Platelet Dysfunction in Glycogen Storage Disease Type I

By Emily E. Czapek, Daniel Deykin, and Edwin W. Salzman

A hemorrhagic tendency has been observed in patients with glycogen storage disease Type I (GSD-I). We have studied the hemostatic mechanism in six patients with GSD-I who have mild to severe bleeding tendencies. All exhibited abnormalities of platelet function (decreased prothrombin consumption, abnormal aggregation reactions, prolonged bleeding time, and low platelet adhesiveness). The degree of dysfunction correlated with the patients' general clinical condition: when patients were acidicotic and severely lipemic, platelet function was strikingly impaired. Two patients received a course of continuous intravenous alimentation. As their general metabolic state approached normal, abnormal platelet function was corrected. We found normal platelets to contain no glucose-6-phosphatase. There was no consistent increase in platelet glycogen levels in patients with GSD-I. These data indicate that the bleeding disorder in GSD-I is an acquired defect rather than a primary platelet abnormality.

A hemorrhagic diathesis has been observed in patients with glucose-6-phosphatase deficiency or Type I glycogen storage disease (GSD-I). Affected individuals frequently have a history of easy bruising, epistaxis, and excessive bleeding following dental and surgical procedures. Previous investigations have implicated a disorder of platelet function in the etiology of such bleeding.1-3 Linneweh et al. attributed the platelet dysfunction to platelet glucose-6-phosphatase deficiency and platelet glycogen accumulation.4,5 Since the development of newer methods of assessing platelet function, only one study of platelet function in GSD-I has been published. In a brief communication, Corby et al.6 described prolonged bleeding times, decreased platelet adhesiveness, abnormal platelet aggregation, and normal platelet factor 3 in patients with various glycogenoses, but the etiology of the platelet dysfunction was not discussed. Our study was undertaken to define further the nature of the hemorrhagic diathesis in GSD-I.

We were afforded the unique opportunity of studying two patients with GSD-I during a course of intravenous hyperalimentation, enabling us to investigate the relationship between platelet function and changing metabolic state.

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MATERIALS AND METHODS

Subjects

Six patients from two families with GSD-I were studied in detail. A seventh patient from a third family was studied to a limited degree. Three patients had biopsy-proven hepatic glucose-6-phosphatase deficiency. The diagnosis in the remaining four patients was based on a clinical course compatible with the disease and a proven enzyme deficiency in a sibling. All patients had a history of marked bruising following minimal trauma. Three had a history of frequent epistaxis and bleeding following dental or surgical procedures although none had experienced life-threatening bleeding. Five unaffected members (parents and three siblings) of one family were also studied. In addition, one patient with marked postprandial hyperlipemia (total lipids 1.5 g/100 ml) and one with Type IV hyperlipemia (total lipids 1.5 g/100 ml) were studied. Normal controls for all coagulation tests were derived from a known population of individuals with no history of a hemorrhagic diathesis. Neither the patients nor the controls had ingested any drugs for 10 days prior to study.

Blood Collection and Processing

Blood was drawn through a 19- or 21-gauge scalp vein needle with a double-syringe technique. Plastic or siliconized glass materials were employed for collection and processing of samples. Samples for platelet glucose-6-phosphatase assays, glycogen determinations, and electron microscopy were collected in acid-citrate-dextrose (ACD) anticoagulant (1 part ACD: 5 parts blood). All other samples were collected in 3.8% sodium citrate (1 part citrate: 9 parts blood). (Addendum A).

Tests of the Soluble Clotting Mechanism

The prothrombin time (PT) and activated partial thromboplastin time (aPTT) were determined by standard techniques. Factors II, V, VII-X, VIII, IX, and XI were assayed by methods previously described. Fibrinogen was determined by the Ellis and Stransky or Clauss methods.

Platelet Function Tests

Platelet factor 3 activity (PF₃) was assayed according to the method of Hardisty and Hutton, and platelet adhesiveness to glass beads was measured by the Salzman technique. Platelet aggregation was performed based on the method of Born and O'Brien, using collagen prepared from (Sigma) bovine tendon as described by Hovig and (Sigma) adenosine diphosphate (ADP) and epinephrine bitartrate. Platelet-rich plasma (PRP) samples were blanked against platelet-poor plasma (PPP) samples from the same individual. In patients with hyperlipemia, there was no appreciable clearing of lipid during preparation of the PPP blank. Three-hour prothrombin consumption in plastic was measured by a modification of the method of Goldstein et al. Bleeding times were performed by the Ivy technique using a Mielke template. Platelet counts were done on a Coulter Model B counter, except for the platelet adhesiveness test, lipid levels precluded an accurate machine count, at which times counts were performed by phase microscopy. Platelet ATP was determined by the method of Strehler and Totter.

Platelet Electron Micrographs

Nine milliliters of paraformaldehyde-cacodylate fixative were added to 1 ml platelet-rich plasma and allowed to stand for 40 min at room temperature. This suspension was centrifuged for 20 min at 3000 g, room temperature, to separate the platelet pellet. The pellet was washed overnight in 0.01 M cacodylate buffer, pH 7.4, containing 7.8 g/100 ml sucrose. It was then dehydrated through alcohol, fixed in osmium, and finally stained with lead. The specimens were examined in a Phillips Model 200 electron microscope.
Platelet Glucose-6-Phosphatase

Platelet glucose-6-phosphatase was determined by a modification of the Eibl and Lands technique. Platelet pellets were obtained from approximately 60 ml of PRP by centrifuging at 2700 g for 5 min at 4°C. The platelets were washed twice by gently resuspending in 0.04 M sucrose (with 0.001 M EDTA) at pH 6.5 and recentrifuging as above. They were resuspended in 0.7 ml of the sucrose-EDTA solution, and a platelet count was performed. One-half milliliter of the suspension was pipetted into the bottom of a motorized tissue homogenizer and was homogenized at 1700 rpm for 4 min at 4°C. The homogenate was quantitatively rinsed from the homogenizer and made up to a final volume such that 1 ml contained approximately 30 mg protein as assayed by the Folin-Lowry method. Care was taken to keep the platelet preparation at 0°C throughout the above procedures. Incubations were conducted with 0.1-0.2 ml of platelet homogenate representing approximately 3-4 mg protein added to 5.4 ml of a buffer containing 4 mM EDTA, 7.3 mM L-histidine, 1 mM NaF, and 60 μg Triton X-100 at pH 6.8. This represents approximately three times the amount of protein necessary to assay for liver glucose-6-phosphatase activity. The reactions were initiated by the addition of 100 μmoles of glucose-6-phosphate, repurified from the Boehringer-Mannheim product, to contain less than 10 nmoles P1/100 moles glucose-6-phosphate. The samples were incubated at 37°C with constant mixing. One and one-half milliliter samples were removed at 15, 30, and 60 min, and the reaction was stopped by adding 0.15 ml cold 80% TCA. After standing for 15 min at 0°C, the samples were centrifuged at 3000 g for 10 min to remove precipitated protein. The supernatants were then assayed for inorganic phosphate (P1) according to the method of Eibl and Lands or the method of Ames. The following additional samples were incubated simultaneously as controls: (1) one containing no glucose-6-phosphate, (2) one containing 100 μmoles β-glycerophosphate instead of glucose-6-phosphate, and (3) one with 80% TCA added before the addition of glucose-6-phosphate. All determinations were performed in duplicate.

Glucose-6-phosphatase was also determined on digitonin-treated platelets by the method of Linneweh et al. measuring inorganic phosphate release.

Platelet Glycogen

Platelet glycogen content was determined after the method of Johnson et al. One milliliter PRP was centrifuged at 2700 g for 5 min at 4°C, and the PPP was decanted. To minimize interference by large amounts of lipid, 2 ml of cold, modified Gaintner's buffer without glucose (0.65 g KH2PO4, 5.52 g NaH2PO4·H2O, 6.29 g NaCl/liter, pH 6.5) were then added to the tube. The platelet pellet was not resuspended but was recentrifuged as above. This modified washing procedure was repeated twice, with care taken to keep the preparation 0°C. After washing, the platelet pellet was lysed by freeze-thawing six times in acetone and dry ice. It was then resuspended in 0.9 ml water. Diazyme hydrolysis of glycogen was performed by adding 1 ml of filtered Diazyme solution [200 mg Diazyme (Miles Laboratories) in 100 ml 0.1 M KH2PO4] to the platelet lysate, mixing, and incubating for 1½ hr at 37°C with constant shaking. Thereafter, specific glucose was measured by the Glucostat (Worthington) method. A sample containing distilled water instead of glycogen served as a control. All determinations were performed in duplicate. Calculation of glycogen content was based on a standard glycogen curve derived from purified commercial glycogen also subjected to Diazyme hydrolysis.

Various control experiments were performed to confirm the validity of our method for determining platelet glycogen. The total glycogen content of samples was directly proportional to the number of platelets incubated over the range of 0.2 × 10^9-1 × 10^10 platelets. The glycogen content of platelets lysed once was slightly lower than that of platelets lysed six times, suggesting there was no major loss during repeated lysis. Recovery of commercial glycogen added to platelet preparations was 100%. Time-course studies showed no significant decrease in glycogen content of platelets assayed within 3 hr of venipuncture; thereafter, glycogen content decreased slowly. The normal values for platelet glycogen agree with those of other workers.
Platelet Acid Phosphatase

Platelet acid phosphatase was measured by the method of Zucker and Borrelli\textsuperscript{31} using Sigma reagents.

RESULTS

We were unable to detect glucose-6-phosphatase activity in normal human platelets. Both homogenized and digitonin-treated platelets incubated with glucose-6-phosphate released only 0.2 µmoles Pi/min/10\textsuperscript{11} platelets. This is approximately 1/30 the amount of Pi released from an equivalent amount of rat liver tissue (Table 1). Substitution of another substrate, β-glycerophosphate, for glucose-6-phosphate, resulted in release of 0.25 µmoles Pi/min/10\textsuperscript{11} platelets. Since β-glycerophosphate has not been reported to be present in platelets, liberation of the same amount of Pi from β-glycerophosphate as from glucose-6-phosphate implies that substrate degradation is secondary to the action of nonspecific phosphatases.

Platelets contain a large amount of acid phosphatase.\textsuperscript{30} Although platelet acid phosphatase is minimally active at pH 6.8 (the pH optimum for glucose-6-phosphatase), actual platelet acid phosphatase measurement at pH 6.8 revealed 32.5 Sigma units/10\textsuperscript{11} platelets to be present. This amount of acid phosphatase is sufficient to liberate 0.36 µmoles Pi/min/10\textsuperscript{11} platelets liberated using glucose-6-phosphate as a substrate.

Tests of Soluble Clotting Factors

Results of tests of the soluble clotting mechanism are shown in Table 2. The PT was minimally prolonged only in instances of extreme hyperlipemia. However, in those instances, specific levels of factors II, V, and VII-X were normal, and it was thought the PT prolongation was due to an artifact of the hyperlipemic plasma. The aPTT was not significantly prolonged in any instance.

Platelet Studies

The platelet count was normal (200,000–600,000) in all patients. Platelet function was impaired to some degree in all patients (Table 3). The prothrombin consumption was uniformly decreased; the bleeding time was prolonged on at least one occasion in five of seven patients, and the platelet adhesiveness was decreased in six of seven patients. Platelet aggregation with adenosine diphosphate (ADP), epinephrine, and collagen was diminished.

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Activity*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>4.7 ± 0.37 µmoles Pi/min/g (n=7) (3.2 ± 0.47 µmoles Pi/min/100 mg protein)</td>
</tr>
<tr>
<td>Platelets</td>
<td>0.2 ± 0.04 µmoles Pi/min/10\textsuperscript{11} platelets (n=10) (0.12 ± 0.06 µmoles Pi/min/100 mg protein)</td>
</tr>
</tbody>
</table>

*Mean ± SEM.
<table>
<thead>
<tr>
<th>Name</th>
<th>PT (sec)</th>
<th>aPTT (sec)</th>
<th>Fibrinogen (mg/100 ml)</th>
<th>Factor IX (%) Normal</th>
<th>Factor VIII (%) Normal</th>
<th>Factor IX (%) Normal</th>
<th>Factor VIII (%) Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>S.M.</td>
<td>11.2-1.5</td>
<td>24.1-35.8</td>
<td>142-490</td>
<td>75-125</td>
<td>75-125</td>
<td>75-125</td>
<td></td>
</tr>
<tr>
<td>a. b.</td>
<td>12.9</td>
<td>22.7</td>
<td>92</td>
<td>92</td>
<td>100</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>G.M.</td>
<td>14.2</td>
<td>32.0</td>
<td>100</td>
<td>180</td>
<td>315</td>
<td>68</td>
<td></td>
</tr>
<tr>
<td>a. b.</td>
<td>15.2</td>
<td>35.0</td>
<td>303</td>
<td>180</td>
<td>110</td>
<td>400</td>
<td></td>
</tr>
<tr>
<td>P.D.</td>
<td>16.0</td>
<td>30.3</td>
<td>284</td>
<td>284</td>
<td>284</td>
<td>284</td>
<td></td>
</tr>
<tr>
<td>N.D.</td>
<td>14.2</td>
<td>37.8</td>
<td>241</td>
<td>241</td>
<td>241</td>
<td>241</td>
<td></td>
</tr>
<tr>
<td>M.D.</td>
<td>14.0</td>
<td>38.9</td>
<td>485</td>
<td>485</td>
<td>485</td>
<td>485</td>
<td></td>
</tr>
<tr>
<td>Pat. D.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
to a variable degree in all cases. Representative tracings are shown in Fig. 1. Abnormalities ranged in severity from disaggregation with $5 \times 10^{-6} \text{M ADP}$ to no reaction to any reagents used. Addition of one part of patient’s platelet-poor plasma to four parts of normal platelets did not significantly impair aggregation with collagen, ADP, and epinephrine. Clot retraction was normal in all patients; platelet factor 3 activity was normal in five patients, and platelet ATP content was normal in the four patients tested. The five unaffected members of the D. family studied all had normal bleeding times and platelet adhesiveness tests. In addition, Mrs. D. had a normal prothrombin consumption, platelet factor 3 activity, and aggregation studies. Both the patient with postprandial hyperlipemia and the patient with Type IV hyperlipemia had normal platelet function studies.

**Platelet Glycogen**

Platelet glycogen determined in samples from 15 normal volunteers was $0.495 \pm 0.068 \mu \text{moles/10}^9 \text{platelets (mean } \pm \text{ SEM). The glycogen content of washed platelets was slightly lower, } 0.38 \pm 0.02 \mu \text{moles/10}^9 \text{ platelets. This was not unexpected and can be accounted for by a variety of processes, such as leakage of glycogen through a damaged cell membrane, increased glycogenolysis stimulated by washing, or by the rupture of some platelets during the washing procedure. In patients with glycogen storage disease, platelet glycogen is...**

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**Table 3. Platelet Studies in GSD-I Patients**

<table>
<thead>
<tr>
<th>Name</th>
<th>Bleeding Time (min)</th>
<th>Platelet Adhesiveness (%)</th>
<th>Prothrombin Consumption (% Consumed)</th>
<th>PF3 Activity (sec)</th>
<th>Platelet ATP ($38.8 \pm 0.77 \times 10^{-9} \text{ moles/10}^9 \text{ Platelets}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal values</td>
<td>&lt;7</td>
<td>&gt;25</td>
<td>&gt;60</td>
<td>&lt;45</td>
<td>—</td>
</tr>
<tr>
<td>S.M.</td>
<td>a. 12</td>
<td>37</td>
<td>25</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>b. 8.5</td>
<td>—</td>
<td>16</td>
<td>40.0</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>c. 4</td>
<td>67</td>
<td>27</td>
<td>41.5</td>
<td>—</td>
</tr>
<tr>
<td>G.M.</td>
<td>a. 12</td>
<td>0</td>
<td>&lt;35</td>
<td>38.3</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>b. 13.5</td>
<td>0</td>
<td>0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>P.D.</td>
<td>13</td>
<td>1</td>
<td>—</td>
<td>—</td>
<td>0.38</td>
</tr>
<tr>
<td>N.D.</td>
<td>a. 7.5</td>
<td>19</td>
<td>—</td>
<td>—</td>
<td>0.39</td>
</tr>
<tr>
<td></td>
<td>b. 10</td>
<td>11</td>
<td>0</td>
<td>36.4</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>c. 12</td>
<td>23</td>
<td>45</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Pu.D.</td>
<td>a. 9.5</td>
<td>13</td>
<td>—</td>
<td>—</td>
<td>0.37</td>
</tr>
<tr>
<td></td>
<td>b. 5</td>
<td>10</td>
<td>7</td>
<td>40.1</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>c. 10.5</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>M.D.</td>
<td>a. 15.5</td>
<td>7</td>
<td>—</td>
<td>—</td>
<td>0.35</td>
</tr>
<tr>
<td></td>
<td>b. &gt;20</td>
<td>22</td>
<td>51</td>
<td>31.1</td>
<td>—</td>
</tr>
<tr>
<td>R.J.</td>
<td>4</td>
<td>13</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

*Mean $\pm$ SEM.
PLATELET DYSFUNCTION IN GLYCOGEN STORAGE DISEASE

Fig. 1. Representative platelet aggregation tracings in two GSD-I patients. Platelets from S.M. failed to respond to high doses of collagen, ADP, or epinephrine. Platelets from P.D. showed a primary response to ADP only.

Platelet glycogen varied from well within the normal range to slightly above the upper range of normal (Table 4). In no instance was platelet glycogen greatly increased.

Life-line Studies

Two patients with GSD-I, to be reported elsewhere, were given continuous intravenous hyperalimentation. On this therapy, previously abnormal values for pH, CO₂ content, blood lactate, plasma lipid level, BUN,
and serum uric acid were restored to normal or near normal levels. In both children, platelet function was abnormal prior to initiation of intravenous feedings, as evidenced by a prolonged bleeding time, decreased prothrombin consumption, decreased aggregation of platelets with ADP, epinephrine, and collagen, and in one child, decreased platelet adhesiveness. During a 14-day course of intravenous hyperalimentation, platelet function reverted dramatically toward normal in both patients. Representative data from one patient are shown in Fig. 2. Serum lipid levels are shown as an arbitrary indicator of the patient's general clinical condition. As serum lipid levels fell from 16 g/100 ml to approximately 1 g/100 ml over a period of 7–12 days, the prothrombin consumption increased from 0% to 55%, the platelet adhesiveness increased from 0% to 42%, and the bleeding time shortened from 12 min to 5 min. Platelet glycogen content did not change significantly. The

Table 4. Platelet Glycogen Content

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Platelet Glycogen (µmoles/10⁶ Platelets)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normals (n=15)</td>
<td>0.38 ± 0.02* (Range 0.24–0.54)</td>
</tr>
<tr>
<td>GSD-I patients</td>
<td></td>
</tr>
<tr>
<td>G.M.</td>
<td>0.55</td>
</tr>
<tr>
<td>S.M.</td>
<td>0.39</td>
</tr>
<tr>
<td>Pu.D.</td>
<td>0.44</td>
</tr>
<tr>
<td>N.D.</td>
<td>0.40</td>
</tr>
<tr>
<td>M.D.</td>
<td>0.22</td>
</tr>
</tbody>
</table>

*Mean ± SEM.
improvement in platelet response to aggregating agents is shown in Fig. 3. Prior to intravenous therapy, the patient’s platelets failed to aggregate with 100 μl collagen, $10 \times 10^{-6}$ M ADP, and $5 \times 10^{-6}$ M epinephrine. Following 12 days of therapy, the patient’s platelets reacted normally to all three agents.

Electron Microscopic Studies

There was no difference in the appearance of the platelets from patients with GSD-I than from normal platelets. Representative micrographs of normal and GSD-I platelets, before and during life-line therapy, are shown in Fig. 4.

DISCUSSION

The hemorrhagic diathesis in patients with GSD-I has been attributed to platelet dysfunction.1-3 Abnormal platelet function has been postulated to be secondary to platelet glucose-6-phosphatase deficiency with accumulation of platelet glycogen.4,5 Our studies confirm the presence of a defect in platelet function in patients with GSD-I. The prothrombin consumption was decreased in all patients, and the bleeding time and platelet adhesiveness were abnormal in most instances. The response of platelets to collagen, epinephrine, and ADP was decreased or absent.

Impaired prothrombin consumption in the face of a normal soluble clotting
Fig. 4. Electron micrographs of normal and GSD-I platelets. (A), normal platelets; (B), platelets from patient G.M. before life-line therapy; (C), platelets from G.M. during life-line therapy when platelet function had returned to normal.

system indicates platelet dysfunction. The discrepancy between decreased prothrombin consumption and normal platelet factor 3 activity in our patients most likely reflects a difference in the sensitivity of the two tests. We have observed such a discrepancy in some patients with platelet dysfunction syndromes on other occasions in our laboratory, and we believe this reflects the heightened sensitivity of the retarded prothrombin consumption test\textsuperscript{16} and the relative insensitivity of the kaolin-activated platelet factor 3 test.

We were unable to demonstrate glucose-6-phosphatase activity in normal human platelets. In our samples, the small amount of inorganic phosphate produced could be explained by the action of nonspecific, residual acid phosphatase. We were also unable to confirm the presence of greatly increased platelet glycogen levels in patients with GSD-I. Glycogen determinations did not exceed the upper limits of normal.

The electron micrographs of platelets of our patients with GSD-I also failed to demonstrate an increase in platelet glycogen granules. In studying many sections of platelets, we were able to find platelets from both normal subjects and patients that contained a large number of glycogen granules. In both cases, platelets could also be found that contained very little glycogen. Our findings are in contrast to electron micrographs of platelets from GSD-I patients published elsewhere, showing an increase in platelet glycogen.\textsuperscript{2} Because of the variability in number of glycogen granules among individual platelets and in different areas of the same platelet, the apparent increase previously reported might perhaps have been due to a sampling error. In theory, if the platelet dysfunction in GSD-I is not secondary to glucose-6-phosphatase deficiency, there is no reason to expect the platelet to accumulate excess glycogen.

The above data indicate that the platelet dysfunction in GSD-I is not secondary to platelet glucose-6-phosphatase deficiency and platelet glycogen accumulation. Rather, the platelet dysfunction appears to be related to some aspect of the abnormal metabolism of patients with GSD-I.
this hypothesis is derived from both clinical observations and laboratory data. Physicians following members of the D. family over the past several years noted that as the children grew older their general clinical condition improved. Concomitantly, their hemorrhagic tendency, manifested by frequent nosebleeds and easy bruising, became less pronounced, although a bleeding diathesis was still evident when the hemostatic mechanism was severely challenged by surgery. More concrete evidence for a correlation between platelet function and general metabolic state is afforded by the studies obtained on S.M. and G.M. prior to and during intravenous hyperalimentation. Both patients showed almost total correction of platelet function as values for pH, CO₂, BUN, serum lipids, and uric acid approached normal. Following cessation of intravenous therapy, platelet function deteriorated progressively.

None of the specific metabolic abnormalities, such as hyperlipemia, hyperuricemia, hyperglycemia, chronic metabolic acidosis, and increased lactate and pyruvate levels found in patients with GSD-I has definitely been shown to cause platelet dysfunction. In some respects, these patients are analogous to patients with uremia; both have hyperuricemia and chronic acidosis and both have a disorder of platelet function frequently characterized by a prolonged bleeding time, decreased platelet adhesiveness, and abnormal aggregation. However, the BUN in patients with GSD-I usually does not approach the levels seen in uremic patients with platelet dysfunction. Triglyceride infusions in normal individuals have been shown to decrease platelet adhesiveness. However, in the individuals tested there was no prolongation of the bleeding time. In our limited study of patients with other forms of hyperlipemias, we did not observe impaired platelet function. We were not able to find patients with grossly elevated lipid levels who were not receiving therapy directed at their hyperlipemia. Hyperuricemia accompanying other clinical conditions has not been associated with a hemorrhagic diathesis. Finally, the time course (several days) of correction of platelet function in S.M. and G.M. suggests that metabolic abnormalities corrected within hours of institution of intravenous therapy, such as acidemia and hypoglycemia, are less likely to be related to the platelet dysfunction.

From the above studies, we conclude that the defect in platelet function in patients with GSD-I is not secondary to platelet glucose-6-phosphatase deficiency. Instead, the finding of normal platelet function in GSD-I patients receiving hyperalimentation suggests the platelet dysfunction is an acquired consequence of the abnormal metabolism that characterizes this disease.

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