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Differential Effects of Enzyme Supplementation Therapy on Manifestations of Type 1 Gaucher Disease

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BACKGROUND: In type 1 Gaucher disease (GD), the accumulation of glucocerebroside in macrophages, caused by deficient activity of glucocerebrosidase, results in a variety of disease manifestations. In addition to the characteristic features of hepatosplenomegaly, cytopenia, and bone abnormalities, resting energy expenditure (REE) and glucose production are increased. In this study the effects of enzyme supplementation therapy on metabolic parameters in relation to other disease manifestations in type 1 GD patients are investigated.

PATIENTS AND METHODS: In 12 adult type 1 GD patients, measurements of REE (by indirect calorimetry), liver and spleen volume (by spiral computerized axial tomography [CT]) and hemoglobin and platelet count were obtained before and after 6 months of alglucerase therapy (15 U/kg per month). In 7 of the 12 patients hepatic glucose production was measured by infusing 3-3H glucose. For comparison, REE and glucose metabolism were studied in 7 weight- and age-matched healthy subjects.

RESULTS: REE and glucose production were increased in GD patients as compared with controls (REE: 29.8 kcal/kg/24 h ± 3.6 and 23.1 ± 2.3 kcal/kg/24 h, respectively, P < 0.05; glucose production: 14.00 μmol/kg/min ± 0.51 and 10.77 μmol/kg/min ± 0.26, respectively, P < 0.03). There were no differences in plasma glucose concentrations. Whereas the elevated REE decreased after 6 months of alglucerase therapy from 129% to 120% of predicted values (P < 0.01), the increase in hepatic glucose production did not change. An increase in weight occurred after 6 months of treatment (1.7 ± 0.8 kg, P < 0.001), which was accounted for by an increase in fat mass of 1.6 ± 1.5 kg (P < 0.02). Hemoglobin levels increased from 11.2 mg/dL to 12.1 mg/dL (P = 0.05) and platelet counts rose from 84 × 10⁹/L to 113 × 10⁹/L (P < 0.05). Although liver and spleen volumes decreased by ~10% and ~20%, respectively, there was no correlation between the decrease in organ volumes and the decrease in REE.

CONCLUSIONS: Treatment with alglucerase improves hypermetabolism and organomegaly in GD, whereas the increase in glucose production persists. Therefore, the dose-response effects of alglucerase are variable for the different manifestations of type 1 GD. Am J Med. 1997;103:185–191. © 1997 by Excerpta Medica, Inc.

Gaucher disease (GD) is the most frequently encountered lysosomal storage disorder in humans.¹ Deficient activity of the lysosomal enzyme glucocerebrosidase (glucosylceramidase; EC 3.2.1.45) results in accumulation of its substrate, glucocerebroside, in macrophages. The clinical manifestations of type 1 GD are highly variable and cannot be predicted from the properties of mutant glucocerebrosidase.¹,² In general, the altered size, number, and function of macrophages result in a variety of disease manifestations. The presence of lipid-laden macrophages results in a number of clinical signs such as splenomegaly, hepatomegaly, bone lesions, and cytopenia. In addition many patients suffer from fatigue, weight loss, and intolerance to fasting. These symptoms may be related to metabolic changes. Abnormal liver function in GD is indicated by the considerably increased hepatic glucose production, presumably as a result of the interaction of hepatocytes with lipid-laden macrophages.³ GD is also associated with other metabolic abnormalities such as an increased resting energy expenditure (REE).³,⁴ It has been suggested by others that the hypermetabolism is related to the Gaucher cell burden.⁴

Enzyme supplementation therapy with purified glucocerebrosidase is aimed at partially restoring the defective activity of glucocerebrosidase within mac-
Targeting of the enzyme to macrophages was attained by modifying the oligosaccharide chain to expose terminal mannose residues, resulting in uptake by macrophages through their mannose receptors. This mannose-terminated glucocerebrosidase is now commercially available as alglucerase (Ceredase; Genzyme Co., Boston, Massachusetts). Alglucerase has proven to be effective in improving the manifestations of GD such as hepatosplenomegaly and cytopenia. It is presently unknown whether the metabolic abnormalities improve similarly in relation to the other symptoms. Therefore the aim of the present study was to evaluate the effect of enzyme supplementation therapy on metabolic parameters in relation to changes in hepatic and splenic volumes, hemoglobin level, and platelet count. Type 1 GD patients were investigated with respect to REE (n = 12) and glucose metabolism (n = 7) before and after 6 months of treatment with alglucerase. For comparison, identical metabolic measurements were obtained in seven healthy control subjects.

### PATIENTS AND METHODS

#### Patients

Twelve adult type 1 GD patients were investigated (age 23 to 52 years). All patients who started enzyme supplementation therapy between January 1993 and March 1994 and gave informed consent were included. A diagnosis of GD was biochemically and/or genetically confirmed. Table I shows the characteristics of the patients. The severity of the disease was mild to moderate according to the severity scoring index. All patients had liver and spleen enlargement. Five patients were splenectomized. None of the patients had evidence of a recent acute illness such as a bone crisis, splenic infarction, or infection and no medication was used.

Seven healthy control subjects with normal medical history and physical examination served as a control group. Patients and controls consumed a weight maintaining diet of at least 250 g of carbohydrates for 3 days before the study. All subjects were informed of the nature, purpose, and possible risks involved in the study before giving their consent to participate. The studies were approved by the Institutional Ethics and Isotope Committees.

#### Protocol

Measurements were performed before and after 6 months of alglucerase treatment.

**Alglucerase treatment.** Alglucerase treatment in GD patients was started at a dose of 1.15 U/kg intravenously, 3 times weekly (1 U of alglucerase hydrolyzes 1 nmol of glucocerebroside per hour). After di-

### Table I

<table>
<thead>
<tr>
<th>Patient Characteristics before Alglucerase Treatment</th>
<th>Platelet Count (10^11/L)</th>
<th>Hb level (mg/dL)</th>
<th>Fat Mass (kg)</th>
<th>Fatfree Mass (kg)</th>
<th>Height (m)</th>
<th>Liver Volume (mL)</th>
<th>Spleen Volume (mL)</th>
<th>Hb level (mg/dL)</th>
<th>Platelet Count (10^11/L)</th>
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<tbody>
<tr>
<td><strong>Patient</strong></td>
<td><strong>Gender</strong></td>
<td><strong>Age (yrs)</strong></td>
<td><strong>Age at Splenectomy (yrs)</strong></td>
<td><strong>SSI</strong></td>
<td><strong>Weight (Kg)</strong></td>
<td><strong>Fat Mass (Kg)</strong></td>
<td><strong>Fatfree Mass (Kg)</strong></td>
<td><strong>Height (m)</strong></td>
<td><strong>Liver Volume (mL)</strong></td>
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<td>5</td>
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<td>11.2</td>
<td>5.3</td>
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</tbody>
</table>

**Mean ± SE**

**Patients 39**

**Controls (n = 7)**  

*SSI* refers to the severity scoring index (11). *Sx* refers to splenectomized status.
lution in 100 mL of saline, the drug was infused over 45 minutes.

Liver and spleen volumes were measured by spiral computerized axial tomography (spiral CT). The accuracy for liver and spleen volume measurements using conventional CT is reported to be 3% to 5%.\textsuperscript{15,16} The use of spiral CT allows measurement of 26 cm of the length of an organ within a single breath-hold, eliminating misregistration of adjacent scan slices.\textsuperscript{17} Reductions in organ volumes were calculated as percent reduction from the volume measured 6 months earlier and corrected for a change in body weight.\textsuperscript{18} Liver and spleen volumes were not measured in the control subjects. Hemoglobin levels and platelet count were determined at baseline and after 6 months of treatment.

**Metabolic measurements.** Patients and control subjects fasted from the evening (6:00 AM) preceding the investigation until the end of the investigation. The patients were confined to bed during the study. On the study day, at 7:00 AM a 19-gauge catheter was placed retrogradely in a hand vein. This hand was placed in a heated (65°C) box for sampling of arterialized venous blood.\textsuperscript{19} Another 19-gauge catheter was inserted in a forearm vein of the contralateral arm for primed (120 nCi/kg), continuous (1.5 nCi/kg/min) infusion of 3-3H-glucose (Amersham, Den Bosch, The Netherlands), started at 08:00 AM and continued throughout the study until 10:15 AM. The catheters were kept patent by a slow saline drip. Plasma samples were collected for 3-3H-glucose specific activity at 8:00 AM (basal value), at 10:00, 10:05, 10:10, and 10:15 AM. In the blood samples of 10:00 and 10:05 AM concentrations of glucose, insulin, C-peptide, glucagon, epinephrine, norepinephrine, cortisol, growth hormone, free fatty acids (FFA), glycerol, lactate, β-hydroxybutyrate, and acetoacetate were measured.

**Resting energy expenditure measurement by indirect calorimetry.** Final measurements for determination of REE by indirect calorimetry were performed between 9:00 and 10:00 AM as described elsewhere,\textsuperscript{20,21} using the method of the ventilated hood with a mass flow meter, a zirconium oxygen sensor, and an infrared absorption carbon dioxide (CO\textsubscript{2}) analyzer (Model 2900; Computerized Energy Measurement system, Sensor Medics, Anaheim, California). The mass flow meter and the oxygen (O\textsubscript{2}) and CO\textsubscript{2} analyzers were calibrated and subsequently verified before each measurement. Moreover, before each series of experiments, the equipment was checked by alcohol burn. O\textsubscript{2} consumption and CO\textsubscript{2} production were measured continuously for at least 30 minutes. During the measurements, the room was darkened and subjects were asked to close their eyes. To allow for adaptation to the hood, the results of the first 10 minutes were discarded. Body composition and lean body mass (LBM) were assessed by a body impedance analyzer (BIA 109; Akern, Florence, Italy).\textsuperscript{22}

**Assays**

All measurements were performed in duplicate. Plasma glucose was measured by the glucose oxidase method (Beckman Glucose Analyzer; Beckmann Instruments Inc., Mijdrecht, The Netherlands). Plasma glucose specific activity was measured as described elsewhere.\textsuperscript{20,21} Plasma insulin concentration was measured by commercial radioimmunoassay (RIA) (Pharmacia Diagnostics, Upplands, Sweden), C-peptide by commercial RIA (RIA-Matt, Malinckrodt Diagnostics, Dietzenbach, Germany), glucagon by RIA (Daiichi Radioisotope Labs, Tokyo, Japan), catecholamines by high pressure liquid chromatography and electrochemical detection, after purification on Biorex 70 and concentration by solvent extraction,\textsuperscript{23} cortisol by fluorescence polarization immunoassay on TDx (Abbott Laboratories, North Chicago, IL), and growth hormone by immunoradiometric analysis (Nichols Institute, Los Angeles, California). Serum FFA concentration was measured by an enzymatic method (NEFAC, Wako Chemical GmbH, Neuss, Germany), plasma glycerol, lactate, β-hydroxybutyrate, and acetoacetate by enzymatic methods (Boehringer Mannheim, Almere, The Netherlands) on a Cobas Bio Centrifugal Analyzer. Plasma alanine was measured by aminoacid analyzer (Chromco 500; Kontron, Italy).

**Calculations**

Glucose turnover was calculated by dividing the infusion rate of 3-3H-glucose by the plateau of 3-3H-glucose-specific activity. Glucose clearance was calculated by dividing total glucose turnover by plasma glucose concentration and given as mL/kg/min. Net glucose and fat oxidation rates were calculated according to published methods,\textsuperscript{24–26} with the following constants. The respiratory quotient for oxidation of lipid is 0.707 and for carbohydrate 1.000. Oxygen consumed is 966.3 mL/g protein, 748.8 mL/g glucose, and 2019.3 mL/g fat; by oxidation of 1 g of protein N, 773.9 mL of CO\textsubscript{2} is produced (1 g of nitrogen is equivalent to 6.25 g of protein). Protein oxidation rates were obtained from urinary nitrogen excretion (urine collected between 8:00 AM and 4:15 PM), after correction for changes in plasma urea levels.\textsuperscript{24} The predicted values of REE were calculated by the formulas of Harris-Benedict.

**Statistics**

The results are presented as mean ± SD. Differences between patients and controls were tested by
rank sum test. Differences between data obtained before and after 6 months of alglucerase therapy were tested by the signed rank test. A P value of <0.05 was considered to represent a significant difference.

RESULTS

Subjects

Table I shows the characteristics of the GD patients. There were no statistical significant differences between the 7 patients that were studied in more detail (patients 6 to 12) and the healthy controls as to weight (72 ± 4 kg versus 78 ± 5 kg), height (1.77 ± 0.05 m versus 1.81 ± 0.02 m), fat free mass (52.3 ± 3.3 kg versus 59.4 ± 4.4 kg) and fat mass (19.6 ± 0.9 kg versus 18.1 ± 1.1 kg).

Nonmetabolic Parameters

Six months of alglucerase treatment resulted in a decrease in hepatosplenomegaly (Table II). The mean decrease in liver volume was 10 ± 4.2% (n = 10; P = 0.005) and in spleen volume 20 ± 9.1% (n = 7; P < 0.03). Excluded from this analysis were patient 6, because no liver volume was made at the appropriate time point, and patient 12 because the liver volume was normal before treatment. Hemoglobin levels were assessed in patients with pretreatment levels of 12.7 mg/dL or less (n = 10) and platelet counts of 150 × 10^9/L or less (n = 9). Hemoglobin levels increased from 11.2 mg/dL to 12.1 mg/dL (P = 0.05) and platelet counts rose from 84 × 10^9/L to 113 × 10^9/L (P = 0.03, Table II).

Resting Energy Expenditure and Weight

The observed REE before treatment was increased by ~20% (29.8 kcal/kg/24 h ± 3.6) as compared with the predicted REE (23.1 ± 2.3 kcal/kg/24 h) in the GD patients and by ~25% as compared with the controls (23.7 ± 0.8 kcal/kg/24 h). After 6 months of therapy, there was a significant increase in weight (mean 1.7 ± 0.8 kg, P < 0.01). This was associated with a decrease of 9% in the observed REE (REE at 6 mo: 27.1 ± 3.2 kcal/kg/24 h, P < 0.01; Table II). Fat mass increased by 1.6 ± 1.5 kg (P < 0.02) whereas fat free mass did not change significantly.

Relation Between REE, Hepatic Glucose Output, and Organ Volumes

In Table II the measurements of weight, organ volumes, REE, and hepatic glucose output are given before and after 6 months of treatment. No association between the extent of increase in REE and the degree of increase in hepatic glucose output was seen. Before treatment, no correlation between the REE and liver and spleen volumes was found. The decrease in REE did not correlate with the change in organ volumes (r = 0.02 for liver, r = 0.40 for spleen, and r = 0.37 for liver and spleen).

Substrate Metabolism

Table III shows the parameters of substrate metabolism before and after 6 months of alglucerase therapy in patients and controls. Plasma glucose and FFA concentrations were not different between the two groups and were not affected by enzyme supplementation therapy. Basal glucose production was ~23% higher in patients than in controls (P < 0.01). Glucose clearance was also ~24% higher in GD patients. However, despite 6 months of alglucerase therapy, there was no change in glucose production or glucose clearance. Net glucose and fat oxidation rates were not different between patients and controls and were unaffected by alglucerase therapy.

Hormone Concentrations

Table IV shows the hormone concentrations in patients and controls. Insulin levels were higher in patients than in controls (P < 0.05), although C-peptide levels were not statistically significant different. The differences in REE between patients and con-

<table>
<thead>
<tr>
<th>TABLE II</th>
</tr>
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<tbody>
<tr>
<td>Weight, Organ Volumes, REE, and Hepatic Glucose Output before and after 6 Months of Alglucerase Treatment</td>
</tr>
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<tr>
<td></td>
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<tr>
<td>12</td>
</tr>
<tr>
<td>Sx refers to splenectomized status.</td>
</tr>
<tr>
<td>REE = resting energy expenditure; HGO = hepatic glucose output;</td>
</tr>
</tbody>
</table>
## DISCUSSION

The spectrum of manifestations of type 1 GD is highly heterogeneous. In accordance with previous studies, enzyme supplementation therapy was found to improve the nonmetabolic symptoms of the disease. In addition, we established that hypermetabolism, reflected in increased REE in GD patients improves during enzyme supplementation therapy, although normalization was not achieved. This improvement of REE was associated with an increase in body weight. Basal glucose production is another metabolic parameter that is elevated in GD. However, in contrast to many other features of GD, this increase in glucose production was not affected by alglucerase treatment. We studied a rather circumscribed population of mild to moderately affected patients with GD, treated with a very low dose of alglucerase. Therefore it is possible that patients on higher doses of enzyme or with more severe disease respond differently with respect to the metabolic parameters. Nonetheless, these data illustrate that the features of type 1 GD do not respond similarly to enzyme supplementation therapy in the low range of alglucerase used in this study. The effects of different doses on the other disease manifestations, including liver and spleen volumes, are the subject of debate. Comparison of different studies is hampered by the diversity of patients and treatment protocols. However, at 6 months of treatment the changes in liver and spleen volumes with a dose of 15 U/kg per month as used in this study are not clearly different from the reductions achieved with doses of 30 to 130 U/kg per month. Nonetheless, we can not exclude the possibility that a higher dose of alglucerase would have resulted in a greater decrease of REE and/or a decrease in glucose production.

### TABLE III

Parameters of Postabsorptive Glucose and Fat Metabolism before (m0) and after 6 Months (m6) of Alglucerase Therapy in GD Patients and Controls

<table>
<thead>
<tr>
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<th>Controls (n = 7)</th>
<th>Gaucher Patients (n = 7)</th>
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<tr>
<td></td>
<td>m0</td>
<td>m6</td>
</tr>
<tr>
<td>Glucose concentration</td>
<td>5.1  ± 0.1</td>
<td>5.1  ± 0.2</td>
</tr>
<tr>
<td>Glucose production</td>
<td>10.77 ± 0.26</td>
<td>14.00 ± 0.51*</td>
</tr>
<tr>
<td>Glucose clearance</td>
<td>2.11 ± 0.08</td>
<td>2.78 ± 0.15†</td>
</tr>
<tr>
<td>Glucose oxidation</td>
<td>1.19 ± 0.34</td>
<td>1.23 ± 0.25</td>
</tr>
<tr>
<td>Protein oxidation</td>
<td>0.71 ± 0.05</td>
<td>1.01 ± 0.26</td>
</tr>
<tr>
<td>Lactate concentration</td>
<td>0.57 ± 0.05</td>
<td>0.70 ± 0.04*</td>
</tr>
<tr>
<td>FFA concentration</td>
<td>0.56 ± 0.08</td>
<td>0.62 ± 0.09</td>
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<tr>
<td>Triglyceride concentration</td>
<td>1.08 ± 0.19</td>
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</tr>
<tr>
<td>Fat oxidation</td>
<td>1.00 ± 0.22</td>
<td>1.19 ± 0.18</td>
</tr>
</tbody>
</table>

* Values are given as mean ± SE.
† P < 0.03 GD pts (m0) versus controls.

### TABLE IV

Plasma Concentrations of Thyroid and Glucoregulatory Hormones in the Postabsorptive State Before (m0) and after 6 months (m6) of Alglucerase Therapy in GD Patients and Controls

<table>
<thead>
<tr>
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<th>Controls (n = 7)</th>
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<tbody>
<tr>
<td></td>
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<tr>
<td>Thyroxine</td>
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<td>Triiodothyronine</td>
<td>1.70 ± 0.12</td>
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<td>Insulin</td>
<td>37 ± 5</td>
<td>58 ± 6†</td>
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<tr>
<td>C-peptide</td>
<td>0.76 ± 0.15</td>
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<tr>
<td>Glucagon</td>
<td>94 ± 9</td>
<td>93 ± 9</td>
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<tr>
<td>Adrenaline</td>
<td>115 ± 38</td>
<td>115 ± 22</td>
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<tr>
<td>Noradrenaline</td>
<td>0.96 ± 0.13</td>
<td>0.72 ± 0.11</td>
</tr>
<tr>
<td>Cortisol</td>
<td>0.39 ± 0.09</td>
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<tr>
<td>Growth hormone</td>
<td>1.4 ± 0.7</td>
<td>1.5 ± 0.9</td>
</tr>
</tbody>
</table>

* Values are given as mean ± SE.
† P < 0.05 GD pts (m0) versus controls.

trols were not related to differences in plasma concentrations of catecholamines or thyroid hormones. Alglucerase therapy had no effect on hormone concentrations in the patient group.
Several pathophysiological mechanisms can explain the manifestations of GD. Hepatosplenomegaly and bone lesions are the result of massive, usually inhomogenous, infiltration with lipid-loaden macrophages. In addition, in many patients fibrosis and altered vascularization adds to the organomegaly. It has been suggested that a toxic process, affecting the tissue around the storage cells, contributes to the pathophysiology of GD. In the liver, the hepatocytes are not involved in the storage and liver function is usually not disturbed. In line with this, the mechanism responsible for the increase in basal glucose production in GD cannot merely be the result of increased macrophage mass. Because hepatocytes are the glucose-producing cells within the liver, impairment of hepatocyte function by accumulation of Gaucher cells within the liver would be reflected in decreased glucose production rates, as in cirrhosis. This stimulation of glucose production is not related to classical endocrine mechanisms because GD does not affect the plasma concentrations of glucoregulatory hormones. Interestingly, in vitro studies have provided evidence that glucose production by hepatocytes is modulated by paracrine interaction with liver macrophages through production of adenosine, prostaglandins, and cytokines. In vivo observations also provide support for the hypothesis that paracrine mechanisms are involved in hepatic glucose production. We speculate that in GD the activity of liver macrophages is changed by the metabolic disorder, causing altered paracrine macrophage-hepatocyte interaction that results in increased glucose production. Consequently, the increase in glucose production might be a reflection of altered function of the hepatic Gaucher macrophages rather than of an increase in hepatic Gaucher macrophage mass. The observation in the present study, that partial restoration of defective glucocerebrosidase activity induces a decrease in hepatic macrophage mass (as reflected in decreased liver volume) without any effect on the increased glucose production, supports this. In line with this hypothesis of activation of Gaucher cells is the observation that glucocerebrosidase stimulates lipopolysaccharide-stimulated interleukin-1 production by murine macrophages.

In our previous study we have shown that REE is increased in the GD patients by ~30% compared with healthy controls. This is confirmed by a larger series of patients in the present study. In addition, it is shown that after treatment with alglucerase for 6 months a considerable decrease in hypermetabolism occurs, although REE remains elevated as compared with controls. This decrease in hypermetabolism was associated with an increase in weight, despite a reduction in liver and spleen volume. The observation that an increase in weight in normal subjects is followed by a compensatory increase in energy expenditure suggests that the decrease in REE in our patients may in fact be even more robust than we have measured. Barton et al suggested that the increase in REE in GD patients was correlated to the degree of liver and spleen enlargement, eg, Gaucher cell mass. This was based on calculations from liver and spleen size by isotope scanning and measurements of REE before and after splenectomy. In our study, using a more accurate method of volume measurement by spiral CT, we could not confirm a correlation between the extent of increase in REE and the degree of liver and spleen enlargement. Moreover, we could not establish a correlation between the decrease in REE and the reduction in liver and spleen size after 6 months of alglucerase therapy. Again, there is no simple relation between the elevated REE and Gaucher cell burden as measured by liver and spleen size. Gaucher cell burden may still be a determinant of REE if another important compartment of Gaucher cells, the bone marrow, could be taken into account. Alternatively, the increase in REE could be a reflection of an activation of macrophages affected by GD. In general, conditions with macrophage activation, such as infection and trauma, are associated with hypermetabolism presumably mediated by elaboration of inflammatory mediators such as cytokines. Whether cytokines are involved in the pathophysiology of the increased REE in GD remains to be determined. Measurements of cytokine levels in the direct environment of the affected macrophages in GD patients or studies in animal models are necessary to clarify the postulated mechanisms. In an attempt to correlate other plasma parameters for GD activity with the metabolic changes we investigated the recently discovered enzyme chitotriosidase, which is extremely elevated in GD plasma, in relation to REE and glucose production. However, levels of chitotriosidase did not correlate with either the increased glucose production or REE (data not shown).

The pleiotropic effects of GD on different organs are reflected in a spectrum of manifestations. Conversely, these manifestations can be used to monitor the effects of enzyme replacement therapy on different organs. For instance, postabsorptive glucose production is a reflection of stimulation of hepatocytes, presumably by Gaucher cells. REE is a function of whole body metabolism, which is apparently stimulated. Therefore the evaluation of these metabolic parameters provides additional information to the traditional parameters (eg, blood counts, liver, and spleen volumes) on the pathophysiology and the response to therapy in GD. This knowledge is of clinical relevance because the therapeutic goals and the

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optimal dose of expensive alglucerase therapy have not been firmly delineated.

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