Gel chromatographic profile of dapsone (DDS) and anti-DDS antibody in dissociated CIC for sera of two lepromatous patients. G-200 column (1 x 10 cm); V₀=void volume and Vₜ=total volume of column. Relative titre for anti-DDS (by ELISA*) and DDS concentration (by ELISIT®).

We have no evidence that such complexes play any role in ENL. Nevertheless, screening for antibody to dapsone and for CICs of dapsone/anti-dapsone could be important in longitudinal studies of the response of leprosy patients to chemotherapy.

We thank Mrs M. de Wit for her technical assistance.

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R. J. W. REES

SECONDARY HYPERAMMONEMIA: A POSSIBLE MECHANISM FOR VALPROATE ENCEPHALOPATHY

Sir,—Hyperglycinämia, hyperglycinuria,¹ propionicaiduria,² and Reye’s syndrome³ have been reported in epileptic patients taking the anticonvulsant drug valproic acid (VPA). While investigating possible mechanisms of VPA toxicity we found increased plasma glycine and propionate concentrations in symptom-free patients taking VPA (table I). With informed consent, loading tests with 500 mg VPA orally were done in three children who had experienced severe vomiting, lethargy, or coma while on VPA. Plasma propionate rose from baseline 5 to 82 nmol/l (case 1), 21 to 81 nmol/l (case 2), and 14 to 62 nmol/l (case 3) by 3 h after the dose. However, these data did not explain why some children became ill from VPA; these levels of glycine and propionate are not nearly as high as those found in children ill with inborn errors of metabolism involving these compounds.*⁵

Recently, we observed hyperammonemia in a patient taking VPA who became obtunded but had no evidence of liver disease or drug intoxication. Since hyperammonemia occurs in several metabolic diseases, including propionyl CoA carboxylase deficiency,⁴ we investigated a possible relation between VPA, propionate, and ammonia that might suggest a mechanism of VPA toxicity.

A 4-year-old 15 kg girl taking phenytoin 125 mg, primidone 175 mg, acetazolamide 375 mg, trimethadione 1800 mg, and valproic acid 750 mg daily became lethargic with vomiting and fever and progressive obtundation. Anticonvulsant levels, electrolytes, liver and renal function tests, coagulation studies, blood gases, cell counts, lactic acid, and CSF studies were normal. Ammonia was 80 μmol/l (control 28, normal 11–35) and remained high for 4 days. VPA was discontinued on admission. By day 5 she was alert, and ammonia was 36 μmol/l (control 30). With informed consent a 500 mg VPA load test was done on day 7 (table II). Glycine was determined on a Beckman 119

**TABLE I—GLYCINE AND PROPIONATE CONCENTRATIONS**

<table>
<thead>
<tr>
<th>Aminoacid</th>
<th>Patients (n=26)</th>
<th>Controls (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycine (mmol/l)</td>
<td>374±75</td>
<td>251±99</td>
</tr>
<tr>
<td>Propionate (mmol/l)</td>
<td>33±20</td>
<td>*</td>
</tr>
</tbody>
</table>

*Normal range 1–3 nmol/l.

as those found in children ill with inborn errors of metabolism involving these compounds.*⁵

Recently, we observed hyperammonemia in a patient taking VPA who became obtunded but had no evidence of liver disease or drug intoxication. Since hyperammonemia occurs in several metabolic diseases, including propionyl CoA carboxylase deficiency,⁴ we investigated a possible relation between VPA, propionate, and ammonia that might suggest a mechanism of VPA toxicity.

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**TABLE II—VPA LOADING TEST RESULTS**

<table>
<thead>
<tr>
<th>—</th>
<th>0 min</th>
<th>60</th>
<th>120</th>
<th>180</th>
<th>240</th>
</tr>
</thead>
<tbody>
<tr>
<td>VPA (μg/ml)</td>
<td>2–2</td>
<td>75–4</td>
<td>64–4</td>
<td>51–9</td>
<td>12–1</td>
</tr>
<tr>
<td>Propionate (nmol/l)</td>
<td>0–0</td>
<td>265</td>
<td>60</td>
<td>65</td>
<td>*</td>
</tr>
<tr>
<td>Ammonia (μmol/l)</td>
<td>30</td>
<td>44</td>
<td>32</td>
<td>42</td>
<td>34</td>
</tr>
<tr>
<td>Glycine (μmol/l)</td>
<td>203</td>
<td>257</td>
<td>237</td>
<td>*</td>
<td>*</td>
</tr>
</tbody>
</table>

*Hemolysed.

CL amino-acid analyser, VPA and propionate were measured by gas liquid chromatography, and ammonia by the glutamate dehydrogenase method. 1 h after the loading dose, VPA, propionate, and ammonia levels had increased significantly and the child became lethargic. As the levels returned to normal at the end of the test, she again became alert.

Propionyl CoA inhibits carboxylate phosphate synthetase I (CPS-I) activity in vitro² so that blood ammonia may be increased in patients with propionyl CoA carboxylase deficiency with raised propionate levels. A decreased activity of CPS-I has been reported in such patients.⁹ VPA apparently does not inhibit propionyl CoA carboxylase activity,¹⁰ but metabolic conversion of VPA to propionate and related compounds could explain the increased propionate levels in patients taking VPA. This increase in blood propionate may then inhibit CPS-I, resulting in accumulation of ammonia in the blood and a secondary ammonia encephalopathy. Since propionate may

also interfere with mitochondrial glycine transport. This may account for the hyperglycinemia seen in patients taking VPA. It has been suggested that N-acetylglutamate synthetase is inhibited by increased propionyl CoA concentrations. Since N-acetylglutamate activates CPS-I, inhibited formation of this compound could also reduce the activity of CPS-I.

It seems that secondary hyperammonemia, not due to liver disease, may occur in patients taking VPA, and this may explain why some patients become stuporous or comatose while taking this drug. Blood ammonia levels should be monitored in such patients. The mechanism of ammonia encephalopathy may be different from that of the hyperammonemia seen in patients with hepatitis due to VPA.

This child was on several drugs, and a single load test may not compare with chronic use. Further studies of ammonia metabolism in patients taking VPA should help clarify the mechanism of VPA toxicity.