Childhood Porphyrias: Implications and Treatments

Neil R. Badcock,1, 3 Denise A. O'Reilly,1 Giovanni D. Zuanetti,1 Evelyn F. Robertson,1 and Colin J. Parker2

In describing the clinical, biochemical, and family findings in five children with porphyria, we examine initial treatments and, where appropriate, the effectiveness of long-term therapy. We note that porphyria diagnosis, particularly in childhood, relies heavily on specialist laboratory investigations. Because disease expression in some porphyrias requires exposure to precipitating factors, it may be prevented or delayed by their avoidance.


One of the first inherited metabolic disorders to be recognized as such was a porphyria, namely, congenital erythropoietic porphyria, or Gunther disease. Now, nearly 100 years later, if concurrent or dual porphyrias are included, 15 different types of porphyria have been described. Most are inherited as Mendelian autosomal dominant traits, but some are recessive and others acquired. The acute porphyrias are of the most importance, because attacks of these may be life-threatening. During an attack, patients accumulate in their tissues and excrete in their urine a massive excess of the neurotoxic porphyrin precursors, 5-aminolevulinic acid (ALA) and porphobilinogen (PBG). The nonacute porphyrias are largely dermatological conditions, with signs and symptoms confined to areas exposed to sunlight; concomitant liver disease occurs in some patients. Skin photosensitivity is due to the interaction of light with circulating porphyrins present in cutaneous tissues. A few porphyrias combine the clinical features of acute and cutaneous porphyria.

Patients may have overt, subclinical, or latent disease; manifestation of porphyria is usually delayed until after puberty. This has led, until recently, to the belief that porphyria was essentially an adult disease. It is now much more widely appreciated that it is not the disease but merely the diagnosis that is so rare in childhood. Indeed, the much lower incidence of overt porphyria in susceptible children may simply reflect lack of exposure to one of the necessary precipitating agents, such as drugs (including ethanol), toxins, viruses, fasting, and hormonal factors.

We have performed porphyrin analyses at the Adelaide Children’s Hospital over the past 13 years. For a pediatric institution to be the State Reference Centre for porphyria, analyses must be as rare as the disease itself; however, during the 13 years, ~1700 adults and 400 children have been screened. Of these, 7% (107 with porphyria cutanea tarda; PCT) and 5% (9 with erythropoietic protoporphyria; EPP), respectively, have tested positive. In the following case reports, we describe a few of the childhood porphyrias we have encountered and provide details on the long-term success or otherwise of respective treatments.

Materials and Methods

Blood was collected into a heparinized container and an aliquot was centrifuged for assay of the plasma. Leukocytes were isolated by standard procedures (1). Urine specimens, collected over 24-h periods and (or) random (untimed) collections, both without preservative, were kept in the dark and refrigerated between collections. Feces were collected into a darkened fecal pot. Blood and leukocytes were stored at −70°C until analysis; plasma, urine, and feces were stored at −20°C. Specimens were protected from light at all times.

ALA and PBG in the urine collections were measured by the methods of Maurer and Granick (2) with standard kits from Bio-Rad Labs. (Richmond, CA). Total porphyrins in blood and plasma, urine, and feces were quantified by the methods of Chisolm and Brown (3), Poulos and Lockwood (4), and Lockwood et al. (5), respectively. Plasma was scanned spectrofluorometrically by use of a technique reported previously (6). Individual porphyrins in urine and feces were measured by fluorescence detection after high-performance liquid chromatography of the free acid forms of the porphyrins (7).

Erythrocyte PBG deaminase (PBGD; hydroxymethylbilane synthase, EC 4.3.1.8) and uroporphyrinogen decarboxylase (EC 4.1.1.37) were assayed by the method of Piepkorn et al. (8) and McManus et al. (9), respectively. Leukocyte protoporphyrinogen oxidase (EC 1.3.3.4) and coproporphyrinogen oxidase (COOX; EC 1.3.3.3) activity were determined by the method of Li et al. (10) and Guo et al. (1), respectively, with modifications to COOX

1 Department of Chemical Pathology, and 2 Skin Clinic, Adelaide Children's Hospital, 72 King William Rd., North Adelaide 5006, South Australia, Australia.
4 Nonstandard abbreviations: ALA, 5-aminolevulinic acid; PBG, porphobilinogen; PCT, porphyria cutanea tarda; EPP, erythropoietic protoporphyria; PBGD, porphobilinogen deaminase; COOX, coproporphyrinogen oxidase; HC, hereditary coproporphyria; and AIP, acute intermittent porphyria.

Received June 8, 1992; accepted November 10, 1992.
measurement as outlined by Blake et al. (11). Enzyme activity was determined on two or more different blood collections taken several weeks apart. Reference ranges for enzyme activity were established from determinations made on at least 30 healthy children, ages 2 to 15 years, and on the same number of normal adult subjects.

Patient 1

A 4-year-old girl from a rural community presented in November 1986 with a 2-year history of blistering and fragile skin on the back of the hands, nose, cheeks, and occasionally feet. Symptoms were worse in summer. A red color of the urine had been observed for several months. There was no itching and burning and, at the time, no family history of similar disease. The patient had complained of central abdominal pain once or twice a week and, on occasions, particularly when tired, became pallid and sweaty. She had a history of pesticide exposure but no organochloro compounds were detected in the blood. There was no hepatic disorder and no masses or visceromegaly.

Porphyrin investigations revealed a very high plasma concentration of total porphyrin. The concentration of erythrocyte porphyrin was normal. Urinary uro- (predominantly isomer I) and heptacarboxylic porphyrin were much increased, oxiisocoprotoporphyrin was present, and the hexacarboxylic and pentacarboxylic porphyrins were moderately increased. Concentrations of porphyrin precursors, ALA and PBG, were normal. There was increased fecal excretion of isocopro- and heptacarboxylic porphyrins, with normal fecal concentrations of copro- and protoporphyrin. Erythrocyte uroporphyrinogen decarboxylase activity was ~50% of normal (Table 1). Porphyrin concentrations are shown in Table 2. These results were diagnostic of familial (type II) PCT and excluded other types of porphyria.

In addition to advising protection from sun exposure, treatment was commenced in March 1988 with oral chloroquine, 12.5 mg twice a week. Despite an immediate and dramatic increase in urinary porphyrin excretion, which persisted over several months, the young girl showed an improvement in her well-being and a reduction of the frequency of blistering lesions on the back of the hands and face; however, there were residual milia in these areas. She also had persistent skin fragility secondary to trauma, particularly noticeable on her legs. When reviewed in December 1988, the patient was free of blisters and erosions and the scars had faded considerably; since then, she has been asymptomatic.

Treatment with chloroquine has continued with no evidence of chloroquine toxicity. Despite the absence of cutaneous symptoms and a significant improvement in porphyrin concentrations, the concentrations of urinary porphyrin and particularly uroporphyrin have remained somewhat high. This has led to a strengthening of the therapeutic regime to 20 mg twice a week in August 1990 and to 25 mg twice a week since February 1991. Throughout chloroquine therapy, the patient's liver-function test results have remained normal except for a persistently above-normal activity of alanine aminotransferase (242 U/L in February 1991; reference range 30–120).

Subsequent investigations revealed that the patient's parents were healthy and nonconsanguineous with no cutaneous symptoms. Porphyrin studies of the child's mother showed normal results for porphyrins, porphyrin precursors, and porphyrin-related enzymes. The father refused testing. Two years later, the girl's paternal uncle presented with a recent history of photosensitivity, which had manifested after a job change that brought him into contact with several aromatic hydrocarbons. His clinical and biochemical picture indicated PCT; with an erythrocyte uroporphyrinogen decarboxylase activity ~40% of normal, he too was shown to have the classic familial type II condition.

Patient 2

This 15-year-old prepubertal boy has already been reported (12). He presented in March 1989 with abdominal pain, vomiting, disturbed consciousness, hypertension, dehydration, tachycardia, and malnutrition. He had suffered convulsions since infancy and was being treated with carbamazepine, sodium valproate, and phenytoin; the drug concentrations had always been within the therapeutic range. On admission, his weight was 19 kg. There was no photosensitivity. Because the passage of rose-colored urine and the patient's clinical manifestations raised the possibility of an acute porphyria, specimens were collected for porphyrin analyses.

Results from these investigations are given in Tables 1 and 2. They show greatly increased excretion of ALA and PBG in the urine, together with increased concentrations of porphyrins, particularly uro- and heptacarboxylic porphyrins. Total erythrocyte porphyrin was

---

**Table 1. Porphyrin Enzyme Data for Each Patient**

<table>
<thead>
<tr>
<th>Sample</th>
<th>Reference Interval</th>
<th>Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td><strong>Erythrocytes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uroporphyrinogen decarboxylase, U/L at 37 °C</td>
<td>1.5–3.0</td>
<td>0.8</td>
</tr>
<tr>
<td>Porphobilinogen deaminase, U/L at 45 °C</td>
<td>1.2–3.6</td>
<td>1.4</td>
</tr>
<tr>
<td><strong>Leukocytes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coproporphyrinogen oxidase, at 37 °C</td>
<td>3.0–5.8</td>
<td>-</td>
</tr>
<tr>
<td>Protoporphyrinogen oxidase, at 37 °C</td>
<td>0.037–0.071</td>
<td>-</td>
</tr>
</tbody>
</table>

* Units are picomoles of protoporphyrin produced per minute per milligram of leukocyte protein; † units are nanomoles of protoporphyrin produced per minute per milligram of leukocyte protein.

---

*CLINICAL CHEMISTRY, Vol. 39, No. 6, 1993 1335*
normal, but the concentration of porphyrin in plasma was increased. There was no porphyrin abnormality in a fecal specimen collected 10 days after admission. The patient had normal activities of erythrocyte PBGD and leukocyte protoporphyrinogen oxidase. Porphyrin studies of the child's parents showed normal results and there was no family history of porphyria, although a maternal uncle had died at age 14 years after treatment with a general anesthetic for a minor surgical procedure.

With acute porphyria established, we sought to determine the particular type of porphyria. The patient's normal leukocyte protoporphyrinogen oxidase activity and plasma fluorescence characteristics (6) ruled out variegate porphyria. The biochemical findings also excluded hereditary coproporphyria (HC), a rare inherited disorder distinguished by a marked increase in urinary and fecal excretion of coproporphyrin, mostly isomer III (7), which, with a coproporphyrin III value <40% of total coproporphyrin, did not match the pattern of abnormal porphyrins found in this particular case. Further, the pattern was clearly different from that described in a family with decreased 5-aminolevulinate dehydratase (EC 4.2.1.24) activity (13). Urine and fecal analyses showed that the subject had a pattern typical of acute intermittent porphyria (AIP), in no way differing from results for other patients with this type of porphyria (14). Despite the normal activity of PBGD then and the unavailability of the COOX assay, the clinical and biochemical picture identified this as a case of variant AIP, a subtype of AIP reported earlier (15-18), in which the enzyme defect is expressed in the liver but not in the peripheral blood cells. Precipitation of this porphyria attack was probably a consequence of the patient's anti-convulsant medication, an acute vomiting disease, and the patient's profound emaciation.

The disease resolved spontaneously after the withdrawal of carbamazepine and sodium valproate and the commencement of parenteral nutrition with subsequent carbohydrate loading. After about 9 weeks, he was discharged back to his previous hospital, the porphyrin pattern having returned to normal values several weeks before. The only biochemical abnormality remaining was the mildly increased activities of liver enzymes. Treatment from discharge to the present has included phenytoin and clobazam combined with continuing di-

### Table 2. Blood, Urinary, and Fecal Porphyrin Concentrations

<table>
<thead>
<tr>
<th>Sample</th>
<th>Reference Interval</th>
<th>Patient 1</th>
<th>Diagnosis date:</th>
<th>Last reviewed:</th>
<th>Patient 2</th>
<th>Diagnosis date:</th>
<th>Last reviewed:</th>
<th>Patient 3</th>
<th>Diagnosis date:</th>
<th>Last reviewed:</th>
<th>Patient 4</th>
<th>Diagnosis date:</th>
<th>Last reviewed:</th>
<th>Patient 5</th>
<th>Diagnosis date:</th>
<th>Last reviewed:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythrocytes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total porphyrin, μmol/L</td>
<td>0.4–1.7</td>
<td>0.9</td>
<td>0.5</td>
<td>1.3</td>
<td>1.5</td>
<td>1.1</td>
<td>0.9</td>
<td>21</td>
<td>0.7</td>
<td>0.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total porphyrin, nmol/L</td>
<td>&lt;10</td>
<td>95</td>
<td>21</td>
<td>101</td>
<td>9</td>
<td>4</td>
<td>5</td>
<td>221</td>
<td>6</td>
<td>8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALA, μmol/L</td>
<td>&lt;43</td>
<td>22</td>
<td>20</td>
<td>230</td>
<td>9</td>
<td>40</td>
<td>37</td>
<td>17</td>
<td>20</td>
<td>27</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PBG, μmol/L</td>
<td>&lt;25</td>
<td>2</td>
<td>6</td>
<td>719</td>
<td>11</td>
<td>6</td>
<td>7</td>
<td>4</td>
<td>2</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total porphyrin, nmol/L</td>
<td>&lt;300</td>
<td>2910</td>
<td>795</td>
<td>7400</td>
<td>97</td>
<td>36</td>
<td>106</td>
<td>131</td>
<td>207</td>
<td>124</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Porphyrin/creatinine, μmol/mmol</td>
<td>&lt;35</td>
<td>323</td>
<td>86</td>
<td>2387</td>
<td>34</td>
<td>6</td>
<td>20</td>
<td>33</td>
<td>37</td>
<td>29</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uroporphyrin, nmol/L</td>
<td>&lt;40</td>
<td>2182</td>
<td>581</td>
<td>6919</td>
<td>29</td>
<td>&lt;1</td>
<td>4</td>
<td>3</td>
<td>17</td>
<td>8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heptacarboxylic porphyrin, nmol/L</td>
<td>&lt;6</td>
<td>302</td>
<td>63</td>
<td>247</td>
<td>4</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>1</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coproporphyrin, nmol/L</td>
<td>&lt;150</td>
<td>74</td>
<td>138</td>
<td>233</td>
<td>61</td>
<td>36</td>
<td>&lt;1</td>
<td>101</td>
<td>127</td>
<td>190</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feces</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total porphyrin, μmol/kg dry wt</td>
<td>&lt;200</td>
<td>239</td>
<td>96</td>
<td>43</td>
<td>—</td>
<td>91</td>
<td>—</td>
<td>233</td>
<td>270</td>
<td>211</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coproporphyrin, μmol/kg dry wt</td>
<td>&lt;180</td>
<td>20</td>
<td>33</td>
<td>24</td>
<td>—</td>
<td>30</td>
<td>—</td>
<td>76</td>
<td>59</td>
<td>190</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proporphyrin, μmol/kg dry wt</td>
<td>&lt;180</td>
<td>135</td>
<td>55</td>
<td>8</td>
<td>—</td>
<td>58</td>
<td>—</td>
<td>157</td>
<td>211</td>
<td>12</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isocopro-/coproporphyrin ratio</td>
<td>&lt;0.02</td>
<td>0.50</td>
<td>0.13</td>
<td>0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At first appearance of symptoms</td>
<td>2</td>
<td>15</td>
<td>N.A.</td>
<td>3</td>
<td>N.A.</td>
<td>4</td>
<td>15</td>
<td>6</td>
<td>4</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td>Familial (type II)</td>
<td>Variant AIP</td>
<td>Latent AIP</td>
<td>EPP</td>
<td>Latent HC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Isomer III <40% of total coproporphyrin
* Isomer III >40% of total coproporphyrin
* For porphyrin other than variegate porphyria and porphyria cutanea tarda.

N.A., not applicable.
etary management, i.e., a high calorie intake of carbohydrate and protein, with limited fats. Concentrations of porphyrin and porphyrin precursors have remained normal postpuberty, and there has been no further exacerbation of his acute porphyria condition.

Patient 3

The porphyrin precursor, PBG, was grossly increased at postmortem examination of the 70-year-old paternal grandmother of patient 3. An acute porphyria was diagnosed on the basis of the increased concentration of PBG, qualitatively determined by a referring laboratory using a simple screening test. Her four clinically well grandchildren were subsequently investigated by the same referring laboratory and results for urine, blood, and fecal porphyrin tests were all reported to be normal. As was the case with the grandmother, no tests for enzyme insufficiency were performed.

As a precautionary measure, before administering anesthesia for a minor surgical procedure to the 6-year-old granddaughter (patient 3), blood, urine, and feces were again collected and sent to our laboratory for more comprehensive porphyrin investigations. Records from an operation under general anesthesia 3 years before had noted the patient was “slow to wake up,” with “3½ hours in recovery.” The considerably reduced PBG activity with normal concentrations for porphyrin, PBG, and ALA were consistent with this patient’s being an asymptomatic gene carrier for AIP (Tables 1 and 2). We included with our porphyrin report a list of drugs, unsafe and safe for use in acute porphyria. Subsequent blood and urine collections from two of the other three asymptomatic grandchildren, ages 7 and 11 years, have since shown a similar decrease in PBG activity with normal ALA, PBG, and urine porphyrin excretion patterns. The fourth grandchild, age 3 years, has normal PBG activity.

The operation proceeded uneventfully with a change from the standard anesthetic regime of halothane to isoflurane with nitrous oxide and the avoidance of steroidal relaxants. Moreover, the patient’s asthma medication was changed from theophylline (unsafe drug) to salbutamol and sodium cromoglycate (safe drugs) for the long term.

The three children with reduced enzyme activities have been advised to avoid drugs with established porphyrinogenic properties. Because of the occasional overlap between the normal and abnormal reference intervals for PBG activity (19, 20), our previous recognition of variant AIP in a patient with a quite high enzyme activity, and a report that described low erythrocyte PBG activity in one member of a large kindred with variant AIP (21), thus raising the possibility of variant and classical AIP coexisting within the one family, we could not give unequivocal assurance that the youngest child would not develop the disease—although extra precautions were not recommended. Neither parent has yet submitted samples for testing.

Patient 4

A 4-year-old girl with a normal medical history until the previous summer complained in January 1978 of episodic itching and burning of the skin on the face, hands, and feet immediately on exposure to sunlight. So intense was the burning sensation that the young girl would often immerse her feet in ice and, on many occasions, sleep with her feet in ice-cold water. The symptoms were always accompanied by edema and erythema of the exposed areas. Vesicles, petechiae, and some residual scarring had also occurred, but much less frequently. Symptoms had abated gradually during the winter months. There were reports of several clinically affected relatives.

Laboratory data showed a 10-fold increase in erythrocyte and plasma concentrations of protoporphyrin. Erythrocyte Zn protoporphyrin content was normal. There were no other biochemical alterations; blood coproporphyrin, urinary porphyrin precursors, and urine and fecal porphyrins were all normal. The results were diagnostic of EPP. A 1-year-old brother was later shown to have a latent form of protoporphyrinia.

The patient was treated with 30 mg of β-carotene twice a day and a topical sunscreen. Throughout her childhood, β-carotene therapy has been shown to provide very significant symptomatic amelioration and an increased tolerance to sun exposure, even though her erythrocyte protoporphyrin concentration has remained very high. Plasma β-carotene concentrations were maintained between 8 and 13 μmol/L during this period (reference range 0.2–2.3; plasma concentration at initial diagnosis 1.1 μmol/L). Apart from a distinct yellowing of the skin and despite the fact that carotene is a provitamin A, no vitamin A side effects have been observed. Vitamin A concentrations have remained within the normal range.

In the past 3 years the patient has chosen to discontinue therapy with β-carotene. Moderate to severe cutaneous photosensitivity has returned, together with abdominal pain. Causes such as gallstones and a dual porphyria have been ruled out. Results of liver-function tests remain normal, despite a recent erythrocyte total porphyrin measurement of 103 μmol/L (reference range 0.4–1.7) and a corresponding plasma β-carotene of 0.5 μmol/L. Other porphyrin tests, including urine coproporphyrin and the ratio of its isomers, give normal results. The younger brother continues to be free of cutaneous symptoms, despite a recent erythrocyte total porphyrin concentration of 16.4 μmol/L.

Patient 5

Medical and biochemical evaluation was sought in November 1991 for an 8-year-old boy with a family history of HC. The child had no clinical symptoms of porphyria. An older sister had died at age 5 years after an unknown febrile illness. A regional referring laboratory had found no porphyrin abnormality in the young boy.

Our investigations revealed slightly increased concentrations of coproporphyrin in the urine and feces,
particularly coproporphyrin III; all other porphyrin measurements, including ALA and PBG, were normal. Significantly, the fecal coproporphyrin III:coproporphyrin I (CIII:CI) isomer ratio, recently cited as a new test for diagnosing latent HC (11), was 9.1 (HC > 2, reference range <1.3). A leukocyte COOX determination showing diminished activity confirmed the diagnosis of HC.

HC combines the clinical features of both cutaneous and, even more importantly, acute porphyria. Consequently, like patient 3, this patient, through his parents, will be encouraged to maintain a regular diet and warned about the dangers of certain drugs, including alcohol, in an effort to prevent clinically overt disease. Six months later, he remains asymptomatic. Two younger brothers have normal results for HC enzyme activity and fecal CIII:CI isomer ratios.

Discussion
A deficiency in enzyme activity was established only after the analysis (in duplicate) of at least two different blood specimens collected several weeks apart. This was done to counter any effect on enzyme activity from viral and bacterial infections (22–24). Also, a complete drug history was gathered and a toxicology screen performed to allow drug therapy, particularly anticonvulsant therapy, to be excluded as the cause of abnormal enzyme activity (25). In establishing a reference range for each enzyme, we determined that the mean enzyme activity, as well as the lower and upper range limit, was relatively constant and unrelated to age and sex.

Because patient 1 has familial PCT, we anticipate that long-term chloroquine therapy will be necessary. This contrasts with one of the few reported cases of the sporadic (type I) condition in childhood (26). In that report, a girl, 2 years old at initial diagnosis, has apparently attained permanent remission 20 years later by adhering to a vitamin-rich diet and avoiding potentially porphyrinogenic substances (A. Kanaky, personal communication).

Chloroquine acts by releasing tissue-bound hepatic porphyrinogens and facilitating their excretion in urine (27); it has also been shown to inhibit porphyrin synthesis (28). Phlebotomy is also effective therapy for PCT, but is not recommended for use in children (29). In an attempt to treat PCT in this young child while avoiding the acute hepatotoxic effects of chloroquine, we initiated a very low-dose regime of 12.5 mg orally twice weekly. Previously, treatment of four children with a daily dose of 250 mg of chloroquine orally for 7 days brought about unacceptably high concentrations of liver enzymes and urinary porphyrin (29). Chloroquine introduced at 75 mg twice a week to treat familial PCT (type II) in a 7-year-old child (30) was accompanied by an immediate gross worsening of the patient’s symptoms. The dose was subsequently reduced, then withheld until a successful introduction at a dose of 75 mg and then 100 mg every 10 days (M. Rogers, personal communication). Interestingly, in all of these reports, urinary porphyrin concentrations have fallen well below pretreatment values and the patients have become asymptomatic, but relatively high residual concentrations of urinary porphyrin still remain.

In investigating patient 1, we identified another important distinguishing aspect of the familial and the sporadic condition. Our 18 patients, of all ages, who have tested positive for familial PCT have always had normal γ-glutamyltransferase activities at diagnosis; contrast this with our 57 patients with sporadic PCT, whose plasma γ-glutamyltransferase values have never been <3.5 times the upper normal range at initial diagnosis. The determination of this liver enzyme is less technically demanding than the assay of uroporphyrinogen decarboxylase and is very useful in checking the familial or sporadic status of a PCT condition.

Patients 2, 3, and 5 illustrate the considerable variation that exists in the clinical expression of the enzymatic defect in porphyrias with autosomal dominant inheritance. Further, patients 2 and 3 dramatically contrast in showing expression of the acute porphyria, despite a normal enzyme activity in one instance, and the absence of any clinical manifestation, despite unequivocal enzyme deficiency, in the other. These patients provide further evidence that the detection of latent forms of the porphyrias requires special techniques and is best carried out by reference laboratories. When latent cases are detected, patients can be advised about the precautions necessary to avoid attacks. Precipitating factors in susceptible patients include drugs, hormones (especially estrogens), starvation or dieting, and infections. Some women have regular premenstrual attacks and pregnancy may provoke an exacerbation. Early diagnosis of the disorder and recognition of the precipitants ensure appropriate treatment should an attack occur.

Specific therapies of acute hepatic porphyrias include the use of high carbohydrate intake and infusion with hematin. The regulatory effects of hematin on heme biosynthesis in the liver are multiple and involve not only inhibition of the synthesis of ALA synthase (EC 2.3.1.37) but also inhibition of the enzyme transfer and importantly inhibition of its own catalytic activity (31). Hematin may also repress the synthesis of the mRNA for ALA synthase (32). The effect of hematin on heme formation in erythrocytes may also be suppression of ALA synthase activity (33), although recent evidence suggests that its principal role is to regulate the transport of iron into reticulocytes (34). Like hematin, the "glucose effect" results mainly in suppression of the induction of hepatic ALA synthase (35), and the mechanisms of mediation are multifactorial and imbedded in the highly complex regulation of heme synthesis (36). Its regulatory role remains highly controversial, with concerns beyond the stated carbohydrate repression of enzyme induction to RNA synthesis, transport of ALA synthase, and glucocorticoid activity as well as the role of cAMP and cGMP (37–39).

Although total fecal coproporphyrin excretion was only slightly increased in patient 5, this increase is significant because, apart from descriptions of homozy-
igious HC in children (40–42), whose deficiency of COOX is severe (<10% of normal values), only one other case of increased fecal coproporphyrin has been reported in a child: a prepubertal 12-year-old member of an HC family (43). At the age of 8, patient 5 is the youngest subject with heterozygous HC yet described to have abnormal concentrations of fecal coproporphyrin. Interestingly, this first fecal porphyrin measurement was made while he was undergoing treatment with the antibiotic Bactrim (trimethoprim and sulfamethoxazole; both drugs that exhibit porphyryogenicity). Subsequent total fecal coproporphyrin measurements have been normal, although the CIII:CI ratio has remained increased.

The mechanism by which β-carotene is effective in EPP is unknown, although perhaps it absorbs 400-nm photons or quenches free radicals and singlet oxygen (44). Increased tolerance to sunlight was reported within weeks of patient 4's commencing therapy with β-carotene. Treatment continued to be effective during her several years of compliance with the medication. The obvious clinical carotenemia that developed was well tolerated and there were no other side effects. Despite the fact that in practical terms 6 μg of β-carotene is converted to 1 μg of vitamin A, plasma concentrations of vitamin A remained within the normal range during treatment. This suggests that EPP patients could safely continue with β-carotene therapy during pregnancy without vitamin A toxicity and its associated fetal teratogenicity.

Because of her perception that treatment was no longer effective, patient 4 has recently decided to discontinue therapy with β-carotene. This has coincided with a return of photosensitivity, although much less prominent than when symptoms first developed in childhood—a surprising result considering the very high concentrations of erythrocyte and plasma porphyrin. This apparent lack of correlation between blood porphyrin concentrations and severity of symptoms has been noted previously (44) and may suggest that endogenous compensatory mechanisms for the cutaneous photosensitivity are involved; with the frequent improvement in symptoms after age 10–11 and the decrease in photosensitivity noted during pregnancy in some EPP patients, it is interesting to speculate that hormonal factors may be involved. If hormones do play a positive role in EPP, it is in stark contrast to their action as precipitants in the acute porphyrias. Fortunately, this EPP patient has not yet developed liver disease, despite having several predictive factors for doing so (45, 46): e.g., very high and increasing erythrocyte porphyrin, high plasma porphyrin, and relatively low normal fecal coproporphyrin concentrations. Importantly, urinary coproporphyrin concentrations and its isomer I:III ratios, which when increased are said to serve as a sensitive indicator for the hepatic complication of protoporphyria, remain normal in patient 4. She will continue to be very closely monitored for hepatobiliary disease.

In conclusion, descriptions of porphyrias in children are rare and usually limited to single reports with no follow-up. In outlining the cases above, we have demonstrated the value of providing a comprehensive porphyrin service within a pediatric institution. Surely such institutions are able not only to recognize the existence of overt childhood porphyrias, but also to screen for latent and subclinical carriers. Further, through the ease of monitoring a child's progress several years after initial diagnosis and their better compliance with therapy relative to adults, young patients can be given a prognosis based on historical information, not speculation. The low level of clinical expression despite reduced enzyme activities is a striking feature of juvenile porphyrias in our experience. Early biochemical diagnosis with the avoidance of porphyryogenic factors is very effective treatment.

References

19. Bottomly SS, Bondkowski HL, Kreiner-Birnbaum M. The diagnosis of acute intermittent porphyria, usefulness and limita-


