A Right Royal Porphyria Fallacy

To the Editor:

We were intrigued by the cover image for the November 2011 issue of Clinical Chemistry, which showed a cover picture claiming that Mary Queen of Scots had a diagnosis of acute porphyria. The diagnosis of porphyria is usually assigned when a presenting patient is currently symptomatic; the range of indicative symptoms is diverse but relatively well defined. The 3 most common acute porphyrrias are hereditary coproporphyria, variegate porphyria, and acute intermittent porphyria, all inherited as autosomal dominant disorders. Many individuals who inherit the enzyme abnormalities remain asymptomatic throughout life. Abdominal pain is the most common symptom of an acute attack, although nausea, vomiting, constipation, neuropathies, and psychiatric symptoms may also accompany the abdominal pain. Hormonal changes, drugs, and nutritional factors may precipitate or aggravate the disorder. The definitive diagnosis relies on a combination of biochemical analyses to define the type of porphyria, followed by molecular analysis that enables screening of potentially affected family members. Occasionally, clinicians encounter patients with vague symptoms and an uncertain family history of porphyria, for which testing of the index case may not be possible. In this scenario of a potentially latent porphyria, results of all screening tests may well be normal and molecular testing is not justified. Many clinicians will adopt a “wait and see” approach, collecting samples at the time of an acute attack if one eventuates.

Owing to the complexity of the porphyrias, a retrospective diagnosis based on clinical observation alone is fraught with problems and would seldom be accepted. Recent research has thrown doubt on the assumption based on historical observation that the English Royals, notably King George III and Mary Queen of Scots, had one of the porphyrrias. The array of symptoms attributed to King George III have been presented as meeting the WHO International Classification of Diseases, 10th Revision, criteria for type 1 bipolar affective disorder with mood-congruent delusions, consistent with previous reports of manic depressive psychosis and with subsequent Alzheimer-type dementia, rather than acute porphyria (1, 2). Evidence generated by the computerized diagnostic aid SimulConsult has also shown that King James VI of Scotland and I of England (the son of Mary Queen of Scots) had features strongly suggestive of attenuated Lesch-Nyhan disease and an autistic spectrum disorder, possibly Asperger syndrome (3). Furthermore, a review in the Journal of Clinical Pathology (4) suggests that neither King George nor his relatives had porphyria, a conclusion based on rarity, penetrance, symptoms, and natural history.

Although all of these reports come from a single group, we believe that the evidence underpinning the assertion that Mary Queen of Scots had porphyria is not robust and potentially perpetuates a myth.

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Holotranscobalamin: Not Ready for Prime Time

To the Editor:

In their recent article in Clinical Chemistry (1), Valente and colleagues advocate that holotranscobalamin II (holoTC)1 become the primary diagnostic test of vitamin B12 status. I believe that study flaws undercut the authors’ recommendation. Moreover, the validation difficulties extend to deeper, more basic issues that

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1 Nonstandard abbreviations: holoTC, holotranscobalamin II; MMA, methylmalonic acid; RBC-B12, erythrocyte vitamin B12.