good correlation and concordance with the PCT assay on the Brahms Kryptor in a highly relevant patient group. Thus, the PCT assay from Roche allows easy and accurate measurement of serum PCT on an automated clinical immunochemistry analyzer that is fully integrated in standard hospital care.

Author Contributions: All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.

Authors’ Disclosures of Potential Conflicts of Interest: No authors declared any potential conflicts of interest.

Role of Sponsor: The funding organizations played no role in the design of study, choice of enrolled patients, review and interpretation of data, or preparation or approval of manuscript.

Acknowledgments: We thank N. Ambrosius for excellent technical assistance.

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Previously published online at DOI: 10.1373/clinchem.2008.117655

Familial Dysalbuminemic Hyperthyroxinemia: A Persistent Diagnostic Challenge

To the Editor:

Familial dysalbuminemic hyperthyroxinemia (FDH)¹ is a well-characterized condition associated with increased circulating total thyroxine (T₄) concentrations and normal physiological thyroid function. It is caused by mutations in the ALB (albumin) gene that increase the affinity of albumin for T₄ by approximately 60-fold. When measured by a technique that minimally disturbs the equilibria between T₄ and its serum binding

¹ Nonstandard abbreviations: FDH, familial dysalbuminemic hyperthyroxinemia; T₄, thyroxine; SyD, symmetric dialysis; FT₄, free T₄.
proteins, such as equilibrium or symmetric dialysis (SyD) performed in a near-physiological medium, the free T₄ (FT₄) value is characteristically within the reference interval. Assays that rely on the competition of a T₄ analog with unbound T₄ in the sample can give spuriously high results in FDH patients, because albumin binding of the T₄ analog is enhanced by the FDH mutation. “Two step” methods, in which the T₄ analog never comes into contact with serum albumin owing to a wash step immediately after capture, avoid this problem. Such assay methods are expected to give FT₄ results within the reference interval in FDH patients, but this expectation has been questioned (1, 2).

Thyroid-function tests, including 1- and 2-step methodologies, were examined in 4 affected individuals from different families who had their FDH diagnoses proved genetically by DNA sequencing of exon 7 of the ALB gene. Each individual carried the well-recognized R218H albumin mutation associated with this disorder (R242H, if the signal peptide is included). SyD was chosen as an alternative method, because this technique is unlikely to be affected by abnormalities in serum T₄-binding proteins. The assay was performed as previously described (3) but with a buffer of a more physiological composition (4). FT₄ assays were performed as described by the manufacturers with reagents and equipment provided by Abbott Diagnostics (ARCHITECT®), Beckman Coulter (Access®), PerkinElmer (DELFIA®), Roche (Elecsys E170), Siemens (Immulite® 2500 and ADVIA Centaur®), and Tosoh Bioscience (AIA®-1800). The Siemens, Roche, and Tosoh assays are 1-step analog methods, and the others are 2-step assays. Total T₄ was measured with the PerkinElmer DELFIA method.

Fig. 1 summarizes the FT₄ results for the different assays. The reference intervals used were those provided by the kit manufacturer, which were not necessarily those used by the respective laboratories. The values for thyroid-stimulating hormone were within the reference interval for all assays in all patients. For all methods, except for SyD, at least one of the patient results fell above the recommended reference interval for FT₄.

In FDH patients, the serum FT₄ results obtained with any of these assays can be misleading. The Siemens Centaur 1-step assay performed considerably better than some of the 2-step methods. This finding is consistent with a report on the predecessor of the Centaur that stated that it yielded the same results as equilibrium dialysis with FDH samples (5). If the limited size of the data set is taken into account, the Centaur, DELFIA, and Abbott methods compare reasonably well with SyD, with the differences between the methods possibly representing relatively small assay biases or the use of incorrect reference intervals. The results for 4 methods in routine use, however, show large deviation from those of the SyD method. Theoretically, both the 1-step and 2-step designs are based on valid principles; however, application of the 1-step approach is hampered by the fact that no T₄ analog has been found that fulfills the essential criteria of binding to the anti-T₄ antibody but not to T₄-binding proteins in the serum. Manufacturers have been trying to reduce this problem both by adding extraneous albumin and by adding inhibitors of T₄ binding to albumin (2). Such additions are not required for 2-step methods, although some manufacturers still use them. Addition of inhibitors of T₄ binding to albumin will lead to spuriously high values for FDH samples, because a much larger proportion of T₄ is bound to albumin in FDH samples than in typical samples; therefore, a higher proportion of the T₄ will be released by the action of the inhibitor during incubation. When SyD is performed in a buffer from one of the 2-step assays that yields high results for FDH samples, similarly high results are obtained (data not shown). Because serum samples from FDH patients still have the potential to generate false-positive FT₄ results in both 1- and 2-step immunoassays, it is essential that this benign condition be identified in situations in which measurements of serum samples produce high FT₄ results with thyroid-stimulating hormone values within the reference interval. A diagnosis
of FDH can be excluded by means of biochemical methods and by albumin genotyping. Because all mutations that have been associated with FDH to date involve residue 218 (242 with the signal peptide) in the albumin molecule, molecular genetic testing is comparatively simple and returns an unambiguous result.

**Author Contributions:** All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.

**Authors’ Disclosures of Potential Conflicts of Interest:** Upon manuscript submission, all authors completed the Disclosures of Potential Conflict of Interest form. Potential conflicts of interest:

**Employment or Leadership:** None declared.

**Consultant or Advisory Role:** None declared.

**Stock Ownership:** None declared.

**Honoraria:** None declared.

**Research Funding:** NIHR Cambridge Biomedical Research Centre. O. Rajanayagam, Wellcome Trust; M. Agostini, Wellcome Trust; V.K. Chatterjee, Wellcome Trust.

**Expert Testimony:** None declared.

**Role of Sponsor:** The funding organizations played no role in the design of study, choice of enrolled patients, review and interpretation of data, or preparation or approval of manuscript.

**Acknowledgments:** We are grateful to E.A. Groves, S.C. Martin, J. Slater, and A. Viljoen for providing FT4 assays.

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Previously published online at DOI: 10.1373/clinchem.2008.120303