Correspondence

Porphyrin metabolism in Gilbert’s, Dubin-Johnson, and Rotor’s syndromes

SIR.—I read with interest the study of McColl et al (Gut 1987; 28: 125–30) concerning the enzymatic abnormalities in peripheral blood cells in Gilbert’s syndrome. According to the authors, hyperbilirubinaemia may inhibit the PROTO oxidase (PROTO), and the latter change be compensated by increase of ALA synthase (ALA). This suggestion, however, is undermined by the lack of corresponding significant correlations. These correlations were obviously not tested after rifampicin: the data in Figure 3 speak in favour of a negative bilirubin-PROTO and PROTO-ALA, and a positive bilirubin-ALA correlation. More accurate information about true causal relations between these parameters necessitates larger sample sizes and use of partial correlation.

There appear a few additional biometrical problems with this paper. The non-parametric type of tests was chosen correctly but it should have been applied to the estimates as well, because the sample sizes were too low and the data were skewed. Thus, the appropriate measures—the medians (their lower; upper 95% confidence limits)—differ sometimes substantially from the ‘x±SD’ routine used, being (nmol/g/h) for ALA 158 (140; 199) at normals, 635 (368; 1756) at Gilbert’s syndrome and 929 (353; 2071) at variegate porphyria, and for PROTO 7.8 (4.8; 11.6), 2.4 (1.1; 6.0) and 1.8 (0.7; 5.2), respectively. The multiple comparisons between normals, Gilbert’s syndrome and variegate porphyria require, instead of Mann-Whitney U-test, rather its generalisation—the Kruskal-Wallis test. The seven fold testing of different biochemical parameters listed in Table 1 needs the Bonferroni modification adjusting the claimed probability level α in the term of critical values to α/7. The appropriate method yields in this case identical results but that need not be true generally. The rifampicin data should be treated biometrically, too: the Friedman test would show statistically significant (p<0.001) changes during this process (Fig. 3) but also a significant heterogeneity between individual patients, a feature to be emphasised from the medical point of view.

The similarity claimed for Dubin-Johnson and Rotor’s syndromes ‘in which the hereditary defects in hepatic bilirubin handling involve hepatocellular excretion rather than uptake or conjugation of the pigment’ by the authors, and also by some others, is questionable. The underlying defect in Dubin-Johnson syndrome is supposed to be an impaired excretion of conjugated bilirubin and sulfobromophthalein. In contrast, Rotor’s syndrome is believed to be an uptake, storage and possibly excretory defect. An ‘increased hepatocellular bilirubin concentration’ in this syndrome, unless selectively specified for some intracellular compartment, is therefore an unacceptable idea and cannot explain the abnormal hepatic porphyrin synthesis in this syndrome. By the way, a ‘normal BSP test’ in Rotor’s syndrome (13, Table 13.3) seems to be a printing error because it is contradicted by the excellent updated text of the chapter.

These comments do not detract from the value of the paper which throws some new light on the old ‘cryptogenic’ puzzle, till now not yet completely resolved.

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References

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Reply

sir.—We are grateful for the comments on our recent paper which have been expressed by Dr Mikulecký from the Department of Mathematics, Queensland University. As he rightly suggests, we did not assess the statistical significance of correlations of changes in ALA synthase, PROTO-oxidase and bilirubin during rifampicin therapy because of the small number studied. In addition, we feel that elucidation of the relationship of hyperbilirubinaemia and abnormal haem biosynthesis must depend on in vitro studies which directly assess the effect of bilirubin on haem enzymes rather than on more detailed mathematical analysis of the in vivo observations.

It is reassuring to learn that reanalysis of our data using the Kruskal-Wallis test, Bonferroni modification and Friedman test gives identical results to those we obtained using the less sophisticated Wilcoxon and Mann Whitney U tests.

Finally, we agree that the precise underlying biochemical defects in the hereditary hyperbilirubinaemias remain unresolved. Hopefully, our findings have gone some way to furthering understanding in this area.

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A confidence interval from a crossover trial should be based on within subject comparisons using both periods and not on between group comparisons for one period as suggested by Dr Logan. Our main purpose in writing, however, is to give the strongest possible support to Dr Logan's suggestion that confidence intervals should be used for the main endpoints of clinical trials, regardless of p values.¹

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Reference


Books


This volume is one in the Clinics and Gastroenterology series published by Saunders and consists of a number of chapters on specific topics related to developing areas in gastrointestinal endoscopy. The authors are from around the world, all being at the forefront of their field and writing well. Currently Saunders have divided this Clinics in Gastroenterology series into two with one volume aimed for North America and the other one for Europe. There are no doubt good commercial reasons for this unfortunate development and this volume illustrates well how important it is to have an international authorship of repute and not to become parochial in our view.

The volume provides a valuable update in the selected areas chosen, although unfortunately there is a considerable overlap in the chapters involving ERCP and this perhaps is not surprising bearing in mind the particular expertise of the author, Professor Meinhard Classen. Less overlap would have allowed a further chapter to have been included. The volume is aimed at the practising endoscopist intending to update him in new developments of now familiar techniques. A good illustration of this is a thoughtful chapter on the role of the endoscope in clinical trials, where some of the problems frequently encountered
Porphyrin metabolism in Gilbert's, Dubin-Johnson, and Rotor's syndromes.

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