Diagnosis of Wilson’s disease: an experience over three decades

The paper by Gow et al (Gut 2000;46:415–19) discussed the diagnosis of Wilson’s disease in 30 patients presenting to two different clinical facilities over 28 years (1971–1998). Because a paper of this type is likely to be viewed as an authoritative guide, it is important that the information be valid. For that reason, I call attention to the following significant errors in the paper.

The authors report urine copper values of 5, 4, 7, 4, 5, 2, and 2 µg per 24 hours in seven patients in table 1. These data cannot possibly be valid. The normal range for urine copper is 20–50 µg per 24 hours, and these patients are far below the lower limit of normal. In performing several thousand 24 hour urine copper tests on patients and normal subjects in our own laboratory, I have never seen one below 10 µg per 24 hours, except in copper deficiency. The patients in table 1 have Wilson’s disease, the opposite of copper deficiency, making the data even more unbelievable. I also do not believe the data for two additional symptomatic patients in their table 1 who are reported to have urine copper values of 55 and 44 µg per 24 hours. Urine copper values in untreated symptomatic Wilson’s disease patients are invariably over 100 µg. That is our experience in all of 88 newly diagnosed neurologically presenting patients (urine copper range 106–1880 µg/24 hours) and in all of 18 newly diagnosed patients with hepatic presentation (urine copper range 106–1880 µg/24 hours). Not all liver disease patients with urine copper values over 100 µg will have Wilson’s disease but all untreated patients with Wilson’s disease with clinically presenting liver disease will have a value over 100 µg. If a patient with liver disease does not have a value that high, then look to another diagnosis, or to a laboratory error. No doubt the latter is the case here because the values in seven of the patients are not biologically reasonable. One caveat: if the patient has been treated with a chelating agent, even briefly, and then the drug stopped, there is often a rebound period when urine copper will drop below 100 µg.

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References

Author’s reply
Dr Brewer in his letter raises two points regarding our recent paper (Gut 2000;46:415–9). Most importantly, he questions the diagnosis of Wilson’s disease in two of the patients in this series. Patient Nos 20 and 22 had liver disease but were negative for Kayser-Fleischer rings, had a non-elevated urine copper, and normal ceruloplasmin levels. The diagnosis was supposed made in patient No 20 by elevated liver copper. Non-Wilsonian chronic liver disease can also elevate hepatic copper.¹ The diagnosis in this patient is uncertain, and disproved if urine copper is truly low. Patient No 22 also had elevated liver copper and a “positive radiolabelled copper plasma clearance test.” Again, hepatic copper is not proof of the diagnosis. The normal radiocopper test is supportive but Wilson’s heterozygotes, comprising about 1% of the population, are often falsely positive.² Urine copper of 44 µg, if valid, would rule out the diagnosis.

In summary, Wilson in the current paper were to be believed (nine of 22 patients with low or normal copper values), it would appropriately denigrate the great usefulness of urine copper analysis for the diagnosis of symptomatic Wilson’s disease. Secondly, the liver copper value is not an absolute in the presence of chronic liver disease. Sometimes a therapeutic trial is the only way to come to a decision in these patients.

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Small intestinal bacterial overgrowth, intestinal permeability, and non-alcoholic steatohepatitis

In a recent issue, Wigg and colleagues (Gut 2001;48:206–11) reported that small intestinal bacterial overgrowth (SIBO), as diagnosed by a combined "C-oxylose/actulose breath test, is significantly more common in patients with non-alcoholic steatohepatitis (NASH) than in control subjects without liver disease. The authors investigated the possible pathogenic significance of this observation by examining whether intestinal permeability and circulating levels of endotoxin and tumour necrosis factor α are increased in NASH patients with SIBO compared with those without. No significant differences in any of these parameters could be demonstrated in the two groups.

An important factor influencing the validity or otherwise of these findings is the diagnostic accuracy of the "C-oxylose and lactulose breath tests for SIBO. Our experience, using a sterile endoscopic technique to sample small intestinal secretions under direct vision, is that these breath tests lack sensitivity and specificity for culture proven SIBO. Endogenous CO2 production and colonic metabolism of o-xylene are important factors inherently limiting the accuracy of the "C-oxylose breath test for SIBO. Furthermore, reliance on the finding of the "double peaks" in serial breath hydrogen or methane levels after ingestion of lactulose to improve the accuracy of the "C-oxylose breath test, or as a diagnostic marker in its own right, is problematic. In a study in which a scintigraphic tracer was administered concurrently

with lactulose, we found that each of the dou-
ble peaks in breath hydrogen values may occur af-
after the arrival of the test meal at the caecum,
paralleling delivery patterns of fermentable
substrate to caecal bacteria. A caecal source of
anaerobic (Enterobacteriaceae) but not obli-
gate anaerobes is not always eradicated
only are required for the catabolism of
Bacteroides spp. We agree with the suggestion that
acetate-bacteroides will catalyze the transport
across the intestinal mucosa. The studies quoted by Riordan
et al on the 

References
1 Riordan SM, McVay CJ, Duncombe WM, et al. Factors influencing the 1-g 14C-D-
2 Riordan SM, McVay CJ, Walker BM, et al. The lactulose breath hydrogen test and small
3 Riordan SM, McVoy CJ, Williams R, Liver damage in human small intestinal bacterial
4 Lichtman SM, Kaku J, Schwab JH, et al. Hepatic injury associated with small bowel bac-
terial overgrowth in rats is prevented by metronidazole and tetracycline.
5 Husebye E, Skar V, Hovestad T, et al. Abnormal intestinal motor patterns explain
enteric colonization with Gram-negative bacilli in late radiation enteropathy.

Authors’ reply
We thank Riordan et al for their own observa-
tions concerning the diagnosis of small intesti-
nal bacterial overgrowth (SIBO) and liver injury
associated with SIBO.
We agree with the suggestion that Bacter-
oides spp may be more important than other bac-
terial species in causing liver injury. This may be
an explanation for our failure to detect
endothelial elevations in those patients diag-
nosed with both NASH and SIBO (endothelin
damage is derived only from Escherichia coli bacteria and not Bacteroides spp) (Gut 2001; 48: 206–11).
We must however correct their statement
that no significant differences were found in
our study between NASH patients and control
subjects for tumour necrosis factor α. A
statistically significant difference was found
between these groups (p<0.001) (Gut 2001; 48: 206–11).
Their comments highlight the longstanding
difficulty in gastroenterology of diagnosing
SIBO. Although the traditional 13C-oxy-
sele test has been associated with a high
sensitivity in some studies,11 the specificity
of this test is unacceptable in our experience.
The high false positive rate associated with
this breath test probably relates to catabolism
of unabsorbed 13C-oxy-sele by the colon,
resulting in 13CO2 expiration. In an attempt to
retain sensitivity and improve specificity, we
have developed a combined 13C-oxy-sele-
lactulose breath test. Lactulose, which is not
absorbed and requires large bacterial concen-
trations for its catabolism to H2 and CH4,
acts as an internal trapper marker of colonic
metabolism. Smaller bacterial concentrations
only are required for the catabolism of
13C-oxy-sele to 13CO2. Thus in SIBO, catabolism
of 13C-oxy-sele by small bowel overgrowths
result in an early 13CO2 peak prior to the
colonic H2 and CH4 peaks. Specificity is
improved because 13CO2 peaks due to colonic
metabolism of unabsorbed 13C-oxy-sele can be
identified when they rise simultaneously with
H2 and CH4 colonic peaks.

When both the 13C-oxy-sele breath test and the
combined breath test were done in a group of
11 patients, only four had positive
combined tests compared with nine positive
13C-oxy-sele breath tests (Gut 2001; 48: 206–
11). This suggests that the combined test has
achieved a greater specificity. We feel that the
combined 13C-oxy-sele-lactulose breath test is
a sensitive and specific non-invasive alterna-
tive to culture of small intestinal aspirates.

We note the concern of Riordan et al of the
use of double H2 peaks for the diagnosis of
SIBO, based on their observations with scinti-
graphic studies. In severe SIBO, a double peak
of H2 and CH4 may be produced due to
catabolism by bacteria in both the small
intestine and colon. As suggested by
Riordan et al, double peaks may reflect catabo-
lism of lactulose by colonic bacteria rather
than by bacteria in the small intestine and
then the colon. Diagnosis of SIBO in our study
was based on early 13CO2 expiration before the
appearance of a H2 or CH4 peak in all cases.
Double H2 or CH4 peaks were observed in only
one of the 16 breath tests recorded as positive
in our study. In this patient, significant 13CO2
was expired prior to the first peak.
The studies quoted by Riordan et al have used
cultures of small intestinal aspirates as the
gold standard for the diagnosis of SIBO. Isolation
of intestinal aspirates under sterile con-
titions is not always a satisfactory gold stan-
dard for the diagnosis of SIBO? This diagnostic
method is not universally accepted. It is likely that
the small volume of proximal intestinal
aspirate contents aspirated does not accurately repre-
sent the bacterial flora of the entire small
intestine. This may explain the problems with
sensitivity and reproducibility described by
some investigators.12 Lack of standardisation of
specimen collection and the invasive nature of the
breath test are further problems, particularly
in the setting of studies involving a healthy
control population. The use of culture of small
intestinal aspirates as a gold standard to assess the
performance of breath tests may therefore not be
valid.
In view of the difficulties associated with
diagnosing SIBO, the association of SIBO with
NASH found in our study requires confirma-
tion by other investigators. Studies using cul-
ture of small intestinal aspirate to diagnose
SIBO, which can also provide qualitative bac-
terial information, will be complementary to
our study using a combined 13C-oxy-sele-
lactulose breath test.

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CORRECTION

Abstract 6/12 in Gut 2001;49(suppl II):A33 contained an error. Q Song should be affiliated with institution 1 (University of Ulm).
In abstract 8/09 (Gut 2001;49(suppl II):A47), the author list should read AT Dubois¹, C Seminomora¹, H Woreta¹, S Doi¹, I Carlstedt¹.¹USUHS: Bethesda, MD, USA; ¹University of Lund: Lund, Sweden.

NOTICES

Broad Medical Research Program—Inflammatory Bowel Disease Grants
Funds for inflammatory bowel disease (IBD) research are available immediately from the Broad Medical Research Program of The Eli and Edythe L. Broad Foundation for innovative projects regarding etiology, therapy, or prevention. Grants totalling approximately US$100,000 per year are available for basic or clinical projects. Larger requests may be considered. Initial letter of interest (no submission deadline), simple application, rapid (60 day) peer review, and funding. Criteria for funding includes new ideas or directions, scientific excellence, and originality. Early exploratory projects, scientists not currently working in IBD, and/or interdisciplinary efforts are encouraged. Further information: Marciana Poland, Research Administrator, Broad Medical Research Program, 10900 Wilshire Blvd., 12th Floor, Los Angeles, CA 90024-6532, USA. Tel: +1 310 954 5091; email: info@broadmedical.org; website: www.broadmedical.org

GI Malignancies Can be Prevented and Treated: from the Bench to the Bedside
This international meeting will be held on 15–20 January 2002 at the Dead Sea, Israel. Further information: Secretariat, GI Malignancies, PO Box 29041, Tel Aviv 61290, Israel. Tel: +972 3 5175150; fax: +972 3 5175155; email: gi@targetconf.com

Malignant Liver Tumours: Basic Concepts and Clinical Management
This Falk Workshop will be held on 24–25 January 2002 in Leipzig, Germany. Further information: Falk Foundation e.V. Congress Division, Leinenweberstr. 5, PO Box 6529, D-79041 Freiburg, Germany. Tel: +49 761 15 14 0; fax: +49 761 15 14 359; email: symposia@falkfoundation.de

European Association for the Study of the Liver: 37th Annual Meeting
The EASL Annual Meeting will be held on 18–21 April 2002 in Madrid, Spain. Further information: EASL Liaison Bureau, c/o Keness International, 17, rue du Cendrier, PO Box 1726, CH-1211 Geneva, Switzerland. Tel: +41 22 908 04 88; fax: +41 22 732 28 50; email: info@easl.ch; website: www.easl.ch

Falk Symposium No 128: Exogenous Factors in Colonic Carcinogenesis
This will be held on 2–3 May 2002 in Würzburg, Germany. Further information: see Falk Workshop details above.

Endoscopic Oncology: Gastrointestinal Endoscopy and Cancer Management
This ASGE Annual Postgraduate Course will be held on 22–23 May 2002 in San Francisco, USA. Further information: American Society for Gastrointestinal Endoscopy. Tel: +1 978 526 8330; fax: +1 978 526 7521; email: asge@shore.net

11th International Symposium on Hepatic Encephalopathy and Nitrogen Metabolism
This meeting will be held on 30 May to 1 June 2002 in Amsterdam, The Netherlands. Further information: Secretariat, Nicolaes Tulp Institute, Academic Medical Center, PO Box 23123, 1100 DS Amsterdam, The Netherlands. Tel: +31 20 566 8585; fax: +31 20 696 3228; email: tulpinst@amc.uva.nl. Deadline for receipt of abstracts: 1 February 2002.

Gastroenterology and Endotherapy European Workshop: XXth Anniversary
This course will be held on 17–19 June 2002 in Brussels, Belgium. Further information: Nancy Beauprez, Gastroenterology Department, Erasme Hospital, Route de Lennik 808, B-1070 Brussels, Belgium. Tel: +32 (0)20 555 49 00; fax: +32 (0)20 555 49 01; email: Beauprez@ulb.ac.be