LETTERS TO THE EDITOR

Coeliac disease and birth defects in offspring

EDITOR,—I read with interest the paper by Martinelli et al (Gut 2000;46:332–335) and letter by Unsworth et al (Gut 2000;47:598) which stress the high prevalence of coeliac disease in anaemic pregnant women. Un-treated coeliac disease can adversely affect the reproductive system and result in infertility, multiple abortions, low birth weight babies, and short breast feeding periods. 1 A low plasma level of folic acid is a common finding in newly diagnosed patients: 2 there are good theoretical reasons for hypothesising that coeliac disease could also be a maternal risk factor for birth defects. 3 "The presence of coeliac women in the study of Martinelli et al had a further pregnancy and reached term. One of them had a boy with a major cardiac malformation; she was the only one on a gluten containing diet.

I examined sera from 40 mothers of children with non-syndromic spina bifida, 37 mothers of children with non-syndromic cleft lip or palate, and 24 mothers of children with isolated cleft palate. 6 I found that 1/40 and 1/37 women were positive for Iga class antidiomysium antibody (AEA). Jejunal biopsy of the mother of a child with cleft lip and palate showed normal villous height/crypt depth ratio and increased number of intraepithelial lymphocytes; jejunal biopsy of the mother of a child with spina bifida was normal. Both AEA positive women were two of the four smallest (<155 cm) among all investigated mothers (n=101). Coeliac patients have acquired the reputation of being short in stature but tall patients do exist. 7 Frequent reports of increased reproduction problems in women with untreated coeliac disease emphasise the importance of early and correct diagnosis followed by adherence to a gluten free diet. Health care professionals need to recognise the manifestations of the disease in women of reproductive age and be prepared to use serological screening tests more frequently to identify patients who could benefit from dietetic treatment.

I suggest that coeliac disease should be considered as a cause of birth defects associated with folic acid deficiency (for example, spina bifida, oro-facial clefts, heart defects) 8 in offspring of women of short stature.

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Reply

EDITOR,—Women affected by untreated coeliac disease have indeed a considerable risk of having low birth weight babies and unfavourable outcome of pregnancy. Very recently in Sweden it was suggested that offspring of coeliac fathers are also at risk of low birth weight. 9 The mean birth weight of offspring of mothers and fathers affected by other autoimmune diseases. The authors of the large population based Swedish study suggest that there are “coeliac” familial risks affecting children with the risk of an unfavourable outcome of pregnancy is considerable.

Folate deficiency is one of the suggested explanations but it is unlikely to explain the large number of isolated cases with no gastrointestinal signs of the disease, and mostly no signs of malabsorption.

Now Hozyasz reports that 1/40 mothers of spina bifida children and 1/37 mothers of children with cleft lip were found to have untreated coeliac disease at endomysium antibody screening, one of whom was confirmed at biopsy. Both of these women were very short in stature, but unfortunately no data on their folate status were reported.

How much do these isolated numbers of women indicate a special risk of untreated coeliac women? Not very much: if we had to compare the data of Hozyasz with the expected prevalence rate among a cohort of pregnant women which would be compatible with the number reported by Hozyasz. The increasing sensitivity of the screening tests now available for coeliac disease (antidiomysium and anti-transglutaminase) is likely to gradually change the estimate of the population prevalence of the disease, but also, repetition of screening over time increases considerably the rate of identification of previously negative cases.

I personally feel that we have little evidence that coeliac disease should be considered “as a cause of birth defects associated with folic acid deficiency...” but I do agree that doctors and obstetricians should widely screen for coeliac disease as they do (often overdo) for many quite rare diseases.

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H pylori and functional dyspepsia

EDITOR,—I read with interest the results reported by Blum et al (Gut 2000;47:473–80) and the editorial which accompanied this article by McColl (Gut 2000;47:461–4). Professor McColl argues that the greater response to acid suppression observed in the Helicobacter pylori positive group compared with the negative subjects in the Blum trial resulted from a lack of blinding of the investigators and the presence of an incentive for categorising subjects as pylori positive responders. In support of this argument, he cites pooled data from two large randomised controlled trials (BOND and OPERA) comparing omeprazole 20 mg, 10 mg, and placebo where overall stimulation of acid secretion between H pylori status and symptom relief was observed. However, there may be other explanations for the results observed by Blum et al.

We have previously reported in pooled data from the BOND and OPERA trials that in the H pylori positive group, 43% on omeprazole 20 mg had complete relief of dyspeptic symptoms (by intention to treat) compared with 33% in H pylori negative patients and 34% and 24% on placebo, respectively. 10 Hence there was a small therapeutic gain observed in H pylori positive patients receiving omeprazole 20 mg versus placebo who were H pylori negative although the differences were not statistically significant. In the pooled data from the BOND and OPERA studies, there was also an association between symptom relief and the presence of an H pylori status. Although this is an observational study, there was a significant reduction in symptom suppression in the H pylori positive group compared with the H pylori negative group. Presumably the decision to conduct statistical analyses separately in H pylori positive and negative patients was exploratory in the Blum trial, as randomisation was not performed stratifying for H pylori status. Although omeprazole, having a valid approach, it is conceivable that the distribution of potential responders to acid suppression in the H pylori positive and negative arms (for example, ulcer-like dyspepsia) was not dissimilar.

Professor McColl suggests that the same therapeutic gain achieved with potent acid suppression may be achieved more permanently by eradication of H pylori. However, this conclusion remains controversial. Moyeed et al recently published a meta-analysis.
of 12 trials reporting that the risk reduction with H pylori eradication therapy from the pooled data was 9% (95% confidence interval (CI) 4%–14%). However, these results are in conflict with a similarly high quality meta-analysis of 10 trials which failed to detect a significant benefit of H pylori eradication (odds ratio for success 1.3, 95% CI 0.89–1.189). The positive and negative trial results in non-ulcer dyspepsia may be reconcilable if H pylori eradication only benefits those with hidden peptic ulcer disease or those predisposed to subsequently developing peptic ulceration which in turn is likely to vary across different populations. If this hypothesis is correct, then eradication therapy in a subset of patients with non-ulcer dyspepsia would be indicated (as the benefits should then outweigh the risks). In the absence of predictors which usefully identify a subset who will achieve symptom relief with eradication therapy, the decision to treat the infection is by necessity on a case by case basis.

Conflict of interest
Professor Talley's original paper to which he refers, the therapeutic gain observed in H pylori infection in functional dyspepsia. There are only two recent high quality meta-analyses of H pylori eradication in functional dyspepsia published as full papers. These both showed unequivocal benefit of the active treatment versus placebo. The other meta-analysis Professor Talley refers to has only appeared in abstract form and is therefore difficult to comment on its quality. In addition, it did not include the most recent studies. None the less, even this study showed a strong trend in favour of eradication therapy over placebo (odds ratio for success 1.2, 95% CI 0.98–1.6).

Reply
Editor—I am very confused by Professor Talley's comments regarding the symptomatic benefit from omeprazole in Helicobacter pylori positive versus negative subjects with functional dyspepsia. In his original paper, he states in the results section that "resolution of dyspepsia in the active treatment arms was not significantly different in the H pylori infected and uninfected patients" and in the abstract that "symptom relief was similar in H pylori positive and negative cases". I was therefore very surprised to read Professor Talley's letter in which referring to the same paper he states that "there was a small therapeutic gain observed in H pylori positive patients versus those who were H pylori negative". He goes on to state that "in the H pylori positive group, 43% on omeprazole 20 mg had complete resolution of dyspepsia symptoms compared with 35% in H pylori negative patients". However, therapeutic gain compares the benefit of the active treatment versus the placebo treatment. The therapeutic gain in the H pylori positive group on omeprazole is 9% and the therapeutic gain in the H pylori negative patients is 11% (fig 1). Therefore, contrary to the comments made in his above letter, Professor Talley's original study showed that the therapeutic gain for omeprazole is similar or less in H pylori positive versus negative patients with functional dyspepsia.

Professor Talley also challenges the therapeutic gain achieved with eradication of H pylori infection in functional dyspepsia. There are only two recent high quality meta-analyses of H pylori eradication in functional dyspepsia published as full papers. These both showed unequivocal benefit of the active treatment over placebo. The other meta-analysis Professor Talley refers to has only appeared in abstract form and is therefore difficult to comment on its quality. In addition, it did not include the most recent studies. None the less, even this study showed a strong trend in favour of eradication therapy over placebo (odds ratio for success 1.2, 95% CI 0.98–1.6).

The number of procedures performed per annum in DGHs was 40–800 (mean 228) and in THs 60–2000 (mean 336), 57.2% of which were therapeutic. Of those performing more than 250 procedures per annum, 82.1% of DGHs and 77.3% of THs held regular radiology meetings to discuss findings. Of those performing less than 250 procedures per annum, 72.9% of DGHs and 75.0% of THs held regular radiology meetings.

Each centre trained up to six trainees per annum, most training one or two. The average number of procedures which trainees could perform per annum was 176 (48–431) in DGHs and 144 (range 54–311) in THs. This was dependent more on the number of trainees per centre than on the type of hospital in which the training was performed with endoscopic retrograde cholangiopancreato-
Before performing the procedure independently. Nevertheless, the general message is accepted that we must look at quality rather than quantity.

Although it is clear that good opportunities do exist for gaining training in units under-taking smaller numbers of procedures, it is difficult to define a precise number that takes into account the needs of the individual trainee in getting the required experience and the numbers required for the trainer to maintain competence.

In the new JAG document, which we hope to publish in the next month, the emphasis has moved away from numbers to other means of assessing competence. We are still of the opinion that those units with lower throughputs should combine with larger units to provide training as part of a regionally organised training scheme. Trainees are already organised regionally and decisions as to who will undertake ERCP training will be made in consultation with the regional training director. Several hospitals have already applied for, and been granted, ERCP training status on the basis of a combined training unit. A total of 74 units have now registered with JAG, of whom 115 have been approved for ERCP training.

The new JAG document makes it clear that trainees should undergo training on endoscopy-specific courses. The first six of these have already been piloted by the Raven Department of Education at the RCS. In future, it will be essential for re-accreditation of units that trainees will have gone on such courses.

Reply

Editor,—We read with interest the letter and enclosed reports of a survey on endoscopic retrograde cholangiopancreatography (ERCP) training. We, like the authors, have been concerned since the initial Joint Advisory Group (JAG) training document that a large extent competence is judged by numbers rather than other measures of endoscopy skills. Indeed, reliance on numbers has been the cause of most of the correspondence that JAG has received following the publication of the initial training document. However, at that time and to a large extent at present, there are few satisfactory measures of competence to replace numbers and time. The authors state in their letter “that only centres that are accredited for training by JAG will be permitted to continue endoscopy training”. Strictly speaking this is not true. Lack of recognition of a unit for training would mean that any training that takes place in that unit would not be recognised by the statutory bodies but this would not prohibit the units from training. They also state that “the guidelines base competence for training in ERCP solely on the number of procedures carried out in the individual centres”. The training does actually require a little more than numbers, for example the training document states that “endoscopists cannot be considered competent in ERCP until they are able to cannulate the desired duct in over 90% of cases and provide biliary drainage. Trainees should carry out at least 100 procedures under supervision and be achieving a high percentage of success before performing the procedure independently”. Nevertheless, the general message is accepted that we must look at quality rather than quantity.

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I might as well get it off my chest first! This is not a good book and I did not enjoy reading it. I would not recommend that you read it or advise your library to purchase it.

In the first instance, the title of the book is wrong. It should be called the “John Hopkins’ Version of Evidence Based Surgery”: 90% of the multitude of authors involved come from that institution. One hesitates to say that the judgement of some of the authors seems to be clouded by institutional bias but words such as “prejudice” and phrases such as “tunnel vision” spring to mind. Like any North American textbook, the rest of the world largely does not exist: 90% of the quoted references are from North American texts with the token British author being a surgeon who has been retired for the last two years.

The first 250 pages are devoted to the principles of evidence based surgery. Within these pages are a series of chapters which have little to do with any healthcare system outside the USA. For those of you who believe that the worst elements of American medicine usually do get across the Atlantic sooner or later, you might wish to dip into this section briefly, especially if you are in the brigade that is totally fed up with the Health Service and wonder just how it can get worse. This book is just the thing to convince yourself that fulfilment in the rest of your existence on this planet will not be in the field of clinical medicine.

To be honest, some chapters were so stultifyingly boring that I just could not finish them, notably “Administrative Data and Evidence-Based Surgery”, although “Leveraging Information Technology” ran it a close second! In the chapter on “Patient Reported Outcome Measures”, we are told that because surgery is primarily palliative for oesophageal malignancies, quality of life assessment may be less important. While it is disappointing to see such nonsense in print, it does hearten me that we have nothing to fear on intellectual grounds at least from the so-called leaders of American surgery.

Turning to the second half of the book which is described as the “Practice of Evidence-Based Surgery”, individual chapters are given up to the recognised surgical specialties. The first six of these are devoted to aspects of gastrointestinal surgery. One of them, the chapter on colon surgery, is well written and should have been given to the other authors as an example of how to write a good chapter on an evidence based element of surgery. The chapter on oesophageal surgery is a classic example of “what do we at Hopkins and why?” Of the 29 references quoted, only one was from a non-USA publication. The chapter on gastric surgery wanders between the old fashioned “R” and the newer “D” notation to describe the extent of gastrectomy. The author’s appraisal of the two European trials which compare D versus D, gastrectomy is particularly superficial and appears to me as if he has only read the abstract or is content to make the same type of uncritical appraisal perpetuated by individuals who do not wish to see the major flaws in both of these trials.

The chapter on pancreatic surgery contains one of the best examples of institutional bias in the entire book. The author quotes his own prospective, randomised, placebo controlled, double blind study to test the hypothesis that erythromycin improves gastric emptying and reduces the incidence of delayed gastric emptying after pancreaticoduodenectomy. The text clearly states that patients who received erythromycin had a shorter duration of nasogastric tube drainage and started foods earlier, and I suppose one could not argue with that and say that the author was not lying because on average, the group receiving erythromycin had their nasogastric tube removed after 5.5 days compared with 6.2 days in the controls and they were able to start solid feeding at 11.3 days versus 12.8 days. You will not be surprised to know that these differences were not statistically significant and it makes you wonder why people should write in this way.

So now you have a fair idea of exactly why I did not like this book. However, I bought my copy from a bookshop, do not waste time on it and in particular, do not be tempted to part with $100.00!

An accessible practical text for doctors and senior health workers at first referral centres in developing countries is indeed a worth-while objective and this WHO sponsored guide largely succeeds. An impressive list of contributors combine to produce a 160 page manual to feeding problems and routine management of children’s progress and an encouragement to audit outcomes are welcome in as the pragmatic approach to human immunodeficiency virus. By virtue of the fact that it is designed with brevity and clarity in mind, it is very didactic however. The reader is not invited to question why for instance “very severe pneumonia” is treated with chloramphenicol, “severe pneumonia” with penicillin, and “pneumonia (non-severely)” with septrin. More leeway is given in the advice to monitor local antibiotic sensitivity patterns in treating Shigella and Salmonella infections. Many may appreciate this approach but some will not.

Designed to complement the Integrated Management of Childhood Illness guidelines, it has the feel of a classic textbook with many simple black and white drawings and tables which are also refreshingly new, given over as they are to demonstrations of practical clinical assessment and diagnostic procedures. There is even an appendix of toys for severely malnourished children. There is also an excellent chapter on supportive care, and solutions to feeding problems and nutrition is an important theme throughout. Monitoring of children’s progress and an encouragement to audit outcomes are welcome in as the pragmatic approach to human immunodeficiency virus. By virtue of the fact that it is designed with brevity and clarity in mind, it is very didactic however. The reader is not invited to question why for instance “very severe pneumonia” is treated with chloramphenicol, “severe pneumonia” with penicillin, and “pneumonia (non-severely)” with septrin. More leeway is given in the advice to monitor local antibiotic sensitivity patterns in treating Shigella and Salmonella infections. Many may appreciate this approach but some will not.

The format of the book is very convenient and helpful to every physician, especially gastroenterologists who treat IBD patients and are frequently confronted with a specific problem or question related to their management and treatment. The 138 chapters cover practically every issue related to the management of ulcerative colitis and Crohn’s disease. Readers will find up to date application of diagnostic tools such as computed tomographic scanning and ultrasonography to the handling of IBD patients. A significant number of chapters are dedicated to the medical treatment not only of straightforward IBD but also its complications, such as pouchitis, severe extraintestinal disease, or to speak of the management of extraintestinal manifestations. Thirty two chapters deal with the surgical aspects of ulcerative colitis and Crohn’s. These chapters provide gastroenterologists with in depth information regarding surgical options, their advantages, and disadvantages. Even though the chapters that relate to surgical intervention of IBD have been written by experienced surgeons, they are easily understandable by medical people, who are usually those who refer patients for surgery. Reading these pertinent chapters will enable the medical man to better understand what is to be expected from the intervention, its details, and place in the therapeutic approach to the treatment of IBD.

The book contains all of the necessary and most current information about the novel medical treatment of IBD. A special chapter deals with anticytokine therapy and another with novel manipulation of the inflammatory mediator pathways. Another feature that characterises this book is inclusion of a rather unusual number of chapters on the humanistic aspects of the management of chronic IBD and patient-physician interactions.

Most of the chapters include a short list of additional references and a brief comment by the editor calling attention to other views and additional references and a brief comment by the editor calling attention to other views and highlighting other areas of potential interest. Because of the broad spectrum of the book, and because the 138 chapters have been written by different authors, repetitiveness is unavoidable and many issues are dealt with more than once. In spite of this drawback, the book is an excellent source of information, practical as well as basic. It will be helpful for clinicians who handle IBD who are looking for a comprehensive resource, containing pertinent information on almost every problem that may arise in the management of patients with ulcerative colitis and Crohn’s disease.

The book contains 138 short chapters on almost all practical issues in the management of patients with inflammatory bowel disease (IBD). It is the second edition of a book published in 1989 entitled Current Management of Inflammatory Bowel Disease. Obviously, in the last 12 years since the publication of the first edition, much has changed both in the medical and surgical therapeutic approaches to IBD. All of the current and most up to date attitudes are well reflected in this book.


Hirschsprung’s disease, or congenital intestinal aganglionosis, was named after Hans Hirschsprung, a Danish paediatrician who gave the first description of the condition in 1886. At first the massive dilatation of the colon was believed to be caused by an abnormality within the dilated colon itself and the condition was therefore called “congenital megacolon”. Sir Frederick Treves (1898) performed the first curative operation. While operating on a six year old girl he noted that although there was massive dilatation of the proximal colon, the lower sigmoid colon and rectum were narrow. He performed an abdominoperineal resection of the distal colon and rectum with anastomosis of the proximal colon to the anal margin. The
The true cause of the disease, which is a congenital absence of ganglion cells in the wall of a variable segment of rectum and colon, was not recognised until 1948. It is now appreciated that the ganglionopathy involves the whole of the autonomic nerve supply to the affected bowel and that the RET proto-oncogene, which is expressed in various cell lines derived from the neural crest, is a major gene for the disease. This genetic abnormality has provided an explanation for the relationship of the disease to other genetic diseases such as multiple endocrine neoplasia and the Waardenburg syndrome. The successful surgical management of congenital aganglionosis now depends on an accurate resection of affected bowel which is aided by the use of histochemical methods for the investigative assessment of the myenteric plexus.

The many facets of this congenital abnormality, which has an incidence of approximately 1 in 5000 live births, have resulted in fascinating studies by physiologists, morphologists, and geneticists. These investigations have led to the recognition of a whole range of abnormalities in the innervation of the gut which include hypoganglionosis and hyperganglionosis as well as the classical aganglionosis.

The book reviewed here is the second edition of a text on Hirschsprung’s disease first published by Holtschneider in 1982. It starts with a brief historical overview, which includes a good description of Swenson’s original pull through operation for the condition in 1948, a procedure designed to conserve the anal sphincter mechanism.

The editors have endeavoured to provide a wide range of current knowledge which they have presented in three main sections—physiology and pathophysiology (including molecular genetics); clinical aspects of the disease; and techniques and results of surgical treatment. Fifty experts in various fields have contributed to the very comprehensive text.

The first section is particularly noteworthy for the reviews of the development and functional anatomy of the enteric nervous system written by JHC Meyers and MD Gershon, respectively. These are nicely presented with excellent overviews of the basic sciences, which is essential knowledge for anyone involved in research of these congenital conditions. The next two chapters focus on molecular genetics and the section concludes with discussions of normal colonic function and pathophysiology.

The second “clinical” section includes chapters on the typical presentation of a range of congenital diseases of the enteric nervous system as well as the radiological, functional, and histological methods of diagnosis. RA Brown and S Cywes have also provided a useful summary of the remarkable number of malformations which have been described in association with Hirschsprung’s disease. This section could perhaps have been enhanced by inclusion of colour illustrations which would have increased the value of the examples of histochemical techniques.

The third “surgical” section begins with a comprehensive description of the six most commonly used surgical techniques in Hirschsprung’s disease, and here the presentation could have been improved by a more consistent approach to the artwork. Further chapters discuss the reported complications of the various techniques and outline their management. I felt that a critical review of these operative techniques, perhaps with a meta-analysis of published data, would have been of interest and might have helped surgeons to decide whether there is a “best buy” among all of these procedures. Consistency in the reference lists, some of which are arranged alphabetically while others follow a strictly numerical system, would also have removed an irritation.

In summary, this book provides a wealth of data about Hirschsprung’s disease and related abnormalities. Although there are a few weaknesses in the editing of the text and artwork I have no hesitation in recommending it as a very useful reference book for surgeons and gastroenterologists, both in their research work and clinical practice.

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