LETTERS TO THE EDITOR

Epidemiology supports oral contraceptives as a risk factor in Crohn’s disease

Editor,—A recent clinical alert (Gut 1999;44:311–12) commented on a study of risk factors for relapse in Crohn’s disease. The author concluded that, unlike the established association with smoking, the link with oral contraceptive use is still controversial. To contribute to this discussion, I have investigated temporal trends in age and sex specific disease incidence and correlated them with the chronology of oral contraceptive use.

The birth control pill was first introduced in 1960 and soon became widely accepted; 10 million American women were taking it by 1973. Concerns about side effects prompted further research, and by the mid-1970s most women taking were taking oral contraceptive pills containing 50 µg or less of oestrogen—a considerable decrease from the 100–150 µg in the pills of the 1960s. Most epidemiological studies of Crohn’s disease (especially those from the USA) have shown a rapid rise in the incidence of disease between the early 1960s and early 1970s, followed by a plateau phase in the 1980s. In my analysis I have used the only two American studies1 for which detailed age and sex incidence distributions were available and correlated them to American data on oral contraceptive use.

Without investigating the incidence trends in a group of 20–29 year old women (these are the most likely users of oral contraceptives), a correlation between the introduction and adoption of oral contraceptives and overall incidence trends of Crohn’s disease would not be sufficient to establish oral contraceptive use as a risk factor. From 1964, both studies showed that there was a striking increase in incidence among the 20–29 year age group, and an increased female to male incidence ratio. Unpublished data from the Olmsted County study2 showed a crude incidence of 26.8 cases per 100 000 person years for this age group in women between 1964 and 1973. This is the highest incidence among all age and sex groups in the entire study period (1940–93), and the highest incidence rise between consecutive time periods. The incidence rise in men for the same period was much less dramatic and the crude rate for the same age group was 17.2. Data for Baltimore showed a 9.46 fold incidence increase for women aged 20–29 between the 1960–3 and 1973 surveys, and only a 2.33 increase for men of the same age group. Again, this jump in female incidence is the most abrupt rise in incidence among all age and sex groups in all periods. Consistent with the introduction of oral contraceptives with a lower oestrogen content, incidence studies of Crohn’s disease reported lessening of predominance in women aged 20–29 from the mid-1970s. Figure 1 shows changing female to male incidence ratio for this age group corresponding to oral contraceptive use.

Although detailed data on incidence and oral contraceptive use were not available, we used two European studies as controls,3 and, in the period 1960–5, both had the highest female to male incidence ratio, which corresponded to the rise in oral contraceptive use and Crohn’s disease, in studies published in the past 15 years.

The author would like to thank Edward V Loftus Jr for contributing unpublished data from the Olmsted County study.

M ALIC
3720 Balboa St, San Francisco, CA 94121, USA


3 Ledochowski M, Sperner-Unterweger B, Fuchs D. Carbohydrate malabsorption syndromes and early signs of mental depression4; similarly, Gwee et al found significant links between anxiety, depression, and somatic complaints in patients with IBS. Our data suggest that non-absorbed carbohydrates interfere with tryptophan metabolism, which may explain the development of anxiety, mental depression, and other signs of somatic dysfunction. Furthermore, most of our patients were diagnosed as having IBS before a diagnosis of carbohydrate malabsorption syndrome was made. Preliminary data indicate that the symptoms of patients who follow a diet that did not include the malabsorbed carbohydrate; we also observed improved depression scores that meant that there was no further need for psychotherapeutical intervention.

In conclusion, we feel that many patients with IBS may have a carbohydrate malabsorption syndrome and may, therefore, develop signs of psychiatric illness. Thus, we suggest that all studies performed on patients with IBS should exclude minor forms of malabsorption syndromes.

M LEDOCHOWSKI
T PROFST
D PUCHS
University of Innsbruck, Landeskrankenhaus, Anichstrasse 35, A-6020 Innsbruck, Austria

Reply

Editor,—I would like to thank Dr Ledochowski and colleagues for their interest in our paper, and for presenting evidence of a possible association between fructose or lactose malabsorption and mental depression. They suggest that psychological symptoms in patients with IBS may be due to carbohydrate malabsorption, caused by the interaction between malabsorbed sugars and the amino acid tryptophan. In contrast, we proposed that psychopathology predisposes to the development of IBS. We observed that neurotic traits, life events occurring before an attack of gastroenteritis, and psychological state at the time of the infection, all seemed to predict which patients would develop IBS.

I would not deny that events in the gut may influence state of mind. Research from our department, and others, has indicated that meals rich in fat induce feelings of calmness,
Table 1 Characteristics of 10 patients with idiopathic pancreatitis

<table>
<thead>
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<th>Patient no</th>
<th>Sex</th>
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<th>Sequence changes</th>
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</thead>
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<td>75</td>
<td>TG11-T7/TG11-T7</td>
</tr>
<tr>
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<td>f</td>
<td>52</td>
<td>41</td>
<td>3041-71A/G</td>
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<tr>
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<td>M</td>
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<td>42</td>
<td>TG0-T7/TG11-T7</td>
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<tr>
<td>4</td>
<td>F</td>
<td>70</td>
<td>69</td>
<td>TG13-T7/G14-T7</td>
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<td>M</td>
<td>41</td>
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<td>38</td>
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<td>M</td>
<td>64</td>
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<td>TG10-T7/G10-T9</td>
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<tr>
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<td>M</td>
<td>72</td>
<td>69</td>
<td>TG10-T7/G11-T7</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>18</td>
<td>NA</td>
<td>TG11-T7/G12-T7</td>
</tr>
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</table>

NA, not available.

In order to document further whether a proportion of adults presenting with idiopathic pancreatitis carry alleles linked to mild abnormalities of CFTR functions, we conducted a complete scan of CFTR sequences by denaturing gradient gel electrophoresis (27 exons) and other appropriate methods (four intronic regions), in a sample of 10 patients with isolated idiopathic pancreatitis (ascertained by standard criteria) in the south of France. As some CFTR alleles of specific DNA marker haplotypes have recently been shown to produce incomplete or less functional CFTR protein, we also thoroughly studied the TGn-Tn loci in the branch/acceptor splice site in intron 8 and the 1540A/G locus (named M470V) in exon 10. Exclusion criteria included the ingestion of more than two alcoholic drinks per day (20 g ethanol), cancer, drug or trauma related pancreatitis, and familial chronic pancreatitis. None of the patients had any clinical manifestation or family history suggestive of cystic fibrosis or CFTR associated diseases. The study was approved by our ethics committee.

Table 1 summarises the CFTR genotypes identified in the 10 patients with idiopathic pancreatitis. Of these, no patient had a cystic fibrosis mutation and seven were instead heterozygous for one or two sequence changes that have been earlier described as DNA sequence polymorphisms/variants (a complete list of these variations can be found on the cystic fibrosis mutation database: www.genet.sickkids.on.ca/cftr).

Although variant 1716G/A (no change at glutamine 528) may result in exon 10 skipping and has been reported in CFTR related diseases, the involvement of this variant in cystic fibrosis remains controversial. The frequency of the IVS8-5T allele (10%) was 2.3 times the observed frequency in the general population (4.3%). It is unlikely, however, that this allele is a variant which predisposes towards idiopathic pancreatitis because it is carried on a TG11-M470 haplotype background, which is not a deleterious combination. Finally, when we screened the whole coding/flanking CFTR sequences of 10 random individuals, six polymorphisms/variants (125G/C and 875+40A/G twice, R79Q, 5T) and one cystic fibrosis mutation (AF508) were observed. In conclusion, extensive analysis of CFTR sequences in a subset of patients from the south of France does not confirm a link between CFTR alterations and isolated idiopathic pancreatitis.

We thank Ms Freis for contributing clinical data and Ms Seguret for statistical advice. This research was supported by the Direction de la Recherche Clinique, CHU, Montpellier, France (U9733).

prostaglandin may inhibit SGLT1, activity. Furthermore, a decrease in active absorption of glucose due to increased levels of intestinal inflammation and surgical patients. 

Can authors explain an alternative mechanism for their findings?

S SOMASUNDARAM
Senior Fellow, VA Medical Centre, Seattle WA 98108, USA

2 Kimberg DV. Cyclic nucleotides and their role in gastrointestinal secretion. Gastroenterology 1974;67:1023–64.
10 Wicks C, Klaeveman G, Comin TP, et al. A discrepancy between our findings and any previous study. In summary, Dr Somasundaram has not presented any evidence that PGE2, lowers SGLT1, activity and acutely or chronically decreases glucose absorption. There is no discrepancy between our findings and any previous study. As PGE2, or any similar hormone or mediator, may have different short term acute and long term chronic actions, and because an appropriate distinction has yet to be made between the state of health and the state of disease, we see no reason for any confusion and no need to provide an alternative mechanism for our findings. We are sure that Dr Somasundaram would be happy to agree.

BUTTINA SCHOLTZKA
FRANK STUEMPHEL
KURT JUNGERMANN
Institute of Biochemistry and Molecular Cell Biology, Georg-August-University, Humboldtallee 23, 37073 Gottingen, Germany


NOTES

11th Annual International Colorectal Disease Symposium

The 11th Annual International Colorectal Disease Symposium will be held at the Marriott Harbor Beach Resort, Port Lauderdale, Florida, USA, on 17–19 February 2000. Further information from: Cleveland Clinic Florida, Department of Continuing Education, 2950 West Cypress Creek Road, Fort Lauderdale, Florida 33309, USA. Tel: +1 954 978 7060; fax: +1 954 978 5539; email: jagelms@ccf.org

5th World Congress on Trauma, Shock, Inflammation, and Sepsis

The 5th World Congress on Trauma, Shock, Inflammation, and Sepsis will be held in Munich, Germany, from 29 February to 4 March 2000. Further information from: Prof Eugen Faist, Department of Surgery, Ludwig Maximilians University Munich, Klinikum Grosshadern, Marchioninisstrasse 15, D-81377 Munich, Germany. Tel: +49 89 7095 5461/2461; fax: +4 89 7095 2460; email: faist@gch.med.uni-muenchen.de

Second Annual Gastrointestinal Cancer Update: A Multidisciplinary Approach

The Second Annual Gastrointestinal Cancer Update conference will be held at the Yarrow Hotel and Conference Centre, Park City, Utah, USA, on 15–19 March 2000. Further information from: Rosalie Lamml. Tel: +1 801 581 8664; fax: +1 801 581 3647; email: rosalie.lammlc@hsc.utah.edu

European Courses on Laparoscopic Surgery

The European Courses on Laparoscopic Surgery will be held at the University Hospital Saint Pierre, Brussels, Belgium, on 4–7 April 2000 and 21–24 November 2000. Further information from: Conference Service S.A., Drève des Tumuli, 18, B-1170 Brussels, Belgium. Tel: +32 2 375 1648; fax: +32 2 375 3299; email: conference.services@skynet.be

Third Scandinavian Course on Inflammatory Bowel Diseases

The Third Scandinavian Course on Inflammatory Bowel Diseases will be held at the Wåndereslen, Örebro Medical Centre, Örebro, Sweden, on 12–14 April 2000. Further information from: Kurskansliet, Regionssjukhuset, S-701 85 Örebro, Sweden. Tel: +46 19 15 37 05; fax: +46 19 15 37 95.

XVIIIth European Workshop on Gastroenterology and Endothergy

The XVIIIth European Workshop on Gastroenterology and Endothergy will be held in Brussels, Belgium, on 26–28 April 2000. Further information from: Administrative Secretariat, Ms Nancy Beauprez, Gastroenterology Department, Erasme Hospital, Route de Lennik 808, B-1070 Brussels, Belgium. Tel: +32 2 555 4900; fax: +32 2 555 4901; email: beauprez@ulb.ac.be

Digestive Disease Week

The Digestive Disease Week will be held at the San Diego Convention Centre, San Diego, California, USA, on 21–25 May 2000. Further information from: DDW Administration, 7989 Woodmont Avenue, 7th Floor, Bethesda, Maryland 20814, USA. Tel: +1 301 272 0022; fax: +1 301 654 3978; website: www.ddw.org

International Hepato-Pancreato-Biliary Association 4th World Congress

The International Hepato-Pancreato-Biliary Association 4th World Congress will be held in Brisbane, Australia, from 28 May to 1 June 2000. Further information from: Intermedia Convention and Event Management. PO Box 1280 (Intermedia House, 11/97 Castlemaine Street), Milton, Queensland 4064, Australia. Tel: +61 (0)7 3379 9479; fax: +61 (0)7 3369 1512; email: hpb2000@cem.com.au
Is isolated idiopathic pancreatitis associated with CFTR mutations?

N PALLARES-RUIZ, S CARLES, M DES GEORGES, C GUITTARD, M CLAUSTRES, D LARREY and G PAGEAUX

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