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 with 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 old 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 Unpublished data from the Olmsted County study2 showed a crude incidence of 26.8 cases per 100 000 person years for this age group in women between 1964 and 1973.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 more 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 and other studies have observed the highest incidence among American 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 that shown in the USA. The above epidemiological findings are concordant with Timmer and colleagues' study and support their explanation that previous use of oral contraceptives is more strongly associated with relapse in Crohn's disease than current use. The change in oestrogen content of oral contraceptives may account for the contradictory findings of a link between 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.

trance, sleepiness, and friendliness, while carbohydrate rich meals induce tension and hostility, and increase activity in the sympathetic nervous system.1,2 The bidirectional link between the gut and emotion is so strong that the gut might usefully be regarded as part of the nervous system. However, I remain cynical of the cumbersome and dated tryptophan hypothesis that is so frequently trundled out to explain the effects of food on human mood and behaviour, and would favour a more direct explanation by different nerves.

I have read the paper by Dr Ledochowski and colleagues that was published in Digestive Diseases and Sciences. Of 30 healthy female volunteers, six showed evidence of lactose malabsorption and had higher scores on Beck’s Depression Inventory. Analysis of the individual data presented in this paper is less convincing as they are biased by two lactose malabsorbers who scored very highly for depression. The scores of the remaining women were within the range seen in people that absorbed lactose normally. Although the authors concluded that lactose malabsorption induced anxiety and depression, their data does not seem well explained by the effects of psychological tension on gut function.

Psychological tension can accelerate small bowel transit, which in turn can compromise absorption, particularly of foods that are more slowly absorbed. Most of the world’s adult population is lactose malabsorbers, but they are not all depressed. Indeed, depression seems to be more common in people that absorb lactose and come from Northern Europe.

Finally, is lactose deficiency or fructose malabsorption truly more common in patients with IBS than in normal subjects? The accumulated data are unconvincing. What seems more likely is that the hypersensitive and hyper-reactive gut of patients with IBS responds more vigorously to an osmotic load, by generating symptoms of diarrhoea, bloating, and pain.

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,3 we also thoroughly studied the TgN-Tn loci in the branch/acceptor splice site intron 8 and the 1540/AQ 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 classified as DNA sequence polymorphisms/variants (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,5 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.6 Finally, when we screened the whole coding/flanking CFTR sequences of 10 random individuals, six polymorphisms/variants (125G/C and 875+40A/G twice, 875G/C, 5T, and 1 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 (UF7533).

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Is isolated idiopathic pancreatitis associated with CFTR mutations?

EDITOR,—In one of two recently published studies which looked at a link between mutations of the cystic fibrosis transmembrane conductance regulator (CFTR) gene and idiopathic pancreatitis,1 Cohn et al estimated that 37% of a cohort of 27 patients with idiopathic pancreatitis had at least one abnormal CFTR gene, which is 11 times the expected frequency.1 Furthermore, the authors concluded that additional CFTR mutations might be detected by more comprehensive DNA testing, because they had tested DNA samples for only 16 of the more than 800 mutations associated with cystic fibrosis.

Table 1 Characteristics of 10 patients with idiopathic pancreatitis

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age at diagnosis</th>
<th>Sequence changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>77</td>
<td>3041-71A/G</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>52</td>
<td>4002A/G</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>44</td>
<td>4404C/T</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>68</td>
<td>875+40A/G</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>62</td>
<td>125G/C</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>52</td>
<td>1716G/A</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>44</td>
<td>125G/C</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>36</td>
<td>1506V</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>69</td>
<td>875+40A/G</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>18</td>
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</tr>
</tbody>
</table>

140 A/G (M470V)

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 (UF7533).

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Did prostaglandin E stimulate glucose absorption in rat intestine?

EDITOR,—I read with interest the recent paper by Schotka et al (Gut 1999;44:490–496) which reported that prostaglandin E, (PGE,) stimulated glucose absorption via the sodium dependent glucose transporter-1 in rat intestine. The authors suggested that PGE, raises sodium dependent glucose transporter (SGLT) and thus increases glucose absorption.

However, earlier papers contradicted this theory and we are now in a state of confusion. Kimberg and coworkers1 and Klae- veman and colleagues have suggested that prostaglandins increase membrane bound adenylyl cyclase activity in the small intestinal mucosa, and thus inhibit Na+-K+-ATPase activity of gut mucosa.2 Recently, Sundaram and colleagues reported that inflamed ileums (excess prostaglandin) express low levels of SGLT, in rabbits, which indicates that
prostaglandin may inhibit SGLT1 activity. Furthermore, a decrease in active absorption of glucose due to increased levels of prostaglandins and cytokines has been observed both in patients with severe intestinal inflammation and surgical patients.¹ Can others explain an alternative mechanism for their findings?

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2 Kimberg DV. Cyclic nucleotides and their role in gastrointestinal secretion. Gastroenterology 1974;67:1023–64.

Reply

Editor,—We see no reason for confusion over the acute increase of PGE₂-stimulated glucose uptake into brush border membrane vesicles of rat jejunal enterocytes. By using isolated perfused rat small intestine, we showed that PGE₂ acutely increased glucose and galactose activity in human stomach, indicating that Na⁺/glucose cotransport reduction was secondary to a decrease in the amount of SGLT1; PGE₂ involvement in this acute alteration was not examined.

Somasundaram et al, who used a rat model of extraintestinal inflammation (six hours after formalin injection into hind leg pad), showed that glucose absorption was impaired in the jejunum, and that they did not study the involvement of PGE₂. Finally, Wicks et al concluded that enteral feeding was as effective as total parenteral nutrition in orthotopic liver transplantation; they also did not examine the involvement of PGE₂.

In summary, Dr Somasundaram has not presented any evidence that PGE₂ lowers SGLT1 activity, actively 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.

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NOTES

11th Annual International Colorectal Disease Symposium

The 11th Annual International Colorectal Disease Symposium will be held at the Marriott Harbor Beach Resort, Fort Lauderdale, Florida, USA, on 17–19 February 2000. Further information from: Cleveland Clinic Foundation, Department of Continuing Education, 2950 West Cypress Creek Road, Fort Lauderdale, Florida 33309, USA. Tel: +1 954 978 5902; fax: +1 954 978 5539; email: jagensm@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, Marchioninistrasse 15, 81377 Munich, Germany. Tel: +49 89 7095 5461/2461; fax: +49 89 7095 2460; email: faist@gh.med.uni-muenchen.de

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@sky.net

Third Scandinavian Course on Inflammatory Bowel Diseases

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

XVIIIth European Workshop on Gastroenterology and Endotherapy

The XVIIIth European Workshop on Gastroenterology and Endotherapy 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 21–24 May 2000. Further information from: DDW Administration, 7911 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 07 (3) 336 9178; fax: +61 07 (3) 336 9152; email: hp2000@im.com.au