

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.¹ 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 1973.² 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.³ In my analysis I have used the only two American studies^{4,5} 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 old age group, and an increased female to male incidence ratio. Unpublished data from

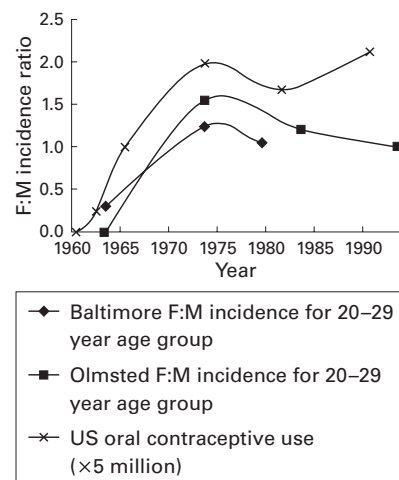


Figure 1 Trends in the use of oral contraceptives and incidence of Crohn's disease as a female to male ratio in the 20-29 year age group.

the Olmsted County study⁵ 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 showed⁴ 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 the highest 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,^{6,7} and, in the period 1960-5, both had the highest female to male incidence ratio, which corresponded to the rise in the USA.

The above epidemiological findings are concordant with Timmer and colleagues' study¹ 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.

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

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The role of psychological and biological factors in postinfective gut dysfunction

EDITOR.—We read with interest the paper by Gwee *et al* (*Gut* 1999;44:400-406) which described the role of psychological and biological factors in postinfective irritable bowel syndrome (IBS). However, these authors did not study fructose or lactose malabsorption in relation to duodenal function. Carbohydrate malabsorption syndromes—

for example, fructose and/or lactose malabsorption, are frequently linked to IBS.¹ Patients with fructose malabsorption often have a clear history of postinfective onset of their symptoms, as Gwee and colleagues found in patients with IBS.

We have shown an association between carbohydrate malabsorption syndromes and early signs of mental depression^{2,3}; similarly, Gwee *et al* found significant links between anxiety, depression, and somatisation scores 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 serotonin deficiency.⁴ 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 with IBS improved on a diet that did not include the malabsorbed carbohydrate; we also observed improved depression scores that meant that there was no further need for psychotherapeutic 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 PROPST
D FUCHS
University of Innsbruck,
Landeskrankenhaus, Anichstrasse 35,
A-6020 Innsbruck, Austria

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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,

tranquility, 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 limbic 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 action via afferent 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 could be equally 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 are 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.

N W READ
Gastrointestinal Motility Unit,
University of Sheffield,
Northern General Hospital,
Sheffield S5 7AU, UK

- 1 Wells AS, Read NW, Uvnas Moberg K, *et al*. Influences of fat and carbohydrate on post-prandial sleepiness, mood and hormones. *Physiol Behav* 1997;61:679–86.
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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,^{1,2} 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

Patient no	Sex	Current age	Age at diagnosis	CFTR genotypes		
				Sequence changes	IVS8 TGn-Tn	1540 A/G (M470V)
1	M	77	75	—/—	TG11-T7/TG11-T7	G/G
2	F	52	41	3041-71A/G 4002A/G	TG11-T7/TG11-T9	A/G
3	M	44	42	4404C/T	TG10-T7/TG11-T7	A/G
4	F	70	69	875+40A/G	TG11-T5/TG11-T7	A/G
5	M	62	61	125G/C	TG11-T7/TG11-T7	G/G
6	F	52	50	1716G/A	TG11-T5/TG10-T7	A/A
7	M	41	38	125G/C	TG11-T7/TG12-T7	A/G
8	M	64	36	—/—	TG10-T7/TG10-T9	A/A
9	M	72	69	1506V 875+40A/G	TG10-T7/TG11-T7	A/G
10	F	18	NA	—/—	TG11-T7/TG12-T7	A/G

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,³ 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 classified 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,^{4,5} 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.³ Finally, when we screened the whole coding/flanking CFTR sequences of 10 random individuals, six polymorphisms/variants (125G/C and 875+40A/G twice, R75Q, 5T) and one cystic fibrosis mutation (ΔF508) 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.

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N PALLARES-RUIZ
S CARLES
M DES GEORGES
C GUITTARD
M CLAUSTRÉS
Laboratoire de Génétique Moléculaire,
Institut de Biologie,
CHU et IGH-CNRS UPRI142,
34060 Montpellier, France
D LARREY
G PAGEAUX
Hôpital Saint-Eloi,
Service d'Hépatogastro-entérologie,
34000 Montpellier, France

Correspondence to: Dr Claustres (email: Mireille.Claustres@igh.cnrs.fr).

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Did prostaglandin E₂ 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 E₂ (PGE₂) stimulated glucose absorption via the sodium dependent glucose transporter-1 in rat intestine.

The authors suggested that PGE₂ raises sodium dependent glucose transporter (SGLT₁) and thus increases glucose absorption. However, earlier papers contradicted this theory and we are now in a state of confusion. Kimberg and coworkers^{1,2} and Klæveman and colleagues³ have suggested that prostaglandins increase membrane bound adenylate cyclase activity in the small intestinal mucosa, and thus inhibit Na⁺-K⁺-ATPase activity of gut mucosa.^{4,5} Recently, Sundaram and colleagues⁶ reported that inflamed ileums (excess prostaglandin) express low levels of SGLT₁ 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 inflammation⁷ and surgical patients.^{8,9}

Can the authors explain an alternative mechanism for their findings?

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

- 1 Kimberg DV, Field M, Johnson J, *et al*. Stimulation of intestinal mucosal adenylcyclase by cholera enterotoxin and prostaglandins. *J Clin Invest* 1974;50:1215–30.
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Reply

EDITOR.—We see no reason for confusion over the acute increase of PGE₂-stimulated glucose absorption via SGLT₁ in rat small intestine. By using isolated perfused rat small intestine and rat villus tip enterocytes, we showed that PGE₂ acutely increased glucose and galactose absorption via SGLT₁ with cAMP, raised by the actions of PGE₂ receptor subtypes 2 and 4, which served as the second messenger.

As the maximum PGE₂ effect was reached after four minutes, the underlying mechanism can only have been stimulation of SGLT₁ activity, rather than an increase in the amount of SGLT₁ by de novo synthesis. Our findings are concurrent with previous data which showed that forskolin (an adenylate cyclase activator) stimulated a glucose dependent inward current of Na⁺ acutely, in the jejunum of CFTR knockout (cystic fibrosis) mice, and that cAMP increased glucose uptake into brush border membrane vesicles of rat jejunal enterocytes.²

Dr Somasundaram now claims that earlier reports contradict this theory. Kimberg, Klaeveman and colleagues showed that prostaglandins stimulated membrane bound adenylate cyclase activity in the small intestine, which is in line with our findings. Mozsik *et al* showed that 5'-AMP, cyclic 2',3'-AMP, and cyclic 3',5'-AMP inhibited Na⁺/K⁺-ATPase activity in human stomach, indicating that this effect was not specific. Furthermore, Parkinson *et al* found that Na⁺/K⁺-ATPase activity in plasma membrane preparations of rabbit jejunum decreased three hours after

cholera toxin treatment; they did not study the direct acute effect of cAMP or PGE₂. Sundaram and colleagues, using a rabbit model of chronic ileal inflammation (cells isolated 13–15 days after intragastric inoculation with *Eimeria magna* oocytes), concluded that Na⁺-glucose cotransport reduction was secondary to a decrease in the amount of SGLT₁; PGE₂ involvement in this chronic 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 this impairment could be prevented by the anti-inflammatory drug, oxyphenbutazone; again PGE₂ involvement was not investigated. Ohri and colleagues reported that monosaccharides were malabsorbed in coronary artery bypass patients, because of significant hypoperfusion of the intestine; 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 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.

BETTINA SCHOLTKA
FRANK STUEMPEL
KURT JUNGEMANN

*Institute of Biochemistry and Molecular Cell Biology,
Georg-August-University,
Humboldtallee 23,
37073 Göttingen, Germany*

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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 Florida, Department of Continuing Education, 2950 West Cypress Creek Road, Fort Lauderdale, Florida 33309, USA. Tel: +1 954 978 5056; 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, Marchioninstrasse 15, 81377 Munich, Germany. Tel: +49 89 7095 5461/2461; fax: +49 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 Lammle. Tel: +1 801 581 8664; fax: +1 801 581 3647; email: rosalie.lammle@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 Services 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 Wilanderselen, 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, 7910 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 3369 0477; fax: +61 (0)7 3369 1512; email: hpb2000@im.com.au