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 Unpublished data from the Olmsted County study[5] showed a crude incidence of 26.8 cases per 100 000 person years for this age group in women between 1964 and 1973.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[4] a 9.46-fold incidence increase for 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.

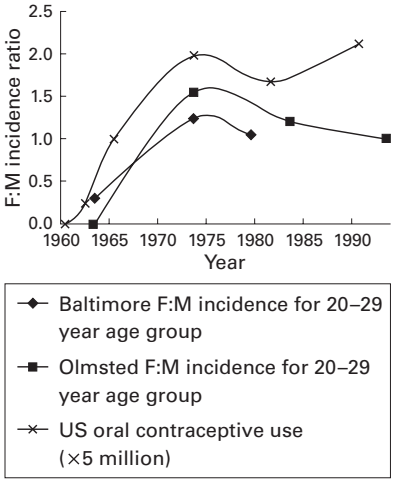

Figure 1 Trends in the use of oral contraceptives and incidence of Crohn's disease as a female to male ratio in the 20–29 year age group.

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' study[1] 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.

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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 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.

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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.

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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	CFTR genotypes: IVS8 TGn-Tn	CFTR genotypes: 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	I506V 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/variations (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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Did prostaglandin E_2 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_2 (PGE_2) stimulated glucose absorption via the sodium dependent glucose transporter-1 in rat intestine.

The authors suggested that PGE_2 raises sodium dependent glucose transporter ($SGLT_1$) 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 Klaeveman and colleagues[3] 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 colleagues[6] reported that inflamed ileums (excess prostaglandin) express low levels of $SGLT_1$ in rabbits, which indicates that