

adenomas, but by an accelerated evolution of the adenoma-carcinoma sequence.^{1,2} Can the conflicting data be reconciled? The central issue is the identification of genuine HNPCC families. A high proportion of our findings are based on a small number of very large families, one of which is known to harbour a point mutation in *hMSH2*.³ Conversely, a high proportion of tumours originating from smaller families is now turning out to be negative for the mutator phenotype (lacking in DNA replication errors). Thus, different genetic factors must be operating in these families, if any. It is clear that HNPCC mutations may be successfully transmitted through multiple generations.⁴ Geographic regions showing a relative high frequency of HNPCC families have turned out to harbour a single, highly extended family.⁴ The frequency of HNPCC in other regions of the same country may be considerably lower. It would therefore appear that the frequency of HNPCC may be lower than 5% and that the most typical presentation of the syndrome may be within rare but relatively large, extended families. Authentic descriptions of the pathological spectrum within HNPCC must be based either on very large families or families known to carry an HNPCC gene mutation. Conversely, the main practical and logistic problems posed by familial colorectal cancer may lie outside classic HNPCC.

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Reply

EDITOR,—Professor Jass comments that our finding of an increased frequency of adenomas, particularly in the proximal colon in 127 subjects from 69 HNPCC families compared with subjects with less of a family history, is somewhat at variance with the colonoscopic findings in his study of 197 'at-risk' subjects from 29 HNPCC families.¹ His study showed no significant increase in the frequency of adenomas in subjects from HNPCC families compared with a necropsy population. His findings are at variance, however, with another publication of the results of colonoscopy examination of 161 first degree relatives of affected members from 28 HNPCC families,² in which the same group reported an increased prevalence of adenomas similar to what we observed. The increased prevalence of adenomas persisted in all ages. We did not have a control group of subjects with general population risk and it could be argued that our reference group of non-HNPCC subjects may have had an increased risk of adenomas compared with the rest of the pop-

ulation. This would tend to underestimate the increased prevalence of adenomas in our HNPCC group. In our study, however, the colonoscopies were performed mostly by the same operator and at least by the same technique. We cannot be sure in their study that they are comparing like with like – that is, in comparing findings at colonoscopy with those at postmortem examination.

We disagree with Jass that any apparent differences in findings can be reconciled by consideration of family size. All of our HNPCC families were defined by the Amsterdam criteria, as were those of Jass. These are very strict criteria and highly specific for this diagnosis. Thus our description of the pathological spectrum in subjects from relatively smaller families that fulfil the Amsterdam criteria is likely to be as accurate as that obtained from the Jass series. Indeed, to understand the true spectrum of this disease, information from members of large numbers of families in addition to large sized families is required.

We agree with Professor Jass that the jury is still out regarding the proportion of families with HNPCC among those with familial clustering of colorectal cancer, and that the HNPCC may be uncommon.

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Cholecystokinin and transient lower oesophageal sphincter relaxation

EDITOR,—The paper by Ledebøer *et al* (*Gut* 1995; **36**: 39–44) clearly shows that CCK infusion does not affect the occurrence of transient lower oesophageal sphincter relaxations (TLOS) in humans. In contrast, we have recently shown that in dogs CCK infusion dramatically increases the frequency of TLOS.¹ A hasty conclusion would be that the dog is not an adequate model. There are arguments, however, suggesting that the difference between the two results is caused by the use of different forms of CCK: CCK-33 in the paper of Ledebøer *et al* and CCK-8 in our work. CCK-33 is one of the major molecular forms found in the plasma² while CCK-8 can be considered as the neuronal form synthesised in nerve cell bodies and released at nerve endings.³ It can indeed be postulated that CCK-8, but not CCK-33, is able to trigger TLOS, which are known to depend on the vago-sympathetic pathway.⁴

Moreover, a comparison between the control of TLOS and satiety, which also requires vagal afferent fibres integrity,⁵ shows the difference of the two CCK forms in question. The inhibition of food intake by administration of exogenous CCK-8 is well reported. However, increase of endogenous plasmatic CCK⁶ or administration of exogenous CCK-33⁷ has been found unable to induce satiety.

In conclusion, despite the absence of effect of CCK-33, a CCKergic control of transient lower oesophageal sphincter relaxations and gastro-oesophageal reflux cannot be excluded.

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Diverticular distraction

EDITOR,—Aldoori *et al* (*Gut* 1995; **36**: 276–82) claim to show an inverse relation between physical activity and symptomatic diverticular disease. Their data do not support such a conclusion, and it is unfortunate that such flawed conclusions have been so widely broadcast (the *Times*, *BMJ* 1995; **310**: 476, *Hospital Doctor*).

Despite the paper's title, this was not truly a prospective study, but a retrospective look at a prospective study of heart disease and cancer to which diverticular questions were opportunistically appended while the main study was underway. This study's original hypotheses did not include diverticular disease, and the design did not include a rationale, or a means of systematically detecting diverticula, most of which are asymptomatic.¹

Symptomatic diverticular disease is not a meaningful term. Diverticula probably cause systems only when they bleed or perforate causing peritonitis. Do diverticuli themselves cause symptoms? We think not. When subjects found to have diverticula on barium enema were blindly compared with controls they were no more likely to have bowel symptoms, and the bowel symptoms were mainly those of the irritable bowel (IBS).^{2–4} The authors claim that there is no basis for the diagnosis of IBS, yet there are published criteria.^{5–6} IBS occurs in 10 to 20% of adults.^{7–8} Therefore the abdominal pain and changed bowel habit found in the reported patients of Aldoori *et al* are most probably due to IBS in people who happen to have been found to have diverticular disease.

The authors have not shown that exercise prevents diverticular disease, symptomatic or not. What they might have shown is that exercise prevents functional bowel symptoms, but a better designed study is needed to confirm that. We have certainly seen patients whose