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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- 1 Jass JR, Stewart SM, Stewart J, Lane MR. Hereditary non-polyposis colorectal cancer – morphologies, genes and mutations. *Mutation Res* 1994; **310**: 125–33.
- 2 Jass JR, Stewart SM. Evolution of hereditary non-polyposis colorectal cancer. *Gut* 1992; **33**: 783–6.
- 3 Van de Water N, Jeevaratnam P, Browett PJ, Stewart SM, Lane MR, Jass JR. Direct mutational analysis in a large family with hereditary non-polyposis colorectal cancer. *Aust NZ J Med* 1994; **24**: 682–6.
- 4 Nystrom-Lahti M, Sistonen P, Mecklin J-P, Pylkanen L, Aaltonen LA, Jarvinen H, et al. Close linkage to chromosome 3p and conservation of ancestral founding haplotype in hereditary non-polyposis colorectal cancer families. *Proc Natl Acad Sci* 1994; **91**: 6054–8.

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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- 2 Jass J, Smyrk T, Stewart S, Stewart M, Lane M, Lanspar S, et al. Pathology of hereditary non-polyposis colorectal cancer. *Anticancer Res* 1994; **14**: 1631–4.

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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- 2 Eysselein VE, Eberlein GA, Hesse WH, Schaeffer M, Grandt D, Williams R, et al. Molecular variants of cholecystokinin after endogenous stimulation in humans: a time study. *Am J Physiol* 1990; **258**: G951–7.
- 3 Dockray GJ, Gregory RA, Tracy HJ, Zhu WY. Transport of cholecystokinin-octapeptide-like immunoreactivity toward the gut in afferent vagal fibres in cat and dog. *J Physiol (Lond)* 1981; **314**: 501–11.
- 4 Martin CJ, Patrikios J, Dent J. Abolition of gas reflux and transient lower oesophageal sphincter relaxation by vagal blockade in the dog. *Gastroenterology* 1986; **91**: 890–6.
- 5 Ritter RC, Ladenheim EE. Capsaicin pretreatment attenuates suppression of food intake by cholecystokinin. *Am J Physiol* 1985; **248**: R501–4.
- 6 Smith GP, Greenberg D, Falasco JD, Avilion AA, Gibbs J, Liddle RA, et al. Endogenous cholecystokinin does not decrease food intake or gastric emptying in fasted rats. *J Physiol (Lond)* 1989; **257**: R1462–6.
- 7 Lieverse RJ, Jansen JBMJ, Van de Zwan A, Samson L, Masclee AAM, Lamers CBHW. Effects of a physiological dose of cholecystokinin on food intake and postprandial satiation in man. *Regul Peptides* 1993; **43**: 83–9.

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

IBS followed cessation of vigorous exercise, but it is also possible that symptoms of IBS would deter some people from athletic pursuits. Did the authors consider the possibility that what they call 'symptomatic diverticular disease' might prevent exercise?

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- 1 Gear JSS, Ware A, Fursdon P, *et al*. Symptomless diverticular disease and intake of dietary fibre. *Lancet* 1979; i: 511-4.
- 2 Thompson WG, Patel DG, Tao H, Nair RC. Does uncomplicated diverticular disease produce symptoms? *Dig Dis Sci* 1982; 27: 605-8.
- 3 Sim GPG, Scobie BA. Natural history of diverticulosis of the colon. *NZ Med J* 1982; 95: 611-3.
- 4 Otte JJ, Larsen L, Andersen JR. Irritable bowel syndrome and symptomatic diverticular disease - different diseases. *Am J Gastroenterol* 1986; 81: 529-31.
- 5 Thompson WG, Creed F, Drossman DA, Heaton KW, Mazzacca G. Functional bowel disorders and functional abdominal pain. *Gastroenterology International* 1992; 5: 75-91.
- 6 Talley NJ, Phillips SF, Melton LJ, Mulvihill C, Wiltgen C, Zinsmeister AR. Diagnostic value of the Manning criteria in irritable bowel syndrome. *Gut* 1990; 31: 77-81.
- 7 Thompson WG, Heaton KW. Functional bowel disorders in apparently healthy people. *Gastroenterology* 1980; 79: 283-8.
- 8 Heaton KW, O'Donnell LJD, Braddon FEM, Mountford RA, Hughes AO, Cripps PJ. Symptoms of irritable bowel syndrome in a British urban community: consultants and non-consultants. *Gastroenterology* 1992; 102: 1962-7.

Reply

EDITOR.—Most of the points of Drs Thompson and Heaton were already considered and discussed in our article. The Health Professionals Follow up Study (HPFS) is indeed a prospective study that began in 1986 when cohort members completed a baseline questionnaire about dietary intake, history of medical conditions, and about other risk factors. Follow up questionnaires were sent in 1988, 1990, and 1992. The 1990 and 1992 follow up questionnaires contained specific questions pertaining to whether diverticular disease had been diagnosed during the previous two years. For this reason, our follow up for diverticular disease was from 1988 to 1992. To maintain the prospective design of our study, we used the 1986 baseline questionnaire for the assessment of several variables such as self reported physical activity, as this provides the only strictly prospective data for all cases. It is worth mentioning that the HPFS assessed many medical conditions in addition to heart disease and cancer (please refer to the study population in the method section). In prospective studies, the relevant exposures may or may not have occurred at the beginning of the study but the outcomes have not yet occurred,¹ which was the case in our study. While in the retrospective cohort study, however, both the exposures and the outcomes of interest have already occurred when the study began.¹ Although this difference in design is very basic, it is unfortunate that such a distinction is not always appreciated.

Biased recall of physical activity was unlikely because the physical activity data were collected before the diagnosis of symptomatic diverticular disease, and we controlled for several potential risk factors such as age, dietary fibre, and other dietary and non-dietary factors. Most of these aspects were not considered in previous case control studies of diverticular disease, which therefore limited

their interpretation. We have doubts that a 'better' and practical design to study diverticular disease is as Dr Heaton once suggested 'provided the ethical problem of radiographing normal people can be overcome, we need a large survey of the general population for diverticulosis and colon spastic symptoms so that diet histories can be obtained from groups of people with neither disorder, with each disorder on its own and with both disorders. It would be a formidable undertaking, but without it doubts will remain.'² As this would not be a prospective study, the recall of past diet would be subject to reporting bias.

Drs Thompson and Heaton are again suggesting that diverticular disease may be an asymptomatic condition, and that the symptomatic presentation is due to existing irritable bowel syndrome (IBS). Strong evidence exists that the two conditions are separate entities sharing a common presentation, which is abdominal pain. We have discussed some of the evidence and emphasised in our article that as both conditions are common, some overlap between them might exist (please see the discussion section). The prevailing understanding, however, is that diverticula can cause symptoms, which vary from a mild left quadrant pain to severe abdominal pain, and in extreme cases perforation or bleeding. Painter has suggested that because of the abnormal motility of the colonic muscle and the pain it is associated with, diverticular disease may cause symptoms whether or not diverticula are inflamed.³ Moreover, it was shown that intraluminal pressure was significantly higher in diverticular disease patients than controls, unlike patients with IBS, who had lower pressure than controls.⁴ High intracolonic pressure is necessary for the formation of the diverticula, and with the excessive segmentation leads to intermittent colonic obstruction, which may produce pain.³ Finally, it is worth mentioning that even among the limited number of diverticular disease cases in our study who presented only with bleeding, physical activity was inversely associated with the risk of diverticular disease (RR=0.46 (95% CI 0.14, 1.49)). We would like to think of this article as a 'Diverticular Contribution' and not a 'Distraction'.

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- 1 Hennekens CH, Buring JE. *Epidemiology in Medicine*. 2nd ed. Boston: Little, Brown, 1987.
- 2 Heaton KW. Diet and diverticulosis: new leads. *Gut* 1985; 26: 541-3.
- 3 Painter NS. The cause of diverticular disease of the colon; its symptoms and its complications. *J R Coll Surg Edinb* 1985; 30: 118-22.
- 4 Trotman IF, Misiewicz JJ. Sigmoid motility in diverticular disease and the irritable bowel syndrome. *Gut* 1988; 29: 218-22.

BOOK REVIEWS

Diagnosis and Management of Liver Disease. Edited by R Kirsch, S Robson, C Trey. (Pp 327; illustrated; £29.95). London: Chapman & Hill, 1995. ISBN 0-412-57570-1.

There are quite a few books on liver disease, but this medium size (327 pages) one takes an interesting approach in that each chapter is written by a member of a research unit in South Africa and then international experts were invited to complete each chapter. The result is a readable, authoritative, and clear book with a good mixture of pathophysiology and disease plus two useful chapters on immunology and molecular biology for the practising doctor. There is some transatlantic spelling.

I think the main weakness of the book, apart from too many scattered typing errors, is that some conditions that can be important to the gastroenterologist are only mentioned, including Wilson's disease, diabetes mellitus, methotrexate induced liver disease, post-operative jaundice, extracorporeal shockwave lithotripsy and endoscopic lithotripsy, Gilbert's syndrome and benign recurrent cholestasis. There is also no description of the lobule and acinus, which are important in an understanding of the function and anatomy of the liver, while there were rather obscure words such as scissura and incisura, when describing the surgical anatomy of the liver and photoferic, referring to a red cell scan. There was also confusion between aminotransferase and transaminase, even on the same page. I suspect these are errors of editing and no doubt the gaps can be filled in in the next edition.

I would have welcomed more diagrams and tables, while some of the scans reproduce poorly. Two radiographs of biliary ascari are no doubt prize exhibits in a slide collection but seem excessive!

In general, I therefore recommend it as a useful textbook of liver disease, although clearly a larger textbook would be required for deeper reading and reference lists.

The authors have apparently donated their royalties to charity but, despite that, it seems rather expensive at close on £30 for a soft back.

Perhaps this illustrates how little the financial rewards given by publishers to their authors contribute to the overall cost of books.

R P H THOMPSON

Paediatric Gastroenterology. Edited by B S Kirschner, J A Walker-Smith. (Pp 228; illustrated; £27.50). London: Bailliere Tindall, 1994. ISBN 0-7020-1866-X.

The number of publications catering for the postgraduate medical education (that is, training after qualification) and continuing medical education (that is, keeping yourself up to date after being fully trained) market continues to increase. These publications divide into those that present brief highlights of the recent literature, and those that present an in depth review of key topics in the field. Ideally those for the postgraduate medical education market need to consider topics that will probably appear in examinations and those for the continuing medical education market need to consider topics of interest to the generalist in the specialty. It would be interesting to know if the current interest in documenting (in the form of credits) the uptake of continuing medical education has led to an increase in the number of people reading these publications, to no change, or indeed to a decrease (how much you read is not counted in the credit tally).

The first volume of this series appeared two years ago. It fits into the 'in depth review of