developing fatal colorectal cancer. Aspirin seems to have immunostimulatory and tumoricidal properties in the colon[1 2] thus accounting for the protection. It is these properties that may also make low dose aspirin useful in the chemoprevention of colorectal cancer in high risk patients.[3] This is supported by the data of Manzano *et al.* Pre-neoplastic ulcerative colitis is associated with T lymphocyte immunosuppression and this may permit immunologically unchallenged malignant degeneration in a chronically inflamed mucosa. Aspirin may therefore be useful in the chemoprevention of colorectal cancer by augmenting the immune system thus destroying early tumours.

This principle also applies in the oesophagus as there are several similarities between the carcinogenesis of colorectal and oesophageal cancer. Chronic inflammation may be a pre-neoplastic lesion in both organs[4] while Barrett's oesophagus is also associated with immunosuppression.[5] NSAIDs may thus be useful in the chemoprevention of both colorectal and oesophageal cancer[6] in patients with pre-neoplastic disease. I agree with Choi and Zelig that longterm studies of low dose NSAID prophylaxis are warranted in patients receiving surveillance.

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Reply

EDITOR,—In our study (*Gut* 1994; **35:** 955–60), we have found that T lymphocytes from ulcerative colitis patients exhibit a deficient interleukin 2 conditioned proliferation pathway. This functional T lymphocyte abnormality is not connected to the activity of the disease, as it is also seen in asymptomatic patients. The cause and the pathogenic signification of this T lymphocyte deficiency remain elusive.

It seems that T lymphocytes play an important part in the surveillance function of the immune system against the growth and dissemination of tumours.[1] A potential association between the impaired T lymphocyte function found in ulcerative colitis patients and their enhanced incidence of colorectal tumours might be a certain hypothesis. But, it has not been shown yet.

Aspirin has an antiprostaglandin effect. It has been shown that prostaglandin E_2 may suppress the function of some immune cells including T lymphocytes.[2] However, the effect of the use of aspirin upon T lymphocyte function in patients with ulcerative colitis is unknown.

Despite the encouraging promise of aspirin as an agent for preventing colon cancer, further studies are required for indicating its widespread antitumour prophylactic use in ulcerative colitis.

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Acid and gastric metaplasia in the duodenum

EDITOR,—I am writing with reference to the letter to the editor (Savarino *et al Gut* 1994; **35:** 1151) and the reply concerning the paper by Noach *et al* (*Gut* 1993; **34:** 1510–4). In this paper they support the concept that gastric metaplasia of the duodenum is a response to acid hypersecretion and may be a defence mechanism.[1–3] An alternative concept is that it is a pathological change resulting in a loss of mucosal resistance to acid and pepsin. The small study that we reported comparing light and electron microscopy appearances of the duodenal mucosa in healed duodenal ulcer patients after one year's maintenance treatment with either cimetidine or sucralfate showed little change in the presence of gastric metaplasia and of *Helicobacter pylori* in 64% of the cimetidine group, and an appreciable reduction or absence of both in 73% of the sucralfate group.[4 5] If gastric metaplasia were a response to acid the reverse would be expected, with a reduction in the group receiving cimetidine. Over the next two years the relapse rates were 69% and 18% respectively.

Gastric metaplasia of the duodenal mucosa is almost invariably found accompanying duodenal ulceration. In the absence of gastric metaplasia *H pylori* cannot survive in the duodenum. Opportunistic colonisation of the metaplastic mucosa by *H pylori* may be an additional factor either in the initial formation of an ulcer or in delayed healing or relapse.

It is of interest that Noach *et al* reported no reduction in the extent and prevalence of gastric metaplasia after 12 months of eradication of *H pylori*. This means that these patients could be at risk of recolonisation and possible recurrence of duodenal ulceration. This emphasises the need for a treatment that will restore normal duodenal mucosa. Treatment with longterm sucralfate is one possibility, but alternatively there may be dietary factors that can achieve the same effect and thereby restore normal mucosal resistance.[6]

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Reply

EDITOR,—We thank Dr Tovey for his comments on our study. We are aware of his findings and results of other studies that the duodenal mucosa does not return to normal after treatment with cimetidine.[1] In agreement with this, we found no reduction of gastric metaplasia during chronic use of H_2 receptor antagonists. Acid suppression during treatment with these agents is comparatively weak, however, and does not exclude a causal relation between acid production and gastric metaplasia. Our finding that gastric metaplasia is virtually absent in patients receiving omeprazole and after highly selective vagotomy lends further support to the concept that gastric metaplasia is related to acid secretion.

As we did not study the grade of duodenal inflammation after eradication of *H pylori*, we have no data to support the theory that gastric metaplasia primarily is a pathological change of the duodenal mucosa with secondary loss of resistance to acid and pepsin. From other studies, however, it is known that signs of gastritis gradually disappear within a year after eradication of *H pylori*.[2] Theoretically, the persistence of gastric metaplasia may render patients at risk for recolonisation. Overwhelming evidence exists, however, that duodenal ulceration does not recur after eradication of *H pylori* whether or not gastric metaplasia persists.[3] We would therefore prefer the use of anti-*H pylori* regimens rather than longterm maintenance treatments.

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Pathogenesis of bacterial colitis

EDITOR,—The leading article on the pathophysiology of bacterial colitis was timely and informative (*Gut* 1994; **35:** 872–4). Some aspects of this fascinating topic may, however, warrant additional discussion.

As the authors pointed out, the cytotoxic toxins of *Shigella dysenteriae* type 1 and *Escherichia coli* O157:H7 are structurally

similar.[1] Moreover, it has been known for several years that these bacterial protein toxins are also structurally similar to ricin and abrin.[1 2] These plant toxins are, respectively, present in seeds of the castor bean plant (*Ricinus communis*) and the jequirity bean (*Abrus precatorius*), which are not closely related to each other.[3] There is compelling evidence that the cytotoxic effect of all these toxins is mediated by an identical mechanism. The toxin molecules consist of an A subunit and one or more B subunits. After binding of the B subunit(s) to a cell surface receptor, the A subunit enters the cell, where it cleaves an adenine residue from ribosomal RNA molecules.[1 2] The end result is that protein synthesis stops and the affected cells die.

This mechanism almost certainly explains the diarrhoea (with or without rectal bleeding) that follows ingestion of castor or jequirity beans,[3 4] the colonic inflammation that occurs in *S dysenteriae* type 1 and *E coli* O157:H7 infections, and the endothelial cell damage that accompanies the haemolytic uraemic syndrome.[5] The traditional equation of bacterial haemorrhagic colitis with bacterial invasion of the mucosa is clearly an over simplification. At least in the case of *E coli* O157:H7 and *S dysenteriae* type 1 infections, the important issue is the production of a cytotoxic toxin, irrespective of whether the bacteria invade the mucosa.

To date, ricin achieved its greatest notoriety in the 1978 'umbrella murder' of the Bulgarian broadcaster Georgi Markov.[6] It is intriguing that the systemic effect of ricin in this unfortunate episode can be directly compared with the pathophysiology of bacterial colitis.

Finally, polymerase chain reaction amplification of *E coli* O157:H7 DNA encoding part of the cytotoxic toxin molecule may facilitate the detection of this bacterium in clinical specimens and in contaminated food.[7]

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Reply

EDITOR,—We appreciate the comments from Dr Heyworth. Further details about toxin structure:function relations may be found in reference 21[1] in the leading article (*Gut* 1994; **35:** 872–4). We have been proponents of the critical role of Shiga family toxins in the pathogenesis of bloody diarrhoea for over two decades, a concept that has become more tenable since the discovery of the 'non-invasive' toxin producing enterohaemorrhagic *E coli*, but which is still far from conclusively proved in human clinical disease.

While we pointed out the importance of rapid detection of this group of organisms in our leading article, and urged that a search for enterohaemorrhagic *E coli* becomes routine when any stool is examined for causes of bloody diarrhoea (an idea recently endorsed and recommended by a Consensus Conference of the American Gastroenterological Association that took place in July 1994), we do not believe that polymerase chain reaction is the best way at present to proceed, as Dr Heyworth suggests. This is because as of today, and for the foreseeable future, most clinical laboratories will not be doing polymerase chain reaction diagnosis at all. Our laboratory has developed monoclonal antibodies and an EIA toxin detection system for direct evaluation of free toxin in patient stools, which has been substantially increased in its sensitivity by Meridian Diagnostics of Cincinnati, Ohio. The preliminary clinical evaluation of this test, which is not restricted to the detection of *E coli* O157:H7 but detects all serotypes of toxin producing organisms, has been highly favourable. Meridian is carrying out further testing and evaluation to obtain approval by the US Food and Drug Administration. It would seem at this moment that a clinically useful early diagnostic test for enterohaemmorhagic *E coli* infection, independent of sorbitol fermentation patterns and the potential impact of antimicrobials on the viability of the micro-organisms, is imminent and could become available within a year's time. This test, in contrast with polymerase chain reaction, could be immediately used in all clinical laboratories that conduct routine microbiological, immunological, and serological assays for the diagnosis of infectious enteritis.

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Unethical research relating to *Helicobacter pylori*?

EDITOR,—We are writing concerning the paper by Vincent *et al* (*Gut* 1994; **35:** 313–6) regarding the prevalence of *Helicobacter pylori* infection in cohabiting children. In that study, the authors examined the prevalence of *H pylori* infection among mentally retarded children residing in an institution. *H pylori* infection was confirmed by gastroscopy. 'Informed consent' was obtained from the families.

We believe that this study raises important ethical questions and concerns. Research involving children always raises the 'ethical' flag and the use of invasive procedures requires a very critical look at the risk versus benefit obtained. In most instances invasive procedures will be deemed to be unjustified in asymptomatic children. The problem is somewhat easier if you are dealing with a population of symptomatic children, but even in that group the motivation and clinical practices of a group reporting the results of invasive procedures for diagnosis must be questioned.

This study describes endoscopic investigations in asymptomatic mentally retarded children. It is extremely difficult to imagine any benefit that the children could have gained from participation in the study. We are hard pressed to come up with any ethical justification for doing the study. Hammerschmidt and Gross[1] note that when a journal accepts a paper for publication after peer review that 'acceptance constitutes at least a *nihil obstat* [no objection] if not an *imprimatur* [official licence to print]. Authority of the journal has been placed behind the paper announcing that it has been subjected to scrutiny and has been found to pass muster in terms of basic quality, novelty and potential importance.' There are two questions: firstly, should the study have been done at all and secondly should it have been accepted for publication?

We recognise that these concerns are serious, but they must be considered and considered now as the role of *H pylori* in the paediatric population is coming under increasing scrutiny.

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Reply

EDITOR,—Ethical aspects regarding our paper (*Gut* 1994; **35:** 313–6) were asked by one of the reviewers, and the necessary answers were given. Study protocol was much more detailed in the first version of our paper, but was shortened afterwards according to the reviewers' recommendations. Finally, only epidemiological and microbiological aspects were described in the published version.

We agree that such a study should not be done only for epidemiological purposes. Our study took place in a clinical context with therapeutic concerns as in the first instance, three cases of *H pylori* endoscopic gastritis were found in this institution and then treated with clinical ameliorations. These three children had endoscopy because of suspected oesophagitis and macroscopic nodules were seen in the antrum. This led us to perform biopsies, which showed the presence of *H pylori* gastritis. Specific *H pylori* treatment was given because we could not distinguish the potential role of the infection in the upper gastrointestinal complaints of these patients.

In severely neurologically impaired children, gastro-oesophageal reflux is common.[1] In our experience, 20·5% of these children suffer from gastro-oesophageal reflux. If not controlled in time, the disease can evolve and lead to severe complications such as oesophageal stricture or Barrett's oesophagus. In these children, gastro-oesophageal reflux is often associated with other disorders (nutritional, metabolic, respiratory, urological, or digestive diseases). It is widely admitted that gastro-oesophageal reflux is difficult to recognise on clinical grounds in mentally retarded