We agree that not all patients with duodenal ulcer disease secrete more acid than normal. Patients with duodenal ulceration, however, on average produce more acid than normal. As gastric metaplasia is an almost constant finding at the margins of duodenal ulcers, increased acid flux may at least be a contributory factor to the development of gastric metaplasia. This is substantiated by many experimental findings and clinical studies. Indeed, the high prevalences of gastric metaplasia in duodenal ulcer patients in general suggests that other, still unknown factors, may also be involved.

The short term lack of regression of gastric metaplasia of H pylori may also point to the multifactorial nature of gastric metaplasia, including ongoing robust acid secretion during the first year after eradication of H pylori. Evidence emerges that gastrin mediated acid output regresses over time in patients with chronic H pylori in duodenal ulcer disease. To up to now, we cannot exclude that gastric metaplasia may be slowly reversible in the long term as has been seen after vagotomy. Again, other factors such as acid and H pylori infection may be responsible for the persistence of gastric metaplasia in other patients.

We do not agree with Savarino et al that the presence of gastrin-mediated acid output in duodenal ulcer patients is diminished by the fact that gastric metaplasia failed to regress in the short term follow up after eradication of H pylori. In our opinion, the almost invariable presence of gastric metaplasia at the margins of duodenal ulcers shows that both gastric metaplasia and (ulcerogenic strains of) H pylori are required for the development of duodenal ulceration. Longer follow up studies will be necessary to find out if, to what extent, and with what velocity gastric metaplasia regresses in duodenal ulcer and non-duodenal ulcer subjects.


Risk factors for the development of gall bladder disease

EDITOR,—I enjoyed reading the article by Murray et al (Gut 1994; 35: 107–11). I am surprised that the authors have published data where there is no confirmatory evidence of gall stones in most of their patients. I agree it is unlikely that the general practitioners in the study changed their diagnoses in patients with upper abdominal pain on the basis of smoking habit. On the other hand it is quite conceivable that smokers could be predisposed to episodes of acute upper abdominal pain because of peptic ulceration or reflux disease.

With 80% of patients not even admitted to hospital and no indication of the percentage of patients who had confirmed gall stone disease this paper cannot fully consider the effect of smoking on gall stone disease. It tells us that smokers experience more upper abdominal pain than non-smokers. Whether or not this results from gall stones is another question, which remains unanswered.

L A NOACH
T M ROLF
N B ROGSA
M SPCHWARTZ
J OOSTING
E A J RAUTS
G N J TYTGT
Department of Gastroenterology, Academic Medical Centre, 1105 Amsterdam, The Netherlands

Ileal and colonic epithelial metabolism in quiescent ulcerative colitis

EDITOR,—The paper by Drs Finnie et al (Gut 1993; 34: 1552–8) showing that mucosal biopsy specimens from sufferers of quiescent ulcerative colitis possess a normal ability to oxidise butyrate is in direct contradiction to our findings where we showed a reduced capability.1 We used an almost identical technique, which has been validated and exhibits a similar degree of reproducibility.2 We would concur with the conclusions of Finnie et al on tissue viability, effects of lymphocytes, and of contaminating bacteria (although assaying 100 µl of faecal fluid would not reflect accurately what would be true for different adherent bacteria on the mucosal surface in disease and controls) on the assay. It is difficult to account for the differences in the results of the two studies. We would like to make a few points to complement those of Professor Roediger (Gut 1993; 34: 1646).

The rates of oxidation of glutamine and butyrate found by Finnie et al were about 100-fold greater than ours using biopsy specimens, and other workers using isolated colonicocytes.3 Working through the calculations of Finnie et al it would seem that the protein content of their specimens was far less than would be expected from the wet weights of the specimens.

This problem may be illustrated by reference to the data shown in Fig 2 where specimens of about 10 mg wet weight were incubated in 1 ml of medium containing 1 mM [1-14C] labelled butyrate (1 µmol butyrate in total) for up to three hours. After two hours about 200 µCi (0.07 mCi) was produced for each µg of tissue protein present in the incubation. As the complete oxidation of butyrate results in four molecules of carbon dioxide this represents the utilisation of 0.97 nmol of butyrate per µg tissue protein. At this rate of utilisation all the butyrate in the incubation medium would have been oxidised in two hours by a specimen containing 20 µg of protein. It is therefore possible that our 100 µCi would yield no more than 20 µg protein.

This same problem can be considered from another angle, without assuming complete oxidation of the butyrate. One µCi (37 KBg) of labelled butyrate was added to 1 µmol of butyrate, thus the specific activity was 2220 disintegrations per minute (DPM) per nmol. Finnie et al quote a range of 24000–115000 DPM for butyrate. This represents 11–52 nmol of labelled butyrate for 0·55–2·6 nmol/mg wet weight/hour. From Table 1 and Fig 4 the mean rate of butyrate oxidation is about 75 nmol/mg protein/hour. Thus a specimen weighing 10 mg wet weight would produce 2.5 nmol and 150 µCi of protein. In our experience a colonic biopsy specimen with a wet weight of about 10 mg is equivalent to about 800 µg protein weight, which is much closer to the ratio found by other workers.

It is difficult to comment in detail without seeing the raw data but it is possible that the division of the biopsy sample into very small pieces led to the shedding of a significant amount of material as cell clusters during the incubation period. The use of perchoric acid to terminate the reaction and liberate the carbon dioxide may then have also resulted in the precipitation of protein, which was lost to the assay.

All our experiments, as Finnie et al correctly pointed out, were performed in the presence of 5 mM glutamine and 5 mM butyrate. It is known that the presence of 5 mM glutamine supports the complete oxidation of glutamine in the rat colonicocytes.4 If this holds true for the human it is difficult to draw conclusions from the work of Finnie et al, as in vivo both glutamine and butyrate will be present.

We while that there is evidence to suggest that butyrate concentrations greater than 2 mM may be toxic to certain cell lines there is no evidence to suggest that concentrations of less than 40 mM are toxic to isolated colonicocytes.5 Finnie et al found that using concentrations of either 1 mM or 5 mM butyrate had no significant effect on the ability of the specimens to oxidise butyrate (Fig 3). In our experiments we used a butyrate concentration of 5 mM.

The finding that the ratio of butyrate/glutamine oxidation in the distal colon is greater than that in the proximal colon and that this relation is lost in the diseased group suggests that this second group has a lower dependency on butyrate and is more reliant on glutamine as a fuel source. It may be speculated that this is a response to an inability to oxidise butyrate and explains why inflammation is more commonly seen in the distal rather than proximal colonic colon.

The results from the ileal mucosal biopsy specimens are at variance with our previously published results6 and we wonder if con-
striking change in the contribution of different fuels to total oxygen consumption was the increased metabolism of glucose in quiescent colitis.

With regard to the appropriate choice of glutamine concentration there is no clear answer. As Chapman et al themselves point out there is likely to be little or no glutamine available from the colonic lumen because it is so readily utilised by colonic flora and peripheral blood concentrations of glutamine are less than 0·5 mM, so culture in the presence of 5 mM glutamine cannot be considered physiological.

We were interested in some results from ileal mucosal biopsy specimens reported by Chapman et al in their abstract. We suspected that the reduced metabolism of butyrate that they have shown in the terminal ileum of patients undergoing colectomy, particularly for severe colitis, might be to some extent a reflection of the severe illness combined with backwash ileitis. For this reason we chose to study ileal biopsy specimens obtained at colonoscopy from patients in clinical remission. The figures for coefficients of variation we published were for all specimens, ileal and colonic included (20% for butyrate metabolism and 23% for glutamine metabolism). The coefficients of variation for the ileal butyrate metabolism were 20% and for butyrate 18%, not 50% as stated by Chapman et al. There was, if anything, a very slight trend towards increased ileal butyrate metabolism in our ulcerative colitis in our study. We have subsequently increased the numbers of ileal biopsy specimens studied to 18 in all and the conclusion remains the same.

There clearly are some interesting differences in mucosal metabolism in ulcerative colitis but our view is that most of these differences are likely to reflect changes occurring secondary to hyperplasia.

Reply

EDITOR,—We thank Mr Chapman for his comments regarding our paper and are grateful to the editor for the opportunity to respond to the points raised.

At the outset, we agree with Mr Chapman that he has correctly identified an error on our part. The units quoted throughout our paper for butyrate and glutamine metabolism should have been nmol substrate metabolised/living patient-day. We urge apology for the confusion that has resulted. The statistical analysis and conclusions for all the data remain as stated.

The critical difference between our study and that of Chapman et al is that we have examined butyrate metabolism in the presence of glucose but not glutamine, whereas their study was performed in the presence of all three energy substrates. Our own studies and those of Roediger (but not those of Chapman et al) have shown increased metabolism of glutamine in ulcerative colitis.

It seems likely that this may be a reflection of hyperplasia, as rapidly dividing cells have increased metabolism of glutamine.1 In the absence of excess glucose we have failed to find any defect in metabolism of butyrate, and suspect that the results of Chapman et al may reflect the predilection of the mucosa for glutamine metabolism, but may not necessarily reflect the ability to metabolise butyrate. To some extent a similar conclusion can be reached from part of Roediger’s original study. He showed that the rate of oxygen uptake by the presence of butyrate as the sole energy substrate was normal in quiescent ulcerative colitis and only reduced in acute colitis, and although production of carbon dioxide from butyrate was reduced in ulcerative colitis, the most

Risk factors for Helicobacter pylori

EDITOR,—The findings of the EUROGAST Study Group on risk factors for H pylori infection (Gut 1993; 34: 1672–6) interested us because of the relation between this disease and the aetiology of peptic ulceration. The principal finding was that the presence of H pylori infection in 5LH of the group was a positive correlation between infection and low educational standard. They suggested this showed that social class was a relevant factor. In 1966 we found an association between atrophic gastritis on gastric biopsy and social class in a series of 221 patients suffering from non-ulcer dyspepsia. The prevalence of gastritis increased with descending social class, and increased with age in all classes, becoming roughly equal in each class at 50 years and over.

Unlike the EUROGAST study our data suggested a positive correlation also between atrophic gastritis and excessive cigarette smoking, excessive alcohol consumption, and drinking hot tea.

The study by Vincent et al (Gut 1994; 35: 313) showed a high prevalence of H pylori in children cared for in a medical centre for mentally retarded children. The authors thought that factors related to close contact with other children were probably the cause of the high prevalence.

We were puzzled by our findings nearly 30 years ago. It is of interest that Bateson’s review of H pylori infection mentions its higher prevalence, and at an earlier age, in the developing world. Perhaps, if there is a relation between atrophic gastritis (and H pylori infection) and social factors it is mediated through interacting elements of living conditions probably associated with low grade education: financial hardship, restricted accommodation with people in close proximity and possibly sharing food and cooking utensils, poor hygiene, and low social class.

F C EDWARDS
78 Old Road,
Oxford OX3 7LP

N F COGHILL
28 The Grove,
Ealing,
London W5 3LH