Markers to study human colonic cell proliferation

EDITOR,—We noted with interest the paper by Kubben et al (Gut 1994; 35: 530–5) on a comparison between proliferating cell nuclear antigen (PCNA) and ex vivo bromodeoxyuridine (BrdU) labelling. We have compared PCNA labelling in 86 human colorectal tumours to iododeoxyuridine (IudR) labelling after in vivo administration using both flow cytometric and immunohistochemical methods.1

In contrast with the authors’ findings, we have not found a significant correlation between the two labels. This was despite correcting for the presence of IudR labelled daughter nuclei (a problem that has not been discussed in this paper) and using a variety of fixatives when assessing PCNA labelling. In our experience, the strongest correlation seen has been on comparison between IudR labelling assessed immunohistochemically and PCNA labelling after fixation in methanol (r=0.38, p<0.01). Fixation methods seem to affect the identification of PCNA in different parts of the cell cycle2 and the apparently higher expression of PCNA than BrdU in Kubben’s paper reflects this.

As we have stated before,3 the way we feel that in comparisons such as this, it is necessary to analyse a much greater number of specimens from a greater number of subjects and attach less clinical significance to a weak correlation that is statistically significant.

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Reply

EDITOR,—We thank Drs Baron and Harris for their interest. We reply to their four points below.

1 The mean duration of the first half hour was 5·1 min (SD 3·8 min). The mean duration of the second half hour (because the first half hour is not a reliable estimate of the basal rate) was: H2 pylori positive (n=41), basal acid output 5·1 mmol/h, Vg 111 mmol/h; H2 pylori negative (n=21), basal acid output 4·97 mmol/h, Vg 110 mmol/h. (2) We do not know why only 68% of our duodenal ulcer group were H2 pylori positive, although some evidence bearing on this point has been submitted for publication. We agree that 95% is commonly quoted, but in five recent publications the values were 67.2%, 52·6%, 66.4%, 76% and 50% (weighted average 68·7%). (3) The plateau/average values (SD of duodenogastic reflux (Va) ml/min and (4) The positive and negative patients did not differ significantly from each other. (4) Body biopsy specimens were not taken, hence the speculative nature of our suggestion. Some of the patients had their H2 pylori eradicated. Acid output was not measured after eradication.

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Letters

DUODENAL ULTRASMALLER, gastric acid, and Helicobacter pylori

EDITOR,—Professor Hobsey’s group (Gut 1994; 35: 1033–6) found significant decrease in duodenal ulcer gastric acid secretion corrected for pyloric loss, duodenogastic reflux, and stature in patients with duodenal ulcer or non-ulcer dyspepsia who were H2 pylori positive. We have four questions. (1) What were the results with the one hour basal acid output? (2) Why were only 68% (21 of 31) of the duodenal ulcer group H2 pylori positive with active chronic gastritis? The usual proportion of H2 pylori positivity in duodenal ulcer is 95%, and superficial or atrophic antral gastritis is almost invariable in duodenal ulcer. (3) The decrease in acid was significant only in the corrected data. Was either pyloric loss significantly reduced or duodenogastic reflux significantly increased in those infected with H2 pylori? (4) They speculate that the reduced acid in the H2 pylori positive duodenal ulcer group results from destruction of parietal cells: what reasons are there? (5) In our study we ascribe to the fixation method used.

Two populations of PCNA are present during S phase. One is nucleopolasmic, present in short G2 phase, and not apparent in cells fixed in organic solvents such as methanol or ethanol. The other form is associated with DNA replication sites and cannot be extracted with organic solvents.1–3

Our results are comparable with those of Weisgerber et al.4 who used an organic solvent as fixative as well, and slightly lower of those of Risio et al.,5 who used formalin fixation (Table). Risio showed a decreasing correlation between PCNA and BrdU immunohistochemical staining with increasing dysplasia of the tissue under investigation.

The progressive increase of PCNA expression with increasing dysplasia seems to be related to both hyperproliferation and neoplastic deregulation of PCNA synthesis. Although they do not provide sufficient technical details, the interesting results of Wilson and Schofield are in agreement with our study and the work of Weisgerber et al and Risio et al.

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3 Yu CCW, Filipe ML. Update on proliferation-associated antibodies applicable to formalin-fixed paraffin-embedded tissue and their clinical applications. Histocom 1993; 25: 843–53.

