LETTERS TO THE EDITOR

Why use Buscopan during diagnostic upper gastrointestinal endoscopy?

EDITOR,—In their audit of upper gastrointestinal endoscopy (*Gut* 1995; **36:** 462–7), Quine *et al* considered the issues surrounding the use of anticholinergic agents during upper gastrointestinal endoscopy. They found that although most procedures were performed without the use of either hyoscine butylbromide (Buscopan, Boehringer Ingleheim) or atropine these agents were still in use in certain centres and their findings indicate that Buscopan (dose range 10–40 mg) was used in 29% of procedures in East Anglia compared with 20·6% in the North West region and atropine (0·6 mg intravenously) was used in 11·2% procedures in the North West region and only 0·3% in East Anglia.

Buscopan is a spasmolytic or smooth muscle relaxant drug with anticholinergic activity. Its anticholinergic activity lasts for about 15–20 minutes and infusion experiments suggest that it is rapidly inactivated or excreted. It also has a sympathetic ganglion blocking action but this effect is unimportant in humans at the conventional dose of 20 mg commonly used. Its actions on the gastrointestinal tract include inhibition of motility in the stomach and colon, reduction of gastric acid secretion, and slowing transit through the small bowel. It also causes transient pylorospasm. Some studies have shown that oesophageal peristalsis is reduced by Buscopan[1] and that it relaxes the lower oesophageal sphincter.[2]

What is the rationale for the routine use of anticholinergic agents during diagnostic upper gastrointestinal endoscopy? The use of atropine to dry up secretions and for 'cardiac protection' is a benefit postulated[3] without there being any controlled data available. Reports have shown that anticholinergic premedication does not improve the quality of diagnostic endoscopy or reduce patient discomfort.[4 5] These investigators found no differences between groups with respect to gastric motor function or endoscopic quality as judged by the endoscopist or discomfort during endoscopy as judged by the patient.[4] Though atropine decreased both the amplitude and frequency of gastric peristalsis this objective effect of atropine did not have any effect on the outcome of the endoscopy.[5]

Anticholinergic premedication does not have any effect in reducing the incidence of cardiac arrhythmias during upper gastrointestinal endoscopy.[6] The audit by Quine *et al* reports on a total of eight patients who experienced significant cardiac arrhythmias that required treatment, including five patients who arrested. Four of these had been given Buscopan (two had been given doses of 40 mg). In another prospective study[7] comparing the use of Buscopan and Glucagon it was found that with intravenous Buscopan 20 mg the heart rate increased from a baseline of 94·4±11·1 to 126±19·5 beats per minute and there was a fall in the mean systolic, diastolic, and mean arterial pressure by 20–50 mm Hg in the Buscopan group. Four patients (aged 76–80 years) had hypotensive episodes immediately after intravenous Buscopan that lasted one to seven minutes. Thus Buscopan can cause both hypotension and a tachycardia.

Buscopan significantly reduces pressure in the lower oesophageal sphincter and in theory may facilitate gastro-oesophageal reflux.[2] The effect of an intravenous injection of 20 mg Buscopan on gastro-oesophageal reflux was evaluated in 112 consecutive patients undergoing barium meal evaluation.[8] This study concluded that the routine use of Buscopan was unlikely to spuriously increase the frequency or degree of gastro-oesophageal reflux seen during barium studies. However, radiological evaluation is an insensitive method of detecting gastro-oesophageal reflux and there are no data on oesophageal pH measurement after intravenous administration of Buscopan. Gastro-oesophageal reflux induced by Buscopan could predispose to the development of aspiration pneumonia. The audit by Quine *et al* reported 11 patients to have had pneumonia shortly after the procedure and 10 of these patients had received pharyngeal anaesthesia, which when combined with the presence of the fibreoptic endoscope interferes with glottic closure and swallowing and may cause pulmonary aspiration. We have no information on the use of anticholinergic agents in this group and wonder if these agents had any role in the development of pneumonia. Thus except for procedures such as injection of oesophageal varices and endoscopic retrograde cholangiopancreatography where the use of anticholinergic agents is clearly beneficial we would question their routine use during diagnostic upper gastrointestinal endoscopy.

K CHOPRA
D WESTABY
I MURRAY-LYON
Gastrointestinal Unit,
Chelsea and Westminster Hospital,
369 Fulham Road, London SW10 9NH

1 Liu C. Visualization of oesophageal varices by Buscopan. *Am J Roentgenol* 1974; **121:** 232–3.
2 Cooper JD, Gill SS, Nelems JN, Pearson FG. Intraoperative and postoperative findings with Collis gastroplasty and Belsey hiatal hernia repair for gastroesophageal reflux. *J Thorac Cardiovasc Surg* 1977; **74:** 744–51.
3 Cotton PB, Williams CB. Diagnostic upper endoscopy. *Practical gastrointestinal endoscopy.* 3rd ed. Great Britain: Blackwell Science, 1990: 23–55.
4 Hedenbro JL, Frederiksen SG, Lindblom A. Anticholinergic medication in diagnostic endoscopy of the upper gastrointestinal tract. *Endoscopy* 1991; **23:** 199–202.
5 Cattau LE, Artnack EJ, Castell DO, Meyer GW. Efficacy of atropine as an endoscopic premedication. *Gastrointest Endosc* 1983; **29:** 285–8.
6 McCloy R, Chiti CC. ECG changes during fibreoptic upper GI endoscopy and colonoscopy [Abstract]. *Gastrointest Endosc* 1976; **22:** 231.
7 Rameh B, Jabbar M, Morden A, Huddy SPJ, Wyke RJ. Changes in blood pressure and duodenal atony during ERCP – studies of the influence of Buscopan and Glucagon [Abstract]. *Gut* 1994; **35** (suppl 5): S50.
8 McLoughlin RF, Mathieson JR, Chipperfield PM, Grymalowski MR, Wong AD. Effect of hyoscine butylbromide on gastroesophageal reflux in barium studies of the upper gastrointestinal tract. *Can Assoc Radiol J* 1994; **45:** 452–4.

Reply

EDITOR,—The authors share Dr Chopra's concern about the use of anticholinergic medication for routine diagnostic upper gastrointestinal endoscopy and endorse the view that it should be reserved for therapeutic endoscopy where the benefit may outweigh the risks. Of the 11 cases of pneumonia reported six patients had received Buscopan and five had not. Therefore the use of Buscopan or Atropine did not seem to have an obvious effect on the risk of pulmonary aspiration though it is an interesting hypothesis.

A QUINE
Audit Unit,
British Society of Gastroenterology,
3 St Andrews Place
Regent's Park, London NW1 4LB

The nurse endoscopist

EDITOR,—As the advent of the nurse endoscopist seems ever more certain, I wish to raise my concerns about the provision of clinical information to the histopathologist who reports on the biopsy specimens.

We are already in a situation where most liver and gut biopsy specimens are sent by endoscopists or radiologists who are not primarily involved in the clinical care of the patient, and whose knowledge of their clinical history and medication is derived from a quick scan of the notes between appointments in a hectically busy department. Most pathologists will already be familiar with the terse statement 'raised LFTs', which is totally inadequate for a clinically useful assessment of a liver biopsy specimen. Two recent confusing samples received in this department were rendered interpretable only when histories of multiple myeloma and pelvic irradiation were eventually disclosed. Chasing clinicians and case notes is very time consuming and counterproductive.

Clearly the present situation, from the histopathologist's point of view, is not as good as it might be despite the fact that qualified medical practitioners are scanning the notes and entering clinical details on the request forms. But how will we fare when non-medical personnel are sending us specimens? Who will ensure the flow of accurate and relevant clinical information? Their training may encompass aspects of anatomy and physiology (*Gut* 1995; **36:** 795) but this is hardly sufficient training to rapidly assimilate and then distil the essence from a patient's medical case notes.

A P GRIFFITHS
Department of Histopathology,
Morriston Hospital,
Swansea SA6 6NL

Reply

EDITOR,—Dr Griffiths is understandably concerned about the provision of clinical information to the histopathologist by nurse endoscopists. Clinical information on histopathology forms is clearly of the greatest importance and this is one of many issues that will be covered in the training programme for nurse endoscopists.

However, I do not think he need fear that pathologists are suddenly going to receive a lot of incompetently filled forms with the advent of nurse endoscopists. Often forms are poorly filled in because of the 'hectically busy' life that most medical endoscopists lead. It is also well recognised that doctors are frequently poor form fillers. By contrast it is my experience that nurses are very diligent in this respect. I am sure that with the increasing numbers of gastrointestinal nurse specialists, obtaining appropriate clinical information from the notes will be well within the nurses' ability. I actually foresee a higher standard of

Gut: first published as 10.1136/gut.38.3.473-c on 1 March 1996. Downloaded from http://gut.bmj.com/ on November 27, 2023 by guest. Protected by copyright.

form filling with better clinical information coming from nurses than from their medical colleagues.

M D HELLIER
Secretary, Endoscopy Committee of the BSG, Princess Margaret Hospital, Okus Road, Swindon SN1 4JU

Measurement of morphokinetic status in experiments on intestinal adaptation

EDITOR,—The protracted debate concerning appropriate measurements of morphokinetic status in experiments on intestinal adaptation, seems to have passed Reilly *et al* (*Gut* 1995; **37:** 81–6). There are several points of major concern in their paper.

(1) 'Crypt cell proliferation rate (is determined) by bromodeoxyuridine incorporation'. How? The references quoted are to BrdU in different systems and cannot be used to assess the methodology of Reilly *et al.* The measurement, called 'crypt cell proliferation (%)', is not one we recognise: could it be the percentage of BrdU labelled cells? But then, percentage of what? It is surely no longer acceptable in such studies to be allowed to give such measurements without giving readers an indication of the target interphase nuclear population and counting statistics; of course, BrdU does not measure 'crypt cell proliferation', but only one indirect component of it – the S phase fraction. The changes in crypt depth (Table II) show that the several groups have different sized crypt populations: therefore the putative increases in labelling index in SCFA/control, saline/gastrin receptor blockade, and SCFA/gastrin receptor blockade may in fact be modified because of changes in the interphase nuclear population. Such problems are simply avoided by using the whole crypt as a denominator, as is now widely used.[1]

(2) The fact that both groups receiving the gastrin blocker (saline/gastrin receptor blockade and SCFA/gastrin receptor blockade) show a significant increase in labelling index compared with saline control, and that the SCFA/gastrin receptor blockade group is significantly larger than the SCFA control receives no mention in the discussion; these differences are also reflected in the crypt depth and villous height measurements (Table II). What is going on here: does the gastric receptor antagonist itself stimulate cell proliferation?

Some light may be cast on this by the weight data: both gastrin receptor blockade groups gained significantly more weight than the control group. Food intake in the various groups is an important modulator of intestinal proliferation and was evidently not monitored: it is certainly not mentioned. Consequently, a possible interpretation is that gastrin receptor blockade increases food intake and hence intestinal cell proliferation: the addition of SCFA in this model fails to further increase cell proliferation. And to argue that other measures such as DNA and protein, support the interpretation is neither here nor there: it is difficult to support such measurements for critical work.[2] What is meant by 'jejunum'? Clarke pointed out many years ago that rats do not have jejunums and ileums, so what does jejunal weight mean? We assume that 'crypt death' measurements were a figment of inadequate proof reading.

It is difficult, if not impossible, to make any conclusions from this study: it will no doubt have to be repeated, monitoring food intake or feeding rats parenterally, with more critical measurements.

N A WRIGHT
R A GOODLAD
Histopathology Unit, 35–43 Lincoln's Inn Fields, London WC2A 3PN

1 Goodlad RA. Microdissection-based techniques for the determination of cell proliferation in gastrointestinal epithelium: application to animal and human studies. In: Celis JE. *Cell biology: a laboratory handbook.* San Diego: Academic Press, 1994.
2 Wright NA, Alison MR. *The biology of epithelial cell populations.* Vol 2. Oxford: Oxford University Press, 1984.

Reply

EDITOR,—George Bernard Shaw once said 'England and America are two countries divided by a common language'.[1] The letter by Wright and Goodlad personifies this divisiveness. Citing their own studies of the crypt cell production rate (CCPR) as the purported 'gold standard' for measurement of intestinal proliferation, Wright and Goodlad question our measure with bromodeoxyuridine (BrdU) and wonder why we did not use their technique. Interestingly, we are not the first 'nonconformists' to incur the vent of their partisan wrath, as expressed in another vituperative letter by Goodlad 'Defective denominators or will people never learn?' (*Gastroenterology* 1995; **108:** 1963). On this side of the pond, experienced investigators use tritiated-thymidine incorporation to quantify 'S' phase cells, proliferating cell nuclear antigen (PCNA), and BrdU to measure proliferating cells, or enzyme markers such as thymidine kinase or ornithine decarboxylase as indicators of cell proliferation. Flow cytometry is also used in combination with some of the staining techniques. We believe all of these methods are valid comparisons within a single experiment. There is clearly not a general agreement on a 'gold standard' for this measure. BrdU immunohistochemistry, performed in our study, is used by many to yield semi-quantitative information that directly correlates with cell proliferation in many in vitro and in vivo experimental systems. The accuracy of BrdU labelling indices to study in vivo proliferation in the digestive tract in rats has been clearly shown.[2]

We agree that BrdU immunohistochemistry is an imperfect measure of crypt cell proliferation because (similar to tritiated-thymidine) it only measures the number of cells cycling through the 'S' phase of the cell cycle. Readers of *Gut* and most gastrointestinal scientists are well aware of this characteristic. The reality remains that although imperfect, BrdU labelling indices (as well as labelling indices obtained by tritiated-thymidine or PCNA) are to date widely accepted as accurate and reliable indices of intestinal proliferation, which can be used for internal comparisons within a single experiment.

It is well accepted that labelling indices can be expressed as the number of labelled cells, divided by the total cells (labelled plus unlabelled) in the entire crypt. Many investigators multiply this ratio by 100, such as performed in our study, to express the index as a percentage value rather than a fraction.[3–8] One of the references included in our paper clearly explains this simple calculation[3] (Table I, page 700), information seemingly overlooked by Wright and Goodlad. Perhaps the confusion stems, in part, from the unintended omission of the number of crypts counted per rat. As indicated in our report for the measurements of villous height and crypt depth, 20 well oriented crypts per animal were randomly selected for assessment of BrdU labelled and unlabelled cells. Labelling index was then calculated by counting the number of BrdU labelled cells and expressing the results as percentage of the total cells (labelled plus unlabelled) counted in the crypts assayed in each rat.

Many scientists[4–8] choose to study intestinal proliferation by BrdU incorporation assessed and expressed as labelling index percentage such as described in our study. This sample of references is woefully incomplete but serves to strengthen our point. These publications include in vitro and in vivo studies all of which use BrdU labelling indices as a measure of intestinal proliferation in the same manner as reported in our paper. While Wright and Goodlad continue to express their bias for the CCPR technique, a search of Current Contents Article Records using the key words 'proliferation' and 'intestine' yielded 89 publications in 1995, only two of which reported use of the CCPR. While the majority may not rule in science, it is clear that the majority have not embraced CCPR.

Wright and Goodlad correctly state that 'food intake is an important modulator of intestinal proliferation.' We agree that controlled dietary intake, such as provided by total parental nutrition, gastrostomy feeding, or pair feeding is important in nutritionally oriented studies. Moreover, we have used these methods extensively in other investigations.[9–10] These methods were not used in this study based upon pilot data (unpublished) showing no significant differences in dietary intake between the gastrin receptor blocker and control groups. Despite the results of our unpublished pilot investigations, the gastrin receptor blockade groups collectively gained more weight than the control groups in the published study. There was no observed increase in dietary intake in the gastrin receptor blockade groups, however, actual food intake was not measured and it may have been increased in the gastrin receptor blockade groups. Nevertheless, we intend to repeat these studies with controlled dietary intake.

Wright and Goodlad quibble about our use of the terms 'jejunum' and 'ileum' to describe the anatomy of the small intestine in the rat. We would like to point out that they have extensively and correctly used the terms jejunum and ileum in many of their previous publications.[11–14] Thus a review of their own work, in addition to a standard textbook on the anatomy of the laboratory rat[15] is strongly recommended.

In summary, an objective review of the literature clearly shows that there are widespread fundamental differences as to whether there is a single best measurement of cell proliferation and what that measure should be. The weight gain in our gastrin receptor blockade groups may have influenced some of the morphometric measures, and further studies with controlled dietary intake are planned. Wright and Goodlad's comments that 'rats do not have jejunums and ileums' is incorrect. To return to Shaw, 'No man fully capable of his own language ever masters another'.[16]

K J REILLY
W L FRANKEL
A M BAIN
J L ROMBEAU
Department of Surgery, Hospital of the University of Pennsylvania, 3400, Spruce Street, Philadelphia PA 19104, USA

Gut: first published as 10.1136/gut.38.3.473-c on 1 March 1996. Downloaded from http://gut.bmj.com/ on November 27, 2023 by guest. Protected by copyright.