LETTERS TO THE EDITOR

Towards safer endoscopic retrograde cholangiopancreatography (ERCP)

EDITOR,—Diagnostic and therapeutic ERCPs are the most dangerous procedures regularly performed by medical gastroenterologists. The leading article from Thornton and Axon (*Gut* 1993; **34**: 721–4) discussing safety aspects is pertinent and helpful, but omits several key points and references.

The first problem is knowing what published figures mean. Bad outcomes cannot be discussed, studied, or minimised, without clear definitions. Suggested definitions for complications (and severity) were made recently after a consensus conference involving 25 experts in ERCP.[2] Reported data vary according to the completeness of their collection. Most retrospective (certainly multicenter) studies minimise the problems, and prospective analyses almost always show higher rates. Another issue is that the risk of a bad outcome is certainly influenced by the severity of the patient's presenting illness and burden of concomitant diseases. We cannot assess our results, or compare them with others, without being able to describe the risk factor spectrum of our patient material.[2] Furthermore, the significance of any risk of complication must be judged against the available alternative techniques in that specific clinical context.

Pancreatitis is the commonest complication of ERCP. Thornton and Axon give it only a few lines, stating that 'clinically significant pancreatitis occurs in only about 2% of procedures.' It depends what you mean by 'clinically significant'. Much higher figures have been published.[3] We are still seeing this complication with distressing frequency at Duke University Medical Center. In a strict prospective computer based study using agreed definitions, we have recorded a total of 160 complications in 3001 ERCP procedures performed over the last three years. One hundred and thirteen (71%) were pancreatitis, an incidence of 3·7%; most cases (55%) were graded as mild (less than three days in hospital). Sphincter of Oddi manometry carries a 12% pancreatitis rate at this institution.

The whole problem of pancreatitis after ERCP has been discussed exhaustively by Sherman and Lehman recently in an important review article, with 181 references.[3] Unfortunately there have been no major breakthroughs in understanding or prevention. The hope that non-ionic contrast materials might be safer has not been realised in a large randomised controlled trial.[4] Many studies have failed to show any protective value of drugs given before ERCP; the latest showed that prophylactic somatostatin actually increased the risk of pancreatitis.[5,6]

It is surprising that the leading article has nothing to say about training, as emphasised by my colleagues in the accompanying letter. Although difficult to prove, it is probable that quality training and substantial ongoing experience have some effect on the results of our interventions. Indeed, there is a danger that widespread application of these potentially dangerous techniques in inexperienced hands will cause them to fall into disrepute.

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1 Cotton PB, Lehman G, Vennes J, Geenen JE, Russell RCG, Moyers WG, *et al*. Endoscopic sphincterotomy complications and their management: an attempt at consensus. *Gastrointest Endosc* 1991; **37**: 383–93.
2 Cotton PB. Endoscopic management of bile duct stones (apples and oranges). *Gut* 1984; **25**: 587–97.
3 Sherman S, Lehman GA. ERCP- and endoscopic sphincterotomy-induced pancreatitis. *Pancreas* 1991; **6**: 350–67.
4 Bedford RA, Johnson GK, Geenen JE, Lehman G, Frakes J, Ryan M, *et al*. Does the use of non-ionic contrast prevent post-ERCP pancreatitis: results of a prospective multicenter study. *Gastrointest Endosc* 1993; **39**: 315.
5 Sternlieb JM, Aronchick CA, Retig JN, Dabezies M, Saunders F, Goosenberg E, *et al*. A multicenter, randomized, controlled trial to evaluate the effect of prophylactic octreotide on ERCP-induced pancreatitis. *Am J Gastroenterol* 1992; **87**: 1561–6.
6 Meier PB. Preventing ERCP-induced pancreatitis. *Am J Gastroenterol* 1992; **87**: 1536–9.

EDITOR,—Drs Thornton and Axon recently reviewed issues pertinent to the safety of ERCP. We feel, however, that the lack of any discussion about the role of training is a serious omission. Historically, scant attention has been paid to how endoscopists acquire their skills. Training in ERCP ranges from self instruction to the highly structured 'Third Tier' programmes for gastroenterology fellows currently popular in the United States. We have considered these enormous variations in training, as well as assessment of procedural competence, elsewhere.[1,2] These issues cannot be ignored, however, if the safety record of ERCP is to be maintained or – preferably – improved. As Cotton has pointed out,[3] a complication is an adverse and undesired outcome that does not necessarily reflect negligence or poor technique. We cannot eliminate complications of ERCP entirely, but appropriate supervised training, insistence on at least basic diagnostic and therapeutic skills, and ensuring that those who perform ERCP maintain and enhance their skills should minimise avoidable complications.

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1 Jowell P, Baillie J. Endoscopic training, present and future. *Gastrointest Endosc Clinics of North America* 1992; **2**: 299–311.
2 Baillie J, Ravich WJ. On endoscopic training and procedure competence. *Ann Intern Med* 1993; **118**: 73–4.
3 Cotton PB. Complications, comparisons and confusion: commentary. *Annual of GI Endoscopy*. London: Current Science, 1970: 7–9.

Reply

EDITOR,—We are grateful to our colleagues from Duke University for drawing attention to our leading article. We agree with the points that they have made. We concentrated mainly on the areas in ERCP where innovations have led to greater safety and as Dr Cotton points out few advances have been made recently where pancreatitis occurs after ERCP.

The question of endoscopy training is of particular relevance in preventing complications, not just in ERCP but in other forms of endoscopy too and our colleagues are correct in drawing attention to this. Regulations governing training in endoscopy in the United Kingdom are at present non-existent and although the British Society of Gastroenterology has made recommendations, the Royal Colleges and the Joint Committees for Higher Medical and Surgical training do not insist either on certification of endoscopists or accreditation of endoscopy units for training purposes. We understand that recent moves have been made to support the concept of the accreditation of endoscopy units for training purposes and that BSG guidelines with some modification are probably the criteria that will be used in the accreditation process.

If this does happen then it is to be welcomed. It is unlikely that endoscopists in the UK will have to undergo a certification or recertification procedure as in the United States, but training in endoscopy is on the agenda of committees in the European Community and this may in the future lead to legislation that will restrict endoscopy to those who have received suitable training.

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Location of superoxide anion in the human colonic mucosa

EDITOR,—We read with interest the article by Oshitani *et al* (Gut 1993; **34**: 936–8) regarding the location of superoxide anion generation in the human colonic mucosa. We have some concern about the interpretation and the significance of the data, which have apparently led the authors to characterise superoxide as the oxygen radical generated in the colonic mucosa especially in ulcerative colitis. The methodological approach used in the study was based on the morphological evaluation of nitroblue tetrazolium (NBT) reduction by endothelial, epithelial, and infiltrating mononuclear cells in the colonic mucosa. Undoubtedly, NBT is reduced by superoxide anion[1,2]; however, the reduction of NBT is not so specific, and other molecules can favour its reduction in the cell environment. Accordingly, xanthine oxidase (which is localised in the endothelium[3]) readily reduces NBT also by a superoxide independent way, which is probably related to a direct NBT electronic transfer with a bypass of the superoxide forming enzyme flavin centre.[4,5] Furthermore, cell dehydrogenase enzyme systems reduce NBT physiologically, so that morphological techniques based on tetrazolium dyes reduction-precipitation have been largely used to quantify myocardial infarct size, because necrosis areas lack dehydrogenase activity and therefore fail to reduce NBT and to stain.[6] There is evidence that the spontaneous reduction of NBT mediated by tissue homogenates can be inhibited by iron and copper chelators, as well as by mitochondrial electron transport chain blockers,[2] thus pointing to a role for transition metals and mitochondria in tissue NBT reduction. In this context, it is noteworthy that the radicals generated by inflammatory cells may increase tissue 'free' iron and copper concentrations, as a result of ferritin iron mobilisation[7]

and thiol-copper biochemical sites denaturation.[8] Another potential source of error in the use of NBT as a superoxide colorimetric detector may be related to the presence in some cell systems of a NBT reductase activity capable of directly reducing the dye without any superoxide participation.[1] It is clear that a 'true' superoxide mediated NBT reduction must be inhibited by superoxide dismutase, this being a fundamental criterion for assignment of a function of superoxide.[9] In such a context, studies dealing with oxygen radical production in cerebral vascular injury resulting from acute hypertension have shown that NBT reduction in brain microvasculature was inhibited by superoxide dismutase, thus showing superoxide participation in this pathophysiological event.[10] In Oshitani's study, superoxide dismutase failed to inhibit NBT reduction, though inhibition was seen with anaerobiosis and para-benzoquinone, which, however, are apparently not specific enough to discriminate superoxide as the species responsible for NBT reduction. Indeed, anaerobiosis may inhibit the mitochondria, and para-benzoquinone may react not only with superoxide but also with other reductants and radical species.

The authors have hypothesised that superoxide dismutase could have been ineffective in their model as a result of a lack of enzyme tissue permeability. Some much smaller molecules with a potential cell permeability, however, such as the cimetidine-copper complex, display a significant superoxide dismutase activity.[11] Moreover, superoxide dismutase conjugated to polyethylene glycol can enter cells, such as the endothelial, and maintain activity much longer than unconjugated superoxide dismutase.[12] We believe that these molecules should have been used by Oshitani *et al* to more precisely assign a role to superoxide in their investigation. Without similar experimental evidence, it does not seem correct to entitle the paper 'Location of superoxide anion generation in human colonic mucosa obtained by biopsy'.

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1 Oberley LW, Spitz DR. Assay of superoxide dismutase activity in tumor tissue. *Methods Enzymol* 1984; **105**: 457–64.
2 Spitz DR, Oberley LW. An assay for superoxide dismutase activity in mammalian tissue homogenates. *Anal Biochem* 1989; **179**: 8–18.
3 Jarasch E-D, Bruder G, Heid HW. Significance of xanthine oxidase in capillary endothelial cells. *Acta Physiol Scand* 1986; **548** (suppl): 39–46.
4 Topham RW, Jackson MR, Joslin SA, Walker MC. Studies of the ferroxidase activity of native and chemically modified xanthine oxidoreductase. *Biochem J* 1986; **235**: 39–44.
5 Bolann Bj, Ulvik RJ. Release of iron from ferritin by xanthine oxidase. *Biochem J* 1987; **243**: 55–9.
6 Fishbein MC, Meerbaum S, Rit J, Lando U, Kanmatsuse K, Mercier JC, *et al*. Early phase acute myocardial infarction: validation of the triphenyl tetrazolium chloride tissue enzyme staining technique. *Am Heart J* 1981; **101**: 593–600.
7 Biemond P, van Eijk HG, Swaak AJG, Koster JF. Iron mobilization from ferritin by superoxide derived from stimulated polymorphonuclear leukocytes. Possible mechanism in inflammation disease. *J Clin Invest* 1984; **73**: 1576–9.
8 Schechinger T, Hartmann H-J, Weser U. Copper transport from Cu(I)-thionein into apocaeuroplasmin mediated by activated neutrophils. *Biochem J* 1986; **240**: 281–3.
9 Halliwell B, Gutteridge JMC. Free radicals in biology and medicine. Oxford: *Clarendon Press*, 1989.
10 Kontos H. Oxygen radicals in cerebral vascular injury. *Circ Res* 1985; **57**: 508–16.
11 Goldstein S, Czapski G. Determination of the superoxide dismutase activity of cimetidine-Cu(II) complexes. *Free Rad Res Comms* 1991; **12–13**: 205–210.
12 Beckman JS, Minor RL, White CW, Repine JE, Rosen GM, Freeman BA. Superoxide dismutase and catalase conjugated to polyethilene glycol increases endothelial enzyme activity and oxidant resistance. *J Biol Chem* 1988; **263**: 6884–92.

Reply

EDITOR,—Thank you for giving us the opportunity to reply to the comments by Drs Lapenna and Cuccurullo. There is no specific probe to detect in situ generation of superoxide; nitroblue tetrazolium (NBT) is the most suitable probe available to detect generation of superoxide in in situ assay. Although inhibition of NBT reduction by superoxide dismutase is essential to prove the contribution of superoxide in the assay, it seems to be impossible to show an inhibitory effect of superoxide dismutase in organ culture, because it does not easily penetrate biopsy specimens.

In the organ culture system, specificity of the xanthine oxidase and interference of dehydrogenases or mitochondrial enzymes with the NBT reduction are important problems. Although a superoxide independent mechanism of releasing iron from ferritin by xanthine oxidase exists,[1–4] 70–95% of the aerobic reduction has been reported to be superoxide dependent,[2–4] hence direct reduction by the xanthine oxidase might not be an important pathway in NBT reduction. NBT reduction in the organ culture system is unique because of the permeability of the reagent. NBT probably does not penetrate the intact cells,[5,6] cytoplasmic enzymes and the mitochondrial respiratory chain might not interfere with the reduction under these conditions. The only interference found was the reduction of NBT by epithelial brush border enzymes, which was found to be non-specific to inflammation. Furthermore, the inability of mitochondrial respiratory chain inhibitor, KCN, to inhibit aerobic NBT reduction in the organ culture system and the inhibition of NBT reduction under anaerobic condition[7] might represent the participation of superoxide in this system. Based on these indirect findings, superoxide might participate in NBT reduction in the organ culture system.

In addition, we have already found that allopurinol combined with copper-cimetidine did inhibit NBT reduction by endothelium and infiltrating cells of the inflamed mucosa in this system.

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1 Topham RW, Jackson MR, Joslin SA, Walker MC. Studies of the ferroxidase activity of native and modified xantine oxidoreductase. *Biochem J* 1986; **235**: 39–44.
2 Bolann BJ, Ulvik RJ. Release of iron from ferritin by xanthine oxidase. *Biochem J* 1987; **243**: 55–9.
3 Williams DM. Lee GR, Cartwright GE. The role of superoxide anion radical in the reduction of ferritin iron by xanthine oxidase. *J Clin Invest* 1974; **53**: 665–7.
4 Thomas CE, Morehouse LA, Aust SD. Ferritin and superoxide-dependent lipid peroxidation. *J Biol Chem* 1985; **260**: 3275–80.
5 Kontos HA. Oxygen radicals in cerebral vascular injury. *Circ Res* 1985; **57**: 508–16.
6 Peskin AV, Khramtsov AV, Morozov IA, Zemskov VM, Zbarsky IB. Visualization of reactive oxygen species formation by phagocytizing macrophages. *Exp Cell Res* 1984; **151**: 247–51.
7 Oshitani N, Kitano A, Okabe H, Nakamura S, Matsumoto T, Kobayashi K. Location of nitroblue tetrazolium-reducing activity in human colonic mucosa obtained by biopsy. *Dig Dis Sci* 1993; **38**: 546–50.

Selective affective biasing in recognition memory in the irritable bowel syndrome

EDITOR,—The account by Gomborone *et al* (*Gut* 1993; **34**: 1230–3) of selective perception, evaluation, and recall of emotionally loaded material by patients with irritable bowel syndrome (IBS) is fascinating. While their findings are resonant with personal clinical experience, they need to be seen and interpreted in a wider context before being judged representative of all patients with IBS.

The one year prevalence of IBS in the general population is about 20%; in other words, one in five adults selected at random from population registers meet the clinical criteria for a diagnosis of IBS when responses to a validated postal questionnaire are analysed.[1] A further substantial group of people have a complex of syndromes described as 'dysmotility like dyspepsia', which may represent a form of IBS predominantly affecting the proximal gut. Only about one third of these subjects, however, seek medical advice for their symptoms and the decision to do so is related to a number of factors.

In dyspepsia, symptom frequency and severity are poor predictors of the likelihood to consult, while concern about the significance of symptoms in terms of serious disease is much more strongly associated with consultation.[2] In IBS, consulting patients report more severe abdominal pain than those who do not consult; they are similarly concerned about the possibility of serious disease, particularly cancer, while those who do not consult are often positively dismissive of their symptoms.[3] In IBS the consulting patients are more often anxious or depressed, or both than the patients who do not consult.[3] This finding is consistent with other reports that conclude that psychological or frank psychiatric disorder is not a component of IBS in itself, but rather is an attribute of consulting patients and possibly a reason for consultation.[4]

The patients studied at St Bartholomew's were a selected group attending the hospital clinic, presumably because of severity or intractability of their symptoms. They also had a high level of psychiatric morbidity and cannot be regarded as representative of the much larger population of IBS patients without either of these characteristics. It would, therefore, be of great interest to know whether IBS patients in the community or consulting for the first time in primary care behave in the same way as this hospital based group. Other research questions arise from the findings of Gomborone *et al*. Do patients with other somatic symptoms for which a physical cause is difficult to find have similarly abnormal affective biases? Do these biases apply to perception, evaluation, and recall of physical symptoms as well as words? If they do, a key management question concerns the ways in which it is possible to investigate, diagnose, and treat irritable bowel syndrome without continually increasing anxiety, concern, and misinterpretation of symptoms.

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1 Jones R, Lydeard S. Irritable bowel syndrome in the general population. *BMJ* 1992; **304**: 87–90.
2 Lydeard S, Jones R. Factors affecting the decision to consult with dyspepsia: comparison of consulters and non-consulters. *J R Coll Gen Pract* 1989; **39**: 495–8.
3 Kettell J, Jones R, Lydeard S. Reasons for consultation in irritable bowel syndrome: symptoms and patient characteristics. *Br J Gen Pract* 1992; **42**: 459–61.