LETTERS TO THE EDITOR

Towards safer endoscopic retrograde cholangiopancreatography (ERCP)

EDITOR,—Diagnostic and therapeutic ERCPs are the most dangerous procedures regularly performed by gastroenterologists. Indeed, our experience have some effect on the results of this procedure. Somatostatin (which reduces the risk of post-ERCP pancreatitis) has been shown to be helpful, but omits several important considerations.

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. Reported data vary according to the completeness of their collection. Most retrospective (certainly multicenter) studies minimise the problems, and prospective analyses allocate always higher rates. Another question 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.

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’ complications occur in only 2% of procedures. If depending on what you mean by ‘clinically significant’, much higher figures have been published. 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 thirty cases of pancreatitis were diagnosed, for an incidence of 3.7%; most cases (55%) were graded as mild (less than three days in hospital). Splinter 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. Unfortunately, there have been too many breakdowns in understanding or prevention. The hope that non-ionic contrast materials might be safer has not been realised in a large randomised controlled trial. 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.

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.

P B COTTON
Division of Gastroenterology, Duke University Medical Center, Durham, North Carolina 27710, USA


Location of superoxide anion in the human colonic mucosa

EDITOR,—We read with interest the article by Oshinazi 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 significance of the data, which probably 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 monocellular cells in the colonic mucosa. Undoubtedly, NBT is reduced by superoxide anion; 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) 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 cent. Furthermore, cell delimitation enzymatic system can reduce NBT physiologically, so that morphological techniques based on tetrazolium dyes reduction-precipitation have been largely used to quantify myocarcial infarct size, because necrosis areas lack of superoxide anion activity and therefore fail to reduce NBT and to stain. 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, 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.

P S JOWELL
JBAULIE
Division of Gastroenterology, Duke University Medical Center, Durham, NC 27710, USA


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. Regular 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 establish 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 well lead to legislation that will restrict endoscopy to those who have received suitable training.

AXON
J THRONTON
The Centre for Digestive Diseases, The General Infirmary and Leeds General Infirmary, Leeds LS1 3EX

and thiol-oxidoreductase biochemical sites denaturate.
Another potential source of error in the use of NBT as a superoxide dismutase in a cell 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.11 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.11 In such a context, studies dealing with NBT oxidative 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.12 In Oshitani's study, superoxide dismutase failed to inhibit NBT reduction, though inhibition was seen with aneroidos and para-benzoquinone, which, however, are apparently not specific enough to discriminate superoxide as the species responsible for NBT reduction. Indeed, aneroidos 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 studies because of low enzyme activity and permeability. Some much smaller molecules with a potential cell permeability, however, such as the cimetidine-copper complex, display a significant superoxide dismutase activity. 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 the potential reagent should have been used by Oshitani et al more precisely as an assay to superoxide in their investigation. Without similar experimental evidence, it does not seem correct to entitle the paper 'Location of superoxide anion production in human colonic mucosa obtained by biopsy'.

D. LAPPENAPUCCURULLOCattedra di Patologia SperimentaleMedica, Universita'GD'Annunzio,Presidencia Facolta' di MedicinaViale dei Vestini66100Chieti, Italy


Reply

EDITOR,—Thank you for giving us the opportunity to reply to the comments by Drs Lapenna and Cuccurullo.2 Their 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 brush border superoxide 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 tissue.

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 dismutase mechanism of releasing iron from ferritin xanthine oxidase exists,75-90% of the aerobic reduction has been reported to be superoxide dependent, hence direct reduction of xanthine oxidase might 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,2 cytoplastic 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 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.

N OSHITANIThird Department of Internal Medicine, Osaka City University Medical School, 1-5-5, Asahi-cho, Abeno-ku, Osaka, 545, Japan


Selective afferent biasing in recognition memory in the irritable bowel syndrome

EDITOR,—The account by Gobomore et al Gut 1993; 34: 1230-3 of selective perception, evaluation, and recall of emotionally loaded material by patients with irritable bowel syn-

drome (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 a wider patient population.

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 are affected. If these figures are correct, then 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. In IBS the consulting patients are more often anxious or depressed, or both than the patients who do not consult. Patients with IBS often consult 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.

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 psychosomatic morbidity which 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 Gobomore 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 appear 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 misinter-

R H JONESUMDS Department of Gastroenterology, 80 Kennington Road, London, SE1 6SP

3. Kettell J, Jones R, Lydeard S. Reasons for consul-