LETTERS TO THE EDITOR

Mucus synthesis by the human gall bladder

EDITOR,—I was interested to read the papers by Rhodes and colleagues concerning mucus synthesis by the human gall bladder, its apparent inhibition by aspirin, and other non-steroidal anti-inflammatory drugs (NSAIDs), and the suggestion that aspirin might prevent cholesterol gall stone formation by this action (*Gut* 1992; 33: 1109–12 and 1113–7). As gall bladder mucus glycoprotein (mucin) is a secretory product, however, estimates of mucin synthesis must take account of secreted mucin as well as tissue mucin concentrations. These papers have reported tissue concentrations only. This is curious, especially as it is the secreted component that is thought to play a part in cholesterol gall stone formation.¹ It cannot be assumed that secreted mucin necessarily reflects tissue concentrations (it ranges from 30–50% of total mucin synthesis in the prairie dog model).²

Although aspirin and other NSAIDs reduced mucin concentrations in gall bladder explants in vitro their effects on mucin secretion in vivo were not presented. In the in vivo trial performed by the authors, however, mucin concentrations in the gall bladder bile of patients treated with aspirin were no lower than those in controls. These papers have not shown an effect of aspirin or other NSAIDs on gall bladder mucin synthesis or secretion. The case remains unproved.

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- 1 Lee SP, LaMont JT, Carey MC. Role of gallbladder mucus hypersecretion in the evolution of cholesterol gallstones. Studies in the prairie dog. *J Clin Invest* 1981; 67: 1712–23.
- 2 O'Leary DP, LaMorte WW, Scott TE, Booker ML, Stevenson J. Inhibition of prostaglandin synthesis fails to prevent gallbladder mucin hypersecretion in the cholesterol-fed prairie dog. *Gastroenterology* 1991; 101: 812–20.

Reply

EDITOR,—We thank Mr O'Leary for his interest in our papers but find his comments a little difficult to follow. He is quite correct when he states that we did not measure secreted mucin in the supernatant of our culture plates and this would provide additional information about the actions of aspirin in vitro. His conclusion that these papers 'have not shown any effect of aspirin on gall bladder mucin synthesis' is, however, incorrect. Both in vitro and in vivo we were able to show consistent inhibition of mucin synthesis.

Aspirin and NSAIDs undoubtedly have significant actions on the human gall bladder. This is confirmed by epidemiological findings,¹ biochemical studies such as these and other work in humans,² and motility work.³ Whether these actions are clinically or therapeutically significant does indeed remain open to question but no doubt will be answered through the

pages of this and other journals over the next five years.

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- 1 Hood K, Gleeson D, Rupp DC, Dowling RH. Prevention of gallstone recurrence by non-steroidal anti-inflammatory drugs. *Lancet* 1988; ii: 1223–5.
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Treatment of achalasia

EDITOR,—Mr Spencer in his editorial review (*Gut* 1993; 34: 148–9) has given a somewhat biased surgeon's view of the treatment of achalasia, favouring cardiomyotomy over balloon dilatation. We, as physicians, would regard balloon dilatation as being so good that surgery is almost never required.

As Mr Spencer rightly points out, although the debate over the choice of treatment would ideally be solved by carrying out prospective randomised trials, this is difficult, given the rarity of the disease. In support of cardiomyotomy, he quotes the solitary prospective randomised study that has been carried out to date – that of Csendes *et al.*¹ Although this study reported excellent results in 95% of patients after myotomy, but in only 65% of patients after one to two dilations, the data need to be viewed with caution. The dilations in the study were carried out for only 10–20 seconds, repeated twice. This is a considerably shorter dilatation time than in series reporting better success rates. Furthermore, the atropine premedication favoured by Csendes may have relaxed the lower oesophageal sphincter, thus rendering the dilations less effective.² These factors may account for the poor success rate after dilatation in this study.

We carry out balloon dilations for a three minute period, and in our published series of 66 patients,³ 98% reported an immediate and appreciable improvement in symptoms after their initial dilatation. Only two patients developed a perforation (3%), both successfully managed conservatively, and three (4.5%) developed gastro-oesophageal reflux. Fifty eight patients were followed up for 1–12 years (median 55 months), and 91% of these remained dysphagia free after only one to two dilations; a success rate comparable with that of Csendes' surgical series. Reflux rates are higher after cardiomyotomy in most series despite antireflux procedures, which may indeed sometimes recreate dysphagia. More-over six days in hospital is required for cardiomyotomy, compared with only 24 hours for balloon dilatation. Lastly age, general frailty, and concomitant serious cardiorespiratory disease need not bar patients from selection for balloon dilatation.

We are now firmly of the opinion that surgery has little to offer in most cases of achalasia. Surgery for achalasia has not so much become unfashionable, as undesirable.

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- 1 Csendes A, Braghetto I, Henriquez A, Cortes C. Late results of a prospective randomised study comparing forceful dilatation and oesophagomyotomy in patients with achalasia. *Gut* 1989; 30: 299–304.
- 2 Vantrappen G, Janssens J. To dilate or to operate? That is the question. *Gut* 1983; 24: 1013–9.
- 3 Banerjee S, Pugh S, Smith PM. Pneumatic balloon dilatation in achalasia: A long term follow up. *Gullet* 1992; 2: 28–32.

Reply

EDITOR,—I have read with interest the comments by Drs Banerjee, Pugh, and Smith on my editorial review. They agree with me that in so rare a disease it is difficult to obtain controlled data, but this seems a poor reason to reject out of hand the only controlled data available, and then accuse me of bias.

I had only two significant points to make. Firstly, that available data support rather than reject surgical treatment. The response to most trials that give results of which we disapprove is to say that those participating in the trial were doing it all wrong anyway. But is there controlled evidence that a longer dilatation gives better results than a shorter one? Or that anti-cholinergics decrease the effectiveness of dilatation? This in particular would be difficult to imagine, let alone prove. It is clear that excellent results may be obtained by dilatation, but with widely different complication rates, perforation occurring in 1–12%.^{1,2}

My second point was that this scene is changing. In many centres laparoscopic (or thoracoscopic) cardiomyotomy is replacing open operation. It offers precise treatment. Radiological studies reported by Dr Smith and his colleagues, show that dilatation produces considerable tearing of the cardia; in an unpredictable few this tear leads to clinical perforation.³ Precisely controlled myotomy can be performed at laparoscopy under excellent visualisation, and is tolerated by patients extremely well. Minimally invasive treatment no longer needs to be blind treatment.

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Injection sclerotherapy in portal hypertension

EDITOR,—We read with interest the article by Dr Heaton and Dr Howard (*Gut* 1993; 34: 7–10) because we are in the early stages of a prospective study of percutaneous transjugular intrahepatic portosystemic shunt (TIPS) in recurrent variceal bleed. While we acknowledge that the article was mainly directed at injection sclerotherapy, the authors discuss the role of emergency surgical procedures in the management of acute variceal bleeding after failed injection sclerotherapy, but have failed to include in their discussion any reference to TIPS. We believe that early results suggest that TIPS should be considered before surgery,

where there are appropriate facilities, in all patients with recurrent variceal haemorrhage.

Intrahepatic portosystemic shunts were first created experimentally by Rosch in 1969.¹ The first human studies were reported in 1982 by Colapinto *et al.*² Interest in the technique has been revived by the introduction of metal stents to maintain shunt patency.³ In this procedure a suitable hepatic vein is selectively cannulated through an internal jugular vein approach, and hepatic venography is performed. Under ultrasound control a needle is advanced into a portal vein branch and the track is dilated with an angioplasty balloon. A metal stent is then deployed across the tract to maintain patency. Decompression of the portal tract is immediate.

La Berge *et al.*⁴ have suggested that TIPS is of benefit in patients with acute variceal haemorrhage, and is associated with an acceptable morbidity and mortality. It offers immediate control of bleeding, and rebleeding is uncommon as long as the shunt remains patent. Patency at two years is up to 80%.⁵ It can be performed, under general anaesthetic or with sedation, on very unfit patients. The reported risk of encephalopathy is low and depends on shunt size.⁶ Surgical access for subsequent hepatic transplantation is not impeded by previous TIPS.

The role of TIPS needs to be defined by prospective studies and longer follow up. Comparative studies are needed with both traditional portosystemic shunts and with endoscopic sclerotherapy. At present we offer TIPS to patients who have rebled despite variceal injection sclerotherapy and before performing either oesophageal transection or a surgical portosystemic shunt. If further studies confirm initial promise it is possible that TIPS may become the treatment of choice for the management of complicated portal hypertension.

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- 1 Rosch J, Hanafee WN, Snow H. Transjugular portal venography and radiologic portacaval shunt: an experimental study. *Radiology* 1969; 92: 1112-4.
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- 6 Haskal ZJ, Ring EJ, La Berge JM, *et al.* Role of parallel transjugular intrahepatic portosystemic shunts in patients with persistent portal hypertension. *Radiology* 1992; 185: 813-7.

Reply

EDITOR, — Although our leading article did not really concern the technical details of portosystemic shunt construction we were interested in the results of Pugh and Sissons who have used the new procedure of TIPS. We have also been impressed with this technique, which was recently introduced into our hospital by Dr J Karani, and it has provided us with a valuable

addition to the range of procedures that are necessary for the comprehensive management of all types and complications of portal hypertension.

TIPS is, of course, not applicable to the management of patients with extrahepatic portal hypertension or to infants and children. The technique may also fail in approximately 10% of patients because of unusual intrahepatic anatomy, particularly in the distribution of the hepatic veins. Contraindications also include severe coagulopathy, polycystic liver disease, and hepatic neoplasms.¹

TIPS is still under evaluation but we believe that the guidelines for its use should not differ appreciably from those enumerated in our article for more conventional surgical portosystemic shunting. The risk of post shunt encephalopathy, clearly documented in the early days of shunt surgery, remains a significant hazard in the patient with cirrhosis and has already been recorded in 10-20% of patients who have been treated with an intrahepatic shunt.¹ We are convinced that TIPS should not displace injection sclerotherapy as the primary treatment for bleeding oesophageal varices except, perhaps, in the case of a bleeding adult patient with cirrhosis awaiting transplantation.

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1 Conn HO. Transjugular intrahepatic portal-systemic shunts: The state of the art. *Hepatology* 1993; 17: 148-58.

BOOK REVIEWS

The puzzle people: memoirs of a transplant surgeon. By Thomas E Starzl. (Pp 364; illustrated; \$24.95.) Pittsburgh: University of Pittsburgh Press, 1992.

Dr Thomas Starzl is a living legend, a man who has made outstanding contributions to transplant surgery by the continuous one directional pursuit of each objective as it came into his focus. He has been successful in overcoming both surgical and immunological difficulties in organ grafting. He has a powerful, mesmeric personality, and an almost unbelievable capacity for hard work.

The writing of an autobiography usually marks the end of an active career but this is certainly not the case for Dr Starzl. Although no longer operating, he is still actively engaged in research and has recently directed the two transplant operations from baboon to man, and he continues to produce more papers in scientific journals than any other writer. His father was a journalist and this may have influenced Starzl in his delight and facility in the use of words. The book is well written and entertaining both for the medical and lay reader as would be expected by someone who has achieved such eminence in his profession. Starzl's early scholastic record was excellent and he achieved outstanding grades in all the subjects that he took.

The story responsible for the title *The puzzle people* is centred on Starzl's life work in transplantation, particularly of the liver and

this is appropriate as Starzl performed the first liver graft in man in 1963. Despite terrible results with the early clinical cases, Starzl persisted and eventually succeeded with good results following the introduction of the immunosuppressive drug cyclosporin. Liver transplantation has been accepted as the main treatment option for those with end stage liver disease and the results are constantly improving. The longest survivor in the world is a patient of Dr Starzl's, now 23 years since her operation and for the last 18 years she has had no immunosuppressive drugs. The patients are 'puzzle people' in the sense that they contain pieces from other individuals. As far as the doctors and nurses who look after the patients are concerned, the challenge has always been severe and they still understand only part of the story of what causes graft rejection and how it can be controlled.

Until he was head of his own unit, Dr Starzl did not seem to stay anywhere for very long, probably because of his exceptional abilities that frightened off people with less capacity for hard work and dedication, which would apply to almost everybody else in surgery. It is not surprising that with a life so specifically targeted, normal family relations were not easy to fit into the work programme and some aspects of this are covered in the book. In the main, however, it is a story of facing and overcoming enormous surgical hurdles and well orchestrated attempts of hospital and university administrators to block specifically his progress.

To the rest of the transplant community, Dr Starzl is an innovator with a keen intellect, an almost photographic memory and a determination to succeed. He worked for years in the laboratory, developing a surgical method of transplanting the liver in the dog. Independently, Dr Moore in Boston was pursuing the same aim. Both achieved success with somewhat different technical solutions to the physiological disturbance that follows clamping the portal and caval circulations. To remove the liver from the recipient it is necessary to obstruct the portal and inferior caval veins, which causes a rapid and damaging rise of blood pressure in the dammed up circulation. The bowels become congested and cyanosed and when relapsed into the circulation, the acidic stagnant blood, high in potassium ions, is likely to cause cardiac arrest. Both Starzl and Moore decided that orthotopic liver transplantation could not be possible unless blood was shunted from the portal vein and inferior vena cava to the superior caval drainage system, thus decompressing the clamped vessels when the recipient liver was removed and the donor liver was sewn in place. It was only after successful decompression that survivors with liver grafts could be studied. At the same time, Starzl was one of the early pioneers of kidney transplantation working in Denver with Dr Waddell.

I first met Dr Starzl in 1961 when he was recording multiple observations in kidney transplant patients using a large flow sheet. This longitudinal analysis of the progress of patients proved to be extremely valuable and has now been adopted by all transplant units all over the world. He was enthusiastic in the use of corticosteroids in addition to azathioprine as the main method of immunosuppression used at that time and the programme from Denver was very active with large number of cases and good results.

Starzl is a man with extremes of enthusiasm; at one time for smoking cigarettes in prodigious numbers so as to form huge pyramids of stub