Progress report

The vagus, the bile, and gallstones

The most frequently used operation for the treatment of duodenal ulcer in the United Kingdom is vagotomy combined with a drainage procedure. Probably the first abdominal vagotomy was performed by Exner in 1911 but it was only after the pioneering work of Lester Dragstedt in the late 1940s that vagotomy came to be adopted for the treatment of duodenal (and, in some centres, gastric) ulceration. The popularity of a stomach operation which incorporated a vagotomy increased with the growing awareness of the complications likely to follow gastric resections of various sorts. Nevertheless it has become apparent that sectioning of the vagi is not without side effects, and these may include disordered biliary function and gallbladder disease. It is of value, therefore, to review the role of the vagus in the physiology of the biliary system and examine the evidence for the claims that gallstones follow vagotomy with increasing frequency.

The vagi are the largest of the cranial nerves and have many connexions and ramifications within the thorax and abdomen. The anterior vagus is derived from the left vagal trunk and, via the hepatic plexus, supplies the liver, bile ducts, and gallbladder. The posterior vagus derives from the right vagal trunk and has no direct hepatic supply^{1,2}.

Hepatic bile is believed to be formed by an admixture of at least two solutions which differ in origin and composition³. A basal rate of bile is produced at a cannalicular level while additional cannalicular bile is formed at a rate directly proportional to the secretion rate of bile salts⁴. Ductular concentration of the cannalicular bile is believed to occur, but in addition the ductules are thought to secrete an alkaline fluid rich in bicarbonate and poor in chloride⁵. This latter mechanism is independent of the influence of bile salts.

The original work of Bayliss and Starling⁶ suggested that duodenal extracts are capable of producing increased bile flow and there is now evidence that both natural and synthetic secretin have a potent choleric action^{7,8}. Secretin acts by stimulating the production of the alkaline fluid from the ductules and this has been demonstrated in the intact animal⁹, in the isolated perfused liver^{10,11}, and in man¹². This stimulatory effect of secretin is independent of the action of bile salts⁵. Another hormone with choleric action is gastrin. This was demonstrated by Jones and Brookes¹³ who reported that antrectomy abolished the choleric response to insulin hypoglycaemia. The studies of Zaterka and Grossman on dogs with total gastrectomy showed clearly that gastrin stimulates an increase in biliary flow and bicarbonate concentration¹⁴. The choleresis induced by gastrin is similar to, but weaker than, that following the administration of secretin. None of the neural or humoral stimuli elicited by ingesting food is capable of increasing the hepatic production of bile salts^{15,16,17}. Not all the reports are in agreement and Pissidis *et al*¹⁸, using the isolated calf liver, were unable to show a choleric response to gastrin; but there are many factors, including species difference, hepatic denervation, and the viability of the preparation, which might explain the disparity.

Vagal stimulation results in an increase in bile volume and solid output. This has been demonstrated in cholecystectomized dogs¹⁹ as well as in humans²⁰. Furthermore after vagotomy the output of bile is reduced^{19,20}, and in man the choleresis is eliminated by a vagal-blocking dose of atropine. Fletcher and Clark²¹ also made the unexpected observation, which requires confirmation, that there is a fall in biliary cholate concentration following vagotomy. It remains to be established whether vagotomy influences the release of secretin from the duodenal mucosa, independently that is of the reduced output of secretin and cholecystokinin/pancreozymin which would be expected to accompany the reduction in gastric acidity.

The neurohumoral factors controlling gallbladder function are well recognized: the major determinant is cholecystokinin/pancreozymin which induces gallbladder contraction. It is probable that this hormone is also responsible for the relaxation of the sphincter of Oddi²². Vagal influences seem to be less important, and it is still uncertain whether the vagus has a direct motor effect on the gallbladder muscle or whether its role is to sensitize the gallbladder to cholecystokinin/pancreozymin via a local nerve plexus. It may well be that nervous factors are more important in maintaining tone than in influencing contractility.

Surprisingly there is no general agreement over the effect of gastric surgery and vagotomy on gallbladder function, perhaps because it is not possible to make precise measurements of gallbladder size and volume *in vivo*. In one of the earliest studies Johnson and Boyden²³ reported that the fasting gallbladder volume doubles in patients following a total vagotomy while Cox *et al*²⁴ noted decreased contraction of the gallbladder after truncal vagotomy. Rudick and Hutchinson²⁵ assessed gallbladder function by means of oral cholecystography and intravenous cholangiography, and reported that vagotomy is followed by both dilatation and impaired emptying of the gallbladder. They concluded that 'the important factor influencing gallbladder volume was the vagotomy since the type of drainage procedure did not seem to affect subsequent volume or emptying of the gallbladder'. This opinion has received support from Inberg and Vuorio²⁶, whereas Tinker and Cox²⁷ observed marked reduction in gallbladder emptying but do not mention whether the gallbladder was dilated or not. Clave and Gaspar²⁸ found contraction to be normal in the vagotomized gallbladder, and they made the interesting suggestion that any increase in fasting volume is limited to the first two years after the operation. On the other hand, neither Glanville and Duthie²⁹ nor Williams and Irvine³⁰ found any change in human gallbladder function following total vagotomy, and a similar conclusion has been reached by Benneventano *et al*³¹ in acute experiments in dogs.

It is likely that the dilatation of the gallbladder observed after partial gastrectomy follows division of the hepatic branch of the vagus. Although Rudick and Hutchinson²⁵ reported no alteration in the size of the gallbladder after anterior selective vagotomy, Tinker and Cox²⁷ showed that the gallbladder is denervated after both truncal and selective vagotomy. Ellis and Wastell³² in a recent review have concluded that selective vagotomy has no advantage over total vagotomy in regard to biliary tract function. There is as yet no firm evidence that vagotomy affects gallbladder mucosal histology or function.

Reports on the effect of vagotomy on the motor function of the bile duct and sphincter are contradictory, no doubt because of the various techniques used to infer or measure contractility and pressure changes. Thus Stassa and Grafe³³ concluded, on the basis of cineradiographic studies in dogs, that vagotomy does not influence the responsiveness of the sphincter mechanism, and this has been confirmed in anaesthetized cats³⁴. Yet in acute experiments in vagotomized dogs a reduction was observed in the pressure required to overcome the choledocho-duodenal sphincter³¹, thus confirming the earlier

observations of Mallet-Guy *et al*³⁵. A contrasting observation is that of Williams and Huang³⁶ who found that biliary pressure is increased in the canine bile duct following vagotomy. These were long-term studies, and, although no measurements were made across the sphincter, the authors inferred that sphincter resistance had increased.

Taking into account the foregoing considerations it is not surprising that interest has been shown in the possible contribution of gastric surgery, and vagotomy in particular, to the development of gallstones and gallbladder disease. In one of the earliest reports of the association Majoor and Suren³⁷ reviewed 174 patients after gastric surgery and found six to have gallstones. Other authors who have reported an increased frequency of gallstones following gastric operations are Griffiths and Holmes³⁸, Krause³⁹, and Lundman *et al*⁴⁰. But this association has been denied by Turunen and Anttila⁴¹ and Schriber *et al*⁴². Similarly there are conflicting views on whether the increased prevalence of gallstone disease follows irrespective of the type of gastric operation or is related to a particular procedure^{30,40}.

There have been a number of case reports incriminating vagotomy as a factor in cholelithiasis. These have been summarized by Clave and Gaspar²⁸ who reported an increased frequency of gallstone disease in 116 patients who had undergone truncal vagotomy. Unfortunately many of the studies are not free from criticism. Thus in the study mentioned no control group was analysed and the figure of 22.8% for those developing gallstones after vagotomy²⁸ may not be much greater than the frequency in control populations. The frequency of gallstones is generally arrived at on the basis of necropsy studies⁴³ and there are no reliable data on the incidence of stones in living populations. Then too, gallstone disease becomes commoner with advancing age so that the incidence in patients after stomach operations would be expected to increase the longer the patients are followed⁴⁴. While it has been denied that there is an association between peptic ulcer and gallbladder disease³⁸, at least one author has claimed that gallstones are commoner in patients with peptic ulcer than in the general population⁴²—but again the conclusions can be criticized because the peptic ulcer population was a carefully followed group which would be investigated more readily than a random sample from the general population.

Among the explanations given for the possible association of cholelithiasis and gastric surgery is that a depressed release of gastric acid, and consequently secretin, will result in a concomitant reduction in bile flow. This, together with a dilated, poorly contracting gallbladder, might favour gallstone formation. A reduced concentration of bile salts²¹ will be an important factor (in the absence of associated changes in the cholesterol and phospholipid concentrations) favouring cholesterol precipitation in the bile following vagotomy. However, it must be stressed that there are many basic factors leading to stone formation and growth which are poorly understood⁴⁵. Another possibility is that vagotomy in some manner leads to preexisting gallstones becoming symptomatic. Experimental studies suggest that acute cholecystitis may supervene in a normal gallbladder containing a stone if a vagotomy is performed⁴⁶.

This subject has been approached experimentally in a number of ways. Barnett and Hilbun⁴⁷ studied the rate at which human gallstones disappeared after being placed in the gallbladders of dogs. The animals were studied with and without vagotomy. There was significant reduction in the rate of gallstone dissolution in those animals with vagotomy; the gallstones in gallbladders of dogs subjected to selective vagotomy dissolved at similar rates to stones placed in gallbladders with intact vagi. Unfortunately these observations have not been confirmed⁴⁸. The induction of allodeoxycholic acid stones in rabbits^{49,50} is a useful model for the study of certain aspects of gallstone disease, including the effect of vagotomy on the development of gallstones.

Conflicting results have been published, probably because of different experimental designs. Thus claims that the operation does not influence the development of stones⁵¹ have been counterbalanced by the report that gallstone formation is enhanced⁵².

Conclusions

Hormonal factors are more important than nervous influences in bile secretion and biliary dynamics. Nevertheless after vagotomy and various gastric operations there is a reduction in bile flow and a tendency for the gallbladder to dilate, although gallbladder emptying is probably unaltered. In this respect selective vagotomy does not seem to differ from total vagotomy. Despite the theoretical reasons for an increased tendency to gallstone formation following vagotomy the clinical evidence is against there being any such association, an opinion also reached by Fletcher and Clark⁵³ in their excellent review of the subject. However, most of the clinical surveys have been inadequate. It is apparent that there is a need for a well designed, well controlled prospective study to test the possible association of cholelithiasis, peptic ulcer disease, and gastric surgery.

I. A. D. BOUCHIER

*Department of Medicine,
The Royal Free Hospital,
London WC1*

References

- ¹Mitchell, G. A. G. (1940). A macroscopic study of the nerve supply of the stomach. *J. Anat.*, **75**, 50-63.
- ²Holt, G. W. (1966). The vagi: medical and surgical implications. *Amer. J. med. Sci.*, **251**, 86-103.
- ³Wheeler, H. O., and Ramos, O. L. (1960). Determinants of the flow and composition of bile in the unanaesthetized dog during constant infusion of sodium taurocholate. *J. clin. Invest.*, **39**, 161-170.
- ⁴Wheeler, H. O., Ross, E. D., and Bradley, S. E. (1968). Cannicular bile production in dogs. *Amer. J. Physiol.*, **214**, 866-874.
- ⁵Preisig, R., Cooper, H. L., and Wheeler, H. O. (1962). The relationship between taurocholate secretion rate and bile production in the unanaesthetized dog during cholinergic blockade and during secretin administration. *J. clin. Invest.*, **41**, 1152-1162.
- ⁶Bayliss, W. M., and Starling, E. H. (1902). The mechanisms of pancreatic secretion. *J. Physiol. (Lond.)*, **28**, 325-353.
- ⁷Vagne, M., Stening, G. F., Brooks, F. P., and Grossman, M. I. (1968). Synthetic secretin: comparison with natural secretin for potency and spectrum of physiological actions. *Gastroenterology*, **55**, 260-267.
- ⁸Jones, R. S., and Grossman, M. I. (1969). Choleretic effects of secretin and histamine in the dog. *Amer. J. Physiol.*, **217**, 532-535.
- ⁹Jonson, G., Sundman, L., and Thulin, L. (1964). Influence of chemically pure secretin on hepatic bile output. *Acta physiol. scand.*, **62**, 287-290.
- ¹⁰Hardison, W. G., and Norman, J. C. (1967). Effect of bile salt and secretin upon bile flow from the isolated perfused pig liver. *Gastroenterology*, **53**, 412-417.
- ¹¹Hardison, W. G. M., and Norman, J. C. (1968). Electrolyte composition of the secretin fraction of bile from the perfused pig liver. *Amer. J. Physiol.*, **214**, 758-763.
- ¹²Waitman, A. M., Dyck, W. P., and Janowitz, H. D. (1969). Effect of secretin and acetazolamide on the volume and electrolyte composition of hepatic bile in man. *Gastroenterology*, **56**, 286-294.
- ¹³Jones, R. S., and Brooks, F. P. (1965). The pyloric antrum as a mediator of insulin induced cholerisis. *Physiologist*, **8**, 202.
- ¹⁴Zaterka, S., and Grossman, M. I. (1966). The effect of gastrin and histamine on secretion of bile. *Gastroenterology*, **50**, 500-505.
- ¹⁵Nahrwold, D. L., and Grossman, M. I. (1967). Secretion of bile in response to food with and without bile in the intestine. *Gastroenterology*, **53**, 11-17.
- ¹⁶Nahrwold, D. L., Cooke, A. R., and Grossman, M. I. (1967). Cholerisis induced by stimulation of the gastric antrum. *Gastroenterology*, **52**, 18-22.
- ¹⁷Ross, H., Saubermann, A., and Silen, W. (1969). The effect of gastric antral stimulation upon the secretion of hepatic bile. *Proc. Soc. exp. biol. (N.Y.)*, **130**, 278-283.
- ¹⁸Pissidis, A. G., Bombeck, C. T., Merchant, F., and Nyhus, L. M. (1969). Hormonal regulation of bile secretion: a study in the isolated, perfused liver. *Surgery*, **66**, 1075-1084.
- ¹⁹Fritz, M. E., and Brooks, F. P. (1963). Control of bile flow in the cholecystectomized dog. *Amer. J. Physiol.*, **204**, 825-828.
- ²⁰Baldwin, J. Heer, F. W., Albo, R., Peloso, O., Ruby, L., and Silen, W. (1966). Effect of vagus nerve stimulation on hepatic secretion of bile in human subjects. *Amer. J. Surg.*, **111**, 66-69.
- ²¹Fletcher, D. M., and Clark, C. G. (1969). Changes in canine bile-flow and composition after vagotomy. *Brit. J. Surg.*, **56**, 103-106.

- ²²Magee, D. F. (1965). Physiology of gall-bladder emptying. In *The Biliary System*, edited by W. Taylor, pp. 233-247. Blackwell, Oxford.
- ²³Johnson, F. E., and Boyden, F. A. (1952). The effect of double vagotomy on the motor activity of the human gall-bladder. *Surgery*, 32, 591-601.
- ²⁴Cox, H. T., Doherty, J. F., and Kerr, D. F. (1958). Changes in the gallbladder after elective gastric surgery. *Lancet*, 1, 764-766.
- ²⁵Rudick, J., and Hutchison, J. S. F. (1965). Evaluation of vagotomy and biliary function by combined oral cholecystography and intravenous cholangiography. *Ann. Surg.*, 162, 234-240.
- ²⁶Inberg, M. V. and Vuorio, M. (1969). Human gallbladder function after selective gastric and total abdominal vagotomy. *Acta chir. scand.*, 135, 625-633.
- ²⁷Tinker, J., and Cox, A. G. (1969). Gall-bladder function after vagotomy. *Brit. J. Surg.*, 56, 779-782.
- ²⁸Clave, R. A., and Gaspar, M. R. (1969). Incidence of gallbladder disease after vagotomy. *Amer. J. Surg.*, 118, 169-176.
- ²⁹Glanville, J. N., and Duthie, H. L. (1964). Contraction of the gallbladder before and after total abdominal vagotomy. *Clin. Radiol.*, 15, 350-354.
- ³⁰Williams, E. J., and Irvine, W. T. (1966). Functional and metabolic effects of total and selective vagotomy. *Lancet*, 1, 1053-1057.
- ³¹Beneventano, T. C., Rosen, R. G., and Schein, C. J. (1969). The physiological effect of acute vagal section on canine biliary dynamics. *J. Surg. Res.*, 9, 331-334.
- ³²Ellis, H., and Westell, C. (1969). Selective vagotomy. In *After Vagotomy* edited by J. A. Williams and A. G. Cox. Butterworths, London.
- ³³Stassa, G., and Grafe, W. R. (1968). The cineradiographic evaluation of the biliary tract after drug therapy following cholecystectomy, sphincterotomy, and vagotomy. *Radiology*, 91, 297-301.
- ³⁴Liedberg, G., and Halabi, M. (1970). The effect of vagotomy on flow resistance at the choledochoduodenal junction. *Acta chir. scand.*, 136, 208-212.
- ³⁵Mallet-Guy, P., Descotes, J., Ahualli, A., and Venturini, A. (1953). Analyse experimentale des effets operations de vagotomie sur les tonus des voies biliaires. *Lyon chir.*, 48, 685-703.
- ³⁶Williams, R. D., and Huang, T. T. (1969). The effect of vagotomy on biliary pressure. *Surgery*, 66, 353-356.
- ³⁷Majoor, C. L. H., and Suren, T. J. J. (1947). Gall-bladder complications following resection of stomach for peptic ulcer. *Brit. med. J.*, 2, 8-11.
- ³⁸Griffiths, J. M. T., and Holmes, G. (1964). Cholecystitis following gastric surgery. *Lancet*, 2, 780-782.
- ³⁹Krause, U. (1963). Long term results of medical and surgical treatment of peptic ulcer. *Acta chir. scand.*, Suppl. 310.
- ⁴⁰Lundman, T., Orinius, E., and Thorsen, G. (1964). Incidence of gallstone disease following partial gastric resection. *Acta chir. scand.*, 127, 130-133.
- ⁴¹Turunen, M., and Antila, L. (1964). Gallbladder disease following gastrectomy. *Acta chir. scand.*, 127, 134-137.
- ⁴²Schreiber, H. W., Luchmann, A. and Koch, W. (1968). Partial gastrectomy and cholelithiasis. *Germ. med. Mth.*, 13, 117-120.
- ⁴³Bouchier, I. A. D. (1969). Postmortem study of the frequency of gallstones in patients with cirrhosis of the liver. *Gut*, 10, 705-710.
- ⁴⁴Horwitz, A., and Kirson, S. M. (1965). Cholecystitis and cholelithiasis as a sequel to gastric surgery. *Amer. J. Surg.*, 109, 760-762.
- ⁴⁵Bouchier, I. A. D., and Freston, J. W. (1968). The aetiology of gallstones. *Lancet*, 1, 340-344.
- ⁴⁶Schein, C. J., Rosen, R. G., Warren, A., and Gliedman, M. L. (1969). A vagal factor in cholecystitis. *Surgery*, 66, 345-352.
- ⁴⁷Barnett, W. O., and Hilbun, G. R. (1966). Dissolution of human gallstone in the dog's gallbladder after various degrees of vagotomy. *Surgery*, 60, 840-843.
- ⁴⁸Loeb, M., and Nicoloff, D. M. (1968). Gallbladder function in the dog following subtotal gastric resection or vagotomy and pyloroplasty. *Surgery*, 63, 806-809.
- ⁴⁹Mosbach, E. H., and Bevans, M. (1956). Formation of gallstones in rabbits fed 3-beta-cholestanol. *Arch. Biochem.*, 63, 258-259.
- ⁵⁰Freston, J. W., Bouchier, I. A. D., and Newman, J. (1969). Biliary mucous substances in dihydrocholesterol-induced cholelithiasis. *Gastroenterology*, 57, 670-678.
- ⁵¹Freston, J. W. (1967). Experimental cholelithiasis. PhD Thesis, University of London.
- ⁵²Amberg, J. R. (1968). Effect of vagotomy on cholestanol cholelithogenesis in the rabbit. *Invest. Radiol.*, 3, 239-242.
- ⁵³Fletcher, D. M., and Clark, C. G. (1968). Gall-stones and gastric surgery. *Brit. J. Surg.*, 55, 895-899.