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 vagus 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 supply1,2.

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 choleretic action7,8. 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 liver10,11, and in man12. This stimulatory effect of secretin is independent of the action of bile salts6. Another hormone with choleretic action is gastrin. This was demonstrated by Jones and Brookes13 who reported that antrectomy abolished the choleretic 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 salts15,16,17. Not all the reports are in agreement and Pissidis et al18, using the isolated calf liver, were unable to show a choleretic 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 dogs\(^2\) as well as in humans\(^2\). Furthermore after vagotomy the output of bile is reduced\(^1\),\(^2\), and in man the choleretic is eliminated by a vagal-blocking dose of atropine. Fletcher and Clark\(^2\) 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 Oddi\(^2\). 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 \emph{in vivo}. In one of the earliest studies Johnson and Boyden\(^2\) reported that the fasting gallbladder volume doubles in patients following a total vagotomy while Cox \emph{et al}\(^2\) noted decreased contraction of the gallbladder after truncal vagotomy. Rudick and Hutchinson\(^2\) 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 Vuorio\(^2\), whereas Tinker and Cox\(^2\) observed marked reduction in gallbladder emptying but do not mention whether the gallbladder was dilated or not. Clave and Gaspar\(^2\) 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 Duthie\(^2\) nor Williams and Irvine\(^2\) found any change in human gallbladder function following total vagotomy, and a similar conclusion has been reached by Benneventano \emph{et al}\(^2\) 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 Hutchinson\(^2\) reported no alteration in the size of the gallbladder after anterior selective vagotomy, Tinker and Cox\(^2\) showed that the gallbladder is denervated after both truncal and selective vagotomy. Ellis and Wastell\(^2\) 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 Grafe\(^3\) 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 cats\(^4\). Yet in acute experiments in vagotomized dogs a reduction was observed in the pressure required to overcome the choledocho-duodenal sphincter\(^3\), thus confirming the earlier
observations of Mallet-Guy et al. A contrasting observation is that of Williams and Huang 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 Suren 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 Holmes, Krause, and Lundman et al. But this association has been denied by Turunen and Antila and Schriber et al. 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.

There have been a number of case reports incriminating vagotomy as a factor in cholelithiasis. These have been summarized by Clave and Gaspar 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 vagotomy may not be much greater than the frequency in control populations. The frequency of gallstones is generally arrived at on the basis of necropsy studies 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 patient are followed. While it has been denied that there is an association between peptic ulcer and gallbladder disease, at least one author has claimed that gallstones are commoner in patients with peptic ulcer than in the general population—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 salts 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 understood. 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 performed.

This subject has been approached experimentally in a number of ways. Barnett and Hilbun studied the rate at which human gallstones disappeared after being placed in the gallbladders of dogs. The animals were studied with and without vagotony. 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 confirmed. The induction of alldeloxycolic acid stones in rabbits 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 stones have been counterbalanced by the report that gallstone formation is enhanced.

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 Clark 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 choledolithiasis, peptic ulcer disease, and gastric surgery.

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References

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