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Effects of ethanol on the sphincter of Oddi: an endoscopic manometric study

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SUMMARY The effect of ethanol, given either intragastrically or intravenously, on the sphincter of Oddi was evaluated by endoscopic manometry. In 12 subjects intragastric ethanol (150 ml of 32%) was given over 10 minutes. In five control subjects saline solution (150 ml of 0·9%) was given intragastrically instead of ethanol. In five other subjects ethanol was infused intravenously (6 ml/kg of 10%) for 36 minutes. Ethanol given intragastrically produced a significant inhibitory effect on sphincter of Oddi pressure. Peak pressure fell from a control value of 75·7±26·35 mmHg to 39±15·39 mmHg ($p<0·001$) at 35 minutes. Basal pressure fell from a control value of 30·17±19·47 mmHg to 11·83±6·35 mmHg ($p<0·01$) at 35 minutes. Wave height fell from a control value of 41·33±15·4 mmHg to 27·16±11·25 mmHg ($p<0·02$) at 35 minutes. No effects on sphincter of Oddi wave frequency were observed. No significant modifications of sphincter motor activity were observed after intragastric saline infusion. Ethanol given intravenously also produced an appreciable inhibitory effect on sphincter of Oddi pressure, without affecting its wave frequency.

The association between alcoholism and pancreatic disease is well known. The aetiological role of ethyl alcohol has generally been accepted, although the mechanism has not yet been defined. A widely held theory is that alcohol causes a duodenitis which, in turn, causes pancreatic duct obstruction.[1–3]

Some authors[4–7] have found that ethyl alcohol produces spasm of the sphincter of Oddi; at the same time increased gastric secretion and secretin-release stimulate the pancreas. Thus consumption of alcohol stimulates the pancreas to secrete in the presence of spasm of the sphincter. This view is not shared by other investigators,[8 9] who think that ethanol produces reflux of duodenal contents into the pancreatic and bile duct. There is still controversy on the effect of ethanol on the sphincter of Oddi.

So far, in human subjects, these studies have been performed by indirect methods, mostly through T-tubes in the early postoperative period. Newly developed recording instrumentation and cannulation of the ampulla of Vater by endoscopy have brought about a more accurate direct quantification of sphincter of Oddi motor activity.[10–12]

The purpose of this study was to evaluate, by endoscopic manometry, the effect of ethanol on the sphincter of Oddi, when given intragastrically or intravenously.

Methods

EQUIPMENT

Two catheters, 195 cm long, 1·6 mm external diameter and 1·1 internal diameter, with a 1·1 diameter side hole, 1 cm from their tip, were used for manometric measurement.

In order to obtain recordings from the biliary or pancreatic duct systems and the sphincter of Oddi one catheter was passed through the biopsy channel of a side-view fibrescope (Olympus model JF B3); the end of this catheter was marked by three black rings 1 mm wide and 3 mm apart, to allow endoscopic observation of the depth of insertion into the sphincter of Oddi, bile, and pancreatic ducts. Continuous recording of the intraduodenal pressure was obtained from the other catheter attached to the external surface of the endoscope.

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Both catheters were attached to external transducers (Statham P23Db) and connected to a multichannel direct polygraph (Ormed M19). They were constantly perfused with sterile 0·9 saline at a rate of 0·9 ml/min with syringes from an infusion pump (Harvard 901). This system gives a small increase in baseline pressure (7 mmHg) and a pressure rise rate of 80 mmHg/s. A third catheter, for intragastric alcohol infusion, was taped to the endoscope, so that its tip was 25 cm proximal to the end of the endoscope.

TECHNIQUE OF MANOMETRY

No drugs were given before endoscopy. Once the papilla of Vater was identified, the manometry catheter was passed into the duodenum and the initial duodenal pressure was recorded as a reference. The papilla was then cannulated and the catheter inserted at least 1–2 cm. The position of the catheter was verified by the appearance of bile (green) or of pancreatic juice (colourless) upon gentle aspiration. Ductal pressure was measured; the catheter was then slowly withdrawn until a phasic high pressure zone was located and the sphincter pressure was recorded where maximum activity was present, pausing one minute or longer at each station. During pressure recordings the position of the catheter was continuously monitored by observing the catheter marks relative to the papillary orifice.

After the basal pressure measurements had been recorded, intragastric ethyl alcohol (150 ml of 32%) was given to 12 subjects over a period of 10 minutes. Pressure measurements were then taken at approximately five minute intervals, for 35 minutes, after the beginning of the intragastric infusion.

In five different subjects, after basal measurement, intragastric saline solution (150 ml of 0·9%) instead of alcohol, was given in an identical manner and pressure recorded for 35 minutes at the same time intervals.

In five other subjects, after basal pressure measurements had been taken, intravenous alcohol (6 ml/kg of 10%) was infused for 36 minutes and pressure recordings were taken at approximately three minute intervals starting three minutes after the beginning of the infusion. For statistical analysis of data, we used Student's *t* test. All values are expressed as means ± 1 SEM.

SUBJECTS

A total of 22 subjects (nine woman and 13 men) were included in this study. Twelve subjects (five women and seven men), with a mean age of 49 years (range 27–72 years) took part in the study with intragastric alcohol infusion; of these, five patients had choledocholithiasis (two postcholecystectomy), three had ERCP findings of chronic pancreatitis, while in four of them no abnormality was found at ERCP. Two of the subjects with choledocholithiasis, one of those with chronic pancreatitis, and one of those with normal ERCP had a history of consuming more than 30 g of alcohol per day.

Five subjects (two women and three men), with a mean age of 43 years (range 25–65 years), served as controls in the study with intragastric saline infusion: among them, one patient had choledocholithiasis, one had ERCP findings of chronic pancreatitis, while in three no abnormality was found at ERCP. A history of alcohol excess (more than 30 g per day) was found in the subjects with choledocholithiasis and in one of those with normal ERCP.

The remaining five subjects (two women and three men), with a mean age of 39 years (range 31–56 years), took part in the study with intravenous alcohol infusion: of these, two patients had choledocholithiasis, while in three no abnormality was found at ERCP. One of the patients with normal ERCP had a history of consuming more than 30 g of alcohol per day.

The project was approved by the North Lothian District Medical Committee (Scotland). Permission to perform the study was obtained from all subjects, who voluntarily agreed to take part in it.

Results

Endoscopic manometry showed that the sphincter of Oddi has a basal, steady-state pressure higher than that in the common bile duct, pancreatic duct, and duodenum; phasic activity, composed of rhythmic contractions and relaxations, is superimposed on the basal pressure; no motor activity is present either in the bile duct or the pancreatic duct; there is no relationship between duodenal contractions and sphincter of Oddi activity.

All values were expressed in mmHg, taking duodenal pressure as zero reference. Five individual peaks were read from each section to generate the value for peak pressure. The lowest sphincter of Oddi pressure recorded from each section was considered to be the basal pressure. The difference between peak and basal pressure was termed wave height. The mean basal sphincter of Oddi pressure was 27·5±15·81 mmHg. Mean value of the sphincter peak pressure was 73·59±20·47 mmHg. Mean wave height was 46·52±16·18 mmHg; wave frequency was 4·66±1·24/min.

The effect of intragastric alcohol infusion on the sphincter of Oddi pressure is shown in Fig. 1. The alcohol produced an inhibitory effect on the

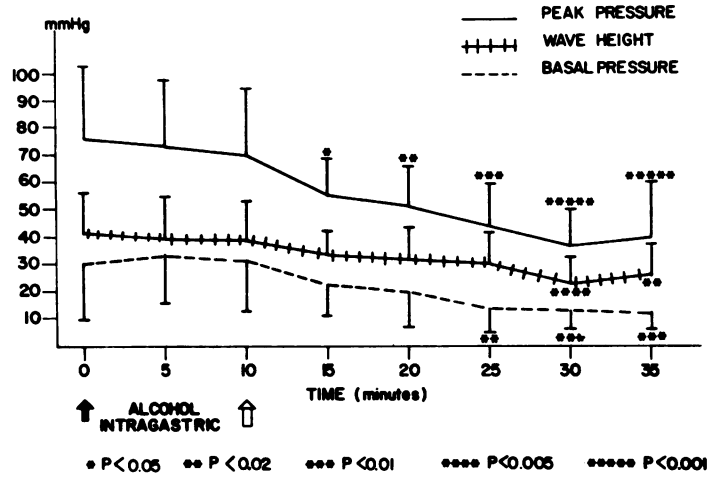

Fig. 1 *Graph showing changes in sphincter of Oddi motor activity after intragastric ethanol infusion (12 subjects). Values are means ± 1 SEM. Black arrow: beginning of infusion. White arrow: end of infusion. Significant difference from control pressure: *p<0·05, **p<0·02, ***p<0·01, ****p<0·005, and *****p<0·001.*

pressure in 11 of 12 patients. In nine of these, alcohol began to reduce the pressure 15 minutes after starting intragastric infusion; this effect lasted for 35 minutes. A typical tracing is shown in Fig. 2.

In two subjects, a mild increase of sphincter of Oddi basal and phasic pressure was observed 15, 20, and 25 minutes after intragastric alcohol infusion had been started; this effect was followed by significant inhibition at 30, 35, and 40 minutes in controls. A typical tracing is shown in Fig. 3. In three subjects, in whom the experiment was continued, the inhibition was still present at 40

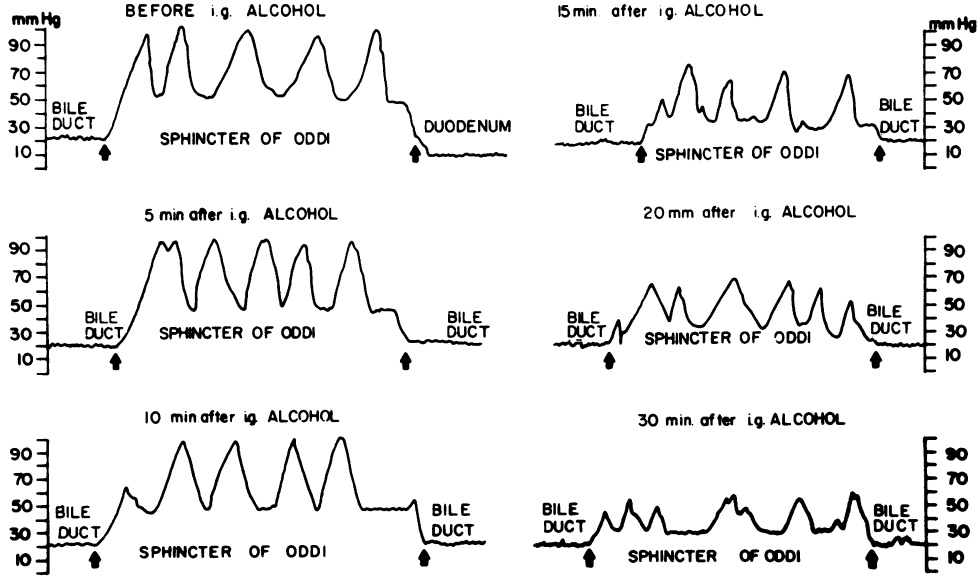

Fig. 2 *Endoscopic manometry recordings from the same subjects before and after intragastric (ig) ethanol infusion; the margins of the sphincter segment are shown by arrows (movements of the catheter across the sphincter). About 15 minutes after starting intragastric infusion the sphincter of Oddi pressure is seen to be reduced.*

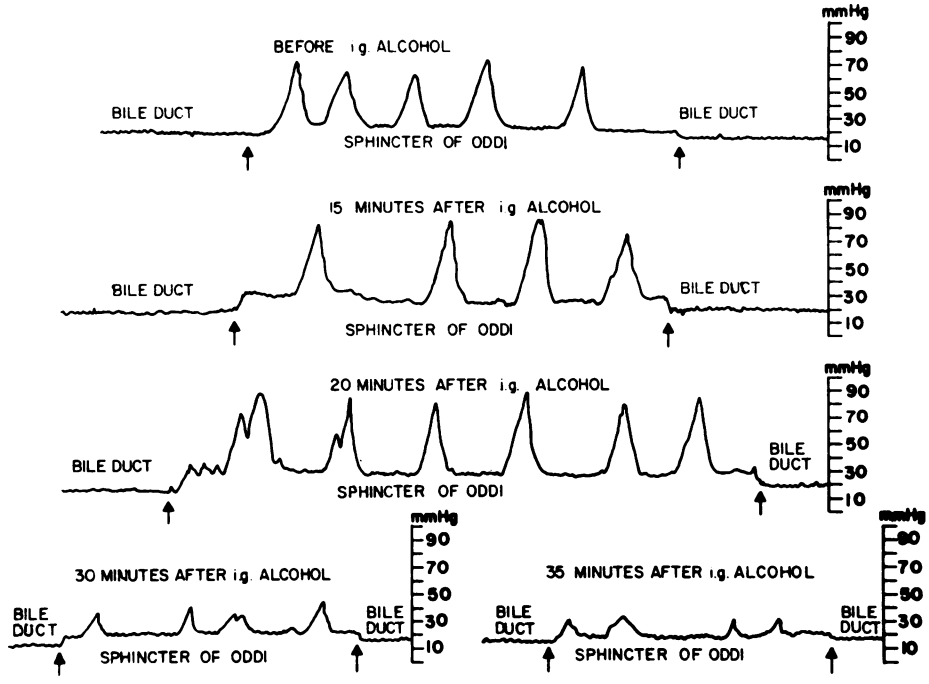

Fig. 3 *Endoscopic manometry recordings from the same subjects before and after intragastric (ig) ethnol infusion. About 15 and 20 minutes after starting intragastric infusion an increase of sphincteric pressure is observed; this increase is followed by an inhibition at 30 and 35 minute controls.*

minutes. In one subject no significant effect on sphincter of Oddi pressure was observed after intragastric alcohol infusion. No effects on the frequency of the sphincter's phasic contractions were observed after intragastric alcohol infusion. Alcohol blood levels achieved after starting intragastric infusion were 2·77±1·32 mmol/l at 10 minutes, 8·53±4·77 mmol/l at 15 minutes, 5·56±3·6 mmol/l at 20 minutes, 3·43±2·84 mmol/l at 30 minutes, and 2·11±2·26 mmol/l at 45 minutes.

No significant modifications of the sphincter's motor activity were observed after intragastric saline infusion.

The effect of intravenous alcohol infusion on the sphincter of Oddi pressure is shown in Fig. 4. The alcohol, given intravenously, produced an inhibitory effect on the sphincter in all five patients; the inhibition began three minutes after starting the infusion and it was present continuously during the infusion. No effects on the frequency of the sphincter's phasic contractions were observed after intravenous alcohol infusion. A typical tracing is shown in Fig. 5.

Duodenal activity, detectable with the catheter in the duodenum, consisted of small undulations of 3–7 mmHg; sporadic, disorganised duodenal contractions, not related to phasic sphincter of Oddi activity, were also observed. Alcohol, given either intragastrically or intravenously, did not provoke any systematic change in duodenal pressure. We have to bear in mind, however, that, because of air insufflation during endoscopy, intraduodenal pressure recordings could not represent real duodenal activity. There were no complications from the procedure.

Discussion

The results show that intragastric or intravenous ethanol infusion causes an inhibition of sphincter of Oddi activity. Ethanol given intragastrically began to produce an effect on the sphincter 15 minutes after starting infusion, almost at the time of the maximum rise in blood alcohol; when it is given intravenously it acts on the sphincter earlier, about three minutes after starting the infusion. These effects lasted 25–30 minutes after the intragastric infusion was ended and during the entire time of intravenous infusion. Alcohol given either intragastrically or intravenously affected neither the

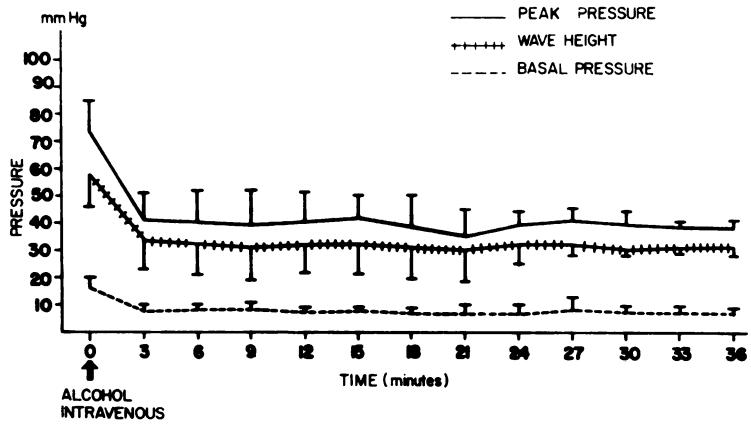

Fig. 4 *Effect of intravenous ethanol infusion on sphincter of Oddi motor activity (five subjects). Values are means ± 1 SEM. The arrow indicates the beginning of infusion. Appreciable changes in peak, basal pressure, and wave heights are observed. The small number of subjects did not allow a statistical analysis.*

frequency of the sphincter's contractions nor duodenal motor activity. At present good evidence exists that motor activity of the sphincter of Oddi is independent of duodenal activity. In fact, the muscular fibres of the sphincter differ from those of the duodenal wall both in structure and embryological developments.[13] Furthermore, simultaneous electromyographic studies of the sphincter of Oddi and the duodenum in rabbit[14 15] and man,[16] and endoscopic manometry in humans[10 12] show that the

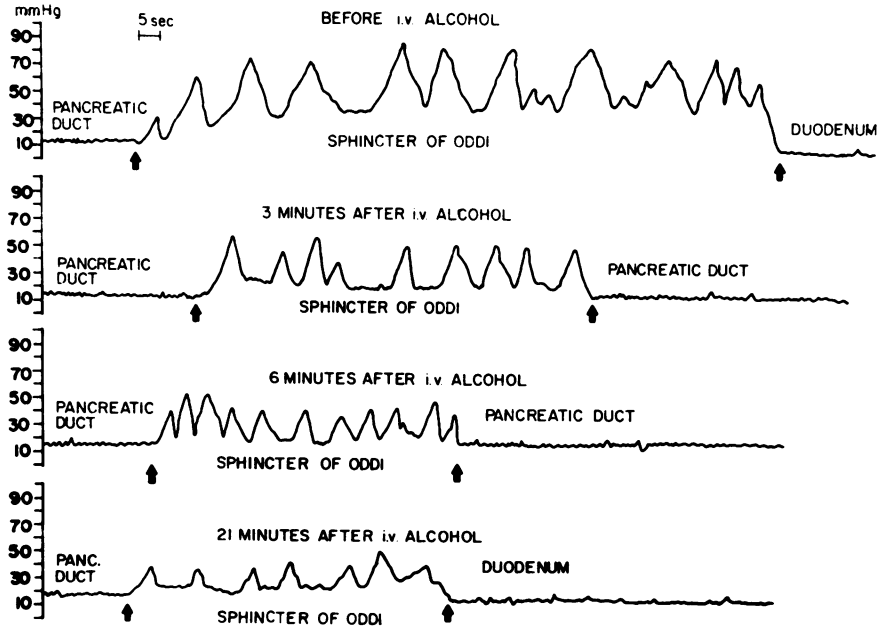

Fig. 5 *Endoscopic manometry recordings from the same subjects before and at different times after the beginning of intravenous (IV) ethanol infusion. The margins of the sphincter segment are shown by arrows (movements of the catheter across the sphincter). An inhibition of sphincteric activity is observed beginning from three minutes after starting the infusion.*

activity of the sphincter is not directly related to duodenal activity.

The regulation of the sphincter of Oddi's motor activity is complex and as yet unclear. A strict interaction between neural and hormonal mechanism, together with an intrinsic automaticity, are probably involved. Experimental studies in cats,[17] dogs,[18 19] and endoscopic manometry in man[12 20] have shown that CCK and CCK-OP have an inhibitory effect *in vivo* on sphincter of Oddi motor activity. Animal studies[18] have shown that secretin relaxes the sphincter. Geenan *et al*[12] observed that intravenous pulse dose of secretin (1 U/kg) elicited a biphasic response of sphincter of Oddi excitation followed by inhibition. This dose was probably non-physiological, so the observed response is, rather, to be considered pharmacological. Carr-Locke and Gregg[21] have found that intravenous secretin infusion, which produces plasma secretin levels such as those observed in the range of postprandial rises, causes selective relaxation of the pancreatic duct sphincter. The same investigators believe that glucagon produces a selective physiological inhibitory action on the bile duct sphincter.

Pentagastrin has been reported to increase sphincter of Oddi motor activity in humans,[12 20] while naloxone, an antagonist of enkephalins, depresses it.[21] It is reasonable to suggest that a physiological role of CCK consists in the relaxation of the sphincter of Oddi while causing gall-bladder contraction; secretin and glucagon may have an accessory role to CCK in inhibiting the tone of the sphincter of Oddi. It is very difficult to establish what physiological role, if any, gastrin, enkephalins, VIP, motilin, and PP have in regulating the sphincter's activity.

The role of the autonomic nervous system in the dynamics of the sphincter of Oddi is not yet known. It has been reported that the sphincter contracts through a cholinergic mechanism.[22–24] α-adrenergic mechanism is also responsible for the contraction, whereas relaxation can be elicited by a β-adrenergic mechanism.[23 25–27] We cannot, at present, determine the physiological role of either cholinergic or adrenergic systems in regulating the activity of the sphincter of Oddi.

It has also been reported that the sphincter can function autonomously.[23 28] This spontaneous activity was shown to be myogenic in origin, as it was not inhibited by agents known to block nervous effects.[23]

The role of the sphincter, whether functional or anatomical, in controlling biliary or pancreatic flow and preventing duodenal reflux into the biliary and pancreatic ducts is controversial. Although some investigators[29 30] believe that the phasic sphincter contractions serve as a peristaltic pump, available evidence suggests that phasic activity retards biliary and pancreatic emptying.[31 32] It also seems likely that sphincter of Oddi basal pressure plays some part in controlling emptying of the pancreatic duct. Finally, it has been suggested that the occlusive competence of the sphincter is accounted for by a mucosal flutter valve.[33]

The integrity of the sphincteric mechanism seems of obvious importance in preventing reflux of bile and duodenal contents back into the pancreatic duct.[34–36] The importance of duodenopancreatic reflux in acute pancreatitis is also stressed by several investigators.[8 35 36] Keynes,[37] in a recent experimental study in dogs, concludes that, while experimental interstitial pancreatitis results from damage to the pancreatic duct system without infection, haemorrhagic pancreatitis results mainly from reflux of bacteria into the pancreatic ducts from the duodenum. Thus the physiological role of basal pressure and phasic contractions in the sphincter of Oddi remains to be determined. We suggest that basal and phasic sphincter of Oddi pressure are of fundamental importance in regulating biliary and pancreatic flow. Reflux of duodenal contents into the biliary and pancreatic ducts is probably avoided mainly by basal pressure.

This study does not allow us to draw conclusions regarding the mechanism of alcohol-induced inhibition. It is possible that alcohol causes a hormone-mediated relaxation of the papillary sphincter, but a nervous or direct mechanism cannot be excluded.

The importance of transampullary duodenal reflux as an aetiological factor in alcoholic pancreatitis is stressed by Rosato *et al.*[9] In their experiments in dogs subjected to measurement of closed duodenal loop pressures, they found that the duodenopancreatic reflux associated with acute pancreatitis occurred at a lower pressure when alcohol was used to distend the loops than when saline was used. Further lowering of the pressure reflux was produced by chronic oral alcohol ingestion.

Jalovaara and Apaja[38] found that bile obtained from chronically alcohol-fed rats caused significantly more serious lesions in the pancreas than did bile from normal rats. Reflux of 'toxic alcoholic' bile into the pancreas might act as an induction factor for alcohol pancreatitis.

Menguy *et al*[5] in experimental dogs and Sarles *et al*[7] in rabbits observed a spasmogenic action of alcohol on the sphincter of Oddi. In previous studies, performed in humans through T-tubes, it has been postulated that alcohol, given intra-

gastrically[4] or intravenously,[6] causes increased tone in the sphincter mechanism at the choledocho-duodenal junction. This study seems to support the theory that alcohol favours reflux through an insufficiency of the sphincter of Oddi. The hypothesis of duodenal reflux would explain why attacks of acute pancreatitis, related to alcohol abuse, follow some 24–48 hours after a bout of drinking. An incubation of bacteria refluxed in the pancreatic duct from the duodenum could explain the delay between alcoholic excesses and the beginning of symptoms of acute pancreatitis.

The part played by an alcohol-induced depression of the activity of the sphincter of Oddi in the pathogenesis of chronic alcoholic pancreatitis and pancreatic cancer is unknown, and, at present, no hypothesis can be formulated. Theoretically, chronic alcohol consumption and repeated episodes of duodenal reflux could produce progressive pancreatic damage, but satisfactory data to support this hypothesis in man are lacking.

The present endoscopic manometry study demonstrates that ethanol given either intragastrically or intravenously inhibits the activity of the sphincter of Oddi but the mechanism of this inhibition and its role in the pathogenesis of pancreatic disease are still unclear. Thus, further investigation is necessary.

References

1 Dreiling DA, Richman A, Fradkin NF. The role of alcohol in the etiology of pancreatitis: a study of the effect of intravenous ethyl alcohol on the external secretion of the pancreas. *Gastroenterology* 1952; **20:** 636–46.

2 Herman RE, Davis JH. The role of incomplete pancreatic duct obstruction in the etiology of pancreatitis. *Surgery* 1960; **48:** 318–29.

3 McKay IR. The effects of alcohol on the gastrointestinal tract. *Med J Aust* 1966; **2:** 372–6.

4 Capitaine Y, Sarles H. Action de l'éthanol sur le tonus du sphincter d'Oddi chez l'homme. *Biol Gastroenterol* 1971; **3:** 231–6.

5 Menguy RB, Hallenbeck GA, Ballman JL, Grindlay JH. Intraductal pressures and sphincteric resistance in canine pancreatic and biliary ducts after various stimuli. *Surg Gynecol Obstet* 1958; **106:** 306–20.

6 Pirola RC, Davis E. Effects of ethyl alcohol on sphincteric resistance at the choledocho-duodenal junction in man. *Gut* 1968; **9:** 557–60.

7 Sarles JC, Devaux MA, Castagnini A. Electromyographie du sphincter d'Oddi chez le lapin: action de la vagotomie, de l'examethonium et de l'alcool. *Biol Gastroenterol* 1976; **9:** 25–32.

8 McCutcheon AD. A fresh approach to the pathogenesis of pancreatitis. *Gut* 1968; **9:** 296–310.

9 Rosato EF, Butter CJ, Grossman R, Mullen JL, Skerrett PV, Rosato FE. Effect of alcohol on duodenal-pancreatic reflux. *Am J Surg* 1973; **125:** 228–30.

10 Carr-Locke DL, Gregg JA. Endoscopic manometry of pancreatic and biliary sphincter zones in man. Basal results in healthy volunteers. *Dig Dis Sci* 1981; **26:** 7–15.

11 Csendes A, Kruse A, Funch-Jensen P, Oster MJ, Ornshalt J, Amdrup E. Pressure measurements in the biliary and pancreatic duct systems in controls and in patients with gallstones, previous cholecystectomy or common bile duct stones. *Gastroenterology* 1979; **77:** 1203–10.

12 Geenen JE, Hogan WJ, Dodds WJ, Stewart ET, Arndorfer RC. Intraluminal pressure recordings from the human sphincter of Oddi. *Gastroenterology* 1980; **78:** 317–24.

13 Boyden EA. The anatomy of the choledochoduodenal junction in man. *Surg Gynecol Obstet* 1957; **104:** 641–52.

14 Ishioka T. Electromyographic study of the choledocho-duodenal junction and duodenal wall muscle. *Tohoku J Exp Med* 1959; **70:** 73–84.

15 Ono K. The discharge of bile into the duodenum and electrical activities of the muscle of Oddi and duodenum. *Jpn J Smooth Muscle Res* 1970; **6:** 123–8.

16 Akasaka YM, Kizn M, Nakajima M, Kawau K. Endoscopic electromyography of the sphincter of Oddi. *Gastroenterol Jpn* 1979; **14:** 306–11.

17 Behar J, Biancani P. Effect of synthetic (CCK-OP) and natural (CCK-N) cholecystokinin on the sphincter of Oddi. (Abstract) *Gastroenterology* 1978; **74:** 1116.

18 Lin TM. Actions of gastrointestinal hormones and related peptides on the motor function of the biliary tract. *Gastroenterology* 1975; **69:** 1006–22.

19 Raih TJ, Ashmore CS, Wilson SD, De Cosse JJ, Hogan WJ, Dodds WJ, Steff JJ. Effect of enteric hormones on the canine choledochal sphincter. (Abstract) *Gastroenterology* 1973; **64:** 787.

20 Nebel OT. Effect of enteric hormones on the human sphincter of Oddi. (Abstract) *Gastroenterology* 1975; **68:** 105.

21 Carr-Locke DL, Gregg JA, Aoki TT. Effects of exogenous glucagon on pancreatic and biliary ductal and sphincteric pressure in man demonstrated by endoscopic manometry and correlation with plasma glucagon. *Am J Gastroenterol.* (In press.)

22 Azuma H. Mechanical responses of sphincter of Oddi and duodenum preparation to certain autonomic drugs and transmural stimulation. *Folia Pharmacol Jpn* 1973; **69:** 711–20.

23 Persson CGA. Adrenoceptor functions in the cat choledochoduodenal junction in vitro. *Br J Pharmacol* 1971; **42:** 447–61.

24 Stasiewiez J, Wormsley KG. Functional control of the biliary tract. *Acta Hepatogastroenterol* 1974; **21:** 450–68.

25 Crema A, Benzi G, Frigo G, Bertè F. Occurrence of α and β receptors in the bile duct. *Proc Soc Exp Biol Med* 1965; **120:** 158–60.
26 Persson CGA. Adrenergic, cholecystokinetic and morphine-induced effects on extra-hepatic biliary motility. *Acta Physiol Scand* Suppl 1972; **383:** 4–32.
27 Persson CGA. Dual effects on the sphincter of Oddi and gallbladder induced by stimulation of the right great splanchnic nerve. *Acta Physiol Scand* 1973; **87:** 334–43.
28 Wyatt AP. The relationship of the sphincter of Oddi to the stomach, duodenum and gallbladder. *J Physiol (Lond)* 1967; **193:** 225–32.
29 Shelhamer J, Goyal RK. Physiology of bile transport: manometric studies of common bile duct and sphincter of Oddi. (Abstract) *Gastroenterology* 1973; **64:** 686.
30 Toouli B, Watts JM. Actions of cholecystokinin-pancreozimin, secretin and gastrin on extrahepatic biliary tract motility in vitro. *Ann Surg* 1972; **175:** 439–47.
31 Ono K, Watanabe K, Suzuki H, Tsuchida Y, Sugiyama Y, Abo M. Bile flow mechanism in man. *Arch Surg* 1968; **96:** 869–74.
32 Geenen JE, Hogan WJ. Endoscopic access to the papilla of Vater. *Endoscopy Suppl* 1980: 47–56.
33 Tansy MF, Salkin LM, Innes DL, Martin JS, Landin WE, Kendall FM. The occlusive competence of the duodenal orifice of the canine pancreatic duct. *Surg Gynecol Obstet* 1977; **144:** 865–8.
34 Keane FB, Dozois RR, Go VLW, Dimagno EP. Interdigestive canine pancreatic juice composition and pancreatic reflux and pancreatic sphincter anatomy. *Dig Dis Sci* 1981; **26:** 577–84.
35 Johnson RH, Doppman J. Duodenal reflux and the etiology of pancreatitis. *Surgery* 1967; **62:** 462–7.
36 Tuzhilin S, Podolsky A, Dreiling DA. The role of insufficiency of the sphincter of Oddi in the pathogenesis of pancreatitis. *Mt Sinai J Med* 1981; **48:** 133–6.
37 Keynes WM. A non pancreatic source of the proteolytic-enzime amidase and bacteriology in experimental acute pancreatitis. *Ann Surg* 1980; **191:** 187–99.
38 Jalovaara P, Apaja M. Alcohol and acute pancreatitis. An experimental study in the rat. *Scand J Gastroenterol* 1978; **13:** 703–9.