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Reviews

Biliary acute pancreatitis: a review

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INTRODUCTION

It is axiomatic that the most effective and soundly based plan of treatment of any disorder is one aimed at the mechanism or mechanisms responsible for its development[1]. This basic notion, coupled with recent reports[2-11] in which, surprisingly there is a total lack of reference to the probable involvement of autonomic-arc-reflexes in the physiopathogenesis of biliary acute pancreatitis have prompted this presentation. Undoubtedly, this disease entity has numerous causes, an obscure physiopathology, few effective remedies, and, often, an unpredictable outcome. At the turn of the century, Opie[12,13] brought to light the association between gallstone migration and acute pancreatitis. When referring to the intimate evolving process, most authors steadily adhere to the Opie's theories: chemical and physical. The former is linked to the common-channel or biliary-reflux mechanism. The latter, to the stone -elicited Wirsung duct obstruction, with the resultant hypertension in the pancreatic ductal tree. What is indeed surprising is the lack of speculation on the subsequent steps that necessarily must follow the initial chemical and/or physical injuries that end up in an episode of acute pancreatitis. The core of our contention is that the pathophysiology of biliary acute pancreatitis is centered on two basic mechanisms: the activation of autonomicarc reflexes and the disruption of the entero-pancreatic feedback loop. Superimposed on the aforementioned pivotal processes we must consider, in some cases, the aggravating role of alcoholism.

In this presentation we will also try to point out those features that justify to consider the Pfeffer method, or of the closed-duodenal-loop, as an experimental surgical model suitable to mimic the clinical condition of acute pancreatitis. Furthermore, we will analyze the properties of local anesthetics that, according to our contention, are valuable agents to either prevent and/or treat efficaciously an episode of biliary acute pancreatitis.

ACTIVATION OF AUTONOMIC-ARC-REFLEXES

The clinical or surgical circumstances that usually evoke an episode of biliary acute pancreatitis, e.g. a stone that migrates into the duodenum or gets impacted in the distal end of the common bile duct[12,13], endoscopic maneuvers (sphincterotomy, sphinctero-manometry, retrograde cholangio-pancreatography), surgical manipulation , in or close to the duodeno-pancreas, percutaneous liver biopsy-associated hemobilia[14], have as a main starting locus of activation of the autonomic-arc-reflexes the peri-Vaterian duodenum. This intestinal segment is the most sensitive area of what we have conceived as the trigger of an imaginary pancreatic revolver (Figure 1). Our choice of this pedagogical reference was suggested, on the one hand, by the morphologic resemblance with the gun that the pancreatic gland offers in its general anatomical outline, and, on the other, by its functional characteristics[15,16]. The exquisite se nsitivity of the trigger zone rests on its innervation density. This has been s uggested, initially, by the macroscopic anatomical dissection findings in human cadavers and dogs[17-19]. Recently , by those observed in rats and the opossum (Figure 2). Subsequently, histochemical studies[20-23] and the utilization of very elaborate tracers[21-23], allowed to fully ratify the initial gross anatomical observations. Some of the nerve fibres that jump the duo deno-pancreatic cleft belong to the vagal system. They arrive to the head segment of the pancreas following a pathway through the gastric and duodenal walls[19,24-34]. Others contingents of nerve fibres are intrinsic to the duodeno-pancreas. They connect the enteric

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nervous system of the stomach and duoden um with the pancreatic gland (Figure 3). Some of them are cholinergic, and many are serotonergic. They end either in the pancreon units[15,16,18,19] and/or the intrapancreatic ganglia[17-19, 20-23, 25,26]. Following the same route, nerve fibres that belong to the afferent component of the autonomic nervous system jump the duodeno-pancreatic cleft in search of either the nodose ganglion of the vagus or the dorsal root ganglia of the spinalcord[35-46]. These duodeno-pancreatic nerve fibres are the basis of duodeno-pancreatic reflexes.

They are short, medium, and long[17-20,24-26,33]. The short duodeno-pancreatic reflex connect the enteric nervous system of the duodenum with the int rapancreatic ganglia and/or the bullets of the pancreatic revolver: the pancre on units and the Langerhansislets[21-23]. The medium duodeno-pancreati c reflex gets its integration in the celiac ganglia. The long duodeno-pancreatic reflex complete the arc reflex loop in the central nervous system, primarily in the hypothalamic-bulbar nuclei. A feature to emphasize is the presence of co mmand neurons in the peri-Vaterian duodenum[28-32]. They exert a pre-programmed control of the interdigestive motor complex. Concerning the source of the duodenal innervation, its proximal segment, at least in the rat, is under the control of the left or anterior vagal nerve. Contrariwise, the peri-Vaterian duodenum is primarily subjected to nervous influences coming from the celiac ganglia[47-61].

The pancreatic gland innervation depends on the following complex systems: the vagal, the splanchnic-celiac, the entero- pancreatic and the sensory-afferent[17-26, 40-46], (Figure 3). In the first two complexes, one should take into consideration the existence of three different kinds of impulses: cholinergic, adrenergic and peptidergic. The above description is valid for both the exocrine and the endocrine pancreas[46]. Summarily, the vagal complex arrive s to the pancreatic gland following the pathways of either the digestive tract wall (stomach-duodenum) or through the celiac ganglia. Its nerve fibres are essentially afferent. It also carries peptidergic influences and efferent impulses, primarily cholinergic. The splanchnic-celiac-ganglia-complex is also a nervous afferent pathway, namely of the pain sensation. From the efferent point of view, this complex is primarily of sympathetic impulses. Secondarily, is a transmitter of peptidergic and cholinergic efferent impulses. The entero-pancreatic-complex is the result of neurons that project from the gut to the pancreas. According to the Gershon group[21-23], the nerve cells are essentially cholinergic and serotonergic. They influence the activity of intrapancreatic neurons and islet cells[46]. The sensory-afferent of the autonomic nervous system , through the mediation of its fine, amyelinic, capsaicin-sensitive type C fibres, constitute the basis of the neurogenic-inflammation[35-39,59-65].

As a preamble to the consideration of the autonomic-arc-reflexes, it seems appropriate to point out that the autonomic ganglia in the extrahepatic bile ducts and the pancreatic gland display similar histoarchitectural and physiologic feat ures to those of the enteric nervous system. This is explainable by their common embryological origin[25,26]. When deprived of all outside neurons influences, the intrapancreatic ganglia can be shown to possess an intrinsic activity. The latter, coupled to outside cholinergic, sympathetic and peptidergic impulses give origin, within the gland, to what has been described, with tacit consensus, as cholinergic tone[15-18, 25-27]. This is involved in an intricate interaction with the hormonal system. It has been ascertained on both pancreon segments: the acinar and the centroacinar-ductal, responsible, respectively, of the ecbolic and the hydrelatic components of the exocrine pancreatic secretion[15,16]. A feature to emphasize is the role of the celiac ganglia as an integration center of different kinds of autonomic arc reflexes[17-19,21-25, 47-61]. The nerve fibres that arrive at the celiac ganglia come from different segments of the digestive tract, the extrahepatic bile ducts and the pancreas. In this autonomic nervous structure they establish an intricate interrelationship. The Faradic electrical stimulation of the celiac ganglia triggers an intrapancreatic ischemic process. This evolves as a result of the opening of arterio-venous shunts[50-57]. We have delineated this autonomic-arc-reflex as sympatho-ischemic (Figure 4). It has been clearly observed subsequent to the instillation of bile or bile salts in the pancreatic ductal tree[53]. The changes in the pancreatic vessels (spasms) and the gland's capillary circulation (ischemia) have been objectivized in plastic casts[53]. The full development of the sympatho-ischemic autonomic - arc-reflex leads to a depression of the pancreon's secretory process. The exocrine pancreatic secretion inhibition can also be evoked through another type of autonomic-arc-reflex. We have pinpointed it as secretory-inhibitor. Its conception arose from our observation in canines equipped with duodenal Thomas can nula and studied in the conscious state (Pavlov frame). Indeed, when intemperate mane uvers are employed, especially if either liquid or air is injected abruptly into the main pancreatic duct (distention), a sudden arrest of exocrine pancreatic secretion is frequently observed. This secretory-inhibitor autonomic-arc-reflex can be elicited from other segments of the digestive tract. We have

observed it in rats when distending with a balloon either the antral-fundic junction of the stomach or the peri-Vaterian duodenum segment. A nervous reflex of this sort has been described by Warkentin *et al*[49] on bile secretion when distending the colon or its nerve supply.

The pathway of this autonomic-arc-reflex is probably that of the afferent component of autonomic nervous system. At pancreas level, an antidromic mechanism (pseudo-axonic), and/or an arc reflex loop integrated either in the intrapancr eatic or the celiac ganglia is a possibility. The involvement of a peptide like CGRP[66], PP[67] or some other agent, like serotonin could be a logical assumption to make. The intimate physiopathogenic mechanism is probably related to with the recent studies of Ohshio *et al*[6] in rats. According to these authors, a short-term pancreatic duct obstruction interferes with the acinar cell secretory process down-stream of hormone-receptor binding, intracellular Ca^{2+} release and protein-kinase activation. The pseudo-axonic autonomic-arc-reflex, that leads to neurogenic inflammation, is evoked as are sult of the irritation of the afferent component of the autonomic nervous system Normally, through these nerve fibres a significant percentage of the information originated in the stomach, duodenum, extrahepatic bile ducts and pancreas reach the central nervous system. The impulses travel through special type of nerve fibres: thin, unmyelinated, capsaicin-sensitive (type C). In their course to the nodose ganglion of the vagus, or the dorsal roots ganglia of the spinal cord, they send collaterals where they exert a modullatory influence on the neural transmission (Figure 3 and 5). It is interesting that capsaicin (red-pepper agent), infused intraduodenally, evokes an exocrine pancreatic secretion equivalent to a 15 % of that obtained with a maximal dose of CCK[63]. This pancreon's secretory response results from the activation of CCK-A receptors by the peptide CGR P released from the afferent nerve fibres. Others vasoactive peptides are involved, like SP, neurokinin-A, VIP, SOM and DYN. After synthesis in the somata of the afferent neurons, the bulk of the peptides is transported to their peripheral endings. The co-released peptides interact in the control of pancreatic function. Their antidromic release elicit vasodilatation and extravasation of plasma proteins and formation of edema (neurogenic inflammation)[35-39,59-65,69-71]. A feature to take into account for its pathophysiologic implications is that SP, and other sensory peptides released in the pseudo-axonic reflex, are capable of activating mast-cells to release histamine and other factors. Furthermore, leukocytes, particularly neutrophils granulocytes, monocytes and lymphocytes are stimulated to adhere to the vascular endothelium and to emigrate to the surrounding tissue. Once neurogenic inflammation is triggered, monocytes release prostaglandins, thromboxane and cytokines[36-39]. Some of the latter agents are vasoactive by themselves and, in addition, can activate afferent nerve endings and thereby provide a positive feedback loop which reinforces the initial stimulation of the afferent component of the autonomic nervous system (Figure 3 and 5). This whole process probably favors the absorption of endotoxin from the gut lumen into the blood stream. This agent is capable of inducing panc reatic lesions, depression of the exocrine pancreatic secretion and, in the liver, on the one hand, inhibition of albumin secretion, and, on the other, enhancing the secretion of both fibrinogen and C-reactive protein[72]. In the afferent component of the autonomic nervous system it should be pointed out the presence of different types of receptors: chemoreceptors, chemonociceptors, polymodal nociceptors and warmth receptors[60]. These nervous structures allow to detect those noxious stimuli that are potentially or actually harmful to the tissues. Besides, they also sense innocuous physiologic stimuli, such as pH, bile, distention. The afferent neurons represent a first line of defense against trauma. or, as in the stomach, to the injurious effects of ethanol[62,63]. It is probable that the same happens in the pancreatic gland. That, normally, in this organ, the afferent component of the autonomic nervous system fulfill some sort of cytoprotective function against the deleterious effects of injurious agents, can be inferred by the fact that its permanent ablation, like the one that results from long-term surgical bilateral splanchnicectomy, aggravates the pancreatic lesions (necrosis) induced by 24h closed-duodenal-loop. This at least has been our experience in unpublished observations in rats[73].

All the foregoing support the notion of autonomic-arc-reflexes involvement in the physiopathogenesis of biliary acute pancreatitis. Their degree of participat ion surely varies in each clinical case. This depending on the intrinsic charact eristics of the injurious agent, its degree of persistence and the patient's neuroendocrine reactivity.

DISRUPTION OF THE ENTERO-PANCREATIC FEEDBACK LOOP

When bile and/or pancreatic juice cannot reach the duodenal lumen, the entero-pancreatic feedback loop gets interrupted. This triggers the rising of blood's CCK levels, and, through the induction of an increased cytosolic Ca^{2+} concentration, a supramaximal stimulation of the pancreon's acinar cells is elicited[74-90]. The foregoing is linked to the

evoking of both positive and negative duodeno-pancreatic reflexes[74]. Indeed, when in the duodenal lumen the influence normally exerted by bile, trypsin and chymotrypsin lessens (bile and/or pancreatic juice diversion bile and/or pancreatic duct obstruction) the releasing of CCK from the duodenal mucosa is markedly enhanced. This peptide through a paracrinic mechanism in the duodenal wall, activates the autonomic nervous system. Thus, a positive duodeno-pancreatic-reflex (increased intrapan creatic cholinergic tone) is induced. This effect is potentiated by a concomit ant annulment of a negative duodeno-pancreatic-reflex. The latter was postulated by us in the eighties[74]. It might have as a pathway the entero-pan creatic nervous complex. A neurotransmitter (SOM ?, PP ?, serotonin ?) induced by the presence in the duodenal lumen of trypsin, chymotrypsin and/or bile, might be at the basis of restricting influences on the pancreon units (Figure 6).

Others features to take into account to better understand the entero-pancreatic feedback loop is that a monitor peptide in the pancreatic juice, and a CCK-releasing peptide, derived from the duodenal mucosa, exert a direct stimulating action on the CCK-releasing cells (I cells). These small peptides are normally in activated by intraduodenal trypsin and chymotrypsin. Concerning bile, this secretion, besides activating the postulated negative duodeno-pancreatic-reflex, normally exerts an indirect feedback inhibition. The latter might result from the stabilization of pancreatic juice's protease by the calciumions in it contained[74,83-90]. A physiologic detail to emphasize is that unblocking of the bile obstruction allows the duodenal mucosa to release secretin[91,92]. This hormone may help to dislodge, through an enhanced exocrine pancreatic secretion of water and bicarbonate, eventual intrapancreatic protein plugs. Besides, it may attenuate the noxious influences of CCK on the pancreon's acinar cells. The latter has been shown, initially by Kanno *et al*[93], subsequently by Renner *et al*[94], and, recently, through an agent (tetrafrenyl actone) that has proved to possess a releasing capacity of this hormone from the intestine[95]. A feature to be emphasized is that both secretin and VIP, through a second messenger (cAMP), either prevent or restore, in the acinar cells, the CCK-induced disrupted microtubules and microfilaments.

Aggravating role of chronic alcoholism

When the usual agents that elicit the biliary acute pancreatitis exert their actions superimposed on a background of chronic alcoholism, the degree and extension of the pancreatic acute inflammatory lesions are significantly enhanced[96,97]. This notion is important because the incidence of a chronic ethanol intoxication as a background of an episode of biliary acute pancreatitis is rampant. This assertion is confirmed by several recent papers[96,97]. Experimentally, Gronr-os *et al*[98-100] have ratified, in rats, our primary contention, described in dogs and rats[101-118], that in the pathophysiology of ethanol-evoked pancreatic lesions two major factors play a crucial role: an elevated intrapancreatic acetylcholine level (high cholinergi c tone) and an enhanced acinar cell response to CCK. At clinical level, Brugge *et al*[119] have provided additional support to this postulation. Recently, we have suggested[115,117,118] that the forementioned changes might be consequence of an alcohol-induced loss of a normal braking mechanism exerted by higher autonomic nervous centers. The braking on the pancreon units might depend on peptides like CGRP[66], PP[67] and/or SOM[120,121].

As eventual aggravating influences associates to alcohol intoxication, one should consider the probable participation of an ethanol-evoked sphincter of Oddi dysfunction. Two reports give support to this assumption. The first one, performed in monkeys[128], has disclosed that after the administration of a 130 mL/L ethanol solution there is a significant increase of the main pancreatic pressure. The second report[121], has put in evidence, in humans, that acute intraduodenal ethanol induces an increase of the Vaterian resistance. This phenomenon is enhanced when performed in chronic alcoholics.

Others additional effects related to ethanol intoxication that merit their consideration are: the reduction of the capillary blood flow[122] and the activation and migration of leukocytes in the pancreatic gland[123].

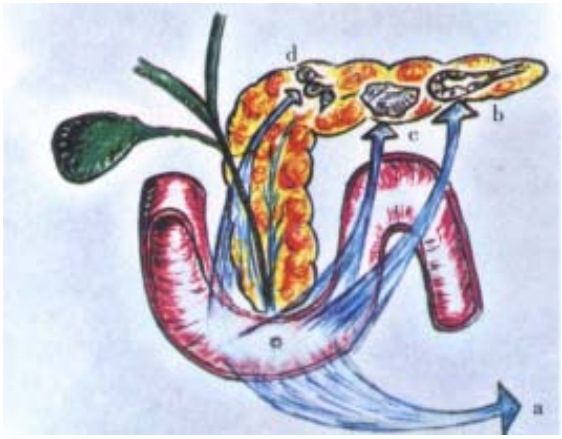

Figure 1 A schematic representation of the duodeno-pancreas. The image pedagogically resorted to is that of a revolver with its trigger represented by the peri-Vaterian duodenum (a) and the bullets by the pa ncreon units (b) and the Langerhans islets (c). The intrapancreatic ganglia (d) are also depicted. The latter integrate different nervous arc reflexes and are pivotal in the generation of the intrapancreatic cholinergic tone.

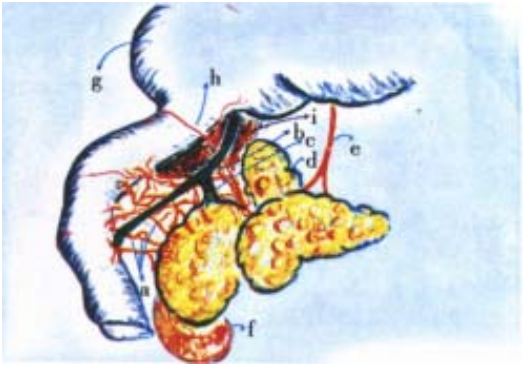

Figure 2 Some anatomical features of the opossum: rich density of nerve fibres jumping the duodeno-pancreatic cleft (a). The joining of the main pancreatic duct (c) with the bile duct (b) giving origin to a long common bile-pancreatic segment before reaching the outlet into the duodenum. The presence of an extension of the pancreatic gland into the hepatic hilum (d). Arriving to the pancreas of the vagus nerve (e). Right kidney (f). Stomach dis placed upward and to the right (g). Duodenal and pyloric branches of the hepatic artery (h). Liver (i)

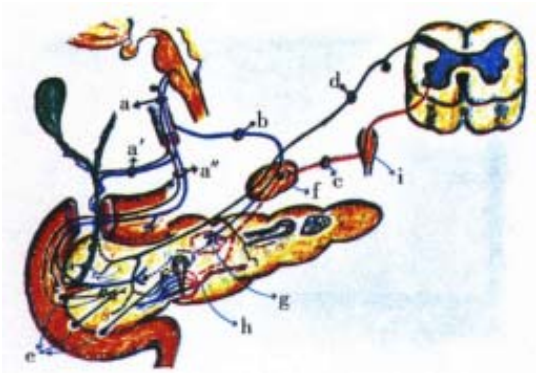

Figure 3 Complex nervous systems that innervate the extrahepatic bile ducts and the duodeno-pancreas. Vagal: Left or anterior vagus nerve (a). Hepatic branch (a'). Gastric branch (a"). Celiac collateral of the right or posterior vagus (b). Splanchnic-celiac: Pre-ganglionic fibre (c). C eliac ganglion with post-ganglionic neuron (f). Sensory-afferent: Afferent fibres and neurons of the dorsal roots ganglia of the spinal cord nerves (f). Enter o-pancreatic: Nerve fibres connecting the neurons of the enteric plexus with the pancreatic gland (e). Parasympathetic synapses in the intrapancreatic ganglion (g). Arterio-venous shunts of the pancreas' microcirculation system (h).Ganglia of the sympathetic chain (i)

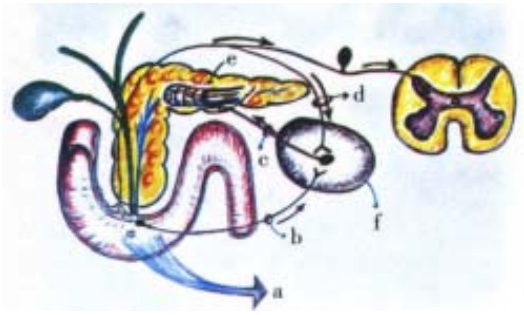

Figure 4 Physiopathogenesis of biliary acute pancrea titis. Activation of autonomic-arc-reflexes.
A: Sympatho-ischemic reflexes.
Trigger of the pancreatic revolver, the peri-Vaterian duodenum region (a). Entero-celiac reflex (b). Celiac-pancreatic reflex (c) giving the origin to the opening of the arterio-venous shunts in the pancreatic gland microcirculation. Celiac ganglia (f)

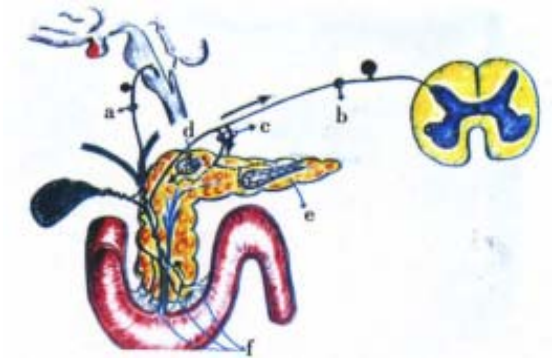

Figure 5 Activation of autonomic-arc-reflexes.
B: Pseudo-axonic reflex. Afferent nerve fibres of the vagal nervous complex (nodose ganglion) (a). Affere nt nerve fibres of the splanchnic-celiac nervous complex (b). Antidromic discha rge through a collateral nervous branch (c). Degranulation of mast cells (d). Pa ncreon units (e). Afferent nerve fibres of the peri-Vaterian duodenum, the trigger zone

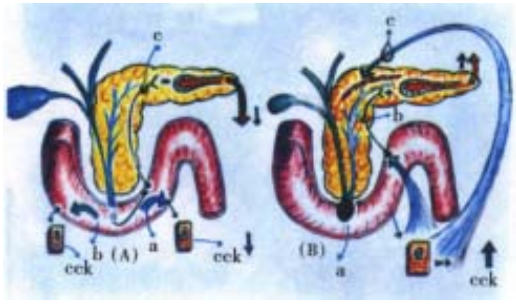

Figure 6 Disruption of the entero-pancreatic feedback loop.
A: Normal condition: Brake of CCK release.
Direct brake (trypsin, chymotripsin) of the CCK-releasing peptide and of the monitor peptide (a). Indirect brake (bilis). Stabilization of trypsin and chymot rypsin (b). Bile-pancreatic secretion activation of a negative duodeno-pancre atic reflex (c).
B: Bile-pancreatic duct obstruction condition
Loss of the normal bile-pancreatic secretion-evoked brake of CCK release. Stone impactation in the Vaterian papilla (a). CCK-induced paracrine-neural duode no-pancreatic reflex (b). CCK-elicited hormonal activation of pancreon units (c). Neural (b) and hormonal (c) mechanisms. Neural (b) and hormonal (c) pathway to the CCK-evoked supramaximal stimulation of the acinar component of the panc reon units.

Figure 7 Experimental mimicking of biliary acute pan creatitis in rats.
Modification of the classical Pfeffer method (closed duodenal loop), the temporary or short-term closed duodenal loop method. Filling of a duodenal loop (a) through the gastric antrum (b) with 7% sodium taurocholate and a few drops of meth ylene blue, at constant pressure. Height of liquid infusion column=110cm (c)

Experimental mimicking of biliary acute pancreatitis

At this stage, it seems relevant to analyze the data afforded by the experimental, surgical-induced acute pancreatitis of the Pfeffer method or of the closed -duodenal-loop[124-131]. This procedure, according to our view, offers a suggestive approximation to those conditions which usually interplay, in a clinical setting, in an episode of biliary acute pancreatitis. Indeed, the closed- duodenal-loop model offers a series of conditions that somehow mimick those frequently seen in human cases of biliary acute pancreatitis, e.g. the distention and chemical injury of the peri-Vaterian duodenum, the bile-pancreatic hypertension, the eventual reflux of the duodenal content into the bile-pancreatic ducts, the disruption of the entero-pancreatic feedback loop due to the exclusion of both bile and pancreatic juice from the intestinal lumen and the bacterial aggression (endotoxemia).

In recent experiments in rats with a short-term closed-duodenal-loop method, that we have modified from Orda *et al*[132] and De Rai *et al*[133], we have observed changes of the pancreatic gland that, taking into account the brevity of the experiments, were unexpected[134]. Indeed, after filling a duodenal loop with a 70 g/L taurocholate solution plus a few drops of blue-methylene, under a constant pressure of a 110 cm fluid column height, and keeping those conditions for only 3 min, the macroscopic evaluation of the pancreatic gland disclosed, 3 hours after, the presence of edema and spotty foci of acinar cell necrosis (Figure 7). Remarkably, the above changes were obtained under the total absence of any reflux of the duodenal content into the bile-pancreatic ducts. This crucial detail was verified by means of a constant visual observation of the duodeno-pancreas. Something we learned from the above test, is that it takes normally more than 20min, and sometimes even more than an hour, to appreciate the reflux of the duo denal content into the bile-pancreatic ducts. When this does indeed occur, a marked pancreatic edema is seen, and quite rapidly, a notorious hemorrhagic acute pancreatitis distinctly develops.

The above described results give further solid support to our contention that the irritation of the duodenum, at the level of the peri-Vaterian duodenum (trigger zone of the pancreatic revolver) is capable of activating autonomic-arc-reflexes. The latter, coupled with the changes evoked by the disruption of the entero-pancreatic feedback loop (bile-pancreatic obstruction) (Figure 6), probably explains, as we have already pointed out, the physiopathogenesis of the pancreatic lesions. This speculations of ours, that biliary acute pancreatit is might pivot around the activation of autonomic-arc-reflexes and a disruption of the entero-pancreatic feedback loop could perhaps be extended to explain, at least partially, the liver changes that recently have been pointed out by Iso gai *et al*[135] in human patients with biliary acute pancreatitis. Indeed, in the reports of these authors, a feature to be emphasized is that both the liver's histopathologic changes and the biochemical abnormalities were of the same order of magnitude in patients with and without impacted stones in the Vaterian region. This set of circumstances allow to infer that besides bile duct hypertension other factors (autonomic reflexes) might be at the basis of the above findings. An anatomical detail that gives support to the precedent contention is that of the rich density of nerve fibres in the hepatic hilum that we have put in evidence in macroscopic dissection studies in human cadavers[17-19].

Another observation that deserves to be emphasized because it affords additional indirect basis to presume an involvement of autonomic-arc-reflexes in the phy siopathogenesis of biliary acute pancreatitis is the one associated to a pure distention of bile ducts without the intervention of any intemperate maneuver or the irritation of a chemical agent. This is what suggestively happens with the acute pancreatic inflammation that have been reported in cases of hemobilia, accidental or iatrogenic (post-percutaneous liver biopsy)[14].

Preventive and therapeutic value of local anesthetics

All the above findings give coherent basis to consider an eventual beneficial effect of local anesthetics either as preventive and/or therapeutic agents of an episode of biliary acute pancreatitis. A long experience in conscious dogs with lidocaine spray in the peri-Vaterian duodenum[19,24,28,30,33] has convinced us, on the one hand, of their efficacy to interrupt noxious autonomic-arc-reflexes and depress the intrapancreatic cholinergic tone, and, on the other, of their relaxing capacity on both the main pancreatic duct outlet and the duodenal motor activity. The above anesthetic-induced changes make easier the catheterization of the Vater papilla in man. Consequently, the changes of it straumatization are significantly reduced. A detail to be emphasized is that of the atropine-like effects evoked by local anesthetics (procaine, lidocaine) in the duodenum and the sphincter of Oddi described by Varela-López *et al*[136,137], by Velasco Su-rez[138,139], Cottini[24] and by our group[24,28,30,33].

The forementioned authors have given convincing evidence of the local anesthetic value no treating clinical cases of sphincter of Oddi dysfunction or bouts of recurrent stone impaction in the distal common bile duct. The procedure most frequently used was of a duodenal infusion of

procaine clorhidrate (20 mL of a 10 g/L solution) or an oral ingestion of this anesthetic (0.2 g up to 1.2 g/24 h). With this latter approach, we succeeded in sparing a sphincterotomy in several patients with common bile duct residual stones following a laparoscopic cholecystectomy.

It is worth remembering that Albanese[69], Longo and Sosa Gallardo[64,65], Salazar[59] and Ochsner[70] have given solid accounts of the clinical therapeutic value of a temporary interruption of the autonomic-arc-reflexes by means of a local anesthetic of the celiac ganglia. This was experimentally ratified by the group of Waisman[58]. Indeed, these authors have shown, in rats subjected to a 24 h closed-duodenal-loop procedure, that those animals in which a single infiltration with lidocaine was performed had a significantly longer survival than the controls.

Local anesthetic bathing of the duodenum, namely at the level of the peri-Vaterian duodenum, or the anesthetic infiltration of the duodeno-pancreatic cleft, and/or of the celiac plexus, during an eventual laparotomy, constitute, according to our postulation, an efficacious means to prevent, or attenuate, the intensity of autonomic-arc-reflexes. Furthermore, they surely contribute to depress the intrapancreatic cholinergic tone. This is important in cases of an episode of biliary acute pancreatitis superimposed on a background of chronic alcoholism. They might do this through the interruption, on the one hand, of cholinergic impulses that course through the gastro duodenal wall, and, on the other, by blocking the CCK release from the "I" endocrine cells and the subsequent evoking of duodeno-pancreatic reflexes[18,19,25,26,63,140]. The latter is suggestively supported by the recent demonstration that vagal mucosal receptors are directly sensitive to CCK-8[141,142]. Besides, as it has been pointed out by Bj-rck *et al*[71] and Mc Cafferty *et al*[143], many other properties of local anesthetics, in addition to those of inhibiting action potentials by blocking sodium channels, are surely involved. The foregoing might explain the therapeutic success reported with intrarectally infused lidocaine in the treatment of ulcerative colitis[71]. In a recent report[144], it has been shown that in patients subjected to ERCP and therapeutic endoscopy (e.g. sphincterotomy, stone removal, etc.) and randomly assigned to have ① 10 mL of 10 g/L lidocaine sprayed onto the ampulla before or after, or, ② saline, either pre or post ERCP, that local anesthesia applied to the ampulla before ERCP facilita tes cannulation of the ampulla and appears to reduce hyperamylasemia whether given before or after ERCP. When considering further experimental evaluation with local anesthetics, related to either the prevention or treatment of biliary acute pancreatitis, one should take into consideration the results recently reported in rats by Mc Cafferty *et al*[143]. Indeed, it is remarkable that the intrarectal administration of 0.5 mL of 25 g/L carboxymethylcellulose, containing lidocaine hydrochloride, at dosis ranging from 5 mg/kg to 100 mg/kg had induced a significative reduction of the colitic score and of the myeloperoxidase activity.

In recent experiments in rats with our "short-term-closed-duodenal-loop" model[134], we showed that previous bathing of the duodenum with lidocaine (20 mg/kg) reduced the histopathologic score of pancreatic necrosis observed in the control group. This was confirmed in a subsequent series[145]. It is our postulation that through the interruption of autonomic-arc-re flexes one could interfere in the release of cytokines at pancreas level[146-154]. This is also suggested by our recent findings in the opossum[155].

Concerning the variable effects of a local anesthetic (lidocaine) on exocrine pancreatic secretion according to the route of administration, e.g. intraduodenal *vs* intravenous, we have acquired a long experience in dogs equipped with a duodenal fistula (Thomas cannula) and tested in the conscious state[33]. From them, we have learned that spraying of the papillar zone (trigger of the pancreatic revolver) with lidocaine (50 mg each, 10 min for 2 h) induces a significant depression (60%) of the plateau levels of all secretin-induced parameters. Remarkably, and coherent with the anatomical details previou sly outlined, the above exocrine pancreatic secretion changes were not observed with lidocaine spraying outside the papillar zone. Other suggestive findings were, firstly, that the intravenous infusion of the same amount of lidocaine (500 mg dissolved in 200 mL physiological saline = 12.5 mg/kg), did not modify any of the exocrine pancreatic secretion parameters and secondly, that when the intraduodenal lidocaine testing was performed in alcohol-fed dogs (2-year), the degree of the anesthetic-induced depression of the exocrine pan creatic secretion was less notorious (35%) than when carried out in controls (65%). We have interpreted this difference as a reflection in the ethanol-fed animals of a higher duodeno-pancreatic cholinergic tone. It is interesting that at clinical level this assertion has been ratified by Brugge *et al*[119]. Other considerations that seem relevant to point out is that of the extraneuronal effects of local anesthetics. In addition to our presumption that through the interruption of autonomic-arc-reflexes they interfere with the release of inflammatory mediators at pancreas level, they inhibit the phospholipase A2 enzyme and its interaction with its specific substrate: the cell membrane phospholipids. The latter was shown by

Aho *et al*[151] following their experiments on acute pancreatitis treated with a procaine solution (40 mg/kg).

Finally, and in order to complete the attempt to interrupt the evolving of the mechanism that we have considered as pivotal in the physiopathogenesis of biliary acute pancreatitis, it would seem logical to add to local anesthetics the simultaneous administration of pancreatic enzymes[75,83,86,87] and, eventually, of a calcium channel blocker[89,152]. Concerning the former, the oral and/or the intragastric-intraduodenal administration of pancreatic enzymes, might accomplish, on the one hand, the depression of the CCK release from the intestinal mucosa, and, on the other, the evoking of our previously described neural mechanism of "pancreon" inhibition, the negative duodeno-pancreatic reflex. In relation with calcium channel blockade, it is interesting to point out the recent finding of Hughes *et al*[153] in rats. Indeed, these authors have shown that the administration of diltiazem is assocated with significant reduction in serum TNF-alfa levels as well as amelioration of pan creatitis by biochemical and pathological criteria. They emphasize that TNF-alfa mediates tissue injury through the activation of inflammatory cells, the up regulation of adhesion molecules, the production of nitric oxide and the release of other cytokines and mediators of inflammation.

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