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Clinical pancreatology I: Pancreatic medical history

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Abstract
The present article and subsequent reviews will not be to report all what has been published, but rather to give an introduction samples that hopefully make the reader eager to read the whole article or articles with "a taste of clinical pancreatology in 2010". The main sources of literatures were PubMed, and the additional Journals such as Pancreas, Pancreatology and Journal of the Pancreas were also scrutinized. Only some full articles in almost all languages were included in the review, other articles, however, that were too superficial or too poor in other ways, were omitted, and the publications of non-human study were excluded.

Keywords: Pancreas, Billroth, stomach, pancreatitis, minimizing toxicity, peritoneal lavage, autodigestion, acute

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German Contributions
Throughout much of history, surgery of the pancreas was restricted to drainage of abscesses and treatment of traumatic wounds. At the turn of the 20th century under the impetus of anesthesia, such surgical stalwarts as Mayo Robson, von Mickulicz, and Sir Moynihan began to deploy laparotomy and gauze drainage in an effort to salvage patients afflicted with severe acute pancreatitis.

After the routine use of ether narcosis and surgical antisepsis, the evolution of surgery experienced fascinating and genuinely surgical technique-related advancements. Surgeons from Germany contributed strongly to the upturn of operative treatment in the second half of the nineteenth century. B von Langenbeck inaugurated in 1852 an osteosynthese device in a patient with pseudoarthrosis and opened up surgery also for softer areas. He is credited to be the very first in introducing the principle of fixateur externe. Theodor Billroth performed in 1873 the first extirpation of the larynx in a patient with a malignant tumor. Postoperatively, the patient was cared with an artificial larynx. The first successful resection of the distal stomach was also inaugurated by Billroth, in 1881, and was later called the Billroth II procedure. Rydygier from Kulm and Billroth from Wien are the first who successfully performed resection of the lower part of the stomach with anastomosis to the duodenum (Billroth I type of resection). In 1883, Theodor Kocher from Bern reported 101 cases of thyroidectomy, the largest single-surgeon experience. L. Rehn from Frankfurt did in 1887 the first successful suturing of a beating heart to repair a large stab wound. A. Braun, Königsberg, presented in 1892 his techniques of side-to-side anastomosis of the intestine to avoid a circular intestinal anastomosis. F. Sauerbruch from Breslau published in 1904 his thoracotomy chamber with space for two surgeons opening routine access to intrathoracic tissues protecting pulmonary ventilation during surgery. Walter Kausch from Berlin reported in 1912 about three successful pancreatic head resections for peripapillary cancer. The first successful pancreatic head resection was performed in 1909 in a patient with a cancer of the papilla. The patient survived for a long term [1].

Over the next thirty years, surgical intervention in severe pancreatitis became the therapy for choice, despite surgical mortality rates that often exceeded 50 percent. When the discovery of the serum test for amylase revealed that clinically milder forms of acute pancreatitis existed that

could respond to nonoperative therapy, a wave of conservatism emerged, For the next quarter century, surgical intervention for severe acute pancreatitis was rarely practiced. However, by the 1960s, conservative mortality rates for severe pancreatitis were reported to be as high as 60 to 80 percent, leading surgeons to not only refine the indications for surgery in severe acute pancreatitis, but also to consider new approaches. Extensive pancreatic resections for severe pancreatitis became the vogue in continental surgical centers in the 1960s and 1970s, but often resulted in high mortality rates and inadvertent removal of viable tissue. Accurate diagnosis of pancreatic necrosis by dynamic CT led to new approaches for management. Some surgeons recommended restricting intervention to those with documented infected necrosis, and proposed delayed exploration employing sequestrectomy and open-packing. Others advocated debridement early in the course of the disease for all patients with necrotizing pancreatitis, regardless of the status of infection. In the 1990s, however, a series of prospective studies emerged proving that nonoperative management of patients with sterile pancreatic necrosis was superior to surgical intervention, and that delayed intervention provided improved surgical mortality rates. The surgical odyssey in managing the necrotizing form of severe acute pancreatitis, from simple drainage, to resection, to debridement, to sequestrectomy, although somewhat tortuous, is nevertheless a notable example of how evidence-based knowledge leads to improvement in patient care. Today's 10 to 20 percent surgical mortality rates reflect not only considerable advances in surgical management, but also highlight concomitant improvements in fluid therapy, antibiotics, and intensive care. Although history documents the important contributions that surgical practitioners have made to acute pancreatitis and its complications, surgeons are rarely complacent, and the recent emergence of minimally invasive techniques holds future promise for patients afflicted with this "... most formidable of catastrophes" [2].

Acute pancreatitis in 20th century

The treatment of acute pancreatitis is based in decades long past but still have impact on the therapy of this disease today. The history identifies in retrospect the correct avenues of research and the blind alleys, and describes the ebb and flow of interest in various forms of management. Acquaintance with the work of previous investigators [3-5] may prevent the unnecessary rediscovery of old principles of treatment.

Principle of minimizing toxicity

It was clear from the outset that acute pancreatitis can be divided into the relatively harmless edematous or interstitial form and the initially often fatal necrotizing form. The necroses were thought to have a toxic effect on the course of the disease. However, the diagnosis of acute pancreatitis was very difficult. In the absence of laboratory tests and imaging procedures, clinical examination was crucial. Diagnostic pointers were a history of biliary colic, obesity, occurrence of the first symptoms after consumption of a large meal, severe cyanosis, and possibly hematemesis. Acute pancreatic necrosis was confirmed by the presence of initial shock [6], so the diagnosis became clear only late in the disease course. Once acute necrotizing pancreatitis had been diagnosed with the aid of the few means at hand, it was considered absolutely necessary to operate immediately and remove the necroses. The surgical treatment initially comprised opening the abdominal cavity to drain off an exudate [7]; it was only later that surgical interventions were performed on the pancreas itself.

One of the first to recommend surgical intervention for pancreatitis was the Chicago surgeon Nicholas Senn [8] cited by Rocha et al [9]. At that time, in the 1880s, pancreatitis was believed to be the response of the pancreas to duodenal disease. Senn recommended drainage and removal of all necrotic tissue. In what was probably the largest study of the time, Schmieden and Sebening [10] reported on 1,278 patients with acute pancreatitis, of whom 654 died, representing a mortality of 51 percent. The authors recommended operation over observation, but described the pancreas as an organ inimical to surgery. Right up to the 1940s, the main cause of death in acute pancreatitis was circulatory shock, undoubtedly a consequence of ignorance of the modern principles of intensive care medicine [11]. Even then, however, some voices warned against operating unnecessarily [12]. Morton [13] found that patients with interstitial pancreatitis, then known as “acute pancreatic edema”, were best left in peace. If operated upon, 27 percent of them died. Nordmann [6] gained the impression that a surgical procedure accelerated the development of necrotizing pancreatitis; this too was perhaps a consequence of the lack of intensive therapy. Parenchymal necrosis varied from 0 to 100 percent of the resected specimen, although at operation all the glands were considered totally or subtotally necrotic. In other words, a large number of surgeons found it hard to distinguish pancreatic and extrapancreatic necroses intraoperatively. The unsatisfactory results of operative treatment led to a move away from surgery at any price towards active conservative therapy [12]. This achieved the first decisive reductions in mortality. The lowering of the overall mortality of necrotizing pancreatitis from around 50 percent to about 25 percent was a great leap forward [14, 15].

In the 1960s and 1970s, the pendulum swung towards rapid operative intervention after diagnosis, but with distinct differences from country to country. In the UK, Watts [16] was the first to successfully perform resection of the head of the pancreas in hemorrhagic necrotizing pancreatitis. Early resection, right up to total pancreatectomy, was also recommended in France [17-20]. In Germany, the Mainz group first advised early operation, i.e. necrosectomy soon after admission [21], and later recommended delayed surgery in order to be able to at least approximately demarcate the necroses [22]. In the middle of the 1980s, Germany and many other countries followed the indications for surgical management und surgical goals formulated by Beger and his group [23]. The principles of

intensive care medicine began to become established. With regard to the pancreas, generous administration of fluids, particularly of human albumin, was a breakthrough [24, 25].

Peritoneal lavage

Corresponding with general clinical experience, it was observed that patients with acute pancreatitis and severe abdominal pain became pain-free immediately after the beginning of peritoneal lavage. This gave rise to the idea that toxic substances could be removed by means of lavage, and thus that lavage could represent a treatment not only for renal insufficiency (a complication of acute pancreatitis), but also for pancreatitis itself. Following the development of a dialysis procedure applicable to rats [26], continuous peritoneal dialysis performed as a treatment for acute experimental taurocholate pancreatitis in the rat significantly prolonged the mean duration of survival and reduced the mortality rate of this experimental disease [27]. Pancreatic ascites fluid given intravenously led to a sharp decrease in blood pressure in healthy dogs [28, 29]. The reason for this effect was unknown, but it was proposed to be partly due to histamine [30, 31]. In a similar experiment, ascites fluid given intraperitoneally also led to a decrease in blood pressure [32]. No follow-up studies were conducted to identify which toxic substance(s) actually led to the fall in blood pressure.

Eight randomized prospective clinical trials evaluating the influence of continuous peritoneal lavage in patients with acute pancreatitis were performed, but led to divergent results [33-40]. A meta-analysis, however, showed that this therapeutic procedure was not associated with any improvement in mortality or morbidity [41]. Furthermore, attempts were made to enhance the efficacy of peritoneal lavage by adding protease inhibitors to the lavage solution. However, neither of two clinical randomized trials showed any significant differences in mortality and morbidity [42, 43].

Principle of inhibition of secretion

Putting the pancreas at rest in acute pancreatitis became a cardinal principle in the 1960s and 1970s. The goal was either to inhibit gastric secretion, thereby indirectly influencing pancreatic secretion, or to inhibit pancreatic secretion directly.

Following reports of possible triggering of acute pancreatitis by cimetidine in the 1970s [44], animal experiments were carried out to ascertain whether this H_2 receptor antagonist could be harmful. Hadas et al [45] found that cimetidine increased the mortality of sodium taurocholate pancreatitis in rats tenfold. However, these findings could not be duplicated in other animal studies [46, 47]. A meta-analysis carried out several years ago [48] covered five randomized controlled trials written in English comparing the effects of H_2 receptor antagonists with those of placebo [49-53]. This meta-analysis [47] showed that cimetidine was not more effective than placebo in reducing acute pancreatitis-related complications and the duration of pain; rather, the use of cimetidine for acute pancreatitis could be associated with higher rates of complications and pain. Thereafter, inhibition of acid secretion was indicated only in severe acute pancreatitis to prevent bleeding from ulcers.

Atropine inhibits gastric and pancreatic secretions and exerts a spasmolytic action on the sphincter of Oddi. These properties would seem to make administration of atropine an ideal therapeutic intervention in acute pancreatitis. These effects cannot be achieved, however, with the dosage that can be administered, i.e. 4 × 0.5 mg/24 h. Higher dosages lead to adverse effects such as amplified symptoms of ileus, tachycardias and atropine psychoses; therefore, particularly after the sole controlled study [54] showed no favorable effect of atropine on the course of acute pancreatitis, this substance was no longer employed. Interestingly, very early reports of the complications of acute pancreatitis included pancreatic encephalopathy, but later, when atropine was no longer used, this adverse effect was not mentioned. Perhaps there is no pancreatic encephalopathy, and the complication that was observed was in fact an atropine psychosis.

Glucagon inhibits the ecbolic and to a lesser extent the hydrokinetic pancreatic secretion. After a first report on the action of glucagon in patients with acute pancreatitis seemed to show a beneficial effect [55], numerous other investigations were conducted. One study showed a favorable influence of glucagon on pancreatitis in pig, but this could not be confirmed in other animal models and species [56-60]. Later clinical controlled studies showed no beneficial effect on the course or the mortality of human acute pancreatitis [61-68]. Therefore, the administration of glucagon in acute pancreatitis was abandoned.

Calcitonin, like glucagon, principally inhibits pancreatic enzyme secretion [69]. However, several clinical studies showed no beneficial effect of calcitonin on the course of acute pancreatitis [70-72].

Principle of inhibition of autodigestion

After numerous studies had failed to show any significant decrease in the mortality of patients with acute pancreatitis under treatment with aprotinin [73], one team of investigators [74] was able to reduce the mortality rate considerably by administering a high dose of aprotinin in biliary and idiopathic acute pancreatitis. However, these findings were not confirmed in subsequent trials [75].

The failure of aprotinin, the first antiprotease drug to be used in clinical trials, was attributed to the molecular weight of the substance (6,500 Da), which was considered too high to permit uptake in pancreatic acinar cells and thus inhibition of intracellular proteases. A low-molecular-weight antiprotease, gabexate-mesilate (417 Da), was synthesized and showed promise. However, controlled studies found that this substance was not effective in preventing complications and mortality in acute pancreatitis [76-78]. A meta-analysis on the effectiveness

of gabexate-mesilate in acute pancreatitis confirmed that it did not affect mortality or the incidence of complications, including those that required surgery, and thus cannot be recommended [79].

Antifibrinolytics such as epsilon-aminocaproic acid and its derivatives, transexamic acid, and p-aminomethylbenzoic acid inhibit plasmin and trypsin and also increase the antitrypsin activity of plasma. In a single controlled study, epsilon-aminocaproic acid had no effect on the course of the disease [80].

Treatment of acute pancreatitis with fresh-frozen plasma, given to replenish important circulating proteins, particularly the naturally occurring antiprotease system, seemed to be successful in an uncontrolled study [81]. However, multiple clinical trials of low- and high-volume fresh-frozen plasma therapy showed no differences between treated and nontreated patients [82, 83].

Principle of inhibition of inflammation

Indomethacin inhibits prostaglandin production in vivo and is a very powerful inhibitor of phospholipase A_2 activity in serum in patients with acute pancreatitis [84]. In the 1970s, oral or intramuscular administration of indomethacin before or shortly after the triggering of an acute pancreatitis attack in rats markedly reduced mortality [85]. Several years later, in a controlled double-blind study, a Danish group achieved a clear reduction in the frequency and intensity of pain in patients with acute pancreatitis by administering indomethacin suppositories 50 mg twice daily for 7 days [86].

Summary of a century of management of acute pancreatitis

The greatest change in the treatment of acute pancreatitis is that surgery has been transformed from an immediate measure in necrotizing disease to a late intervention. Although large prospective, multicenter studies are still lacking, the pendulum has swung towards conservative treatment: across the world, conservative measures are tried first even in the presence of infected necroses. Surgical intervention is reserved for complications in the later stages of the disease. Peritoneal lavage has been discontinued owing to its lack of clinical efficacy. It is unfortunate that no investigations were carried out to establish which substances are responsible for the hypotensive action of ascites fluid; a new principle of therapy might have emerged. The principle of inhibition of autodigestion has been completely abandoned, at least in most countries. Endoscopic sphincterotomy has an established role, while cholecystectomy to prevent recurrence of biliary pancreatitis is undisputed but is still performed too infrequently [87].

Some stars in the pancreatology in 20th century

Joan Braganza

Dr. Joan Braganza, a world expert in the field of chronic pancreatitis, proposed a new template for its pathogenesis based on the role of free radical pathology, in particular the heightened but unmitigated oxidative detoxification reactions via cytochromes P450. Dr. Braganza has gone on to show how pancreatic damage in cystic fibrosis, acute pancreatitis and pancreatic cancer fit into the scheme, paving the way for new treatment modalities. She graduated in Bombay in 1966, having never seen a patient with chronic pancreatitis, but in January 1968 she found herself in a chronic pancreatitis referral unit at the Manchester Royal Infirmary. Its chief was Henry Howat who had introduced pancreozymin – discovered by Alan Harper and colleagues at the University – as an adjunct in the classical secretin test. The finding of secretory impairment was the only way to diagnose chronic pancreatitis pre-operatively. It was clear that chronic pancreatitis was equated with alcoholism, and that duct decompression or resective surgery was the mainstay of treatment for agonizing pain, in apparent support of the notion that calcifying protein plugs in the duct system were the seminal problem that led to strictures, compromising acinar function. In May 1969, soon after she had obtained the MRCP, domestic tragedy forced her to resign. Howat had an ongoing research program on gastric and pancreatic secretion in the anaesthetized cat in response to caerulein analogues. She synthesized the research data into an MSc thesis and wrote four papers for The Journal of Physiology. Her new finding was that Boots secretin – but not the purer gastrointestinal-hormone product from Stockholm – had a potent pepsin-stimulating effect which was not due to a non-specific increase in blood flow, as shown by cannulating the hepatic artery. Howat retired in 1976. Now, with responsibility for some 100 patients with chronic pancreatitis, she switched focus to its etiology. The threefold increase in annual admissions since 1955 was impressive, as was the younger age at presentation. Alcohol was not implicated in 50 percent of the cases. Instead, a threefold increase in the UK consumption of corn oil, essentially linoleic acid, had been documented. In chronic pancreatitis patients, there was a striking excess of copper and also bilirubin soon after secretin, and higher serum levels, too, of caeruloplasmin [88]. The idea that these changes reflected a compensation for excessive copper absorption, in line with a failing pancreas, was supported by rat experiments. The quest for an explanation led to London's Thomas Dormandy – a pioneer in the field of free radical pathology. In patients with chronic pancreatitis it was found high concentrations in secretin- stimulated bile or duodenal aspirate of several lipid-based products of free radical oxidation [89]. Now, the copper aberrations could be interpreted as indicating the mobilization of hepatic antioxidant defense. Moreover, secretin was known to increase the activity of microsomal cytochromes P450 (CYP) and bilirubin transferases in rat liver. Not only are CYP induced by alcohol and corn oil-rich diets, but they detoxify numerous xenobiotics, in the process generating reactive oxygen species and sometimes, as in paracetamol poisoning, also reactive xenobiotic species. Thus, it was proposed that pancreatic disease – not only chronic pancreatitis but also acute pancreatitis and cancer – may be a casualty of hepatic

"detoxification", when reactive material enters the gland in refluxed bile or duodenal juice [89]. David Dreiling was the first to see the potential merit of this hypothesis. Pharmacokinetic studies confirmed an induction of CYP – especially the CYP1 family – in the majority of patients, including those with idiopathic disease. This was rationalized by cigarette smoke constituents, but especially, by regular close exposure to occupational volatile hydrocarbons [90, 91]. These would strike the pancreas directly, bypassing the protective liver sieve. Thus, CP – and also drug-related acute pancreatitis and pancreatic cancer – might actually reflect direct oxidant damage via reactivated pancreatic CYP. That could be the reason why surgical diversion of toxic bile failed to abort attacks. Studies of habitual diets in patients with idiopathic chronic pancreatitis, by reference to a CYP1-induced control group on anticonvulsants, underlined their lower intakes of selenium, vitamin C and methionine. These micronutrients interact in the methionine transsulphuration pathway that yields glutathione and other detoxifiers. Several enzymes in this pathway are vulnerable to oxidative stress, as are the components of the signal transduction route towards exocytosis in the pancreatic acinar cell. Pain reduction was accompanied by a fall in serum 9,11,LA‘ and correction of the poor antioxidant status. These and other concepts were reviewed at a symposium that organized at the 1998 World Gastroenterology Congress in Vienna by Dr. Braganza [92]. Another high point was the finding – in collaboration with Maurice Super and Martin Schwartz – of an increased frequency of mutations in the cystic fibrosis transmembrane regulator (CFTR) gene in patients with chronic pancreatitis [93]. She record the invaluable input during her 25-year "radical journey" of numerous scientists – in physiology (Maynard Case, Sigrid RuMeettishauser), transplant immunology (Ian Hutchinson), surgical science (Anders Borgström), bacteriology (Louis Quesnel), pharmacy (Brian Houston, Martin Jones, John Fell, Frank Leach), biochemistry (Frank Steven, Jop Ubbink, Jessica Douglas, Lance Sandle, Iain Laing), pharmacogenetics (Jeffrey Idle), medical physics (Harbans Sharma), pathology (John Foster, Najeeb Haboubi, Iona Jeffrey), medical statistics (Linda Hunt, Roseanne McNamee, Chris Main), occupational health (Tim Lee, Ian Leck, Nicola Cherry), chemistry (Giocomo Sturniolo, George Smith, Philip Day), dietetics (Patricia Rose, Helen Worthington) and free radical pathology (Thomas Dormandy, John Gutteridge, John Butler) [94].

John A Williams

Dr John A Williams is one of the world's leading physiologists working on signal transduction mechanisms in pancreatic acinar cells. He is worldwide recognized for his contribution to many areas of pancreatology, especially the understanding of GI hormone regulation of pancreatic exocrine function. Having grown up in a small college town in Washington state with an interest in science and natural history he aimed towards a career in medicine, in part because he received a lot of social reinforcement when he mentioned it. He took the chance to enter a summer research program prior to starting medical school at the University of Washington. By a somewhat convoluted logic he was placed in an electrophysiology laboratory and proceeded to fall in love with laboratory research, then took a year off to do research in the middle of medical school after which his mentor, J Walter Woodbury asked him if he wanted to take another year off and earn a PhD. His thesis was on the electrophysiology of the thyroid. He did a 2-year stint in the U.S. Public Health Service at NIH to fulfill my military obligation where he carried out research on thyroid secretion with Jan Woolf. They then moved to Cambridge in the UK where he worked in the laboratory of Keith Mathews adjacent to another postdoc, Ole Petersen, who had come from Copenhagen and was recording intracellularly from pancreas. It then became apparent to that the exocrine pancreas was an ideal tissue with which to study regulated secretion in that it was homogeneous with one predominant cell type and that there were simple assays to measure the enzymatic activity of the secretory products. Petersen and Williams carried out a still (2010) cited study showing the release of intracellular calcium and its relationship to secretion in perfused pancreatic segments stimulated with CCK-PZ. After an enjoyable stay in Cambridge, Williams moved to San Francisco where a faculty position was waiting. Over the first 5 years there, his research work shifted almost entirely to the pancreas. He was able to bridge his interests by studying the effects of insulin on acinar cells and the action of gastrointestinal hormones especially CCK on the exocrine pancreas [95].

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