SPHINCTER OF ODDI DYSFUNCTION (SOD)

THE ENDOSCOPE IS MIGHTIER THAN THE BLADE: PLOWING THROUGH (SOD)

Medical Grand Rounds

June 5, 1997

J. Steven Burdick, MD
The University of Texas Southwestern Medical Center at Dallas

FORWARD

The Sphincter of Oddi is a complex series of muscle bundles which regulates the flow of 2-3 liters of bile and pancreatic fluids per day. Commonly, conditions arise in which the normal progression of these fluids are impaired due to an outflow obstruction. This obstruction may be anatomically fixed "papillary stenosis" or spasmodic "biliary dyskinesia". Overlap of these disease entities, inconsistent definitions, and different techniques of delineation among investigators led to the proliferation of terms used with reference to Sphincter of Oddi dysfunction Other terms included under Sphincter of Oddi dysfunction include biliary dyskinesia, post cholecystectomy syndrome, papillary stenosis, and papillitis. Diagnostically, the inability to pass a 3 mm Blake's choledochoprobe at open cholecystectomy was eventually replaced with endoscopic retrograde cholangiopancreatography and manometric pressure recording instruments. Few today would argue that the patient who suffers with pain and evidence of an obstructed bile duct with associated biliary dilation and abnormal liver function tests are definitively abnormal. However, the intermittent pain syndrome with variable findings of abnormal liver function tests, partial obstruction on cholangiogram or nuclear medicine studies, is more dubious. These intermittent findings have been felt secondary to spasm and have been difficult to reproduce manometrically. Additionally, these patients may have concomitant disorders of irritable bowel syndrome and, thus, the therapy is less consistent. Investigators note the similarities of intermittent spasm with prinzmetal's angina or esophageal spasm, while others remain unconvinced of its reproducibility or science. As 15-20% of patients continue to suffer from pain post-post-cholecystectomy undoubtedly, you will see a patient who continues to suffer from intractable pain after cholecystectomy which you recommended. Sphincterotomy therapy appears to have brought long lasting relief for some patients suffering from Sphincter of Oddi dysfunction. However, the evaluation and therapy of this disorder is not without its attending risks, with complications occurring after sphincterotomy in 21.7% of patients. Careful selection of patients for evaluation is, thus, advised. Enclosed is a critical review of the literature with emphasis on evidence based recommendations.

OUTLINE

1. History

2. Anatomy & Embryology

3. Physiology

4. Pathology

5. Clinical

Dr. Burdick is an Assistant Professor of Medicine at the University of Texas Southwestern Medical Center, Director of Endoscopy at Parkland, and Co-Director of the Fellowship Training Program. He attended medical school at the University of Oklahoma. Afterward he matriculated to the Medical College of Wisconsin to complete an internal medicine residency. Later he served as Chief Medical Resident and Associate Chief of Medicine before entering a three year fellowship in GI/Hepatology with third tier endoscopy training at the Medical College of Wisconsin. He was in private practice until joining the faculty on Sept. 16,1996. Dr. Burdick's interests in therapeutic endoscopy including ERCP and GI oncology including endoscopic ultrasound.

Awards since 1995:
Humanitarian Service Award - Mothers of Charity, 1995
delivered by Mother Theresa
American Gastroenterology Association President's Plenary Award, 1996
American College of College of Surgeons Patton Award, 1996

HISTORY

Our knowledge of the Sphincter of Oddi can retrospectively be divided into anatomy and physiology. The early contributions noted are the anatomical aspects of the sphincter. Later, around 1900, our knowledge of its physiologic properties increased. Ruggero Oddi, for whom the sphincter is named after, provided substantial physiologic contributions to this area.

Reference to the sphincter dates back to 1542 when Vesalius in Fabrica referred to the controversy over the insertion of the "meatus of the bile vesicle". His dissections revealed "that not the smallest portion of the bile vesicle was extended into the stomach except in one oarsman of pontifical trireme". The gallbladder and bile duct were described in detail with the vesicle traveling "down a little obliquely and is implanted in the duodenal jejunum". "Two little membranes which hang loosely at each side of the orifice easily yielding to the weight of the inflowing bile and obstructing the way least anything can flow back into the passage". (1) Our understanding of anatomy in reference to the biliary tree would remain largely static for the next 100 years until the anatomy of the sphincter was further elucidated by Francis Glisson (1597-1677), the Regius Professor of Physick at Cambridge and reader of anatomy at the College of Physicians. In Anatomica Hepatis he gave a description of a "ring-like structure which occupied not only the opening of the duct itself, but also the whole oblique tract". He concluded that this structure "prevents the regurgitation of contents into the bile duct". Further, he conducted experiments in which he watched the opening of the sphincter "contract by spontaneous motion". (2) Despite these accurate descriptions of the bile duct, the first pictorial representation of the confluence of the bile duct and pancreatic duct had been given to Godefridus (Govert) Bidloo of Layden in 1685, while physician to King William III of England. (3)

The major papilla is also known as the duodenal papilla or ampulla of Vater. The papilla is named after Abraham Vater who described the area is 1720 as a tubercle or diverticulum.(4) Vater additionally recognized the complex fusion of the bile duct and pancreatic duct. This observation was elucidated by the technique of injection which had previously been developed by Frederick Rusch as noted in Dilucidation valvularum, the Hague, 1665. Vater was unable to find spiral valves as previously described in the cystic duct by Heister. Of note, we currently recognize that his description of a tubercle is

seen in only 10% of cases. Giovanni Domenico Santorini (1681-1737) had previously described the pancreatic duct and bile duct confluence, but had described the area as valvular like structure. Santorini died in 1737 and his work was subsequently published in 1775 Septendecim Tabulae.(5) Thus some authors have felt the description of the ampulla should go to Santorini. Of note, previous authors had described this area before which include Samuel Collins in 1685 and Malpighi, who died in 1694. (6) (7)

The theory of gallbladder filling as a result of contraction of the sphincter can be derived from Jonas Baptisma Bianca's observation in Historia Hepatica, 1725. (8) In this manuscript he wrote in reference to the gallbladder "although a sufficient possibility of the contraction mentioned before might be given, nevertheless there is no assigned cause why, by turns and at unequal intervals, it should come into action ..... therefore, power of this kind must be sought from without; in some adjacent part, perhaps which applied strongly to it by turns, and pressing vigorously, could drive out the liquid contained therein and force it through its own paths". This theory would later be found correct.

The importance assigned to priority was not a preoccupation during this period of time. Questions of plagiarism and priority were much less uncommon in the 17th and 18th centuries. It was felt more important to define and describe these findings better than previous authors and not contribute to "cacographia", "Horribilis Cacophonia" and "Aequivocationes". (9) The stage was thus set for a brash fourth year medical student, who under the direction of his mentor, Marciacci, would perform further evaluation of the sphincter, defining its physiologic properties.(10) His views and work would contribute significantly to our knowledge of this area. However, his scholarship would later be questioned as he minimized Glisson's work as theories reportedly to gain priority.(11) Oddi published in "D'une Disposition a Sphincter Speciale de L'Ouverture du Canal Choledoche" in the Archives Italiennes de Biologie in 1887 as a fourth year medical student.(12) For this manuscript he undertook a series of investigations initially into the anatomical structure of the bile duct and then into the physiologic function of the sphincter. Oddi began by isolating the sphincter in which he made transverse and longitudinal sections of the bile duct at various levels. He performed these sections on various animals including dogs, sheep, oxen, pigs, and man. In all, he found a similar muscular arrangement. He concluded he had found an annular muscularity in

the intramural choledochus that "excludes the possibility that the above mentioned ring is merely an outcome of the duodenal musculature". He correctly theorized that the filling of the gallbladder was secondary to the contraction of the Sphincter of Oddi. "Bile tends to gather in the gallbladder in the biliary ducts of these animals without a gallbladder, contrary to the laws of gravity and hydrodynamics. The norms by which bile refrains from overflowing into the duodenum are unknown. Having demonstrated the existence of a sphincter-like arrangement of the muscles surrounding the lower edge of the choledochus, I believe this is obviously the mechanism that controls biliary flow". Oddi continued his work with a separate publications in 1888 determining the resistance of the sphincter and later focusing on the neural control of the sphincter identified at the spinal center relating to the vagal and sympathetic nerves.(13,14,15) Oddi had additionally published extensively on topics as diverse as obesity, pregnancy, pathways of afferent nerves in the spinal cord, and respiratory status with exercise. At the age of 29 he had been appointed as the Director of the Physiologic Institute of Geneva. Oddi's rise to eminence in research, however, would be short-lived. His career and life are open to interpretation and mystery as little biographical information is available. He retained this position for 7 years until 1901, when a series of catastrophic and ill understood events prompted his removal from this position and loss of his family. Oddi had been quoted later as having "lost the greatest affection that I've ever had and my scientific profession". Records of his wife and children cease during this period of time. There is thus speculation that his family may have disintegrated or been lost in a catastrophe. This coincided with Oddi suffering from a perforated appendix requiring emergent surgery in January, 1898. He required a second surgery in November, 1990 for an intestinal obstruction. A dangerous liaison with Stefano Capranica, the head of the Department of Physiology in Geneva, likely introduced him to drugs. Dr. Capranica was known as a drug addict who later in life underwent a mystic crisis and converted to Christianity donating all of his property to the Genovise curio in 1899. The donation of his property included the physiologic laboratory that Oddi had used for his research. A subsequent accounting revealed serious financial irregularities in the physiologic institute and likely contributed to Oddi's dismissal. Oddi elected to seek a three year contract as a physician in the Congo. In the early 20th century this area was sought out as an area to resolve inner peace. Additionally, from a medical standpoint it was noted to have interesting pathologic conditions and the position was well paid. The

collapse of Oddi's medical career and disintegration of his family life impacted on Oddi with subsequent depression. During this time he came under the care of a Belgium physician for treatment of his depression who converted him to Indian mysticism and drugs capable of altering mental status. The homeopathic preparation used was known as Vitalin and contained pure glycerin, sodium borate, ammonium chloride and alcohol. The Belgium service in the Congo later would judge him too ill or incompetent to adequately perform medical work and he was discharged. He would subsequently be employed intermittently in Spain and Italy, and during this time he would widely advocate the use of Vitalin. In 1906 he wrote a pamphlet promoting this substance.(16) Complications to a patient would occur attributed to Vitalin and authorities then charged him with abusive use of medical products and tried him for voluntary manslaughter. Shortly after this he would leave Italy and seek passage to Tunisia. Historically, it should be noted that this was a domain of the French Foreign Legion during this time. Nevertheless, he died there at the age of 49 in 1913.

Abnormal problems with the biliary tree were being encounter as surgery progressed. It was reported in 1935 "Many surgeons had encountered hepatic congestion, bile stasis, and dilation of the "biliary tree" without being able to demonstrate pathological changes to account for the obstruction."(20) Krukenberg in 1903 reported a case of "gall-stone colic" however, no calculus, infection, or stricture was found.(17) Meltzer in 1917 theorized that a spasm or increased tone of the sphincter of Oddi could act as a mechanical impediment and produce biliary colic and jaundice.(18) This theory was based upon physiologic work of the sphincter under normal circumstances. Different authors then reported the finding of hypertrophy of the sphincter of Oddi.(19) Strauss et al. in 1933 reported 22 cases of obstructive jaundice in which ampullary and duodenal inflammation appeared to be the only cause for the obstruction.(20) The following year Ivy and Sandblom reported on the abnormal motor responses of the gallbladder and the bile ducts in these patients concluding the choledochus was to blame. They coined the term biliary dyskinesia.(21) Others felt this term was not descriptive and thus other terms were utilized to describe the clinical presentations. This includes biliary dysynergia, post-cholecystectomy syndrome, papillary stenosis, papillitis, and others. Defining this entity became based upon the passage of a 3 mm choledochol probe known as a Blakes 3 dilator. The passage of such a device through the papilla and distal choledochus should not meet with resistance. Resistance or

tearing of the area was considered abnormal.(24,25) Unfortunately , therapy based upon this definition did not improve symptoms.(26) A new means of diagnosis would soon become available.

Manometric devices were being utilized in the diagnosis of esophageal disorders. These initial manometry equipment required a high perfusion rate of 6 cc per minute to deliver accurate tracings due to their high compliance. However, during peristaltic waves the rate of perfusion would be impaired or stop resulting in inaccurate data. A significant improvement was the low compliance water perfused system developed by Arndorfer and Hogan as reported in 1977. (22) This coincided with the rapidly developing field of endoscopy in the 70's and 80's. Relating this to the sphincter endoscopic retrograde cholangio-pancreatogram was first performed in the late 60's with endoscopic sphincterotomy in 1973. The Medical College of Wisconsin wishing to embrace this technology sent one of it's recent graduates a clinical faculty member named Dr. Geenen to Germany to bring this technique back to Milwaukee. Endoscopy was proliferating very rapidly and at that time it was typical for the Gastroenterology department to make their own catheters and other endoscopic devices. Shortly after the development of the low compliance water perfused system a catheter was developed for the biliary tree and utilized in the evaluation of the Human sphincter of Oddi in Milwaukee the following year in 1978.

A period of learning was required to recognize abnormal results and which parameters would influence therapy. Abnormal sphincter of Oddi was termed Dysfunction with two subsets. Papillary stenosis was utilized for the stenotic tight ampulla and biliary dyskinesia became the term used for spasm induced ampullary disorders.(27) However, in practice it is often impossible to separate the two entities. Therapy has traditionally been endoscopic but this choice of therapy was undoubtedly related to the therapeutic endoscopist who performed this procedure. The credibility of this technique and it's ability to predict long-term benefits to patients was aided through the publication of The Efficacy of Endoscopic Sphincterotomy After Cholecystectomy in Patients with Sphincter-Of-Oddi Dysfunction in 1989 in the New England Journal of Medicine.(28) Dr. Hogan was received many accolades for his work. He is one of only two who served as president of the American Gastroenterology Association and American Society of Gastrointestinal Endoscopy

receiving their highest honors respectively the Julius Friedenwald Medal and the Schindler Award.

Areas of controversy still exist. Dyskinetic or spasmodic sphincters can not always be reproduced manometrically and some classes of patients do not appear to benefit from endoscopic therapy. The technique for evaluation remains technically demanding and frequented by complications yet non-invasive techniques have not been accurate in recognizing who will benefit.

ANATOMY

The gateway of the bile and pancreatic ducts are the papillary orifice. The papillary orifice is located in the second portion of the duodenum, 10.5 cm ± 1.3 cm from the pylorus. The papillary opening in the second portion of the duodenum is variable and located 30% time in the upper one third, 50% of the time in the middle one third, and 12% of the time in the lower one third. The classification of the pancreatobiliary confluences have previously noted significant variations in the literature with a common channel reported between 5% and 98%.(29,30,31,32) Although, individual differences occur and thus patient selection may influence variances, differences among techniques of evaluation may account for these discrepancies. Previous evaluations have relied upon either histologic or radiographic interpretations. The simultaneous integration of radiographs, tridimensional casts, and histology from the same specimens revealed disparities within these techniques.(33) In particular, radiographs were unable to distinguish short common channel from separate orifices from the same papilla. The following are classifications of the anatomic variance:

TYPE	DESCRIPTION
Y	Short common channel measuring between 1.5 and 10 mm, representing 60%
Y	Long common channel greater than 10 mm, 4%
V	Very short common channel, less than 1.5 mm and represents 14%
U	Separate orifices within the major papilla, 20%
II	Separate papillas, 2%

The septum or frenulum's length at the orifice is thus the predominant influence on pancreatobiliary orifice at the major ampulla. For example, if the frenulum extends to the orifice, then a U type exists. If the frenulum extends to less than 1.5 mm or greater than 10 mm from the orifice, then a V or Y long channel respectively are formed.

Example: A common channel is thus seen in only 80% of cases. Opie's theory of biliary pancreatitis in which a biliary stone impacts at the ampulla resulting in bile regurgitation in the pancreatic duct with resultant activation of pancreatic enzymes is dependent upon this common channel theory.(34) Thus a significant criticism of this theory is the occurrence of pancreatitis in patients without a common channel. Intuitively, stones would impact in the narrowed area in the distal choledochus which is also referred to as Hand's notch which occurs at the upper border of the sphincter of choledochus. The movement of the septum or resultant edema may occlude pancreatic flow. Support for this model is based upon animal models in which the ducts are ligated resulting in pancreatitis. Interestingly, the duration of ligation correlates with the severity of pancreatitis supporting the role of acute intervention in biliary pancreatitis.

The pancreas develops from the fusion of the ventral and dorsal diverticulum in the foregut. Phisalix in 1888 reported that the human pancreas arises from two diverticuli of the foregut.(35) At five weeks in a 3 mm embryo a bud from the base of the liver diverticuli and a second bud from the dorsal side of the duodenum just opposite to the liver diverticulum arise. A fusion of these two diverticulum will later form the pancreas. The dorsal primordium grows faster and later becomes the majority of the pancreas. The ventral diverticulum develops into the gallbladder, bile duct, and ventral pancreas. The left ventral bud atrophies secondary to its location adjacent to the duodenum. The right ventral bud rotates backward adjacent to the posterior and inferior aspects of the dorsal pancreatic primordium. The ventral primordium forms the uncinate process and posterior inferior aspect of the pancreatic head which surrounds the distal common bile duct.(37) Fusion of the ventral bud and the dorsal bud results in the main pancreatic duct communicating with the major papilla. A segment of the dorsal duct develops into an accessory duct which communicates with the minor papilla in approximately 85% of humans. Nonfusion of the ventral and dorsal bud occurs commonly in 1-10% of the population. Nonfusion of the ventral and dorsal buds results in the main pancreatic duct communicating at the minor ampulla and the short ventral pancreas communicating at the major ampulla.(38) There are several variants of this congenital abnormality which is best described as a nonfusion abnormality. Pancreas divisum is a term commonly used to describe this abnormality. The relatively small aperture afforded at the minor ampulla associated with pancreas divisum is theorized to result in a partial obstruction of the pancreas.

This impaired flow may result in increased pressure on the pancreas with resultant pancreatitis.(39) This theory remains a controversial etiology for causes of pancreatitis.(40)

Two theories for development of sphincter musculature are noted. One theory believes the development of the sphincter was derived from the muscle of the duodenal wall. Support for this theory arose from the difficulty in separating the physiologic function of the Sphincter of Oddi from duodenal contractions. The second theory, and most accepted, is based upon embryologic development. The embryo, while only 26 mm in size, passes through the duodenal window composed of mesenchyme. The mesenchymal fibers then elongated and differentiated into muscle fibers starting at the window and progressed toward the ampulla.(41,42) This suggests the sphincter developed independently from the duodenal musculature. Comparative anatomy is supportive of this hypothesis. For example, in the possum the sphincter is entirely extraduodenal. Additionally, slips of duodenal muscle extend from the duodenal window to the sphincter serving to anchor the sphincter muscle for the support of this anatomical theory.

The Sphincter of Oddi consists of circular and longitudinal musculature and has three contiguous component: the ampullary sphincter, the sphincter choledochus, and sphincter pancreaticus.(43) The intramural link of the sphincter averages 14 mm, range of 7-12 mm. The extraduodenal extent averages an additional 5 mm with a range of 1-11 mm. The total length of the sphincter anatomically, therefore, measures, on average, 19 mm. However, the total length of the sphincter physiologically averages only 10 mm in length. This discrepancy may be explained in part by thinning or incomplete muscle codes at the ends resulting in insufficient functional capacity. The circular smooth muscle is completed in 70% of the cases and in the remaining 30% muscle fibers intermingle with the connective tissue fibers and mucus glands, the sacculi of Beale. Examples of variance with clinical importance would include annular pancreas, choledochocele, choledochocyst.

PHYSIOLOGY

Our knowledge of the ampullary sphincter is based on animal and human observations. In interpreting the information from these different species, it is important to be aware of variations in sphincter function. For example, CCK stimulation increases biliary flow in both herbivores and carnivores. However, the Sphincter of Oddi actions are resistive in carnivores and peristaltic in herbivores. CCK causes relaxation of the sphincter in humans, cats, and dogs, while CCK in herbivores causes contractions. Thus, the Sphincter of Oddi actions can be opposite in function among species.

The Sphincter of Oddi in man has two functions. The first is a resistive function to bile flow, thus diverting bile causing the gallbladder to fill. Secondly, the sphincter provides a barrier to inhibit reflux of duodenal contents into the bile duct and pancreatic duct. Evidence to support the sphincter's role in gallbladder filling is based on comparative anatomy and physiologic observations. The concomitant absence of the ampullary sphincter and gallbladder in the rat and horse suggest a teleology link. Hydrostatic filling of the bile duct after sphincterotomy in post mortem humans did not fill the gallbladder. Further, radionuclide labeled biliary flow in the gallbladder did not occur after sphincter ablation. Thus, one must be aware of prior intervention to the sphincter in ordering and interpreting hepatic nuclear medicine imaging as non-uptake of the gallbladder as a proper physiologic response post sphincterotomy. This data supports the argument of the sphincter role in gallbladder regulation.

The ampulla's function as a barrier to reflux is suggested through motility differences and complications occurring after sphincter ablation. For example, CCK8 in man results in duodenal peristalsis and relaxation of the sphincteric baseline pressure. The sphincter pressure, however, remains above the duodenum maintaining a gradient or barrier. The absence of food, debris, or bacterial in histologic specimens is well noted even back to Fabrica in 1542. Physiologically, the bile duct during fasting has antegrade waves or stripping waves to facilitate the removal of debris. Patulous changes to the sphincter created after sphincterotomy may provide further insight into the loss of this barrier. Restenosis and recurrent biliary stones are known complications after sphincterotomy. These stones are made of deconjugated bilirubin believed secondary to reflux of

bacteria and are quite atypical for stones originating in the gallbladder. Collectively, this data supports the role of the sphincter as a barrier.

The neural control of the sphincter is complex and not fully elucidated. Myenteric ganglia are present between the circular and longitudinal muscle layers with abundant nerve bundles found overlying the adventitia. Sympathetic innervation is derived from T7 through T10 and celiac ganglia. Parasympathetic innervation is derived from the vagus nerve. The vagus nerve is 90% sensory afferent and 10% efferent. The comparative influence of the autonomic nervous system vs. the enteric nervous system might be suggested through neuronal histochemical study. Efferent motor neurons of the vagus number in the hundreds which is compared to the millions of neurons in the enteric nervous system. Further vagotomy does not alter the fasting sphincter motility, thus supporting the role of the enteric nervous system over the autonomic nervous system. (45)

Multiple animal models are available for neurotransmitters and neurons present, but a paucity of human data is available. This lack of data is related to the difficulty in obtaining tissue from this area. Endoscopic biopsies have not revealed neurons and rapid degeneration of neuronal elements occur post mortem. An autopsy study of neuronal structural elements and neurotransmitters was performed shortly after death for individuals with and without pancreatobiliary disease. In this study, indirect immunofluorescence technique was performed for S-100 myelin network staining and neuro-immunofluorescent technique antibodies for various neuropeptides found in animal models. Bombesin although present in animal studies was not present in man. The following neurotransmitters were noted from the nervous system.(46)

TABLE
Intrinsic Neurons

Catecholamine
Nonadrenergic/noncholinergic
A. Vasoactive intestinal peptide
B. Peptide-histidine isoleucine
C. Neuropeptide Y
D. Somatostatin
E. Calcitonin gene-related peptide CGRP
F. Galanin
G. Enkephalin
H. Nitric oxide

The function of these neurotransmitters and their role in health and disease, however, are relatively unknown. Nitric oxide production results in sphincter relaxation in animal models and man resulting in reductions in sphincter basal tone.

The nitrous oxide production is thus inhibitory to Sphincter of Oddi function and the lack of nitric oxide production or impairment would, therefore, not allow relaxation. A potential model for impaired nitric oxide production is achalasia involving the lower esophageal sphincter. The inhibitory effectors are impaired or destroyed resulting in decreased nitric oxide production.(48) This syndrome may be considered under the disinhibitory neuron diseases, as there is impairment or loss of inhibitory motor neurons.

TABLE
Disinhibitory Motor Disease

1. Pseudo Obstruction
   A. Chagas
   B. Paraneoplastic
   C. Hirschsprung
   D. Idiopathic
2. Achalasia

An analogy may also be drawn with Hirschsprung disease in which the distal segment is tonically contracted and unable to relax. Electric nerve potential recordings reveal bursts of activity from excitatory neurons . The lack of inhibitory neural input is based on the ability to produce similar tracing in models when the inhibitory neurons are blocked.(49) This model can be compared with the neuronal tracings and pressure measurements from the Sphincter of Oddi. Sphincter of Oddi dysfunction is noted to have several abnormalities which include increase rates of peristalsis "tachyoddia" and elevated baseline pressures (basal sphincter hypertension). (51) The elevated baseline pressures became the accepted definition of Sphincter of Oddi dysfunction secondary to the improved response based on this parameter.(28) Tachyoddia, defined as an increased frequency or burst of phasic contractions, has not produced the sustained responses to therapy and therefore has not become as accepted as direct therapy, but is frequently seen. In Sphincter of Oddi dysfunction the administration of CCK produces a paradoxical response.(51) The baseline pressure becomes elevated and bursts of phasic waves occur. This may be explained by the loss of inhibitory effector neurons, thus relaxation is not seen. CCK has a direct effect on circular muscle which, without inhibitory controls, causes contraction resulting in paradoxical increase in basal pressure and spasm. The similarities of Sphincter of Oddi manometry in Sphincter of Oddi dysfunction is thus very similar to the tracing of Hirschsprung disease in which there is a loss of inhibitory effectors as a common pathway.

Sphincter of Oddi activity is the result and neuronal and enteric nervous system regulation mediated through excitatory inhibitory effectors. The inhibitory system appears mediated as a response of CCK induced neuronal relaxation causing nitric oxide production. Another inhibitor is secretin. Secretin is inhibitory to the sphincter function. However, in physiologic doses, only the pancreatic segment appears affected. The sphincter is additionally influenced through reflexes. For example, the Sphincter of Oddi is inhibited with increased gallbladder wall tension. In comparison, low gallbladder wall tension causes an increase in sphincter baseline tone. The bile duct wall tension appears to have similar reflux models to the gallbladder upon influencing sphincter response. These effects can be blocked with lidocaine or tetrodotoxin.

The Sphincter of Oddi pressure as measured above the duodenal pressure is referred to as baseline pressure. Contractile waves are

termed phasic waves with their amplitude frequency and propagation recorded. Waves seen propagating from the duodenum to the liver hilum are termed retrograde waves. Waves which propagate to the duodenum are termed antegrade. Waves may propagate in both directions simultaneously.

Sphincter activity is integrated with the inter-digestive phases 1, 2, and 3. In phase 1 we observe quiescence with consistently elevated baseline sphincter tones. In phase 2 irregular phasic waves with increasing frequency and regularity are noted. In phase 3 the migrating motor complex has antegrade propagating contractions and maximal frequency. The Sphincter of Oddi phase 3 response generally precludes are the duodenal propagating peristalsis response. Inter-digestive phases interrupted with food intake, which inhibits baseline pressure and phasic wave amplitude, facilitating biliary and pancreatic flow. Initially, attempts to measure for stenosis included the interoperative passage of a 3 mm Blake's dilator for the sphincter choledochus and a 2 mm lacrimal probe for the sphincter pancreaticus. Based upon the findings of tearing or resistance, it was declared stenotic and intraoperative sphincteroplasty was performed. The response to this evaluation and therapy was suboptimal. During this period of time manometric evaluation became available with the advent of the low compliance water perfused system. Manometry recordings could then be performed intraoperatively, transcystic, transhepatic or retrograde with ERCP.

The baseline pressure is defined as the pressure between phasic waves sustained for 20 to 120 seconds. Generally this wave form is read in the mid-expiratory phase. Some investigators prefer the end respiratory phase taking the mean of the lowest sustained elevations. Selective cannulation of the bile or pancreatic duct is required with position confirmed radiographically and/or with aspiration of the bile or pancreatic fluid. The pressure is recorded in the duodenum and within the desired duct with sphincter pressures obtained at interval pull through of .5 to 1 mm in 2 or more radial axis around the catheter.

Normal values have been obtained from 50 volunteers.(52) These evaluations were repeated on 2 occasions in 10 subjects and found to be quite reproducible. This study and others have established normal values for intraductal pressure, basal sphincter pressure, and phasic wave parameters to three standard deviations. The

pancreatic duct is noted to have higher pressure than the common bile duct, but the difference is not statistically significant.

Manometry in Normal Individuals

	ERCP #1	ERCP #2
Duct	6.7 mm	7.1 mm
Basal Pressure	18.9	17.6
Phasic Pressure	133.5	124
Duration	4.8 sec	5.0 sec
Frequency	5.5 /min	5.7 /min

n=10 CBD only

Digestive Diseases & Sciences 90 pg 38

SO Manometry

	CBD	PD
Duct	7.4	8.0
Basal	16.2	17.3
Phasic		
Amplitude	136.5	127.5
Duration	4.7 sec	4.8 sec
Frequency	5.7 /min	5.8 /min

20 patients

Digestive Diseases & Sciences 90 pg 38

SO Manometry Normals

	CBD	PD
Phasic		
Antegrade	34 (0-70)	35 (10-70)
Retrograde	11 (0-40)	12 (0-40)
Simultaneous	55 (10-100)	53 (10-90)

20 patients

Digestive Diseases & Sciences 90 pg 38

PATHOPHYSIOLOGY

The ampullary sphincter may become involved with inflammation, neoplasia or have anatomical distortion. Although some prefer to define Sphincter of Oddi dysfunction as purely a benign disease, roughly 5% of patients referred for evaluation will be found to have a neoplastic process.(53,54) The importance of biopsy should not be overlooked in this setting. Endoscopic biopsies are typically limited to the mucosa and occasionally some submucosa, but after sphincterotomy a more direct biopsy can be obtained. Thus, endoscopic biopsy to assess sphincter fibrosis are generally not technically possible with endoscopic techniques. In patients with sphincter of Oddi dysfunction endoscopically obtained ampullary biopsies of mucosa and submucosa have yielded chronic inflammatory changes in 30 out of 67, and rarely acute inflammation or ulceration in less than 5%.(54) Surgical septectomy specimens note chronic inflammatory change usually associated with fibrosis which extends transmurally into the sphincter. Circular muscle bundles become separated by collagen bands with chronic inflammatory changes. Others have reported hypertrophy/hyperplasia and adenomyosis.

What causes these changes? The passage of stones appear to be a major contributing factor. Several papers have noted histologic change of the papillitis after choledocholithiasis. For example, in patients who are noted to have acute pancreatitis associated with gallstones and later fecal recovery of gallstones, acute papillitis is a noted surgical finding. (55) Further support for the stenotic ampulla from gallstones may be obtained from careful chemical analysis of T tube fluid post cholecystectomy. T-tube aspirates were obtained from patients with a common channel and ampullary patency on cholangiogram. Pancreatic isoenzymes were measured from the T tube aspirates in 3 different sub-groups of patients. The sub-groups included uncomplicated gallstones, common bile duct stones, and gallstone pancreatitis. After a test meal to stimulate pancreatic output, they are re-evaluated. Pancreatic amylase was increased in patients who had previous common bile duct stones and gallstone pancreatitis. The relative outflow obstruction of the ampulla is presumed to cause reflux of pancreatic juice into the hilum.(56) From this histologic data and physiologic data , the passage of stones through the common bile duct is likely associated with sphincter stenosis.

Infections are associated with inflammatory ampullary changes. This previously had been noted with infected bile and strongyloides. In impaired immune systems such as AIDS, there are noted multiple opportunistic infections. AIDS has been associated with intrahepatic ductal changes, papillary stenosis, and diffuse disease involving the papilla, extrahepatic bile duct, and intrahepatic bile duct.(57) Biopsies obtained from the ampulla and have noted crypto sporidium in up to 40-50% of patients with these conditions. The outbreak of crypto-sporidium diarrheal disease in Milwaukee in 1993 was followed by an increased presentation of AIDS related biliary disease, particularly in patients with CD4 count of less than 250.(58) However, a direct cause and effect relationship has not been shown. Other opportunistic infection could be suggested including cytomegalovirus and mycobacteria disease but, share the same criticisms as cryptospordium with a lack of cause and effect.

The duodenal wall and the angulation created results in increased resistance and pressure. The duodenal wall thus contributes to the ampullary sphincter pressure. Periampullary diverticuli are seen in 10% of patients. These diverticuli may impinge upon the duct and cause obstruction rarely. Pancreatitis has been noted to cause inflammatory change and resultant fibrosis. Additionally, complications of pancreatitis would include pseudocysts which can cause obstruction of the ampullary area.

Sphincter of Oddi Diseases

1. Lithiasis and microlithiasis
2. Inflammatory
3. Neoplastic
4. Anatomic
   a. Pseudocysts
   b. Diverticular
5. Infections
   a. Bacterial
   b. Parasitic
   c. Viral
   d. Mycobacterial
6. Muscular hyperplasia/ Hypertrophy
7. Adenomyosis

Sphincter of Oddi normal patterns and values were thus established in healthy volunteers. Patients who continued to suffer abdominal pain post-cholecystectomy without a cause became the focus of evaluation. Roughly, 10-20% of patients continue to suffer from their symptoms post-cholecystectomy. This subset of patients upon evaluation were noted to have the following motility pattern abnormalities and the motility patterns were compared. Normal values to 3 standard deviations had previously been obtained. These abnormal findings included an increased basal pressure, increased phasic wave amplitude, increased number of retrograde waves or discoordination, an increased phasic wave frequency tachyoddia, and a paradoxical response following intravenous injection of cholecystokinin (CCK). (51)

The randomization of patients to sphincterotomy versus sham procedure followed by careful analysis of these manometric findings suggested basal pressure elevation to predict a clinical response to sphincterotomy. In an effort to define the subgroups of patients who are evaluated clinical criteria were proposed. All patients have biliary pain these criteria included biliary tree dilation, biliary drainage of contrast at ERCP, and liver function tests.(27) Biliary dilation and biliary drainage of contrast in the supine position were previously established for endoscopic retrograde cholangiopancreatography.(62) It is noted that there is good inter-observer variation and reproducibility of normal and stenotic sphincters. However, dyskinetic sphincter may be inconsistently seen. This finding was noted when patients were randomized to sham sphincterotomy and reevaluated 3 months later. Dyskinesia could not be reproduced in 50% of the patients who were previously abnormal. (59)

Biliary Type I

1. SGOT and alkaline phosphatase greater than 2 times normal on 2 or more occasions.
2. Delayed Contrast Drainage from the common bile duct greater than 45 minutes in the supine position.
3. Dilated common bile duct of greater than 12 mm

Biliary Type II

1. Patient with biliary pain and one or two of the previously mentioned criteria

Biliary Type III

1. Patients have pain only about the abnormalities described in biliary groups I and II.

One should be aware that not all causes of alkaline phosphatase and SGOT are the result of the liver. For example, SGOT can released from muscle and recently I was referred a woman with intractable abdominal pain and isolated SGOT elevations with pain. A reversible ischemic defect was found on stress thallium. A subsequent coronary angiogram revealed diffuse right coronary disease. Thus laboratory results should not be a substitute for sound clinical judgment.

This classification system has limitations. It fails to separate patients with abnormal findings which may not meet these criteria from patients without any abnormalities. The most common criticism is the liver enzymes which both SGOT and AP must be two times normal on two or more occasions. Mild liver enzyme changes may not meet these criteria. The application of these criteria however can be predictive of long-term response to therapy. Biliary class I and II patients with basal hypertension have excellent long-term responses to sphincterotomy. However, the response of biliary type III patients in several series appears limited.

It has been noted that dyskinesia may be intermittent and, thus, not found manometrically, although strongly suspected clinically. It is thus appropriate to ask, "Is there a situation when manometry should not be performed?". (60,61) Limited data is available but in biliary type I patients only 85% of the time can an abnormal manometry tracing be obtained. However, the sphincterotomy response even when normal is near 90% . This correlates with the 90% response if manometry is abnormal.(61) Thus, manometry may be unnecessary in this group. However, abnormal manometric findings correctly predict response rates for type II and type III

patients with sphincterotomy. Therefore, empiric sphincterotomy should clearly be avoided in these subgroups.

Sphincterotomy Regardless of Manometry Results

Biliary	Manometry Abnormal	Response Tx	
		Abnormal	Normal
Type I	85%	90%	90%
Type II	55%	85%	35%
Type III	5-50%	55-65%	Less than 10%

Sphincter of Oddi response to endoscopic therapy is not always long-lasting. The gallbladder motility including response to CCK has been shown to abnormal in irritable syndrome. The poor response to sphincter of Oddi therapy was been linked to concomitant symptoms of irritable bowel syndrome. Soffer and Johlin found SOD in the sphincter choledochus in 215 patients who were treated with sphincterotomy. 26 of 215 patients with Sphincter of Oddi dysfunction treated with biliary sphincterotomy failed to improve. Twenty -five of the 26 patients were later found to have pancreatic sphincter hypertension and were treated with septotomy. Nine patients remained symptomatic. Six of the nine who failed response to septotomy and seven of the sixteen who improved were evaluated with duodenal-jejunal manometry. Manometry was abnormal in four of the six patients who failed septotomy but present in only 1 of seven who benefited from septotomy.(64) A second group noted the abnormal response to cholecystokinin was present predominately in patients who additionally suffered from irritable bowel syndrome.(65) Evans et al. noted 33% of their patients with SOD Class I and II fulfilled the modified Rome criteria for irritable bowel syndrome. They noted the typical response to CCK with relaxation and loss of phasic waves was not a consistent finding in their IBS subgroup as compared To SOD without irritable bowel syndrome. In their paper post-cholecystectomy pain was present in 42 consecutive patients. They were unable to obtain manometry in two patients and CCK challenge was not given to all patients. Manometry was abnormal in 8 Of 13 with IBS and 18 of 27 without IBS. The paradoxical response to CCK was seen in 5 of 12 with IBS but only 1 of 23 without IBS $p = 0.01$.

Acute pancreatitis has been associated with Sphincter of Oddi abnormalities.(60) Initially, investigators only evaluated the sphincter choledochus, but recently investigators have been finding frequent abnormalities in the pancreatic segment. The incidence of Sphincter of Oddi dysfunction in association with acute pancreatitis was 17/116 patients in one series.(72) Pancreatic manometry has been performed in patients with biliary pain. Elevated pancreatic sphincter pressure has been shown in 30-50% of patients with biliary type pain who had previously failed therapy. There are limited studies which have reported a response rate to pancreatic sphincter ablation in both acute pancreatitis and refractory pain settings. (69,70,71) This is an area of ongoing investigation at this time and not widely accepted. Few conclusive recommendations can be made for this form of pancreatic evaluation and therapy at this time.

Pancreatic Type I

1. Includes patients with acute recurrent pancreatitis with greater than two times elevation of amylase or lipase on two or more occasions.

2. Dilation of the pancreatic duct greater than 6 mm in the head, 5 mm in the body, and
3. Delayed pancreatic contrast time of greater than 9 minutes as evaluated on ERCP in the prone position.

Pancreatic Type II

1. Patients with pancreatic pain or recurrent pancreatitis and one or two of the previously mentioned criteria.

Pancreatic Type III

1. Includes patients with pancreatic pain only without any of the previous established criteria

Risks of Sphincter of Oddi Manometry:

We've discussed the benefits of therapy but one must consider the potential risks for any procedure. The main complication of Sphincter of Oddi manometry is pancreatitis. The rate of pancreatitis appears increased over diagnostic or therapeutic ERCP. Interpreting this data is difficult as injection, manometry, and therapy are often rendered in the same setting. Additionally, investigators have not always stated whether manometry was performed of the biliary or pancreatic sphincter, or both. The indication for the procedure will likely influence manometry of the biliary and or pancreatic sphincter. When pancreatic pain or pancreatitis is noted, the pancreatic sphincter is more likely to be evaluated. The risk of evaluation of the patients with a prior history of pancreatitis and elevation of the pancreatic sphincter appear to be a risk factors for complications.(66) Reviewing this literature, the definition of pancreatitis was variable among institutions. Hyperamylasemia is often seen after ERCP. Separating the chronic pain which some of these individuals suffer from the indications for the procedure is often difficult to separate. In order to develop a standard for post-ERCP pancreatitis a committee was formed with the following definition proposed.(68) Pancreatic type abdominal pain associated with amylase greater than three times normal occurring post-ERCP .The length of hospitalization and presence of complications was used to develop three class of severity.

Mild	2-3 days
Moderate	4-10 days
Severe	Greater than 10 days or the association of any of the following complications: pseudocyst, phlegmon, hemorrhage, ICU admission, surgery, or requiring any other intervention.

The unforgiving nature of the pancreas has multiple potential causes but trauma with manipulations due to multiple cannulations and over distention of the pancreas have been shown.(67) The pancreatic ductal system typically accepts up to 3 cc of contrast before acinarization occurs. Typically water perfused catheters with 3 lumens perfused at the rate of 0.25 cc per minute delivers 0.75 cc in 1 minute's time. acinarization would thus occur after 2-4 minutes of manometry within the pancreatic duct. It is known that

pancreatic intraductal pressures rise 15 mm Hg within 2 minutes of pancreatic sphincter manometry. Guelrud et al. in their study of normal controls did not report any complication.(52) He utilized pancreatic drainage with his catheter prior to removal. However, he did not perform amylase and lipase and a systematic follow-up to record complications was not used. Sherman et al. were able to reduce the incidence of ERCP induced pancreatitis with a modified catheter in which the fluid within the pancreatic duct was aspirated. (65)However, this catheter alteration comes at the expense of a recording type which may decrease it's accuracy. Additionally, this study demonstrated the increased risk of pancreatitis when manometry of both the pancreatic duct and bile duct was compared to biliary manometry alone. Others series noted an increased incidence of ERCP pancreatitis if the patient had a prior history of pancreatitis.(66)

Severity of Pancreatitis Associated with Manometry

	Mild	Moderate	Severe
Cattau	6.5%	0%	0.4%
Sherman	11.0%	2.6%	1.3%
Roiny	0%	6.8%	1.4%

Pancreatitis Post-ERCP

Indication	PD Cannulation	Pancreatitis Incidence
Pancreatitis	22	32%
No Pancreatitis	73	4%

Gut 1990 pg 621-624

Pancreatitis Risk Factors Sphincterotomy

Univariate	Power
Acinarization	<0.01
SO Manometery	<0.01
Hx ERCP Pancr.	<0.01
Hx Pancreatitis	<0.01
Female	<0.01

NEJM 96 Vol 335 pg 907-918

Pancreatitis Risk Factors Sphincterotomy

Multivariate	Power	Odds Ratio
suspected SOD	<0.01	5.01 (2.7-9.2)
young age	<0.01	2.14 (1.4-3.2)
precut	<0.01	4.34 (1.710.9)
difficult entry	<0.01	2.40 (1.1-5.4)
pancreatic inj	<0.01	1.35 (1.0-1.75)

NEJM 96 Vol 335 pg 907-918

Microtransducers have been placed in the bile duct and may allow prolonged ambulatory monitoring. Prolonged monitoring may allow attacks of pain which occur intermittently to be may be captured. These catheters are approximately 1.3 mm or 4 French in diameter and do not require perfusion. (73) These are compared to the 5 to 6 French catheters required for water perfused manometry. These devices have been placed through a T tube or endoscopically, but have been associated with pancreatitis which did not appear until greater than 24 hours post procedure. Additionally, these transducers are subject to baseline drift, fragile, and expensive. Thus, their use has been quite limited.

The difficulty in performing manometry and the risks have lead to the evaluation of provocative non-invasive testing. Several tests have been proposed. Morphine is known to cause increased phasic waves and elevated basal pressure. 20ug/kg of morphine intravenously elevated the basal pressure 26.6 mmHg. This is the equivalent of 1.4mg in a 70kg person. It was theorized that spasm of the sphincter created by morphine will cause a transient obstruction of bile flow with resultant pain and abnormal liver function tests. Unfortunately, it was not reliable. Secretin and CCK stimulate pancreatic and biliary flow. Secretin stimulates pancreatic secretion. Normally the pancreatic duct increases in diameter in response to secretin. However, a dysfunctional papilla under increased flow might dilate further than the normal dilation of 2 mm. The response of the pancreatic duct dilation can be followed under ultrasound. CCK is release following a fatty meal. CCK causes contraction of the gallbladder and increased biliary flow. However , in a stenotic papilla or a papilla with a paradoxical response to CCK biliary dilation could occur. Quantitative hepatobiliary imaging with measurement of biliary drainage from the bile duct and gallbladder ejection fraction have been evaluated for their usefulness as a non-invasive technique. The gallbladder function is linked to the sphincter by nerves in animals which can be abolished with lidocaine or tetrodotoxin. In humans when the gallbladder is distended the sphincter pressure is low. Previous studies have shown a decreased gallbladder ejection fraction with obstructions of the distal choledochus. Conversely increased gallbladder flow occurs with sphincterotomy. It is thus reasonable in theory that a low gallbladder ejection fraction would correlate with high sphincter choledochal pressures. Unfortunately, noninvasive testing has not been

correlated well with manometry. Gallbladder ejection factions were 41% in SOD patients versus 46% in patients with normal biliary manometry. The sensitivity of gallbladder ejection fraction was 33% with a specificity of 63%.(74) Isolated centers have reported small numbers with several of the above techniques. However, the results have not been duplicated at other centers and the numbers generated have been small.

ALTERNATIVE THERAPIES

1) Medical
2) Stent
3) Botulinum toxin
4) Surgery

Sphincterotomy is the accepted standard of therapy for Sphincter of Oddi dysfunction. The difficulty between distinguishing papillary stenosis from biliary dyskinesia and the history of surgical therapy for this disease likely lead to initial use of sphincterotomy. The excellent results in pain relief for Biliary Type I and II patients with long-term relief made few ask if another therapy would be of value. . However, sphincterotomy has significant risk acutely and now we are beginning to appreciate some long -term risks. Additionally, the Biliary Type III patients response to sphincterotomy is sub-optimal.

Other treatment options are available. Surgical therapy with sphincteroplasty and or with septectomy were the initial forms of treatment. They where limited in their diagnostic ability utilizing the choledochal and pancreatic probes to diagnosis SOD. The resultant alleviation of symptoms was suboptimal at 40% improved and less invasive means to diagnosis and therapy became available with endoscopic technique. Currently surgical options are being reinvestigated for cases which fail to respond to biliary sphincterotomy and recurrent pancreatitis.

Medical therapy may not cure Sphincter of Oddi dysfunction but may control symptoms. Few trials are available to compare outcomes in this patient population. Two classes of medications nitrates and calcium channel blockers are associated with reductions in basal

pressure. However, they did not reduce sphincter pressures to normal in patients with SOD. Sand et al utilized nifedipine in patients who would fit the biliary type II category, but did not perform manometry. Nifedipine diminished the number of days patients experienced pain $p< 0.05$ but, did not significantly influence a reduction in pain medications.(78) Nitroglycerin exerts a pronounced reduction in Sphincter of Oddi pressure. Several authors have noted a reduction in basal pressure and amplitude with unchanged phasic wave frequency. This effect has been used to separate papillary stenosis from dyskinesia and to allow extraction of stones without a sphincterotomy. Antispasmodic agents N-butylscopamine Buscopan and Hymecromone have reduced basal SO pressure with Buscopan having an additional effect of decreasing the phasic wave amplitude and pressure. Dipyrone (Metamizol) is a pyrazolone derivative which is an analgesic and spasmolytic drug with effects likely mediated through central and peripheral modes of action. It results in a reduction in basal pressure and frequency of phasic waves.(79)

Botulinum toxin is a potent inhibitor of the release of acetylcholine from nerve endings. Botox when injected into the lower esophageal sphincter of patients with achalasia reduced the LES basal pressure and improved symptoms.(50) The response appears short lived averaging 19 months before symptoms reoccurred. Currently the John Hopkins group is investigating this treatment for SOD. In an initial report sphincter pressure was reduced by 50 % in 2 patients. Unfortunately neither patient normalized their pressures or was afforded pain relief. (77)

Manometry requires skills and equipment not available universally. Additionally sphincterotomy may not offer relief thus endoscopic stenting in theory could reduce the pressure and avoid manometry. It was thought that a temporary trial of stenting may predict response to sphincterotomy. However, in practice the complication rate exceeded the complication rate for manometry and it should not be advocated. (80)

REFERENCES

1. Vesalius (1514-1564) Fabrica (1542) A.D.
2. Glisson F. (1597-1677) Anatomica Hepatis.1654.
3. Godefridus (Govert) Bidloo of Leyden Anatomia.1685.
4. Vater, Abraham. Dissertatio anatomica qua novum bilis diverticulum circa orificium ductus cholodochi ut et valvulosam colli vesicae felleae constructionem...1720; Wittenbergae, Lit. Gerdesianus, 4to.
5. Santorini, Giovanni Domenco. Septendecium tabulae quas nunc primum edit atque explicat itsque iddit de structura Parmensi universitae anatomes professor primarius etc. 1775; Parme ex regia typographia. Fol.
6. Collins S. A systeme of anatomy, treating of the body of man, beasts, birds, fish, insects and plants. Illustrated with many schemes, consisting of variety of elegant figures, drawn from the life, and engraven in seventy-four Folio copper plates and after every part of man's body hath been anatomically described, its diseases, cases and cures are concisely exhibited.1685.
7. Adelmann H. Marcello Malpighi and the evolution of embryology. (5 vols.) 1966: Cornell University Press.
8. Bianchus, Johannes Baptista. 1725. Historia Hepatica.
9. Pechlin, Johann Nicholaus: wrote under pseudonym Janus Leonicenus Veronensis. Metamorphosis aeseulapii et apollinis pancreatici.1673. Lugd. Batau:Apud Phillippum Bonum 8va.
10. Oddi R. "D'une disposition a sphincter speciale de l'ouverture du canal choledoche." Archives Italiennes de Biologie.1887;8:317-322.
11. Boyden E. The pars intestinalis of the common bile duct, as viewed by the older anatomists: Vesalius, Glisson, Bianchi, Vater, Haller, Santorienni, etc. Anat Rec.1936;66:217-232.
12. Modlin IM, Ahlman H. Oddi: The paradox of the man and the sphincter. Arch Surg 1994;129:549-556.
13. Oddi R. Sulla tonicita dello sfintere del coledoco. Arch Sci Med.1888;12:333-339.
14. Oddi R. Sul centro spinale dello sfintere del coledoco. Lo Sperimentale Sez Biologica.1894;48:180-191.
15. Oddi R. Sulla esiutenza di speciali gangli nervosi in prossimita del coledoco. Monitore Zooll Ital. 1894; 5:216-219.
16. Oddi R. Nuova terapia delle malatti d'infezione e delle cachessie maligne. Modo di prevenirle e curarle:La vitalina Gatchkowskj. Citta di Castello. 1906.

17. Krutzenberg H. Veber gallenblasen koliken ohne gallesteine. Koine Wechschr.1903;40:660.
18. Melzer SJ. Diseases of the bile ducts and gallbladder. Am J Med Sci. 1917;153:469.
19. Giordano AS, Mann FC. Sphincter of choledochus. Arch Path. 1927;4:943-957.
20. Best RR, Hicken NF. Biliary dyssynergia:Physiological obstruction of the common bile duct. Surg Gynecol Obstet. 1935;61:721-729.
21. Ivy AC, Sandblom P. Biliary dyskinesia. Ann Int Med. 1934;8:115-122.
22. Arndorfer DE, Stef JJ, Dodd W, Linehan JH, Hogan WJ. Improved infusion system for intraluminal esophageal manometry. Gastroenterology.1977;73:23-27.
23. Vondrasek P, Eberhardt G, Classen M. Endoscopic semiconductor manometry. Int J Med.1974;3:188-192.
24. Braash JW, McCann JC. Normal luminal size of choledochoduodenal junction as determined by probe at choledostomy. Surgery.1967;62:258-259.
25. Schein CJ, Beneventans TE. Choledochoduodenal junction stenosis in the post-cholecystectomy syndrome. Surgery. 1968;64:1039-1046.
26. Moody FG, Becker JM, Potts JR. Transduodenal sphincteroplasty and transampullary septectomy for post-cholecystectomy pain. Ann Surg. 1983;197:627-636.
27. Hogan WJ, Geenen JE. Biliary dyskinesia. Endoscopy. 1988;20:179-188.
28. Geenen GE, Hogan WJ, Dodds WJ, Toouli J, Venu RP. The efficacy of endoscopic sphincterotomy after cholecystectomy in patients with sphincter of Oddi dysfunction. N Engl J Med. 1989;320:82-87.
29. Fernandez-Cruz L, Pujol-Soler R. Etude comparative de la cholangiographie selection et de l'examen anatamo-pathologique du sphincter d'Oddi. Rev Med Suisse. 1978;98:548-552.
30. Delmont J. Le sphincter de Oddi:Anatomie traditionelle et anatomie functionelle. Gastroenterol Clin Biol. 1979;3:57-65.
31. DiMagno EP, Shorter RG, Taylor WF, Long VW. Relationship between pancreaticobiliary ductal anatomy and pancreatic ductal and parenchymal histology. Cancer.1982;49:36-38.
32. Barraga L, Pujol-Soler R, Vergneaux JP. La Region Oddi-enne. Anatomie millimetrique Press Med. 1971;55:2527-2534.

33. Flati G, Flati D, Porowstra B, Ventura T, Catarci M, Carboni M. Surgical anatomy of the papilla of Vater and biliopancreatic ducts. Am Surg. 1994;60:712-718.
34. Opie EL. The etiology of acute haemorrhagic pancreatitis. Johns Hopkins Hosp Bull. 1901;12:182-188.
35. Philsalix C. Etude d'un embryon humain de 10 millimetres. Arch Zool Exper Gen Hist Nat Morph Histol Evol Animaux Ser 2. 1888;6:279.
36. Odgero PNB. Some observations on the development of the ventral pancreas in man. J Anat.1930;65:1-7.
37. Suda K, Matsumoto Y, Miyano T. Narrow duct segment distal to choledochal cyst. Am J Gastroenterol.1991;86:1259-1263.
38. Kozu T, Suda K, Toti F. Pancreatic development and anatomical variation. Gastrointest Endosc Clin NA.1995;5:1-30.
39. Bernard JP, Sahel J, Giovannini M et al. Pancreas divisum is a probable cause of acute pancreatitis. A report of 137 cases. Pancreas. 1990;5:248-254.
40. Cotton PB. Pancreas divisum-curiosity or culprit. Gastroenterology.1985;89:1431-1435.
41. Schwegler R, Boyden E. The development of the pars intestinalis of the common bile duct in the human fetus, with special reference to the origin of the ampulla of Vater and the sphincter of Oddi. I. The involution of the ampulla. Anat Rec. 1937;67:441.
42. Schwegler R, Boyden E. The development of the pars intestinalis of the common bile duct in the human fetus, with special reference to the origin of the ampulla of Vater and the sphincter of Oddi. II. The early development of the musculus proprius. Anat Rec. 1937;68:17.
43. Schwegler R., Boyden E. The development of the pars intestinalis of the common bile duct in the human fetus, with special reference to the origin of the ampulla of Vater and the sphincter of Oddi. III. The composition of the musculus proprius. Anat Rec. 1937;68:193.
44. Boyden E. The sphincter of Oddi in man and certain representative mammals. Surgery. 1937;1:25.
45. Johnson. Textbook of Gastrointestinal Physiology. 1994.
46. Sand J, Jainioh FL, Nordbach I. Peptidergic innervation of human sphincter of Oddi. Dig Dis Sci. 1994;39:293-300.
47. Slivka A, Chuttani D, Carr-Lock DL. Inhibition of sphincter of Oddi function by nitric oxide. Carrier S-nitroso N-acetylcysteine in rabbits and humans. J Clin Invest.1994;94:1792-1798.
48. Mearin F, Movrelle M, Guarnu F, Salas A, et al: Patients with achalasia lack nitric oxide synthase in the gastro-oesophageal

junction. European Journal of Clinical Investigation. 1993; 23(11):724-8.
49. Wood JD: Electrical activity of the intestine of mice with hereditary megacolon and absence of enteric ganglion cells. American Journal of Digestive Diseases. 1973;18(5):477-488.
50. Pasricha PJ, Ravich WJ, Hendrix TR, Sostre S, Jones B, Kalloo A: Intrasphincteric botulinum toxin for the treatment of achalasia. NEJM. 1995;322:774-778.
51. Toouli J, Roberts-Thomson IC, Dent J, Lee J: Manometric disorders in patients with suspected sphincter of Oddi dysfunction. Gastroenterology. 1995;88:1243-50.
52. Guelrud M, Mendoza S, Rossiter G, Villegas MI: Sphincter of Oddi manometry in healthy volunteers. Digestive Diseases and Sciences. 1990;35(1):38-46.
53. Khan MAM, Thomas DM, Howard ER: Pancreatitis in childhood associated with villous adenoma of the ampulla of Vater. British Journal of Surgery. 1996;83:1211.
54. Ponchon T, Aucia, Mitchell R, Chavalla A, Borg R, Hedelius F: Biopsies of the ampullary region in patients suspected to have sphincter of Oddi dysfunction. Gastrointestinal Endoscopy. 1995;42(4):296-300.
55. Acosta JM, Ledesma CL: Gallstone migration as a cause of acute pancreatitis. NEJM. 1974;290:484-487.
56. Hernandez C, Lerch M: Sphincter stenosis and gallstone migration through the biliary tract. Lancet. 1993;341:1371-1373.
57. Cello JP, Chan MF: Long-term follow-up of endoscopic retrograde cholangiopancreatography sphincterotomy for patients with acquired immune deficiency syndrome papillary stenosis. The American Journal of Medicine. 1995;99:600-603.
58. Vakil NB, Schwartz SM, Buggy BP, et al: Biliary crypto-sporidiosis in HIV-infected people after the waterborne outbreak of cryptosporidiosis in Milwaukee. NEJM. 1996;334:19-23.
59. Thune A, Scicchitano J, Roberts-Thomson I, Toouli J: Reproducibility of endoscopic sphincter of Oddi manometry. Digestive Diseases and Sciences. 1991;36(10):1401-1405.
60. Sherman S, Troiano FP, Hawes RH, O'Connor KW, Lehman GA: Frequency of abnormal sphincter of Oddi manometry compared with the clinical suspicion of sphincter of Oddi dysfunction. American Journal of Gastroenterology. 1991;86(5):586-590.
61. Rolny P, Geenen JE, Hogan WJ: Post-cholecystectomy patients with "objective signs" of partial bile outflow obstruction: clinical characteristics, sphincter of Oddi manometry findings and results of therapy. Gastrointestinal Endoscopy. 1993;39:778-781.

62. Belsito A, Marta JB, Cramer GE, et al: Measurement of biliary tract size and drainage time. Radiology. 1977;122:65-69.
63. Evans PR, Dowsett JF, Bak YT, Chan YK, Kellow JE: Abnormal sphincter of Oddi response to cholecystokinin in postcholecystectomy syndrome patients with irritable bowel syndrome. Digestive Diseases and Sciences. 1995;40(5):1149-1156.
64. Soffer EE, Johlin FC: Intestinal dysmotility in patients with sphincter of Oddi dysfunction. Digestive Diseases and Sciences. 1994;39(9):1942-1946.
65. Sherman S, Hawes RH, Troiano FP, Lehman GA: Pancreatitis following bile duct sphincter of Oddi manometry: utility of the aspirating catheter. Gastrointestinal Endoscopy. 1992;38:347-350.
66. Rolny P, Anderberg B, Ihse I, Lindstrom E, Olaison G, Arvill A: Pancreatitis after sphincter of Oddi manometry. Gut. 1990;31:821-824.
67. Freeman ML, Nelson DB, Sherman S, Haber G, et al: Complications of endoscopic biliary sphincterotomy. NEJM. 1996;335:909-18.
68. Cotton PB, Lehman G, Vennes JA, et al: Endoscopic sphincterotomy complications and their management: an attempt at consensus. Gastrointestinal Endoscopy. 1991;37:383-393.
69. Toouli J, DiFrancesco V, Saccone G, et al: Division of the sphincter of Oddi for treatment of dysfunction associated with recurrent pancreatitis. British Journal of Surgery. 1996;83:1205-1210.
70. Gregg JA, Carr-Locke DL: Endoscopic pancreatic and biliary manometry in pancreatic, biliary, and papillary disease, and after endoscopic sphincterotomy and surgical sphincteroplasty. Gut. 1984;25:1247-1254.
71. Kelly SB, Rowlands BJ: Transduodenal sphincteroplasty and transampullary septectomy for papillary stenosis. HPB Surgery. 1996;9:199-207.
72. Venu RP, Geenen JE, Hogan W, Stone J, Johnson GK, Soergel K: Idiopathic recurrent pancreatitis: an approach to diagnosis and treatment. Digestive Diseases and Science. 1989;34(1):56-60.
73. Tanaka M, Ikeda S: Sphincter of Oddi manometry: comparison of microtransducer and perfusion methods. Endoscopy. 1988;20:184.188.
74. Kalloo AN, Sostre S, Meyerrose GE, Pasricha PJ, Szabo Z: Gallbladder Ejection Fraction: nondiagnostic for sphincter of Oddi dysfunction in patients with intact gallbladders. Clinical Nuclear Medicine. 1994;19(8):713-719.

75. Madacsy L, Velosy B, Lonovics J, Csernay L: Differentiation between organic stenosis and functional dyskinesia of the sphincter of Oddi with amyl nitrite-augmented quantitative hepatobiliary scintigraphy. European Journal of Nuclear Medicine. 1994;21:203-208.
76. Ruffolo TA, Sherman S, Lehman GA, Hawes RH: Gallbladder ejection fraction and its relationship to sphincter of Oddi dysfunction. Digestive Diseases and Sciences. 1994;39(2):289-292.
77. Pasricha PJ, Miskovsky EP, Kalloo AN: Intrasphincteric injection of botulinum toxin for suspected sphincter of Oddi dysfunction. Gut. 1994;35:1319-1321.
78. Sand J, Nordback I, Koskinen M, Matikainen M, Lindholm TS: Nifedipine for suspected type II sphincter of Oddi dyskinesia. The American Journal of Gastroenterology. 1993;88(4):530-535.
79. Brandstatter G, Schinzel S, Wurzer H: Influence of spasmolytic analgesics on motility of sphincter of Oddi. Digestive Diseases and Sciences. 1996;41(9):1814-1818.
80. Goff JS: Common bile duct sphincter of Oddi stenting in patients with suspected sphincter dysfunction. American Journal of Gastroenterology. 1995;90(4):586-589.