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Acute Idiopathic Gastric Dilatation With Gastric Necrosis in Individuals With Prader-Willi Syndrome

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Individuals with Prader-Willi syndrome (PWS) have excessive appetite with the ability to consume large quantities of food. Absence of vomiting and a high pain threshold are considered manifestations of the disorder. We present 6 patients with PWS with acute dramatic gastric distention. In 3 young adult women with vomiting and apparent gastroenteritis, clinical course progressed rapidly to massive gastric dilatation with subsequent gastric necrosis. One individual died of overwhelming sepsis and disseminated intravascular coagulation. In 2 children, gastric dilatation resolved spontaneously. Gastrectomy specimens—in 2 cases subtotal and distal, in the other with accompanying partial duodenectomy and pancreatectomy—showed similar changes. All cases demonstrated signs of ischaemic gastroenteritis. All specimens showed diffuse mucosal infarction with multifocal transmural necrosis. Vascular dilatation and small bifrin thrombi were apparent within the infarcted areas. These 6 women with PWS had acute idiopathic gastric dilatation. It is possible that a predisposition to acute gastric dilatation may be related to abnormal gastric homeostasis on a genetic basis. Understanding the mechanisms responsible for this event could increase the understanding of gastrointestinal and appetite regulation in individuals with PWS. Am. J. Med. Genet. 73:437–441, 1997.

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INTRODUCTION

We present 6 cases, with 2 deaths, of unexplained massive gastric dilatation in individuals with Prader-Willi syndrome (PWS). Three women with profound dilatation developed gastric necrosis. One other woman with gastric dilatation but without necrosis died of sudden cardiac arrest. Two girls with PWS developed acute gastric distention with subsequent spontaneous improvement without gastric sequelae. The occurrence of 6 cases of gastric dilatation in females with PWS with subsequent gastric necrosis in 3 individuals might indicate abnormal gastric homeostasis on a genetic basis. The presentation of this disorder in females only should be considered coincidental at this stage. Understanding the mechanisms responsible for this event could increase the understanding of gastrointestinal and appetite regulation in this syndrome.

CLINICAL REPORTS

Patient 1

A 36-year-old woman with PWS due to uniparental disomy was admitted to the hospital with fever, vomiting, and abdominal pain. Fluorescent in situ hybridization (FISH) studies using SNRPN probe for region A and GABRB3 for region B plus a chromosome 15 marker probe were performed. The presence of a 6.0 kb band and the absence of a 4.4 kb band detected by methylation was indicative of maternal disomy and consistent with the diagnosis of PWS. Five days before admission, mild, transient, midepigastric pain without fever, diarrhea, or nausea developed. The epigastric pain recurred intermittently for the next 2 days. One day before admission, the patient experienced vomiting associated with abdominal pain. The following day she noted her abdomen to be distended. Her vomiting continued, and she was referred to the hospital.

There was no history of diarrhea, alcohol use, gall-

stones, or peptic ulcer disease. She had a history of 45.4 kg gradual weight loss 5 years before admission. She was taking no medications. She denied ingestion of caustic substances or recent bingeing.

On examination the patient appeared acutely ill. Blood pressure was 90/60 mm Hg, heart rate was 120 beats/min, RR was 30/min, temperature was 38.5°C, weight was 55.4 kg, and height was 147.4 cm. She had evident PWS with abdominal distention and mild right midepigastric tenderness with voluntary guarding. There was no rebound. Her bowel sounds were hypoactive. Rectal findings were normal, and stool was guaiac negative. A nasogastric tube demonstrated guaiac-positive brown liquid. Her hematocrit was 54.6%; leukocyte count 37,500/cmm with 74% neutrophils, 10% bands, 13% lymphocytes, 2% monocytes. The platelet count was 230,000/cumm. Her amylase was 524 units/L. Blood urea nitrogen was 36 mg/dl and serum creatinine was 1.5 mg/dl. A plain film of the abdomen showed a nonspecific gas pattern. No free air was detected. Abdominal ultrasonography showed a dilated gallbladder with no evidence of gallstones. The pancreas was obscured by overlying bowel gas. An abdominal computed tomography scan demonstrated a distended gallbladder without gallbladder wall thickening. The head of the pancreas appeared large relative to the remainder of the pancreas, possibly due to focal pancreatitis. The stomach and proximal duodenum were distended to the level of the third portion of the duodenum. No mass was identified. No intraluminal contrast was seen. There was ascites in abdomen and pelvis. Oral intake was discontinued, and she was treated with antibiotics.

The patient's condition deteriorated. The day after admission, she had diffuse abdominal tenderness with involuntary guarding. Bowel sounds were absent. Her pulmonary status worsened, and she required intubation and mechanical ventilation as well as pressor support. Two days after admission, an exploratory laparotomy for a presumptive diagnosis of pancreatitis and acute acalculus cholecystitis was performed. At laparotomy, a grossly distended and necrotic stomach was evident. The necrosis extended from 2–3 cm distal to the gastroesophageal junction to the antrum. There was a focal perforation and subdiaphragmatic abscesses. She underwent subtotal gastrectomy with gastrojejunostomy, cholecystectomy, and jejunostomy tube placement.

Her postoperative course was complicated by adult respiratory distress syndrome, sepsis, low-grade disseminated intravascular coagulation, and prolonged intubation with mechanical ventilation. She has recovered fully.

Patient 2

A 23-year-old woman with PWS and deletion of 15q11-13 presented to the emergency department with mild diffuse abdominal pain and vomiting of recent onset. She denied alcohol use or recent food bingeing. She lived in an adult group residence where admission was based on documentation of PWS. Her food intake was supervised closely. She was taking no medications. Findings were reported as benign, and she was discharged with a diagnosis of viral gastroenteritis. She returned to the emergency department 14 hours later due to persistent vomiting and severe abdominal pain. At this time she was acutely ill with hypotension and tachycardia. She was afebrile. A radiograph of her abdomen demonstrated massive gastric dilatation and free air under the left hemidiaphragm. At laparotomy, she had a grossly distended and necrotic stomach and multiple subdiaphragmatic abscesses. Her abdomen was closed, and she was transferred to another hospital where she underwent a subtotal gastrectomy with gastrojejunostomy. Her condition remained unstable during the second surgical procedure. She died of sepsis and respiratory failure 1 day after the second surgery.

Patient 3

A 21-year-old woman with PWS presented to an emergency department with fever and abdominal pain of short duration. She lived in a closely supervised setting, and her weight had been maintained carefully over the past year. She was taking no medications. FISH analysis demonstrated SNRPN probes hybridized to both chromosome 15 in each of 10 metaphases. Southern blot analysis using probe PW71B (locus D15S63) with a Bgl IICfo I digest demonstrated an abnormal methylation pattern suggestive of the presence of maternal UPD. The results were consistent with the diagnosis of PWS. On examination she appeared acutely ill. Blood pressure was 100/60 mm Hg, heart rate was 136/min, RR was 40/min, and temperature was 38.3°C. Her abdomen was distended and rigid. She had a leukocyte count of 24,000/cumm with a marked left shift. Abdominal radiographs showed an abdomen wide air-fluid level consistent with a perforated viscus. Laparotomy demonstrated undigested food in her abdominal cavity. She had a perforation of the stomach with gastric necrosis beginning at the gastroesophageal junction and involving 80% of the stomach. The patient underwent a proximal gastrectomy with gastroesophageal anastamosis and pyloroplasty.

Postoperatively, she required total parenteral nutrition, mechanical ventilation, and a tracheotomy. A surgical reexploration of her abdomen for fever 3 weeks following her admission documented multiple intraabdominal abcesses from retained food.

Patient 4

A 37-year-old woman with PWS and deletion of 15q11-13 had a cardiac arrest at her residential group home. Clinical history and review of a photograph taken shortly before her death confirmed the diagnosis of PWS. She had been well and was taking no medications. Two days before her death she complained of a stomach ache and had watery diarrhea. Her primary care physician prescribed oral medication that transiently improved her condition. However, the next day she again had watery diarrhea and was incontinent of stool. The following morning she complained to another resident at the group home of not being able to fasten her pants because her stomach was bloated. She then

returned to her room, coughed up black-brown material, and collapsed. She could not be resuscitated.

Autopsy demonstrated a well-nourished woman of approximately 62 kg. There was marked distention of the stomach without ulcerations, induration, or obstruction. Cultures from the gastrointestinal tract were all negative for infectious pathogens.

Patient 5

A girl with PWS and deletion of 15q11-13 had 2 documented episodes of acute gastric dilatation at age 3.5 and 7 years. Clinical presentation and findings were consistent with the diagnosis of PWS. At age 3.5 years, she experienced abdominal pain, distention, and vomiting. On examination she was afebrile, although tachycardic and tachypneic. She was also pale and lethargic. A radiograph of her abdomen showed pronounced dilatation of her stomach with a large amount of food residue. Gaseous distention continued throughout the gastrointestinal tract, and there were several small fluid levels. She was treated with intravenous fluid, and a nasogastric tube was placed. A subsequent barium meal showed no evidence of malrotation and normal motility.

Patient 6

A 6-year-old girl with PWS and deletion of 15q11-13 experienced several episodes of sudden painful abdominal swelling within 1 year. Phenotype (as examined by one of the authors, R.H.W.) was consistent with the diagnosis of PWS. None of the episodes were associated with excess food intake, medication, or flu-like symptoms, and the patient did not vomit during any of the episodes. Her mother reported that the girl's abdomen "felt hard" during the episodes of distention, which all resolved spontaneously within 60 minutes.

Pathologic Findings

Gastrectomy specimens—in 2 cases subtotal and distal, in the other with accompanying partial duodenectomy and pancreatectomy—showed essentially similar changes. In all cases, the viable mucosa beyond the necrotic areas was remarkable for the presence of fibrin deposition and mucosal gland dropouts, features of ischaemic gastroenteritis (Fig. 1).

All specimens showed diffuse mucosal infarction with multifocal transmural necrosis. Vascular dilatation and small fibrin thrombi were apparent within the infarcted areas. Acute serositis without obvious fat necrosis was seen. The submucosal myenteric plexus appeared intact. In one case, the necrosis appeared limited to the proximal corpus, the other showing duodenal involvement. The viable mucosa beyond these areas was remarkable for the presence of ischaemic-like changes with fibrin deposition and gland dropouts. Ghostly outlines of mucosal glands were visible in many areas, with only mild inflammatory changes and no obvious perforation or granulation tissue, suggesting that the process was acute (24–48 hours duration). In one case, an area of preserved submucosa appeared fibrotic, but otherwise no evidence of previous injury was determined. Despite extensive sampling, no convincing causal agent could be found; in particular no vasculitis, infectious agent, major vessel thrombosis, embolus, or vascular malformation was seen. Evidence of volvulus or other cause of mechanical vascular obstruction was not apparent at surgery.

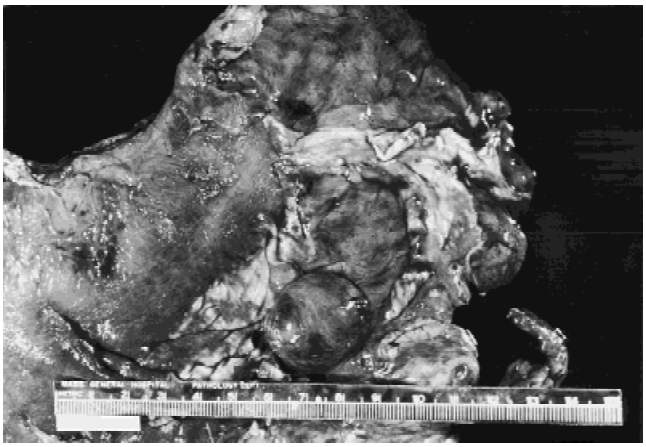

Fig. 1. Gastrectomy specimen with glistening red normal mucosa and abrupt transition to grey-black infarcted mucosa.

DISCUSSION

Two of these 6 women with PWS presented to emergency departments with symptoms suggesting a diagnosis of viral gastroenteritis. They had mild abdominal distention, were afebrile, had no peritoneal signs, and were discharged without intervention. A third woman presented acutely ill following a brief illness. In each of these women, symptoms began with vague abdominal pain and progressed to vomiting. Their symptoms all evolved rapidly to gastric rupture, peritonitis, and shock. Pathology in Patients 1 and 2 showed total gastric necrosis, whereas Patient 3 had 80% necrosis of the stomach.

These three women all had a history of morbid obesity (greater than 200% ideal body weight). Each had

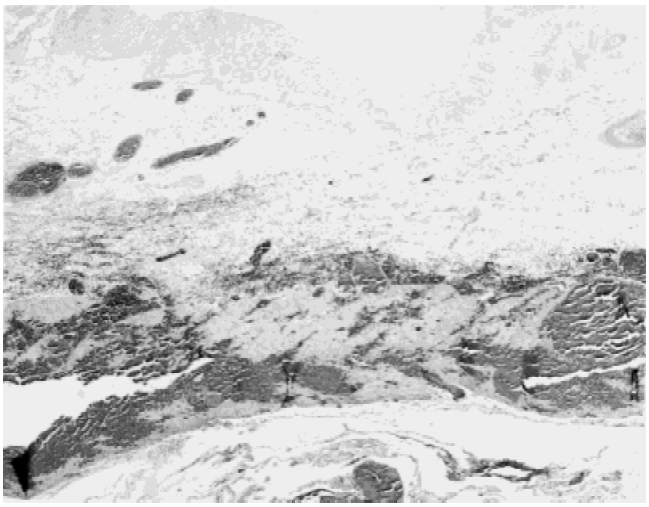

Fig. 2. Complete mucosal infarction without inflammation. The ghostly outlines of dead glands are preserved.

gradually lost more than 45 kg at an average rate of approximately 1 kg/week after their entries into separate group residence programs providing strict regulation of dietary intake. Although their weights tended to fluctuate, they had maintained weights below 140% ideal body weight for longer than 1 year.

An additional woman developed profound dilatation with catastrophic sequelae, although without gastric necrosis, whereas 2 girls developed apparent gastric dilatation but with spontaneous resolution. A medical evaluation of one of these girls (Patient 5) failed to uncover a cause for the dilatation. The other girl's dilatation (Patient 6), was clearly documented by parental observation, although not confirmed by medical evaluation. These additional cases add supportive evidence to the presence of this clinical phenomenon and together suggest the presence of a variable, occasionally benign presentation.

Total gastric necrosis is an extremely uncommon event. In a series of more than 23,000 autopsies, Cohen [1951] identified only 4 cases. Extensive gastric blood supply typically protects the stomach against widespread damage [Edlich et al., 1970]. However, when gastric necrosis does occur, it is catastrophic and often fatal. The reported causes of gastric necrosis are varied and include intrathoracic gastric herniation [Gibbons, 1968], volvulus of the stomach [Sellors and Papp, 1955], acute necrotizing gastritis [Strauss et al., 1978], ingestion of caustic material [Nicosia et al., 1974], and acute gastric dilatation [Patel et al., 1966; Kerstein et al., 1974; Willems et al., 1976; Koyazounda et al., 1985; Reeve et al., 1988] usually secondary to psychogenic polyphagia. Vascular compromise—such as that due to embolization of atherosclerotic plaques [Harvey et al., 1972], thrombosis of the stomach's major arterial supply [Cohen, 1951], and occlusion of gastric arteries by Gelfoam [Bradley and Goldman, 1976]—can occasionally produce the syndrome. However, the stomach is ordinarily protected from arterial ischaemia and gangrene due to its rich collateral blood supply from extensive intramural anastomoses [Babkin et al., 1943; Somervell, 1945]. In experimental preparations, both venous and arterial occlusion are required to produce infarction [Babkin et al., 1943].

One possible explanation for gastric necrosis in these cases is acute necrotizing gastritis. Several cases were described by Rosenthal and Tobias [1943], Behrand et al. [1954], and Nicosia et al. [1974]. The patients presented with abdominal pain and vomiting and were found to have dilated and grossly necrotic stomachs, with only small areas of normal mucosa. In these cases, no thrombosis or occlusion of the major vessels was found at operation, but a sharp line of demarcation between necrotic and healthy tissue at the pylorus was seen.

Acute necrotizing gastritis has been attributed to a variety of causes. Strauss et al. [1978] postulated that this condition derives from a spreading infection of the stomach that results primarily in necrosis and gangrene of the stomach rather than the abscesses seen in classic phlegmonous suppurative gastritis. In some of these cases, Gram-stained microscopic sections reveal that stomach mucosa is massively infiltrated with bacteria. Nevertheless, definitive proof of an infectious cause for these cases of gastric necrosis is lacking. No significant bacterial infiltration was seen on pathologic examination in our cases.

Another possible cause for the gastric necrosis in these particular women is acute gastric dilatation due to polyphagia. However, acute gastric dilatation associated with psychogenic polyphagia is often characterized by lack of vomiting. Massive distention of the stomach seen with psychogenic polyphagia can lead to a decrease in intramural blood flow when the intragastric pressure exceeds 30 cm H_2O [Edlich et al., 1970]. Evans [1968] showed that the stomach could be distended to a volume in excess of 4 L before mechanical rupture occurred. In one case of psychogenic polyphagia, a gastric volume of 15 L was recorded [Kerstein et al., 1974]. In the patients reported here, a markedly distended stomach was noted at the time of laparotomy. However, although occasional episodes of increased food intake are probable in Patients 1 and 2 and although there was significant abdominal contents of food at laparotomy in Patient 3, these woman were under strict supervision and there is no information to suggest bingeing before their clinical presentation.

Even with bingeing, individuals with PWS generally have a documented ability to ingest large quantities of food without experiencing abdominal pain or vomiting. In one study evaluating appetite behavior and gastric peptides, 9 subjects with PWS were presented with 100 sandwich quarters without restrictions on their consumption. Eight of 9 subjects ate continually during the hour food was available, with 1 subject consuming 100 sandwich quarters. No abdominal discomfort, gastric distention, or vomiting were reported by any of the subjects or an observer. Blunted responses of pancreatic polypeptide and gastrin [Zipf and Bernston, 1987; Wharton et al., 1988] have been detected. In addition, in a study to evaluate gastric emptying, preliminary results demonstrated no abnormalities.

The presence of vomiting and pain in these cases is distinctly unusual for individuals with PWS. In several cases in which children with PWS have received ipecac following the ingestion of potentially harmful agents, vomiting has not resulted (Wharton RH, personal communication). In fact, an inability to vomit and an increased threshold for pain are clinical signs supporting the diagnosis of PWS [Holm et al., 1993]. Therefore, in retrospect, the presence of these two clinical signs might have served as a warning of significant underlying gastrointestinal pathology.

The dramatic alteration in stomach muscle integrity from pronounced weight loss in individuals with PWS, although gradual, may have been a predisposing factor for gastric necrosis. Gastric necrosis was reported in individuals with weight loss resulting from anorexia nervosa [Abdu et al., 1987]. Several studies have suggested that the stomach undergoes atony and muscular atrophy directly following a period of starvation. [Evans, 1968; Markowski, 1947]. Rapid weight loss and relative malnutrition may predispose to the development of a direct neurogenic gastric paralysis [Scobie, 1973]. The sudden ingestion of food in this setting can

lead to paralysis of an already weakened stomach and acute dilatation followed by rupture.

An additional potential causes of gastric necrosis includes the ingestion of unusual substances. The initial assumption in Patient 2 was that she ingested a caustic substance believing it to be food. However, her autopsy did not demonstrate signs of caustic ingestion, and investigation at her residence produced no substance capable of causing her catastrophic event.

Therefore, these 3 women with PWS had profound gastric necrosis without a clear cause. Two girls had gastric distention without necrosis, and 1 had gastric distention with sudden death. These cases raise the possibility that a predisposition to acute gastric dilatation may be related to abnormal gastric homeostasis that is a feature of the syndrome. The variable clinical courses may suggest that older individuals who have undergone significant stretching of their stomachs over time may be vulnerable to severe sequelae, such as gastric necrosis resulting from distention.

PWS is associated with a paternal gene absence in chromosome 15q11-13, suggesting that clinical features of PWS are caused by a deficiency in one or more maternally imprinted genes in this region. Recently, a mouse gene that maps to the critical region of 15q11-13, *Snrpn*, encoding a brain-derived small nuclear ribonucleoprotein was shown to play a role in mRNA processing [Leff et al., 1992]. Further, SmN may function as a *trans*-acting factor promoting calcitonin gene-related peptide (CGRP) mRNA production. In addition to functioning as a hypothalamic peptide, CGRP is also believed to regulate gastrointestinal homeostasis. One may therefore speculate that abnormalities in gastric CGRP expression in individuals with PWS may predispose these individuals to unusual gastric homeostasis with resulting gastric injury.

SUMMARY

Vomiting, pain, and other more typical signs of gastric distress merit a prompt and vigorous evaluation in any individual with PWS to rule out a silent underlying disease process. In addition, severe gastric dilatation, especially in older individuals in whom there have been recurrent alterations in gastric size, should be considered a sign of possible impending abdominal catastrophe. The self-resolving symptoms present in the younger patients suggest that acute idiopathic gastric distention may be underreported and perhaps a not uncommon additional clinical feature in individuals with PWS.

ADDENDUM

Shortly after this manuscript was submitted a 27-year-old man with PWS was admitted to hospital due to vomiting and dehydration. Three days prior to admission he began to vomit and complain of abdominal pain. His vomiting and pain persisted for three days. He had no fever, diarrhea, or nausea. On examination he was an ill-looking man. His vital signs were stable. He was afebrile. A CT scan of his abdomen reported massive gastric dilatation. A biopsy of gastric mucosa demonstrated diffuse mucosal infarction with multifocal transmural necrosis. A subtotal gastrectomy was performed and the patient subsequently made a complete recovery.

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REFERENCES

Abdu RA, Garritano D, Culyer O (1987): Acute gastric necrosis in anorexia nervosa and bulimia. Arch Surg 122:830–832.

Babkin PB, Armour JA, Webster DR (1943): Restoration of the functional capacity of the stomach when deprived of its main arterial blood supply. Can Med Assoc J 48:1–5.

Behrand A, Katz AB, Robertson JW (1954): Acute necrotizing gastritis. Arch Surg 69:18.

Bradley E, Goldman ML (1976): Gastric infarction after therapeutic embolization. Surgery 79:421.

Cohen EB (1951): Infarction of the stomach: Report of 3 cases of total gastric infarction and one case of partial infarction. Am J Med 5:645–652.

Edlich RF, Borner JW, Kuphal J (1970): Gastric blood flow. Am J Surg 120:35.

Evans DS (1968): Acute dilatation and spontaneous rupture of the stomach. Br J Surg 55:940–942.

Gibbons WD (1968): Gangrenous intrathoracic stomach. Med J Aust 1: 4451.

Harvey RL, Doberneck RC, Black WC (1972): Infarction of the stomach following atheromatous embolization. Gastroenterology 62:469.

Holm VA, Cassidy SB, Butler MG, Hanchett JM, Greenswag LR, Whitman BY, Greenswag F (1993): Prader-Willi syndrome: Consensus diagnostic criteria. Pediatrics 91:398–402.

Kerstein MD, Goldberg B, Panter B, Tilson D, Spiro H (1974): Gastric infarction. Gastroenterology 67:1238–1239.

Koyazounda A, LeBaron JC, Abed N (1985): Necrose gastrique par dilatation gastrique aigue. J Chir 122:403–407.

Leff SE, Brannan CI, Reed ML, Ozcelik T, Francke U, Copeland NG, Jenkins NA (1992): Maternal imprinting of the mouse *Snrpn* gene and conserved linkage homology with the human Prader-Willi syndrome region. Nat Genet 2:259–264.

Markowski B (1947): Acute dilatation of the stomach. Br Med J 2:128–130.

Miller AL, Smith B, Rogers AL (1975): Phlegmonous gastritis. Gastroenterology 68:231.

Nicosia JF, Thornton JP, Folk FA (1974): Surgical management of corrosive gastric injuries. Ann Surg 180:139–143.

Patel J, Hepp J, Cormier JM (1966): La rupture spontanee de l estomac chez l adulte. Lyon Chir 62:121–124.

Reeve T, Jackson B, Scott-Conner C, Sledge C (1988): Near-total gastric necrosis caused by acute gastric dilatation. South Med J 81:515–517.

Rosenthal J, Tobias MJ (1943): Acute phlegmonous gastritis with multiple perforations. Am J Surg 59:117.

Scobie BA (1973): Acute gastric dilatation and duodenal ileus in anorexia nervosa. Am Med J 2:932–934.

Sellors TH, Papp C (1955): Strangulated diaphragmatic hernia with torsion of the stomach. Br J Surg 43:289.

Somervell TH (1945): Physiological gastrectomy. Br J Surg 33:146.

Strauss RJ, Friedman M, Platt N, Gassner W, Wise L (1978): Gangrene of the stomach: A case of acute necrotizing gastritis. Am J Surg 135:253–257.

Wharton RH, Synder JD, Wolfe MM (1988): Gastric motility and regulatory peptides in Prader-Willi syndrome. Prader-Willi Syndrome Scientific Papers. Abstract.

Willems PH, Kraft F, Morin A (1976): Les perforations et necrosis disatiques de l estomac de l adulte. Lyon Chir 72:175–180.

Zipf WB, Bernston GG (1987): Characteristics of abnormal food-intake patterns in children with Prader-Willi syndrome and study of affects of naloxone. Am J Clin Nutr 46:277–281.