“The past is only the present become invisible and mute.”
-M. Webb

James Cromie
8/16/10
Background: Acute Pancreatitis

- 250,000 hospitalizations annually
  - > 90% cases caused by EtOH or gallstones
  - Annual costs > $2 billion
- Acute Necrotizing pancreatitis (ANP)
  - 10-20% of cases
  - 12% mortality, sterile
  - 30% mortality, infected

Most common
- Choledocholithiasis
- Ethanol abuse
- Idiopathic

Less common
- Endoscopic retrograde cholangiopancreatography
- Hyperlipidemia (types I, IV, and V)
- Drugs
- Pancreas divisum
- Abdominal trauma

Least common
- Hereditary (familial)

Necrotizing pancreatitis

- **Two phase disease process**
  - Early phase < 14 days:
    - hypovolemia,
    - Systemic inflammatory response
    - Multiple organ dysfunction

- Late phase
  - Septic phase – infected necrosis in 40 – 70% of cases
    - Nonoperative mortality approaches 100%
    - Operative mortality 20 – 36%
History

- 1652:
  - Nikolaus Tulp, Dutch anatomist.
    - First recorded description of necrotizing pancreatitis. Postmortem exam on young man with “apocalyptic attack of abdominal pain”, fatal after 5 days. Pancreas found to be “rotten”

- Mid-late 19th century
  - Sporadic surgical case reports uniformly ending in death
  - 1886: Senn. Animal experiments on necrotizing pancreatitis.
    - “… gangrene as one of the diseases of the pancreas which should be treated by operative measures…”
1889

Reginald Fitz, Professor of Pathoanatomy at Harvard, student of Virchow and Billroth.

- First clinico-pathologic classification system.
- Surgery would not benefit patients with acute pancreatitis, and mortality is not prevented by “operative meddling”.

Later admitted that surgical debridement in some severe cases was beneficial.
1894:
- 48 y/o obese F, severe pancreatitis
  - Debridement of large pancreatic abscess
    1 month after onset
  - Placed iodoform gauze-wrapped drains, with repetitive changes.
  - Discharged 5 months later.

“In the acute stage, surgical treatment is not recommended, wherein patients have the propensity for cardiovascular collapse. If pancreatic apoplexy occurs, surgical treatment cannot help. Later, when we can prove that a purulent collection is arising from the gland, surgery is indicated.”
Early 1900’s

- **1927: Schmiedon, et al.**
  - 1278 cases of surgical management for ANP
  - Overall mortality: 51%
    - compared to 60% prior to surgical management
  - Advocated early surgical intervention within days of onset.

- **1929: Elman (surgical resident)**
  - Introduced serum amylase assay as a means of diagnosing pancreatitis
  - Surgical management of pancreatitis became extremely rare until 1950’s

Late 1900’s

- Extensive resections frequently found to have areas of viable tissue
- Evolution of necrosectomy – limited debridement, with multiple re-operations
- Advances in diagnosis and severity assessment

Evaluating severity / prognosis

- Ranson’s Criteria for prediction of severe acute pancreatitis
  - At presentation:
    - Age > 55yrs
    - Blood Glucose > 200 mg/dL
    - WBC > 16,000/mm3
    - LDH > 250 U/L
  - At 48hrs
    - Hct > 10% decrease
    - Calcium < 8 mg/dL
    - Base deficit > 4 mEq/L
    - BUN > 5mg/dL increase
    - Fluid sequest > 6L
    - PaO2 < 60 mmHg

Score > 3-4 =
Severe pancreatitis
Mortality > 16%

65 M necrotizing pancreatitis.

A = admission
B = 7 days later
C = 14 days later

1984:
> 90% diagnostic accuracy
Development of current open necrosectomy technique

- Hans Beger, Germany:
  - = 5.1 days from symptomatic onset
  - Surgery indicated for all patients with CT evidence of necrosis, regardless of infection
  - Overall mortality 8.1%

- 2005 collective experience:
  - 13.1% Mortality in 107 operated patients
    - > 25% required re-operative management
  - 6.2% mortality in non-operative patients

Infected necrosis

- Necrosis occurs in 10 – 20% of severe pancreatitis cases
  - Non-operative mortality approaches 100%
  - Infection arises in 40 – 70% of cases
  - > 50% necrosis associated with 8x increase rate of infection.

<table>
<thead>
<tr>
<th>% Extent of Necrosis</th>
<th>% Sterile</th>
<th>% Infection</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30 of the pancreas</td>
<td>56</td>
<td>10</td>
<td>&lt;.00001</td>
</tr>
<tr>
<td>30–50 of the pancreas</td>
<td>28</td>
<td>10</td>
<td>NS</td>
</tr>
<tr>
<td>&gt;50 of the pancreas</td>
<td>16</td>
<td>80</td>
<td>&lt;.00001</td>
</tr>
</tbody>
</table>

## Open Necrosectomy

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>No. Patients</th>
<th>No. Deaths</th>
<th>Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Borie et al(^{38})</td>
<td>1994</td>
<td>157</td>
<td>28</td>
<td>17.8</td>
</tr>
<tr>
<td>Armbruster et al(^{39})</td>
<td>1998</td>
<td>108</td>
<td>30</td>
<td>27.8</td>
</tr>
<tr>
<td>Bradley(^{40})</td>
<td>1999</td>
<td>176</td>
<td>23</td>
<td>13.1</td>
</tr>
<tr>
<td>Kriwanek et al(^{41})</td>
<td>1999</td>
<td>100</td>
<td>19</td>
<td>19.0</td>
</tr>
<tr>
<td>Gotzinger et al(^{19})</td>
<td>2002</td>
<td>340</td>
<td>133</td>
<td>39.1</td>
</tr>
<tr>
<td>Rau et al(^{27})</td>
<td>2005</td>
<td>285</td>
<td>71</td>
<td>24.9</td>
</tr>
<tr>
<td>Farkas et al(^{42–45})</td>
<td>2006</td>
<td>281</td>
<td>39</td>
<td>13.9</td>
</tr>
<tr>
<td>Olakowski et al(^{45})</td>
<td>2006</td>
<td>126</td>
<td>26</td>
<td>20.6</td>
</tr>
<tr>
<td>Reddy et al(^{46})</td>
<td>2006</td>
<td>118</td>
<td>45</td>
<td>38.1</td>
</tr>
<tr>
<td>Howard et al(^{47})</td>
<td>2007</td>
<td>102</td>
<td>12</td>
<td>11.8</td>
</tr>
<tr>
<td>Rodriguez et al(^{48})</td>
<td>2008</td>
<td>167</td>
<td>19</td>
<td>11.4</td>
</tr>
</tbody>
</table>
## Open vs. Closed drainage

<table>
<thead>
<tr>
<th>Method</th>
<th>Fistula</th>
<th>Hernia</th>
<th>Bleeding</th>
<th>Abscess</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Open Packing (n=138)</td>
<td>50%</td>
<td>32%</td>
<td>17%</td>
<td>12.7%</td>
<td>26.8%</td>
</tr>
<tr>
<td>Closed Drainage (n = 64)</td>
<td>15.6%</td>
<td>--</td>
<td>5.7%</td>
<td>10.7%</td>
<td>18.8%</td>
</tr>
</tbody>
</table>

Review of 5 prospective trials using open packing technique vs 2 trials using closed drainage technique, as described by Beger.

Early vs. Late Necrosectomy

- Prospective randomized Study
  - 1997:
    - Early Surgery (48 – 72 hrs)
      - N = 25
      - 56% mortality
    - Delayed surgery (>12 days)
      - N = 11
      - 3 additional pts. Avoided surgery
      - 27% mortality
- Necrosectomy ideally delayed 2-4 weeks to allow demarcation

Study terminated early because of OR of 3.39, in favor of delayed necrosectomy

Minimally Invasive Techniques

- Percutaneous drainage / necrosectomy
- Endoscopic
- Video Assisted Retroperitoneal Debridement “VARD”
Percutaneous Drainage / Necrosectomy

- 1997: First report of percutaneous necrosectomy and drainage for INP
  - European International Hepato-pancreato-biliary Association Congress, Bologna

- Regensberg, Germany experience
  - Retrospective single institution review
  - 18 patients between 1992 – 2004
  - Median Ranson’s at admission: 2
  - Median APACHE II : 22
Percutaneous Necrosectomy

- 30 Fr catheter used for necrosectomy
- 56% (10 / 18) patients required surgical debridement
- Overall Mortality 22%

Percutaneous technique:

- Necrotic cavity defined by contrast
- Necrosectomy performed with Dormia Basket and soft tip catheters
Percutaneous Necrosectomy

- Freeny: aggressive irrigation and drainage alone
  - 29% success in patients with **central** gland necrosis.
- Mann: use of dormia baskets and continuous lavage
- Echenique: similar technique.
  - None had hemodynamic instability pre-procedure
  - Lesser disease severity
- Mean fistula complication rate: 50%

### Percutaneous Necrosectomy Trials. 1998 - 2001

<table>
<thead>
<tr>
<th>Studies</th>
<th>Patients, n</th>
<th>Infected, %</th>
<th>Mortality, n (%)</th>
<th>Success, n (%)</th>
<th>Complications, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Freeny et al(^19)</td>
<td>34</td>
<td>100</td>
<td>4 (12)</td>
<td>16 (47)</td>
<td>Fistulas, 23.5*</td>
</tr>
<tr>
<td>Mann et al(^20)</td>
<td>29</td>
<td>100</td>
<td>8 (27)</td>
<td>20 (69)</td>
<td>Fistulas, 8</td>
</tr>
<tr>
<td>Echenique et al(^24)</td>
<td>20</td>
<td>100</td>
<td>0</td>
<td>20 (100)</td>
<td>Fistulas, 50</td>
</tr>
<tr>
<td>Gouzi et al(^25)</td>
<td>32</td>
<td>81</td>
<td>5 (15)</td>
<td>21 (65)</td>
<td>Fistulas, 53</td>
</tr>
<tr>
<td>Szentkereszty et al(^28)</td>
<td>24</td>
<td>Not stated</td>
<td>3 (12.5)</td>
<td>3 (12.5)</td>
<td>None</td>
</tr>
</tbody>
</table>

*Eight patients had fistula formation, although the relation to catheter drainage could not be proven conclusively.
Endoscopic Necrosectomy

- First reported by Baron et al. 1996
  - All retrospective reports
  - Transgastric or transduodenal drainage catheters placed nasally, +/- EUS guidance
  - Tract dilated up to 18 - 20 mm
  - Require median of 3 - 4 procedures

Summary of Endoscopic Trials 1996 - 2008

<table>
<thead>
<tr>
<th>Studies</th>
<th>Patients, n</th>
<th>Infected, %</th>
<th>Mortality, %</th>
<th>Success, n (%)</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baron and Morgan\textsuperscript{32}</td>
<td>11</td>
<td>27</td>
<td>0</td>
<td>9 (81)</td>
<td>Bleeding, 9%; infection, 36</td>
</tr>
<tr>
<td>Papachristou et al\textsuperscript{33}</td>
<td>53</td>
<td>49</td>
<td>0</td>
<td>43 (81)</td>
<td>11 (21%); bleeding, n = 9</td>
</tr>
<tr>
<td>Charnley et al\textsuperscript{37}</td>
<td>13</td>
<td>85</td>
<td>0</td>
<td>12 (92)</td>
<td>None</td>
</tr>
<tr>
<td>Voemans et al\textsuperscript{40}</td>
<td>25</td>
<td>100</td>
<td>0</td>
<td>23 (93)</td>
<td>Major bleeding, 4%; minor bleeding, 30%</td>
</tr>
<tr>
<td>Gardner et al\textsuperscript{35}</td>
<td>25</td>
<td>24</td>
<td>0</td>
<td>22 (88)</td>
<td>Bleeding, 32%</td>
</tr>
<tr>
<td>Navaneethan et al\textsuperscript{42}</td>
<td>8</td>
<td>50</td>
<td>12.5</td>
<td>7 (87.5)</td>
<td>Perforation of cyst wall, 12.5%</td>
</tr>
<tr>
<td>Mathew et al\textsuperscript{43}</td>
<td>6</td>
<td>100</td>
<td>0</td>
<td>5 (83.3)</td>
<td>None</td>
</tr>
</tbody>
</table>
Endoscopic Necrosectomy

- Voermans, et al. 2007
  - 25 patients with organized pancreatic necrosis
  - EUS guided drainage using cystoenterostomy or cystogastrostomy
  - 93% overall success rate (2/25 needing surgery)

- All endoscopic reports demonstrate high success rates

  - Limitations:
    - Possible only for contiguous walled off pancreatic necrosis
    - Require high level of expertise
    - Transgastric approach may be dangerous, causing continuous retroperitoneal contamination
    - Frequent inadequate debridement
Laparoscopic Necrosectomy

- 2008: prospective review of 8 patients with INP
  - Ranson score 2-4
  - 20 - 90% pancreatic necrosis
  - Preoperative drainage in all patients
    - 75% underwent prior laparotomy

- Laparoscopic necrosectomy delay:
  - 31 d (13 - 59 days)
  - Procedure indicated in patients with continued sepsis despite prior laparotomy or percutaneous drainage.
  - 0% mortality, 1 patient required repeat laparoscopy

**Laparoscopic Necrosectomy**

- Critically ill patients may not tolerate pneumoperitoneum
- Risk of infection transmission through peritoneal cavity or bowel injury
- Vast majority of patients had prior drainage
- Poor patient characterization in all studies, and no description of degree of necrosis

<table>
<thead>
<tr>
<th>Studies</th>
<th>Patients, n</th>
<th>Infected, %</th>
<th>Mortality, n (%)</th>
<th>Success, n (%)</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhu et al&lt;sup&gt;47&lt;/sup&gt;</td>
<td>10</td>
<td>0</td>
<td>1 (10)</td>
<td>9 (90)</td>
<td>Bleeding, 9%; infection, 36%</td>
</tr>
<tr>
<td>Parekh&lt;sup&gt;49&lt;/sup&gt;</td>
<td>19</td>
<td>95</td>
<td>2 (11)</td>
<td>43 (81)</td>
<td>No direct complications related to the procedure</td>
</tr>
<tr>
<td>Bucher et al&lt;sup&gt;52&lt;/sup&gt;</td>
<td>8</td>
<td>100</td>
<td>0</td>
<td>8 (100)</td>
<td>None</td>
</tr>
</tbody>
</table>
Retrospective review of necrosectomies 1997 - 2003

- Early and Late outcomes
- 88 patients, non-randomized
  - Open versus minimally invasive necrosectomy

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>% or (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimally invasive necrosectomy</td>
<td>47</td>
<td>53</td>
</tr>
<tr>
<td>Open necrosectomy</td>
<td>41</td>
<td>47</td>
</tr>
<tr>
<td>Median postoperative APACHE II</td>
<td>9</td>
<td>(0-22)</td>
</tr>
<tr>
<td>Patients with complications</td>
<td>82</td>
<td>93</td>
</tr>
<tr>
<td>In-hospital deaths</td>
<td>25</td>
<td>28</td>
</tr>
<tr>
<td>Median total hospital stay of survivors (days)</td>
<td>93</td>
<td>(8-300)</td>
</tr>
<tr>
<td>Median postoperative hospital stay of survivors (days)</td>
<td>54</td>
<td>(5-272)</td>
</tr>
<tr>
<td>Median postoperative stay in ICU of survivors (days)</td>
<td>1</td>
<td>(0-66)</td>
</tr>
</tbody>
</table>

In hospital complications in 88 patients who underwent pancreatic necrosectomy

<table>
<thead>
<tr>
<th>Complication</th>
<th>Number (%)</th>
<th>Mortality N</th>
<th>Univariate analysis (P)</th>
<th>Multivariate analysis (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients with one or more complications</td>
<td>82 (92%)</td>
<td>25 (28%)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Patients with organ failure</td>
<td>44 (50%)</td>
<td>19</td>
<td>.004</td>
<td>.05</td>
</tr>
<tr>
<td>Portal and/or splenic vein thrombosis</td>
<td>11 (13%)</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>*Cardiovascular complications</td>
<td>14 (16%)</td>
<td>5</td>
<td>NS</td>
<td>NA</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>4 (5%)</td>
<td>2</td>
<td>NS</td>
<td>NA</td>
</tr>
<tr>
<td>Colonic necrosis</td>
<td>2 (2%)</td>
<td>2</td>
<td>.08</td>
<td>.77</td>
</tr>
<tr>
<td>Gastrointestinal fistulae (upper gastrointestinal tract/colonic)</td>
<td>3/1 (5%)</td>
<td>1</td>
<td>NS</td>
<td>NA</td>
</tr>
<tr>
<td>Secondary hemorrhage</td>
<td>10 (11%)</td>
<td>7</td>
<td>&lt;.01</td>
<td>.03</td>
</tr>
<tr>
<td>Secondary fungal infection</td>
<td>28 (32%)</td>
<td>13</td>
<td>&lt;.01</td>
<td>.19</td>
</tr>
</tbody>
</table>

- Overall mortality: 28%
- In-hospital complication rate: 92%
- Long term complication rate: 62% (of 63 survivals)
- MIPN group: 12 / 47 (26%) required subsequent debridement
Comparison of minimally invasive necrosectomy to open necrosectomy.

Comparison of outcomes

<table>
<thead>
<tr>
<th></th>
<th>Open necrosectomy (N=41)</th>
<th>MIPN (N=47)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>41 (range, 19-85)</td>
<td>56 (range, 18-83)</td>
<td>NS</td>
</tr>
<tr>
<td>Etiology (stones/alcohol)</td>
<td>28 (68%)</td>
<td>28 (60%)</td>
<td>NS</td>
</tr>
<tr>
<td>&gt;50% necrosis</td>
<td>29 (71%)</td>
<td>42 (89%)</td>
<td>.03</td>
</tr>
<tr>
<td>Infected necrosis at first procedure</td>
<td>31 (76%)</td>
<td>38 (81%)</td>
<td>NS</td>
</tr>
<tr>
<td>Time to operation (days since admission)</td>
<td>36 (range, 1-95)</td>
<td>28 (range, 3-161)</td>
<td>NS</td>
</tr>
<tr>
<td>Preoperative ICU admission</td>
<td>18 (44%)</td>
<td>16 (34%)</td>
<td>NS</td>
</tr>
<tr>
<td>Preoperative APACHE II score</td>
<td>8.5 (range, 0-20)</td>
<td>8 (range, 0-17)</td>
<td>NS</td>
</tr>
<tr>
<td>Postoperative APACHE II score</td>
<td>10 (range, 0-21)</td>
<td>7 (range, 0-22)</td>
<td>.02</td>
</tr>
<tr>
<td>Mortality</td>
<td>16 (39%)</td>
<td>9 (19%)</td>
<td>.06</td>
</tr>
<tr>
<td>Patients with complications</td>
<td>39 (95%)</td>
<td>43 (92%)</td>
<td>NS</td>
</tr>
<tr>
<td>Organ failure</td>
<td>24 (59%)</td>
<td>20 (43%)</td>
<td>NS</td>
</tr>
<tr>
<td>Cardiovascular complications</td>
<td>7 (17%)</td>
<td>7 (15%)</td>
<td>NS</td>
</tr>
<tr>
<td>Pulmonary complications</td>
<td>3 (7%)</td>
<td>1 (2%)</td>
<td>NS</td>
</tr>
<tr>
<td>Bleeding</td>
<td>4 (10%)</td>
<td>6 (13%)</td>
<td>NS</td>
</tr>
<tr>
<td>PV/splenic vein thrombosis</td>
<td>1 (2%)</td>
<td>10 (21%)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Colonic necrosis</td>
<td>0</td>
<td>2 (4%)</td>
<td>NS</td>
</tr>
<tr>
<td>Gastrointestinal fistula</td>
<td>2 (5%)</td>
<td>2 (4%)</td>
<td>NS</td>
</tr>
<tr>
<td>ICU stay postoperative (survivors)</td>
<td>4 (range, 0-56)</td>
<td>0 (range, 0-66)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>LOS postoperative (survivors)</td>
<td>50 (range, 5-158)</td>
<td>64 (range, 15-272)</td>
<td>.04</td>
</tr>
</tbody>
</table>
• Shortcomings of MIPN:
  • Inadequacy for pancreatic head or uncinate process necrosis debridement
  • Inability to assess for evaluation and treatment of evaluation of coexisting disease
PANTER: 2010 Multicenter randomized controlled trial

- Intent to treat
- 88 patients randomized between 2005 - 2008
  - N = 43. “Step-up” necrosectomy (primary percutaneous drainage followed by MIPN)
  - N = 45. Primary open necrosectomy
- Surgery delayed > 4 weeks if possible
Exclusion:
- Flare up of chronic pancreatitis
- Previous laparotomy during current episode
- Previous drainage or surgery
- Pancreatitis caused by abdominal surgery
- Acute intra-abdominal event (ACS)

Combined primary endpoint:
- New-onset MOF
- Enterocutaneous fistulae
- Visceral peroration
- Intra-abdominal hemorrhage
Only major complication significantly lower for Step Up approach is for new onset MOF: 12% vs 42%

Mortality not significantly different
Health Care Utilization

- Open necrosectomy: 40% requiring new ICU admission
- Step Up: 16%

Cost / patient:

- Step up: $116,016
- Open necrosectomy: $131,979
- Does not provide direct comparison of minimally invasive to open necrosectomy
- No mortality benefit demonstrated for minimally invasive procedure
Conclusions

- Surgery indicated for infected necrotizing pancreatitis or sterile disease not improving over time
- Delayed Open necrosectomy with closed drainage remains the standard surgical treatment
- Percutaneous drainage / necrosectomy may reduce
- Endoscopic necrosectomy effective in WOPN, but limited to centers of excellence
- VARD:
- As early non-operative management evolves, more localized patterns of necrosis are being observed, making minimal access management more feasible.