Helicobacter Connections

Barry Marshall
“The greatest obstacle to knowledge is not ignorance, it is the illusion of knowledge.”

Daniel Boorstein - Historian
Peptic Ulcers

Duodenal Ulcer (DU)

Gastric Ulcer (GU)
SMITHKLINE’S ULCER MEDICINE “HOLY WAR”

SmithKline Beckman’s patent on Tagamet, the pale green pill that cures ulcers, has been the next best thing to a license to print money. For seven delightfully profitable years, the company enjoyed a virtual monopoly. But competition was bound to rear its head sooner or later. Glaxo Holdings of Britain has brought out a drug, Zantac, that does the same job. A success in Europe, Zantac has just come to market in the U.S., and the competitive struggle shaping up will undoubtedly give some SmithKline executives stomach pains.
Activities 1981

- Study patients with HP
  - No new information
- Take biopsies from consecutive cases
  - And from “normal” mucosa unaffected by a local lesion (away from the ulcer)
- Search the literature
- Treat one patient
- Try to culture the “CLO”
  - “Lee” method, microaerophilic
Ito biopsied his own stomach and discovered that he was colonised with a spiral organism. This image was published in 1966 in a well known text book.
Prospective Study: 1982

- 100 Elective Patients
- Prospective consent
  - clinical data (travel, pets, drugs, teeth)
- Endoscopy
  - appearance (ulcers, oesophagitis, cancer)
- Biopsy of “normal” antral mucosa
  - Histology (blind) to JRW
  - Culture and Gram stain (blind to JP)
Results:
Bacteria were cultured from 12 patients

- Easter Thursday 1982
  - Patient 37, 70 y.o. male
  - DU, GU, artificial valve, anticoagulants
- MRSA epidemic at Royal Perth
  - Overworked microbiology technologists
  - No time to check the culture on Saturday
  - Not examined until Tuesday
  - Gram negative rods seen in pure culture
- We had been using the right methods for
  - Cultures were being discarded after 48 hours
## Association of Bacteria with Endoscopic Diagnoses

<table>
<thead>
<tr>
<th>Endoscopic Appearance</th>
<th>Total</th>
<th>With Bacteria</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric Ulcer</td>
<td>22</td>
<td>18 (77%)</td>
<td>0.0086</td>
</tr>
<tr>
<td><strong>Duodenal Ulcer</strong></td>
<td>13</td>
<td>13 (100%)</td>
<td>0.00044</td>
</tr>
<tr>
<td>All Ulcers</td>
<td>31</td>
<td>27 (87%)</td>
<td>0.00005</td>
</tr>
<tr>
<td>Oesophagus Abnormal</td>
<td>34</td>
<td>14 (41%)</td>
<td>0.996</td>
</tr>
<tr>
<td>Gastritis</td>
<td>42</td>
<td>23 (55%)</td>
<td>0.78</td>
</tr>
<tr>
<td>Duodenitis</td>
<td>17</td>
<td>9 (53%)</td>
<td>0.77</td>
</tr>
<tr>
<td>Bile in Stomach</td>
<td>12</td>
<td>7 (58%)</td>
<td>0.62</td>
</tr>
<tr>
<td>Normal</td>
<td>16</td>
<td>8 (50%)</td>
<td>0.84</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>100</td>
<td>58 (58%)</td>
<td></td>
</tr>
</tbody>
</table>

Gastritis and Duodenal Ulcer

- Magnus 1952
  - GU: gastritis in 80%
  - DU: gastritis is 100%

- NSAID’s
  - Gastric ulcers with normal histology are commonly NSAID associated
A new species

Bacteria linked to gastritis

“since the new bacteria are associated with gastritis as described by Warren, then they may play a role in other poorly understood gastric diseases i.e. peptic ulcer and gastric cancer.”
Disease Associations for *Helicobacter pylori*

If the bacteria could be eliminated, would the ulcer be cured?
Known Facts about Ulcer Disease

- The stomach was sterile
- Ulcers were caused by
  - Lifestyle (stress)
  - Diet, alcohol, drugs
  - Genetically determined
- Work rejected because the results were outside the current paradigm
- This was the pattern for the next 8 years
Was Hp a pathogen?
Testing the hypothesis

1. Do patients have antibodies?
2. Do antibacterials heal gastritis?
3. Have Koch’s postulates been fulfilled?
4. What is the disease process?
   1. How does it infect?
   2. How does it survive in the acid stomach?
A new look at the literature:

- Heavy metals were antibacterial
  - Arsenic and Mercury for syphilis
- Bismuth had been used to treat gastric diseases for 200 years
- Bismuth was also an ulcer treatment
  - Relapse after bismuth treatment was lower
- Was bismuth killing CLO?
Bacterial cause explains why a heavy metal cures the disease in 40%.

Some thoughtful gastroenterologists noticed that drug therapy affected relapse rates.
In-vitro

In-vivo
Bismuth Based Therapy Could be Used in Clinical Trials

- Placebo controlled study of ulcer patients
  - H2RA (cimetidine) vs. Antibiotic
    » Unethical!
  - H2RA vs. Bismuth
    » H2RA+Antibiotic
    » Bismuth+Antibiotic
    » H2RA alone
    » Bismuth alone
An attempt to fulfil Koch’s postulates: preliminary steps

- A red rag to a bull
  - “Dr Marshall, these changes seem very subtle..”
  - “..these commensal bacteria merely infect people with ulcers.”
- Failed attempts to infect pigs
- Serology shows 40% of population has Hp
- First treatment success
  - bismuth + metronidazole cures 75%
  - Excellent clinical responses
    - Patients
    - GP’s
    - Own experience
An attempt to Fulfill Koch’s Postulates for *Campylobacter pyloridis*

Med J. Aust 1984
An attempt to fulfil Koch’s postulates: the experiment

- Cultured a patient with gastritis
- Underwent baseline endoscopy
- Treated the patient successfully
- Drank bacteria $10^9$ c.f.u.
  - d3-5 vague illness, halitosis
  - d5-8 vomiting, **no acid present**!
  - d8 – endoscopy and biopsy
- Histological gastritis
  - Hp is a pathogen
Day 8: The Infection Takes Hold

The time has come for Marshall to put his hypothesis to the critical test... with agonizing trepidation, Marshall undergoes an endoscopy to determine once and for all if the bacteria have eaten their way into his stomach lining...

If only there were a simple, quick test to diagnose this bacteria! Then I would be spared this burdensome procedure!

Marshall! Your stomach lining is dangerously inflamed!
Koch’s Postulates fulfilled for Gastritis
Gastric Mucosa, H&E, Day 8
Achlorhydric Gastritis in Children

“examination of the vomitus reveals as a rule, absence of hydrochloric acid and sometimes the presence of volatile fatty acids.”
Epidemic gastritis with hypochlorhydria

- The acute attack of Hp
  - In early childhood
  - Lasts a few days
  - Lifelong colonization with Hp
How does Hp survive in the stomach?

- **Urease enzyme**
  - Gastric urease discovered in 1926
  - Association with Hp noted in 1984

- **Urea absent from gastric juice of patients with Hp**
  - Hp splits urea to make ammonia and HCO3⁻
  - Hp protects itself from acid

- **Biopsy Urease test**
  - As accurate as Gram Stain
  - Takes a few minutes
  - Anyone can now diagnose Hp!
Implementation

- Effective therapy
  - Bismuth and antibiotic
  - PPI (Losec) with two antibiotics (1996)
- Non invasive breath test for H. pylori
  - Now GP’s can treat Hp!
  - Non-invasive follow-up possible
  - Bye bye gastroenterologists!
Validation 1985-7

- Double blind study
  - 100 patients
  - H2 Blocker vs. Bismuth+antibiotic
  - Cure rate 80% vs 10%

- Replication by others
  - 1990: Rauws and Tytgat, Amsterdam
  - 1991: Graham, Houston Tx
  - 1993: Hentschel, Vienna
Week after healing of duodenal ulcers

Hentschell NEJM, 1993
Acceptance

- NIH Consensus conference
  - Washington DC
  - February 1994
Postscript

Nobel Prize in Physiology or Medicine
J. Robin Warren and Barry J. Marshall

Thank You
Alfred Nobel and Helicobacter
Alfred Nobel and His Health Problems

During most of his life, Alfred Nobel suffered from poor health. He complained of indigestion, headaches and occasional spells of depression. Already as a young man, he spent several weeks at health resorts. His first stay at a spa was at Franzenbad in Bohemia in 1854. The inactivity at the health resorts made him restless and bored. He cannot have been impressed by the medical treatment offered at the spas. It consisted of baths, resting, and drinking well water. Toward the end of his life, Alfred Nobel suffered from a heart condition marked by paroxysms of intense pain (angina pectoris). The real nature of his health problems at a younger age are not clear, but one may well imagine that he was simply overworked or under serious mental stress. Often he felt lonely and without friends.
Urea and Urease Enzyme

\[ \text{NH}_2 \quad | \quad \text{C}=\text{O} \quad +2\text{H}_2\text{O} +\text{H}^+ \xrightarrow{\text{urease}} 2\text{NH}_4^+ + \text{HCO}_3^- \]