A Case Study on Peptic Ulcers

What causes peptic ulcers?
THE
LONDON ENCYCLOPAEDIA,
or
UNIVERSAL DICTIONARY
OF
SCIENCE, ART, LITERATURE, AND PRACTICAL MECHANICS,
COMPRISING
A
POPULAR VIEW OF THE PRESENT STATE OF KNOWLEDGE.

ILLUSTRATED BY
NUMEROUS ENGRAVINGS, A GENERAL ATLAS,
AND APPROPRIATE DIAGRAMS.

BY THE ORIGINAL EDITOR OF THE ENCYCLOPEDIA METROPOLITANA,
ASSISTED BY EMINENT PROFESSIONAL AND OTHER GENTLEMEN.

IN TWENTY-TWO VOLUMES

VOL. XVI.

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and WHITTLE & LAWRENCE, Salem, North America.

1829.
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OYS 417

OYSTER SHELLS are an alkali far more powerful than is generally allowed, and in all probability much better medicines than many of the more costly and pompous alkalis of the same class. These shells produce very sensible effects on the stomach, when it is injured by acid humors.

OYOLAVA, one of the larger Navigator's Islands, in the South Pacific, in long. 121° 24 W., and lat. 14° S., separated from Macaoa, or Massacre Island, by a channel about nine leagues wide; and, according to Perouse, Otagoheie can scarcely be compared with it for beauty, extent, and fertility. When his vessel was within three leagues of the coast it was surrounded by canoes laden with bread-fruit and other provisions, and the island seemed very populous from the central mountain to the shore.

OSTER, n. 1. Belg. cent.; Lat. ostrea. A well-known sea fish: the oyster wench and oyster woman are women employed in sale of this fish; and generally, any low woman.

I will not lend to a penny,
—When then the world's mine oyster, which I with sword will open.
Shakespeare, Merry Wives of Windsor.

Off goes his bonnet to an oysterman. Shakespeare, Vol. XVI.

OZANAM (James), an eminent French mathematician, born at Belguem in Bresse, in 1640. His father designed him for the church; but his mathematical genius showed itself so early that he made that study his profession, and taught that science at Lyons. In 1702 he was admitted into the Royal Academy of Sciences; and died of an apoplexy in 1717. He was of a mild and serene temper, and a cheerful disposition. His works are very numerous, and have met with approbation. The principal are, 1. Practical Geometry, 12mo. 2. A Mathematical Dictionary. 3. A Course of Mathematics, 4 vol. 4. Mathematical and Philosophical Recreations, the most complete edition of which is that of 1724, in 4 vol. 5. An Easy Method of Surveying. 6. New Elements of Algebra, a work much commended by M. Leibnitz. 7. Theoretical and Practical Perspective, &c.
Gastric Diseases
Gastric Diseases
Design an Experiment

- In small groups design an experiment to test the “excess acid” hypothesis.
- Be specific about how you would treat your experimental groups and what you would measure.
Which option is the best test of the excess acid hypothesis?
What step in the scientific method does this test represent?
A Possible Study Design

- Patients suffering from ulcers were divided into two groups
  - Group 1 received antacids and were instructed to take them 3X/day
  - Group 2 received sugar pills (a placebo) and were instructed to take them 3X/day
- After 3 months, the number of patients with ulcers was assessed.
- Neither the doctor evaluating the patients nor the pathologist assessing the patient biopsy samples knew which patients had been given the antacids and which had been given the sugar pills. The study was “double-blind”.
How would you label the two groups?
Why is it important that the trial be “double-blind”?
Prediction

Predict what the results of the trial would look like after 3 months if the excess acid hypothesis was correct.
Which graph most closely matches your predicted results?

A)  

B)  

C)  

D)  

Ex  |  C
---|---
Ex  |  C
Ex  |  C
Ex  |  C
Anecdotal Evidence for the Excess Acid Hypothesis

- Unfortunately, controlled, double-blind studies were assessing the number of patients with ulcers were not conducted.
- There was abundant anecdotal evidence and even controlled studies in which antacids relieved the SYMPTOMS of gastric ulcers.
- However, the antacids did not cure the ulcers. The relapse rate was high.
- Drug companies spend millions on developing and testing new antacids and chemicals that block stomach acid production.
A Technological Breakthrough

Fiberoptic endoscopy allowed gastroenterologists to take biopsies.
Collaboration with Dr. Barry Marshall

Marshall cultivates a bacterium from gastric biopsies.

Tuesday, January 24, 2012
UNIDENTIFIED CURVED BACILLI ON GASTRIC EPITHELIUM IN ACTIVE CHRONIC GASTRITIS

Sir,—Gastric microbiology has been sadly neglected. Half the patients coming to gastroscopy and biopsy show bacterial colonisation of their stomachs, a colonisation remarkable for the constancy of both the bacteria involved and the associated histological changes. During the past three years I have observed small curved and S-shaped bacilli in 135 gastric biopsy specimens. The bacteria were closely associated with the surface epithelium, both within and between the gastric pits. Distribution was continuous, patchy, or focal. They were difficult to see with haematoxylin and eosin stain, but stained well by the Warthin-Starry silver method (figure).

I have classified gastric biopsy findings according to the type of inflammation, regardless of other features, as "no inflammation", "chronic gastritis" (CG), or "active chronic gastritis" (ACG). CG shows more small round cells than normal while ACG is characterised by an increase in polymorphonuclear neutrophil leucocytes, besides the features of CG. It was unusual to find no inflammation. CG usually showed superficial oedema of the mucosa. The leucocytes in ACG were usually focal and superficial, in and near the surface epithelium. In many cases they only infiltrated the necks of occasional gastric glands. The superficial epithelium was often irregular, with reduced mucinogenesis and a cobblestone surface.

When there was no inflammation bacteria were rare. Bacteria were often found in CG, but were rarely numerous. The curved bacilli were almost always present in ACG, often in large numbers and often growing between the cells of the surface epithelium (figure). The constant morphology of these bacteria and their intimate relationship with the mucosal architecture contrasted with the heterogeneous bacteria often seen in the surface debris. There was normally a layer of mucous secretion on the surface of the mucosa. When this layer was intact, the debris was spread over it, while the curved bacilli were on the epithelium beneath, closely spread over the surface (figure).

The curved bacilli and the associated histological changes may be present in any part of the stomach, but they were seen most consistently in the gastric antrum. Inflammation, with no bacteria, occurred in mucosa near focal lesions such as carcinoma or peptic ulcer. In such cases, the leucocytes were spread through the full thickness of the nearby mucosa, in contrast to the superficial infiltration associated with the bacteria. Both the bacteria and the typical histological changes were commonly found in mucosa unaffected by the focal lesion.

Curved bacilli on gastric epithelium.

Section is cut at acute angle to show bacteria on surface, forming network between epithelial cells. (Warthin-Starry silver stain; bar = 10 µm.)

Determinative Bacteriology. The stomach must not be viewed as a sterile organ with no permanent flora. Bacteria in numbers sufficient to see by light microscopy are closely associated with an active form of gastritis, a cause of considerable morbidity (dyspeptic disease). These organisms should be recognised and their significance investigated.

Department of Pathology, Royal Perth Hospital, Perth, Western Australia 6001

J. ROBIN WARREN
Why were most doctors skeptical of Warren and Marshall’s hypothesis that bacteria caused ulcers?
Do bacteria cause ulcers?

- *Drs. Warren and Marshall hypothesize that bacteria may cause gastric ulcers.*
- *What are some alternative hypotheses to explain the presence of bacteria in the stomach.*
A Pilot Study

Fig. 3: Data Tables Published in The Lancet by Warren and Marshall in 1984

<table>
<thead>
<tr>
<th>Table II: Association of Bacteria with Endoscopic Diagnosis</th>
<th>Table III: Histological Grading of Gastritis and Bacteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endoscopic Appearance*</td>
<td>Bacterial Grade</td>
</tr>
<tr>
<td>Total</td>
<td>With Bacteria</td>
</tr>
<tr>
<td>------</td>
<td>----------------</td>
</tr>
<tr>
<td>Gastric ulcer</td>
<td>22</td>
</tr>
<tr>
<td>Duodenal ulcer</td>
<td>13</td>
</tr>
<tr>
<td>All ulcers</td>
<td>31</td>
</tr>
<tr>
<td>Oesophagus abnormal</td>
<td>34</td>
</tr>
<tr>
<td>Gastritis\textsuperscript{T}</td>
<td>42</td>
</tr>
<tr>
<td>Duodenitis\textsuperscript{T}</td>
<td>17</td>
</tr>
<tr>
<td>Bile in stomach</td>
<td>12</td>
</tr>
<tr>
<td>Normal</td>
<td>16</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
</tr>
<tr>
<td>*More than one description applies to several patients.</td>
<td></td>
</tr>
<tr>
<td>\textsuperscript{T}Refers to endoscopic appearance, not histological inflammation.</td>
<td></td>
</tr>
</tbody>
</table>

*Gastritis grades 0 and 1 are normal.  
\textsuperscript{T}1 case showed bacteria on gram stained smear.
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Prediction

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Which graph most closely matches your predicted results?

A)  

B)  

C)  

D)
Prediction

Predict what the results of the trial would look like after 3 months if the bacterial hypothesis was correct.
Which graph most closely matches your predicted results?

A) 

B) 

C) 

D)
Epilogue

- Medical doctors worldwide were not easily convinced. Warren and Marshall needed more evidence.

- Marshall began treating patients with antibiotics, which appeared to work, but this was not a controlled experiment.

- Marshall attempted to infect pigs with bacterium but was unsuccessful.
Epilogue

- In desperation Marshall drank 30 ml of the bacterial culture. Within 8 days he developed stomach pain, vomited and developed ulcers. Her cured himself with antibiotics.

- In 2005, Warren and Marshall were awarded the Nobel prize in Medicine and Physiology.