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Doctor's World

A Scientist, Gazing Toward Stockholm, Ponders "What If?"

By LAWRENCE K. ALTMAN, M.D.

For Dr. A. Stone Freedberg, a 97-year-old retired Harvard scientist, the presentation of the Nobel Prize in Medicine on Saturday to two Australians for discovering a bacterial cause of stomach ulcers will be bittersweet.

In 1940, Dr. Freedberg identified curved bacteria, now known as *Helicobacter pylori*, in the stomachs of ulcer patients in Boston. But he abandoned that line of research after other scientists failed to confirm his findings, and his boss, Dr. Herrman L. Blumgart, told him to move on to something easier to prove.

But what if that confirmation had come and Dr. Freedberg had pursued ulcer research?

Dr. Freedberg might have become a Nobel laureate long ago. Antibiotics would have cured millions more people of their ulcers and spared them from surgically parting with much of their stomachs, a standard treatment for chronic ulcers.

"What ifs" are as plentiful in medicine as any other field. In conducting research, doctors are guided by a number of philosophical questions: is the aim to create a new paradigm? To try to disprove a well-accepted theorem? Or to refine existing understandings?

Most scientists say that they settle on making minor advances, because grants from the National Institutes of Health and other federal agencies usually support that type of research.

Also, young researchers face tremendous career risks in seeking to upset conventional thinking and scientific dogma. Ulcers are a case in point: for decades doctors believed that stress caused ulcers and were slow to accept them as an infectious disease and to prescribe antibiotics.

Dr. Freedberg's interest in stomach ulcers as a young researcher at the Harvard-affiliated Beth Israel Hospital in Boston grew out of his investigations into another condition. His initial focus was on learning the effects of fever on the heart and circulatory system when it collapsed into shock from infections.

Dr. Freedberg learned from reading scientific reports that patients who had this condition often developed tiny ulcers in the stomach and small bowel that sometimes bled, even severely,

He also learned that since at least 1906, doctors had seen curved bacteria in the stomachs of patients with ulcers, but rarely in people without them. Dr. Freedberg was puzzled. "The stomach was very acid and did not seem to be the kind of place where bugs would grow," he said. "So how could bugs be there? And what were they doing there?"

All these findings were in dead people, raising the possibility that the bacteria were contaminants or that they took up residence after death.

So Dr. Freedberg decided to determine whether the bacteria were present in living patients by examining pieces of stomach removed during operations for ulcers and other illnesses.

A surgeon friend agreed to provide Dr. Freedberg with these tissues. A pathologist gave him a work space and supplies to examine the stomach tissue under a microscope after the staff had gone home.

In performing these tests, Dr. Freedberg relied on techniques he had learned in 1936 and 1937 while training as a specialist in pathology and microbiology at the Rhode Island Hospital in Providence. He abandoned that career choice because he could find no permanent pathology job, he said in interviews.

Initially, Dr. Freedberg could not see any bacteria when he used standard chemicals to stain the stomach tissue. But the bacteria stood out when he used a silver stain. He found the bacteria in 13 of 35 patients, or 37.1 percent.

"I still remember the surprise and good feeling I had when I first saw the S-shaped organisms" in the mucosa, or surface lining, of the stomach, Dr. Freedberg said.

Dr. Freedberg thought they were not normal inhabitants of the stomach, but he lacked evidence that the microbes had any pathological significance. Still, a fundamental question needed answering: what were the bacteria? The only way to know was to grow them in a laboratory.

“Obviously if I could grow the bacteria, there were things you could do with them,” Dr. Freedberg said.

A microbiologist colleague whose main interest was virology, not bacteriology, tried to culture the bacteria. But about four months later he stopped because nothing grew.

So Dr. Freedberg wrote a paper describing his findings and *The American Journal of Digestive Diseases* published it in 1940. In a discussion section, published as a follow-up to Dr. Freedberg’s paper, Dr. Frank D. Gorham of St. Louis said that for 10 years he had found that intramuscular injections of bismuth helped heal ulcers. Bismuth was a popular remedy.

In 1850, a German doctor recommended the mineral for stomach ulcers and by 1900 Norwich Eaton sold Bismosal for relief of gastric ulcers and acute gastritis.

To determine whether bismuth worked because ulcers might be an infection, Dr. Gorham’s colleagues at Washington University examined 242 stomachs obtained from autopsies and found curved bacteria in 43 percent. But these colleagues could not establish a definite causative link between the presence of the bacteria in the stomach and serious gastric disease. Dr. Gorham urged additional searches for an ulcer-causing microbe.

Dr. Freedberg said he was “very upset that my findings weren’t confirmed” because it implied that his work was wrong. Also, the inability to grow the bacteria “bothered me,” Dr. Freedberg said, because his findings “had to be important” for ulcers, which were an important health problem.

But Dr. Freedberg’s superiors squelched any thoughts of continuing the research. “I was discouraged by everybody,” he said.

Dr. Freedberg said that Dr. Blumgart, the chief, told him, “Maybe you made a mistake,” and that it did not make any sense to continue because it would be a waste of time, when diseases of the heart and blood vessels were the main focus of the department’s research.

The longstanding attitude in the department was “if you find it difficult to pursue a problem, drop it and switch to something you could learn something from, because there is so much unknown in our area of medicine,” Dr. Freedberg said.

Though some doctors continued to raise suspicions about an infectious cause of ulcers, researchers consistently failed to find the evidence. For example, in 1954, Dr. Eddy D. Palmer of the Walter Reed Army Hospital in Washington reported finding no bacteria among 1,180 stomach specimens he examined.

Dr. Freedberg said that “what Palmer did, was to essentially destroy interest in a bacterial cause of ulcers:” until 1984, when two Australians, Dr. Barry J. Marshall and Dr. J. Robin Warren, identified *H. pylori* among ulcer patients.

They will receive their Nobel Prizes on Saturday in Stockholm.

Dr. Freedberg, who went on to have a distinguished career as a professor of cardiology at Harvard, gave up practice this year, but he remains active by advising former patients and regularly attending concerts in Boston. He said he was “really happy when Marshall found the bugs,” because the discovery confirmed his theory.

He met with the Australians when they received an award in Boston in 1994. Dr. Freedberg tried to go back and study his old specimens and lab notebooks after the initial Australian reports, he said, but the Beth Israel Hospital had discarded them.

Editors of medical journals insist that other experts review new findings before they are published and reported to the public.

The purpose of this peer review is to help ensure accuracy and to exclude false findings. But publication of papers that fail to confirm initial positive findings in peer reviewed journals illustrates that the publication of poorly researched negative findings can be as dangerous, if not more so, as publishing sloppy positive findings.

Dr. Marshall, asked in a telephone interview whether he would have won his Nobel Prize if Dr. Freedberg had been able to pursue his ulcer research, said, “No way.”

“If Dr. Freedberg’s team had been able to culture *H. pylori*,” Dr. Marshall said, “they would have seen that bismuth kills the bacteria and they could have developed a treatment in a few years.”

He added: “They would have won the Nobel Prize about 1951 as I was getting born. So it was just a bit of bad luck for a lot of people.”

class assignment #3

This assignment is due no later than 1:30 p.m. on Friday, 25 January. You may e-mail your answers (subject is 102#3 Your Name) or turn them in *word processed* at lecture or my office. Scores based on 12 points, with 4 additional points extra credit possible.

Write four questions related to this article.

- **Your questions may be factual (asking for information such as dates, places, times, people, etc., that can either be found in the article or that can be looked up using references). Factual questions are worth 1 point each; supplying correct answers double their value. OR**
- **Your questions may go beyond the facts and require some level of synthesis, thought and/or analysis. Opinion questions are acceptable for this latter category. Synthesis questions are worth 2 points each; supplying well-reasoned answers double their value. OR**
- **You may write a combination factual and synthetic questions, to round out your four questions.**

You must identify each question as either “factual” or “synthesis.”

For example (you cannot use either of these for your questions!):

Factual: On what date was this article written? (answer: 6 December 2005)

Synthesis: What caused Dr. Marshall to develop his dedication to research in order to drink bacteria-filled broth to prove the hypothesis—nature, nurture, or mad scientist? (answer: pick one and justify your choice)