Testing The Most Curious Subject -- Oneself

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One July day in 1984, Barry Marshall, a medical resident at the Fremantle Hospital in Perth, Western Australia, walked over to his lab bench, pulled down a beaker, and mixed a cocktail. The key ingredient: about a billion Helicobacter pylori bacteria. Marshall hoped to show that the microorganism causes ulcers. He gulped the concoction, describing it as "swamp water."

PHYSICIAN, STUDY THYSELF: Barry Marshall's daring experiment eventually garnered him awards. One hundred years earlier, Max von Pettenkofer, a chemist in Munich, Germany, performed a similar experiment. Von Pettenkofer was eager to prove the recently identified Vibrio cholerae bacterium could not, on its own, cause cholera. His cocktail ingredients: bouillon and the deadly cholerae. He, too, gulped his potion.

Marshall was correct. He suffered an inflamed stomach. Von Pettenkofer was incorrect. He was fortunate to survive. Both researchers risked their health-and, perhaps, their lives-to prove a scientific point. And they are not alone.

Since the earliest days of medicine, self-experimenting researchers have swallowed microbes, injected vaccines, followed deprivation diets, and even performed their own surgeries. Aside from health hazards, these unorthodox experimenters risk the incredulity of peers accustomed to formal subject studies. If a self-experiment is unsuccessful, an investigator's reputation -- and funding -- may be in jeopardy.

So why self-experiment? Belief in a hypothesis. Curiosity. Convenience. Ethics. Desperation. A medley of motivations stands behind self-experimentation. Usually, researchers double as subjects because it appears both practical and ethical.

"I was so frustrated," recalls Marshall, now a gastroenterologist at the University of Virginia. "I had been trying to infect animals with H. pylori. I really needed to prove this organism could infect a healthy human stomach. So I decided to put my money where my mouth was" (B.J. Marshall et al., Medical Journal of Australia, 142:436-9, 1985).

No one knows how many scientists have experimented on themselves. Some researchers try a new therapy or technique without approval from a university institutional review board (IRB). Marshall, for example, did not receive

institutional approval for his self-testing. Such experiments may remain anecdotal, outside of the peer-reviewed literature. Other investigators may simply include themselves in a pool of subjects. Lawrence Altman, a reporter for the New York Times and author of Who Goes First? The Story of Self- Experimentation in Medicine (New York, Random House, 1986), resorted to tracking self-experiments in old medical journals, which listed subjects' initials. If the investigator's initials were included, Altman speculated, he or she had probably self-experimented.

Fortunately, many self-experiments are documented. Self-dosing researchers have played a part in developing a dozen vaccines. Self-experimenters helped create drugs that prevent organ- transplant rejection, treat bacterial and fungal infections, and halt anemia. And countless scientists first tested revolutionary equipment, like positron emission tomography (PET), on themselves.

For example, Hilary Koprowski, director of the Center for Neurovirology at Thomas Jefferson University in Philadelphia, has self-injected versions of vaccines for Colorado tick fever and rabies that he helped create. In 1951, he became the first person to swallow a live polio vaccine. Each self-experiment was instrumental to the vaccines' development.

Koprowski took the experimental rabies vaccine with a team of three colleagues in 1971 at the Wistar Institute in Philadelphia, where he was director from 1957 to 1991. During the course of tests, 12 other Wistar staff also got the vaccine. It worked, and it was soon available across the world.

Koprowski says he did not hesitate to take the risk of catching the disease at hand. "Worrying about risk is stark nonsense," he declares. "The real danger is that these drugs should not exist. You always take a small amount of risk."

Altman's book notes that self-experiment risk can sometimes be fatal. In 1900, Jesse W. Lazear, a surgeon with the United States Army, died from intentional exposure to a yellow fever-carrying mosquito during an experiment. The same experiment may have contributed to the death of a colleague, James Carroll, seven years later. More fortunately, a dozen researchers at Washington University in St. Louis recovered in the hospital from experiment-induced illness. Several scientists, for example, grew ill after experimental blood transfusions from patients with leukemia and other disorders.

Occasionally, self-experiments even have led to public-health disasters. In von Pettenkofer's time, a Spanish physician named Jaime Ferrán y Clua created a dangerously crude cholera vaccine. After testing it on himself, Ferrán y Clua allowed his vaccine-which contained still-active cholera bacteria -- to be distributed to 50,000 people. Some died. Similarly, in the 1930s, at least a dozen children became paralyzed after receiving early, still-active versions of a polio vaccine that had been self-tested by John Kolmer, then a physician at Temple University in Philadelphia.

Today, the public is protected from hastily created therapies by IRBs, ethics committees, and peer review. According to Robert Levine, a professor of medicine at Yale University and chairman of Yale -- New Haven Medical Center's human investigation committee, human research adheres to standards set by a few key agencies. For example, the U.S. Department of Health and Human Services stipulates that in any research approved by an IRB, "risks to subjects are minimized by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk."

Today's IRB-approved self-experimentation is relatively tame, involving studies of exercise, nutrition, and blood. "Around the country, most IRB literature doesn't even mention self- experiments," notes Levine. "When it is [mentioned], it is only to say that self-experiments follow the same restrictions as any other. A self-experimenter would submit a protocol to the university IRB."

"It doesn't come up often," adds Gary Ellis, director of the Office for Protection from Research Risks at the National Institutes of Health. Regulators and ethicists worry much more about research subjects, according to Ellis.

Still, Altman thinks investigators may often "work out the bugs" of a new therapy with themselves as subjects before launching a full-fledged experiment. "That's hard to learn about," he notes. "people don't know that it goes on. Therefore, they assume it doesn't. Unapproved self-experiments like Marshall's occasionally change medicine forever. Some researchers say it is only fair for the investigator to be the first subject.

"One could regard it as rather unethical to not try a new procedure on yourself first," asserts Michel Ter-Pogossian, a radiation physicist at Washington University in St. Louis who helped create the PET scan and first tried the machine on himself. "If you are going to ask volunteers to be tested, you should be willing to do it yourself."

It was 1961. Victor Herbert was losing weight. A 34-year-old researcher at the Thorndike Memorial Laboratory at Boston City Hospital, Herbert had dropped 20 pounds in roughly four months. A uniquely bland diet was to blame. Before eating anything -- chicken, hamburger, applesauce -- Herbert made sure it had been boiled three times.

"I was determined not to eat anything with folic acid," recalls Herbert, now a professor of medicine at Mount Sinai Medical Center in New York. "I drank a lot of coffee." Folic acid is an essential vitamin found largely in leafy green vegetables. Herbert had a hunch that a diet low in folic acid could cause anemia. He decided to find out.

He asked the hospital staff to boil all his food for 30 minutes, which would degrade the folic acid. After five months of boiled meals -- through the

Thanksgiving holiday and family get-togethers -- Herbert's hypothesis was confirmed. A blood test revealed a weak red blood cell count. Herbert had become anemic.

His ensuing research report (V. Herbert, Transactions of the Association of American Physicians, 75:307-20, 1962) was one of the first to establish the link between folic acid deficiency and anemia. Today, physicians routinely prescribe folic acid to pregnant women. It is a recommended daily vitamin.

The unsavory self-experiment was a time-honored tradition at Thorndike. Herbert's mentor, researcher William Castle, was known for an experiment on pernicious anemia, a type of anemia in which red blood cells fail to mature. Castle wanted to show that pernicious anemia resulted from a missing "intrinsic factor" in a patient's stomach, not simply a deficiency of the vitamin B12. In a famous experiment, Castle ate rare beef and then used a gastric tube to extract the food -- mingled with gastric juice -- from his stomach. Castle then fed the mixture to anemic patients, who were cured.

"Castle was a mentor for many self-experimenters," Herbert recalls.

At the time, self-experiments were common at Washington, Duke, and Yale universities, as well, according to Herbert. "It was the atmosphere at institutions where the fire of research burned strong. For me, self-experimenting meant that I knew my patient would follow orders. I knew that when I told my patient -- namely me -- not to eat any foods other than those prepared in the [hospital] kitchen, that's what I would do."

Strict human-subject review did not then exist. In fact, only a handful of human-research regulations existed. The first was the 1947 Nuremberg Code, which stipulated that: "No experiment should be conducted where there is an a priori reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where experimenting physicians also serve as subjects."

"Back then, there was a perception that nobody as rational as physicians would expose themselves to unwarranted risks," notes Yale's Levine. "Now, of course, we know that a lot of physicians will expose themselves to risk."

Herbert, for one, still self-experiments. In 1994, he and his colleagues joined volunteer subjects in taking an experimental drug to treat diabetes. "Every month, I also have my blood taken as a control in studies," Herbert says. "I'll always be a guinea pig."

Another current self-experiment involves French physician Daniel Zagury of the Pierre-et-Marie Curie University in Paris. In 1986, Zagury became the first person to receive an experimental AIDS vaccine -- which he helped create. Zagury showed that, at least initially, the vaccine was safe and stimulated an immune response. He was not infected with HIV.

Reporting on this and a subsequent experiment with volunteer subjects in Zaire, Zagury's research team wrote, "We would wish to overcome any limitations . . . before we could properly consider any large-scale clinical trial of the vaccine" (D. Zagury et al., Nature, 326:249-50, 1987).

Future headline-winning self-experimenters will emerge, predicts Ter-Pogossian, who estimates he's performed 200 self- experiments over the past 25 years. "I would guess these experiments are more common than you think," he says. "Investigators, you know, have a tendency to be curious."

In his experiment to prove everyone is both good and evil, Robert Louis Stevenson's Dr. Jekyll exhibited one fatal flaw: bias. Swallowing the potion that transformed him into Edward Hyde, the doctor remained confident that he could control -- and evaluate -- the outcome. He was wrong. Edward Hyde's personality took control. In a rare, desperate moment of lucidity, Jekyll overdosed on the potion, essentially committing suicide.

Fortunately, real self-experimenters don't face the gruesomeness of Dr. Jekyll and Mr. Hyde. But they do face the same challenge. "Any time you are the subject, there is a real potential bias in evaluating data," states Richard Galbraith, associate dean for patient-oriented research at the University of Vermont College of Medicine. "It is too easy to find what you want to find. For that reason, I think, IRBs and institutions frown upon self-experimentation, and it is becoming exceedingly rare."

Ernest Prentice, associate dean for research at the University of Nebraska Medical Center in Omaha, concurs. "We discourage self-experimentation, principally because the individual is not in a terribly objective position," states Prentice. "They have a vested interest, and they are sometimes willing to submit to considerable risk that IRBs would not find acceptable."

COOPERATIVE SUBJECT: Victor Herbert says he self-experimented because "I knew my patient -- namely me -- would follow orders."
But self-experimenting researchers are adamant that such investigations have their place. "I don't think we'd have half as many medical advances as we do without self-experiments," Herbert maintains. "I totally agree," says Koprowski. What's ironic, he notes, is that early studies that revolutionized American medicine would not be approved now. "Because of all these safety concerns, the oral polio vaccine and rabies vaccine that we created would never be licensed today."

Ter-Pogossian, Herbert, and Marshall did not seek prior approval before launching their experiments. Yet, important medical findings might not have occurred had they been unwilling to act as subjects.

The personal payoff for taking a chance on a self-experiment is big. Take Marshall's pivotal H. pylori experiment. At first, his critics lambasted both his ulcer theory and his approach, denouncing him as "crazy" (T. Monmaney, "Marshall's Hunch," New Yorker, Sept. 20, 1993, pages 64-72).

But further experiments soon showed Marshall was correct. He accepted a position at the University of Virginia, where he is now a clinical associate professor of internal medicine. This fall, he received the Albert Lasker Clinical Research Award (N. Sankaran, The Scientist, Oct. 16, 1995, page 1) as well as the John Scott Award, presented by the Board of Directors of City Trusts of the City of Philadelphia (see Notebook, page 30).

Of course, the self-experiment route to success isn't always smooth. "Actually," says Marshall, "a self-experiment might have a negative effect on funding. Usually, researchers reviewing grants tend to be bench scientists doing important basic research that doesn't get a lot of publicity. People who end up in the media [by garnering publicity for self-experimentation] before they get funded may be at a disadvantage. Not to mention the physical risks of such an experiment."

In the end, though, is a good self-experiment worth the risk? Marshall doesn't hesitate: "You bet."

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