THE FORTNIGHTLY CLUB

of

REDLANDS, CALIFORNIA

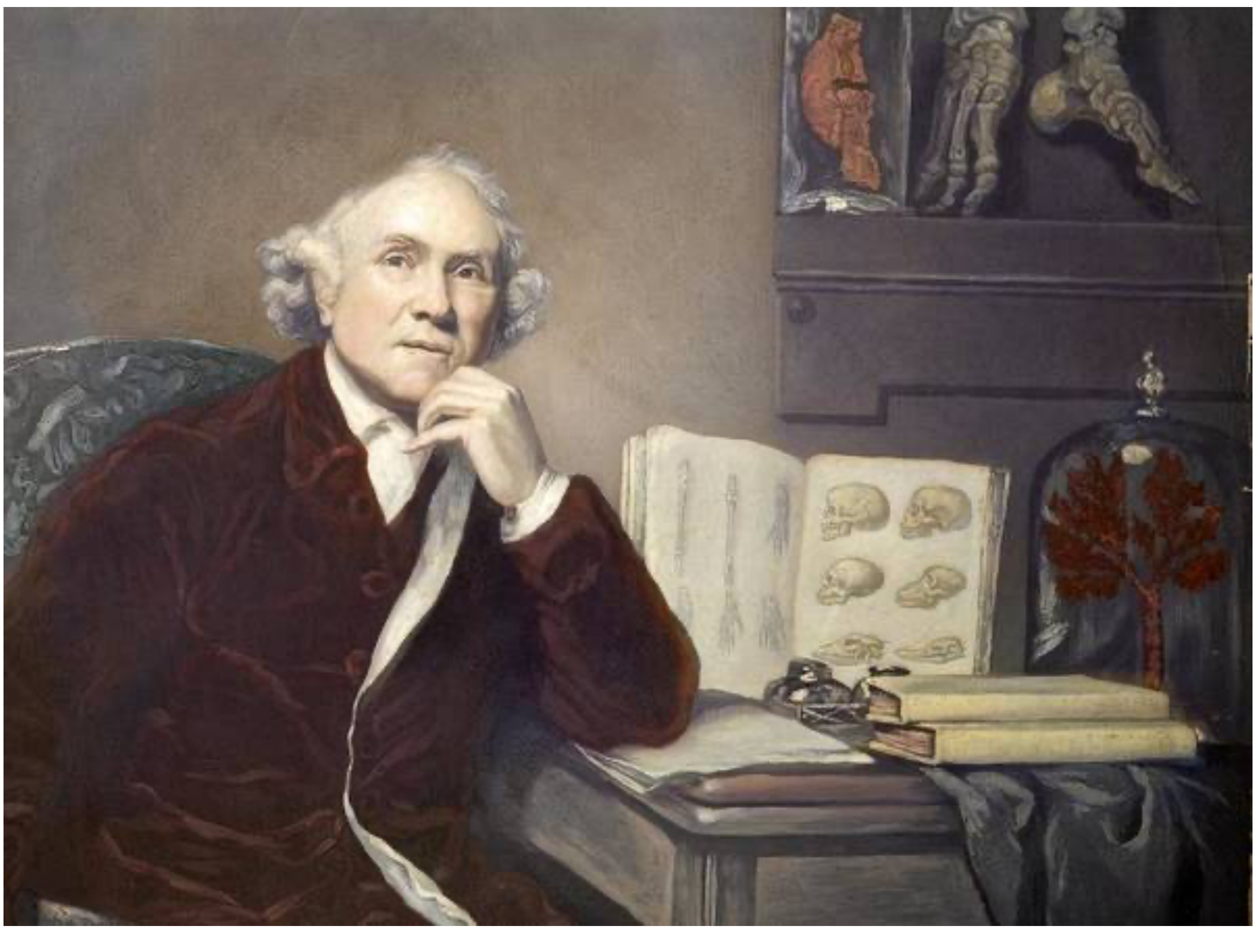
Founded 24 January 1895

Meeting Number 1977

March 2, 2023

4:00 P.M.

Self-Experimentation by Physicians



John Hunter

By William Patton, MD

Assembly Room, A. K. Smiley Public Library

Self-Experimentation by Physicians

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Summary:

In the last 250 years there have been roughly 700-800 recorded self-experiments. At least eight physicians died from their self-experiments, the last in 1928, and 10 physicians won a Nobel prize for their self-experiments, the most recent in 2005.

The most famous of these was done in 1765 by John Hunter, the father of scientific surgery. He inoculated himself with syphilis and gonorrhea and wrote in detail about the symptoms, signs, and course of the disease as he experienced it.

This paper presents the fascinating stories of other self-experimenters whose research was important in the development of anesthesia, the control of yellow fever, the beginnings of cardiac catheterization, and the causes and treatment of stomach ulcers and some kinds of stomach cancer. As the saying goes, "you can't make this stuff up."

There are no ethical rules that say that self-experimentation shouldn't be done. Many researchers reason "how can I expect another person to subject themselves to an experiment that I wouldn't consider doing on myself."

The Nuremberg trials of Nazi war criminals in 1945-1946 resulted in some useful, widely accepted guidelines for human experiments. Principle number 5 reads: "No experiment should be conducted where there is *a priori* reason to believe that death or disabling injury will occur, <u>except, perhaps, in those experiments where the experimental physicians also serve as subjects</u>."

Biographical Sketch for Bill Patton, MD

Bill grew up in Merna, Nebraska (pop. 400), graduating from Merna High School in 1961. He received his BA in Chemistry from Union College in Lincoln, NE in 1965, then attend Loma Linda University School of Medicine, where he received his MD degree in 1969. After an Internal Medicine Internship and an Ob/Gyn Residency at Loma Linda, he completed a Fellowship in Reproductive Endocrinology and Infertility at Harvard Medical School in 1975.

He joined the ob/gyn faculty at Loma Linda in 1975 where he has remained to the present, with a current rank of Professor. He is double board certified in Ob/Gyn and Reproductive Endocrinology and Infertility. He served as Chief of the Section of Reproductive Endocrinology and Infertility for 15 years and had been Department Chair of Ob/Gyn for 6 years at the time of his retirement from clinical practice in 2010.

As an academic physician he published the usual papers and received the usual honors such physicians receive. Following retirement from clinical practice, he has continued to actively teach and mentor medical students, residents, and faculty as a volunteer faculty member.

He has been an avid amateur astronomer since 1957, has lectured on astronomy to many different groups, and has been an active member of the Riverside Astronomical Society for many years. He loves boating--power, sail, row, and paddle--and has built a sailboat, a sliding-seat rowboat, and a kayak. He also enjoys cycling (has ridden every street in Redlands), and is an avid reader of science, medicine, history, and current events.

He has lived in Redlands since 1975, where he and his wife, Julie, have raised 2 sons.

Self-Experimentation by Physicians

By Bill Patton, MD

Alexander Pope (who lived from 1688-1744) famously said "the proper study of mankind is man." This is the basis of human medical experimentation and, of course, self-experimentation, the most basic form of human experimentation.

When I started researching this topic, I thought it was probably quite rare. For many years I've been teaching about the first known physician self-experimenter, John Hunter, the father of modern scientific surgery (who lived from 1728-1793.) In 1765 when he was 37, Hunter deliberately gave himself syphilis and then wrote a classic treatise about his symptoms and signs and the progression of the disease. He thought that syphilis and gonorrhea were one disease, and the experiment was done to prove or disprove that theory.

He obtained some pus from a patient with a urethral discharge and scratched his penis with a needle that had been dipped in the pus. He also put some pus under his foreskin. Within a few days, he developed the discharge and burning characteristic of gonorrhea, and then several weeks later, he developed a typical syphilitic sore (chancre), leading him to conclude that they were one disease. The patient likely had both gonorrhea and syphilis so Hunter's conclusion that they were one disease was incorrect. Hunter may well have paid for this experiment with his life. Advanced syphilis affects many organs and tissues including the aorta and coronary arteries. Hunter developed angina pectoris several years before his death which occurred during an anginal attack.

Hunter was the tenth child of ten in a poor family. He hated school and was largely self-educated in science by roaming the woods, examining plants and animals, and dissecting hundreds of small animals. His older brother, William was a surgeon in London and John apprenticed to medicine, surgery, and anatomy under him. Hunter eventually became the surgeon to George III, king of England. He made seminal contributions to the physiology of wound healing and inflammation, the care of battlefield gunshot wounds, the separateness of maternal and fetal blood circulations, and the role of the lymphatic system. He even transplanted human teeth-- into a cock's comb--and did the first recorded human artificial insemination for a man with hypospadias.

As I researched further, I discovered that self-experimentation is much more common that I had thought. In the last 250 years there have been roughly 700-800 recorded self-experiments in medicine, almost all by physicians. At least eight physicians died from their self-experiments, the last, Alexander Bogdanov, in 1928. He was researching the possibility of treating premature aging by blood transfusions. and died after giving himself the 12th transfusion in a short period---likely incompatible blood. Ten physicians won a Nobel prize for their self-experiments, the most recent Barry Marshall, in 2005.

In the next few minutes, I want to tell you a few of the amazing stories about these courageous --perhaps foolish--physicians and what they did to themselves in the name of curiosity and discovery. These men (and they were all men in those days) contributed to our knowledge about anesthesia, yellow fever, cardiac catheterization, and gastric ulcers.

At the time of the development of general anesthesia in the 1840's, surgery was often demonstrated in the amphitheater, a circular room with a large skylight, a wood floor covered with sawdust to absorb blood, a wooden table in the center surrounded by raised seating for observers, and a wood stove in the corner. The usual arrangement was for the patient to be held down by several strong assistants and often "bite the bullet", a small wad of leather. The patient would receive some liquor and perhaps a sponge soaked in a tincture of poppy seeds to suck on.

Surgery was done very quickly. Robert Liston, considered at the time to be the greatest surgeon in England, often would ask to be timed as he "performed" the amputation of a leg. Thirty-five seconds seems to have been his record. Most good surgeons took a minute or two. (We still use the term "performed" today to describe doing surgical procedures and Liston was certainly a performer.) One can only imagine the pain involved for the patient during those terrible seconds.

A number of self-experimenters contributed to the development of general anesthesia. Laughing gas parties (nitrous oxide) were popular forms of entertainment dating from the 1700's. A showman would come to town, reserve a hall, and people would come and pay to see their friends and neighbors inhale nitrous oxide (contained in a silk bag) and then make fools of themselves as their speech and balance became impaired. In December 1844 a Hartford dentist named Horace Wells attended a laughing gas party and noticed that he did not feel any pain when he bumped his leg hard as he stumbled when he returned to his seat after inhaling the nitrous oxide gas. He obtained a small silk bag containing some of the gas from the showman, and the next day took it to his office, persuading his partner to pull one of his teeth after he had inhaled the gas. He felt no pain.

In 1846, after using it successfully on a number of his patients, he persuaded a well-known Harvard surgeon, John Collins Warren, to allow him to demonstrate it as an anesthetic for a tooth extraction in front of the faculty and students of Harvard Medical School in the amphitheater at the Massachusetts General Hospital. During this demonstration by Wells and Warren, the patient wasn't given enough nitrous oxide, and he cried out in pain during the procedure, even though he claimed afterwards that he had felt no pain and remembered nothing. This was greeted by cries of "humbug" from the observers in the gallery. Medical students, residents, and academic physicians are among the most skeptical of all people.

At about the same time William Morton, a 27-year-old dentist and former partner of Wells, who was using his dental practice to pay for attending Harvard Medical School, was experimenting with sulfuric ether as an anesthetic, both by inhalation and by rubbing it on a patient's gums. He also inhaled it himself, once even exhaling it into an open flame to test its safety. He was extremely lucky that it didn't ignite since ether is known to be very flammable.

On October 16, 1846, Morton administered ether to a patient who needed removal of a benign tumor of his jaw. This demonstration was done in the same amphitheater by the same surgeon, John Collins Warren, who had operated nearly two years before on Wells' patient. This time the patient lay quietly asleep, didn't move, didn't make a sound, and said he had felt no pain, nor did he remember the operation. At the end Warren turned to the observers and said "Gentlemen, this is no humbug!" General anesthesia was born.

In Scotland an obstetrician, James Young Simpson, was experimenting with pain relief for childbirth. He would try different potentially useful volatile liquids to observe their effects on dinner guests as they sat around a table on which was placed an open dish of the liquid selected for the experiment. When he tried chloroform, all the guests, including himself, awoke sometime later lying on the floor or slumped over the table, and realized that they had been rendered unconscious by the fumes.

Simpson began to use chloroform for childbirth, but it met some opposition from physicians who considered pain in labor as a useful and necessary part of normal birth and the Presbyterian clergy who felt that God ordained pain with labor as punishment for Eve's original sin. Simpson pointed out that when God made Eve "the Lord caused a deep sleep to fall upon

Adam," a very early record of anesthesia indeed. Chloroform became widely accepted after Simpson gave it to Queen Victoria in 1853 for the birth of Prince Leopold.
Chloroform is a much more dangerous anesthetic than ether with a much smaller margin of safety between desired effect and dangerous toxicity. US doctors preferred ether and nitrous oxide, but chloroform was still used occasionally in Scotland until 1980.

Ether and chloroform were used in the Civil War, but not widely. The problem of infection was still the gorilla in the room for civil war surgery and casualties. Joseph Lister published his famous paper on germ theory and antiseptic surgery in 1865, but it wasn't really accepted in the US until well into the 1880's after being brought to America by a man destined to be the most famous of all American surgeons, William Stewart Halsted (1852-1922).

Halsted was the son of a wealthy man, went to Yale, was a top student, captained the first 11-man football team in the country, and lived the life of a frat boy. He became interested in medicine and went to Columbia College of Physicians and Surgeons in New York City, one of the top medical schools of the day, graduating in 1877 at the top of his class. At that time, the world's centers of medical learning and research were in Germany and Austria, and so Halsted went there in the late 1870's to "walk the wards" as many young surgeons of means did in his day, studying under the great surgeon Theodore Billroth, among others.

He learned and came to believe the Listerian principles of antiseptic surgery, but when he returned to New York City he found that those principles were not accepted in America yet, so he set up his own sophisticated tent on the Bellevue hospital grounds to do his own surgery there. His results, of course, were excellent in comparison to other surgeons who were not using antisepsis, and he quickly became the leading surgeon in New York City.

In 1885 he became interested in using cocaine as a local anesthetic. Let me tell you a little of the story of cocaine and how it came to be used as a local anesthetic. Chewing coca leaves had been practiced for centuries by South American peoples (the Incas called it "the divine plant") to improve high altitude tolerance and endurance. The leaves were glowingly described by the famous German explorer, Alexander von Humboldt after his first contact with them in 1801, but cocaine was not isolated and purified from the leaves until 1859. It was initially developed by several pharmaceutical companies but none so successfully as Parke-Davis in Detroit, who marketed the drug as a cure-all for everything, including opiate addiction. For a brief period beginning in 1885, Parke-Davis even took control of *Index Medicus* (the print index of every medical publication in the world), and the company's illustrated ads for cocaine were found among its pages.

In 1883 a young physician in the mental wards of the large Vienna Krankenhaus hospital named Sigmund Freud had begun to self-experiment with pure cocaine, hoping it would be a means to help his best friend, a surgeon, overcome an addiction to morphine. He found that it gave him more strength and faster reaction times as measured by some special instruments he developed. He also noted it gave him pleasurable feelings of well-being and that it made his tongue and cheeks numb, but he failed to recognize the potential of the drug as a local anesthetic, something he would always regret.

He wrote the first definitive book about cocaine, Uber Coca, published in 1885, incorporating his own experiences and feelings as well as his scientific observations. Unfortunately, it didn't cure his friend's morphine addiction and they both became addicted to cocaine.

One of his friends, an ophthalmologist named Karl Koller found through animal and then self-experimentation that cocaine was a very effective local anesthetic in the eye. He presented this at a large meeting in Heidelberg in 1884, and he is given the credit for discovering local anesthesia. Cocaine is still used as a local anesthetic for eye surgery.

Coca Cola was introduced in 1886 as a patent medicine and tonic. Coca Cola contained coca leaves and cola nuts dissolved in alcohol and water and it sold well. Koller was, of course, soon nicknamed "Coca Koller" by Freud Cocaine was removed from Coca Cola in 1903 but coca leaves were retained for flavor.

There were no laws or regulations dealing with drugs or addiction in the late 19th century. Prescriptions were not required. Cocaine was readily available, but quite expensive.

William Stewart Halsted in New York City, heard of Freud's work and began in 1884 to do a carefully controlled series of experiments with cocaine as a local anesthetic on himself. He used the hypodermic syringe that had been invented in 1853 to inject the drug through his skin and into tissues close to nerves. It was very effective as a local anesthetic and nerve block. He also discovered that sniffing the powder relieved his weariness and created a sense of well-being.

The addictive potential and dangers of cocaine were not well understood nor widely publicized at that time, so of course, he became addicted. Halsted's friend, William Henry Welch, from his Bellevue training days, helped him to successfully get off cocaine by hospitalizing him for several months in Rhode Island. He also gave him morphine, but then Halstead quickly became addicted to morphine.

Welch, who by then was dean of the new Johns Hopkins Medical School in Baltimore believed that Halstead had overcome his morphine addiction, when in 1892 he appointed him the first Professor of Surgery. Halstead joined the other 3 famous original professors there--William Welch, pathology, William Osler, medicine, and Howard Kelly, gynecology. The four were captured by John Singer Sargent's famous 11'x10' painting of 1906 which hangs in the Great Hall of the Welch Memorial Library at Hopkins.

Halsted became famous as the father of modern surgery, developing new techniques and operations for inguinal hernia repair (still used today), radical mastectomy for breast cancer, thyroid surgery, gall bladder surgery, and bowel surgery, to name a few. He introduced the new methods of aseptic surgery, nurtured the careers of the men who founded neurosurgery and urology, and developed a world-famous surgical training program. He was truly the "Johnny Appleseed of surgery in America"--his trainees "seeded" surgery departments to this day.

How he came to invent the rubber glove for surgery is a romantic story. His OR scrub nurse, Carolyn Hampton, had to dip her bare hands repeatedly in carbolic acid, and other irritating chemicals to kill germs. They became red and raw. Halstead was attracted to her and later married her. He went to the Good Year Tire and Rubber Company and, together they developed the rubber surgical glove to save her pretty hands.

He remained addicted to morphine for the rest of his life, and would occasionally go away for cocaine binges, keeping it all a secret until his death in 1922 at age 69 from mouth cancer that he acquired from chain-smoking cigars.

Cocaine also found a use for spinal anesthesia. In 1886 it was discovered that a needle could be inserted between the vertebral spines into the spinal canal to obtain spinal fluid--a so-called spinal tap. In Germany in 1898 a surgeon, August Bier (1861-1949) and his assistant, August Hildebrandt (1868-1954) did major surgery on 5 patients by injecting a cocaine solution to replace the withdrawn spinal fluid. This caused numbing of the lower body, but there were side effects afterwards not too different from those of general anesthesia, so they decided to experiment on each other to clarify doses and techniques.

For the first experiment, August Hildebrandt planned to inject August Bier. He put the needle in, got back some spinal fluid, but then found that the syringe he had that contained the cocaine solution didn't fit on the needle hub and this prevented him from injecting enough cocaine to provide much anesthetic effect.

Four or five hours later, after getting a syringe that would fit, Bier injected Hildebrandt. A good level of anesthesia was obtained from the waist down within a few minutes. Bier then tested the level of anesthesia on his friend Hildebrandt. A curved needle driven deep through the skin of his thigh produced no pain. A needle was then driven into the tibia without sensation. Several hammer blows to the shins, touching a lighted cigar to the thigh, and pulling out of some hunks of pubic hair followed--still no pain or sensation. The final test was grabbing Hildebrand's testicles, squeezing, and pulling hard--well tolerated. Apparently, they were still friends after all this. Hildebrandt had a bad headache the next day, a known common complication after spinal anesthesia.

When a patient is given a general anesthetic like ether they go to sleep, become unaware and amnesic, and then, if more and more anesthetic is given, their muscles get relaxed. Still deeper levels of anesthesia can cause cardiac arrhythmias and death. When someone's abdomen is opened, muscle relaxation is desirable, so the intestines are not pushed out through the wound making it difficult to see and get at the area of interest. This all requires careful regulation of the concentration of anesthetic gas. Those of you who have done or seen surgery know that there is a constant tension between the surgeon who wants as much relaxation as possible and the anesthesiologist who wants to give the minimum amount of anesthetic needed to do the job to avoid the dangers of anesthetic overdose.

One development to keep patients relaxed without having to use deep levels of anesthesia with their attendant risks was to use a paralyzing agent such as curare. This is the arrow poison made from plant leaves that South American Indians used in hunting. It had been known since Europeans arrived in the 15th century, but was not purified until the 1850's, and not used in surgery until the 1940's.

By 1944 a purified, standardized preparation of d-tubocurarine was being produced by Burroughs-Wellcome pharmaceuticals in England. Dr. Frederick Prescott, head of research at the company, proposed a protocol for testing doses of the drug using himself as the experimental subject. His vital signs would be closely monitored and recorded, and a noted anesthesiologist would be present ready to assist him should he encounter complications. The first experiment involved IV injection of a low dose of the drug and within a few minutes produced facial paralysis, inability to speak, double vision, and weakness, but not failure of respiration. He could still cough and swallow.

A week later, a double dose produced more rapid onset of slightly more severe paralysis with recovery in about 15 minutes, as before. Two weeks later a triple dose was given. Within 2 minutes Prescott was completely paralyzed except for very weak breathing and could not speak or open his eyes. The team had not worked out any set of signals, so when, at 3 minutes Prescott was intubated and ventilated, no one could know that he felt like he was suffocating and drowning in his own secretions and was terrified, even though he was pink. His pain sensation was tested by tearing off strips of adhesive that had been attached to his chest and legs. He felt the pain clearly.

About the same time Dr. Scott Smith in Utah who did not know of Prescott's work, which was yet unpublished, became the subject of similar experiments to test for pain sensation, awareness, and memory after being given curare. Pre-arranged signals were in place. Smith found no pain relief and complete preservation of awareness and memory. Muscle relaxants, often relatives of curare are used today along with narcotics to help with pain, and inhaled gases and other IV agents to induce loss of consciousness and to cause amnesia. This is called balanced anesthesia.

Our next experimenters worked with yellow fever, known as the yellow jack, after the yellow signal flag for "Q". ("I request free pratique"--permission to enter port after inspection for absent contagious disease(s) on board). Yellow fever originated in West Africa and came to the Caribbean with the slave trade in the 17th century. Epidemics were common in colonial times along the eastern and southern seaboards as far north as Portsmouth, New Hampshire. It's a very serious disease with no effective treatment and a mortality rate of 20-30%. It attacks the liver with high fever, jaundice, and internal hemorrhages from the stomach and esophagus with vomiting of black blood (a result of liver damage). In the 1793 epidemic in Philadelphia, 10% of the population died. No one knew the cause.

In 1802 a 17-year-old medical student in Philadelphia named Stubbins Ffirth observed that the disease wasn't obviously transmitted from person to person. Nurses, relatives, and others who had close contact with a patient wouldn't usually get the disease. He conducted about 30 experiments on himself, rubbing various body secretions from sick patients on his skin, sleeping on the dirty linen of sick patients, encouraging patients to breathe in his face, ingesting black vomit taken directly from a sick patient, and even injecting himself with the blood of a sick patient--all without getting sick himself.

He was lucky with the blood. We now know that the yellow fever virus is only present in the blood during the first 2-3 days of the disease even though the disease becomes much more serious thereafter and death or recovery usually takes about two weeks to occur. He probably injected blood from a patient who was past the blood infection stage, but still very ill. Ffirth published his findings, which were largely ignored. After all, at that time everyone "knew" that most disease was caused by miasmas--so-called foul-smelling "bad air."

Beginning about 1880 Dr. Carlos Finlay (1833-1915), who practiced in Havana, postulated that mosquitos transmitted the disease, noting that it occurred in the northern cities only during summer, and there were often reports of large numbers of mosquitos during epidemic years. In the next 19 years he did over 100 experiments, but none on himself, trying to show transmission of yellow fever by allowing infected mosquitos to bite people under observation without clear success.

We now know that the mosquito has to bite a yellow fever victim in the first 3-4 days of the 2 week disease and will not transmit yellow fever until she has incubated the virus in her body for about 10-14 days. We also now know that such a mosquito remains infectious for 60 -70 days. Finley had likely allowed his infected mosquitos to bite test subjects too soon.

More soldiers died from disease than bullets in all American wars until WWII. The short Spanish-American war of 1898 was no exception and many American soldiers fighting in Cuba contracted yellow fever and many died.

In 1900 Army Surgeon General George Sternberg, considered the father of American bacteriology, created the US Army Yellow Fever Commission headed by Major Walter Reed, assigning it to Havana, and charging it with investigating the cause of the disease and how to prevent its occurrence. Three other military physicians--Aristides Agramonte, James Carroll, and Jesse Lazear--were also appointed to the Commission. All were trained pathologists and/or bacteriologists.

Based on Finlay's work the Reed Commission decided to focus on mosquitos and in early August the four of them made a pact to experimentally expose themselves to yellow fever to aid in their research. Interestingly, Walter Reed left to go back to Washington the day after the pact was made, and he never directly participated in the subsequent experiments.

A female mosquito of the *Stegomyia fasciata* (later renamed *Aedes aegypti*) species was allowed to bite a yellow fever victim, then she was placed in a test tube with a cotton plug in the end. After several days, the test tube was inverted on the forearm of the test subject, the cotton plug was slipped out, and she would fly down and bite for several minutes.

Jesse Lazear allowed such a potentially infectious mosquito to bite him, and eight other soldier volunteers were bitten by other infected mosquitos. None came down with yellow fever. Most likely the mosquitos had not harbored the virus long enough for it to multiply sufficiently---the same mistake Finley made.

James Carroll was next. The mosquito that bit him had bitten a patient with severe yellow fever 12 days previously. About 10 days after his test bite he developed a slight fever and headache. The fever increased in the next few days to 104. Any exposure to light caused severe headache. He sweated profusely, his back ached, his gums were swollen, and his skin and eyes turned bright yellow. But he was lucky--he did not bleed internally, and he gradually recovered.

On September 13 Jesse Lazear allowed another bite, and this time he contracted a severe case of yellow fever, and he died on September 25. Additional human experiments by the remaining members of the team (not on themselves) convinced them that mosquitos transmitted yellow fever. This led to the famous work of Dr. William Crawford Gorgas begun in 1901 to eradicate yellow fever in Cuba and the Panama Canal construction zone by killing mosquitos or preventing them from hatching by eliminating all standing water. The disease disappeared from the US in 1905 and the last case in Panama was in 1906.

But still no bacterium had been identified in yellow fever patients. The submicroscopic concept of viruses was advanced in 1898, but it wasn't until 1927 that yellow fever became the first human virus to be isolated. The yellow fever virus is 40-50 nm in diameter. For comparison, the average bacterium is 1000 nm, a red blood cell is 7000 nm, and the period on a page is 500,000 nm. A good light microscope can resolve objects down to about 200 nm.

In 1938 a South African, Max Theiler (1899-1972), developed a live, attenuated vaccine, weakening the virus by passing it sequentially through multiple animal hosts (mouse and chicken embryos). He was the first to get the vaccine, injecting it into himself--believing it would be safe, but not knowing for sure whether it would infect him. He got a little fever and a sore arm. The vaccine was given to large numbers of people in Brazil and shown to be very effective. That same vaccine is the one still used today. Max Theiler received the Nobel Prize for this work in 1951.

I often use the story of yellow fever in teaching the history of medicine, because it spans 140 years or so from Stubbins Ffirth to Max Theiler, the time period of the major transformation of medicine from a primitive art to a modern science.

Our next brave (or foolish) self-experimenter was a German physician named Werner Forssmann (1904-1979) who catheterized his own heart. In 1929 he had just finished medical school and was interning at a small hospital near Berlin. He had seen a sketch in one of his textbooks showing a catheter being passed into the jugular vein of a horse's neck and then down into the heart. He asked his chief of surgery if he could try this on a dying patient, but was refused permission, and was told to experiment first on animals. He didn't want to be bothered with that, so he decided to do it secretly on himself. In order to get access to the OR and needed equipment, he cultivated the good will of the 45-year-old nurse in charge, Gerda Ditzen, who became very interested and excited about what he wanted to do. She agreed to help, but only on the condition that she, not he, would be the test subject.

They went to the OR during the noon-hour one day and prepared the instruments and a ureteral catheter that they would need for the experiment. The rubber ureteral catheter was about 30" long--the only catheter they could find that was long enough and small enough to reach the heart from the vein in the elbow. (The ureter, the tube conveying urine from the kidney to the bladder, is usually catheterized from inside the bladder). Gerda lay down on the table, allowing him to restrain her arms and legs so she wouldn't move them during the procedure. Werner proceeded to prep the equipment behind her, and while she patiently waited for him to get ready, dabbed the elbow crease of his left arm with iodine solution and injected local anesthetic.

While he waited for it to take effect, he returned to Gerda and prepped her arm with iodine as well. He went behind her again and cut down with a scalpel to the vein in the elbow crease of his own left arm. He inserted a large hollow needle into the vein, and then passed the catheter through it up the vein toward his shoulder. He could feel the catheter make the corner in his shoulder and begin to go down toward his heart, but it was not particularly painful.

About then Gerda wondered what was going on and asked when he was going to continue with her. He stepped over to her, released her arms and legs, and showed her the catheter in his own arm. She was furious, but he convinced her to help him get to the X-ray department in the basement to get a film to see where the catheter was and to help pass it the rest of the way into his heart.

They persuaded the X-ray tech who was there to help them with fluoroscopy, which is done with a screen in real time, to locate the catheter. Gerda held a mirror so Werner could see to guide it further into his heart. The catheter was just long enough to reach into the right atrium but did not pass into the right ventricle. They took an X-ray to document the position of the catheter and the success of the experiment. Forssmann was lucky that the catheter was too short to enter the ventricle. When the endocardium, the lining of the heart, is touched, particularly in the ventricle, dangerous, sometimes fatal cardiac arrhythmias can result.

When Forssmann's surgery chief learned of the illicit experiment, he was initially very upset and lectured the young intern about disobedience. But then he asked to see the X-ray, and he became excited when he realized the significance of the experiment. He took Forssmann to dinner to celebrate. Forssmann was allowed to repeat the experiment on himself several more times in the next month. A paper describing the experiment was published in the leading German medical journal, *Klinische Wochenschrift*, and it generated a sensation in the press.

Forssmann then went on to attempt injections of X-ray contrast into the heart to obtain clearer outlines of the chambers and valves. He did animal experiments with several species and several chemicals before finding success with sodium iodide in dogs. Again, he became the first human subject, succeeding in obtaining somewhat poor-quality images of the contrast in his heart. By now he had worn out the arm veins in both arms and was using the large femoral vein in his groin for the catheter insertion site. He ultimately catheterized his own heart 9 times.

In 1935 the daring Forssmann had a colleague attempt to inject dye into his aorta by stabbing a long needle directly into the aorta through his upper back. The first attempt was unsuccessful and was so painful that he didn't persist with this line of inquiry. This pleased his urologist physician wife who pleaded with him to stop experimenting on himself. He also became a practicing urologist, but it was hard for him to find work because of his controversial self-experiments.

Forssman became a Nazi during the 1930's, and was offered unlimited experimental subjects, but refused and was able to keep clear of the unethical experiments done during that era by the Nazi physicians. During WWII he was captured by the Allies and put in a prison camp. After the war, he couldn't practice medicine in West Germany because of his Nazi history, so he became a laborer. In the 1950's West Germany rescinded the prohibitions on former Nazi physicians, and he was able to practice urology in a small farming community with his wife.

In 1956 he was awarded the Nobel prize in medicine and physiology along with two physicians at New York's Bellevue Hospital, Andre Cournand, and Dickenson Richards who had built on his work.

I remember that I got to do a cut-down and pass a catheter into a patient's heart when I was an intern--under the watchful eye of a cardiologist of course. About all we could do then was inject contrast and measure pressure gradients across valves. Now cardiac catheterization is an everyday procedure, allowing sophisticated diagnostic imaging and testing, coronary artery clot removals and stent placement, and even aortic valve replacement through a catheter--all avoiding open heart surgery

The last story I want to tell involves ulcers, one of the major breakthroughs in medicine in the last few decades, and the most recent self-experimenter to win the Nobel prize. Most of us have long believed that ulcers are caused by stress or hot foods. That is not true. As a result of this experiment and its resulting further research, we now know that most ulcers are caused by a corkscrew-shaped bacterium named *Helicobacter pylori*. The remarkable self-experiments of Dr. Barry Marshall (born in 1951) in Australia in 1984 helped establish this bacterium as the cause of stomach ulcers, gastritis, and some types of stomach cancer.

Dr. Robin Warren, a pathologist (born 1937) had seen a little spiral bacterium under the microscope in stomach biopsies from patients with gastritis and, together with Dr. Barry Marshall, a fellow in gastroenterology, had been attempting to culture it unsuccessfully. They succeeded because of a fortuitous accident. When a lab does a culture on a plate, the bacteria being sought usually grow rapidly in a day or two, are identified, and then the plate is discarded because during further incubation there is overgrowth of many other superfluous organisms. One of their experimental cultures was left in the lab over the weekend instead of being thrown out, and the bacterium grew after 4-5 days.

Marshall subjected himself to a gastroscopy, obtaining cultures and biopsies of his own stomach lining to be sure he didn't already have this little organism --now called *Helicobacter pylori*--that lives in the crevices of the stomach lining. Everything looked good.

Three weeks later a positive culture was obtained from a patient with dyspepsia, and it was confirmed that the organism was sensitive to the antibiotic tinidazole. Marshall then drank a "brew" composed of a broth made from two positive culture plates. He figured he might get an asymptomatic infection and maybe an ulcer perhaps months or years later.

He describes it best. "After five days, I started to have bloating and fullness after the evening meal, and my appetite decreased. My breath was bad, and I vomited clear watery liquid, without acid each morning at 0600."

Another gastroscopy now revealed that he had severe acute gastritis and *H. pylori* was cultured from the biopsies of affected areas. He continues: "After 14 days, I repeated the endoscopy and then, before the results were known, began taking antibiotics (on my wife's orders)." The symptoms disappeared within 24 hours. "However *H. pylori* were not seen on that biopsy so I might have already had a spontaneous cure. Robin Warren believes that the bacteria were still lurking and would have been detected on culture, but by then I was already treated. The paper was published in the third person, but it gradually became known that the 'male volunteer' was me."

The relationship between this organism and ulcers, gastritis and stomach cancer has been confirmed and amplified by much subsequent research that continues. There are now good tests for screening and diagnosis. The cure is a short regimen of common antibiotics. Barry Marshall and Robin Warren received the Nobel prize in 2005 for this discovery. Both are still living.

There are no ethical rules that say that self-experimentation shouldn't be done. Many researchers consider them to be the right thing to do. They reason "how can I expect another person to subject themselves to an experiment that I wouldn't consider doing on myself."

The Nuremberg trials of Nazi war criminals in 1945-1946 resulted in some useful, widely accepted guidelines for human experiments called the Nuremberg principles of human experimentation. Principle number 5 reads: "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 the experimental physicians also serve as subjects."

All institutions supervising research today have an IRB--institutional research board--that reviews and gives approval and permission for any human trials conducted in that institution. Some, but not all institutions, insist that self-experiments should also receive such IRB approval. What do <u>you</u> think?

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