Mason, 7th grade student, thrusts up his hand: “Ms. Rainey, in our discussion of diseases, you mentioned that many drugs are being discovered. Can you tell me why new drugs cost so much? My mom has rheumatoid arthritis, I think it is called. Her current medicine doesn’t work too well, and the doctor has prescribed a new drug that should work better. But my folks are always complaining about how much the new treatment costs. Thanks to this new drug, I’ll probably have to wait forever for that new bike I’ve been wanting!”

Ms. Rainey replies, “Well, Mason, what do you know about how new drugs get discovered?” Mason twists his mouth and with furrowed brow says, “I guess some biologists make a discovery about what causes a disease, and then chemists make a compound that blocks that cause. … or maybe counteracts the bad effects.”

Not fully satisfied with that answer, Ms. Rainey continues, “If you were developing a new drug for a disease, what would you expect the drug to do?”

“Well obviously,” Mason says with a smirk, “the drug ought to work. And I guess if there are other drugs for that disease, it ought to work better than what is already available.”

Now Ms. Rainey smiles, “Very good, Mason. There is one more thing you would need. Do you know what that is? Think about the fact that all drugs have side effects.”

“Oh, I see. The drug must be safe. At least there ought to be a dose that is effective and yet safe. There shouldn’t be too many side effects, and those it does have shouldn’t be too bad.”

“Well done, Mason. Now how does one find these things out?”

Mason pauses to rub his arm he hurt in yesterday’s game and then replies, “I guess you have to do some experiments to see if the drug is safe and effective. Oh, and I guess you need to know what dosage to use. Too much of any drug would be a poison.”

As a smile crosses Ms. Rainey’s face, she continues “Right! These experiments or tests are called *clinical trials*. In these, many people with the disease are put into groups and each group, except one, receives a different dose of the drug being tested. That one group serves as a control and unknowingly receives a fake drug. All new drugs first go through pre-clinical testing on lab animals. All these trials cost a lot of money. Now do you see why new drugs cost so much?”

For centuries, medical doctors had very little training. In fact, there wasn't much known at all about diseases and how to treat them. This led to all sorts of bizarre treatments. "Medicine men" developed all sorts of chants and rituals to ward off "evil spirits" that were at the time believed to cause disease and illness.

One particularly dangerous early "medical" treatment was blood-letting, widely practiced from about the 3rd century BCE in Egypt until well past medieval times. The idea behind bloodletting was that disease was caused by "bad blood. It was believed that draining out the "bad blood" would rid the body of the disease. Of course, it didn't. If the patient managed to recover, they did so despite of, not because of, bloodletting. As medicine advanced with the introduction of drugs and various surgical procedures, it became clear that a system was needed to establish if new treatments were safe and effective. The system that evolved has become known as "Clinical Trials."

Meet the Scientists

James Lind (1716-1794) and Others

No one scientist developed a system for drug development. Drug development has a long history involving numerous people, beginning with some ancient times to the first randomized controlled trial conducted in 1946 for the development of the antibiotic, streptomycin.

The first clinical trial might have been conducted by Babylon's King Nebuchadnezzar (605 – 562 BCE). He thought that a diet of only meat and wine would make subjects healthy. He ordered everyone to go on such a diet. Vegetarians objected. So, he let them stay on their diet so he could compare the results of the two groups. After 10 days, it seemed that those who ate only plants and drank only water were a little healthier. These results led to a public policy decision allowing vegetarianism.

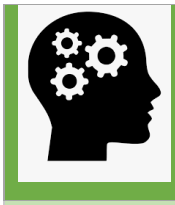
The modern methods of clinical trials stem from a pioneering experiment performed in the 1747 by James Lind, a Scottish physician. Lind's father was a merchant in Edinburgh, and his mother's social connections with medical people led Lind to become a physician. In those days, medical training was rather unstructured and informal. In his initial medical training, Lind did not actually enroll in the Edinburgh university medical school, but he did attend lectures sometimes. He apprenticed to be a surgeon, and after that training, he joined the British navy in 1738. His first assignment was on a battle vessel that the British used to attack Spanish merchant ships. In 1748, Lind quit the navy and went back to the University of Edinburgh to complete formal M.D. training. He married and set up medical practice in the same town.

Ten years later, he received a letter of appointment as Chief Physician to His Majesty's Royal Hospital at Haslar and left his private practice. While working at the hospital, Lind continued to experiment and publish, which enabled him to gain some recognition among medical professionals in England. Because of his navy background, he developed an interest in the diagnosis and treatment of scurvy, a disease usually occurring in sailors. Lind wrote a lengthy and somewhat confusing book about scurvy. Of the book's 450 pages, only four gained lasting

significance. They described the first controlled clinical trial that tested six possible treatments for scurvy. Nobody knew how to treat scurvy, because the cause was unknown. Initially, Lind believed there were multiple causes of scurvy, including diet, foul air, and lack of exercise. His shipboard experiments revealed that the cause was inadequate diet.

Many scientists created the principles and procedures used today in the development of new drugs (pharmaceuticals) and surgical procedures. We will explain each of the following:

- Randomization
- Placebo
- Blindness to treatment conditions
- Ethical standards
- Preclinical testing on laboratory animals



Think About It!

In your notebook:

- Summarize the discussion between Mason and Ms. Rainey.
- Write a few words that sumarize what each idea means.

Randomization

In Lind's time, scurvy was especially common in sailors who spent many months at sea, with everyone eating the same, limited diet. Lind was called to treat sick sailors on the ship *Salisbury*, which was enforcing a blockade in the English Channel. The sailors all had similar symptoms: putrid gums, skin spots, low energy, and weakness of the knees. All the sailors onboard ate the same diet: water gruel sweetened with sugar in the morning; fresh mutton broth, light puddings, or boiled biscuit with sugar for lunch; and barley and raisins, rice and currants, sago and wine for supper.

Not knowing how to treat the sailors' condition, Lind thought the cause might be due to a deficiency in their diet, because that was the one thing common to all who were ill. To test this idea, Lind randomly assigned the sailors to different diets. For this test, he randomly picked two sailors to receive different diet additives. Those additives were:

- A quart of cider a day.
- Twenty-five drops of elixir vitriol three times a day.
- Two spoonsful of vinegar three times a day.
- A course of seawater.
- Two oranges and one lemon every day.

- A mixture of powders in a honey base.

Within just a week, clear improvement occurred in the two sailors who had received the oranges and lemon. No other treatment worked, though some minor improvement did occur in the cider group.

Why did Lind include the citrus fruit in the test? It might have been due to the rumors from some hundred years earlier that were attributed to the explorer Sir Richard Hawkins, who had claimed that oranges and lemons prevented scurvy in his sailors.

Lind apparently never realized that he had discovered the cause and treatment of scurvy. Though impressed with the rapid improvement after eating citrus fruit, he never became a big supporter of citrus as a treatment. He even advocated other, much less effective foods for treating scurvy. Perhaps not surprisingly, the British navy failed to recognize the importance of Lind's discovery for many decades. It was not until 1795, that the Admiralty insisted that its sailors have citrus fruit added to their diet.

Placebo

Obviously with many diseases, a patient may recover without any treatment. So, an appropriate test design should include at least one group that gets no treatment (a placebo). Thus, in the case of testing a new drug, for example, patients might receive sugar pills to make them think they are getting treatment.

Blindness to Treatment Conditions

Patients should not know to the treatment group to which they are assigned. Not only do they not know if the medicine is real or a placebo, they also do not know what the dose is. The reason for "treatment blindness is that psychological effects can influence the course of a disease. This reduces the risk of clinical trial patients "talking themselves into" being sick or recovering.

Many years passed after Lind's test of treatment in 1747 before placebos were routinely used in testing. However, it was only in 1863 that United States physician Austin Flint planned the first clinical study comparing a dummy remedy (placebo) to an active treatment for rheumatism.

Many more years passed before researchers realized that they could unintentionally affect trial results. They could be biased in interpreting test results if they knew in advance from which test group each trial data set came. Therefore, a so-called "double-blind" design was developed, wherein neither patient nor researcher knows in advance which treatment the patient is receiving.

The first randomized double-blind control trial tested the antibiotic streptomycin in the treatment of pulmonary tuberculosis. The trial was conducted in 1946 and included coordination of the physicians at the participating hospitals. The design included an untreated control group. A special feature of this trial's design was that chest x-rays were evaluated by experts who did not know which treatment the patients received. Patients did not know to which group they were assigned.

Ethical Standards

The basis for developing ethical standards can be found in the ancient Hippocratic Oath, which says that a physician should do no harm. However, this pledge was frequently violated in clinical trials until after WWII. Today, some ethical concerns remain about the use of placebos, especially in studies where the disease is progressing rapidly, and one of the treatments is likely to be beneficial.

The first International Guidance on the ethics of medical research involving subjects was the Nuremberg Code formulated in 1947. A key feature of the Code was that experimental subjects had to willingly consent to participate in the test. Later, the code was amended to require that patients had to know the risks that might occur from participation.

General principles and specific guidelines turned into U.S. legislation with the US National Research Act of 1974. Government laws and regulations have been progressively strengthened in more recent years and are enforced by the US Department of Agriculture (USDA; for animal research) and the Food and Drug Administration (FDA; for human research).

The FDA was founded in 1862 as a scientific institution and became a law enforcement organization after the U.S. Congress passed the Food and Drug Act of 1906. After that, legislation demanded progressively greater accountability for the marketing of food and drugs, and the need for testing drugs in clinical trials increased.

Today, all research institutions must have separate "compliance committees" for human and animal experimentation. No experiments are allowed until the researchers submit and receive approval of highly detailed. Plans must state specific procedures to be followed to protect the rights and welfare of the subjects.

All these regulations and others have made research very expensive. For that reason, many drug companies are moving much of their research to foreign countries. Many countries have less demanding laws and regulations and lower labor costs. Even so, research results must meet U.S. standards for safety and efficacy for the drug to be sold here.

Preclinical Testing on Laboratory Animals

It is much easier and less expensive to do much of the biomedical research on animals than on humans. The earliest known testing on animals was performed by Aristotle (384 – 322 BC) and Erasistratus (304 – 258 BC). A 12th century Arab physician in Spain used animal testing as an experimental method for testing surgical procedures before applying them to human patients.

We know of many incidents of the harm to humans from the use of substances that have not been first tested on animals. For example, in 1937 a drug company created the drug sulfanilamide that used the solvent diethylene glycol (DEG). Unknown to the developers was the fact that DEG was poisonous. The preparation led to mass poisoning and deaths of more than a hundred people. No animal testing had been done prior to the sale of the drug. This and other similar disasters led to

the passing of the 1938 Federal Food, Drug, and Cosmetic Act that required safety testing of drugs on animals before those drugs could be marketed for human use.

Another tragic drug fiasco occurred in the late 1950s and early 1960s with thalidomide. It was found to act as an effective tranquilizer and painkiller and was proclaimed a 'wonder drug' for a variety of ailments in addition to relief of anxiety. Because thalidomide suppressed morning sickness in pregnant women, thousands of pregnant women took the drug to relieve their symptoms. No testing on pregnant animals had been performed before the drug was used in humans. Thus, more than 10,000 children in 46 countries were born with malformations or missing limbs. The drug was withdrawn from the market in 1961.

We see from these stories of drug development testing that the need for testing for safety and efficacy was recognized early. But it took many decades to evolve the set of procedures that we rely on today. There are still some unresolved issues, such as the high cost and time delays of testing new drugs, vaccines, and medical procedures. Another problem is the requirement of placebos in clinical trials where seriously ill patients receiving placebos are more likely to die because they did not get the drug or medical procedure that might have saved them. Sometimes, there are no easy answers.

Sources:

Bhatt, Arun, (2010). Evolution of clinical research: A history before and beyond James Lind. Perspect. Clin. Res. 19(1), 6-10. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3149409/

Hajar, Rachel (2011). Animal testing and medicine. Heart Views. 12(1), 42. doi: 10.4103/1995-705X.81548 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3123518/

Milne I (2012). Who was James Lind, and what exactly did he achieve? The James Lind Library. http;// https://www.jameslindlibrary.org/articles/who-was-james-lind-and-what-exactly-did-he-achieve/

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