Legumes, lemons and streptomycin: A short history of the clinical trial

The first documented experiment resembling a clinical trial was not conducted by a scientist or doctor, but by an ingenious military leader who dabbled in architecture and is perhaps best known for the 7 years he spent roaming the wilderness eating grass. His name was King Nebuchadnezzar, and he ruled Babylon for almost 60 years, his reign ending in 562 BC.

At some point during his rule, according to the "Book of Daniel" in *The Bible*, Nebuchadnezzar ordered his people to eat only meat and drink only wine, a diet he believed would keep them in perpetual fine fettle.

But several youth of royal blood and herbivorous bent objected.

Far from being angry, the king, his curiosity piqued, permitted the dissenters to instead follow a diet of legumes and water — but only for 10 days, after which he would assess their health.

"It looks, historically, like man has always been curious and always looked to see if things can be improved," says Dr. Madhu Davies, a United Kingdom-based pharmaceutical medicine consultant and coeditor of the book *A Quick Guide to Clinical Trials*. "If you need a written, documented, citable source, then it's pretty much back to the Old Testament."

When Nebuchadnezzar's experiment ended, the bean-loving teetotallers appeared better nourished than the mandated meat-eaters, so the king allowed them to continue their diet. Not exactly a randomized, double-blinded, placebo-controlled clinical trial, but the modest experiment may have been one of the first times in human history that a medical test, however rudimentary, guided a decision about public health.

Today, a clinical trial is defined as a multiphase study conducted by researchers on human subjects to test a medical treatment or prevention strategy. The medical treatment under examination could be a drug, a surgical procedure, a medical device or a therapy. Prevention strategies subject to clinical study include lifestyle changes, dietary modifications and health education.

The most common type of clinical trial (Box 1, Box 2) is a parallel-arm experiment, in which subjects are divided into at least 2 groups. Ideally, the members of each group are identical in every way except one: some receive the treatment under test (active group); others don't (control group).

Researchers consider a treatment to work, or at least to have some effect, when the people in an active group have significantly better health outcomes than those in a control group. If the outcomes vary little, however, the treatment glides a few degrees farther along a trajectory into medical history's waste bin.

The first person to conduct a parallel-arm medical experiment was British physician Dr. James Lind, whom many scientists consider, with all due respect to King Nebuchadnezzar, the true father of the clinical trial. In 1747, after several weeks at sea, many in the crew of the British naval ship Salisbury had been forced prone by an all-too-common-at-the-time affliction among seafarers: scurvy. Where most saw only misery, Lind, the ship's surgeon, saw opportunity.

Lind selected 12 ill sailors and divided them into groups of 2. All the subjects displayed similar symptoms. ("They all in general had putrid gums, the spots and lassitude, with weakness of knees," he wrote in his 1753 paper *A Treatise on the Scurvy).* Isolated from the rest of the crew, the men were given the same rations, but each pair received a different scurvy treatment: either cider, a few drops of a weak acid, vinegar, seawater, nutmeg and barley water, or oranges and lemons. After 6 days, the

Box 1: Types of clinical trials

Clinical trials are typically classified by their purpose. By that standard, there are 5 different types:

Treatment: Tests new drugs (or combinations thereof), therapies, devices or surgeries.

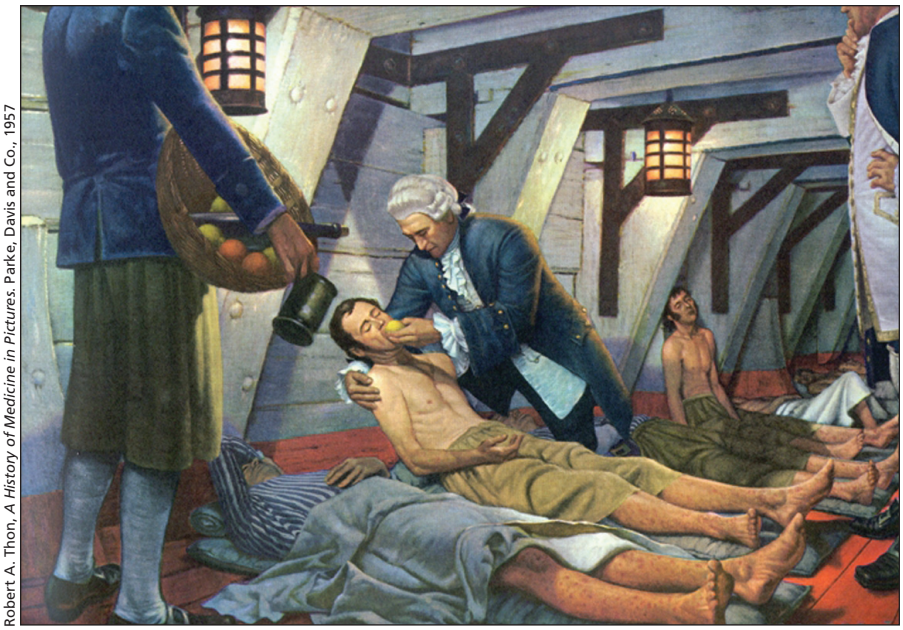
Prevention: Tests new means to prevent disease: medicines, vaccines, lifestyle changes, etc.

Diagnostic: Tests new ways of diagnosing diseases or conditions.

Screening: Tests new ways of detecting diseases or conditions.

Quality of life: Tests new ways of improving quality of life for people with chronic illnesses.

Source: US National Institutes of Health.



Robert A. Thon, *A History of Medicine in Pictures*. Parke, Davis and Co., 1957

In 1747, Dr. James Lind tested several scurvy treatments on crew members of the British naval ship Salisbury and discovered that lemons and oranges were most effective in treating the dreaded affliction.

Box 2: Clinical trial phases

Clinical trials are conducted in 4 phases, with each having a different purpose.

Phase I: Initial testing of a new drug or treatment on a small group of human subjects to evaluate a drug or treatments safety, as certain a safe dosage range and identify side effects.

Phase II: The therapy is tested on a larger group to determine its efficacy, (i.e., whether it works under ideal circumstances). For example, a phase II trial would ask whether an antihypertensive lowers blood pressure.

Phase III: Randomized controlled multicentre trials on even larger patient groups to confirm effectiveness, (i.e., whether the drug does more good than harm under usual care conditions). In the case of the antihypertensive, the trial might ask whether it lowers the risk of stroke.

Phase IV: Post-market studies gathering data on whether the drug affects population groups differently, or whether there are side effects associated with its long-term use.

Source: US National Library of Medicine.

ship's supply of fruit was spent, but by then it hardly mattered; the 2 men on the citrus treatment were already back on their feet. The others, to paraphrase Lind's description of their original condition, remained weak in the knees.

It would be more than a century before the emergence of another cornerstone of the modern-day clinical trial: the placebo. The word *placebo* first appeared in medical literature in the early 1800s. *Hooper's Medical Dictionary* of 1811 defined it as "an epithet given to any medicine more to please than benefit the patient."

But it wasn't until 1863 that United States physician Austin Flint conducted the first medical experiment comparing a dummy remedy to an active treatment. He treated 13 patients suffering from rheumatism with an herbal extract instead of an established remedy.

"This was given regularly, and became well known in my wards as the 'placeboic remedy' for rheumatism," Flint wrote in his 1886 book *A Treatise on the Principles and Practice of Medicine*. "The favourable progress of the cases was such as to secure for the remedy generally the entire confidence of the patients."

Control groups and placebos allowed researchers to compare treatments (and the fact that both are mainstays of clinical trials today attests to their importance) but problems remained — none worse than the creeping influence of bias.

"It is only in the late 18th century onwards, when elite medicine bifurcates and becomes enmeshed in a tug-of-war between mainstream and unconventional medicine that the imperative to demonstrate medical outcomes uncorrupted by poor judgement, illusion, over-enthusiasm, imagination and fraud becomes an urgent matter," according to Harvard Medical School researchers (*IJE* 2004;33[2]:247-51).

Thus the challenge became deciphering between health claims derived from legitimate medical inquiry and those made by hucksters with pockets full of magic crystals. Out of this dilemma rose 2 concepts that would become vital in ensuring the integrity of a clinical trail: blinding and randomization.

Blinding, also called masking, is the practice of reducing bias by keeping people in the dark about which study subjects are in the active group and which are in a control group. A single-blind study keeps those collecting and assessing the data blinded to group assignment. In a double-blind study, the participants are also unaware if they are taking the treatment under test, an alternate remedy or a placebo.

It might be difficult, however, to blind assessors or participants if the group-assignment process was not itself free of bias. Noticeable patterns might emerge if subjects were deliberately selected for active or control groups, a problem addressed by randomization. Randomly assigning subjects to groups reduces the odds that one could predict who is receiving the active treatment and who isn't.

Despite efforts to rid experiments of bias, however, researchers sometimes fail. For example, in a trial involving the antibiotic rifampicin, researchers found that "the slightly red color in urine during the rifampicin phase did not allow a true blinding" (*BCPT* 2006;98[6]:555-8).

The first widely publicized randomized clinical trial was a 1948 test of streptomycin for treating pulmonary tuberculosis (*BMJ* 1948;2:769-82). Though some contest that an earlier experiment to test the efficacy of immunization against whooping cough was the first truly randomized trial, the streptomycin test was published earlier and is the best known (*BMJ* 1998;317:1217-20). It's been referred to as the "1948 watershed."

British statistician Austin Bradford Hill is generally credited for designing the trial, an accomplishment that earned him widespread fame.

"He was the father of modern clinical research. Basically, he cracked it, and what we've done since is refined what he proposed," says Davies. "It was the beginning of the modern era in terms of trial design."

One way today's researchers have refined Hill's ideas on trial design has been to put more emphasis on establishing appropriate end points before testing begins. "The primary outcome should be stated explicitly in the trial hypothesis and is typically the variable that is used to determine sample size," writes Dr. Lawrence Appel, a professor of medicine at John Hopkins University, in a clinical trials primer (*Clin J Am Nephrol* 2006;1[6]:1360-7). And determining the appropriate sample size is vital to a trial's success.

Trials with an inadequate number of participants have larger margins of errors. It is also difficult to ensure people with important risk factors are evenly distributed among randomly assigned groups if the sample size is too small.

"The 2 most important variables in a clinical trial are the randomization and outcome variables," says Appel. "You have to spend a lot of time making sure those are done right." — Roger Collier, *CMAJ*

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