The Ethics of Clinical Research

Brendan's Big Book of Bioethics | Brendan Shea, Ph.D. (Brendan.Shea@rctc.edu)

1 CONTENTS

2 WHAT IS A CLINICAL TRIAL?

Brendan's Note: **I've adapted some of the material in this set of lecture notes from the National Institutes of Health (NIH).**

Clinical research is medical research involving people. There are two types, observational studies and clinical trials. In this chapter, we'll be focusing primarily (but not exclusively) on clinical trials.

Observational studies observe people in normal settings. Researchers gather information, group volunteers according to broad characteristics, and compare changes over time. For example, researchers may collect data through medical exams, tests, or questionnaires about a group of older adults over time to learn more about the effects of different lifestyles on cognitive health. These studies may help identify new possibilities for clinical trials.

By contrast**, clinical trials** are research studies performed in people that are aimed at evaluating a medical, surgical, or behavioral intervention. They are the primary way that researchers find out if a new treatment, like a new drug or diet or medical device (for example, a pacemaker) is safe and effective in people. Often a clinical trial is used to learn if a new treatment is more effective and/or has less harmful side effects than the standard treatment.

Other clinical trials test ways to find a disease early, sometimes before there are symptoms. Still others test ways to prevent a health problem. A clinical trial may also look at how to make life better for people living with a life-threatening disease or a chronic health problem. Clinical trials sometimes study the role of caregivers or support groups.

Before the U.S. Food and Drug Administration (FDA) approves a clinical trial to begin, scientists perform laboratory tests and studies in animals to test a potential therapy's safety and efficacy. If these studies show favorable results, the FDA gives approval for the intervention to be tested in humans.

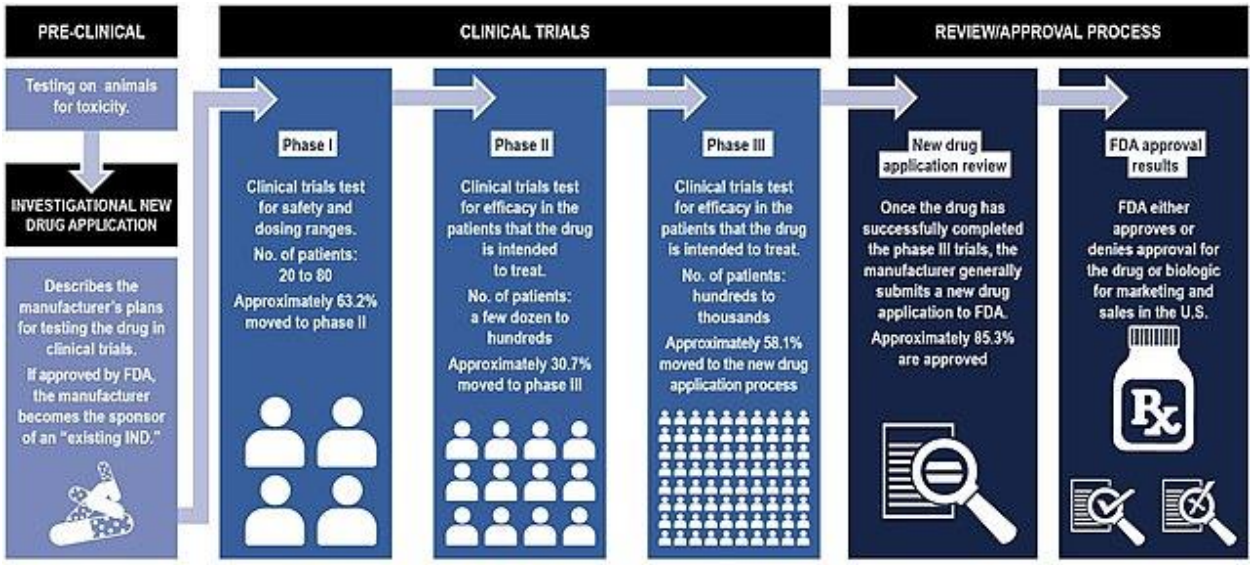
Many clinical trials are structured as **randomized-control trials (RCTs),** about which we'll say more a bit later.

2.1 WHAT ARE THE FOUR PHASES OF CLINICAL TRIALS?

Clinical trials advance through four phases to test a treatment, find the appropriate dosage, and look for side effects. If, after the first three phases, researchers find a drug or other intervention to be safe and effective, the FDA approves it for clinical use and continues to monitor its effects.

Clinical trials of drugs are usually described based on their phase. The FDA typically requires Phase I, II, and III trials to be conducted to determine if the drug can be approved for use.

- A **Phase I trial** tests an experimental treatment on a small group of often healthy people (20 to 80) to judge its safety and side effects and to find the correct drug dosage.
- A **Phase II trial** uses more people (100 to 300). While the emphasis in Phase I is on safety, the emphasis in Phase II is on effectiveness. This phase aims to obtain preliminary data on whether the drug works in people who have a certain disease or condition. These trials also continue to study safety, including short-term side effects. This phase can last several years.
- A **Phase III trial** gathers more information about safety and effectiveness, studying different populations and different dosages, using the drug in combination with other drugs. The number of subjects usually ranges from several hundred to about 3,000 people. If the FDA agrees that the trial results are positive, it will approve the experimental drug or device.
    - This is the "crucial" step for testing, and requires far more time/effort than the previous two steps.
- A **Phase IV trial** for drugs or devices takes place after the FDA approves their use. A device or drug's effectiveness and safety are monitored in large, diverse populations. Sometimes, the side effects of a drug may not become clear until more people have taken it over a longer period of time.



Source: GAO analysis of FDA data and a 2016 collaborative study by Biotechnology Innovation Organization, Biomedtracker, and Amplion.* | GAO-17-564

In general, such trials can take between 2 and 5 years or longer. However, in cases of medical urgency, things proceed much more quickly, so long as adequate experimental subjects (and researchers!) can be found. For example, in COVID vaccine development during 2020-21, phase 1 trials started in Feb/March (almost immediately after the disease was discovered), and phase 2 trials started a few months later. By mid-summer 2020, huge phase 3 trials (enrolling upwards of 30,000 participants) were under way, which led to eventual emergency approval around December 2020. Enrolling this many participants (and having the research staff to support them and analyze data) is possible only in the highest-priority medical problems.

2.2 Seven Rules for Ethical Clinical Trials

As we'll be discussing later, there have been *many* clinical trials that have ended up harming patients. This has led to a fair amount of discussion (by scientists, bioethicists, lawyers, and many others) as to the "principles" for making sure a clinical trial is ethically OK. The following set of seven conditions[1] provides one influential answer.

2.2.1 The Research Must Have Social and Clinical Value

Every research study is designed to answer a specific question. Answering certain questions will have significant value for society or for present or future patients with a particular illness. An answer to the research question should be important or valuable enough to justify asking people to accept some risk or inconvenience for others. In other words, answers to the research question should contribute to scientific understanding of health **(social value)** or improve our ways of preventing, treating, or caring for people with a given disease **(clinical value)**. Only if society will gain useful knowledge — which requires sharing results, both negative and positive — can exposing human subjects to the risk and burden of research be justified.

2.2.2 The Research Must Have "Scientific Validity"

A study should be designed in a way that will get an understandable answer to the valuable research question. This includes considering whether the question researchers are asking is answerable, whether the research methods are valid and feasible, and whether the study is designed with a clear scientific objective and using accepted principles, methods, and reliable practices. It is also important that statistical plans be of sufficient

[1] Ezekiel J. Emanuel, David Wendler, and Christine Grady, "What Makes Clinical Research Ethical?," *JAMA* 283, no. 20 (May 24, 2000): 2701–11, https://doi.org/10.1001/jama.283.20.2701.

power to definitively test the objective, for example, and for data analysis. Invalid research is unethical because it is a waste of resources and exposes people to risk for no purpose

2.2.3 Research Subjects Must Be Selected Fairly

Who does the study need to include, to answer the question it is asking? The primary basis for recruiting and enrolling groups and individuals should be the scientific goals of the study — not vulnerability, privilege, or other factors unrelated to the purposes of the study. Consistent with the scientific purpose, people should be chosen in a way that minimizes risks and enhances benefits to individuals and society. Groups and individuals who accept the risks and burdens of research should be in a position to enjoy its benefits, and those who may benefit should share some of the risks and burdens. Specific groups or individuals (for example, women or children) should not be excluded from the opportunity to participate in research without a good scientific reason or a particular susceptibility to risk.

2.2.4 The Research Must Have a Favorable risk-benefit ratio

Uncertainty about the degree of risks and benefits associated with a drug, device, or procedure being tested is inherent in clinical research — otherwise there would be little point to doing the research. And by definition, there is more uncertainty about risks and benefits in early-phase research than in later research. Depending on the particulars of a study, research risks might be trivial or serious, might cause transient discomfort or long-term changes. Risks can be physical (death, disability, infection), psychological (depression, anxiety), economic (job loss), or social (for example, discrimination or stigma from participating in a certain trial). Has everything been done to minimize the risks and inconvenience to research subjects, to maximize the potential benefits, and to determine that the potential benefits to individuals and society are proportionate to, or outweigh, the risks? Research volunteers often receive some health services and benefits in the course of participating, yet the purpose of clinical research is not to provide health services.

2.2.5 There Must Be Regular Independent Review of the Research

To minimize potential conflicts of interest and make sure a study is ethically acceptable before it even starts, an independent review panel with no vested interest in the particular study should review the proposal and ask important questions, including: Are those conducting the trial sufficiently free of bias? Is the study doing all it can to protect research volunteers? Has the trial been ethically designed and is the risk–benefit ratio favorable? In the United States [and most other developed countries], independent evaluation of research projects is done through granting agencies, local **institutional review boards (IRBs**), and data and safety monitoring boards. These groups also monitor a study while it is ongoing.

Note: An **institutional review board (IRB)** is a local group (often associated with a hospital, university, or governmental agency) whose job it is to protect human subjects of research. It consists of scientific experts and at least one "community member" who does NOT work for the institution in question. Similar boards exist for animal research, often with slightly different names. Mayo Clinic, Olmsted Medical Center, and the University of Minnesota all have institutional review boards that oversee the biomedical research done at their institutions.

2.2.6 The Research Subjects Must Give Informed consent

For research to be ethical, most agree that individuals should make their own decision about whether they want to participate or continue participating in research. This is done through a process of informed consent in which individuals (1) are accurately informed of the purpose, methods, risks, benefits, and alternatives to the research, (2) understand this information and how it relates to their own clinical situation or interests, and (3) make a voluntary decision about whether to participate.

There are exceptions to the need for informed consent from the individual — for example, in the case of a child, of an adult with severe Alzheimer's, of an adult unconscious by head trauma, or of someone with

limited mental capacity. Ensuring that the individual's research participation is consistent with his or her values and interests usually entails empowering a proxy decision maker to decide about participation, usually based on what research decision the subject would have made, if doing so were possible.

2.2.7 Respect for potential and enrolled subjects

Individuals should be treated with respect from the time they are approached for possible participation—even if they refuse enrollment in a study—throughout their participation and after their participation ends. This includes:

1. Respecting their privacy and keeping their private information confidential.
2. Respecting their right to change their mind, to decide that the research does not match their interests, and to withdraw without penalty.
3. Informing them of new information that might emerge in the course of research, which might change their assessment of the risks and benefits of participating.
4. Monitoring their welfare and, if they experience adverse reactions, untoward events, or changes in clinical status, ensuring appropriate treatment and, when necessary, removal from the study.
5. Informing them about what was learned from the research. Most researchers do a good job of monitoring the volunteers' welfare and making sure they are.

2.3 Review Questions

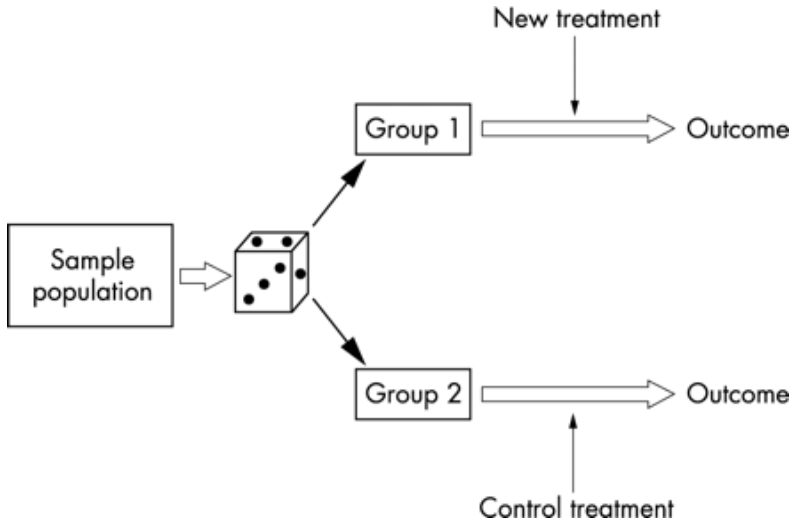
1. In your own words, describe how clinical trials differ from observational studies.
2. What are the four stages each clinical trial must go through? Do a web search to see if you can find some examples of current research at each stage.
3. What does it mean to "violate" the ethical rules of clinical research? Choose 1 or 2 of the seven "principles" laid out above, and describe what sort of clinical trial might "break" this rule.

3 Other Issues in Clinical Research Ethics

Historically, many writers have argued that there is distinction between **clinical ethics** (the professional ethics relevant to medical staff concerned with the care of patients) and **research ethics**[2] (the professional ethics relevant to biological and medical research staff). Beauchamp and Childress (2020), among others, argue that there is no reason to make this distinction, as clinical staff increasingly face many of the same problems as research staff:

- **How can medical professionals minimize the "therapeutic misconception"?** The **therapeutic misconception** occurs when patients believe that participating in a research trial is likely to benefit *them,* when it is much more likely to benefit patients in the *future.* This false belief can sometimes lead patients to take unwarranted risks.
- **How can randomized control trials respect patients' best interests?** Most medical research involves **randomized control trials (RCTs)** in which subjects are randomly assigned to (1) an **experimental** group that receives the treatment being tested or (2) a **control** group that does NOT receive this treatment (but instead receive an inactive **placebo** that "looks" like the drug in question, an **active control** using an alternate treatment, or no treatment).

[2] See the SEP article on clinical research ethics: David Wendler, "The Ethics of Clinical Research," in *The Stanford Encyclopedia of Philosophy*, ed. Edward N. Zalta, Winter 2017, 2017, https://plato.stanford.edu/archives/win2017/entries/clinical-research/.



This figure [3] provides a graphical depiction of how a **randomized control trial (RCT)** works. The study subjects are *randomly* divided into two (or more) groups, with one group receiving the treatment that is being tested. The "control" group may receive (a) no treatment, (b) a "fake" treatment (placebo), or (c) an alternative drug (such as the current "standard of treatment.)

- **When should patients be withdrawn from RCTs?** During the course of an RCT, evidence may start to accumulate that (1) the new treatment is much more effective than the control or (2) the new treatment is much less effective than the control. This means that researchers are no longer in a state of clinical equipoise, and must seriously consider moving *all* the subjects to the more effective treatment (though this must be balanced against the benefits of finishing the RCT).

3.1 THE DEBATE OVER CLINICAL EQUIPOISE

Some medical ethicists hold that RCTs are appropriate only when the scientific community is in a state of **clinical equipoise** with regard to the treatment that is being tested**,** which occurs when there is no reason to think that patients will be "better off" in either the control group or the experimental group. Another way of putting this: clinical equipoise occurs when scientists are *genuinely unsure* whether a new drug/treatment is better, worse, or equal to the existing treatment. The intuition is that we should not do research on humans (or animals) unless it teaches us something we don't already know.

Other ethicists think that it can sometimes be *perfectly fine to carry out (some) experiments even when we aren't in state of clinical equipoise, and instead have a good guess on how the experiment will (probably) turn out.* For example, suppose drug A is known to cure about 40% of patients with disease D. Drug B has been tested in rats, and it cured around 50% of rats. While there is no guarantee it would have similar effects on humans, there is no particular reason to think that it wouldn't.

- Proponents of clinical equipoise would approve of testing drug B, *so long as the control group received drug A and NOT a placebo.* Why? Proponents of this view hold that giving patients a placebo would be immoral, when we know that there is an effective treatment. Placebos should be used only when there is genuine ignorance about how to treat the disease at all.
- Critics of clinical equipoise would also approve of the trial, although they would probably favor a placebo-controlled trial, since these can have more "statistical power" than do active control trials—that is, they make it much easier for statisticians to tell whether the drug is working and thus, whether it would be worthwhile to start using it for treatment. Active controls may lead to a *good* drug being rejected.

[3] J. M. Kendall, "Designing a Research Project: Randomised Controlled Trials and Their Principles," *Emergency Medicine Journal* 20, no. 2 (March 1, 2003): 164–68, https://doi.org/10.1136/emj.20.2.164.

- One can also adopt a moderate position: Placebo-control trials should be used only when necessary, and subjects must be informed of why and how the placebos are being used (even though they won't know if they themselves will receive placebos). For example, they hold it would be wrong to give cancer patients "placebo" anti-nausea drugs, as has happened in the past.

Proponents and critics of clinical equipoise also disagree about what to do if a new drug seems to be *working* (for example, suppose that 18 out of the first 20 patients treated with drug B survive). Proponents of clinical equipoise would generally support making the drug more widely available (and perhaps ending the trial early, in order to put *everyone* on the drug). Again, the critics would emphasize that this would make it much more difficult to figure out how well the drug actually worked[4].

3.2 REVIEW QUESTIONS

1. What is the "therapeutic misconception"? Why is it important for researchers to help patients avoid this?
2. What is a randomized control trial (RCTs)? What roles do the experimental and control groups play? What is a "placebo" and what role do they play in some RCTs?
3. Clinical equipoise is an idea about the conditions under which it is ethically OK to conduct research. In your own words, explain what this idea is.
4. Do you agree or disagree with the claim that "clinical research is morally OK only in a state of clinical equipoise." Why or why not?

4 BIOETHICS IN HISTORY: TUSKEGEE SYPHILIS STUDY[5]

In 1932, the Public Health Service, working with the Tuskegee Institute, began a study to record the natural history of syphilis in hopes of justifying treatment programs for blacks. It was called the "Tuskegee Study of Untreated Syphilis in the Negro Male."…The study initially involved 600 black men – 399 with syphilis, 201 who did not have the disease. The study was conducted without the benefit of patients' informed consent. Researchers told the men they were being treated for "bad blood," a local term used to describe several ailments, including syphilis, anemia, and fatigue. In truth, they did not receive the proper treatment needed to cure their illness. In exchange for taking part in the study, the men received free medical exams, free meals, and burial insurance. Although originally projected to last 6 months, the study actually went on for 40 years.

In July 1972, an Associated Press story about the Tuskegee Study caused a public outcry that led the Assistant Secretary for Health and Scientific Affairs to appoint an Ad Hoc Advisory Panel to review the study…The panel found that the men had agreed freely to be examined and treated. However, there was no evidence that researchers had informed them of the study or its real purpose. In fact, the men had been misled and had not been given all the facts required to provide informed consent…The men were never given adequate treatment for their disease. Even when penicillin became the drug of choice for syphilis in 1947, researchers did not offer it to the subjects. The advisory panel found nothing to show that subjects were ever given the choice of quitting the study, even when this new, highly effective treatment became widely used…The advisory panel concluded that the Tuskegee Study was "ethically unjustified"--the knowledge gained was sparse when compared with the risks the study posed for its subjects."

[4] For a recent (and influential) critique of clinical equipoise, see Franklin G. Miller and Steven Joffe, "Equipoise and the Dilemma of Randomized Clinical Trials," *New England Journal of Medicine* 364, no. 5 (February 3, 2011): 476–80, https://doi.org/10.1056/NEJMsb1011301.

[5] "Tuskegee Study and Health Benefit Program - CDC - NCHHSTP," October 3, 2018, https://www.cdc.gov/tuskegee/index.html.

The response to this study marked the beginning of modern "research ethics," which emphasizes the importance of **voluntary informed consent** and regular oversight of research by **institutional review boards.**]

4.1 QUESTIONS

1. Use the seven rules for ethical clinical research to analyze "what went wrong" in Tuskegee.
2. Suppose contemporary researchers wanted to do a long-term study of drug-resistant syphilis in a similar community (generally poor, and with little knowledge about the relevant condition or its treatment). If you were on the institutional review board, what safeguards might you require before you let the study go ahead?
3. Some research has suggested that Tuskegee (and similar experiments) led to a long-lasting mistrust of medicine and science among African Americans, with bad consequences for their health. If this is true, what could medical and scientific workers do to "earn back that trust"?

5 READING: UNETHICAL EXPERIMENTS' PAINFUL CONTRIBUTIONS TO TODAY'S MEDICINE (BY NINA AVRAMOVA)[6]

Chinese scientist He Jiankui sent shockwaves around the world last year **[in 2018]** with his claim that he had modified twin babies' DNA before their birth. The modification was made with gene editing tool CRISPR-Cas9, he said, and made the babies resistant to HIV. Scientists from China and around the world spoke out about the experiment, which many say was unethical and not needed to prevent the virus. The scientist had also been warned by peers not to go down this path.

His experiments, which are still clouded with the uncertainty of his claims and his whereabouts, open a Pandora's box of questions around ethics in experiments with humans -- even though these dilemmas aren't new.

Historic examples of human experimentation include wartime atrocities by Nazi doctors that tested the limits of human survival. Another led to the creation of the hepatitis B vaccine prototype. Wendell Johnson, who made several contributions to the field of communication disorders, tried to induce stuttering in normally fluent children. In the 1940s, prisoners in Illinois were infected with malaria to test anti-malaria drugs.

Such experiments have been criticized as unethical but have advanced medicine and its ethical codes, such as the Nuremberg Code.

When He made his claim of genetically altering humans, the response from the global medical community was swift and condemning.

"It is out of the question that the experiment is unethical," said Jing Bao Nie, professor of bioethics at the University of Otago in New Zealand. Without "medical necessity, it is not ethical to carry out" gene editing.

Sarah Chan, director of the University of Edinburgh's Mason Institute for Medicine, Life Sciences and the Law, adds that the balance of risks and benefits make it hard to justify this experiment. Genome editing of

[6] Nina Avramova, "Unethical Medical Experiments: The Good, the Bad and the Debates," CNN, January 21, 2019, https://www.cnn.com/2019/01/09/health/unethical-experiments/index.html.

embryos is still not fully established, and "virtually all scientists will say we don't yet know enough about It to be able to recommend that we just go ahead with it clinically," she said.

If it were the case of a life-threatening disease that will cause tremendous pain, and the only way to alleviate the pain would be a risky experimental procedure, then Chan thinks "given the immense benefit, we could produce perhaps taking that risk is justified."

When it comes to medical ethics, different principles need to be weighed against each other by an institutional review board, deciding over experiments involving human participants.

5.1 A DEFINITION OF MEDICAL ETHICS

Medical ethicists and researchers commonly hold that there are **seven general rules** for an ethical experiment involving humans, explained Govind Persad, assistant law professor at the University of Denver.

[Brendan's Note: Compare these explanations of the rules with those above.]

Experiments should be socially valuable and scientifically valid, and people have to be selected fairly and respected. The risks and benefits to participants and the benefits to society need to be weighed against each other, and there needs to be an independent outside review of the ethics of the experiment, Persad said.

The risks and benefits equation sometimes includes third-party consideration, such as tests of a vaccine that includes a virus that can "shed" and infect others who are not research participants, Persad said. Research on smallpox vaccine is one example.

If He's experiment produced any mutations, these could be passed down to the twins' children and then diffuse into the general population, which didn't consent to that change, Persad explained.

"I don't know how large of a risk that is," Persad said. "Because again, it depends on the odds of the mutation, whether the mutation was one that would end up staying in the population or whether it would be selected out over time."

Many of national and international protocols, like the 2005 UN Declaration on Human Rights and Bioethics, include some of these seven principles, Persad said. But as with most international documents, these protocols are not legally binding.

The first document outlining how research should be done in a fair way was a product of Nazi war atrocities.

During the 1940s, Nazi doctors conducted human experiments on prisoners in concentration camps. In all of these experiments, which one study by the Jewish Virtual Library describes as "acts of torture," prisoners were forced into danger, nearly all enduring mutilation and pain, and many experiments had fatal outcomes. Most famously, experiments were conducted by Dr. Josef Mengele, who was interested in twins and performed "agonizing and often lethal" research on them.

Renate Guttmann was one of the "Mengele Twins," according to the Holocaust Encyclopedia, subjected to experiments such as injections that made her vomit and have diarrhea, and blood being taken from her neck.

Twenty Nazi doctors were sentenced in the 1945-46 Nuremberg trials. The process resulted in the first ethics document, the **Nuremberg Code**, a 10-point declaration on how to conduct ethical scientific research.

But some doctors felt that this code did not apply to them.

A decade later, pediatrician Dr. Saul Krugman was asked to do something about rampant hepatitis in the **Willowbrook State School** for children with intellectual disabilities on Staten Island, New York. Krugman found that over 90% of children at the school were infected.

Contracting hepatitis was "inevitable" and "predictable" due to poor hygiene at the overcrowded school, according to the first study Krugman and his colleagues carried out in Willowbrook. He decided to try to develop a vaccine, and parents were informed and asked for consent.

Krugman's experiment helped him discover two strains of hepatitis -- A and B -- and how these spread, A spreading via the fecal-oral route and B through intimate contact and transfer of body fluids. Fifteen years later, he developed a prototype hepatitis B vaccine.

In his paper, Krugman agrees with criticism that the ends do not justify the means but says he does not believe that to apply to his own work, since all children at the school were constantly exposed to the risk of acquiring hepatitis.

The subsequent debate pointed out that the central ethical question around Krugman's work is whether it can be acceptable to perform a dangerous experiment on a person, in this case the Willowbrook students, who will themselves see no benefit from it.

Kelly Edwards, professor of bioethics at the University of Washington, thinks back to the needed balance of risks and benefits in an experiment. "We had a trend of saying 'this group of people is already suffering,' " she says, which inspired researchers to study these populations for some generalizable knowledge that would help others. "But we still are really taking advantage of this one group of people suffering."

She believes there are now other methods that would have brought the same results. But because the vaccine was acquired in this unethical way and we are using the "tainted data" -- results from unethical experiments -- Edwards says we owe some recognition to "the children who contributed to that knowledge."

[Brendan's Question: Had you heard of the Willowbrook case before this? What do you think of Krugman's defense of his work?]

5.2 TAINTED MEDICAL PAST

The need for retribution and compensation is found in a famously unethical experiment: the Tuskegee syphilis study. Syphilis was seen as a major health problem in the 1920s, so in 1932, the US Public Health Service and the Tuskegee Institute in Alabama began a study to record the natural progression of the disease.

The study observed 600 black men, 201 of whom did not have the disease. In order to incentivize participants, they were offered free medical exams, meals and burial insurance. But they were not informed of what was being investigated; instead, they were told that they would receive treatment for "bad blood" -- a local term that the Centers for Disease Control and Prevention says was used to describe several illnesses, including syphilis, anemia and fatigue.

Those who carried the diseases were not treated for syphilis, even when penicillin became an effective cure in 1947.

After the first reports about the study in 1972, an advisory panel was appointed to review the Tuskegee study. Their conclusion was that the knowledge gained "was sparse" compared to the risks to the subjects. The study concluded in October of that year.

Shortly after, a class-action lawsuit was filed on behalf of the participants and their families. A $10 million settlement was reached.

The Tuskegee Health Benefit Program was established to pay compensation such as lifetime medical benefits and burial services to all living participants and their wives and children. President Bill Clinton publicly apologized for the study in 1997.

Edwards noted that many medicines and vaccines now in routine use were obtained initially through unethical means, "and some of them are not even as much on our consciousness."

The birth control pill was tested in 1955 on women in Puerto Rico who were not told that they were involved in a clinical trial or that the pill was experimental and had potentially dangerous side effects.

The 1979 **Belmont Report** into ethical guidelines for scientific research made informed consent US law and therefore such experiments illegal.

The commission responsible for the Belmont report also wrote topic-specific reports, one of which was on the use of prisoners in experiments. "It was a pretty widespread practice to use prisoner populations," Edwards said, because it was seen as offering them a way to repay their debts to society.

One place where prisoners were used in experiments was **Holmesburg Prison in Philadelphia** in the 1950s. Dermatologist Dr. Albert M. Kligman, famous for patenting the acne treatment Retin-A, conducted many tests on these inmates. Retin-A was partially based on Kligman's experiments on prisoners at Holmesburg, according to a report. Some included studying the reaction to dangerous chemicals, such as dioxin, an Agent Orange ingredient, the removal of thumbnails to see how fingers react to abuse, or the infestation of inmates with ringworm.

One psychiatrist working at Holmesburg at the same time as Kligman reported that tranquilizers, antibiotics and Johnson & Johnson toothpaste and mouthwash were all tested on inmates, according to Sana Loue in "Textbook of Research Ethics: Theory and Practice."

Participating in these experiments was one of way for prisoners to earn money and a further means to control them, Loue said.

Prisoners' inability to give consent because their lives are completely controlled by others and the large risk of coerciveness are what inspired the Belmont report to rule out experiments with this vulnerable population, Edwards said.

5.3 THE PRESENT AND FUTURE OF ETHICS

The reports that followed these experiments were used to draw up laws and governance bodies, such as **institutional review boards**. These boards are made up of a small group of representatives from the institution that would like to carry out the experiment and one non-scientific community representative; they decide whether an experiment is ethical and should go ahead.

Edwards says the institutional review boards offer a small one-time assessment of the situation. She hopes for more ongoing ethical review practices during experiments, like data safety monitoring, used mainly in clinical trials. This monitoring tool can halt an experiment at any time.

Chan also sees the need for more discussions around ethics. He's experiment and the second international human genome editing summit in Hong Kong, where He publicly defended his work, showed that there "is a real will to have these discussions seriously [and] to consider both what the benefits are but also to consider very carefully the conditions under which we should be using these technologies," she said.

[Brendan's Question: As this article explains, there has been a fair amount of unethical research in the past. To what extent will the changes we've made over the years stop this from happening in the future? What else, if anything, would you like to see happen?]

6 READING: GENTLE MEDICINE COULD RADICALLY TRANSFORM MEDICAL PRACTICE (BY JACOB STEGENGA)[7]

Numerous criticisms of medical science have been articulated in recent years. Some critics argue that spurious disease categories are being invented, and existing disease categories expanded, for the aim of profit. Others say that the benefits of most new drugs are minimal and typically exaggerated by clinical research, and that the harms of these drugs are extensive and typically underestimated by clinical research. Still others point to problems with the research methods themselves, arguing that those once seen as gold standards in clinical research – randomised trials and meta-analyses – are in fact malleable and have been bent to serve the interests of industry rather than patients. Here is how the chief editor of *The Lancet* medical journal summarised these criticisms in 2015:

> *Afflicted by studies with small sample sizes, tiny effects, invalid exploratory analyses, and flagrant conflicts of interest, together with an obsession for pursuing fashionable trends of dubious importance, science has taken a turn towards darkness.*

[Brendan's Note: This is sometimes called the "replication crisis." Starting around 2012, researchers began to discover that a lot of scientific results they'd "taken for granted" couldn't actually be replicated, especially in areas such as psychology and medicine. There's been quite a bit of recent work trying to figure out "what went wrong" and how to fix it.]

These problems arise because of a few structural features of medicine. A prominent one is the profit incentive. The pharmaceutical industry is extremely profitable, and the fantastic financial gains to be made from selling drugs create incentives to engage in some of the practices above. Another prominent feature of medicine is the hope and the expectation of patients that medicine can help them, coupled with the training of physicians to actively intervene, by screening, prescribing, referring or cutting. Another feature is the wildly complex causal basis of many diseases, which hampers the effectiveness of interventions on those diseases – taking antibiotics for a simple bacterial infection is one thing, but taking antidepressants for depression is entirely different. In my book *Medical Nihilism* (2018), I brought all these arguments together to conclude that the present state of medicine is indeed in disrepair.

How should medicine face these problems? I coined the term **'gentle medicine'** to describe a number of changes that medicine could enact, with the hope that they would go some way to mitigating those problems. Some aspects of gentle medicine could involve small modifications to routine practice and present policy, while others could be more revisionary.

Let's start with clinical practice. **Physicians could be less interventionist than they currently are.** Of course, many physicians and surgeons are already conservative in their therapeutic approach, and my suggestion is that such therapeutic conservatism ought to be more widespread. Similarly, the hopes and expectations of patients should be carefully managed, just as the Canadian physician William Osler (1849-

[7] Jacob Stegenga, "How Gentle Medicine Could Radically Transform Medical Practice | Aeon Ideas," Aeon, May 13, 2020, https://aeon.co/ideas/how-gentle-medicine-could-radically-transform-medical-practice.

1919) counselled: 'One of the first duties of the physician is to educate the masses not to take medicine.' Treatment should, generally, be less aggressive, and more gentle, when feasible.

Another aspect of gentle medicine is how the medical research agenda is determined. Most research resources in medicine belong to industry, and its profit motive contributes to that 'obsession for pursuing fashionable trends of dubious importance'. It would be great if we had more experimental antibiotics in the research pipeline, and it would be good to have high-quality evidence about the effectiveness of various lifestyle factors in modulating depression (for example). Similarly, it would be good to have a malaria vaccine and treatments for what are sometimes called 'neglected tropical diseases', the disease burden of which is massive. The current coronavirus pandemic has displayed how little we know about some very basic but immensely important questions, such as the transmission dynamics of viruses, the influence of masks on mitigating disease transmission, and the kinds of social policies that can effectively flatten epidemic curves. But there is little industry profit to be made pursuing these research programmes. Instead, great profit can be made by developing 'me-too' drugs – a new token of a class of drugs for which there already exist multiple tokens. A new selective serotonin reuptake inhibitor (SSRI) could generate great profit for a company, though it would bring little benefit for patients, given that there are already many SSRIs on the market (and, in any case, their demonstrated effect sizes are extremely modest, as I argued in a recent Aeon essay).

A policy-level change, for which some now argue, is **to reduce or eliminate the intellectual property protection of medical interventions**. This would have several consequences. It would, obviously, mitigate the financial incentives that appear to be corrupting medical science. It would probably also mean that new drugs would be cheaper. Certainly, the antics of people such as Martin Shkreli would be impossible. Would it also mean that there would be less innovative medical research and development? This is a tired argument often raised to defend intellectual property laws. However, it has serious problems. The history of science shows that major scientific revolutions typically occur without such incentives – think of Nicolaus Copernicus, Isaac Newton, Charles Darwin and Albert Einstein. Breakthroughs in medicine are no different. The most important breakthroughs in medical interventions – antibiotics, insulin, the polio vaccine – were developed in social and financial contexts that were completely unlike the context of pharmaceutical profit today. Those breakthroughs were indeed radically effective, unlike most of the blockbusters today.

Another policy-level change would be to **take the testing of new pharmaceuticals out of the hands of those who stand to profit from their sale.** A number of commentators have argued that there should be independence between the organisation that tests a new medical intervention and the organisation that manufactures and sells that intervention. This could contribute to raising the evidential standards to which we hold medical interventions, so that we can better learn their true benefits and harms.

Returning to the issue of the research agenda, we also need to have **more rigorous evidence about gentle medicine itself.** We have a mountain of evidence about the benefits and harms of initiating therapy – this is the point of the vast majority of randomised trials today. However, we have barely any rigorous evidence about the effects of terminating therapy. Since part of gentle medicine is a call to be more therapeutically conservative, we ought to have more evidence about the effects of drug discontinuation.

For example, in 2010 researchers in Israel applied a drug discontinuation programme to a group of elderly patients taking an average of 7.7 medications. By strictly following treatment protocols, the researchers withdrew an average of 4.4 medications per patient. Of these, only six drugs (2 per cent) were re-administered due to symptom recurrence. No harms were observed during the drug discontinuations, and 88 per cent of the patients reported feeling healthier. We need much more evidence like this, and of higher quality (randomised, blinded).

Gentle medicine doesn't mean easy medicine. We might learn that regular exercise and healthy diets are more effective than many pharmaceuticals for a wide range of diseases, but regular exercise and healthy eating are

not easy. Perhaps the most important health-preserving intervention during the present coronavirus pandemic is 'social distancing', which is completely non-medical (insofar as it doesn't involve medical professionals or medical treatments), though social distancing requires significant personal and social costs.

In short, as a response to the many problems in medicine today, gentle medicine suggests changes to clinical practice, the medical research agenda, and policies pertaining to regulation and intellectual property.

[Brendan's Question: Do you agree with the idea that we ought to move toward "gentle medicine"? Why or why not? What do think of Stegenga's proposals?]

7 READING: A LASTING GIFT TO MEDICINE THAT WASN'T REALLY A GIFT (BY DENISE GRADY)[8]

Fifty years after Henrietta Lacks died of cervical cancer in the "colored" ward at Johns Hopkins Hospital, her daughter finally got a chance to see the legacy she had unknowingly left to science. A researcher in a lab at Hopkins swung open a freezer door and showed the daughter, Deborah Lacks-Pullum, thousands of vials, each holding millions of cells descended from a bit of tissue that doctors had snipped from her mother's cervix.

Ms. Lacks-Pullum gasped. "Oh God," she said. "I can't believe all that's my mother."

When the researcher handed her one of the frozen vials, Ms. Lacks-Pullum instinctively said, "She's cold," and blew on the tube to warm it. "You're famous," she whispered to the cells.

Minutes later, peering through a microscope, she pronounced them beautiful. But when she asked the researcher which were her mother's normal cells and which the cancer cells, his answer revealed that her precious relic was not quite what it seemed. The cells, he replied, were "*all* just cancer."

The vignette comes from a gripping new book, "The Immortal Life of Henrietta Lacks" (Crown Publishers), by the journalist Rebecca Skloot. The story of Mrs. Lacks and her cells, and the author's own adventures with Mrs. Lacks's grown children (one fries her a pork chop, and another slams her against a wall) is by turns heartbreaking, funny and unsettling. The book raises troubling questions about the way Mrs. Lacks and her family were treated by researchers and about whether patients should control or have financial claims on tissue removed from their bodies.

The story began in January 1951, when Mrs. Lacks was found to have cervical cancer. She was treated with radium at Johns Hopkins, the standard of care in that day, but there was no stopping the cancer. Her doctor had never seen anything like it. Within months, her body was full of tumors, and she died in excruciating pain that October. She was 31 and left five children, the youngest just a year old. She had been a devoted mother, and the children suffered terribly without her.

Neither Mrs. Lacks nor any of her relatives knew that doctors had given a sample of her tumor to Dr. George Gey, a Hopkins researcher who was trying to find cells that would live indefinitely in culture so researchers could experiment on them. Before she came along, his efforts had failed. Her cells changed everything: they multiplied like crazy and never died.

[8] Denise Grady, "A Lasting Gift to Medicine That Wasn't Really a Gift," *The New York Times*, February 1, 2010, sec. Health, https://www.nytimes.com/2010/02/02/health/02seco.html.

A cell line called HeLa (for Henrietta Lacks) was born. Those immortal cells soon became the workhorse of laboratories everywhere. **HeLa cells** were used to develop the first polio vaccine, they were launched into space for experiments in zero gravity and they helped produce drugs for numerous diseases, including Parkinson's, leukemia and the flu. By now, literally tons of them have been produced.

Dr. Gey did not make money from the cells, but they were commercialized. Now they are bought and sold every day the world over, and they have generated millions in profits.

The Lacks family never got a dime. They were poor, with little education and no health insurance, and some had serious physical or mental ailments. But they didn't even know that tissue had been taken or that HeLa cells even existed until more than 20 years after Mrs. Lacks's death. And they found out only by accident, when her daughter-in-law met someone from the National Cancer Institute who recognized her surname and said he was working with cells from "a woman named Henrietta Lacks."

The daughter-in-law rushed home and told Mrs. Lacks's son, Lawrence, "Part of your mother, it's alive!"

When they learned that their mother's cells had saved lives, the family felt proud. But they also felt confused, a bit frightened, used and abused. It had never occurred to anyone to ask permission to take their mother's tissue, tell them that her cells had changed scientific history or even to say thank you. And certainly no one had ever suggested that they deserved a share of the profits.

Some of the Lackses later gave blood to Hopkins researchers, thinking they were being tested for cancer, when really the scientists wanted their genetic information to help determine whether HeLa cells were contaminating other cultures. When Ms. Lacks-Pullum asked a renowned geneticist at the hospital, Victor McKusick, about her mother's illness and the use of her cells, he gave her an autographed copy of an impenetrable textbook he had edited, and, Ms. Skloot writes, "beneath his signature, he wrote a phone number for Deborah to use for making appointments to give more blood."

The bounds of fairness, respect and simple courtesy all seem to have been breached in the case of the Lacks family. The gulf between them and the scientist's race, class, education was enormous and made communication difficult.

A less charitable view is that it might have made the Lackses easier to ignore. When the family's story became known in the black community in Baltimore, Ms. Skloot writes, it was seen as the case of a black woman whose body had been exploited by white scientists.

[Brendan's Question: What do you think of the case of Henrietta Lacks?]

Ideas about informed consent have changed in the last 60 years, and the forms now given to people having surgery or biopsies usually spell out that tissue removed from them may be used for research. But Ms. Skloot points out that patients today don't really have any more control over removed body parts than Mrs. Lacks did. Most people just obediently sign the forms.

Which is as it should be, many scientists say, arguing that Mrs. Lacks's immortal cells were an accident of biology, not something she created or invented, and were used to benefit countless others. Most of what is removed from people is of no value anyway, and researchers say it would be too complicated and would hinder progress if ownership of such things were assigned to patients and royalties had to be paid.

But in an age in which people can buy songs with the click of a mouse, that argument may become harder to defend.

So far, the courts have sided with scientists, even in a case in the 1980s in which a leukemia patient's spleen and other tissues turned out to be a biomedical gold mine for his doctor. The patient, John Moore, sued his doctor after discovering that the doctor had filed for a patent on his cells and certain proteins they made, and had created a cell line called Mo with a market value estimated at $3 billion. Mr. Moore ultimately lost before the California Supreme Court.

As Ms. Skloot writes in her last chapter, this issue is not going away. If anything, it may become increasingly important, because the scale of tissue research is growing, and people are becoming savvier about the money to be made and also the potential for abuse if tissue samples are used to ferret out genetic information.

The notion of "**tissue rights"** has inspired a new category of activists. The question that comes up repeatedly is, if scientists or companies can commercialize a patient's cells or tissues, doesn't that patient, as provider of the raw material, deserve a say about it and maybe a share of any profits that result? Fewer people these days may be willing to take no for an answer.

[Brendan's Question: What do you think of the idea of "tissue rights"? Do we "own" the right to our body and tissues, if these could help medical research? Does this change after we die?]

8 READING: TUSKEGEE TRUTH TELLER (BY CARL ELLIOTT)

[Brendan's Note: The author of this piece—Carl Elliott—is a University of Minnesota philosopher and medical doctor. He "blew the whistle" on unethical psychiatric experiments that were going on there in the early 2000s, but was not well-liked for it! The University's failure to deal with the problems he pointed out eventually led to the government shutting down all psychiatric research for a time.]

Peter Buxtun, like many medical whistleblowers, got little thanks for exposing a notorious scandal

One July evening in 2016, at the Viva Goa restaurant in San Francisco, I was sitting across from a silver-haired gentleman named Peter Buxtun. We had just ordered our meal when a loud thud sounded from across the room. Buxtun, who was nearly 80, leaped up from the table and rushed over to help a dazed-looking woman sprawled on the floor. "Did you hit your head?" Buxtun asked. "Are you okay?" When she didn't answer right away, Buxtun switched to German. Yes, she was fine, although very embarrassed; apparently she had misjudged the location of her seat and sat down in empty space.

As he was helping the woman to her feet, a waiter pushed his way between them to fill her water glass. The waiter was intent on pretending that nothing unusual had taken place, even though it had been only seconds since the woman had crashed to the floor. When Buxtun returned to our table, he was still shaking his head, baffled by the the waiter's behavior. This reaction, I have learned, is not uncharacteristic of Buxtun. Despite his easy laugh and genial manner, he has the air of a man who fears the world is populated by blockheads and scoundrels.

In 1972, Buxtun exposed the most notorious medical research scandal in American history. For 40 years, the U.S. Public Health Service had deceived and exploited hundreds of poor black men with syphilis near Tuskegee, Alabama, using free meals and burial insurance to lure them into an experiment in which they would receive no treatment for a potentially deadly disease. Very few employees of the health service apart from Buxtun saw anything wrong with this. Only when Associated Press reporter Jean Heller wrote about the abuse, using documents provided by Buxtun, did the Tuskegee study eventually end. Buxtun's revelations triggered Senate hearings, a federal inquiry, a class-action lawsuit, and in concert with several other research scandals of the period, a lasting set of federal guidelines and institutional structures intended to protect the subjects of medical research.

It would be difficult to name a figure in the history of American medical ethics whose actions have been more consequential than Buxtun's. Yet most ethicists have never heard of him, and many accounts of the Tuskegee scandal do not even mention his name. Buxtun did not appear in Jean Heller's 1972 exposé, nor was he mentioned in the first major scholarly article about the scandal, written in 1978 by Harvard historian Allan M. Brandt. In the well-known play (and later, film) based on the scandal, *Miss Evers' Boys,* Buxtun is completely absent. His name is rarely uttered along with the other notable whistleblowers of his era, such as Daniel Ellsberg, Karen Silkwood, and Frank Serpico. If the role played by Buxtun in exposing the scandal is at all familiar, it is largely because of James H. Jones's influential 1981 history of the Tuskegee study, *Bad Blood,* and Wellesley College historian Susan Reverby's 2009 book, *Examining Tuskegee.*

Included in *Bad Blood* is a photo of Buxtun as a bearded young man in 1973, posing next to Senator Ted Kennedy. For many years that photo—plus the knowledge that Buxtun lived in San Francisco during the 1960s—had placed a certain image of him in my head. If asked to describe it, I would have mentioned radical politics, psychedelic drugs, and maybe the Grateful Dead. Nothing could be less accurate. Buxtun is a lifelong Republican, a member of the National Rifle Association, and a collector of vintage weapons. When I told him about a recent visit I had made to the City Lights bookshop, famous as the home of San Francisco's Beat poetry scene in the '50s, he replied, "Sometimes I like to go there and ask to see their military history section." Buxtun left the Public Health Service in 1968, moving on to law school and then to a career in investments, but he has lived in the same Telegraph Hill apartment for more than 50 years. In front of a large bay window overlooking San Francisco Bay is a set of German aviation binoculars mounted on a tripod. The walls of his apartment are lined with bookshelves, including one shelf devoted to books he keeps solely for their names. One is titled *The Romance of the Gas Industry.*

Maybe the most unusual thing about Buxtun is how few counterparts he has. The past half century has seen many medical research scandals, but few of them have been exposed by whistleblowers. In many scandals, even those that came well after Tuskegee, doctors and nurses have stayed silent even after seeing research subjects being shamefully mistreated. In cases where medical insiders have worked up the courage to speak out publicly, the result has often been professional vilification. **This raises a larger question: In a research enterprise supposedly built on a humanitarian ethos, why are whistleblowers like Buxtun so rare? [Brendan's Note: This is a big question! Think about this as you read the article.]**

Buxtun never planned to work for the Public Health Service. Raised on a ranch in Oregon, he had enlisted in the army and trained as a psychiatric social worker after he finished a political science degree at the University

of Oregon. In 1965, he was doing graduate work in history when he saw a job flier. The health service was funding a venereal disease program in San Francisco. Buxtun says, "I found this thing and thought: San Francisco, working in VD control? What a stitch!"

Soon he had become a venereal disease tracker. "A typical day would be, Come in, look in your mail slot to see if you had some other people's names," Buxtun says. "Charlie Jones, met in a gay bar by another gay guy, and they had gay sex, the other guy had syphilis. Okay, chase this guy down. How do you find the guy? Well, there are a lot of ways to do it, and we had some of the resources that a typical detective in a police department would get—reverse directories and things like that." Once Buxtun had tracked his subject down—sometimes in a flophouse, sometimes in one of the city's better neighborhoods—he would persuade the person to be tested. Those who tested positive were treated effectively with penicillin. "Men could get a sore that would scare the hell out of you," Buxtun says. "One of them looked like a dog had taken a bite out of a weenie."

One day in the coffee room, Buxtun overheard a coworker talking about a syphilis patient in Alabama. "The family knew that he was really ill, that something was really wrong," Buxtun says. "He was plainly insane, had symptoms, and for some reason they took him some distance away to a doctor they knew of." The doctor diagnosed tertiary syphilis (the later stages of infection, which can damage the central nervous system) and gave the man a shot of penicillin. But when Public Health Service officials found out, they got very upset. The doctor, unaware of the Tuskegee study, had treated a research subject who was not supposed to be treated.

The next day Buxtun was on the phone with someone at the Communicable Disease Center (now the Centers for Disease Control). "I said, 'Hey, what do you have on this Tuskegee study?' He said, 'Oh, I've got a lot on it. What do you want?' I said, 'Send me everything.' Damned if I didn't get—and I've still got it—a brown Manila envelope." It had about 10 reports of what were called roundups—the occasions when the subjects were found and brought in for examination. What Buxtun read about the Tuskegee study in that envelope contradicted everything that he'd been advising doctors to do with a syphilis patient. "You treat him. You don't let him get back out in society and infect someone else," Buxtun says. Yet in Tuskegee, the researchers were simply following patients to see what would happen if they went without therapy. "It was an autopsy-oriented study," Buxtun says. "They wanted these guys dead on a pathology table."

The research subjects were all black men in Macon County, Alabama, many of them sharecroppers. Nearly 400 had syphilis and another 200 or so served as healthy controls. The syphilitic men were never told they had an infectious disease, only "bad blood," nor were they offered any treatment apart from tonics and pills such as aspirin for aches and pains. Many subjects underwent painful lumbar punctures (spinal taps) to determine whether the infection had spread to the nervous system. The researchers persuaded them to enroll in the study by giving them free meals and minor remedies and by promising to pay their burial expenses in exchange for permission to autopsy their bodies. When the Tuskegee study began in 1932, treatment for syphilis involved a lengthy, toxic course of arsenic-based therapy. By 1943, however, the disease was easily curable with penicillin. The consequences of untreated syphilis are summed up on a yellow matchbook that Buxtun and his colleagues used to distribute in bars and bathhouses: "Blindness, heart injury, insanity, death."

Buxtun took the roundup reports with him to the city library. "I wanted to look up German war crimes proceedings," he says. Buxtun had come to America as an infant in 1937, the son of a Jewish Czech father and a Catholic Austrian mother. He knew that the "Doctors' Trial" in Nuremberg, in which German physicians were indicted for experimenting on concentration camp prisoners—seven were executed—had led to the modern code of research ethics. The very first principle of the Nuremberg Code states, "The voluntary consent of the human subject is absolutely essential." The code also directs researchers to protect subjects

from disability, injury, or death, no matter how remote the possibility. Buxtun remembers, "It was toward the end of the evening in that library downtown, and I thought: I've got to do something."

The first thing he did was prepare a report on the Tuskegee study. "I directly compared the work of the CDC in Atlanta, in Tuskegee, to what the Nazis had done," Buxtun says. He showed the report to his boss and said he planned to send it to William Brown, the head of the Venereal Disease Section of the Public Health Service. He recalls his boss saying, "When they come to fire you, or do whatever they're going to do, forget my name. I've got a wife and a couple of kids. I want to keep my job."

[Brendan's Question: How do you think most people would react to finding out about the Tuskegee study? Like Buxtun? Or like his Boss? Why?]

It is unclear whether Brown ever read that report, but he certainly read a letter Buxtun sent him in November 1966. "Have any of the men been told the nature of this study?" Buxtun asked. "In other words, are untreated syphilitics still being followed for autopsy?" Brown drafted a reply assuring Buxtun that the subjects were volunteers who were "completely free to leave the study at any time." But he apparently never sent it and instead decided to talk to Buxtun in person.

"To my surprise, I got orders to go to Atlanta, from Dr. Brown and company," Buxtun says. "I was being called on the carpet, and they thought from the high position that they had that they were going to correct an errant employee. Maybe I was an alcoholic, or a lunatic of some sort." The March 1967 summons to Atlanta coincided with an annual conference for healthcare workers specializing in venereal disease. Buxtun was scheduled to meet Brown after the first session. "So these stern-looking bureaucrats come out," he says. They led him to a meeting room with a large, dark wooden table. "All these guys came in and sat at one end of the table, so I went a little way down the table, sat down, and put my things down," Buxtun says. "They were sitting right in front of the American flag and the flag of the Public Health Service. The leader of the group was Brown, who turned out to be a mousy little bureaucrat," Buxtun says. The real enemy in the room was **John Cutler**, an assistant surgeon general and venereal disease specialist who was deeply involved in the Tuskegee study. "He was bursting with rage," Buxtun remembers. "He couldn't wait for the door to be shut to that meeting room."

"That guy pinned my ears back," Buxtun says. "He proceeded to give me a tongue-lashing. 'See here, young man. This is serious work we are doing. You are talking about harm to these black sharecroppers? This is something they are doing as volunteers.' " Buxtun responded by reading from one of Cutler's own reports, which stated clearly that the subjects would never have agreed to the study without the "suasion" of burial expenses. Buxtun remembers Cutler saying, "I didn't write that! I didn't write that! It must have been written by one of my colleagues!" At that point, Buxtun says, everyone in the room began to look nervous.

"It's tough being a whistleblower when you don't even know you're a whistleblower," Buxtun told me. When he began his work with the Public Health Service, the word was completely unknown. "Would I have known the term whistleblower in 1972? I don't know. I might have," he says. "But it wouldn't have the connotations that it carries now."

In Buxtun's era, people who called out wrongdoing in their own organizations were more likely to be called turncoats, snitches, or squealers. In the introduction to a 1972 book on whistleblowing, historian Taylor Branch writes that it is difficult to find in history or mythology any case where people are honored for having publicly exposed the actions of their superiors. "Whistle-blowing is severely hampered by the image of its most famous historical model, Judas Iscariot," Branch writes. "Martin Luther seems to be about the only figure of note to make much headway with public opinion after doing an inside job on a corrupt organization."

[Brendan's Question: Why do you think that whistleblowers have such a bad reputation?]

Anyone who has studied the notorious research scandals of Buxtun's era cannot help being struck by the absence of whistleblowers—or even any real public dissent—in studies that often lasted years. It took decades, for example, for someone to finally blow the whistle, in 1972, about the federal government's practice of testing the toxic effects of radioactive substances on unwitting citizens. Nor did anyone act when University of Pennsylvania dermatologist Albert Kligman tested organophosphates and other toxic chemicals on inmates at Holmesburg Prison in Philadelphia. In Montreal, McGill University faculty members remained silent for a decade while CIA-funded psychiatrist **Ewen Cameron [Brendan's Note: You can look up the "MKULTRA" project for more details.]** subjected his patients to some of the most bizarre experimental techniques imaginable—drug-induced comas lasting weeks, repeated high-voltage electroconvulsive therapy, the administration of powerful psychoactive drugs ranging from LSD to PCP, helmets broadcasting taped "psychic driving" messages into their ears. In a famous 1966 article in *The New England Journal of Medicine,* Harvard anesthesiologist Henry Beecher identified 22 stunningly abusive studies that had been published in medical journals over a period of years, seemingly without prompting any ethical objections whatsoever.

Of course, this was also a time when public trust in institutional authority was plummeting—the era of the My Lai massacre and the Watergate cover-up, of *Eichmann in Jerusalem* and *Unsafe at Any Speed.* In 1978, more than 900 Americans committed suicide by drinking cyanide-laced Kool-Aid at the People's Temple religious commune in Guyana, on the orders of their minister, Jim Jones. By the end of the 1970s, the consequences of such blind obedience to authority had given whistleblowing a measure of cultural respectability.

Today whistleblowers in medical research are not as rare as they once were. For instance, it was largely the actions of whistleblower John Pesando, an oncologist at the Fred Hutchinson Cancer Research Center in Seattle, that in 2001 exposed a series of ill-conceived, deceptive cancer studies. Yet many other scandalous studies in recent decades have taken place without public disclosure. Some were conducted by private companies, such as Pfizer's Trovan trials during a meningitis epidemic in Nigeria in the '90s, which resulted in the deaths of 11 children. But many others occurred in academic health centers: the controversial treatment withdrawal study of patients with schizophrenia at UCLA in the 1980s, the recent "bacteria-in-the-brain" studies at University of California–Davis, the infamous "symptom provocation" studies on schizophrenic patients at (for example) Yale University, Columbia University, the National Institute of Mental Health, and the University of Cincinnati. My own institution, the University of Minnesota, has endured a series of research scandals in its psychiatry department dating back to the early '90s, many of which remained hidden for years until mistreated research subjects or their family members contacted reporters. **[Brendan's Note: It was Elliott, as much as anybody, who ended up making the University of Minnesota change their ways.]**

In the decades since the Tuskegee study, the moral standing of whistleblowers has become more complicated. As in such movies as *Serpico* and *The Insider,* Hollywood portrays them as brave, conscience-tortured martyrs who triumph in the end, but in reality, people who try to blow the whistle on wrongdoing often fail and face brutal punishment. In 2010, scholars at the universities of Chicago and Toronto studied 216 cases of corporate fraud. They found that more than 82 percent of cases with named employees who reported fraud were fired, quit under duress, or were punished in some other way. Many never worked again. The scholars concluded, "Not only is the honest behavior not rewarded by the market, but it is penalized. Why employers prefer loyal employees to honest ones is an interesting question that deserves separate study."

This pattern is consistent across a whole array of organizations, both public and private: engineering firms, banks, military bases, government agencies, and hospitals. Even nurses who speak up about dangers to patients are often punished. One study found that 28 percent of nurses who reported misconduct had been

formally reprimanded, and every single nurse surveyed had suffered some kind of informal retaliation, such as ostracism or pressure to resign. Ten percent were asked to see a psychiatrist. **[Brendan's Question: Why do you think whistleblowers are treated so poorly? (Even nurses who are looking out for their patients!)]**

Although no such studies of whistleblowers in clinical research have been conducted, there is little reason to think that the results would be much different. One of the most demoralizing recent assessments of medical whistleblowing came from a Harvard study of 26 people who had exposed fraud and corruption in pharmaceutical companies using *qui tam* lawsuits. The purpose of *qui tam* lawsuits is to encourage whistleblowers by allowing them to collect a share of the resulting financial settlement. Many of the 26 whistleblowers eventually collected millions of dollars, yet few felt that it was worth the personal devastation. Often they had been asked to take extraordinary risks, such as smuggling files out of the company or wearing a wire to meetings, yet federal investigators treated them with suspicion, as if they were complicit in the crimes. Nearly half of the whistleblowers experienced stress-related illnesses, and more than 30 percent were financially ruined.

Research whistleblowers have even fewer protections. The federal research oversight system has no formal mechanism for dealing with whistleblower complaints. The Food and Drug Administration will not even tell whistleblowers whether it is investigating a complaint. If an FDA investigation is undertaken and completed, the only way for a member of the public to find out the result is to file a Freedom of Information Act request. Even worse, those who dare to blow the whistle on abuses at their own institution do so at their own risk. No federal statute offers them any legal protection. (In some states, however, they may have protection under other laws.)

Even back in 1967, Buxtun was well aware that his efforts to stop the Tuskegee study might backfire on him. "You bet I thought about having to find another job, perhaps in another city and probably outside of government," Buxtun tells me. "Make no mistake, my confrontation with the CDC aristocracy was intended to get rid of me. They knew it, and I knew it.'"

… **[Brendan's Note: I cut out some material here, in interest of length. You can find the full text on the website].**

The natural assumption is that Buxtun's actions were the consequence of his extraordinary character and tenacity. Not many people would take up a moral cause on behalf of strangers and stick with it for seven years without any discernible success. "Once Peter gets something in his head, he's going to pursue it and give it 100 percent," author James Jones told me. That Buxtun persisted so long and eventually succeeded, without the help of like-minded colleagues, sets him apart from even the most determined crusaders.

But it is also important to note the social factors that made it more likely that Buxtun would resist authority. He was not a doctor, so he had not been trained to see senior doctors as his superiors. Nor was he committed to a career in public health. He lived some 2,000 miles from Macon County, Alabama, and the authority figures he answered to in San Francisco were not involved in the Tuskegee study. By the time Buxtun met Brown and Cutler, he had already committed himself deeply to dissent. He never saw the Tuskegee doctors as legitimate authorities and never surrendered his moral agency to them.

Many whistleblowers see their actions as the defining event of their lives and never let go of their bitterness over the difficulties they have faced. Buxtun, in contrast, seems remarkably free of rancor. "I've moved on," he says. "A lot of good things have happened." The only figure in the Tuskegee scandal he still seems to harbor any resentment toward is Cutler, the man who gave him a tongue-lashing in Atlanta and remained unrepentant for decades. In 2010, President Obama issued a formal apology to victims after Susan Reverby discovered that Cutler had also directed Public Health Service experiments in Guatemala in the 1940s, in

which researchers intentionally gave syphilis and gonorrhea to soldiers, prisoners, and mentally ill patients. "He's my villain for all of this," Buxtun says of Cutler. "I can see Dr. Mengele saluting this guy."

If Buxtun carries any resentment about his relative anonymity, he hides it well. "I don't want to be embarrassed by an oversupply of compliments," he says. "I am who I am. There's nothing to try to change, up or down." I told him I was gratified to see he had recently been given a Freedom of Information prize by a journalism association in Northern California. Buxtun replied that he was not the only person honored that night. Then he added, "Another recipient was arrested the following week for public corruption and gun trafficking."

9 CASE STUDY: THE PERNKOPF ATLAS

From: NATIONAL HIGH SCHOOL ETHICS BOWL Case Set for 2020 National Competition. Parr Center for Ethics. AUTHORS: Dustyn Addington, David Boonin, Chris Blake-Turner, Alex Campbell, Guido Chiriboga, Ramona Ilea, Audra Jenson, Clare LaFrance, Chris Ng, Alexander Partridge, Savannah Pearlman, Maddy Troilo, Jacky Wang, Jessica Wang, APPE

Steve, a recent graduate of a prestigious medical school, is working his first full shift as a surgeon at a rural hospital near his hometown. The first operation Steve is scheduled to perform is an emergency appendectomy. Appendectomies are common, and are generally considered safe and low-risk procedures. However, as is the case with any surgery, complications are still possible. Just before beginning the first operation of his professional career, Steve becomes nervous and disoriented, feeling the need to consult an anatomical reference book. The hospital staff provides Steve with an old copy of the so-called *Pernkopf Atlas*, originally published in 1937 by medical doctor and known supporter of the Nazi movement in 20th century Germany, Eduard Pernkopf. Steve, loosely aware of the history of this particular reference book, asks a nurse for another but is told that this is the only reference book available. Steve knows that without consulting the reference book, he is putting the patient at a higher risk. However, given the nature of the procedure, if Steve chose not to consult the Atlas, the increased risk would be a small one with any kind of complications remaining unlikely.

Like many anatomical reference books of its day, the *Pernkopf Atlas* was designed to be a detailed rendering of human anatomy for study and surgical practice. Almost 80 years later, the *Pernkopf Atlas* is still considered by many medical professionals to be one of the most detailed and anatomically correct reference books ever created. The Atlas itself has been out of print since 1994, but the drawings created by Pernkopf can still be found in current medical textbooks and original copies sell for many thousands of dollars.[9] While doctors and educators get great use of the Atlas, its history is troubling for reasons beyond Pernkopf's Nazi party affiliation. In 1998, Pernkopf's former employer, the University of Vienna, conducted a study that found that during Nazi occupation the University had received the corpses of executed prisoners and political dissidents.[10] Of the 800 drawings in the Atlas, at least half have so far been determined to be based on surgical experimentation on the bodies of those prisoners. While in the past, efforts were made to conceal the origins of the Atlas by airbrushing out insignias and removing references to the Nazi party, there is more effort today to come to terms with the resource's history.[11]

[9] https://www.statnews.com/2019/05/30/surgical-dilemma-only-nazi-medical-text-could-resolve/

[10] https://science.sciencemag.org/content/329/5989/274.2

[11] https://www.bbc.com/news/health-49294861

Those who might argue in support of using the Atlas could claim that to not use it would be to erase the suffering of the victims and that, while its origins are unfortunate, the medical benefits that it yields are enormous. In a recent survey, 69% of neurosurgeons indicated that they were comfortable using the Atlas, and 13% said they still use the Atlas in their practice. Additionally, some Rabbinic authorities have stated that while its origins are fraught it is permissible to use the Atlas as long as its history is made known.[12] Those who might oppose Steve's use of the Atlas could claim that, while there are benefits to using it, the drawings in the Atlas were obtained in such a morally reprehensible way that it is difficult to justify using it.

9.1 STUDY QUESTIONS

1. Is it morally permissible for Steve to use the Pernkopf Atlas to inform his medical practice? Why or why not?
2. Is it permissible to commit morally impermissible acts in the service of some greater good, like the reduction of overall suffering? Why or why not?
3. How should we treat scientific advances made by repressive or totalitarian regimes?

[12] https://www.bbc.com/news/health-49294861