



FIRST, DO HARM

In the 1940s, US doctors deliberately infected thousands of Guatemalans with venereal diseases. The wound is still raw.

BY MATTHEW WALTER

The injections came without warning or explanation. As a low-ranking soldier in the Guatemalan army in 1948, Federico Ramos was preparing for weekend leave one Friday when he was ordered to report to a clinic run by US doctors.

Ramos walked to the medical station, where he was given an injection in his right arm and told to return for another after his leave. As compensation, Ramos's commanding officer gave him a few coins to spend on prostitutes. The same thing happened several times during the early months of Ramos's two years of military service. He believes that the doctors were deliberately infecting him with venereal disease.

Now 87 years old, Ramos says that he has suffered for most of his life from the effects of those injections. After leaving the army, he returned to his family's remote village, on a steep mountain slope northeast of Guatemala City. Even today, Las Escaleras has no electricity or easy access to medical attention. It wasn't until he was 40, nearly two decades after the injections, that Ramos saw a doctor and was diagnosed with syphilis and

gonorrhoea. He couldn't pay for medication.

"For a lack of resources, I was here, trying to cure myself," says Ramos. "Thanks to God, I would feel some relief one year, but it would come back." Over the decades, he has endured bouts of pain and bleeding while urinating, and he passed the infection onto his wife and his children, he told *Nature* last month in an interview at his home.

Ramos's son, Benjamin, says that he has endured lifelong symptoms, such as irritation in his genitals, and that his sister was born with cankers on her head, which led to hair loss. Ramos and his children blame the

United States for their decades of suffering from venereal disease. "This was an American experiment to see if it caused harm to human beings," says Benjamin.

Ramos is one of a handful of survivors from US experiments on ways to control sexually

US doctors experimented on patients with psychiatric disorders without consent.

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transmitted diseases (STDs) that ran in semi-secrecy in Guatemala from July 1946 to December 1948. US government researchers and their Guatemalan colleagues experimented without consent on more than 5,000 Guatemalan soldiers, prisoners, people with psychiatric disorders, orphans and prostitutes. The investigators exposed 1,308 adults to syphilis, gonorrhoea or chancroid, in some cases using prostitutes to infect prisoners and soldiers. After the experiments were uncovered in 2010, Ramos and others sued the US government, and US President Barack Obama issued a formal apology. Obama also asked a panel of bioethics advisers to investigate, and to determine whether current standards adequately protect participants in clinical research supported by the US government.

When details of the Guatemalan experiments came to light, US health officials condemned them as 'repugnant' and 'abhorrent'. Last September, the Presidential Commission for the Study of Bioethical Issues went further, concluding in its report¹, that "the Guatemala experiments involved unconscionable violations of ethics, even as judged against the researchers' own understanding of the practices and requirements of medical ethics of the day" (see 'Evolving ethics').

Yet that report and documents written by the researchers involved in the Guatemalan work paint a more complex picture. John Cutler, the young investigator who led the Guatemalan experiments, had the full backing of US health officials, including the surgeon general.

"Cutler thought that what he was doing was really important, and he wasn't some lone gunman," says Susan Reverby, a historian at Wellesley College in Massachusetts, whose discovery of Cutler's unpublished reports on the experiments led to the public disclosure of the research².

Cutler and his superiors knew that some parts of society would not approve. But they viewed the studies as ethically defensible because they believed that the results would have widespread benefits and help Guatemala to improve its public-health system. Those rationalizations serve as a warning about the potential for medical abuses today, as Western clinical trials increasingly move to developing countries to take advantage of lower costs and large populations of people with untreated disease. Bioethicists worry that laxer regulations and looser ethical standards in some countries allow researchers to conduct trials that would not be allowed at home. "The strongest lesson should be that the same rules, same principles, same ethics should apply no matter where you are," says Christine Grady, acting chief of the Department of Bioethics at the National Institutes of Health (NIH) Clinical Center in Bethesda, Maryland, and a member of the bioethics commission.

THE WAR AGAINST SYPHILIS

In the early decades of the twentieth century, US health officials were consumed by the battle against STDs, much as subsequent generations of researchers have fought cancer and HIV. In 1943, Joseph Moore, then chairman of the US National Research Council's Subcommittee on Venereal Diseases, estimated that the military would face 350,000 new infections of gonorrhoea annually, "the equivalent of putting out of action for a full year the entire strength of two full armored divisions or of ten aircraft carriers". The government launched vigorous campaigns of research, treatment and advertising to combat the problem. "She may look clean — but pick-ups, 'good time' girls, prostitutes spread syphilis and gonorrhea", read one poster issued by the US Public Health Service, which promotes health initiatives and medical research.

Many of the country's leading health officials were veterans of that fight. The surgeon general who would approve the proposal for the Guatemalan experiments, Thomas Parran, had previously run the Public Health Service's Venereal Disease Research Lab (VDRL) in New York, and had written two books on the topic. And the associate director of that lab went on to serve as the chief of the research grants office at the NIH, which would fund the Guatemalan work in early 1946.

"You had a very active venereal-disease division," says John Parascandola, a former historian of the Public Health Service and author of *Sex, Sin and Science: A History of Syphilis in America* (Praeger, 2008). Even after researchers demonstrated in 1943 that penicillin was an effective treatment for syphilis and gonorrhoea, they had many questions about

EVOLVING ETHICS

Sexually transmitted diseases (STDs) were a prime concern for health officials in the 1940s, and many medical studies — including the US experiments in Guatemala — used methods that would be considered unethical today. Although standards improved over the decades, clinical researchers continued to push the boundaries of acceptable science.

A 12-month old baby in California is deliberately infected with herpes as part of an experiment. One editor objects to publishing the work, but it appears in 1942 in the *Journal of Pediatrics*.

Penicillin demonstrated to be an effective treatment for syphilis and gonorrhoea.



The US military and Public Health Service combat STDs through an all-out campaign of research, treatment programmes and advertising.



John Cutler works on a prison experiment in Terre Haute, Indiana, in which inmate volunteers are infected with STDs to test a prophylactic method.

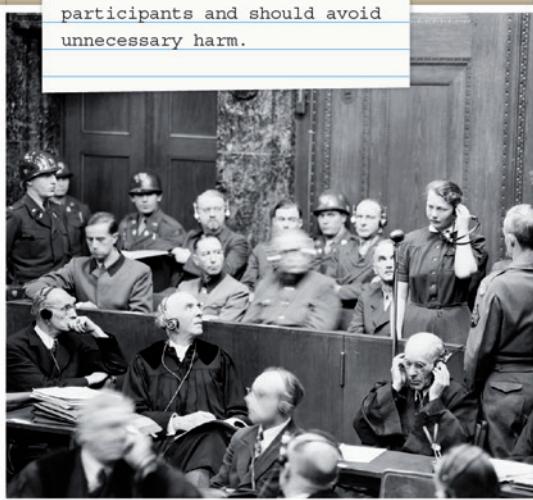
1946

Cutler starts experiments in Guatemala that eventually expose 1,308 prisoners, soldiers and patients at a psychiatric hospital to STDs. The US team also takes blood from 1,384 children to assess STD diagnostic tests. Evidence suggests that the participants in the study did not give their consent.



1946-7

The trial of Nazi doctors leads to the establishment of the Nuremberg Code of medical ethics, which holds that experimenters must obtain voluntary consent from participants and should avoid unnecessary harm.



1953

Cutler starts an experiment at Sing Sing prison in New York, in which he injects syphilis into inmate volunteers, some of whom had received an experimental vaccine.

preventing and treating those diseases and others. "You still had all these people who cut their teeth with venereal diseases and were interested in that topic. Certainly, the venereal-disease division in the 1940s didn't think the problem was licked."

The military, in particular, wanted to develop prophylactic techniques better than the 'pro kit' that had been in use for decades. After sex, servicemen were supposed to inject a solution containing silver into their penises to prevent gonorrhoea, and rub a calomel ointment over their genitals to prevent syphilis. The methods were painful, messy and not very effective.

To test treatments and prophylaxis, the Public Health Service had argued in late 1942 that it was crucial to give the disease to people under controlled conditions. Officials debated the legality and ethics of this, and even solicited the input of the US attorney general. They decided to do the work at a federal prison in Terre Haute, Indiana, using volunteer inmates.

Cutler was one of the doctors charged with carrying out the work. When the prison study began in September 1943, Cutler was 28, and had finished medical school only two years before. The researchers tried to infect prisoners by depositing bacteria — sometimes gathered from prostitutes arrested by the Terre Haute police — directly on the end of the penis. The experiment established several practices that Cutler would go on to use in Guatemala, including working with local law-enforcement agencies and prostitutes. But the researchers could not develop a means to effectively infect people — a necessary step towards testing prophylactic techniques. Within ten months, the experiments were abandoned.

CAPTIVE POPULATION

After Terre Haute, researchers began to plan a more ambitious study. They wanted to try causing infections through what they called normal exposure, in which people would have sex with infected prostitutes.

In 1945, a Guatemalan health official who was working for a year at the VDRL offered to host studies in his country. As director of the Guatemalan Venereal Disease Control Department, Juan Funes was uniquely positioned to help. Prostitution was legal in his country at the time, and sex workers were required to visit a clinic twice a week for examinations and treatment. Funes oversaw one of the main clinics, so he could recommend infected prostitutes for experiments. Cutler and other scientists at the VDRL were quickly sold on the idea: they proposed a programme, which was approved with a budget of US\$110,450.

According to a Guatemalan report³, the US plan was a clear violation of contemporary Guatemalan law, which made it illegal to knowingly spread venereal diseases. But the country was experiencing political upheaval in the mid-1940s and the bureaucracy did not object to the US plan. Government officials as high up as Luis Galich, head of the Guatemalan ministry of public health, were involved in the US study, and even President Juan José Arévalo, who had been elected in 1945, was at least aware of a syphilis experiment being done by US scientists. The study presented a chance to tap into US funding to upgrade Guatemala's inadequate public-health infrastructure, and to import scientific expertise.

Cutler arrived in the country in August 1946 and began setting up experiments. He planned to assess diagnostic blood tests, and to determine the effectiveness of penicillin and an agent called orvus-mapharsen in preventing STDs. At first, Cutler tried using infected prostitutes to spread gonorrhoea to soldiers: he and his team used various bacterial strains to inoculate sex workers, who then had intercourse with many men. Records show that one prostitute had sex with 8 soldiers in a period of 71 minutes. The team also carried out similar experiments using sex workers at a prison.

But it was hard to induce infections by the 'natural' method. So researchers turned to inoculation, swabbing the urethra with an infected solution, or using a toothpick to insert the swab deep into the urethra. At the National Psychiatric Hospital of Guatemala, scientists scratched male patients' penises before artificial exposure to improve infection rates, and injected syphilis into the spinal fluid of seven female patients.

According to the US bioethics commission's report, Cutler's team exposed 558 soldiers, 486 patients at the psychiatric hospital, 219 prisoners, 6 prostitutes and 39 other people to gonorrhoea, syphilis or

chancroid. But the commission was unable to determine how many people actually developed infections or how many of the participants were treated. Researchers also measured the accuracy of diagnostic tests in experiments that involved orphans and people with leprosy, as well as people from the psychiatric hospital, prison and the army.

The commission says there is no evidence that Cutler sought or obtained consent from participants, although in some cases he did get permission from commanding officers, prison officials and doctors who oversaw the patients at the psychiatric hospital. In a letter to his supervisor, John Mahoney, director of the VDRL, Cutler openly admits to deceiving patients at the psychiatric hospital, whom he was injecting with syphilis and later treating. "This double talk keeps me hopping," Cutler wrote.

Cutler and his colleagues treated some people brutally. In one case, detailed by the bioethics commission, the US doctors infected a woman named Berta, a patient at the psychiatric hospital, with syphilis, but did not treat her for three months. Her health worsened, and within another three months Cutler reported that she seemed close to death. He re-infected Berta with syphilis, and inserted pus from someone with gonorrhoea into her eyes, urethra and rectum. Over several days, pus developed in Berta's eyes, she started bleeding from her urethra and then she died.

Yet Cutler did do some good in Guatemala. He took steps to improve public health, initiating a venereal-disease treatment programme at the military hospital and developing a prophylactic plan for the army. He treated orphans for malaria, lobbied his supervisors to supply the army with penicillin — he was turned down — and trained local doctors and technicians. And he provided treatment for 142 people who may have had venereal disease but had not been exposed to it as part of the research.

At the prison, he reported that "we have found a very ready acceptance of our group, both on the part of the prison officials and the part of the inmates, which we think stems from the fact that we now have given them a program of care for venereal disease, which they have lacked in the past. Thus we feel that our treatment program is worthwhile and fully justified."

In the end, Cutler could claim no real success in his experiments, in part because he was never able to infect people reliably without resorting to extreme methods. He secured an extension to continue the experiments from June to December 1948, and he left Guatemala at the end of that year. Other researchers published some of the blood-test results, but Cutler did not publish his work on prophylactic methods. The experiments were not only unconscionable violations of ethics, the bioethics commission charges, they were also poorly conceived and executed.

A DISTINGUISHED CAREER

Despite the failures, the work burnished Cutler's credentials. A few months after he arrived home, the World Health Organization sent Cutler to India to lead a team demonstrating how to diagnose and treat venereal diseases. In the 1960s, he became a lead researcher in the infamous Tuskegee experiment in Alabama, in which hundreds of black men with syphilis were studied for decades without receiving treatment. He flourished in the Public Health Service and later became a professor of international health at the University of Pittsburgh in Pennsylvania. He died in 2003, well before details of the Guatemala experiments were exposed.

Michael Utidjian was an epidemiologist at Pittsburgh in the late 1960s and co-authored two papers with Cutler. He describes his former colleague as devoted to venereal-disease studies and enthusiastic about international research. "He did some pioneer work out in India using penicillin to treat the commoner STDs." But Utidjian says that Cutler was a flawed researcher. "I wouldn't rank him as a top-flight scientist or designer of studies." The two scientists collaborated on a study to test the effectiveness of a topical prophylaxis in prostitutes at a brothel in Nevada. However, the poor implementation of the experiment led to "pretty worthless" results, says Utidjian.

The participants in Cutler's Guatemalan study fared far worse than the doctor himself. Shuffling among the tin-roofed homes in Las Escaleras, Ramos is bone thin and speaks in a mumble, made worse by his lack of teeth. He says that he put off treatment until about ten years ago, when it became too painful to urinate. His son rushed him to a hospital,

Researchers launch a 15-year study at the Willowbrook State School in New York, where they infect children with mental disabilities with hepatitis.

1956

Doctors inject live cancer cells into elderly residents at the Jewish Chronic Disease Hospital in New York without their consent. Outrage over the experiment helps to spark a debate about research ethics and prompts federal authorities to develop tighter controls on research.

1963



The United States halts a 40-year experiment in Tuskegee, Alabama, where hundreds of African American men with syphilis were observed for decades without being treated.

1972



Historian Susan Reverby exposes the abuses of Cutler's Guatemalan experiments, prompting US President Barack Obama to apologize to Guatemala and launch an investigation, which finds that the experiments involved unconscionable violations of ethics".

2010



Federico Ramos has suffered excruciating symptoms after US experiments.

where doctors inserted a catheter and later performed an operation.

Gonzalo Ramirez Tista lives in the same village as Ramos and says that his father, Celso Ramirez Reyes, also participated in the experiments during his three years in the army. He was required by the scientists to have sex with infected prostitutes. "They gave him an order, and it came from a superior," says Tista. They also gave him injections, and within days he noticed pus coming out of his penis. "He still had these symptoms when he left [the military], and he infected my mother." After his service, gonorrhoea left Reyes with sores, poor eyesight and lethargy.

Like Ramos's family, Tista is a party to the lawsuit seeking compensation from the US government. Neither man could provide documents to support their claims. But Pablo Werner, a doctor with Guatemala's Human Rights Ombudsman's office, has reviewed the cases and found that Ramos's and Reyes's stories are supported by the timing of their military service and details in the medical histories that they gave. Reyes is also named in a database of research participants that was compiled by Guatemala's National Police Historical Archive from Cutler's papers.

NEVER AGAIN

The US Department of Justice requested last month that the compensation case be dismissed, arguing that the courts are not the "proper forum" for it. But last September, a panel of the presidential bioethics commission recommended⁴ that the government set up a general compensation system for test participants harmed by federally funded research.

This January, the US Department of Health and Human Services committed nearly \$1.8 million to improving the treatment of STDs in Guatemala and strengthening ethics training there regarding research on humans. The plaintiffs are not satisfied and intend to press their case, says Piper Hendricks, an international human-rights lawyer with Conrad & Scherer in Fort Lauderdale, Florida, who is representing them.

As the case moves forward, researchers are wrestling with how to judge the actions of Cutler's team, and how to prevent such abuses from happening again. The bioethics commission argues that Cutler and his superiors knew that they were violating the medical ethics of their day, because they had sought the consent of participants in Terre Haute. And in Guatemala, the researchers took steps to suppress knowledge of their work. One colleague told Cutler that the US surgeon general "is very much interested in the project and a merry twinkle came into his eye when he said, 'You know, we couldn't do such an experiment in this country.'"

But the ethical landscape was evolving rapidly at the time. The standards of the 1940s were "a lot murkier" than those of today, says Susan Lederer, a bioethicist at the University of Wisconsin–Madison. "The idea that it was so clear in 1946 to me doesn't ring true."

In late 1946, after Cutler had started his work in Guatemala, 23 Nazi doctors and officials went on trial in Nuremberg, Germany, for the inhuman experiments that they had carried out in concentration camps during the Second World War. From that trial emerged the Nuremberg Code, a set of principles that mandated that experimenters obtain voluntary consent from participants, that participants be capable of giving such consent and that experiments avoid unnecessary physical and mental harm.

Although such tight standards were not entirely foreign to researchers before the Nuremberg trials, few followed them. In 1935, for example, the Supreme Court of Michigan stated that researchers could get consent from caregivers of participants, which Cutler did in a sense when he consulted commanding officers and other officials. Many of Cutler's participants were poor, uneducated people from indigenous populations, whom the scientists viewed as incapable of understanding the experiments.

At the time, some of the United States's top researchers worked without obtaining consent from individuals. Jonas Salk, who later earned fame for developing the polio vaccine, and Thomas Francis Jr, a leading influenza researcher, intentionally infected patients at a psychiatric hospital in Ypsilanti, Michigan, with influenza in 1943 (ref. 5). There is evidence that the patients did not all consent to the experiments.

Cutler and his superiors apparently thought it was acceptable in Guatemala to cross ethical lines that they would not have breached at home — an issue that raises concern today, with Western companies increasingly running clinical trials in foreign countries, particularly in developing nations. In 2010, the US Department of Health and Human Services investigated all requests by companies to market their drugs in the United States, and found that in 2008, nearly 80% of approved applications used data from clinical trials in other countries.

Developing nations often have lower medical standards than developed countries, and can't enforce rules as effectively. In India, for example, human-rights activists and members of parliament say that foreign drug companies often test experimental drugs on poor, illiterate people without obtaining their consent or properly explaining the risks.

And in 2009, the pharmaceutical giant Pfizer agreed to pay up to \$75 million to settle lawsuits over the deaths of Nigerian children who had participated in tests of an experimental antibiotic. Nigerian officials and activists had claimed that the company had acted improperly by, for example, not obtaining proper authorization or consent. But Pfizer denies the allegations and did not admit any wrongdoing in the settlement.

Ethicists also warn about practices viewed as acceptable today, such as testing medications on patients who are extremely ill, and who see new treatments as their only hope, no matter how dangerous they are. Lederer notes that some trials of cancer drugs involve particularly toxic compounds. In the future, she says, "people might say, 'how can people who are so sick make informed decisions?'"

For Grady, the lessons from Guatemala are fundamental tenets of bioethics: not every method is acceptable, transparency is key and scientists should remember that they are working with human beings.

But in clinical research, she says, the ethical lines aren't always well defined. "When you get to the details of what that means in a particular case, people disagree." And that may be the most troubling lesson of the Guatemalan experiments. In any era, many if not most researchers might agree that a certain practice or rule is justified and necessary. But for later generations, the barbarism of the past seems only too obvious. ■ SEE EDITORIAL P.132

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1. Presidential Commission for the Study of Bioethical Issues *Ethically impossible: STD Research in Guatemala from 1946 to 1948* (2011).
2. Reverby, S. M. J. *Policy Hist.* **23**, 6–28 (2011).
3. Comisión Presidencial para el Esclarecimiento de los Experimentos Practicados con Humanos en Guatemala, durante el periodo 1946 a 1948 *Consentir el Daño* (2011).
4. Presidential Commission for the Study of Bioethical Issues *Research Across Borders* (2011).
5. Francis, T. Jr, Salk, J. E., Pearson, H. E. & Brown, P. N. *J. Clin. Invest.* **24**, 536–546 (1945).