The Best Possible Intentions

Testing Prophylactic Approaches on Humans in Developing Countries

Ilana Löwy, PhD

Debates on human experiments in developing countries focus on ethical principles such as informed consent, accountability, involvement of the concerned communities, and the improvement of local health services. Public health specialists who conducted human experiments in Rio de Janeiro (1902–1905) and in Guatemala (1947–1948) believed, however, that they were acting in the best interests of local populations, were aware of the importance of informed consent, were closely collaborating with local health professionals, and were contributing to the development of local health structures. Nevertheless, their investigations went dramatically wrong. An initial desire to conduct ethically and scientifically sound studies was undermined by pressure to obtain results and to save the researchers' initial investment, the possibility of freely using hospitalized patients as experimental participants, uncritical help from local professional elites, and structural pitfalls of experimenting with severely deprived people. These elements can still be found in trials of preventive methods in the Global South. (*Am J Public Health*. 2013;103:226-237. doi:10.2105/AJPH.2012.300901)

"Distinguished Dr. Cutler, It's a privilege for us to manifest to you, by means of these lines, our everlasting gratitude which will remain for ever in our hearts because of your noble and gentlemanly way with which you alleviated the suffering of the guards and prisoners in this penitentiary. You have really been a philanthropist, your disinterestedness, your constancy are evident samples of your nobleness."

—Roberto Robles Chinchilla, chief of the medical service of Guatemala's Central Prison, December 8, 1948[1]

"I'm asking the Minister of Colonies permission to honor the members of the Mission for the Study of Yellow Fever, MM Simond et Marchoux, for their outstanding contribution to the Mission's work and the impressive intelligence they brought to this extremely difficult and dangerous endeavor."

—Letter sent to the French minister of colonies, November 23, 1905[2]

ROBERTO ROBLES CHINCHILLA'S tribute to John Cutler's "noble and gentlemanly ways," and praise of his "philanthropy" and "disinterestedness," refer to studies of the prevention of venereal disease conducted in Guatemala in 1947 and 1948 and funded by the US Public Health Service (PHS) through a grant to the Pan American Sanitary Bureau (PASB). It is reasonable to assume that Cutler (1915–2003) was proud of this letter; he placed it on the first page of his 1955 report on his studies of syphilis in Guatemala. Cutler probably did not view these studies, in which hundreds of people—prisoners, soldiers, and psychiatric patients—were infected with venereal diseases without their consent, as problematic. In 1990, he transmitted

his documents on the Guatemala studies to the University of Pittsburgh archives. As a consequence, the historian of medicine Susan Reverby found them while researching Cutler's role in the Tuskegee syphilis study, and started a chain of events that led to an apology to the Guatemalans issued by US Secretary of State Hillary Clinton and Secretary of Health and Human Services Kathleen Sebelius and a call from US President Barack Obama to Guatemala's president, Alvaro Colom.[3]

Cutler and his colleagues in Guatemala had studied the prevention of sexually transmitted diseases. Human experiments were often motivated by scientists' enthusiastic and sometimes obsessive search for new scientific knowledge.[4] From the 1970s on, human experiments in developing countries often have been conducted by pharmaceutical firms that are testing new drugs, a practice that has led to fears of the exploitation of vulnerable populations.[5] Studies like the one conducted by PHS researchers in Guatemala belong to a third category of human experiments: public health investigations.[6] Such studies are often conducted by investigators who sincerely strive to alleviate the burden of disease and reduce human suffering.[7]

I examine two preventive experiments using human participants: studies of yellow fever conducted by Pasteur Institute scientists in Rio de Janeiro and Petropolis, Brazil, in 1902 through 1905 and studies of venereal diseases performed by PHS researchers in Guatemala in 1947 and 1948. These experiments were conducted in radically different political contexts. Early 20th-century Brazil was a truly (not only formally) independent country, and public health interventions were seen as a part of an effort to consolidate its national identity.[8] French researchers were welcome in Rio de Janeiro because of their country's cultural cachet, not because of France's political influence in Brazil. By contrast, in the 1940s and 1950s Guatemala was dominated by the United States. Guatemala's subordinate status may explain the extraordinary freedom of the US PHS researchers there.[9] Moreover, the two experiments were not identical: studies of yellow fever involved fewer participants and were more dangerous.[10] Nevertheless, the Brazilian and the Guatemalan projects shared important traits. In both, the starting point of the study was the infection of healthy people with a transmissible disease, the main stumbling block was the discovery that such an infection was more difficult to treat than initially believed, and researchers increasingly deviated from their original project to produce artificial contamination. The result was an increasingly chaotic experimental design, poorly executed studies, and ethically questionable interventions.

Scholars who have attempted to explain why investigators sincerely committed to public health ideals conducted unethical human experiments have evoked the belief that they were warriors fighting against an insidious and cruel enemy, but were also ignorant of ethical principles and affected by hubris and racism.[11] These are surely plausible explanations. On the other hand, an exclusive focus on personal failings of individual researchers may mask structural causes that favor the conduct of unethical human experiments in developing countries: pressure to obtain results and save the researchers' initial investment, gray zones of experimentation on hospitalized or institutionalized patients, local professional elites' wish to achieve new developments in science and medicine, and the difficulty of conducting ethical experiments on severely deprived participants.[12] All these elements can also be found in present-day human experiments. Good intentions are not enough to prevent messy outcomes.

SAVING THE EXPERIMENT: HOW GOOD INTENTIONS UNRAVEL

The Pasteur Institute Mission to Rio de Janeiro was funded by the French Ministry of Colonies, eager to limit the economic harm produced by yellow fever in French colonies in Africa and the Caribbean islands.[13] The members of the mission were Paul Luis Simond (1858–1947), a researcher who had already made a name for himself through studies of the role of fleas in the transmission of plague, Emile Marchoux (1862–1943), and Alexandre Taurelli Salimbeni (1867–1942). They arrived in Rio de Janeiro in November 1901.[14] At that time, Walter Reed and his colleagues from the US Army Mission to Cuba had already established, through human experiments conducted in Havana in 1900, that yellow fever was transmitted by *Stegomyia fasciata* mosquitoes (today, *Aedes aegypti*).[15]

Members of the Pasteur Institute Mission established a bacteriology laboratory in the São Sebastião hospital, the main yellow fever hospital in Rio de Janeiro.[16] However, in 1902 possibilities for studying yellow fever in the laboratory were very

limited. There were no diagnostic tests, no animal models, no ways to cultivate the disease's agent, and no cure.[17] In September 1902, Simond complained that in spite of their intensive efforts the results they had obtained so far were very modest.[18] In March 1902, Emile Roux, who was supervising the work of the Pasteur Institute Mission, proposed that they focus on investigating sera from patients and convalescents.[19] He speculated on the possibility of protecting people from yellow fever through the administration of inactivated serum, and added, "[I]t's really a pity you cannot conduct experiments on men of good will, as was done in Cuba."[20]

A year later, the French researchers found a way to conduct such experiments. Volunteers—all new immigrants to Brazil—were gathered in a camp in Petropolis, a town near Rio de Janeiro, too high in the mountains to allow the survival of the *S fasciata* mosquito.[21] Human experiments started in mid-April 1903. According to the published report of these experiments, they were conducted on 27 consenting participants: "The men who participated in our experiments were warned before witnesses about the risks involved in these experiments, and all freely agreed to it."[22] In their publication, the Pasteur Institute scientists arranged their experiments in a logical order. Simond's notebook from that period gives a very different picture—of studies conducted in a chaotic and opportunistic way.[23] Most of the experimental participants were injected with inactivated serum from yellow fever patients and then exposed to contaminated mosquitoes to check their resistance to infection.[24] The quantity of injected serum and its origin, the treatment and the intervals between injections, all varied greatly and with no apparent logic. Moreover, entirely negative outcomes—in which the experimental participant did not develop yellow fever—were difficult to interpret.[25] Not every bite of an infected mosquito transmitted yellow fever, and Simond was not sure that all the experimental participants were susceptible to the disease.[26]

In the meantime, the Pasteur Institute scientists were required to justify the investment in their studies. Simond and Marchoux had had a major falling out, and news about their disagreements had reached Paris. In May 1903, Roux urged Simond to transmit as rapidly as possible their results up to then to the Ministry of Colonies, to neutralize the bad impression they had created. He also told Simond about growing difficulties in obtaining the money that had been allocated to the mission.[27] Roux's message might have put additional pressure on the French researchers. In late May, 13 experimental participants who had not developed yellow fever were exposed to bites of freshly infected mosquitoes. Only two of them subsequently developed the disease. In June, the remaining 11 men were injected with infected blood.

On June 3, 1903, Simond recorded the murder of an experimental participant named Sollers. The same day, he noted that another experimental participant, Rolf, had "escaped"—an event that was perhaps related to Sollers's murder.[28] On June 10 and 11, four experimental participants were injected with the blood of yellow fever patients. On June 17, one of them, Geronimo, came down with a fever. On June 15, the remaining seven men were injected with the blood of Bardach, an experimental participant who had developed a severe case of yellow fever.[29] Bardach died in the early morning of June 18. The same morning, Geronimo escaped from the Petropolis camp. As Simond recorded it in his notebook,

> He takes the 7h30 train to Rio de Janeiro, arrives at Rio da Serra, gets off the carriage with his luggage and starts to walk along the rails. He stops after several hundred meters. He is brought to the station by the station's workers, and dies there after two or three hours.[30]

On June 18, two experimental participants from the Petropolis camp had just died from yellow fever, and three of those injected with infected blood had high fever. On June 19, the five men inoculated with Bardach's blood who remained healthy received 10 cubic cemtimeters each of a convalescent's blood, probably in a hurried attempt to protect them from a deadly disease. The last entries in Simond's notebook are from the morning of June 20.

In their publication of the Petropolis experiments, members of the Pasteur Mission affirmed that "experiments on man are legitimate only if they produce new and important results."[31] However, nearly all the results reported in their heavily edited retelling of their experiments either confirmed observations made by other researchers, were inconclusive, or could not be repeated.[32] In hindsight, in the absence of an animal model of yellow fever, Pasteur Institute scientists' efforts to find a way to protect people from this disease were highly unlikely to succeed.[33] The human experiments conducted in 1903 by Marchoux,

Salimbeni, and Simond in Rio may be described as illegitimate, even according to their own criteria.

Human experiments in Guatemala were sponsored by the Venereal Diseases Section of the PHS and conducted officially under the supervision of the PASB and by a grant from the National Institutes of Health. They were viewed as a continuation of studies made in the Terre Haute federal penitentiary in 1943 and 1944. In these experiments, prisoners who volunteered to be infected with gonorrhea received accurate information on the nature of the experiment. The PHS investigators, however, had difficulty in artificially infecting people with gonorrhea. The head of the Guatemalan Venereal Disease Control Department, Juan Funes, who in 1945 worked as a one-year fellow at the PHS's Venereal Diseases Research Laboratory in Staten Island, New York, proposed to study venereal disease prevention in Guatemala. In that country, prisoners were allowed to pay for the services of a prostitute, making it possible to produce a "natural" infection through sexual intercourse with a contaminated sex worker. The availability of penicillin, the PHS researchers believed, made such an infection practically risk free.[34] PHS put in charge of this study a junior researcher, John Cutler.

The original project, however, rapidly ran into a major difficulty: the "natural" transmission of venereal disease was also found to be inefficient. In addition, the plan to use volunteers from the federal penitentiary in Guatemala in the syphilis studies did not work as expected. Prisoners were difficult to control. Cutler therefore welcomed an offer by the director of the Insane Asylum, Carlos Salvado, to conduct experiments on the asylum's inmates.[35] Most of the syphilis experiments, and some of the chancroid experiments, were conducted on psychiatric patients.[36] PHS researchers used two additional groups of people: children from an orphanage, a source of normal sera for the calibration of serological tests, and soldiers, used in studies of gonorrhea and chancroid.[37] A study that originally should have relied on well-informed volunteers ended by almost exclusively using people who did not know they were participating in a medical experiment, and were often deceived about the true aims of the researchers' activities.[38] Moreover, the persistent difficulty of infecting healthy people with venereal diseases led to a gradual drift of the experimental design toward an increasingly "unnatural," aggressive, painful, and potentially harmful experimentation, especially on psychiatric patients.[39]

Cutler's papers indicate that PHS-sponsored studies in Guatemala were not only ethically questionable, but also poorly executed and difficult to interpret.[40] One of the reasons for the chaotic conduct of the experiments might have been Cutler's belief that he should provide results rapidly; otherwise, he might lose financial support and therefore "a scientific opportunity which comes only rarely."[41] In the fall of 1947, Cutler's hierarchical superior John Mahoney was worried about negative reactions to the slow progress of the Guatemala investigations:

> In the event of the prophylaxis angle proving to be impossible of resolution, we will have left only the serology study and the work in penicillin therapy. We would surely have difficulty in selling an expensive project of this kind to the Service.[42]

The PHS investigators' willingness to bend rules to produce results may have been related to their wish to justify the considerable investment in the Guatemala project.[43] At the same time, they seem to have been aware how questionable their approach was. In 1948, when Thomas Parran was scheduled to leave his job as surgeon general, Mahoney wrote to Cutler that with this change:

> We know that we have lost a very good friend and that it appears to be advisable to get ducks in line. In this regard we feel that the Guatemala project should be brought to *the innocuous stage* as rapidly as possible.[44]

Pasteur Institute investigators had explained that risky human experiments could be justified only when the results were truly new and important, but they had conducted badly planned and poorly executed studies. PHS researchers observed sound scientific principles and ethical rules in the Terre Haute penitentiary, but abandoned these rules in Guatemala. The isolation of a small group of researchers in a foreign country may partly explain their failure to respect the principles they themselves proclaimed.[45] In addition, however, such behavior may have been prompted by external pressure from hierarchic superiors who wanted to justify costly experiments abroad, and by internal pressure felt by scientists who had found out that their project was not working as expected. They might have been led to hurried attempts to infect participants by their belief that otherwise everything would be lost: their goals, ambition, and reputation, along with the time, money, and effort invested in

their study up to then, but also their sincere hopes to alleviate the plight of people who suffered from transmissible diseases.

HUMAN EXPERIMENTS IN HOSPITALS: GRAY ZONES AND FUZZY MARGINS

Before they started experiments on healthy people, the Pasteur Institute researchers attempted to treat patients at the São Sebastião hospital with convalescent sera. Seven of the treated patients stayed alive and four died.[46] Human experiments at the hospital continued in 1905 and 1906. In 1906, Simond and Marchoux believed they held conclusive proof that the yellow fever agent could pass from an infected female mosquito to her female offspring.[47] This conviction was grounded in a single human experiment. A young immigrant was bitten by mosquitoes hatched in the laboratory from the eggs of an infected female and developed mild but typical yellow fever. To confirm that the disease was indeed yellow fever, mosquitoes that had fed on a deadly case of yellow fever were allowed to bite the same participant. He remained healthy.[48] In 1912, Simond recognized that the experiment was not conclusive: other investigators had failed to repeat it.[49] Simond's notebook for 1904 and 1905 indicates that Simond (and perhaps Marchoux) conducted other "unofficial" human experiments. Simond's notes from that period are very fragmentary and mainly cover February and March 1905. We learn nevertheless about attempted experimental infection of seven additional participants; their subsequent fate remains unkown.[50]

In his 1955 report, Cutler explained that he had abandoned his original plan to use volunteers recruited in the national penitentiary because the prisoners had refused repeated blood drawings. Members of the Presidential Commission on Bioethical Issues noted, however, that the experiments in the Insane Asylum started only a few days later than those in the prison.[51] It seems possible that Cutler and his colleagues could not resist the temptation to conduct experiments on humans without going to the trouble of negotiating an agreement. Psychiatric patients were never informed that they were being artificially infected with syphilis, and even some of the asylum's staff believed at first that the "inoculation" was part of a treatment.[52] The sum of $1500, originally intended to pay volunteers in the prison, was given to the psychiatric hospital's administration to acquire equipment that would benefit the community. The US researchers also supplied the asylum with an antiepileptic drug, Dilantin.[53] Cutler believed that this was a fair arrangement:

> Although we gave medicines and supplies to the institution the patients were not aware of it and it would have meant nothing even though the patients had been mentally fit and cognizant of the fact.[54]

Bioethical debates on experimentation on human beings usually focus on activities clearly labeled "experiments," and tend to neglect regular medical practice. This is problematic because not infrequently physicians—driven by the wish to "do something" for people they are treating, and by poor judgment, hubris, and a desire to advance their career, or a mixture of these motivations—conduct scientifically unsound and ethically doubtful experiments on their patients. Such experiments tend to remain invisible.[55]

LOCAL SCIENTIFIC COMMUNITIES AND HUMAN EXPERIMENTS

Schematic views of human experiments in developing countries sometimes oppose "Western scientists" to "local communities," and overlook the complicated role of the mediating entity "local scientific communities." The Pasteur Institute scientists in Rio de Janeiro benefited from the protection of Oswaldo Cruz, the head of Rio de Janeiro's Department of Public Health, and were greatly helped by the director of the São Sebastião hospital, Carlos Siedl.[56] Cruz had studied bacteriology at the Pasteur Institute, and in the early stages of his career presented himself as a student and follower of Emile Roux and a promoter of "pasteurian science."[57] Siedl was flattered that his establishment was elected to host illustrious French researchers.[58] Siedl's and Cruz's strong support may explain why the French researchers did not face the hostile press and "malignant gossip" that complicated the task of the United States Army Mission to Cuba.[59]

Siedl went out of his way to provide the best possible working conditions for the French researchers. He gave them laboratory space, scientific collaborators, and technical help, and even hired a French cook to prepare their meals.[60] More importantly, he gave them access to the hospital's patients, an indispensable source of the yellow fever virus and potential experimental participants.[61] In return, the French

scientists shared their knowledge of laboratory methods. They brought with them a complete set of equipment from a bacteriology laboratory, organized a formal bacteriology course for the São Sebastião physicians, and provided tutoring in bacteriological techniques.[62] At the end of their mission, Simond and Marchoux left all their laboratory equipment, with the exception of the microscopes, at the São Sebastião hospital.[63] The members of the Pasteur Mission in Rio de Janeiro, Siedl explained later, taught their Brazilian colleagues how to study human diseases in the laboratory and how to conduct a scientific investigation.[64]

John Cutler and his colleagues were invited to Guatemala by Juan Funes.[65] The PHS's sponsored research was strongly supported by numerous other Guatemalan officials, such as Constantino Alvarez, division chief at the Guatemalan Ministry of Health, Luis Galich, director of public health of Guatemala, and Carlos Tejeda, chief of the Medical Services of the Military Hospital.[66] Helping the PHS scientists provided Guatemalan doctors with opportunities to advance their careers. Salvado, the director of the Insane Asylum, received a scholarship to work in the United States. In 1948, Salvado and Funes were hired by the PHS to continue the observations started by Cutler and his collaborators, and in the early 1950s Funes became vice-chairman of the World Health Organization's syphilis study commission.[67] Abel Luna, a physician from the Guatemala Public Health Service who helped the PHS researchers, received a fellowship to study in the Venereal Disease Research Laboratory in Staten Island, New York. Salvado and Funes continued to send biological material (sera and spinal fluid) to the United States, and Carlos Tajeda, chief of Guatemala's army medical department, made arrangements to open in Guatemala a training center in tropical diseases for American physicians from the PHS, the US Army, and the US Navy.[68] Moreover, when the PHS project in Guatemala came to an end in summer 1948, the PASB laboratory was transformed into a permanent center for training of Latin American scientists and the standardization of syphilis tests.[69]

Scientists in "peripheral" countries hope to gain access to knowledge and practices elaborated in recognized scientific centers.[70] In exchange for such access, their Western colleagues may get an opportunity to use interesting "research material," including human participants. Their help in organizing human experiments may thus provide important professional benefits for local scientists.[71] At the same time, they can easily persuade themselves that such experiments are advancing medical research in their country and contributing to the improvement of its inhabitants' health.[72] Scientists who work today in developing or intermediary countries are probably no less eager than their predecessors to collaborate with colleagues from prestigious scientific centers and reap the intellectual and practical advantages of such collaborations. A sincere wish to use human experiments to promote biomedical research and the development of local health structures may become hopelessly entangled with ambitious professionals' desire to advance their own interests.

"The majority of the volunteers recruited for experiments on the transmission and prevention of yellow fever in Cuba and Brazil were in all probability attracted by the promise of considerable financial compensation."[73]

CUTTING-EDGE SCIENCE IN LANDSCAPES OF MISERY

Healthy participants in risky medical experiments may be motivated by an altruistic wish to help a scientific inquiry, but more often they are lured by the possibility of material advantages. The majority of the volunteers recruited for experiments on the transmission and prevention of yellow fever in Cuba and Brazil were in all probability attracted by the promise of considerable financial compensation.[73] Simond's record of the Petropolis experiments starts with a list of people paid by the French scientists.[74] In his description of Reed's experiments in Cuba, Paul de Kruif dissociates "true" volunteers—US soldiers ready to risk their life in the interest of science—from the mercenary participants,

> ignorant immigrants, hardly more intelligent than animals. . . . there were five of these mercenary fellows—whom I shall simply call Man 1, 2, 3, 4—just as microbe hunters often mark animals: Rabbit 1, 2, 3.[75]

The Insane Asylum in Guatemala, Cutler explained in his 1955 report, lacked basic equipment, did not have essential drugs, and was severely understaffed.[76] Cutler and his colleagues seem to have accepted

this situation as normal. The decision to buy for the asylum a supply of the antiepileptic drug Dilantin was legitimated by the observation that it would facilitate the conducting of syphilis studies.[77] PHS researchers exploited the inmates' extreme material and emotional deprivation to advance their goals:

> The institute's staff was so small that the group of experimental workers appreciably increased the amount of a physician's time given to each inmate. As reported earlier, cigarettes were a most valuable, even indispensable, adjunct to the whole program. . . . The patients would often attempt to make numerous trips past the physicians, for blood letting, cisternal puncture or examination, just to augment their supply of tobacco.[78]

"Without the availability of cigarettes," Cutler explained, "the type of patients management [*sic*] that we were able to achieve, we feel, would have been impossible."[79]

The experiments conducted by PHS experts in Guatemala are an extreme case of abuse of participants in research, but debates on clinical trials in the Global South continue today. In the second half of the 20th century, such debates focused on three issues: clinical testing and mass diffusion of contraceptives, transfer of clinical trials of new drugs to developing and intermediary countries, and clinical trials of preventive strategies, especially the reduction of HIV infection. Each issue is different. Population experts presented mass diffusion of contraceptives as a way to help people in poor countries to better their condition. It is seen today by many scholars as an effort to disarm the "population bomb," perceived at that time as a major threat to the Western way of life.[80] The testing of new drugs on people who often cannot afford access to them stems mainly from the pharmaceutical companies' desire to reduce the costs of research and development.[81] Questionable practices, such as the testing of the antibiotic Trovan in Nigeria, undermined confidence in Western medicine and led to efforts to better regulate this activity.[82] Finally, clinical trials of HIV vaccines or methods to prevent HIV transmission from mother to fetus were designed (mainly) to limit AIDS epidemics in Africa and Asia, but some were criticized for their ethical failings.[83]

The AIDS crisis has intensified debates on human experiments in developing countries, increasingly conducted with the active participation of experts from the Global South.[84] These debates usually focus on informed consent, the ethics of trials against placebo, the importance of securing benefits for participating communities, and the need to protect local populations and researchers against exploitation.[85] They rarely problematize the polysemic term "community," evoke the possibility that the interests of local professional elites may conflict with those of other social groups, or examine the consequences of conducting experiments on severely deprived populations.[86]

One notable exception to the paucity of attention on the role of deprivation was the debate over field trials of anti-HIV microbicides (substances applied locally and meant to protect women from HIV infection). Activists who promoted such trials had found that

> it is very difficult to balance the need to make a reliable trial with a right understanding of what organizers of this trial can do—and what they cannot—in order to avoid bothersome meddling with local health structures, raising non realistic expectations, and doing more harm than good.[87]

Organizers of clinical trials of anti-HIV microbicides were unable to find a satisfactory way to ensure that women who became infected with HIV during a prevention trial could access care and treatment after the study was over. They were obliged to recognize that research often could not help rectify long-standing inequities in access to global health resources, and that even the most carefully crafted protocols could not address the root causes of disintegrating health systems, such as poverty and gender inequalities.[88]

When people who volunteer to participate in a clinical experiment are driven by an inability to fulfill an elementary need—be it of care or of subsistence—the notion of informed consent becomes very questionable. Many doctors and bioethicists believe that experimenting on humans is not a problem if they are willing participants. They forget that the individual or collective decision to participate in an experiment may be founded on misinformation, misplaced trust in the profession, or, not infrequently, on pecuniary circumstances.[89] The insistence on informed consent without paying sufficient attention to the circumstances of receiving such consent may lead to a perilous dissociation of the process of consent from its clinical and social setting.[90] A guard at Pennsylvania's Holmesburg Prison, where dermatologists from the University of Pennsylvania conducted painful and sometimes risky experiments on prisoners, explained to

a social researcher surprised by such "volunteering," "Look, you and I wouldn't do it, sell ourselves for chump change to some strange college doctors, but. . . this is their only way to make money in jail."[91] Informed consent is about the possibility to choose, but it is not a choice when options are severely limited.

STUDYING "REALLY EXISTING" HUMAN EXPERIMENTS

Present-day reflections on human experiments, and evaluations of past experiments, are shaped by contemporary bioethical debates.[92] Such debates have been stimulated by revelations of severe ethical failings in the conduct of such experiments. Names such as Tuskegee, Willowbrook—and, today, Guatemala—have become synonyms of scientific misconduct.[93] Other past experiments on humans are presented as ethical, sometimes on the strength of partial evidence. In an oft-quoted text on "Ethics and Human Experimentation," David Rothman presents two historical examples of principled behavior of scientists. One is Louis Pasteur's first test of the rabies vaccine. Pasteur, Rothman explains, agonized about the decision to treat the first victim of a rabid dog, consulted with two colleagues, and decided in favor of treatment only when he was assured that otherwise the victim's death appeared inevitable.[94] The source of this often-told story is a hagiographic biography of Pasteur, written by his son-in-law.[95] Other sources present a very different image of Pasteur's human experiments, including "unofficial" experimentation and falsification of evidence.[96] Rothman's second case is studies carried out by PHS researchers in the Terre Haute penitentiary in 1943 and 1944. Scientists who conducted these studies were aware of their problematic legal and ethical aspects and established special protocols of informed consent, elements that did not exist in the Guatemala experiments supervised by the same people.[97]

Walter Reed's yellow fever studies are another frequently cited example of ethical human experiments.[98] Reed's biographer explains that all the volunteers in the Cuban experiments signed a contract that enumerated their risks and benefits and specified that

> the undersigned binds himself not to leave the bounds of this camp during the period of the experiment, and will forfeit all the rights to the benefits named in this contract if he breaks this agreement.[99]

The notion of a freely respected contract is, however, at odds with General William Gorgas's description of Reed's experiments:

> They established an experimental station in the country and half-a-mile or more from any habitation, *placed non-immunes in the camp under military control so that they could not leave it*, kept them there a sufficient length of time to be certain that they had not contracted yellow fever, and then experimented upon them.[100]

In Gorgas's version, a key element of the success of Reed's experiments was not a signed contract but the presence of armed guards.

If no new documents come to light, we may never know how participants in the Cuban yellow fever experiments reacted to their confinement. Without the chance arrival of Simond's laboratory notebooks in the Pasteur Institute Archives in the 1990s, the only source of information about the Petropolis experiments would have been the heavily edited official report of the Pasteur Institute Mission.[101] The relative abundance of documents on the PHS studies in Guatemala is probably an exception. It is difficult to count on the possibility that researchers will keep potentially compromising records.[102]

Obstacles to finding out what really happened during a given human experiment are not limited to historical studies. Discussions on present-day experiments tend to be centered on rules and regulations, institutional reviews and protocols, declared goals and proposed results. The final report of The Presidential Commission on Bioethical Issues, *Moral Science: Protecting Participants in Human Subjects Research*, released in December 2011, focuses on elements that should promote such protection: informed consent, increased accountability, expansion of education in bioethics, compensation for research related injury, and the promotion of "community engagement."[103] *Moral Science* does not dwell, however, on the need to supervise ongoing human experiments and gather reliable information on what is actually going on in these experiments, especially in those conducted in developing and intermediary countries. To avoid the risk of investigating the "bioethics of the imaginary," it may be important to considerably increase the number of observational studies of human experiments, including those with public health goals.[104] Such studies should help to answer the "how" question—What should be

done to reduce the risk of unethical behavior?—but also the "whether" question: What are the political, socioeconomic, and institutional conditions under which experiments on humans should not take place, even when the researchers who plan to conduct them have the best possible intentions? ■

About the Author

Ilana Löwy is with Centre de recherche, médecine, sciences, santé, santé mentale, société (INSERM, CNRS, EHESS, Paris V), Paris, France.

Correspondence should be sent to Ilana Löwy, CERMES 3, site CNRS, 7 rue Guy Moquet, 94801 Villejuif cedex, France (e-mail: lowy@vjf.cnrs.fr). Reprints can be ordered at http://www.ajph.org by clicking the "Reprints" link.

This article was accepted May 9, 2012.

Acknowledgments

This study was partly funded by Agence Nationale de Recherche sur le Sida (grants 2009-436 and 2010-375), in the framework of a larger study on the history and present uses of the prevention of sexually transmitted infections.

I thank Denise Ogilvie and Daniel Demellier of the Pasteur Institute Archives for their invaluable assistance with Paul Louis Simond's papers, and the *Journal*'s anonymous reviewers, who greatly helped me to improve this article.

Endnotes

1. Letter of Dr. Roberto Robles Chinchilla, chief of the medical service of Guatemala's central prison, Guatemala, December 8, 1948. Dr. John Cutler's documents, syphilis papers, file 1 (final report, syphilis), p. 4. National Archives, Washington, DC, http://www.archives.gov/research/health/cdc-cutler-records (accessed October 29, 2011). (Henceforth called "Cutler's papers.")

2. Letter to Etienne Clémentel, French minister of colonies, November 23, 1905. Pasteur Institute Archives, file Paul Louis Simond (henceforth, "Simond's papers") SIM/9. Simond and Marchoux, both members of the French corps of colonial physicians (corps des médecins des colonies), were promoted; in addition, Simond was named chevalier (knight) of the Legion d'Honneur, and Marchoux was advanced to the grade of officer.

3. "Read-Out of the President's Call With Guatemalan President Colom," October 1, 2010, http://www.whitehouse.gov/the-press-office/2010/10/01/read-out-presidents-call-with-guatemalan-president-colom (accessed October 29, 2011).

4. On earlier human experiments, see, for example, George Chamayou, *Les corps vils: Experimenter sur les êtres humains au XVIIIe et XIXe siècle* (Paris, France: La Decouverte, 2008); Susan Lederer, *Subjected to Science: Human Experimentation in America Before the Second World War* (Baltimore, MD: Johns Hopkins University Press, 1995).

5. Adriana Petryna, Andrew Lakoff, and Arthur Kleinman, *Global Pharmaceuticals: Ethics, Markets, Practices* (Durham, NC: Duke University Press, 2006); Adriana Petryna, *When Experiments Travel: Clinical Trials and the Global Search for Human Subjects* (Princeton, NJ: Princeton University Press, 2009).

6. There are exceptions to this rule; for example, the recent development of the human papillomavirus vaccine. Keith Wailoo, Julie Livingstone, and Steven Epstein, eds., *Three Shots at Prevention: The HPV Vaccine and the Politics of Medicine's Simple Solutions* (Baltimore, MD: Johns Hopkins University Press, 2010).

7. Such striving can and often does coexist with a wish to promote one's career. The ethical aspects of the PHS's experiments in Guatemala are analyzed in three excellent publications: Susan Reverby, "'Normal Exposure' and Inoculation Syphilis: A PHS 'Tuskegee' Doctor in Guatemala, 1946–1948," *Journal of Policy History* 23 (2011): 6–28; John Douglas, "CDC Report on Findings From the US Public Health Service Sexually Transmitted Disease Inoculation Study of 1946–1948, Based on Review of Archived Papers of John Cutler, MD, at the University of Pittsburgh," September 29, 2010, http://www.hhs.gov/1946inoculationstudy/std_inoc_st (accessed October 29, 2011); Presidential Commission for the Study of Bioethical Issues, "Ethically Impossible: STD Research in Guatemala, 1946 to 1948," September 2011, http://www.bioethics.gov (accessed October 29, 2011).

8. On the role rise of public health system in Brazil in the early 20th century in the construction of Brazilian nation, see, for example, Gilberto Hochman, *A Era do Saneamento—As bases da política de saúde pública no Brasil* (São Paulo, Brazil: Hucitec/ANPOCS, 1998).

9. Reverby discusses the role of Guatemala's political subordination to the United States in shaping the PHS's syphilis study. Reverby, "Normal Exposure," 11. On the other hand, the 1944 overturning of the military regime in Guatemala, followed by the presidency of Juan José Arévalo, opened a period of relative freedom, favorable to the growth of local professional elites. Such relative freedom ended with the 1954 military coup. Piero Gleijeses, *Shattered Hope: The Guatemalan Revolution and the United States, 1944–1954* (Princeton, NJ: Princeton University Press, 1991).

10. Report of Pasteur Institute Yellow Fever Mission, Pasteur Institute Archives, Simond's papers, SIM/ 9; Ilana Löwy, *Virus, moustiques et modernité: La fièvre jaune au Brésil entre science et politique* (Paris, France: Archives de l'Histoire Contemporaine, 2001); John Douglas, "CDC Report," 24; *Ethically Impossible*, 37–44.

11. Allan Brandt, "Racism and Research: Case of the Tuskegee Syphilis Study," *Hastings Center Report* 8 (1978): 21–29; Interview with Susan Reverby, *BU Today*, August 31, 2010; *Ethically Impossible*, 104–106.

12. Some of these elements were evoked by Reverby; see David A. Walsh, "An Interview With Susan Reverby," *Spero News*, October 9, 2010, http://www.speroforum.com/a/41331/An-interview-with-Susan-Reverby-Guatemala-syphilis-experiments-Island-of-Dr-Moreau (accessed October 29, 2011); *Ethically Impossible.*

13. Decree no. 2240 of the French Parliamentary Session of March 7, 1901, established the Yellow Fever Mission and allocated to it a budget of 150 000 francs (approximately €550 000 in 2011).

14. Salimbeni participated in the early investigations of the Pasteur Institute Mission, and then poor health obliged him to leave Rio de Janeiro.

15. On Reed's mission, see, for example, Nancy Stepan, "The Interplay Between Socio-Economical Factors and Medical Science: Yellow Fever Research in Cuba and in the United States," *Social Studies of Sciences* 8 (1978): 397–423; François Delaporte, *Histoire de la fièvre jaune* (Paris, France: Payot, 1989); Mariola Espinola, *Epidemic Invasions: Yellow Fever and the Limits of Cuban Independence, 1878–1930* (Chicago, IL: Chicago University Press, 2009). In 1900, a Cuban physician, Juan Guiteras, attempted to produce immunity to yellow fever by exposing people to bites of mosquitoes fed on mild cases of yellow fever. Three of his eight subjects died, a telling demonstration of the impossibility of controlling experimental yellow fever. Juan Guiteras, "Experimental Yellow Fever at the Inoculation Station of the Sanitary Department of Havana, With a View of Producing Immunization," *American Medicine* (November 23, 1901): 809–817; William Bean, "Water Reed and Yellow Fever," *Journal of the American Medical Association* 250 (1983): 659–662.

16. Paul Louis Simond, Journal, Rio de Janeiro, Simond's papers, SIM/9 ; Carlos Siedl, "Renascença: A missao Pasteur," *Revista Brasil Médico* (April 1905): 166–172.

17. The Pasteur Institute scientists conducted innovative epidemiological studies that demonstrated a high frequency of mild cases of yellow fever, and the importance of young children as a reservoir of the disease's agent. Emile Marchoux and Paul Louis Simond, "Etudes sur la fièvre jaune: Troisième memoire," *Annales de l'Institut Pasteur* 20 (1906): 104–147; Emile Marchoux and Paul Louis Simond, "Etudes sur la fièvre jaune: quatrième memoire," *Annales de l'Institut Pasteur* 20 (1906): 161–205.

18. Letter of Paul Louis Simond to Pierre Charin, September 9, 1902, Simond's papers, SIM/9.

19. Reed and his colleagues had shown that while it was possible to transmit yellow fever through the injection of a patient's serum, such a serum rapidly loses its capacity to infect other people when heated to 56°C or exposed for several days to air. Walter Reed, "Recent Researches Concerning the Etiology, Propagation and Prevention of Yellow Fever, by the United States Army Commission," *Journal of Hygiene* 2 (1902): 101–119.

20. Letter of Emile Roux to (probably) Antonio Salimbeni, March 28, 1902, Simond's papers, SIM/4. Roux possibly had in mind vaccination with an inactivated yellow fever agent present in heated serum drawn from patients during an infectious stage of this disease. He also mentioned passive protection by antibodies present in a convalescent's serum. Roux was at that time vice-director of the Pasteur Institute. He became the institute's director in 1904.

21. One may argue that the main reason Pasteur Institute scientists conducted human experiments in Brazil and not in Europe was that yellow fever was endemic there. This is partly true: Pasteur and his followers did experiment on humans in conditions today judged as ethically doubtful . Gerald Geison, *The Private Science of Louis Pasteur* (Princeton, NJ: Princeton University Press, 1996). On the other hand, "Pasteurian science" was closely related with the French colonial enterprise. The institute supplied vaccines and sera for the colonial army, trained colonial doctors in bacteriology, and recruited its researchers among these doctors. Anne Marie Moulin, "Patriarchal Science: The Network of Overseas Pasteur Institutes," in *Science and Empire*, ed. Patrick Petitjean, Catherine

Jami, and Anne Marie Moulin (Dordrecht, Netherlands: Kluwer, 1992), 307–322. On the links between early bacteriological and virological research and colonial and neocolonial endeavors, see, for example, Warwick Anderson, "When Every Prospect Pleases and Only Man Is Vile: Laboratory Medicine as Colonial Discourse," *Critical Inquiry* 18 (1992): 506–529; Michael Worboys, "The Colonial World as Mission and Mandate: Leprosy and Empire 1900–1940," *Osiris* 15 (2000): 207–218.

22. Emile Marchoux, Alexandre Salimbeni, and Paul Louis Simond, "La fièvre jaune: Rapport de la mission française," *Annales de l'Institut Pasteur* 17 (1903): 665–680 (citation, 671). We do not know how the (stated) "warning before witnesses" was worded and what it meant to experimental subjects.

23. Löwy, *Virus, moustiques et modernité*, 75–77. It is difficult to correlate the experimental subjects described in Simond's notebook with those described in the published text. The order of the experiments is different, and the data on the experimental subjects are not identical. Moreover, Simond's notebook gives the impression that he might have relied on a preexisting sets of notes: important details are occasionally missing, and some dates seem to be wrong.

24. Nineteen of the 30 subjects listed in Simond's notebook received injections of inactivated serum from a yellow fever patient. Notebook, April–June, 1903, Simond's papers, SIM/10.

25. By contrast, the induction of mild yellow fever was seen as a success: it demonstrated both the sensitivity of the subject and evidence of the protective effect of the injection of serum. Marchoux, Salimbeni, and Simond, "La fièvre jaune: Rapport de la mission française." This interpretation, however, was contradicted by the Pasteur Institute's scientists' epidemiological observation that a natural infection with yellow fever agent sometimes produced a very mild disease. Marchoux and Simond, "Etudes sur la fièvre jaune: Troisième memoire."

26. Since mild forms of yellow fever produced immunity, immigrants who had already stayed a short time in Brazil could have become immunized without being aware of the fact. The same objection was valid for experiments that attempted (and failed) to transmit yellow fever in unorthodox ways. A positive result would have been conclusive, but the meaning of a negative one was uncertain. Notebook, April–June, 1903, Simond's papers, SIM/10.

27. Letter of Roux to Simond, May 5, 1903, Simond's papers, SIM/4.

28. Short entries in Simond's notebook are (for now) the only source of information on these events. Rolf might have been accused of Soller's murder, or scared by it, or his escape might have been an independent event.

29. Bardach arrived in Pernambuco from Hamburg on May 5, and in Rio de Janeiro on June 1. He was bitten by two infected mosquitoes on June 10 and developed a high fever on June 14. Simond's notebook, April–June, 1903, Simond's papers, SIM/10. It seems likely that Bardach, infected at a late stage of the experimental series in Petropolis (no. 22 in Simond's notebook), is the individual described as "case 2" in the 1903 paper by Marchoux, Salimbeni, and Simond. His infection was described as a preliminary test, conducted to confirm Reed's findings: "once this point was established, we could safely start our vaccination essays." Marchoux, Salimbeni, and Simond, "La fievre jaune: Rapport de la mission française," 672.

30. Notebook, April–June, 1903, Simond's papers, SIM/10.

31. Marchoux, Salimbeni, and Simond, "La fièvre jaune: Rapport de la mission française," 671.

32. For example, Marchoux, Simond, and Salimbeni claimed that the yellow fever's agent could pass through a porcelain filter with medium size pores (Chamberland F) but not one with smaller pores (Chamberland B). Simond recognized in 1912 that other investigators had found that the yellow fever agent was able to pass through Chamberland filter B. Paul Louis Simond, "Fievre Jaune," in *Traité de Pathologie exotique, clinique et therapeutique*, ed. C. Grall and A. Clarac (Paris, France: J.B. Ballière, 1912), 30–75 (p. 34). The original observation that the yellow fever agent is a "filterable virus" was made by Reed and his collaborators in Cuba.

33. When an animal model became available, it was possible to verify some of the Pasteur Institute researchers' insights, such as the protective properties of convalescent serum. Such serum attenuated the effects of live virus when administered together with such a virus as a vaccine, but was not used as protection from natural infection. Wilbur Sawyer, S.F. Kitchen, and Wray Lloyd, "Vaccination Against Yellow Fever With Immune Serum and Virus Fixed for Mice," *Journal of Experimental Medicine* 55 (1932): 945–969.

34. *Ethically Impossible*, 27–29. Reverby stresses that at that time the interest in using penicillin for prophylaxis of sexually transmitted disease was waning in the United States. Reverby, "Normal exposure."

35. Cutler's correspondence suggests, however, that Salvado did not have precise information on the nature of the PHS studies.

36. Cutler's papers, file syphilis, no. 1, 17–20.

37. They were contaminated either through contact with an infected sex worker or through the injection of bacteria. *Ethically Impossible*, 45–51; 69.

38. Reverby, "Normal Exposure"; Douglas, "CDC Report"; *Ethically Impossible*. These texts point out to ethical failing, not only according to present-time standards but also according to those applied in 1947.

39. Douglas, "CDC Report," 10–12; *Ethically Impossible*, 61–68. These methods included abrasion of skin on the penis with a needle, then exposure of the abraded surface to treponemal solution and direct injection of germs to cerebrospinal fluid through a cisternal puncture. Cutler argued that these extremely artificial ways of infecting their experimental subjects would make possible the study of prophylaxis methods under more severe conditions than those occurring normally. Cutler to Mahoney, September 18, 1947, Cutler's papers.

40. Douglas, "CDC Report," 20; *Ethically Impossible*, 95–96. See also interview with John Arras, a member of the Presidential Commission for the Study of Bioethical Issues, *BioEdge*, September 26, 2011, http://www.bioedge.org/index.php/bioethics/bioethics_article/9749 (accessed October 29, 2011).

41. Cutler to Mahoney, September 20, 1947, Cutler's papers.

42. Mahoney to Cutler, September 8, 1947, Cutler's papers. At that time, the study, planned to last two years, was in its first year.

43. Cutler to Mahoney, June 22, 1947; Richard Arnold to Cutler, April 19, 1948; Cutler's papers.

44. Mahoney to Cutler, February 19, 1948, Cutler's papers. Italics are mine.

45. *Ethically Impossible*, 104–107. On the other hand, Cutler and Simond were in regular contact with their hierarchic superiors.

46. Marchoux, Salimbeni, and Simond, "La fievre jaune: Rapport de la mission française," 679. The French researchers added that such failures were to be expected, because people, like horses, produce more or less potent protective sera. They omitted to add that they had no way to test the preventive properties of a given convalescent serum, a major obstacle for the interpretation of their attempts to protect healthy people from yellow fever by the injection of such serum.

47. Emile Marchoux and Paul Louis Simond, "Etudes sur la fièvre jaune: Deuxième memoire," *Annales de l'Institut Pasteur* 20 (1906): 16–40. Marchoux and Simond explained that a trans-generational transmission of the yellow fever agent (if it exists) is probably a marginal phenomenon in endemic zones, but may play an important role in the exportation of yellow fever outside such zones.

48. Ibid, 20–22. The article describes two additional successful attempts to infect humans with yellow fever: one to prove that an experimental subject who failed to be infected by a second-generation mosquito was sensitive to the disease, another to demonstrate that mosquitoes fed on the bodies of infected mosquitoes can transmit yellow fever.

49. Simond, "Fievre Jaune," 73. Simond recognized that since their experiment was conducted in Rio, it was impossible to exclude the possibility that, in spite of their supervision, their experimental subject was accidentally bitten by an infected mosquito.

50. On February 15, 1905, subject no. 171 was bitten by an infected mosquito. The same day, yellow fever patient no. 180 was bitten by bedbugs; on February 19, subject no. 196 was exposed to infected bedbugs, and remained healthy. On March 6, subject no. 214 was bitten by infected mosquitoes to check whether he became immune to yellow fever. On March 10, subjects no. 236, 241, and 243 were bitten by infected mosquitoes and developed a mild disease, believed to be yellow fever. Simond's notebook, January 1904–March 1905, Simond's papers, SIM/10. It is not known how representative Simond's fragmentary notes are of his and Marchoux's activities in the São Sebastião hospital.

51. Cutler, 1955 summary of the syphilis experiments, file "syphilis" no. 1, Cutler's papers. Members of the Presidential Commission for the Study of Bioethical Issues contest this version, because the experiments in the penitentiary and the asylum started at the same time. *Ethically Impossible*, 57.

52. File "syphilis" no. 1, p. 23, Cutler's papers. The PHS researchers relied on the help of the Insane Asylum staff, paid with small sums of money or US cigarettes. File "syphilis" no. 1, p. 33, p. 42, Cutler's papers.

53. Cutler to Mahoney, May 19, 1948, Cutler to Mahoney, February 6, 1948; Cutler, file "syphilis" no. 1, p. 23, p. 25, Cutler's papers. The psychiatric hospital received (or was helped to purchase) a refrigerator, a sound projector, and metal cups and plates.

54. Cutler, file "syphilis" no. 1, p. 41, Cutler's papers.

55. This point was made in 1948 by Professor Tadeusz Kielanowski, dean of Marie Curie University, Lublin, in his comment on a paper by the pioneer of the sociology of science, Ludwik Fleck, on the regulation of human experiments. Ludwik Fleck, "W sprawach doswiadczen lekarskich na ludziach" ("On Human Medical Experiments"), *Polski Tygodnik Lekarski* (*Polish Medical Weekly*) 35 (1948): 1052–1054; Tadeusz Kielanowski, "W sprawie artykulu prof. dra Flecka o doswiadczeniach lekarskich na ludziach" ("On the Article of Dr. Fleck on Human Medical Experiments"), *Polski Tygodnik Lekarski* 43 (1948): 1292–1293. Fleck had a strong personal interest in experimentation on humans. As a prisoner in Buchenwald, he witnessed Nazi studies that involved deliberate infection of healthy people with typhus, and testified about these studies at the I.G. Farben trial in Nuremberg, February 12, 1948. Persecution documents no. 2224 and 2226, I.G. Farben trial, reproduced in *Ludwik Fleck: Style myslowe i fakty: artykuly i swiadectwa*, ed. Sylwia Werner, Claus Zittel, and Florian Schmaltz (Warsaw, Poland: IFiS-PAN, 2007), 358–365.

56. Marchoux, Salimbeni, and Simond, "La fièvre jaune: Rapport de la mission française," 671.

57. Letter of Oswaldo Cruz to Emile Roux, August 9, 1903, Oswaldo Cruz's correspondence, Archives of Casa Oswaldo Cruz, Fiocruz. On Cruz's sanitary campaign, see, for example, Nara Britto, *Oswaldo Cruz* (Rio de Janeiro, Brazil: Editora Fiocruz, 1995).

58. Paula Maria de Olivera, *Hospital de Sao Sebastiao (1889–1905): um lugar para a ciência e um lazareto contra as epidemias,* unpublished master's dissertation (Rio de Janeiro, Brazil: Fiocruz, 2005), 71.

59. William Beam, "Walter Read and the Ordeal of Human Experiments," *Bulletin of the History of Medicine* 51 (1977): 75–92 (quotation on p. 87).

60. Joal Pedro Leao de Aquino, "A Hopital Sanatorio Sao Sebastiao," *Revista Médica Municipal, Rio de Janeiro* (May–June 1945): 393–394. Quoted in Olivera, *Hospital de Sao Sebastiao*, 71–73.

61. Marchoux, Salimbeni, and Simond, "La fievre jaune: Rapport de la mission française," 679.

62. Leao de Aquino, "A Hopital Sanatorio Sao Sebastiao." The bacteriology course started in February 1903. On medical research in Brazil at that time, see Nancy Stepan, "Initiation and Survival of Biomedical Research in a Developing Country: The Oswaldo Cruz Institute of Brazil, 1900–1920," *Journal of the History of Medicine* 8 (1975): 303–325.

63. Letter of Minister of the Colonies Etienne Clémetel to Emile Roux, March 20, 1905, Simond's papers, SIM/4.

64. Siedl, "Renascença: A missao Pasteur," 169. Siedl explained that thanks to their contacts with the French scientists, Brazilian researchers grasped for the first time the importance of careful execution of experiments, their repetition, and the need for appropriate controls.

65. File "syphilis" no. 1, Cutler's papers; *Ethically Impossible*, 28–29.

66. The collaboration with US scientists might also have been favored by the fact that this was a period of liberalization in Guatemala. Gleijeses, *Shattered Hope.*

67. Mahoney strongly promoted Funes's career. Mahoney to Cutler, June 2, 1948; Mahoney to Cutler, June 26, 1948; Cutler's papers.

68. William McAnally, head of the Caribbean section of the PABS, to Fred Soper, the PASB's director, July 3, 1948, Cutler's papers.

69. This transformation was made upon the request of Guatemala's director of public health, Luis Galich. Cutler to PASB's director, Fred Soper, June 22, 1948; Mahoney to Cutler, July 16, 1948. Moreover, the PHS and the PASB promoted the training of Guatemalan scientists in the use of the electron microscope, a new, advanced research technology. John Mahoney and John Murdock (the PASB's vice-director) to John Cutler, July 13, 1947, Cutler's papers.

70. On the problematic notions of "center" and "periphery" in science, see, for example, Kapil Raj, *Relocating Modern Science: Circulation and the Construction of Knowledge in South Asia and Europe, 1650–1900* (New York, NY: Palgrave Macmillan, 2007).

71. Training in a leading scientist's center was often a first stage in the career of a young scientist, while one of the ways to maintain close contact with one's former colleagues was to facilitate their studies abroad. Human experiments were sometimes an element in a complex network of gift exchanges.

72. The Presidential Commission for the Study of Bioethical Issues stressed the importance of the involvement of local communities in the organization of such experiments, and the use of experiments to improve local health services. *Research Across Borders: Proceedings of the International Research Panel of the Presidential Commission for the Study of Bioethical Issues*, August 30, 2011, http://bioethics.gov/cms/node/346 (accessed October 29, 2011).

73. Volunteers in such experiments might also have been attracted by the argument that immigrants to an endemic country cannot escape yellow fever, and therefore it may be safer to contract this disease in a protected environment. Beam, "Walter Read and the Ordeal of Human Experiments."

74. Simond's notebook, Petropolis experiments, 1903, SIM/9, Simond's papers. The 24 entries in this list (out of 30 people mentioned in the notebook) are divided into two categories: people who developed experimental yellow fever and those who did not develop the disease. The French scientists did not speak about "volunteers" but about "men of good will" or "men who submitted to our experiments." Letter of Roux to (probably) Salimbeni, March 28, 1902, Simond's papers, SIM/4; Marchoux, Salimbeni, and Simond, "La fievre jaune: Rapport de la mission française."

75. Paul de Kruif, *Microbe Hunters* (New York, NY: Harcourt, Brace and Company, 1926), 133.

76. Cutler, file "syphilis" no. 1, p. 19, Cutler's papers.

77. Cutler to Mahoney, March 1, 1948, Cutler's papers. Similarly, the decision to give antimalaria therapy (the drug Aralen) to children at the orphanage where they collected blood for studies of the serology of syphilis was justified by the needs of the serological research. Cutler to Mahoney, June 6, 1947, Cutler's papers.

78. File "syphilis" no. 1, p. 33, Cutler's papers.

79. Cutler, file "syphilis" no. 1, p. 41, Cutler's papers.

80. On the efforts to prevent population explosion, see Betsy Hartmann, *Reproductive Rights and Wrongs: The Global Politics of Population Control* (New York, NY: Harper and Row, 1987) and Mathew Connelly, *Fatal Misconception: The Struggle to Control World Population* (Cambridge, MA: Harvard University Press, 2008); on ethically doubtful clinical trials of contraceptives in the Global South, see, for example, Mahmood Mamdani, *The Myth of Population Control: Family, Caste and Class in an Indian Village* (New York, NY: Monthly Review Press, 1972); Annette B. Ramírez de Arellano and Conrad Seipp, *Colonialism, Catholicism, and Contraception: A History of Birth Control in Puerto Rico* (Chapel Hill, NC: University of North Carolina Press, 1983); Barbara Mintzes, Anita Hardon, and Jannemieke Hanhart, eds., *Norplan: Under Her Skin* (Amsterdam, Netherlands: Women's Health Action Foundation, 1993); Laura Briggs, *Reproducing Empire: Race, Sex, Science, and US Imperialism in Puerto Rico* (Berkeley, CA: University of California Press, 2002).

81. Adriana Petryna, Andrew Lakoff, and Arthur Kleinman, eds., *Global Pharmaeuticals: Ethics, Markets, Practices* (Durham, NC: Duke University Press, 2006); Adriana Petryna, "Clinical Trials Offshored: On Private Sector Science and Public Health," *Biosocieties* 2 (2007): 21–40; Adriana Petryna, *When Experiments Travel: Clinical Trials and the Search for Human Subjects* (Princeton, NJ: Princeton University Press, 2009).

82. Marcia Angell, "The Body Hunters," *New York Review of Books* (October 6, 2005): 52–58; Joe Stephens, "Panel Faults Pfizer in '96 Clinical Trial in Nigeria," *Washington Post*, May 7, 2006, http://www.washingtonpost.com/wp-dyn/content/article/2006/05/06/AR2006050601338.html (accessed October 30, 2012); Ayodele Samual Jegede, "What Led to the Nigerian Boycott of the Polio Vaccination Campaign?" *PLoS Medicine* 4 (2007): e73.

83. Michelle Barry, "Ethical Considerations on Human Investigation in Developing Countries: The AIDS Dilemma," *New England Journal of Medicine* 319 (1988): 1083–1085; Peter Lurie and Sidney Wolfe, "Unethical Trials of Interventions to Reduce the Perinatal Transmission of the Human Immunodeficiency Virus in Developing Countries," *New England Journal of Medicine* 337(1997): 853–855; David B. Resin, "The Ethics of HIV Research in Developing Nations," *Bioethics* 12 (1998): 286–306; Peter Lurie, Ruth Faden, and Nancy Kass, "HIV Research, Ethics and the Developing World [editorial]," *American Journal of Public Health* 88 (1998): 548–550.

84. See, for example, Prahan Phanuphak, "Ethical Issues in the Studies in Thailand of the Vertical Transmission of HIV," *New England Journal of Medicine* 338 (1998): 834–835; Salim Abdool Karim, "Placebo Controls in HIB Perinatal Transmission Trials: A South African Viewpoint," *American Journal of Public Health* 88 (1998): 564–566.

85. Michele Barry and Malcom Molyneux, "Ethical Dilemmas in Malaria Drugs and Vaccine Trials: A Bioethical Perspective," *Journal of Medical Ethics* 18 (1982): 189–192; Marcia Angell, "The Ethics of Clinical Research in the Third World," *New England Journal of Medicine* 337(1997): 847–849; Harold Varmus and David Sather, "Ethical Complexities of Conducting Research in Developing Countries," *New England Journal of Medicine* 337(1997): 1003–1005; Carlos del Rio, "Is Ethical Research Feasible in Developed and Developing Countries," *Bioethics* 12 (1998): 328–330; Grieg Kosli and Stuart Nightingale, "Research Involving Human Subjects in Developing Countries," *New England Journal of Medicine*

345 (2001): 136–138; Harold Shapiro and Eric Meslin, "Ethical Issues in the Design and Conduct of Clinical Trials in Developing Countries," *New England Journal of Medicine* 345 (2001): 139–141; Ezkiel Emanuel, David Wendler, Jack Killen, and Christine Grady, "What Makes Clinical Research in Developing Countries Ethical? The Benchmarks of Ethical Research," *Journal of Infectious Diseases* 189 (2004): 930–937.

86. A frequently nonreflexive use of the term "community" in debates on the ethical aspects of human experiments in the Global South sharply contrasts with the nuanced uses of this term by scholars interested, for example, in women's or minority rights. In the latter context, "community" is often presented as a dynamic and evolving entity and a site of numerous conflicting interests and power struggles. Male "community elders" may act against the interests of women in that "community," "modernizers" may clash with "traditionalists," etc. See, for example, Susan Moller Okin, *Is Multiculturalism Bad for Women* (Princeton, NJ: Princeton University Press, 1999).

87. Lori Heise and Susan Wood, *Rethinking the Ethical Roadmap for Clinical Testing of Microbicides,* (Washington, DC: Global Campaign for Microbicides, May 2005), 23.

88. Lorie Heise, Katherine Shapiro, and Katie West Slevin, *Mapping the Standards of Care at Microbicide Clinical Trial Sites* (Washington, DC: Global Campaign for Microbicides, 2005), 70–74.

89. Jordan Goodman, Anthony McElligott, and Lara Marks, "Introduction," in *Useful Bodies: Humans in the Service of Medical Science in the Twentieth Century,* ed. Jordan Goodman, Anthony McElligott and Lara Marks (Baltimore, MD: Johns Hopkins University Press, 2003), 1–25 (p. 13).

90. Oonagh Corrigan, "Empty Ethics: The Problem With Informed Consent," *Sociology of Health and Illness* 25 (2003): 768–792.

91. Allen M. Hornblum, *Acres of Skin: Human Experiments at Holmesburg Prison* (New York, NY: Routledge, 1998), p. xiv.

92. On the shaping of present-day bioethics, see, for example, *Social Sciences Perspectives on Bioethics*, ed. George Weisz (Philadelphia, PA: University of Pennsylvania Press, 1991); Charles Rosenberg, "Meanings, Policies and Medicine: On the Bioethical Enterprise and Its History," *Daedalus* 128 (1999): 27–46; Roger Cooter, "The Ethical Body," in *Companion to Medicine in the Twentieth Century*, ed. Roger Cooter and John Pickstone (London, UK: Routledge, 2000), 451–469; Renée Fox and Judith Swazey, *Observing Bioethics* (Oxford, UK: Oxford University Press, 2008), 21–76; Duncan Wilson, "Creating the 'Ethics Industry': Mary Warnock, In Vitro Fertilisation and the History of Bioethics in Britain," *BioSocieties* 6 (2011): 121–141.

93. On Tuskegee, see, for example, James Howards Jones, *Bad Blood: The Tuskegee Syphilis Experiment* (New York, NY: Free Press, 1981); *Tuskegee Truths*: *Rethinking the Tuskegee Syphilis Study*, ed. Susan Reverby (Chapel Hill, NC: University of North Carolina Press, 2000); Susan Reverby, *Examining Tuskegee: The Infamous Syphilis Study and Its Legacy* (Chapel Hill, NC: University of North Carolina Press, 2009), on Willowbrook, see Joel Howell and Rodney Hayward, "Writing Willowbrook, Reading Willowbrook," in *Useful Bodies*, 190–213.

94. David Rothman, "Ethics and Human Experimentation," *New England Journal of Medicine* 317 (1987): 1195–1199 (p. 1196).

95. René Valery Radot, *Pasteur: A Great Life in Brief*, transl. Alfred Joseph (New York, NY: Knopf, 1958).

96. According to Gerald Geison, before his highly publicized treatment of the child Joseph Meister, Pasteur conducted "private," unreported human experiments with rabies vaccine; Geison, *Private Science of Louis Pasteur*. Later, in all probability, Pasteur's collaborators, with Pasteur's tacit agreement, falsified evidence to hide a death produced by the rabies vaccine; Adrien Loir, *À l'ombre de Pasteur* (Paris, France: Le Mouvement Sanitaire, 1938).

97. Rothman, "Ethics and Human Experimentation," 1197–1198. Rothman attributed the PHS researchers' decision to experiment on vulnerable populations to a wartime environment that legitimized putting people's lives at risk to sustain war efforts and prevent defeat. On the contrast between the Terre Haute and Guatemala experiments, see *Ethically Impossible*, 13–23. It is not clear, however, if people deprived of liberty can provide truly informed and freely granted consent.

98. These studies are quoted, for example, by the Presidential Commission for the Study of Ethical Issues as an example of early awareness of the importance of informed consent and risk reduction; *Ethically Impossible*, 97.

99. Beam, "Walter Read and the Ordeal of Human Experiments," 87. One of the aims of this consent form might have been to disarm local critics. Reed explained in 1900 that he was not at all disturbed by the malignant gossip spread by hostile Cuban newspapers, because the Spanish consul "assures us that we shall have his support as long as we do not use minors and the individual gives us written consent." Ibid.

100. William C. Gorgas, "Recent Experiences of the United States Army With Regard to Sanitation of Yellow Fever in the Tropics," *Journal of Tropical Medicine* 6 (1903): 49–52 (quotation, p. 50). Italics are mine.

101. Simond's papers, collected between 1993 and 1997, were a gift from Simond's nephew, Marc Simond. Fonds d'archives Paul-Louis Simond, Institut Pasteur, Service des Archives, http://www.pasteur.fr/infosci/archives/sim1.html (accessed October 29, 2011).

102. Cutler's documents, however rich, provide only a very partial image of the events in Guatemala. *Ethically Impossible*, 5.

103. Report of The Presidential Commission on Bioethical Issues, *Moral Science: Protecting Participants in Human Subjects Research* (released December 14, 2011), http://bioethics.gov/cms/node/558 (accessed January 17, 2012).

104. I borrow the term "bioethics of the imaginary" from Ludwik Fleck, who explained in 1929 that epistemologists who investigate scientists' principles and declarations, but fail to observe their work in the laboratory, produce "epistemologia imaginalis." Ludwik Fleck, "On the Crisis of 'Reality,'" in *Cognition and Fact: Materials on Ludwik Fleck*, ed. Robert Cohen and Thomas Schnelle (Dordrecht, Netherlands: Reidel, 1986), 59–78. The original article was published in *Die Naturwissenschaften* 18 (1929): 425–430.