From: Lightman, B., 2016, A Companion to the History of Science, Wiley Blackwell,Malden, MA.

CHAPTER NINE

The Human Experimental Subject

ANITA GUERRINI

Humans have been experimental subjects in Western science for almost as long as experimentation has taken place. As Western-style biomedicine has come to dominate most of the world in the past century, so Western-style experimentation has also taken root. Medical anthropologist Margaret Lock notes, "medical knowledge and practices in all societies are inevitably associated with moral judgments and with ideas about what is normal and abnormal" (Selin 2003, 155). Experimenting on humans has come to be considered normal. The definition of experimentation varies widely over time and place, and includes external observation and manipulation; the testing of toxins in poisons, foods, or diseases; and vivisection, the surgical cutting open of the body, among other interventions in a body's normal functioning. But experimental subjects over the centuries have generally been drawn from a few classes of people, what historian Grégoire Chamayou has referred to as "vile bodies." These include prisoners, orphans, prostitutes, people with disabilities, the mentally ill, hospital patients, slaves, and the colonized (Chamayou 2008, 7). To these might be added certain racial and economic groups, and soldiers. But it is not inevitable that these people would become experimental subjects, and how one became a "vile body" has shifted with time and circumstance. The critical relationship is one of power: those who possess political or medical authority have deemed that certain individuals occupy the boundaries of health, or the law, or the state and that they are therefore expendable as experimental subjects for a greater good. Yet self-experimentation among researchers constitutes a significant category of experimentation that these definitions do not cover. Human experimental subjects have only recently become subjects of historical scrutiny, as knowledge-making has come to be viewed more broadly.

Only in the twentieth century did ethical theories and accompanying statutes emerge in Western nations to limit, mitigate, and in some cases forbid human experimentation. Not coincidentally, that century also witnessed the most flagrant violations of human bodily integrity, at times despite legal restrictions. Historians have argued that the concept of consent is the most important legacy of twentieth-century

A Companion to the History of Science, First Edition. Edited by Bernard Lightman.

bioethics, and that revelations of Nazi atrocities during the Nuremberg trials in 1946 led to the codification of consent of the subject as a prerequisite for experimenting. But the story is more complicated: both Chamayou (2008) and Lederer (1995) have shown that researchers viewed consent as necessary long before 1946. Moreover, numerous studies beginning with the revelations of Maurice Pappworth and Henry Beecher in the 1960s have shown that the criterion of consent continues to be inconsistently applied.

"Informed consent," the notion that the human experimental subject must be advised of potential risks and benefits, also has a long history before Nuremberg. But its definition continues to be imprecise, and legal and ethical obligations do not entirely coincide. Factors such as fear, hope, respect for authority, and financial incentive may make consent less than free and informed, particularly among the populations most likely to become experimental subjects.

This account offers a selective look at some of the categories of human subjects over history: prisoners, slaves, children, patients, and self-experimenters. For much of history, the greater public has viewed human experimentation with horror and disgust; this has made it an easy shorthand to vilify political or ideological enemies. Sometimes this vilification has been justified. My story ends in 1993 with the revelation of secret human experiments conducted by the US government, which led to further regulations. New arenas for experimentation and abuse emerged with the biotechnology revolution of the late 1990s and 2000s.

Prisoners

Although there are surgical traditions in many parts of the world, there are few instances of dissection outside Greco-Roman medical culture (Selin 2003). During the eras in Western science when human dissection was allowed for research, the bodies of executed criminals were most commonly used. Dissection therefore entailed collusion between researchers and the executing authorities. The British Murder Act of 1752 codified what was usually a local transaction, specifying that the corpses of those executed for murder would be available for dissection. Whether criminals or prisoners of war, the incarcerated have historically also been the primary "vile bodies" employed as experimental subjects. Imprisonment for whatever reason places humans completely under another's control. Even more than slavery, it effaces individual identities and rights.

Alexander the Great founded the city of Alexandria in Egypt in 331 BCE as a cosmopolitan center of learning. Its combination of willing physicians, ambitious rulers, and what historian Heinrich von Staden has called "scientific frontiersmanship" (von Staden 1989, 141) allowed the dismissal of old taboos, including Greek prohibitions of the mutilation of the human body, living or dead. There is good evidence that, around 280 BCE, Herophilus of Chalcedon and his younger contemporary Erasistratus dissected humans. In addition, the king granted them condemned criminals to dissect alive to investigate further the workings of the human body. But the Alexandrians' moment was short, and sanctioned human dissection did not reappear for over 1500 years.

When human dissection began again around 1300, executed criminals were the most common subjects. Although some anatomists dreamt longingly of the

days of Herophilus, human vivisection remained unthinkable; but as dissection became increasingly practiced after 1500, rumors abounded that the most prominent anatomists, including Jacopo Berengario da Carpi and Andreas Vesalius, did not always wait for their anatomical subjects to expire before cutting them open. In Oxford in 1650, Anne Greene, convicted and hung for infanticide, was not the first to revive at the touch of the anatomist's knife.

The use of prisoners to test poisons, drugs, and remedies also has a long history. King Attalus III of Pergamon around 150 BCE tested poisons and their antidotes on criminals condemned to death. Shortly after, the notorious King Mithradates of Pontus also tested poisons on prisoners, as well as on members of his court. Between antiquity and the Renaissance, information about experimentation is scanty. A hostile commentator attributed to the thirteenth-century Holy Roman Emperor Frederick II a number of experiments involving prisoners, but modern historians have dismissed these accounts as exaggerated. However, medieval prisoners of war were treated harshly, and the line between torture and experimenting might have been thin.

The first modern use of prisoners as test subjects came in the context of smallpox variolation (deliberately infecting with smallpox to induce immunity) in London in the early 1720s. In the wake of Lady Mary Wortley Montagu's successful variolation of her own children, royal physician Hans Sloane arranged for an experimental trial with six prisoners from London's Newgate prison, three men and three women. Once inoculated, five came down with smallpox and survived; it turned out one had already had the disease. The prisoners gained their release, but one of them, Elizabeth Harrison, aged 19, further proved her immunity by nursing smallpox victims.

Prison itself could be an experiment. The Pennsylvania System of incarceration based on isolation, introduced in 1829 at the Eastern State Penitentiary in Philadelphia, has subsequently been viewed as a wide-scale (and long-term) human experiment in the effects of prolonged solitary confinement. Intended to induce penitence, solitary confinement often led to insanity. Charles Dickens wrote of it in 1842, "I hold this slow and daily tampering with the mysteries of the brain to be immeasurably worse than any torture of the body; and because its ghastly signs and tokens are not so palpable to the eye,… and it extorts few cries that human ears can hear" (Dickens 1842). This system endured until the early twentieth century. But by that time, scientists and prison administrators began to realize that prison populations provided ample human material for a variety of experiments.

Amnesty or a reduced sentence for participation in experiments proved to be a powerful incentive. The 1915 pellagra experiments of Joseph Goldberger in Mississippi provided a model for subsequent use of prisoners in experiments. Goldberger, a physician with the US Public Health Service, believed that the cause of pellagra, which was endemic in the South, was not a germ but a dietary deficiency. He had tested this hypothesis in two Mississippi orphanages and a Georgia mental asylum. With the agreement of the state's governor, Goldberger then embarked on a controlled dietary experiment with prison volunteers. All of the chosen volunteers where white; Goldberger argued that because pellagra was less common among whites, this would offer a more convincing demonstration, and the telltale rash was more easily discernible on lighter skin. But historian Jon Harkness has argued that the predominance of white subjects in this and other prison experiments reflected social and racial divisions in prison culture, where participation in experiments (and its rewards) was

viewed as a privilege (Harkness 1996). The experiment successfully demonstrated the relation between pellagra and diet, but critics remained and Goldberger resorted to self-experimentation to make his case. There was little criticism, however, of his use of prisoners.

Between 1915 and the early 1970s, many experiments were conducted on American prison populations, ranging from testicular implants to research on tuberculosis, cancer, and malaria. The peak of prison experimenting occurred between 1951 and 1974 at Holmesburg Prison in Philadelphia, which journalist Allen Hornblum described in his book *Acres of Skin* (1999). Directing these experiments was dermatologist Albert Kligman. In exchange for payments of between $10 and $300, inmates tested consumer products such as detergents and hair dyes as well as radioactive, hallucinogenic, infectious, and toxic materials for pharmaceutical companies and government agencies. Kligman developed the popular acne medication Retin-A from experiments at Holmesburg. Following the Tuskegee revelations in 1972, experimenting stopped at Holmesburg and Federal laws enacted in 1978 restricted prison experimenting to studies with minimal risk to inmates. Some have argued that this law goes too far and that therapeutic experiments on prisoners should be allowed.

Slaves

Next to prisoners, slaves undoubtedly had the least agency and were therefore quintessential "vile bodies." Roman *praegustatores* or food tasters, who were slaves or freedmen, continued earlier traditions of servants in noble households who tasted food to ensure its safety. Historians have recently argued that, far from being unwitting victims of poisoners, the *praegustators* were skilled toxicologists who prided themselves on their ability to detect poisons, employing a variety of methods (Johnston 2013).

Slaves were of increasing importance in the global economy in the eighteenth century, and they were often too valuable to use in experiments. Eighteenth-century physicians such as Zabdiel Boylston, who practiced variolation in Boston, or Thomas Fowler, who published "trials" of the therapeutic uses of tobacco and arsenic, preferred to use their patients. Historian Londa Schiebinger cites the colonial physician John Quier's variolation of black slaves in Jamaica in the 1760s as an example of experimentation on slaves. But Quier's variolation did not differ from standard general practices and the slaves were also his patients (Quier 1780; Schiebinger 2004, 401–2). In the United States, however, historian Todd Savitt argues that in the antebellum south, "Blacks were considered more available and more accessible" to medical research, owing particularly to their legal invisibility (Savitt 1982, 332). In the nineteenth century, a developing scientific medicine based on clinical observation demanded human subjects, alive and dead. In the south the majority of hospital patients were black, solicited by offers to slave owners of free medical care, and most student dissections were performed on black bodies.

Several historians cite two more sinister uses of slaves for the advancement of medical knowledge. In Georgia in the 1820s and 30s, Dr. Thomas Hamilton subjected a slave named Fed to experiments on heat stroke. On several occasions, Fed sat in a pit surrounded by hot embers to test various remedies. In the 1840s, Dr. James Marion Sims tested surgical techniques in the repair of vesico-vaginal fistula on three slave women in Alabama. Each woman experienced around thirty operations, which

in this pre-anesthetic, pre-antiseptic age were both painful and risky. Sims finally succeeded, and found that his white patients on whom he subsequently operated seemed much less tolerant of pain than the slave women, perpetuating a myth of racial difference in pain perception. Other examples of surgical trials on slaves included tests of ovariotomy, anaesthesia, and caesarian section (Savitt 1982, 346–7).

World War II victims of medical experimenting by the Axis powers may more properly be defined as slaves than as prisoners, since their incarceration was a function of who they were rather than the result of a crime. The experiments at Nazi concentration camps and the Manchurian site known as Unit 731 have been thoroughly documented. In Germany, medical scientists had elaborated long before World War II the distinctively German strain of eugenics known as *Rassenhygiene* or racial hygiene, which classified certain ethnic groups, particularly Jews and Roma, along with homosexuals and the mentally ill, as threats to the nation's health. These groups became the "vile bodies" of Nazi experimentation. Bioethicist Arthur Caplan has argued that "mainstream biomedicine in Germany boarded the Nazi bandwagon early, stayed for the duration of the Nazi regime, and suffered few public second thoughts or doubts about the association even after the collapse of the Reich" (Caplan 1992, 57).

Although Nazi physicians at the "doctors' trial" at Nuremberg in 1946–47 claimed that they were merely following orders in wartime, the ideological basis of Nazi science made such arguments unconvincing, and revelations of mass euthanasia in concentration camps made any claims for the scientific value of Nazi experiments equally dubious. However, debate has continued on the ethics of using Nazi experimental data. Does the nature of the experimental subjects make the data invalid? In the 1980s, some scientists argued that the use of Nazi data on hypothermia would recognize the sacrifice of the experimental subjects, but in 1990 physician Robert Berger showed that the experiments were deeply flawed (Berger 1990). On the other hand, Nazi physician Eduard Pernkopf compiled what is widely regarded as one of the most accurate anatomical atlases ever produced. It has become increasingly clear that Pernkopf used victims of Nazi violence to compile his atlas, and researchers continue to disagree about the ethics of its use (Pringle 2010).

Although the Japanese physicians who experimented with chemical and biological warfare at Unit 731 believed, like the Nazis, that their victims—mostly Chinese and Russian—were racially inferior, they were prisoners of war, political prisoners, and others identified as subversive; in other words, their identity as "vile bodies" was political rather than ideological. Of course, these motivations made little difference to the victims themselves. However, unlike with Nazi doctors, the occupying Americans did not try Japanese physicians for war crimes, instead appropriating their research on biological weapons. In 1949, the USSR tried 12 Japanese officers in connection with experiments on Russians, but full revelation of Japanese experiments only occurred from the 1980s onward (Harris 1994).

Patients

By the seventeenth century, human dissection had become increasingly common not only for medical instruction, but for research into human structure and function. The English physician William Harvey tied tourniquets on arms in order better to observe

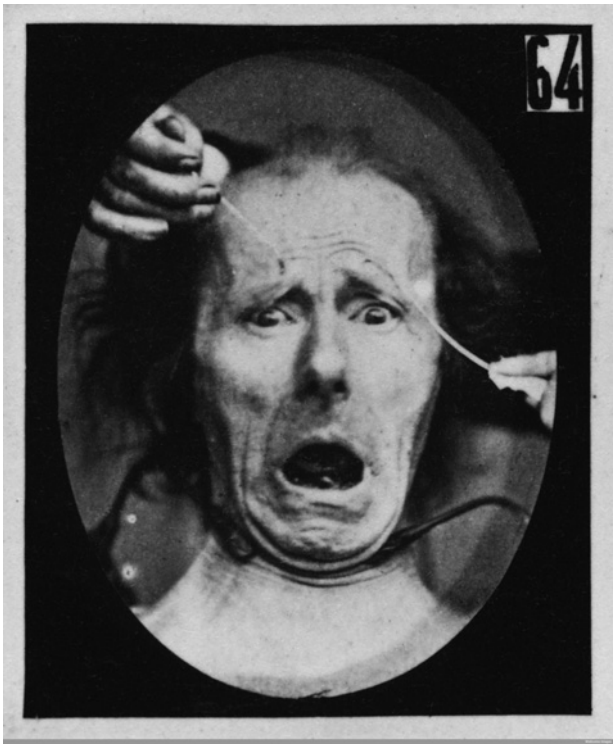

Figure 9.1 The expression of terror as induced by electrical stimulation of facial muscles. Duchenne used his patients for his experiments on the electrical stimulation of muscles. G.-B. Duchenne. 1862. *Mécanisme de la physionomie humaine*. Paris: Renouard, Plate 7, Image 64. Wellcome Library, London.

the veins and arteries, but that was the extent of his research on live humans. His concept of the circulation of the blood (1628) led to a number of experiments on blood transfusion in the 1660s, especially in England and France. Transfusion experiments had begun with animals, but the therapeutic potential of exchanging old, sick blood for fresh, young blood seemed too promising to pass up. With little understanding of the composition of blood, experimenters believed that the blood of young animals such as calves or lambs could be particularly beneficial for humans. The first transfusions, of seriously ill people, were inconclusive. Trials were then made on mentally ill (but otherwise healthy) subjects. In London, Arthur Coga survived two transfusions of lambs' blood and his "too warm" brain calmed; in Paris, however, Antoine Mauroy died, either from the effects of the transfusions or from some other cause. (Figure 9.1)

Human transfusion then ceased until 1818, when James Blundell, a London obstetrician, suggested blood transfusion as a way to mitigate the consequences of uterine hemorrhage after birth. After numerous experiments with dogs (during which he determined that injecting blood from other species was fatal), Blundell transfused blood from one human into another in 1825, and several times subsequently. Not all of his patients survived, but some did. A few others adopted his procedures with

mixed success. Until greater knowledge of blood types and anticoagulants emerged in the twentieth century, blood transfusion remained a hit-or-miss procedure. Little is known about Blundell's subjects, but it is likely that they were his hospital patients rather than from his private practice, and therefore were poor women.

I have argued elsewhere (Guerrini 2003) that smallpox inoculation in the eighteenth century was the first large scale human experiment, conducted largely by doctors on their patients. While early trials of the procedure were made on the "vile bodies" of prisoners, variolation soon became widespread and eagerly sought by populations across Europe. Smallpox was common and greatly feared: contagious, disfiguring, and in up to a third of cases, fatal. Survivors were unlikely to contract it again, but the nature of immunity was not understood. In parts of Asia and Africa, children had long been variolated. The most common method involved inserting some dried scabs into a scratch on the arm, although powdered scabs were sometimes inhaled.

An account of this practice in Constantinople appeared in the *Philosophical Transactions* of the Royal Society of London in 1714; a few years later, Lady Mary Wortley Montagu, the wife of the British ambassador to the Ottomans, had her young son inoculated by the embassy's surgeon. Back in London when a smallpox epidemic broke out in 1721, her daughter was also inoculated. The girl contracted a mild case of smallpox and survived, and the medical world took notice. Following the experimental trial with six prisoners, variolation spread among the British population.

Meanwhile, an epidemic broke out in New England. The clergyman and fellow of the Royal Society Cotton Mather had learned of variolation from the *Philosophical Transactions* as well as from his African slave. He persuaded only one Boston physician, Zabdiel Boylston, to try it, who inoculated his sons, his slaves, and several patients. Boston physicians debated the efficacy of variolation, but statistics—a very new science—was on Boylston's side; only 12 of the 400 he inoculated died, versus 500 out of 3600 natural cases. In the late 1720s, the British physician James Jurin made a larger statistical case for variolation, determining that only 1 in 60 died of it in Britain, versus 1 in 8 of natural smallpox.

Widely practiced, variolation remained experimental. It did not always work: induced cases of smallpox were not always mild, and the inoculated could spread the disease to others. The statistical methods of Jurin and later Daniel Bernoulli (1700–1782) in France also turned individual patients into numbers, a step toward the depersonalization of the experimental subject. Variolation and later vaccination introduced statistics and an early version of cost-benefit analysis to human experimentation. But it also amounted to doctors experimenting on their patients. Because smallpox was such a feared disease, it could even be argued that the consent of those who volunteered for variolation was not entirely uncoerced. These issues would arise again.

Hospital patients became experimental subjects by the eighteenth century, and some argue they remain so. Until the end of the nineteenth century, those who could afford it received care from a physician in their homes. Those who could not went to hospitals. Historical opinion differs on the level of care provided in these institutions, but they were fruitful ground for the observation of diseases and for research into remedies and their effectiveness. Most therapies were experimental in that their actions and effectiveness were poorly understood, and therefore any patient, in or out of hospital, might be considered an experimental subject. Hospital patients provided

a captive and largely powerless pool of subjects. Slave patients in antebellum hospitals were therefore doubly captive.

By the early nineteenth century, the practice of therapeutic experimentation had become standardized; in 1814 French physician Auguste Chomel summarized the rules that medical students should follow in such experiments. He distinguished two varieties of trials, one to determine the action of a therapeutic agent against a known illness, the other to find the specific body function that the therapy affected. One must therefore know the remedy, the experimental subject, and the illness (Chamayou 2008, 206). Experiments, added Chomel, should aim to cure a patient, not to make him ill. Over a century later, Beecher and Pappworth detailed dozens of harmful experiments that took place in hospitals in the 1950s and 60s.

In the heyday of colonialism in the eighteenth and nineteenth centuries, colonial subjects were deemed excellent experimental subjects; in status they fell between slaves and their European rulers. For example, in the 1840s, Scottish surgeon James Esdaile experimented in Calcutta on Indian subjects on the efficacy of mesmerism as an anesthetic (Winter 1998). The discovery of the mosquito vector for malaria in the 1890s included experiments on British colonial subjects and patients in China and India.

The most famous human experimental subject in the nineteenth century was neither a slave nor a hospital patient, and the experiments had no connection to therapy. In 1822, a French-Canadian voyageur in upper Michigan named Alexis St. Martin (1794–1880) received a gunshot wound in his side. The wound did not close, leaving an opening into his stomach. This gastric fistula provided a window into still mysterious digestive processes, and his doctor, Army surgeon William Beaumont (1785–1853), decided to investigate these. St. Martin could not continue fur-trapping and served in Beaumont's household as a handyman. As historian Alexa Green has pointed out, St. Martin's agreement with Beaumont was an employment contract rather than one protecting his rights as an experimental subject (Green 2010).

Beaumont poked bits of food into St. Martin's stomach through the fistula. He also took samples of gastric fluid and inserted a long thermometer, which was quite painful. Between 1825 and 1833 Beaumont performed hundreds of experiments on St. Martin, and published several articles and a book that made them both famous. St. Martin disliked the experiments and periodically ran away. He left Beaumont's household permanently in 1833, and although he lived in poverty, he resisted the surgeon's pleas to return for more experiments. St. Martin was hardly an equal in the relationship with Beaumont; like hospital patients, his poverty and low social status made him particularly susceptible to exploitation as a "vile body."

The noted French physiologist Claude Bernard greatly admired Beaumont's work. In the preface to his influential *Introduction to the Study of Experimental Medicine* (1865), Bernard echoed Chomel in justifying human experimentation in certain circumstances; yet none of these applied to St. Martin:

> It is our duty and our right to perform an experiment on man whenever it can save his life, cure him or gain him some personal benefit. The principle of medical and surgical morality, therefore, consists in never performing on man an experiment which might be harmful to him to any extent, even though the result might be highly advantageous to science. … So, among the experiments that may be tried on man, those that can only

> harm are forbidden, those that are innocent are permissible, and those that may do good are obligatory (Bernard 1957, 101–2).

A dozen years after these lines were written, the emergence of the germ theory of disease afforded a new set of experimental imperatives for medicine, in the development of the clinical trial. The modern clinical trial tests a medical treatment or a prevention strategy (Collier 2009). In the mid-eighteenth century, Scottish physician James Lind tested the efficacy of citrus juice in the prevention and treatment of scurvy on 12 sailors; only the two fed citrus recovered from the disease. While notions of placebo and control group developed in the nineteenth century, the additional concepts of blinding and randomization only emerged in the late 1940s. In a blind and randomized trial, neither the researcher nor the experimental subject knows who is receiving the treatment being tested and who receives a placebo; furthermore, assignment to each group is random. These measures minimize researcher bias.

This design was not fully realized when researchers from the United States Public Health Service began a project in 1932 to examine the effects of syphilis. This study was not a clinical trial, but an observational study of the effects of untreated syphilis in black men, although the 600 subjects, poor southern men, included 201 who did not have the disease and served as controls. They received free medical examinations and burial insurance. They did not, however, receive information about the nature of the study when they consented to participate. It continued for 40 years, and even when penicillin, highly effective in the early stages of the disease, became available in the 1940s, the men were not offered it. The study was finally terminated in 1972 after its revelation in the press led to public outcry. On the heels of the whistle-blowing of Beecher and Pappworth, the Tuskegee case led to a reexamination of human subjects protection in the US, culminating in the National Research Act of 1974, which codified written consent and established Institutional Review Boards to evaluate human subjects research. The act also set up a National Commission on the Protection of Human Subjects to identify the basic ethical principles underlying human research. Building on the 1964 Helsinki Declaration of the World Medical Association and subsequent amendments, the commission's 1979 Belmont Report named three key principles: respect for persons, beneficence, and justice.

Children

A thirteenth-century chronicler claimed that Emperor Frederick II caused several orphaned children to be raised in complete silence to determine if they would spontaneously speak Hebrew, thought to be the original language of the world and therefore the language of God. Orphans and other institutionalized children, like prisoners, had no one to speak for them other than institutional authorities. After Sloane conducted his smallpox trial at Newgate Prison, a group of orphans received inoculation. Only then did it gain royal approval.

Not all children were as vulnerable as these. But the threat of a deadly disease could compel parents to offer their children as guinea pigs. Vaccination is one example. Edward Jenner, an English country physician, knew of many cases of milkmaids and dairymen who had contracted cowpox—a bovine disease with minor effects in humans—and then seemed resistant to smallpox. He tested this hypothesis in 1796

on an eight-year-old boy, James Phipps, inoculating him with cowpox matter from a milkmaid. James fell ill with cowpox but recovered, and Jenner then inoculated him with smallpox with no effect. Vaccination (from the Latin *vacca*, cow) quickly supplanted variolation.

We don't know what the parents of James Phipps (who were poor farm laborers) thought when Edward Jenner injected him with cowpox. But the mother of nine-year-old Joseph Meister took him to Paris in the summer of 1885 to see the celebrated scientist Louis Pasteur. Joseph had been bitten by what appeared to be a rabid dog, and Pasteur had recently announced that he had developed a rabies vaccine that was effective in dogs. It had not, however, been tried in humans. Pasteur agreed to treat Joseph, who survived.

The development of the polio vaccine in the mid-twentieth century affords many examples of children as experimental subjects. Poliomyelitis, also known as "infantile paralysis," was a virus that particularly attacked children. A common and largely unrecognized disease before 1900, new sanitation and public health measures ironically made it less common and more virulent. Most cases of polio did not result in paralysis, but those that did made it a much-feared disease in the first half of the twentieth century, particularly in the US (Oshinsky 2006).

Public pressure to develop a vaccine was enormous. Two researchers in the mid-1930s announced they had developed a vaccine. Maurice Brodie first tested his killed-virus vaccine on himself and some of his lab assistants before inoculating a dozen children who had been volunteered by their parents. Brodie eventually inoculated 9000 children. Several developed allergic reactions to the vaccine, which turned out to be ineffective. Around the same time, John Kolmer developed a live (but weakened) virus vaccine. He too tested it on himself and on his own children and then on a sample of 23 children with parental consent before inoculating some 10,000 children. A dozen or more became ill, and nine died.

After World War II, many researchers sought a polio vaccine, and children continued to be experimental subjects. In this post-Nuremburg era, consent of parents or guardians was required. In 1950, Hilary Koprowski tested a live-virus vaccine on 20 children in a New York state facility for intellectually disabled children. Two years later, Jonas Salk tested his killed-virus vaccine on two groups of institutionalized children, including both the physically and the intellectually disabled. Neither of these were clinical trials; the purpose was to determine whether the vaccines produced antibodies. Many of the children in these institutions were under the guardianship of the state, which gave consent. Koprowski had already tested his vaccine on himself; Salk injected himself and his family after these first human trials.

The success of Salk's trials led to a massive field trial of his polio vaccine on 600,000 children, the first large randomized double-blind clinical trial. A second parallel trial of 1,000,000 children did not administer a placebo, but simply observed the non-vaccine subjects. Parents overwhelmingly agreed to allow their children to become "Polio Pioneers." Salk's field trial concluded in June 1954; six months later, Albert Sabin tested his live-virus vaccine on 12 prison volunteers. Koprowski and Sabin later conducted wide-scale field trials, mainly on children, in what were then the Belgian Congo and the USSR. Salk's vaccine was licensed for use in 1955, Sabin's in 1961.

Goldberger in 1915 manipulated the diets of Mississippi orphans before his prison experiments. Although there was some criticism of Koprowski and Salk for their use

of institutionalized children for their early trials, the extent of the use of such children did not become clear until much later. Between 1946 and 1953, more than 100 boys at the Fernald State School in Massachusetts were fed oatmeal laced with radioactive iodine and calcium to trace the absorption of nutrients. At the Willowbrook School on Staten Island, experiments with Hepatitis A between 1956 and 1970 included deliberately infecting children. The Willowbrook experiments were revealed in the early 1970s and became part of the greater revulsion over Tuskegee. But the Fernald experiments only came to light, with other radiation experiments, in the 1990s.

Self-experiment

Researchers have experimented on themselves for centuries. Who could be a better research subject? The ancient king Mithradates also tried out poisons on himself. He discovered that by giving himself tiny doses of certain poisons he became over time immune to their noxious effects (Mayor 2009, 237–46).

Journalist Lawrence Altman's *Who Goes First?* (1998) remains the classic study of self-experimentation in medicine. In the early seventeenth century, Italian physician Santorio Santorio spent the better part of 30 years sitting for several hours a day on a large balance of his own design. By measuring his bodily intake and discharges, Santorio sought to understand metabolism. He concluded that the body lost a quantity of fluid each day in what he called "insensible perspiration." A century later, his countryman Lazzaro Spallanzani studied digestion by swallowing cloth bags and wooden tubes filed with food and then vomiting them up. He also swallowed and retrieved a sponge to obtain a sample of gastric fluid. Around the same time, the renowned London surgeon John Hunter reported injecting pus from a patient with gonorrhea into the penis of an unnamed experimental subject. Most historians agree that he was the subject, and that he probably contracted both gonorrhea and syphilis from the experiment.

Before chemical assays were developed (and even after), smelling, tasting, and ingesting foreign substances were standard methods of identification. In the early nineteenth century, inhaling was added to this list. The English chemist Humphry Davy discovered the anesthetic (and pleasurable) properties of nitrous oxide by trying it on himself. In the 1840s, American and British doctors tested a number of potential anesthetics on themselves. Some, like acetone and benzene, had no effect. Ether, like nitrous oxide, was a recreational drug and its medicinal uses were recognized almost by accident. Chloroform, also effective, was less flammable than ether. But it was also addictive, as the dentist Horace Wells discovered. Later in the century, first Sigmund Freud and then the Americans Richard Hall and William Halsted experimented with the use of cocaine as a local anesthetic. Hall and Halsted became addicted, and Halsted weaned himself off cocaine with morphine, to which he remained addicted for the rest of his illustrious surgical career.

While the germ theory of disease illuminated the causes of many diseases, it obscured the causes of others. Goldberger's prison experiments on pellagra had convinced him that its cause was dietary, but his contemporaries remained skeptical. He therefore convened what he called a "filth party." He and his assistant injected blood from a pellagra victim into each other. In addition, they swabbed out secretions from the nose and throat of another victim and applied them to their own noses and throats,

and even gave each other capsules they had made of the scabs from pellagra rashes. Goldberger's wife later joined the party. None of them got pellagra, but their critics remained unconvinced (Harkness 1996).

Throughout the twentieth century, doctors infected themselves or took drugs they hoped would kill microbes or offer immunity. In 1900, the four physicians of the US Yellow Fever Commission in Cuba—Walter Reed, Aristides Agramonte, Jesse Lazear, and James Carroll—decided to test on themselves the new theory that a mosquito was the disease vector before testing soldier volunteers. Lazear and Carroll allowed themselves to be bitten by mosquitoes, and both fell ill with yellow fever. Carroll survived, but Lazear died. Half a century later, many early polio researchers tested their vaccines on themselves and their families before proceeding to human trials. And in the 1970s, David F. Clyde allowed himself to be bitten thousands of times by malarial mosquitoes in order to test an experimental vaccine before trials on prison volunteers.

Conclusion

The year 1993 proved to be a turning point in human experimentation in the US. The revelation of long-term secret human experiments on the part of the US government, particularly those conducted under the auspices of the US Atomic Energy Commission between 1947 and 1974, led to an outcry even greater than over the Tuskegee experiments twenty years earlier. The Tuskegee case was one of neglect; experiments revealed in 1993 included injection of radioactive substances, administration of drugs, and other examples of deliberate exposure across the spectrum of human subjects: patients, prisoners, children, the handicapped, the poor: all had been secretly used as guinea pigs in the two decades that followed the Nuremberg trials. A presidential Advisory Committee on Human Radiation Experiments, appointed in 1994, further emphasized the necessity of informed consent that the Belmont Report had established. While the regulatory framework is stronger than it has ever been in history, one may not assume that abuses, errors, or failed experiments no longer occur. Moreover, stronger regulation in the US and Europe has led to the export of clinical trials to poorer nations with more lax oversight (Shah 2006).

The biotechnology revolution that began in the late 1990s has complicated the ethical and regulatory picture. Older laws do not cover new techniques such as cloning, gene therapy, genetic engineering, and stem cell therapy. New reproductive and therapeutic technologies call into question the very definition of human. The human experimental subject of the future may indeed be a cell.

References

Altman, Lawrence. 1998. *Who Goes First? The Story of Self-Experimentation in Medicine*. Berkeley: University of California Press.

Beecher, Henry K. 1966. "Ethics and clinical research." *New England Journal of Medicine*, 274: 1354–60.

Berger, Robert L. 1990. "Nazi science—The Dachau hypothermia experiments." *New England Journal of Medicine*, 322: 1435–1440.

Bernard, Claude. 1957. *An Introduction to the Study of Experimental Medicine*. Translated by Henry Copley Greene. New York: Dover.
Caplan, Arthur (ed.) 1992. *When Medicine Went Mad: Bioethics and the Holocaust*. Totowa, NJ: Humana Press.
Chamayou, Grégoire. 2008. *Les corps vils. Expérimenter sur les êtres humains aux XVIIIe et XIXe siècles*. Paris: La Découverte.
Collier, Roger. 2009. "Legumes, lemons and streptomycin: A short history of the clinical trial." *Canadian Medical Association Journal*, 180: 23–4.
Dickens, Charles. 1842. *American Notes for General Circulation*. New York: Harper & Brothers.
Green, Alexa. 2010. "Working Ethics: William Beaumont, Alexis St. Martin, and medical research in antebellum America." *Bulletin of the History of Medicine*, 84: 193–216.
Guerrini, Anita. 2003. *Experimenting with Humans and Animals. From Galen to Animal Rights*. Baltimore: Johns Hopkins University Press.
Harkness, Jon M. 1996. "Prisoners and pellagra." *Public Health Reports*, 111: 463–7.
Harris, Sheldon H. 1994. *Factories of Death. Japanese Biological Warfare, 1932–45, and the American Cover-up*. London: Routledge.
Hornblum, Allen M. 1999. *Acres of Skin: Human Experiments at Holmesburg Prison*. New York: Routledge.
Johnston, Chelsea. 2013. *Beware of that Cup! The Role of Food-tasters in Ancient Society*. M.A. thesis, University of Otago.
Lederer, Susan. 1995. *Subjected to Science: Human Experimentation in America before the Second World War*. Baltimore: Johns Hopkins University Press.
Mayor, Adrienne. 2009. *The Poison King: The Life and Legend of Mithradates, Rome's Deadliest Enemy*. Princeton, NJ: Princeton University Press.
Oshinsky, David M. 2006. *Polio: An American Story*. New York: Oxford University Press.
Pappworth, Maurice. 1967. *Human Guinea Pigs: Experimentation on Man*. London: Routledge and Kegan Paul.
Pringle, Heather. 2010. "Confronting anatomy's Nazi past." *Science*, 329: 274–5.
Quier, John. 1780. *Letters from Mr John Quier, Practitioner of Physic in the Island of Jamaica, to Dr D. Monro, Jermyn-street, London, on the Small-pox and Inoculation, Measles, &c.* In *Medical commentaries. … Collected and published by Andrew Duncan*. London: printed for Charles Dilly.
Savitt, Todd. 1982. "The use of Blacks for medical experimentation and demonstration in the Old South." *Journal of Southern History*, 48: 331–48.
Schiebinger, Londa. 2004. "Human experimentation in the 18th century: Natural boundaries and valid testing." In *The Moral Authority of Nature*, edited by Lorraine Daston and Ferdinando Vidal, 384–408. Chicago: University of Chicago Press.
Selin, Helaine (ed.) 2003. *Medicine across Cultures: History and Practice of Medicine in Non-Western Cultures*. Dordrecht: Kluwer.
Shah, Sonia. 2006. *The Body Hunters. Testing New Drugs on the World's Poorest Patients*. New York: New Press.
Von Staden, Heinrich. 1989. *Herophilus. The Art of Medicine in Early Alexandria*. Cambridge: Cambridge University Press.
Winter, Alison. 1998. *Mesmerized. Powers of Mind in Victorian Britain*. Chicago: University of Chicago Press.