Historical Reflections on the Ethics of Human Subjects Research

Jason E. Glenn
Associate Professor
Department of History and Philosophy of Medicine
University of Kansas Medical Center

September 5, 2019
Objectives:

- Discuss the history of human subject research ethics within the transformation of the practice of medicine, 19th – 20th centuries.
- Contextualize this history within the conceptual revolution of the 19th century that for the first time conceives what it means to be human in biological terms
- Understand the relevance of this legacy to contemporary challenges in research ethics
Broadening the Foucault Hypothesis

- Investigates 19th century as the point where “Man” becomes an object of study
- “Man’s” biology takes special significance as “Man” gets defined for the first time as a purely biological being.
- The production of biological knowledge and the idea of laws of biology, for the first time, become thinkable.
The Birth of the Clinic

Doctors able to gain an exclusive knowledge of anatomical and biological function through *dissection* and *microscopic examination*, gazing into the open body, which allowed them to differentiate the normal body from the pathological one.
The Foucault Hypothesis

- This knowledge of biological function allowed doctors to match internal pathology to specific outer signs and symptoms, and thereby develop a standardized nosology.

- Doctors gained cultural authority by defining the clinic as their scientific laboratory where biomedical knowledge is produced under their exclusive expertise.
For Foucault, these new epistemological, ontological, technical reshapings of medical perception led to the “clinical gaze” focused at the **molecular level**, that reduces human existence to biological processes.

The **gaze** necessitated new objects of focus that could be opened, explored, and experimented upon to understand the biological laws that dictated how they worked.

Scholars traditionally point to the “**clinical gaze**” as the source of the **impersonal** and **detached** nature of the contemporary **doctor-patient relationship**.

*From Martini, Timmons, & Tallisch, Human Anatomy, 7th Ed.*
Until the enactment of new regulations ~38 years ago, throughout the history of anatomical and biomedical research the vast majority of subjects of study were persons confined and/or institutionalized: persons in prisons, asylums, mental hospitals, and sometimes those held as slaves.

The institutionalized populations were often mentally ill, terminally ill, orphans, but most were prisoners.
Roots in Antiquity

- Greek Physicians **Herophilus of Chalcedon and Erasistratus of Chios** around 250 B.C.E. were given permission to cut into a *living* criminal condemned to death and soon scheduled for execution.

- Animal dissection for research had been a long established practice, championed and ardently practiced by Aristotle a half century earlier.

- Strong taboos against the mutilation of the human body existed, however, so Aristotle felt that mammalian animals could be used as suitable substitutes for understanding human structure.
During the Renaissance Andreas Vesalius, researching human anatomical structure, used nearly all executed prisoners. Bodies given by the state to doctors for research. It was because of their moral transgressions that such bodies were deemed no longer deserving of the honor and dignity of a proper and timely burial.
Vesalius and Prisoners

- *De humani corporis fabrica* famously pokes fun at how bodies were acquired.
- These persons were considered to have such corrupted souls as to allow others to look upon their deceased bodies as detached from any redeemable human value.
Anatomy Theatres in 1600s

- Scientific Anatomy blossomed in the 17th century.
- Thousands flocked to amphitheaters to watch human dissections.
- To cut open a person after death, dismember them, and then expose them – nameless and naked – before an audience of strangers was seen as the utmost in shame and dishonor.
- Anatomy demonstrations offered a macabre combination of curiosity, sex, crime and punishment – as subjects were all executed prisoners.
17th Century Blood Transfusion Experiments

- In 1667, Richard Lower and Edmund King performed a transfusion on an mad house patient giving him the blood of a lamb.
- Researchers tried to treat madness by transfusing the blood of a docile animal into the mad man, believing his madness caused by the excessive heat of his blood (humoral theory of medicine).
Growing Demand from Medical Schools and Universities

- The 18th and 19th centuries saw growing demand for the use of prisoners for the production of anatomical and biomedical knowledge.

- Britain passed the **Murder Act in 1751**, *forbid* the burial of executed murderers and *mandated* that they be sent to an anatomist to be dissected in public.

- The **Anatomy Act in 1832** broadened the category of legitimately dissectible and dismemberable subjects to include the destitute and anyone who died in prison, the asylum, or a workhouse.
Use of Blacks in American South

- Black bodies in particular, both alive and dead, were used for experimentation and education throughout 19th century.
- Med schools competed for students by advertising their access to clinical material.
- Dissecting tables, operating amphitheaters, classroom demonstrations, and in laboratories.
- Particularly huge demand for Black cadavers, usu. executed prisoners granted by the state and those stolen from graves.
Classic Era of Human Experimentation, 20\textsuperscript{th} Century

- Early phase pre-WWII: dozens of less formalized research studies conducted investigating the causes and vectors of transmission of infectious diseases.
- Emphasis on those that most heavily impacted U.S. shipping commerce and military efforts.
- Subjects were nearly all U.S. prisoners and prisoners held in various U.S. colonies
1906 Bubonic Plague & Cholera Study in the Philippines

- Inmates paid in cigarettes and cigars to let researchers infect them.
- Subjects were not told the nature nor the severity of the experiments.
- Subjects suffered at least 18 deaths, paralysis, mental disorders, and heart damage.
1906 Beriberi Study in the Philippines

- Conducted by **Dr. Richard Strong** in 1906-1907.
- Withheld proper nutrition from 29 prisoners in order to create beriberi (thiamine deficiency).
- Participants experienced loss of sensation in their hands and feet, paralysis in their legs, mental deterioration and speech difficulties, chronic pain, nystagmus, and routine vomiting.
1915-1935 Mississippi State Prison Pellagra Study

- US researchers try to discern the cause of pellagra (niacin deficiency), orig. thought to be an infectious disease.
- Inmates were subjected to extreme malnourishment, resulting in severe dermatitis, diarrhea and dementia
- Subjects were mostly Black
- Promised early parole
- Suffered skin eruptions, gastro-intestinal sickness, nervous disturbances and mental deterioration.
Dr. Leo L. Stanley removed the testicles from goats and executed prisoners and surgically implanted them into 500 older inmates demonstrating signs of senility.

The extracted testicles were either inserted into the prisoner’s scrotum or into the abdominal wall.

Undeterred by early negative results that killed some subjects, the study was allowed to continue for four years.
1931 Puerto Rican Prison Cancer Study

- Dr. Cornelius Rhoads, pathologist from the Rockefeller Institute for Medical Research in New York, used prisoners in Puerto Rico to test whether cancer could be spread by direct injection of malignant cells into a non-cancerous person.
- Purposefully hid details of the experiment from subjects
- At least 13 of the subjects died from Rhoads’ study.
Dr. Rhoads’ Hidden Agenda

In a letter to another doctor, leaked to the Puerto Rican Nationalist Party, Rhoads wrote:

*The Porto Ricans* [sic] *are beyond doubt the dirtiest, laziest, most degenerate and thievish race of men ever inhabiting this sphere. It makes you sick to inhabit the same island with them.... What the island needs is not public health work, but a tidal wave or something to totally exterminate the population. It might then be liveable [sic]. I have done my best to further the process of extermination by killing off eight and transplanting cancer into several more. The latter has not resulted in any fatalities so far.... The matter of consideration for the patients' welfare plays no role here - in fact, all physicians take delight in the abuse and torture of the unfortunate subjects.*
Dr. Rhoads Gets Promoted!

- Allowed to return to New York and continue his job at the Rockefeller Institute.
- Hired as VP of NY Academy of Medicine
- During WWII, rejoined military and promoted to Colonel in the Army and Chief Medical Officer for the Chemical Warfare Division.
- Established chemical weapons laboratories for Army in Utah, Maryland, and Panama.
- Oversaw the testing of poison gas on over 60,000 unwitting U.S. service members, many of them Puerto Ricans.
- Subjects suffered the horrific effects of nerve gas: emphysema, eye damage, genital scarring, psychological damage, etc.
- For this work, he was awarded the Legion of Merit in 1945.
Dr. Rhoads Gets Promoted Again!

Named the Director of the Sloan Kettering Institute after WWII, where he conducted chemotherapy and radiation experiments on human subjects for the U.S. Dept. of Energy…
US RADIATION EXPERIMENTS, 1937-1971

Experiments included:

- Removing bodies from graveyards to test them for radiation
- Irradiating the heads of children as a “treatment” for hookworm
- Feeding radioactive material to mentally disabled children
- Exposing U.S. soldiers and prisoners to high levels of radiation
- Irradiating the testicles of prisoners, which caused severe birth defects
- Giving lethal doses of radiation to cancer patients under the guise of treatment
US Radiation Experiments: Cancer Patients:

- Most selected from US public hospitals, at UC San Francisco, Berkeley, Iowa, Massachusetts, UTMB, and Cincinnati General Hospital
- Hospitals had secret contract with military
- Poor, often Black charity patients, not all terminally ill, most irradiated during early stage of their cancer.
- Subjects told they were being treated for their cancer
US Radiation Experiments, cont.

- Some subjects given total body radiation in one massive dose to simulate soldiers’ exposure to nuclear war
- Military level of radiation had no chance of improving subjects’ health
- Thousands of participants in all, exact numbers unknown.
- Patients suffered nausea and vomiting from acute radiation sickness and intense pain from burns on their bodies.
- Estimated 25% died within 1 month as result of radiation exposure, most died within a year
US Public Health Service
Syphilis Study in Guatemala

- Intentionally infected **1700** Guatemalan prisoners and mental institution patients with syphilis and other STDs to test the efficacy of penicillin.

- Hired prostitutes, infected them with syphilis and forced them to have sex with prisoners and patients in mental institutions.

- If a syphilitic infection did not occur “naturally” they gave the men and women abrasions on their genitalia and forced them to have sex again.

*If that still did not work, men were given syphilis by spinal injection.*
US Public Health Service
Syphilis Study in Guatemala

- Conducted 1946-1948 by many of the *same personnel who conducted Tuskegee study*.
- Co-sponsored by the PHS, the NIH, the Pan American Health Sanitary Bureau (now the Pan American Health Organization), and the Guatemalan government.
- The study ended in 1948 when they knew definitively that penicillin cured syphilis.
US PHS Syphilis Study in Guatemala, cont.

- Many cases of gonorrhea and syphilis were left untreated.
- At least 83 subjects died due to unspecified complications of the disease.
- Same PIs who worked on Guatemalan study and who knew penicillin was an effective cure for syphilis were also the ones who insisted that the Tuskegee subjects NOT be treated.
Illinois Stateville Prison Malaria Study

- Doctors infected 441 prisoners with malaria to test possible drug cures, 1944-1946.
- Inmates only told they were helping the war effort, promised early parole.
- In addition to suffering from the disease, many also suffered from the toxic effects of the experimental drugs.
- One researcher told the BMJ (1963): “Criminals in our penitentiaries are fine experimental material - and much cheaper than chimpanzees.”
RESEARCH BY GERMAN DOCTORS DURING THE NATIONAL SOCIALIST PERIOD

- Hypothermia studies
- High altitude studies
- Experiments on the best forms of sterilization
- Studies simulating war injuries including mustard gas exposure
- Vaccination trials for malaria and typhus
- All on prisoners of war
Nuremberg Tribunal

- A group of 24 were on trial for War Crimes and Crimes Against Humanity
- Of particular concern was the human experimentation conducted by the Nazi doctors
- International “Directives for Human Experimentation” drafted as a result.
1. The voluntary consent of the human subject is absolutely essential. This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision.
The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.

No experiment should be conducted where there is an a priori reason to believe that death or disabling injury will occur.

The experiment should be conducted only by scientifically qualified persons.

During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible.
German Doctors cited U.S. research practices in their defense

- Despite presenting evidence of similar American research, seven Nazi doctors were sentenced to death by hanging, others to long prison terms.

- In the face of the Nuremberg trials and sentencing, egregious U.S. research practices **actually** expanded post WWII as government sponsorship increased.
Henry Knowles Beecher

- Chief of Anesthesia at MGH, 1936-1969.
- Ground-breaking research on the placebo effect
- Championed double-blind placebo-controlled studies
- Led Harvard University’s fight against full implementation of the Nuremberg Code
Henry Knowles Beecher, cont.

- Argued that the character and integrity of the medical profession in the U.S. was adequate to make full implementation of the Nuremberg Code’s requirement of “informed voluntary consent” an unnecessary constraint on research and researchers.

- He thus led fight against the U.S. implementing the informed consent portion of the Nuremberg Code in 1947

- “The Nuremberg Code was written for Nazis. We’re not Nazis.”
Dr. Saul Krugman fed fecal matter to mentally disabled children of Willowbrook in NY.

Fecal matter was mixed with the children’s chocolate milk and fed to them for 15 years.

Krugman began gingerly, with a 1:100,000 dilution, working his way up to a 1:5 dilution.

Claimed conditions at the school were so filthy that the children would catch hepatitis anyway.
Holmesburg prison became the training ground for med students and residents in dermatology.

By late 1960s was the largest and best known in the country.

Expansive Phase 1 testing of pharmaceutical and commercial products.

Prisoners subjected to radioactive isotopes, dioxin, hallucinogenic incapacitants, and various other chemical warfare, viral, and cancer studies.
Dr. Albert Kligman

- Recruited to Holmesburg due to recurring athlete’s foot outbreaks.
- Conducted prior research infecting mentally disabled institutionalized children with ringworm.
- “All I saw before me were acres of skin… and anthropoid colony, mainly healthy under perfect control conditions… like a farmer seeing a fertile field for the first time.”
- Made UPenn the national center for Dermatology studies and education
1963-1971 Oregon Prison Testicular Radiation Study

- Endocrinologist **Dr. Carl Heller** conducted study on over 100 inmates at Oregon State Prison
- Heller was paid **$1.12 million by the US Atomic Energy Commission** to research the effects of radiation on male reproductive function
- Heller performed experiments radiating the testes of his subjects and checking their function after
- Subjects paid $5 per month and $25 per testicular tissue biopsy in compensation
- In a eugenic twist, subjects also received $100 at end of study for submitting to mandatory vasectomies
Began his career as a part-time physician at Oklahoma State Penitentiary in 1939.

Started a business extracting blood from inmates to meet growing plasma demand after WWII.

In selling blood products he also realized there was a market for drug testing.

Expanded partnerships to include Arkansas and Alabama state prisons systems.

Enrolled thousands of inmates in phase II drug studies, paying them $1 per day.

Conducted over 130 drug trials for 37 drug companies, including Wyeth, Bristol-Myers, Squibb, Merck, etc.
Dr. Austin Stough drug and plasma experiments, 1963-1969

- Extracted and sold their blood plasma as drug studies continued.
- Stough earned nearly $1 million/year.
- By 1969 it was estimated that Stough’s research accounted for 25-50% of all Phase II drug testing in the U.S.
- Hepatitis epidemics broke out in prisons due to conditions of “gross contamination.”
- Many prisoners “died slowly in a very painful fashion.” Exact #s concealed.

The Stough Group, 1965
Dr. Austin Stough drug and plasma experiments, 1963-1972

- Some prison plasma studies discontinued, but drug studies allowed to persist until 1979.
- The millions made off prisoners helped grow the company into the multinational conglomerate it is today, diversifying into real estate development in 1980s.
Reform in the Civil Rights Era

- Stough’s Research exposed in 1969
- Radiation experiments become public in 1971
- Details of US Public Health Service Syphilis Study at Tuskegee made more public
- Congressional creation of the National Commission for the Protection of Human Subjects (1973); included in Code of Federal Regulations of 1974
- Federalized Ethical Principles and Applications *The Belmont Report*, 1979
THE AIDS CLINICAL TRIALS GROUP (ACTG) STUDY - 1994

- **Placebo-controlled** study of Zidovudine (ZVD or AZT) in maternal-infant transmission of HIV showed a reduction of nearly 70% in the risk of transmission.

- Zidovudine became the standard of care afterward.

- Subsequent research funded by the U.S. Centers for Disease Control and **NIH** continued placebo-controlled trials in poor countries.

- Patients in trials in the US had unrestricted access to the drug, while those in poor countries did not.

- Good ethical practice is to compare standard of care to experimental treatment **plus** standard of care, not to placebo.

- Responding to criticism, PIs initially changed the study design in Thailand but not Africa.
Gene Transplant Therapies: Jesse Gelsinger

- Teen died in September 1999, 1 month after gene transplant therapy
- Investigators failed to disclose their financial interests in the company that developed the therapy
- Family not told all the risks, that the therapy proved fatal in primate trials, and had not been told about other adverse events.
Artificial Heart Transplant: James Quinn

- Died of stroke in August of 2002, 9 months after artificial heart transplant
- Perfect example of therapeutic misconception: experimental procedure of the highest risk with little to no chance of patient benefit.
- Widow sued manufacturer and hospital, alleging negligence and fraud, saying Quinn was not well informed of the ordeal he would face.
- Drexel University College of Medicine exclaimed: “We donated thousands of hours to Mr. Quinn's care, and we did so with pride.”
City Homes Inc. Lead Abatement Study, 1991-2000

- Attempted to find more cost-effective measures to remove lead paint
- Non-profit org contracted with private company to “neutralize” lead paint
- Families told that houses were lead-free, not that houses were a part of a research study for the company.
- Families were paid to move into houses that once had dangerously-high lead content but that underwent new removal treatment.
- Over a dozen children developed permanent cognitive and behavioral disabilities due to lead exposure in a public-funded lead abatement study in Baltimore, Maryland (U.S.A.)
- Children in the study displayed developmental issues consistent with lead poisoning, yet researchers did not stop the study, inform the families, or inform the institutional review board.
Good Intentions

Good intentions, without **critical historical reflection**, lead to a **utilitarian approach** to conducting research:

* A risk to others becomes worth a benefit to us.
Contemporary Challenges

- Political, career, economic, and social interests continue to pose *inextricable* conflicts of interests that undermine protection and respect for research subjects.
- Widespread collecting of genetic information that cannot be completely de-identified.
- Federal and state disinvestment from education and research, pushing more and more investigators to the private sector, which has a fiduciary responsibility to investors and stock holders, not to patients.
Thanks!

♦ Contact:
Jason E. Glenn
jglenn4@kumc.edu
Sources