

# HISTORICAL PERSPECTIVES AND THEIR SIGNIFICANT IMPACT ON THE DEVELOPMENT OF ETHICAL STANDARDS GOVERNING RESEARCH USING HUMAN PARTICIPANTS

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The following narratives are extracted from Cynthia McGuire Dunn & Gary Chadwick *Protecting Study Volunteers in Research: A Manual for Investigative Sites* (1999) CenterWatch, Inc., University of Rochester Medical Center, 1999, p 2-4.

There have been slight adaptations by Amy Henderson-Harr.

## I. Background

### The Nuremberg Doctors Trial of 1946

At the beginning of WWII, Germany was the most scientifically and technologically advanced country in the world and even had a proposed code of research ethics. In the field of medicine, the Nazi government supported midwifery, homeopathy and nutrition programs as well as research into ecology, public health, human genetics, cancer, radiation and asbestos. They were the first to ban smoking in public buildings. Women were denied tobacco ration coupons because of concern about the effect of nicotine on the fetus. German physicians stressed the importance of preventive medicine rather than curative medicine. The Nazis, however, exploited people's trust in physicians to disguise discrimination and murder as public health.

*Medical Experiments-* A legitimate concern of the German Air force was the survival of pilots at extremely high altitudes and determining the maximum safe altitude for bailing out of damaged aircraft. In one series of experiments, researchers placed victims in vacuum chambers that could duplicate the low air pressure and lack of oxygen at altitudes as high as 65,000 feet (about two to three times the maximum altitude that aircraft were flying). Approximately 200 internees at Dachau were used in these experiments, and about 40% died as a result. Some deaths were caused by extended anoxia; others were attributed to lungs rupturing from the low pressures in the chamber.

Another concern was survival time after parachuting into the cold water of the North Atlantic. Some victims of this research were immersed for hours in tubs of ice water; others were fed nothing but salt water for days. Still others were penned outside, unclothed and unsheltered in sub-freezing temperatures from 12 to 14 hours. Some of these "freezing victims" were sprayed with cold water. No attempts were made to relieve the tremendous pain and suffering caused by these experiments. Three hundred Dachau prisoner-subjects suffered a mortality rate of 30%.

Experiments involving battlefield medicine included treatment of gunshot wounds, burns, traumatic amputations and chemical and biological agent exposures. In these experiments, the wound was first inflicted upon the victim (by gunshot, stabbing, amputation or other traumatic method) and then treated using various techniques. For example, in a study of sulfanilamide at the Ravensbrueck camp, Polish women were shot and slashed on the legs. The resulting wounds were stuffed with glass, dirt and various bacteria cultures, and sewn shut. The infected wounds were then treated with experimental anti-infective agents. In another experiment, a mixture of phosphorus and rubber was applied to the skin of victims and ignited. After burning for up to two minutes, the fire was extinguished and the resultant

burns treated with various chemicals and ointments. Another series of experiments involved amputation of upper and lower limbs, and attempted treatment with transplanted bones, muscle and nerves. Neither the victim nor the tissue ‘donor’ did well in these studies; about half of the amputation victims died, the rest were maimed for life.

Experiments on treating exposure to chemical-warfare agents were ongoing throughout the war years. Prisoners were forced to drink poisoned water and breathe noxious gases. Some were shot with cyanide-tipped bullets or given cyanide capsules. A mortality rate of 25% was typical.

“The Nazi Doctors Trial,” was held from December 9, 1946 to August 8, 1947. The 23 defendants (including 20 physicians) were charged with murder, torture and other atrocities committed in the name of medical science. When the trial was over, 15 of the 23 defendants were found guilty. Seven were sentenced to death. Although the trial was called “The Trial of the Century,” it would probably have been forgotten except for the fact that the judgment included a set of standards known as the Nuremberg Code. The Code, was the ‘ethical yardstick’ by which the defendants had been measured and guilt determined. The ‘Modern’ era of human research protections is routinely dated from the promulgation of the Nuremberg Code. The Code stated that: informed consent of volunteers must be obtained without coercion; human experiments should be based upon prior animal experimentation; anticipated scientific results should justify the experiment; only qualified scientists should conduct medical research; physical and mental suffering and injury should be avoided; and there should be no expectation of death or disabling injury from the experiment.

## The ‘Milgram Study’ (1963)

Stanley Milgram was a researcher in social psychology at Yale University who, after reading accounts of the Nazi Holocaust, became interested in obedience and humans’ response to authority. The German citizenry’s seeming acceptance of and complacency in regard to the atrocities presented an interesting question. In 1963, he published the results of a study on obedience that raised a firestorm of criticism with implications even today.

*The Experiment-* Adult participants were recruited by means of a newspaper advertisement asking for volunteers for a study of ‘memory and learning.’ Participants were paid a modest amount for the one hour experiment. Study participants were part of a triad that consisted of themselves, the investigator and a third person. The investigator explained that the experiment was to study learning and memory, specifically what role punishment played. The participant was to play the role of ‘teacher’ while the third person was to be the ‘learner.’ The investigator would monitor the process and record the data.

The learner was placed in what appeared to be an electric chair, that is, wire leads ran from a control panel to the chair and were attached to the learner’s wrists. The control panel had switches labeled from 15 volts to 450 volts.

For the experiment, the teacher asked the learner a question (word-pair matching) and when the wrong answer was given, the investigator would instruct the teacher to administer ‘punishment’ to the learner in the form of electric shocks in an escalating amount. The learner would display evidence of receiving pain from the shocks. After one-third of the shock levels had been given, the learner demanded to stop. At this point, the teacher would usually ask the investigator to stop, but the investigator insisted that the

procedure continue. After two thirds of the shocks had been administered, the learner fell silent and non-responsive (a non-response was treated as a wrong answer and punished). When they continued to seek permission to stop, the highly conflicted teachers were told that the experiment was important to complete for the advancement of science. Fully 60% of teachers were persuaded into administering shocks up to and including the highest level.

What the teachers did not know was that the third person who played the role of learner was in fact a confederate of the investigator. No shocks were administered. The learner (who deliberately gave wrong answers) only pretended to be hurt. The real intent of the experiment was to see how far the participant could be pushed under the guise of complying with authority. At the completion of the experiment (either after the maximum shock was ostensibly given or upon firm refusal by the participant to continue), the confederate came out of his room and demonstrated to the participant that he was uninjured. A debriefing with the participant was held that explained the deception and the real purpose of the study. During the debriefing interviews, participants often justified their actions by saying that they were only following instructions. (A similar line was taken by the Nazi defendants).

Milgrim, in his *Obedience to Authority* stated, “*I observed a mature and initially poised businessman enter the laboratory smiling and confident. Within twenty minutes he was reduced to a twitching, stuttering wreck, who was rapidly approaching a point of nervous collapse.*”

*Impact* - Criticism of the study centered upon the extreme psychological stress experienced by some participants and on the fact that due to the deception involved, informed consent had not been obtained. The role of deception in human participant’s research continues to be debated even today. As a result of this and other behavioral studies, the federal guidelines specifically instruct investigators and IRBs to consider not just physical harms that may be attached to research, but also other harms including psychological, social, legal and economic.

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(Dunn & Gary Chadwick, ps. 5-7)

The following narrative was in part extracted and in part paraphrased by Amy Henderson-Harr from two separate sources:

Cynthia McGuire Dunn & Gary Chadwick *Protecting Study Volunteers in Research: A Manual for Investigative Sites* (1999) CenterWatch, Inc., University of Rochester Medical Center, 1999, p 2-4.

The National Institutes of Health Human Participant Protections Education for Research Teams online tutorial, available from the National Cancer Institute <http://cme.cancer.gov/c01/>.

## **The Tuskegee Syphilis Study (1932-1972)**

The most notorious example in the United States of prolonged and knowing violations of the rights of a vulnerable group of research participants was the long-term study of black males conducted at the Tuskegee Institute by the United States Public Health Service (later known as the Center for Disease Control). Tuskegee Institute was located in Macon County, Alabama, and selected as the site for a project to examine the natural history of untreated syphilis because previous epidemiological studies had shown an extremely high rate of the disease within the black community.

To secure the cooperation of the black subjects, the participation of black physicians was seen as essential. A local nurse who had trained at the Tuskegee Institute was hired to be the on-site representative. More than 400 black men with syphilis participated, and about 200 men without syphilis served as controls. The men were recruited without informed consent and, in fact, were misinformed that some of the procedures done in the interest of research (e.g., spinal taps) were actually "special free treatment."

By 1936, it was apparent that many more infected men than controls had developed complications, and 10 years later, a report of the study indicated that the death rate among those with syphilis was about twice as high as it was among the controls. In the 1940s, penicillin was found to be effective in the treatment of syphilis. However, during WWII, to keep the syphilis research participants from receiving treatment, it was arranged with the local draft board to exempt them from the military. By 1951, penicillin was widely available as the treatment for syphilis, but it continued to be withheld from the study participants. Actually, the availability of penicillin was used by the study investigators as justification for continuing the study because it made the protocol a 'never-again' scientific opportunity. Neither the ethical issues nor the fact that the supposedly untreated participants had received some minimal treatment were addressed. No connection was made between the Syphilis Study and the Nazi experiments.

The first accounts of this study appeared in the *New York Times* and the *Washington Star* on July 25, 1972 by investigative reporter Jean Heller from the Associated Press. The resulting public outrage led to the appointment of an ad hoc advisory panel by the Department of Health, Education and Welfare to review the study and advise on how to ensure that such experiments would never again be conducted. By 1973, Senator Edward Kennedy held hearings on experimentation using human participants in research. In March 1973 the Syphilis Study was stopped, treatment was given, and by 1975 the government extended treatment to the wives and children who had been born with congenital syphilis. In 1997, President Clinton apologized to study participants and their families and called for renewed emphasis on research ethics.

In 1974, Congress passed the National Research Act. The Act required regulations for the protection of human participants that included requirements for informed consent and review of research by institutional review boards (IRBs). This Act also created the National Commission for the Protection of Human Subjects of Biomedical and Behavior Research, who in 1979 wrote the "Belmont Report."

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The following narratives are extracted from the National Institutes of Health Human Participant Protections Education for Research Teams online tutorial, available from the National Cancer Institute <http://cme.cancer.gov/c01/>

## **The Jewish Chronic Disease Hospital Study (1963)**

In 1963, studies were undertaken at New York's Jewish Chronic Disease Hospital to understand whether the body's inability to reject cancer cells was due to cancer or debilitation. Previous studies had indicated that healthy persons reject cancer cells promptly, and the researchers allegedly believed that the debilitated patients would also reject the cancers but at a substantially slower rate when compared to healthy participants.

These studies involved the injection of foreign, live cancer cells into 22 senile patients who were hospitalized with various chronic debilitating diseases. Patients were not told that they would receive cancer cells because the researchers felt it would unnecessarily frighten them. Researchers defended this view with the assertion that they had good cause to predict that the cancer cells were going to be rejected.

In subsequent review proceedings conducted by the Board of Regents of the State University of New York, it was found that the study had not been presented to the hospital's research committee and that the physicians responsible for the patients' care had not been consulted. The researchers were found guilty of fraud, deceit, and unprofessional conduct.

## **II. The Development of Codes of Research Ethics**

### **The Nuremberg Code (1947): Voluntary consent; benefits outweigh risks; ability to withdraw**

The Nuremberg Code (<http://ohsr.od.nih.gov/nuremberg.php3>) served as the first set of principles outlining professional ethics for medical researchers. The Code is comprised of ten points including the statement that "voluntary consent of the human subject is absolutely essential." The Code also established that animal experimentation should precede human experimentation; all unnecessary physical and mental suffering and injury should be avoided; the degree of risk to participants should never exceed the "humanitarian importance of the problem" and should be minimized through "proper preparations"; and that participants should always be at liberty to withdraw from experiments. The Code has been the model for many professional and governmental codes since the 1950s and has, in effect, served as the first international standard for the conduct of research.

### **Declaration of Helsinki (1964): Concern for the interest of the participant must prevail**

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The Declaration of Helsinki (<http://www.wma.net/e/policy/b3.htm>) was developed by the World Medical Association for use by the medical community following dissemination of the Nuremberg Code. The Declaration considers the conduct of clinical research and makes an important distinction between therapeutic and nontherapeutic research, which was later removed. Like the Nuremberg Code, the Declaration made informed consent a central requirement for ethical research while allowing for surrogate consent when the research participant is incompetent, physically or mentally incapable of giving consent, or a minor. The Declaration also states that research with these groups should be conducted only when the research is necessary to promote the health of the population represented and when this research cannot be performed on legally competent persons. It further states that when the participant is legally incompetent but able to give assent to decisions about participation in research, assent must be obtained in addition to the consent of the legally authorized representative. The Declaration is the first significant effort of the medical community to regulate itself.

### **Belmont Report (1979): Ethical concepts of respect, beneficence and justice**

In the 1950s and 1960s, Federal funding for biomedical research increased dramatically. Along with increased interest and funding, there was heightened public concern about research abuses such as the Tuskegee Study and other reported biomedical abuses. In response to this public outcry, in 1974, Congress passed the National Research Act which established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The primary task of the National Commission was to identify the ethical principles that would guide all research involving humans. In 1979, the National Commission wrote the Belmont Report, which serves as the cornerstone of ethical principles upon which Federal regulations for the protection of human research participants are based. The Belmont Report addressed the ethical principles of respect, beneficence and justice and can be found at the following site: <http://ohrp.osophs.dhhs.gov/humansubjects/guidance/belmont.htm>.