From Involuntary to Participatory: The Role of Humans in Research

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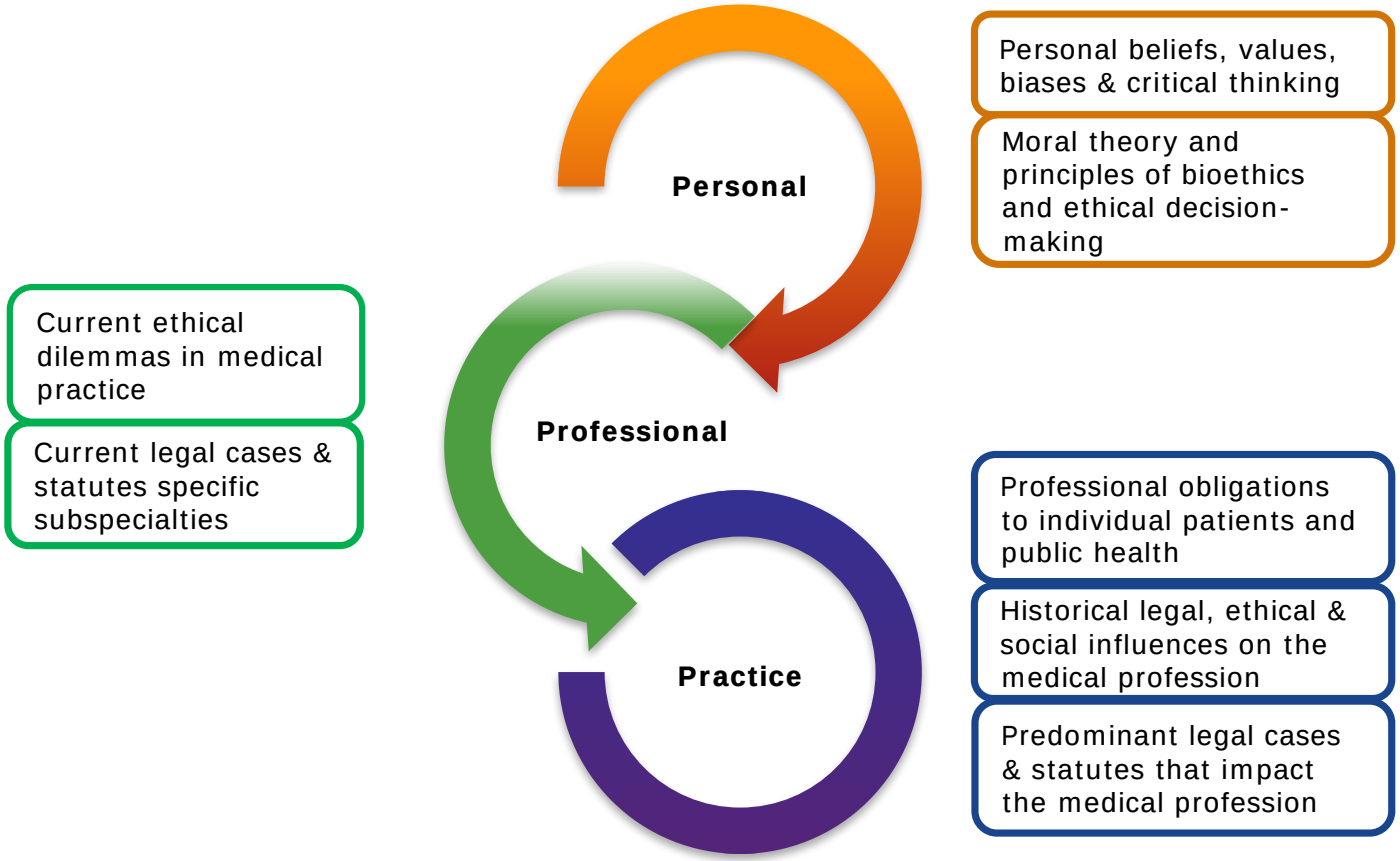
2017

MEDICINE *of* THE HIGHEST ORDER

UNIVERSITY *of* ROCHESTER MEDICAL CENTER

PERSONAL, PROFESSIONAL, PRACTICE



Shaw, Margie H.; D'Angio, Carl T; and Dadiz, R. "Personal, Professional, and Practice: A Framework for Ethics Education." *NeoReviews*. 2016;17:2, e61-e69. Modified for this presentation.

GOALS

1. Describe historical events that influenced the development of safety policies for subjects participating in research

2. Describe activities, and the reasoning behind engagement in those activities, by research teams to promote the safety and well-being of research subjects

3. Identify challenges to regulatory protections for humans in research.

CHALLENGE

Scientific knowledge is created by humans in an environment of inherent and accepted uncertainty.

- Scientific uncertainty
- Ethical uncertainty

Let's think about the humans …

RESEARCH ETHICS

1796 Cowpox human inoculations

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1932-1972 Tuskegee Syphilis study

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1979 The National Commission releases the Belmont Report

1996 (Nicole) Wan Hoi-yan died at the University of Rochester

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2003 The Havasupai Tribe approved “Banishment Order”

2017 US Department of Health and Human Services Final Rule on Common Rule

2017 San people of Southern Africa adopt a code

FIRST, PRINCIPLES

Autonomy

Beneficence

Non-Maleficence

Justice

Social and clinical value

Scientific validity

Fair subject selection

Favorable risk-benefit ratio

Independent review

Informed consent

Respect for potential and enrolled subjects

HUMAN RESEARCH?

What is the purpose of human research?

Why do we undertake research on humans?

What constitutes research?

On which humans do we conduct research?

Has our thinking about these questions changed over time? And if so, how?

OBSERVATION

Lithography depicting the inoculation of James Phipps

By Gaston Mélingue

(circa 1894)

EXPERIMENTATION

June 6, 1822

Beaumont tended gunshot wound on Alexis St. Martin

Beaumont and St. Martin

By Dean Cornewell, (circa 1938)

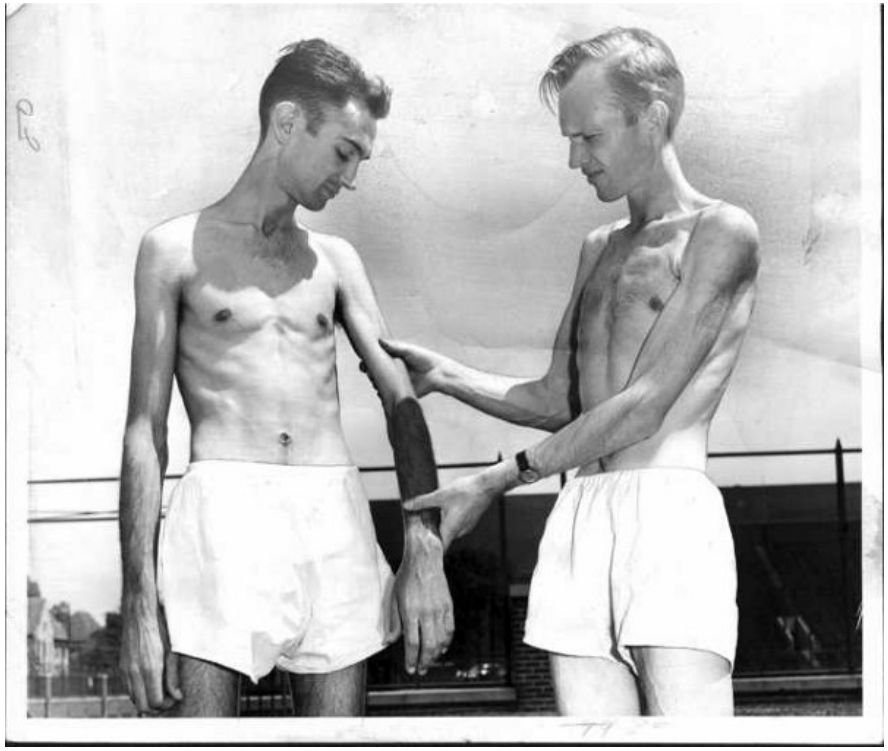
WWII

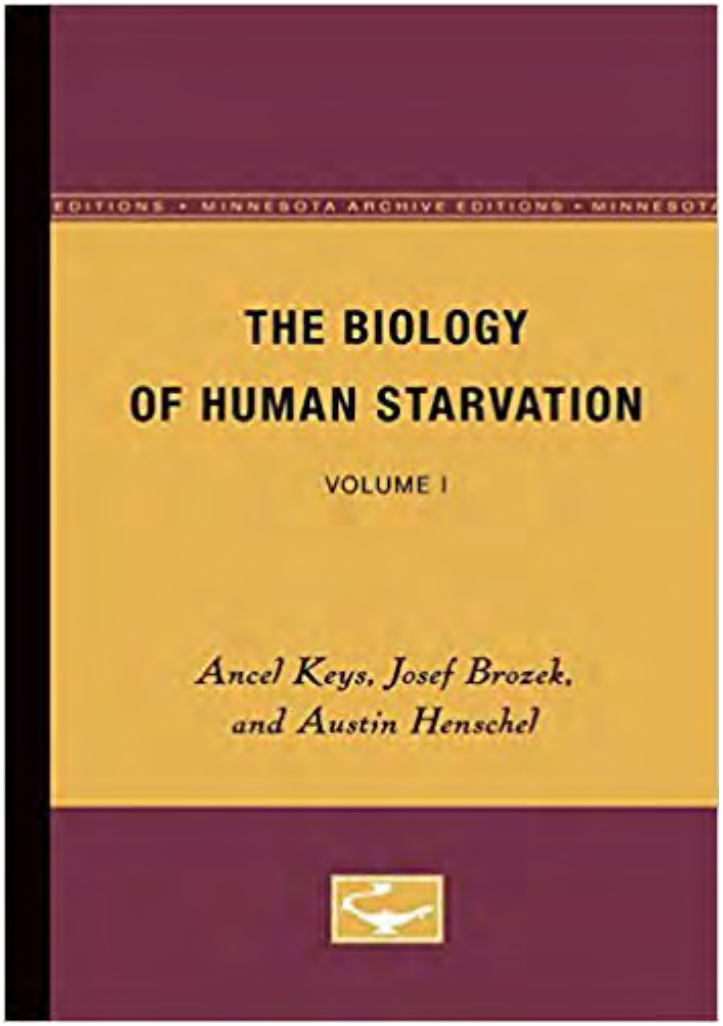
President Franklin D. Roosevelt signing the Declaration of War against Japan, December 8, 1941. 79-AR-82. National Archives Identifier: 520053

34,506,923 men registered for the U.S. draft

72,354 applied for conscientious objector (CO) status.

“I was young and I wanted to show that I was not a coward,” Neil Hartman.





Edward F. Adolph, Ph.D.

“Adolph's research interests at Rochester over a period of sixty-two years included investigations into the physiological regulation of size, body fluids and temperature, the physiology of man in the desert, physiological adaption, and the ontogeny of regulations.”

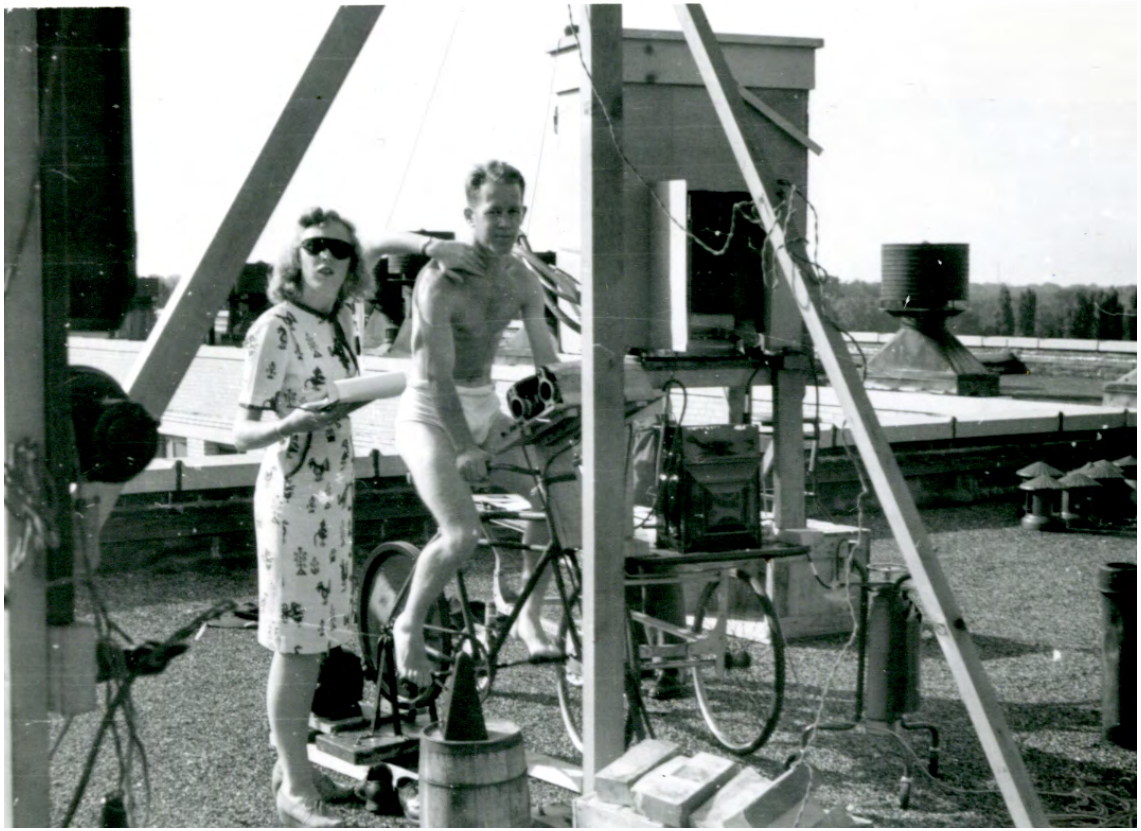
https://www.urmc.rochester.edu/libraries/miner/historical_services/archives/Faculty/adolph.cfm

Adolph, E. F. 1947. *Physiology of man in the desert*. New York: Interscience.

"The research team was charged with determining water and food requirements, sweat rates, energy balance, heat tolerance, work capacity, and survival rates while soldiers were living and working under desert conditions."

"Other studies considered how long men could survive without water under a variety of conditions, including men on life rafts at sea. A sobering result of some of these studies was a series of maps of the world's oceans identifying estimated survival time for men on life rafts without water by season and location."

URMC ROOFTOP EXPERIMENTS



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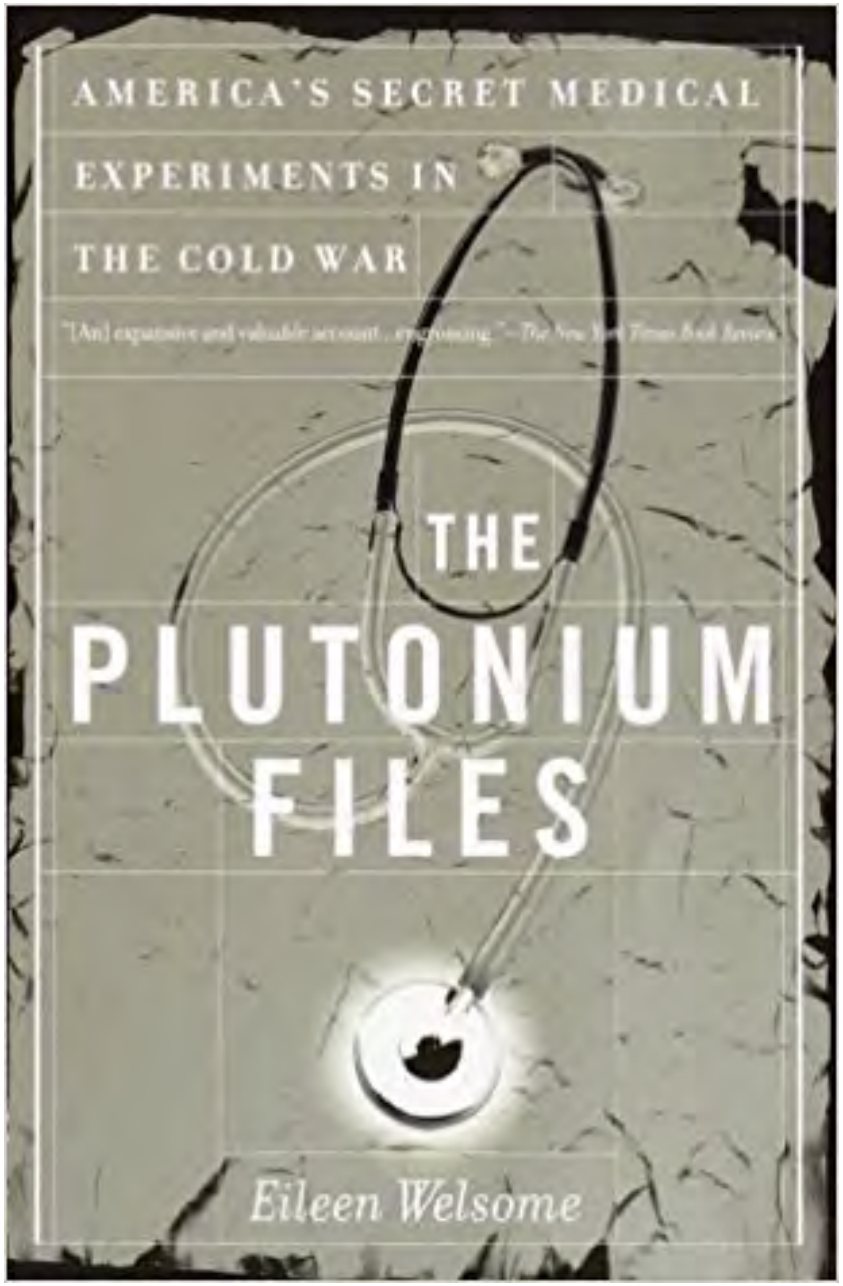
Chapter 13: The Rochester Production Line



https://www.amazon.com/Plutonium-Files-Americas-Medical-Experiments/dp/0385319541

MANHATTAN ANNEX, 1943

1945 RADIATION EXPERIMENTS

Patients were injected with plutonium

- The selection of subjects is entirely up to the Rochester group. … **It is of primary importance that the subjects have relatively normal kidney and liver function, as it is desirable to obtain a metabolic picture comparable to that of an active worker.** Undoubtedly the selection of subjects will be greatly influenced by what is available. The above points, however, should be kept in mind.
  (Wright Langham, "Revised Plan of 'Product' Part of Rochester Experiment," ACHRE No. DOE-121294-D. p. 2) **Emphasis added.**

Some were injected with uranium

Some were given polonium

Amedio Lovecchio, HP1 (1878-1960)

"Lovecchio had two fig trees in his backyard. Each fall he bent the trees to the ground and buried them deep in the soil to protect them from the harsh winter. Each spring he gave the first fig to a pregnant daughter-in-law."

PERSPECTIVE

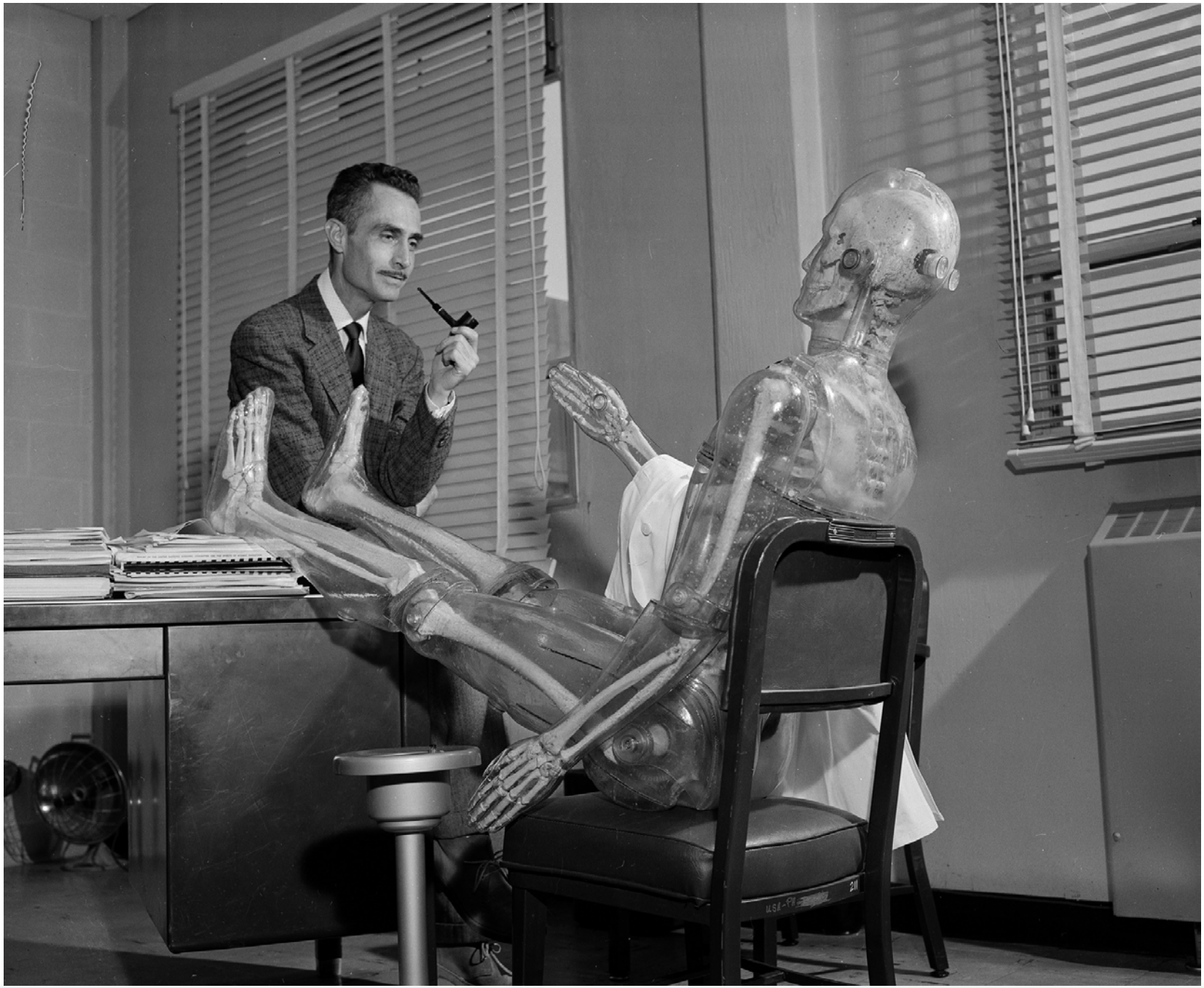
"Your letter of February 27 regarding Hp 11 was startling, to say the least. . . . In case you should decide to do another terminal case, I suggest you use 50 micrograms instead of 5. This would permit the analysis of much smaller samples and would make my work considerably easier. I have just received word that Chicago is performing two terminal experiments using 95 micrograms each. **I feel reasonably certain there would be no harm in using larger amounts of material if you are sure the case is a terminal one."**

[Wright Langham to Samuel Bassett, March 13, 1946, ACHRE No. DOE-121294-D.] **Emphasis added.**

"She [Dr. Waterhouse] believes that follow-up of these persons is an important project and is willing to cooperate to the fullest. She still sees two of the people on a regular basis and has contacted the physician who has been caring for the third patient known to be still living. She believes that all three persons would be agreeable to providing excretion samples and perhaps blood samples, but they are all quite old--in their middle or late 70's and cannot travel far. **More important, they do not know that they received any radioactive material."**

[Patricia Durbin, December 9, 1971, ACHRE No. DOE-121294-D.]

Emphasis added.



DISTRESS

“Classification (prolonged) and the passage of many years before even classified publication of the findings led to his [Dr. Langham's] eventual responsibility for analysis and publication of the results. He is, I believe, distressed by this and other aspects of the study itself--particularly the fact that the injected people in the HP series were unaware that they were the subjects of an experiment.”

[Patricia Durbin, December 10, 1971, ACHRE No. DOE-121294-D.]

The voluntary consent of the human subject is absolutely essential.

THE NUREMBERG CODE

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. This latter element requires that, before the acceptance of an affirmative decision by the experimental subject, there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person, which may possibly come from his participation in the experiment.

The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity.

2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.

3. The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study, that the anticipated results will justify the performance of the experiment.

4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.

5. No experiment should be conducted, where there is an a priori reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.

6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.

7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death.

8. The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.

9. 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 seemed to him to be impossible.

10. During the course of the experiment, the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of the good faith, superior skill and careful judgement required of him, that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

["Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law No. 10", Vol. 2, pp. 181-182. Washington, D.C.: U.S. Government Printing Office, 1949.]

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Declaration of Helsinki

World Medical Association Declaration of Helsinki

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964; amended by the 29th WMA General Assembly, Tokyo, Japan, October 1975; 35th WMA General Assembly, Venice, Italy, October 1983; 41st WMA General Assembly, Hong Kong, September 1989; 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996, and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000

Duty of physician is to promote and safeguard health of the people.

A. Introduction

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.

2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.

6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.

7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.

8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. Basic principles for all medical research

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the

Bulletin of the World Health Organization, 2001, **79** (4)

It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

The subjects must be volunteers and informed participants in the research project.

HHS.gov U.S. Department of Health & Human Services

Office for Human Research Protections

The Belmont Report

Office of the Secretary
Ethical Principles and Guidelines for the Protection of Human Subjects of Research
The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

April 18, 1979

AGENCY: Department of Health, Education, and Welfare.

ACTION: Notice of Report for Public Comment.

SUMMARY: On July 12, 1974, the National Research Act (Pub. L. 93-348) was signed into law, there-by creating the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. One of the charges to the Commission was to identify the basic ethical principles that should underlie the conduct of biomedical and behavioral research involving human subjects and to develop guidelines which should be followed to assure that such research is conducted in accordance with those principles. In carrying out the above, the Commission was directed to consider: **(i)** the boundaries between biomedical and behavioral research and the accepted and routine practice of medicine, **(ii)** the role of assessment of risk-benefit criteria in the determination of the appropriateness of research involving human subjects, **(iii)** appropriate guidelines for the selection of human subjects for participation in such research and **(iv)** the nature and definition of informed consent in various research settings.

The Belmont Report attempts to summarize the basic ethical principles identified by the Commission in the course of its deliberations. It is the outgrowth of an intensive four-day period of discussions that were held in February 1976 at the Smithsonian Institution's Belmont Conference Center supplemented by the monthly deliberations of the Commission that were held over a period of nearly four years. It is a statement of basic ethical principles and guidelines that should assist in resolving the ethical problems that surround the conduct of research with human subjects. By publishing the Report in the Federal Register, and providing reprints upon request, the Secretary intends that it may be made readily available to scientists, members of Institutional Review Boards, and Federal employees. The two-volume Appendix,

Respect for persons
Beneficence
Justice

(NICOLE) WAN HOI-YAN

19 years old

Sophomore at the University of Rochester

Studying to become a nurse

Volunteered (compensated $150)

Bronchoscophy: Tube inserted to collect lung cells performed under local anesthetic (Lidocaine)

“There is the question of when is a procedure more invasive than a 19-year-old should have the power to consent to. As a parent I wouldn't want my child to consent to this.” Dr. Debuono, NY State Health Commissioner

NEW YORK SEEKS TO TIGHTEN RULES ON MEDICAL RESEARCH

By ELISABETH ROSENTHAL SEPT. 27, 1996

Prompted by the case of a healthy 19-year-old college student who died of a heart attack after volunteering for a medical research project, state health officials yesterday assailed the researchers and called for stricter state rules for such experiments.

After a four-month investigation, the state reported that the researchers at the University of Rochester Medical Center had violated their own guidelines by increasing the dose of an anesthetic for the student, Nicole Wan, who had agreed to participate for $150.

Health Commissioner Barbara A. DeBuono said Ms. Wan's death also raised a broader question of whether medical researchers in general paid enough attention to the potential risks faced by their volunteers.

The Research Subject

http://www.hpsnetwork.org

The Research Subjects

Research Participants

Guiding Principles for Community-Engaged Research

Long-term engagement

Mutual benefit

Mutual respect

Shared findings

Enhanced community capacity

Shared responsibility

Evidence-based

Collaborative from start to finish

Responsive to community priorities and perspectives

RESEARCH OBJECTIVES

Engaging more effectively with community organizations, agencies, and diverse population groups to identify research questions critical to the community and to improve methods to reflect community preferences;

Developing more effective strategies for recruitment and retention of participants in clinical studies;

Improving the dissemination of information from health promotion interventions and/or clinical trials to increase the community's knowledge of health promotion and disease prevention.

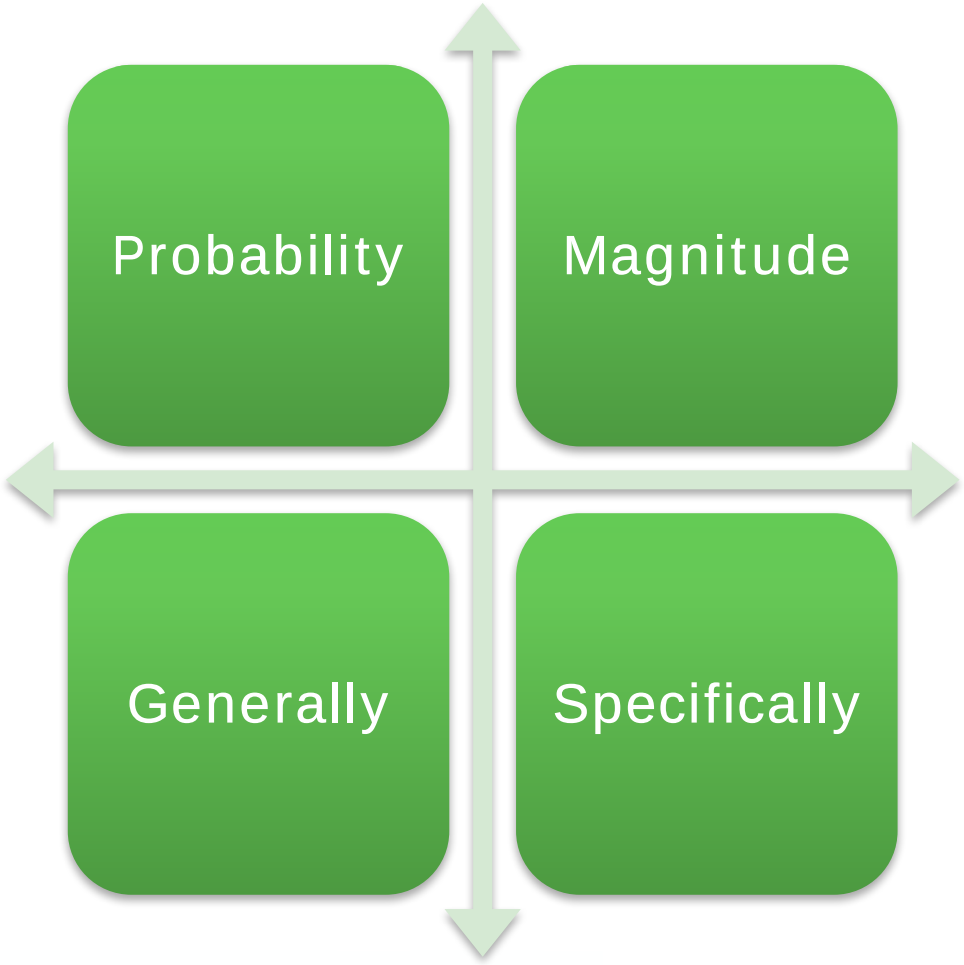
https://www.urmc.rochester.edu/community-health/about-us.aspx

RISK ASSESSMENT

"Research that poses greater risk should receive more attention and deliberation than less risky research, and the degree and type of oversight should be commensurate with the level of risk."

Department of Health and Human Services, 2015, p. 53941.

The Precautionary Principle & the Sanguinity Principle



SUMMARY

Slow **PROGRESS** over time

Even with good processes humans make mistakes

Requires exquisite attention to how individuals and teams make IRB/REC decisions

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MELIORA

Thank you.