Historical Look at Research Ethics and the Concern for Vulnerability

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Arkansas Children's
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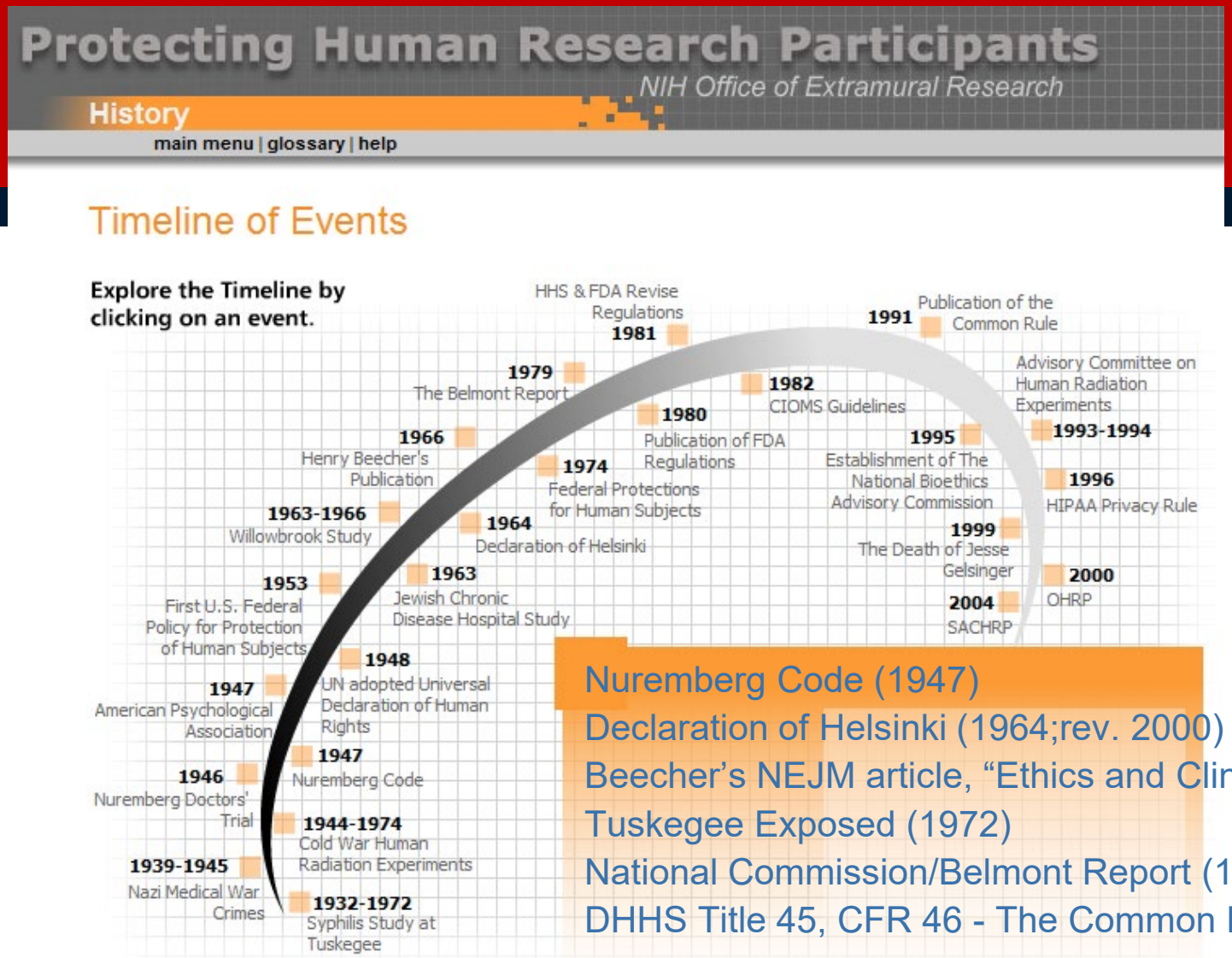


Nuremberg Code (1947)
Declaration of Helsinki (1964;rev. 2000)
Beecher's NEJM article, "Ethics and Clinical Research" (1966)
Tuskegee Exposed (1972)
National Commission/Belmont Report (1976-79)
DHHS Title 45, CFR 46 - The Common Rule (1991; rev. 2018)

GETTING HISTORICAL 20TH CENTURY LANDMARKS

Nuremburg and Helsinki

- Nuremburg Code's 10 principles, including…
  - Voluntary Consent
  - Yield Fruitful Results
  - Prior Animal Studies
  - Risk Should Not Exceed Potential Promise
  - Volunteers Can Withdraw at Any Time

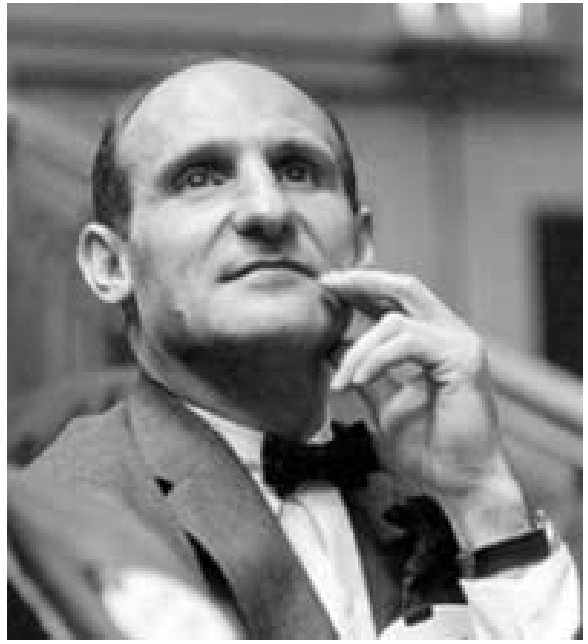
- Helsinki Declaration's Protections (selected)
  - Well-being of the participant should take precedence of the scientific interests
  - Potential Benefit Must Outweigh Risks, and Risks Must Be Manageable
  - Participants Must Be
    - Voluntary
    - Informed
    - Respected (including privacy provisions)
    - Can Gain Consent from a Legal Guardian

Codes Shmodes

"The Nuremberg Code was conceived in reference to Nazi atrocities and was written for the specific purpose of preventing brutal excesses from being committed or excused in the name of science. The code ... is in our opinion not necessarily pertinent to or adequate for the conduct of medical research in the United States"

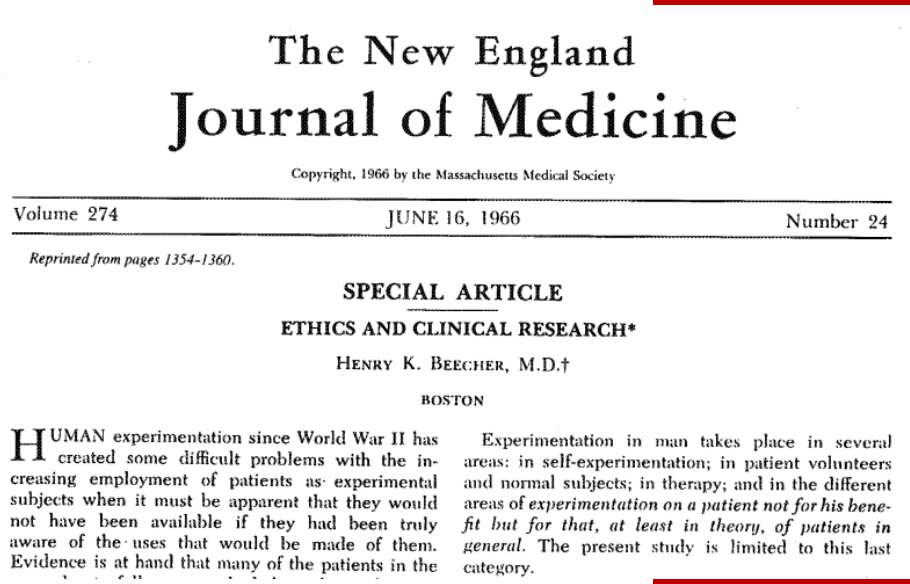
Joseph Gardella, MD (1962)

Assistant Dean of Students, Harvard Medical School



Watershed Moments: Beecher's Response to Gardella

- "Ethics and Clinical Research" (NEJM, 1966)
  - Author: Henry Beecher, MD
    - Dissenting member of Gardella's committee
  - Published an annotated list of 22 ethically problematic published research trials
    - Injecting cancer cells into non-consenting elderly patients
    - Exposing institutionalized children to hepatitis
    - No-therapy control groups in serious, treatable diseases



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SPECIAL ARTICLE

ETHICS AND CLINICAL RESEARCH*

HENRY K. BEECHER, M.D.†

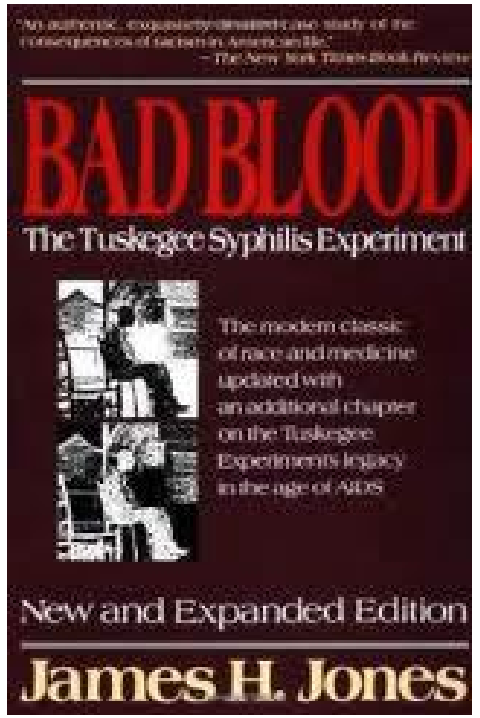
BOSTON

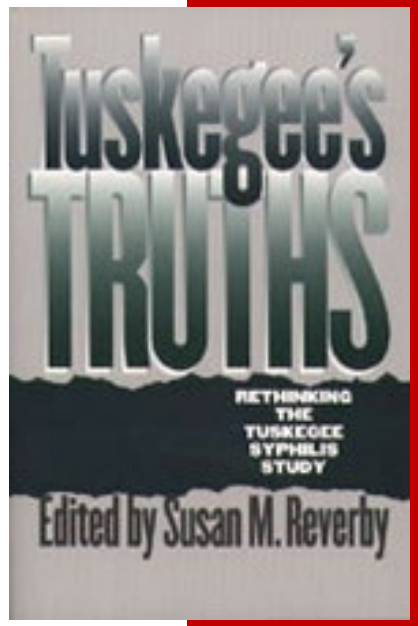
HUMAN experimentation since World War II has created some difficult problems with the increasing employment of patients as experimental subjects when it must be apparent that they would not have been available if they had been truly aware of the uses that would be made of them. Evidence is at hand that many of the patients in the

Experimentation in man takes place in several areas: in self-experimentation; in patient volunteers and normal subjects; in therapy; and in the different areas of *experimentation on a patient not for his benefit but for that, at least in theory, of patients in general.* The present study is limited to this last category.

Watershed Moments: Tuskegee Syphilis Study

- Public Health Service Study, 1932-72
  - Piggy-backing off a prevalence study, 1929
- 399 w/syphilis; 201 w/out (as control)
  - African American males from Macon County, AL
- Volunteered to be part of a health project
  - Inducements included
    - free lunch
    - transportation
    - health checks
    - burial insurance
  - Not told they had syphilis
  - Subjected to tests (including lumbar punctures)
- Penicillin available by late 1940s





Macon County Health Department

ALABAMA STATE BOARD OF HEALTH AND U.S. PUBLICH HEALTH SERVICE COOPERATING WITH TUSKEGEE INSTITUTE

Dear Sir:

Some time ago you were given a thorough examination and since that time we hope you have gotten a great deal of treatment for bad blood. You will now be given your last chance to get a second examination. This examination is a very special one and after it is finished you will be given a special treatment if it is believed you are in a condition to stand it.

If you want this special examination and treatment you must meet the nurse at _____ on _____at _____ M. She will bring you to the Tuskegee Institute Hospital for this free treatment. We will be very busy when these examinations and treatments are being given, and will have lots of people to wait on. You will remember that you had to wait for some time when you had your last good examination, and we wish to let you know that because we expect to be so busy it may be necessary for you to remain in the hospital over one night. If this is necessary you will be furnished your meals and a bed, as well the examination and treatment without cost.

REMEMBER THIS IS YOUR LAST CHANCE FOR SPECIAL FREE TREATMENT. BE SURE TO MEET THE NURSE.

Macon County Health Department

U. S. PUBLIC HEALTH SERVICE

25

This certificate is awarded to

In grateful recognition of 25 years of active participation in the Tuskegee medical research study.

Awarded 1958

Surgeon General

The New York Times

Syphilis Victims in U.S. Study Went Untreated for 40 Years

By JEAN HELLER
The Associated Press

WASHINGTON, July 25—For 40 years the United States Public Health Service has conducted a study in which human beings with syphilis, who were induced to serve as guinea pigs, have gone without medical treatment for the disease and a few have died of its late effects, even though an effective therapy was eventually discovered.

The study was conducted to determine from autopsies what the disease does to the human body.

Officials of the health service who initiated the experiment have long since retired. Current officials, who say they have serious doubts about the morality of the study, also say that it is too late to treat the syphilis in any surviving participants.

Doctors in the service say they are now rendering whatever other medical services they can give to the survivors while the study of the disease's effects continues.

Dr. Merlin K. DuVal, Assistant Secretary of Health, Education and Welfare for Health and Scientific Affairs, expressed shock on learning of the study. He said that he was making an immediate investigation.

The experiment, called the Tuskegee Study, began in 1932 with about 600 black men,

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
OFFICE OF THE SECRETARY

TO : Director
Center for Disease Control
THROUGH: Administrator, HS

DATE: NOV 16 1972

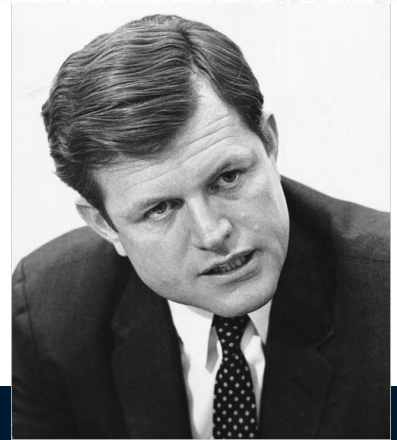
11/22

FROM : Assistant Secretary for Health

SUBJECT: Termination of USPHS Study of Untreated Syphilis (the Tuskegee Study)

As recommended by the Tuskegee Syphilis Study Ad Hoc Advisory Panel, I have decided that the "Tuskegee Study" as a study of untreated syphilis must be terminated. I will advise you of the necessary steps to be taken to assure that appropriate medical care be given to all remaining participants in the "Tuskegee Study" as a part of the close-out phase of the project.

Merlin K. DuVal, M.D.

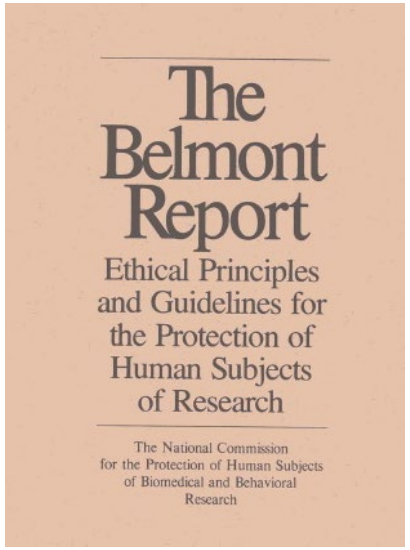


National Commission, Belmont Report (1979): Principles and Applications

- Defines differences among
  - *Practice*: "interventions that are designed solely to enhance the well-being of an individual patient…that have reasonable expectation of success"
  - *Experimentation*: an "innovation" that "departs in a significant way from standard accepted practice"; it is "new, untested, or different"
  - *Research*: "an activity designed to test an hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge"

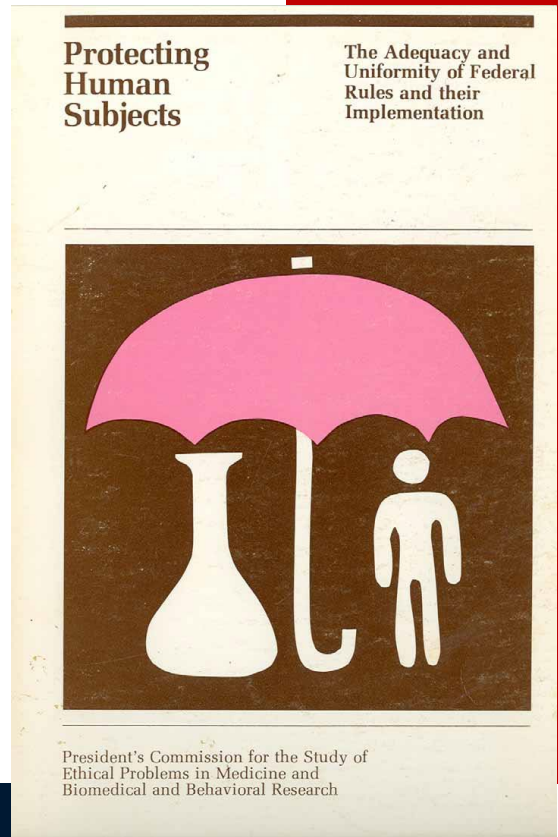
- Identifies comprehensive "prescriptive judgments"

Principles	→	Applications
Respect for Persons	→	Informed Consent
Beneficence	→	Harms v. Benefits
Justice	→	Subject Selection



President's Commission: Protecting Human Subjects (1981)

- Need for common federal regulations
- Need for a DHHS office to protect human subjects in research
- Need to have regular updates from PIs
- Need for protection of vulnerable populations
- Need for negative consequences to befall those who are guilty of misconduct



The Common Rule (1991; updated 2019)
45 CFR 46

- Regulations for Federally Funded Human Subjects Research
  - Endorsed by Most Federal Agencies
    - FDA has its own human subjects regulations (21 CFR 50)
- Applies to research on human subjects
  - Exemptions include certain forms of educational research, “masked” video recordings, biospecimens that meet certain criteria, some research of federal programs
- Four Main Sections
  - Human Subjects Research and IRBs (45 CFR, Subpart A - 46.1xx)
  - Pregnant Women, Fetuses, Neonates (45 CFR, Subpart B - 46.2xx)
  - Prisoners (45 CFR, Subpart C - 46.3xx)
  - Children (45 CFR, Subpart D - 46.4xx)

The Common Rule: Definitions (45 CFR 46.102)

- Definitions include
  - ***Research***: “a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge.”
  - ***Human Subject***: “a living individual about whom an investigator (whether professional or student) conducting research:

    (i) Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or

    (ii) Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens

How the History of Research Ethics Affects Us: Federal Wide Assurance (FWA)

- Human subjects research must be guided by principles
  - Belmont, Declaration of Helsinki, or other approved set
- Covers all research that falls under The Common Rule
  - The Common Rule covers all federally funded human subjects research
- Must comply with The Common Rule (and other applicable federal regulations)
  - Latest revision is 2019 – know the new regulations!
- Must have written procedures for reporting
  - Reporting existing research as well as any misconduct
- Must have adequate support for IRB efforts
  - Can use external IRB, but must assure that all regulations are followed by that IRB

What Makes a Group or Person “Vulnerable”?

VULNERABILITY: PARTICIPANTS AT RISK

Vulnerability: What It Is and How to Respond

Vulnerability is

- Susceptibility to harm
- Risk of exploitation

- Three responses
  - Acquiescence
  - Protection
  - Empowerment

Forms of Potential Vulnerability

- Age?
- Ethnicity?
- Educational background?
- Institutional status?
- Economic status?
- Mental or medical health status?

BALANCING PROTECTION AND ACCESS

Protecting the Vulnerable

- Regulations are written that identify a few special/vulnerable populations
  - Pregnant women, fetuses or *in vitro* fertilization
    - Condition of women can heighten risks
    - Fetuses are developmentally fragile
  - Prisoners
    - Captive population where coercion may affect autonomous decision making
  - Children
    - Minors lack decisional capacity
- Other special/vulnerable populations to consider
    - Cognitively impaired
    - Addicted individuals
    - Students or employees or military personnel
    - Non English-speaking participants
    - Economically or educationally disadvantaged

Providing Access

- Restricting access to research participation can
  - Compromise scope of knowledge about the effects of interventions on entire populations
    - Research may lead to improve health status for target populations
  - Exclude individuals for potential positive health outcomes
    - Research may provide health benefits for participants

- Need to balance the need for protection with the benefits of participation in research

RESEARCH W/CHILDREN

Issues with Children in Research

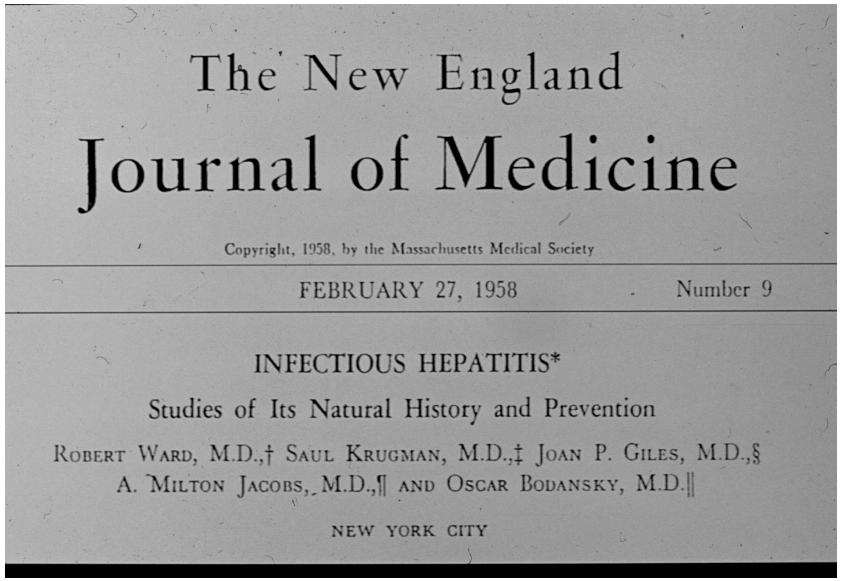
- The Vulnerability of Children
  - Evaluation of Risk/Harm
  - Restricting Access
- The Lack of Good Pediatric Data
  - Unavailability of researched dosing levels in children
  - “Off-label” use of drugs in children
  - Identifying research needs in the pediatric population
- Role of Parental Authority
  - Status of a Child’s Dissent

The “Pediatric Tuskegee”

WILLOWBROOK

The Story

- Institutionalized, developmentally delayed children
- Injected ("introduced" or "fed") a cohort of children with (to) hepatitis
  - Blood serum, purified from stool
- Attempted to use gamma globulin to create immunity



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FEBRUARY 27, 1958 Number 9

INFECTIOUS HEPATITIS*

Studies of Its Natural History and Prevention

ROBERT WARD, M.D.,† SAUL KRUGMAN, M.D.,‡ JOAN P. GILES, M.D.,§
A. MILTON JACOBS, M.D.,¶ AND OSCAR BODANSKY, M.D.‖

NEW YORK CITY

November 15, 1958

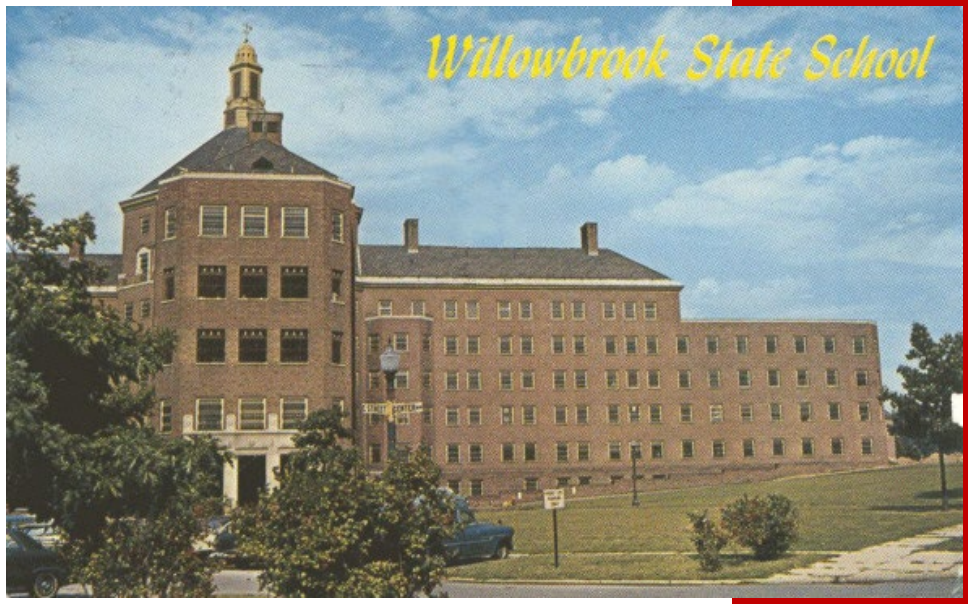
Dear Mrs. _____:

We are studying the possibility of preventing epidemics of hepatitis on a new principle. Virus is introduced and gamma globulin given later to some, so that either no attack or only a mild attack of hepatitis is expected to follow. This may give the children immunity against this disease for life. We should like to give your child this new form of prevention with the hope that it will afford protection.

Permission form is enclosed for your consideration. If you wish to have your child given the benefit of this new preventive, will you so signify by signing the form.

The Institution – Willowbrook State School

- Institution for children with developmental delay (aka, “retardation” or “mental defect”)
- Designed to house 3,000 children, population eventually exceeded 6,000
  - Primarily African American and Puerto Rican
  - Many were unclothed
  - Ratio of children to attendants was 50-to-1
- 40 buildings, little-to-no furniture
  - One section dedicated to research



The Leader – Saul Krugman, MD

- According to the National Academy of Sciences
  - One of the most honored pediatricians, Saul Krugman, contributed to the elimination of more pediatric infectious diseases than any other scientist of his time. His research led to the measles vaccine in 1963 and the rubella vaccine in 1969. He was the first scientist to determine the distinction between infectious hepatitis A and serum hepatitis B. He found that hepatitis A was transmitted orally or through consumption of infected materials and that hepatitis B was transmitted intravenously and through sexual contact. However, Krugman's most significant discoveries were that hepatitis B was preventable by administering a specific immune globulin and that the virus could be actively immunized by injection of a heated virus-containing serum. This led to the development of the hepatitis B vaccine, and it increased global treatability of the virus. Krugman established one of America's first comprehensive children's health clinics at Bellevue Hospital and laid the foundation for modern medical clinics. He was also co-author of a widely-used classic medical textbook entitled *Infectious Diseases of Children*.

The Fallout, Response, and Legacy

- Fallout
  - Kennedy's complaints (1964); Rivera's expose (1972)
  - Beecher's condemnation (1966/1970); Rothman's rebuke (1984)
- Response
  - Krugman (1967/1986)
  - Robinson/Unruh (2008)
- Legacy
  - Identified hepatitis A & B strains
    - Proved "passive immunity" theory in hepatitis
  - The "pediatric Tuskegee"
    - Restricted use of children in research

THE CURRENT REGULATORY CONTEXT

Definition of “Children” in The Common Rule (45 CFR 46)*

Children are persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted [402(a)]

- Assent applies only to *children*
- States may have laws that adjust the age of *consent* to research
  - That is, some state laws may speak to whether or not a minor meets certain criteria such that s/he is granted the authority to *consent* to research for him/herself
  - These laws do not affect *assent* issues in research

*in relation to the issues discussed in the presentation, the FDA regs mirror The Common Rule

The Common Rule: Part D (45 CFR 46.4xx)

46.404: Research not involving greater than minimal risk

- One parent (or LAR) must give permission (consent)
- Child's assent is necessary

46.405: Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects

- One parent (or LAR) must give permission (consent)
- **Child's dissent may be overridden in cases where no therapeutic alternatives exist**

46.406: Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition

- Both parents (or LARs) must give permission (consent)
- Child's assent is necessary

46.407: Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children

- Both parents (or LARs) must give permission (consent)
- Child's assent is necessary

46.408: Requirements for permission by parents or guardians and for assent by children

Consent/Permission

- Parents (or LARs) must give permission (consent)

Assent as process

- All minors capable of assent (per IRB determination) must be "assented"

Regulation Regarding Assent/Dissent
The Common Rule (45 CFR 46.408)

…adequate provisions [must be] made for soliciting the assent of the children, when in the judgment of the IRB the children are capable of providing assent. In determining whether children are capable of assenting, the IRB shall take into account the ages, maturity, and psychological state of the children involved. This judgment may be made for all children to be involved in research under a particular protocol, or for each child, as the IRB deems appropriate. [408(a)]

Regulation Regarding Assent/Dissent
The Common Rule (45 CFR 46.408)

…If the IRB determines that the capability of some or all of the children is so limited that they cannot reasonably be consulted or that *the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research, the assent of the children is not a necessary condition for proceeding with the research*. [408(a)]

Assent as Product and/or Process
The Common Rule (46.4xx)

Assent means a child's affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent. [408(b)]

- This is a “product” definition

Adequate *provisions are made for soliciting* the assent of the children and permission of their parents or guardians, as set forth in §46.408. [emphasis added; 405(c)]

- This is a “process” expectation

Proceeding with Research: Necessary/Sufficient Conditions*

Minor Assent	Necessary as Process	Necessary as Product	Sufficient in either form
404	Yes	Yes	No
405	Yes	No	No
406	Yes	Yes	No
407	Yes	Yes	No

Parental Permission	Necessary	Sufficient
404	Yes	No
405	Yes	Yes
406	Yes	No
407	Yes	No

*when child minor is capable of assent and IRB requires assent

Planning for Dissent: When Process is Required but Product is not "Necessary"

- If assent is sought, dissent is possible
- Provisions should be made for what an investigator will do in the face of dissent
  - Dissent may be overridden by parental permission if the trial holds out the "prospect of direct benefit"
    - Not all teens have their own long-term best interests in mind

  OR
  - Dissent may be honored by the investigator (even if there is the "prospect of direct benefit") if put into exclusion criteria
    - Not all parents are in tune with their teen's needs/interests/experiences
    - A dissenting teen may not dissent passively
    - Teen may have good reasons for dissenting

Why Callout 405 Protocols?

- High Stakes?
  - Protection → Benefit (Wilkinson, *JME* 2012)
    - 405 research purports to provide possible benefit where no other reasonable options for benefit exist
  - Sliding scale for capacity (cf. Unguru, et al., *Pediatrics* 2010)
    - Complex and higher stakes considerations require higher bar for "capacity," which children do not often meet
- Parental Authority?
  - Acknowledgment of wide scope (cf. Ross, *Children in Medical Research* 2006)
    - Parents have right to exercise their authority over the important decisions made on behalf of their children

Treating Children as *Participants*

- All research subjects should be treated as *participants*
  - Should not treat decisional capacity or authoritative autonomy as necessary conditions for participation
- Affirmative agreement is neither sufficient nor necessary to be treated as a participant
  - Even dissenting individuals may be considered "true" participants
- Requiring a robust assent *process* treats children as participants
  - Cheah/Parker (*BMC Medical Ethics* 2014) argue assent is not well-conceived as "agreement," since this implies the capacity to make decisions for oneself and one's well-being
    - Assent is best understood a "respectful and sensitive engagement."
  - Giesbertsz, et al. (*Eur J of Hum Gen* 2014) argue for "personalized assent" based on the premise that engagement in a process, not outcome of decision making, is what matters to respecting children.

Q&A

THANK YOU