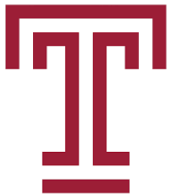
Ethical and IRB Issues in Biomedical Research

3.14.19

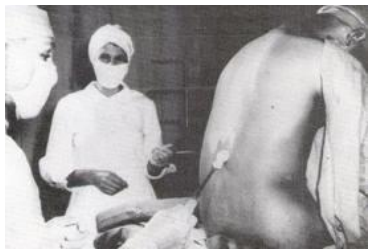
Nora L. Jones, PhD
Associate Director | Director of Education



Center for Bioethics, Urban Health, & Policy
Lewis Katz School of Medicine at Temple University

Goals:

- Historical perspective on the development of research ethics and IRBs
- Overview of subject protections - What makes research ethical?
- A take-away toolkit for clinician researchers

Birth of Bioethics:

Nuremberg and the
Nazi Doctor Trials - 1946/7

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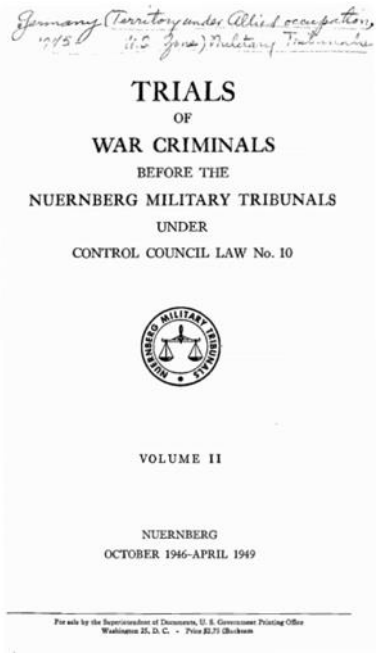
Research Abuses → Regulations


Germany (Territory under Allied occupation, 1945- U.S. Zone) Military Tribunals

TRIALS
OF
WAR CRIMINALS
BEFORE THE
NUERNBERG MILITARY TRIBUNALS
UNDER
CONTROL COUNCIL LAW No. 10

VOLUME II

NUERNBERG
OCTOBER 1946-APRIL 1949

For sale by the Superintendent of Documents, U. S. Government Printing Office
Washington 25, D. C. - Price $2.75 (Buckram

Nuremberg Code, 1949

1. Voluntary consent absolutely essential. Legal capacity to consent, without coercion, full IC (risk/benefit)
2. Must yield fruitful results for the good of society; should not be attainable in other ways; cannot be random or unnecessary
3. Should be based on animal experimentation
4. Should avoid unnecessary physical and mental suffering/injury
5. Death cannot be an expected outcome
6. Risk can never outweigh humanitarian importance
7. Right to withdraw
8. Scientist must be prepared to terminate in adverse circumstances

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History of Research Ethics Regulation

EVENT	Nazi Doctor Trials – 1945-49			
POLICY RESPONSE	Nuremberg Code 1947 (research); Declaration of Helsinki, 1964 (clinical research)			
PUBLIC RESPONSE	Outrage – anger at the 'others'			
FOCUS	Unwitting research 'subjects'			

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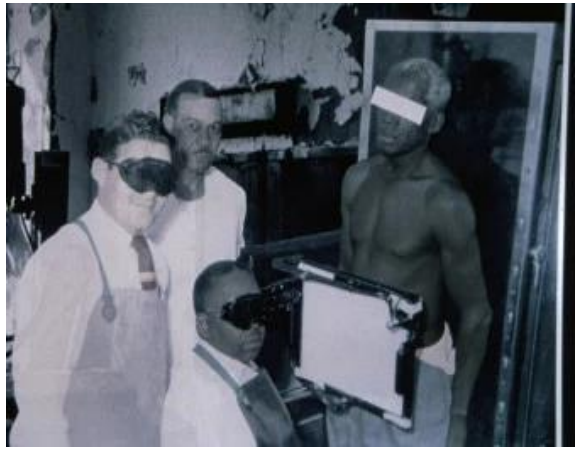
Research Ethics comes to the United States:

USPHS Tuskegee Study of Untreated Syphilis, 1932-1972



USPHS Guatemalan Syphilis Study

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Research Abuses → Regulations

National Commission, 1974

Belmont Report, 1979

1. Respect for persons: protecting autonomy, IC with truthfulness and without deception
2. Beneficence: doing no harm to the subject while maximizing the project's benefits
3. Justice: distributing costs and benefits fairly and equally among participants and potential participants

Common Rule, 1981

→ IRBs

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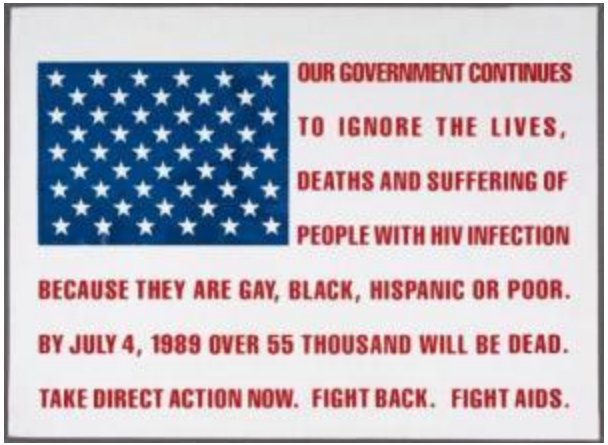
A shift…



"A Drug Trial is Health Care Too"

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Treatment IND (1987/2009)

- Promising new drugs, not yet approved
- Available to persons with serious and life-threatening illnesses (for whom no other comparable or satisfactory alternative exists)
- Outside of clinical trial
- ONLY in the following conditions:
  - Serious/life-threatening illness, with no other options
  - Potential benefit justifies the the risk (and risks not unreasonable in the context of the disease/condition being treated)
  - IND use will NOT interfere with clinical trials (in progress or completed)
- Evidence of effectiveness generally from phase 3 or phase 2 of a clinical trial

‘Right to try’

- Ethical pro argument….
- Unethical anti argument:
  - False hope
  - Not-needed
  - Allows for losing insurance coverage for hospice and home health care if experimental new drugs are tried
  - Presumes that drugs that have completed Phase I are safe
  - “Empty, unethical, feel-good legislation.”

HEALTH

The Disingenuousness of ‘Right to Try’

The new law has a catchy name, but it will only make it more difficult to know if medication is effective or safe.

JAMES HAMBLIN JUN 2, 2018

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PUBLIC RESPONSE	Outrage – anger at the 'others'	Outrage – anger at the medical establishment for abuses of power and subjects	From gay community – call for greater funding and more/faster research; Power to the people	
FOCUS	Unwitting research 'subjects'		Willing but unable research subject/patient	

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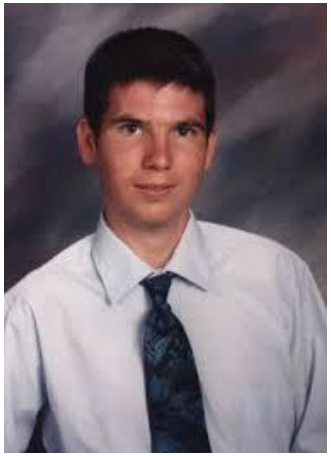
Gelsinger and 'Gene Therapy'

- Sep 13, 1999, UPenn: Jesse Gelsinger, 18, is injected with adenoviral vector in clinical trial
  - Jesse had ornithine transcarbamylase deficiency, under control with diet, meds
  - Trial to see if gene therapy would help babies with condition
- Sep 17, 1999: Jesse dies, having suffered from massive immune response to vector
  - First gene therapy clinical trial death
- Subsequent FDA investigation reveals improper procedures in clinical trial by UPenn scientists, raises issues of informed consent
  - Jesse included as substitute for another volunteer improperly
  - Failure to report serious side effects of two patients
  - Failure to report death of monkeys in animal trials on informed consent form
  - Potential financial conflicts of interest



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Weak ← **Pendulum of Protectionism** → **Strong**

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Will stronger protectionist policies make research more ethical? Absolve investigators of certain responsibilities? Something else?

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What makes research ethical?

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Emanuel et al's 7 requirements cited 2164 times since 2000

1. Value (social or scientific) (Useful)
    - Distributive Justice; Social Justice (non-exploitation)
2. Scientific Validity (Good design)
    - Distributive Justice; Social Justice
3. Fair Subject Selection
    - Social Justice (Beneficence, Non-maleficence)
4. Favorable Risk Benefit Ratio
    - Non-maleficence, beneficence, non-exploitation
5. Independent Review
    - Public accountability; minimizing COI
6. Informed Consent
    - Respect for Autonomy
7. Respect for subjects (potential and enrolled)
    - Respect for Autonomy

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Rhodes' Rethinking Research Ethics

Cited 175 times since 2005; named AJOB's 'Most Controversial Article'

"In the context of constituting gross violations of the negative golden rule, serious inequality, egregious injustice, and worthless study designs, pointing at the failure to obtain informed consent as the ethical downfall of Nazi research seems to miss the target entirely."

- Issue with dogma of Informed Consent
- Too narrow a focus on subject protection
- Wants a more 'reasonable' balance of assessment of risk, efficacy, justice, respect
- Research participation as a social duty

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Scientist avoiding thinking about ethics

- Scientists wary of ethical scrutiny; generally reluctant to engage the public in moral conversation about their work

Paul Root Wolpe – Reasons scientists avoid thinking about ethics, *Cell* 2006

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- "I'm not trained in ethics."

- "Ethics is arbitrary."

- "Ethicists mostly say 'no' to new technologies."

- "Others will make the ethical decisions."

- "The public does not know what it wants."
- "Knowledge is intrinsically good."
- "If I don't do it, someone else will."

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- "I'm not trained in ethics."
  - NIH requires ethics training (grants, funded programs) on human subjects protections
    - Should also work on reinforcing the importance of the bigger questions – What is science for? How do I advance the cause of scientific progress? Whom does my research serve?
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  - Not enough of a justification to do something that would otherwise be ethically questionable.

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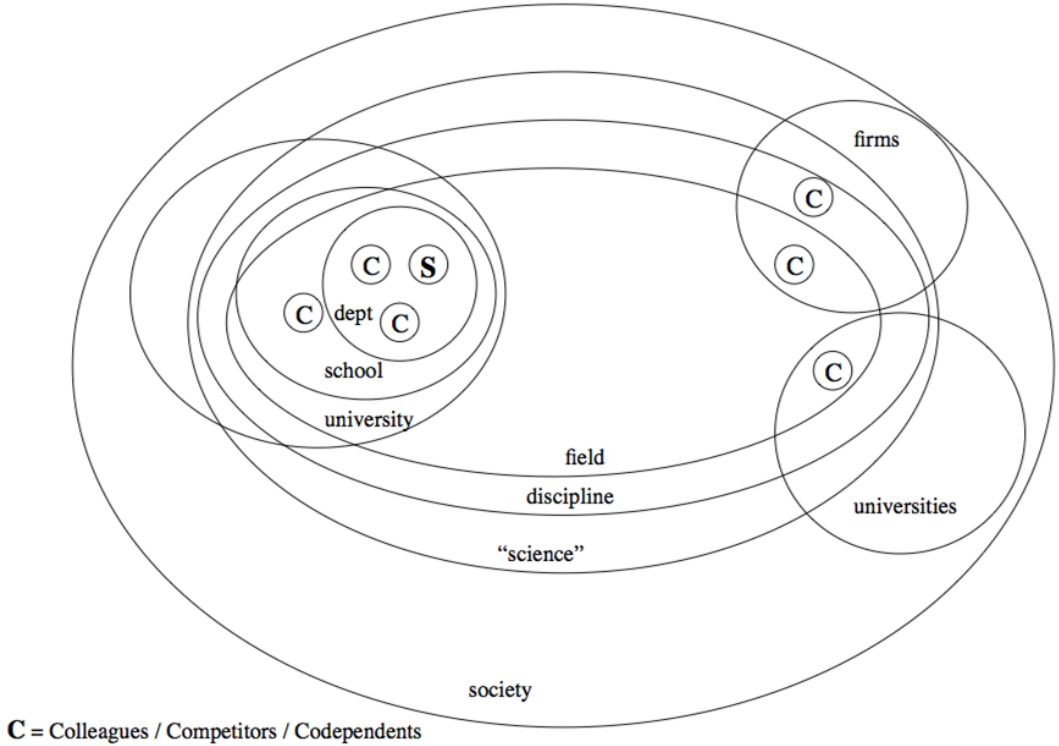
No **S**cientist is an Island



From Jon Merz, JD, PhD

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General Research Ethics

- Abuse of data

Abuse of Data - Sugar

- Sept 2016 – How the Sugar Industry Shifted Blame to Fat
  - 1967 – Sugar Research Foundation paid 3 Harvard scientists $6,500 (~$50,000 today) to publish a review on sugar, fat, and heart disease
    - Counter to rising # of studies hinting at link between sugar and heart disease
      - Studies hand-picked by the Sugar Industry
      - "Then we can publish the data and refute our detractors."
      - "Let me assure you this is quite what we had in mind."
  - One response has been to push harder that all research be publicly funded
    - One of the scientists, D. Mark Hegsted, became head of nutrition at the USDA, where in 1988 he helped draft the forerunner to the federal government's dietary guidelines.
- http://nyti.ms/2cynHoS

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General Research Ethics

- Publication, authorship, and peer review
  - "'Cut-throat academia leads to 'natural selection of bad science', claims study" – The Guardian, Sept 20, 2016
    - "As long as the incentives are in place that reward publishing novel, surprising results, often and in high-visibility journals above other, more nuanced aspects of science, shoddy practices that maximize one's ability to do so will run rampant."
    - "The pressure to publish is corrosive and anti-intellectual. Scientists are just humans, and if organizations are dumb enough to rate them on sales figures, they will do discounts to reach the targets, just like any other sales person."

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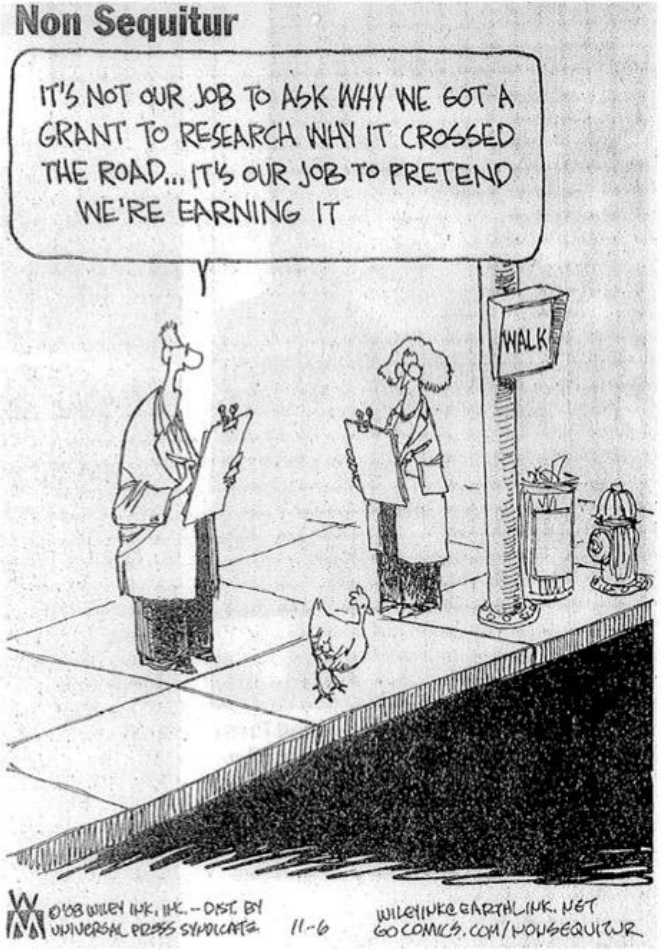
General Research Ethics

- Integrity of research
  (social stewardship of resources)



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General Research Ethics

- Recognizing wrong-doing (micro)

"Behind one door is tenure - behind the other is flipping burgers at McDonald's."

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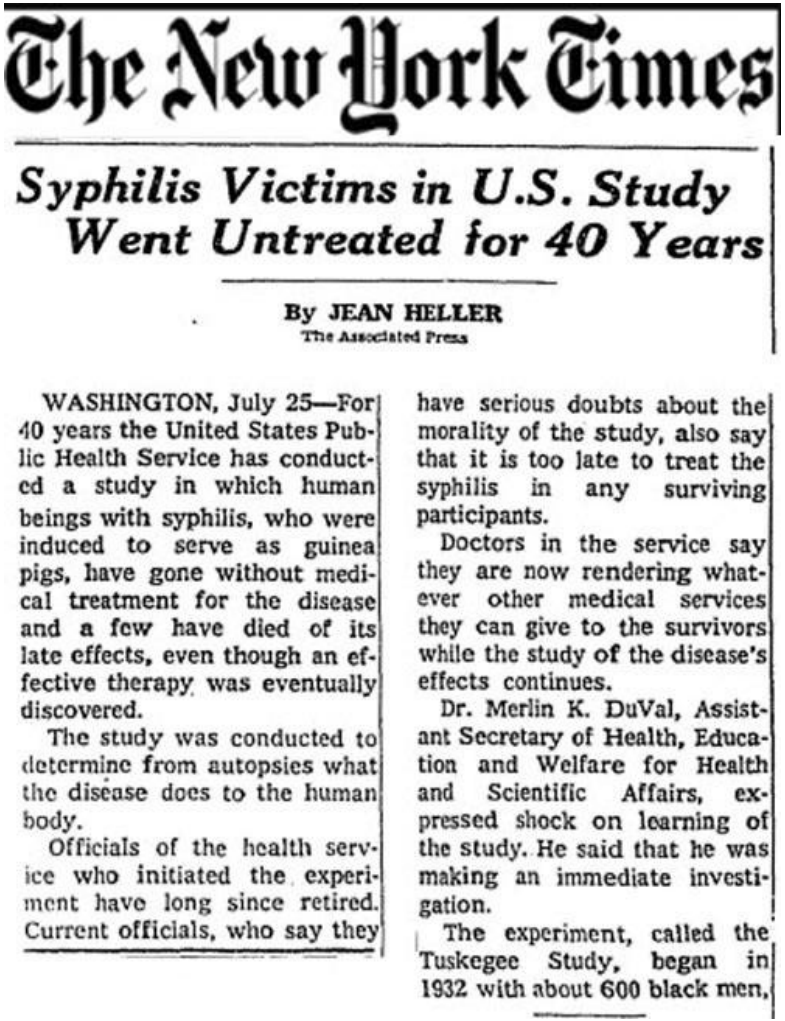
General Research Ethics

- Recognizing wrong-doing



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,

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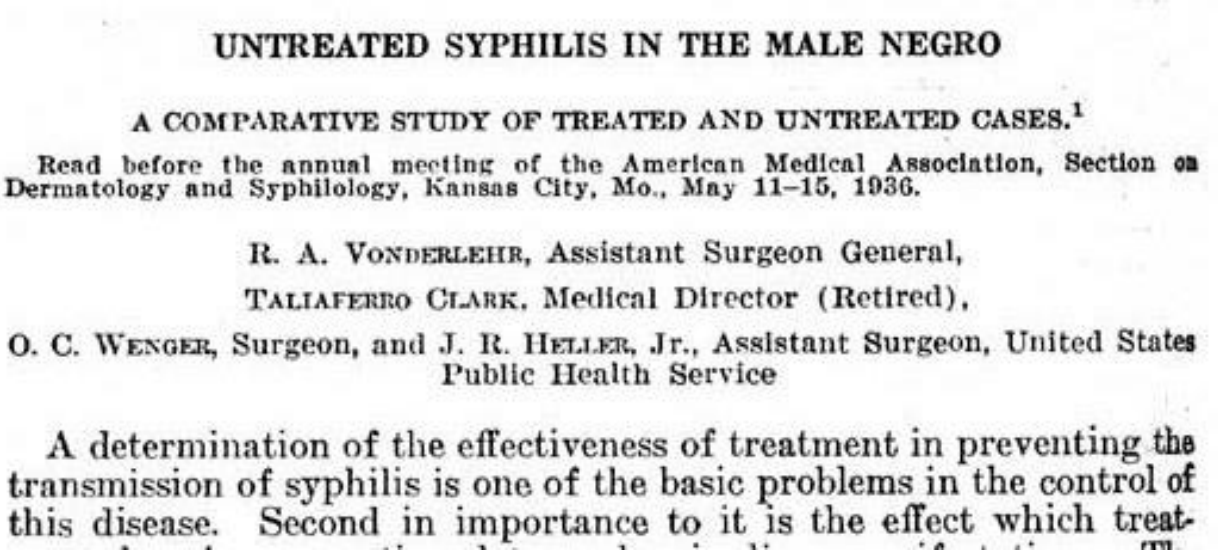
General Research Ethics

- Recognizing wrong-doing

1936 - JAMA



UNTREATED SYPHILIS IN THE MALE NEGRO

A COMPARATIVE STUDY OF TREATED AND UNTREATED CASES.[1]

Read before the annual meeting of the American Medical Association, Section on Dermatology and Syphilology, Kansas City, Mo., May 11–15, 1936.

R. A. VONDERLEHR, Assistant Surgeon General,
TALIAFERRO CLARK, Medical Director (Retired),
O. C. WENGER, Surgeon, and J. R. HELLER, Jr., Assistant Surgeon, United States Public Health Service

A determination of the effectiveness of treatment in preventing the transmission of syphilis is one of the basic problems in the control of this disease. Second in importance to it is the effect which treat-

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1956 – Journal of Chronic Diseases

Untreated Syphilis in the Male Negro

Twenty-Two Years of Serologic Observation in a Selected Syphilis Study Group

SIDNEY OLANSKY, M.D., Durham, N. C.
AD HARRIS
JOHN C. CUTLER, M.D.
and
ELEANOR V. PRICE, Chamblee, Ga.

Since 1932 there has been carried on a study of the outcome of untreated syphilis in the male Negro.* Although the primary objective of this study is the determination

to 22 years. The initial sero
tion in 1932-1933 was based
complement fixation and F
flocculation tests for syphilis
the National Institute of H
1938-1939 and subsequent su
testing has been done by the
ease Research Laboratory
Staten Island, N. Y., and
Chamblee, Ga.). Although

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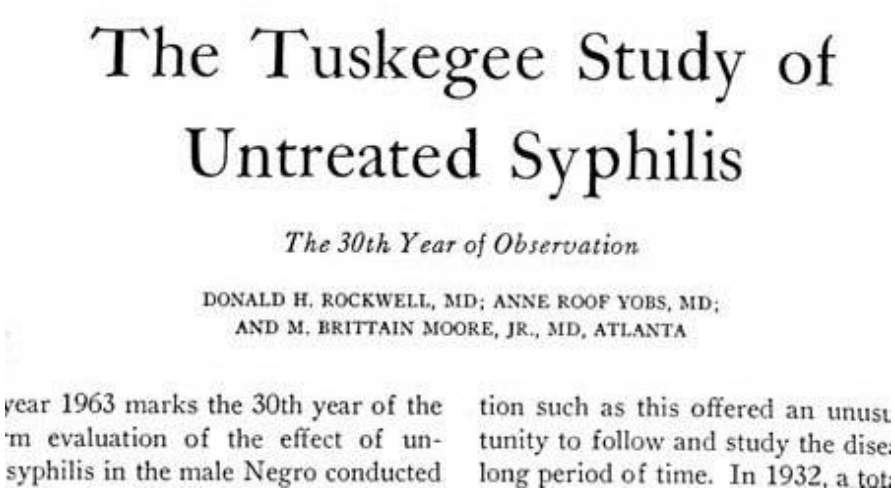
General Research Ethics

1964 – Archives of Internal Medicine



The Tuskegee Study of Untreated Syphilis

The 30th Year of Observation

DONALD H. ROCKWELL, MD; ANNE ROOF YOBS, MD; AND M. BRITTAIN MOORE, JR., MD, ATLANTA

year 1963 marks the 30th year of the 'm evaluation of the effect of un- syphilis in the male Negro conducted

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Other 'scientific' studies published as late as 1973
As early as 1978 critical analyses of the study begin to be published

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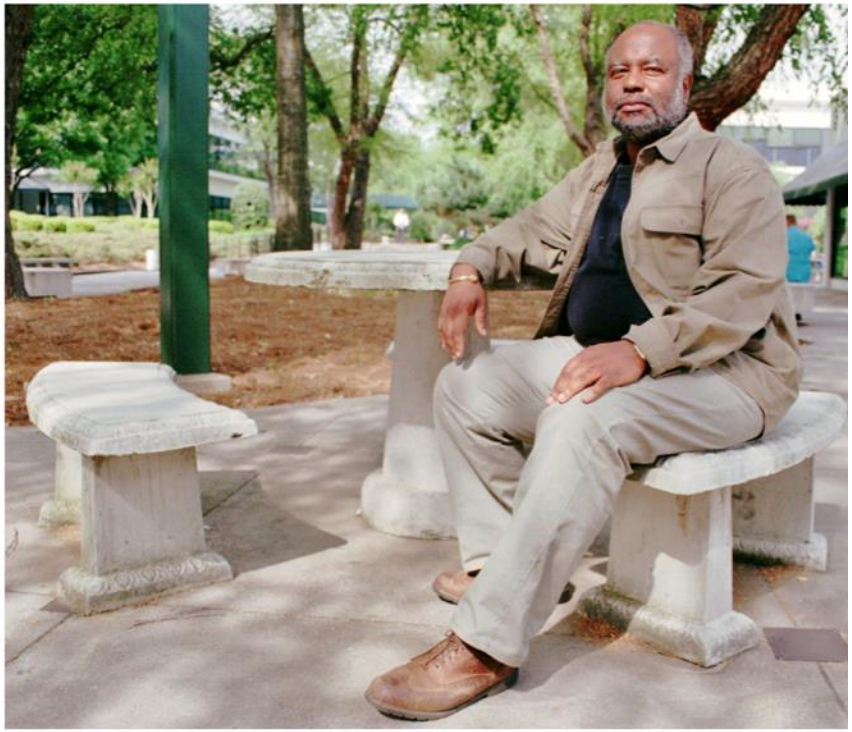
Bill Jenkins, Who Tried to Halt Tuskegee Syphilis Study, Dies at 73



Bill Jenkins in 1997. He denounced the government's unethical Tuskegee syphilis experiment aimed at black men, and spent his career working against injustice in health care. Alan Mothner/Associated Press

By Katharine Q. Seelye

Feb. 25, 2019

Dr. Irwin Schatz – rare Tuskegee Study critic (1932-2015)

Note only rare, but relatively un-talked about. Let's change that.

In 1964, Dr. Schatz wrote a 3-sentence letter to the editors of Archives of Internal Medicine in response to Rokewell et al's article "The Tuskegee Study of Untreated Syphilis: The 30th Year of Observation." Dr. Schatz wrote:

"I am utterly astounded by the fact that physicians allow patients with potentially fatal disease to remain untreated when effective therapy is available. I assume you feel that the information which is extracted form observation of this untreated group is worth their sacrifice. If this is the case, then I suggest the United States Public Health Service and those physicians associated with it in this study need to re-evaluate their moral judgments in this regard."

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IRB: A Necessary Good

By Mike Jacobs, Professor of Pharmaceutical Studies

Professor Jacobs stepped down from the medical intervention IRB after serving for 11 years as its chair and over 30 as a member. The Editor asked him to reflect on what his long (and selfless!) service had taught him.

Call it what you like, the Human Research Protection Program, the Ethics Committee, or the Institutional Review Board (IRB); it is the committee that apparently all clinical researchers across the country love to hate. It doesn't matter if it is medical or social-behavioral research. Any researcher who has had to deal with this committee will at one time or another face some level of frustration in having to deal with the IRB. But a well-functioning IRB is essential to a robust program for protecting the rights and welfare of human research participants, itself crucial to the good clinical research at the heart of Temple's mission.

An Urban Research Ethics

Individual → Community

How do we adapt IRB and ethical practice in a setting of extreme health inequities?

How can we (should we?) privilege social justice and equity over abstract individual autonomy?

Are we researching the things most of concern to the community?

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Thank you!

nora.jones@temple.edu

temple.edu/bioethics

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Summer 2019 - **Reproductive Justice** with Liz Kukura, JD, MA