The Changing Landscape of Human Subjects Research

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Agenda

• 50th Anniversary of Beecher paper
  – Who was Henry Beecher?
  – Why was his paper so important?
• What has happened in 50 years?
  – Changes in research/researchers
  – Changes in public perceptions
• Have we met Beecher’s criteria?
Henry Beecher
1904-1976

Named Chief of Anesthesia at Massachusetts General Hospital in 1936
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 examples to follow never had the risk satisfactorily understood.

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.
• 22 published studies with questionable ethics
• No names or citations given
• “These examples are not cited for the condemnation of individuals; they are recorded to call attention to a variety of ethical problems found in experimental medicine....it has become apparent that thoughtlessness and carelessness, not a willful disregard of the patient’s rights, account for most of the cases encountered.”
• Known effective treatment withheld
  – Complications of streptococcal infections
    • Example 1: 109 received placebo (not Pen)
    • Example 2: 500 denied Pen
  – Relapse rate of typhoid fever
    • Example 3: chloramphenicol withheld in 157/408 charity patients
Study of therapy
- Example 4
- TriA (triacetyloleandomycin)
- Study of hepatic toxicity in 50 patients
  - 13-39 yo; some with mental deficiency; some inmates at a children’s center
- Study stopped because of hepatotoxicity
  - 8 transferred to hospital and had liver bx
  - 4 had repeat challenge after LFT normalized
  - 1/4 had a 2nd challenge
• Physiologic studies
  – Example 5: chloramphenicol hemato-toxicity
    • 20 patients given 2 gm/day: 2/20 \(\rightarrow\) BM suppression
    • 21 patients given 6 gm/day: 18/21 \(\rightarrow\) BM suppression

  – Example 6: effect of thymectomy on skin grafts
    • CHD patients 3.5 mo – 18 yr
    • 7 controls and 11 total thymectomy
    • Full thickness skin grafts sutured to chest wall
• Highlightes the importance of ethical approach to research
  – Two most important components
    • Informed consent (although difficult/if not impossible, must try)
    • Presence of “an intelligent, informed, conscientious, compassionate, responsible investigator.”

• Making people aware of the problem would hopefully be sufficient

• Did not suggest regulatory oversight
"Among the experiments that may be tried on man, those that can only harm are forbidden, those that are innocent are permissible, and those that may do good are obligatory. It is immoral then, to make an experiment on man when it is dangerous to him, even though the result may be useful to others. It is essentially moral to make experiments on an animal, even though painful and dangerous, if they may be useful to man." (*)

http://www.claude-bernard.co.uk/page13.htm
Bernard's scientific discoveries were made through vivisection:

“The physiologist is no ordinary man. He is a learned man, a man possessed and absorbed by a scientific idea. He does not hear the animals' cries of pain. He is blind to the blood that flows. He sees nothing but his idea, and organisms which conceal from him the secrets he is resolved to discover.”

Bernard practiced vivisection, to the disgust of his wife and daughters who had returned at home to discover that he had vivisected their dog. The couple was officially separated in 1869 and his wife went on to actively campaign against the practice of vivisection.

http://www.claude-bernard.co.uk/page13.htm
The importance of:
- “direct benefit is likely”
- “full consent”

Otherwise “the sacred cord which blinds physician and patient snaps instantly.”

William Osler
1849-1919

“The father of modern medicine”

Walter Cannon proposed to the AMA in 1916: The need for definition of conditions necessary for acceptable human experimentation, including formal, prior patient consent.

Dr. Peabody feared that the concept of patient consent might detract from a virtuous physician’s responsibility to act unilaterally for the patient’s welfare. To him the character of the researcher was the principle issue and Peabody noted that, fortunately, those who pursued a career in scientific medicine were generally ‘among the more high-minded of the profession.’

† Apparently the AMA committee agreed: they failed to adopt Cannon’s resolution.”

Still More Meanderings in Medical History. M. Nevins. 2013
The Nuremberg Trials
The Nuremberg Code. 1949

- Ten principles
- No enforcement
- Inappropriately seen as specific to the perpetrators of the Nazi atrocities
  - ‘Them not us’ mentality
1. The voluntary consent of the human subject is absolutely essential.

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.
50 years ago

- Lyndon Johnson was President
- Beginning of Medicare
- Best Picture: Sound of Music
- Synthetic insulin produced in China
- FDA considered “the pill” safe for human use
- First episode of Star Trek
  - Man trap (creatures suck salt out of human bodies)
50 years later

- Barack Obama is President
- Medicare going bankrupt?
- Best Picture: Spotlight (not a happy musical)
- Synthetic biology boon
- Increased access to “the morning after pill”
- Star Trek Beyond
What has changed?

• Computers and the Intranet
• Explosion of science and technology
• Public involvement
Information Flow
The printing press and the internet

• Before the printing press
  – Information ‘owned’ by the few

• The printing press
  – Democratized access to books
  – No longer needed the sage for information

• The intranet
  – Perhaps the printing press on steroids
Increase in Information Flow
Being connected

• Computing capacity and the Internet
  – Sharing ideas and data
  – Storing and analyzing data
  – Expanding audiences
  – Democratization of data
  – Social media and ‘on-line’ communities
Scientific Advances
The Genetic Revolution

- Changed the study of disease and health
- Changed diagnostics
- Changed therapeutic decisions
- Basic component of precision medicine
- Became therapy: gene transfer
- Opened up new doors
  - CRISPR-CAS9 (Gene editing)
Imaging

- Plain radiographs
- CT scans
- MRIs
- Positron Emission Tomography (PET)
- Elastography
- Tactile Imaging
- Photoacoustic
- Thermography
- Functional near infrared spectroscopy
"Synthetic biology is an emerging area of research that can broadly be described as the design and construction of novel artificial biological pathways, organisms or devices, or the redesign of existing natural biological systems."

Source: UK Royal Society

Synthetic Biology: Mission possible: Rewriting the genetic code.

J. Bohannon
Science. 2016Aug 19;353(6301)
Biologists are transforming the proteinmaking instructions of *Escherichia coli*.

Biologists are close to reinventing the genetic code of life
‘Radically rewritten’ bacterial genome unveiled

The altered *Escherichia coli* represent the most extensive reengineering yet of an organism’s genetic code.

Erika Check Hayden

18 August 2016

Stem Cells and Cloning

• Dolly the sheep
Stem cells and cloning

- New ways to study human development
- New tools for studying disease
- Potentially new ‘replacement’ therapies
  - E.g.,
    - Stem cell derived beta cells for Diabetes
    - Dopaminergic cells for Parkinson’s disease
Increase in the ‘possibilities of science’

- Nanotechnology
- BIG DATA
- 3-D printing
- And more
Scientific Advances Advance new Ethical Questions

• Examples from
  – Genetics
    • The results
      – What do they mean?
    • Should the genome be edited?
  – Stem cells
    • Embryo questions
    • Chimeras
  – BIG Data and Social Media
    • Who can access what for what?
GENETIC MISDIAGNOSES AND THE POTENTIAL FOR HEALTH DISPARITIES

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BACKGROUND

For more than a decade, risk stratification for hypertrophic cardiomyopathy has been enhanced by targeted genetic testing. Using sequencing results, clinicians routinely assess the risk of sudden death. Yet, understanding the clinical utility of these results remains challenging.
Cautionary Tale Of Genetic Testing: You May Drop Dead! Oops, Never Mind

August 18, 2016
By Carey Goldberg
WBUR
Imprecise Medicine: Genetic Tests Lead To Misdiagnosis
August 17, 2016 by Larry Husten

–Some black Americans were wrongly told they had a high risk for hypertrophic cardiomyopathy.
Precision medicine offers the promise of an accurate assessment of individual risk for serious conditions like hypertrophic cardiomyopathy (HCM). But a new report published in the New England Journal of Medicine,” which the authors describe as “a cautionary tale of broad relevance to genetic diagnosis,” makes clear that the utility of genetic tests may be limited by the lack of diversity of people included in the underlying genetic databases used to assess risk.

No hunger. No pollution. No disease.

And the end of life as we know it.
The Genesis Engine.

Editing DNA is now as easy as cut and paste. Welcome to the post-natural world.

CRISPR-CAS 9
Stem cells and cloning
New Questions

• Embryonic stem cells
  – Embryo donation
    • Commodification of embryos
  – Embryo creation for research
  – Somatic cell nuclear transfer
    • Commodification of eggs
  – Creation of chimeras

• Induced pluripotent stem cells
  – ‘Routine’ tissue donation – adequate or not
BIG Data and Social Media
Tastes, ties, and time: A new social network dataset using Facebook.com

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ABSTRACT

Scholars have long recognized the potential of Internet-based communication technologies for improving network research—potential that, to date, remains largely underexploited. In the first half of this paper, we introduce a new public dataset based on manipulations and embellishments of a popular social network site, Facebook.com. We emphasize five distinctive features of this dataset and highlight its advantages and limitations vis-à-vis other kinds of network data. In the second half of this paper, we present descriptive findings from our first wave of data. Subgroups defined by gender, race/ethnicity, and socioeconomic status are characterized by distinct network behaviors, and students sharing social relationships as well as demographic traits tend to share a significant number of cultural preferences. These findings exemplify the scientific and pedagogical potential of this new network resource and provide a starting point for future analyses.
Taste, Ties and Time

- Three year study at an ‘anonymous’ NE university
- Facebook profiles and university residential forms downloaded to study how friendships and interests evolve.
- 1,700 profiles: gender, home state/country, major, political views, network of friends, romantic preferences and cultural tastes in books, music and movies.
- NOTE:
  - Students unaware of the research
  - Some had configured their profile to be visible only to Facebook friends.
  - Details in the profiles made it easy to determine that the “anonymous” university was, in fact, Harvard itself.
On May 6, a group of Danish researchers publicly released a dataset of nearly 70,000 users of the online dating site OkCupid, including usernames, age, gender, location, what kind of relationship (or sex) they’re interested in, personality traits, and answers to thousands of profiling questions used by the site.
OkCupid

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• When asked whether the researchers attempted to anonymize the dataset:
  – “No. Data is already public.”

https://www.wired.com/2016/05/okcupid-study-reveals-perils-big-data-science/
Social Network Research

- Researchers take online content without interacting with any individuals and not considering them human subjects.
- In aggregate data may be used to identify individuals.
- Researchers argue that the data is public.
Consider Other Changes in Research

• The science is simply more complex
• Everything with a ‘genetic angle’
• Mining large data sets and social networks
• Multi-site
• Multi-state if not multi-national
• Population studies
• Precision Medicine
• Learning HealthCare Systems
Learning Health Care Systems

• Bridging the gap between clinical care and research
• Learning from what we do
• Admitting that many healthcare decisions are based on no and/or flawed data
Question: which of two FDA approved and similar anti-hypertensive drugs is the better choice?

Both drugs used clinically, chosen by physician-preference. No data to suggest one is better.

THE STUDY:
- 50:50 randomization to each drug
- Randomization unit is at the primary care clinic level
  - Eg., if your doctor works in the 5th floor clinic – you will be randomized to Drug A.
  - Of note, your MD routinely prefers Drug B
Please vote:

☐ This is research and each patient should be asked for consent

☐ This is comparing two accepted therapies, consent is not required.
Please vote:

☐ This is research and each patient should be asked for consent

☐ This is comparing two accepted therapies, consent is not required.

* If your doctor is on the 5th floor....does your vote change?
The public has also changed

- Democratization of science and research
- I want my research results returned to me
  - I want the research results of my family members
- I want to be a partner in the research
  - PCOR (Patient Centered Outcomes Research)
  - Different roles:
    - Consultant, true partner in design, conduct and reporting
- Citizen Science – I can do my own research
Consider

- Melanie Swan, investment advisor developed smartphone app: drug efficacy related to certain genes
- Trial: effect of different types of vitamin B on homocysteine levels (connected to heart-disease risk)
- N=7: Two forms of vitamin B ($300 out of pocket)
- Design:
  - 2 wks of each vitamin source separated by 2 wk wash-out
  - Weekly homocysteine levels: results uploaded by subjects
- Results presented (by invitation) at Scripps Research Institute

Concerns

• Quality of data collection
  – Integrity of data collection
  – Potential bias (lack of blinding)
• Inadequate sample sizes
• Premature conclusions
• Generalizations from anecdotal data
• Falls outside oversight
• Potential medical risk – participation without medical supervision
Vitamin B study

• Ms. Swan suggested to other trial participants that they pursue a more professional tack—including getting approval from an institutional review board.

• No support – participants felt Ms. Swan was introducing too much bureaucracy.
WASHINGTON — The Food and Drug Administration approved the first drug to treat patients with the most common childhood form of muscular dystrophy.
Controversy at FDA: Dr. Ellis Unger

“By allowing the marketing of an ineffective drug, essentially a scientifically elegant placebo, thousands of patients and their families would be given false hope in exchange for hardship and risk,” he wrote in a July 18 dispute report. “I argue that this would be unethical and counterproductive. There could also be significant and unjustified financial costs — if not to patients, to society.”

He added that approval “would send the signal that political pressure and even intimidation — not science — guide FDA decisions... A standard this low would undercut FDA’s ability to ensure that drugs that are approved are effective; it would call into question much of what we do. Lowering the bar to this level would be tantamount to rolling back the 1962 Kefauver-Harris Drug Amendments to the Federal Food, Drug and Cosmetic (FD&C) Act, which have served Americans well for some 54 years.”

Distrust in Science

Multi-factorial

• Lack of understanding re: the process of research
• Low health and science literacy
• Politicization of science and research
Distrust in Science

• 2012 NSF survey
  – 25% think that the sun orbits the earth
• 2014 AP-GFK survey
  – 40% doubt evolution
  – >50% question the Big Bang
  – 40% do not believe pollution \(\rightarrow\) climate change
  – 15% do not believe in efficacy of vaccines

WHY THE REJECTION OF SCIENTIFIC THEORIES?
"Anything that doesn't fit into the political appointees' ideological, theological or political agenda is often ignored, marginalized or simply buried," Carmona* testified.

* Former Surgeon General
Politicization of Science

• SCAM: Scientific Certainty Argumentation Method
  – Argue for full scientific certainty – without certainty it cannot be relied upon as fact

"Doubt is our product since it is the best means of competing with the 'body of fact' that exists in the mind of the general public. It is also the means of establishing a controversy."

'THE REPUBLICAN WAR ON SCIENCE,' BY CHRIS MOONEY', Political Science, Review by JOHN HORGAN, Published: December 18 2005

Original "Doubt is our product..." memo". University of California, San Francisco. 21 August 1969. Retrieved 3 October 2012
Have we met Beecher’s Criteria?

• “An intelligent, informed, conscientious, compassionate, responsible investigator.”
• Informed consent
• No call for more regulations
Explosion of regulations

• True Federal Regulations
  – Common Rule
  – HIPAA
  – CT.gov

• ‘Regulations’ associated with grant award
  – Stem cell guidelines
  – Data sharing – dbGaP, many Institute-specific
  – Conflict of interest mandates

• Mandates from outside
  – International Council of Medical Journal Editors
Have we fixed informed consent?

• No
• May be more broken than before
  – Not enough focus on process
  – Forms are
    • Longer
    • More legalistic
• But – we still try
Are researchers more “intelligent, informed, conscientious, compassionate, responsible”

• Uncertain
• Researchers must wear too many hats
• Too often spend time being the coordinator
• The regulatory burden is exhausting
We still have a long way to go