

History of Clinical Research and Choosing a Research Question

John I. Gallin, M.D.
Director, NIH Clinical Center



October 27, 2008



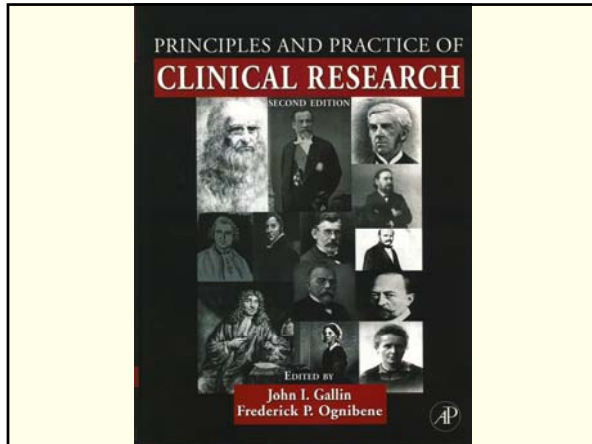
Outline

- Course Overview
- History of Clinical Research
- Picking a Research Project

2008-2009 IPPCR Enrollment Data*

# enrolled at the NIH:	346
# enrolled at 19 remote locations:	442
Total enrollees (as of 10/24/08):	788

*10/24/08



Chinese Translation of Second Edition

Beijing, China
November 10-15, 2008

IPPCR Administrative Comments

Video Archive

- video of each lecture will be posted within 48hrs following presentation

Questions

- will be taken by the faculty at the end of each presentation

Exam/Certificates

- at completion of course, exam posted on course website
- certificates - final exam grade of 75% or higher

Questions regarding course: (301) 496-9425

Introduction to the Principles & Practice of Clinical Research	
Module I -	Statistical Methods
Module II -	Ethical Issues and Regulation of Human Subjects Research
Module III -	Monitoring Patient-Oriented Research and Regulatory Issues
Module IV -	Preparing and Funding a Clinical Research Study

Introduction to the Principles & Practice of Clinical Research	
Module I - Statistical Methods	
<ul style="list-style-type: none"> • Choosing a research question • Study development • Clinical trials design • Measurement • Analyzing and presenting data <ul style="list-style-type: none"> - Biostatistics in clinical trials - Meta analysis - Economic analysis 	

Introduction to the Principles & Practice of Clinical Research	
Module II - Ethical Issues and Regulation of Human Subjects Research	
<ul style="list-style-type: none"> • Ethical Principles in Clinical Research • Legal Issues • Researching an Ethics Question • Scientific Conduct • Mock IRBs 	

Introduction to the Principles & Practice of Clinical Research

Module III - Monitoring Patient-Oriented Research and Regulatory Issues

- Data management in clinical trials
- Quality control in clinical trials
- Relations with the FDA
- Product development
- Data and safety monitoring boards
- The clinical researcher and the media

Introduction to the Principles & Practice of Clinical Research

Module IV - Preparing and Funding a Clinical Research Study

- Evaluation of a protocol budget
- How to succeed in NIH peer-review grants process
- ProtoType and protocol mechanics
- Inclusion of women and minorities in clinical trials
- Technology transfer
- Concepts in the management of projects
- Design of case report forms

Introduction to the Principles & Practice of Clinical Research

Special Lectures:

Human Genome Project and Clinical Research
Christopher Austin, M.D., NHGRI

Clinical Research from a Patient's Perspective
Susan Butler, B.A., M.A.,
Exec Dir, DC Cancer Consortium

Outline

- Course Overview
- History of Clinical Research

Definition of Clinical Research

- Patient-Oriented Research
Research conducted with human subjects (or on material of human origin such as tissues, specimens and cognitive phenomena) for which an investigator (or colleague) directly interacts with human subjects...includes:
 - Development of new technologies
 - Mechanisms of human disease
 - Therapeutic interventions
 - Clinical Trials
- Epidemiologic and Behavioral Studies
- Outcomes Research and Health Services Research

*From NIH Director's Panel on Clinical Research, 1996

History of Clinical Trials



"Then Daniel said to the steward...

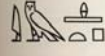
Test your servants for ten days; let us be given vegetables to eat and water to drink. Then let our appearance and the appearance of the youths who eat the king's rich food be observed by you, and according to what you see, deal with your servants.

So he hearkened to them in this matter; and tested them for ten days.

At the end of ten days it was seen that they were better in appearance and fatter in flesh than all the youths who ate the king's rich food. So the steward took away their rich food and the wine they were to drink, and gave them vegetables."

Daniel 1:11 – 16
c. 530 BC

Imhotep in Ancient Egypt c2850 B.C.



- Imhotep was a known scribe, chief lector, priest, architect, astronomer and magician (medicine and magic were used together)
- Diagnosed and treated over 200 diseases, performed surgery and practiced some dentistry
- Extracted medicine from plants and knew the position and function of the vital organs and circulation of the blood system



Important Contributions of Chinese Medicine



Sampling of Chinese texts available at National Library of Medicine (>2,000 volumes of Chinese medical classics)


Ancient Chinese Medicine

2737 B.C.
Emperor Shen Nung experimented with poisons and classified medical plants.

He is reputed to have eaten 365 medicinal plants over the course of his life, turned green and died.



Shen Nung (c. 2800 B.C.)



李時珍
Li Shih-chen
1518 -1593

Wrote Pen ts'ao kang mu, general catalog of herbs, which summarizes herbal medicine discoveries through the 16th century



Pulse chart from a 1693 edition of Secrets of the Pulse, originally written by Pien Ch'iao in the 6th or 5th century BC

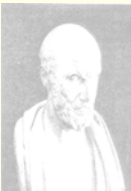
Insight from the Bedside

Hippocrates

- Greek physician born about 460 BC; died about 370 BC
- Hippocratic method

- Observation paramount: "A great part of the Art is to be able to observe."

- Description of pulmonary edema: "Water accumulates; the patient has fever and cough; the respiration is fast; the feet become edematous; the nails appear curved and the patient suffers as if he has pus inside, only less severe and more protracted. One can recognize that it is not pus but water...If you put your ear against the chest you can hear it seethe inside like sour wine."



Hippocrates' Accomplishments

- Dissociated medicine from theology and philosophy
- Established science of medicine
- Provided physicians the highest moral inspiration they have



Galen



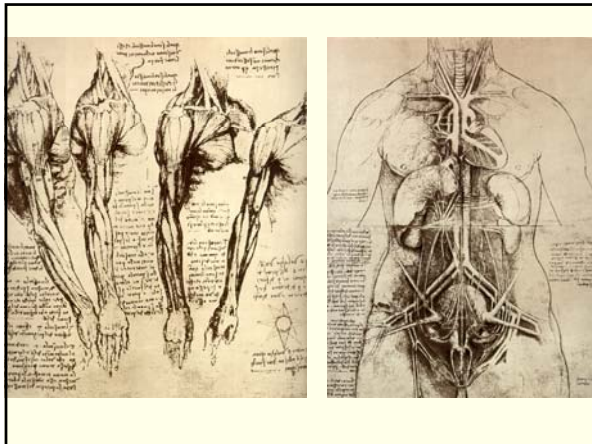
- Greek physician lived 6 centuries after Hippocrates (A.D. 129- ca. 216)
- Crystallized all the best work of the Greek medical schools
- Blood consists of 4 humors: black bile, yellow bile, phlegm, and blood.
- Remained an unchallenged authority for >1,000 years

Leonardo daVinci



(1453-1519)

*Born near the town of Vinci
in Florence, Italy*





**Antonj
Van Leeuwenhoek
(1632-1723)**
Born in Delft, Netherlands

- Invented microscope
- Described protozoa, bacteria, striated muscle, crystalline lens, RBCs, sperm

Hematology

- **William Harvey (1578 - 1657)**
Defined the circulatory system
- **Sir Christopher Wren (1632 - 1723)**
First intravenous injections (in dogs)
- **Richard Lower and Edmund King (1667)**
First blood transfusion in man

Sir Christopher Wren (1632-1723)

Born in Wiltshire, England

- Anatomical drawings of the brain
- First IV needle (1656) used for first blood transfusions (1667)
- Instrument to measure angles
- Instruments for surveying
- Machines to lift water
- Military devices for defending cities
- Significant contributions to architecture



A full human brain, drawn by Christopher Wren and included in *The Anatomy of the Brain and Nerves*, Feindel, W., ed., Montreal: 1965. From Zimmer, C. *Soul Made Flesh*, NY, 2004, p.2

History of Clinical Trials

James Lind - 1753

- Scurvy was a major health problem for the British Navy in the 1700's.
- William Harvey had recommended lemons to treat scurvy, but had argued that the therapeutic effect was a result of the acid in the fruit.
- James Lind, a naval surgeon, conducted a clinical trial in 1747 to assess the utility of three therapies for scurvy.



History of Clinical Trials

James Lind - Experimental Design

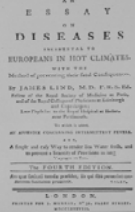
- 12 sailors with classical scurvy, divided into six groups of two each; all given identical diets, the various groups supplemented with:
 - vinegar
 - diluted sulfuric acid
 - cider
 - sea water
 - nutmeg, garlic, and horseradish mixture
 - two oranges and one lemon, daily



History of Clinical Trials

James Lind - Experimental Design (cont'd)

Treatment Arm	Cured	P Value*
Sulfuric Acid	0/2	NS
Vinegar	0/2	NS
Sea Water	0/2	NS
Cider	0/2	NS
Physician's Remedy	0/2	NS
Citrus Fruit	2/2	NS!!!!



*Compared to patients in the the other 5 arms of the trial; no placebo group

Story of Smallpox



Girl with smallpox

- (1) Al-Razi (Rhazes) – 1st description of smallpox c 900 AD (Persian)
- (2) In the 11th century, protective measures for smallpox included:
 - Putting scabs from smallpox pustules in the nostrils
 - Wearing the clothing of someone who had the disease
 - Ingesting powdered fleas from infected cows (may have perceived relationship of cowpox to smallpox)

Small Pox in American History

- **Biological warfare** - used by Lord Jeffrey Amherst in 1763 during Pontiac's Rebellion, a conflict between British and Native Americans following the French and Indian War
- **George Washington and the Continental Army**
 - 1775 quarantine
 - use of immune troops
 - variolation 1776 approved by Continental Congress July 3, 1776



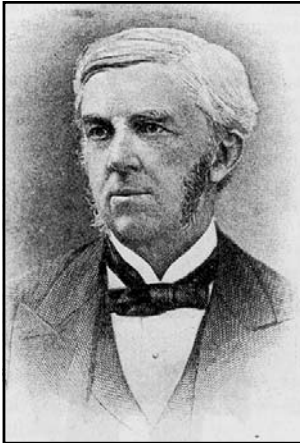
Edward Jenner
(1749-1823)
Born in Gloucestershire, England

Illustration of Edward Jenner vaccinating James Phipps
Artist unknown. Undated illustration

Washing Hands

Wound Management

- "...if water was used for irrigation, it had to be very pure or boiled, and the hands and nails of the operator were to be cleansed." Hippocrates, 460 BC – 370 BC
- Spreading of disease by water and soil
Ibn Sina (Avicenna), Persian, c. 900 AD



**Oliver Wendell
Holmes
(1809 - 1894)**

*Born in Cambridge, Massachusetts,
USA*

Advocated hand-
washing in obstetrics
(no data)



**Ignaz P. Semmelweis
(1818-1865)**

Born in Budapest, Hungary

History of Clinical Trials

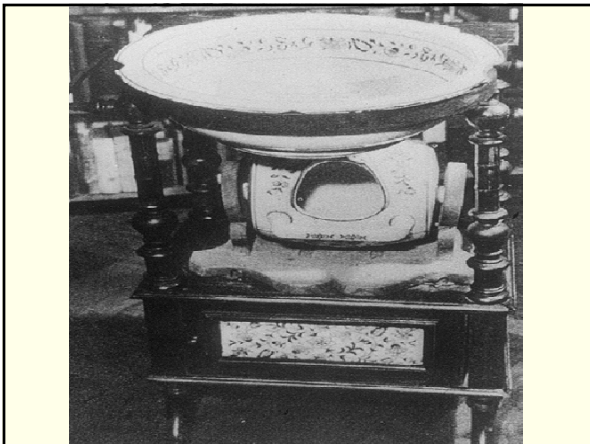
Semmelweis, 1848 - 1863

- Semmelweis studied puerperal sepsis in Vienna over the protestations of his chief; he noted that the sepsis rate was three times higher in Division 1 than in Division 2; Divisions identical except medical students taught in Division 1, Midwives in Division 2.
- Death of a friend following infection of an autopsy-related wound led to his primary hypothesis that the infection was transported from the autopsy room to uninfected patients by the students.

History of Clinical Trials

Semmelweis - Experimental Design

- Students to wash hands in chlorinated lime solution.
- Mortality rate dropped from 18.3% to 1.3% per year; in some months in 1848 the mortality rate was 0%.
- His chief did not believe his data; one year later he was fired.



History of Clinical Trials

Semmelweis, 1848 - 1863 (continued)

- He returned to Budapest, Hungary where he was placed in charge of an obstetrical unit plagued with an epidemic of puerperal sepsis. He repeated his earlier experiment and again the mortality rate declined precipitously (mortality remained less than 1% during his six-year tenure vs. 10 to 15% in Vienna and Prague).
- His major paper, "The etiology, understanding, and prevention of puerperal sepsis" was rejected by the Vienna Medical Journal and he ultimately had to pay to get his work published.

Story of Antisepsis

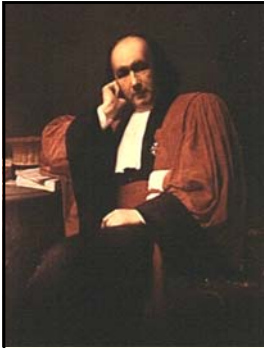


Joseph Lister
(1827-1912)
Born in Essex, England



Lister's careful trials with antiseptics were the beginning of the end of post-op sepsis. The carbolic sprays he advocated (shown in this 1882 engraving) were initially messy and unpleasant.

Physiology/Pathology



**Claude Bernard
(1813-1878)**

*Born in the village of
Saint-Julien, France*

- Pancreas in digestion
- Glycogenic function of liver
- Vaso-motor system (vaso-dilator and vasoconstrictor nerves)
- Curare



**Rudolph Virchow
(1821-1902)**

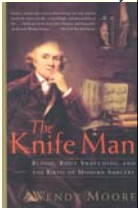
Born in Świdwin, Poland

- Leukemia
- *Omnis cellula e cellula*” every cell originates from another cell (1858)
- Pulmonary emboli (thromobosis and embolism)


Surgery

John Hunter (1728 – 1793)
The Man who Changed the Nature of Surgery

- Scottish anatomist and surgeon
- Purchased services of grave robbers
- To determine the nature of venereal disease, inoculated himself with infected material from a sufferer (gave him syphilis which over the years severely damaged his heart)




Immunology



- Introduced Petri dish, use of blood agar pour plates to culture bacteria
- First to describe anthrax infection (1872)
- Cultured *M. tuberculosis* and developed TB skin test
- Described water-borne epidemics
- Koch's postulates
- In 1905 he was awarded the Nobel Prize for Physiology or Medicine "for his investigations and discoveries in relation to tuberculosis"

Robert Koch
(1843-1910)
Born in Hanover, Germany



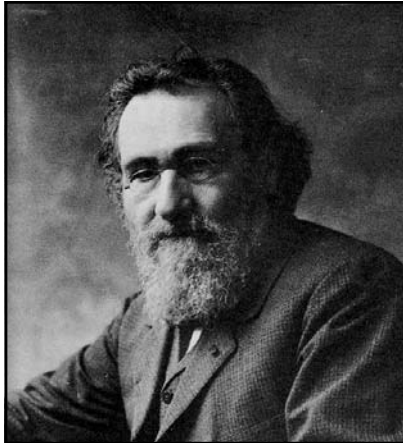
Anthrax bacillus from a paper published by Koch in 1877

The complex block contains a portrait of Robert Koch on the left, a list of his contributions in the center, and a micrograph of an anthrax bacillus on the right. Below the micrograph is a caption identifying it as an anthrax bacillus from a paper published by Koch in 1877.



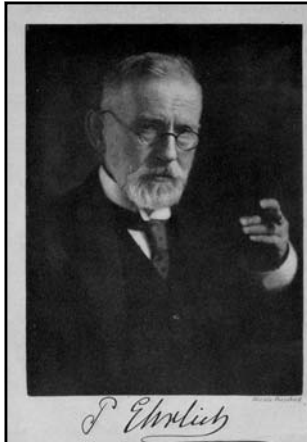
Louis Pasteur
(1822-1895)
Born in Dole, France

- Germ basis of fermentation, germ theory of infectious diseases
- Discovered staphylococci as cause of boils
- Described *Streptococcus pyogenes* as cause of puerperal sepsis
- Vaccine for anthrax
- Vaccine for rabies



Elie Metchnikoff
(1845-1916)
Born in Kharkiv, Ukraine

- Phagocytosis in host defense
- Cellular elements of immunity
- In 1908 he shared the Nobel Prize for Physiology or Medicine with Paul Ehrlich in recognition of their work on immunity



Paul Ehrlich
(1854-1915)
Born in Strehlen, Poland

- Described eosinophils
- Described complement pathway and humoral immunity
- Arsenic for treatment of syphilis



**Emil von Behring
(1854-1917)**

*Born in
Deutsch-Eylau, Germany*

- Discovered antibodies (diphtheria antitoxin)
- First use of passive immunization
- In 1901 he was awarded the Nobel Prize for Physiology or Medicine "for his work on serum therapy, especially its application against diphtheria..."

**End of 19th Century:
Women in
Clinical Research**



**Florence Nightingale
(1820-1910)**

Born in Florence, Italy

- Famous work in nursing
- Accomplished mathematician
- Math expertise dramatized needless deaths caused by unsanitary conditions in hospitals and need for reform
- Major contributions during Crimean War in promoting sanitary conditions for soldiers



Marie Curie (1867 - 1934)

Born in Warsaw, Poland

Accomplishments:

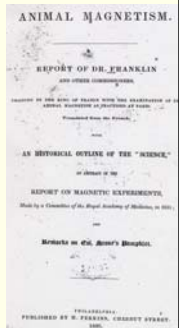
- Discovery of radium
- Realization that radioactivity is an intrinsic atomic property of matter
- Pioneered a mobile x-ray unit for the French army in WWI
- Founded a radiological school for nurses
- With her husband, she was awarded half of the Nobel Prize for Physics in 1903, for their study into the spontaneous radiation discovered by Becquerel (awarded the other half of the Prize)
- In 1911 she received a second Nobel Prize in Chemistry, in recognition of her work in radioactivity.
- Daughter, Irene Joliot-Curie, was awarded the Nobel Prize for chemistry in 1935 jointly with her husband for their discovery of artificial radioactivity

Blind Studies and Placebo Effect

Benjamin Franklin

In 1784:

- King Louis XVI of France appointed Franklin to a Royal Commission
- Purpose: judge legitimacy of animal magnetism as a medical cure
- Single-blind, placebo-controlled trial used by Commission
- Placebo effect noted



Borrowed Ideas: Blinding

- **Torald Sollmann** suggested a placebo control and blinded observer as a solution to investigator bias as early as 1930
- **Blindfold Tests:** widely used by advertisers and consumer groups in the 1930s and 1940s



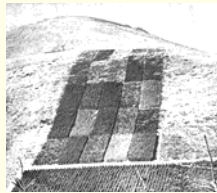
Testing gelatins at Consumers Union, 1945

Statistics – Randomization

Borrowed Ideas: Randomization



Sir Ronald Aylmer Fisher (1890-1962)

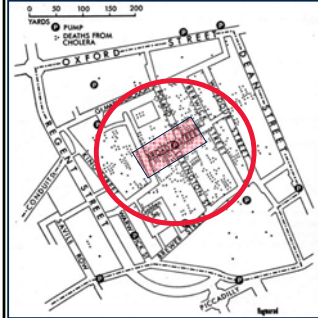



Rothamsted Agricultural Station

- Introduced application of statistics to experimental design
- Farming and plant fertility: concept of randomization and analysis of variance

Epidemiology

John Snow (1813-1858)
Born in York, England



...gist
for work in outbreak in

- Spot map illustrates cases of cholera centered around pump
- Statistics illustrate connection between quality of water source and cholera cases
- Study was major event in public health history

History of Informed Consent

1767: Slater v. Baker & Stapleton
“...it is reasonable that a patient should be told what is about to be done to him.”

1898: Osler, William
“To deliberately inject a poison of known high degree of virulency into a human being, unless you obtain a man’s sanction...is criminal.”
(In response to an oral presentation by Giuseppe Sanarelli on discovery of the etiologic agent of yellow fever)

Informed Consent at the NIH Clinical Center

Minutes of Meeting
MEDICAL BOARD
Tuesday, June 9, 1953, 3:00 p.m.
Chairman: Dr. Luther Terry

Report submitted to Medical Board by Clinical Research Committee addressed "how to provide each patient with a reasonable understanding of his role in a study project and the means for obtaining evidence of such understanding and consent."

Medical Research Ethics

History of Medical Research Ethics

1947	Nuremberg Code International code of Ethics
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Post World War II Nuremberg Trials 1946-1947

German physicians conducted pseudoscientific medical experiments on thousands of concentration camp prisoners without their consent.



Most prisoners died or were permanently crippled as a result.

History of Medical Research Ethics

1947	Nuremberg Code International code of Ethics
1953	NIH CC Medical Board: Call for informed consent and protocol review

History of Medical Research Ethics

1947	Nuremberg Code International code of Ethics
1953	NIH CC Medical Board: Call for informed consent and protocol review
1963	FDA requires Informed Consent
1974	Institutional Review Board procedures established <i>(U.S. administrative law)</i>
1979	<p>Belmont Report <i>(issued by U.S. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research)</i></p> <p>Principle of Respect: Recognizes autonomy of humans and requires clear informed consent.</p> <p>Principle of Beneficence: Research must be shown to be beneficial and reflect the Hippocratic idea of do no harm.</p> <p>Principle of Justice: The benefits to some must be balanced against the risks to subjects</p>

Outline

- Course Overview
- History of Clinical Research
- Picking a Research Project

The Ten Commandments for Picking a Research Project

- I. Anticipate the Results Before Doing the First Study.
- II. Pick an Area on the Basis of the Interest of the Outcome.
- III. Look for an Underoccupied Niche that has Potential.
- IV. Go to Talks and Read Papers outside Your Area of Interest.

From C. Ronald Kahn, M.D., NEJM, 330: 1530, 1994.

The Ten Commandments for Picking a Research Project

- V. Build on a Theme.
- VI. Find a Balance Between Low-Risk and High-Risk Projects, but Always Include a High-Risk, High Interest Project in Your Portfolio.
- VII. Be Prepared to Pursue a Project to any Depth Necessary.

From C. Ronald Kahn, M.D., NEJM, 330: 1530, 1994.

The Ten Commandments for Picking a Research Project

- VIII. Differentiate Yourself from Your Mentor.
- IX. Do Not Assume that Outstanding, or Even Good Clinical Research is Easier Than Outstanding Basic Research.
- X. Focus, Focus, Focus.

From C. Ronald Kahn, M.D., NEJM, 330: 1530, 1994.

Conclusion

- (1) The history of clinical research can be traced to all cultures.
- (2) The future requires information exchange to maximize progress in health care.
- (3) "What's past is prologue"
(William Shakespeare, The Tempest)
