

Introduction to the Principles & Practice of Clinical Research

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LECTURE OUTLINE

- I. Course Overview
- II. Historical Overview
- III. Picking a Research Question

2005-2006 IPPCR Student Enrollment Data

of students enrolled at the NIH: 317

of students enrolled at remote locations: 334

Total students enrolled (as of 10/13/05): 651

IPPCR Participating Off-Campus Sites

- Children's National Medical Center (Washington, DC)
- Harbor UCLA Medical Center (Torrance, CA)
- Howard University College of Medicine (Washington, DC)
- Morehouse School of Medicine (Atlanta, GA)
- National Institute on Aging (Baltimore, MD)
- National Institute of Environmental Health Sciences (NC)
- State University of New York (Syracuse, NY)
- Universidad Autónoma de Nuevo León (Monterrey, Mexico)
- University of California at Los Angeles (Los Angeles, CA)
- University of Puerto Rico (San Juan, PR)
- U.S. Naval Medical Research Center Detachment (Lima, Peru)
- Walter Reed Army Medical Center (Washington, DC)

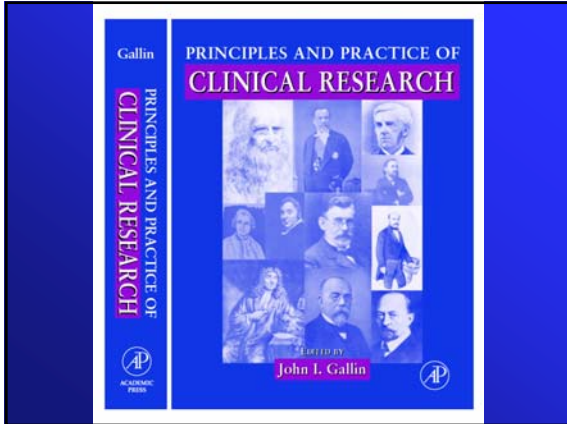
IPPCR Archived Content

- National Cancer Center in Singapore
- National Institute of Hygiene in Rabat, Morocco
- Seoul National University College of Medicine in Korea
- University of Bergen in Norway
- University of Maryland School of Nursing
- University of Southern California School of Dentistry

IPPCR Administrative Comments

Course Textbook

- Principles and Practice of Clinical Research
- Available: FAES Bookstore, Bldg 10, Rm B1L101
- Handouts will be posted on course website
<http://www.cc.nih.gov/researchers/training/ippcr.shtml>
- Lecture evaluations will be conducted via e-mail



IPPCR Administrative Comments

Video Archive

- video of each lecture will be posted within one week 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 for final exam grade of 75% or higher

Questions regarding course: (301) 496-9425

Continuing Medical Education

To comply with the Accreditation Council for Continuing Medical Education (ACCME) guidelines:

All speakers are required to disclose any financial interest or relationship that they or their spouse/partner may have with the manufacturer or provider of any commercial product, service, technology, or program as it relates to their presentation.

A summary of this information is available at the registration table outside of Lipsett or through your event liaison at off-site locations.

Introduction to the Principles & Practice of Clinical Research

Module I - Epidemiologic 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 - Epidemiologic Methods

- Choosing a research question
- Study development
- Clinical trials design
- Measurement
- Analyzing and presenting data
 - 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

- 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 the NIH peer-review process for grants
- 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:

Unanticipated Risk in Clinical Research

Human Genome Project and Clinical Research

Clinical Research from a Patient's Perspective

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. This area of research 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

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I. Course Overview

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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 your 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

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



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.)

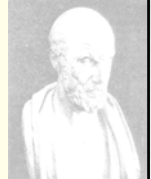


Doctor examining
patient by feeling
pulse, perhaps the
most important
feature of ancient
Chinese medical
diagnosis

Insight from the Bedside

Hippocrates

- 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."



Insight from the Bedside

Hippocrates on 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."

Galen



GALENI IN LIBRVM HIPPOCRATIS

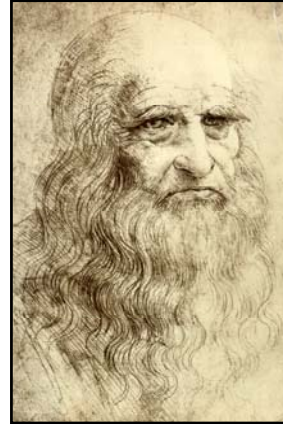
Shows the surgical procedures
described by Galen on the head, eye,
leg, mouth, bladder, and genitals
-still practiced in the 16th century

- Lived 6 centuries after Hippocrates (130 - 200 A.D.)
- Crystallized all the best work of the Greek medical schools
- 4 humors defined: blood, yellow bile, phlegm, black bile
- Remained an unchallenged authority for >1,000 years

Ancient Hindus Excelled in Surgery

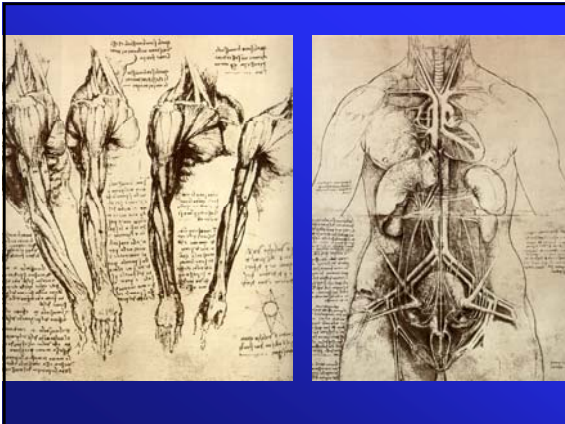
Susruta: 380 – 450, Father of Indian Surgery

- Resided at the court of the Gupta kings during golden age of Hindu culture
- Wrote medical texts about surgery
- Advocated the sterilization of wounds



Leonardo da Vinci

1453-1519



Antonj
Van Leeuwenhoek
(1632-1723)

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

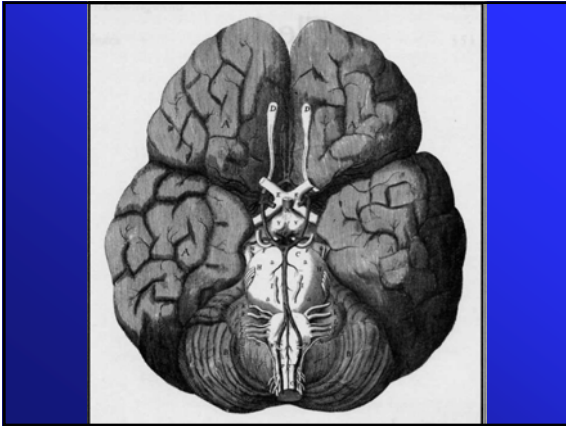


Leeuwenhoek and his microscope.

(From Dubos, R. 1962. *The Unseen World*. Rockefeller University Press, New York.)

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



Chelsea Royal Hospital

Founded by King Charles II
completed in 1692
Designed by Sir Christopher Wren



Statue of King Charles II is 7ft 6in and stands in the central court of the Hospital

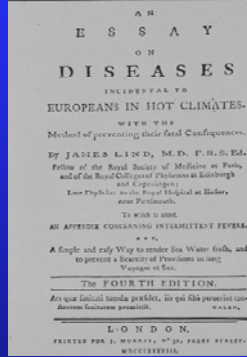
Wren's career discoveries:

- Anatomical drawings of the brain
- Developed a blood transfusion method, an instrument to measure angles, instruments for surveying, machines to lift water, military devices for defending cities

•Significant contributions to architecture



James Lind (1716 - 1794)



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 five arms of the trial; no placebo group



Small Pox




Girl with smallpox

In the 11th century, protective measures for smallpox included:

- (1) Putting scabs from smallpox pustules in the nostrils
- (2) Wearing the clothing of someone who had the disease
- (3) Ingesting powdered fleas from infected cows (may have perceived relationship of cowpox to smallpox)

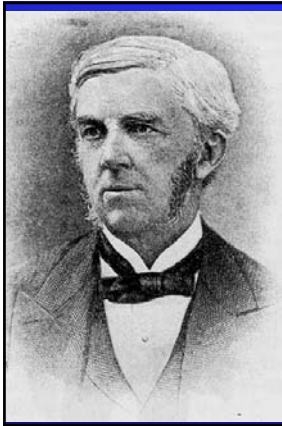
Small Pox in American History

- Biological warfare-Lord Jeffrey Amherst and 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)
First Inoculation 1778

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



Oliver Wendell Holmes
(1809 - 1894)

Advocated hand-washing in obstetrics (no data)



Ignaz P. Semmelweis
(1818-1865)

History of Clinical Trials

Semmelweis, 1848 – 1863

- Semmelweis studied puerperal sepsis (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.

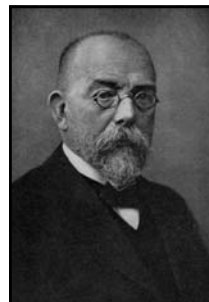
Story of Antisepsis



Joseph Lister
(1827-1912)

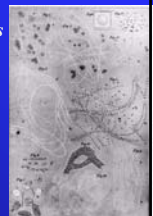


Lister's careful trials with antiseptics were the beginning of the end of post-op sepsis. The carbolic sprays he advocated (shown in this 1882 engraving) were initially messy and unpleasant



Robert Koch
(1843-1910)

- 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



Anthrax bacillus from a paper published by Koch in 1877



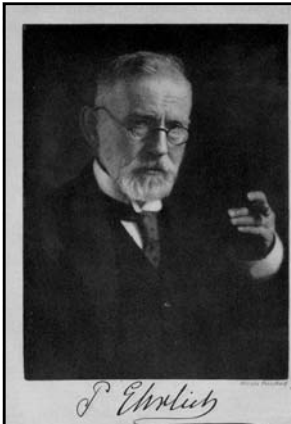
Louis Pasteur (1822-1895)

- 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



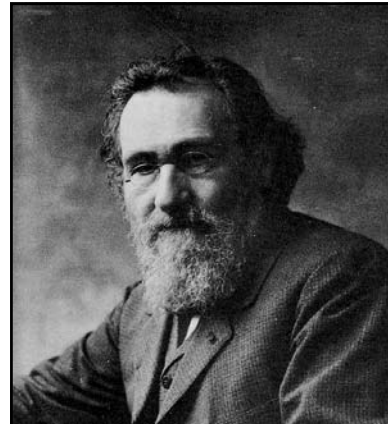
Emil von Behring (1854-1917)

- Discovered antibodies (diphtheria antitoxin)
- First use of passive immunization



Paul Ehrlich (1854-1915)

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

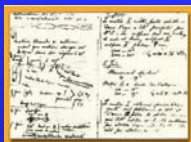


Elie Metchnikoff (1845-1916)

- Phagocytosis in host defense
- Cellular elements of immunity



Marie Curie (1867 - 1934)



A page from the Curies' lab notebook of 1898. On the left, in Pierre's hand, sublimation procedure. On the right, in Marie's hand, chemical processing.

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

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)

Standards for Clinical Research Within the NIH Intramural Program



- Clinical Informatics, Data Management and Protocol Tracking
- Biostatistics Support
- Quality Assurance and Quality Control
- Protocol Review
- Human Resources and Physical Plant
- Training and Education

LECTURE OUTLINE

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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.