

History of Clinical Research

A Merging of Diverse Cultures

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Happy 20 Year Anniversary, IPCCR!!!!

IPPCR Administrative Pointers

Course Textbook

Principles and Practice of Clinical Research,

Third Edition

Available on-line or at NIH FAES Bookstore new location, Bldg 10, 1st floor, near Masur Auditorium

Handouts posted on course website

Lecture evaluations link will appear on the course website following the lecture

IPPCR Administrative Comments

Video Archive

Video of each lecture will be posted within 48hrs following presentation

Questions

Questions can be submitted to course coordinator, Mr. Daniel McAnally at [daniel.mcanally@nih.gov](mailto:daniel.mcanally@nih.gov)

Exam Certificates

At completion of course, examination will be posted on the course website

Certificates final exam grade of 75% or higher

Questions regarding course 301 496-9425

Discussion Board Feature

Introduction to the Principles & Practice of Clinical Research

Module I Study Design, Measurement, and Statistics

Choosing a Research Question and Implications for Efficient Clinical Trials

Overview of Clinical Study Design

Design of Epidemiologic Studies

Clinical Research from the Patient's Perspective

Study Participant Selection

Issues in Randomization

Overview of Hypothesis Testing

Sample Size and Power

Conceptual Approach to Survival Analysis

Measures

Quality of Life

Designing and Testing Questionnaires

Using Large Datasets for Population-Based Health Research

Secondary Data/Meta-Analysis

## Module II – Ethical, Legal, Monitoring, and Regulatory Considerations

Legal Issues in Clinical Research

Ethical Principles in Clinical Research

Data and Safety Monitoring Committees

Institutional Review Boards

Mock IRB

Research with Vulnerable Participants

## Module III – Preparing and Implementing Clinical Studies

Developing Protocols and Manuals of Operating Procedures

Evaluation of a Protocol Budget

Scientific Conduct

Inclusion of Women and Minorities in Clinical Trials

Pharmaceutical Development: Management of Projects

NIH Peer Review Process

FDA Product Regulation

Data Management and Case Report Form Development in Clinical Trails

Electronic Health Records and Clinical Data Interchange Standards

Quality Management in Clinical Research

Clinical Trial Registration and Results Reporting

Information Resources for Clinical Research



## Module IV – Addition Study Designs and Miscellaneous Topics

Technology Transfer

Dissemination and Implementation Research

Health Disparities Research

Health Disparities and Community-Based Participatory Research

The Clinical Researcher and the Media

## 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

Sir Isaac Newton

(1642-1727)

Born in Lincolnshire, England

If I have seen a little further, it is by standing on the shoulders of giants

## Imhotep in Ancient Egypt

c. 2850 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.

## Malaria, an Ancient Disease

China: symptoms described in ancient medical writings

2700 BC, several characteristic symptoms of malaria described in the Nei Ching

Qinghao plant (*Artemisia annua*): was described in the medical treatise, 52 Remedies, found in the Mawangdui Tomb

In 340 AD, the antifever properties of Qinghao first described by Ge Hong of the East  
Yin Dynasty

Active ingredient of Qinghao, known as artemisinin, isolated by Chinese scientist, Professor Tu Youyou in 1971 (Nobel Prize 2015)

Sushruta: Father of Indian Surgery

Resided at the court of the Gupta kings

~600 B.C. (unclear)

Wrote medical texts about surgery

most famous: Sushruta Samhita, an encyclopedia of medical learning

Counted 300 bones in human body

Advocated sterilization of wounds

Discussed options for instruments; hand: best instrument



## 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."

Insight from the Bedside

Hippocrates

Greek physician born about 460 B.C.;

died about 370 B.C.

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

## 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.”

Iranian Medicine: Al Rhazi and Ibn Sina

Al Rhazi (865-925):

Discovered use of alcohol and mercurial compounds as antiseptics

Contributions to medicine, alchemy, and philosophy

1st treatise on pediatrics

recorded in over 184 books and articles

Ibn Sina - Avicenna (973-1037):

Leader in pharmacy, philosophy, medicine and pharmacology

Wrote the Canon of Medicine, main European medical textbook of 14th – 16th c.

Text contains 1st known treatise on clinical trials – provided foundation for systematic approach to drug testing

Ibn Sina (Avicenna)

“The Canon of Medicine”

7 conditions for experimentation

Drug must be pure

Drug must be tested for only 1 condition

Drugs must be tested in contradictory disease states

Strength of drug must be proportionate to severity of diseases

Time of therapeutic effect must be considered

Drug must be observed for continued action

Drug must be tested in humans before judgment

Leonardo daVinci

## History of the Microscope

1st C AD: Glass tested by Romans who recognized when thick in middle and thin on edges yielded magnification

13th C: Eye glasses invented; first eyeglasses made in Germany ~1286

1590: Zaccharia Janssen and son, Han invented compound microscope with 2 lenses in a cylinder

1609: Galileo added focusing device



Antony Van Leeuwenhoek

(1632-1723)

1660: worked in dry good store counting threads in woven cloth

Made small lenses with greater curvature resulting in 270X magnification

Described bacteria, yeast, sperm, striated muscle, crystalline lens, RBCs

## Hematology

William Harvey (1578 - 1657)

Defined the circulatory system

## Rare Diseases: Window on Nature?

Nature is nowhere accustomed more openly to display her secret mysteries than in cases where she shows traces of her workings apart from the beaten path; nor is there any better way to advance the proper practice of medicine than to give our minds to the discovery of the usual law of nature, by the careful investigation of cases of rarer forms of disease.

~ William Harvey, Letter IX,  
to John Vlackveld, 24 Apr 1657

## Hematology

William Harvey (1578 - 1657)

Defined the circulatory system

Sir Christopher Wren (1632 - 1723)

First intravenous injections (in dogs)

Sir Christopher Wren (1632-1723)

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

## Hematology

William Harvey (1578 - 1657)

Defined the circulatory system

Sir Christopher Wren (1632 - 1723)

First intravenous injections (in dogs)

Jean-Baptiste Denis (1667)

Richard Lower and Edmund King (1667)

First blood transfusions in man

Jean-Baptiste Denys

June 15, 1667 – Transfused about twelve ounces of sheep blood into a 15-year old boy – who survived

Richard Lower

November 1667 –

transfused sheep's blood into man



Hematology

James Blundell (1828)

First modern (man-to-man;  
man-to woman) transfusion

## History of Clinical Trials

James Lind

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

James Lind - Experimental Design (cont'd)

## Story of Smallpox

Girl with Smallpox

Al-Rhazi– 1st description of smallpox ~900 A.D.

(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)

Smallpox in 1700's

By 1720's: Variolation practiced in Africa, China, India

1721: Lady Mary Worley Montague, wife of the British Ambassador, observed inoculation in Constantinople and introduced practice in London (inoculated her 2 children)

1745: London Smallpox Inoculation Hospital founded

Benjamin Jesty

1736 – 1816

Jesty was a farmer who lived in village of Yetminster in North Dorset, UK.

Convinced milkmaids who contracted cowpox were protected from small pox, in 1774 he inoculated himself, wife and 2 sons with cowpox lymph from underside of cow udder.

In 1805 publically inoculated son Robert with live small pox to demonstrate he was still protected.



Edward Jenner

(1749-1823)

Born in Gloucestershire, England

Illustration of Edward Jenner

vaccinating James Phipps

Artist unknown. Undated illustration

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

July 3, 1776: variolation approved by Continental Congress

## Eradication of Small Pox

D.A. Henderson, MD, MPH

1966: head of WHO's global smallpox

eradication campaign

1974: In India during one of the largest

epidemics of 20th C he initiated global

immunization program

Last case of smallpox in Somalia

in 1977, not until 1980 that WHO confident smallpox completely eradicated

## Genetics

Mendel, the Father of Genetics

Experiments in Plant Hybridization lead to a new theory of inheritance

Inheritance is a “particulate” process

Genetic factors come in pairs

Genes are on chromosomes and passed on from parents to offspring during sexual reproduction

Barbara McClintock, PhD

1902 – 1992

American scientist and one of the world's most distinguished cytogeneticists

Groundbreaking research in developing the technique for visualizing maize chromosomes

Used microscopic analysis to demonstrate many fundamental genetic ideas

Discovered transposition and used it to demonstrate that genes are responsible for turning physical characteristics on and off

1983: Nobel Prize in Physiology or Medicine "for her discovery of mobile genetic elements"

## Charles Darwin and Evolutionary Theory

Charles Darwin (1859) "On the Origin of Species"

In his Theory of Evolution by Natural Selection, Darwin provides a mechanistic explanation of adaptation based on natural laws, not supernatural or religious actions. "Nothing in Biology makes sense without Evolution"

Created first tissue bank and demonstrated importance of meticulous records.

Epidemiology

John Snow

(1813-1858)

Born in York, England

British physician, anesthesiologist

Medical hygiene pioneer

Father of modern epidemiology for work in tracing the source of a cholera outbreak in Soho, England (1854)

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



## Washing Hands

~600B.C., Sushruta advocated sterilization of wounds

~400 B.C., Hippocrates promoted clean hands for wound management

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 worked 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%.

Puerperal Fever

## History of Clinical Trials

Semmelweis, 1848 - 1863 continued

His chief did not believe his data; one year later he was fired.

He moved to his original home in Budapest, Hungary where he repeated his earlier experiment with the same results.

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

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.

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)

Anesthesia

William T. G. Morton 1819-1868, dentist

Demonstrated use of "letheon" (ether) Oct 16, 1846 at Mass General Hospital

## Birth of the Pharmaceutical Industry

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)

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

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

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..."



Paul Ehrlich

(1854-1915)

Born in Strehlen, Poland

Described eosinophils

Described complement pathway and humoral immunity

Treatment of syphilis

First Antibiotic for Syphilis

Salvarsan (Hoechst), an arsenobenzene was 32% arsenic and toxic

Later, Neosalvarsan (compound '914') was less toxic

Ehrlich coined term "magic bullet"

"We must search for magic bullets. We must strike the parasites, and the parasites only, if possible, and to do this, we must learn to aim with chemical substances!"

Sir Alexander Fleming (1881-1955)

Born in Lochfield, Scotland

In 1928 while working on influenza virus, observed mold on a staph culture plate with a bacteria-free circle around itself.

Penicillin discovery spawned expansion of pharmaceutical industry

Awarded the Nobel Prize in Physiology or Medicine 1945

## The Insulin Story

May –August 1921:

Material extracted from the islets of Langerhans (called "insulin," from Latin for "island") given to diabetic dogs; result: abnormally high blood sugars were lowered.

Within 6 weeks, product purified and given to 14-year-old boy dying of diabetes. Injection lowered blood sugar and cleared urine of sugars and other signs of disease.

February, 1922: Banting and Best published paper on their discovery.

In 1923: Nobel Prize was awarded to Banting and Macleod for the discovery, and each shared their portion of the prize money with other project researchers (including Best)

Polio Story

Jonas Salk, MD

(1914 – 1995)

American medical researcher and virologist

Developed the first successful inactivated polio vaccine, one of the most rapid examples of bench-to-bedside translation in medicine

In 6 year span:

Key basic lab discoveries facilitating the development of the vaccine were made

Optimization/safety testing completed in both animals and human volunteers

largest clinical trial in history of 1.8 M children conducted, and the results released

Associated incidents:

Lab manufacturing errors with Cutter and Wyeth vaccine lots

Questions re: statistical design

Albert Bruce Sabin, MD

(1906 – 1993)

1954: Sabin vaccine first tested

Sabin vaccine consists of weakened forms of the viruses that cause polio

1956-1960: Sabin worked with Russian colleagues to perfect the oral vaccine

1955-1961: oral vaccine tested on ~100 million people in USSR, parts of Eastern Europe, Singapore, Mexico, the Netherlands

## 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

Rosalyn Sussman Yalow, PhD

(1921 – 2011)

American medical physicist

Collaborated with Solomon Berson, MD to develop radioimmunoassay (RIA)

Co-winner of the 1977 Nobel Prize in Physiology or Medicine

with Roger Guillemin and Andrew Schally for development of the radioimmunoassay technique

1st female and 1st nuclear physicist to win the Albert Lasker Award for Basic Medical Research

for the discovery and development of the technique of radioimmunoassay

Janet Davison Rowley, MD

(1925 – 2013)

American human geneticist

1970's: 1st scientist to identify a chromosomal translocation as the cause of leukemia and other cancers:

abnormal Philadelphia chromosome implicated in certain leukemias was involved in a translocation with chromosome 9 in some cases

Awards included:

National Medal of Science

Presidential Medal of Freedom

Lasker Award in Clinical Medical Research

with Alfred Knudson, Jr., Peter Nowell: “for incisive studies in patient-oriented research that paved the way for identifying genetic alterations that cause cancer in humans and that allow for cancer diagnosis in patients at the molecular level”

## 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

## Statistics – Randomization



Borrowed Ideas: Randomization

Sir Ronald Aylmer Fisher (1890-1962)

Introduced application of statistics to experimental design

Farming and plant fertility: concept of randomization and analysis of variance

Medical Research Council trial led by  
Sir Austin Bradford Hill  
1948

First clinical trial with a properly randomized control group

## Medical Research Ethics

Gerhard Armauer Hansen

(1841-1912)

Born in Bergen Norway

## History of Informed Consent

1898: William Osler

“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

Minutes of Medical Board

MEDICAL BOARD

Tuesday, June 9, 1953, 3:00 p.m.

Chairman: Dr. Luther Terry

“...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.”

1962:

Kefauver-Harris amendment to Food and Drug Act stipulating subjects must be told whether a drug is being used for investigational purposes

Surgeon General requires peer review (IRBs) for all PHS grants.

1967:

FDA required all new drug sponsors obtain informed consent for use of investigational drugs in humans.