History of Clinical Research
A Merging of Diverse Cultures
October 19, 2009
Outline

Course Overview

History of Clinical Research
2009 – 2010 IPPCR Enrollment Date

# enrolled at the NIH: 409

# enrolled at 25 remote locations 719

Total enrollees (as of 10/19/09) 1,128
IPPCR
25 Participating Off-Campus Sites

NIH
National Cancer Institute – Frederick

U.S.
Children’s National Medical Center
Franklin Square Hospital
Meharry Medical College
Harbor Hospital
Harbor UCLA Medical Center
Union Memorial
Morehouse School of Medicine
UCLA K30 Program
Unity Health System
Walter Reed Army Medical Center
Washington DC Veteran’s Administration Medical Center
Washington Hospital Center
Howard University GCRC
Oklahoma State University
Washington University School of Medicine

International
Don-A University Medical College, Busan Korea
Universidade Federal de Santa Maria-UFSM, Samta Maria Brazil
U.S. Naval Medical Research Center Detachment, Lima, Peru
Universidad Peruana Cayetano Heredia, Lima. Peru
University of Puerto Rico, San Juan, PR
Affiliated Union Hospital, Tongi Medical College, Huazhong University of
Science and Technology, Wuhan, China
Centro Internacional de ENtrenaminete e Investigaciones Medicias, Cali,
Columbia
ImpactaPeru, Lima, Peru
World Map of pinpointing locations of remote locations.

Over 16,000 students world-wide have participated in the NIH Curriculum in Clinical Research
IPPCR Administrative Comments

Course Textbook: Principles and Practice of Clinical Research, Second Edition

Available: NIH FAES Bookstore, Building 10, Room B1L101 or on-line

Handouts: posted on course website:
http://www.cc.nih.gov/training/training/ippcr/info.html

Lecture evaluations: via email
Chinese Translation of Second Edition

Photo: Cover of Principles and Practice of Clinical Research, Chinese Edition

Courses in China: November 10-15, 2008 and April 6-10, 2009
IPCPR Administrative Comments

Video Archive: video of each lecture will be posted within 48 hours following the presentation

Questions: should be sent to the course mailbox and answers posted on course website
od_ippcr@mail.cc.nih.gov

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

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
Scientific Conduct
Quality of Life
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
ProtoType and Protocol Mechanics
Inclusion of Women and Minorities in Clinical Trials
Health Disparities Research
Community-based Participatory Research
Technology Transfer
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.
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
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 kings' rich food be observed by you, and according to what you see, deal with your servants.

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

And 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

picture of book in the upper right corner
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 practices some dentistry

Extracted medicine from plants and know the position and function of the vital organs and circulation of the blood system

Photo of hieroglyphics and Egyptian statue
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.

Painting of Shen Nung (c. 2800 B.C.)
Pulse chart from a 1693 edition of Secrets of the Pulse, originally written by Pien Ch’iao in the 6th of 5th century B.C.

Drawing of pulse chart

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

Painting of ancient Chinese physician feeling a patient’s pulse
Susruta: Father of Indian Surgery

Resident at the court of the Gupta kings – 600 B.C. (unclear)

Wrote medical texts about surgery
    Most famous: Susruta Samhita, an encyclopedia of medical learning
Counted 300 bones in human body
Advocated sterilization of wounds
Discussed options for instruments; hand: best instrument

Drawing of Susruta in upper right hand
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 sever and more
protracted. Once 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.”

Photo of Hippocrates in upper right corner
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.”

Hippocrates, 460 BC – 370 BC
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

Photo of Galen in the middle of the page
“…help or at least to do no harm”
Hippocrates, Epidemics, Bk.1, Sect. XI.

“Primum non nocere...”
Galen
Iranian Medicine: Al Rhazi and Ibn Sina

Al Rhazi (865-925)
- Discovered use of alcohol as anticeptic
- Contributions to medicine, alchemy, and philosophy
- 1st treatise on pediatrics
- Recorded in over 184 books and articles

Picture of Al Rhazi

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

Picture of Ibn Sina
Ibn Sina (Avicenna)  
“The Canon of Medicine”  
7 conditions for experimentation  

1. drug must pure  
2. drug must be test for only 1 condition  
3. drugs must be tested in contradictory disease states  
4. strength of drug must be proportionate to severity of diseases  
5. time of therapeutic effect must be considered  
6. drug must be observed for continued action  
7. drug must be tested in humans before judgment  

Photo of “The Canon of Medicine”
Leonardo da Vinci (1453 – 1519)
Born near the town of Vinci in Florence, Italy

Drawing of Leonardo da Vinci
Two drawings of human anatomy
Anton 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 or defending cities  
Significant contributions to architecture


Painting of Sir Christopher Wren in the upper right corner  
Painting of the human brain in the lower left corner
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

Painting of James Lind
1716-1794
Born in Edinburgh, Scotland
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 or Clinical Trials

James Lind – Experimental Design (cont’d)

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Cured</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfuric Acid</td>
<td>0/2</td>
<td>NS</td>
</tr>
<tr>
<td>Vinegar</td>
<td>0/2</td>
<td>NS</td>
</tr>
<tr>
<td>Sea Water</td>
<td>0/2</td>
<td>NS</td>
</tr>
<tr>
<td>Cider</td>
<td>0/2</td>
<td>NS</td>
</tr>
<tr>
<td>Physician’s Remedy</td>
<td>0/2</td>
<td>NS</td>
</tr>
<tr>
<td>Citrus Fruit</td>
<td>2/2</td>
<td>NS!!!!!</td>
</tr>
</tbody>
</table>

*Compared to patients in the other 5 arms of the trial; no placebo group
Story of Smallpox
Girl with smallpox

(1) Al-Rhazi – 1st description smallpox ~900 AD
(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)

Chinese rendition of a girl with smallpox on left side of page
Small Pox in American History

- 1721 – Reverend Cotton Mather (Boston) learned of Variolation from African slaves and concluded variolation protected from smallpox; Mather introduced variolation to Boston
- 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

Picture of George Washington holding American Flag
Illustration of Edward Jenner vaccinating James Phipps on left side of the page
Artist unknown. Undated illustration

On the right side of the page: Portrait of Edward Jenner (1749-1823)
Born in Gloucestershire, England
Washing Hands
Oliver Wendell Holmes (1809-1894)
Born in Cambridge, Massachusetts, USA

Advocated hand-washing in obstetrics (do data)

Portrait of Oliver Wendell Holmes
Ignaz P. Semmelweis (1818 – 1865)
Born in Budapest Hungary

Portrait on left side of page
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 that 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.
Photo of an old fashioned sink
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

Lister’ 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.

Portrait of Joseph Lister (1827 – 1912)
Born in Essex, England
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

Painting of Claude Bernard on the right side of the paper
Rudolph Virchow (1821-1902)
Born in Seidwin, Poland

Lukemia

Omnis cellula e cellula every cell originates from another cell (1858)

Pulmonary emboli (Thrombosis 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)

Cover of book The Knife Man by Wendy Moore in the right lower corner
Immunology
Robert Koch (1843-1910)
Born in Hanover, Germany

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 postulated

In 1905 he was awarded the Nobel Prize for Physiology of Medicine “for his investigations and discoveries in relation to tuberculosis”

Portrait of Robert Koch in the upper left corner of the page
Drawing of anthrax bacillus from a paper published by Koch in 1877 in the lower right corner of the page
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

Vaccines for anthrax

Vaccine for rabies

Portrait of Louis Pasteur on the left side of the page
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.…”

Portrait of Emil von Behring on the left side of the page
Elie Methcnikoff (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 

Portrait of Paul Ehrlich
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

Portrait of Florence Nightingale in upper left corner of the page
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

Portrait of Marie Curie in the upper left corner of the page
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

Portrait of Benjamin Franklin at the bottom of the page in the middle
Copy of Animal Magnetism report on the right side of the page
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.

Photo: 3 women in blindfolds testing gelatins at Consumers Union, 1945.
Statistics – Randomization
Borrowed Ideas: Randomization

Introduced application of statistics to experimental design

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

Photo: Sir Ronald Aylmer Fisher (1890-1962) on the left side of the page
Photo: Rhamsted Agricultural Station on the right side of the page
Epidemiology
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

Portrait of John Snow (1813-1858)
Born in York, England on the upper right corner of the page

Picture of spot map on the left side of the page
Medical Research Ethics
History of Informed Consent

1767: Slater v. Baker & Stapelton
“…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

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

Copy of portion of cover page from a Medical Board meeting
Conclusion

The history of clinical research can be traced to all cultures.

The future requires information exchange to maximize progress in health care.
History of Clinical Research
A Merging of Diverse Cultures

Photo of the globe being held up by hands of people from different cultures/backgrounds
Questions???
sshould be sent to the course mailbox and answers will be posted to the course
website od_ippcr@mail.cc.nih.gov