History of Clinical Research
- A Merging of Diverse Cultures -

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Director, NIH Clinical Center

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Outline

• Course Overview
• History of Clinical Research

2009-2010 IPPCR Enrollment Data*

# enrolled at the NIH: 409
# enrolled at 26 remote locations: 719
Total enrollees (as of 10/19/09): 1,128

*10/19/09
IPPCCR
26 Participating Off-Campus Sites

<table>
<thead>
<tr>
<th>NIH Sites</th>
<th>International Sites</th>
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<tbody>
<tr>
<td>Children's National Medical Center</td>
<td>Universidad Federal de Santa Maria, Brazil</td>
</tr>
<tr>
<td>Emory University Hospital</td>
<td>U.S. Naval Medical Research Center Detachment, Lima, Peru</td>
</tr>
<tr>
<td>Harbor UCLA Medical Center</td>
<td>Universidad Autonoma de Nuevo Leon, Mexico</td>
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<tr>
<td>Memorial Hospital</td>
<td>Universidad Peruana Catedrático, Lima, Peru</td>
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<tr>
<td>Johns Hopkins School of Medicine</td>
<td>University of Puerto Rico, San Juan</td>
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<tr>
<td>UCLA K23 Program</td>
<td>Centro Internacional de Entrenamientos e Investigaciones Médicas, Cal, Colombia</td>
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<tr>
<td>Unity Health System</td>
<td>Centro Internacional de Entrenamientos e Investigaciones Médicas, Cal, Colombia</td>
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<tr>
<td>Walter Reed Army Medical Center</td>
<td>Centro Internacional de Entrenamientos e Investigaciones Médicas, Cal, Colombia</td>
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<tr>
<td>Washington DC Veteran's Administration Medical Center</td>
<td>Centro Internacional de Entrenamientos e Investigaciones Médicas, Cal, Colombia</td>
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<td>Oklahoma State University</td>
<td>Centro Internacional de Entrenamientos e Investigaciones Médicas, Cal, Colombia</td>
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<tr>
<td>Washington University School of Medicine</td>
<td>Centro Internacional de Entrenamientos e Investigaciones Médicas, Cal, Colombia</td>
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</table>

Over 16,000 students worldwide have participated in the NIH Curriculum in Clinical Research.

### IPPCCR Administrative Comments

- **Course Textbook:**
  - *Principles and Practice of Clinical Research, Second Edition*
  - Available: NIH FAES Bookstore, Bldg 10, Rm B1L101 or on-line

- **Handouts:** posted on course website:
  - [http://www.cc.nih.gov/training/training/ippcr/info.html](http://www.cc.nih.gov/training/training/ippcr/info.html)

- **Lecture evaluations:** via e-mail
Chinese Translation of Second Edition

Courses in China:
November 10-15, 2008
April 6 – 10, 2009

IPPCR Administrative Comments

Video Archive
• video of each lecture will be posted within 48hrs following 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.
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 harkened 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

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.)

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

Doctor examining patient by feeling pulse, perhaps the most important feature of ancient Chinese medical diagnosis
Susruta: Father of Indian Surgery

- Resided 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

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
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

“...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 antiseptic
- 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

1. Drug must be pure
2. Drug must be tested 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

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

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**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.

**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)

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Cured</th>
<th>P Value*</th>
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<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 the other 5 arms of the trial; no placebo group

Story of Smallpox

(1) Al-Rhazi – 1st description of 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)

Girl with smallpox

Chinese artist rendition of a girl with smallpox

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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

Edward Jenner
Born in Gloucestershire, England

Washing Hands
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.

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 (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)
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 postulates
- In 1905 he was awarded the Nobel Prize for Physiology or Medicine “for his investigations and discoveries in relation to tuberculosis”

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
Emil von Behring (1854-1917)
Born in Deutsch-Eylau, Germany
- Discovered antibodies (diptheria 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...”

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
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
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

- 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

Medical Research Ethics

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 virulence 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 his role in a study project and the means for obtaining evidence of such understanding and consent.”

Conclusion

- The history of clinical research can be traced to all cultures.
- The future requires information exchange to maximize progress in health care.
QUESTIONS

Should be sent to the course mailbox and answers will be posted to the course website od_lppcr@mail.cc.nih.gov