

History of Clinical Research and Choosing a Research Question

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October 15, 2007



Outline

- * **Course Overview**
- * **Vignettes**
- * **Study Design**
- * **History of Informed Consent**
- * **Protocol Review Process**
- * **Choosing a Research Question**

2007-2008 IPPCR Enrollment Data

enrolled at the NIH: 360

enrolled at 17 remote locations: 399

Total enrollees (as of 10/12/07): 759

IPPCR

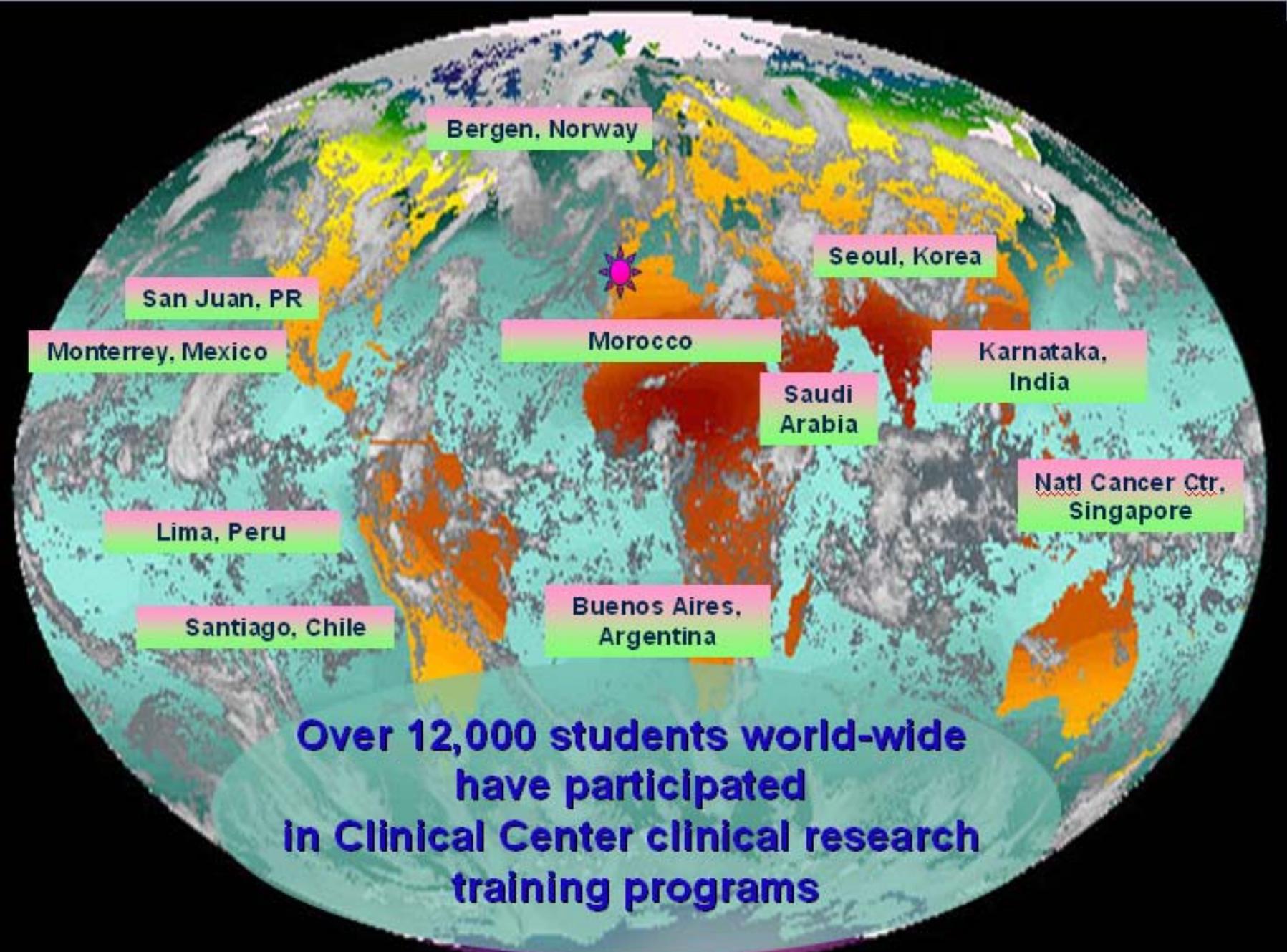
Participating Off-Campus Sites

NIH Sites
National Cancer Institute - Frederick
National Institute on Aging
National Institute of Environmental Health Sciences

National Sites
Children's National Medical Center
George Washington University Rheumatology Fellowship Program 'Informal Site
Harbor UCLA Medical Center
Howard University College of Medicine
Morehouse School of Medicine
Naval National Medical Center
SUNY Upstate Medical Center
UCLA K30 Program
Walter Reed Army Medical Center
Washington Hospital Center <u>MedStar Health</u>

International Sites
U.S. Naval Medical Research Center Detachment, Lima
Universidad <u>Autonoma de Nuevo Leon</u> , Mexico
Universidad <u>Peruana Cayetano Heredia</u> , Lima
University of Puerto Rico

New Sites



Bergen, Norway

San Juan, PR

Monterrey, Mexico

Morocco

Seoul, Korea

Saudi Arabia

Karnataka, India

Natl Cancer Ctr, Singapore

Lima, Peru

Santiago, Chile

Buenos Aires, Argentina

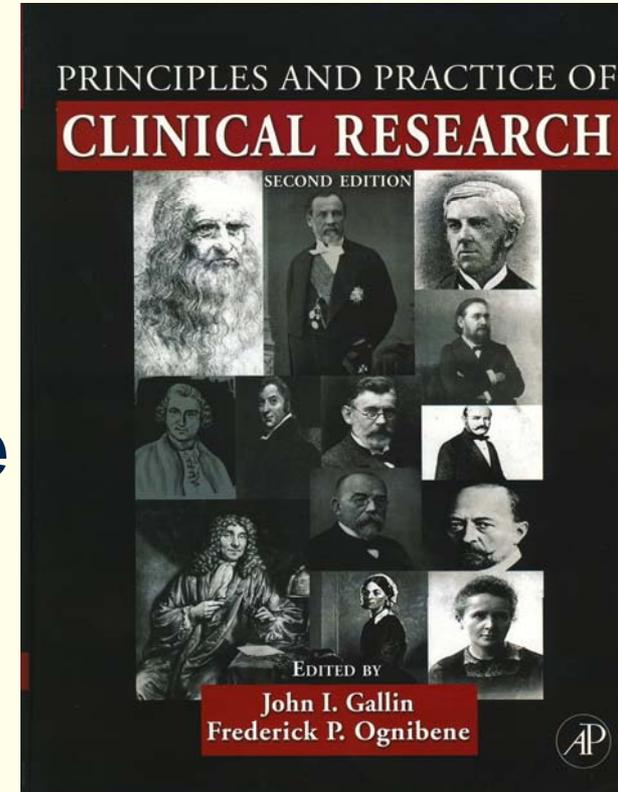
**Over 12,000 students world-wide
have participated
in Clinical Center clinical research
training programs**

IPPCR Administrative Comments

Course Textbook:

Principles and Practice of
Clinical Research, 2nd Edition

Available: NIH FAES Bookstore
Bldg 10, Rm B1L101 or on-line



Handouts will be posted on course website:

<http://clinicalcenter.nih.gov/researchers/training/ippcr.shtml>

Lecture evaluations will be via e-mail

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

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 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

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...includes:

- Development of new technologies
- Mechanisms of human disease
- Therapeutic interventions
- Clinical Trials

* Epidemiologic and Behavioral Studies

* Outcomes Research and Health Services Research

Outline

- * **Course Overview**
- * **Vignettes**

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.

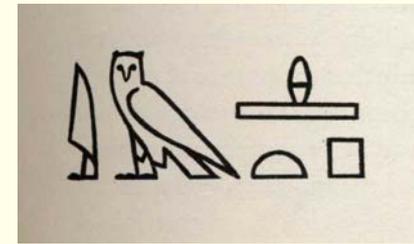
So he harkened to them in this matter; and tested them for ten days.

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.)

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





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

陽居於二陰之義靜則合乎水動則合乎火此生成自然之理
 人身之根本也世人多以右尺爲命門者亦有說焉因右尺有
 少火山心火而生心者君主之官君火不至令相火代之此火
 存則可以生脾土曰生此火滅則不能生脾土曰死既能診候
 生死故呼之爲命門實非命門也殊不知命門在兩腎中間主
 脊骨從上數下第十四節從下按上第七節經曰七節之傍而
 有小心是也今引內經設圖以正其說爲人司命者不可不知
 也

內經三部診候圖

左手 右手

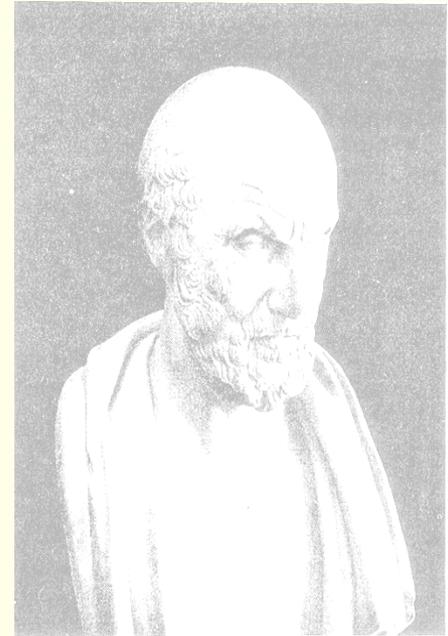


Pulse chart from a 1693 edition of Secrets of the Pulse, originally written by Pien Ch'iao in the 6th or 5th century B.C.

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.”



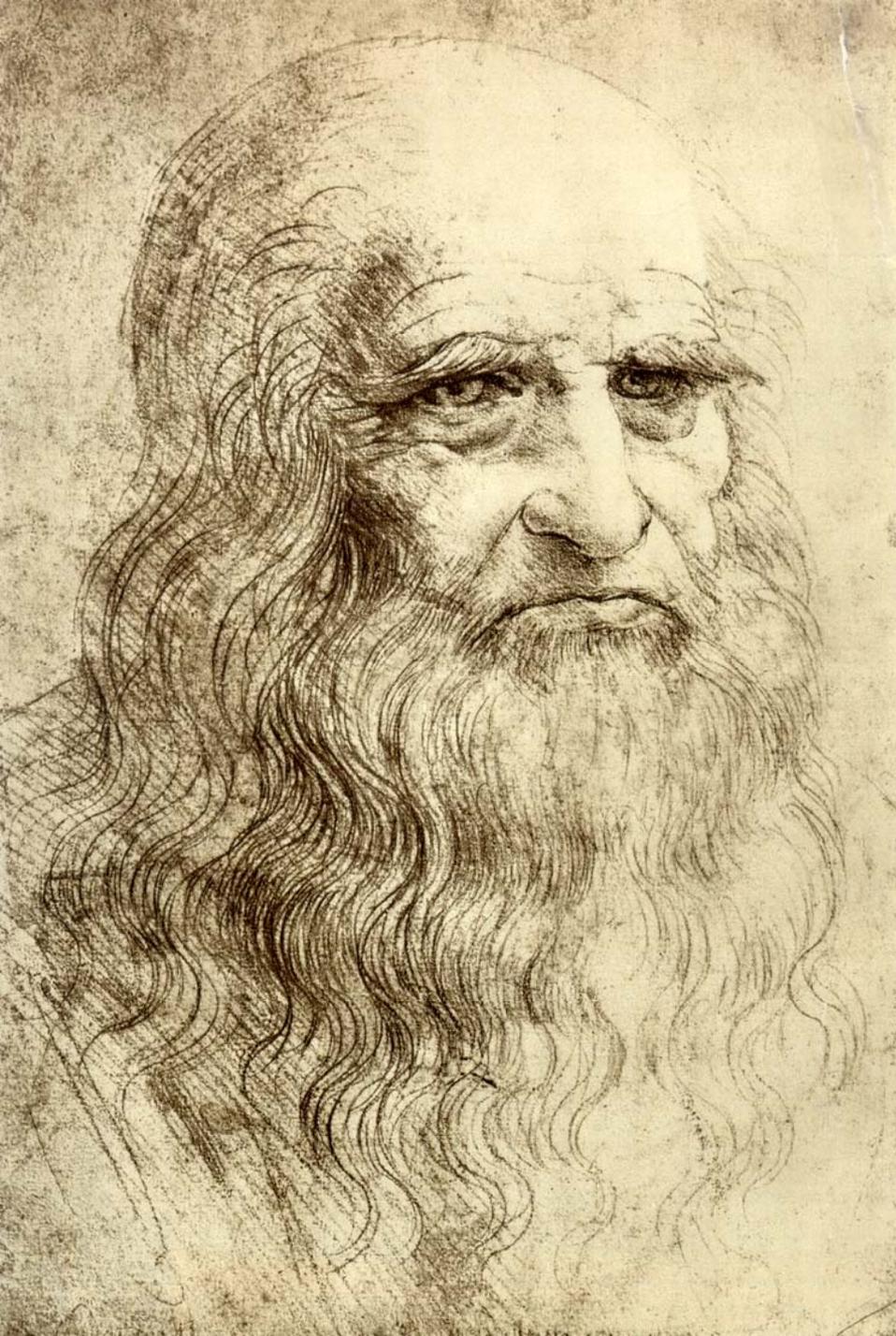
Hippocrates' Accomplishments

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

Galen



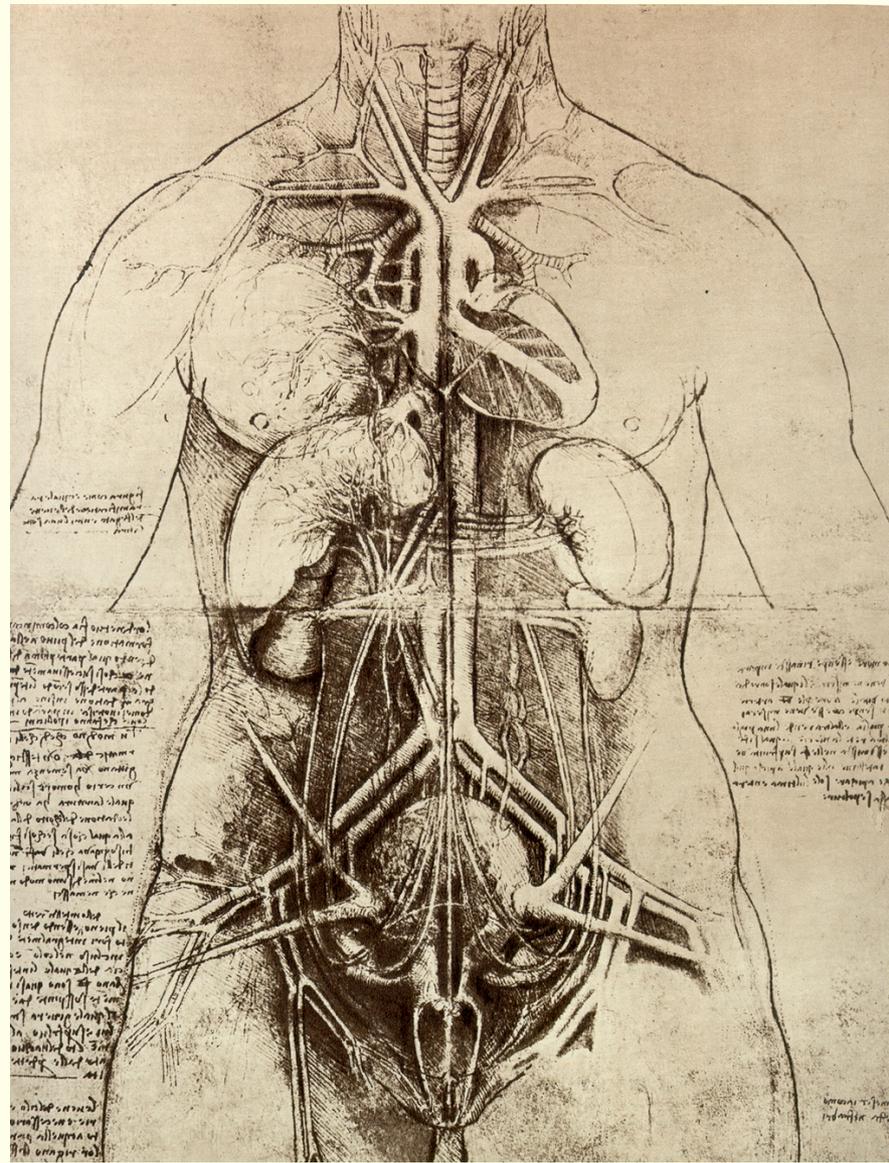
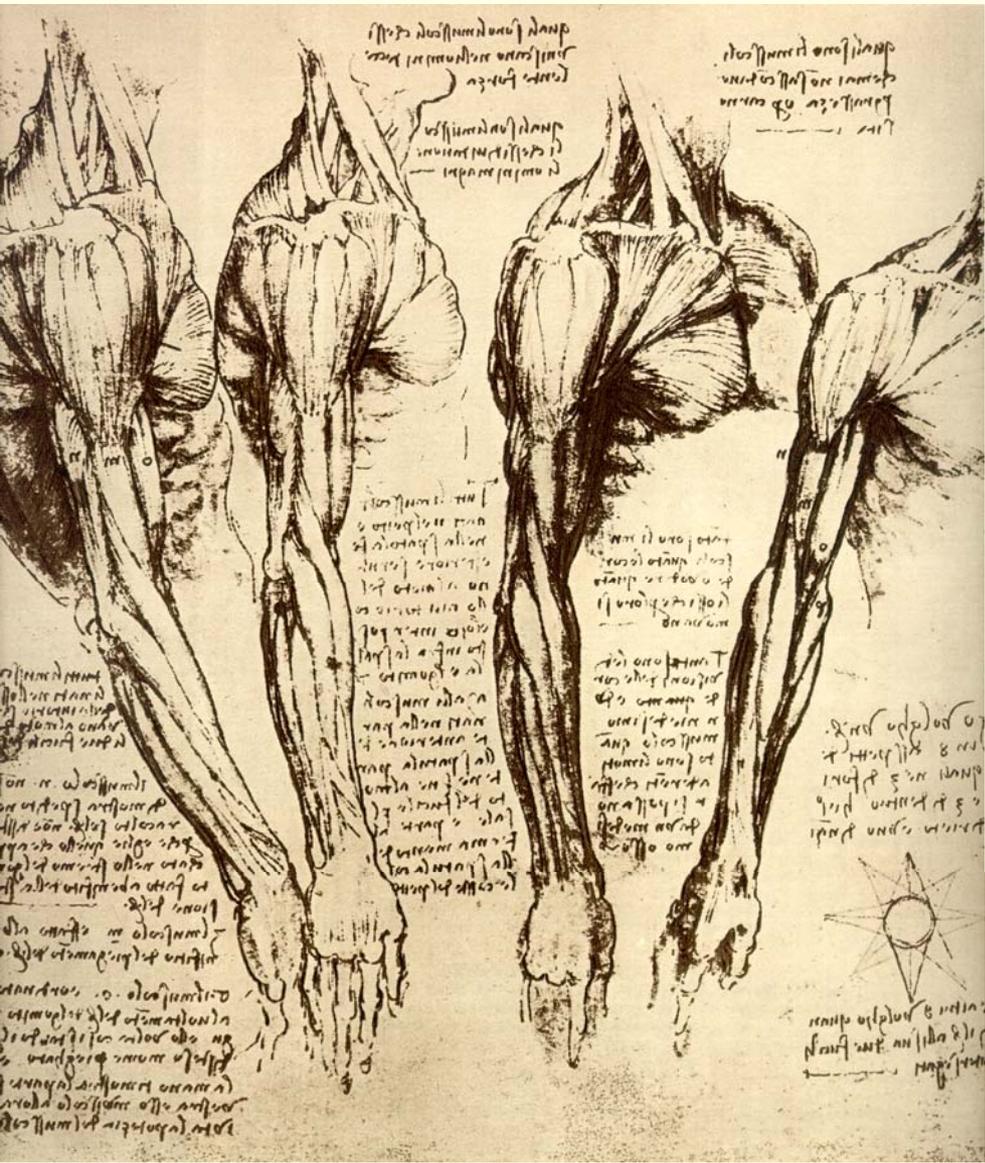
- * **Greek physician lived 6 centuries after Hippocrates (A.D. 129- ca. 216)**
- * **Crystallized all the best work of the Greek medical schools**
- * **Blood consists of 4 humors: black bile, yellow bile, phlegm, and blood.**
- * **Remained an unchallenged authority for >1,000 years**



Leonardo da Vinci

(1453-1519)

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





**Antonj
Van Leeuwenhoek
(1632-1723)**

Born in Delft, Netherlands

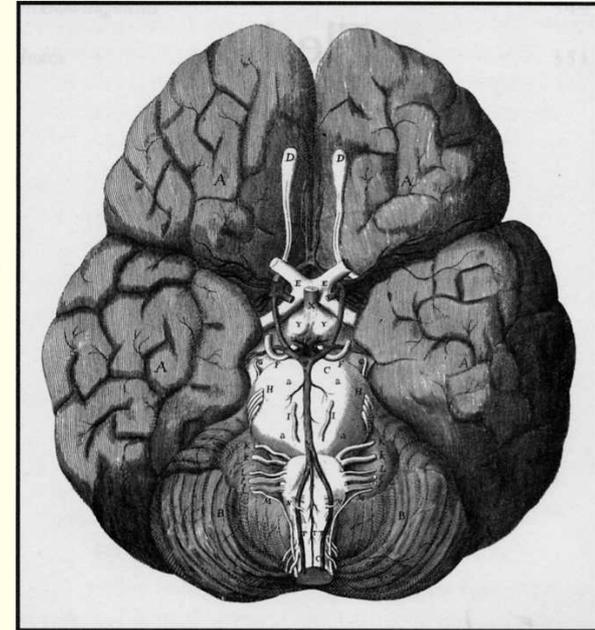
- * Invented microscope
- * Described protozoa, bacteria, striated muscle, crystalline lens, RBCs, sperm

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

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



James Lind (1716 – 1794)
*Born in Edinburgh,
Scotland*



AN
E S S A Y
O N
D I S E A S E S
I N C I D E N T A L T O
E U R O P E A N S I N H O T C L I M A T E S .
W I T H T H E
M e t h o d o f p r e v e n t i n g t h e i r f a t a l C o n s e q u e n c e s .
B y J A M E S L I N D , M . D . F . R . S . E d .
F e l l o w o f t h e R o y a l S o c i e t y o f M e d i c i n e a t P a r i s ,
a n d o f t h e R o y a l C o l l e g e s o f P h y s i c i a n s a t E d i n b u r g h
a n d C o p e n h a g e n ;
L a t e P h y s i c i a n t o t h e R o y a l H o s p i t a l a t H a l l a r ,
n e a r P o r t s m o u t h .
T o w h i c h i s a d d e d ,
A N A P P E N D I X C O N C E R N I N G I N T E R M I T T E N T F E V E R S .
A N D ,
A s i m p l e a n d e a s y W a y t o r e n d e r S e a W a t e r f r e s h , a n d
t o p r e v e n t a S c a r c i t y o f P r o v i s i o n s i n l o n g
V o y a g e s a t S e a .
T h e F O U R T H E D I T I O N .
A r t s q u a e s a n i t a t i t u e n d a e p r a e s t a t , i i s q u i s i b i p a r u e r i n t c o n -
s t a n t e m s a n i t a t e m p r o m i t t i t . G A L E N .
L O N D O N ,
P R I N T E D F O R J . M U R R A Y , N ° 3 2 , F L E E T S T R E E T .
M D C C L X X V I I I .

Pioneered early clinical trials that demonstrated the efficacy of citrus fruits in combating scurvy while discrediting many traditional remedies

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

一子九歲



毒湧掀腫痘形十六

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** - 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





**Illustration of Edward Jenner
vaccinating James Phipps**

Artist unknown. Undated illustration



**Edward Jenner
(1749-1823)**

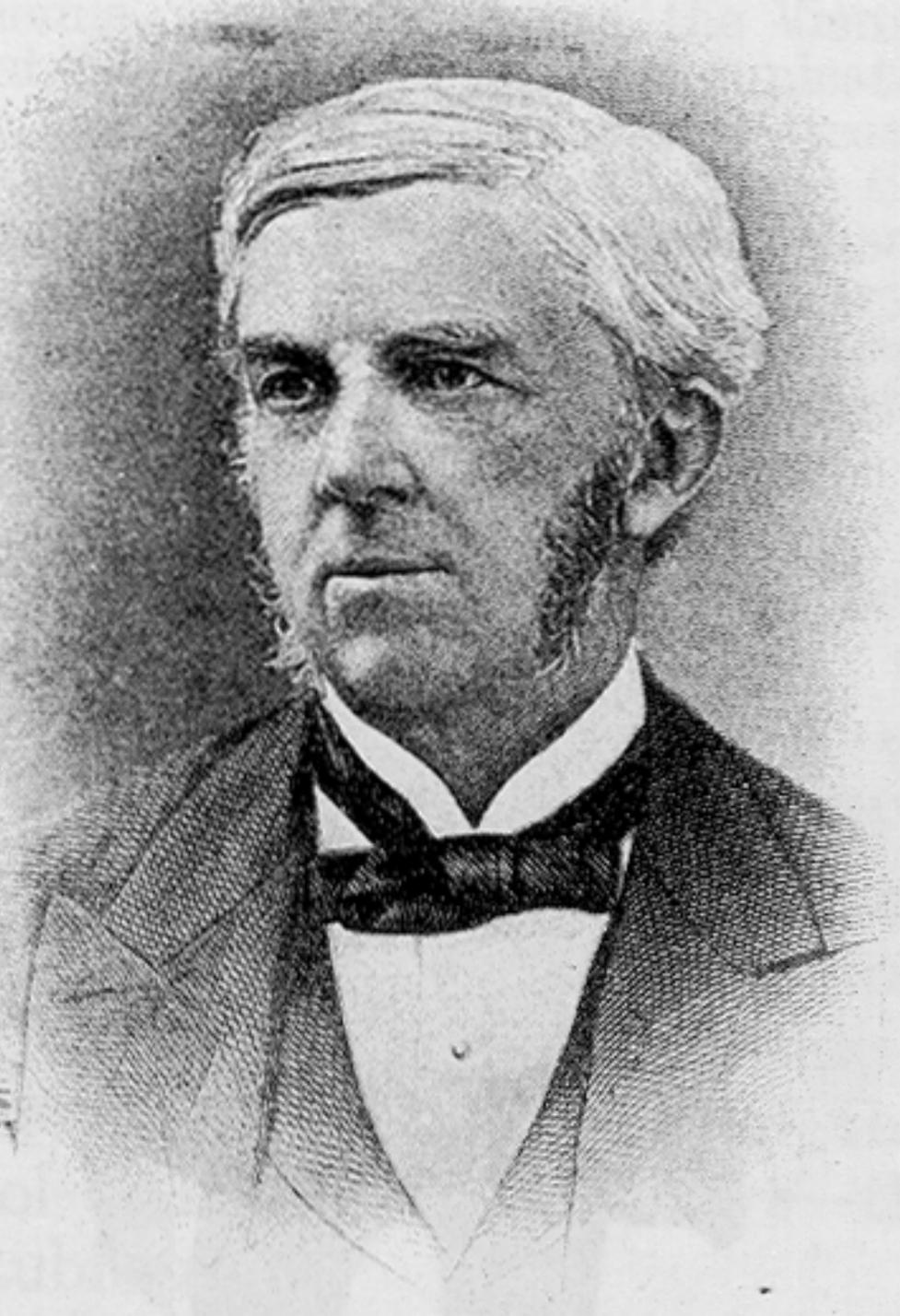
Born in Gloucestershire, England

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



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

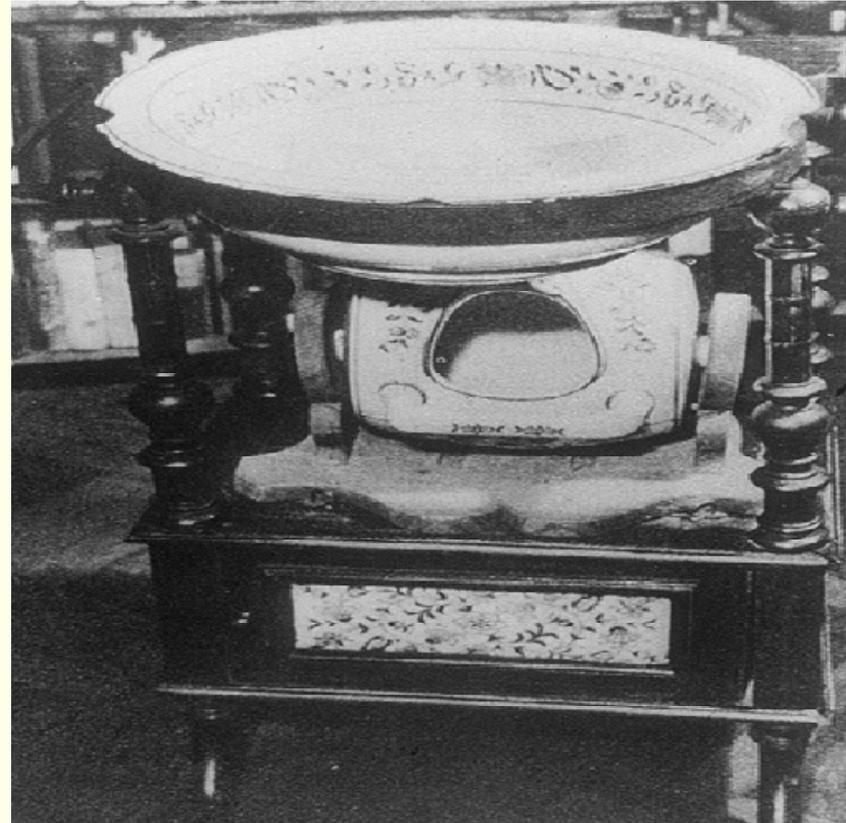
Semmelweis, 1848 - 1863

- * 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)

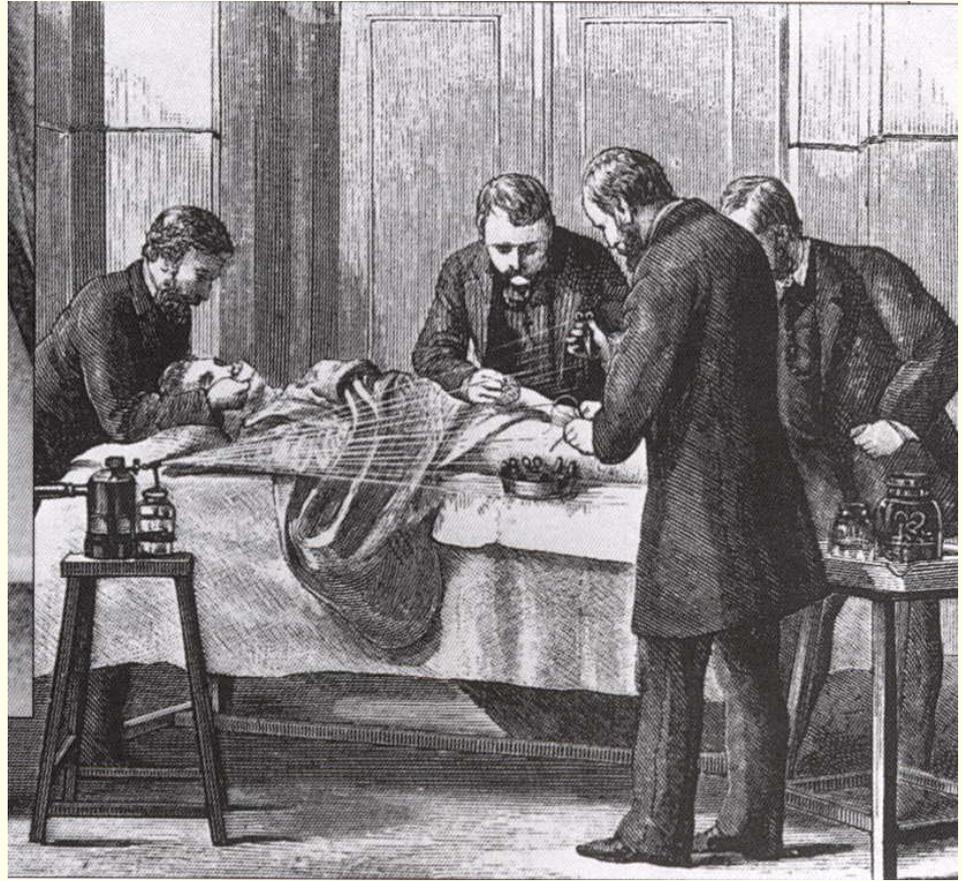
- * He returned to Budapest, Hungary where he was placed in charge of an obstetrical unit plagued with an epidemic of puerperal sepsis. He repeated his earlier experiment and again the mortality rate declined precipitously (mortality remained less than 1% during his six-year tenure vs. 10 to 15% in Vienna 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



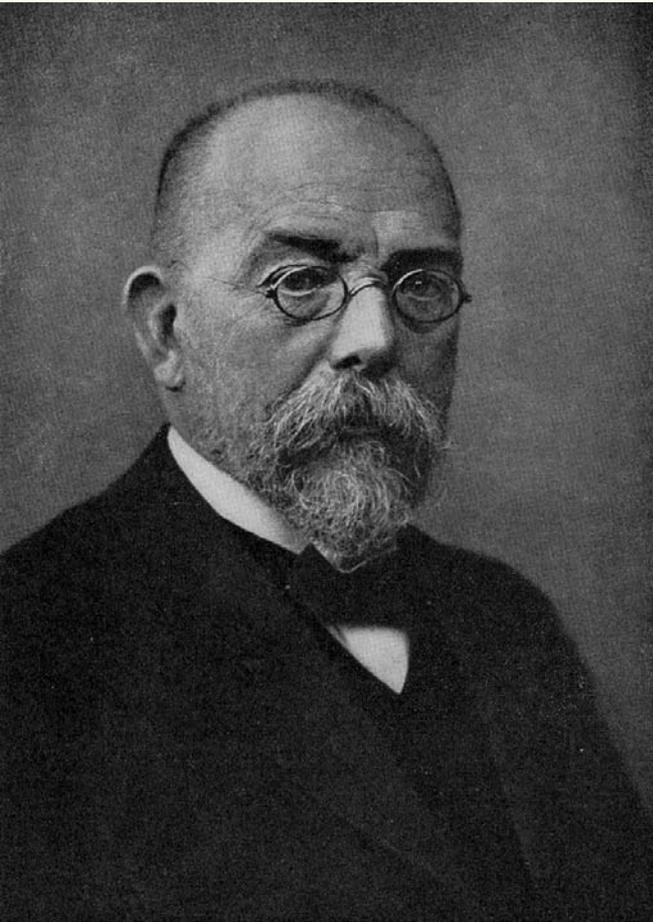
Joseph Lister
(1827-1912)

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.

Immunology

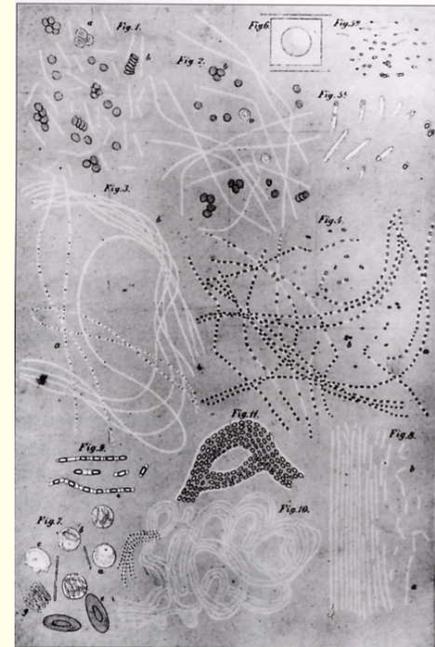


Robert Koch

(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"



Anthrax bacillus from a paper published by Koch in 1877

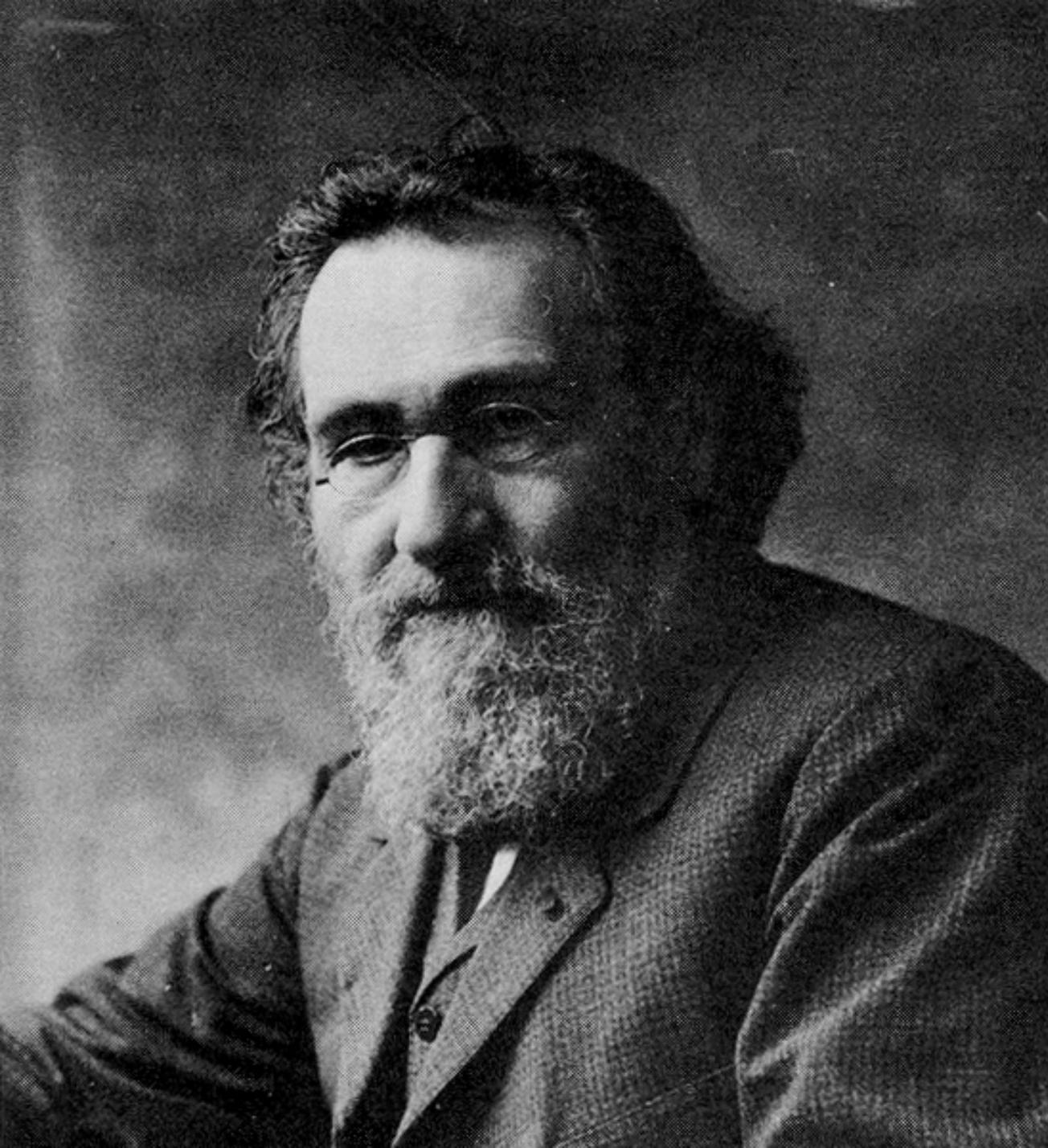


Louis Pasteur

(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 1905 he shared the Nobel Prize for Physiology or Medicine with Paul Ehrlich in recognition of their work on immunity



Nicola Perscheid

P Ehrlich

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 History**



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.**

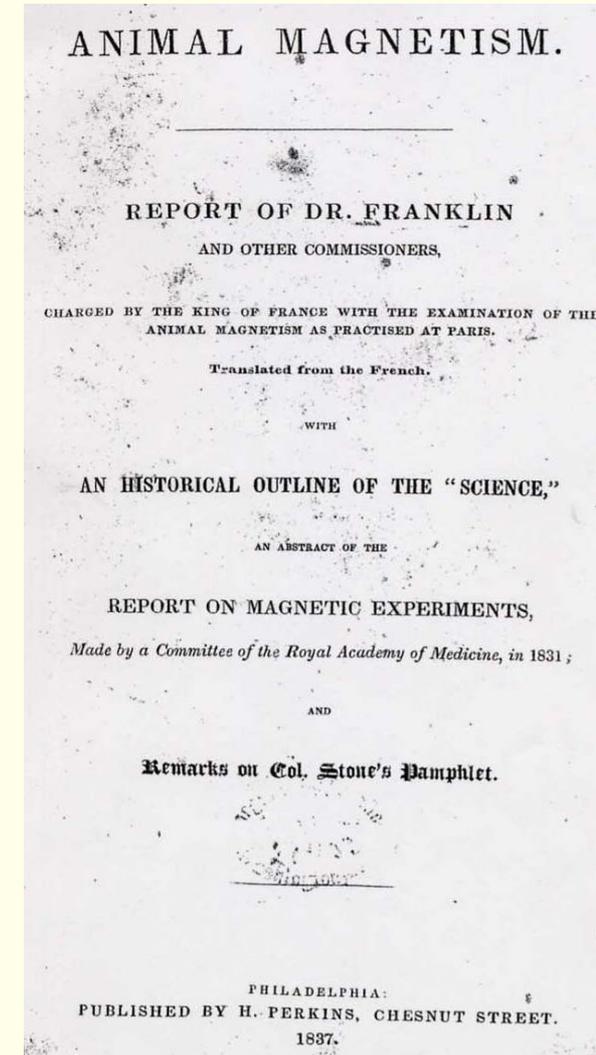
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- * **Course Overview**
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- * **Study Design**

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
- * Recognized placebo effect



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

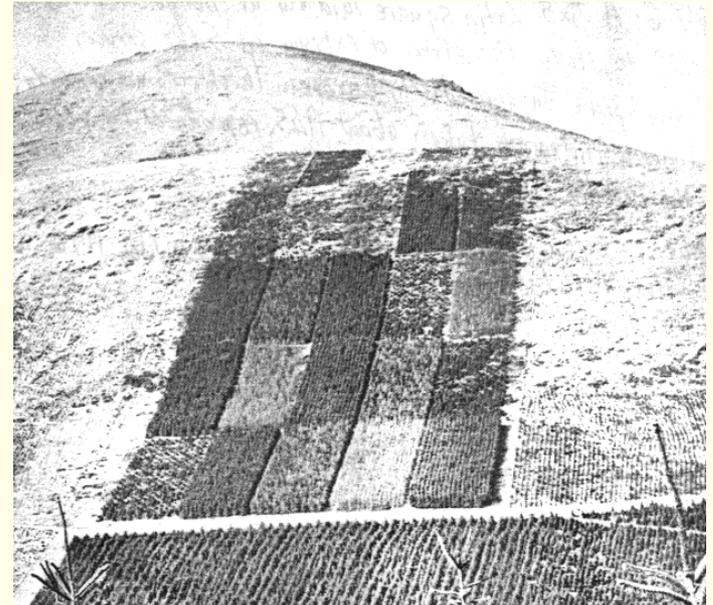


Testing gelatins at
Consumers Union, 1945

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

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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)

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- * **Protocol Review Process**

**1971
Protocol
Review
Process**

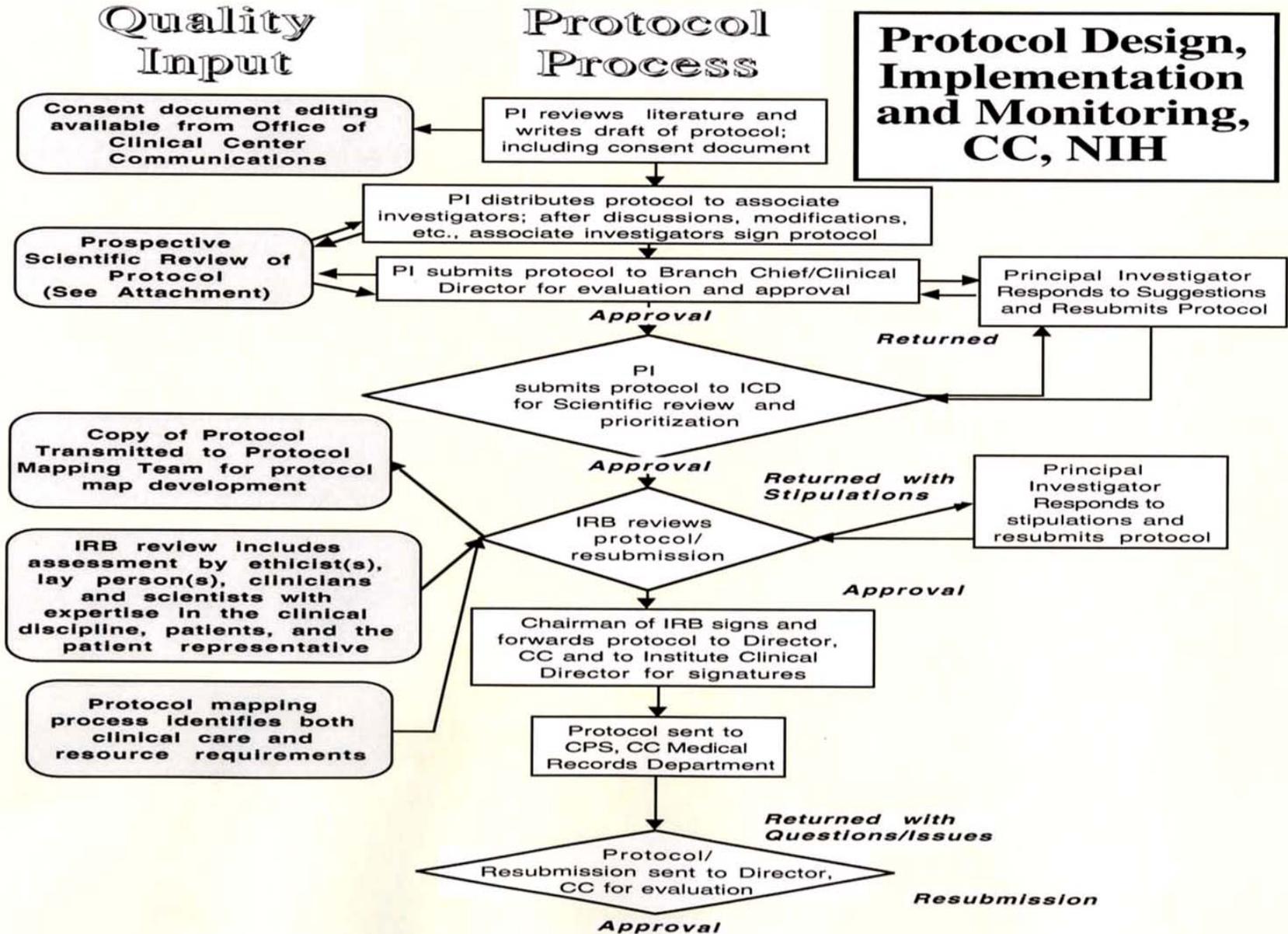
***Principal Investigator
Writes Protocol***

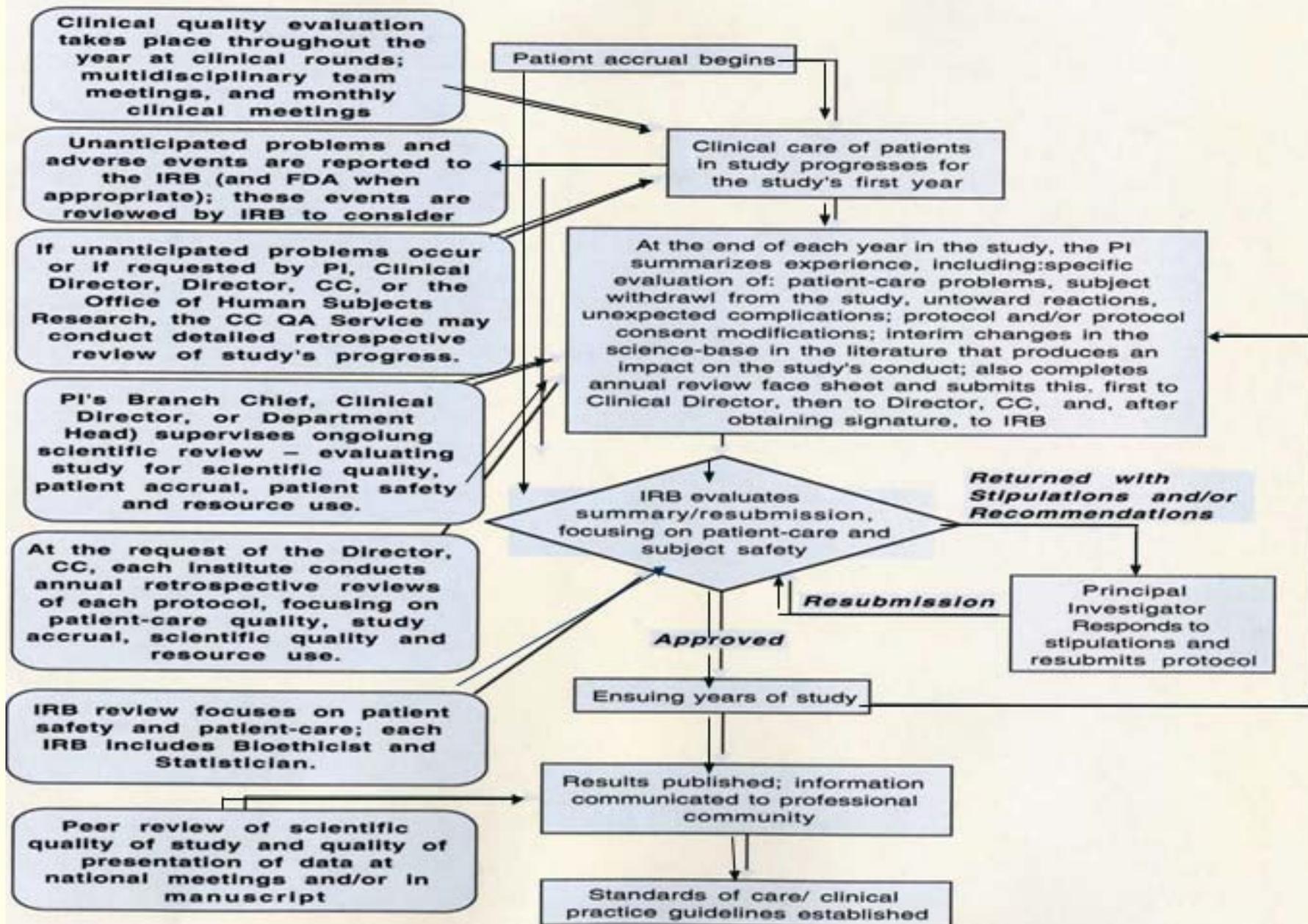
***IRB
Review***

***Revisions to
Protocol Requested***

***Final IRB
Approval***

2007 Protocol Review Process





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The Ten Commandments for Picking a Research Project

- 1. Anticipate the Results Before Doing the First Study.**
- 2. Pick an Area on the Basis of the Interest of the Outcome.**
- 3. Look for an Underoccupied Niche that has Potential.**
- 4. 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

- 5. Build on a Theme.**
- 6. Find a Balance Between Low-Risk and High-Risk Projects, but Always Include a High-Risk, High Interest Project in Your Portfolio.**
- 7. 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

- 8. Differentiate Yourself from Your Mentor.**
- 9. Do Not Assume that Outstanding, or Even Good Clinical Research is Easier Than Outstanding Basic Research.**
- 10. Focus, Focus, Focus.**

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