

Principles and Ethics of Clinical Research

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Goals of clinical research

- New therapies
- Improving outcomes
- Reducing toxicities/side effects

History of clinical research

- Herophilos (335-280 BC)
- Avicenna (980-1037)
- Edward Jenner (1749-1823)
- Walter Reed (1851-1902)

Herophilos (335-280 BC)

- Began to use scientific inquiry in medicine.
- -used dissection
- -recognized brain as center of nervous system
- -described difference between arteries and veins
- -described changes in the pulse with disease



<http://www.hsl.virginia.edu/historical/artifacts/antiqua/alexandrian.cfm>

Courtesy of Historical Collections & Services, Claude Moore Health Sciences Library,
[University](#) of Virginia.”

<http://egyptian12.blogspot.com/2008/06/ancient-egypt.html>

Avicenna (980-1037)

- Introduced experimentation into medicine and the idea of a clinical trial.



www.sacred-destinations.com/uzbekistan/images



images.travelpod.com/users/uzbekland_okie

<http://www.newworldencyclopedia.org/entry/Avicenna>

© Paul Halsall, August 1998

Ibn Sina

- TB
- Diabetes



<http://www.newworldencyclopedia.org/entry/AvicennaPersian.jpg>



The Canon of Medicine

Avicenna

- 1. The drug must be free from any extraneous accidental quality.
- 2. It must be used on a simple, not a composite, disease.
- 3. The drug must be tested with two contrary types of diseases, because sometimes a drug cures one disease by its essential qualities and another by its accidental ones.
- 4. The quality of the drug must correspond to the strength of the disease. For example, there are some drugs whose heat is less than the coldness of certain diseases, so that they would have no effect on them.
- 3. The time of action must be observed, so that essence and accident are not confused.
- 4. The effect of the drug must be seen to occur constantly or in many cases, for if this did not happen, it was an accidental effect.
- 5. The experimentation must be done with the human body, for testing a drug on a lion or a horse might not prove anything about its effect on man.

Image: This image is from Avicenna's [Canon], Courtesy of the National Library of Medicine. The NLM caption reads, "Represented in the two miniatures shown here are the three basic stages of a physician's visit with a patient; the examination of the patient, the consultation with attendants, and possibly a written prescription or treatment procedure."

Stuff we still think about

- The effect of the drug must be seen to occur constantly or in many cases, for if this did not happen, it was an accidental effect.
- The experimentation must be done with the human body, for testing a drug on a lion or a horse might not prove anything about its effect on man."

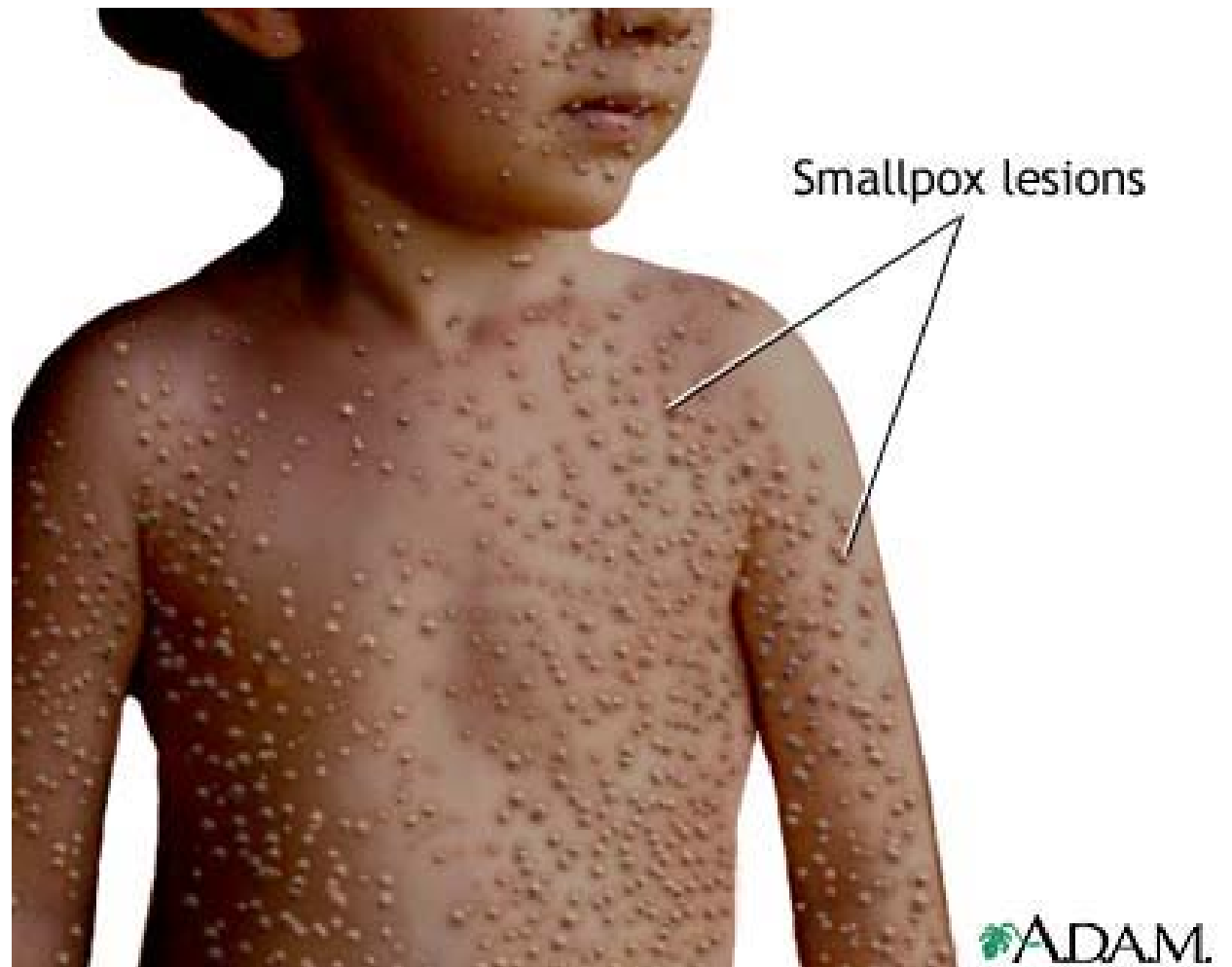
Edward Jenner (1749-1823)

- “Don’t think, try.” William Harvey



Smallpox

- In late 1700's about 20% of people died of smallpox.

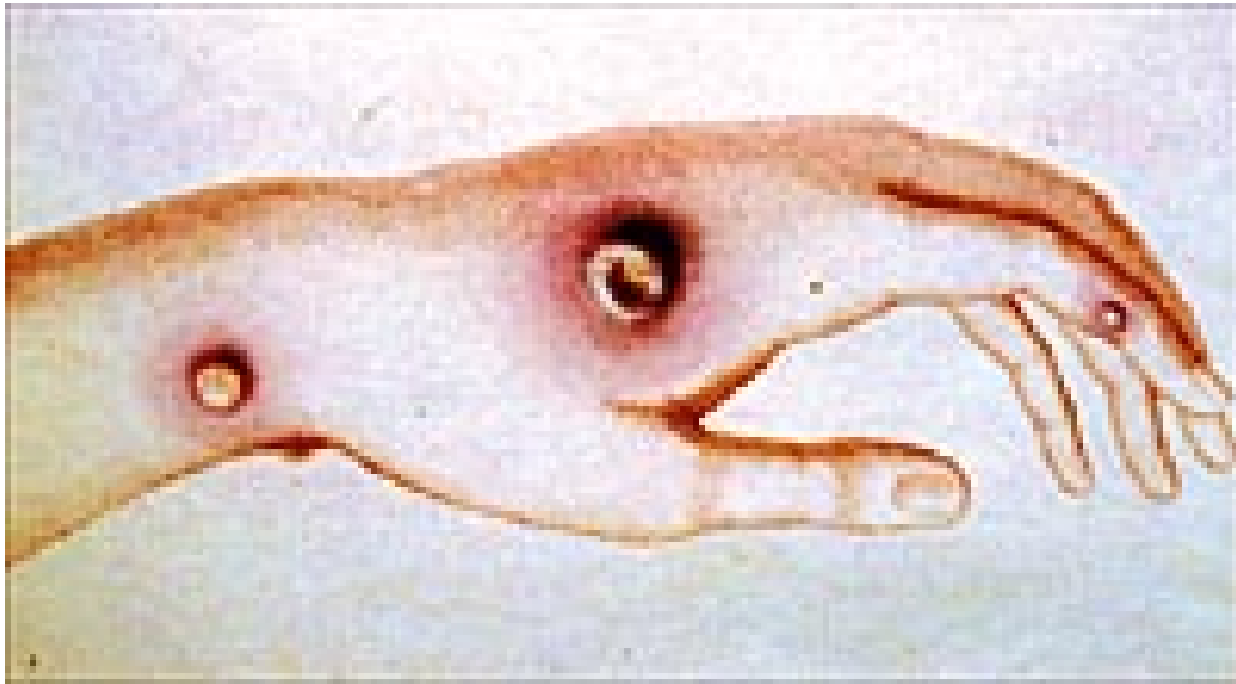


Observation

- Milkmaids didn't get smallpox.

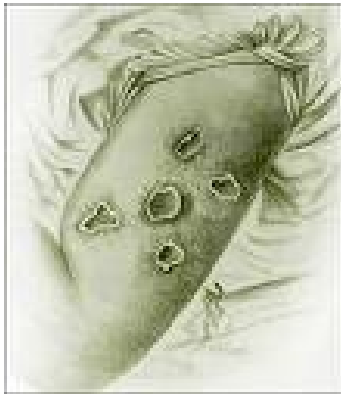


They got cowpox.



Experiment

- Jenner inoculated 17 people with the pus from cowpox blisters including James Phipps with blister pus from Sarah Nelmes after she got cowpox from Blossom the cow.



Clinical trials as of 1800

- Make an observation and develop a hypothesis.
- Try your idea on a person.

Walter Reed (1851-1902)

- Army Doctor, born in Virginia.



Walter Reed at UVa
1869

Experiments on Yellow Fever in Cuba

- Dirty bedding or Mosquitos??



<http://etext.virginia.edu/healthsci/reed/commission.html>

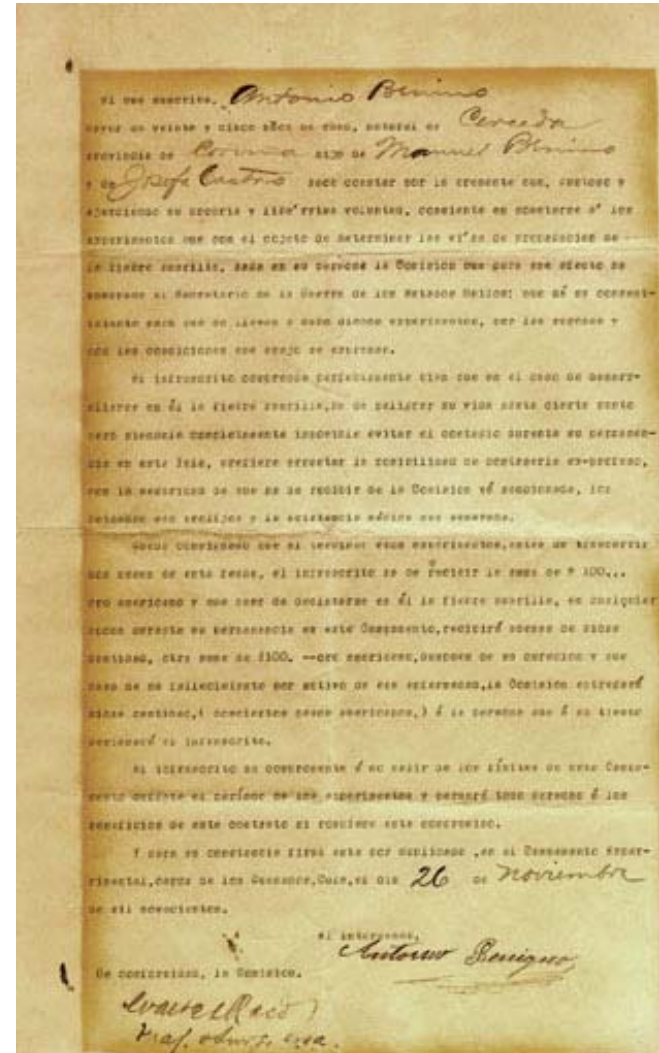
<http://ocp.hul.harvard.edu/contagion/panamacanal.html>

Reed thought patients involved in medical experiments should consent to their participation

- This was the first informed consent.

Informed consent document (in Spanish) for Antonio Benigno, November 26, 1900.

PHILIP S. HENCH WALTER REED
YELLOW FEVER COLLECTION



Reed's informed consent

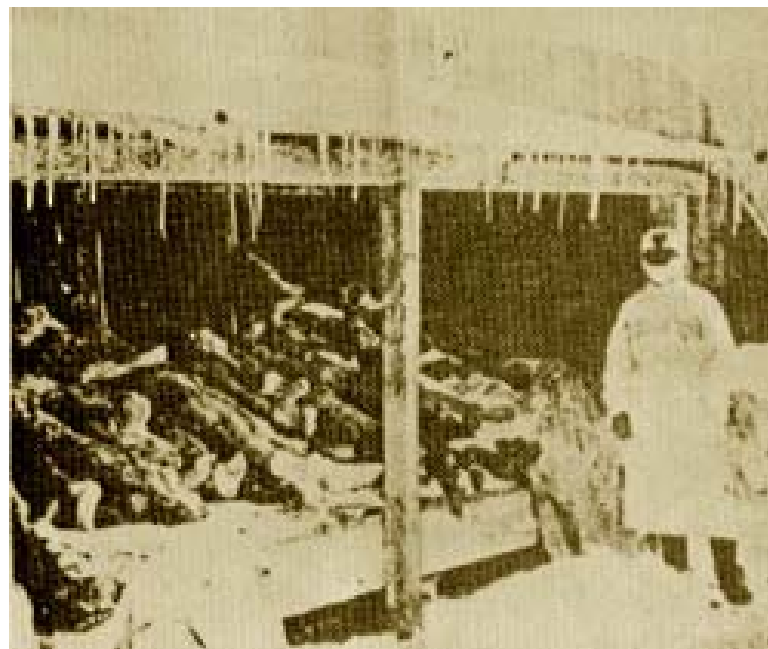
- Each volunteer explicitly consented to participate, and balanced the certainty of contracting yellow fever in the general population against the risks of developing an experimental case, followed by expert and timely medical care. The volunteers agreed to remain at Camp Lazear for the duration of the experiments, and as a reward for participation would receive \$100 "in American gold," with an additional hundred-dollar supplement for contracting yellow fever.



Reed and his daughter
Blossom, 1901

<http://etext.virginia.edu/healthsci/reed/reed.html>





Nuremberg Code

- Informed consent required for experiments.
- Experiments must be scientifically necessary and conducted by qualified personnel.
- Human trials should be preceded by animal studies and surveys of a disease's natural history.
- Benefit to science must be weighed against risks and suffering of experimental subjects.

Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law No. 10, Vol. 2, pp. 181-182.. Washington, D.C.: U.S. Government Printing Office, 1949.

The rules become better defined.

- A policy statement made by the World Medical Association in 1964, The declaration of Helsinki, forms the basis for ethical research on human subjects.

Declaration of Helsinki

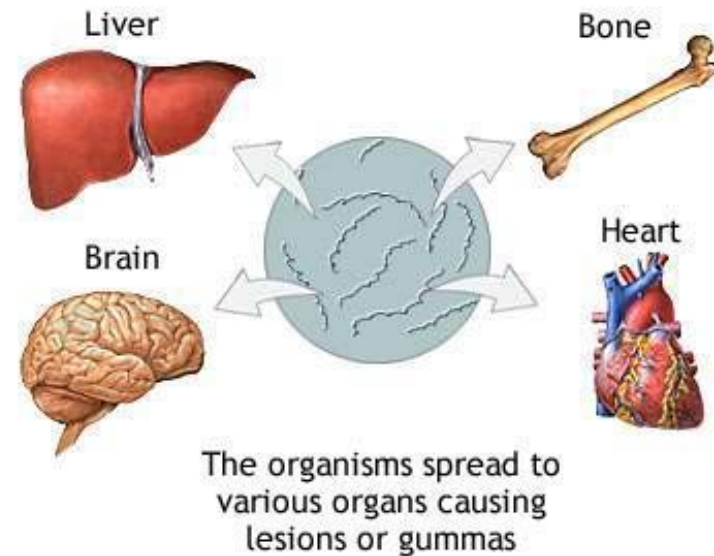
- Clinical research should be based on animal and laboratory experiments.
- Clinical research should be conducted and supervised only by qualified medical workers.
- Clinical research should be preceded by a careful assessment of risks and benefits to the patient.
- Human beings should be fully informed and must freely consent to the research.
- Responsibility for the human subject must always rest with a medically qualified person, and never with the subject.
- Results of experiments that do not comply with ethical guidelines should not be accepted for publication.
- Special care must be taken with informed consent of minors.
- Also mentions consideration of the welfare of animal subjects and the environment.

Declaration of Helsinki

- Respect for the individual
- Right to self determination
- Right to make informed decisions (informed consent)
- Needs of subject always comes before needs of society

Tuskegee Syphilis Study (1932-1972)

- 399 black men thought to have syphilis were recruited and followed to determine the course of the disease (what would happen to them).
- Penicillin was known to be an effective treatment for syphilis by about 1947.
- The subjects were not informed of what was being studied or of the treatment alternatives available.





Belmont Report

- Principal of Respect: recognizes the autonomy of humans and requires clear informed consent.
- Principal of Beneficence: Research must be shown to be beneficial and reflect the Hippocratic idea of do no harm.
- Principle of Justice: The benefits to some must be balanced against the risks to subjects.

Thalidomide



<http://engineering.cua.edu/biomedical/faculty/kirtley/synergy/&usg>

Food and Drug Act

- Requires that drugs be shown to be safe before marketing.

The 1906 Food and Drugs Act imposed purity standards and forbid adulterated or misbranded food and drugs



Life Magazine, April 29, 1909

The Federal Food, Drug, and Cosmetic (FDC) Act of 1938

- Requiring new drugs to be shown safe before marketing-starting a new system of drug regulation.
- Providing that safe tolerances be set for unavoidable poisonous substances.

1962 Kefauver-Harris Drug Amendments

- ensure drug efficacy and greater drug safety
- To show a drug works you need a clinical trial

How were we doing?

Beecher article

- Cited 22 examples of unethical human research
- Suggested that publishers should exercise judgement about whether researchers obtained informed consent and properly weighed the risks and gains, before deciding to publish results
- “Special Article: Ethics and Clinical Research,” NEJM 274 (1966), 1354-60.

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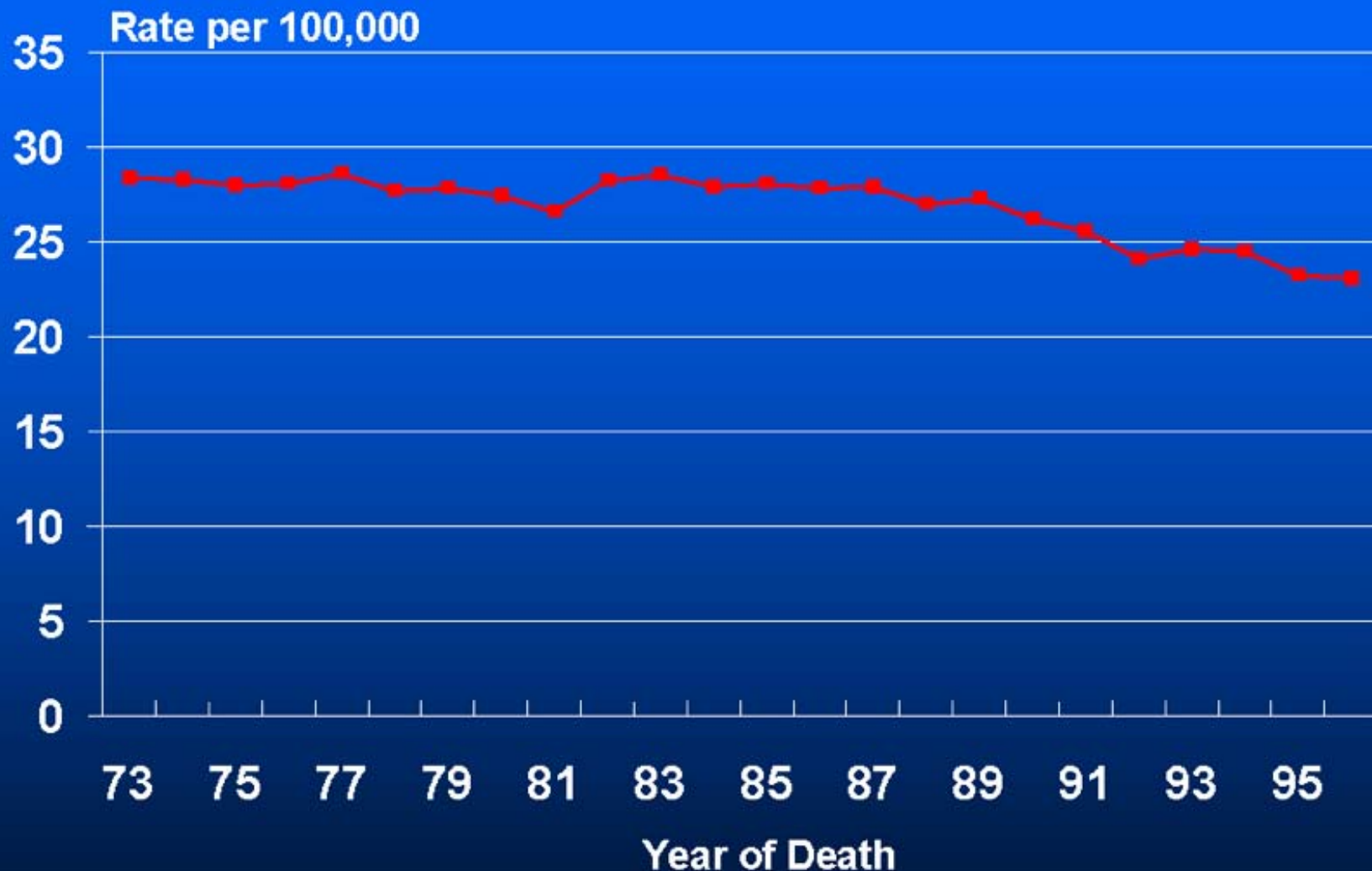
Bringing a therapy to market

- Preclinical trials
- Phase I
- Phase II
- Phase III

Application

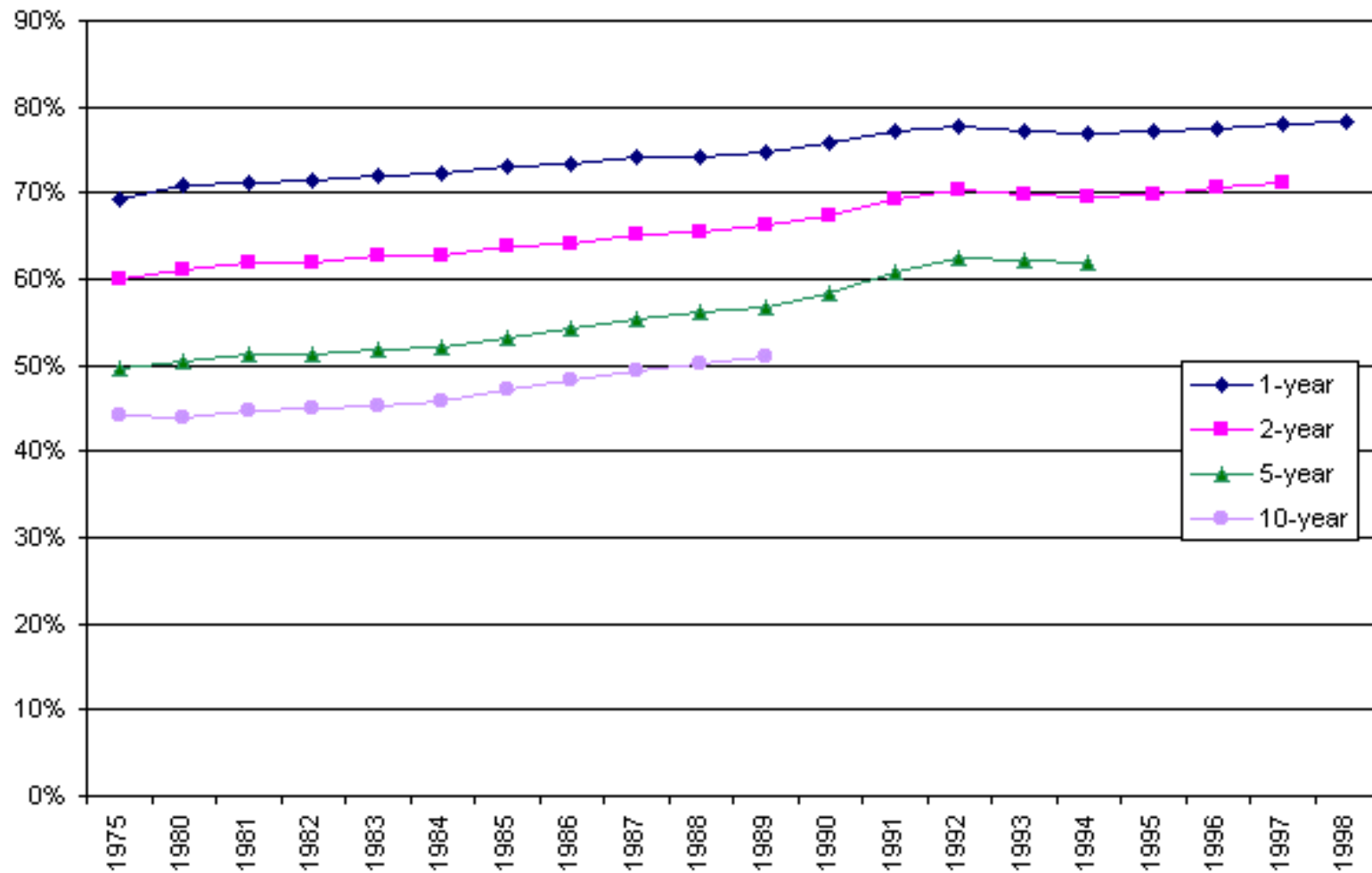
- POG/CCG/COG
- Cancer care for kids vs. adults

Female Breast Cancer Mortality, California, 1973-1996

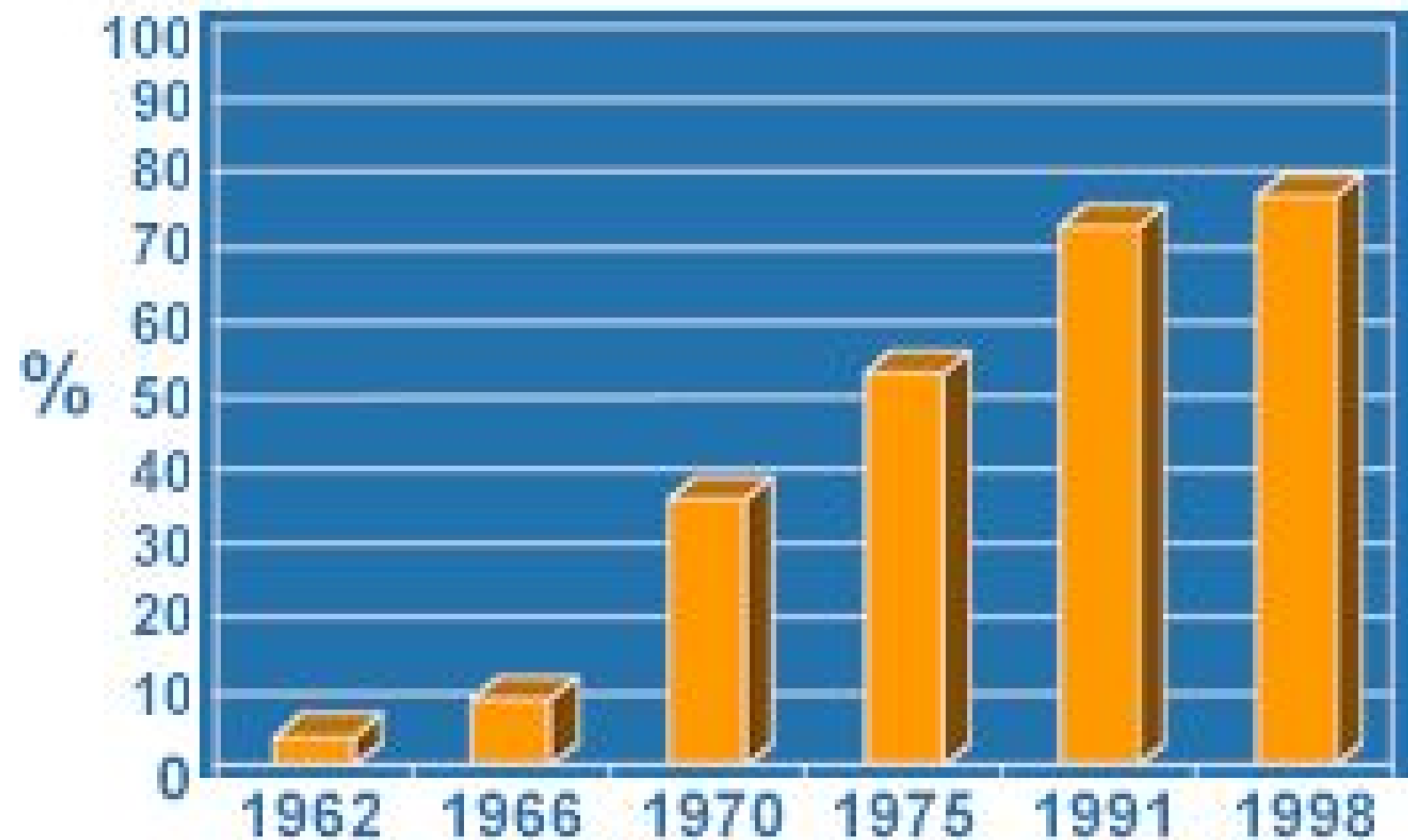


Rates are age-adjusted to the 1970 US population. Prepared by the
California Department of Health Services, Cancer Surveillance Section.

Cancer Survival Rates, All Sites



5 Year Event-Free Survival Acute Lymphoblastic Leukemia



Are clinical trials an ethical imperative?
