

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 states



Avicenna (980-1037)

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



Ibn Sina

- TB
- Diabetes



The Canon of Medicine

Avacenna

- 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."

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."

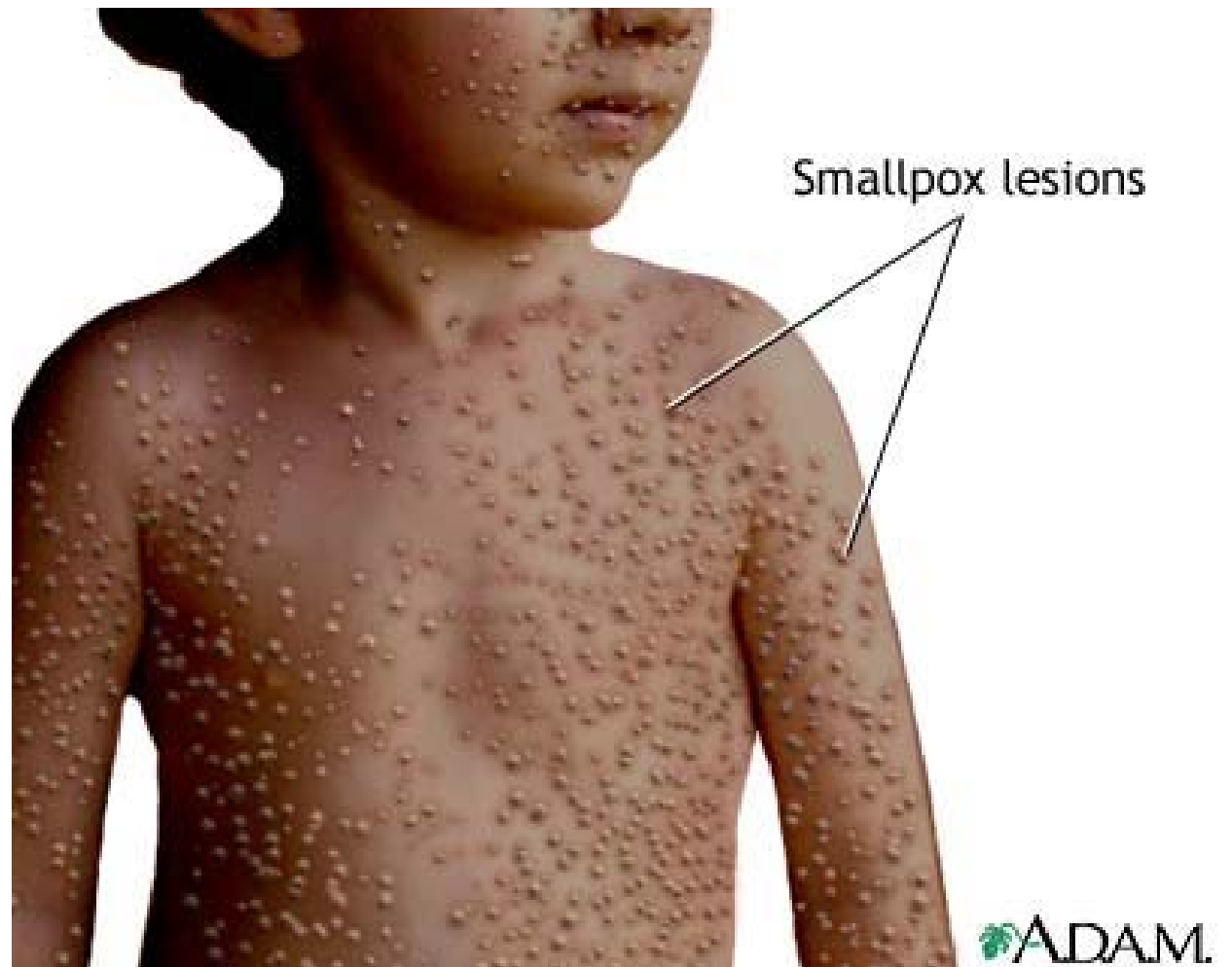
Edward Jenner (1749-1823)

- “Don’t think, try.” William Harvey



Smallpox

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



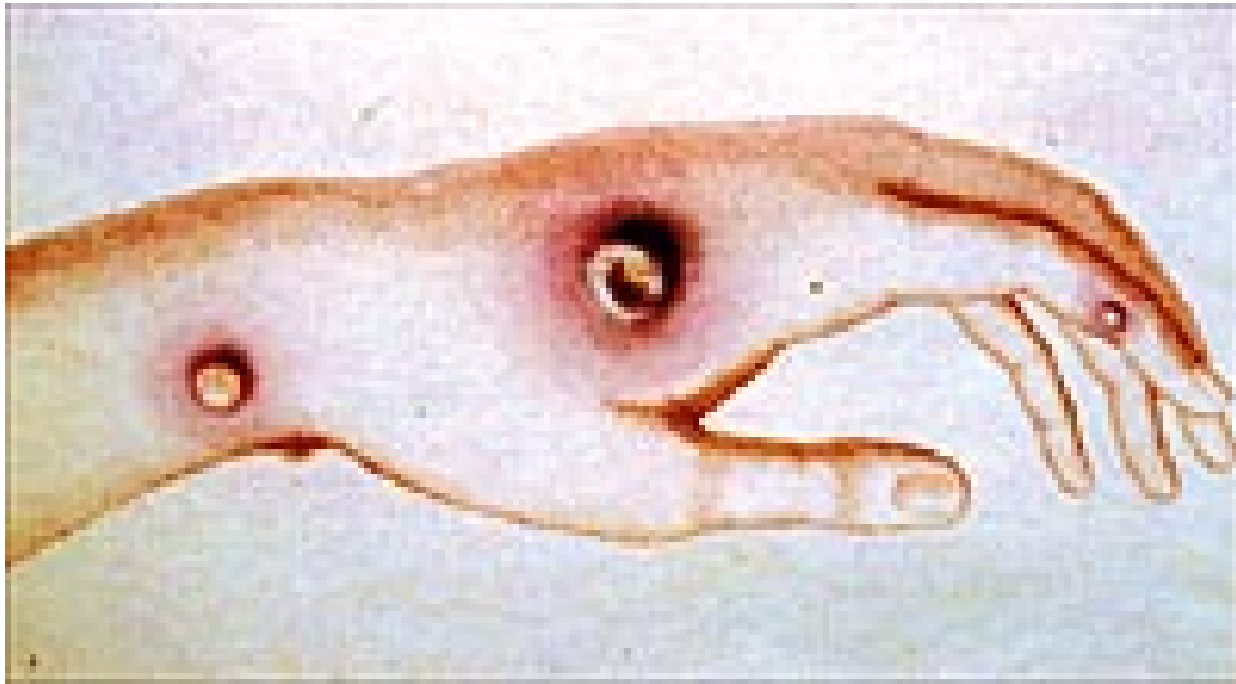
Observation

- Milkmaids didn't get smallpox.



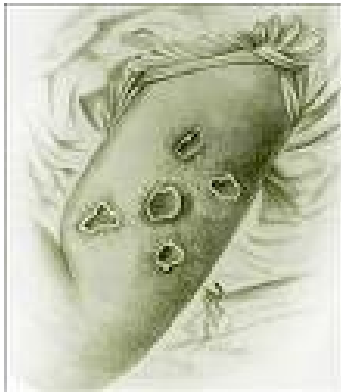
Julien Dupre

They got cowpox.



Experiment

- Jenner inoculated 17 people with the pus from cowpox blisters including James Phipps with blister pus from Sarah Nelms 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.



Research in Cuba on Yellow Fever

- Was yellow fever transmitted by fomites or a live vector?



Building Number Two (Mosquitoes)



Building Number One (Fomites)

First Informed Consent

The undersigned, *Antonio Benigno*
being more than twenty-five years of age, native of Corcega,
in the province of Corima, the son of Manuel Benigno
and Josefa Castro here states by these presents, being in
the enjoyment and exercise of his own very free will, that he consents
to submit himself to experiments for the purpose of determining the
methods of transmission of yellow fever, made upon his person by the
Commission appointed for this purpose by the Secretary of War of the
United States, and that he gives his consent to undergo the said ex-
periments for the reasons and under the conditions below stated.

The undersigned understands perfectly well that in case of the
development of yellow fever in him, that he endangers his life to a
certain extent but it being entirely impossible for him to avoid the
infection during his stay in this island, he prefers to take the
chance of contracting it intentionally in the belief that he will
receive from the said Commission the greatest care and the most skill-
ful medical service.

It is understood that at the completion of these experiments, with-
in two months from this date, the undersigned will receive the sum of
\$100 in American gold and that in case of his contracting yellow fever
at any time during his residence in this camp, he will receive in addi-
tion to that sum a further sum of \$100 in American gold, upon his re-
covery and that in case of his death because of this disease, the
Commission will transmit the said sum (two hundred American dollars)
to the person whom the undersigned shall designate at his convenience.

The undersigned binds himself not to leave the bounds of this camp
during the period of the experiments and will forfeit all right to the
benefits named in this contract if he breaks this agreement.

And to bind himself he signs this paper in duplicate, in the Experi-
mental Camp, near Quemados, Cuba, on the 26th day of November
nineteen hundred.

On the part of the Commission:
Walter Reed
Maj. & Surg., U.S.A.

The contracting party,
Antonio Benigno

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.

Coincidence?



Reed and his daughter
Blossom, 1901



Lowlights and Progress

Food Drug and Cosmetics Act 1938

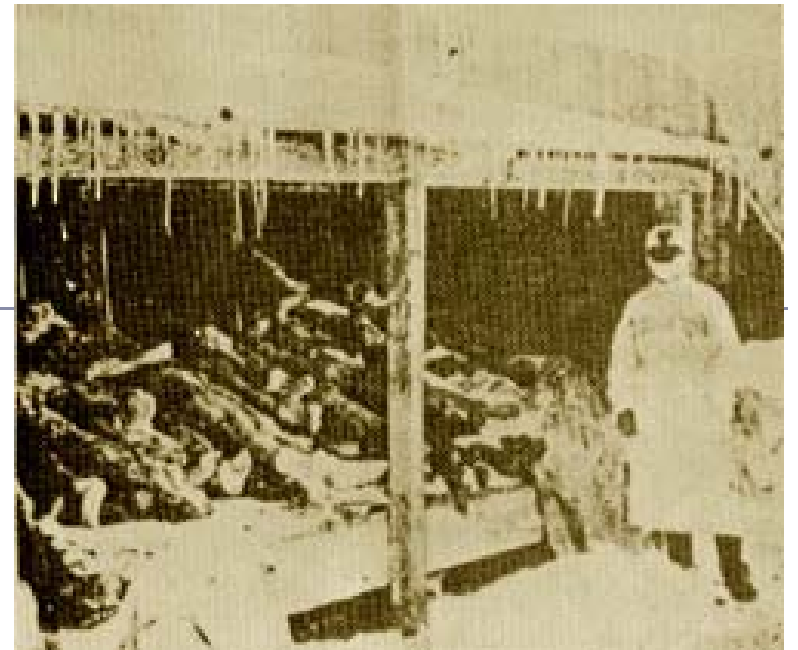
- Requires that drugs be shown to be safe before marketing. This leads to the need for human trials.



Thalidomide







Nuremberg Code 1947

- 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.

Declaration of Helsinki 1964



- 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.

Beecher article 1966

- 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.



Belmont Report 1979

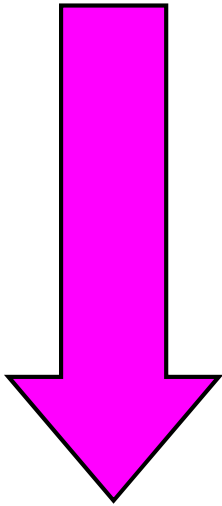
- **Principal of Respect:** recognizes the **autonomy** of humans and requires clear informed consent.
- **Principal of Beneficence:** Research must be shown to be beneficial and reflect the Hippocratic idea of do no harm.
- **Principle of Justice:** The benefits to some must be balanced against the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

Belmont report

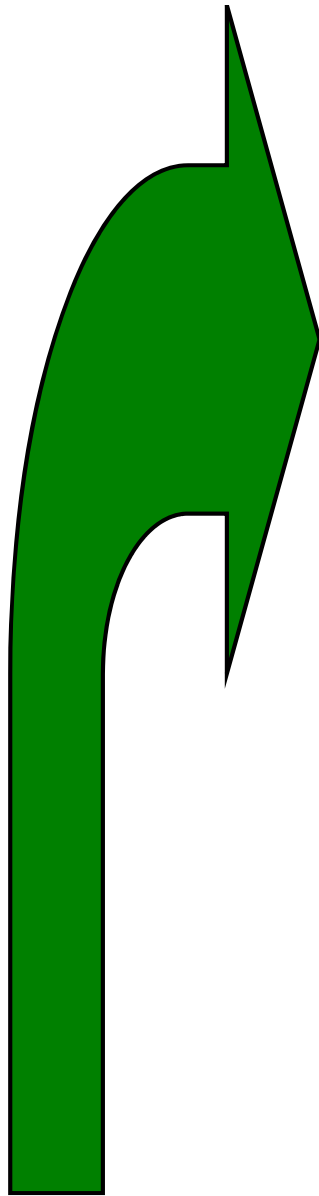
- Principles of ethical research involving human subjects
- Respect for persons
 - Autonomy
 - Protection
- Beneficence
 - Do not harm
 - Maximize benefits while minimizing possible harm
- Justice
 - Exploitation of vulnerable populations
 - Public funding and intended treatment population

How do we find new drugs?

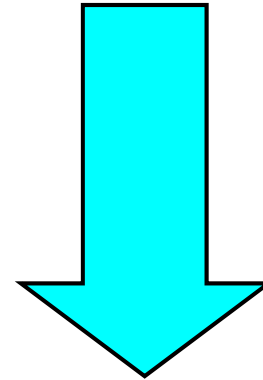
Idea



Identify Target



Find Drug



**Test in Cells
and Animals**

This takes a long time

How do we start testing it in people?

IRB

INSTITUTIONAL REVIEW BOARD
UMDNJ New Brunswick / Piscataway Campus

Phase I trial

- Is it safe to give to people?
- What is the correct dose?



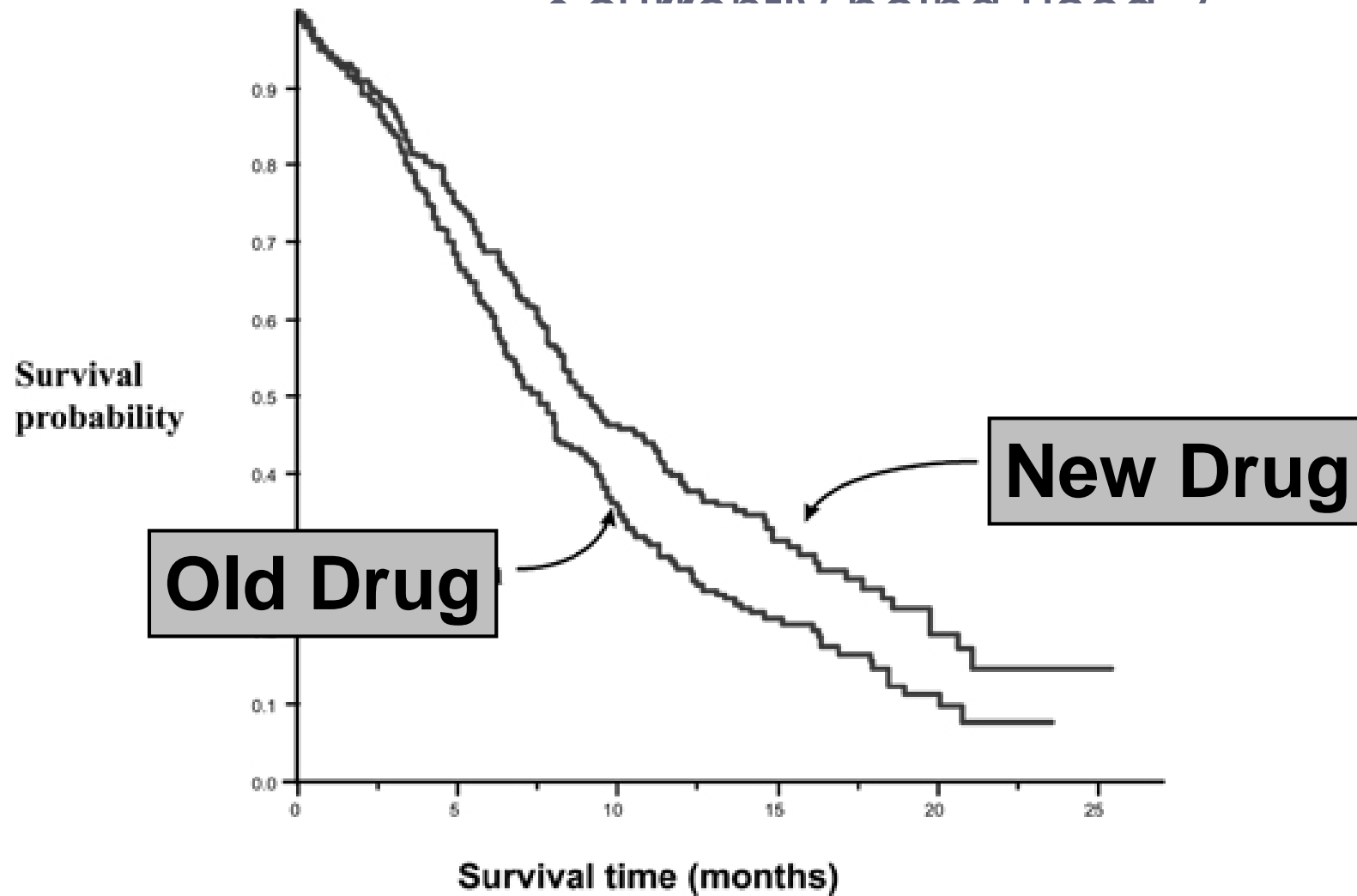
Phase II Clinical Trial

- Does it work?



Phase III Clinical Trial

- Does it work better than what is currently being used?



If a drug works in animal models and in the lab why do we still need to test it in people?

Remember Avicenna

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.

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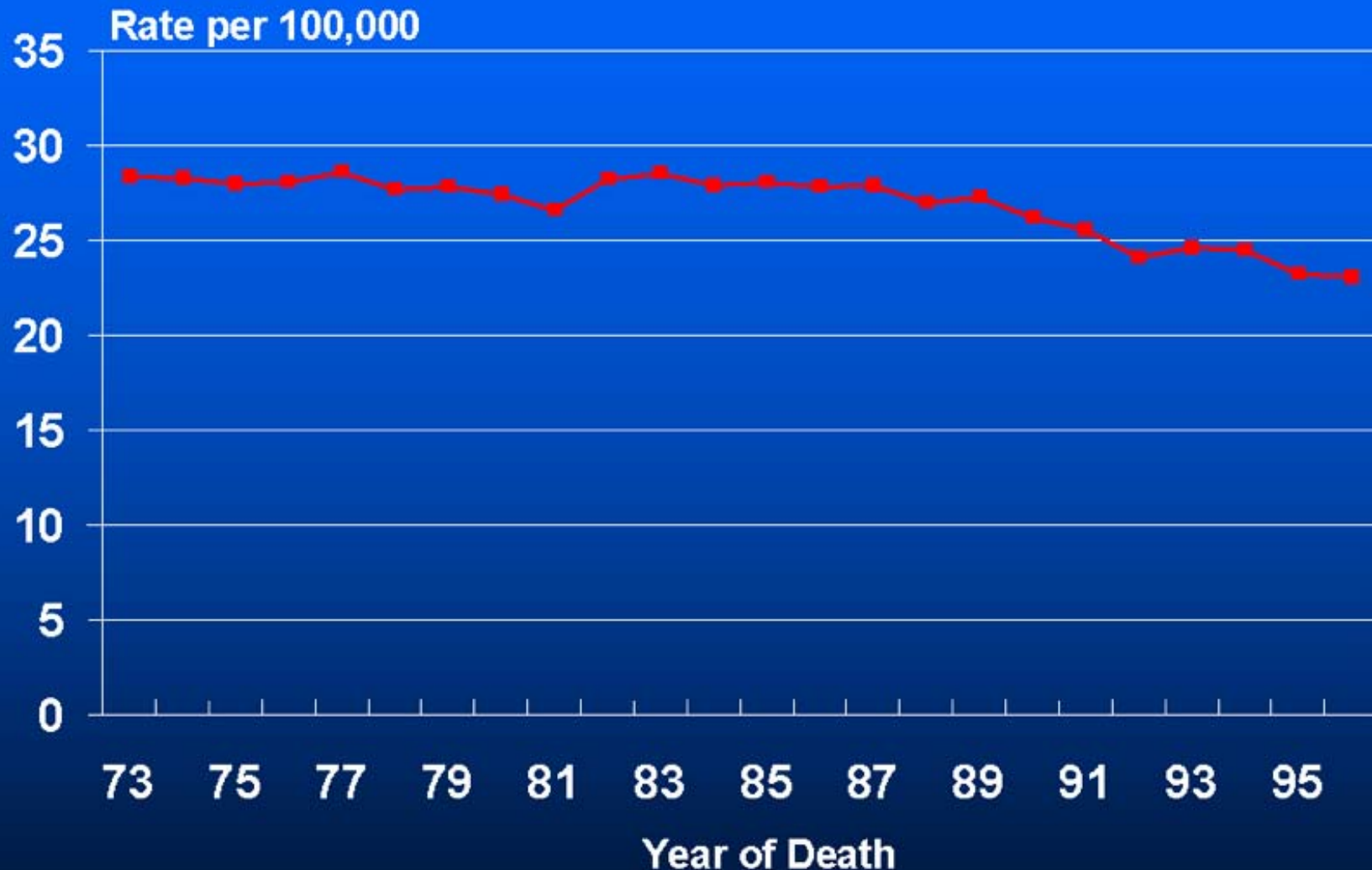
Why do clinical research?

Do clinical trials really make a difference?

- Benefit to future patients.
- Benefit to Current Patients.

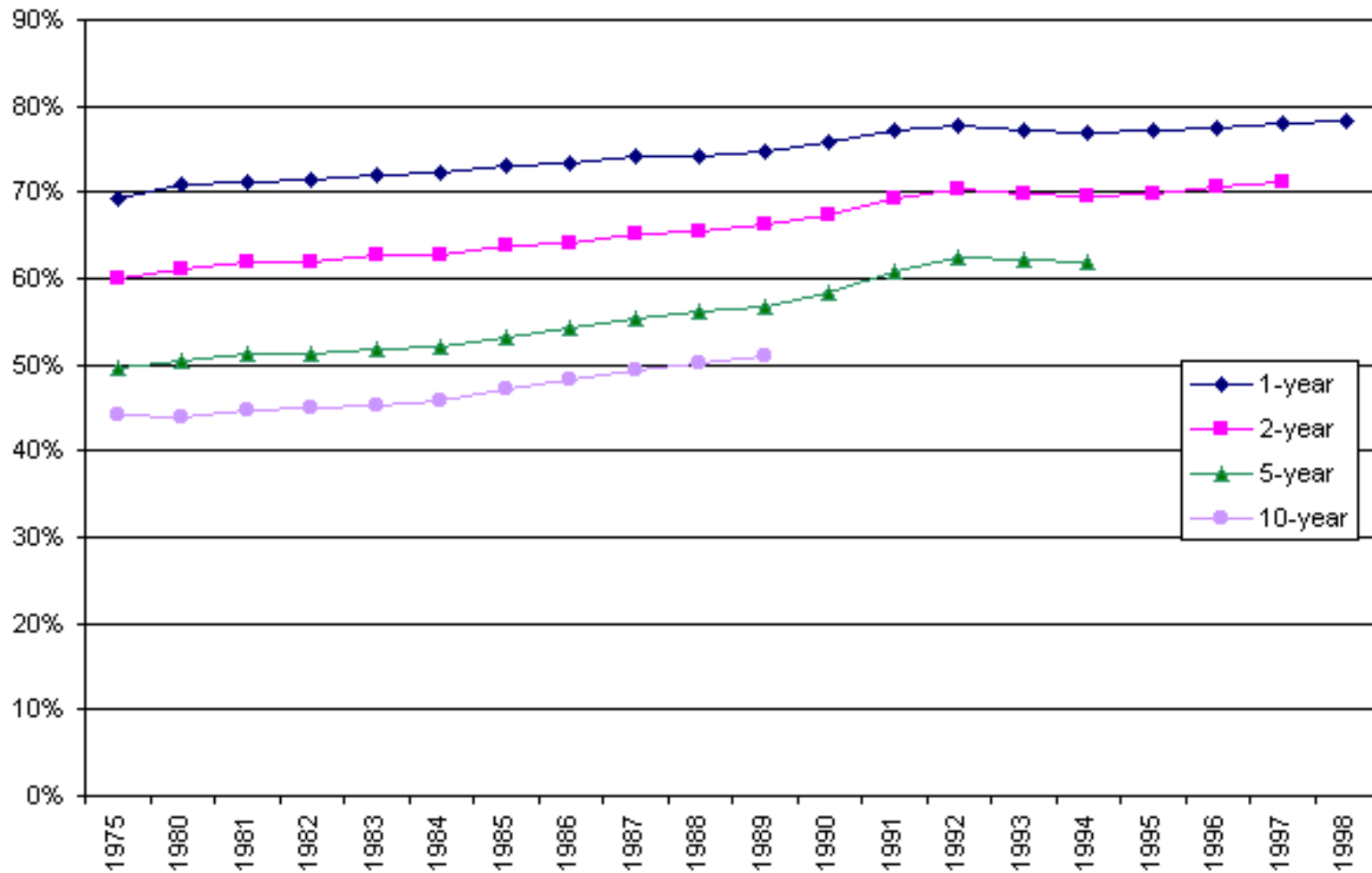


Female Breast Cancer Mortality, California, 1973-1996

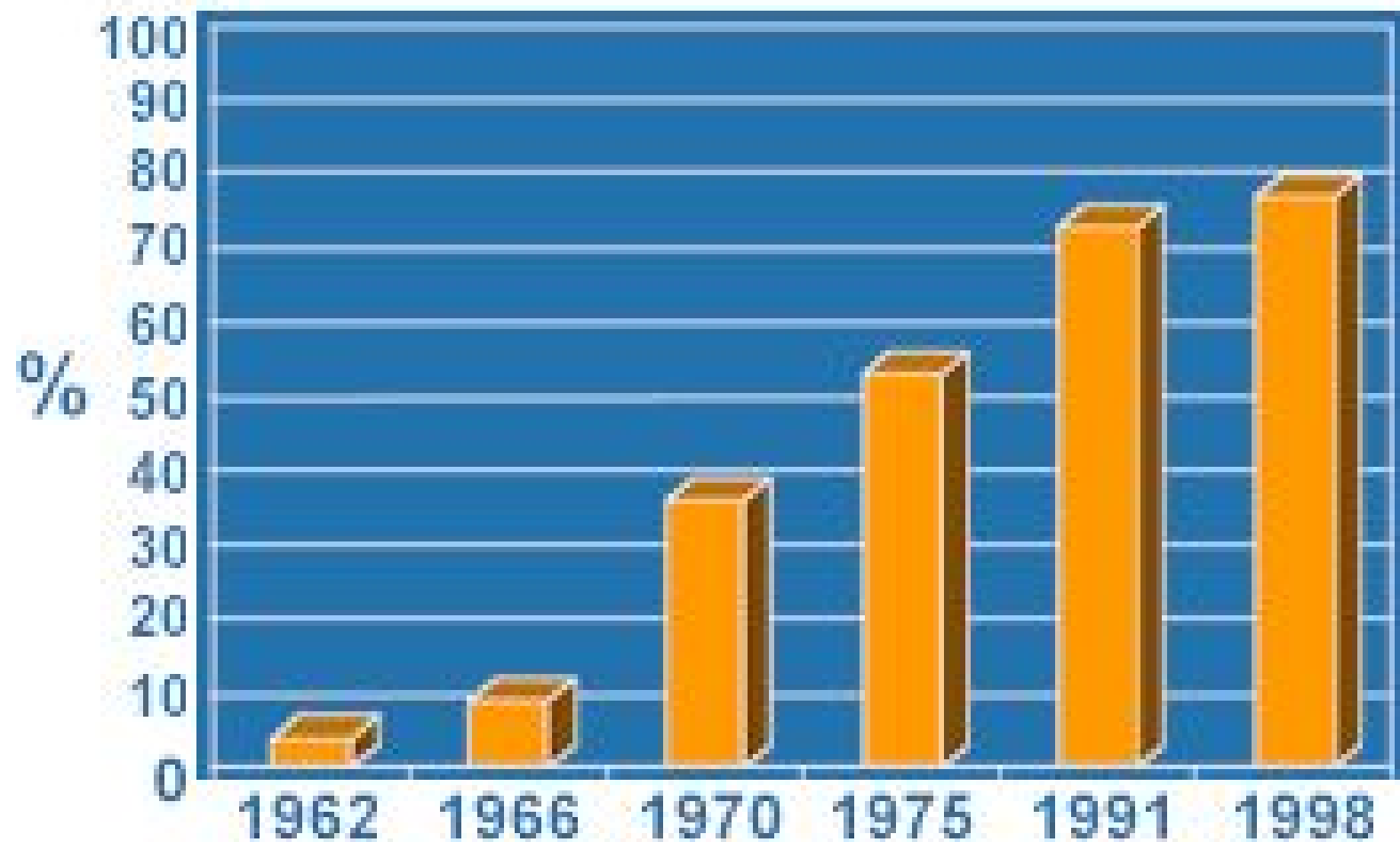


Rates are age-adjusted to the 1970 US population. Prepared by the
California Department of Health Services, Cancer Surveillance Section.

Cancer Survival Rates, All Sites



5 Year Event-Free Survival Acute Lymphoblastic Leukemia



Challenges for the future.

- How do we protect patient's privacy?
- How can we go through drugs more rapidly?
- Can we divide diseases into smaller groups?