RESEARCH 101
Session 1:

Research History and Background, Evolution of Regulations and Guidance

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Key Points

The Science - Clinical Trial Study Design

The Ethics - Protection of Human Subjects

U.S. Regulations and Guidance ---Study Conduct

Objectives:

Recognize the events in history that led to the drafting of ethical and regulatory guidelines for clinical research in the U.S.

Explain the major provisions of the national Research Act of 1974 - Include the impact on the ethical and regulatory considerations for clinical studies.

Clinical Research
is
Research involving Humans

- To examine physical, mental and/ or behavioral attributes of an individual or group of people

- To collect information that contributes to our collective memory and general knowledge about individuals and groups of people

Clinical Trials

A special type of Clinical Research that evaluate the effects of an intervention on biomedical or health–related outcomes.

The function of the controlled clinical trial is not the "discovery" of a new drug or therapy. The function of the formal controlled clinical trial is to separate the relative handful of discoveries which prove to be true advances in therapy from a legion of false leads and unverifiable clinical impressions, and to delineate in a scientific way the extent of and the limitations which attend the effectiveness of drugs."

William Thomas Beaver, MD
PHARMA v. Robert Finch and Herbert Ley
1969

Contributions to “The Science”

These early physician /investigators through their ***Curiosity, Observation, and Documentation*** pioneered a rigorous research method for new treatments.

Study Design

First Documented Clinical Study

Problem: Daniel and his friends cannot eat the food ordered by the king

Daniel Refusing the King's Meat and Wine, by Del Parson, © 1983 IRI

(Daniel 1:5-16).

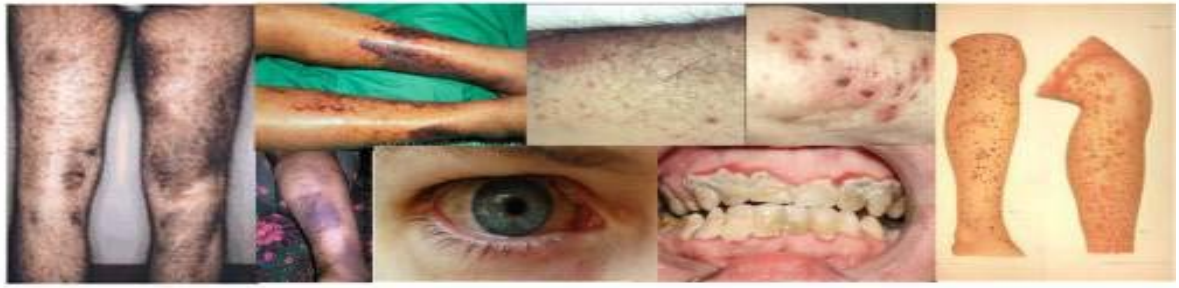
First Novel Therapy

Problem: Gunshot wounds (guns used in battle for the first time in 16th century)

Ambroise Pare
1537, Siege of Turin

First Controlled Clinical Trial

Problem: Sea Scurvy



James Lind's Experiment, 1747

Twelve sailors with same symptoms of scurvy; each pair received one of the following interventions

- Quart of cider a day
- 25 drops vitriol 3x a day
- 2 spoons of vinegar 3x a day
- Half pint of sea water a day
- Paste of garlic, mustard seed, dried radish and myrrh
- An orange and two lemons

Although the benefits of citrus had been known for centuries, Lind's study confirmed the addition of citrus fruit to the diet as superior to other remedies.

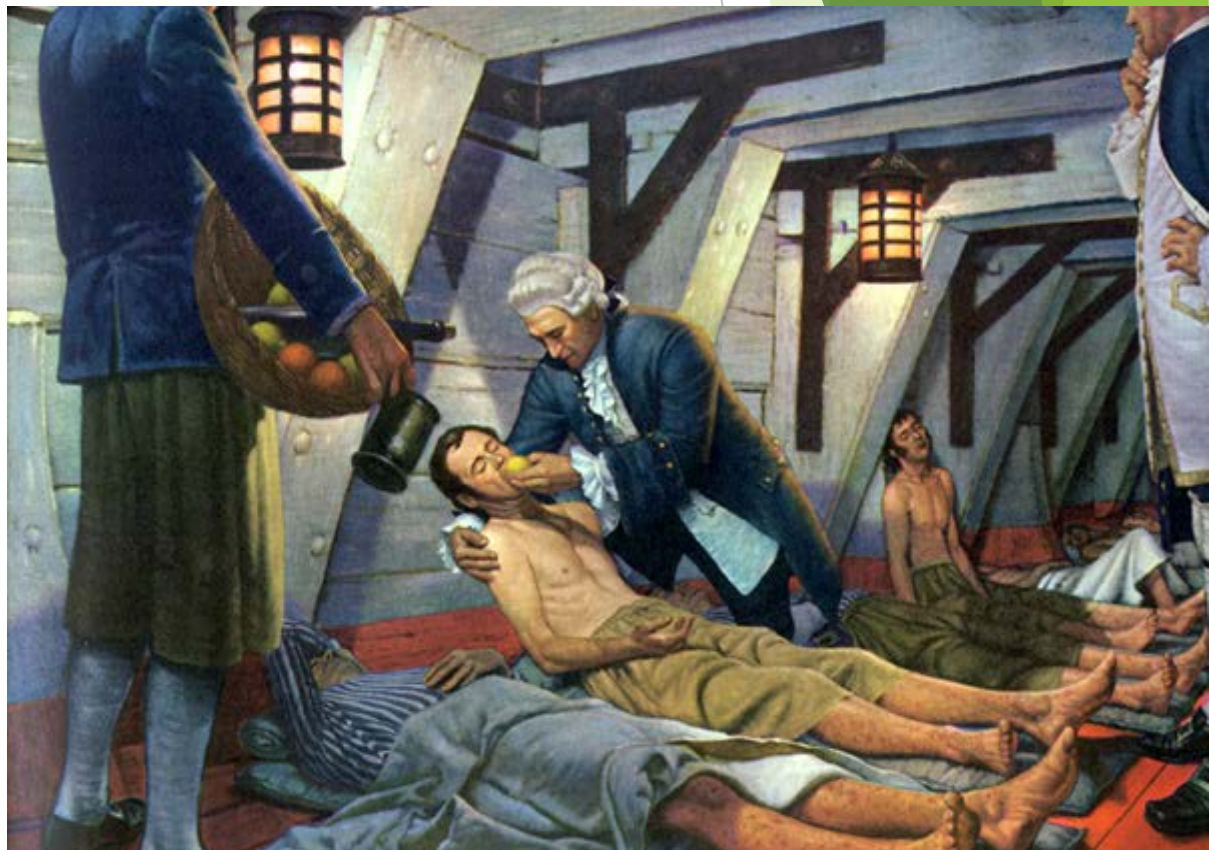
All were treated the same except for the tx

A common laxative

Vitriol is sulfuric acid

Published his finding on scurvy in a treatise in 1753

Navy did not adopt the changes for another 42 years



First Double Blind Controlled Clinical Trial

Proble : The Common cold

British Medical Research Council- 1943 – 44
Multi-center study to compare Patulin to placebo.

Patulin a fungal metabolite (mycotoxin) from rotting apples (Penicillium patulum) was compared to placebo

W. A. Hopkins, M.D.
Bradford Hill, M.D.
Army and Navy Trials

"An Apple a Day…"

First Randomized, Double–blind Controlled Clinical Trial 1948

Problem: Penicillin ineffective against Pulmonary Tuberculosis

… tuberculosis was the most important cause of death (50% mortality) of young adults in Europe and North America. Study was to measure the efficacy of Streptomycin to treat Pulmonary tuberculosis

Bradford Hill, M. D.

Phillip D'Arcy Hart

The randomized, double blind controlled trial is still considered the gold standard for today's clinical investigations.

“The Ethics” - Protection of Human Subjects

Prior to the twentieth century, research ethics were primarily governed by physicians’ conscience and professional codes of conduct.

In the previous examples “patients/subjects” were not informed that they were involved in experimental treatments.

Patients expected that the treatment or intervention was for therapeutic purposes

Early U.S. Court Cases

Carpenter V. Blake, 1871

Earliest significant contribution to human subject protections

The Carpenter court held that a doctor who departs from the usual, established method of treatment is liable for any resulting problems.

Fortner v. Koch, 1935

For the first time, the court recognized that some human experimentation must be permitted – specifically , *Therapeutic Research*, experiments that could potentially benefit the patient.

The court imposed two important limits on such experimentation, namely that the subject must consent and that the procedure not deviate too much from established practice.

In the meantime – in Europe

The Berlin Code of Ethics, 1900

"Prussian Standards"

- First regulations by a state authority for human experimentation
- Became a part of physician employment contracts
- Binding under German law

The Royal Prussian Minister of Religious, Educational and Medical Affairs

Directive to all medical directors of university hospitals, polyclinics, and other hospitals

I. I advise the medical directors of university hospitals, polyclinics, and all other hospitals that all medical interventions for other than diagnostic, healing, and immunization purposes, regardless of other legal or moral authorization, are excluded under all circumstances, if

(1) the human subject is a minor or not competent due to other reasons;

(2) the human subject has not given his unambiguous consent;

(3) the consent is not preceded by a proper explanation of the possible negative consequences of the intervention.

II. At the same time I determine that

(1) interventions of this kind are to be only performed by the medical director himself or with his special authorization;

(2) in all cases of these interventions the fulfillment of the requirements of I (1-3) and II (1), as well as all further circumstances of the case, are documented in the medical record.

III. The existing instructions about medical interventions for diagnostic, healing, and immunization purposes are not affected by these instructions.

Berlin, 29 December 1900
The Minister for Religious ec. Affairs
Studt

Guidelines for New Therapy and Human Experimentation'
“Reich Instructions”

1931

Expanded on the Berlin Code of Ethics

1) No experimentation on patients who were poor or socially disadvantaged.

2) Proportionality of risk and benefit must be respected, and

3) that experiments should first be done in animals.

4) Experimentation with dying persons not permissible, and

5) Made the head of the institution personally and professionally responsible for the design, implementation and review of human experimentation

Rise of Adolf Hitler and the Third Reich, 1933

The earlier human protection directives were reversed and laws were passed to control reproduction and achieve racial cleansing.

1. Sterilization Act of 1933 - Protect the Hereditary Health of the German People

2. Reich Citizenship law

3. Nuremberg Laws of 1935 - Safeguard Marital Health

Euthanasia Program - “life unworthy of life, ”1939

- This program authorized doctors to identify and destroy those who were “undesirable” in the population.
- In Berlin, a state organization was formed, which allowed doctors to examine hospital and clinic records.
- Between 1939 and 1941, doctors sentenced 70,000-100,000 Germans to death through their experiments in “perfecting methods of group killings”
- Public forced a shut down of the domestic euthanasia program – Hitler set up the death camps

Nazi Doctors' Trial, 1946: USA vs. Karl Brandt, et al

Prosecution of 23 doctors and administrators participating in war crimes and crimes against humanity in the form of medical experiments and medical procedures inflicted on prisoners and civilians without their consent

The specific crimes charged included more than twelve series of medical experiments concerning the effects of and treatments for high altitude conditions, freezing, malaria, poison gas, sulfanilamide, bone, muscle, and nerve regeneration, bone transplantation, saltwater consumption, epidemic jaundice, sterilization, typhus, poisons, and incendiary bombs.

"Permissible Medical Experiments" (Nuremberg Code)

Considered the basic text of modern medical ethics for human experimentation

First *INTERNATIONAL* document that advocated for informed consent and voluntary participation and imposed limits on how experiments could be conducted.

Compliance and enforcement left to the investigator

Nuremberg Code

1. *The voluntary consent of the human subject is absolutely essential*

2. *The experiment should aim at positive results for society that cannot be procured in some other way.*
3. *It should be based on previous knowledge (like, an expectation derived from animal experiments) that justifies the experiment.*
4. *The experiment should be set up in a way that avoids unnecessary physical and mental suffering and injuries.*
5. *It should not be conducted when there is any reason to believe that it implies a risk of death or disabling injury.*
6. *The risks of the experiment should be in proportion to (that is, not exceed) the expected humanitarian benefits.*
7. *Preparations and facilities must be provided that adequately protect the subjects against the experiment's risks.*
8. *The experiment should be conducted only by scientifically qualified persons.*
9. *The human subjects must be free to immediately quit the experiment at any point when they feel physically or mentally unable to go on.*
10. *Likewise, the medical staff must stop the experiment at any point when they observe that continuation would be dangerous.*

Post Nuremberg ---1947 – 1974

Novel therapies and experiments continued to be performed on unsuspecting US populations by researchers without consent including those populations that we would now consider “vulnerable”.

- Pregnant Women
- Children
- Mentally disabled
- Prisoners
- Military personnel
- Elderly
- Terminally ill
- Infants

Especially egregious were the experiments on the US population and military by the Atomic Energy Commission.

First Federal Policy for Protection of Human Subjects 1953

The first U.S. Federal policy for the protection of human subjects was put into place for research conducted at the Clinical Center, NIH.

This system is the model for the current IRB system.

NIH Policy, 1966

It required prospective review of human subjects research, taking into account the rights and welfare of the subjects involved, the appropriateness of the methods used to secure informed consent, and the risks and potential benefits of the research.

Declaration of Helsinki, 1964

Many in the medical community saw the Nuremberg Code as imposing strict legal obligation on Doctors.

World Medical Association prepared recommendations as a guide to every physician in biomedical research involving human subjects.

Informed consent requirement based on whether the research was considered Therapeutic or Non-therapeutic.

Obedience to Authority Study

Stanley Milgram
Yale University
Deception in Research

"Tuskegee Study of Untreated Syphilis in the Negro Male," 1932- 1972

Based on finding of the Oslo Study of the natural history of 2000 cases of untreated syphilis 1890 – 1910 and follow up 1921 – 1928

(Aus der Dermatologischen Universitätsklinik in Oslo.)

Über das Schicksal der nicht spezifisch behandelten Luetiker.

Von

E. Bruusgaard.

(*Eingegangen am 23. Oktober 1928.*)

Aus den pathologisch-anatomischen Instituten in Eppendorf sowie aus denen der Charité und des Rudolf Virchow-Krankenhauses sind eine Reihe größerer Statistiken über die syphilitischen Arterienaffektionen

National Research Act, 1974

Three major provisions

1. Office of Protection from Research Risks (OPRR) in the NIH
2. Promulgated 45 CFR 46 Public Welfare Regulations for the Protection of Human Subjects
3. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research*

- Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research

45 CFR 46
Public Welfare, Protection of Human Subjects

National Research Act required DHEW to adopt the 1966 NIH policy for protecting human subjects as part of the public welfare regulations.

The 1974 regulations at 45 CFR 46 were amended and re-issued in **1981** **with provision that they only applied to federally funded research**

Oversight of federally funded human research was assigned to
Office of Protection from Research Risks in the NIH

1991
45 CFR 46 subpart A was adopted by 17 federal agencies – called the “Common Rule”

Regulations & Guidance: Good Clinical Practice

- Is comprised of the FDA Regulations and guidance documents, the ICH guidelines for good clinical practice and ethical codes of conduct in clinical trials such as the Declaration of Helsinki and the Belmont Report

- Is a standard for the design, conduct, performance, monitoring, recording, analysis and reporting of clinical trials

- Ensures the rights, safety and welfare of subjects are protected and the integrity of the study data is maintained

Good Clinical Practice in Clinical Trials

Concurrent to the drafting of ethical guidelines and regulations , authorities began to recognize the need for controlling medical therapies early in the 20th Century

Predecessor office to the current Food and Drug Administration (FDA) was the Chemistry Division, a scientific department, in the Department of Agriculture established in 1862.

Major function was to test pesticides and other agricultural products
(included preservatives in foodstuffs)

FDA consumer oversight function of food and drug products began in 1906

The role of the FDA as a consumer protection agency has evolved and expanded

“FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation’s food supply, cosmetics, and products that emit radiation.”

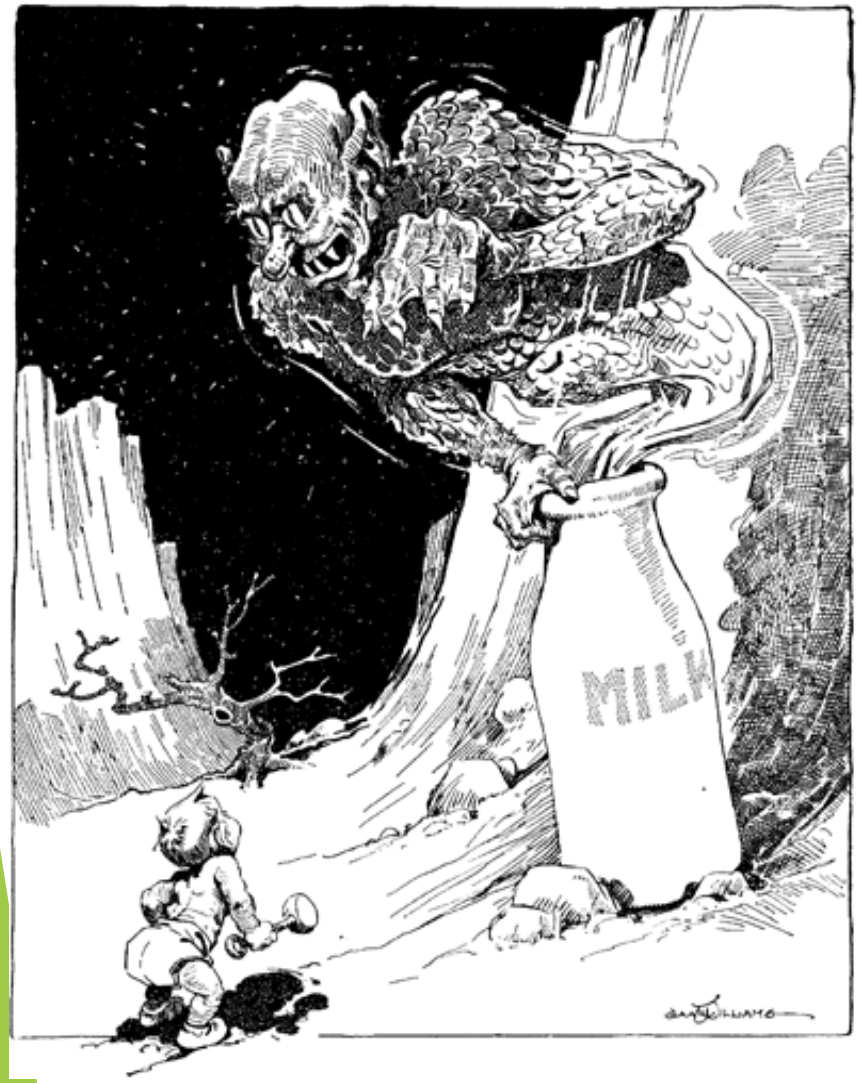
Turn of the Century in the United States - 1900

“Adulterated Foods”

“Patent Medicines” trade

Publication of “The Jungle”

Adulterated Foods

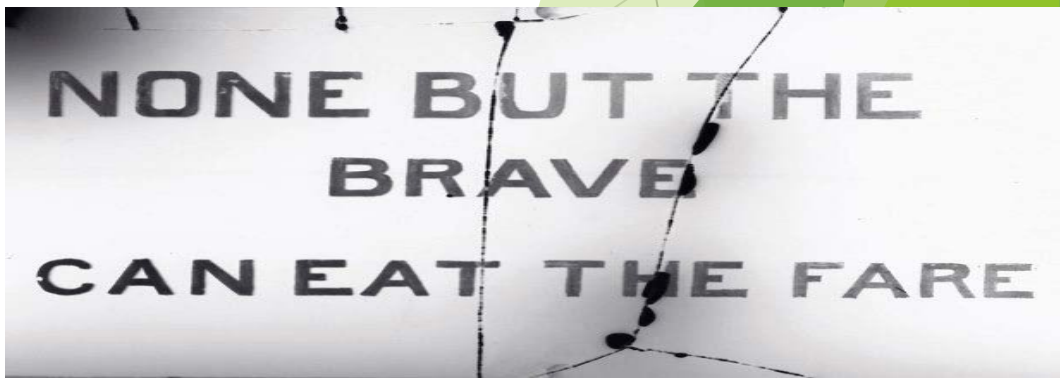


Chemistry Division, Department of Agriculture

"…investigate the character of food preservatives, coloring matters, and other substances added to foods, to determine their relation to digestion and to health, and to establish the principles which should guide their use."

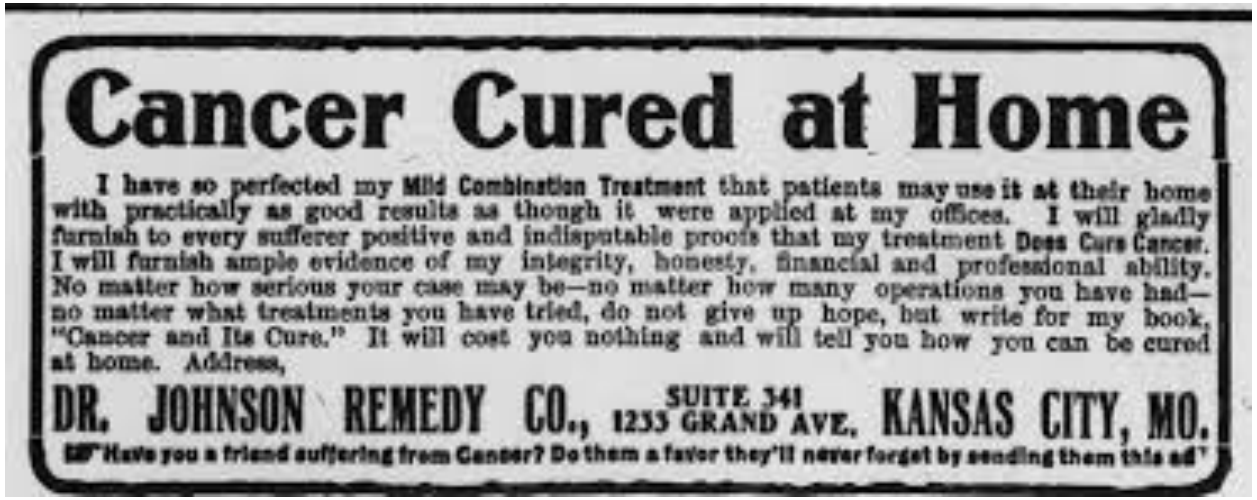
Common Additives/ Preservatives

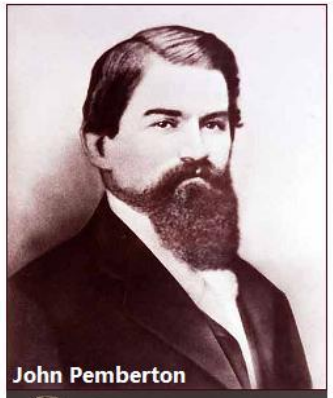
- Borax
- Copper Sulfate
- Sulfuric Acid
- Potassium Nitrite
- Benzoic Acid
- Alum
- Formalin

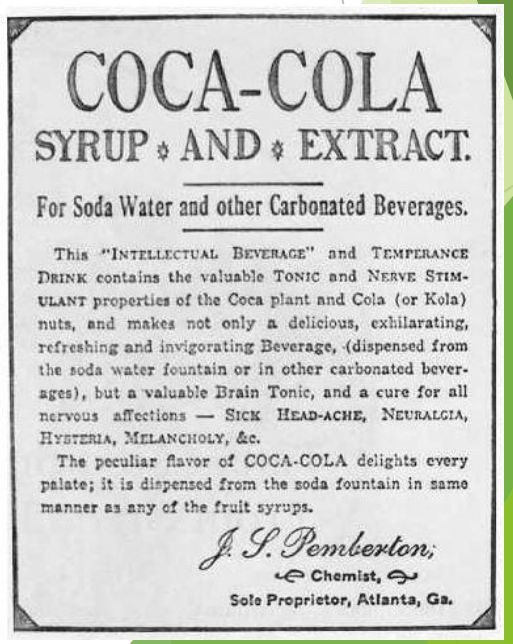


The Patent Medicine Trade

Outrageous Advertising - “Secret” Ingredients

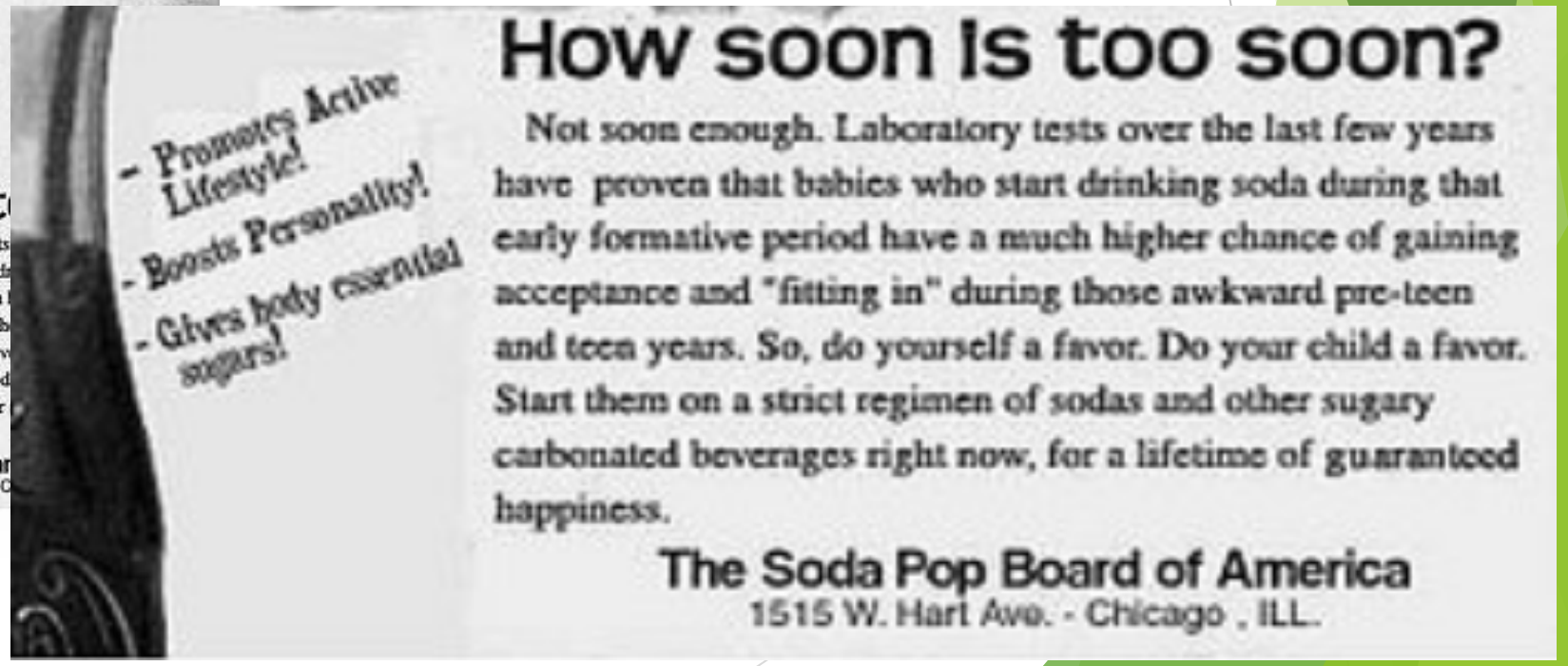






http://thecitydesk.net

"Brain Tonic"



The Jungle

Sinclair wrote how diseased, rotten, and contaminated meat products were processed, doctored by chemicals, and mislabeled for sale to the public.

…how workers would process dead, injured and diseased animals after regular hours when no meat inspectors were around – or paid them off

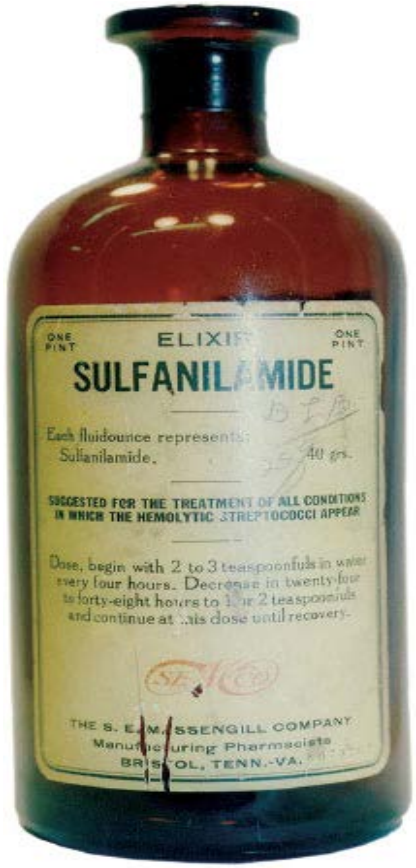
The Pure Food and Drug Law of 1906

LANDMARK LEGISLATION

The federal government assumed permanent and comprehensive (law enforcement) responsibility for the health and safety of the American food and drug supply for the first time.

First U.S. Consumer Protection law of the 20th Century

Sulfanilamide Disaster, 1937



"…to realize that six human beings, all of them my patients, one of them my best friend, are dead because they took medicine that I prescribed for them innocently, and to realize that that medicine which I had used for years in such cases suddenly had become a deadly poison in its newest and most modern form, as recommended by a great and reputable pharmaceutical firm in Tennessee: well, that realization has given me such days and nights of mental and spiritual agony as I did not believe a human being could undergo and survive"

A.S. Calhoun, MD

Food, Drug and Cosmetic Act of 1938

The only remedy for such a situation (Sulfanilamide Disaster) is the enactment by Congress of an adequate and comprehensive national Food and Drugs Act which will require that all medicines placed upon the market shall be safe to use under the directions for use. ...“

Required

“substantial” evidence that a new drug was safe for use and be reported to the FDA*
Required a FDA approval of new drug for market

**Doesn’t specifically require animal testing in the law: however animal testing has become the default standard for the FDA and the agency will generally ask for toxicity test results using at least two species of animals*

Thalidomide Tragedy, 1957 – 1961

Synthesized in Germany and marketed over the counter in 1957 as a sedative under the trade name Kevadon.

Distributed in 46 countries -------wildly popular as the only non-barbiturate sedative available

An Australian obstetrician discovered that the drug also alleviated morning sickness. He started recommending this off-label use of the drug to his pregnant patients, setting a worldwide trend.

Thalidomide Tragedy

- In 1960 the FDA was petitioned to approve distribution in the US.
- Dr. Francis Kelsy held up the application for over a year –by then reports of the birth defects were being associated with Thalidomide use.

Linked to Malformed Babies

'Heroine' of FDA Keeps Bad Drug Off of Market

By Morton Mintz
Staff Reporter

This is the story of how the skepticism and stubbornness of a Government physician prevented what could have been an appalling American tragedy, the birth of hundreds or indeed thousands of armless and legless children.

The story of Dr. Frances Oldham Kelsey, a Food and Drug Administration medical officer, is not one of inspired prophesies nor of dramatic research breakthroughs.

She saw her duty in sternly simple terms, and she carried it out, living the while with insinuations that she was a bureaucratic nitpicker, unreasonable — even, she said, stupid. That such attributes could have been ascribed to her is, by her own acknowledgement, not surprising, considering all of the circumstances.

What she did was refuse to be hurried into approving an application for marketing a new drug. She regarded its safety as unproved, despite considerable data arguing that it was ultra safe.

It was not until last April, 19 months after the application was filed with the FDA, that the terrible effects of the drug abroad were widely reported in this country. What remains to be told is how and why Dr. Kelsey blocked the introduction of the drug before those effects were suspected by anyone.

Dr. Kelsey invoked her high standards and her belief that the drug was "peculiar" against these facts:

The drug had come into widespread use in other countries. In West Germany, where it was used primarily as a sedative, huge quantities of it were sold over the counter before it was put on a prescription basis. It gave a prompt, deep, natural sleep that was not followed by a hangover. It was cheap. It failed to kill even the would-be suicides who swallowed massive doses.

And there were the reports on experiments with animals. Only a few weeks ago the American licensee told of giving the drug to rats in doses 6 to 60 times greater than the comparable human dosage. Of 1510 offspring, none was delivered with "evidence of malformation."

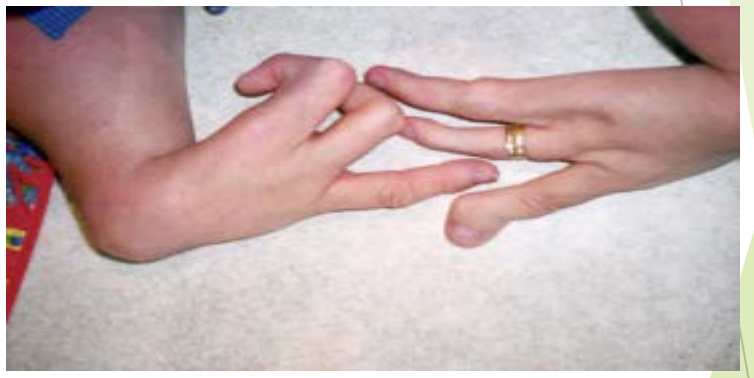
In a separate study, one rat did deliver a malformed offspring, but the dosage had been 1200 times the usual one. Rabbits that were injected with six times the comparable human dose also were reported to have produced no malformed births.

Recently, the FDA publicly

See DRUG, A8, Col. 1

The Washington Post

DR. FRANCES O. KELSEY
. . . skepticism wins



Kefauver – Harris Amendment to the Food Drug and Cosmetic Act, 1962

For a new drug application: the amendment

- Required Manufacturers to provide substantial proof of "**Efficacy**" **through well controlled clinical trials**
- Codified the informed consent requirement
- Set the rules for investigations
- Required the FDA specifically approve marketing applications
- Required adverse events be reported

Laid the ground work for the New Drug Regulations

Investigational Drug Regulations, 1963

21 CFR 312 - **IND Application Regulations**

21 CFR 314 - **New Drug Application** for market approval

Food Drug and Cosmetic Act

Many other amendments through the years (24)

1951 Durham Humphrey Act
1976 Medical Device Amendments
1983 Orphan Drug Act
1992 Prescription Drug User Fee Act
2003 Pediatric Research Equity Act

1981

FDA and OHRP regulations were harmonized to the extent allowed by statute.

1991

45 CFR 46 Subpart adopted as the “Common Rule”

Helpful to Remember!

OHRP has regulatory oversight clinical research funded or supported by the federal government. (45 CFR 46)

FDA has regulatory oversight of clinical investigations of FDA regulated products regardless of the source of funding.

21 CFR 11, 50, 54, 56, 312, 314, 812, 814

International Conference on Harmonization Guidance Documents , 1996

ICH Guidelines / Work Products /

The ICH topics are divided into four categories and ICH topic codes are assigned according to these categories.

Quality Guidelines

Harmonisation achievements in the Quality area include pivotal milestones such as the conduct of stability studies, defining relevant thresholds for impurities testing and a more flexible approach to pharmaceutical quality based on Good Manufacturing Practice (GMP) risk management.

Safety Guidelines

ICH has produced a comprehensive set of safety Guidelines to uncover potential risks like carcinogenicity, genotoxicity and reprotoxicity. A recent breakthrough has been a non-clinical testing strategy for assessing the QT interval prolongation liability: the single most important cause of drug withdrawals in recent years.

Efficacy Guidelines

The work carried out by ICH under the Efficacy heading is concerned with the design, conduct, safety and reporting of clinical trials. It also covers novel types of medicines derived from biotechnological processes and the use of pharmacogenetics/genomics techniques to produce better targeted medicines.

Multidisciplinary Guidelines

Those are the cross-cutting topics which do not fit uniquely into one of the Quality, Safety and Efficacy categories. It includes the ICH medical terminology (MedDRA), the Common Technical Document (CTD) and the development of Electronic Standards for the Transfer of Regulatory Information (ESTRI).

International Conference on Harmonization Guidance Documents

Efficacy (E) - 20 Guidelines

Concerned with the design, conduct, safety and reporting of clinical trials.

E8 GENERAL CONSIDERATIONS FOR CLINCIAL TRIALS

The Guideline provides an introduction to clinical development, quality design of clinical studies and a focus on those factors critical to the quality of the studies.

E6 (R2) GOOD CLINCIAL PRACTICE

Outlines expectations of all participants in the conduct of clinical trials, including investigators, monitors, sponsors and IRBs. GCP E6 covers aspects of monitoring, reporting and archiving of clinical trials, and incorporates addenda on Essential Documents and on the Investigator's Brochure. The revised guidance updates and improves approaches to clinical trail design, conduct, oversight, recording and reporting including standards regarding electronic records and essential documents.

E2 PHARMACOVIGILANCE

E2A – Clinical Safety Data management: Definitions and Standards for Expedited Reporting

Useful Resources

Nuremburg Code
Declaration of Helsinki
Belmont Report
https://www.hhs.gov/ohrp/international/ethical-codes-and-research-standards/index.html

Compare OHRP and FDA regulations
https://www.fda.gov/science-research/good-clinical-practice-educational-materials/comparison-fda-and-hhs-human-subject-protection-regulations

Milestones in FDA History
https://www.fda.gov/about-fda/fdas-evolving-regulatory-powers/milestones-us-food-and-drug-law-history