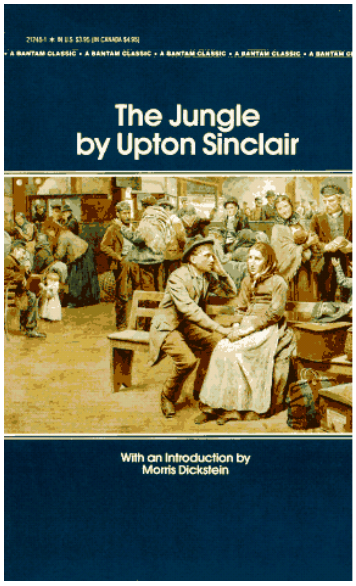
INTRODUCTION

The medical advances of the twentieth century came at great human cost. The triumphs, from the eradication of once-common scourges of mankind to seeming miracles at the cutting edge of medical research, are well known. What is not generally known is that the standards for clinical trials, the basic process by which medical treatments for human beings are developed, were defined in reaction to abuses and scandals ranging from the unconsciously negligent, to the systematic and criminal.

Up to the beginning of the last century, regulations for medical experiments involving humans, or for production and commercialization of medicines, did not exist. Formulas for medical products were kept secret. Sales and distribution were by means of fairs and traveling carnivals, with an emphasis on colorful posters advertising glorified benefits. Single medications were promoted for such wide-ranging illnesses as gout, mental disorders or general weakness.

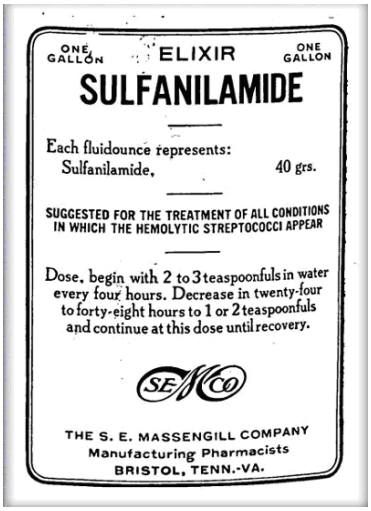
In 1906, Upton Sinclair, a prominent US journalist writing for the Kansas newspaper Appeal to Reason, published a series of articles exposing appalling sanitary practices in Chicago meat-packing plants. The articles were later combined into a book titled The Jungle, referring to the human subsisted in, a savage survival-of-the-fittest environment. Although Sinclair's work focused on labor conditions, resulting public outrage centered on the unsanitary meat being sold to unsuspecting buyers.



The Jungle infuriated Americans, from President Theodore Roosevelt down to common consumers. In short order, protests before congress resulted in the enactment in 1906 of the Pure Food and Drug Act. This law created the US Food and Drug Administration (FDA). Over the years, the regulatory scope of this federal agency has been expanded beyond regulation of food products, dietary supplements and drugs, (for humans and animals), to include cosmetics, medical devices, and biological and blood products. As a first line of defense for consumers, The Pure Food and Drug Act prohibited the manufacture and sale of adulterated or deceptively

labeled products. Unfortunately, the law as passed only required that medicines meet standards of purity and dosage and be correctly labeled. The onus was left on the FDA to prove that a product did not comply, to be able to force its removal from the market.

Upton Sinclair changed the course of history in a way that he had not intended. The Jungle resulted in the passage of the Pure Food and Drug act and the creation of the FDA, which would have far-reaching consequences for medical research and the pharmaceutical industry. But Sinclair always regretted that the labor social justice appeal in his book got few results. In appraising the effect of The Jungle, Sinclair said, "I aimed at Americans' heart, but instead I hit them in the stomach."


ONE GALLON ELIXIR ONE GALLON

SULFANILAMIDE

Each fluidounce represents:
Sulfanilamide, 40 grs.

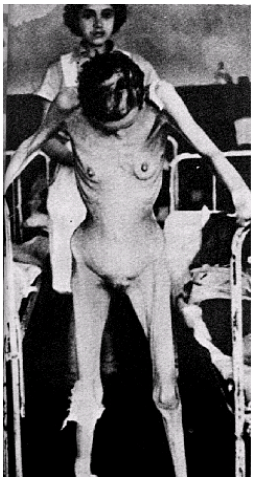
SUGGESTED FOR THE TREATMENT OF ALL CONDITIONS IN WHICH THE HEMOLYTIC STREPTOCOCCI APPEAR

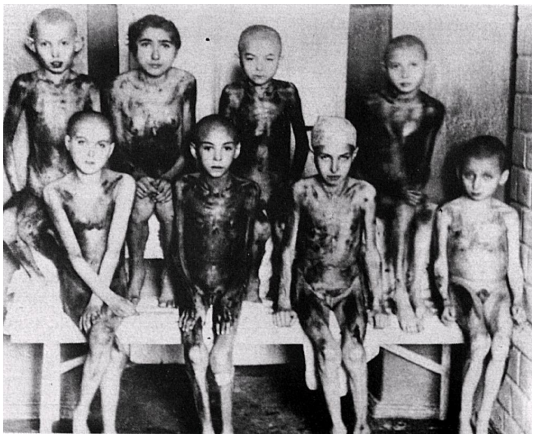
Dose, begin with 2 to 3 teaspoonfuls in water every four hours. Decrease in twenty-four to forty-eight hours to 1 or 2 teaspoonfuls and continue at this dose until recovery.

SEMCO

THE S. E. MASSENGILL COMPANY
Manufacturing Pharmacists
BRISTOL, TENN.-VA.

In 1937 a new public health tragedy outraged the American public. More than a hundred persons died from consuming "Strep Elixir" for the treatment of streptococcus infections. This concoction contained sulfanilamide as the active ingredient, but mixed with diethylene glycol, an anti-freezing which we now know is highly toxic to human beings. The product had been examined for smell, color and appearance, but its safety had not been tested before authorizing sale. The legal framework within which the scandal unfolded further inflamed public opinion. The victims or their relatives were only able to file lawsuits under the technicality that Strep Elixir, because it contained no alcohol, was mislabeled as an elixir. Had the concoction been correctly labeled as a "solution," no legal action would have been possible. The Strep Elixir case prompted the US Congress to approve the Food, Drug and Cosmetic Act in 1938. This law mandated that manufacturers of pharmaceutical products test their safety before commercialization.





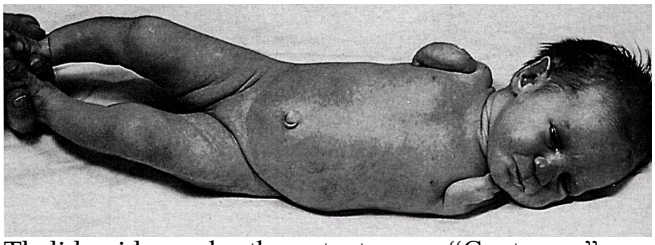
The atrocities committed by Nazi doctors at concentration camps during WWII are the darkest pages in the history of research involving human beings. The uncovering of these systematic abuses and violations of human rights stupefied the world scientific community. Innocent human beings, mostly Jews, were subjected to cruel experiments in the name of "science." Gunpowder burns were purposely inflicted on children, to provide test cases for treatments of their injuries. Men and women were subjected to prolonged, extreme fasting, to study the effects of starvation on a living body. Needless to say, these and other extreme cruelties were inflicted without consent and caused pain, suffering and death.

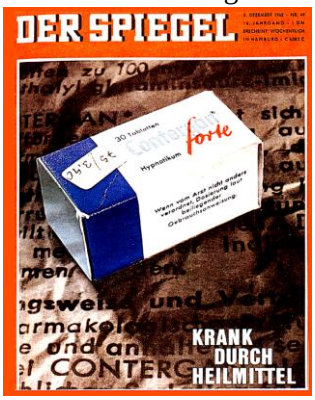
At Nurenberg in 1945, an International Military Tribunal established by the governments of England, France, the Soviet Union and the USA found 15 Nazi doctors guilty of crimes against humanity. Seven received the death penalty. The accused

doctors showed no remorse whatsoever, maintaining to the last that their actions had been legitimate scientific research.

The most important legacy of the "Trial of the Century" was the establishment of the Nurenberg Code: the first international regulation for medical investigation involving human beings. This document is still valid, without modification, and has become an almost obligatory point of departure for bioethics codes and legislation throughout the world.

Towards the end of the 1950s, thousands of children in Europe, Canada and Latin America were born with missing or abnormal limbs. The pattern was called "Dysmelia Syndrome", and at first was considered a new disease. The syndrome was eventually linked to consumption of Thalidomide, a drug taken by mothers of the affected children during their pregnancies.





Thalidomide, under the patent name "Contergan", was primarily a sleep aid that also had antiemetic effects. Because of the latter characteristic, Contergan was prescribed to pregnant women to reduce morning sickness symptoms. The product was launched for sale in October 1957, after trials on more than 300 patients, none of whom manifested significant toxic effects. Between October 1957 and November 1961 more than five million people had taken the medicine, with only very scarce reports of mild secondary effects. But Thalidomide had not been subjected to tests to rule out teratogenesis. On 27 November 1967, the manufacturing company removed the product from the market.

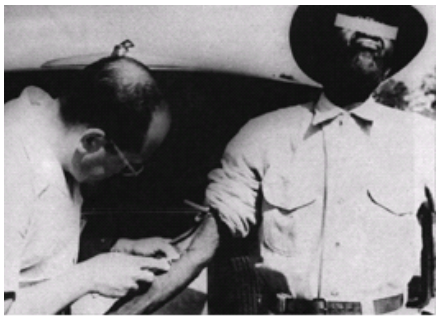
Once more, concerned US consumers pressured Congress for action. The "Kefauver-Harris Amendment" to the Food, Drug and Cosmetic Act, approved in 1962, mandated that pharmaceutical companies establish scientific efficacy and safety tests for all new products destined for use by humans.

Driven by the Thalidomide tragedy, in June 1964 the World Medical Association approved the Helsinki Declaration at its XVIII meeting in Finland. This was the first global attempt to establish protection standards for people who participate as subjects in clinical research. The landmark document introduced the concept of independent Ethical Scientific Committees, to assure safeguarding of participants and adherence to ethical principals in clinical research. The Helsinki Declaration has been revised seven times at meetings of the WMA: Tokyo 1975, Italy 1983, Hong Kong 1989, South Africa 1996, Edinburg 2000, Washington 2002, Tokyo 2004, Seoul 2008 and Brazil 2013. Helsinki Declaration modifications are not without controversy: changes relating to the use of placebos and availability of investigational products to participants when the study is concluded, introduced at Edinburg 2000, have been contentious issues. In 2001 the FDA declined to recognize the 2000 revision, due to the Declaration's restricted stance on placebo control trials in economically developing countries. On October 29, 2008, the FDA formally discontinued it reliance on the Declaration and replaced it by the guideline of the Good Clinical Practice of the International Conference of Harmonization. Nevertheless, the Helsinki Declaration remains an invaluable reference point for all parties involved in clinical research.

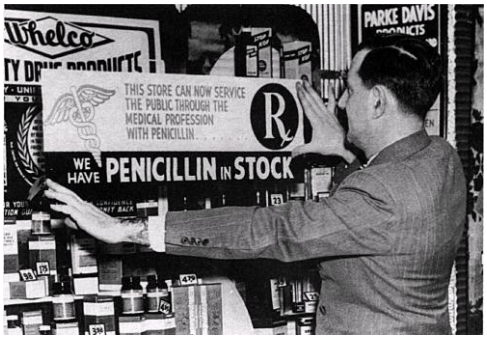
In 1972, when the scientific community was finally recovering from the stigma of the Nazi experiments and the Thalidomide tragedy, the journalist Jean Heller ignited public opinion with a

report on a new scandal: The Tuskegee Syphilis Experiment. The article appeared in both the New York Times and the Washington Star on 25 July 1972.

The experiment began in 1932 under the sponsorship of the US Government, through its Public Health Service. Six hundred subjects from the state of Alabama participated, all African-Americans from very poor socio-economic backgrounds suffering from syphilis. Three hundred and nine subjects conformed the experimental group and 201 the control group. All were offered "free treatment for bad blood," a euphemism used to describe syphilis, which at the time was endemic in Tuskegee County. Informed consent was never obtained from the subjects, who willingly signed up on the basis of such incentives as free physical check-ups, transportation expenses, warm food on check-up days and the promise of remuneration of $50.oo at the end of the study.



The experiment lasted four decades. Participating patients were never given any treatment for syphilis, despite the fact that, from 1946 onwards, the use of penicillin against that pathology became widespread. The Tuskegee Syphilis Experiment was seen as immoral and scandalous due to the lack of informed consent, the exploitative participation incentives and, above all, the denial of access to easily available treatment for a potentially life-threatening disease to poor black people.



A public apology from President Bill Clinton in 1997, medical treatment for survivors and financial compensation to the victims and their families all fell short of overcoming the negative impact of this reprehensible event. US Government reaction included the National Research Act in 1974, the Code of Federal Regulations in 1977, and the Belmont Report in 1978.

In 1974, the US Congress passed the National Research Act, which created the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. This commission produced a document entitled Ethical Principles and Guidelines for Research Involving Human Subjects, which came to be known as the Belmont Report upon publication in 1978. The Belmont Report quickly became the most important reference document in the field of human research ethics, establishing the three basic principles of autonomy or respect for persons, benefit and justice.

In 1977, the FDA published the Code of Federal Regulations. This document contains two sections directly related to clinical research. Title 21 CRF is dedicated to food and drugs and includes Part 50 (Protection of Human Subjects), Part 56 (Institutional Review Boards), Part 312 (Investigational New Drug Application), Part 600 (Biological Products) and Part 812 (Investigational Device Application). Title 45 CRF is entirely dedicated to the protection of human subjects. The Code establishes compulsory norms for all drug, biological product and medical device research subject to FDA regulation. This legislation introduced the concept of "Good Clinical Practice," placing an

emphasis on the quality of data obtained from clinical research, as an additional requirement to the ethical principles established in the Nurenberg Code and the Helsinki Declaration.

In 1991, the US Government standardized requirements for sponsorship of research by federal agencies. Known as the Common Rule, these compulsory norms are extracted from Title 45, Part 46 of the Code of Federal Regulations. The Common Rule establishes three protection mechanisms for subjects participating in clinical trials: review by an independent ethical-scientific committee, informed consent of all participants, and institutional commitment to compliance with all regulations.

On the multilateral level, at the end of the 1970s, both the Council for International Organizations of Medical Sciences (CIOMS) and the World Health Organization (WHO) took up the issue of medical trials involving human beings. Their joint efforts resulted in widespread circulation, starting in 1982, of a document entitled "Proposed Ethical Guidelines for Biomedical Research Involving Human Subjects." In February 1992 a committee appointed by CIOMS presented a final draft which was reviewed and approved by more than 150 participants from all over the world, including representatives of health ministries, professionals in medicine and related disciplines, ethicists, philosophers and lawyers. The resulting International Ethical guidelines for Biomedical Research Involving Human Subjects, known as the CIOMS Document, contain an introduction and fifteen general guidelines for the protection of the rights and welfare of subjects participating in clinical research.

Apart from the preceding international institutional effort at developing principles and rules for clinical trials, the governments of the United States, France, Germany, the United Kingdom, the Nordic Community, the European Economic Community and Japan all developed their own internal regulations throughout the 1980s. While the rules of each had many elements in common, differences among them prevented the emergence of an international standard. To fill this void, representatives from the European Union, the United States and Japan met at the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. In May 1996 this commission issued the Guidelines for Good Clinical Practice (GCP). This document establishes mandatory quality, ethical and scientific standards for clinical research in any of the subscribing regions. These Guidelines quickly became the standard for clinical research anywhere in the world. They incorporate norms not only from the countries that participated in the harmonization conference, but also from Australia, Canada, the Nordic countries and the World Health Organization. GCP standards now have legal force in Canada, the European Community and Japan.

The United Nations has also contributed to development of a legal and ethical framework for medical research involving humans, starting with its landmark 1948 Universal Declaration of Human Rights. In November 1997, at its 29th General Conference, UNESCO unanimously adopted the Universal Declaration on the Human Genome and Human Rights. This document, endorsed by the UN General Assembly in 1998, is the first universal instrument in the biology area, and strikes a balance between the need to ensure freedom of research and safeguarding human rights and fundamental freedoms.

Through UNESCO, the United Nations has continued its activity in fast developing and globalizing human medical research fields. At its 32nd Session in 2003, UNESCO adopted the International Declaration on Human Genetic Data, and at its 33rd Session in 2005, the Universal Declaration on Bioethics and Human Rights.

The previously listed documents, though treating matters that can (or should) be applied to all mankind, have varying degrees of legal enforceability, from country to country. They are all in the public domain, and accessible through the internet and by other means.

The documents in the compilation herein attached were all obtained from their original sources. All are the most recent versions, as of the date of this writing. For the Helsinki Declaration, all amendments to date are included.

The tragedies and abuses described in this introduction are isolated cases. In some the pain, suffering and/or deaths were the result of unfortunate accidents. In others, the subjects were victims of unscrupulous researchers who put their appetites for recognition, power, money or fame above basic ethics and respect for human rights. Unfortunately, the negative press that these undeniably heart-wrenching cases generate cast a shadow of doubt over the work of thousands of competent and moral medical researchers, who dedicate their lives to the search for new treatments for the benefit of mankind.