… *Ethical Implications of Human-Subjects Research Oversight …*
A Generation of Vipers …

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Disclosures

- John Gillon has no financial or non-financial relationships to disclose relating to the content of this presentation.
- The views expressed in this presentation are those of John Gillon, and reflect neither the official policy nor position of the Department of Defense, or the U.S. Government.
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Learning Objectives

At the conclusion of this activity, participants will be able to:

1. Explain the history that compelled the development of the U.S. research oversight structure.
2. Summarize the elements of human-subjects research oversight.
3. Comprehend the Department of Defense (DoD) Instruction 3216.02, *Protection of Human Subjects and Adherence to Ethical Standards in DoD-Conducted and Supported Research*.

… ethical implications of human-subjects research oversight … a generation of vipers …

Snake … serpent … viper

(Wikipedia, n.d.)

One comes to know the snake/serpent/ viper in myth, religion, and nature.

In some traditions it is a benefit, a tool.

(Wikipedia, n.d)

Snake … serpent … viper

(Wikipedia, n.d.)

In others it is a danger, a threat—even a weapon to be used against another.

Two edges— that of tool and of a weapon.

(Wikipedia, n.d.)

And **that** is about as close as we will come to philosophy in this discussion.

Os & Qs: Look back and around …

… to know and understand where one is now and where one is going, it is necessary to know where "we"—those of and in the field and/or education system and/or practice—were and the route we took to the "now" … the history.

…has an initial failure, or apparent failure set up continuing failure … or later success; and, in either case, how has that played out along the way?

…what are the weaknesses we find in the history of health science and practice, including those in the educational processes?

… and …

Caveat:

Audiens-Inspectoris (Listener-Viewer) Beware:

Along the way this discussion will move forwards and backwards through time, and you may feel it moves side-to-side in space. Time may be lineal, but issues and their effects have a habit of arising at different times in different places.

…note…

Occasionally you will see at the bottom of a slide a hypertext link in tiny, tiny type. You may worry you can't read that tiny, tiny type. Most often you'll find it's an underlying source … with a hypertext link, to take you to those source websites available online.

BTW (By the way) …

No …

Neither

George Santayana

nor

Winston Churchill

said ...

“Those who cannot remember the past are condemned to sit through a lecture on it.”

Disclosure

There are elements of this presentation that may disturb, even anger you.

… disclosure (cont'd)

Why?

… disclosure (cont'd)

Well, often we will be talking here about history … and with a particular focus on American history.

And as we have been reminded in recent times, as often as not, many of America's history pictures were and are not pretty.

… disclosure (cont'd)

And there is another aspect to this condition … .

As you likely have come to find across your time in the study and practice of your aspect of science and/or patient healthcare, the processes of learning and studying and practice are environs of trial … and error.

… disclosure (cont'd)

Yes, Alexander Pope wrote in An *Essay on Criticism*:

"To err is human, to forgive, divine."

- *"An Essay on Criticism," (Part II)*, Alexander Pope (Pope, 1709) http://olympos.cz/Antika/Uceni/Sarkissian/Pope.pdf
- *To Err is Human: Building a Safer Health System* (Kohn et al., 2000) https://www.nap.edu/download/9728
- *Patient Safety and Quality: An Evidence-Based Handbook for Nurses*, Chapter 3: "An Overview of To Err is Human: Re-emphasizing the Message of Patient Safety," (Hughes et al, 2008) https://www.ncbi.nlm.nih.gov/books/NBK2673/pdf/Bookshelf_NBK2673.pdf

… disclosure caution …

But … sometimes those errors arise out of something other than the reasoned effort to overcome knowledge gaps in science and/or practice.

And, in those cases, the errors may be due to negligence … or even intentional acts.

A distinction

While some may equate

the term

Morality

with the term

Ethics …

… distinctions with differences …

The term **Morality**:

- is used descriptively to refer to certain codes of conduct put forward by a society or a group (such as a religion), or accepted by an individual for their own behavior, but
- mistakenly, I think, is seen normatively to refer to a code of conduct that, given specified conditions, would be put forward by all rational persons.

- *Stanford Encyclopedia of Philosophy* (Gert et al., 2002) https://plato.stanford.edu/entries/morality-definition/

… distinctions with differences … (cont'd)

While the term **Ethics** refers to a guide:

- to behavior wider in scope than morality, **not** limited by religious requirements—*e.g.*, fasting, or Kosher and Halal dietary laws; and
- which an individual adopts as his or her own guide-to-life, as long as it is a guide that the individual views as a proper one for others.

- *Stanford Encyclopedia of Philosophy* (Gert el al., 2002) https://plato.stanford.edu/entries/morality-definition/

Question: How'd we get where we are …

FDA Historian Wallace F. Janssen wrote (*FDA Consumer*, June 1981):

"Conditions in the U.S. food and drug industries [in the late 19th/early 20th centuries] can hardly be imagined ***. Use of chemical preservatives and toxic colors was virtually uncontrolled. *** ."

- https://wayback.archive-it.org/7993/20170111191530/http://www.fda.gov/AboutFDA/WhatWeDo/History/Overviews/ucm056044.htm (Janssen, 1981)

… the way things were …

"*** Changes from an agricultural to an industrial economy *** made it necessary to provide the rapidly increasing city population with food from distant areas. ... sanitation was primitive ... . *** The great pioneers of bacteriology were just starting their string of victories over infectious diseases."

- https://wayback.archive-it.org/7993/20170111191530/http://www.fda.gov/AboutFDA/WhatWeDo/History/Overviews/ucm056044.htm (Janssen, 1981)

… the way things were …

"In the [1890s], thousands of so called 'patent' medicines such as 'Kick-a-poo Indian Sagwa' and 'Warner's Safe Cure for Diabetes' reflected both the limited medical capability of the period and public acceptance of the doctrine that the buyer could and should look out for himself."

- https://wayback.archive-it.org/7993/20170111191530/http://www.fda.gov/AboutFDA/WhatWeDo/History/Overviews/ucm056044.htm (Janssen, 1981)

… the way things were …

"Medicines containing *** opium, morphine, heroin, and cocaine were sold without restriction. *** Labels did not list ingredients ***. What information the public received came frequently from bitter experience."

- https://wayback.archive-it.org/7993/20170111191530/http://www.fda.gov/AboutFDA/WhatWeDo/History/Overviews/ucm056044.htm (Janssen, 1981)

… the way things were …

Attorneys and commentators Merrill and Francer's "Organizing Federal Food Safety Regulation," notes that "[a] coalition [that included] the American Medical Association, the American Public Health Association, labor unions, and consumer groups formed to support the [proposed Pure Food and Drug Act (PFDA) and Meat Inspection Act (MIA)], and to overcome the opposition of food producers."

- http://scholarship.shu.edu/cgi/viewcontent.cgi?article=1334&context=shlr (Merrill et al., 2000)

… the way things were …

They also wrote that the "publication of Upton Sinclair's *The Jungle* helped persuade President Theodore Roosevelt to support, and Congress to pass, the PFDA [—which banned interstate traffic in adulterated or mislabeled food and drug products—] and MIA on the same day in 1906."

http://scholarship.shu.edu/cgi/viewcontent.cgi?article=1334&context=shlr (Merrill et al., 2000)

… the way things were …

And "Dr. Harvey Wiley, Chief of the Bureau of Chemistry from 1883 until 1912, had long been an advocate for the federal government's responsibility for food safety, and had actively advised the congressional committees that drafted the PFDA."

http://scholarship.shu.edu/cgi/viewcontent.cgi?article=1334&context=shlr (Merrill et al., 2000)

… the way things were …

However, “Organizing Federal Food Safety Regulation” reminds:

“The Bureau of Chemistry suffered an important defeat in 1908: President Theodore Roosevelt, who took saccharin every day on the advice of his doctor, became enraged when he learned that the Bureau was considering banning the sweetener as an adulterant.

http://scholarship.shu.edu/cgi/viewcontent.cgi?article=1334&context=shlr (Merrill et al., 2000)

… the way things were …

"Roosevelt had previously appointed Dr. Ira Remsen, the discoverer of saccharin, to chair a new Board of Consulting Scientific Experts to help resolve issues of food and drug safety … ."

http://scholarship.shu.edu/cgi/viewcontent.cgi?article=1334&context=shlr (Merrill et al., 2000)

… the way things were …

Now, whatever one might be tempted to say about the Congress of the United States ... and others have spoken to that subject …

… the way things were …

John Adams,

Second President of the United States,

spoke to that subject

"In my many years I have come to a conclusion that one useless man is a shame, two is a law firm, and three or more is a Congress."

… the way things were …

Mark Twain,

Lecturer, Writer, Humorist,

also spoke to that subject

"Suppose you were an idiot, and suppose you were a member of Congress; but I repeat myself."

… the way things were …

One may conclude that Congress is a demonstration of what George Santayana did

say ...

… the way things were …

"Those who cannot remember the past are condemned to repeat it."

—Jorge Agustín Nicolás Ruiz de Santayana y Borrás (George Santayana):

- *The Life of Reason* (Vol. 1: Reason in Common Sense) (Santayana, 2005) https://www.gutenberg.org/files/15000/15000-h/15000-h.htm

… the way things were …

History demonstrates that it took a series of catastrophes to compel Congress to act to the extent it has ... .

Throughout the 20th century major public health crises forced Congress to revisit the scope of federal drug legislation.

- *AIM*, 15 March 1995, "Elixirs, Diluents, and the Passage of the 1938 Federal Food, Drug and Cosmetic Act," (Wax, 1995)
  https://www.acpjournals.org/doi/pdf/10.7326/0003-4819-122-6-199503150-00009

… the way things were …

Sulfanilamide had been safely used in caplet form to treat streptococcal infections.

- *AIM*, 15 March 1995, "Elixirs, Diluents, and the Passage of the 1938 Federal Food, Drug and Cosmetic Act," (Wax, 1995) https://www.acpjournals.org/doi/pdf/10.7326/0003-4819-122-6-199503150-00009
- BR Rossen, 18 April 2008, "FDA's Proposed Regulations to Expand Access to Investigational Drugs For Treatment Use: The Status Quo in the Guise of Reform," (Rossen, 2008) https://dash.harvard.edu/bitstream/handle/1/8965551/Benjamin%20Rossen%20course%20and%203L%20Paper%20-%20Proposed%20Rules%20to%20Expa.pdf

… the way things were …

However, scientists at the S.E. Massengill, Co., said they responded to consumer demand, and developed a liquid version of the drug.

- *AIM*, 15 March 1995, "Elixirs, Diluents, and the Passage of the 1938 Federal Food, Drug and Cosmetic Act," (Wax, 1995) https://www.acpjournals.org/doi/pdf/10.7326/0003-4819-122-6-199503150-00009
- BR Rossen, 18 April 2008, "FDA's Proposed Regulations to Expand Access to Investigational Drugs For Treatment Use: The Status Quo in the Guise of Reform," (Rossen, 2008) https://dash.harvard.edu/bitstream/handle/1/8965551/Benjamin%20Rossen%20course%20and%203L%20Paper%20-%20Proposed%20Rules%20to%20Expa.pdf

… the way things were …

Had the S.E. Massengill, Co., conducted tests for safety, it would have discovered that the solution used to dissolve the sulfanilamide—diethylene glycol, the equivalent of modern day antifreeze—was a deadly poison.

- *AIM*, 15 March 1995, "Elixirs, Diluents, and the Passage of the 1938 Federal Food, Drug and Cosmetic Act," (Wax, 1995) https://www.acpjournals.org/doi/pdf/10.7326/0003-4819-122-6-199503150-00009
- BR Rossen, 18 April 2008, "FDA's Proposed Regulations to Expand Access to Investigational Drugs For Treatment Use: The Status Quo in the Guise of Reform," (Rossen, 2008) https://dash.harvard.edu/bitstream/handle/1/8965551/Benjamin%20Rossen%20course%20and%203L%20Paper%20-%20Proposed%20Rules%20to%20Expa.pdf

… the way things were …

With the elixir sulfanilamide catastrophe as the second wake-up call of the 20th century, in 1938, Congress enacted the Federal Food, Drug and Cosmetic Act.

- *AIM*, 15 March 1995, "Elixirs, Diluents, and the Passage of the 1938 Federal Food, Drug and Cosmetic Act," (Wax, 1995) https://www.acpjournals.org/doi/pdf/10.7326/0003-4819-122-6-199503150-00009
- BR Rossen, 18 April 2008, "FDA's Proposed Regulations to Expand Access to Investigational Drugs For Treatment Use: The Status Quo in the Guise of Reform," (Rossen, 2008) https://dash.harvard.edu/bitstream/handle/1/8965551/Benjamin%20Rossen%20course%20and%203L%20Paper%20-%20Proposed%20Rules%20to%20Expa.pdf

… the way things were …

The 1938 Federal Food, Drug and Cosmetic Act required for the first time that drug manufacturers test all new drugs for safety and obtain FDA approval prior to any commercial distribution.

- *AIM*, 15 March 1995, "Elixirs, Diluents, and the Passage of the 1938 Federal Food, Drug and Cosmetic Act," (Wax, 1995) https://www.acpjournals.org/doi/pdf/10.7326/0003-4819-122-6-199503150-00009
- BR Rossen, 18 April 2008, "FDA's Proposed Regulations to Expand Access to Investigational Drugs For Treatment Use: The Status Quo in the Guise of Reform," (Rossen, 2008) https://dash.harvard.edu/bitstream/handle/1/8965551/Benjamin%20Rossen%20course%20and%203L%20Paper%20-%20Proposed%20Rules%20to%20Expa.pdf

… the way things were …

The 1938 Food Drug and Cosmetic Act required manufacturers of any "new drug" to file a new drug application (NDA) with FDA and detail in the application medical and scientific data about the drug's safety for human consumption.

- *AIM*, 15 March 1995, "Elixirs, Diluents, and the Passage of the 1938 Federal Food, Drug and Cosmetic Act," (Wax, 1995) https://www.acpjournals.org/doi/pdf/10.7326/0003-4819-122-6-199503150-00009
- BR Rossen, 18 April 2008, "FDA's Proposed Regulations to Expand Access to Investigational Drugs For Treatment Use: The Status Quo in the Guise of Reform," (Rossen, 2008) https://dash.harvard.edu/bitstream/handle/1/8965551/Benjamin%20Rossen%20course%20and%203L%20Paper%20-%20Proposed%20Rules%20to%20Expa.pdf

… the way things were …

To permit the clinical trials intended to determine drug safety, Congress specifically authorized FDA to promulgate regulations exempting "drugs intended solely for investigational use by experts qualified by scientific training and experience to investigate the safety of drugs."

- *AIM*, 15 March 1995, "Elixirs, Diluents, and the Passage of the 1938 Federal Food, Drug and Cosmetic Act," (Wax, 1995) https://www.acpjournals.org/doi/pdf/10.7326/0003-4819-122-6-199503150-00009
- BR Rossen, 18 April 2008, "FDA's Proposed Regulations to Expand Access to Investigational Drugs For Treatment Use: The Status Quo in the Guise of Reform," (Rossen, 2008) https://dash.harvard.edu/bitstream/handle/1/8965551/Benjamin%20Rossen%20course%20and%203L%20Paper%20-%20Proposed%20Rules%20to%20Expa.pdf

… the way things were …

The 1938 act also gave the FDA the power to set standards in safety testing and to prevent unsafe drugs from ever reaching the market—which marked a major shift toward consumer protection through risk regulation.

- *AIM*, 15 March 1995, "Elixirs, Diluents, and the Passage of the 1938 Federal Food, Drug and Cosmetic Act," (Wax, 1995) https://www.acpjournals.org/doi/pdf/10.7326/0003-4819-122-6-199503150-00009
- BR Rossen, 18 April 2008, "FDA's Proposed Regulations to Expand Access to Investigational Drugs For Treatment Use: The Status Quo in the Guise of Reform," (Rossen, 2008) https://dash.harvard.edu/bitstream/handle/1/8965551/Benjamin%20Rossen%20course%20and%203L%20Paper%20-%20Proposed%20Rules%20to%20Expa.pdf

… the way things were …

However the 1938 act provided that a new drug application automatically became effective after sixty (60) days unless FDA provided affirmative notice to the contrary.

- *AIM*, 15 March 1995, "Elixirs, Diluents, and the Passage of the 1938 Federal Food, Drug and Cosmetic Act," (Wax, 1995) https://www.acpjournals.org/doi/pdf/10.7326/0003-4819-122-6-199503150-00009
- BR Rossen, 18 April 2008, "FDA's Proposed Regulations to Expand Access to Investigational Drugs For Treatment Use: The Status Quo in the Guise of Reform," (Rossen, 2008) https://dash.harvard.edu/bitstream/handle/1/8965551/Benjamin%20Rossen%20course%20and%203L%20Paper%20-%20Proposed%20Rules%20to%20Expa.pdf

… the way things were …

Less than a decade later there was

Chemie Grünenthal

… the way things were …

Chemie Grünenthal was created in West Germany in the wake of WWII and was rooted in a business owned for generations by the Wirtz family of Stolberg.

- *Newsweek*, 12 September 2012, "The Nazis and Thalidomide: The Worst Drug Scandal of All Time," (Williams, 2012) http://www.newsweek.com/nazis-and-thalidomide-worst-drug-scandal-all-time-64655

… the way things were …

Thus, *Chemie Grünenthal* was created out of a Wirtz-family enterprise—that until then had focused mostly on soap, perfumes, and cleaning products—and combined with other businesses that were taken from Jewish families (*e.g.,* the maker of *Tabac* products) in the pre-WWII "Aryanization" of German businesses.

- *Newsweek*, 12 September 2012, "The Nazis and Thalidomide: The Worst Drug Scandal of All Time," (Williams, 2012) http://www.newsweek.com/nazis-and-thalidomide-worst-drug-scandal-all-time-64655

… the way things were …

Thereafter, *Chemie Grünenthal* was the creator, maker and marketer of Contergan.

- *Newsweek*, 12 September 2012, "The Nazis and Thalidomide: The Worst Drug Scandal of All Time," (Williams, 2012) http://www.newsweek.com/nazis-and-thalidomide-worst-drug-scandal-all-time-64655
- *WP*, 15 July 1962, "'Heroine' of FDA Keeps Bad Drug Off Market," (Mintz, 1962) http://www.washingtonpost.com/wp-srv/washtech/longterm/thalidomide/keystories/071598drug.htm
- *MED-CARE*, November 2012, "Pharmaceuticals and the Health of the Public: Use, Safety, Cost, Access, Ethics, and Quality," (Zito, 2012) https://www.jstor.org/stable/pdf/41714597.pdf

… the way things were …

Defense Health Agency

Contergan …

as in …

- *Newsweek*, 12 September 2012, “The Nazis and Thalidomide: The Worst Drug Scandal of All Time,” (Williams, 2012) http://www.newsweek.com/nazis-and-thalidomide-worst-drug-scandal-all-time-64655
- *WP*, 15 July 1962, “'Heroine' of FDA Keeps Bad Drug Off Market,” (Mintz, 1962) http://www.washingtonpost.com/wp-srv/washtech/longterm/thalidomide/keystories/071598drug.htm
- *MED-CARE*, November 2012, “Pharmaceuticals and the Health of the Public: Use, Safety, Cost, Access, Ethics, and Quality,” (Zito, 2012) https://www.jstor.org/stable/pdf/41714597.pdf

… the way things were …

- *Newsweek*, 12 September 2012, "The Nazis and Thalidomide: The Worst Drug Scandal of All Time," (Williams, 2012) http://www.newsweek.com/nazis-and-thalidomide-worst-drug-scandal-all-time-64655

… the way things were …

Contergan

Chemically known as *α-(N-phthalimido) glutarimide*

- *Newsweek*, 12 September 2012, "The Nazis and Thalidomide: The Worst Drug Scandal of All Time," (Williams, 2012) http://www.newsweek.com/nazis-and-thalidomide-worst-drug-scandal-all-time-64655

- FDA, "Frances Oldham Kelsey: Medical reviewer famous for averting a public health tragedy," (FDA, 2018) https://www.fda.gov/about-fda/virtual-exhibits-fda-history/frances-oldham-kelsey-medical-reviewer-famous-averting-public-health-tragedy

… the way things were …

α-(N-phthalimido) glutarimide

known generically as thalidomide.

- FDA, June, 2019, "Thalidomide (alpha-(N-phthalimido) glutarimide)," (FDA, 2019) https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020785s067lbl.pdf

… the way things were …

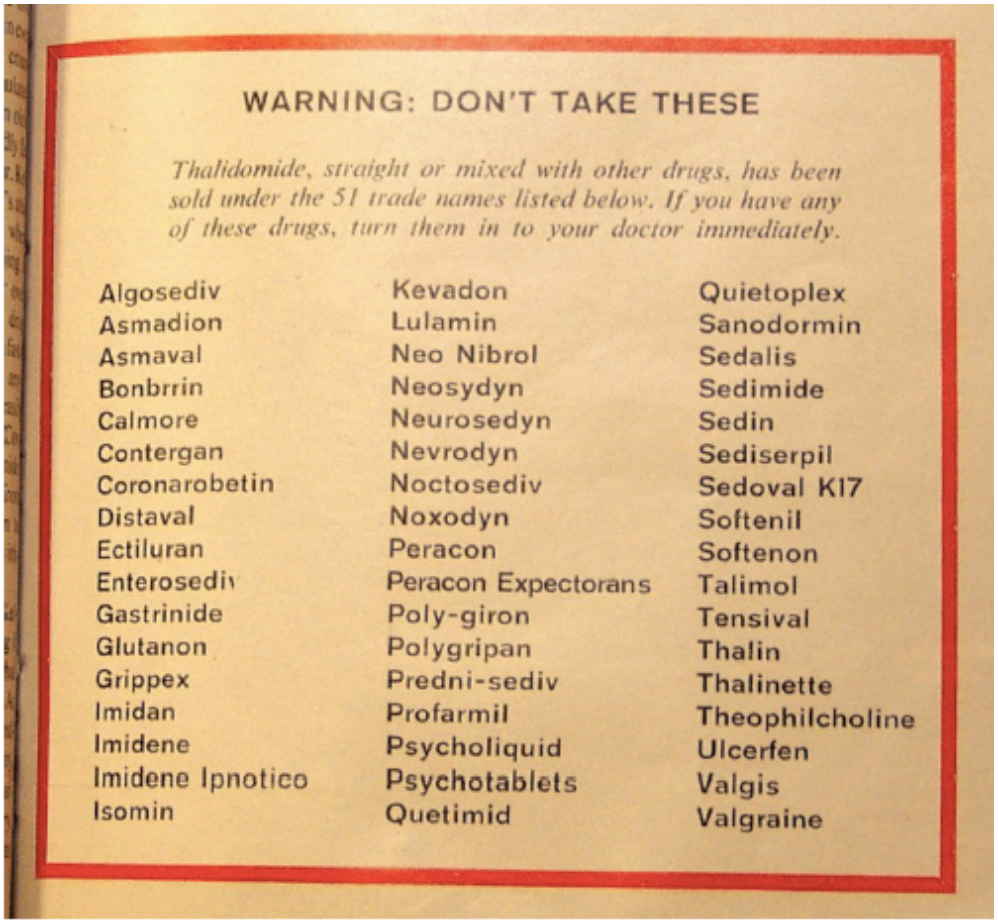
Thalidomide

known by fifty-one (51) different commercial names …

- *LIFE*, 10 August 1962, at 29 (Bunde, 1962) http://books.google.com/books?id=Hk4EAAAAMBAJ&pg=PA29&source=gbs_toc_r&cad=2#v=onepage&q&f=false

- FDA, "Frances Oldham Kelsey: Medical reviewer famous for averting a public health tragedy," (FDA, 2018) https://www.fda.gov/about-fda/virtual-exhibits-fda-history/frances-oldham-kelsey-medical-reviewer-famous-averting-public-health-tragedy

… the way things were …



WARNING: DON'T TAKE THESE

Thalidomide, straight or mixed with other drugs, has been sold under the 51 trade names listed below. If you have any of these drugs, turn them in to your doctor immediately.

Algosediv	Kevadon	Quietoplex
Asmadion	Lulamin	Sanodormin
Asmaval	Neo Nibrol	Sedalis
Bonbrrin	Neosydyn	Sedimide
Calmore	Neurosedyn	Sedin
Contergan	Nevrodyn	Sediserpil
Coronarobetin	Noctosediv	Sedoval K17
Distaval	Noxodyn	Softenil
Ectiluran	Peracon	Softenon
Enterosediv	Peracon Expectorans	Talimol
Gastrinide	Poly-giron	Tensival
Glutanon	Polygripan	Thalin
Grippex	Predni-sediv	Thalinette
Imidan	Profarmil	Theophilcholine
Imidene	Psycholiquid	Ulcerfen
Imidene Ipnotico	Psychotablets	Valgis
Isomin	Quetimid	Valgraine

- *LIFE*, 10 August 1962, at 29, (Bunde, 1962) http://books.google.com/books?id=Hk4EAAAAMBAJ&pg=PA29&source=gbs_toc_r&cad=2#v=onepage&q&f=false

- FDA, "Frances Oldham Kelsey: Medical reviewer famous for averting a public health tragedy," (FDA, 2018) https://www.fda.gov/about-fda/virtual-exhibits-fda-history/frances-oldham-kelsey-medical-reviewer-famous-averting-public-health-tragedy

… the way things were …

Thalidomide

was marketed in Europe as an hypnotic—an aid to sleep—and then promoted as an aid to control morning sickness in pregnant women.

- (Rossen, 2008) (https://dash.harvard.edu/bitstream/handle/1/8965551/Benjamin%20Rossen%20course%20and%203L%20Paper%20-%20Proposed%20Rules%20to%20Expa.pdf?sequence=1
- *LIFE*, 10 August 1962, at 29, (Bunde, 1962) http://books.google.com/books?id=Hk4EAAAAMBAJ&pg=PA29&source=gbs_toc_r&cad=2#v=onepage&q&f=false
- http://www.section216.com/history/Kelsey.pdf

… the way things were …

Defense Health Agency

Contergan (thalidomide)

… was formulated "by accident" in 1954 and sold in most nations around the world— except in the United States ... but, then, it arrived *via* other mechanisms.

- *Suffer the Children: The Story of Thalidomide,* Insight Team of The Sunday Times of London (Archer, 1979); see also: http://www.unz.org/Pub/SaturdayRev-1962sep01-00035
- *LIFE*, 10 August 1962, at 29, (Bunde, 1962) http://books.google.com/books?id=Hk4EAAAAMBAJ&pg=PA29&source=gbs_toc_r&cad=2#v=onepage&q&f=false

… the way things were …

In its effort to market thalidomide in the States the William S. Merrell Corporation—by this time known as Richardson-Merrell—obtained from *Chemie Grünenthal* and distributed to 1,267 physicians 2.5 million thalidomide tablets—more than 1,970 tabs per doctor. The company stated: "We have firmly established the safety, dosage and usefulness [and doctors] need not report results."

- By Prescription Only, 2nd ed., (Mintz, 1967)

… the way things were …

At the FDA Dr. Frances Oldham Kelsey, an FDA medical officer, was in line to receive and review the next application to be filed. So the Richardson-Merrell NDA for thalidomide—known as "Kevadon" in the U.S. application, "Distaval" in Britain, and "Talivol" in Dr. Kelsey's native Canada —went to her in September 1960.

- *WP*, 15 July 1962, "'Heroine' of FDA Keeps Bad Drug Off Market," (Mintz, 1962) http://www.washingtonpost.com/wp-srv/washtech/longterm/thalidomide/keystories/071598drug.htm
- "Frances Oldham Kelsey: FDA Medical Reviewer Leaves Her Mark on History" (FDA, 2018) free full text link: http://www.ncbi.nlm.nih.gov/pubmed/11444245

… the way things were …

Dr. Kelsey had gone to work for the agency only a month earlier, and this was her first assignment.

- WP, 15 July 1962, "'Heroine' of FDA Keeps Bad Drug Off Market," (Mintz, 1962) http://www.washingtonpost.com/wp-srv/washtech/longterm/thalidomide/keystories/071598drug.htm

- "Frances Oldham Kelsey: FDA Medical Reviewer Leaves Her Mark on History" (FDA, 2018) free full text link: http://www.ncbi.nlm.nih.gov/pubmed/11444245

… the way things were …

Dr. Kelsey regarded Richardson-Merrell's evidence of thalidomide's safety as "incomplete in many respects": the drug was not intended for grave diseases, or for the relief of intolerable suffering, but primarily for sleeplessness, for which many drugs of known safety were already on the market.

- *WP*, 15 July 1962, "'Heroine' of FDA Keeps Bad Drug Off Market," (Mintz, 1962) http://www.washingtonpost.com/wp-srv/washtech/longterm/thalidomide/keystories/071598drug.htm
- "Frances Oldham Kelsey: FDA Medical Reviewer Leaves Her Mark on History"; (FDA, 2018) free full text link: http://www.ncbi.nlm.nih.gov/pubmed/11444245

… the way things were …

Dr. Kelsey wrote Richardson-Merrell when each 60-day deadline for action on the application came due that the company's proof of safety of the drug was inadequate—each time a new 60-day deadline drew near, out went another letter: insufficient proof of safety.

- *WP*, 15 July 1962, "'Heroine' of FDA Keeps Bad Drug Off Market," (Mintz, 1962) http://www.washingtonpost.com/wp-srv/washtech/longterm/thalidomide/keystories/071598drug.htm

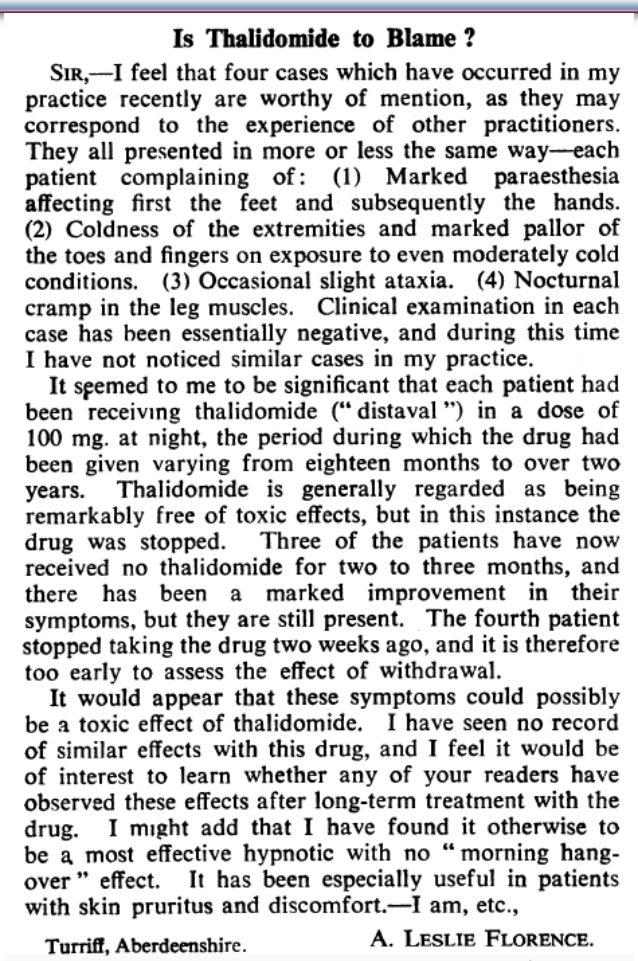
- "Frances Oldham Kelsey: FDA Medical Reviewer Leaves Her Mark on History" (FDA, 2018) free full text link: http://www.ncbi.nlm.nih.gov/pubmed/11444245

… the way things were …

In February 1961, Dr. Kelsey read in the 31 December 1960 issue of the *British Medical Journal*—now the *BMJ*—a letter from physician A. Leslie Florence questioning whether certain instances of peripheral neuritis, a sometimes irreversible tingling numbness in the feet and the fingers, might not be due to intake of thalidomide ... to Dr. Kelsey this was a danger signal.

- *LIFE*, 10 August 1962, at 29, (Bunde, 1962) http://books.google.com/books?id=Hk4EAAAAMBAJ&pg=PA29&source=gbs_toc_r&cad=2#v=onepage&q&f=false
- http://www.section216.com/history/Kelsey.pdf

… the way things were …



Is Thalidomide to Blame ?

SIR,—I feel that four cases which have occurred in my practice recently are worthy of mention, as they may correspond to the experience of other practitioners. They all presented in more or less the same way—each patient complaining of: (1) Marked paraesthesia affecting first the feet and subsequently the hands. (2) Coldness of the extremities and marked pallor of the toes and fingers on exposure to even moderately cold conditions. (3) Occasional slight ataxia. (4) Nocturnal cramp in the leg muscles. Clinical examination in each case has been essentially negative, and during this time I have not noticed similar cases in my practice.

It seemed to me to be significant that each patient had been receiving thalidomide ("distaval") in a dose of 100 mg. at night, the period during which the drug had been given varying from eighteen months to over two years. Thalidomide is generally regarded as being remarkably free of toxic effects, but in this instance the drug was stopped. Three of the patients have now received no thalidomide for two to three months, and there has been a marked improvement in their symptoms, but they are still present. The fourth patient stopped taking the drug two weeks ago, and it is therefore too early to assess the effect of withdrawal.

It would appear that these symptoms could possibly be a toxic effect of thalidomide. I have seen no record of similar effects with this drug, and I feel it would be of interest to learn whether any of your readers have observed these effects after long-term treatment with the drug. I might add that I have found it otherwise to be a most effective hypnotic with no "morning hang-over" effect. It has been especially useful in patients with skin pruritus and discomfort.—I am, etc.,

Turriff, Aberdeenshire. A. LESLIE FLORENCE.

The letter from physician A. Leslie Florence in the 31 December 1960 *British Medical Journal* (now *BMJ*)

- *BMJ*—1960-12-31—"Is Thalidomide to Blame?" (Florence, 1960) (https://www.bmj.com/content/2/5217/1954.1)

… the way things were …

On 18 November 1961 the German paper *Welt am Sonntag* reported on a study finding that pregnant women who had been taking thalidomide were giving birth to babies with gross deformities.

- *C&EN*, 20 June 2005, "Thalidomide" (Rouhi, 2005) http://pubs.acs.org/cen/coverstory/83/8325/8325thalidomide.html

… the way things were …

By 27 November 1961 "*** *Grünenthal* had pulled the drug off the market, blaming the sensationalism of the press," Philip J. Hilts wrote in his 2003 work, *Protecting America's Health: The FDA, Business, and One Hundred Years of Regulation.*

- C&EN, 20 June 2005, "Thalidomide" (Rouhi, 2005) http://pubs.acs.org/cen/coverstory/83/8325/8325thalidomide.html

… the way things were …

But that was only in Germany. Meanwhile, sales elsewhere were allowed to continue ... until, that is, a letter came to the editors of *The Lancet* from New South Wales, Australia, and the office of Dr. William G. McBride.

- *C&EN*, 20 June 2005, "Thalidomide" (Rouhi, 2005) http://pubs.acs.org/cen/coverstory/83/8325/8325thalidomide.html

- *Suffer the Children: The Story of Thalidomide* (Archer, 1979)

… the way things were …

Dr. McBride wrote: “THALIDOMIDE AND CONGENITAL ABNORMALITIES: SIR, Congenital abnormalities are present in approximately 1.5% of babies. In recent months I have observed that the incidence of multiple severe abnormalities in babies delivered of women who were given the drug thalidomide (‘Distaval’) during pregnancy, as an anti-emetic or as a sedative, to be almost 20%.”

- *The Lancet*—1961-12-16, “THALIDOMIDE AND CONGENITAL ABNORMALITIES,” (McBride, 1961) https://www.jameslindlibrary.org/wp-data/uploads/2010/05/McBride_WG_1961.pdf
- *Suffer the Children: The Story of Thalidomide* (Archer, 1979)

… the way things were …

"These abnormalities are present in structures developed from mesenchyme—*i.e.*, the bones and musculature of the gut. Bony development seems to be affected in a very striking manner, resulting in polydactyly, syndactyly, and failure of development of long bones (abnormally short femora and radii).

- *The Lancet*—1961-12-16, "THALIDOMIDE AND CONGENITAL ABNORMALITIES," (McBride, 1961) https://www.jameslindlibrary.org/wp-data/uploads/2010/05/McBride_WG_1961.pdf
- *Suffer the Children: The Story of Thalidomide* (Archer, 1979)

… the way things were …

"Have any of your readers seen similar abnormalities in babies delivered of women who have taken this drug during pregnancy?

—W.G. McBride—Hurstville, New South Wales"

- *The Lancet*—1961-12-16, ""THALIDOMIDE AND CONGENITAL ABNORMALITIES," (McBride, 1961) https://www.jameslindlibrary.org/wp-data/uploads/2010/05/McBride_WG_1961.pdf
- *Suffer the Children: The Story of Thalidomide* (Archer, 1979)

… the way things were …

Meanwhile: What Richardson-Merrell Did

Saturday Review reported FDA records revealed at least 46 mail, telephone and in-person contacts by Richardson-Merrell representatives (*e.g.*, F. Joseph Murray, executive assistant to its director of research) with the FDA.

- *The Saturday Review*, 1 September 1962, "The Unfinished Story of Thalidomide," (Lear, 1962) https://www.unz.com/print/SaturdayRev-1962sep01-00035

… the way things were …

Those 46 contacts by Richardson-Merrell:

- were directed to Dr. Kelsey, to then-chief of FDA's new drug branch/medical division Dr. Ralph Smith, and to assisting chemist Ms. Lee Geismar; and
- occurred between the 12 September 1960 filing and the 8 March 1962 withdrawal of the application.

- *The Saturday Review*, 1 September 1962, "The Unfinished Story of Thalidomide," (Lear, 1962) https://www.unz.com/print/SaturdayRev-1962sep01-00035

… the way things were …

Putting pencil to paper …

… across something less than 18 months,

Richardson-Merrell contacted FDA personnel (roughly) every 11.72 calendar days.

- *The Saturday Review*, 1 September 1962, "The Unfinished Story of Thalidomide," (Lear, 1962) https://www.unz.com/print/SaturdayRev-1962sep01-00035

… the way things were …

FDA records revealed that Dr. Kelsey wrote to Richardson-Merrell on 11 April 1962 to ask whether the drug was still undergoing investigational use, and—if so—to request to be informed what had been done to warn physicians of the dangers of the drug.

- *The Saturday Review*, 1 September 1962, The Unfinished Story of Thalidomide," (Lear, 1962) https://www.unz.com/print/SaturdayRev-1962sep01-00035

… the way things were …

Dr. Kelsey also asked for:

- the measures the company took to inform doctors of the association between the drug and fetal abnormalities at the time the association first became known to the firm; and
- a complete, up-to-date list of all physicians who'd been supplied with the drug for "investigational purposes."
- *The Saturday Review*, 1 September 1962, "The Unfinished Story of Thalidomide," (Lear, 1962) https://www.unz.com/print/SaturdayRev-1962sep01-00035

… the way things were …

Defense Health Agency

What Richardson-Merrell Didn't Do

Richardson-Merrell learned in November 1961 of *Grunenthal's* withdrawal of thalidomide from the German market, but made only cursory efforts to notify clinical investigators through July 1962.

- *By Prescription Only*, 2nd ed.,Morton Mintz (Mintz, 1967)
- "Frances Oldham Kelsey: FDA Medical Reviewer Leaves Her Mark on History" (FDA, 2018) free full text link: http://www.ncbi.nlm.nih.gov/pubmed/11444245

… the way things were …

Remember:

Because FDA had no authority to supervise clinical testing of new drugs, millions of tablets of thalidomide had been distributed to U.S. physicians in preparation for human testing.

- Benjamin Rossen, April 2008, "FDA's Proposed Regulations to Expand Access to Investigational Drugs For Treatment Use: The Status Quo in the Guise of Reform," (Rossen, 2008) https://dash.harvard.edu/bitstream/handle/1/8965551/Benjamin%20Rossen%20course%20and%203L%20Paper%20-%20Proposed%20Rules%20to%20Expa.pdf

… the way things were …

Remember also:

Dr. Kelsey had not withheld approval of thalidomide based on any *indicia* of danger in the NDAs themselves (as no such data were present) but rather due to "insufficient information."

- Benjamin Rossen, April 2008, "FDA's Proposed Regulations to Expand Access to Investigational Drugs For Treatment Use: The Status Quo in the Guise of Reform," (Rossen, 2008) https://dash.harvard.edu/bitstream/handle/1/8965551/Benjamin%20Rossen%20course%20and%203L%20Paper%20-%20Proposed%20Rules%20to%20Expa.pdf

… the way things were …

Thus, while there was an outbreak of infantile deformity (phocomelia) in Western Europe in 1961 and 1962 from the drug thalidomide, developed in West Germany, the drug never got a foothold in the States because one FDA medical officer in the Bureau of Medicine—Dr. Frances Kelsey—withheld approval of its new-drug application.

- *DAED*—1969-04—"Governmental Regulation of the Use of Human Subjects in Medical Research—The Approach of Two Federal Agencies" (Curran, 1969)

… the way things were …

The response of Congress to the thalidomide crisis was the Kefauver Harris Amendment, more properly known as the Drug Amendments of 1962. President John F. Kennedy signed the Act on 10 October 1962. The legislative package made fundamental changes in basic laws regulating ethics in the drug industry.

- Benjamin Rossen, April 2008, "FDA's Proposed Regulations to Expand Access to Investigational Drugs For Treatment Use: The Status Quo in the Guise of Reform," (Rossen, 2008) https://dash.harvard.edu/bitstream/handle/1/8965551/Benjamin%20Rossen%20course%20and%203L%20Paper%20-%20Proposed%20Rules%20to%20Expa.pdf

… the way things were …

The Drug Amendments of 1962 expanded FDA's mandate with regard to new drug approvals, requiring FDA to determine a new drug's effectiveness in addition to its safety and obligating drug sponsors to collect data through "adequate and well controlled investigations, including clinical investigations" conducted by experts.

- Benjamin Rossen, April 2008, "FDA's Proposed Regulations to Expand Access to Investigational Drugs For Treatment Use: The Status Quo in the Guise of Reform," (Rossen, 2008) https://dash.harvard.edu/bitstream/handle/1/8965551/Benjamin%20Rossen%20course%20and%203L%20Paper%20-%20Proposed%20Rules%20to%20Expa.pdf

… the way things were …

The Drug Amendments of 1962 instituted the first true requirement of affirmative FDA pre-market approval for new drugs, eliminating the old regime where an NDA could become effective automatically after 60 days.

- Benjamin Rossen, April 2008, "FDA's Proposed Regulations to Expand Access to Investigational Drugs For Treatment Use: The Status Quo in the Guise of Reform," (Rossen, 2008) https://dash.harvard.edu/bitstream/handle/1/8965551/Benjamin%20Rossen%20course%20and%203L%20Paper%20-%20Proposed%20Rules%20to%20Expa.pdf

… the way things were …

The Drug Amendments of 1962 required drug sponsors to gain FDA approval prior to undertaking any clinical trials—expanding FDA authority to regulate the development of new drugs before a sponsor sought marketing approval.

- Benjamin Rossen, April 2008, "FDA's Proposed Regulations to Expand Access to Investigational Drugs For Treatment Use: The Status Quo in the Guise of Reform," (Rossen, 2008) https://dash.harvard.edu/bitstream/handle/1/8965551/Benjamin%20Rossen%20course%20and%203L%20Paper%20-%20Proposed%20Rules%20to%20Expa.pdf

… the way things were …

The Drug Amendments of 1962 did not include any statutory provision for investigational use of unapproved drugs for treatment, and limited the IND exemption only to use in clinical investigations.

- Benjamin Rossen, April 2008, "FDA's Proposed Regulations to Expand Access to Investigational Drugs For Treatment Use: The Status Quo in the Guise of Reform," (Rossen, 2008) https://dash.harvard.edu/bitstream/handle/1/8965551/Benjamin%20Rossen%20course%20and%203L%20Paper%20-%20Proposed%20Rules%20to%20Expa.pdf

… the way things were …

Defense Health Agency

A Couple of Worthwhile Reads

- Insight team of the Sunday Times of London (1979)
- (Mintz, 1967)

Two additional examples …

… of drug companies' failure to disclose … won't be discussed detail, but are mentioned for awareness …

Companies failed to reveal …

Diethylstilbestrol (DES)—synthetic form of the hormone estrogen prescribed to pregnant women (1940-1971) to prevent miscarriage, premature labor, related pregnancy complications: women taking DES during pregnancy have increased risk of breast cancer; their daughters have increased risks of clear cell adenocarcinoma of the vagina, cervix and breast cancer, and of fertility problems.

- National Cancer Institute, October 2011, "Diethylstilbestrol (DES) and Cancer," (NCI, 2011) http://www.cancer.gov/cancertopics/causes-prevention/risk/hormones/des-fact-sheet
- Akron Law Review (or ALR), 1987, "DES and the Identification Problem", (Roberts et al., 1987) https://ideaexchange.uakron.edu/cgi/viewcontent.cgi?article=1894&context=akronlawreview

… and …

Vioxx (Rofecoxib)—important because, *inter alia*, sometime between December 2000 and June 2001, Merck & Co. had in hand data demonstrating the dangers of the drug—*i.e.*, increased risk of heart attack and stroke—but didn't withdraw the drug from the market until 30 September 2004.

- *Ann.IM*, 19 August 2008, "The ADVANTAGE Seeding Trial: A Review of Internal Documents" (Hill et al., 2008) http://annals.org/article.aspx?articleid=742239
- *Arch.IM*, 23 November 2009, "Pooled Analysis of Rofecoxib Placebo-Controlled Clinical Trial Data: Lessons for Post-Market Pharmaceutical Safety Surveillance" (Ross, 2009) http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2830805/pdf/nihms178569.pdf

BTW: A look-back you may find of interest and value …

NOTE:

On 28 January 2020 *PBS American Experience* aired "The Poison Squad—The American People Had No Idea What They Were Eating."

You can access information on this at: https://www.pbs.org/wgbh/americanexperience/films/poison-squad/ .

… moving on …

So, now let's take a look-back at, for example, human-subjects research in the U.S., two of the earliest-stage questions that arise well could be:

Why and how did Tuskegee happen?

Was it simply that the Tuskegee researchers were bigots?

Actually, the search for the answers to those questions begins in Europe, not in the States … .

One needs remember that in 1932 little was known about the nature of syphilis.

There were some treatments, and some claimed cures … .

… but the treatments were risky at best, and those treatments in included injecting patients with mercury and arsenic compounds, and other heavy metals.

- *MLI*—2005-06—"More subject, less human ... ." (Gillon, 2005)

Syphilis treatments in Europe

Treatments of syphilis also included infecting patients with malaria using *Plasmodium vivax*.

The medical claim was that the intense fevers killed the syphilis spirochetes.

- *MLI*—2005-06—"More subject, less human ... ." (Gillon, 2005)

The process, termed “pyrotherapy,” earned its creator, Julius Wagner-Jauregg, the 1927 Nobel Prize in physiology or medicine.

- *MLI*—2005-06—“More subject, less human ... .” (Gillon, 2005)

It's worth noting that the award occurred the decade before Wagner-Juaregg tumbled completely into a virulent, eugenics-supporting anti-semitism and sought membership in the *Nationalsozialistische Deutsche Arbeiterpartei* (*NSDAP*) ... the Nazi party.

- *JRSM,* August 2012, "Julius Wagner-Jauregg: pyrotherapy, simultanmethode, and 'racial hygiene'," (Gartlehner et al., 2012) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3423136/pdf/JRSM-12-K049-JL.pdf
- *Bulletin of the History of Medicine*—1996-04—"Julius Wagner-Jauregg [1857-1940] Review" (Sengoopta, 1996)

The indication is that Wagner-Jauregg's application for membership in the Nazi party was rejected because ...

- *JRSM,* August 2012, "Julius Wagner-Jauregg: pyrotherapy, simultanmethode, and 'racial hygiene'," (Gartlehner et al., 2012) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3423136/pdf/JRSM-12-K049-JL.pdf
- *Bulletin of the History of Medicine*—1996-04—"Julius Wagner-Jauregg [1857-1940] Review" (Sengoopta, 1996)

... his first wife was Jewish.

- *JRSM,* August 2012, "Julius Wagner-Jauregg: pyrotherapy, simultanmethode, and 'racial hygiene'," (Gartlehner et al., 2012) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3423136/pdf/JRSM-12-K049-JL.pdf
- *Bulletin of the History of Medicine*—1996-04—"Julius Wagner-Jauregg [1857-1940] Review" (Sengoopta, 1996)

Also in Europe

We know that, for decades in Oslo, the Norwegians treated leprosy and syphilis (known as *radesyken*—an old Nordic name for "the wicked disease") at the national hospital, or *Rikshospitalet*.

The first of the noted clinicians was Jens Johan Hjort, at the *Rikshospitalet*, from 1825 until his resignation/retirement in 1871.

- *GENIT-MED, June* 1994, "The history of venereology in Norway," (Fyrand et al., 1994) https://europepmc.org/article/med/8039789#free-full-text

Hjort's successor was Carl Wilhelm (C.W.) Boeck, first professor in dermatovenereology, surgery and pathology in 1851, and chief of the department from 1871 to 1875, his death. C.W. Boeck claimed that radesyke was caused by a "syphilitic virus" or "poison," and conventional treatment of syphilis with mercury ointments, solutions, pills and fumigations disastrously effected physiological disease resistance.

- *GENIT-MED, June* 1994, "The history of venereology in Norway," (Fyrand et al., 1994) https://europepmc.org/article/med/8039789#free-full-text

C.W. Boeck "vaccinated patients with 'constitutional syphilis' (syphilis in the second or third stage of the disease), using pus from veneral soft or hard chancres in order to stimulate the natural resistance of the organism, according to the modern vaccination therapy of Jenner."

(The originator of "syphilisation" was a French doctor, Auzias Turenne.)

- *GENIT-MED, June* 1994, "The history of venereology in Norway," (Fyrand et al., 1994) https://europepmc.org/article/med/8039789#free-full-text

Between 1852 and 1870, C.W. Boeck treated 1,075 patients using syphilisation at his clinic. When he died in 1875, the clinic abandoned syphilisation. Thereafter, his nephew—Caesar Boeck—was elected chief of the department. Caesar Boeck, who won international fame in 1899 for his description of sarcoidosis (*Morbus Boeck*), followed his uncle's regime of not using mercury in the treatment of syphilitic patients.

- *GENIT-MED, June* 1994, "The history of venereology in Norway," (Fyrand et al., 1994) https://europepmc.org/article/med/8039789#free-full-text

Intending to stimulate resistance, Caesar Boeck treated about 2,000 patients between 1890 and 1910 with roborant, or strengthening, meals and rest until their syphilitic symptoms disappeared. In 1910 he started to use the organoarsenic compound salvarsan and, later, neo-salvarsan.

- *GENIT-MED, June* 1994, "The history of venereology in Norway," (Fyrand et al., 1994) https://europepmc.org/article/med/8039789#free-full-text

In Caesar Boeck's records, patients' lesions were described on admission, and the regression and time of disappearance of the lesions were noted.

Caesar Boeck was succeeded by Edvin Bruusgaard, who in 1925 investigated Caesar Boeck's well-kept records.

- *GENIT-MED, June* 1994, "The history of venereology in Norway," (Fyrand et al., 1994) https://europepmc.org/article/med/8039789#free-full-text

In his 1925 study, Bruusgaard wanted to show "how syphilis progresses when little or no treatment is given and the patient's defence mechanism is allowed to combat the disease alone."

And Caesar Boeck's patients would be studied again at the dermatological department at the *Rikshospitalet* in 1948.

- *GENIT-MED, June* 1994, "The history of venereology in Norway," (Fyrand et al., 1994) https://europepmc.org/article/med/8039789#free-full-text

In that 1948 *Rikshospitalet* look-back, of 1,978 original patients, 20% were randomly analyzed, and the study showed that of those infected:

- 23.6% experienced clinical secondary relapse;
- 15.8% experienced benign tertiary syphilis;
- 10.4% experienced cardiovascular syphilis;
- 6.6% experienced neurosyphilis; and
- 10% died of the disease.
- *GENIT-MED, June* 1994, "The history of venereology in Norway," (Fyrand et al., 1994) https://europepmc.org/article/med/8039789#free-full-text

It was with the foundations of Bruusgaard's 1925 study, **and** the thinking of doctors in 1932 that:

- after the disease passed into later stages, the syphilis treatments were more dangerous than the disease and possibly of no benefit, and
- there might be racial disparities in the progress and nature of the disease,

the researchers then designed and began the Tuskegee Study of Untreated Syphilis (TSUS).

- *MLI--2005-06--*"More subject, less human ...." (Gillon, 2005)

Keep in mind that, in 1932:

- the United States was three years into the Great Depression, and many people lined up for food at soup kitchens and bread lines—they couldn't afford to eat, much less obtain medical care;
- for someone who was poor during the Great Depression, the ongoing medical attention available in the Tuskegee study likely was more than most other citizens would get.
- *MLI--2005-06--*"More subject, less human ...." (Gillon, 2005)

Please know…

This is **not** a defense of Tuskegee.

Rather, this is an effort first of all to place Tuskegee into the medical, historical, economic and social context of when and how the Tuskegee study began in 1932, in the United States, in the South.

So…

So, what were the issues—the ethical issues—with Tuskegee?

The real issues of Tuskegee

The subjects of the US Public Health Service (USPS) Tuskegee study were, for many reasons, a "vulnerable population":

- most were ill, and
- all were African-American sharecroppers: poor, poorly educated, politically and economically powerless men.

And there was no clear and full disclosure to the men who were the human subjects of the study.

- *MLI*--2005-06--"More subject, less human ..." (Gillon, 2005)

The real problems of Tuskegee (cont'd)

It is clear that no one told the men either:

- the nature of the study: explained what would happen to them in the study, or gave them the option to participate or not; or
- the name or nature of the disease they did or did not have (the expression used was "bad blood," a euphemism of the times for conditions as varied as fatigue, anemia and venereal disease).

- *About the USPHS Syphilis Study,* (Tuskegee University, 2019) https://www.tuskegee.edu/about-us/centers-of-excellence/bioethics-center/about-the-usphs-syphilis-study
- *MLI*--2005-06--"More subject, less human ..." (Gillon, 2005)

The real problems of Tuskegee (cont'd)

The Tuskegee study didn't have a definitive

end- or stopping-point: no event, time or result that would trigger the study's end or Reformation. And more than 20 years after Mayo Clinic researchers discovered, then determined the efficacy and safety of penicillin as a treatment for syphilis (1946-48), the Tuskegee human subjects still had not been provided that treatment.

- *About the USPHS Syphilis Study,* (Tuskegee University, 2019) https://www.tuskegee.edu/about-us/centers-of-excellence/bioethics-center/about-the-usphs-syphilis-study
- *MLI*--2005-06--"More subject, less human ..." (Gillon, 2005)

… jumping ahead for a moment across the decades …

Again, please remember that between 1946 and 1948, researchers at the Mayo Clinic determined—and then confirmed—that penicillin was a successful and, for the most part, safe treatment for syphilis.

- *GENIT-MED, June* 1994, "The history of venereology in Norway," (Fyrand et al., 1994) https://europepmc.org/article/med/8039789#free-full-text
- *Pharmacy in History (*Vol. 43, No. 1), 2001, "John Mahoney and the Introduction of Penicillin to Treat Syphilis," (Parascandola, 2011) https://www.jstor.org/stable/41112709
- *MLI*--2005-06--"More subject, less human ... " (Gillon, 2005)

The "nail in the coffin" of the TSUS …

No one told the TSUS participants about the existence of a successful and safe treatment for syphilis using penicillin, or provided that treatment.

- *GENIT-MED, June* 1994, "The history of venereology in Norway," (Fyrand et al., 1994) https://europepmc.org/article/med/8039789#free-full-text
- *Pharmacy in History (*Vol. 43, No. 1), 2001, "John Mahoney and the Introduction of Penicillin to Treat Syphilis," (Parascandola, 2001) https://www.jstor.org/stable/41112709
- *MLI*--2005-06--"More subject, less human ... " (Gillon, 2005)

… returning to the real problems of Tuskegee …

News-wire investigative reporter Jean Heller's interviews of US Public Health Service (USPS) epidemiologist Peter Buxton revealed in 1972—40 years after TSUS began, 24 years after Mayo Clinic researchers determined the efficacy, safety of penicillin as treatment for syphilis (1946-48)—that the Tuskegee human subjects never got treatment.

- *AP/ Washington Star*, 25 July 1972, *NYT,* 25 July 1972, "Syphilis Victims in U.S. Study Went Untreated for 40 Years," (Heller, 1972) https://www.nytimes.com/1972/07/26/archives/syphilis-victims-in-us-study-went-untreated-for-40-years-syphilis.html
- *About the USPHS Syphilis Study,* (Tuskegee University, 2019) https://www.tuskegee.edu/about-us/centers-of-excellence/bioethics-center/about-the-usphs-syphilis-study

So …

How did we come to human-subjects protections in the United States—and when did we do that?

… we must step back in time again …

By September 1945, the last of the winds of war had blown through Europe and the Pacific. With that, the world was discovering the horrors of:

- the German death camps, and
- Japan's research facility, Unit 731, which used human subjects in developing and testing agents of biological warfare, including but not limited to anthrax, plague, cholera and tularemia.
- *MLI*--2005-06--"More subject, less human ..." (Gillon, 2005)

Nuremberg

In Europe, trials of defendants accused of war crimes—among them, the "Doctors' Trial" (December 1946 - August 1947): *United States v. Karl Brandt, et al.*—began in Nuremberg. U.S. prosecutors asked for a medical expert to assist, and the American Medical Association (AMA) named Dr. Andrew Ivy—formerly the civilian director of the Naval Medical Research Institute, Bethesda, Maryland—the prosecutors' consultant.

- *MLI*—2005-06—"More subject, less human ..." (Gillon, 2005)

Dr. Andrew Ivy's rules

Dr. Ivy set out for the Nuremberg prosecutors—and the Court—his "Rules for Human Experimentation":

1. Consent of human subject must be obtained ... all must be volunteers ... Absent coercion in any form ... subjects must be informed of the hazards.

- *MLI*—2005-06—"More subject, less human ..." (Gillon, 2005)

Dr. Ivy's rules (cont'd)

2. An experiment must be designed/based on results of animal experiments and knowledge of natural history of disease under study ... anticipated results must justify the experiment ... yielding results for good of society unprocurable by other methods ... and must not be random/unnecessary in nature.

- *MLI*—2005-06—"More subject, less human ..." (Gillon, 2005)

Dr. Ivy's rules (cont'd)

3. An experiment must be conducted only by scientifically qualified persons ... to avoid all unnecessary physical/mental suffering and injury ... based on prior adequate animal experimentation, with no *a priori* reason to believe death or disabling injury will occur—except where experimenters also serve as subjects (*e.g.,* Yellow Fever experiments).

- *MLI*—2005-06—"More subject, less human ..." (Gillon, 2005)
- *Military Medicine* "Clara Maass, Yellow Fever and Human Experimentation" (Chaves-Carballo, 2013) https://academic.oup.com/milmed/article/178/5/557/4222873

However …

It is important to note that while Dr. Ivy presented to the Nuremberg Court his "Rules for Human Experimentation" as those in force in the U.S., those rules did not exist at the time of Dr. Ivy's testimony before the Nuremberg Court.

- *MLI—2005-06—*"More subject, less human ..." (Gillon, 2005)
- *BMJ*, 7 December 1996, "The Nuremberg Code (1947)," http://www.cirp.org/library/ethics/nuremberg/

Before his testimony …

Before he testified, Dr. Ivy had attempted to have his hand-picked committee of physicians adopt those "Rules for Human Experimentation" in the U.S., but was unable to obtain adoption.

- *MLI—2005-06—"*More subject, less human ..." (Gillon, 2005)

The Nuremberg Court

The Nuremberg Court opened its decision with the declaration of the "Absolute Requirements of Legitimate Medical Research," which have since been known as the Nuremberg Code.

- *MLI—2005-06—*"More subject, less human ..." (Gillon, 2005)
- *BMJ—1996-12-07—*" The Nuremberg Code (1947)" http://www.cirp.org/library/ethics/nuremberg/
- *JAMA*—2017-09-05—"The Nuremberg Code 70 Years Later" (Moreno et al., 2017) https://jamanetwork.com/journals/jama/fullarticle/2649074

After Nuremberg …

Following Dr. Ivy's testimony at Nuremberg, the AMA began in the 1950s to update its "Principles of Medical Practice," and commenced formulation of its own Code of Conduct for human-subjects research. For a look at some of the issues involved, see the the December 2015 issue of the *AMA Journal of Ethics* (formerly *Virtual Mentor*).

- *AMA-JoE—2015-12—*"Clinical Research Ethics" (Williams et al., 2015) *https://journalofethics.ama-assn.org/sites/journalofethics.ama-assn.org/files/2018-09/joe-1512.pdf*

And at the National Institutes of Health (NIH)

In 1953 the Director of the National Institutes of Health (NIH) established a Code of Research Conduct, which mandated consent by the patient volunteers at the Clinical Research Center.

- *Daedalus,* Spring 1969-04—"Governmental Regulation of the Use of Human Subjects in Medical Research--The Approach of Two Federal Agencies," (Curran, 1969) https://pubmed.ncbi.nlm.nih.gov/11609508/ , https://www.jstor.org/stable/20023891

Historical Notes: Germany

Even before World War II, the 1931 rules of the German Minister of the Interior—"Regulations for Modern Therapy for the Performance of Scientific Experiments on Human Beings"—covered both therapeutic and non-therapeutic research, which were more thorough than the Nuremberg Code or the AMA Code of Conduct.

- *MLI*—2005-06—"More subject, less human ..." (Gillon, 2005)

Historical Notes (cont'd): Guatemala

We learned on 1 October 2010 that from 1946 through 1948 doctors of the U.S. Public Health Service infected prisoners and mental patients in Guatemala with syphilis—without their knowledge—to then test the safety and efficacy of penicillin as a treatment and cure. It's not clear that all those infected were treated/cured.

- *"'Normal Exposure' and Inoculation Syphilis: A PHS 'Tuskegee' Doctor in Guatemala, 1946-48* (Reverby, 2011) *www.wellesley.edu/WomenSt/Reverby%20Normal%20Exposure.pdf*

Historical Notes (cont'd): the Bowery

Beginning in 1951, and for more than a decade thereafter, researchers made lower Manhattan Skid Row alcoholics an offer: Agree to a surgical biopsy of the prostate, and they could get a few days of a clean bed and three square meals plus free medical care/treatment if they had prostate cancer.

- *NYT*—2013-10-17—"Decades Later Condemnation for a Skid Row Cancer Study" (Kolata, 2013)
- *AJPH*—2013-10-17—"Screening for Prostate Cancer in New York's Skid Row--History and Implications" (Aronowitz, 2014)
- *BHM*—2013-10-19—"From Skid Row to Main Street--the Bowery series and transformation of prostate cancer 1951-1966" (Aronowitz, 2014)

Historical Notes (cont'd): the Military …

Nuclear "Volunteers"—1946-1962: About 400,000 American soldiers, sailors watched nuclear explosions a few miles from ground zero: 200-plus atmospheric tests. No information or consent—only orders.

- *NYT*—2019-02-14—"Atomic Soldiers" (Knibbe, 2019) https://www.nytimes.com/2019/02/12/opinion/atomic-soldiers.html
- AHF—2019-06-17—"Atomic Veterans 1946-1962" https://www.atomicheritage.org/history/atomic-veterans-1946-1962
- Faden, R—*HCR*—1996-09—"The Advisory Committee on Human Radiation Experiments: Reflections on a Presidential Commission" Faden, 1996) http://pdfs.semanticscholar.org/727d/b374f4af1d8cd79bd84f69b09cc79f013105.pdf
- MH—2002-10—" Undue risk: secret state experiments on humans" (Wiendling, 2002) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1044582/pdf/medhist00005-0152.pdf

Historical Notes: the Military (cont'd) …

Boxes of research-study records—documents from the Walter Reed Army Institute of Research—that were supposed to be shredded turned up in a trash bin. A resident of a suburban Washington neighborhood near the Army medical research campus found the boxes and alerted Montgomery County, Maryland, police.

WP-AP—2007-08-21—"Army Lab Documents Found in Trash Bin" (Whitlock, 2011)

http://www.washingtonpost.com/wp-dyn/content/article/2007/08/21/AR2007082100496.html

Historical Notes: the Military (cont'd)—see also Appendix i

Dating to 2003, top officials at Walter Reed Army Medical Center, including the Army's then-surgeon general, were told by family members, veterans groups and Congress about outpatient neglect. Yet, years later Pentagon and Walter Reed officials expressed surprise about the living conditions and bureaucratic nightmares faced by wounded soldiers staying at the D.C. facility.

WP—2007-03-01—" Hospital Officials Knew of Neglect" (Priest et al., 2007)
http://www.washingtonpost.com/wp-dyn/content/article/2007/02/28/AR2007022801954.html

The National Research Act: Its when and how …

After Jean Heller's July 1972 national revelation of the TSUS, in 1974 the National Research Act created the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research—which created a guidance document that became in 1976 the *Belmont Report*.

- HHS-CDC, "How Tuskegee Changed Research Practices," (CDC, n.d.) https://www.cdc.gov/tuskegee/after.htm
- *Belmont Report*, (OHRP, 1979) https://www.hhs.gov/ohrp/sites/default/files/the-belmont-report-508c_FINAL.pdf

The Belmont Report

The *Belmont Report* summarized the three ethical principles which should guide human research:

- **Respect for persons**: All individuals should be treated as autonomous agents; persons with diminished autonomy are entitled to protection.

- HHS-CDC, "How Tuskegee Changed Research Practices," (CDC, n.d.) https://www.cdc.gov/tuskegee/after.htm
- *Belmont Report*, (OHRP, 1979) https://www.hhs.gov/ohrp/sites/default/files/the-belmont-report-508c_FINAL.pdf
- J Health Care Poor Underserved, Aug. 2010 August More than Tuskegee: Understanding Mistrust about Research Participation, (Darcell et al., 2010) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4354806

The Belmont Report

- **Beneficence**: Researchers should maximize possible benefits and minimize possible harm.
- **Justice**: All persons are to be treated equally, and the selection of research subjects should be scrutinized so that no one is systematically selected on the basis of race, ethnicity, class or other factors.

- HHS-CDC, "How Tuskegee Changed Research Practices," (CDC, n.d.) https://www.cdc.gov/tuskegee/after.htm
- *Belmont Report*, (OHRP, 1979) https://www.hhs.gov/ohrp/sites/default/files/the-belmont-report-508c_FINAL.pdf

… the Regulations of the National Research Act …

The National Research Act set out Title 45, Part 46 of the Code of Federal Regulations (45 CFR 46), "Protection of Human Subjects," and since amended, which required researchers to get voluntary informed consent from persons taking part in human-subject research studies.

- 45 CFR 46 (pre-1918), https://www.govinfo.gov/content/pkg/CFR-2016-title45-vol1/pdf/CFR-2016-title45-vol1-part46.pdf; 45 CFR 46 (effective 19 July 2018, https://www.ecfr.gov/cgi-bin/retrieveECFR?gp=&SID=83cd09e1c0f5c6937cd9d7513160fc3f&pitd=20180719&n=pt45.1.46&r=PART&ty=HTML
- HHS-CDC, "How Tuskegee Changed Research Practices," (CDC, n.d.) https://www.cdc.gov/tuskegee/after.htm

… the "Common Rule …

The Federal Policy for the Protection of Human Subjects or the "Common Rule" was published in 1991 and subsequently codified in separate regulations signed by sixteen (16) Federal departments and agencies, with two (2) more under Executive Order and two (2) more stating an intent to sign.

- Federal Policy for the Protection of Human Subjects ("Common Rule"), (OHRP, 2016) https://www.hhs.gov/ohrp/regulations-and-policy/regulations/common-rule/index.html

Acquired Immune Deficiency Syndrome (AIDS)

With the 5 June 1981 issue of the *Morbidity and Mortality Weekly Report* (*MMWR*), Centers for Disease Control and Prevention (CDC), came the first notice of Acquired Immune Deficiency Syndrome (AIDS), which placed the FDA in the position of exacerbating a health care crisis by impeding development of, and access to, new medications.

- HHS-CDC, 12 August 2020, "HIV and AIDS Timeline," (CDC, 2020) https://npin.cdc.gov/pages/hiv-and-aids-timeline#1980
- HHS-CDC-MMWR, 5 June 1981, "Pneumocystis Pneumonia --- Los Angeles," (Gottlieb et al., 1981) https://www.cdc.gov/mmwr/preview/mmwrhtml/june_5.htm

AIDS (cont'd)

AIDS rapidly became known as a highly lethal infectious disease for which there were no conventional therapies. In consequence, those suffering from the disease were desperately in need of new forms of treatment, no matter how experimental or unorthodox.

- *NYU-J-L&PP*, 2000, "AIDS, Experimental Drug Approval, And The FDA New Drug Screening Process," (Greenberg, 2000) http://www.nyujlpp.org/wp-content/uploads/2012/10/Michael-D-Greenberg-AIDS-Experimental-Drug-Approval-and-the-FDA.pdf

AIDS (cont'd)

For individuals facing imminent death from AIDS, the possibility that an experimental treatment could be unsafe or ineffective was largely irrelevant.

- *NYU-J-L&PP*, 2000, "AIDS, Experimental Drug Approval, And The FDA New Drug Screening Process," (Greenberg, 2000) http://www.nyujlpp.org/wp-content/uploads/2012/10/Michael-D-Greenberg-AIDS-Experimental-Drug-Approval-and-the-FDA.pdf

AIDS (cont'd)

Unsurprisingly, the paternalistic and risk-averse procedures for FDA drug approval were widely viewed in the AIDS community as politically unresponsive and a death sentence for many persons with AIDS.

- *NYU-J-L&PP*, 2000, "AIDS, Experimental Drug Approval, And The FDA New Drug Screening Process," (Greenberg, 2000) http://www.nyujlpp.org/wp-content/uploads/2012/10/Michael-D-Greenberg-AIDS-Experimental-Drug-Approval-and-the-FDA.pdf

AIDS (cont'd)

In the early years of AIDS, the disease affected primarily politically unpopular minorities such as homosexuals and intravenous drug users, as a result of which mainstream society largely failed to respond—despite the presence of a serious public health crisis—and through 1987 AIDS had not become a major political issue.

- "FDA's Proposed Regulations to Expand Access to Investigational Drugs For Treatment Use: The Status Quo in the Guise of Reform," (Rossen, 2008) http://dash.harvard.edu/bitstream/handle/1/8965551/Benjamin%20Rossen%20course%20and%203L%20Paper%20-%20Proposed%20Rules%20to%20Expa.pdf?sequence=1

AIDS (cont'd)

Government research expenditures remained relatively small, and FDA had not approved a single treatment for the disease.

- *NYU-J-L&PP*, 2000, "AIDS, Experimental Drug Approval, And The FDA New Drug Screening Process," (Greenberg, 2020) http://www.nyujlpp.org/wp-content/uploads/2012/10/Michael-D-Greenberg-AIDS-Experimental-Drug-Approval-and-the-FDA.pdf

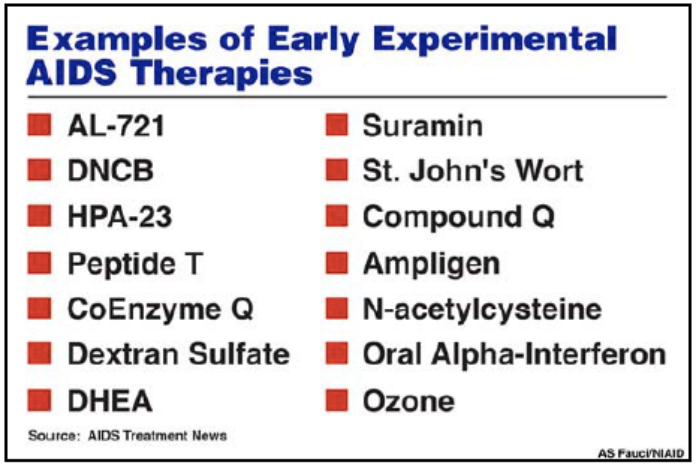
AIDS (cont'd)

Meanwhile, desperately ill and dying victims of the disease, lacking any legitimate treatment and facing imminent death, fervently pursued any available glimmer of hope—no matter how far-fetched or unlikely.

- *NYU-J-L&PP*, 2000, "AIDS, Experimental Drug Approval, And The FDA New Drug Screening Process," (Greenberg, 2020) http://www.nyujlpp.org/wp-content/uploads/2012/10/Michael-D-Greenberg-AIDS-Experimental-Drug-Approval-and-the-FDA.pdf

AIDS (cont'd)

Late 2014 in Baltimore, Maryland, Dr. Anthony Fauci, director of the National Institute of Allergy and Infectious Disease (NIAID) at NIH, spoke to the times, the activists' search for relief, and some of the items on their lists of ... desperation:



(PRIM&R/AER Conference, 2014)

AIDS (cont'd)

Dr. Fauci spoke of how he was characterized by the AIDS-activist community in those days:

(PRIM&R/AER Conference, 2014)

(PRIM&R/AER Conference, 2014)

AIDS (cont'd)

He spoke to how he and those AIDS-activists came to hear and understand one another, and co-operate, even in the face of FDA opposition:

San Francisco Chronicle

June 24, 1989

By Randy Shilts

Top U.S. Researcher and AIDS Official Urges Expanded Drug Testing

"The federal government's top AIDS researcher yesterday called for opening up a "parallel track" of drug testing that would greatly expand the availability of new treatments for AIDS sufferers..."

Los Angeles Times

June 24, 1989

Ease AIDS Drug Rules, Health Chief Urges

The New York Times

June 25, 1989

AIDS Researcher Seeks Wide Access to Drugs in Tests

AS Fauci/NIAID

(PRIM&R/AER Conference, 2014)

AIDS (cont'd)

And he told of how the FDA came to accept the proposals of AIDS-activists ... and him, though those events had taken almost a decade to come to pass:

(PRIM&R/AER Conference, 2014)

1989 and beyond …

Looking back at Dr. Fauci's telling of the consensus forged with the HIV-AIDS community by 1989, if one takes that year as something of an HIV-AIDS drug-trials turning point and marks the calendar from then, there were nineteen (19) statutes passed by Congress in the next 26 years.

See: Appendix ii for ten (10) legislative examples in the 1996-2011 window.

Meanwhile …

… a segment of the pharmaceutical industry demonstrated a powerful flex of Congressional muscle …

… that flex of Congressional muscle …

"... by the early 1990s, the [FDA] had become uneasy about the growing number of [companies'] exotic product and health claims, particularly after more than 20 deaths were attributed to a 'natural' sleep remedy. After the agency conducted raids across the country to confiscate supplements deemed unsafe or sold for unapproved uses. [Senator Orrin G.] Hatch came to the rescue."

- *NYT*, 20 June 2011, "Support is Mutual for Senator and Utah Industry," (Lipton, 2011) http://www.nytimes.com/2011/06/21/us/politics/21hatch.html

… that flex of Congressional muscle (cont'd) …

http://www.nytimes.com/2011/06/21/us/politics/21hatch.html?pagewanted=all

THE CHAMPIONS

Support Is Mutual for Senator and Utah Industry

Xango — Senator Orrin G. Hatch visited the headquarters of the Xango company, which makes a $40-a-bottle juice made from a Southeast Asian fruit called the mangosteen.

By ERIC LIPTON
Published: June 20, 2011

SALT LAKE CITY — A drive along mountain-lined Interstate 15 here shows why Senator Orrin G. Hatch is considered a hero in this region nicknamed the Silicon Valley of the nutritional supplement industry.

The Champions

A 'Natural Ally'

Articles in this series will look at members of Congress and their advocacy for favorite industries or causes. (Go to website for selection of articles: http://www.nytimes.com/topic/timestopic/se/t/thechampions/index.html.).

In the town of Lehi is the sprawling headquarters of Xango, where company officials praised Mr. Hatch, a Utah Republican, late last year for helping their exotic fruit juice business "operate without excessive intrusion" from Washington.

(Lipton, 2011)

The Dietary Supplement Health and Education Act of 1994

"Under legislation [the 'Dietary Supplement Health and Education Act of 1994'] he pushed through Congress, nutritional supplement companies could introduce products without F.D.A. approval, and make general health claims without proving their effectiveness or safety." (emphasis supplied)

- *NYT*, 20 June 2011, "Support is Mutual for Senator and Utah Industry," (Lipton, 2011) http://www.nytimes.com/2011/06/21/us/politics/21hatch.html

The Dietary Supplement Health and Education Act of 1994 (cont'd)

Which provides insight as to why it was the State Attorney General of New York—rather than the FDA—which acted in early February of 2015 to remove "supplement" products alleged to have been adulterated and/or otherwise dangerous or fraudulent

- *NYT*, 3 February 2015, "New York Attorney General Targets Supplements at Major Retailers," (O'Connor, 2015) http://well.blogs.nytimes.com/2015/02/03/new-york-attorney-general-targets-supplements-at-major-retailers
- *NYT*, 3 February 2015, "What's in Those Supplements?" (O'Connor, 2015) https://well.blogs.nytimes.com/2015/02/03/sidebar-whats-in-those-supplements/

Post the AIDS crisis, if not post AIDS …

Those in need of new therapies—and others who would use them for their own purposes—went to school on the "mediazation" methodologies of 1980s HIV-AIDS activists.

With those tools in hand, the "right-to-try" movement—advocating, *inter alia*, state laws that it claims will give critically ill patients the right to try medications that have not been approved by the FDA—has grown.

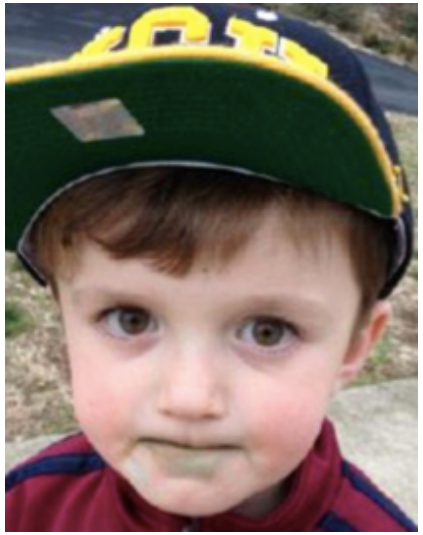
“Right-to-Try” (for greater detail, see Appendix iii …)

Some faces employed for the “right-to-try” movement

(WP, 2001)

(Lakeland PBS, 2017)

(Statesman, 2014)



(FLS,2016)

(NYT, 2015)

(l-r)Abigail Burroughs, Jacob Gunvalson, Andrea Sloan, Josh Hardy, Larry Kutt

The FDA view …

The FDA view of drugs is three-tiered:

- approved drugs;
- drugs in clinical trials;
- drugs in "expanded access"

For a discussion of the FDA view of these three (3) tiers, see: Appendix iv

FDA--2015-0202--"Expanded Access Programs for Drugs and Biologics—When All Else Fails," (FDA, 2015) https://www.fda.gov/media/97846/download

The fault, is not in our stars …

Adverse Event Triggered Event Reporting for Devices

—

Report of a Food and Drug Administration Supported Feasibility Pilot of Automated Adverse Event Reporting"

- *JCL* (Reed et al., 2016) http://journals.lww.com/jcejournal/Abstract/2016/04000/Adverse_Event_Triggered_Event_Reporting_for.12.aspx

… the fault is in ourselves …

"Despite US Food and Drug Administration (FDA) requirements for reporting medical device adverse events, only an estimated 10% of events are actually reported, and many of those lack important data. ***[T]he FDA sponsored a pilot project of the Adverse Event Triggered Event Reporting for Devices (ASTER-D) system … ." (emphasis supplied)

- *JCL*, (Reed et al., 2016) http://journals.lww.com/jcejournal/Abstract/2016/04000/Adverse_Event_Triggered_Event_Reporting_for.12.aspx

… and in ourselves …

Ellen Roche, a 24 year old woman who was previously healthy, volunteered for a research project, and died as a result of her participation in the project.

- *NYT*, 17 July 2001, "Johns Hopkins Admits Fault in Fatal Experiment," (Koolata, 2001) https://www.nytimes.com/2001/07/17/us/johns-hopkins-admits-fault-in-fatal-experiment.html
- *BMJ*, 30 June 2001, "Healthy woman dies in research experiment," (Joefson, 2001) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1173356/pdf/1565a.pdf
- *JME*, 1February 2002, "The hexamethonium asthma study and the death of a
- normal volunteer in research," (Savulescu, 2002) https://jme.bmj.com/content/medethics/28/1/3.full.pdf

… and in ourselves … (sigh)

Maryland Court compares two cases of research with children to the TSUS and that of the Nazis.

- MD-CT-APP, 16 August 2001, Ericka GRIMES v. Kennedy Krieger Institute, Inc, (Findlaw, 2001) https://caselaw.findlaw.com/md-court-of-appeals/1236870.html
- *JoHCL&P*, Vol. 6 (1) 2002, "Whose Duty is it Anyway?: the Kennedy Krieger Opinion and its Implications for Public Health Research," (Hoffmann et al., 2002) https://digitalcommons.law.umaryland.edu/cgi/viewcontent.cgi?article=1081&context=jhclp
- *JoHCL&P*, Vol. 6 (1) 2002, "The Kennedy Krieger Case: Judicial Anger and the Research Enterprise," (Schwartz, 2002) https://digitalcommons.law.umaryland.edu/cgi/viewcontent.cgi?article=1082&context=jhclp
- *AJPH*, July 2002, "Risk and Responsibility: Ethics, Grimes v Kennedy Krieger, and Public Health Research Involving Children," (Mastroianni, et al., 2002) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1447191/pdf/0921073.pdf

Some materials of interest

- *Principles of Biomedical Ethics* (Eighth Edition, 2019)—Tom Beauchamp and James Childress

- Tuskegee Study of Untreated Syphilis (TSUS) http://www.tuskegee.edu/about_us/centers_of_excellence/bioethics_center/about_the_usphs_syphilis_study.aspx

- CDC: "U.S. Public Health Service Syphilis Study at Tuskegee," http://www.cdc.gov/tuskegee/index.html

See Appendix v for additional materials of interest

A “pecking order” in law …

There is an authority “pecking order” where:

- a constitution has more authority than a statute, which has more authority than a regulation (or “rule”), which has more authority than an agency manual or directive ... ; and
- a tradition of making the law as we go along: the case-law structure of the Common Law tradition.

Institutional Review Boards (IRBs)

- Most IRBs in the States are creatures of the institutions at/in which they are resident. (This is the condition at the five (5) IRBs on which I've served (for the most part *pro bono*) since 2002.)

- Question: Can there be an IRB that does not exist within a research institution?

IRBs (cont'd) …

- Across the past two decades "commercial" IRBs—private business enterprises—have come into existence, and now flourish.
- They say that they seek to serve their "customers," but for the commercial IRB, is the customer the drug company, device maker, the research investigator?
- And if so, does that present a conflict: *i.e.*, the duty to the "customer" vs. the duty to protect research subjects?

IRBs (cont'd) …

… not sayin' … just askin' …

IRBs (cont'd) …

Consider:

- Commercial IRBs have done what humans and their institutions do: they began "mating"—*i.e.*, merging one with another—and now there are a few very large commercial IRBs.
- Venture-capital (VC) firms saw how profitable commercial IRBs were, and began "investing" in them—stated more directly, the VC firms bought, acquired commercial IRBs.

IRBs (cont'd) …

Consider: VC firms were not satisfied with those acquisitions, and they acquired, for example:

- a company doing "product development ... prototyping ... validation and testing" for medical device makers; and
- "... the leading provider of model-based drug development and data analytics software and consulting services to the biopharmaceutical research and development market." (19 December 2013) ...

IRBs (cont'd) …

… and further VC firm acquisitions:

- an enterprise that is a "provider of compliance service solutions that enable hospitals to create, oversee and effectively manage their contractual agreements in compliance with regulations."

- a clinical services organization ensuring safety, transparency, and "accelerating progress of clinical research" (clinical trials).

Documents revealing potential conflicts of interest (COIs)

A colleague asked my thoughts about something they'd found in a Material Transfer Agreement (MTA), which is a document executed between institutions doing research together, whereby they share, for example, tissue—*e.g.*, blood—for research analysis. My colleague found in the MTA language that ... well, troubled.

Documents revealing potential COIs …

The MTA stated:

"... cells, tissue, tumor tissue, or other biological specimens removed from the subject during the course of sample collection for the DNA [collection entity] or the genetic material (DNA) removed from such specimens may be valuable for scientific, research, or teaching purposes or for the development of a new medical product ...

Documents revealing potential COIs …

"... by agreeing to participate in the DNA ... repository, subjects authorize [the institution] and members of its staff to use their cells, blood, or other specimens (DNA) for use in future studies ... in the event specimens in the DNA [repository] are used in a research project that results in a product that could be sold commercially, [the institution] and its collaborators will assert the exclusive right to any revenue from the sale of such a product." (emphasis supplied.)

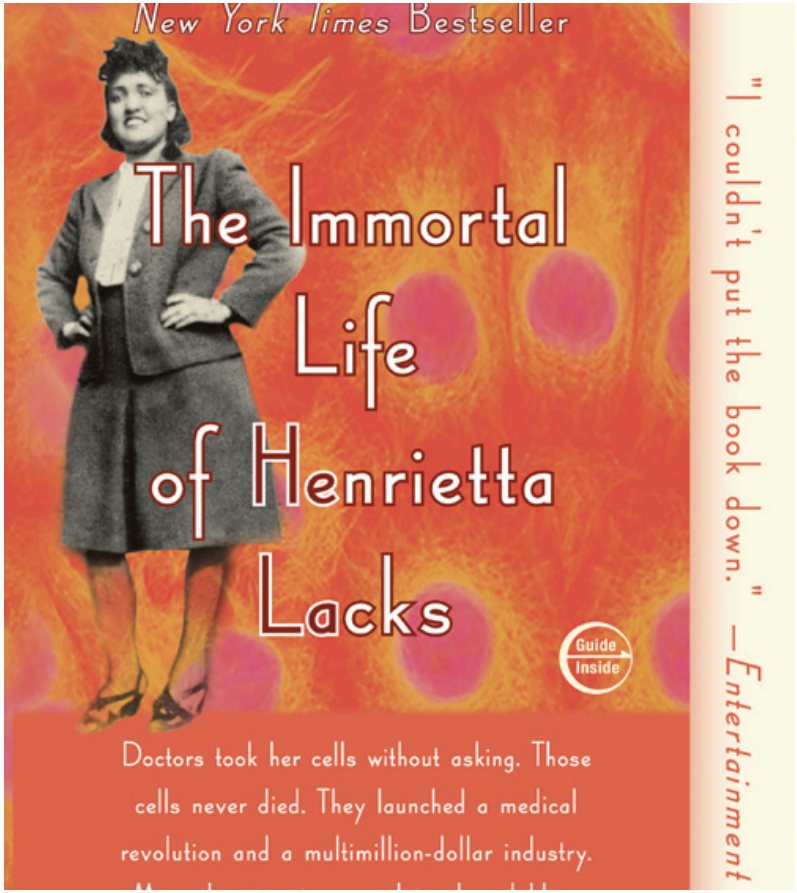
Documents revealing potential COIs …

My colleague had spotted the language in the MTA, but apparently no one else had. The principal investigator hadn't noted the language for the oversight panel—he/she may never have noticed it—and apparently no institution reviewer had noted or considered it. The receiving institution was taking possession and ownership of the tissue, its DNA content(s) and any products that might be developed from them.

Documents revealing potential COIs …

This further was complicated by the fact that there were two of these MTA documents from two different—and so "competing"—receiving institutions. Further, no one informed the research subjects as to either of these MTA documents--or of the similarly acquisitive Cooperative Research and Development Agreements (CRADAs) that each institution had with its respective pharmaceutical company partner(s).

Biological material(s) removed from a patient or subject …



(Skloot, 2001)

You likely are familiar with *The Immortal Life of Henrietta Lacks*, the book telling the true story of a dying patient from whom cancer tumor cells were removed in the early 1950s, and the first to be cultured successfully, and then used for research and for drug development.

Biological material(s) removed from patient/subject (cont'd) …

The story of Ms. Lacks might be explained as having begun in a less-informed time and, in/at that time without a profit motive by the treating physician—who originally simply sought to culture the cancer cells and study them to care for his patients.

Please know that I don't suggest by this that the down-stream events should be excused.

Biological material(s) removed from patient/subject (cont'd) …

Nonetheless, what my colleague found could not be explained that way.

For your further consideration, contrasting tacks:

- *G3: Genes|Genomes|Genetics*, 11 March 2013, "The genomic and transcriptomic landscape of a HeLa cell line," (Landry et al., 2013) https://www.g3journal.org/content/ggg/early/2013/03/11/g3.113.005777.full.pdf
- *Science*, 13 January 2013, " Identifying personal genomes by surname inference," (Gymrek et al., 2013) https://www.gwern.net/docs/genetics/2013-gymrek.pdf
- Moore v. Regents of the University of California, 51 Cal. 3d 120; 271 Cal. Rptr. 146; 793 P.2d 479 (1990), http://biotech.law.lsu.edu/cases/consent/Moore_v_Regents.htm

April revisions to DoDI 3216.02

On 15 April 2020, the US Department of Defense (DoD) released a revision of DoD Instruction (DoDI) 3216.02.

Apparently, there was neither a companion listing of changes within the document; nor "tracked" version which allowed the reader to see on first-reading what changes had been made.

- DoDI 3216.02—Protection of Human Subjects and Adherence to Ethical Standards in DoD-Conducted-and-Supported Research (2020) https://www.esd.whs.mil/Portals/54/Documents/DD/issuances/dodi/321602p.pdf

April revisions to DoDI 3216.02

However, civilian staff of Walter Reed Army Institute of Research (WRAIR) detailed—and generously shared—a listing of the changes observed:

- (JJG: Particularly problematic?) DoD eliminated the requirement of a DoD Research/Medical Monitor—the loss of a second and independent eye. The IRB must decide what to do with the currently approved Greater than Minimal Risk (GtMR) studies having research monitors.

April revisions to DoDI 3216.02

- Waivers of 10 USC 980 are matter exclusive to the Secretary of Defense. However, in this new regime that authority seems to move down the chain-of-command, possibly to the DOHRP.
- The DoD component must conduct a component-level administrative review (CLAR)) of all non-exempt HSR when the HSR: is conducted in a foreign country, unless by a DoD overseas institution; or involves only DoD-affiliated personnel who are U.S. citizens.

April revisions to DoDI 3216.02

- The revised DoDI no longer requires that IRB members be federal employees.
- The DoDI now requires post-approval compliance monitoring (PACM) for studies conducted or supported by a DoD Institution.
- The DoDI revision uses the term “Key Investigator” rather than “Principal Investigator.”

April revisions to DoDI 3216.02

- Large-scale genomic data (LSGD) collected from DoD affiliated personnel (Sec, 1.2.h) are subject to several requirements, including reviews for DoD Component Security and by the Office for Human Research Protections (DOHRP).
- DoD will permit use of broad consent in DoD-conducted and collaborative research (DOHRP guidance), with DoD Component notification to the DOHRP that a DoD institution intends to use broad consent in a research protocol.

April revisions to DoDI 3216.02

- When a DoD institution believes that the research is not subject to the provision listed in 32 CFR 219.114(b), there is a mechanism to deviate from the single IRB requirement.

- An Institutional Agreement for IRB Review (IAIR) will no longer be necessary when an IRB relies upon another DoD institution for ethical and regulatory review.

April revisions to DoDI 3216.02

- Previously, to rely upon a non-DoD IRB, the Human Subjects Protection Branch (HSPB) had to demonstrate it had a secondary role in research and the work packet was subject to a component-level administrative review (CLAR). While several requirements remain (*e.g.*, non-DoD IRBs apply DoD regulations, policies, etc.), these two items have been eliminated. AHRPO will need to approve the IAIR.

April revisions to DoDI 3216.02

- Currently, the Defense Federal Acquisition Regulation (DFARS) clause conflicts with the revised DoDI and contracts will need to be modified to reflect the revised DoDI.
- In limited circumstances (*e.g.*, no extramural partners), the DoDI allows for a DoD IRB's review to constitute the HRPO review. Possibly HRPO will conduct an initial review, but return a decision that its review no longer is necessary.

April revisions to DoDI 3216.02

- For DoD-supported exempt and research not involving human subjects (NHSR), the DoDI requires that the packet be sent to HRPO (per the same requirements) but it is silent as to a review. HRPO may consider delegating this review to the HSPB.
- The DoDI redefines "assistance." A DoD component may waive some procedures for DoD-supported HSR when the DoD support is limited to "assistance."

April revisions to DoDI 3216.02

- For non-DoD Institutions, reporting of pregnancy to AHRPO is required is immediately when pregnancy occurs during a study that lists this as an exclusion.

Operation Warp Speed (OWS)

Operation Warp Speed—a partnership among DHHS (*e.g.*, the CDC, the FDA, the NIH), the Biomedical Advanced Research and Development Authority (BARDA), and DoD—seeks to deliver 300 million doses of a safe, effective vaccine for COVID-19 by January 2021, and accelerate development, manufacturing, and distribution of COVID-19 vaccines, therapeutics, and diagnostics.

- DHHS,"Fact Sheet: Explaining Operation Warp Speed," (DHHS, 2020) https://www.hhs.gov/about/news/2020/06/16/fact-sheet-explaining-operation-warp-speed.html

Again: takeaways: Os & Qs …

Recalling our original queries …

Q: Look back, and around …

- How might one benefit by teasing out from the route taken to the "now" to know, understand where one is now and where one is going?
- Has an initial failure, or apparent failure set up continuing failure … or later success; and, in either case, how has that played out to date?
- What are the weaknesses found in health science, practice and education history—and how can those be minimized, if not eliminated, going forward?

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- **Michael Grippaldi, JD**—for DoDI 3216.02 guidance.
- **Marianne Elliott**—for asking the WHYs about this presentation that even my internal perpetual five-year-old failed to ask

Defense Health Agency

Questions?

BTW: A final thought …

… going forward, the only **truly** stupid question is the one not asked.

Key Takeaways

•In human-subjects research and its oversight, we must have an appreciation of from whence we have come to understand and appreciate where we are, and where we must go in the future;

•the foundations of clinical and research ethics--aka bioethics--the foundations must be built on respect for others; and

•while one may not need know the details of human-subjects research and its oversight as it is practiced abroad--e.g., the European Union and its General Data Protection Regulation (GDPR)--but one needs know that the requirements exist and know where to go to ask the questions necessary

Thank You!

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Appendix i: Historical Notes: the Military …

The US Air Force dumped the incinerated partial remains of at least 274 American troops in a Virginia landfill before halting the secretive practice in 2008. Air Force officials said the landfill dumping was concealed from families who had authorized the military to dispose of the remains in a dignified and respectful manner.

WP—2011-12-07—" Air Force dumped ashes of more troops' remains in Va. landfill than acknowledged" (Whitlock et al., 2011) https://www.washingtonpost.com/world/national-security/air-force-dumped-ashes-of-more-troops-in-va-landfill-than-acknowledged/2011/12/07/gIQAT8ybdO_story.html

Appendix i (cont'd): Historical Notes: the Military …

The Office of the Inspector General, Department of Veterans Affairs, investigated allegations of, *inter alia*, patient care and administrative issues at the Bay Pines VA Medical Center (BPVAMC), and the deployment of the Core Financial and Logistics System (CoreFLS). The investigation confirmed many of those allegations.

DVA-OIG—2004-08-11—"Issues at VA Medical Center Bay Pines, Florida and Procurement and Deployment of the Core Financial and Logistics System (CoreFLS)" (VA, 2004)
https://www.va.gov/oig/52/reports/2004/VAOIG-04-01371-177.pdf

Appendix i (cont'd): Historical Notes: the Military …

The Indonesian government ordered the US Naval Medical Research Unit No. 2 (NAMRU-2), a key player in the fight against avian flu set up in Jakarta in 1970, to cease all research by year-end 2005. Researchers said that closing the unit would be a major blow to efforts to control the avian flu outbreaks affecting humans and poultry across the country. The Indonesian military was opposed to the center's presence.

NATURE—2005-12-07—"Avian flu centre put under threat of closure" (Butler, 2005)
https://www.va.gov/oig/52/reports/2004/VAOIG-04-01371-177.pdf

Appendix ii: Some Food and Drug Legislation: 1997-2011

- Food and Drug Administration Modernization Act (FDAMA) of 1997—PL105-115 (21 November 1997)
- Best Pharmaceuticals for Children Act—PL 107-109 (4 January 2002)
- Medical Device User Fee and Modernization Act (MDUFMA) of 2002—PL 107-250 (26 October 2002)

Appendix ii (cont'd): Some Food and Drug Legislation: 1997-2011

- Animal Drug User Fee Act of 2003—PL 108-130 (18 November 2003)
- Pediatric Research Equity Act of 2003—PL 108-155 (3 December 2003)
- Minor Use and Minor Species Animal Health Act of 2004—PL 108-282 (2 August, 2004)
- Dietary Supplement and Nonprescription Drug Consumer Protection Act—PL 109-462 (22 December 2006)

Appendix ii (cont'd): Some Food and Drug Legislation: 1997-2011

- Food and Drug Administration Amendments Act (FDAAA) of 2007—PL 110-85 (27 September 2007)
- Family Smoking Prevention and Tobacco Control Act (Public Law 111-31)—PL 111-31 (22 June 2009)
- FDA Food Safety Modernization Act—PL 111-353 (4 January 2011)

Appendix iii: Faces used in the "right-to-try" movement …

- Abigail Burroughs—*WP*, 12 June 2001, "Student Dies After Fight With Drug Firms," (Ginsberg, 2001) https://www.washingtonpost.com/archive/local/2001/06/12/student-dies-after-fight-with-drug-firms/8ce428fc-6772-4fb7-ad96-dabbc945bc15/

- Jacob Gunvalson—*Lakeland PBS*, 21 September 2017, "Gonvick Man Living With Muscular Dystrophy Shares His Experience," (Clotter, 2017) https://lptv.org/gonvick-man-living-with-muscular-dystrophy-shares-his-experience/

- Andrea Sloan—*Statesman*, 3 January 2014, "Austin woman dies after battle for access to experimental cancer drug," (Ball, 2014) https://www.statesman.com/article/20140103/NEWS/301039693

Appendix iii (cont'd): Faces used in the "right-to-try" movement …

- Josh Hardy—*FLS,* 22 September 2016, "'Now he is healed;' Mourning the death of 10-year-old Josh Hardy," (Dyson, 2016) https://fredericksburg.com/news/local/now-he-is-healed-mourning-the-death-of-10-year-old-josh-hardy/article_3da24a7a-ee8b-5c74-89a8-f58adeb0ff31.html

- Larry Kutt —*NYT,* 10 January 2015, "Patients Seek 'Right to Try' New Drugs," (Turkewitz, 2015) https://www.nytimes.com/2015/01/11/us/patients-seek-right-to-try-new-drugs.html

Appendix iv: The FDA view …

The FDA view of drugs is three-tiered:

- approved drugs
- drugs in clinical trials
- drugs in "expanded access"

- FDA, "Expanded Access Programs for Drugs and Biologics—When All Else Fails," (FDA, 2015) https://www.fda.gov/media/97846/download

Appendix iv (cont'd): The FDA view …

To the FDA, approved drugs are drugs that:

- have been studied and characterized;
- are labeled;
- have the broadest availability; and
- have been cleared for third-party reimbursement

- FDA, "Expanded Access Programs for Drugs and Biologics—When All Else Fails," (FDA, 2015) https://www.fda.gov/media/97846/download

Appendix iv (cont'd): The FDA view …

To the FDA, drugs in clinical trials are drugs that are:

- in a process of providing necessary data to determine safety and effectiveness; and
- on an efficient path to market and broad availability

- FDA, "Expanded Access Programs for Drugs and Biologics—When All Else Fails," (FDA, 2015) https://www.fda.gov/media/97846/download

Appendix iv (cont'd): The FDA view …

To the FDA, "expanded access" drugs are:

- drugs that represent an opportunity for a patient when other options have been exhausted—and the goal is access to treatment

- FDA, "Expanded Access Programs for Drugs and Biologics—When All Else Fails," (FDA, 2015) https://www.fda.gov/media/97846/download

Appendix v: Some materials of interest …

- Advisory Committee on Human Radiation Experiments (ACHRE), http://www2.gwu.edu/~nsarchiv/radiation/

- National Academy of Sciences (NAS) report: "Intentional Human Dosing Studies for EPA Regulatory Purposes: Scientific and Ethical Issues": http://www.nap.edu/download.php?record_id=10927

For more materials of interest, see: Appendix v

Appendix v: Some materials of interest (cont'd) …

- Moore v. Regents of the University of California, 51 Cal. 3d 120; 271 Cal. Rptr. 146; 793 P.2d 479 (1990), http://biotech.law.lsu.edu/cases/consent/Moore_v_Regents.htm
- Jesse Gelsinger (1999): *Science*, 8 May 2009, "A History Lesson for Stem Cells," https://science.sciencemag.org/content/sci/324/5928/727.full.pdf
- Also: *bioethics.net*, 31 January 2008, "A comment from Paul Gelsinger on gene therapy and informed consent," http://www.bioethics.net/2008/01/a-comment-from-paul-gelsinger-on-gene-therapy-and/

Appendix v: Some materials of interest (cont'd) …

- TGN 1412 (2006), http://news.bbc.co.uk/2/hi/uk_news/england/london/4807042.stm
- "Ethics of 2 cancer studies questioned—India studies funded by Gates Foundation, National Cancer Institute draw scrutiny" (2013-14), http://www.azcentral.com/news/articles/20130213ethicscancer-studies-india-questioned.html

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