Wasted Money in United States Biomedical and Agricultural Animal Research

Jim Keen

University of Nebraska-Lincoln

Follow this and additional works at: https://www.wellbeingintlstudiesrepository.org/bioamres

Part of the Animal Experimentation and Research Commons, Animal Studies Commons, and the Other Medical Sciences Commons

Recommended Citation

Keen, J. (2019). Wasted money in United States biomedical and agricultural animal research. In Animal Experimentation: Working Towards a Paradigm Change (pp. 244-272). Brill.
Background

To kill an error is as good a service as, and sometimes even better than, the establishing of a new truth or fact.

CHARLES DARWIN, 1879

Biomedical and agricultural animal research uses millions of experimental animals and dozens of animal species each year by choice, precedent, or regulatory mandate in basic and applied life science research and toxicity testing of drugs, chemicals, and consumer products. Animal research is a large component of the international US$270 billion government-subsidized, biomedical industrial ecosystem (Chakma et al., 2014). In the United States (US) and presumably elsewhere, about half of these funds support animal research and testing (Institute of Medicine and National Research Council, 2012). Each year at least 115 million experimental animals (mostly mice and likely a significant underestimate) are used worldwide (Akhtar, 2015). The status quo animal research environment provides “ecosystem services” to a large number of inter-dependent “species”, including governments, academia, biotechnology, agri-food and pharmaceutical industries, and publishers. Losers in this system are the conscripted animals (for “labor”) and taxpayers (for “capital”).

Animal research squanders precious public and private monies directly, indirectly, by opportunity cost, and by unintended negative consequences. There is no doubt that biomedical and agricultural animal research have delivered societal dividends. Nevertheless, the questionable benefit-cost ratio and the unquestionable negative repercussions of animal research are enormous for taxpayers, patients, and the public at large. Precise animal research investments and attendant waste are impossible to ascertain, in part because the research community and the US government obfuscate financial and animal use data. However, estimated US tax dollars wasted on animal use in biomedical and
agricultural research range, conservatively, from US$5 billion to US$9 billion per year. Even though exact monetary and animal use data are unobtainable, in this chapter I use the best available, if imprecise, estimates. The estimates themselves are arguable, yet the underlying conclusions remain valid.

2 Biomedical Animal Research

Animal experiments are of two types: basic (e.g., investigation of biological phenomena and animal models) and applied (e.g., drug research and development (R&D), and toxicity and safety testing). Applied research can also be preclinical (e.g., molecular biology, cell culture, animal models) or clinical (e.g., human drug or vaccine efficacy trials). The preclinical research goal in animal experimentation is to generate candidate drugs, bio-medical technology or devices and diagnostic tests to evaluate downstream for clinical testing and possibly commercialization, a laboratory-to-patient process called translation. Preclinical research also entails toxicity testing of drugs, vaccines, chemicals, cosmetics, and other consumer products, usually in mice and dogs. Veterinary biomedical animal research is structured essentially the same as its human counterpart albeit on a much smaller scale. The desired outcome of preclinical research, mostly performed by government and academia, are scientific papers, the currency (along with grant funds) of research success. The desired outcome of applied research, mostly performed by biotechnology and pharmaceutical firms, are patented biomedical products that reflect successful translation and new revenue streams. Public acceptance of animal research, especially if invasive and painful, is contingent on substantial human benefits and fiscal accountability. Unfortunately, taxpayers often support animal research under the false hype of “breakthrough” animal model-based medical progress.

Most preclinical research is publicly funded. The US National Institutes of Health (NIH), the world’s largest biomedical research organization with a 2019 budget of US$39.2 billion, emphasizes infectious diseases and oncology (NIH, 2019). The biotechnology and pharmaceutical sectors favor product development and commercialization (e.g., bio-engineered drugs, vaccines and clinical trials for cancer, analgesics, anti-diabetic drugs, and some rare diseases). The public sector generally relies more on animals than the private sector. However, the private sector depends indirectly on publicly funded animal research as a pipeline for candidate drugs or technologies to convert into marketable biomedical products (Dorsey et al., 2009; Moses et al., 2015).

Tax-supported animal research and testing is conducted or sponsored by several US agencies, especially the NIH. Federal laws mandate animal testing
of pharmaceuticals, vaccines, and other chemicals to assess their safety and efficacy. The Environmental Protection Agency and the Food and Drug Administration (FDA) are appropriated vast funds for animal testing. Other US agencies that require and/or conduct animal testing include the Department of Agriculture (USDA), the Consumer Product Safety Commission, the Department of Defense, the National Institute of Environmental Health Sciences, and the Department of Transportation. The private sector has decreased animal testing in some areas, especially in pharmaceuticals (due to high cost and animal model failure) and in cosmetics (due to consumer pressure). However, millions of animals are still used annually by private industry for internal or regulatory safety and efficacy testing of agrochemicals, vaccines and other biologics, and chemicals in consumer products (61.8%; US$71 billion). Private industry is followed by the US government (31.5%; US$45 billion) nonprofits and charities (3.8%; US$4.4 billion), and academia (3.0%; US$3.5 billion). About US$56.4 billion (49%) is spent on preclinical research, with the NIH providing most funding. About 47% of preclinical research uses animals, of which 51% to 89% is flawed. Thus, US$14 billion to US$25 billion (9 million to 15 million out of 17 million laboratory animals) of US animal research is wasted (Freedman, Cockburn and Simcoe, 2015; Moses et al., 2015; National Anti-Vivisection Society, 2018).

2.1 Many Animals
Precise animal numbers utilized in US biomedical research are unknown because the large majority (at least 95%) are exempt from the monitoring, care, and reporting requirements of the USDA’s Animal Welfare Act (AWA). Mice, rats, birds, and fish are exempt. As a result, it is impossible to know how many mice and rats are used each year for research in the US, for what purposes, and the pain and/or distress these animals experience because this data is not gathered or reported (American Anti-Vivisection Society, 2017). The USDA reported 820,812 AWA-covered animal species used for research, testing, teaching, and experimentation in 2016. About 40% of these animals were reported to be subjected to painful procedures, some with and some without anesthesia or analgesia (USDA, 2017). However, this USDA AWA data (animal numbers, species, painful procedures, etc.) is facility self-reported and thus unverified.

It is estimated that roughly 95% of the animals used in US laboratories are mice and rats. Assuming relative species use comparability of European Union data on vertebrate animals (i.e., mice, rats, birds, fish, and all cold-blooded animals), and an AWA non-exempt research animal population of 821,000, about 16 million mice are used annually. However, the estimated US research mouse population varies between 10 million and 100 million animals, many
genetically engineered (Guarino, 2015). Mouse numbers are growing rapidly (Goodman, Chandna and Roe, 2015). Extrapolation from Goodman, Chandna and Roe’s study estimates the US research mouse population at 86 million.

2.2 The Biomedical Industrial Complex

The biomedical industrial complex is an international multi-billion-dollar business. Animal experimentation in the biomedical industrial complex (BIC) is pervasive, secretive, profitable, and government-sanctioned. The term “industrial complex” is from the famous and prescient 1961 farewell speech by US President Dwight Eisenhower to “beware the military industrial complex”, the semi-opaque, complicated “dark state” network of relationships between governments, the armed forces and the corporate military/security sector that supplies them. Like the military industrial complex, the biomedical industrial complex is an impenetrable, taxpayer-money driven eco-system, where the stated bio-medical and public health missions are sometimes subservient to more self-serving ones (Orzechowski, 2012). This does not impugn or discredit most animal researchers, who usually have good, if misguided, intentions.

There are innumerable inter-dependent BIC beneficiaries. These include millions of investigators (salaries, prestige), thousands of universities and foundations (overhead, patents, jobs), hundreds of funding organizations (jobs, power), numerous biotechnology and pharmaceutical corporations (jobs, profits, patents, products) and venture capitalists (return on investment, ROI). Moreover, there is a vast subtler army of allied industries (e.g., equipment, reagent and animal suppliers, consultants, bureaucrats, veterinarians, regulators, and publishers).

Like all taxpayer subsidized enterprises affiliated with human medicine, prices for products and services are highly inflated. Animal suppliers breed animals, from genetically engineered mice to monkeys, to satisfy researcher demands. A New Zealand white rabbit can cost US$350, a monkey US$8,000. In 2010, the Jackson Laboratory sold 2.9 million mice for a revenue of US$98.7 million. Suppliers of feed, cages, and equipment have profitable businesses. A mouse treadmill may cost US$10,000. The US scientific publishing industry generates US$10 billion in annual revenue (Jarvis and Williams, 2016). Biomedical research, with or without animals, is particularly lucrative for US universities who charge overhead (facilities and administrative fees) on every research dollar, typically at a 50% rate. About 80% (US$29.8 billion/year) of NIH’s US$37.3 billion annual funding is awarded to universities and research institutes as extramural competitive grants. Academic “administrative costs” consume one in three research grant dollars, approximately US$9.3 billion (one-fourth) of the
entire NIH budget. Overhead primarily pays high university executive salaries and building depreciation costs and only marginally supports research and investigators. By comparison, typical overhead (fixed costs) for a private US business is approximately 25% of sales, salaries, and benefits, inclusive.

3 The Failure of the Animal Model Paradigm in Biomedical Research

The problem is that it [animal research] hasn’t worked, and it’s time we stopped dancing around the problem [...] We need to refocus and adapt new methodologies for use in humans to understand disease biology in humans [...] You’ve lost the debate if you lose sight of the taxpayers and the patients.

ZERHOUNI, former head of the US NIH, in McManus, 2013

The cornerstone of modern biomedical investigation is animal experimentation, but this practice is in the midst of an existential crisis. Up to 88% of preclinical biomedical experiments, especially those involving animals, are invalid, i.e. derived candidate drugs or vaccines are clinically ineffective or toxic (Freedman et al., 2015; Bock, 2016). This results from poor experimental practices intertwined with the abject failure of synthetic disease in animals, from mice to chimpanzees, to serve as more than skin-deep human disease surrogates.

Animal research has always been ethically contested, but there is now indisputable evidence of animal model failure to recapitulate human disease and provide clinical value (Pound and Blaug, 2016). Public support for animal research is dropping. From 2009 to 2014, Americans opposing animal use in scientific research increased from 43% to 50% (Pew Research Center, 2015). Failed animal models are the root cause of disappointing and diminishing returns on biomedical investments. Poorly designed preclinical animal studies lead to downstream expensive but fruitless clinical trials, exposing people to false hopes, potentially harmful drugs, or withheld beneficial treatments. Poorly conducted studies produce unreliable findings and suffering in millions of animals, nullifying the social and moral justification of laboratory animal use (Pound and Bracken, 2014).

4 Failure and Waste in Preclinical Animal Research

4-1 Of Mice Not Men: Animals Are Not People

Hundreds of thousands of peer-reviewed publications are based on the assumption that human-animal similarities enable knowledge from “animal
models” to be extrapolated to people. The belief is entrenched in scientific funding agencies and animal experimentalists. However, even if animal research is conducted faultlessly, animal models have limited success in predicting human clinical outcomes because of inherent evolutionary, genomic, epi-genomic, physiological, and other human-animal differences. Human diseases are artificially induced in animals but fail to reproduce the complexity of human ailments. Animal models are typically generated through genetic manipulation, surgical intervention, or injection of foreign substances, producing ailments with signs similar to a human disease. A common current mouse cancer model harvests human tumor cells, grows them in a petri dish and then transplants tumor tissue beneath the skin of immuno-compromised mice, so that the mice avatars cannot reject the implanted tumors. These so-called patient-derived xenografts are then exposed to drugs whose killing efficiency and toxicity profiles are extrapolated to treat “personalized” human cancers. The cancer research community published an extraordinary 361,693 experimental studies and journal papers according to a PubMed database search I conducted on 8 August 2018 using the terms “Mice” and “Cancer”. PubMed was unable to identify how many successful anti-cancer mouse drugs became FDA-approved for human use but that number is certainly miniscule. Billions of lost dollars clearly show that mice as human disease surrogates are no more analogous than artificially flavored grape drink is to fine French wine. The chimpanzee, who shares 99% of its DNA sequence with humans and should best predict human outcomes, has largely failed as an animal model, certainly in dozens of HIV vaccine trials over the past three decades (Bailey, 2008). A 1% DNA difference apparently outweighs a 99% similarity.

5 Irreproducibility

Science has two aims: to be reproducible (confirmatory) and to contribute to cumulative knowledge (discovery). Confirmatory science has higher value because it defines scientific truth, i.e. the non-repeatable is false. An estimated 51% to 89% of preclinical animal research (US$13.3 billion to US$23 billion) is unreliable (see Table 10.1).

About 1.5 million biomedical scientific papers are published per year. Irreproducible but published animal research constitutes severe literature pollution, leading other researchers to follow false leads, amplifying waste (see Figure 10.1).

Some cogent and expensive examples of non-repeatable animal experiments are shown in Table 10.2.
TABLE 10.1 Annual US biomedical and agricultural R&D investment and estimated wasted animal research monies

| Source                  | Total research investment: basic, applied, preclinical, and clinical | Total basic or preclinical (assume 49% of total)\(^a\) | Total animal (assume 47% of preclinical)\(^b\) | Wasted money due to flawed animal research (assume 51% to 89% failure rate)\(^a\) |
|-------------------------|---------------------------------------------------------------|--------------------------------------------------------|------------------------------------------------|----------------------------------------------------------------------------|
| All                     | US$124 billion (100%)                                        | US$56 billion                                          | US$26 billion                                  | US$13.3–US$23 billion                                                     |
| Industry                | US$71 billion (61.8%)                                        | US$34.8 billion                                        | US$16.4 billion\(^d\)                         | US$8.4–US$14.6 billion                                                   |
| Government              | US$45 billion (31.5%)                                        | US$22 billion                                         | US$10.4 billion                                | US$5.3–US$9.3 billion                                                   |
| Non-profits and charities | US$4.4 billion (3.8%)                                      | US$2.2 billion                                         | US$1.1 billion                                 | US$560–US$970 million                                                   |
| Academia                | US$3.5 billion (3%)                                          | US$1.7 billion                                         | US$800 million                                 | US$410–US$700 million                                                   |

Biomedical—basic/preclinical and applied/clinical\(^a\)

Animal agriculture—basic and applied\(^c\)

| All                      | US$1.4 billion (100%)                                        | US$686 million\(^e\)                                   | US$686 million                                 | US$350–US$611 million                                                  |
| Industry                | US$500 million (36%)                                        | US$245 million                                         | US$245 million                                 | US$125–US$218 million                                                 |
| Government              | US$900 million (64%)                                        | US$441 million                                         | US$441 million                                 | US$225–US$393 million                                                 |

All 2017 biomedical and agricultural animal research

| All                      | US$125.4 billion                                             | US$61.5 billion                                       | US$28.9 billion                                 | US$14.7–US$25.7 billion                                             |
| Source        | Total research investment: basic, or preclinical, and clinical | Total basic (assume 49% of preclinical) | Total animal (assume 47% of preclinical) | Wasted money due to flawed animal research (assume 51% to 89% failure rate) |
|--------------|---------------------------------------------------------------|----------------------------------------|----------------------------------------|---------------------------------------------------------------|
| Industry     | US$ 71.5 billion                                               | US$ 35 billion                         | US$ 16.6 billion                       | US$ 8.5–US$ 14.8 billion                                      |
| Government   | US$ 45.9 billion                                               | US$ 22.4 billion                       | US$ 10.5 billion                       | US$ 5.3–US$ 9.3 billion                                       |

- **a** Freedman et al., 2015
- **b** National Anti-Vivisection Society, 2018
- **c** Clancy, Fugile and Heisey, 2016
- **d** Probably an overestimate, as industry has a downstream clinical research focus and relies much less on upstream animal research than government or academia.
- **e** Since animal models are rarely used or needed in agricultural animal research, total basic research and total animal research dollars are assumed to be the same.

The most alarming exemplar of irreproducibility is a 2012 Amgen study that reproduced key findings in only six of 53 (11%) *landmark* preclinical cancer papers, mostly from mouse models, published in premier scientific journals (Begley and Ellis, 2012). NIH director Francis Collins recently wrote, “A growing chorus of concern, from scientists and laypeople, contends that the complex system for ensuring the reproducibility of biomedical research is failing and is in need of restructuring [...] *Preclinical research, especially work that uses animal models, seems to be the area that is currently most susceptible to reproducibility issues*” (emphasis added, Collins and Tabak, 2014). Why do we continue to spend so much on flawed animal models that lack validity, resilience, and repeatability?

6 Non-publishable Research and Publication Bias

A hypothesized treatment in an animal model may be ineffective or toxic, a “failure” considered a “negative result”. Scientists do not want to submit, and
Figure 10.1 The animal model of human disease as a major driver of wasted money and translational failure in biomedical research.

Journals do not want to publish negative findings because they lack the prestige of novel discoveries. This leads to unnecessary repetition of failed (unknown) research, amplifying wasted money. Published animal trials overestimate by 30% the likelihood of treatment success because of “missing” unpublished negative findings (Sena et al., 2010).

Unpublished or unpublishable results bias the biomedical literature, favoring positive over negative findings and leading to duplicate studies that unnecessarily endanger animal and human subjects and waste resources. Clinical trials funded by NIH (almost exclusively based on the false animal-as-human paradigm) and registered within ClinicalTrials.gov (clinicaltrials.gov), an NIH-run trial registry and results database, showed that fewer than half of 635 NIH funded clinical trials between 2005 and 2008 were published in a
### Table 10.2  Examples of non-repeatable animal experiments

| Research field | Repeatability failure | Estimated wasted money | Reference |
|----------------|-----------------------|------------------------|-----------|
| Drug discovery: Cancer, women’s health, cardiovascular | Bayer reports 43 of 67 (65%) new drug targets failed to repeat academic journal findings. | US$67 million<sup>a</sup> | Mullard, 2011; Begley and Ellis, 2012 |
| Drug discovery: All biomedical disciplines | 50% of published academic studies in top-tier journals cannot be repeated with same conclusions by industrial labs. | Many millions | Osherovich, 2011 |
| Drug discovery: Cancer | Amgen researcher unable to reproduce the findings in 47 of 53 (89%) landmark cancer papers from top journals. | US$53 million<sup>a</sup> | Begley and Ellis, 2012 |

<sup>a</sup> Cost to repeat preclinical work in industrial labs varies from US$500,000 to US$2 million per compound and three to 24 months. I used a value of US$1 million per drug target (see Freedman, Cockburn and Simcoe, 2015).

Peer reviewed biomedical journal within 30 months of trial completion. Furthermore, those that were published omitted key, usually detrimental, details (Ross et al., 2012). A 2016 study of 4347 interventional clinical trials across 51 US academic medical centers reported dissemination of results within 24 months of completion ranging from 16.2% to 55.3%. This occurred in spite of a 2008 (unenforced) federal law requiring reporting of clinical trial results within 12 months of completion or termination with a (never applied) $10,000 per day fine for non-compliance (Chen et al., 2016). My current home institution, the University of Nebraska, is the most flagrant violator of clinical trial reporting among academic institutions, disclosing less than 20% of clinical trial findings from 2015 to 2017 (Pillar and Bronshtein, 2018). *En toto,* the
non-transparent delayed or non-reporting of human clinical trials represents
the dual wasteful and unethical suffering of many thousands of laboratory
animals, the compromised safety and squandered sacrifice of thousands of
participant human subjects and a total disregard for public accountability to
US taxpayers.

7 Failure to Translate: Downstream Human Clinical Consequences
of Flawed Animal Research

The history of cancer research has been a history of curing cancer in the
mouse. We have cured mice of cancer for decades and it simply didn’t
work in humans. We need to acknowledge the fact that use of animals
will not make us better scientists, but bitter scientists.

RICHARD KLAUSNER, former director of the US National Cancer Institute, 1998, in
MANDAL and PARIJA, 2013

As the above quote attests, animal model failure has been well known for
decades at the highest levels. Animal experiments have contributed to
understanding mechanisms of disease and normal animal physiology and bio-
chemistry. However, their record in predicting effectiveness, toxicity of treat-
ment, or preventive strategies in human trials is dismal. In fact, clinical trials
are essential precisely because animal studies do not predict with sufficient
certainty what will happen in people (van der Worp et al., 2010). The pharma-
aceutical industry bemoans the near empty pipeline over the past 30 years of
new drugs that enter and survive the clinical trial gauntlet to gain FDA approv-
al. Serious biases in animal studies makes it nearly impossible to rely on animal
data to predict whether or not an intervention will be toxic or have a favorable
clinical benefit-risk ratio in humans (Ioannidis, 2012). Excessive translational
risk occurs even though there has never been more public and private money,
trained researchers, and better infrastructure, facilities, and biotechnological
tools (e.g., “humanized” mice) than at present. Nearly all candidate drugs de-
derived from preclinical research, entailing immense expenditures and use of
animal models in which the drugs work well against artificially-induced dis-
 ease, fail in human trials (Kaur, Sidhu and Singh, 2016). Well-known examples
of animal model-to-human clinical failure, costing billions of public and pri-
vate dollars, are shown in Table 10.3.

Drivers of translation failure include:
- Irreproducibility: For decades, the pharmaceutical industry has internally
  replicated preclinical research findings, published or otherwise, as standard
TABLE 10.3 Examples of non-translatable clinical science based on laboratory animal research, mostly mouse models. The drugs or other interventions “worked” (non-toxic, clinically effective) in animal models but were abandoned for use in people due to toxicity or lack of therapeutic efficacy

| Research field                                                                 | Repeatability failure                                                                                                                                                                                                                                                                                                                                 | Estimated wasted money | Reference                                                                 |
|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------|--------------------------------------------------------------------------|
| Type 1 diabetes                                                                | All 195 methods that prevented or delayed development of type 1 diabetes in mice failed in people.                                                                                                                                                                                                                                                  | Billions                | Roep, Atkinson and Herrath, 2004                                         |
| Human immune-deficiency virus (HIV): pre-clinical, and Phase I, II and III vaccine trials | 30–40 vaccines in approx. 90 clinical trials, involving more than 20,000 human volunteers, failed; all vaccines worked in non-human primates, especially chimpanzees injected with HIV; one vaccine increased human HIV risk.                                                                                                                     | Billions; not one HIV vaccine FDA-approved after 30 years | Bailey, 2008                                                            |
| Alzheimer’s disease; preclinical in mice, clinical trials in people             | 300 different interventions reported effective in the amyloid precursor mouse model; none effective in human trials. Of 1,200 clinical trials, only 5 drugs approved, which treat symptoms but not disease progression.                                                                                                                                                  | Billions                | Zahs and Ashe, 2010; Cavanaugh, Pippin and Barnard, 2014                |
| Ischemic stroke                                                                | Two of 500 neuroprotective interventions against stroke successful in human clinical trials; one of the two beneficial drugs was aspirin.                                                                                                                                                                                                          | Billions                | van der Worp et al., 2010                                               |
TABLE 10.3  Examples of non-translatable clinical science based on laboratory animal research, mostly mouse models. The drugs or other interventions “worked” (non-toxic, clinically effective) in animal models but were abandoned for use in people due to toxicity or lack of therapeutic efficacy (cont.)

| Research field                  | Repeatability failure                                                                 | Estimated wasted money | Reference               |
|---------------------------------|--------------------------------------------------------------------------------------|-------------------------|-------------------------|
| Inflammation and sepsis         | 150 clinical trials that tested candidate agents intended to block the inflammatory response all worked in mice; all failed in critically ill patients. | Billions                | Seok et al., 2013       |
| Amyotrophic lateral sclerosis (ALS) | 100 potential drugs in established animal models, of which eight entered clinical trials with thousands of people, failed. Clinical trials of 24 compounds in 51 studies of 13,000 ALS patients, found 1 beneficial compound. | Billions                | Perrin, 2014; Petrov et al., 2017 |

operating procedure to validate drug targets and initiate internal drug discovery. Non-repeatable results have been disappointing and expensive (see Table 10.2). The pharmaceutical industry has heavily divested and decreased reliance on animals because each translational failure causes significant losses of invested capital. European drug companies decreased animal use by 25% from 2005 to 2008 (Pound and Bracken, 2014).

- **False positive animal model success:** Industry researchers must give up when a drug is poorly absorbed, unsafe, or does not work. Only five in 5,000 compounds that enter preclinical testing make it to human testing. Only one of the five is safe and effective enough to be marketed (FDA, 2017). More than 90% of promising new compounds fail when tested in humans because they are ineffective or toxic, even though each drug performed well in prior multi-species animal tests.
- **False negative toxicity (iatro-epidemics):** Severe unintended human harms and billions of dollars in damages occur when FDA-approved drugs are non-toxic in laboratory animals but cause serious, sometimes fatal iatro—(medically caused) epidemics after marketplace entry. These adverse drug reactions may cause 100,000 US deaths annually, although this is likely a highly inflated number (Lazarou, Pomeranz and Corey, 1998). The FDA Adverse Events Reporting System (FAERS) is a computerized information database designed to support the agency's post-marketing safety surveillance program for all approved drug and therapeutic biologic products. The FAERS contains almost 16 million reports of adverse events and reflects data from 1969 to 2018 suggesting limitations to the validity of animal drug or biologics toxicity screening (FDA, 2018). For example:
  - The arthritis drug rofecoxib (Vioxx) was safe in eight studies in African green monkeys and five other animal species but caused 140,000 heart attacks and 60,000 to 100,000 deaths before withdrawal in 2004. Merck paid US$950 million to settle damages in 2011 (Pippin, 2012).
  - Analysis of 780 chemical agents listed in a cancer database found the positive predictivity of animal bioassays, for a definite or probable human carcinogen, to be 20% (Knight, 2007). In addition to risking human welfare from the low predictability of animal bioassays, each assay requires up to millions of dollars and years to execute (Akhtar, 2015).
  - The diet drug, fen-phen (fenfluramine-phentermine), worked well as an appetite suppressant in rats without toxicity. However, this popular drug damaged heart valves and caused pulmonary hypertension in some people in the 1990s. The FDA withdrew it in 1997. The drug's maker settled damage claims for US$3.75 billion (Kolata, 1997; Morrow, 1999).
- **False positive drug toxicity:** Just as ineffective and dangerous drugs are approved based on erroneous safety in animals, useful drugs may be toxic in animals but safe for people. Aspirin was patented in 1900, decades before mandated animal testing. When later evaluated, aspirin produced birth defects in mice, rats, guinea pigs, rabbits, cats, dogs, sheep, and monkeys. Post-approval toxicity of penicillin (killed guinea pigs) and tamoxifen (liver cancer in rats) was absent in people. If the animal toxicity were known, these safe drugs would unlikely be on the market today (Akhtar, 2015).
- **Costs of failed clinical trials:** Clinical human research relies on and extends preclinical animal research. Unsound animal research leads to precarious clinical research outcomes. The FDA drug approval process is stringent and tightly controlled and consists of four phases (Phase I to Phase IV). Phase I: Is the drug safe in healthy people?; Phase II: Does the drug work in patients?
Phase III: Pivotal trials: How does the drug compare to existing treatments?
Phase IV: Post-marketing surveillance: What unknown drug effects (good or bad) happen? Only one in 5000 to 10,000 new chemical compounds derived from preclinical testing proceed to Phase I (Akhtar, 2015). Phase transition success rates are: Phase I to Phase II: 63%; Phase II to Phase III: 31%; Phase III to new drug approval: 85%. The overall success rate from Phase I to FDA-approval is 9.6% (Batelle, 2015).

The immense attrition of drugs entering human clinical trials has made big pharma cautious, even skeptical, of preclinical animal research. In 2013, the average time and cost to develop a new drug was 10 years and us$2.6 billion (Batelle, 2015). Candidate drugs that fail anywhere in the clinical trial process, prior to FDA-approval, still lose millions of dollars. Drug development losses are recouped as higher prices for pharmaceuticals already on the market. Promising preclinical animal studies that require extensive time, labor, and money rarely translate into successful human therapies. The overwhelming preclinical tendency to use animal models, in spite of their near universal translation failure, invokes the “law of the hammer”, a cognitive bias involving over-reliance on a familiar tool (Kaplan, 1964). Abraham Maslow (1966) said, “I suppose it is tempting, if the only tool you have is a hammer, to treat everything as if it were a nail”. The laboratory mouse is certainly a worn-out bio-hammer.

8 Animal Agriculture Research: Less Money, Fewer Animals, but Great Waste All the Same

According to the USDA, in 2016, approximately 80,000 farm animals (pigs, sheep, goats, and cattle) were used in animal testing or biomedical research. This excludes federal government owned agricultural-research animals who are AWA exempt (approximately 50,000 animals). About us$1.4 billion was spent on US agricultural animal research in 2016, including us$900 million in public funds (mostly USDA) and us$500 million by private industry (Clancy, Fuglie and Heisey, 2016) (see Table 10.1). Animal agriculture research has approximately 1% of the budget and uses approximately 0.8% of the animals used in biomedical research. Since experiments are performed directly on the target livestock species, animal research in agriculture has the distinct advantage of not relying on animal models.

8.1 The Animal Agriculture Industrial Complex
Animal agricultural research is a cog in the large industrial agri-business ecosystem. It directly and indirectly supports an entourage of scientists, government
agencies, livestock commodity groups, lobbyists, and the animal health, feed and other allied industries (Twine, 2012). The dominant raison d'être of livestock research is to benefit people via support of the industrial ("factory farm" or "prison") paradigm, i.e. intensively managed and densely confined pigs, feedlot beef cattle, dairy cattle, and poultry (Imhoff, 2010). There are three common aims:

- To optimize so called production efficiency of meat, milk and eggs i.e. generate the greatest output with the fewest inputs. Three tools accomplish this: genetic selection, feed efficiency and animal health, writ large, including growth promoting drugs, disease suppressing antibiotics and numerous vaccines.
- To maximize consumption of animal agriculture products.
- To address unintended consequences of industrial animal agriculture (e.g., food safety risk, zoonotic pathogens, antibiotic resistance, and pollution from animal wastes).

9 Case Studies in Wasted Money from Animal Research

The Mad Cow Disease iatro-pandemic and new variant Creutzfeldt-Jakob Disease (nvCJD): The best feed for cows ... is cows!

"The road to hell is paved with good intentions"

Saint Bernard of Clairvaux, 1150

Because feed is the greatest expense in raising livestock (65%–75% of total cost), there is an ongoing quest to lower feed costs. A dominant research goal is to increase feed efficiency (feed inputs/outputs of growth, eggs or milk). Feed efficiency research focuses on: (1) drugs (hormones and antibiotics); (2) genetic selection; (3) better nutrition; and (4) low cost "waste products" as feedstuffs.

While corn and soybeans are mainstays in us industrialized livestock rations, less savory ingredients also become animal feeds, especially to meet expensive protein needs. Only 60% of a slaughtered cow is edible (i.e. suitable as human food). The remaining “inedible” 40% (including hides, bones, entrails, lungs, spleens, hooves, fat and gristle, and fetuses, among others), known euphemistically as "by-products", are not permitted to be used as human food. They can, however, be used in livestock and poultry feeds and pet foods. Rendering plants transform slaughter by-products and animals that are unsuitable for human consumption into animal feed products using grinding, cooking, and pressing processes. Livestock are fed rendered animal fat and protein from slaughtered food animals and their wastes, including chicken feathers, egg shells, poultry litter (bedding and feces), blood, hair, bone marrow, pig
manure, and rumen ingesta. So called “4D” animals (dead, dying, diseased, disabled) also become livestock feed and pet foods. Cost driven same-species feeding (cannibalism) is common and industry-supported in livestock and poultry in most countries (Denton et al., 2005).

Meat and bone meal (MBM, dried and ground), also known as “animal flour”, was a small-scale livestock feed for much of the twentieth century. The Agricultural Research Service, the internal USDA research arm, studied feeding bovine MBM to dairy cattle in the 1960s (Brundage and Sweetman, 1963). However, commercial rendering, industry-sponsored research at the University of Nebraska-Lincoln, in the early 1980s, discovered the “by-pass protein effect” when cattle are fed high protein MBM from dead cattle (Rampton and Stauber, 1997). Proteins from rendered bovine MBM, unlike plant proteins, withstand rumen microbial digestion and are delivered intact to the small intestine, maximizing growth and lactation in high-yield dairy cattle. Additional University-sponsored research confirmed the MBM by-pass protein effect, resulting in many peer-reviewed papers (e.g., Stock et al., 1981; Santos et al., 1998). It should be no surprise that rumen microbes, evolutionarily designed over millions of years to digest forage, are unable to digest MBM, completely foreign nutrients. By analogy, humans would have a difficult time digesting sawdust. By the mid-1980s, MBM bypass protein was widely accepted, especially in Western Europe, as a dairy cattle protein source. MBM use in animal feed was heavily dependent on its price relative to the price of alternative ingredients (e.g., soybeans) with similar nutrient values.

However, this anti-nature Faustian bargain of high milk production in exchange for cannibalism resulted, starting in the mid-1980s, in the bovine spongiform encephalopathy (BSE, “Mad Cow”) pandemic. This new fatal prion (infectious protein) disease spread to cattle eating prion-contaminated bovine MBM, amplified by “recycling” rendered cattle that died of BSE into even more prion-contaminated MBM. In Britain, 185,000 live cattle were BSE-infected, 44 million were slaughtered during the 1986–1998 eradication program, and perhaps a million BSE-infected cattle entered the human food chain. Cattle in 30 countries were infected. Thousands of European dairy farmers lost their livelihoods (Brown et al., 2001). Since the 1996 discovery that BSE was transmissible to humans from eating prion-contaminated beef, at least 231 persons in 13 countries died from new variant Creutzfeldt-Jakob Disease (nvCJD), the zoonotic manifestation of BSE (Maheshwari et al., 2015). Since the first US BSE case in 2003, the US cattle industry has forfeited billions of dollars from lost exports, decreased product value, lower consumption, and new regulatory burdens. This tragic MBM cow cannibalism story shows that “production efficiency” research can have incredible negative sequelae and vividly demonstrates
the myth of so-called peer-reviewed sound science. Unfortunately, the BSE experience has not completely tempered the feeding of animal protein to herbivores.

9.1  **Livestock Research at the USDA US Meat Animal Research Center (US MARC)**

I worked at the USDA Agricultural Research Service of the Meat Animal Research Center (MARC) in Nebraska from 1988 to 2014 in various veterinary clinical and research positions for the USDA and the University of Nebraska-Lincoln (UNL). The USDA and UNL jointly operate MARC, the world’s largest livestock research center. It has a federal appropriation of US$22 million per year, plus approximately US$5 million in annual revenue from livestock sales, a cumulative US$1.3 billion budget over the half century it has existed. MARC is essentially a 55 square mile (14,200 hectare) ranch surrounding a research campus. Each year, MARC’s 6,800 brood cows raise 6,000 calves, 600 sows produce 14,000 piglets, and 2,800 ewes birth 5,000 lambs; 35,000 animals in total. Almost all Agricultural Research Service livestock and meat research is directed toward helping large producers and processors. In particular, much current Agricultural Research Service research addresses the untended negative consequences of industrial animal agriculture, for example food safety risk, zoonotic pathogens, drug residues, antibiotic resistance and pollution from animal wastes.

A former MARC Director told me directly that since an executive branch agency (such as the Agricultural Research Service) cannot lobby Congress (the Hatch Act of 1939), he would tell the livestock trade and lobbying associations what research MARC wanted to do. These associations would then lobby Congress on MARC’s behalf, often resulting in new funding for MARC, frequently as budgetary earmarks. In return, MARC would (and still does) perform taxpayer-subsidized research directly addressing pressing priority livestock and meat industry concerns.

Thus, in addition to its multi-million dollar federal research budget, MARC performs targeted research on behalf of, or funded by, livestock commodity groups. For example, the National Cattlemen’s Beef Association (NCBA), a trade association and lobbying group for mostly large US beef producers and slaughter processors, has a very close and decades-long association with MARC. The NCBA funded at least 52 research projects at MARC between 1999 and 2017. These included one project in genetic selection, nine in meat quality, and 42 in beef safety (zoonotic bacteria and antibiotic resistance). Each NCBA proposal typically provides funding of US$100,000 for one year and does not cover MARC labor or equipment costs. Thus, this represents a US$5.2 million
NCBA research investment in MARC over 18 years (National Cattlemen’s Beef Association, 2017). However, since MARC provides “free” labor (~80% of the cost of research), this $5.2 million industry “investment” in MARC signifies a taxpayer gift of at least $20.8M to the NCBA over 18 years, an impressive return in investment. The North American Meat Institute, a meat and poultry trade association representing meat packers and processors is also a frequent funder of industry research at MARC.

MARC’s mission is to apply science and technology for red meat production efficiency to benefit consumers, producers, and animal agri-business, with a genetic selection focus. Among livestock producers, animal scientists, and beef geneticists, MARC is a world-famous, NIH-Mayo Clinic equivalent for red meat livestock R&D. Like all industrial livestock based-systems, MARC achieves “production efficiency” using three tools:

- **Genetic selection**: Choose a desirable and heritable production trait (e.g., many offspring; large muscles) and vigorously (hyper) select for this attribute over many generations.

- **Feed efficiency**: Maximize via genetic selection and/or experimental low-cost feeds. For example, in the early 1980s, MARC scientists fed high pH cement kiln dust (a by-product of cement manufacturing) to feedlot steers, sheep, and pigs as a calcium feed supplement and to buffer the dangerously acidic rumen or stomach pH of animals fed high-energy corn rations (Wheeler et al., 1981; Pond et al., 1982). Cement kiln dust is the fine-grained, solid, highly alkaline waste removed from cement kiln exhaust gas by air pollution control devices. Toxicity led to abandonment of these experiments.

- **“Factory farm-ecology”**: Use drugs to improve feed efficiency and promote fast lean growth, such as anabolic steroids (hormone implants), antibiotics, ionophores, and beta-agonists (repartitioning agents that convert fat to muscle) (Petersen, 2012). The cumulative drug effects are rapid growth and maximized lean muscle mass.

As a cogent example of MARC funding of industry research, USDA and UNL investigated the growth and “welfare” (body temperature and mobility) effects of zilpaterol, a beta-agonist growth promotant, on MARC feedlot steers (Boyd et al., 2015). Zilpaterol is a failed human asthma drug whose undesirable human side effect of turning fat into muscle was a very desirable outcome in cattle. This drug is approved for use in livestock in only five countries (Centner, Alvey and Stelzleni, 2014). Zilpaterol was voluntarily removed from the market by Merck in 2013 due to serious animal welfare concerns. This zilpaterol research at MARC, tri-funded by USDA, UNL and the Nebraska Beef Council,
not surprisingly reported no welfare problems in using this fat-to-muscle repartitioning agent. Of interest in this MARC feedlot study are: (1) all nine authors were livestock scientists; no person with animal or livestock welfare training or expertise was part of the study; (2) an unreferenced and invalidated meat industry-developed 5-level ordinal lameness scoring metric was employed (Tyson mobility scoring, Tyson Foods, Springdale, AK) and; (3) evaluators were not blinded as to treatment group, a dominant source of experimental bias.

I will recount three examples of MARC research principles in action, all with animal welfare repercussions and massive waste of taxpayer dollars.

9.2  **Twiner Beef Cattle**
Rationale: Cows usually have one offspring. The natural twinning rate in cattle is 1%–2%. Production efficiency would double if cows had twins instead of singlets.

Results: From 1981 until 2011, the twinning rate in a MARC herd rose to approximately 50% (1.6 calves per cow) via intense genetic selection.

Problems: (1) It is bio-unnatural for cows to have twins, fighting against millions of years of evolution favoring singlets; (2) Dystocia, C-sections, mastitis, early calf deaths, and sterile female calves.

Outcome: The project was abandoned after 30 years and approximately 100 million tax dollars. There was no market for twinning cows. Most farmers cull cows with twins due to the well-known problems described above. A beef geneticist said in 2016, “There are animals in this world that God made to have twins or triplets; cows are made to have one” (Simmons, 2016).

9.3  **“Double muscled” Beef Cattle**
Rationale: Cattle with more muscle mass have greater productivity. Belgium blue cattle can have a mutant *myostatin* gene, causing skeletal muscles to grow continuously, producing massive animals.

Results: MARC scientists co-identified the *myostatin* gene mutation as causative for double muscling and developed a test for its genetic selection worldwide. Production efficiency experiments conducted over many years produced cattle with very large muscle mass.

Problems: Dystocia, low fertility, low stress and heat tolerance, poor calf viability.

Outcome: The project started in 1997 and was abandoned after many years and millions of tax dollars. There is no market for these cattle (Elstein and Peabody, 2004; Bassett, 2009).
9.4 "Easy care" Sheep

Rationale: The US commodity sheep industry is becoming extinct. In 2015, there were less than 5 million sheep, a 91% decline since 1950. Labor is costly.

Solution: Increase sheep production efficiency by developing a cross-bred fecund breed. This "easy care" sheep has hair (since US wool has negative economic value) and births twins or triplets. Use brutal neo-Darwinian selection via hands-off husbandry to select sheep that raise lambs, who require minimal labor, feed inputs, and human attention.

Results: From 2002 to 2017, approximately 1,500 easy care ewes gave birth to 3,000–5,000 lambs per year. Rather than the usual summer pasture and winter shed housing and lambing, "easy care" sheep were kept on isolated pastures year-round without shelter or shade. Shepherds were prohibited, by experimental protocol, from intervening to care for ewes or lambs in need. Ewes that survived and reared lambs under these heinous conditions were considered "successfully genetically selected".

Problems: Predictably, human-dependent domestic sheep treated like wild sheep fared very poorly. Lamb mortality ranged from 10% to 50% per year (normal rates are 1%–5%). Over 15 years, 15–20 thousand lambs died (the expected number was 1,200) from coyote predation, starvation, exposure, abandonment, dystocia, and disease.

Outcome: Like the Twinner cattle, the "easy care" sheep project used intense long-term genetic selection in an anti-nature, poor welfare manner to attempt to create a product without commercial demand. The easy ("No") care sheep research failed completely, unsurprisingly, to reach its scientific goal of a new sheep breed with low labor needs. Over 15 years, the project spent approximately 15 million tax dollars. No scientific papers resulted from this work.

These three MARC projects share several commonalities:
- Intense genetic selection created or attempted to create a livestock product no one wanted where production efficiency at all (animal and taxpayer) costs was the focus.
- Genetics were used as a biological hammer to select for abnormal, exaggerated, or unnatural traits that were both costly and harmful to livestock well-being.
- Projects were internally and non-competitively funded for decades with millions of tax dollars.
- MARC livestock, like all federal government-owned agricultural research livestock, are AWA-exempt and subject to almost no internal or external animal welfare oversight which are mandated for other US research animals.
The industrial animal agriculture system does not merit research funding from the public treasury, as exemplified by the decades of failed and unnecessary research and multi-millions of wasted tax dollars at MARC. It is almost impossible to justify research support for an unsustainable system that produces Mad Cow disease, antimicrobial resistance, pollution from livestock wastes, food-borne pathogens (e.g., *E. coli* O157), and horrible livestock and poultry welfare. "Cheap" factory-farmed eggs, beef, pork and chicken enabled by intensive agricultural animal research are incredibly expensive (Pew Charitable Trusts, 2008).

### Conclusions

Publicity is justly commended as a remedy for social and industrial diseases. Sunlight is said to be the best of disinfectants; electric light the most efficient policeman.

*LOUIS D. BRANDEIS, 1914*

It is an economic and ethical imperative to reduce wasted money and animals used in US biomedical and agricultural animal research. These imperatives are unlikely to manifest in the current animal research environment due to perverse incentives. Complete transparency (e.g., costing, specific animal usage, outcomes, evidence of translational success, mandatory public reporting of all government funded research regardless of results) in both the public and private domains will likely be the most effective driver of fiscal responsibility and refining (minimizing experimental suffering), reducing (minimizing animal numbers), and replacing (with non-animal alternatives) research animal use. This will require, at a minimum, sustained public pressure, policy and regulatory changes (e.g., removal of species or institutional exemptions from the AWA), adequate resourcing, and enforced (new or old) legislation.

Animal research is losing its immunity from criticism or challenge. However, it is a multi-billion-dollar industry in which government, academia and private business have high financial stakes (Pound and Bracken, 2014). It is critical to recognize that wasted money in animal research is only germane to laboratory animals and to people excluded from the animal research industrial complex (i.e., taxpayers, patients, investors, and consumers). To those within the animal research ecosystems, there is no waste or cost, only sustenance and benefit. This is a major reason why wasteful, unproductive, and even
counterproductive use of research animals not only continues but is fiercely defended despite obvious limitations and dangers. Supporters of animal research rely on expert opinion (one of the least valid types of evidence) and the occasional translational success story. Opponents have billions of wasted dollars, millions of scientific papers, and decades of evidence against their continued use. Government sponsored animal experiments may continue because they are taxpayer-subsidized and incentivized. The pharmaceutical and biotechnology industries may reduce laboratory animal use in drug discovery and development, because they cannot invest heavily in such an unreliable methodology. Unfortunately, scientific precedent, legal liability concerns, and regulatory approval mandates will ensure enormous use of laboratory animals in the private sector to assess safety of drugs, medical devices, biologics, chemicals, and consumer products and to test vaccines (for potency and by batch), at least in the near term or until regulatory requirements change.

Available and emerging non-animal research approaches and technologies can provide better return on investment, more valid and valuable findings, and better human well-being outcomes and save billions of taxpayer dollars and millions of animal lives (D’Urbino, 2016). Goals should include:

- Abandoning molecular reductionism (e.g., as manifested in genetically modified or “gene knock out” mice).
- Investigating complex naturally-occurring disease in humans and animals instead of artificial and incongruent animal models.
- Implementing more in vitro (human or animal cell-based assays) and in silico (computer modeling) technologies.
- Resourcing development, validation, and regulatory acceptance of non-animal alternatives (e.g., the Interagency Coordinating Committee on the Validation of Alternative Methods, ICCVAM (National Toxicology Program, 2018)).
- Defunding public biomedical research that uses animal disease models.
- Eliminating non-competitive internal government research funding and halving extramural grant overhead rates.
- Discontinuing the failed research focus in agriculture on industrial livestock “production efficiency” in favor of humane sustainable agricultural research.

References

American Anti-Vivisection Society (2017). Animal in Science—Which Animals Are Used—Mice and Rats. [online] Available at: http://aavs.org/animals-science/animals-used/mice-rats/ [Accessed 9 August 2018].
Akhtar, A. (2015). The Flaws and Human Harms of Animal Experimentation. *Cambridge Quarterly of Healthcare Ethics, 24*(4), pp. 407–419.

Bailey, J. (2008). An Assessment of the Role of Chimpanzees in AIDS Vaccine Research. *Alternatives to Laboratory Animals, 36*(4), pp. 381–428.

Bassett, A. (2009). Welfare and Belgium Blue Cattle. *Animal Welfare Approved Technical Fact Sheet. PCE.4vi-TAFS 1.* [online] Available at: https://agreenerworld.org/wp-content/uploads/2018/05/TAFS-1-Welfare-and-Belgian-Blue-Cattle-v1.pdf [Accessed 25 July 2018].

Battelle (2015). *Biopharmaceutical Industry-Sponsored Clinical Trials: Impact on State Economies.* [online] Available at: http://phrma-docs.phrma.org/sites/default/files/pdf/biopharmaceutical-industry-sponsored-clinical-trials-impact-on-state-economies.pdf [Accessed 25 July 2018].

Begley, C.G. and L.M. Ellis (2012). Drug Development: Raise Standards for Preclinical Cancer Research. *Nature, 483*(7391), pp. 531–533.

Bock, E. (2016). Much Biomedical Research Is Wasted, Argues Bracken. *NIH Record, LXVIII*(14). [online] Available at: https://nihrecord.nih.gov/newsletters/2016/07_01_2016/story3.htm [Accessed 13 August 2017].

Boyd, B.M., S.D. Shackelford, K.E. Hales, T.M. Brown-Brandl, M.L. Bremer, M.L. Spangler, T.L. Wheeler, D.A. King and G.E. Erickson (2015). Effects of Shade and Feeding Zilpaterol Hydrochloride to Finishing Steers on Performance, Carcass Quality, Heat Stress, Mobility, and Body Temperature. *Journal of Animal Science, 93*, pp. 5801–5811.

Brandeis, L.D. (1914). *Other People’s Money and How the Bankers Use It.* New York: Frederick A. Stokes.

Brown, P., R.G. Will, R. Bradley, D.M. Asher and L. Detwiler (2001). Bovine Spongiform Encephalopathy and Variant Creutzfeldt-Jakob Disease: Background, Evolution, and Current Concerns. *Emerging Infectious Diseases, 7*(1), pp. 6–16.

Brundage, A.L. and W.J. Sweetman (1963). Meat and Bone Meal as a Protein Supplement for Lactating Dairy Cattle. *Journal of Dairy Science, 46*(10), pp. 1081–1084.

Cavanaugh, S.E., J.J. Pippin and N.D. Barnard (2014). Animal Models of Alzheimer Disease: Historical Pitfalls and a Path Forward. *Alternatives to Animal Experimentation, 31*(3), pp. 279–302.

Centner, T.J., J.C. Alvey and A.M. Stelzleni (2014). Beta Agonists in Livestock Feed: Status, Health Concerns, and International Trade. *Journal of Animal Science, 92*, pp. 4234–4240.

Chakma, J., G.H. Sun, J.D. Steinberg, S.M. Sammut and R. Jagsi (2014). Asia’s Ascent Global Trends in Biomedical R&D Expenditures. *New England Journal of Medicine, 370*(1), pp. 3–6.

Chen, R., N.R. Desai, J.S. Ross, W. Zhang, K.H. Chau, B. Wayda, K. Murugiah, D.Y. Lu, A. Mittal and H.M. Krumholz (2016). Publication and reporting of clinical trial results: cross sectional analysis across academic medical centers. *British Medical
Journal, p. 352-1637. [online] Available at: https://www.bmj.com/content/352/bmj.637 [Accessed 8 August 2018].

Clancy, M., K. Fuglie and P. Heisey (2016). US Agricultural R&D in an Era of Falling Public Funding. Amber Waves. [online] Available at: https://www.ers.usda.gov/amber-waves/2016/november/us-agricultural-rd-in-an-era-of-falling-public-funding/ [Accessed 8 August 2018].

Collins, F.S. and L.A. Tabak (2014). NIH Plans to Enhance Reproducibility. Nature, 505(7485), pp. 612–613.

Darwin, C., 1879 [2008]. Letter to A.S. Wilson, March 5, 1879. In: F. Darwin and A.C. Seward, eds., More Letters of Charles Darwin, vol. 2, Charleston, SC: BiblioBazaar.

Denton, J.H., C.N. Coon, J.E. Pettigrew and C.M. Parsons (2005). Historical and Scientific Perspectives of Same Species Feeding of Animal By-products. Journal of Applied Poultry Research, 14(2), pp. 352–361.

Dorsey, E.R., J.P. Thompson, M. Carrasco, J. De Roulet, P. Vitticore, S. Nicholson, S.C. Johnston, R.G. Holloway and H. Moses (2009). Financing of US Biomedical Research and New Drug Approvals Across Therapeutic Areas. PLoS One, 4(9), p. e7015. [online] Available at: http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0007015 [Accessed 13 August 2017].

D’Urbino, L. (2016). The Mischief of Mice. The World’s Favourite Lab Animal Has Been Found Wanting, But There Are New Twists in the Mouse’s Tale. The Economist. [online] Available at: https://www.economist.com/news/christmas-specials/21712058-evolution-scientific-mainstay-worlds-favourite-lab-animal-has-been-found [Accessed 13 August 2017].

Elstein, D. and E. Peabody (2004). Can You Have Your Beef and Eat It Too? Agricultural Research, 52(7), pp. 10–11.

FDA (2017). The Beginnings: Laboratory and Animal Studies. [online] Available at: https://www.fda.gov/drugs/resourcesforyou/consumers/ucm143475.htm [Accessed 13 August 2017].

FDA (2018). FDA Adverse Event Reporting System (FAERS) Public Dashboard. [online] Available at: https://fis.fda.gov/sense/app/d10be6bb-494e-4cd2-82e4-0135608ddc13/sheet/7a47a261-d38b-4203-a8aa-6d3021737452/state/analysis [Accessed 26 July 2018].

Freedman, L.P., I.M. Cockburn and T.S. Simcoe (2015). The Economics of Reproducibility in Preclinical Research. PLoS Biology, 13(6), p. e1002165. [online] Available at: http://journals.plos.org/plosbiology/article?id=10.1371/journal.pbio.1002165 [Accessed 13 August 2017].

Goodman, J., A. Chandna and K. Roe (2015). Trends in Animal Use at US Research Facilities. Journal of Medical Ethics, 41, pp. 563–566.

Guarino, B. (2015). How Many Lab Mice Did American Researchers Kill in 2015?. [online]. Available at: https://www.inverse.com/article/9316-how-many-lab-mice-did-american-researchers-kill-in-2015 [Accessed 16 February 2018].
Imhoff, D. (2010). *CAFO (Concentrated Animal Feeding Operations): The tragedy of industrial animal factories*. San Rafael, CA: Earth Aware.

Institute of Medicine and National Research Council (2012). *International Animal Research Regulations: Impact on Neuroscience Research: Workshop Summary*. Washington, DC: The National Academies Press. p. 23. [online] Available at: https://www.nap.edu/catalog/13322/international-animal-research-regulations-impact-on-neuroscience-research-workshop-summary [Accessed 13 August 2017].

Ioannidis, J.P. (2012). Extrapolating from Animals to Humans. *Science Translational Medicine*, 4(151), pp. 1–4.

Jarvis, M.F., M. Williams (2016). Irreproducibility in Preclinical Biomedical Research: Perceptions, Uncertainties, and Knowledge Gaps. *Trends in Pharmaceutical Science*, 37(4), pp. 290–302.

Kaplan, A. (1964). *The Conduct of Inquiry: Methodology for Behavioral Science*. San Francisco: Chandler Publishing Co., p. 28.

Kaur, R., P. Sidhu and S. Singh (2016). What Failed BIA 10-2474 Phase I Clinical Trial? Global Speculations and Recommendations for Future Phase I Trials. *Journal of Pharmacology and Pharmacotherapeutics*, 7(3), pp. 120–126.

Knight, A. (2007). Systematic Reviews of Animal Experiments Demonstrate Poor Human Clinical and Toxicological Utility. *Alternatives to Laboratory Animals*, 35, pp. 641–659. [online] Available at: http://animalstudiesrepository.org/cgi/viewcontent.cgi?article=1085&context=acwp_arte [Accessed 13 August 2017].

Kolata, G. (1997). How Fen-Phen, a Diet “Miracle,” Rose and Fell. *New York Times*. [online] Available at: https://www.dartmouth.edu/~chance/course/Syllabi/97Dartmouth/day-2/fen-phen-1.pdf [Accessed 13 August 2017].

Lazarou, J., B.H. Pomeranz and P.N. Corey (1998). Incidence of Adverse Drug Reactions in Hospitalized Patients: A Meta-analysis of Prospective Studies. *Journal of the American Medical Association*, 279(15), pp. 1200–1205.

Maheshwari, A., M. Fischer, P. Gambetti, A. Parker, A. Ram, C. Soto, L. Concha-Marambio, Y. Cohen, E.D. Belay, R.A. Maddox and S. Mead (2015). Recent US Case of Variant Creutzfeldt-Jakob Disease—Global Implications. *Emerging Infectious Diseases*, 21(5), pp. 750–759.

Mandal, J. and C. Parija (2013). Ethics Involving Animal Research. *Tropical Parasitology*, 3(1), pp. 4–6.

Maslow, A.H. (1966). *The Psychology of Science: A Reconnaissance*. New York: Harper & Row, p. 15.

McManus, R. (2013). Ex-Director Zerhouni Surveys Value of NIH Research. *NIH Record*, LXV(13). [online] Available at: https://nihrecord.nih.gov/newsletters/2013/06_21_2013/story1.htm [Accessed 13 August 2017].

Morrow, D. (1999). Fen-Phen Make to Pay Billions in Settlement of Diet-injury Cases. *New York Times*. [online] Available at: http://www.nytimes.com/1999/10/08/business/fen-phen-maker-to-pay-billions-in-settlement-of-diet-injury-cases.html [Accessed 13 August 2017].
Moses, H., D.H. Matheson, S. Cairns-Smith, B.P. George, C. Palisch and E.R. Dorsey (2015). The Anatomy of Medical Research: us and International Comparisons. *Journal of the American Medical Association*, 313(2), pp. 174–189.

Mullard, A. (2011). Reliability of “New Drug Target” Claims Called into Question. *Nature Reviews Drug Discovery*, 10, pp. 643–644.

National Anti-Vivisection Society (2018). *The Animal Testing and Experimentation Industry*. [online] Available at: https://www.navs.org/the-issues/the-animal-testing-and-experimentation-industry/#.W23Egy3Mw6i [Accessed 10 August 2018].

National Cattlemen’s Beef Association (2017). *Beef Research*. [online] Available at: http://www.beefresearch.org/search.aspx?as=no&qaw=&qal=Meat%20Animal%20Research%20Center&qep=&qw=1&scp=1&sc=1&startPage=1&sort=Rank&rpp=10&sortDirection=Desc http://www.beefresearch.org/ [Accessed 13 August 2017].

National Toxicology Program (2018). *About ICCVAM*. [online] Available at: https://ntp.niehs.nih.gov/pubhealth/evalatm/iccvam/index.html [Accessed 26 July 2018].

NIH (2019). Budget. Available at: https://www.nih.gov/about-nih/what-we-do/budget [Accessed 30 January 2019].

Orzechowski, K. (2012). *Animal Experimentation: The Industries Behind the Industry*. [online] Available at: http://www.onegreenplanet.org/lifestyle/animal-experimentation-the-industries-behind-the-industry/ [Accessed 13 August 2017].

Osherovich, L. (2011). Hedging Against Academic Risk. [online] *SciBX: Science-Business eXchange*, 4(15). [online] Available at: https://www.nature.com/scibx/journal/v4/n15/pdf/scibx.2011.416.pdf [Accessed 13 August 2017].

Perrin, S. (2014). Make Mouse Studies Work. *Nature*, 507, pp. 423–425.

Petersen, M. (2012). As Beef Cattle Become Behemoths, Who Are Animal Scientists Serving? *The Chronicle Review, The Chronicle of Higher Education*. [online] Available at: http://www.chronicle.com/article/As-Beef-Cattle-Become/131480/ [Accessed 13 August 2017].

Petrov, D., C. Mansfield, A. Moussy and O. Hermine (2017). ALS Clinical Trials Review: 20 Years of Failure. Are We Any Closer to Registering a New Treatment?. *Frontiers in Aging Neuroscience*, 9, p. 68. [online] Available at: https://www.frontiersin.org/articles/10.3389/fnagi.2017.00068/full [Accessed 16 February 2018].

Pew Charitable Trusts (2008). *Putting meat on the table: Industrial farm animal production in America*. Washington, DC: PEW Charitable Trust, pp. 11–19. [online] Available at: http://www.pewtrusts.org/-/media/legacy/uploadedfiles/peg/publications/report/pcifapfinalpdf.pdf [Accessed 13 August 2017].

Pew Research Center (2015). Chapter 7: Opinion About the Use of Animals in Research. *American Politics and Science Issues*, pp. 141–144. [online] Available at: http://www.pewinternet.org/2015/07/01/chapter-7-opinion-about-the-use-of-animals-in-research/ [Accessed 13 August 2017].
Piller, C. and T. Bronshtein (2018). Faced with public pressure, research institutions step up reporting of clinical trial results. STAT. [online] Available at: https://www.statnews.com/2018/01/09/clinical-trials-reporting-nih/ [Accessed 8 August 2018].

Pippin, J.J. (2012). Animal Research in Medical Sciences: Seeking a Convergence of Science, Medicine, and Animal Law. South Texas Law Review, 54, pp. 469–512.

Pond, W.G., J.T. Yen, D.A. Hill, C.L. Ferrell and L. Krook (1982). Bone Lesions in Growing Swine Fed 3% Cement Kiln Dust as a Source of Calcium. Journal of Animal Science, 54(1), pp. 82–88.

Pound, P. and R. Blaug (2016). Transparency and Public Involvement in Animal Research. Alternatives to Laboratory Animals, 44(2), pp. 167–173.

Pound, P. and M.B. Bracken (2014). Is Animal Research Sufficiently Evidence Based To Be a Cornerstone of Biomedical Research?. British Medical Journal, 348.

Rampton, S. and J. Stauber (1997). Mad Cow USA. Monroe, ME: Common Courage Press, pp. 69–70. [online] Available at: http://www.srwolf.com/reports/mcusa.pdf [Accessed 13 August 2017].

Roep, B.O., M. Atkinson and M. von Herrath (2004). Satisfaction (Not) Guaranteed: Re-evaluating the Use of Animal Models. Nature Reviews Immunology, 4(12), pp. 989–997.

Ross, J.S., T. Tse, D.A. Zarin, H. Xu, L. Zhou and H.M. Krumholz (2012). Publication of NIH funded trials registered in ClinicalTrials.gov: cross sectional analysis. British Medical Journal, 344:d7292.

Santos, F.A.P., J.E.P. Santos, C.B. Theurer and J.T. Huber (1998). Effects of Rumen-Undegradable Protein on Dairy Cow Performance: A 12-year Literature Review. Journal of Dairy Science, 81(12), pp. 3182–3213.

Sena, E.S., H.B. van der Worp, P.M. Bath, D.W. Howells and M.R. Macleod (2010). Publication Bias in Reports of Animal Stroke Studies Leads to Major Overstatement of Efficacy. PLoS Biology, 8(3), p. e1000344. [online] Available at: http://journals.plos.org/plosbiology/article?id=io.1371/journal.pbio.1000344 [Accessed 13 August 2017].

Seok, J., H.S. Warren, A.G. Cuenca, M.N. Mindrinos, H.V. Baker, W. Xu, D.R. Richards, G.P. McDonald-Smith, H. Gao, L. Hennessy and C.C. Finnerty (2013). Genomic Responses in Mouse Models Poorly Mimic Human Inflammatory Diseases. Proceedings of the National Academy of Sciences, 110(9), pp. 3507–3512.

Simmons, S. (2016). Double the Trouble? Twins Increase Labor, Beef Production. Tri State Livestock News. [online] Available at: http://www.tsln.com/news/double-the-trouble-twins-increase-labor-beef-production/ [Accessed 13 August 2017].

Stock, R., N. Merchen, T. Klopfenstein and M. Poos (1981). Feeding Value of Slowly Degraded Proteins. Journal of Animal Science, 53(4), pp. 1109–1119.

Twine, R. (2012). Revealing the “Animal-Industrial Complex”—A Concept and Method for Critical Animal Studies?. Journal for Critical Animal Studies, 10(1), pp. 12–39.
USDA (2017). *Annual Report Animal Usage by Fiscal Year, Fiscal Year 2016*. [online] Available at: https://www.aphis.usda.gov/animal_welfare/downloads/reports/Annual-Report-Animal-Usage-by-FY2016.pdf [Accessed 13 August 2017].

van der Worp, H.B., D.W. Howells, E.S. Sena, M.J. Porritt, S. Rewell, V. O’Collins and M.R. Macleod (2010). Can Animal Models of Disease Reliably Inform Human Studies?. *PLoS Medicine*, 7(3), p. e1000245. [online] Available at: http://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1000245 [Accessed 13 August 2017].

Wheeler, W.E., C.H. Noller and J.L. White (1981). Comparison Between Limestone and Cement Kiln Dusts of Similar Rates of Reactivity Used in High Concentrate Diets for Beef Steers. *Journal of Animal Science*, 52(4), pp. 873–881.

Zahs, K.R. and K.H. Ashe (2010). “Too Much Good News”—Are Alzheimer Mouse Models Trying to Tell Us How to Prevent, Not Cure, Alzheimer’s Disease?. *Trends in Neurosciences*, 33(8), pp. 381–389.