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Animal Research in Medical Sciences: Seeking a Convergence of Science, Medicine, and Animal Law

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Physicians Committee for Responsible Medicine

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ANIMAL RESEARCH IN MEDICAL SCIENCES: SEEKING A CONVERGENCE OF SCIENCE, MEDICINE, AND ANIMAL LAW

JOHN J. PIPPIN*

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I. INTRODUCTION

As of April 2013, the Animal Legal Defense Fund lists 144 U.S. and Canadian law schools that offer courses in animal law,¹ and 190 U.S. and international student Animal Legal Defense Fund chapters.² This is remarkable growth from only nine animal law courses available at U.S. and Canadian law schools in 2001,³ and the emergence of an energized animal

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1. *Animal Law Courses*, ANIMAL LEGAL DEF. FUND, http://aldf.org/userdata_display.php?modin=51 (last visited Apr. 21, 2013).

2. *Student Animal Legal Defense Fund Chapters*, ANIMAL LEGAL DEF. FUND, http://aldf.org/userdata_display.php?modin=62 (last visited Apr. 21, 2013).

3. *Where Should You Go to Law School?*, ANIMAL LEGAL DEF. FUND, <http://aldf.org/article.php?id=426> (last visited Apr. 21, 2013).

law community has engendered fear and apprehension in the animal research community.⁴

As the intersection of animal law and animal research becomes congested, it is appropriate to establish the scientific context in which laws regarding the use and care of research animals will operate. There are at least three components of this context that set the terms of the debate: ethics, science, and the legal status of animals. The following discussion will not address ethics; not because it isn't important, but because it exists along a spectrum of objective and subjective positions that are often unassailable by argument and data. I can assure you as a former animal researcher that even in the most compassionate hands, animal research is cruel, sad, and deadly for animals. The pro-research ethics argument can only be that this research is a "necessary evil" for the advancement of science and medicine, and thus worth the cost in animal misery.

It is my belief that it is not essential to engage the ethics argument because the science of animal research is more than sufficient to discredit the practice. If this is true—and as a former practitioner and longtime critic I fervently believe it is—then the animal research community must face the reality that when the "necessity" is not there, then only the "evil" remains. That is perhaps what will motivate the animal law community to help achieve a convergence of science, medicine, and animal law.

II. THE LAW AS APPLIED TO ANIMAL RESEARCH

There are nearly 100 federal animal protection-related statutes, including those directly addressing protection and others with either animal protection components or directed toward activities involving animals.⁵ Additionally, there are animal cruelty laws in all fifty U.S. states, the District of Columbia, Puerto Rico, Guam, the Virgin Islands, American Samoa, and the Northern Mariana Islands.⁶ These state and territorial statutes vary in their numbers, definitions, exemptions, and effectiveness in addressing animal cruelty. In nearly all cases, those statutes exempt both animal research and agricultural animal use from prosecution, either

4. See P. Michael Conn, *A Legal Challenge to Animal Research*, SCIENTIST, Dec. 1, 2009, <http://www.the-scientist.com/?articles.view/articleNo/27814/title/A-Legal-Challenge-to-Animal-Research>.

5. See HENRY COHEN, CONG. RESEARCH SERV., RL94731, BRIEF SUMMARIES OF FEDERAL ANIMAL PROTECTION STATUTES (2009), available at http://www.animallaw.info/articles/art_pdf/aruscohen2009fedlawsummaries.pdf.

6. See 2011 U.S. Animal Protection Laws Rankings, ANIMAL LEGAL DEF. FUND (Dec. 13, 2011), <http://aldf.org/article.php?id=1894>; STEPHAN K. OTTO, ANIMAL LEGAL DEF. FUND, 2011 U.S. ANIMAL PROTECTION LAWS RANKINGS: COMPARING OVERALL STRENGTH & COMPREHENSIVENESS 7–8 (2011), <http://aldf.org/downloads/ALDF2011USRankingsReport.pdf>.

explicitly or in practice.⁷ A very useful two-part review of the history of U.S. animal laws since 1972 is available.⁸

Despite the large number of animal protection laws promulgated, the only federal statute that regulates the treatment of animals in research, exhibition, transport, and by dealers is the Animal Welfare Act (AWA), which was passed by Congress in 1966 and amended in 1970, 1976, 1985, 1990, 2002, 2007, and 2008; and enforced by the U.S. Department of Agriculture (USDA), Animal and Plant Health Inspection Service (APHIS), Animal Care Program (AC).⁹ The definition of animals covered by the AWA is restrictive and has become patchwork as amended over four decades:

The term “animal” means any live or dead dog, cat, monkey (nonhuman primate mammal), guinea pig, hamster, rabbit, or such other warm-blooded animal, as the Secretary may determine is being used, or is intended for use, for research, testing, experimentation, or exhibition purposes, or as a pet; but such term excludes (1) birds, rats of the genus *Rattus*, and mice of the genus *Mus*, bred for use in research, (2) horses not used for research purposes, and (3) other farm animals, such as, but not limited to livestock or poultry, used or intended for use as food or fiber, or livestock or poultry used or intended for use for improving animal nutrition, breeding, management, or production efficiency, or for improving the quality of food or fiber. With respect to a dog, the term means all dogs including those used for hunting, security, or breeding purposes.¹⁰

As a result of this definition of *animal*, specifically as diminished by USDA regulation in 1971¹¹ and subsequently by congressional amendment of the AWA in 2002¹² to exclude birds, rats, and mice bred for research,¹³ about 95% of animals used for research in the U.S. are excluded from coverage under the AWA. Despite several lawsuits against the USDA and

7. Paige M. Tomaselli, *International Comparative Animal Cruelty Laws*, ANIMAL LEGAL & HIST. CENTER (2003), <http://www.animallaw.info/articles/ddusicacl.htm>.

8. See generally Joyce Tischler, *The History of Animal Law, Part I (1972–1987)*, 1 STAN. J. ANIMAL L. & POL’Y 1 (2008) [hereinafter Tischler, *Part I*]; Joyce Tischler, *A Brief History of Animal Law, Part II (1985–2011)*, 5 STAN. J. ANIMAL L. & POL’Y 27 (2012) [hereinafter Tischler, *Part II*].

9. Animal Welfare Act of 1966, 7 U.S.C. § 2131 (2011); *Animal Welfare Act*, ANIMAL WELFARE INFO. CENTER, <http://awic.nal.usda.gov/government-and-professional-resources/federal-laws/animal-welfare-act> (last modified Apr. 5, 2013).

10. 7 U.S.C. § 2132(g) (2006).

11. See 9 C.F.R. § 1.1 (2000).

12. Farm Security and Rural Investment Act of 2002, Pub. L. No. 107-171, 116 Stat. 134 (2002).

13. *Id.* § 10301, 116 Stat. at 491; D. Smith, *Rats, Mice and Birds Excluded from Animal Welfare Act*, AM. PSYCHOL. ASS’N., <http://www.apa.org/monitor/julaug02/rats.aspx> (last visited Feb. 16, 2013).

establishment of standing for specific plaintiffs, “the courts allowed the USDA and industry to circumvent the will of Congress, leaving the AWA as a paper tiger.”¹⁴ Regulations guiding the interpretation and enforcement of the AWA, developed by AC, are published annually in the Code of Federal Regulations, Title 9, Chapter 1, and may be accessed on the USDA APHIS website.¹⁵

In practice, enforcement of the AWA focuses on animal *treatment* rather than animal *use*, utilizes a checklist approach to assess compliance with specific elements of the AWA, and does not address the suitability or justification for animal use—a function AC reserves for institutional animal care and use committees. Thus, the AWA does not prohibit any research protocols from approval and implementation, no matter how useless, painful, or wasteful they are.

AC de-emphasizes penalties when enforcing the AWA, and minor violations are allowed to be corrected by a stated date without establishing a violation of the AWA. More serious “noncompliances” may generate a warning letter, and very serious or repeated violations may result in an investigation of the facility by the USDA’s Investigative and Enforcement Services (IES). When an IES investigation confirms the alleged AWA violation(s), civil penalties are typically applied, which may include fines of up to \$10,000 per violation.¹⁶ Criminal penalties are also available to AC but are seldom employed.

Available remedies notwithstanding, AC has faced criticism that its enforcement of the AWA is weak and ineffective. The bar for receiving a fine or other penalty is high, fines are often redirected to the violating facilities, and settlements are encouraged that substantially discount fines, avoid federal charges, and allow the cited facilities to neither admit nor deny the alleged violations.

Periodic audits by the USDA Office of Inspector General (OIG) of AC enforcement of the AWA have been supportive of these criticisms and are quite critical of AC enforcement practices. The most recent OIG audit report broadly addressing AWA enforcement cited numerous serious deficiencies, including the following:

- ◆ Failure of AC’s Eastern Region to aggressively pursue “enforcement actions against violators of the AWA” despite recommendations from its facility inspectors.

14. Tischler, *Part II, supra* note 8, at 66.

15. 9 C.F.R. § 1, available at http://www.aphis.usda.gov/animal_welfare/downloads/awr/awr.pdf.

16. Animal Welfare Act of 1966, 7 U.S.C § 2149(b) (2006).

- ◆ Failure to use enforcement measures rather than repeated educational measures in addressing facility violations, thereby undermining the authority and damaging the morale of its Veterinary Medical Officers.
- ◆ Failure to refer violators for investigation by the USDA IES as appropriate, and failure to implement the recommendations of the IES following investigations.
- ◆ Failure to fine violators sufficiently (typically discounting fines by 75%), creating a climate in which “violators consider the monetary stipulation as a normal cost of conducting business rather than a deterrent for violating the law.”
- ◆ Failure on the part of the USDA’s Veterinary Medical Officers to ensure that facilities provided them with basic data on the research facilities, such as “the number of animals used in research” and the number of “unexpected animal deaths.”
- ◆ Failure on the part of Institutional Animal Care and Use Committees (IACUC) to effectively monitor animal care activities (veterinary care, review of painful procedures).
- ◆ Failure on the part of IACUCs to ensure the use of nonanimal methodologies where such research avenues exist.¹⁷

USDA APHIS issued a lukewarm point-by-point response to the OIG audit report,¹⁸ and it is questionable whether substantive improvements have resulted from the audit report, which has no enforcement mandate.

Therefore, the only federal statute regulating the use and care of animals in research seems not to be up to the task. In an effort to improve AC facility inspections and prevent useless, unnecessary, and arguably illegal animal use under the auspices of the AWA, in September 2012 the Physicians Committee for Responsible Medicine (PCRM) petitioned for a meeting with the USDA Office of General Counsel (OGC). Among the claims stated by PCRM are that the USDA has broad authority to interpret and enforce the statute, that the agency would better serve its enforcement role by expanding its interpretation to permit denial of animal use protocols when valid alternatives to animal use are available, and justification for disregarding those alternatives is inadequate.¹⁹ The agency has previously opined that “[t]he AWA does not permit APHIS to interrupt the conduct of

17. U.S. DEP’T OF AGRIC., REPORT NO. 33002-3-SF, AUDIT REPORT: APHIS ANIMAL CARE PROGRAM INSPECTION AND ENFORCEMENT ACTIVITIES i–ii (2005), available at <http://www.usda.gov/oig/webdocs/33002-03-SF.pdf>.

18. See *id.* at 45–51 (Exhibit E).

19. See *Illegal Experiments: Physicians File Lawsuit Against UCSF for Violating Animal Welfare Law*, PCRM, <http://www.pcrm.org/search/?cid=569> (last visited Apr. 7, 2013).

actual research or experimentation.”²⁰ But PCRM believes the more expansive interpretation proposed is within the USDA’s broad interpretive authority and allows better implementation of the AWA. Nevertheless, in December 2012 the USDA OGC confirmed its previous opinion, and the proposed meeting did not occur.

III. ANIMAL USE IN MEDICAL SCIENCE RESEARCH

Proponents of animal experimentation often make the sweeping claim that almost every major advance in human medicine during the last century has been attributable to animal research. This claim was first reported—without supporting citation—by the U.S. Public Health Service in 1994,²¹ and it has become almost rote among researchers, research institutions, and many funding agencies. But the claim has crumbled under scrutiny. Perhaps most succinctly, Robert Matthews’s analysis demonstrates that this claim has not been (and cannot be) validated, and he further describes the inadequacies of the predictive value and evidential weight from animal experimentation.²²

It may reasonably be stated that most medical advances have *included* animal experimental use; for decades this has been the default approach. But it has not been demonstrated that such animal use has been *essential* or even *reliable* for medical advancement. Thus, the claim that animal research contributes importantly to human health is analogous to claiming that white coats cure patients—yes, doctors wear white coats, but the white coats are not essential for the practice of medicine. Animal research occurs in the medical sciences, but it is not essential for favorable human outcomes. In fact, the unreliability of animal research and its many wrong turns have frequently delayed or derailed medical advances and exposed patients to ineffective and dangerous treatments.

Numerous reports demonstrate this unreliability of animal experimentation for investigation of human diseases and the development of safe and effective treatments, and describe the suitability of nonanimal

20. U.S. DEP’T OF AGRIC., ANIMAL CARE FACTSHEET: THE ANIMAL WELFARE ACT (Nov. 2012), http://www.aphis.usda.gov/publications/animal_welfare/2012/animal_welfare_act_english.pdf.

21. Pub. Health Serv., U.S. Dep’t of Health & Human Servs., *The Importance of Animals in Biomedical and Behavioral Research*, 5 ANIMAL WELFARE INFO. CENTER NEWSL., no. 2, 1994, available at <http://www.nal.usda.gov/awic/newsletters/v5n2/5n2phs.htm>.

22. Robert A.J. Matthews, *Medical Progress Depends on Animal Models—Doesn’t It?*, 101 J. ROYAL SOC’Y. MED. 95, 95, 97 (2008), available at <http://jrsm.rsmjournals.com/content/101/2/95.full.pdf+html>.

methods to replace them.²³ Persistence of many scientists' belief in the animal experimentation paradigm despite the preponderance of contrary evidence, and their resistance to change, has been attributed to technological and institutional lock-in.²⁴

Unknown to most of the public, entire fields of medical discovery have derived little or nothing of value for humans from decades of animal experimentation. Many of the major causes of morbidity and mortality among humans are eye-opening examples of this failure of animal experimentation, including but not limited to HIV/AIDS, stroke, cancers, menopausal hormone therapy, spinal cord injury (paralysis); and numerous other neurological, immunological, cardiovascular, and endocrine (most prominently diabetes mellitus) diseases.

A. HIV/AIDS Vaccine Research

Although to date, more than eighty-five HIV/AIDS vaccines have been both safe and effective in animal studies (predominantly using nonhuman primates), none has been successful in more than 200 human trials either for the prevention or treatment of HIV infection.²⁵ As of April 2013, the National Library of Medicine website, ClinicalTrials.gov, lists 130 human trials of preventive HIV vaccines²⁶ and 54 human trials of therapeutic HIV vaccines.²⁷ None of these trials has demonstrated a conclusive benefit either

23. See, e.g., Daniel G. Hackam & Donald A. Redelmeier, *Translation of Research Evidence from Animals to Humans*, 296 JAMA 1731, 1731–32 (2006); David F. Horrobin, *Modern Biomedical Research: An Internally Self-Consistent Universe with Little Contact with Medical Reality?*, 2 NATURE REV. DRUG DISCOVERY 151, 152–53 (2003); John P.A. Ioannidis, *Evolution and Translation of Research Findings: From Bench to Where?*, PLOS CLINICAL TRIALS (Nov. 17, 2006), <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1851723>; Gill Langley et al., *Replacing Animal Experiments: Choices, Chances, and Challenges*, 29 BIOESSAYS 918, 918–24 (2007), available at http://www.animalexperiments.info/studies/alternatives/replacement_langley_et_al_2007_assets/Replace%20Langley%20et%20al%202007%20Bioessays.pdf; Pablo Perel et al., *Comparison of Treatment Effects Between Animal Experiments and Clinical Trials: Systematic Review*, BRIT. MED. J. 1, 5 (Dec. 15, 2006), <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1781970/pdf/bmj-334-7586-res-00197-el.pdf>; Pandora Pound et al., *Where Is the Evidence that Animal Research Benefits Humans?*, 328 BRIT. MED. J. 514, 514, 516–17 (2004); Geoff Watts, *Animal Testing: Is It Worth It?*, 334 BRIT. MED. J. 182, 182–83 (2007).

24. Joshua Frank, *Technological Lock-in, Positive Institutional Feedback, and Research on Laboratory Animals*, 16 STRUCTURAL CHANGE & ECON. DYNAMICS 557, 572–573 (2005).

25. See Jarrod Bailey, *An Assessment of the Role of Chimpanzees in AIDS Vaccine Research*, 36 ALTERNATIVES TO LABORATORY ANIMALS 381, 381–82, 419 (2008), available at http://cms.neavs.org/docs/Chimps_AIDS_research_J_Bailey.pdf.

26. CLINICALTRIALS.GOV., <http://www.clinicaltrials.gov> (search performed using term “HIV preventive vaccines”) (last visited Apr. 21, 2013).

27. CLINICALTRIALS.GOV., <http://www.clinicaltrials.gov> (search performed using term “HIV therapeutic vaccines”) (last visited Apr. 21, 2013).

for prevention or control of HIV infection, and no HIV vaccine has been approved for human use.

In fact, only a handful of vaccine candidates have even progressed to phase III clinical trials, the final step before submission for FDA approval. The vast majority of vaccines tested on humans have failed during phase I and II trials designed to test vaccine safety and efficacy on smaller numbers of participants. Among the few vaccines that have reached phase III, the results from perhaps the two most-highly-touted vaccines are illustrative.

The Step Study²⁸ was the culmination of more than two decades of basic science research and failed human trials, and was viewed as employing a vaccine that had surmounted previous shortcomings believed to have prevented successful translation of animal results to humans. The study of 3,000 participants at high risk for HIV infection was designed to assess the ability of the Merck vaccine to prevent HIV infection and its effectiveness in controlling the viral burden among participants who contracted HIV during the study.²⁹ The Step Study was halted after the first interim data analysis confirmed that the vaccine did not prevent HIV infection or reduce viral burden.³⁰

The HIV/AIDS research community was rocked by the additional finding that participants who received the vaccine had a *higher* rate of HIV infection than those who received the placebo.³¹ A four-year follow-up study of infected participants documented a persistent 40% increased risk for HIV infection among vaccine recipients compared to placebo recipients.³²

The ALVAC-AIDSVAX clinical trial, conducted by the U.S. Army and the Thai government, included 16,402 men and women in Thailand.³³ Its goals were to assess the vaccine's ability to prevent HIV infection and its effectiveness in controlling the viral burden among those who contracted HIV during the trial.³⁴ No statistically significant decrease in HIV infections

28. SUSAN P. BUCHBINDER ET AL., EFFICACY ASSESSMENT OF A CELL-MEDIATED IMMUNITY HIV-1 VACCINE (THE STEP STUDY): A DOUBLE-BLIND, RANDOMISED, PLACEBO-CONTROLLED, TEST-OF-CONCEPT TRIAL (2008), http://www.hvti.org/media/Buchbinder_STEParticle_13Nov08.pdf.

29. *Id.* at 1, 3–5.

30. *Id.* at 1, 10.

31. *Id.* at 8.

32. Ann Duerr et al., *Extended Follow-Up Confirms Early Vaccine-Enhanced Risk of HIV Acquisition and Demonstrates Waning Effect Over Time Among Participants in a Randomized Trial of Recombinant Adenovirus HIV Vaccine (Step Study)*, 206 J. INFECTIOUS DISEASES 258, 258 (2012).

33. Supachai Rerks-Ngarm et al., *Vaccination with ALVAC and AIDSVAX to Prevent HIV-1 Infection in Thailand*, 361 NEW ENG. J. MED. 2209, 2210 (2009).

34. *Id.*

was seen among vaccinated participants, and no benefit in control of viral burden was seen in the three-and-a-half year trial period.³⁵ A subsequent study designed to assess the longer-term effect of the vaccine on viral burden and disease progression among 114 participants who contracted HIV during the initial trial showed no benefits for the vaccine after two additional years.³⁶

At an urgent HIV/AIDS summit convened in March 2008 after the failure of the Step Study, summit co-chair Warner C. Greene, M.D. from the University of California, San Francisco, stated: “Despite hundreds and hundreds of millions of dollars, the reality in 2008 is that an HIV vaccine clearly remains beyond our grasp.”³⁷ The National Institute of Allergy and Infectious Diseases website explains precisely why this is still true five years later: “It has been difficult to study HIV because the virus exclusively infects and causes disease in humans. As a result, there is no ideal animal model that can imitate the natural history and pathogenesis of HIV/AIDS in the human body.”³⁸

B. Stroke Research

Stroke due to cerebrovascular disease is the number-four killer of Americans, causing nearly 130,000 deaths a year.³⁹ About 90% of strokes are caused by atherosclerosis and thrombosis in blood vessels supplying the brain.⁴⁰ Animal research, predominantly using rodents but also larger mammals such as rabbits and nonhuman primates, has for decades been the default scientific approach to studying the human disease and developing stroke treatments.⁴¹

35. *Id.* at 2209.

36. *Follow-up Study to RV144 HIV Vaccine Trial Shows No Effect on Disease Progression in Infected Volunteers*, U.S. MILITARY HIV RES. PROGRAM (Sept. 16, 2011), <http://www.hivresearch.org/news.php?NewsID=220>.

37. Bob Roehr, *Research into HIV Vaccines Needs to Change Direction*, 336 BRIT. MED. J. 743, 743 (2008), available at <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2287264>.

38. *Evaluation of Vaccine Candidates in Animal Models*, NAT’L INST. OF ALLERGY & INFECTIOUS DISEASE, <http://www.niaid.nih.gov/topics/HIVAIDS/Research/vaccines/Pages/candidates.aspx> (last updated July 27, 2012).

39. Donna L. Hoyert & Jiaquan Xu, *Deaths: Preliminary Data for 2011*, 61 NAT’L VITAL STAT. REP. 1, 3–4 (2012), available at http://www.cdc.gov/nchs/data/nvsr/nvsr61/nvsr61_06.pdf.

40. Véronique L. Roger et al., *Heart Disease and Stroke Statistics—2012 Update: A Report from the American Heart Association*, 125 CIRCULATION e2, e68 (2012), available at <http://circ.ahajournals.org/content/125/1/e2.full.pdf+html>.

41. See Juliana B. Casals et al., *The Use of Animal Models for Stroke Research: A Review*, 61 COMP. MED. 305, 307 (2011), available at <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3155396/pdf/cm2011000305.pdf>; see also

Numerous reviews have documented the futility of animal research for developing treatments to reverse or ameliorate human stroke.⁴² Malcolm R. Macleod and colleagues reported more than 4,000 studies identifying more than 700 successful neuroprotective drugs in animal experiments.⁴³ Macleod subsequently reported that every one of about 150 human drug trials for stroke has failed to improve survival, and he estimated that about 250,000 animals had been used between 1985 and 2005 in this futile effort.⁴⁴

In a large meta-analysis of 525 publications regarding sixteen therapeutic interventions tested in animal studies, only ten studies (2%) correctly reported no overall benefit for the tested treatment, and only six studies did not report at least one statistically significant favorable finding.⁴⁵ Yet the only intervention that provided short-term symptomatic improvement for stroke patients was recombinant tissue plasminogen activator, which was already in clinical use for myocardial infarction, can only be given to about 5% of stroke patients, and does not improve survival.⁴⁶ As succinctly stated by *Annals of Neurology* editor S. Claiborne Johnston in 2006: “Ischemic stroke is a case study in failed translation.”⁴⁷

Michael E. Sughrue et al., *Bioethical Considerations in Translational Research: Primate Stroke*, 9 AM. J. BIOETHICS 3, 4 (2009).

42. See, e.g., Victoria E. O’Collins et al., *1,026 Experimental Treatments in Acute Stroke*, 59 ANNALS NEUROLOGY 467, 467 (2006); A. Richard Green & Ashfaq Shuaib, *Therapeutic Strategies for the Treatment of Stroke*, 11 DRUG DISCOVERY TODAY 681, 683–84 (2006); Ulrich Dirnagl, *Bench to Bedside: The Quest for Quality in Experimental Stroke Research*, 26 J. CEREBRAL BLOOD FLOW & METABOLISM 1465, 1465–67, 1469, 1475 (2006); Alan I. Faden & Bogdan Stoica, *Neuroprotection: Challenges and Opportunities*, 64 ARCHIVES NEUROLOGY 794, 794–95 (2007); Casals et al., *supra* note 41, at 305, 307; Gary H. Danton & W. Dalton Dietrich, *The Search for Neuroprotective Strategies in Stroke*, 25 AM. J. NEURORADIOLOGY 181, 181, 191 (2004).

43. Malcolm R. Macleod et al., *Pooling of Animal Experimental Data Reveals Influence of Study Design and Publication Bias*, 35 STROKE 1203, 1203 (2004).

44. Malcolm R. Macleod, *What Can Systematic Review and Meta-Analysis Tell Us About the Experimental Data Supporting Stroke Drug Development?*, 1 INT’L J. NEUROPROTECTION & NEURODEGENERATION 201 (2005).

45. Emily S. Sena et al., *Publication Bias in Reports of Animal Stroke Studies Leads to Major Overstatement of Efficacy*, PLOS BIOLOGY (Mar. 30, 2010), <http://www.plosbiology.org/article/info%3Adoi%2F10.1371%2Fjournal.pbio.1000344>.

46. See Nat’l Inst. of Neurological Disorders & Stroke rt-PA Stroke Study Grp., *Tissue Plasminogen Activator for Acute Ischemic Stroke*, 333 NEW ENG. J. MED. 1581, 1581–82, 1586 (1995); Al-Buhairi AR & Jan MM, *Recombinant Tissue Plasminogen Activator for Acute Ischemic Stroke*, PUBMED.GOV (Jan. 23, 2002), <http://www.ncbi.nlm.nih.gov/pubmed/11938357> (abstract).

47. S. Claiborne Johnston, *Translation: Case Study in Failure*, 59 ANNALS NEUROLOGY 447, 447 (2006).

C. Neurological and Brain Research

Spinal cord injuries (SCI) with paralysis are devastating events that have proven resistant to reversal or improvement despite decades of animal experiments primarily using rodents, as well as cats, dogs, and nonhuman primates. Akhtar and colleagues have provided a comprehensive review of this topic, addressing mechanistic, anatomical, and biological reasons for the inability of animal models of SCI to translate to human benefit.⁴⁸ Their subsequent review of methylprednisolone details the failures of this most-tested therapy for SCI.⁴⁹

Every one of ten randomized prospective controlled trials involving 2,717 patients, and numerous other clinical trials of treatments for acute SCI that were successful in animals, have failed to confirm benefits for humans.⁵⁰ Charles H. Tator, M.D., Ph.D., section editor of the *Journal of Neurotrauma*, concluded in 2006: “The field of spinal cord injury (SCI) is remarkable for the high number of treatment trials in humans. Unfortunately, none has produced a major improvement in neurological recovery or a meaningful increase in function, although much effort and resources have been expended.”⁵¹ Six years later, in his extensive updated review of SCI animal research, Dr. Tator and colleagues repeated that “no agents that produce major benefit have been proven to date.”⁵²

In the related field of traumatic brain injury (TBI), the failure of animal experimentation is equally evident. TBI is the most common cause of morbidity and mortality worldwide in persons less than forty-five years old,⁵³ largely due to the proliferation of automobile travel and constant warfare on the planet.⁵⁴ Animal studies have been unable to approximate

48. See Aysha Z. Akhtar et al., *Animal Models in Spinal Cord Injury: A Review*, 19 REV. NEUROSCIENCES 47, 47 (2008).

49. See Aysha Z. Akhtar et al., *Animal Studies in Spinal Cord Injury: A Systematic Review of Methylprednisolone*, 37 ALTERNATIVES TO LABORATORY ANIMALS 43, 43, 57 (2009).

50. See Charles H. Tator, *Review of Treatment Trials in Human Spinal Cord Injury: Issues, Difficulties, and Recommendations*, 59 NEUROSURGERY 957, 957–58, 966 (2006); Michael G. Fehlings & Darryl C. Baptiste, *Current Status of Clinical Trials for Acute Spinal Cord Injury*, 36 INJ., INT. J. CARE INJURED 113, 113 (2005); Dennis Maiman, *Symposium on Spinal Cord Injury Models: Introduction*, 11 J. AM. PARAPLEGIA SOC'Y 23, 23 (1988).

51. Tator, *supra* note 50, at 957.

52. Charles H. Tator et al., *Translational Potential of Preclinical Trials of Neuroprotection Through Pharmacotherapy for Spinal Cord Injury*, 17 J. NEUROSURGERY SPINE 157, 157 (2012).

53. Robert Vink & M. Ross Bullock, *Traumatic Brain Injury: Therapeutic Challenges and New Directions*, 7 NEUROTHEAPEUTICS: J. AM. SOC'Y EXPERIMENTAL NEUROTHEAPEUTICS 1, 1 (2010).

54. See J.W. Finnie & P.C. Blumbergs, *Animal Models: Traumatic Brain Injury*, 39 VETERINARY PATHOLOGY 679, 679 (2002).

the complexities of human TBI,⁵⁵ and instead, researchers have relied on animal models that are affordable, simple, and widely applicable,⁵⁶ rather than closely representative of human TBI.

Although rodents are most commonly used to model human TBI, researchers acknowledged the severe restrictions imposed by the major brain and spinal cord anatomical and structural differences between rodents and humans, as well as the large discrepancies between rodent and human physiological and behavioral responses to neurological trauma.⁵⁷ Even nonhuman primate studies have been discordant with the mechanisms and outcomes of human TBI, and the use of any other species is also known to produce immutable differences in injury outcomes.⁵⁸

There appears to be general surrender among researchers regarding the translation of animal research findings to human TBI⁵⁹—which is highlighted by the 2010 report by Maas and colleagues of twenty-seven phase III clinical trials and six unpublished trials that universally failed to show benefits for TBI patients, despite showing benefit in animal studies.⁶⁰ The role of in vitro models of TBI has gained favor among some researchers.⁶¹ These models are usually compared to the discredited animal models of TBI rather than to human TBI pathology, which complicates the assessment of their relevance for humans.⁶²

Numerous other neuroscience research areas have also been unproductive in terms of human benefit, despite many years of animal experimentation. As of 2005, more than fifty publications reported therapeutic agents that prolonged survival in the standard SOD1 mouse

55. See generally D.M. Morales et al., *Experimental Models of Traumatic Brain Injury: Do We Really Need to Build a Better Mousetrap?*, 136 NEUROSCIENCE 971, 972 (2005) (examining many animal studies and concluding that no one animal study can reproduce the entire spectrum of human TBI); see also Finnie & Blumbergs, *supra* note 54, at 679 (“No single animal model can reliably replicate the full spectrum of human TBI.”).

56. Hong-Cai Wang & Yan-Bin Ma, *Experimental Models of Traumatic Axonal Injury*, 17 J. CLINICAL NEUROSCIENCE 157, 157–58 (2010).

57. Ibolja Cernak, *Animal Models of Head Trauma*, 2 NEURORX 410, 411 (2005).

58. See Finnie & Blumbergs, *supra* note 54, at 679.

59. See, e.g., Cernak, *supra* note 57, at 410; Alan I. Faden, *Neuroprotection and Traumatic Brain Injury: Theoretical Option or Realistic Proposition*, 15 CURRENT OPINION NEUROLOGY 707, 707 (2002); Kathryn Beauchamp et al., *Pharmacology of Traumatic Brain Injury: Where Is the “Golden Bullet”?*, 14 MOLECULAR MED. 731, 737 (2008).

60. Andrew I.R. Maas, et al., *Clinical Trials in Traumatic Brain Injury: Past Experience and Current Developments*, 7 NEUROTHERAPEUTICS 115, 115 (2010).

61. See, e.g., Barclay Morrison III et al., *In Vitro Central Nervous System Models of Mechanically Induced Trauma: A Review*, 15 J. NEUROTRAUMA, 911, 917 (1998); Barclay Morrison III et al., *In Vitro Models of Traumatic Brain Injury*, 13 ANN. REV. BIOMEDICAL ENGINEERING 91, 93 (2011); A. Kumaria & C.M. Tolia, *In Vitro Models of Neurotrauma*, 22 BRIT J. NEUROSURGERY 200, 200 (2008).

62. See *In Vitro Models of Traumatic Brain Injury*, *supra* note 61, at 99.

model for amyotrophic lateral sclerosis (ALS).⁶³ Yet not a single phase III clinical trial in four decades has shown any convincing benefit for ALS patients. Benatar's 2007 review detailed the internal inconsistencies and lack of translation for eighty-five ALS animal studies reporting seventy-eight different treatment modalities.⁶⁴ Traynor and colleagues identified 113 promising ALS drugs from animal studies and early stage clinical trials, but none of these translated to patient benefits.⁶⁵

Only one drug, riluzole, is approved for use in ALS in the United States, and that drug may only marginally slow disease progression for some patients while not prolonging survival. The animal studies that led to clinical testing of riluzole could not be replicated by Scott and colleagues, who concluded that the purported benefit of riluzole was merely statistical noise.⁶⁶ Most recently, the much-anticipated EMPOWER clinical trial of Biogen Idec's dexamipexole, which had "shown neuroprotective properties in multiple in vitro and in vivo studies,"⁶⁷ failed to demonstrate any benefit among 943 ALS patients for improving either function or survival.⁶⁸

Animal research has also produced no effective treatments for the other major motor neuron diseases, including primary lateral sclerosis, progressive muscular atrophy, spinal muscular atrophy, progressive bulbar palsy, and pseudobulbar palsy.⁶⁹ The sad reality is that spontaneous symptom regression and arrested disease progression are more common than any treatment benefits for ALS and the other motor neuron diseases.

63. See, e.g., Jeffrey D. Rothstein, *Preclinical Studies: How Much Can We Rely On?*, 5 *ALS & OTHER MOTOR NEURON DISORDERS* 22, 22–23 (2004) (discussing what has been learned from past preclinical studies); Niranjana Nirmalananthan & Linda Greensmith, *Amyotrophic Lateral Sclerosis: Recent Advances and Future Therapies*, 18 *CURRENT OPINION NEUROLOGY* 712, 712 (2005).

64. See Michael Benatar, *Lost in Translation: Treatment Trials in the SOD1 Mouse and in Human ALS*, 26 *NEUROBIOLOGY DISEASE* 1, 3 (2007).

65. B.J. Traynor et al., *Neuroprotective Agents for Clinical Trials in ALS: A Systematic Assessment*, 67 *NEUROLOGY* 20, 21 (2006).

66. Sean Scott et al., *Design, Power, and Interpretation of Studies in the Standard Murine Model of ALS*, 9 *AMYOTROPHIC LATERAL SCLEROSIS* 4, 4 (2008).

67. *Biogen Idec and Knopp Biosciences Announce Enrollment of The First Patient in a Global Phase III Study of Dexamipexole for ALS*, BIOGEN IDEC (Mar. 31, 2011), http://www.biogenidec.com/press_release_details.aspx?id=5981&reqid=1544596.

68. *Biogen Idec Reports Top-Line Results from Phase 3 Trial Investigating Dexamipexole in People with Amyotrophic Lateral Sclerosis (ALS)*, BIOGEN IDEC (Jan. 3, 2013), http://www.biogenidec.com/PRESS_RELEASE_DETAILS.aspx?ID=5981&ReqId=1770780.

69. *Motor Neuron Diseases Fact Sheet*, NAT'L INST. OF NEUROLOGICAL DISORDERS & STROKE, http://www.ninds.nih.gov/disorders/motor_neuron_diseases/detail_motor_neuron_diseases.htm (last updated Dec. 28, 2012).

Experimental autoimmune encephalitis (EAE) is the animal model pathology developed to replicate human multiple sclerosis (MS), using primarily mice but also rats, guinea pigs, rabbits, and nonhuman primates. Animal research reviews have reported that over the past few decades, literally thousands of drugs have been used successfully in EAE animals,⁷⁰ and that it is possible to control immune-mediated disease at any point during the relapsing disease process in animal models.⁷¹ However, these ubiquitous animal model successes are incapable of predicting benefits for patients, and the mantra among some EAE researchers has become, “Everything stops EAE, nothing cures MS.”⁷²

Some of these treatments actually worsen MS or cause severe and sometimes lethal adverse effects undetected in animal studies, including liver failure, heart damage, infertility, acute myelogenous leukemia, and progressive multifocal leukoencephalopathy.⁷³ Even the few drugs that have been shown to decrease relapse frequency for relapsing-remitting MS patients have not been consistently effective in modifying MS symptoms and disease progression.⁷⁴ Additionally, there is no effective treatment for the progressive forms of MS.

Animal research studying the related dementias Alzheimer disease (AD) and frontotemporal dementia (FTD) has employed genetically modified mouse models that attempt to replicate the putative etiology and hallmarks of AD in humans, brain deposition of amyloid- β peptide aggregates and tau protein tangles.⁷⁵ AD is the most common cause of dementia in older patients,⁷⁶ while FTD causes half of dementias in patients

70. Hanna M. Vesterinen et al., *Improving the Translational Hit of Experimental Treatments in Multiple Sclerosis*, 16 MULTIPLE SCLEROSIS 1044, 1044–45 (2010).

71. See generally Gareth Pryce et al., *Autoimmune Tolerance Eliminates Relapses but Fails to Halt Progression in a Model of Multiple Sclerosis*, 165 J. NEUROIMMUNOLOGY 41 (2005) (showing the poor correlation between EAE models in rodents and the progression of MS).

72. David Baker et al., *Critical Appraisal of Animal Models of Multiple Sclerosis*, 17 MULTIPLE SCLEROSIS J. 647, 652 (2011).

73. See Alastair Compston & Alasdair Coles, *Multiple Sclerosis*, 359 LANCET 1221, 1228 (2002); Giancarlo Comi, *Treatment of Multiple Sclerosis: Role of Natalizumab*, 30 NEUROLOGICAL SCI. S155, S156 (Supp. II 2009); see generally Helen Tremlett & Joel Oger, *Hepatic Injury, Liver Monitoring and the Beta-Interferons for Multiple Sclerosis*, 251 J. NEUROLOGY 1297 (2004).

74. See Heather J. MacLean & Mark S. Freedman, *Multiple Sclerosis: Following Clues from Cause to Cure*, 8 LANCET NEUROLOGY 6, 7 (2009).

75. See Todd E. Golde, *The A β Hypothesis: Leading Us to Rationally-Designed Therapeutic Strategies for the Treatment or Prevention of Alzheimer Disease*, 15 BRAIN PATHOLOGY 84, 85 (2005); see generally Todd E. Golde et al., *Targeting A β and Tau in Alzheimer's Disease: An Early Interim Report*, 223 EXPERIMENTAL NEUROLOGY 252 (2010).

76. See Jürgen Götz & Lars M. Ittner, *Animal Models of Alzheimer's Disease and Frontotemporal Dementia*, 9 NATURE REV. NEUROSCIENCE 532, 532 (2008).

younger than sixty years.⁷⁷ No therapies have been developed that prevent, ameliorate, slow progression, affect mortality, or provide cure for patients with AD or FTD,⁷⁸ and some commonly used drugs can worsen functional impairment and hasten cognitive decline.⁷⁹ Several of the interspecies barriers that explain these failures have been reviewed.⁸⁰

All of the amyloid- β targeted drugs to reach phase III clinical trials have failed to impact symptoms or outcomes.⁸¹ The latest and most hopeful drug tested in AD patients is Dimebon (latrepirdine), which showed no evidence for efficacy in a phase III trial involving 598 patients⁸² after being hyped with the headline “Dimebon shines as Alzheimer’s therapy”⁸³ following a phase II trial involving 155 patients.⁸⁴ Consistent failure to translate animal-derived treatments aimed at preventing or removing pathological brain protein accumulations in patients, combined with other inconsistencies, puts the AD amyloid protein hypothesis in jeopardy, and thus potentially discredits more than two decades of AD animal research.⁸⁵

D. Menopausal Hormone Therapy Research

For six decades after the 1942 FDA approval of conjugated equine estrogen (Premarin) for treatment of menopausal symptoms such as hot flashes, mood swings, and disordered sleep, women were informed and reassured about the therapeutic and preventive health properties of estrogen

77. *Id.*; see also Carlo Ballatore et al., *Tau-Mediated Neurodegeneration in Alzheimer’s Disease and Related Disorders*, 8 NATURE REV. NEUROSCIENCE 663, 663 (2007).

78. See Götz & Ittner, *supra* note 76, at 541; David M. Holtzman, *Moving Towards a Vaccine*, 454 NATURE 418, 418 (2008); Lon S. Schneider et al., *Treatment with Cholinesterase Inhibitors and Memantine of Patients in the Alzheimer’s Disease Neuroimaging Initiative*, 68 ARCHIVES NEUROLOGY 58, 64 (2011).

79. Schneider et al., *supra* note 78, at 58, 60, 62.

80. See generally Hugo Geerts, *Of Mice and Men: Bridging the Translational Disconnect in CNS Drug Discovery*, 23 CNS DRUGS 915 (2009).

81. Eric Karran et al., *The Amyloid Cascade Hypothesis for Alzheimer’s Disease: An Appraisal for the Development of Therapeutics*, 10 NATURE REV. DRUG DISCOVERY 698, 698 (2011).

82. Roy W. Jones, *Dimebon Disappointment*, 2 ALZHEIMER’S RES. THERAPY 25, 25–26 (2010), available at <http://alzres.com/content/pdf/alzrt49.pdf>.

83. Daniel J. DeNoon, *Dimebon Shines as Alzheimer’s Therapy*, WEBMD (July 30, 2008), <http://www.webmd.com/alzheimers/news/20080730/dimebon-shines-as-alzheimers-therapy>.

84. Rachelle S. Doody et al., *Effect of Dimebon on Cognition, Activities of Daily Living, Behaviour, and Global Function in Patients with Mild-to-Moderate Alzheimer’s Disease: A Randomised, Double-Blind, Placebo-Controlled Study*, 372 LANCET 207, 207 (2008).

85. See, e.g., Rachael L. Neve & Nikolaos K. Robakis, *Alzheimer’s Disease: A Re-examination of the Amyloid Hypothesis*, 21 TRENDS NEUROSCIENCES 15, 15 (1998); John Hardy & Dennis J. Selkoe, *The Amyloid Hypothesis of Alzheimer’s Disease: Progress and Problems on the Road to Therapeutics*, 297 SCIENCE 353, 353–54 (2002); Karran et al., *supra* note 81, at 708–09.

replacement. After it was reported in 1975 that unopposed estrogen therapy caused a several-fold increase in endometrial cancers,⁸⁶ and the next year that estrogen use may increase breast cancer risk, estrogen prescriptions plummeted.⁸⁷ But it was soon found that adding progestin to estrogen maintained estrogen's relief of menopausal symptoms and eliminated the increased risk for endometrial cancer. This combination was used for nearly two decades, and a fixed-dose estrogen and progestin combination pill (Prempro) was approved by the FDA in 1995. At the turn of the millennium, menopausal hormone therapy (MHT), formerly known as hormone replacement therapy, using Premarin and Prempro generated more than sixty-five million prescriptions annually, and more than six million American women were taking an estrogen and progestin combination drug.⁸⁸

Preclinical animal experiments indicated to Wyeth Pharmaceuticals (part of Pfizer, Inc. since 2009) that estrogen and the estrogen and progestin combination were protective regarding heart and vascular diseases, and the company pursued numerous experiments in various animal species to identify mechanisms and outcomes for this suspected protective effect. Using a diet-induced atherosclerosis nonhuman primate model (cynomolgus macaque) and postmortem assessment, Adams and colleagues found that estrogen with or without progestin reduced the development of coronary atherosclerosis by about half over thirty months.⁸⁹ The same researchers demonstrated links between decreased atherosclerosis in the high-estrogen state of pregnancy⁹⁰ and increased atherosclerosis in the low-estrogen state of surgical menopause,⁹¹ leading to the conclusion that estrogen is protective regarding atherosclerosis. A subsequent coronary arteriography study in cynomolgus macaques suggested that the protective effect of

86. Harry K. Ziel & William D. Finkle, *Increased Risk of Endometrial Carcinoma Among Users of Conjugated Estrogens*, 293 NEW ENGL. J. MED. 1167, 1167 (1975); Thomas W. McDonald et al., *Exogenous Estrogen and Endometrial Carcinoma: Case-control and Incidence Study*, 127 AM. J. OBSTETRICS GYNECOLOGY 572, 572-73 (1977).

87. Amanda Spake, *The Menopausal Marketplace*, U.S. NEWS & WORLD REP., Nov. 10, 2002, http://health.usnews.com/usnews/health/articles/021118/archive_023268_print.htm.

88. *Id.*

89. Michael R. Adams et al., *Inhibition of Coronary Artery Atherosclerosis by 17-Beta Estradiol in Ovariectomized Monkeys*, 10 ARTERIOSCLEROSIS, THROMBOSIS, & VASCULAR BIOLOGY 1051, 1051, 1056 (1990).

90. Michael R. Adams et al., *Pregnancy-Associated Inhibition of Coronary Artery Atherosclerosis in Monkeys: Evidence of a Relationship with Endogenous Estrogen*, 7 ARTERIOSCLEROSIS, THROMBOSIS, & VASCULAR BIOLOGY 378, 378 (1987).

91. Michael R. Adams et al., *Ovariectomy, Social Status, and Atherosclerosis in Cynomolgus Monkeys*, 5 ARTERIOSCLEROSIS, THROMBOSIS, & VASCULAR BIOLOGY 192, 192, 199 (1985).

estrogen is mediated by improved vascular function,⁹² consistent with an earlier study that showed similar results in baboons.⁹³

Clarkson and colleagues demonstrated a protective effect of estrogen for coronary artery atherosclerosis⁹⁴ and carotid artery atherosclerosis⁹⁵ in postmenopausal cynomolgus macaques,⁹⁶ and later showed the same protective effect for coronary atherosclerosis in postmenopausal long-tailed macaques.⁹⁷ Other beneficial direct and mediated vascular effects of estrogen related to lowering cardiovascular risk have been demonstrated in rabbits,⁹⁸ mice,⁹⁹ rats,¹⁰⁰ cows,¹⁰¹ and nonhuman primates.¹⁰²

92. J. Koucky Williams et al., *Estrogen Modulates Responses of Atherosclerotic Coronary Arteries*, 81 CIRCULATION 1680, 1680, 1683 (1990).

93. Alan L. Lin et al., *Estradiol 17 β Affects Estrogen Receptor Distribution and Elevates Progesterone Receptor Content in Baboon Aorta*, 6 ARTERIOSCLEROSIS, THROMBOSIS, & VASCULAR BIOLOGY 495, 495 (1986).

94. Thomas B. Clarkson et al., *A Comparison of Tibolone and Conjugated Equine Estrogens Effects on Coronary Artery Atherosclerosis and Bone Density of Postmenopausal Monkeys*, 86 J. CLINICAL ENDOCRINOLOGY & METABOLISM 5396, 5401 (2001).

95. Thomas B. Clarkson et al., *Comparison of Tibolone and Conjugated Equine Estrogens Effects on Carotid Artery Atherosclerosis of Postmenopausal Monkeys*, 33 STROKE 2700, 2702 (2002).

96. Adams et al., *supra* note 91, at 192 (“Socially dominant intact females were protected against advanced atherosclerotic lesions (plaques) of the coronary arteries, while subordinate females and ovariectomized females were not.”).

97. Susan E. Appt et al., *Low Dose Estrogens Inhibit Coronary Artery Atherosclerosis in Postmenopausal Monkeys*, 55 MATURITAS 187, 187–88 (2006) (“[M]onkeys treated with low dose CEE had marked reductions in coronary artery atherosclerosis plaque extent (intimal area) in all three main coronary arteries.”).

98. See, e.g., Katti Fischer-Dzoga et al., *The Effect of Estradiol on the Proliferation of Rabbit Aortic Medial Tissue Culture Cells Induced by Hyperlipemic Serum*, 39 EXPERIMENTAL & MOLECULAR PATHOLOGY 355, 355 (1983); Jane L. Hough & Donald B. Zilversmit, *Effect of 17 Beta Estradiol on Aortic Cholesterol Content and Metabolism in Cholesterol-Fed Rabbits*, 6 ARTERIOSCLEROSIS, THROMBOSIS, & VASCULAR BIOLOGY 57, 57 (1986); Jens Haarbo & Claus Christiansen, *The Impact of Female Sex Hormones on Secondary Prevention of Atherosclerosis in Ovariectomized Cholesterol-Fed Rabbits*, 123 ATHEROSCLEROSIS 139, 139 (1996).

99. See, e.g., Richard H. Karas et al., *Estrogen Inhibits the Vascular Injury Response in Estrogen Receptor β -Deficient Female Mice*, 96 PROC. NAT'L ACADEMY SCIENCES 15133, 15133 (1999); Mark D. Iafrafi et al., *Estrogen Inhibits the Vascular Injury Response in Estrogen Receptor α -Deficient Mice*, 3 NATURE MED. 545, 545 (1997); Richard H. Karas et al., *Effects of Estrogen on the Vascular Injury Response in Estrogen Receptor α,β (Double) Knockout Mice*, 89 CIRCULATION RES. 534, 534 (2001); Theodore R. Sullivan, Jr. et al., *Estrogen Inhibits the Response-to-Injury in a Mouse Carotid Artery Model*, 96 J. CLINICAL INVESTIGATION 2482, 2482 (1995).

100. See, e.g., Chang Wen-Chang et al., *Stimulation of Prostacyclin Biosynthetic Activity by Estradiol in Rat Aorta Smooth Muscle Cells in Culture*, 619 BIOCHIMICA ET BIOPHYSICA ACTA 107 (1980); Grace M. Fischer, *In Vivo Effects of Estradiol on Collagen and Elastin Dynamics in Rat Aorta*, 5 ENDOCRINOLOGY 1227, 1227, 1231 (1972).

101. John C. Beldekas et al., *Effects of 17 β -Estradiol on the Biosynthesis of Collagen in Cultured Bovine Aortic Smooth Muscle Cells*, 20 BIOCHEMISTRY 2162, 2162 (1981).

As if to confirm the extensive animal studies, the Nurses' Health Study, an observational study of 32,317 postmenopausal nurses, identified a protective effect of estrogen for heart disease.¹⁰³ However, contemporaneous data from a much smaller cohort of women in the Framingham Heart Study reported opposite effects of estrogen for heart disease risk.¹⁰⁴ A ten-year follow-up report from the Nurses' Health Study reiterated the decreased heart disease risk with estrogen therapy for a larger cohort of 48,470 postmenopausal nurses,¹⁰⁵ and this outcome was also supported by other observational studies.¹⁰⁶ These studies are in sharp contrast to the *increased* heart disease risk seen in the Framingham Heart Study, and also contrast the failure of Premarin or Prempro to prevent coronary artery disease progression in the Estrogen Replacement and Atherosclerosis Trial.¹⁰⁷

Despite the lockstep uniformity of cardiovascular benefits in numerous mechanistic and outcome-focused animal studies of MHT, and despite the marked preponderance of confirmatory outcomes in observational clinical studies of MHT, *all of these findings were wrong*. And the consistency of animal studies of MHT in showing opposite effects, as compared to the effects in prospective clinical trials of postmenopausal women, is a strong indictment of the animal research paradigm.

102. J. Kouody Williams et al., *A Comparison of Tibolone and Hormone Replacement Therapy on Coronary Artery and Myocardial Function in Ovariectomized Atherosclerotic Monkeys*, 9 MENOPAUSE 41, 47, 50 (2002).

103. Meir J. Stampfer et al., *A Prospective Study of Postmenopausal Estrogen Therapy and Coronary Heart Disease*, 313 NEW ENG. J. MED. 1044, 1044 (1985).

104. See Peter W.F. Wilson et al., *Postmenopausal Estrogen Use, Cigarette Smoking, and Cardiovascular Morbidity in Women Over 50: The Framingham Study*, 313 NEW ENG. J. MED. 1038, 1038 (1985).

105. Meir J. Stampfer et al., *Postmenopausal Estrogen Therapy and Cardiovascular Disease: Ten-Year Follow-Up from the Nurses' Health Study*, 325 NEW ENG. J. MED. 756, 756, 761 (1991).

106. See, e.g., Deborah Grady et al., *Hormone Therapy to Prevent Disease and Prolong Life in Postmenopausal Women*, 117 ANNALS INTERNAL MED. 1016, 1016 (1992); Francine Grodstein et al., *A Prospective, Observational Study of Postmenopausal Hormone Therapy and Primary Prevention of Cardiovascular Disease*, 133 ANNALS INTERNAL MED. 933, 933 (2000); Robert H. Knopp, *The Effects of Postmenopausal Estrogen Therapy on the Incidence of Arteriosclerotic Vascular Disease*, 72 OBSTETRICS & GYNECOLOGY 23S, 23S (1988); Helen A. Jonas et al., *Current Estrogen-Progestin and Estrogen Replacement Therapy in Elderly Women: Association with Carotid Atherosclerosis*, 6 ANNALS EPIDEMIOLOGY 314, 320 (1996); Cristina Varas-Lorenzo et al., *Hormone Replacement Therapy and Incidence of Acute Myocardial Infarction: A Population-Based Nested Case-Control Study*, 101 CIRCULATION 2572, 2572 (2000); Susan R. Heckbert et al., *Duration of Estrogen Replacement Therapy in Relation to the Risk of Incident Myocardial Infarction in Postmenopausal Women*, 157 ARCHIVES INTERNAL MED. 1330, 1330 (1997).

107. David M. Herrington et al., *Effects of Estrogen Replacement on the Progression of Coronary-Artery Atherosclerosis*, 343 NEW ENG. J. MED. 522, 522 (2000).

Though the noted Framingham Heart Study results raised a red flag, the first major blow to the animal research results came from the randomized prospective Heart and Estrogen/Progestin Replacement Study (HERS) reported in 1998. HERS demonstrated no protection from heart attacks and cardiac deaths for estrogen/progestin therapy among 2,763 women with coronary heart disease.¹⁰⁸ The Women's Health Initiative (WHI) clinical trials of MHT further unraveled the purported cardiovascular protective benefits of MHT with word of the premature termination of the WHI estrogen and progestin trial in 2002. Designed to evaluate the effects of Prempro on the incidence of cardiovascular disease, cancers, and bone fractures, this landmark trial of 16,608 postmenopausal women was halted by its data and safety monitoring board due to increased risk for breast cancer among MHT recipients.¹⁰⁹

Complete data analysis at mean 5.2 years of follow-up confirmed 26% increased breast cancer risk, but also identified increased risks of 29% for coronary heart disease, 41% for stroke, 107% for deep vein thrombosis, and 113% for pulmonary embolism.¹¹⁰ All findings were confirmed in subsequent intermediate-term data analyses.¹¹¹

The parallel WHI Premarin study of 10,739 women with hysterectomies also was terminated prematurely due to increased stroke risk, and data analysis showed no cardiovascular protection from estrogen.¹¹² In addition, the risks for hormone-related breast cancer, thrombosis, and pulmonary embolism were further confirmed in the UK Million Women Study.¹¹³ The preponderance of failed estrogen and

108. Stephen Hulley et al., *Randomized Trial of Estrogen Plus Progestin for Secondary Prevention of Coronary Heart Disease in Postmenopausal Women*, 280 JAMA 605, 605 (1998).

109. See Writing Grp. for the Women's Health Initiative Investigators, *Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women: Principal Results from the Women's Health Initiative Randomized Controlled Trial*, 288 JAMA 321, 321 (2002).

110. *Id.* at 326.

111. See, e.g., JoAnn E. Manson et al., *Estrogen Plus Progestin and the Risk of Coronary Heart Disease*, 349 NEW ENG. J. MED. 523, 523 (2003); Rowan T. Chlebowski et al., *Influence of Estrogen Plus Progestin on Breast Cancer and Mammography in Healthy Postmenopausal Women: The Women's Health Initiative Randomized Trial*, 289 JAMA 3243, 3243 (2003); Sylvia Wassertheil-Smoller et al., *Effect of Estrogen Plus Progestin on Stroke in Postmenopausal Women. The Women's Health Initiative: A Randomized Trial*, 289 JAMA 2673, 2673 (2003); Jane A. Cauley et al., *Effects of Estrogen Plus Progestin on Risk of Fracture and Bone Mineral Density: The Women's Health Initiative Randomized Trial*, 290 JAMA 1729, 1729 (2003).

112. The Women's Health Initiative Steering Comm., *Effects of Conjugated Equine Estrogen in Postmenopausal Women with Hysterectomy: The Women's Health Initiative Randomized Controlled Trial*, 291 JAMA 1701, 1701 (2004).

113. See Million Women Study Collaborators, *Breast Cancer and Hormone-Replacement Therapy in the Million Women Study*, 362 LANCET 419, 419 (2003); see also S. Sweetland et al., *Venous Thromboembolism Risk in Relation to Use of Different Types of Postmenopausal*

estrogen/progestin randomized trials is summarized by Ouyang and colleagues.¹¹⁴

The failure of MHT to prevent or mitigate cardiovascular disease has been cemented by a meta-analysis published shortly after the initial WHI estrogen and progestin study,¹¹⁵ a 2010 analysis of continued coronary heart disease risk among WHI participants,¹¹⁶ a 2012 systematic review of MHT studies published since 2002,¹¹⁷ and the updated U.S. Preventive Services Task Force 2013 guidelines for MHT.¹¹⁸ There can be little doubt that consistently misleading animal research results contributed to decades of inappropriate MHT, thereby causing substantial morbidities and mortality for postmenopausal women.

E. Cancer Research

The use of animals to investigate human cancers and to develop cancer treatments has been unreliable and sometimes damaging to patients. This is perhaps most succinctly explained by former U.S. National Cancer Institute director Richard Klausner, M.D., who stated in 1998: “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.”¹¹⁹ The clinical failure rate of cancer drugs developed from animal research is at least 95%, higher than for any other disease category.¹²⁰ With rare exceptions, such as the success of Gleevec (imatinib) in treating chronic

Hormone Therapy in a Large Prospective Study, 10 J. THROMBOSIS & HAEMOSTASIS 2277, 2277, 2282 (2012).

114. See generally Pamela Ouyang et al., *Hormone Replacement Therapy and the Cardiovascular System: Lessons Learned and Unanswered Questions*, 47 J. AM. C. CARDIOLOGY 1741 (2006).

115. See Heidi D. Nelson et al., *Postmenopausal Hormone Replacement Therapy: Scientific Review*, 288 JAMA 872, 874 (2002).

116. See Sengwee Toh et al., *Coronary Heart Disease in Postmenopausal Recipients of Estrogen Plus Progestin Therapy: Does the Increased Risk Ever Disappear?: A Randomized Trial*, 152 ANNALS INTERNAL MED. 211, 216 (2010).

117. See Heidi D. Nelson et al., *Menopausal Hormone Therapy for the Primary Prevention of Chronic Conditions: A Systematic Review to Update the U.S. Preventive Services Task Force Recommendations*, 157 ANNALS INTERNAL MED. 104, 104 (2012).

118. See Virginia A. Moyer, U.S. Preventive Servs. Task Force, *Menopausal Hormone Therapy for the Primary Prevention of Chronic Conditions: U.S. Preventive Services Task Force Recommendation Statement*, 158 ANNALS INTERNAL MED. 47, 47 (2013).

119. Marlene Cimon et al., *Cancer Drugs Face Long Road from Mice to Men*, L.A. TIMES, May 6, 1998, <http://articles.latimes.com/print/1998/may/06/news/mn-46795>.

120. Lisa Hutchinson & Rebecca Kirk, *High Drug Attrition Rates—Where Are We Going Wrong?*, 8 NATURE REV. CLINICAL ONCOLOGY 189, 189 (2011); see also Ismail Kola & John Landis, *Can The Pharmaceutical Industry Reduce Attrition Rates?*, 3 NATURE REV. DRUG DISCOVERY 711, 712 (2004); Thomas G. Roberts Jr. et al., *Trends in the Risks and Benefits to Patients With Cancer Participating in Phase 1 Clinical Trials*, 292 JAMA 2130, 2130 (2004).

myelogenous leukemia patients,¹²¹ Dr. Klausner's conclusion is just as true fifteen years later.

Since President Richard Nixon signed the National Cancer Act in December 1971, stating the goal of curing cancer by the nation's bicentennial five years later, more than a quarter *trillion* dollars has been spent to investigate and develop treatments for cancers.¹²² Today, the annual budget of the U.S. National Cancer Institute exceeds five billion dollars,¹²³ and billions more are spent annually through other federal and state agencies, research facilities, private and charitable organizations, and pharmaceutical companies.

During the first two decades of Nixon's program (dubbed the "war on cancer"), U.S. age-adjusted cancer mortality *increased* by 8%—twice the increase that occurred in the previous two decades.¹²⁴ The administrator of the program, John C. Bailar III, M.D., reported in 1986 that "some 35 years of intense effort focused largely on improving treatment must be judged a qualified failure,"¹²⁵ a conclusion he repeated more than a decade later.¹²⁶ Recognizing the failed approach directed primarily toward animal research and drug development, Dr. Bailar noted that improvements in cancer mortality were attributable to prevention and early detection, and concluded: "The most promising approach to the control of cancer is a national commitment to prevention, with a concomitant rebalancing of the focus and funding of research."¹²⁷

Indeed, of the three determinants of cancer mortality—prevention, early detection, and treatment—cancer treatment has contributed least to improved outcomes.¹²⁸ Prevention efforts such as smoking cessation, dietary improvements, and physical activity have decreased the incidence of

121. See *infra* text accompanying notes 149–50.

122. See Clifton Leaf, *Why We're Losing The War On Cancer [And How to Win It]*, CNNMONEY, Mar. 22, 2004, http://money.cnn.com/magazines/fortune/fortune_archive/2004/03/22/365076/index.htm; Susan M. Gapstur & Michael J. Thun, *Progress in the War on Cancer*, 303 JAMA 1084, 1084 (2010).

123. *NCI Budget Information*, NAT'L CANCER INST., <http://www.cancer.gov/aboutnci/servingpeople/nci-budget-information> (last updated Nov. 1, 2011).

124. David M. Cutler, *Are We Finally Winning the War on Cancer?*, 22 J. ECON. PERSP. 3, 3 (2008).

125. John C. Bailar III & Elaine M. Smith, *Progress Against Cancer?*, 314 NEW ENG. J. MED. 1226, 1231 (1986).

126. See John C. Bailar III & Heather L. Gornik, *Cancer Undeclared*, 336 NEW ENG. J. MED. 1569, 1573 (1997).

127. *Id.* at 1569.

128. See Cutler, *supra* note 124, at 4; Bailar III & Smith, *supra* note 125, at 1231; Bailar III & Gornik, *supra* note 126, at 1573.

new cancer diagnoses for both men and women.¹²⁹ Screening for breast,¹³⁰ cervical,¹³¹ and colorectal¹³² cancers has contributed to better patient outcomes with early intervention. Other than for those fortunate patients for whom cancer is localized and initial treatment is curative, however, treatments for established cancers have seldom led to significant improvements in survival, and only rarely to cures.

Though overall U.S. cancer death rates are only about 5% lower in the last six decades,¹³³ there has been a 20% decline in age-adjusted cancer mortality since the peak mortality year of 1991, predominantly due to prevention and screening efforts.¹³⁴ And with few exceptions—such as some childhood cancers, testicular cancer, and Hodgkin disease—metastatic cancer may be slowed but remains incurable, even with the advent of the latest generation of targeted cancer drugs.¹³⁵

Standard xenograft models of human cancers, in which human cancer cells are transplanted beneath the skin of rodents, have been reported to have “few predictive achievements and many notable failures,” and it is acknowledged that “many agents that show consistent and potent anticancer activity in specific xenograft models prove to be of limited use in the therapy of human cancer.”¹³⁶ These and other animal models of cancer have also fared poorly when compared to research using human cancer cell lines. A National Cancer Institute of Canada study of thirty-one cancer drugs found that human cancer cell lines were superior to the two most prominent

129. See Christie Ehemann et al., *Annual Report to the Nation on the Status of Cancer, 1975–2008, Featuring Cancers Associated with Excess Weight and Lack of Sufficient Physical Activity*, 118 *CANCER* 2338, 2362 (2012); see also *Reduce Your Cancer Risk*, AM. INST. FOR CANCER RES. (Feb. 20, 2013), <http://www.aicr.org/reduce-your-cancer-risk>.

130. U.S. Preventive Servs. Task Force, *Screening for Breast Cancer: U.S. Preventive Services Task Force Recommendation Statement*, 151 *ANNALS INTERNAL MED.* 716, 716–17 (2009); Ellen Warner, *Breast-Cancer Screening*, 365 *NEW ENG. J. MED.* 1025, 1025 (2011).

131. See Virginia A. Moyer, U.S. Preventive Servs. Task Force, *Screening for Cervical Cancer: U.S. Preventive Services Task Force Recommendation Statement*, 156 *ANNALS INTERNAL MED.* 880, 881 (2012).

132. See Evelyn P. Whitlock et al., *Screening for Colorectal Cancer: A Targeted, Updated Systematic Review for the U.S. Preventive Services Task Force*, 149 *ANNALS INTERNAL MED.* 638, 638 (2008); Amir Qaseem et al., *Screening for Colorectal Cancer: A Guidance Statement from the American College of Physicians*, 156 *ANNALS INTERNAL MED.* 378, 378 (2012).

133. Gina Kolata, *As Other Death Rates Fall, Cancer’s Scarcely Moves*, *N.Y. TIMES*, Apr. 24, 2009, <http://www.nytimes.com/2009/04/24/health/research/24cancerside.html>.

134. Rebecca Siegel et al., *Cancer Statistics, 2013*, 63 *CA: CANCER J. FOR CLINICIANS* 11, 11 (2013); Cutler, *supra* note 124, at 4.

135. See Editorial, *The End of the Beginning?*, 5 *NATURE REV. DRUG DISCOVERY* 705 (2006).

136. Norman E. Sharpless & Ronald A. DePinho, *The Mighty Mouse: Genetically Engineered Mouse Models in Cancer Drug Development*, 5 *NATURE REV. DRUG DISCOVERY* 741, 741–43 (2006).

mouse models for predicting drug efficacy in clinical trials,¹³⁷ and the standard mouse models have been widely discredited as a means for studying and treating human cancers.¹³⁸ The U.S. National Cancer Institute recognized this problem more than thirty years ago and developed the DTP Human Tumor Cell Line Screen, a panel of sixty human tumor cell lines, to replace unreliable animal testing for identification of drugs with anti-tumor effects.¹³⁹

In addition to displaying poor translation to human medicine, animal research regarding cancer has not even been reproducible, thus unmasking the unreliability of the laboratory research and its inapplicability to the care of cancer patients. Begley and Ellis reported that only six of fifty-three selected landmark preclinical cancer studies could be duplicated by Amgen scientists.¹⁴⁰ Asadullah and colleagues reported that fewer than one-fourth of forty-seven early-stage cancer projects at Bayer HealthCare were reproducible, and that nearly two-thirds of those projects were either scrapped or markedly delayed when the preclinical research could not be validated.¹⁴¹ Some of this irreproducible research had stimulated numerous secondary publications that built on the false results. Alarming, related clinical studies subjected cancer patients to treatments that had little chance to succeed.¹⁴² And while targeted cancer treatments had unpredictable and erratic results, simply changing housing conditions for mice reportedly reduced the sizes of melanomas and colon cancers by as much as three-fourths.¹⁴³

Many reasons other than poor reproducibility have been documented for the failure of the animal research paradigm for the study of human

137. Theodora Voskoglou-Nomikos et al., *Clinical Predictive Value of the in Vitro Cell Line, Human Xenograft, and Mouse Allograft Preclinical Cancer Models*, 9 CLINICAL CANCER RES. 4227, 4227, 4229, 4237 (2003).

138. Ken Garber, *Realistic Rodents? Debate Grows Over New Mouse Models of Cancer*, 98 J. NAT'L CANCER INST. 1176, 1176 (2006); *The End of the Beginning?*, *supra* note 135, at 705; Edward A. Sausville & Angelika M. Burger, *Contributions of Human Tumor Xenografts to Anticancer Drug Development*, 66 CANCER RES. 3351, 3351 (2006); Voskoglou-Nomikos et al., *supra* note 137, at 4227, 4232.

139. See Robert H. Shoemaker, *The NCI60 Human Tumour Cell Line Anticancer Drug Screen*, 6 NATURE REV. CANCER 813, 813 (2006); see also *NCI-60 DTP Human Tumor Cell Line Screen*, SCREENING SERVICES, <http://dtp.nci.nih.gov/branches/btb/ivclsp.html> (last visited Feb. 24, 2013).

140. C. Glenn Begley & Lee M. Ellis, *Raise Standards for Preclinical Cancer Research*, 483 NATURE 531, 532 (2012).

141. See Florian Prinz et al., *Believe It or Not: How Much Can We Rely on Published Data on Potential Drug Targets?*, NATURE REV.: DRUG DISCOVERY (Sept. 2011), <http://www.nature.com/nrd/journal/v10/n9/full/nrd3439-c1.html>.

142. Begley & Ellis, *supra* note 140, at 532.

143. See Lei Cao et al., *Environmental and Genetic Activation of a Brain-Adipocyte BDNF/Leptin Axis Causes Cancer Remission and Inhibition*, 142 CELL 52, 52, 62 (2010).

cancers. No animal models replicate the tumors that are grafted onto them in terms of tumor architecture, growth rate, metastatic potential, interaction with nonhuman tissue elements, or response to drugs.¹⁴⁴ Because rodent models are intentionally immune-deficient to permit unregulated tumor growth, they present an unrealistic biological milieu and are unable to replicate the behaviors of tumors in a patient or the combined effects of the human immune system and cancer drugs. And though scientists and physicians have long known that 90% of cancer deaths are due to metastatic tumor spread,¹⁴⁵ the mechanisms and treatments of metastatic cancer are rarely addressed in animal models due to the complexity involved.

Many human tumor cell lines used in animal studies are inadequately characterized or internally inconsistent, thus introducing irreproducibility even before animal studies are conducted.¹⁴⁶ And the functions of human cancer-promoting or cancer-suppressing genes transferred into animals are often different in direction and magnitude from their human hosts. Chemicals that cause cancers in animals seldom do so in humans. For example, in a recent study using rodents, of the thirty-eight chemicals that caused pancreatic cancer and thirty-nine chemicals that caused colorectal cancer in the rodents, none caused cancer in humans.¹⁴⁷ And a protein that *triggers* colorectal cancers in animal models was found to *suppress* cancer growth in humans.¹⁴⁸ The implication of this finding is frightening, because clinical trials of drugs that deactivate production of this protein would likely stimulate rather than suppress cancer growth, possibly killing patients rather than helping them.

Let's look back at a success story from cancer research mentioned above—the development and testing of Gleevec (imatinib). Gleevec was developed directly from identification and targeting of a specific genetic mutation that occurs in 95% of chronic myelogenous leukemia patients, designated the Philadelphia chromosome. But studies of the drug in mice, rats, rabbits, dogs, and monkeys detected serious adverse effects, and in particular, severe liver damage in dogs appeared to preclude clinical trials in

144. Hutchinson & Kirk, *supra* note 120, at 189.

145. See Anne Trafton, *How Cancer Cells Break Free from Tumors*, MITNEWS (Oct. 9, 2012), <http://web.mit.edu/newsoffice/2012/how-cancer-cells-break-free-from-tumors-1009.html>.

146. Begley & Ellis, *supra* note 140, at 532.

147. See Jeffrey W. Card et al., *Lack of Human Tissue-Specific Correlations for Rodent Pancreatic and Colorectal Carcinogens*, 64 REG. TOXICOLOGY & PHARMACOLOGY 442, 455–56 (2012).

148. Wei Tang et al., *A Genome-Wide RNAi Screen for Wnt/ β -Catenin Pathway Components Identifies Unexpected Roles for TCF Transcription Factors in Cancer*, 105 PROC. NAT'L ACAD. SCI. 9697, 9697, 9701 (2008).

humans.¹⁴⁹ However, the Novartis research team also conducted studies of the drug in human cell assays and did not identify liver toxicity. Early clinical trials confirmed the absence of significant liver toxicity, and also revealed the pronounced favorable responses of patients to Gleevec, leading to the drug's 2001 FDA approval to treat chronic myelogenous leukemia.¹⁵⁰ Far from being a success of animal research, Gleevec is a success of rational drug design and human-based drug testing—a life-prolonging success that would have been lost if the results of animal research had prevailed.

But Gleevec is an anomaly, and even other drugs in the same class have failed to prolong survival in various types of cancer. More typical results are the barren twenty-seven years of animal-tested drugs for small-cell lung cancer in more than 10,000 patients,¹⁵¹ the consistent failures of therapeutic vaccines for melanoma and other cancers,¹⁵² and the persistent failure to cure metastatic cancers. Also more representative of the poor outcomes for cancer therapies is a 2008 review of 624 cancer drugs that progressed to the final (phase III) stage of testing.¹⁵³ This review revealed that between 50% and 75% of the drugs fail even at this final stage.¹⁵⁴ And the true failure rate is likely even higher because the review excluded all uncompleted trials and most unreported trials,¹⁵⁵ two additional categories with especially high drug failure rates.

A discouraging and perhaps predictable result of the cancer clinical trial wasteland and its animal research underpinnings is the FDA's low bar for approval of new cancer drugs. Many, if not most, approvals are for drugs that only impede cancer progression by a few months or a few weeks, may or may not prolong survival, do not cure anyone, commonly cause serious or even lethal adverse effects, and often provide poor quality of life

149. *Application Number: NDA 21-335 Pharmacology/Tox Review(s)*, CENTER FOR DRUG EVALUATION & RES. (May 7, 2001), http://www.accessdata.fda.gov/drugsatfda_docs/nda/2001/21-335_Gleevec_pharmr_P1.pdf.

150. *See id.*; *see also* Elisabeth Buchdunger & Juerg Zimmerman, *The Story of Gleevec*, http://www.innovation.org/index.cfm/StoriesofInnovation/InnovatorStories/The_Story_of_Gleevec (last visited Apr. 8, 2013).

151. Isao Oze et al., *Twenty-Seven Years of Phase III Trials for Patients with Extensive Disease Small-Cell Lung Cancer: Disappointing Results*, 4 PLOS ONE, e7835, Nov. 2009, at 1, <http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0007835>.

152. Steven A. Rosenberg et al., *Cancer Immunotherapy: Moving Beyond Current Vaccines*, 10 NATURE MED. 909, 913 (2004).

153. *See generally* Benjamin Djulbegovic et al., *Treatment Success in Cancer: New Cancer Treatment Successes Identified in Phase 3 Randomized Controlled Trials Conducted by the National Cancer Institute—Sponsored Cooperative Oncology Groups, 1955 to 2006*, 168 ARCHIVES INTERNAL MED. 632, 632–633 (2008).

154. *See id.* at 641.

155. *See id.* at 632.

at great expense.¹⁵⁶ Tarceva was approved in 2005 to treat pancreatic cancer after a clinical trial claiming to improve median survival by only ten days.¹⁵⁷ Vectibix was approved in 2006 to treat colorectal cancer after a clinical trial that showed a delay of just five days in cancer progression and no prolonged survival.¹⁵⁸ Avastin was approved in 2006 to treat a subgroup of patients with non-small cell lung cancer after showing a survival advantage of two months, and only for men.¹⁵⁹ A later study of Avastin in the same cancer type showed prolonged time to cancer progression of only twelve to eighteen days for the two doses tested.¹⁶⁰ The important difference between a statistical endpoint and meaningful impact on quality of life and survival is now at the forefront, and recommendations include targeting clinical trials toward life-related outcomes. In their review of eighteen clinical trials of FDA-approved cancer drugs since 2000, Ocana and Tannock found that most trials reported minimal advantages in either progression-free interval or overall survival, and none showed as much as five months improved survival.¹⁶¹

These and many other cancer drug outcome measures are statistically and objectively dubious, clinically irrelevant, and probably irreproducible—as suggested by the subsequent withdrawal of numerous cancer drugs after post-marketing study data showed that the original clinical trials were wrong and the drugs were not effective after all. Mylotarg was withdrawn for acute myelogenous leukemia treatment in 2010 after a decade on the market.¹⁶² Avastin was withdrawn for breast cancer treatment in 2011 after

156. See, e.g., Hannah Hoag, *Cancer Drugs Should Add Months, Not Weeks, Say Experts*, 17 NATURE MED. 7 (2011); Tito Fojo & Christine Grady, *How Much is Life Worth: Cetuximab, Non-Small Cell Lung Cancer, and the \$440 Billion Question*, 101 J. NAT. CANCER INST. 1044, 1044–45 (2009); Martin H. Cohen et al., *FDA Drug Approval Summary: Bevacizumab (Avastin) Plus Carboplatin and Paclitaxel as First-Line Treatment of Advanced/Metastatic Recurrent Nonsquamous Non-Small Cell Lung Cancer*, 12 ONCOLOGIST 713, 717 (2007); Alberto Ocana & Ian F. Tannock, *When Are “Positive” Clinical Trials in Oncology Truly Positive?*, 103 J. NAT’L CANCER INST. 16, 16–20 (2011).

157. See Malcolm J. Moore et al., *Erlotinib Plus Gemcitabine Compared with Gemcitabine Alone in Patients with Advanced Pancreatic Cancer: A Phase III Trial of the National Cancer Institute of Canada Clinical Trials Group*, 25 J. CLINICAL ONCOLOGY 1960, 1962 (2007).

158. Eric Van Cutsem et al., *Open-Label Phase III Trial of Panitumumab Plus Best Supportive Care Compared with Best Supportive Care Alone in Patients with Chemotherapy-Refractory Metastatic Colorectal Cancer*, 25 J. CLINICAL ONCOLOGY 1658, 1660–61 (2007).

159. See Cohen et al., *supra* note 156, at 716.

160. Martin Reck et al., *Phase III Trial of Cisplatin Plus Gemcitabine with Either Placebo or Bevacizumab as First-Line Therapy for Nonsquamous Non-Small-Cell Lung Cancer: AVAiL*, 27 J. CLINICAL ONCOLOGY 1227, 1227 (2009).

161. See Ocana & Tannock, *supra* note 156.

162. *Gemtuzumab Ozogamicin Voluntarily Withdrawn from U.S. Markets*, NAT’L CANCER INST. (June 24, 2010), <http://www.cancer.gov/cancertopics/druginfo/fda-gemtuzumab-ozogamicin>.

nearly four years on the market.¹⁶³ Iressa was withdrawn for lung cancer treatment in 2012 after nine years on the market.¹⁶⁴ And the FDA estimates that when post-marketing studies are performed (this occurs in a minority of approved drugs), more than 10% of cancer drugs are not confirmed to be effective¹⁶⁵—often several years and sometimes more than a decade after original approval, and after unsuccessful use in many thousands of cancer patients.

In 1999, cancer supplanted heart disease as the leading cause of death among Americans younger than eighty-five years,¹⁶⁶ which is 98% of the U.S. population. By 2008, cancer became the leading cause of death worldwide.¹⁶⁷ The use of animals to study and develop treatments for cancer has consumed enormous resources and several decades without substantially advancing the control and cure of cancer. It frequently happens that cancer researchers gain sterling reputations, career success, and millions of dollars in research funding without helping even one cancer patient gain even one extra day of life. Such is the disconnection between the results of basic science and the needs of human medicine.

This failed animal research paradigm for cancer is openly acknowledged by some cancer researchers. Carlo Maley, Ph.D. of the University of California-San Francisco stated, “We’ve been banging our heads against this cure thing for three, four decades now and really made almost zero progress.”¹⁶⁸ And Bert Vogelstein, M.D., director of the Ludwig Center for Cancer Genetics and Therapeutics at Johns Hopkins University School of Medicine, adds perspective: “Unfortunately our track record shows that far less than 1 percent of our promising approaches actually make the grade in patients.”¹⁶⁹ More than forty years into the war on cancer, that war is still being lost in animal research laboratories.

163. *FDA Commissioner Announces Avastin Decision*, U.S. FOOD & DRUG ADMIN. (Nov. 18, 2011), <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm280536.htm>.

164. AstraZeneca Pharmaceuticals LP; Withdrawal of Approval of a New Drug Application for IRESSA, 77 Fed. Reg. 24,723, 24,723 (Apr. 25, 2012).

165. Peggy Eastman, *ODAC Backs FDA’s Strong Stance on Need for Post-Marketing Studies on Accelerated-Approval Cancer Drugs*, 33 ONCOLOGY TIMES 8, 9 (2011).

166. Ahmedin Jemal et al., *Cancer Statistics, 2005*, 55 CA: CANCER J. FOR CLINICIANS 10 (2005).

167. *Cancer*, WORLD HEALTH ORG. (Jan. 2013), <http://www.who.int/mediacentre/factsheets/fs297/en>.

168. Nadia Drake, *Forty Years on from Nixon’s War, Cancer Research “Evolves,”* 17 NATURE MED. 757, 757 (2011).

169. Nicholas Wade, *New Cancer Treatment Shows Promise in Testing*, N.Y. TIMES, June 28, 2009, <http://www.nytimes.com/2009/06/29/health/research/29drug.html>.

IV. ANIMAL USE IN DRUG DEVELOPMENT AND TESTING

For seventy-five years, the default preclinical testing methods for the efficacy and safety of drugs have relied heavily on the use of animals. Historically based on regulatory responses to two tragic drug-related events, the animal-testing paradigm has nonetheless never been validated to predict or correlate with human outcomes. Former FDA pharmacology and toxicology reviewer Anita O'Connor stated in 1998: "Most of the animal tests we accept have never been validated. They evolved over the past 20 years and the FDA is comfortable with them."¹⁷⁰ The deaths of more than 100 persons—many of them children—from taking sulfanilimide elixir in 1937 led to the Federal Food, Drug, and Cosmetic Act of 1938, which among other measures mandated that drugs be shown to be safe before use in humans.¹⁷¹ The thalidomide disaster in the late 1950s and early 1960s caused more than 10,000 cases of severe birth deformities in forty-six countries, including seventeen thalidomide-related birth defects in the U.S.¹⁷² This disaster led to passage of the 1962 Kefauver-Harris Amendments to the Federal Food, Drug, and Cosmetic Act of 1938, which required FDA approval of all drugs before marketing in the U.S., and subsequent FDA regulatory measures established animal experiments as the default method for gaining FDA approval for clinical trials.¹⁷³

After animal testing identifies an apparently safe and effective drug candidate, and after the FDA approves an Investigational New Drug application, the drug is tested in a series of clinical trials:

- ◆ *Phase I*: Small trials typically enrolling about ten to 100 healthy volunteers, and designed to assess drug safety and metabolism at various doses. If the drug displays no serious adverse effects, it will usually advance to the next clinical trial phase.
- ◆ *Phase II*: Larger trials typically enrolling a few hundred patients with the target disease, usually employing a randomized design comparing the drug to placebo or to a comparator drug, and

170. Andre Menache, *Non-Animal Methods of Research—Who Is Responsible for Holding Back Progress?*, HUMANE RES. AUSTL. (Sept. 2006), <http://www.humaneresearch.org.au/LiteratureRetrieve.aspx?ID=46580>.

171. Carol Ballentine, *Sulfanilamide Disaster*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/AboutFDA/WhatWeDo/History/ProductRegulation/SulfanilamideDisaster> (last updated Oct. 7, 2010).

172. Linda Bren, *Frances Oldham Kelsey: FDA Medical Reviewer Leaves Her Mark on History*, U.S. FOOD & DRUG ADMIN., http://permanent.access.gpo.gov/lps1609/www.fda.gov/fdac/features/2001/201_kelsey.html (last visited Apr. 9, 2013).

173. Pat Clarke, *50 Years Ago: How an FDA Reviewer Saved Lives and Spurred Legislation*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/Drugs/NewsEvents/ucm320924.htm> (last updated Dec. 11, 2012).

designed to determine if the drug is effective and safe as it is likely to be used in clinical medicine. If this “proof of concept” is successful, the drug will usually advance to the next clinical trial phase.

- ◆ *Phase III*: Large final-stage trials before applying for FDA marketing approval, typically enrolling several hundred to several thousand patients with the target disease and employing a randomized design comparing the drug to placebo or to a comparator drug. More detailed information is obtained about drug toxicity.

Drug testing using animals has proven to be very poor for predicting efficacy and toxicities in humans as determined in the subsequent clinical trials. The FDA has reported that the failure rate of drugs tested safe and effective in preclinical studies (including animal tests) is 92%,¹⁷⁴ and current data confirm this very high drug attrition rate. Analyses of drug failure rates from 2007 to 2010 by Thomson Reuters Life Science Consulting demonstrate that in recent years, the phase II failure rate has increased from 72% to 82%,¹⁷⁵ and the phase III failure rate has increased to 50%.¹⁷⁶ The worsening phase III failure rate has been attributed to the commercially hopeful but scientifically unwise advancement of drugs that show marginal, if any, benefits during phase II trials,¹⁷⁷ and the conclusion is that the 82% phase II failure rate should be even higher. The resulting failure of all but a small percentage of drugs during phase II trials would be a further serious indictment of the animal modeling paradigm because phase II trials are designed to offer proof of the efficacy and safety findings arising primarily from animal studies.

The cumulative clinical trial failure rate was 86% in 1985, increased to 92% by 2003,¹⁷⁸ and continues to increase today,¹⁷⁹ despite all efforts to

174. See Ashish Singh & Preston Henske, *Has the Pharmaceutical Blockbuster Model Gone Bust?*, BAIN & CO. (Dec. 8, 2003), <http://www.bain.com/about/press/press-releases/has-the-pharmaceutical-blockbuster-model-gone-bust.aspx>; see also U.S. DEPT. OF HEALTH & HUMAN SERVS., FOOD & DRUG ADMIN., CHALLENGE AND OPPORTUNITY ON THE CRITICAL PATH TO NEW MEDICAL PRODUCTS 8 (2004) [hereinafter CHALLENGE AND OPPORTUNITY], available at <http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/CriticalPathInitiative/CriticalPathOpportunitiesReports/ucm113411.pdf>.

175. See John Arrowsmith, *Phase II Failures: 2008–2010*, 10 NATURE REV. DRUG DISCOVERY 328, 328 (May 2011).

176. John Arrowsmith, *Phase III and Submission Failures: 2007-2010*, 10 NATURE REV. DRUG DISCOVERY 87, 87 (Feb. 2011).

177. See *id.*; see also Tamara Elias et al., *Why Products Fail in Phase III*, IN VIVO 1, 5 (2006).

178. See Singh & Henske, *supra* note 174; see also CHALLENGE AND OPPORTUNITY, *supra* note 174, at 8; Mike Mitka, *Guidelines Aim to Speed Drug Approval While Protecting Human Subjects*, 295 JAMA 988, 988 (2006).

improve the predictability of animal testing. Professor Robin Lovell-Badge of the MRC National Institute for Medical Research, London, calculates the current clinical trials failure rate to be 94%.¹⁸⁰ Recently reported phase-specific data may be even more damning, showing up to a 56% failure rate for phase I,¹⁸¹ 82% for phase II,¹⁸² and 50% for phase III¹⁸³—a cumulative 96% failure rate.

This pattern of worsening drug candidate attrition is stark evidence that efforts over the past quarter century to improve identification and development of drugs using animal models of human diseases have failed. And why do these drugs fail when tested in humans? Half fail because they simply do not work—efficacy testing in animals was wrong.¹⁸⁴ Another 30% fail because they are unsafe—safety testing in animals was wrong.¹⁸⁵ And 20% fail because they are no better or safer than other available drugs.¹⁸⁶

Additionally, about half of those few drugs that succeed in clinical trials and receive FDA marketing approval are later relabeled or withdrawn for serious or lethal adverse effects not detected during animal testing.¹⁸⁷ Further, more than 90% of approved drugs work for fewer than half of patients, and response rates (not cures) are as low as 25 to 30% for oncology and neurology drugs.¹⁸⁸

The FDA classifies at least three-fourths of approved drugs as category S drugs that provide “little or no therapeutic gain” compared to currently available drugs (commonly referred to as “me too” drugs).¹⁸⁹ The

179. See Robin Lovell-Badge, *Nine Out of Ten Statistics Are Taken Out of Context*, UNDERSTANDING ANIMAL RES. (Jan. 23, 2013), <http://www.understandinganimalresearch.org.uk/news/2013/01/nine-out-of-ten-statistics-are-taken-out-of-context>; see also Arrowsmith, *supra* note 175, at 328; Arrowsmith, *supra* note 176, at 87; Bernard H. Munos & William W. Chin, *How to Revive Breakthrough Innovation in the Pharmaceutical Industry*, 3 SCI. TRANSLATIONAL MED. 1, 2 (June 29, 2011).

180. Lovell-Badge, *supra* note 179.

181. *Id.*

182. See Arrowsmith, *supra* note 175, at 328.

183. Arrowsmith, *supra* note 176, at 87; Heidi Ledford, *4 Ways to Fix the Clinical Trial*, 477 NATURE 526, 526 (2011).

184. Elias et al., *supra* note 177, at 1.

185. *Id.* at 1–2.

186. *Id.* at 2; see also Arrowsmith, *supra* note 176, at 87.

187. U.S. GEN. ACCOUNTING OFFICE, FDA DRUG REVIEW: POSTAPPROVAL RISKS 1976-85 24 (1990), available at <http://161.203.16.4/d24t8/141456.pdf>.

188. Steve Connor, *Glaxo Chief: Our Drugs Do Not Work on Most Patients*, COMMON DREAMS (Dec. 8, 2003), <http://www.commondreams.org/headlines03/1208-02.htm>; see also Brian B. Spear et al., *Clinical Application of Pharmacogenetics*, 7 TRENDS IN MOLECULAR MED. 201, 201–02 (2001).

189. See FOOD & DRUG ADMIN., CDER APPROVAL TIMES FOR PRIORITY AND STANDARD NDAS AND BLAS: CALENDAR YEARS 1993–2008, available at <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedand>

percentage of new drugs that are better or safer than available drugs has been reported elsewhere to be even lower, ranging from just 14%¹⁹⁰ to as low as 11%.¹⁹¹ The lower figure is confirmed in an often-cited pharmaceutical industry report of all internationally marketed drugs over a two-decade period.¹⁹²

Thus, it takes on average more than 100 drugs that are safe and effective in preclinical testing (including animal testing) to produce just one unique, effective, and safe drug for humans, which then works only in a minority of patients and is not curative for most disease categories. Nor is animal drug safety testing reliable when viewed retrospectively. A recent study found that only 19% of ninety-three serious adverse drug reactions in patients were seen in preclinical animal studies.¹⁹³

There could hardly be stronger cumulative evidence that animal use for drug testing is extremely unreliable and does not contribute to drug efficacy or safety. And the consequences of this translation failure are much worse than just the costs in time and money, because the current animal-based drug testing approach contributes to the approval and widespread use of dangerous drugs. The arthritis drug Vioxx (rofecoxib) was safe in at least eight studies in African green monkeys and five other animal species, but resulted in an estimated 140,000 heart attacks and 60,000 deaths in the U.S.—more American deaths than the Vietnam War.¹⁹⁴ The diabetes drug Avandia (rosiglitazone) was safe in mice, rats, dogs, and monkeys but was reported to increase risks for heart attacks, strokes, heart failure, and

Approved/DrugandBiologicApprovalReports/UCM123957.pdf (stating that the total number of new drug approvals from 2000–2008 was 780, of which 612 (78%) were category S drugs); see also *Proposed New Drug, Antibiotic, and Biologic Drug Product Regulations*, U.S. FOOD & DRUG ADMIN. (June 9, 1983), <http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm119443.htm> (commenting on the effectiveness of Type IC drugs, now known as category S).

190. *A Look Back at Pharmaceuticals in 2006: Aggressive Advertising Cannot Hide the Absence of Therapeutic Advances*, 16 *PRESCRIBER INT'L*, 80, 84 (2007).

191. See JOHN ABRAHAM, *SCIENCE, POLITICS AND THE PHARMACEUTICAL INDUSTRY: CONTROVERSY AND BIAS IN DRUG REGULATION* 243 (1995).

192. See Donald W. Light & Joel Lexchin, *Will Lower Drug Prices Jeopardize Drug Research? A Policy Fact Sheet*, 4 *AM. J. BIOETHICS*, no. 1, 2004 at W1, W2 (citing P.E. BARRAL, 20 YEARS OF PHARMACEUTICAL RESEARCH RESULTS THROUGHOUT THE WORLD: 1975–1994 (Paris, Rhone-Poulenc Rorer Found. 1996)).

193. Peter J.K. van Meer et al., *The Ability of Animal Studies to Detect Serious Post Marketing Adverse Events Is Limited*, 64 *REG. TOXICOLOGY & PHARMACOLOGY* 345, 345 (2012).

194. See Manette Loudon, *The FDA Exposed: An Interview with Dr. David Graham, the Vioxx Whistleblower*, *NATURALNEWS.COM* (Aug. 30, 2005), http://www.naturalnews.com/011401_Dr_David_Graham_the_FDA.html; David J. Graham et al., *Risk of Acute Myocardial Infarction and Sudden Cardiac Death in Patients Treated with Cyclo-Oxygenase 2 Selective and Non-Selective Non-Steroidal Anti-Inflammatory Drugs: Nested Case-Control Study*, 365 *LANCET* 475, 475 (2005); Eric J. Topol, *Failing the Public Health—Rofecoxib, Merck, and the FDA*, 351 *NEW ENG. J. MED.* 1707, 1707–08 (2004).

cardiovascular deaths compared to placebo or other diabetes drugs.¹⁹⁵ Perhaps as many as 100,000 such events are attributable to Avandia.¹⁹⁶

Very instructive is the case of the monoclonal antibody TGN1412, developed to treat B-cell chronic lymphocytic leukemia and arthritis. TGN1412 was tested successfully for safety and efficacy in mice, rats, rabbits, and two species of monkeys.¹⁹⁷ Yet TGN1412 caused rapid critical immune system activation in all six young men who received the drug in the first stage of clinical testing at London's Northwick Park Hospital in 2006. This "cytokine storm" was nearly lethal for these healthy volunteers, causing multiple organ failure for all six victims and leading to amputations of toes and fingertips for one participant.¹⁹⁸ Even though monkey and human TGN1412 binding sites and cellular mechanisms were identical, the hyperactivation of the participants' immune systems was the opposite of the immune suppression response in monkeys at up to 500 times the dosage tested in the volunteers.¹⁹⁹ It is difficult to construct a more definitive animal-based prediction of human response and safety, yet all six men have permanent immune system and organ damage.

In the same way that ineffective and dangerous drugs can be approved based on erroneous animal research, useful drugs can also fail animal testing for the same reason. A sterling example is aspirin, which was patented for human use in 1900, decades before animal testing was employed for drugs. When aspirin was later tested for teratogenicity (birth defect causation), it was found to produce birth defects in all eight species tested—mice, rats, guinea pigs, rabbits, cats, dogs, sheep, and monkeys.²⁰⁰

195. See generally Steven E. Nissen & Kathy Wolski, *Rosiglitazone Revisited: An Updated Meta-Analysis of Risk for Myocardial Infarction and Cardiovascular Mortality*, 170 ARCHIVES INTERNAL MED. 1191, 1192, 1198–99 (2010); Steven E. Nissen & Kathy Wolski, *Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes*, 356 NEW ENG. J. MED. 2457, 2459, 2467 (2007); Clifford J. Rosen, *Revisiting the Rosiglitazone Story: Lessons Learned*, 363 NEW ENG. J. MED. 803, 803–04 (2010); David J. Graham et al., *Risk of Acute Myocardial Infarction, Stroke, Heart Failure, and Death in Elderly Medicare Patients Treated with Rosiglitazone or Pioglitazone*, 304 JAMA 411, 411, 414, 416–17 (2010); David N. Juurlink, *Rosiglitazone and the Case for Safety Over Certainty*, 304 JAMA 469, 469 (2010).

196. Richard Knox, *Diabetes Drug Poses Safety Test for FDA*, NAT. PUB. RADIO (June 29, 2010), <http://www.npr.org/templates/story/story.php?storyId=128174678>.

197. E. William St. Clair, *The Calm After the Cytokine Storm: Lessons from the TGN1412 Trial*, 118 J. CLINICAL INVESTIGATION 1344, 1346 (2008).

198. *Id.* at 1345.

199. See Thomas Hanke, *Lessons from TGN1412*, 368 LANCET 1569, 1569 (2006); M.J.H. Kenter & A.F. Cohen, *Establishing Risk of Human Experimentation with Drugs: Lessons from TGN1412*, 368 LANCET 1387, 1387–89 (2006).

200. See, e.g., RONALD D. MANN, MODERN DRUG USE: AN ENQUIRY ON HISTORICAL PRINCIPLES 610–11 (1984); Phil Young, *Aspirin and Non-Steroidal Anti-Inflammatory Agents: Pregnancy*, IPCS INCHEM, <http://www.inchem.org/documents/ukpids/ukpids/ukpid03.htm> (last updated Jan. 1997); Richard T. Robertson et al., *Aspirin: Teratogenic Evaluation in the Dog*, 20

However, aspirin is safe for women during all stages of pregnancy. Similarly, penicillin launched the hugely important antibiotic era in the 1940s and saved countless lives, despite causing birth defects in rats,²⁰¹ and killing guinea pigs²⁰² and hamsters.²⁰³

The dramatic clinical failures of drugs such as Vioxx and TGN1412, and the falsely alarming animal testing results for drugs such as aspirin and penicillin, demonstrate that no level of certainty from animal testing can reliably predict drug effects in humans. It is just this immutable barrier that led British immunotherapeutics expert David Glover to state: “The relevance of animal testing, whether artificially created disease models or healthy animals for toxicology, has to be very seriously questioned for testing of human-specific biologic drugs,”²⁰⁴ and former Huntingdon Research Centre scientific director Ralph Heywood to conclude: “Toxicology . . . is a science without a scientific underpinning.”²⁰⁵

The reasons for the failed animal testing paradigm for drugs can be traced to the level of genes and gene regulation, but the practical manifestations are revealed at the level of interspecies pharmacology. The five fundamental elements in the science of drug testing are drug absorption, drug distribution in the body, drug metabolism by the liver and other organs, drug elimination from the body, and drug toxicity (collectively labeled ADMET). Some interspecies differences in toxicities have been noted in the foregoing paragraphs, but there are substantial and unresolvable differences between humans and other animals regarding each component of ADMET. One stark example of these differences is that the two human enzymes that metabolize more than 70% of marketed drugs

TERATOLOGY 313, 316 (1979); J.D. McColl, *Drug Toxicity in the Animal Fetus*, 9 APPLIED THERAPEUTICS 915, 916 (1967); Duane D. Sanders & Trent D. Stephens, *Review of Drug-Induced Limb Defects in Mammals*, 44 TERATOLOGY 335, 349 (1991); K.S. Khera, *Teratogenicity Studies with Methotrexate, Aminopterin, and Acetylsalicylic Acid in Domestic Cats*, 14 TERATOLOGY 21, 25 (1976); J.G. Wilson et al., *Comparative Distribution and Embryotoxicity of Acetylsalicylic Acid in Pregnant Rats and Rhesus Monkeys*, 41 TOXICOLOGY & APPLIED PHARMACOLOGY 67, 67 (1977).

201. Kaye H. Kilburn & Rex A. Hess, *Neonatal Deaths and Pulmonary Dysplasia Due to D-Penicillamine in the Rat*, 26 TERATOLOGY 1 (1982).

202. Dorothy M. Hamre et al., *The Toxicity of Penicillin as Prepared for Clinical Use*, 206 AM. J. MED. SCI. 642, 642 (1943).

203. S. Stanley Schneierson & Ely Perlman, *Toxicity of Penicillin for the Syrian Hamster*, 91 PROC. SOC'Y FOR EXPERIMENTAL BIOLOGY & MED. 229, 229 (1956).

204. Peter Mitchell, *Critics Pan Timid European Response to TeGenero Disaster*, 25 NATURE BIOTECHNOLOGY 485, 486 (2007).

205. Arthur Allen, *Of Mice or Men: The Problems with Animal Testing*, SLATE (June 1, 2006),

http://www.slate.com/articles/health_and_science/medical_examiner/2006/06/of_mice_or_men.html.

work very differently in mice, making mice unreliable for testing the safety and efficacy of these and similar drugs.²⁰⁶

Aspirin is again a representative example of the differences in each respective species' drug metabolism rates that invalidate translation of animal research findings to humans. Aspirin has a half-life in humans of fifteen to twenty minutes (which means that half the drug is eliminated from the circulation in that time period after ingestion), while the active metabolite of aspirin (salicylate) has a half-life of about three hours at standard doses, which extends to as long as thirty hours at high doses.²⁰⁷ The aspirin half-life for rats is only eight minutes,²⁰⁸ and for dogs and cats it is about eight hours and forty hours, respectively.²⁰⁹

Similarly, the metabolism and related effects of Valium (diazepam) are markedly different for humans and other animals. For example, diazepam half-life in humans is 43 ± 13 hours, which may be as long as 100 hours when active metabolites are considered,²¹⁰ and is prolonged by the minimal contribution of liver metabolism. In contrast, diazepam half-life is less than one hour in dogs, and liver metabolism is rapid and extensive.²¹¹ Treatment of refractory seizures in dogs may require very large doses of diazepam administered intravenously due to the rapid liver metabolism. The dose required to terminate refractory seizures in a large dog would be lethal for a human. Diazepam half-life is intermediate for cats (five and a half hours), but a single small dose can be lethal due to acute liver necrosis specific for cats.²¹²

So how do these examples compare to the larger picture of drug metabolism in humans and other animals? Interspecies differences in drug metabolism are ubiquitous and are extensively reviewed by Val Beasley,

206. Frank J. Gonzalez & Ai-Ming Yu, *Cytochrome P450 and Xenobiotic Receptor Humanized Mice* 5 (Apr. 17, 2006) (author manuscript), available at <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1440291/pdf/nihms9214.pdf>.

207. *Aspirin Tablets BP 300mg*, DRUGS.COM, <http://www.drugs.com/uk/aspirin-tablets-bp-300mg-spc-10476.html> (last updated June 10, 2010).

208. M. Guillaume Wientjes & Gerhard Levy, *Nonlinear Pharmacokinetics of Aspirin in Rats*, 245 J. PHARMACOLOGY & EXPERIMENTAL THERAPEUTICS 809, 809 (1988).

209. *Specific Nonsteroidal Anti-Inflammatory Drugs*, MERCK VETERINARY MANUAL, <http://www.merckvetmanual.com/mvm/index.jsp?cfile=htm/bc/191606.htm> (last updated Mar. 2012); Peter D. Hanson & Jill E. Maddison, *Nonsteroidal Anti-Inflammatory Drugs and Chondroprotective Agents*, in SMALL ANIMAL CLINICAL PHARMACOLOGY 287, 304 (Jill E. Maddison et al. eds., 2008).

210. *Diazepam*, NAT'L HIGHWAY TRAFFIC SAFETY ADMIN., <http://www.nhtsa.gov/people/injury/research/job185drugs/diazepam.htm> (last visited Mar. 22, 2013).

211. See Barbara Lynn Sherman & Mark G. Papich, *Drugs Affecting Animal Behavior*, in VETERINARY PHARMACOLOGY AND THERAPEUTICS 509, 519 (Mark G. Papich et al. eds., 9th ed. 2009).

212. *Id.*

D.V.M.,²¹³ and the absence of correlations is graphically depicted for rodents, dogs, nonhuman primates, and humans in Figure 1.²¹⁴

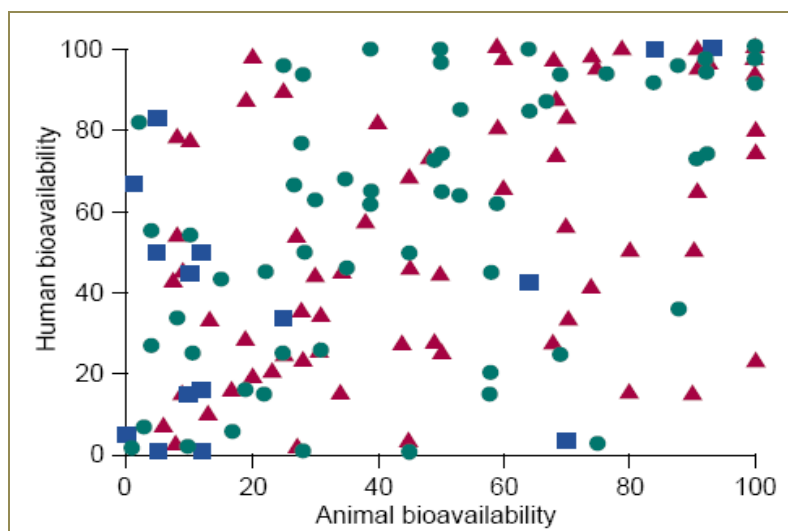


Figure 1: Absolute bioavailability of various drugs in dogs (triangles), primates (squares), and rodents (circles) versus the absolute bioavailability reported in humans. Three observations can be made: (i) there is no apparent relationship between animal bioavailability and human bioavailability; (ii) the number of false negatives is high; and (iii) the number of false positives is high.

Moreover, the FDA has acknowledged the inadequacy of animal testing for drug safety in its response to the Institute of Medicine report, *The Future of Drug Safety: Promoting and Protecting the Health of the Public*, stating: “The FDA is involved in an ongoing scientific collaboration intended to yield more sensitive, specific, and informative tests for drug organ toxicity than the toxicology screening techniques currently in use.”²¹⁵

213. V. Beasley, *Absorption, Distribution, Metabolism, and Elimination: Differences Among Species*, INT’L VETERINARY INFO. SERVICE (Aug. 9, 1999), www.ivis.org/advances/beasley/appc/ivis.pdf.

214. George M. Grass & Patrick J. Sinko, *Effect of Diverse Datasets on the Predictive Capability of ADME Models in Drug Discovery*, 6 DRUG DISCOVERY TODAY S54–S56 (2001).

215. U.S. DEP’T OF HEALTH & HUMAN SERVS., FOOD & DRUG ADMIN., *THE FUTURE OF DRUG SAFETY—PROMOTING AND PROTECTING THE HEALTH OF THE PUBLIC: FDA’S RESPONSE TO THE INSTITUTE OF MEDICINE’S 2006 REPORT 10* (2007), available at

But until the FDA eliminates the longstanding—but unvalidated—default status of animal testing for drugs, the pharmaceutical industry is poorly positioned to replace animal tests with human-based methods. As stated by a pharmaceutical company vice president of drug innovation: “[A]nimal models in these disease areas are not predictive, yet regulatory agencies require preclinical investigational new drug (IND) packages to contain *in vivo* animal efficacy and data based on nonpredictive or nonrelevant disease models.”²¹⁶

Unfortunately, the FDA appears to be ill-equipped to spearhead the transition from the discredited paradigm of animal testing for drugs to the human-based future of drug testing. A scathing report from its own science board criticized the inadequacy of the FDA’s science expertise for the task of leading and regulating the drug approval process, concluding: “Today, not only can the Agency not lead, it cannot even keep up with the advances in science.”²¹⁷

V. WHY ANIMAL RESEARCH IS A FAILED PARADIGM AND WHAT SHOULD BE DONE

The straightforward reason that the use of animals to study human diseases and develop drugs is unacceptable is because it has not worked in any predictable, reliable, reproducible, or translatable sense to advance human medicine and conquer human diseases. Some of the evidence for this claim is referenced in the above sections, and reviews of the outcomes of highly touted animal research findings are perhaps definitive on this issue. Contopoulos and colleagues reported the outcomes of 101 highly touted treatments that promised major clinical applications and were published in top basic science journals between 1979 and 1983.²¹⁸ These “best-of-the-best” treatments were reviewed two decades later, and the findings were both discouraging and revealing: only twenty-seven of the 101 treatments ever advanced to clinical trials, only five were approved for human use, and only one—a blood pressure drug—remains in regular use.

<http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM171627.pdf>.

216. Youssef L. Bennani, *Drug Discovery in the Next Decade: Innovation Needed ASAP*, 16 *DRUG DISCOVERY TODAY* 779, 784 (2011).

217. FDA SCIENCE BOARD, *FDA SCIENCE AND MISSION AT RISK: REPORT OF THE SUBCOMMITTEE ON SCIENCE AND TECHNOLOGY* 3 (2007), available at http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4329b_02_01_fda%20report%20on%20science%20and%20technology.pdf.

218. See Despina G. Contopoulos-Ioannidis et al., *Translation of Highly Promising Basic Science Research into Clinical Applications*, 114 *AM. J. MED.* 477, 477 (2003).

Lindl and colleagues reported the results of citations for published animal research results in Germany for a two-year period. Of ninety-seven such citations, only four made a direct correlation between the animal research results and the clinical findings, and in none of those four instances was the animal research result duplicated.²¹⁹ As also noted above, for the development of safe, effective, and unique drugs, the success rate for even the most promising animal-derived treatments is not more than 1%. This can be called good fortune for that 1%, but it cannot be called science.

Though most promising findings from animal research are not subjected to attempts at replication, those that are scrutinized are frequently markedly modified or even refuted, an outcome termed the Proteus phenomenon.²²⁰ Often, the initial promising results continually diminish and eventually disappear in later studies,²²¹ and the original research is discredited—in many instances only after the erroneous results have been implemented for patients. This is but one explanation for the growing consideration that most breakthrough published medical research is false.²²²

Decades ago, scientists' knowledge of comparative biology, physiology, and genetics was inadequate to understand that animals in laboratories are not convenient miniature versions of humans. With the advances achieved in the new millennium—and particularly due to the enormous growth of genetics knowledge resulting from the Human Genome Project and subsequent human and nonhuman animal genetic studies—we now know that the factors that preclude translation of animal research to human benefit reflect differential evolutionary influences. These differences exist at cellular, subcellular, molecular, and submolecular levels. We have learned that interspecies differences in the composition and regulation of genes are both explanatory and immutable regarding the failure of animal research to reliably inform human medicine.

This understanding also explains why the renaissance in medical science promised from the use of genetically modified (GM) animals—

219. Toni Lindl et al., *Tierversuche in der Biomedizinischen Forschung* [Animal Experiments in Biomedical Research], 22 ALTERNATIVES TO ANIMAL EXPERIMENTATION 143, 143 (2005) (Ger.).

220. John P.A. Ioannidis & Thomas A. Trikalinos, *Early Extreme Contradictory Estimates May Appear in Published Research: The Proteus Phenomenon in Molecular Genetics Research and Randomized Trials*, 58 J. CLINICAL EPIDEMIOLOGY 543, 547 (2005).

221. John P.A. Ioannidis, *Evolution and Translation of Research Findings: From Bench to Where?*, PLOS CLINICAL TRIALS, e36, Nov. 2006, at 1.

222. See John P.A. Ioannidis, *Why Most Published Research Findings Are False*, 2 PLOS MED. 696, 696 (2005); John P.A. Ioannidis, *Contradicted and Initially Stronger Effects in Highly Cited Clinical Research*, 294 JAMA 218, 218 (2005); Ramal Moonesinghe et al., *Most Published Research Findings Are False—But a Little Replication Goes a Long Way*, 4 PLOS MED. 218, 218 (2007).

predominantly rodents—has not occurred. To the contrary, it has been demonstrated repeatedly that purported gene links to human diseases are often not valid or reproducible and seldom have meaningful effects on disease risk,²²³ and that species-specific differences in the regulation of genes invalidate gene-disease associations.²²⁴ Additionally, identical genes often function differently in rodents and humans,²²⁵ and even function differently for genetically identical laboratory animals.²²⁶

Finally, human identical twins, who are members of the species of interest and share all their genes, nonetheless have different and changing patterns of gene regulation and thus different disease risks and drug responses.²²⁷ The findings arising from the genetics revolution of the last

223. See, e.g., Thomas M. Morgan et al., *Nonvalidation of Reported Genetic Risk Factors for Acute Coronary Syndrome in a Large-Scale Replication Study*, 297 JAMA 1551, 1558–59 (2007); Monya Baker, *The Search for Association*, 467 NATURE 1135, 1135 (2010); David B. Goldstein, *Common Genetic Variation and Human Traits*, 360 NEW ENG. J. MED. 1696, 1696 (2009); Wayne D. Hall et al., *Being More Realistic About the Public Health Impact of Genomic Medicine*, 7 PLOS MED., e1000347, Oct. 2010, at 1; Peter Kraft & David J. Hunter, *Genetic Risk Prediction—Are We There Yet?*, 360 NEW ENG. J. MED. 1701, 1701 (2009); Nina P. Paynter et al., *Association Between a Literature-Based Genetic Risk Score and Cardiovascular Events in Women*, 303 JAMA 631, 631 (2010); Sudha Seshadri et al., *Genome-Wide Analysis of Genetic Loci Associated with Alzheimer Disease*, 303 JAMA 1832, 1832, 1839 (2010); Themistocles L. Assimes et al., *Lack of Association Between the Trp719Arg Polymorphism in Kinesin-Like Protein 6 and Coronary Artery Disease in 19 Case-Control Studies* 10 (Nov. 2, 2011) (author manuscript), available at <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3084526/pdf/nihms287126.pdf>; Jemma C. Hopewell et al., *No Impact of KIF6 Genotype on Vascular Risk and Statin Response Among 18,348 Randomized Patients in the Heart Protection Study*, 57 J. AM. C. CARDIOLOGY 2000, 2004, 2006 (2011).

224. Caroline L. Relton & George Davey Smith, *Epigenetic Epidemiology of Common Complex Disease: Prospects for Prediction, Prevention, and Treatment*, 7 PLOS MED., e1000356, Oct. 2010, at 1; ENCODE Project Consortium, *An Integrated Encyclopedia of DNA Elements in the Human Genome*, 489 NATURE 57, 71 (2012).

225. Ben-Yang Liao & Jianzhi Zhang, *Null Mutations in Human and Mouse Orthologs Frequently Result in Different Phenotypes*, 105 PROC. NAT'L ACAD. SCI. 6987, 6987 (2008).

226. See Cynthia M. Rohde et al., *Metabonomic Evaluation of Schaedler Altered Microflora Rats*, 20 CHEMICAL RES. TOXICOLOGY 1388, 1391 (2007).

227. See, e.g., Mario F. Fraga et al., *Epigenetic Differences Arise During the Lifetime of Monozygotic Twins*, 102 PROC. NAT'L ACAD. SCI. 10604, 10604, 10609 (2005); Valerie W. Hu et al., *Gene Expression Profiling of Lymphoblastoid Cell Lines from Monozygotic Twins Discordant in Severity of Autism Reveals Differential Regulation of Neurologically Relevant Genes*, BIOMED CENTRAL 2, 13 (May 18, 2006), <http://www.biomedcentral.com/content/pdf/1471-2164-7-118.pdf>; Terrance P. O'Hanlon et al., *Gene Expression Profiles from Discordant Monozygotic Twins Suggest that Molecular Pathways Are Shared Among Multiple Systemic Autoimmune Diseases*, ARTHRITIS RES. & THERAPY 8, 12–13 (April 26, 2011), <http://arthritis-research.com/content/pdf/ar3330.pdf>; Arjun Raj et al., *Variability in Gene Expression Underlies Incomplete Penetrance*, 463 NATURE 913, 913 (2010); Adrian Streit & Ralf J. Sommer, *Random Expression Goes Binary*, 463 NATURE 891, 891–92 (2010); Arturas Petronis et al., *Monozygotic Twins Exhibit Numerous Epigenetic Differences: Clues to Twin Discordance?*, 29 SCHIZOPHRENIA BULL. 169, 169 (2003).

decade undermine the very premise on which GM animal science is based, and they provide the scientific foundation that should relegate animal research for human diseases and drugs to the historical dustbin. After all, if identical twins are not always reliable predictors for each other, what can we expect to learn from other species about human diseases and drug responses?

The solution to the failed animal research paradigm is of course to replace animal use with research methods that more closely reflect human diseases and drug responses. These methods range from the use of human cells, tissues, and organs to computer-based analysis, advanced imaging, and genetic studies. It is not practical to review these methods in detail here, but a brief mention of some of the available and developing methods follows.

Cultures of human cells and tissues permit many of the cellular and subcellular experiments performed on animals to be performed instead on the species of interest—humans.²²⁸ These may include immortal cell lines, cell and tissue cultures that may be used for personalized approaches to therapy, organotypic cultures that combine cellular elements to replicate tissue and tumor environments, engineered three-dimensional tissue environments, and other constructs. A particularly promising and advancing method is the use of various categories of human stem cells to study human diseases and develop drugs for human use.²²⁹ While these human-based cell and tissue studies will not always replicate results in the “whole animal,” they are more accurate for the questions studied and more translatable than research on the wrong “whole animal.”

Computer-based analysis of the likely efficacy and adverse effects of drugs and chemicals can be performed by a process called QSAR (quantitative structure-activity relationships), which employs large databases of information on human diseases and treatments.²³⁰ The related area of bioinformatics involves the accumulation and sharing of human disease and drug data.²³¹ Genetic screening and testing techniques such as

228. See, e.g., Margaret Clotworthy, *The Application of Human Tissue for Drug Discovery and Development*, 7 EXPERT OPINION ON DRUG DISCOVERY 543, 543 (2012); Chris Hillier & David Bunton, *Functional Human Tissue Assays*, 12 DRUG DISCOVERY TODAY 382, 382 (2007).

229. See, e.g., Allison D. Ebert & Clive N. Svendsen, *Human Stem Cells and Drug Screening: Opportunities and Challenges*, 9 NAT. REV. DRUG DISCOVERY 367, 367 (2010); Colin W. Pouton & John M. Haynes, *Embryonic Stem Cells as a Source of Models for Drug Discovery*, 6 NAT. REV. DRUG DISCOVERY 605, 606, 612 (2007).

230. See (Q)SAR, ALTOX.ORG, <http://alttox.org/trc/emerging-technologies/qsar> (last visited Mar. 20, 2013).

231. See generally Tanita Casci, *Bioinformatics: Next-Generation Omics*, 13 NATURE REV. GENETICS 378, 378–79 (2012).

microarray methods²³² and pharmacogenomics²³³ contribute to patient-specific drug safety and efficacy prediction without using animals.

Microdosing is a technique that uses advanced imaging methods to track the metabolism and excretion of drugs administered to humans at doses that are far too small to produce either therapeutic or adverse effects.²³⁴ Its accuracy is such that it has the “ability to detect a liquid compound even after one litre of it has been diluted in the entire oceans of the world.”²³⁵ Already employed by many pharmaceutical companies, microdosing can eliminate the need to obtain such metabolic data from animals, which as discussed earlier is inaccurate anyway.

Microfluidics and related chip technologies permit analysis of human cells and tissues in configurations that mimic cellular, tissue, organ, and whole person scenarios and are widely employed for drug development and toxicity testing for drugs and chemicals.²³⁶ The numerous linked fields of tissue engineering have applications for diagnostics, drug testing, and even culturing and auto-transplantation of tissues or organs.²³⁷ Advanced noninvasive imaging methods such as computed tomography, positron emission tomography, accelerator mass spectrometry, various magnetic resonance imaging methods, ultrasound innovations, and other developing techniques are already replacing animal studies for many research and drug development applications.²³⁸

232. See *DNA Microarray Technology*, NAT'L HUMAN GENOME RES. INST., <http://www.genome.gov/10000533> (last updated Nov. 15, 2011).

233. See generally *Pharmacogenomics and Its Role in Drug Safety*, DRUG SAFETY NEWSL. (U.S. Food & Drug Admin., Rockville, Md.), Winter 2008, at 24–26, available at <http://www.fda.gov/downloads/Drugs/DrugSafety/DrugSafetyNewsletter/ucm118970.pdf>; Susan B. Shurin & Elizabeth G. Nabel, *Pharmacogenomics—Ready for Prime Time?*, 358 NEW ENG. J. MED. 1061, 1061 (2008).

234. See K. Stenström et al., *Microdosing for Early Biokinetic Studies in Humans*, 139 RADIATION PROTECTION DOSIMETRY 348, 349 (2010); Malcolm Rowland, *Microdosing: A Critical Assessment of Human Data*, 101 J. PHARMACEUTICAL SCI. 4067, 4067 (2012).

235. MALCOLM ROWLAND, MICRODOSING AND THE 3RS, at 4 (2006), <http://www.nc3rs.org.uk/downloaddoc.asp?id=339&page>.

236. See, e.g., Donna M. Dambach & Hirdesh Uppal, *Pharmaceutical Toxicity: Improving Risk Assessment*, 4 SCI. TRANSLATIONAL MED. 159, 159 (2012); M.B. Esch, T.L. King & M.L. Shuler, *The Role of Body-on-a-Chip Devices in Drug and Toxicity Studies*, 13 ANN. REV. BIOMEDICAL ENGINEERING 55, 59–60 (2011); Uwe Marx et al., *'Human-on-a-chip' Developments: A Translational Cutting-Edge Alternative to Systemic Safety Assessment and Efficiency Evaluation of Substances in Laboratory Animals and Man?*, 40 ALTERNATIVES TO LAB ANIMALS 235, 235 (2012); Pavel Neuzil et al., *Revisiting Lab-on-a-Chip Technology for Drug Discovery*, 11 NAT. REV. DRUG DISCOVERY 620, 620, 622, 625 (2012).

237. See *NIH Definition of Tissue Engineering/Regenerative Medicine*, TISSUE ENGINEERING PAGES, <http://www.tissue-engineering.net/index.php?seite=whatiste> (last visited Mar. 22, 2013).

238. See generally Nathan Blow, *How to Get Ahead in Imaging*, 458 NATURE 925, 925 (2009); Vivek Prabhakaran et al., *Current Status and Future Perspectives of Magnetic Resonance*

More importantly, a shift in emphasis from animal research to human-based methods would accelerate a superior science and hasten the day when basic and applied sciences translate reliably to human medicine. If we knew decades ago what we know now about the failures and consequences of the animal research paradigm, perhaps we would have avoided it and started earlier to develop human-based research methods. But it is often more difficult to undo an erroneous established practice and its accumulated infrastructure than to prevent its adoption in the first place. To the extent that researchers hang on to the old ways, getting there will cost more time, resources, hopes, and human lives.

VI. ANIMAL LAW SHOULD BETTER REFLECT ANIMAL RESEARCH REALITIES

Tying together the brief review of research-related animal law in Section I with the deconstruction of animal research methodology and results in Sections II–IV, the “fatal flaw” of U.S. animal law is evident. While the AWA (poorly) regulates animal treatment and welfare, it does not address the suitability of animal research or seek to define the expectations or goals that “justify” experimentation and the killing of animals in laboratories. The solution is not in the language or intent of the AWA as currently written, and change must come from Congress.

There is evidence of some favorable movement. In December 2011, the Institute of Medicine of the National Academies released its report, *Chimpanzees in Biomedical and Behavioral Research: Assessing the Necessity*, in which the need for chimpanzees in the conduct of nearly all biomedical research was dismissed.²³⁹ This IOM report was game-changing for at least three reasons: it was the first federally sponsored report that began to dismantle a major element of animal research, it addressed the use and abuse of our closest genetic relatives, and it granted credibility to opponents of chimpanzee research, who had been kept down by researchers and funding agencies using the bully pulpit to shape public opinion. NIH director Dr. Francis Collins immediately accepted the IOM report’s

High-Field Imaging: A Summary, 22 *NEUROIMAGING CLINICS N. AM.* 373, 373–74 (2012); M.H. Lee, C.D. Smyser & J.S. Shimony, *Resting-State fMRI: A Review of Methods and Clinical Applications*, *AM. J. OF NEURORADIOLOGY*, Aug. 30, 2012, at 1, 3, 5; Ragnar Hellborg & Göran Skog, *Accelerator Mass Spectrometry*, 27 *MASS SPECTROMETRY REV.* 398, 398, 419 (2008); J. Paul Shea, *Noninvasive Imaging in Drug Discovery and Development. Where to Begin*, *NEXT GENERATION PHARMACEUTICAL*, <http://www.ngpharma.com/article/Noninvasive-Imaging-in-Drug-Discovery-and-Development--Where-to-Begin> (last visited Mar. 22, 2013).

239. INST. OF MED. & NAT’L RESEARCH COUNCIL, *CHIMPANZEES IN BIOMEDICAL AND BEHAVIORAL RESEARCH: ASSESSING THE NECESSITY* 66–67 (Bruce M. Altevogt et al. eds., 2011).

conclusions and recommendations, and he commissioned the advisory NIH Council of Councils to develop guidelines for the implementation of the IOM's recommendations.²⁴⁰

The NIH Council of Councils appointed a Working Group on the Use of Chimpanzees in NIH-Supported Research, which released its report on January 22, 2013, and began a sixty-day public comment period.²⁴¹ Among the working group's recommendations are that most current NIH-sponsored chimpanzee research should be ended, that all but a small number of NIH-owned and supported chimpanzees should be retired to sanctuaries, and that very restrictive criteria should be applied to future requests to perform research using chimpanzees.²⁴² On June 26, 2013, Dr. Collins announced that NIH is adopting twenty-seven of the twenty-eight Council of Councils recommendations, excluding a single provision regarding space allocation for chimpanzees.²⁴³ It is reasonable to expect that the NIH implementation of the IOM's recommendations and the Council of Councils' guidelines will spell the beginning of the end for invasive chimpanzee research in the U.S.

Simultaneously, the Great Ape Protection and Cost Savings Act (GAPCSA) was introduced in both houses of the 112th U.S. Congress (S. 810 and H.R. 1513).²⁴⁴ GAPCSA would establish a timeline to phase out invasive research involving chimpanzees and other great apes, prohibit breeding and transport of great apes for research purposes, and retire all federally owned chimpanzees to sanctuary with lifetime care.²⁴⁵ GAPCSA did not reach a vote in either the Senate or the House of Representatives this session, but the bill will be reintroduced in the 113th Congress.²⁴⁶

240. *Statement by NIH Director Dr. Francis Collins on the Institute of Medicine Report Addressing the Scientific Need for the Use of Chimpanzees in Research*, NIH NEWS (Dec. 15, 2011), <http://www.nih.gov/news/health/dec2011/od-15.htm>.

241. *Working Group Submits Its Report*, COUNCIL OF COUNCILS, DPCPSI, http://dpcpsi.nih.gov/council/working_group_message.aspx (last updated Jan. 23, 2013).

242. See NAT'L INST. OF HEALTH, COUNCIL OF COUNCILS WORKING GROUP ON THE USE OF CHIMPANZEES IN NIH-SUPPORTED RESEARCH REPORT 4-5 (2013), *available at* http://dpcpsi.nih.gov/council/pdf/FNL_Report_WG_Chimpanzees.pdf.

243. See generally NAT'L INST. OF HEALTH, ANNOUNCEMENT OF AGENCY DECISION: RECOMMENDATIONS ON THE USE OF CHIMPANZEES IN NIH-SUPPORTED RESEARCH (2013), *available at* http://dpcpsi.nih.gov/council/pdf/NIH_response_to_Council_of_Councils_recommendations_62513.pdf.

244. *The Great Ape Protection and Cost Savings Act*, PROJECT R&R, <http://www.releasechimps.org/laws/gapcsa> (last visited Mar. 22, 2013).

245. CONG. BUDGET OFFICE, S. 810 GREAT APE PROTECTION AND COST SAVINGS ACT OF 2011, at 1-3 (2012), *available at* <http://www.cbo.gov/sites/default/files/cbofiles/attachments/s810.pdf>.

246. See PROJECT R&R, *supra* note 243.

In September 2011, the U.S. Fish & Wildlife Service (FWS) announced that the agency was undertaking a review of the status of captive chimpanzees in the U.S. in response to a petition to reclassify all these chimpanzees from threatened to endangered.²⁴⁷ In June 2013, FWS announced that it is proposing that all chimpanzees be classified as endangered and further stated that the more than two-decade split-listing of captive chimpanzees was not permitted under the Endangered Species Act of 1973.²⁴⁸ If the proposed reclassification is implemented after a 60-day public comment period, substantial protection of captive chimpanzees from medical research and many other uses will follow. This protection is likely to be enhanced by the announced collaboration between FWS and NIH to coordinate FWS permitting decisions under the Endangered Species Act with NIH research protocol reviews under its new stringent guidelines.

Congress also should consider acting in order to more closely regulate NIH research funding. There is reason to question the science and public health return on investment from the \$31 billion NIH discretionary budget, and it is within Congress's authority to establish guidelines for the NIH regarding the potential returns for public health from the funding of basic science research (more than 40% of the NIH discretionary budget). If Congress is willing to examine and act on the poor returns from animal research and redirect NIH funding to human-based research with the demonstrated potential to improve public health, the road to better science and better medical care will be smoother.

247. See ANNA FROSTIC, HUMANE SOCIETY OF THE U.S., PETITION TO UPGRADE CAPTIVE CHIMPANZEES (*PAN TROGLODYTES*) FROM THREATENED TO ENDANGERED STATUS PURSUANT TO THE ENDANGERED SPECIES ACT OF 1973, AS AMENDED 4 (2010), http://www.humanesociety.org/assets/pdfs/animals_laboratories/chimpanzee_research/fws_endangered_petition.pdf; Endangered and Threatened Wildlife and Plants; 90-Day Finding on a Petition to List All Chimpanzees (*Pan Troglodytes*) as Endangered, 76 Fed. Reg. 54,423, 54,423 (Sept. 1, 2011) (notice of petition finding).

248. *U.S. Fish and Wildlife Service Proposes Protection for All Chimpanzees—Captive and Wild—as Endangered*, U.S. FISH & WILDLIFE SERVICE (June 11, 2013), <http://www.fws.gov/home/newsroom/serviceproposeschimpanzeesNR06112013.html>.