HOW RELIABLE AND PREDICTIVE ARE ANIMAL EXPERIMENTS FOR HUMAN OUTCOMES?

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Obligatory Disclaimer

The opinions here are solely those of Dr. Akhtar and do not necessarily represent the opinions of the US government or the FDA.
Why are Animal Experiments Conducted?

• Basic research
  • Curiosity-driven, exploratory research

• Applied research
  • Addresses specific or practical problems
    • Drug testing & marketing
    • Chemical toxicity testing

• Phases of medical research: pre-clinical, clinical
  (Phase I, II, III, post-marketing)
Ethical Questions

Do potential benefits outweigh potential harms?

1. Is animal experimentation ethical for animals?
   • Are animals adequately protected?
   • Are ethical considerations for animals fair?

1. Is animal experimentation ethical for humans?
   • Is animal experimentation an effective use of resources?
   • Do animal experiments reliably inform human health?
State of Medical Research

Basic research:

2000 Institute of Medicine Report notes a “disconnection between the promise of basic science and the delivery of better health.”
State of Medical Research

Applied research:

92% failure rate in drug development.
Reasons for High Drug Failure Rate

• Potential higher regulatory hurdles.
• Long, expensive clinical trials.
• Poor predictability of animal experiments.

Malcolm Macleod at University of Edinburgh estimates that a quarter of a million of animals have been used between 1985-2005 in this futile effort.

**Animal Experiments in Stroke**

- Number of treatments effective in animal stroke experiments: >700
- Number of these treatments tested in human clinical trials: >150
- Number that have proven effective in humans: 0
<table>
<thead>
<tr>
<th>Animal Experiments in HIV/AIDS</th>
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<tr>
<td>- Number of vaccines effective in animal HIV experiments: &gt;85</td>
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<tr>
<td>- Number of clinical trials: &gt;200</td>
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<tr>
<td>- Number that have proven effective in humans: 0</td>
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Specific Studies


• Fletcher & Heywood: 25% concordance between animal and human toxicity.

  • Heywood R. Toxicology Letters 1981; 8: 349–358
Intrinsic Causes of Failure of Animal Experiments

1. Uncontrollable influences of laboratory environment & procedures.
3. Species and strain-specific differences in physiology, genetics, biochemistry.
Influences of Laboratory Environment and Procedures
Artificially-Induced Animal Models
Discrepancies Between Artificially-Induced Strokes in Animals and Human Strokes

- **Strike 1**: Human stroke develops over decades.

- **Strike 2**: Animal stroke models don't usually include the underlying conditions.

- **Strike 3**: Artificially induced underlying condition.
Interspecies Differences

![Interspecies Brain Diagram]

- Human
- Elephant
- Dolphin
- Gorilla
- Dog
- Macaque
- Cat
- Mouse

5cm Scale
Animal Experiments in Spinal Cord Injury

- Results of Methylprednisolone (MP) studies for treatment of acute spinal cord injury:
  - Cats (6 studies): mostly positive
  - Dogs (3 studies): mostly positive
  - Rats (47 studies): mostly negative
  - Mice (2 studies): all negative
  - Monkey (1 study): positive
  - Sheep (1 study): negative
  - Rabbit (2 studies): equivocal
  - Humans?

Horrobin contends that these three conditions have not been fulfilled for any human disease. I would argue that with few exceptions, we have not met even one of these conditions.

Problems With Animal Models

- **For an effective model, 3 conditions must be met:**
  - Full understanding of the animal model
  - Full understanding of the human disease
  - The above two cases must be substantially congruent in all important respects

  - David F. Horrobin, MD, PhU Nature Reviews Drug Discovery, 2003; 2: 151-154
Does Animal Experimentation Pass the RAP Test?

Are animal experiments:

• **Reliable**?
• **Accurate**?
• **Predictive**?
Consequences of Reliance on Animal Experiments

1. **Human harms**
   - Misleading safety data
   - Misleading effectiveness data
   - Wasted resources & time
   - Possible abandonment of effective therapies

2. **Animal Harms**
   - Significant physical pain
   - Psychological suffering
Human Based Testing Methods

- Three-dimensional cell and tissue cultures (Human organs-on-a-chip)
- Virtual humans
- Systems biology
- Human Immunology Project
- Imaging studies
- Biomarker studies
Thank You

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