

# *Challenges in Designing Surgical Trials for Neurodegenerative Diseases*

Sham Surgery Workshop  
Bethesda  
July 2010

Steven Piantadosi, M.D., Ph.D.  
Cedars-Sinai Medical Center  
Los Angeles, CA



# ***Disclosures***

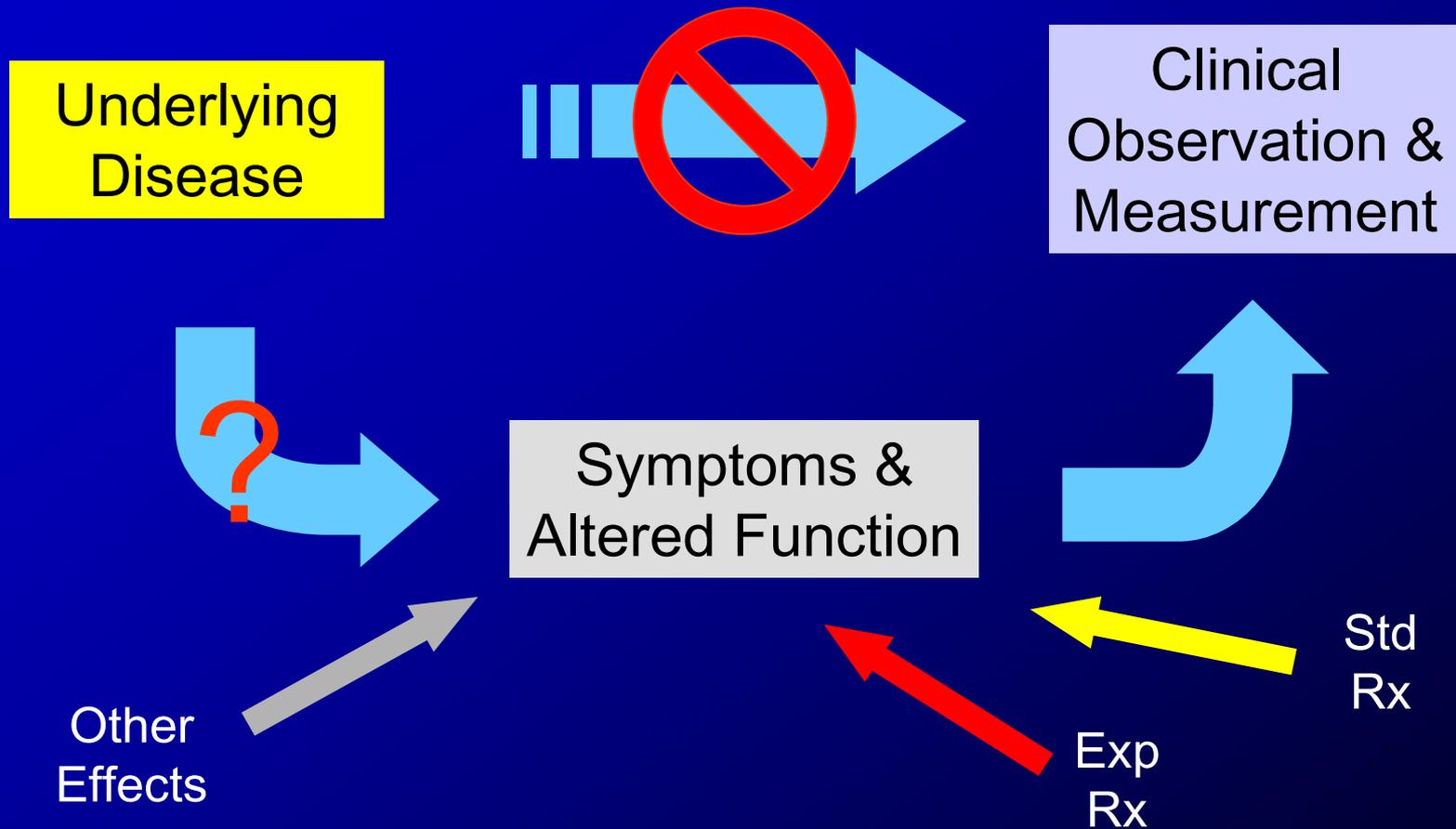
## *Challenges in Neurodegenerative Diseases*

---

None

# Problem #1: Latency

## Challenges in Neurodegenerative Diseases



# ***Latency***

## *Challenges in Neurodegenerative Diseases*

---

- Due to other effects, function and symptoms are not a true surrogate for the disease state, so we have difficulty knowing what the treatment is actually doing.
- Other example diseases where this might be the case?
  - Psychiatric illness
  - Chronic fatigue
  - Diabetes
  - Stroke
  - Viral URI
  - **Emphysema**
  - Sarcoidosis
  - Marfan's

# ***Non-Latency***

## *Challenges in Neurodegenerative Diseases*

---

- Contrast with conditions where the disease process is directly observable
  - Infections
  - Cancer (overt clinical stages)
  - CHD
  - **Emphysema**
  - Trauma
  - Congenital defects
  - AIDS

## Other Problems

# ***Making Latency Even Worse***

## *Challenges in Neurodegenerative Diseases*

---

- Brain taboo
- Observer bias
- Subject bias
- Placebo effect
- Concomitant therapies
- High person to person variability
- Chronicity
- Lack of symptom model
- Developmental pipeline

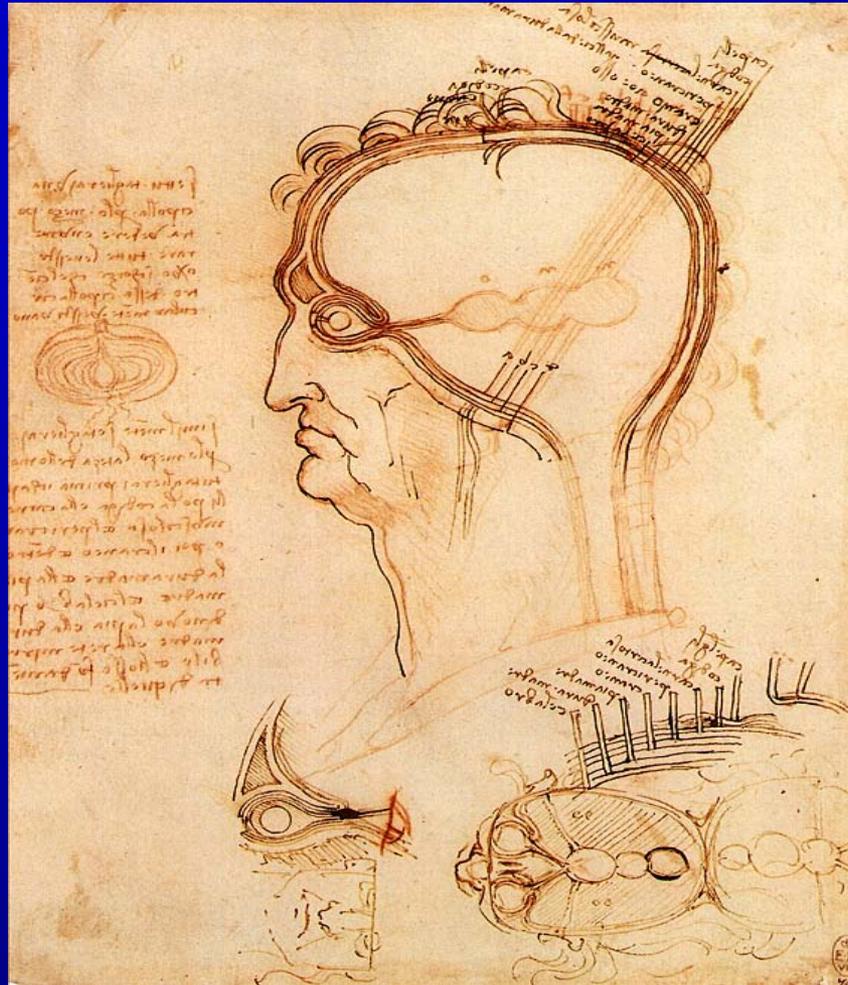
# ***Well-Known Solutions***

## *Challenges in Neurodegenerative Diseases*

---

- Observer bias - masking
- Subject bias - masking
- Placebo effect – internal controls
- Concomitant therapies – randomization, replication
- High person to person variability - replication
- Chronicity – longitudinal studies/outcomes

# Challenges in Neurodegenerative Diseases



# *Observer Bias*

## *Challenges in Neurodegenerative Diseases*

---

- Pertains to observations from all sources
- Potential mitigations or solutions:
  - Objective measurements (e.g., UPDRS, video)
  - Explicit comparisons to control (remember the enthusiasm following uncontrolled fetal tissue transplantation)
  - Masking
  - Removal of placebo effect per se

## Pipeline Issues

# ***Pipeline Issues***

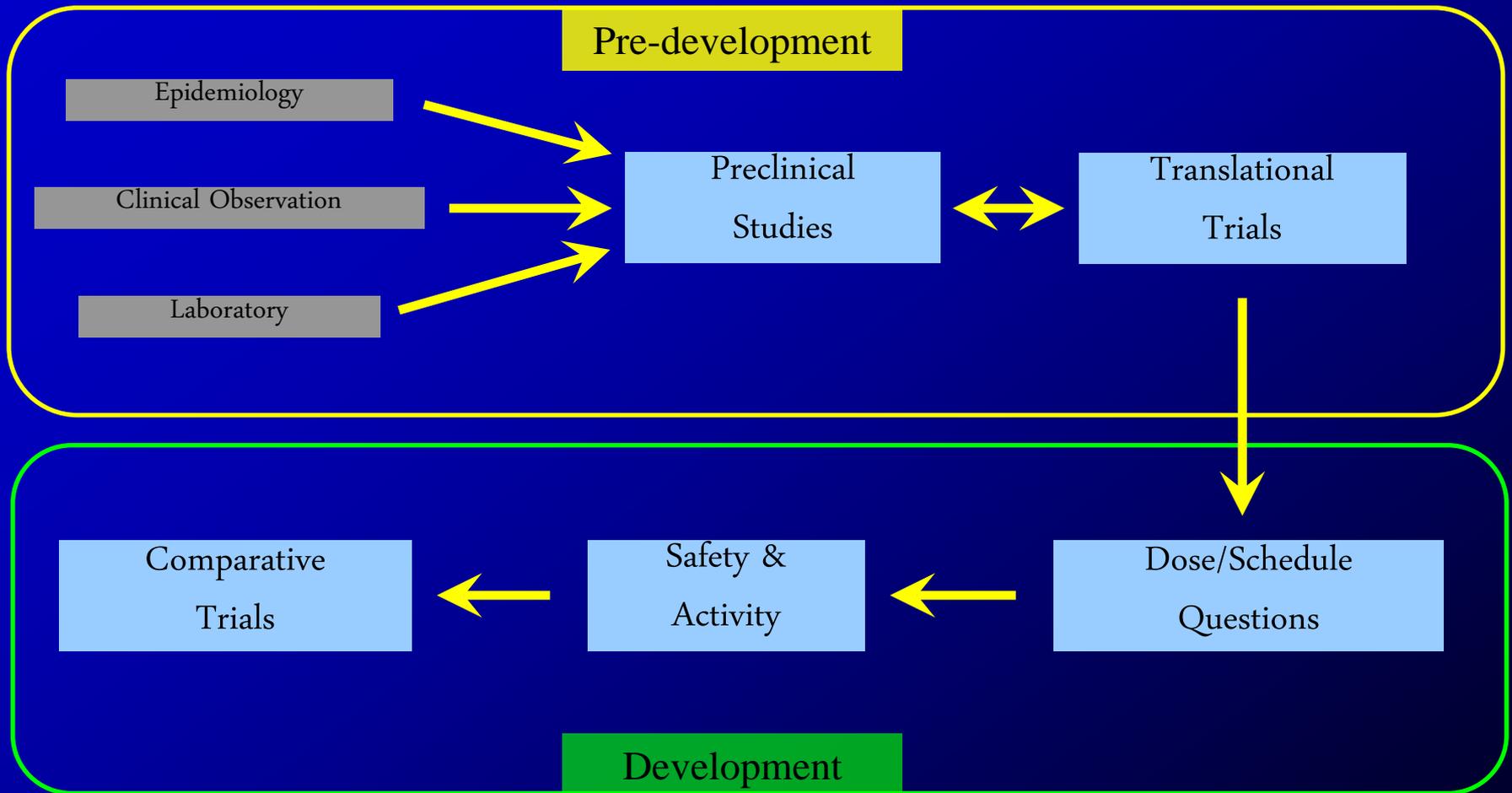
## *Challenges in Neurodegenerative Diseases*

---

- Do we have the right development paradigm?
- De-centralization of effort
- Terminology
- Disadvantages of scale

# *A Developmental Paradigm*

## *Challenges in Neurodegenerative Diseases*



# ***Some Points About the Pipeline***

## *Challenges in Neurodegenerative Diseases*

---

- It evolved under special circumstances
  - Sizeable numbers of subjects
  - Toxic treatment
    - ~ needs a dose-safety titration
    - ~ no placebo effect
  - Many ideas to test, leading to futility studies
  - Directly observable disease
  - Definitive outcome (overall survival)
  - Cooperative groups
- How much of this is shared by neuro-regenerative therapy?

# *Hypothetical New Pipeline*

## *Challenges in Neurodegenerative Diseases*

---

- Step 1: Establish dose
  - PK/PD, microdialysis, csf levels, imaging
  - Avoid dose-efficacy questions
- Step 2: Your baby is ugly
  - Single efficacy outcome futility trial, fixed dose
  - Staged design to kill the loser early
  - Randomized internal control  $N > 60$
- Step 3: Large multi-center randomized trial with extensive peer-reviewed protocol development. Detect effect sizes of .25 or less.

# *Models*

## *Challenges in Neurodegenerative Diseases*

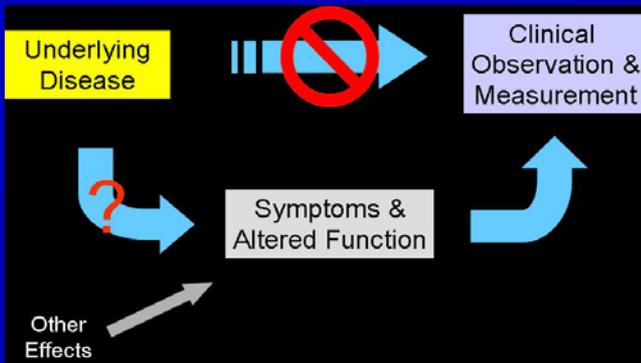
---



Museo La Specola Florence

# Symptom Model

## Challenges in Neurodegenerative Diseases



- If we had the correct model for the relationship between the underlying disease and symptoms and function, then objective clinical observation would inform us directly about the disease (latency would disappear).
- How do we build such models?
- National PD Brain Study: if a PD patient dies prematurely from other causes, the brain and other tissue is donated for study to help build the disease-symptom model.

# ***Disease Modification***

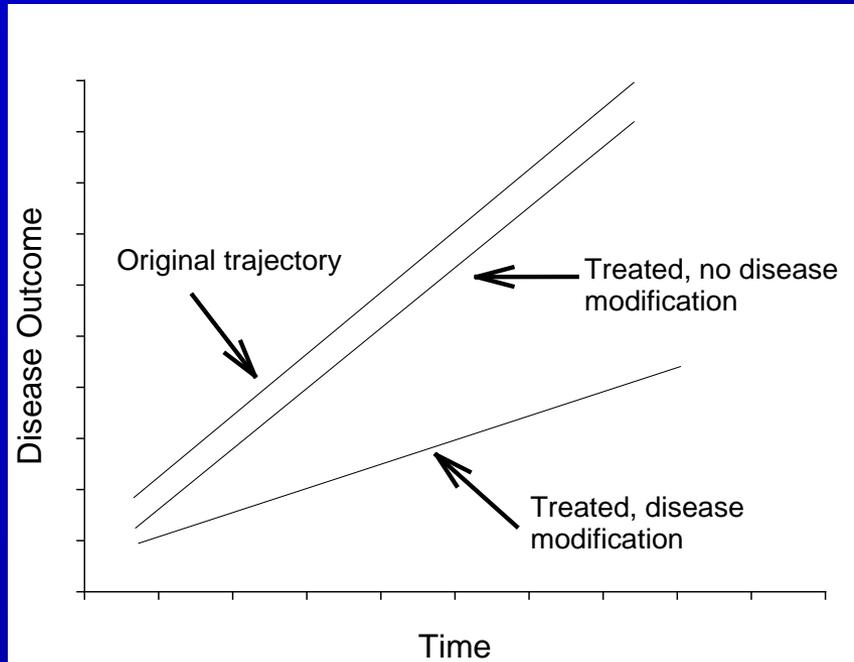
## *Challenges in Neurodegenerative Diseases*

---

- Because of latency, how can we be sure if a therapy is affecting the underlying disease rather than simply temporarily improving symptoms and function?
- Answer: detect “disease modification”
- One recent idea has been the “delayed start study” design – but see Ploeger and Holford  
[http://tucson2008.go-acop.org/pdfs/16-Ploeger\\_FINAL.pdf](http://tucson2008.go-acop.org/pdfs/16-Ploeger_FINAL.pdf)

# Delayed Start

## Challenges in Neurodegenerative Diseases



- Change in position is not disease modification (time shift)
- Change in slope (velocity) is disease modification
- Examples: survival; tumor size; viral load; FEV<sub>1</sub>; UPDRS
- “Delayed start” design detects change in position

# ***Disease Modification***

## *Challenges in Neurodegenerative Diseases*

---

- Some designs that might detect disease modification:
  - Washout
  - Multi-period crossovers
  - Delayed start (under certain conditions)
  - Multi-group delayed start?
  - Ordinary designs with the correct disease-symptom model

## Surgical Context

# *Surgical Context*

## *Challenges in Neurodegenerative Diseases*

---

- Clinical trials have not been as widely applied in surgery or other skill-dependent therapies as in, for example, drug development. This creates certain tensions when they are used in the context of surgery.
- The essential problem in evaluating early studies of surgery and skill dependent therapy is the triple confounding of patient prognosis (selection), the practitioner's skill, and the efficacy of the treatment.
- Surgical treatments are often developed at low cost by a single practitioner or a small group. This can reduce the need for resources and collaboration, and therefore opportunities for methodological rigor.

# *Surgical Context*

## *Challenges in Neurodegenerative Diseases*

---

- Even in a randomized surgical trial, the stress of the operative procedure can differentially affect one treatment group, thereby partially undoing the effects of randomization and leaving a residual bias (e.g., survivor's bias).
- Risk/benefit can change strongly over time with surgery, requiring careful long term observation and definitive endpoints.
- Like devices, surgery often corrects an obvious defect.
  - Some surgical procedures are mitigating rather than corrective and need to be assessed more rigorously
  - A newly feasible procedure does not equate to clinical benefit

# ***Surgical Culture***

## *Challenges in Neurodegenerative Diseases*

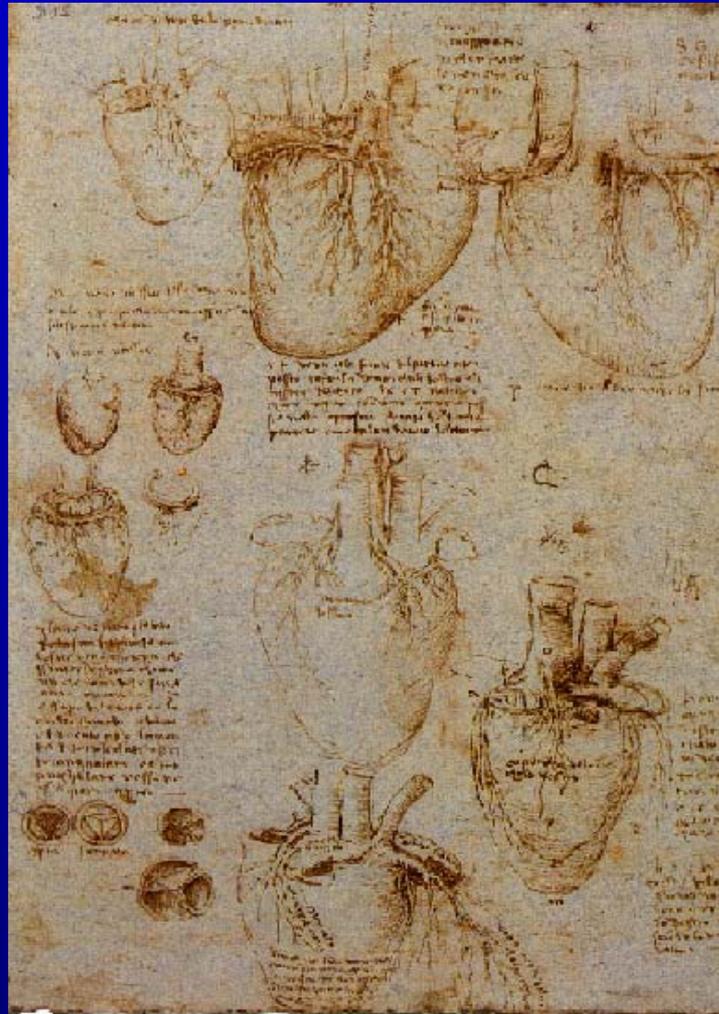
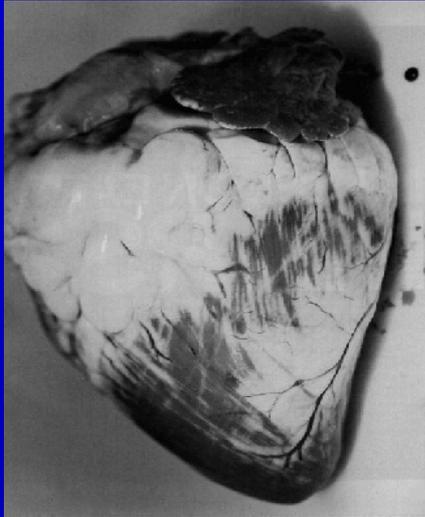
---

- no regulation of surgical therapies
- no widely accepted developmental paradigm
- not enough respect for the potential for bias
- too strong a belief in anecdotal reasoning
- too much respect for expert opinion
- weak support for comparative studies

# Bias

## Challenges in Neurodegenerative Diseases

---



# *Case History/Series*

## *Challenges in Neurodegenerative Diseases*

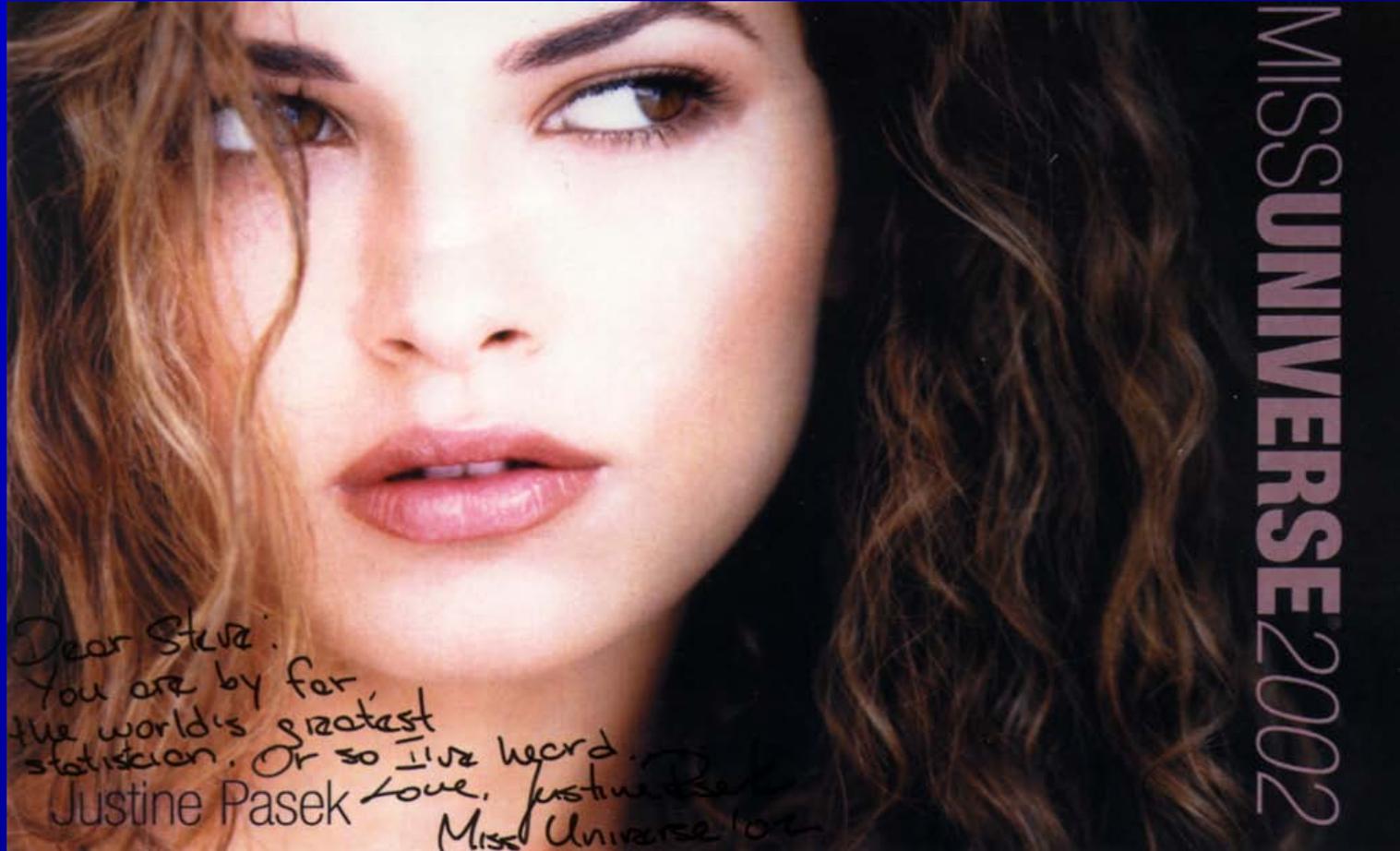
---



# Expert Opinion

## Challenges in Neurodegenerative Diseases

---



# *Surgery Context*

## *Challenges in Neurodegenerative Diseases*

---

- ① Uniformity of the treatment - substantive differences in
  - ▢ practitioners
  - ▢ procedures
  - ▢ supportive care
  - ▢ patient selection
  
- ① Incremental improvement: very relevant, because most procedures evolve from existing feasible operations
  
- ① Expected magnitude of treatment effects: often moderate to large

# *Surgery Effect Size*

## *Challenges in Neurodegenerative Diseases*

---

- Rigorous experimental designs are most needed when the treatment effect is about the same magnitude as natural variation in outcomes and/or the bias from uncontrolled observations.
- When treatment effects are likely to be large,
  - internal controls may not be needed
  - sample sizes could be smaller
  - extraneous sources of variability could be ignored rather than controlled
- Warning: every therapeutic context believes this of itself at first. Also, patients are interested in even small treatment effects.

# *Surgery As Mitigating*

## *Challenges in Neurodegenerative Diseases*

---

- ① Rationale for expecting large treatment effects from surgical therapies
  - ▢ correction of obvious defects
  - ▢ trauma care, control of bleeding
  
- ① Corrective versus mitigating treatments
  - ▢ cancer surgery seems to fall in between
  - ▢ drugs nearly always seem to be mitigating
  - ▢ surgery for NDD is at best mitigating
  
- ① We can't reasonably expect mitigating treatments to have large effects

# ***Final Comments***

## *Challenges in Neurodegenerative Diseases*

---

- The difficult problem of latency can only be helped with either 1) a valid symptom model, or 2) a new way to view the disease state directly
- We must deconstruct the stereotypical developmental model and be sure we have the right one for NDD
- Observer bias and other confounding is especially a problem in evaluating surgery
- The surgical context is challenging in other ways for assessing evidence objectively