Research Design and Methods

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Disclosures

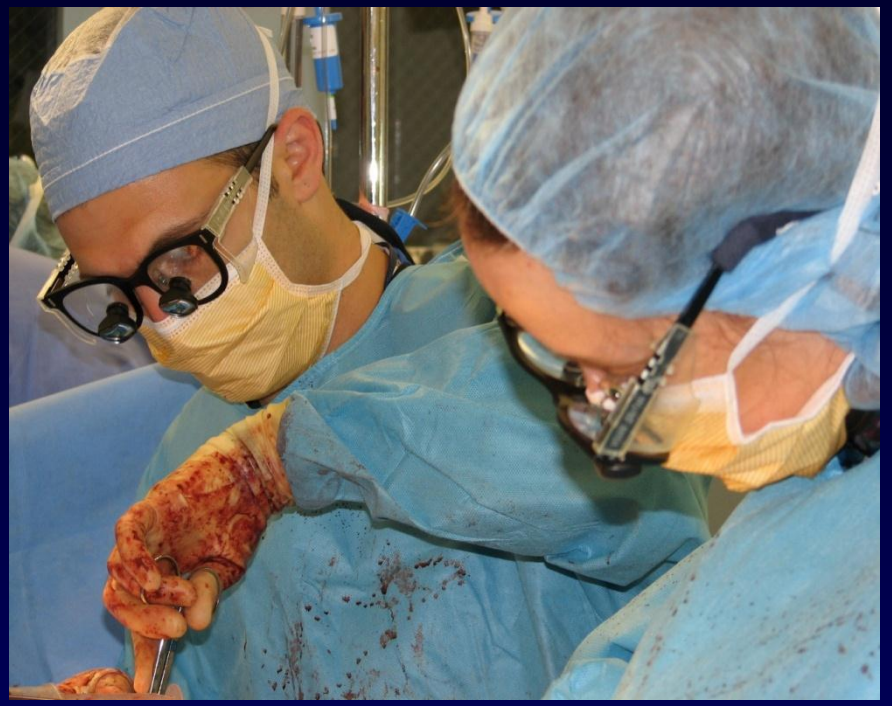
- I have no relevant financial relationships to disclose as it pertains to the content of my presentation.
- I do not intend to discuss an unapproved/investigative use of a commercial product/device in my presentation.

The Surgeon Scientist

- Huggins – hormonal treatment of cancer
- Gibbon and Lillehei – cardiopulmonary bypass and open cardiac surgery
- Murray and Starzl – solid organ transplantation
- Dudrick – development of TPN
- Carrel – organ culture
- Folkman – mechanism of dependence of tumors on blood supply

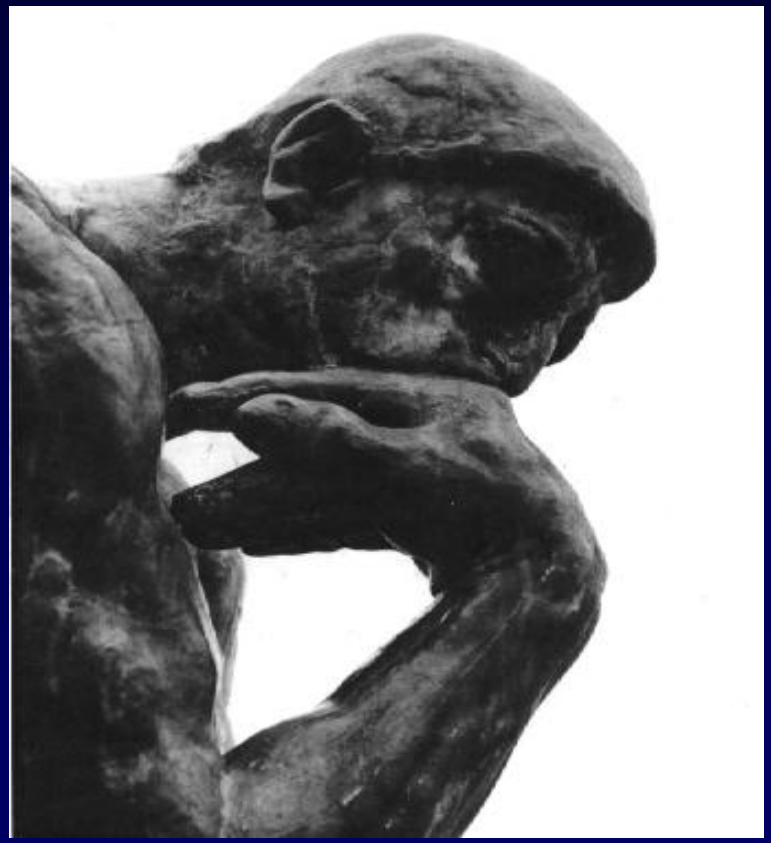
Nina Braunwald (1928-92)
Implanted 1st mitral valve, own design 1960

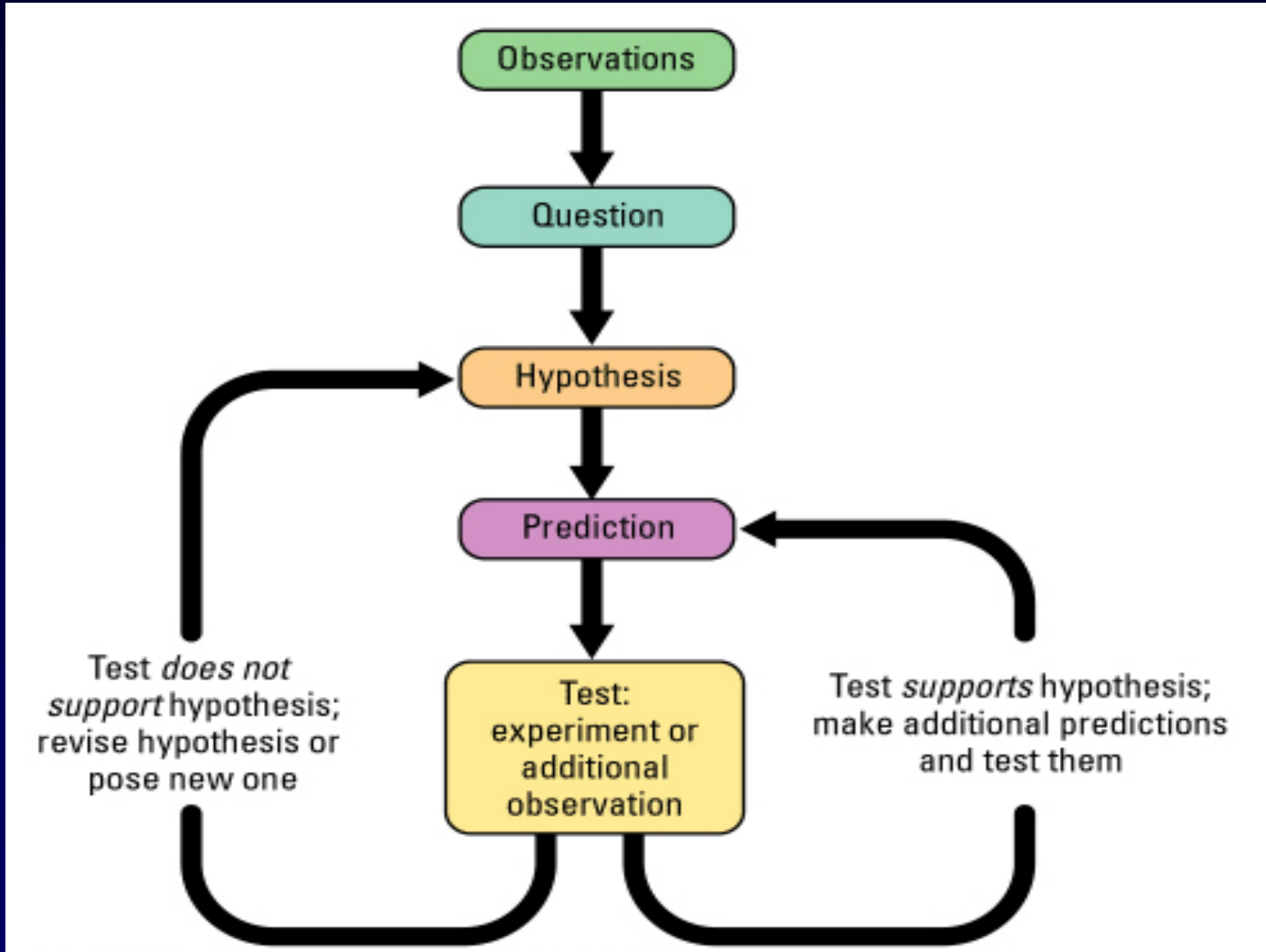
Surgeon-Scientist…



- Goal – to discover and apply new knowledge to problems affecting surgical populations
- In search of better ways of overcoming old problems
- Combination of genetic manipulation, gene therapy, conventional surgery, immunotherapy, chemotherapy

- Read the literature
- Develop a hypothesis
- **Design an experiment**
- **Methods**





Planning the Project

- Detailed literature review
- Developed a testable hypothesis
- Study design
  - —Anticipation of a definitive result
  - —Methodology – Innovation?
    - »Needs to be able to answer the question
  - —Risk/benefit assessment
  - —(Inclusion/exclusion criteria)
  - —Statistical analysis (Power analysis)

Designing an Experiment

Experiment Type

- In vitro
- In vivo
  - Animal
  - Human
    - Case Report
    - Case Series/Retrospective Review
    - Natural History
    - Clinical Trial

Risk/Benefit Assessment

- Is the study properly designed?
- Does the "cost" justify the potential results?
- Are risks/use of animals/humans justified?
- What is the chance & severity of harm?
- Systematic assessment of risk/benefit
  - —Risks limited to those necessary to achieve research objectives while protecting the subjects
  - —Oversight- stopping a study if there is a clear benefit/risk/lack of anticipated contributory result

Methodology

- Be innovative
- Methodology needs to be specific step by step
- The Lab Notebook - document steps actually done carefully
- Be careful about changing proposed method midstream

The Laboratory Notebook –The Goals

- Diary of laboratory experiments of one individual
- Complete record of procedures, reagents, data, active thought process
- Enough detail to be able to repeat experiments
- Enough detail to understand how work was done
- Foster analysis of data
- Legal document - Establish invention conception, integrity

The Laboratory Notebook Documentation

- Record real time
- Add explanation for lapses in time
- Do not leave out (potential for new discovery)
  - Bad experiments
  - Mildest change in technique
  - Source of key materials
- Neat, legible hand writing, proper grammar

The Laboratory Notebook Documentation Don't Forget

- Lot numbers
- Centrifuge speed
- Incubation time
- # washes
- Delays
- Culture medium
- pH
- Percent gel (for western blots)
- Cell passage
- Cell quality
- Etc……

Research Type

- Observational
- Experimental/Quantitative
  - Actively introduce a variable for study
    - Experimental conditions
    - Intervention
    - Treatment
    - Measureable outcome

Study Groups

- Comparison Groups
  - —One intervention/treatment/condition vs. another with both being of interest
- Control Group
  - —Customary care group or placebo group
- Placebo Group
  - —Treatment group with no expected physiological effect

Selection Bias

- What is included?
- What is excluded?
- Is blinding done when/where appropriate?
- Will experimental and control groups be treated equally?

Proper Statistical Testing

- Determine test to be used when the study is designed (i.e., BEFORE experiments begin)
- Test used NOT necessarily the one that gives the best *p* value
- Advent of computer programs may lead the wrong choices in analysis/Determine when a statistician is needed
- Alpha Value - Probability of a type 1 error – rejecting the null hypothesis when it is actually true
- Power - probability of getting a statistical difference if a true difference exists between groups

Findings

- Results should be presented accurately regardless of how they reflect on the hypothesis
- Conclusions must be based on the data obtained – loose interpretation must be avoided

Your Conclusions Can Only Address the Question Asked

Phil Witte, Piedmont, CA
Union of Concerned Scientists Cartoon Competition

Research Integrity

- Information needs to be complete, honest
- Follow the guidelines for documentation
- Be careful on extending the meaning of your results
- Reviewed for misconduct

Special Considerations
Animal-Based Research

- Non-animal alternatives
  - —ALT Web - http://altweb.jhsph.edu/
  - —UCDavis Center for Animal Alternatives Information
- Power analysis to determine sample size
  - —PHS policy is that that no animal life is wasted; the number of animals used in each project must be the minimum necessary to obtain valid and meaningful results

Special Considerations
Animal-Based Research

- Provision of humane care
  - Right thing to do
  - Approved animal care facility
  - Alleviation of pain, discomfort and needless suffering
  - Violation of animal care regulations can result in not only the shut down or research in the lab committing the violation but can lead to a halt of animal research at the institution
  - Follow the mandates
  - Listen to the Animal Care and Use Committee

Special Considerations In Clinical Research

- Protect Patient Rights and Clinical Needs
- Assessment of Risks and Benefits
- Power Analysis to Determine Sample Size
- Informed Consent
- Subject Selection
  - Vulnerable subjects e.g. incompetent, incapable of giving consent, minor
- Data protection/security

Institutional Review Board "The IRB"

Federally Mandated Committee

- Human Protocols
- A committee of physicians, statisticians, researchers, community advocates that ensures a clinical trial is ethical and that the study participants rights are protected
- Require ethics training for all researchers
- Provides initial approval and periodic review of the research to protect the rights of human participants
- Can approve, require modifications or disapprove the plan

Study Validity

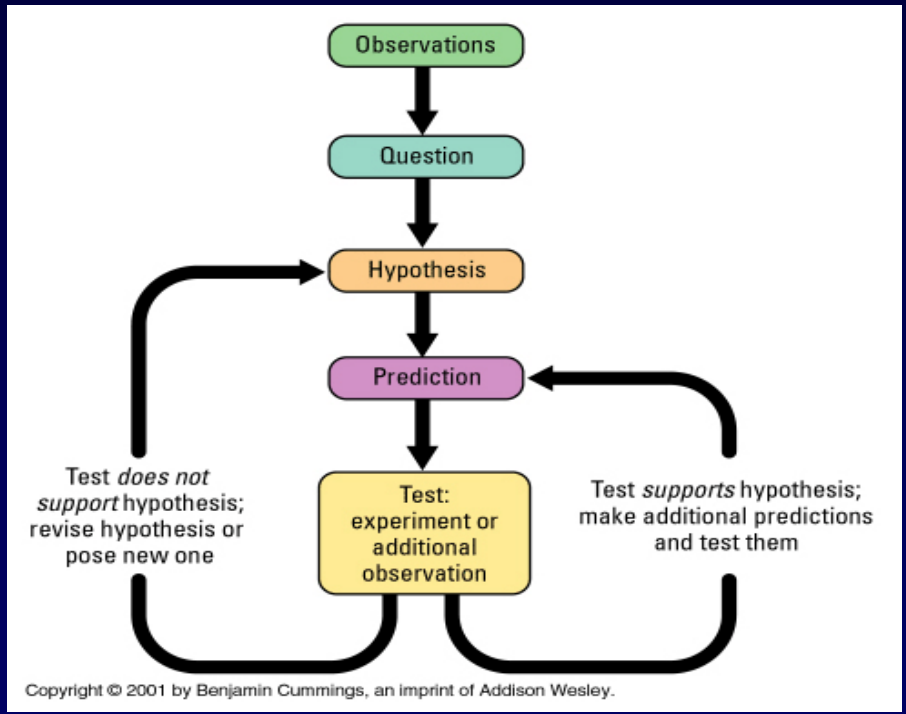
- Internal validity
  - When study groups are comparable in terms of demographics and clinical characteristics
- External validity
  - When study groups are comparable to the target population such as the general public

In Summary…….

- Knowing the literature/what has already been done and where the gaps in knowledge exist is essential
- Research should have a well-defined question to be answered and stated in a hypothesis
- The hypothesis determines the research design
- Research should contribute new information, be timely and relevant

- A series of small advances.

- Research is a continued development of learning from the work of others and yourself…
- Hypothesis development
- Experimental Design
- Experimentation
- Data analysis
- Hypothesis refinement
- Again and again and again……



- Thomas Edison took >1000 attempts to get the light bulb right