1 Design of Experiments

1.1 Controlled Experiments

1. The Salk Vaccine Field Trial (1954)

- experiment to test effectiveness of the Jonas Salk polio vaccine
  produces antibodies against polio
  - dates from prehistory
  - 1916 epidemic, U.S
  - 1928 iron lung
  - 1938 Roosevelt, NFIP

- tested on subjects most vulnerable to polio:
  - children in grades 1, 2, 3

- The National Foundation for Infantile Paralysis (NFIP) Study

  - treatment group (vaccinated): grade 2 (intramuscular injection)
  - "control" group (unvaccinated): grades 1, 2, and 3

  Q. Why not just vaccinate every subject in a given year and compare rate with previous years?

  Q. Year-to-year variability would mask any treatment effect or at least bias it.

  - school districts with high incidence of polio were selected

  - Results:
    | Group          | Size  | Rate per 100,000 |
    |----------------|-------|-----------------|
    | grade 2 (vaccine) | 285,000 | 25 ~ improvement over |
    | grades 1+3 (control) | 725,000 | 44 |
    | grade 2 (no contact) | 125,000 | 44 |
    | --------------------- | ------ | ----------------- |
    | Total                | 1,035,000 | 44 |

- But there are issues with this experimental design.
• **Issue:** children can be vaccinated only with parents' consent

  But permission is associated with higher income, which is associated with higher incidence (due to better hygiene, less exposure to obtain natural immunity)

  Hence: if "treatment group" = "consent group", then there is a bias against the vaccine. There is a group difference confounded with the treatment effect to be measured.

  **Solution:** choose both treatment group and control group from within the consent group.

• **Issue:** polio is contagious and spreads through contact

  Thus polio incidence can be higher or lower in grade 2 than in grades 1 and 3

  Hence: if treatment group is one grade and control group another, then again there is a bias. A difference in groups confounds the difference due to treatment versus no treatment

  **Solution:** make treatment and control groups similar with respect to grades
• Issue: the placebo effect

Sometimes the body can be healthier if we think or know that we are being treated with a preventative measure or a cure. This can also bias the comparison of treatment groups (who know they are vaccinated) with the control group (unvaccinated).

Solution: 1) Also inject the control group (with just a salt solution)
2) Do not inform the subject which they are getting ("subject blinding")

• Issue: diagnosis bias

Many forms of polio are hard to diagnose. In borderline cases, the doctor doing the diagnosis might be influenced by knowing whether the subject was vaccinated. Another source of bias.

Solution: "doctor blinding"

• Issue: Human judgement in assigning to groups

Unconsciously, a professional might want their child to be in that group. Another source of bias.

Solution: randomized assignment (equivalent to tossing a coin for each child)

Because of these issues, the NFIP study was somewhat flawed. A better design was adopted.
- The randomized controlled double-blinded experiment

- both treatment and control groups selected from
  the consent group

- randomized assignment to treatment and control
  groups, with double-blinding

- Results, Group Size Rate
  Treatment 200,000 28
  Control 200,000 71
  No consent 350,000 46

This comparison eliminates several biases
and gives a truer picture of the treatment
effect due to vaccination.

- Q. Could the observed difference be due purely to
  chance?

A: Yes. But incredibly unlikely. Hence we rule out
the "pure chance explanation". We make an
educated gamble.

Subsequent experience confirmed the validity of the
conclusion that the vaccine works.
2. The Porta caval Shunt
   - see text

3. Historical Controls
   - see text

4. Summary
   - see text, pp 10-11

- The PCP
  - see sheets (3, of which 2 on website)

- Excerpts about randomization and blinding, from particular papers
  - see sheet