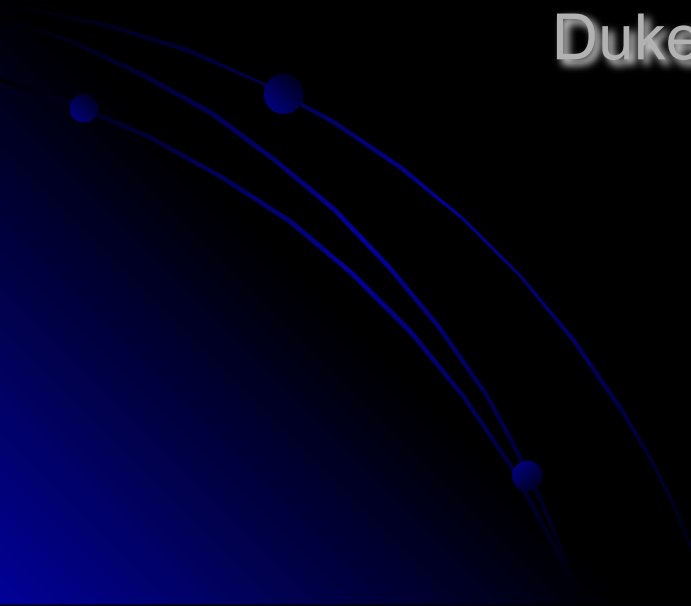


Evidence-Based Ophthalmology

David K. Wallace, MD, MPH

Duke University Eye Center



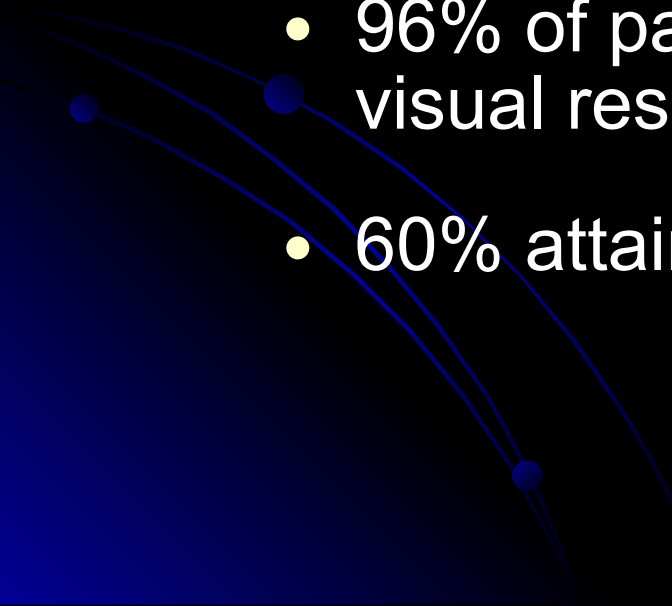
Example: Published Paper

PURPOSE: To determine the effectiveness and side effects of full-time occlusion for the treatment of amblyopia

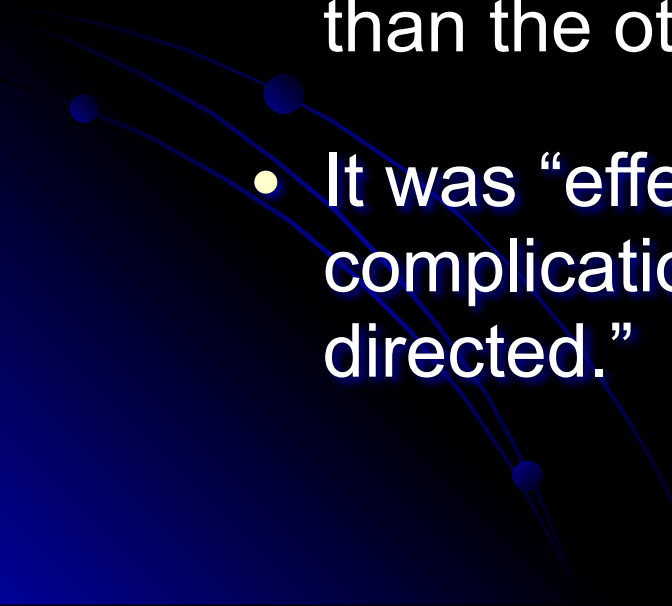
METHODS:

- Patients with... amblyopia were reviewed
- All patients had full-time occlusion
- Success was defined as 20/30 or better or equal visual acuity by fixation pattern

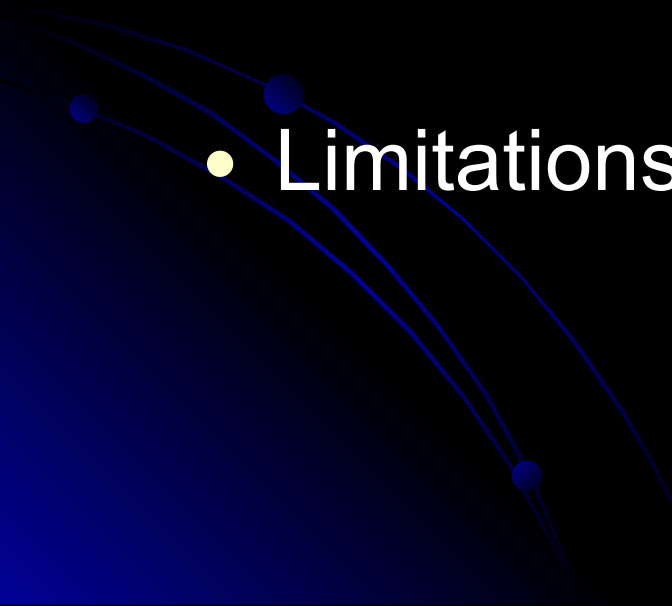
Results

- 600 patients fit the inclusion criteria
 - Mean follow-up of 7.2 years after patching stopped, to age of 10.8 years
 - 96% of patients attained a successful visual result
 - 60% attained equal visual acuity
- 

Conclusions

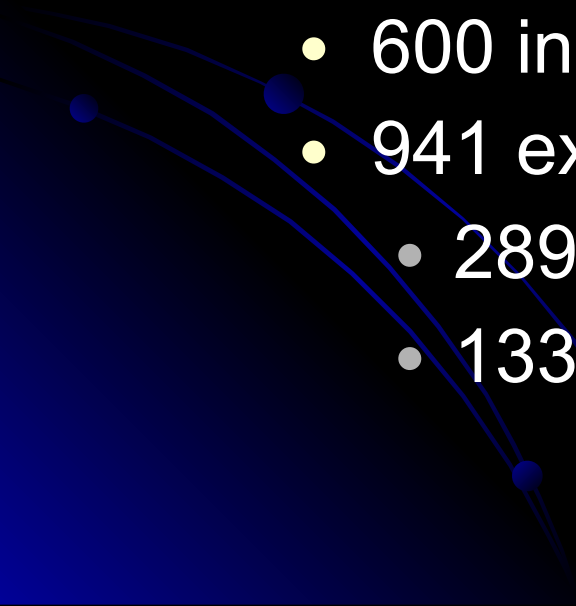
- “The results... demonstrate that full-time patching is effective in obtaining 20/30 or better vision.”
 - It “produces equal vision at a higher rate than the other forms of treatment.”
 - It was “effective with no long-term complications if patients proceed as directed.”
- 

Reader's Conclusions

- Should all patients have full-time patching?
(Hard to argue with “96% success”)
 - Limitations of this study's approach?
- 

Potential Problems

How many patients were excluded and why? Were those included similar to those excluded?

- 1541 charts reviewed
 - 600 included
 - 941 excluded
 - 289 lost to follow-up
 - 133 part-time patching
- 

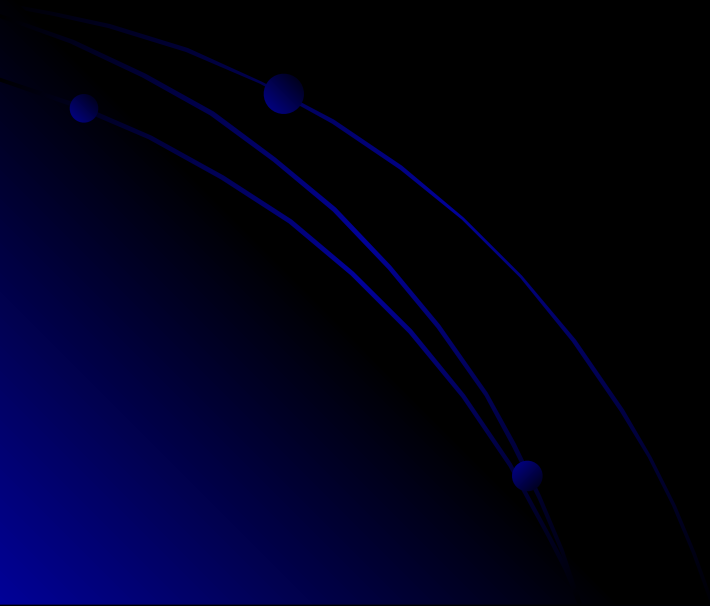
Sensitivity Analysis

- What if all of the patients lost to follow-up or with part-time patching had poor compliance and were unsuccessful?
 - Successes = 576
 - Failures = $24 + 289 + 133 = 446$
 - Success rate = $576 / 1022 = 56\%$

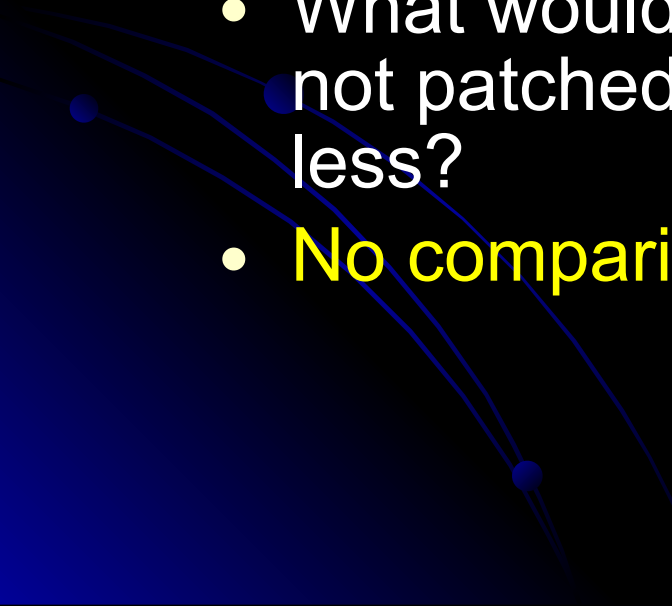
Visual Acuity Measurement

How was vision measured?

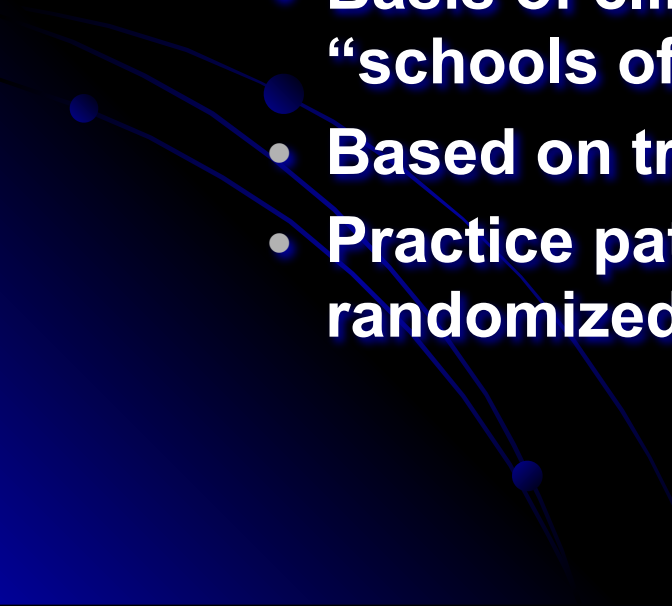
7 different ways



Other Issues

- What other treatments did they receive?
 - Many wore glasses - Which treatment improved vision?
 - What would have happened if children had not patched? What if they had patched less?
 - No comparison or control group
- 

Practice Patterns

- **Until recently, few clinical trials in pediatric ophthalmology / strabismus**
 - **Consequences**
 - **Variability in treatment guidelines**
 - **Basis of clinical practice was primarily “schools of thought”**
 - **Based on training**
 - **Practice patterns were developed with little randomized trial data**
- 

Hierarchy of Studies for Obtaining Evidence in Humans

Editorials or Opinions

Case Reports

Case Series

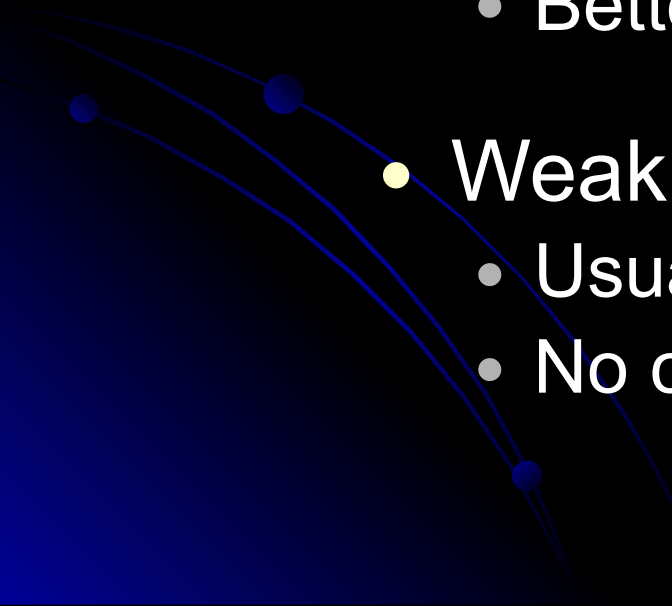
Case Control Studies

Cohort Studies

Randomized Clinical Trials

Meta-analyses of RCT's

Case Reports and Case Series

- Strengths
 - Useful for reporting...
 - Unusual observations
 - Treatment of rare conditions
 - Innovative treatment strategies
 - Better than nothing!
 - Weaknesses
 - Usually small numbers
 - No comparison group
- 


Case-Control Study

- Identify “cases” = those with disease
- Select “controls” = sample from population that produced cases (often those without disease, but not necessarily)
- Measure some exposure / risk factor in each group
- Results expressed as “odds ratio”
- OR = 1 means no association

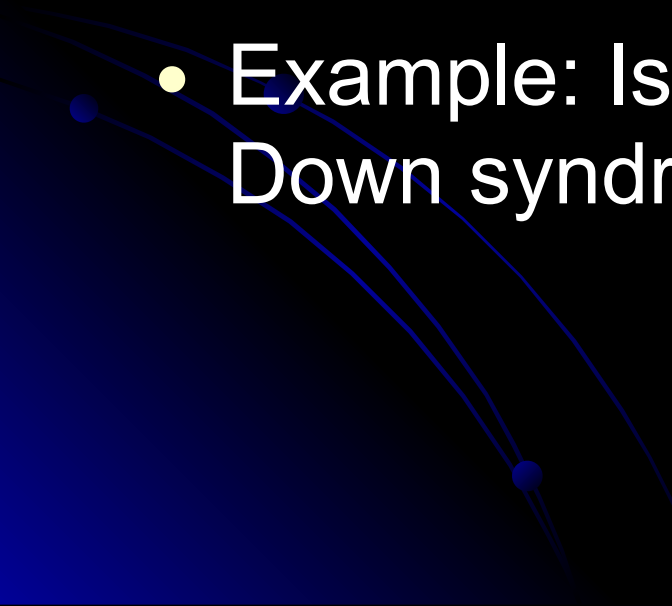
Snow's study

- Epidemic of cholera in 19th century London
- Suspected Broad St. pump was source
- Cases of cholera – where did they draw their water?
- Controls without cholera – water source?
- Showed a strong association between cholera and the Broad St. pump

Case-Control Studies

- Strengths
 - Control group
 - Particularly useful when the disease is rare or has a long induction / latent period
 - Weaknesses
 - Sometimes it is not clear that risk factor precedes the disease
 - Possibility of confounding
- 

Confounding

- Confounding: An observed association between two variables (factors) is due, at least in part, to another variable
 - Example: Is birth order associated with Down syndrome?
- 

Confounding Example

- Fictitious example: in case-control study, lower birth order is found to be associated with Down syndrome
- Confounder = **maternal age**
- Children of lower birth order tended to have older mothers, and maternal age is the important association

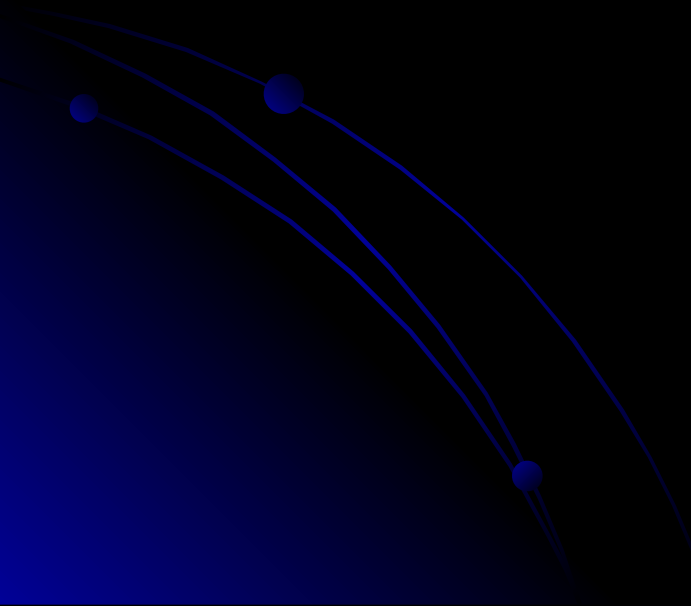
Confounding in Case-Control Studies

- How to deal with confounding:
 - Stratify: among older mothers only, no association between birth order and Down syndrome
 - Adjust statistically using regression analysis techniques
- If potentially confounding variables are not identified, measured, and accounted for, then erroneous conclusions can be reached
- Typically, some confounding variables are not known

Cohort Studies

“Cohort” = a group of subjects experiencing an event in a particular time span

e.g. untreated eyes of infants in the cryotherapy for ROP study constituted a natural history cohort



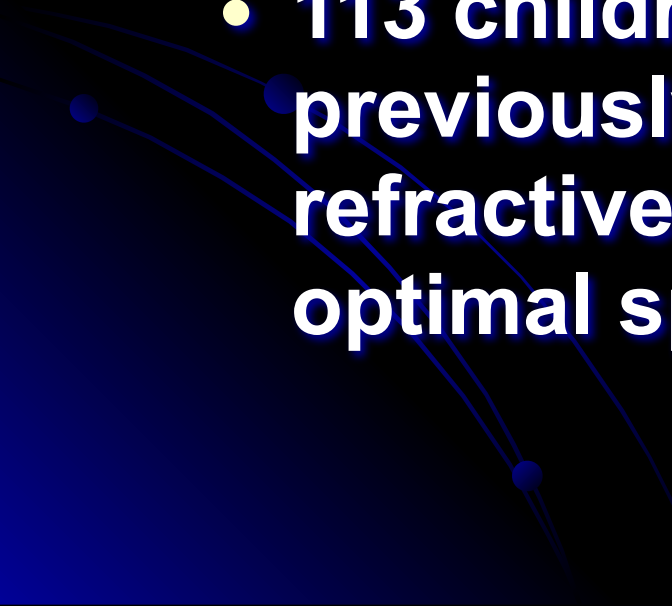
Amblyopia Treatment Study 7

**Treatment of Bilateral Refractive Amblyopia in
Children 3 to <10 Years Old**

Supported by the National Eye Institute



Subjects and Methods

- **Prospective cohort study at 27 sites**
 - **113 children age 3-10 with previously untreated bilateral refractive amblyopia provided with optimal spectacle correction**
- 

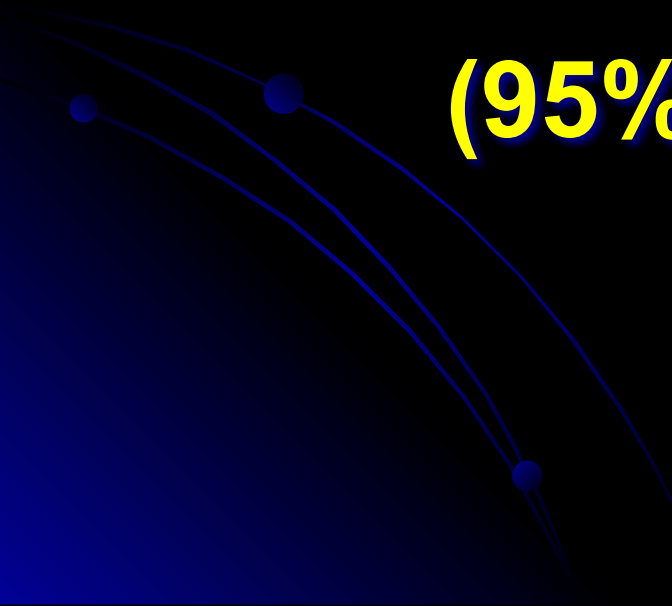
Bilateral Refractive Amblyopia Defined As:

- **20/40 to 20/400 best-corrected *binocular* acuity**
- **Refractive error criteria**
 - $\geq +4.00$ D hypermetropia by spherical equivalent, and/or**
 - ≥ 2.00 D astigmatism in each eye**

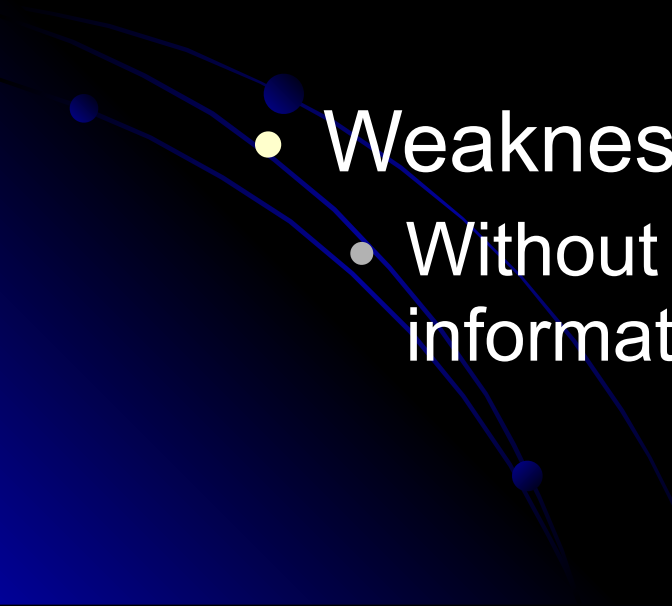
Mean Binocular Visual Acuity Improvement After 1 year

3.9 lines

(95% CI = 3.5 to 4.2)

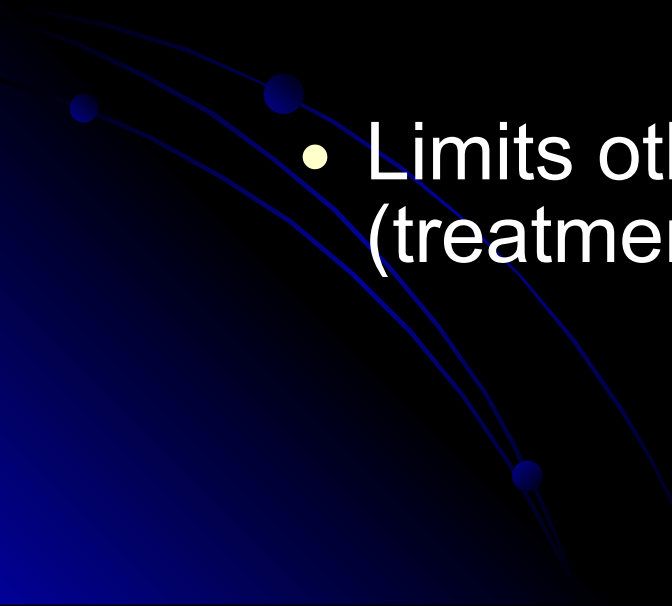


Cohort Studies

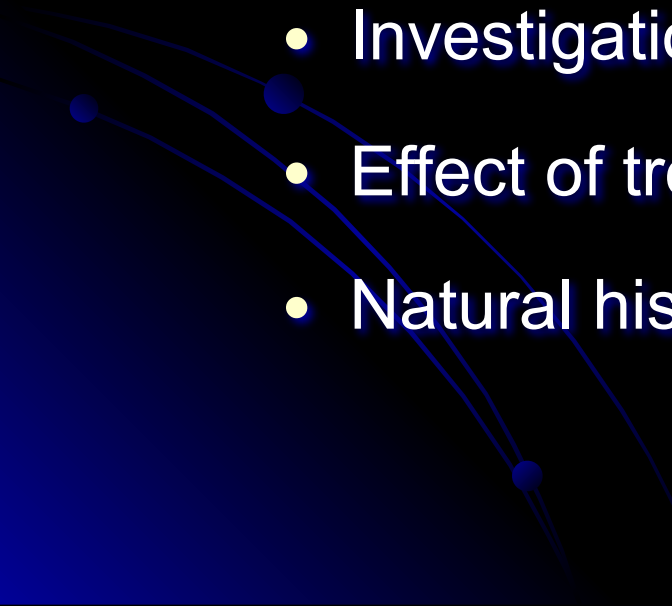
- Strengths
 - Best study design for determining an incidence of an event or prognosis of a condition
 - Standardized data collection
 - Weakness
 - Without comparison group, limited information on effect of treatment
- 

Randomized Clinical Trial *Advantages*


#1 – Randomization!!!

- Controls confounding
 - Limits other potential biases (treatment assignment)
- 

Others Advantages of RCT's

- Standardization of intervention
 - Prospective data collection
 - Masked outcome measures
 - Investigation of adverse events
 - Effect of treatment on 2^o outcomes
 - Natural history data
- 

Why So Few Clinical Trials?

- Requirements for Clinical Trials
 - “Burning” question
 - Equipoise for randomization
 - Feasible – unlikely for rare conditions
 - Disadvantages of Clinical Trials
 - Expensive
 - Time-consuming
 - Challenges of patient recruitment & retention
- 

“A carefully designed therapeutic trial is not only more scientific but also more ethical than the treatment of consecutive patients with a new drug of unproved value”

T. Chalmers, 1968

“One has only to review the graveyard of discarded therapies to realize how many patients would have benefited by being assigned to a control group”



T. Chalmers, 1968

Do we really need an RCT (if we think we already know the answer)?

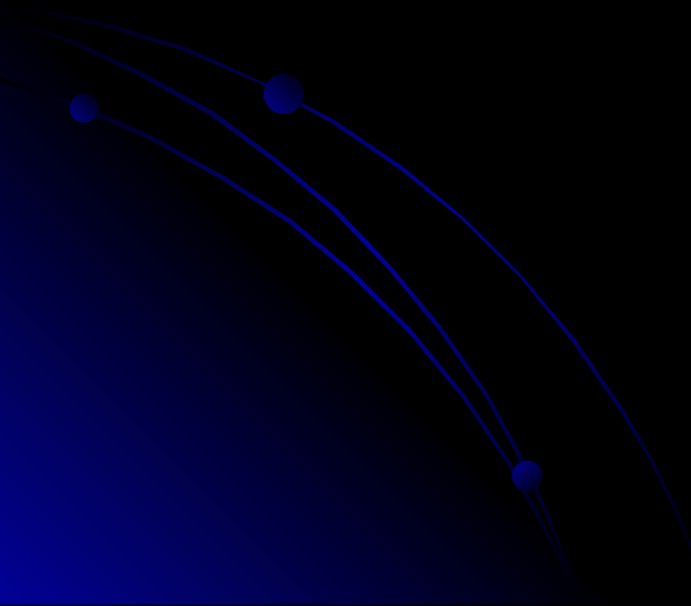
Gaynon et al noted that ROP worsened when supplemental oxygen weaned

They started targeting higher O2 saturations and compared before and after:

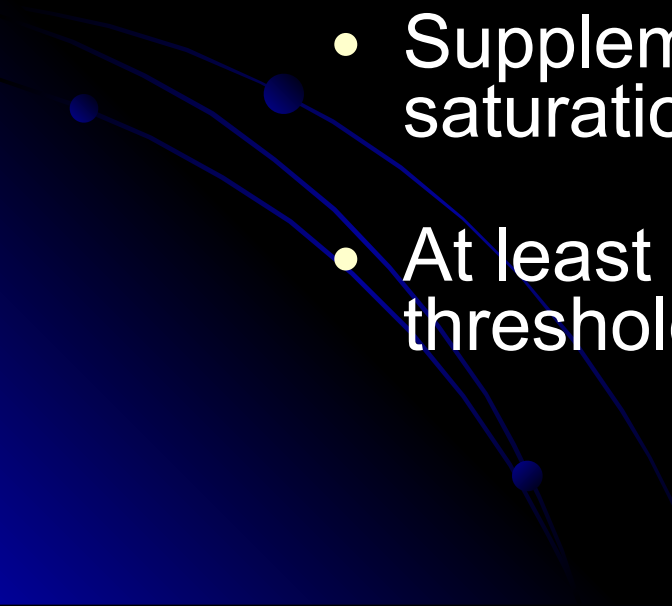
	<u>1985-89</u>	<u>1990-93</u>
Min. O2 sat.	92-96%	99%
Prethreshold	95	58
Threshold	35	4
Percent	37%	7%

STOP-ROP

Primary Question: Does supplemental oxygen reduce the incidence of ROP progression from prethreshold to threshold?



STOP-ROP Methods

- Randomized clinical trial
 - Conventional oxygen arm: 89-94% saturation
 - Supplemental oxygen arm: 96-99% saturation
 - At least 2 weeks & until endpoint of threshold or regression
- 

STOP-ROP Results

- 649 infants enrolled over 5 years
- *Rate of progression to threshold in at least one eye*
 - *Conventional arm* 48%
 - *Supplemental oxygen arm* 41%
- Difference not statistically significant

Adverse Pulmonary Events

- Pneumonia and/or exacerbations of chronic lung disease
 - Conventional arm 8.5%
 - Supplemental oxygen arm 13.2%

- Infants at 50 weeks postmenstrual age

	<u>Supplemental</u>	<u>Conventional</u>	
Hospitalized	6.8%	12.7%	
On oxygen	37.0%	46.8%	
On diuretics	24.4%	35.8%	

Take Home Messages

- RCTs provide the highest quality of evidence
 - Not every study can or should be an RCT
 - Best study design depends on the question being asked
- 