



PROOF AND CONSEQUENCES: THE HISTORY OF CLINICAL TRIALS IN OPHTHALMOLOGY

Pamela C. Sieving, MA, MS

NIH Library

Bethesda, Maryland

MILESTONES IN CLINICAL TRIAL HISTORY

- Daniel
- 1753: 6 Arm, nutritional intervention (Lind)
- 1834: Prospective design, control (Louis)
- 1865: Placebo proposed (Sutton)
- 1915: Randomization proposed (Greenwood & Yule)
- 1927: Masking (Ferguson, Davey & Topley)
- 1948: First randomized, placebo-controlled, double-blind trial (Medical Research Council)



RETROLENTAL FIBROPLASIA

- 1952: Patz, Hoeck & de la Cruz (Am J Ophthalmol 35:1248)
 - 1952: First multi-center RCT
 - 1955: Reese (Am J Ophthalmol 40:267)
 - 1956: Guy (Pediatrics 17:247)
- Cases
 - ↗ 1950: 278
 - ↗ 1951: 363
 - ↗ 1952: 454
 - ↗ 1953: 442
 - ↗ 1954: 170
 - ↗ 1955: 62
 - ↗ 1956: 35
 - ↗ 1957: 10
 - ↗ 1958: 7

OPHTHALMOLOGY

Retrolental Fibroplasia

Cooperative Study of Retrolental Fibroplasia and the Use of Oxygen

V. EVERETT KINSEY, Ph.D.

Detroit

With the Assistance of June Twomey Jacobus, B.A., Detroit,
and F. M. Hemphill, Ph.D., Ann Arbor

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From the Kresge Eye Institute (Dr. Kinsey and Mrs. Jacobus) and the Department of Public Health Statistics, School of Public Health, University of Michigan (Dr. Hemphill).

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The Coordination Committee was composed of the following members: V. Everett Kinsey, Chairman, Kresge Eye Institute; Richard L. Day, State University of New York College of

(Footnotes continued on next page)



Source: SUNY Downstate Medical Center
Evidence-Based Medicine Course

NEW ETHICAL STANDARDS

- Consent, Beneficence, Benefit, Autonomy, Good Science, Equipoise
- Codes
 - *Nuremberg, 1947*
 - *Belmont Report 1979*
 - *Declaration of Helsinki 1964/2000*
 - *ICH Harmonised Tripartite Guideline 1996*
 - *Common Rule, Title 45 1991/2001*
- Rights of Children, Women, Minorities, Mentally Disabled, Prisoners
- Institutional Review Boards
- Data Safety Monitoring Committees
- Recombinant DNA Advisory Committee

NIH SUPPORT

- NINDB: \$51,000 for ROP trial
 - 18 centers
 - *Effect of duration of exposure to O₂ on incidence of development of retrolental fibroplasia*
- 1961 NINDB anniversary:
 - *RF 'the most outstanding discovery in ophthalmology during the past 10 years'*
- 1972 NEI Annual Report:
 - *Education of prospective research subjects proposed*
 - *Fundus photography reading center*
- 1973 NEI Annual Report:
 - *Twin trial of myopia progression*
- 1974: NEI AUPO workshop on clinical trials
- 1976: Diabetic Retinopathy Study results



DIABETIC RETINOPATHY STUDY

- Dissemination to 10,000 ophthalmologists, 3000 MDs who belonged to ADA
- 228 Physicians attended U Michigan CME (JAMA 1979; 241:2622)
 - 43% knew DRS had taken place
 - 28% were aware of results
 - 33% chose DRS-determined therapy for 2 patients
- Trial dissemination studied from citations, 1976-79 (Bull Med Libr Assc 1981; 69:301)
 - 43 ophthalmology journals, 27 non-ophthalmology



THE IDEAS SPREAD

- 1982: Carl Kupfer receives U Penn Dr Med (HC):
 - *“...successful application of collaborative clinical trials to a variety of complicated ophthalmic conditions, most notably diabetic retinopathy”*
- 1990 ICO, Singapore
 - *NEI reports 15 epidemiological studies, 21 multicenter trials*
 - *\$30 million annually*
- 1992: Optic Neuritis Treatment Trial
 - *Dissemination of results*

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A RANDOMIZED, CONTROLLED TRIAL OF CORTICOSTEROIDS IN THE TREATMENT OF ACUTE OPTIC NEURITIS

ROY W. BECK, M.D., PATRICIA A. CLEARY, M.S., MALCOLM M. ANDERSON, JR., P.A.C., JOHN L. KELTNER, M.D., WILLIAM T. SHULTS, M.D., DAVID I. KAUFMAN, D.O., EDWARD G. BUCKLEY, M.D., JAMES J. CORBETT, M.D., MARK J. KUPERSMITH, M.D., NEIL R. MILLER, M.D., PETER J. SAVINO, M.D., JOHN R. GUY, M.D., JONATHAN D. TROBE, M.D., JOHN A. MCCRARY, III, M.D., CRAIG H. SMITH, M.D., GEORGIA A. CHROUSOS, M.D., H. STANLEY THOMPSON, M.D., BARRETT J. KATZ, M.D., MICHAEL C. BRODSKY, M.D., JAMES A. GOODWIN, M.D., CONSTANCE W. ATWELL, PH.D., AND THE OPTIC NEURITIS STUDY GROUP*

Abstract *Background and Methods.* The use of corticosteroids to treat optic neuritis is controversial. At 15 clinical centers, we randomly assigned 457 patients with acute optic neuritis to receive oral prednisone (1 mg per kilogram of body weight per day) for 14 days; intravenous methylprednisolone (1 g per day) for 3 days, followed by oral prednisone (1 mg per kilogram per day) for 11 days; or oral placebo for 14 days. Visual function was assessed over a six-month follow-up period.

Results. Visual function recovered faster in the group receiving intravenous methylprednisolone than in the placebo group; this was particularly true for the reversal of visual-field defects ($P = 0.0001$). Although the differences between the groups decreased with time, at six months the group that received intravenous methylprednisolone still had slightly better visual fields ($P = 0.054$), contrast

sensitivity ($P = 0.026$), and color vision ($P = 0.033$) but not better visual acuity ($P = 0.66$).

The outcome in the oral-prednisone group did not differ from that in the placebo group. In addition, the rate of new episodes of optic neuritis in either eye was higher in the group receiving oral prednisone, but not the group receiving intravenous methylprednisolone, than in the placebo group (relative risk for oral prednisone vs. placebo, 1.79; 95 percent confidence interval, 1.08 to 2.95).

Conclusions. Intravenous methylprednisolone followed by oral prednisone speeds the recovery of visual loss due to optic neuritis and results in slightly better vision at six months. Oral prednisone alone, as prescribed in this study, is an ineffective treatment and increases the risk of new episodes of optic neuritis. (N Engl J Med 1992; 326:581-8.)

OPTIC NEURITIS is an acute demyelinating dis-

treatments for optic neuritis has been debated since

THE IDEAS SPREAD

- 1982: Carl Kupfer receives U Penn Dr Med (HC):
 - “...successful application of collaborative clinical trials to a variety of complicated ophthalmic conditions, most notably diabetic retinopathy”
- 1990 ICO, Singapore
 - NEI reports 15 epidemiological studies, 21 multicenter trials
 - \$30 million annually
- 1992: Optic Neuritis Treatment Trial
- 2000: Evidence-Based Eye Care (now Evidence-Based Ophthalmology)
- 2001:
 - NEI funds CEVG@US
 - Johns Hopkins Symposium to mark anniversaries
 - AREDS results published
- 2002: A. Heijl “On a Mission from God” (Acta Ophthalmol 80:123)



AAO LEADERSHIP

- 1999: Ophthalmology (106:11)
 - *Requires CONSORT data for trial reports*
 - *Promotes AAO initiatives on evidence-based practice, understanding of research methodology*
- 2000: Ophthalmology: Initiates evidence-based clinical updates (107:9)
- 2005: Ophthalmology: Clinical trials the 'gold standard' (103:869)
- 2006:
 - *"The State of Being Noninferior" (Ophthalmology 113:1)*
 - *18 Preferred Practice Patterns*





Clinical Studies Database *Supported by the National Eye Institute*

All Clinical Studies

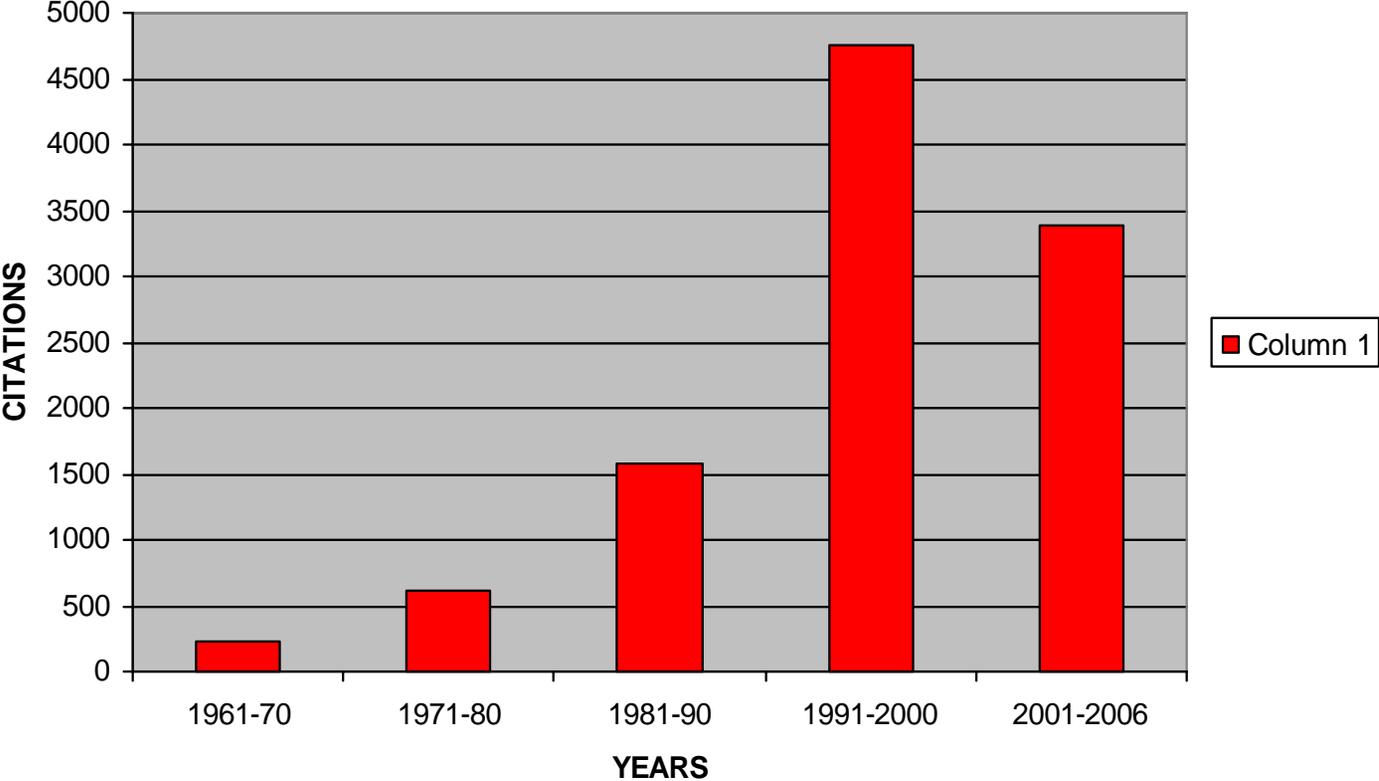
The Clinical Studies Database includes information on major completed and ongoing clinical research supported by the NEI since 1970. This area includes Clinical Trials, Epidemiology and Natural History Studies, and Health Services Research sections of the database.

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- ▶ [Age-Related Eye Disease Study \(AREDS\)](#)
- ▶ [Age-Related Eye Disease Study II \(AREDS II\)](#)
- ▶ [Amblyopia Treatment Study: Occlusion Versus Pharmacologic Therapy for Moderate Amblyopia](#)
- ▶ [Amblyopia Treatment Study: A Randomized Trial to Evaluate 2 Hours of Daily Patching for Amblyopia in Children 3 to <7 Years Old](#)
- ▶ [Berkeley Orthokeratology Study, The](#)
- ▶ [Bilateral Refractive Amblyopia Treatment Study](#)
- ▶ [Branch Vein Occlusion Study](#)
- ▶ [Central Vein Occlusion Study \(CVOS\)](#)
- ▶ [Clinical Trial of Eye Prophylaxis in the Newborn](#)
- ▶ [Collaborative Corneal Transplantation Studies \(CCTS\)](#)
- ▶ [Collaborative Initial Glaucoma Treatment Study \(CIGTS\)](#)
- ▶ [Collaborative Italian-American Clinical Trial of Nutritional Supplements and Age-related Cataract \(CTNS\)](#)

OPHTHALMIC CLINICAL TRIAL REPORTS (MEDLINE)



CLINICAL TRIAL REGISTRIES

- www.clinicaltrials.gov (92 glaucoma trials)
- www.controlled-trials.com (32)
- www.actr.org.au (7)
- www.trialregister.nl (0)
- www.umin.ac.jp/ctr/index/htm (0)



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CEVG Reviews

Systematic Reviews

Cornea and external eye disease

- [Antibiotics for trachoma \(click for abstract\)](#)
- [Antibiotics versus placebo for acute bacterial conjunctivitis \(click for abstract\)](#)
- [Environmental sanitary interventions for preventing active trachoma](#)
- [Face washing promotion for preventing active trachoma \(click for abstract\)](#)
- [Interventions for herpes simplex virus epithelial keratitis \(click for abstract\)](#)

Glaucoma

- [Interventions for normal tension glaucoma \(click for abstract\)](#)
- [Intra-operative Mitomycin C for glaucoma surgery \(click for abstract\)](#)



Applying Cochrane Systematic Review Methodology to Improve Evidence-based Clinical Practice and Practice Guidelines

Monday, May 1, 2006

1:15 - 2:45 PM

Grand Floridian D



Join us at the Association for Research in Vision and Ophthalmology's (ARVO) Annual Meeting, 30 April - 4 May 2006, Fort Lauderdale, Florida for the Special Interest Group (SIG) Session.

Presentations:

- 1:15 - 1:30PM: Introduction - Kay Dickersin, PhD and Roberta Scherer, PhD (Johns Hopkins Bloomberg School of Public Health)
 - 1:30 - 1:45PM: Systematic Review of Aqueous Shunts for Glaucoma - Donald Minckler, MD (University of Southern California, Keck School of Medicine, Department of Ophthalmology)
 - 1:45 - 2:00PM: Systematic Review of Interventions for Slowing Myopia Progression - Karla Zadnik, OD, PhD (The Ohio State University College of Optometry)
 - 2:00 - 2:15PM: The Impact of Systematic Reviews on AAO's Preferred Practice Patterns - Richard Abbott, MD (University of California, San Francisco, Francis I. Proctor Foundation for Research in Ophthalmology)
-

?? THE FUTURE ??

- Clinical Trial Registration
- Education
- Internet:
 - ↗ *Organize, Plan*
 - ↗ *Recruit*
 - ↗ *Transmit Data*
 - ↗ *Disseminate Results*
- Global Research, Worldwide Impact
 - ↗ *US-India Statement of Intent signed August, 2005*
 - ↗ *STAR (Surgery for Trichiasis, Antibiotics to prevent Recurrence): Wolayta Zone, Ethiopia. Arch Ophthalmol 2006; 124:309*



New York Times 3/31/06

References

- Kertes PJ, Conway MD: Clinical Trials in Ophthalmology: A summary and practice guide. Lippincott Williams & Wilkins, 1998.
- Wormald R, Smeeth L, Henshaw K. Evidence-Based Ophthalmology. BMJ Books, 2004

THANK YOU!

PamSieving@nih.gov

