The First Clinical Trials in Vision:
A Brief and Incomplete History

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Financial Disclosure/Conflict of Interest:

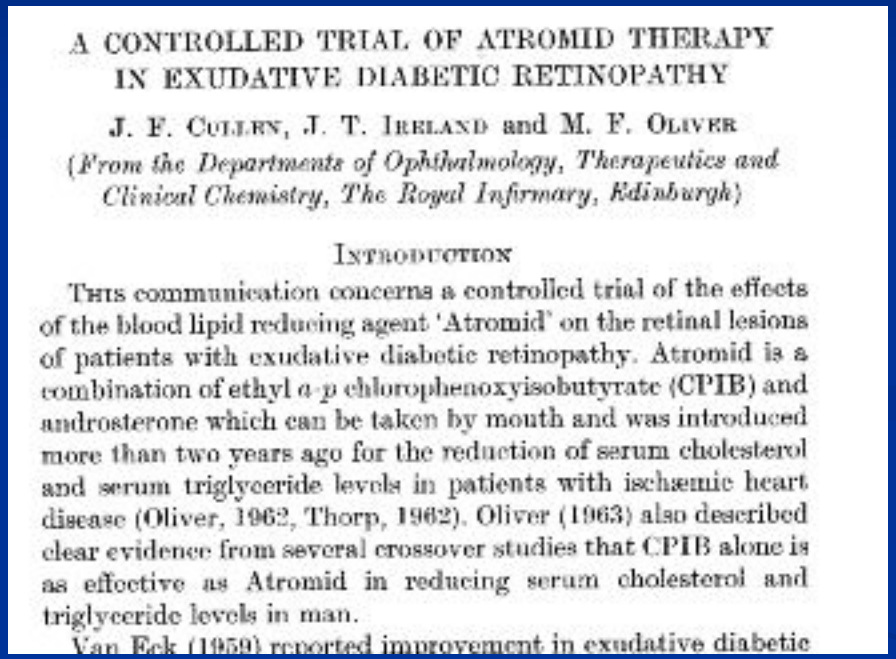
I have no financial interests or relationships to disclose

How to Recognize a Clinical Trial

- Prospective, planned study design
  - Louis, 1834
- Control/placebo
  - Lind, 6 arm, 1753
  - Sutton, 1865
- Randomization
  - Greenwood & Yule, 1915
- Masking ("blinding": single, double, triple)
  - Ferguson, Davey & Topley, 1927

The first multi-center, randomized, placebo-controlled, double blind study: 1948

Earliest Medline-indexed clinical trial in ophthalmology:



A CONTROLLED TRIAL OF ATROMID THERAPY IN EXUDATIVE DIABETIC RETINOPATHY

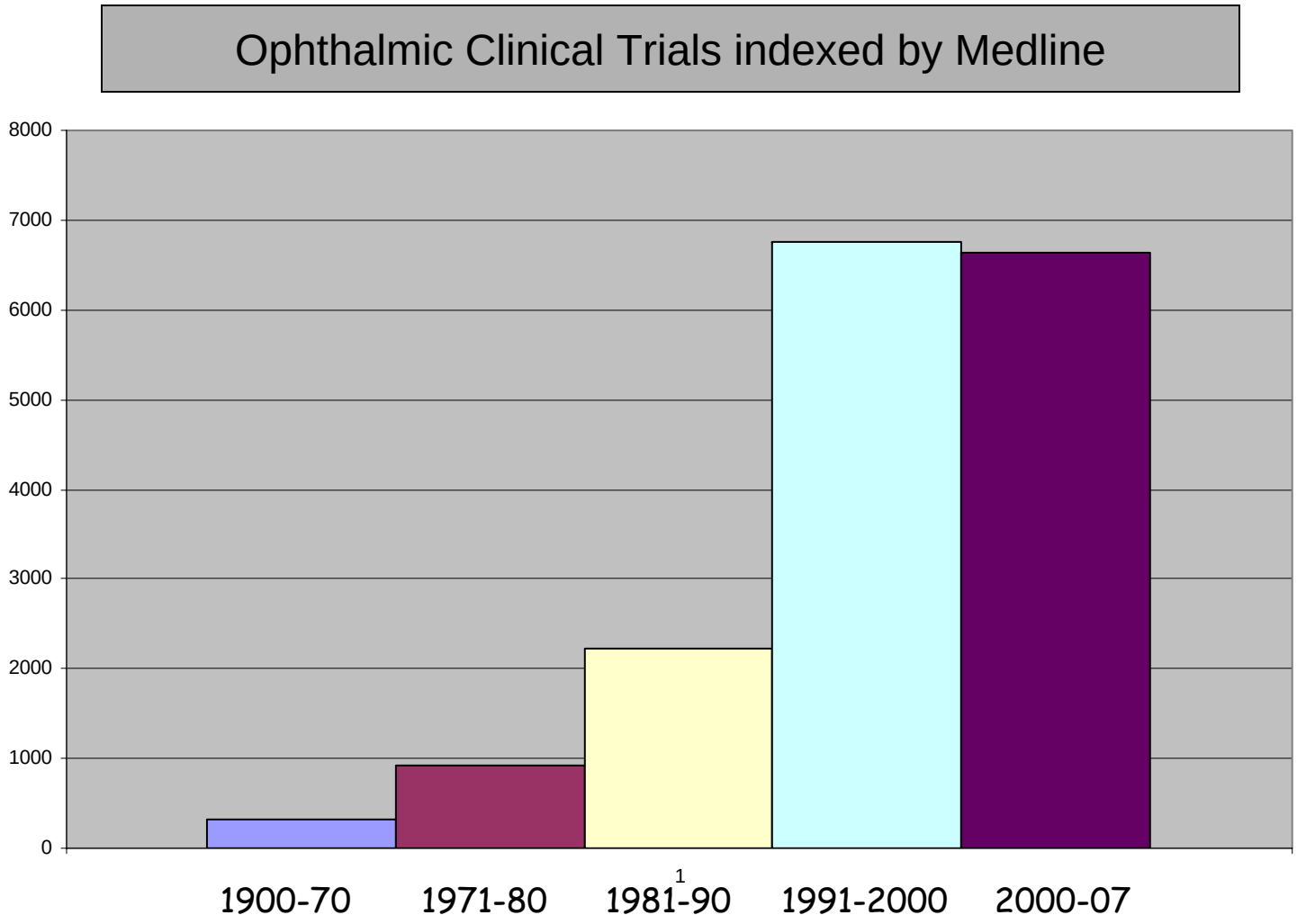
J. F. Cullen, J. T. Ireland and M. F. Oliver
(*From the Departments of Ophthalmology, Therapeutics and Clinical Chemistry, The Royal Infirmary, Edinburgh*)

Introduction

This communication concerns a controlled trial of the effects of the blood lipid reducing agent 'Atromid' on the retinal lesions of patients with exudative diabetic retinopathy. Atromid is a combination of ethyl *a-p* chlorophenoxyisobutyrate (CPIB) and androsterone which can be taken by mouth and was introduced more than two years ago for the reduction of serum cholesterol and serum triglyceride levels in patients with ischæmic heart disease (Oliver, 1962, Thorp, 1962). Oliver (1963) also described clear evidence from several crossover studies that CPIB alone is as effective as Atromid in reducing serum cholesterol and triglyceride levels in man.

Van Eck (1959) reported improvement in exudative diabetic

Trans Ophthalmol Soc UK 1964 v84



Sieving AAO 2007

An even earlier study:

Material and Methods

An initial trial was conducted to compare 0·2 per cent. chlorhexidine/5 per cent. D.D.S. ointment with neomycin ointment. This trial included all cases of superficial ocular infection attending the out-patients department. This preliminary

Brit. J. Ophthal. (1960) **44**, 761.

CLINICAL TRIAL OF CHLORHEXIDINE AND DIAMINODIPHENYLSULPHONE IN SUPERFICIAL OCULAR INFECTIONS*

BY

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In recent years a new antibacterial agent, chlorhexidine ("Hibitane") has become available (Davies, Francis, Martin, Rose, and Swain, 1954; Murray and Calman, 1955). This compound has a wide range of bacteriostatic activity against both Gram-positive and Gram-negative organisms and is of low toxicity. The development of bacterial resistance to chlorhexidine has not been demonstrated. It is now used extensively for general antisepsis, but until recently its application in the conjunctival sac has been limited by the irritant nature of the diacetate salt commonly employed. Recently a less irritant but still soluble salt, chlorhexidine gluconate, has become available. This may be used in strengths of up to 0·2 per cent. as against 0·05 per cent. for the diacetate compound.

the small number of cases available.

In each patient the duration of the symptoms and the presence or absence of previous treatment elsewhere was ascertained, and this information was used to allocate patients to groups of similar duration and previous treatment. The patients were grouped according to 3-day intervals up to 12 days, a fifth group comprising cases of over 12 days' duration. These five groups were then further sub-divided into treated and untreated patients, making ten groups in all. Within each of these ten groups successive patients were allocated to receive one of the four preparations by reference to a table of random permutations.

In this way it was hoped to minimize the effect of variations in the duration of the disease and of previous treatment. The treatment received was unknown to the patient or to the observer, who saw each patient at every attendance.

The ointment was applied 4-hourly during the trial period, and the number of

Early Trial Reports:

- Synthetic mydriatic (Riddell, *Br J Ophthalmol* 1946 v30)
- Erythromycin in trachoma (Agarwal, *Br J Ophthalmol* 1954 v38)
- Pyrimethamine for uveitis (Perkins, *Br J Ophthalmol* 1956 v40)
- Sulfamethoxypyridaxine for trachoma (Bietti, *Rev Int Trachome* 1957 v34)

IODIDE TRICHLORIDE.

	No. of Cases observed.	Percentage of Ophthalmia Neonatorum.	
Buchholz, Dorpat, 1, 4, '92, to 1, 4, '93,	201	1.0	Diss. Dorpat, 1893.
Keilmann, Dorpat u. Breslau,	500	1.4	Schles. Gesellschaft fur vaterl. Cultur., 25, 1, '95.
	701	1.2	

From these tables it will be seen that we have here the results of various treatment in over 54,000 cases, and they are divided as follows:

17,767	births	with no treatment,	9.2	per cent. of ophthalmia of infancy.
24,724	"	2 per cent. solution of silver nitrate,	0.65	per cent.
1,223	"	1 " " "	2.4	"
1,623	"	carbolic acid solutions,	7.7	"
965	"	0.1 per cent. solution of sublimate,	0.6	"
1,396	"	other sublimate solutions,	0.4	"
6,155	"	sterilized water,	2.8	"
701	"	iodide trichloride solutions,	1.2	"

It will be seen that previous to the introduction of Credé's method the records of over 17,000 births, tabulated by thirteen observers, showed that over nine per cent. of the children developed ophthalmia neonatorum. On the contrary, after the introduction of Credé's method, the records of over 24,000 births, tabulated by thirty-one observers, showed only .65 per cent. In other words, the proportion was nearly 15 times more frequent without the Credé method than with it. Attempts have naturally been made to obtain the same results with other agents, and the relative success with these is shown in Kostling's list. It will be seen that all of these methods give a larger percentage of ophthalmia than does Credé's method, with possibly the excep-

First meta-analysis?

Systematic review?

Call to adopt guideline?

Trans Am Ophthalmol Soc 1897 v8

Retrolental Fibroplasia: An Early Success

- 1952: Patz, Hoeck & de la Cruz
  Am J Ophthalmol v35
- 1952:
  First multi-center RCT
- US Cases:
  - 1950: 278
  - 1951: 363
  - 1952: 454
  - 1953: 442

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  - 1951: 363
  - 1952: 454
  - 1953: 442
  - 1954: 170
  - 1955: 62
  - 1956: 35
  - 1957: 10
  - 1958: 7

Success Noted:

- "An epitaph for RF"
  (*Am J Ophthalmol* 1955 v40)
- "The possibility of total elimination of RF by oxygen restriction"
  (*Pediatrics* 1956 v17)
- "The most outstanding discovery in ophthalmology during the past 10 years"
  (NINDB anniversary)

The Floodgates Open

- Trachoma vaccine and therapy
- Bacteriostatic contact lenses
- Oral glycerol in glaucoma
- Pituitary ablation for DR
- Anesthetic agents to control blood loss in strabismus surgery
- Tobacco amblyopia
- Radiological exophthalmolmetry
- Estrogens for traumatic hyphema
- Antiviral drugs for keratitis
- Inclusion conjunctivitis
- Optic neuritis
- Episcleritis-scleritis
- Anticholinesterase drugs for cataract
- Succinylcholine for IOP
- Fructose for diabetic retinopathy
- Lipotriad for AMD

Published in…

- Quarterly Journal of Medicine
- *The Lancet*
- The American Journal of the Medical Sciences
- *Antimicrobial Agents & Chemotherapy*
- Annals of the NY Academy of Sciences
- *American Journal of Epidemiology*
- Der Anaesthesist
- *Clinical Radiology*
- Deutsche Medizinische Wochenschrift

It's in the Air…

- Confounding factors (sanitation, working conditions) identified (Cameron, *Br J Ophthalmol* 1949 v33)
- Documentation of serial changes in retinal pathology in over 50 patients is "a formidable and exacting task" (Joplin, *Q J Med* 1965 v34ns)
- Loss to follow-up noted (Watson, *Br J Ophthalmol* 1966 v50)
- Patients should be stratified for risk factors before randomisation (Gregor, *Br J Ophthalmol* 1977 v61)
- Grant support acknowledged (NB 3576….1967)

Wonderful little, when all is said,
Wonderful little our fathers knew:
Half their remedies cured you dead,
Most of their teaching was quite untrue.

--Rudyard Kipling
(quoted in Duke-Elder System of Ophthalmology v7)

Thank You!

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