THE THERAPY OF AMBLYOPIA: AN ANALYSIS COMPARING THE RESULTS OF AMBLYOPIA THERAPY UTILIZING TWO POOLED DATA SETS*

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ABSTRACT

Context: We previously presented the results of an original pooled data set of 961 amblyopic patients who underwent patching therapy for amblyopia from 1965 to 1994 (study group 1).[1] Three types of amblyopia were considered: anisometropic, anisometropic-strabismic, and strabismic. Analysis of this group's success was related to the age at which therapy was initiated, the type of amblyopia, and the depth of visual loss before treatment was begun. The purpose of the current study is to test the validity of these findings on a second group of 961 amblyopes employing the data set used by Woodruff and associates in their publications[25,26] (study group 2). These 2 data sets, after adjustment to conform to the definitions of age, amblyopia, anisometropia, and similar items utilized in common between the 2 study groups, will be compared for the risk factors predictive of successful occlusion therapy.

Outcome: As in the previous study, the success of occlusion therapy is defined as a visual acuity of 20/40 or better at the end of treatment.

Results: Success by the 20/40 criteria was achieved in 73.7% in study group 1 and in 59.9% in study group 2. By category, the rate of success in study

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group 1 was 77.2% in strabismic amblyopia, 67.2% in anisometropic-strabismic amblyopia, and 66.0% in anisometropic amblyopia. In study group 2, success was 61.2% in strabismic amblyopia, 51.2% in anisometropic-strabismic amblyopia, and 63.0% in anisometropic amblyopia. Study group 1 univariate analysis related success in each group to the age at which therapy was initiated, the type of amblyopia, and the depth of visual loss before treatment in each group. In study group 2, univariate analysis related success of occlusion therapy to age and the depth of visual loss before treatment. Type of amblyopia was not related to outcome success in this group. When the 2 data sets were pooled, the risk factors for success were age and depth of visual loss at onset of treatment.

Conclusions: Factors that appeared closely related to a successful outcome of patching therapy were patient age and depth of visual loss before treatment. These conclusions further support the value of early detection and screening for amblyopia, its prevention, where possible, and its adequate and vigorous treatment when it is detected and diagnosed.

INTRODUCTION

In a previous paper[1] we presented an analysis of the results of occlusion therapy on amblyopic subjects drawn from the pooled raw data of 23 studies.[2-24] This group consisted of 961 amblyopes of 3 types—strabismic, anisometropic, and anisometropic-strabismic—and will be designated study group 1. We sought to address 3 basic questions concerning the outcome of occlusion therapy in treating amblyopia:

- How does occlusion of the dominant eye affect the recovery of vision in the amblyopic eye?
- What risk factors influence this outcome?
- What can we say about recidivism following occlusion therapy?

The results of that study were that occlusion therapy, in the very varied group of patients from 23 studies, was successful in the short term; that the major risk factors for failure were type of amblyopia, age at which therapy began, and depth of the amblyopia at the start of therapy. Recidivism, although it remains a problem in amblyopia therapy, occurs in a minority of patients following successful occlusion therapy. The purpose of this paper is to take those significant findings as hypotheses and test them on an independently gathered data set of some 961 children treated for the same types of amblyopia at 7 orthoptic centers in England during 1983. This group will be designated study group 2. The results of that study have

been reported elsewhere.[25,26] Finally, we will combine the 2 data sets to generate new and testable hypotheses on the nature of the biologic response of the amblyopic visual system to occlusion of its fellow eye.

MATERIALS AND METHODS

POPULATION

Study group 1, its study population, and patient characteristics have been described elsewhere.[1] The patient characteristics of study group 2 are described in the publications of Woodruff and associates.[25,26]

STUDY VARIABLES

In order to make the amblyopic subjects in study group 2 comparable to those in study group 1, we aligned the definitions of the variables listed in Table I between the 2 study groups and eliminated those amblyopic subjects in both study groups that did not conform to these definitions. After using similar definitions, study group 1 was modified to include only children 10 years of age and younger with a specified type of amblyopia, resulting in a sample of 767 patients in this group. In study group 2, we eliminated 372 patients and also led to reclassifying certain patients. The data set for study group 2 consists of 589 patients. Patients classified in the original British data set (group 2) as amblyopic with visual acuities of 20/40 or better were eliminated as not having amblyopia for purposes of this study. Patients classified as anisometropic-strabismic on the basis of a 1 D difference in spherical or cylindrical refractive error were reclassified in the current study as simply strabismic to conform to the definition of anisometropia used in study group 1 of 1.5 D or greater difference in spherical equivalent between the eyes.

TABLE I: EXCLUSIONS FROM STUDY GROUP 2 POPULATION

TOTAL POPULATION	961 AMBLYOPES
Not amblyopic at any time (VA ≥20/40)	-231
Not amblyopic during treatment	-102
Lack acuity data during treatment	-18
Coding errors	-21
Amblyopic population analyzed	589

TYPE OF OCCLUSION

The type of occlusion used in group 2 was partial as defined in the group 1 study: occlusion for any interval less than 24 hours per day was defined

as partial. Since no difference in the outcome (success of treatment) was noted in the former study between total and partial occlusion, this was treated as the uniform variable (occlusion) for both study groups.

PRETREATMENT ACUITY

The various values were converted to their Snellen fraction. These were then converted to (-) log acuity[27] where necessary for analytic purposes. For reporting purposes, acuity values were stratified by octaves (ie, a doubling of acuity value ~20/20 to 20/40 = 1 octave).

REFRACTION AND ANISOMETROPIA

These were converted to spherical equivalent for both the amblyopic and nonamblyopic eye. For purposes of this study, anisometropia was defined as ≥1.5 D spherical equivalent difference between the eyes.

AGE

This was defined as the age in years at which occlusion therapy was begun. Because the data on when the amblyopia itself began was sparse, fragmentary, and unreliable, this was not entered into the database.

DURATION OF THERAPY

Data on this variable, the duration of the first occlusion therapy, was coded in weeks.

SUCCESS OF OCCLUSION

For this study's patient population, success was defined as the attainment of a visual acuity of ≥20/40 at the end of the first application of occlusion therapy. For acuities of less than 20/40, the therapy was deemed a failure.

RECIDIVISM

This was defined by taking the vision at the completion of the first session of occlusion therapy as the result of occlusion for purposes of evaluation of the success or failure of the method. Recidivism occurred when that vision, attained at the end of therapy, declined by one octave. The time required for this until the date of last follow-up visit or date of initiation of new therapy.

STATISTICAL ANALYSIS

As in the previous study, standard statistical methods were used to calculate means, standard deviations, medians, and confidence intervals for the major risk variables of study group 2 and the effect of these on the outcome variable "success." The statistically significant variables were then

compiled in a stepwise logistic model to determine which variables survived as independent predictors of an unfavorable outcome when considered with the effect of all the other variables taken into account. This model was then compared to the model of risk developed from the group 1 data. Finally, the 2 study groups were combined, and risk models including models of relative risk[28] were calculated. Relative risk of failure of occlusion was estimated by logistic regression[29] on the combined data set.

RESULTS

POPULATION DESCRIPTION

Table 2 presents the baseline characteristics of study group 2 broken down by type of amblyopia. For comparison to study group 1, the age at treatment and the pretreatment visual acuity for study group 2 are presented in Fig 1 and 2. When groups 1 and 2 were aligned as described and their demographic characteristics compared, there was no statistical difference between them at the age of onset of their occlusion therapy. The mean age in both groups was 4.0 years(P=1.00, t test). Variables that differed statistically between the 2 populations were visual acuity at the start of therapy (P< .001, t test) and the distribution of type of amblyopic subjects between the two populations (P<.001, chi square). The median acuity was 20/100 in study group 1 and 20/80 in study group 2. Study group 1 had 16.8% anisometropes, 71.8% strabismics, and 11.3% anisometropic-strabimics, while study group 2 had 9.2%,76.2%,and 14.6%, respectively.

OCCLUSION THERAPY

Duration of occlusion was a significant predictor of failure in study group 2, similar to what was found in our previous study.[1] The relationship is inverse: The longer the therapy, the higher the failure rate. Since we had concluded from the result of that previous study that no statistical difference existed between full-time and parttime occlusion, we ignored differences in that variable and dealt only with the duration of occlusion in weeks as the operative independent variable. Because study group 2 data set was far more extensive than study group 1 and included follow-up over months and years, the duration of initial occlusion in weeks was taken as the weeks from the onset of occlusion to the first cessation of therapy for the 3 types of amblyopia (Table III). The duration of therapy was 41.4 weeks in study group 2 versus 23.3 weeks in study group 1. This difference was statistically significant (P <.001).

SUCCESS OF OCCLUSION THERAPY

Table IV and Fig 3 describe the results of occlusion therapy at the end of

TABLE II: BASELINE CHARACTERISTICS BY TYPE OF AMBLYOPIA: STUDY GROUP 2

TYPE OF AMBLYOPIA	ANISOMETROPES(%) N = 54	STRABISMUS(%) N = 449	ANIS/STRAB(%) N = 86	TOTAL (%) N = 589
Sex				
Male	28 (51.9)	225 (49.9)	42 (48.8)	295 (50.1)
Female	26 (48.1)	224 (50.1)	44 (51.2)	294 (49.9)
n	54	449	86	589
(missing)	(0)	(0)	(0)	(0)
Amblyopic eye				
Right	14 (25.9)	206 (45.9)	32 (37.2)	252 (42.8)
Left	40 (74.1)	243 (54.1)	54 (62.8)	337 (57.2)
n	54	449	86	589
(missing)	(0)	(0)	(0)	(0)
Age				
0-3	4(7.4)	230 (51.2)	34 (39.5)	268 (45.5)
4-5	24 (44.5)	140 (31.2)	30 (34.9)	194 (32.9)
6-10	26 (48.1)	79 (17.6)	22 (25.6)	127 (21.6)
n	54	449	86	589
(missing)	(0)	(0)	(0)	(0)
Mean (SD)	5.5 (1.6)	3.7 (1.9)	4.2 (1.9)	4.0 (1.9)
Median (range)	5 (2-10)	3 (0-10)	4 (0-10)	4.0 (0-10)
Acuity				
<20/40 to 20/80	34 (63.0)	218 (56.0)	28 (36.4)	280 (53.8)
<20/80 to 20/160	13 (24.1)	74 (19.1)	18 (23.3)	10.5 (20.2)
<20/160 to 20/320	7 (13.0)	76 (19.5)	14 (18.2)	97 (18.7)
<20/320 to 20/640	0	15 (3.9)	13 (16.9)	28 (5.4)
<20/640	0	6 (1.5)	4 (5.2)	10 (1.9)
n	54	389	77	520
-log (visual fraction)				
Mean (SD)	0.65 (0.19)	0.72 (0.28)	0.88 (0.37)	0.74 (0.29)
Median (range)	20/80 (20/60 to 1/12)	20/80 (20/60 to 1/60)	6/36 (20/60 to 1/60)	20/80(20/60 to 1/60)
(missing)	(0)	(60)	(9)	(69)
Diff in sph eq (D)				
Mean (SD)	3.0 (1.2)	0.38 (0.40)	2.7 (1.4)	1.0 (1.3)
Median (range)	2.8 (1.5 – 7)	0.25 (0 to 1.38)	2.3 (1.5 to 8.5)	0.5 (0 to 8.5)
n	54	429	86	569
(missing)	(0)	(20)	(0)	(20)
Refractive error (D)				
Mean (SD)	2.3 (4.0)	2.3 (2.2)	3.4 (3.1)	2.5 (2.6)
Median (range)	3.5 (-9.5 to 7.0)	2.3 (-8.4 to 9.8)	4.0 (-7.5 to 7.5)	2.5 (-9.5 to 9.8)
n	54	433	86	573
(missing)	(0)	(16)	(0)	(16)

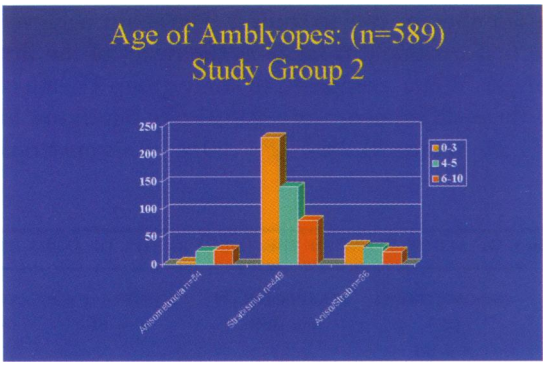

FIGURE 1

Frequency histogram of age distribution of patients in study group 2 by type of amblyopia. There was no statistical difference between study groups 1 and 2 (P=1.000).

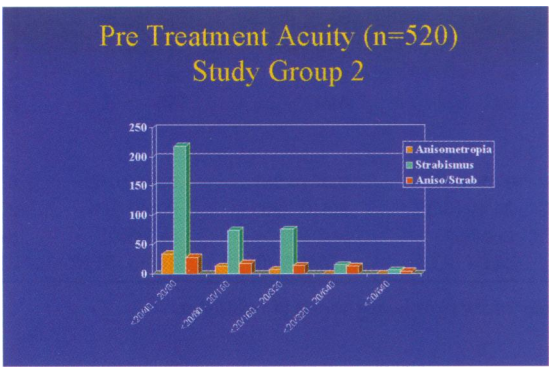

FIGURE 2

Frequency histogram of pretreatment acuity for study group 2. There was a statistical difference between these groups (P<.001).

TABLE III: TREATMENT DURATION BY TYPE OF AMBLYOPIA: STUDY GROUP 2

TYPE OF AMBLYOPIA	ANISTOMETROPES (%) N = 54	STRABISMUS (%) N = 449	ANIS/STRAB (%) N = 86	TOTAL (%) N = 589
Mean (SD	36.4 (54.0)	42.1 (44.0)	41.2 (42.7)	41.4 (44.7)
Median (range)	24 (4-38.3)	27 (2 to 314)	27 (2-276)	27 (2-383)
N	54	449	86	589
(missing)	(0)	(0)	(0)	(0)

the first occlusion therapy trial in study 2. The acuity achieved at the conclusion of the first treatment is taken as the result of the first episode of occlusion therapy. When compared to study group 1's rate of success for the 3 groups, these differences were statistically significant for strabismic amblyopes (77.2% versus 61.2%) ($P < .001$). Anisometropic strabismic

TABLE IV: ACUITY AT END OF TREATMENT BY TYPE OF AMBLYOPIA

ACUITY	ANISOMETROPES (%) N = 54	STRABISMUS (%) N = 449	ANIS/STRAB (%) N = 86	TOTAL (%) N = 589
20/20+	6 (11.1)	55 (12.2)	11 (12.8)	72 (12.2)
<20/20 – 30	12 (22.2)	108 (24.1)	15 (17.4)	135 (22.9)
<20/30 – 40	16 (29.6)	112 (24.9)	18 (21.0)	146 (24.8)
<20/40 – 60	9 (16.7)	89 (19.8)	11 (12.8)	109 (18.5)
<20/60 – 80	8 (14.8)	28 (6.2)	8 (9.3)	44 (7.5)
<20/80 – 160	1 (1.9)	28 (6.2)	6 (7.0)	35 (5.9)
<20/160 – 320	2 (3.7)	24 (5.4)	12 (14.0)	38 (6.4)
<20/320 – 640	0	3 (0.7)	3 (3.5)	6 (1.0)
<20/640	0	2 (0.4)	2 (2.3)	4 (0.7)
n	54	449	86	589
-log (visual fraction)				
Mean (SD)	0.35 (0.23)	0.37 (0.28)	0.50 (0.42)	0.39 (0.31)
Median (range)	20/40 (6/5 to 6/60)	20/40 (6/5 to 1/60)	20/40 (6/6 to 1/60)	20/40 (6/5 to 1/60)
Success rate*	34/54 (63.0)	275/449 (61.2)	44/86 (51.2)	353/589 (59.9)

*Defined as acuity of 20/40 or better at end of treatment.

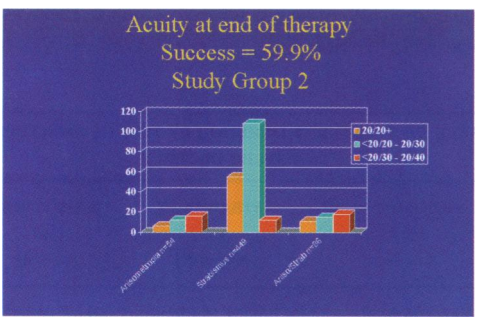

FIGURE 3

Frequency histogram of successful results of occlusion therapy by type of amblyopia for study group 2. There was a statistical difference between study groups 1 and 2. See text for explanation of differences.

amblyopia also had a statistically better success rate in study group 1 (67.2% versus 51.2%) (P=.05). Because strabismic amblyopes so dominated both study groups, this also affected the comparison for the total group (73.7% versus 59.9%) (P<.001).

Explanations for this difference may lie in a selection bias in reported patients, which may have occurred in the 23 different studies in study group 1. Patients who dropped out of therapy were not reported in the studies encompassing the populations of study group 1. Or perhaps a milder approach to occlusion therapy in study group 2. (On average, children who were prescribed less than 90 hours of patching in the first 3 months [average, 1 hour/day] had a final visual acuity of 6/10.8.[26])

RISK FACTORS FOR FAILURE

Table V presents the analysis of the risk factors for failure. Variables that may be important predictors of success or failure are the age at which therapy began (P=.07), duration of treatment (P=.003), and the acuity at the onset of therapy (P<.001). Although there are scattered data on the issue of compliance in the British data set, the data are too sparse to provide a meaningful evaluation of this variable, although it may in fact be the most important of the risk factors for failure of therapy.

LOGISTIC MODELS AND RELATIVE RISK ESTIMATES

The risk model used for analysis of study group 1 was developed from a trial-and-error process employing different parameters and selecting the model that gave the best fit for the most patients in that very varied group of patients. This analysis, when applied to study group 2, resulted in identifying 2 factors: patient age at therapy onset and depth of amblyopia as independent risk factors bearing on the outcome success (or failure) of occlusion. These factors make intuitive clinical sense, although the literature from smaller samples does not always support them. The results are presented in Table VI and Fig 4.

RECIDIVISM

Because of its extensive nature, the British data set permits us to address this question in more depth than was possible with the previous study's data. In Table VII, the data suggest that the results of amblyopia therapy endure particularly if a successful result has been attained. At the conclusion of therapy for successful results (acuity, ≥20/40), 73% retained that vision for 1 year, 61% for 2 years, and 53% for 3 years (Fig 5) using Kaplan-Meier analysis, which adjusts for the length of follow-up after cessation of treatment. Although the numbers of individuals in the cohort diminishes at each of these dates, this method of analysis provides the best estimate

TABLE V: RISK FACTORS FOR FAILURE° BY TYPE OF AMBLYOPIA

BASELINE CHARACTERISTICS	ANISOMETROPES (%) N = 54			STRABISMUS (%) N = 449			ANIS/STRAB (%) N = 86			TOTAL (%) N = 589		
	SUCCESS†	FAILURE	P	SUCCESS†	FAILURE	P	SUCCESS†	FAILURE	P	SUCCESS†	FAILURE	P
Age												
n	34	20	0.64‡	275	174	0.22‡	44	42	0.07‡	353	236	0.07‡
mean	5.6	5.4		3.7	3.9		3.8	4.7		3.9	4.1	
(SD)	(1.7)	(1.4)		(1.8)	(2.0)		(1.6)	(2.1)		(1.8)	(2.0)	
Sex												
Male	16/28	12/28	0.52§	143/225	82/225	0.36§	22/42	20/42	1.00§	181/295	114/295	0.53§
	(57.1)	(42.9)		(63.6)	(36.4)		(52.4)	(47.6)		(61.4)	(38.6)	
	18/26	8/26		132/224	92/224		22/44	22/44		172/294	122/294	
Female	(69.2)	(30.8)		(58.9)	(41.1)		(50.0)	(50.0)		(58.5)	(41.5)	
Amblyopic eye												
Right	8/14	6/14	0.84§	126/206	80/206	1.00§	14/32	18/32	0.40§	148/252	104/252	0.67§
	(57.1)	(42.9)		(61.2)	(38.8)		(43.8)	(56.3)		(58.7)	(41.3)	
	26/40	14/40		149/243	94/243		30/54	24/54		205/337	132/337	
Left	(65.0)	(35.0)		(61.3)	(38.7)		(55.6)	(44.4)		(60.8)	(39.2)	
Diff. in sph Eq												
n	34	20	0.67‡	267	162	0.63‡	44	42	0.12‡	345	224	0.37‡
mean	2.8	3.2		0.4	0.4		2.4	3.0		0.9	1.1	
(SD)	(1.0)	(1.5)		(0.4)	(0.4)		(1.0)	(1.7)		(1.1)	(1.5)	

TABLE V (CONTINUED): RISK FACTORS FOR FAILURE° BY TYPE OF AMBLYOPIA

BASELINE CHARACTERISTICS	ANISOMETROPES (%) N = 54			STRABISMUS (%) N = 449			ANIS/STRAB (%) N = 86			TOTAL (%) N = 589		
	SUCCESS†	FAILURE	P	SUCCESS†	FAILURE	P	SUCCESS†	FAILURE	P	SUCCESS†	FAILURE	P
Duration (wk) of treatment												
n	34	20	0.88‡	275	174	<0.001‡	44	42	0.16‡	353	236	0.003‡
mean	28.6	49.7		34.5	54.1		47.6	34.6		35.6	50.2	
(SD)	(18.4)	(85.1)		(34.2)	(54.0)		(48.0)	(35.6)		(35.3)	(54.8)	
Refraction												
n	34	20	0.12‡	269	164	0.18‡	44	42	0.081‡	347	226	0.15‡
mean	3.3	0.6		2.2	2.4		3.2	3.7		2.5	2.5	
(SD)	(2.6)	(5.2)		(2.0)	(2.4)		(2.6)	(3.5)		(2.2)	(3.0)	
-log (visual fraction)												
n	34	20	0.020‡	250	139	<0.001‡	39	38	<0.001‡	323	197	<0.001‡
mean	0.60	0.73		0.67	0.80		0.67	1.10		0.66	0.85	
(SD)	(0.16)	(0.21)		(0.24)	(0.32)		(0.25)	(0.36)		(0.24)	(0.34)	
Total	**34/54 (63.0)**	**20/54 (37.0)**		**275/449 (61.2)**	**174/449 (38.8)**		**44/86 (51.2)**	**42/86 (48.8)**		**353/589 (59.9)**	**236/589 (40.1)**	**0.19¶**

° Failure is visual acuity worse than 20/40 at end of treatment.
† Success is visual acuity 20/40 or better at end of treatment.
‡ Mann Whitney test.
§ Chi-square test.
¶ Chi-square comparing success rates among types of amblyopia.

TABLE VI: MULTIVARIATE MODEL

RISK FACTOR	COEFFICIENT ± STANDARD ERROR	ODDS RATIO	*P* VALUE
Age (yr)			
0-3	0	Reference group	
3-5	0.76 + 0.23	2.1	<.001
6-10	1.15 + 0.27	3.2	
Initial acuity			
<20/40 – 20/60	0	Reference group	
<20/60 – 20/80	0.55 + 0.29	1.7	<.001
<20/80 – 20/100	*	*	
<20/100 – 20/200	1.23 + 0.24	3.4	
<20/200 – 20/320	1.26 + 0.55	3.5	
<20/320 – 20/640	2.47 + 0.49	11.8	
<20/640	2.86 + 0.83	17.4	
Type of amblyopia			
Anisometropia	0	Reference group	
Strabismus	0.17 + 0.32	1.2	.8
Anisometropia/strabismus	0.27 + 0.40	1.3	

*Only one case in this group; estimate unavailable.

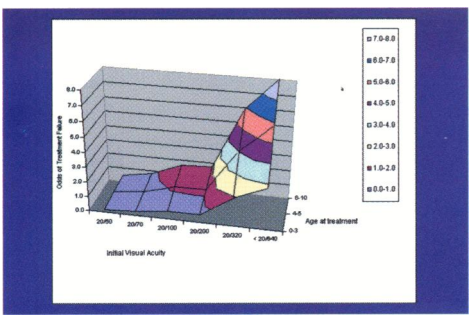

FIGURE 4

Logistic model of how odds of treatment failure are influenced by acuity and age in study group 2. Odds of treatment failure are small (<1:2) for a wide range of patients who began treatment at an early age with reasonable initial acuity (≥20/160).

of how acuity diminishes over time in the cohort of successful results. The challenge for the future is to assure that the results of the therapy remain durable over decades or the lifetime of the individual.

COMBINED DATA SET

The combined data set provided a unique opportunity to study the outcome of occlusion therapy across decades of time, in differing populations

TABLE VII: RECIDIVISM (AFTER END OF FIRST TREATMENT)*

VISION AT END OF TREATMENT	20/20 TO 20/40	<20/40 TO 20/80	<20/80 TO 20/160	<20/160 TO 20/320	<20/320	TOTAL
20/20 – 20/40	219 (66.0)	94 (28.3)	13 (3.9)	5 (1.5)	1 (0.3)	332 (63.8)
<20/40 – 20/80	24 (19.7)	66 (54.1)	23 (18.9)	8 (6.6)	1 (0.8)	122 (23.5)
<20/80 – 20/160	2 (7.1)	7 (25.0)	9 (32.1)	8 (28.6)	2 (7.1)	28 (5.4)
<20/160 – 20/320	0	0	6 (19.4)	24 (77.4)	1 (3.2)	31 (6.0)
<20/320	0	0	0	2 (28.6)	5 (71.4)	7 (1.3)
Total	245 (47.1)	167 (32.1)	51 (9.8)	47 (9.0)	10 (1.9)	520 (100.0)

*Vision after treatment discontinued. Time (wk) treatment was discontinued, $\bar{x}$ = 71.9, SD = 74.3, range (1-379). 229 amblyopes had no further treatment. 291 amblyopes had futher treatment: 149 had 1 treatment; 74 had 2 treatments; 33 had 3 treatments; 18 had 4 treat ments; 11 had 5 treatments; 4 had 6 treatments; 1 had 7 treatments; 1 had 8 treaments.

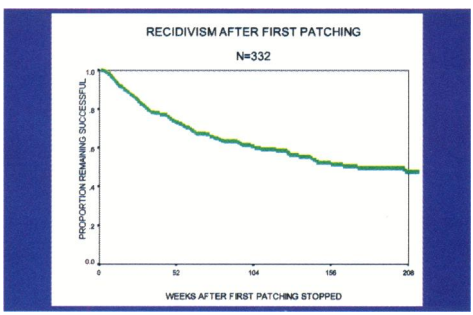

FIGURE 5

Kaplan-Meier survival curve describing behavior of acuity over time following cessation of therapy in weeks in study group 2.

and age-groups, level of onset acuities, refractive errors, types of amblyopia with a large sample size (n=987). The combined data set provided answers to some of the questions posed by the separate analyses of each. In spite of the obvious differences between the 2 data sets, which were gathered under very different circumstances, the first from 23 studies published over 3 decades from 8 different countries and the second gathered during a single year from 7 neighboring centers in a single country, the entity studied (amblyopia) proved remarkably consistent and robust in its effects on the affected subjects. Although statistical differences exist

between the groups, the risk factors, age, and depth of acuity loss were the strongest predictors of outcome of therapy. Fig 6 is a depiction of the odds of occlusion failure for the entire group plotted along the dimensions of age and acuity. From the clinical standpoint, this large sample of patients permitted the construction of a nomogram giving the probability of successful occlusion, given the level of acuity and age at beginning of therapy (Table VIII).

DISCUSSION

The major findings of this study are as follows:

- Amblyopia is treatable successfully, by occlusion therapy, in the majority of cases.

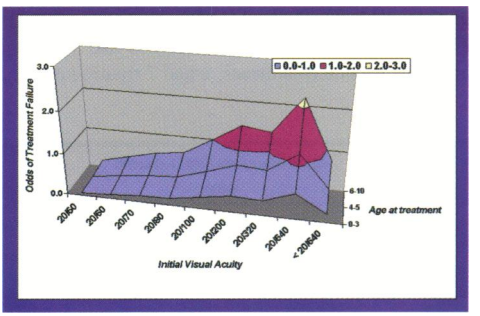

FIGURE 6

Logistic model of combined data set of study groups 1 and 2 to show odds of treatment failure follow pattern shown in logistic model of study group 1.

TABLE VIII: PROBABILITY OF SUCCESS OF AMBLYOPIA THERAPY (N=987)

PRETHERAPY VISION	AGE-GROUP (YR) 0-3	3-5	5-10
>=20/50	0.95	0.91	0.85
20/60	0.91	0.84	0.75
20/70	0.88	0.78	0.66
20/80	0.86	0.76	0.63
20/100	0.78	0.65	0.50
20/200	0.72	0.57	0.42
20/320	0.73	0.58	0.43
20/640	0.62	0.46	0.31
<20/640	0.64	0.47	0.33

- The risk factors for failure are the depth of the amblyopia at the start of treatment, the age of the patient, and, to a lesser extent the type of amblyopia.
- Duration of therapy is an item to be considered in the therapy of amblyopia. It proved to be significantly shorter in study group 1, and since the occlusion was more vigorous in this group, it is plausible that this resulted in a shortening of the time required to reach a goal. Occlusion, it should be remembered is an onerous task for a child.
- Recidivism, although it does occur, is not the problem that it seemed. Once having achieved a successful result in the 20/20 to 20/40 range, this result seems durable in the majority of patients for up to 3 or more years. The challenge is to find ways of maintaining acuity levels in these patients over decades or even a lifetime. As was noted in our previous paper, amblyopia remains an important cause of monocular visual loss in patients reaching age-groups where they are at risk for macular degeneration, retinopathy, and cataract—all causes of binocular visual loss.[30-32] With visual impairment from childhood amblyopia, these patients have only one eye on which to depend. Amblyopia remains a serious yet treatable public health problem.

When the data from the 2 studies are merged, the set lends further support to the risk factors identified from the previous studies, affecting the outcome. It also permits, as a result of its large size (n=987), a determination of the probability of a successful outcome of occlusion therapy using the 2 major risk factors as parameters. This had previously not been possible with smaller sample sizes of published studies. The linearity of the estimates of a successful outcome are striking and arise from the data itself and not from forcing on the part of the statistical programs involved.

Although this study is based on one of the most extensive data sets ever gathered on this subject, it does not address the issue of compliance with occlusion therapy. This remains one of the most difficult problems in amblyopia management. One of the real needs in this field is for the application of modern technology to provide useful information on this question to enable us to separate true treatment failures from failures due to lack of compliance with therapy.

Several other potential biases in this study are the fact that patients who drop out before the completion of therapy are not true tests of the efficacy of that therapy carried out to the limits of its ability to improve visual function. Because this data set was gathered with such rigor and completeness, such patients are simply failures imputed to the method, when, in fact it may be due to the unsolved problem of compliance mentioned previously. Study group 1, which served as the comparison group,

may also have its potential biases in that follow-up data were much less complete and patients who dropped out of therapy for whatever reason may not have been counted as they were in study group 2. It is well to recall that apparent differences in success rates may arise from a bias in follow-up ascertainment. In study group 1, failures may not have been followed as closely as in study group 2. Further publication bias not discernable in the 23 publications that formed the data set of study group 1 may give rise to these differences. Finally, although any or all of these may provide plausible and possible explanations, at present the data do not permit any firm conclusions as to its cause.

Finally, this study was not undertaken for the purpose of providing information bearing on the conclusions of the recent British National Health Service document[33] on screening for amblyopia and its treatment. It is well to recall the specific recommendations of that publication:

- Purchasers and providers are advised not to implement new preschool vision screening programs unless they have been rigorously evaluated
- There is a lack of good quality research into the natural history of the target conditions (*amblyopia chief among them*)....and the efficacy of available treatments
- The findings of the one prospective study do not support the belief that identifying children with amblyopia in the preschool period reduces the prevalence of this condition in children aged 7 years

These are not taken out of context; they are, in fact, the context of that document. Granted, a great deal of progress has not occurred in amblyopia therapy since its inception in the 18th and early 19th centuries in Europe[34] and the British Isles.[31] Nevertheless, existing data sets permit us to begin to identify, in large sample sizes, risk factors that help predict which patient is likely or least likely to benefit from therapy. Randomized trials of other forms of therapy against occlusion are under way (M. Repka, MD, personal communication), and drug therapy, heretofore considered of no value, is being reevaluated in both clinical studies[36,37] and animal models.[38,39]

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DISCUSSION

DR PAUL R. MITCHELL. Dr Flynn and coauthors have presented 2 extremely comprehensive and informative studies analyzing the results of amblyopia therapy. Results of the first were presented at the American Ophthalmological Society meeting 1 year ago and published in the *Transactions*.[1] Data from 23 studies published in 8 countries from 1965 to 1994 were presented. Of 961 patients with amblyopia who underwent patching therapy (group 1), the most common types of amblyopia were strabismic, anisometropic and combined anisometropic-strabismic. All other types of amblyopia were excluded, producing a pool of 689 patients. Successful outcome was defined as visual acuity of 20/40 or better. The percentages published in the Transactions in 1998 and those presented today are slightly different because of modifications in the criteria for classifications. Success was achieved in 74% of all patients in group 1, with 77% success with strabismus, 66% with anisometropia, and 67% with anisometropia-strabismus.

We have learned today that group 2 also consisted of 961 patients who were treated for amblyopia in 1983 in 7 different orthoptic centers in England. Results were published by Woodruff and coworkers in 1994.[2,3] After modification of definitions of study group 1 to align the data, a pool of 589 patients was studied. The success in group 2 was lower and statistically significant as a group and individually by amblyopia type; 60% had

total success, 61% had strabismus, 63% anisometropia, and 51% anisometropia-strabismus.

The mean age at onset of treatment was identical—4 years of age—but the distribution by type of amblyopia was different, with anisometropia being more frequent in group 1 and strabismus and anisometropia-strabismus more frequent in group 2. The duration of initial occlusion was a significant predictor of failure, in an inverse relationship; the longer the duration of therapy, the higher the failure rate.

Successful outcome was related to age at initiation of therapy and depth of visual loss before treatment in both groups and was related to the type of amblyopia only in group 1. Outcome was not related to the total duration of occlusion, the type of occlusion, the refractive error, the sex of the patient, or the eye involved. Dr Flynn's conclusions support the value of early detection and screening for amblyopia, its prevention where possible, and adequate and vigorous treatment when detected and diagnosed. An area that was not addressed by Dr Flynn was fusion, an important factor in stability of strabismus and in vision. In his recent Costenbader Lecture in Toronto, Dr Mazow reviewed treatment results of amblyopia and practice patterns.[4] In Table VIII, courtesy of Dr Mazow, 66.8% of 263 patients had no change in fusion and 1.9% lost fusion, but 31.3% gained fusion, which was extremely important. In a group of 100 patients who lacked fusion before treatment, 44% developed single or subnormal binocular vision over the course of their treatment, and an additional 33% developed peripheral fusion. The remaining 23 patients failed to develop fusion. It would be informative to know the fusion results in both group 1 and group 2 as well as how these data relate to Dr Mazow's findings.

Both Dr Flynn and Dr Mazow have drawn attention to a recent document by Snowdon and Stewart-Brown,[5] which questions the cost-effectiveness and need for vision screening in the National Health Service of the United Kingdom. A number of letters denouncing this paper have been published in the British ophthalmologic literature, and in a subsequent publication,[6] these authors attempt to further explain their reasons for their conclusions. Highlights include:

1. "The review of preschool vision screening commissioned by the NHS. . .could not identify any robust studies showing that amblyopia (the main target condition of pre-school vision screening programmes) causes any problems to children or adults."
2. "The best documented consequence of amblyopia appears to be that blindness may ensue if the good eye becomes damaged or diseased in later life."
3. " . . . people who have suffered from amblyopia since childhood have

difficulty in specifying any way this has affected them."

4. ". . . studies . . .suggest that amblyopia may sometimes regress spontaneously."
5. ". . .many adults and children were clear that the treatment. . .had had an important and negative impact on their quality of life as children and on the lives of their families."
6. ". . .concluded that screening is not effective, not because the screening programme cannot identify children efficiently, but because there is no clear evidence that treatment is effective or necessary."
7. "There is, however, no clear evidence that pre-school children benefit from the correction of the minor refractive errors that are common in childhood, and there is good evidence that children with these defects, who are old enough to make choices for themselves, often choose not to wear glasses. "
8. ". . . the NHS is supporting an intervention for which there is no evidence base. This intervention consumes scarce resources, but more importantly it requires parents to enforce a potentially distressing treatment on their children, on specious premises."
9. "The results of this report suggest that health authorities should stop purchasing pre-school vision screening services . . . therefore . . . unethical to screen in the absence of robust evidence of treatment impact."
10. ". . . a reasonable and ethical compromise could be made that they insist that treatment be offered only after a clear statement of the limits of medical knowledge about the conditions, their treatment, and their side effects. Then parents could make up their own minds about whether the potential benefits are worth the problems that treatment causes."

The majority of this British report contradicts and minimizes the years of dedication to preserving and improving the vision of the patients treated by the members of this Society and ophthalmologists everywhere. The British recommendations and potential repercussions on the quality of childhood vision care are indeed chilling. Use of the term "inconvenient" or "distressing" to describe a treatment is not a valid reason to withhold that treatment. We must continue to study amblyopia, as Dr Flynn so meticulously has, in order to accumulate more data to refute these types of radical and harmful recommendations.

I would like to thank the Society for allowing me to discuss Dr Flynn's paper and to thank Doctor Flynn for sending his manuscript in advance.

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DR LEONARD APT. One of the most difficult amblyopia problems to deal with is the one associated with eccentric fixation; more commonly seen with strabismic amblyopia. Recent reports on amblyopia therapy often neglect to consider the importance of central versus eccentric fixation in the evaluation and response to treatment. Patients with eccentric fixation are less likely to respond well to conventional occlusion therapy because patching the better seeing eye may reinforce the noncentral fixation process and thus prevent improvement in vision. With these comments in mind, I would like to ask Dr Flynn: (1) was the fixation pattern taken into consideration in his amblyopia study? (2) What were the results of treatment of the patients with eccentric fixation? and (3) How did the results of treatment of this special group of patients affect his data? Some 40 years ago Professor Bangerter of Switzerland and Professor Cuppers introduced a therapy called pleoptics to treat patients with amblyopia and eccentric fixation. Using an array of special instruments designed to reestablish the principal foveal visual direction these men claimed improved visual accuity results. Shortly thereafter, at the Jules Stein Eye Institute, we acquired the necessary instruments and personnel that had been trained at both Bangerter and Cuppers' clinics. We studied 79 patients with amblyopia and eccentric fixation and achieved success in 43% of the group; our criteria for success were significant linear vision improvement plus attainment of some binocular function. An analysis of the records of the patients in the "success" group yielded several favorable prognostic features that would be of value to the ophthalmologist if pleoptic therapy were to be considered (*Am Orthopt J* 1974;24:42-46).

DR ROBERT L. STAMPER. I would like to comment on the effectiveness of screening. A paper presented a number of years ago questioned the cost-effectiveness of glaucoma screening because there was no proof that treatment of glaucoma was effective. This was a call to the glaucoma specialists

to make the necessary studies to show whether treatment was effective. We now have at least one long-term prospective study that shows that glaucoma therapy works. Perhaps this will stimulate pediatric ophthalmologists to move in a similar direction. I congratulate Dr Flynn for taking a big step in that direction.

DR EUGENE M. HELVESTON. On the basis of your data, can you either support or refute the statement that a child who attains a certain level of vision, say 20/40, at age 5 or 6 but who recedes to a level of 20/100 at age 10 is capable of returning to the best vision he once had, 20/40 in this case, if it should ever become necessary?

DR JOHN T. FLYNN. First of all, I would like to thank the committee for letting me present this paper and thank my discussants, all 6 of them. To take up the first questions asked by my opening discussant, Dr Paul Mitchell. Unfortunately, Paul, I cannot answer you; I have no data on fusion. In retrospective studies, you have to take what the data will give you. You can't retrospectively invent data. Regarding the British National Health Service report, I look on it as a good thing not a bad thing. Why? Because these two women are sociologists, not ophthalmologists. They have, as far as we know, no bias or axe to grind. They critically looked at 1500 publications, including many of mine, on the subject of amblyopia and faulted these publications for many design flaws. Such flaws were methodology, data which does not support the conclusions and conclusions that went way beyond speculation. This is all good to know because it's a dash of cold water in our faces and tells us to get our act together. Fortunately, through the auspices of the National Institutes of Health, the pediatric investigator's group (PEDIG) is getting together randomized clinical trials comparing methodologies of patching and patching against other treatment such as penalization. We are going to do our homework, which we should have been doing long ago. In answer to Dr Apt: Leonard regarding eccentric fixation, I spent a year with Professor Cüppers and also had a visit to Professor Bangerter in Switzerland. Let me tell a little historical vignette regarding amblyopia in middle Europe. Why did pleotic therapy come about? Why did they get so concerned, post World War II, about amblyopia? It was so, in a culture that is very different than ours, the leading German ophthalmologist of that day, whose name escapes me, said, "We will not touch strabismus nor any of its complications until these children are teenagers." In a sense, this wrote off any chance for fusion and opened the door, at the same time, to the development of amblyopia. After the war, as a consequence, they had an epidemic of teenage and preteen age children with amblyopia. Things like that die hard in a culture,

and this is what German ophthalmologists, and to a lesser extent the Swiss ophthalmologist, followed when I was there in the early 60's. I'm quite sure that we have lost some information by forgetting about eccentric fixation. None of my data has any information about fixation, but if it will make you feel a little better, I still teach our residents to pick up this strange instrument invented by Helmholz in the last century called a direct ophthalmoscope and make them look at the fixation in the amblyopic eye. Regarding Dr Stamper's question, Bob, I'm well aware of that shot across the bow of the glaucoma subspecialty. I think it was Dr Manson Eddy that fired it about twenty years ago. I think that glaucoma treatment today is the better for it, having gotten it's act together about the medical effects and the cost effectiveness of glaucoma treatment. We need to do exactly the same in strabismus therapy. It's not bad that somebody criticizes you from the outside. In answer to Dr Gene Helveston, I think there are 44,000 files in this data set and it is an enormous mass to handle. Regarding the question of recoverability in vision, it lies somewhere in those files. I think that when we see the rate at which, in certain subpopulations of amblyopia, recividism occurs, how quickly it occurs and to what depth it occurs, this will give us at least a partial answer to your question. This is basically the same question as Dr Tasman asked and it's the best I can do to answer it. I would like to thank again my discussants and everyone who stayed overtime to listen to this.