AMBLYOPIA THERAPY*†‡ **RESULTS AT THE GIESSEN CLINIC**

BY

J. T. FLYNN AND E. VEREECKEN§

*From the Department of Orthoptics, Pleoptics, and Motility Disturbances of the Eye,
University of Giessen, Giessen, West Germany (Director: Professor C. Cüppers)*

RESULTS reported from clinics using pleoptic methods for the treatment of amblyopia may be characterized as variable (von Noorden and Lipsius, 1964; Priestley, 1961; Girard, Fletcher, Tomlinson, and Smith, 1962). The purpose of this communication is to present the results at the Giessen Clinic during the authors' tenure there.

Of the 88 beds in the eye hospital of the University of Giessen, 36 are kept fully occupied by strabismus patients undergoing monocular, binocular, and surgical therapy. The cost of prolonged hospitalization (*vide infra*) is borne by public and private health insurance organizations, membership of which is mandatory in West Germany.

Population Surveyed

The choice of patients in the survey was arbitrary. The years 1963–1964 were chosen because the patients would be those treated during our stay there. Of 3,150 admissions during this period, 768 were strabismus patients; 636 of these had diagnoses other than unocular amblyopia, and 44 of the remaining 132 were excluded from this survey for various reasons (Table I).

TABLE I
REASONS FOR EXCLUSION FROM SURVEY OF 44 CASES OF UNIOCLAR AMBLYOPIA

Reason	No. of Cases
Cosmetic Operation Only, without Pleoptic Therapy	25
Organic Retinal Disease (optic atrophy, retinal detachment, macular coloboma, tapeto-retinal degeneration)	8
Congenital Cataracts with Nystagmus	5
Diagnosis Only or Short Follow-up	4
Occlusion Only	1
Orbital Anomalies rendering Pleoptics mechanically Impos- sible	1
Total	44

* Received for publication September 5, 1966.

† Address for reprints: Dr. J. T. Flynn, Bascom Palmer Eye Institute, Department of Ophthalmology, University of Miami School of Medicine, 1638 N.W. 10th Avenue, Miami, Florida, 33136, U.S.A.

‡ This investigation was supported in part by Public Health Service Special Fellowship NB1F10-1319-01, National Institute of Neurological Diseases and Blindness, National Institutes of Health, Bethesda, Maryland.

§ Present address: Dr. E. Vereecken, 21 Lange Steenstraat, Ghent, Belgium.

A series of 88 cases was thus investigated as examples of uniocular amblyopia without demonstrable organic pathology which might directly affect the outcome of therapy. The patients were admitted solely on the basis of their position on the waiting list, over which we had no control.

Diagnostic Categories

Each case of amblyopia was assigned to one of three diagnostic groups:

(1) *Central Inhibition Scotoma* (10).—These represent obligatory central inhibition (Duke-Elder, 1949a), on monocular sensory testing (Vereecken and Flynn, 1967), without loss of the foveal principal visual direction (PVD) (Hering, 1861).

(2) *Eccentric Fixation with Latent Foveal PVD* (42).—This group is characterized by a shift of the PVD from the fovea to a non-foveal locus in addition to obligatory inhibition. By some forms of uniocular sensory testing, however, they show a latent foveal PVD (Cüppers, 1961).

(3) *Eccentric Fixation without Latent Foveal PVD* (36).—These cases are in all respects similar to the above except that they show no evidence of latent foveal PVD by any form of testing.

Definition of Results

For each diagnostic group a definition of the result was established (Table II).

TABLE II
DEFINITION OF RESULTS

Group	Diagnosis	No. of Cases	Positive	Plus/Minus	Negative
1	Central Inhibition Scotoma	10	Visual Acuity: 1-0.83. Symbols in rows with correction at 6 m. Niden Text ⁷ 1 or 2 with correction at 30 cm. No separation difficulties	Not Applicable	Anything less than full visual acuity for distance or near or separation difficulties
2	Eccentric Fixation with Latent Foveal PVD	42	As above	Change of fixation from eccentric to foveal but without full visual acuity for distance or near, or separation difficulties	No change of fixation from eccentric point
3	Eccentric Fixation without Latent Foveal PVD	36	As above	As above	As above

Method of Survey

For each patient several topics were reviewed under four headings (Table III). It was not possible to include every fact which might be relevant, but the development of the amblyopia and the course of therapy were examined; 86 of the 88 patients were re-evaluated in the early months of 1965 to obtain the latest information.

TABLE III
METHOD OF SURVEY

History	<ol style="list-style-type: none"> 1. Family History 2. Pregnancy and Birth 3. Childhood Diseases with Role 4. Age of Onset: Strabismus Monolaterality 5. Previous Therapy <ul style="list-style-type: none"> Glasses—Age—Effect Patch—Eye—Duration—Effect Prior Operations—Effect
Examination on Admission	<ol style="list-style-type: none"> 1. Age at Examination 2. Vision: Distance/Near with correction, Crowding +/— 3. Atropine Refraction 4. Anisometropia 5. Angle of Squint/Method of Measure 6. Motor Status—Torticollis 7. Correspondence: Real/Entopic Object 8. Fixation: Star and Localization <ul style="list-style-type: none"> Haidinger Brush: +/—, Localization After Image +/—, Localization
Therapy	<ol style="list-style-type: none"> 1. Duration 2. Type <ul style="list-style-type: none"> Monocular Monocular and Binocular 3. Occlusion During and Post Therapy 4. Surgery <ul style="list-style-type: none"> Horizontal Vertical Both Change of Localization OP Result
Result of Therapy	<ol style="list-style-type: none"> 1. Type of Result 2. Duration of Result 3. Vision Distance/Near with Correction 4. Fixation 5. Correspondence: Real/Entopic 6. Binocular Functions: <ul style="list-style-type: none"> (A) Simultaneous Macular Perception (B) Fusion (C) Amplitudes (D) Stereopsis 7. Present Occlusion/Ratio

Results of the Survey

I. Historical Data

Family History.—This was positive for strabismus in 29 of the 88 cases (two cases of central inhibition scotoma and 27 of the rest: Table IV, opposite).

These data were analysed by means of the χ^2 test (Doden, 1961) for statistical significance, the two cases of central inhibition scotoma being excluded because for them the definitions of failure and success were different. Within the limitation of

TABLE IV
FAMILY HISTORY RELATED TO RESULTS IN 78 CASES

Family History	Result			
	+	+/-	-	Total
Positive	5	10	12	27
Negative	21	13	17	51
Total	26	23	29	78

$P = 0.13$

the number of patients available, the observed difference in outcome of therapy is of borderline statistical significance ($P = 0.13$). One may thus be 87 per cent. confident that there is a real association between family history and response to therapy. This accords with the clinical impression that the most difficult patients to treat are those with a strong family history of strabismus.

Age at Onset and Unilaterality.—This information depends on the alertness of the observers, in most cases the parents, who vary widely in reliability. Nevertheless, in 61 cases, the strabismus was observed before the second year of life and the eye seen to deviate was the amblyopic eye. In fifteen cases, the strabismus was said to begin in the second to fourth year and in nine cases after this age. In three the age at onset was unknown. The age at onset *per se* was not significantly related to the outcome of therapy ($0.8 > P > 0.7$).

An interesting though small group included those whose strabismus was noted at birth or in the first month of life. There were ten such patients none of whom had any significant history of maternal illness, injury, or obstetric complication. All were eccentric fixers. None received any treatment whatever until the fourth year of life; three had a positive result, three a plus/minus result, and four were failures. This was in spite of the fact that the amblyopic eye had been in the squinting position for at least the first 4 years of life.

Occlusion.—The cases surveyed were ones which could not be treated by occlusion alone and were therefore selected for in-patient treatment. In the vast majority of amblyopes diagnosed early, carefully and conscientiously applied patching will suffice for treatment.

Points which appeared significant with regard to the use of occlusion in this group:

(1) In 26 patients, either no occlusion was given or it was used so irregularly as to be worthless. Thus, in about 30 per cent. of patients, lack of co-operation on the part of the parents prevented the use of this therapy.

(2) Ten cases showed under inverse occlusion a change of fixation towards improvement. There was no correlation between the length of the occlusion, the place and type of fixation, and this change. The cause of this phenomenon remains obscure.

(3) Three cases of unsupervised direct occlusion (done elsewhere) were associated with temporal eccentric fixation in convergent strabismus. They were failures as far as pleoptic therapy was concerned.

(4) Attempts at direct occlusion for from 1 to 4 months failed in seventeen cases and inverse occlusion was prescribed for periods of 3 to 36 months. In these patients and another 24 who had inverse occlusion from the start, no change in fixation was noted in spite of the long duration of treatment.

(5) In eight patients information was inadequate.

II. Examination on Admission

Age at Start of Active Pleoptic Therapy.—The mean ages of the three diagnostic groups were:

Central Inhibition Scotoma: 9.5 years (standard deviation 5.8).

Eccentric Fixation with Latent Foveal PVD: 6.5 years (standard deviation 2.4).

Eccentric Fixation without Latent Foveal PVD: 8.1 years (standard deviation 2.2).

It is customary for German children to start school after their seventh birthday and 54 per cent. of the patients began their pleoptic therapy in the immediate pre-school years. Another 32 per cent. began in the first and second school years and the remainder later.

Vision.—On starting therapy this was taken as the best response of the child to any type of acuity testing (separate symbols or rows) with correction for distance. This was recorded as the vision before therapy.

χ^2 analysis showed that the visual acuity at the outset was associated with the outcome of therapy ($0.001 > P > 0.0001$) and that a patient with vision of 0.1 or better had a better outcome than those below this level. It must be recalled in this connexion that vision at the outset of therapy is a product of at least two factors: the depth of the scotoma and the place of fixation (Figure).

FIGURE.—Visual acuity before therapy related to diagnostic groups.

Refractive Error	No. of Cases
Myopia > -4D	3
-4D > R > -0.5D	9
-0.5D > R > +0.5D	18
+0.5 > R > +4D	34
Hypermetropia > 4D	24
Total	88

These variables would not necessarily be reflected in this analysis but might influence the outcome.

Refraction.—The refractive error in the amblyopic eye was divided into five groups, similar to the classification used by Sorsby, Benjamin, Davey, Sheridan, and Tanner (1957) in a study of refraction in the general population (see Davson, 1962).

Statistical analysis of the refractive error against the results (Table V) showed that the refractive error of the amblyopic eye did affect the outcome of therapy. The results were significantly better among myopes, emmetropes, and low grade hypermetropes as opposed to those in the high hypermetropic range.

TABLE V
REFRACTIVE ERROR RELATED TO RESULTS IN 78 CASES (EXCLUDING CASES OF
CENTRAL INHIBITION SCOTOMA)

Refractive Error	Result			
	+	+/-	-	Total
$> -4 \rightarrow -0.5$	6	1	3	10
$-0.5 \rightarrow +0.5$	8	5	3	16
$+0.5 \rightarrow +4$	11	12	9	32
$+4 <$	1	5	14	20
Total	26	23	29	78

P = 0.005

Anisometropia.—This was defined as a difference of more than 1.5 dioptres between the two eyes. Nineteen cases were found, but anisometropia by itself appeared to play no role in the outcome of therapy ($0.9 > P > 0.8$).

Angle of Squint.—77 cases were convergent and five divergent and in six the angle was so small as to be within the limits of error of the testing method, usually the prism-corneal light reflex method. 46 cases also showed a measurable vertical deviation in the primary position. A decrease in the angle of convergent strabismus (over 6°) without surgery during pleoptic treatment was noted in three cases.

Retinal Correspondence.—It was possible to determine the correspondence at the outset in 45 cases (Table VI). Suppression was so deep in the other 43 that correspondence testing was impossible. In every case of eccentric fixation in which it

TABLE VI
RETINAL CORRESPONDENCE AT START OF PLEOPTIC TREATMENT

Diagnosis	Correspondence			
	Normal	Anomalous	No Data Available	Total
Central Inhibition Scotoma	2	6	2	10
Eccentric Fixation with Latent PVD	1*	21	20	42
Eccentric Fixation without Latent PVD	0	15	21	36
Total	3	42	43	88

* Correspondence alternated between Normal and Anomalous for Entopic Objects.

could be determined, the correspondence was anomalous in all but one, where it alternated between normal and anomalous for entoptic objects only. Except as noted below, the status of the retinal correspondence played no role in the outcome of therapy.

Site of Fixation.—In central inhibition scotoma, the PVD is always foveal and the retinal locus used to view objects is on the border of the scotoma (Aulhorn, 1961). In eccentric fixation however, it is conceivable that the site of fixation may in some way influence the therapeutic result.

Hypothetically stated: Is it more difficult to attain foveal fixation when the eccentric fixation is in the region of the disc than when it is 2° nasal to the fovea?

For purposes of analysis, the cases were divided into those fixing in the neighbourhood of the disc*, those fixing between the disc and macula**, and those fixing in the macular region*** (Table VII). The results showed that the location of the eccentric fixation probably does affect the result of therapy ($0.05 > P > 0.02$), for reasons as yet unknown. A fixation in the region of the macula has a better prognosis than one in the neighbourhood of the disc.

TABLE VII
RESULT OF THERAPY RELATED TO PLACE OF FIXATION IN 78 CASES

Place of Fixation	Result		
	Foveal	Non-Foveal	Total
Disc	19	20	39
Disc to Macula	18	4	22
Macula	12	5	17
Total	49	29	78

($0.05 > P > 0.02$)

Crowding or Separation Difficulty (Bangerter, 1955).—This was defined as a difference of at least 0.2 in the visual acuity between single letters and line acuity. At the onset eleven patients manifested this. In all, the visual acuity was better than 0.2. During the course of therapy 28 more patients developed it and at the end of the survey ten still showed it. All of these last were cases of eccentric fixation without latent foveal PVD.

III. Therapy

Duration of Therapy.—The means for the three diagnostic groups were:

Central Inhibition Scotoma: 7.7 weeks (standard deviation 4.7).

Eccentric Fixation with Latent Foveal PVD: 8.07 weeks (standard deviation 5.4).

Eccentric Fixation without Latent Foveal PVD: 8.6 weeks (standard deviation 5).

This represents a 6-day working week of three to six sessions daily, but they were not necessarily consecutive weeks.

* Disc = Within 2–3° nasal or temporal to disc.

** Disc to Macula = More than 3° nasal to fovea to 3° temporal to disc.

*** Macula = Within 6° of macular diameter.

TABLE VIII
TYPE OF THERAPY IN 87 CASES†

Diagnosis	Type of Therapy		
	Unocular	Unocular and Binocular	Total
Central Inhibition Scotoma	2	8	10
Eccentric Fixation with Latent Foveal PVD	26	16*	42
Eccentric Fixation without Latent Foveal PVD	26*, *	9	35†
Total	54	33	87

† Change of Fixation Operation Only in one case.

* Monocular Diplopia: 3 cases.

Type of Therapy (Table VIII).—Binocular therapy using entoptic objects was employed frequently. As soon as Haidinger's brushes were seen by the amblyopic eye under binocular conditions such therapy was begun. Three patients demonstrated unocular diplopia and pleoptics employing this phenomenon was utilized (Hering, 1861). In one patient only a planned change of fixation operation (Cüppers, 1966) was performed and no other therapy was given.

Surgery.—Sixty patients underwent surgery; 41 had combined horizontal and vertical muscle surgery and in the remaining eighteen only the horizontal muscles were dealt with.

A "change of fixation" operation with the specific object of affecting eccentric fixation by surgery was performed in 24 patients; foveal fixation was achieved in nine of them, but since they all had unocular and binocular therapy as well as surgery, the main factor in success cannot be distinguished. The remaining fifteen of the 24 were failures.

IV. Results of Therapy (Table IX)

The diagnosis is the key factor in formulating a prognosis and judging the results of therapy. The outlook for patients with central inhibition scotoma is better than

TABLE IX
RESULTS OF PLEOPTIC THERAPY

Diagnosis	Result			
	Positive	Plus/Minus	Negative	Total
Central Inhibition Scotoma	10	—	0	10
Eccentric Fixation with Latent PVD	21	12	9	42
Eccentric Fixation without Latent PVD	5	11	20	36
Total	36	23	29	88

that for those with eccentric fixation, while in the latter group, the presence of a latent foveal PVD has a better prognosis ($0.01 > P > 0.001$).

Positive Results (36).—For the results of amblyopia therapy to be significant, the binocular status of each child who attained full vision must be accounted for (Table X). In all cases in which full vision was attained, the results have endured because of the practice of continuing occlusion on a 13 to 1 dominant to non-dominant eye basis until retinal correspondence is normal, the eyes straight, and binocular functions present. Eighteen of the 36 patients with positive results had attained normal retinal correspondence, and of this group fourteen had fusion, eleven with amplitude and six with some form of stereopsis. These represent results which are probably stable. The mean duration of follow-up in this group was 6.2 months (range of 2 to 16). Of the eighteen with still anomalous or transitional forms of correspondence all were under occlusion and awaiting further hospital admission.

TABLE X
BINOCULAR STATUS IN 36 POSITIVE RESULTS

Diagnosis	Correspondence		Binocular Functions in 18 Cases of Normal Retinal Correspondence			
	Anomalous	Normal	Simultaneous Macular Perception	Fusion	Amplitude	Stereopsis
Central Inhibition Scotoma	4	6	6	6	4	3
Eccentric Fixation with Latent Foveal PVD	12	9	6	6	5	1
Eccentric Fixation without Latent Foveal PVD	2	3	3	2	2	2
Total	18	18	15	14	11	6

Plus/Minus Results (23).—Fixation was foveal, but the visual acuity was not full and they cannot be regarded as fully-recovered amblyopes. All were under occlusion on a 13 : 1 basis as in the previous group. During the course of therapy, five developed normal retinal correspondence accompanying the shift of fixation to the fovea. Ten cases represent a transitional phase between anomalous and normal correspondence. Eleven remained anomalous. The average duration of follow-up was 6.1 months (range 2 to 20). Nothing was recognized in a review of the historical data or physical findings to distinguish them as a group from those with positive results. It appeared only that the central scotoma was more recalcitrant to treatment.

Negative Results (29).—This group, though often overlooked in a survey of the results of pleoptic therapy, presents the most challenging aspect of such an analysis. When they were scrutinized to see if they possessed common factors which might explain the failures, the following were found:

(1) The diagnosis, as already noted, was most important, the outlook in cases of eccentric fixation without latent foveal PVD being poor (Table IX).

(2) The ages of the failures did not differ significantly by variance analysis (Harms, 1949) from the others ($P > 0.05$).

(3) Three were cases of temporal eccentric fixation and four others showed harmonious anomalous correspondence with identity between the angle of anomaly and the eccentric fixation point.

(4) Two cases showed evidence of organic macular disease on dark-adaptation perimetry. There was no other evidence of a macular lesion and on ophthalmoscopy the macula appeared normal.

(5) Age at onset, angle of squint, and anisometropia were not statistically significant.

Summary

Analysis of this group of 88 amblyopes permitted the following conclusions:

(1) A positive family history of strabismus is probably the only historical fact implicated in the outcome of therapy.

(2) A visual acuity of 0.1 or better at the start seems to be associated with a better outcome. Care must be taken in interpretation of these results.

(3) It appears easier to achieve foveal fixation when fixation was in the region of the macula. Further study of this problem, particularly with regard to the latency of the foveal PVD, is indicated.

(4) Amblyopes with high hypermetropia seem to have a poorer prognosis than other refractive groups.

(5) Anisometropia in no way affects the outcome.

(6) The duration of treatment was remarkably uniform, the mean being about 7-9 weeks regardless of the type of amblyopia. However, those with central inhibition were older and their spread or variance greater. This may have prolonged the duration of therapy in this group.

(7) Both uniocular and binocular therapy was usually given. Some patients also had surgery designed to change eccentric fixation to foveal.

(8) Success was achieved in 36, 23 regained foveal fixation, and 29 failed to derive any benefit.

The problem of amblyopia is common (Downing, 1945; Helveston, 1965) but by no means simple. This survey of the patient population and results of the Giessen Clinic over a 2-year period shows that much time and intensive effort are required to treat amblyopia by pleoptics. The prolonged hospitalization, multiple daily therapy sessions, and combination of surgery with sensory training are departures from typical methods, but 41 per cent. of the patients reviewed achieved full vision and a further 26 per cent. recovered foveal fixation, while 33 per cent. gained no benefit.

We gratefully acknowledge the invaluable assistance of Dr. Iris M. Keim, Assistant Professor of Biometry, University of Miami School of Medicine, for help in the organization and interpretation of the statistical material.

The patients surveyed in this paper are those of Prof. C. Cüppers; the authors gratefully acknowledge his permission to use this material and are also indebted to him for his kind assistance and advice in preparing this paper.

REFERENCES

- AULHORN, E. (1961). *Wiss. Z. Karl-Marx-Univ. Leipzig, Math-nat. Reihe*, **10**, 694.
 BANGERTER, A. (1955). "Amblyopiebehandlung", 2nd ed. Karger, Basel.
 CÜPPERS, C. (1961). In "Schielen: Pleoptik Orthoptik Operation", ed. F. Hollwich, p. 1-68. ("Bücherei des Augenarztes", heft 38). Enke, Stuttgart.
 — (1966). *Ann. roy. Coll. Surg. England*, **38**, 308.

- DAVSON, H. (1962). "The Eye", vol. 4, p. 143, Academic Press, London.
- DODEN, W. (1961). In "Schielen: Pleoptik Orthoptik Operation", ed. F. Hollwich, p. 69-115. ("Bücherei des Augenarztes", heft 38). Enke, Stuttgart.
- DOWNING, A. H. (1945). *Arch. Ophthalm. (Chicago)*, **33**, 137.
- DUKE-ELDER, S. (1949a). "Text-book of Ophthalmology", vol. 4, pp. 3833-47, Kimpton, London.
- (1949b). *Idem*, pp. 4304-09. Kimpton, London.
- GIRARD, L. J., FLETCHER, M. C., TOMLINSON, E., and SMITH, B. (1962). *Amer. orthopt. J.*, **12**, 12.
- HARMS, H. (1949). *von Graefes Arch. Ophthalm.*, **149**, 1.
- HELVESTON, E. M. (1965). *Amer. J. Ophthalm.*, **60**, 75.
- HERING, E. (1861). "Beiträge zur Physiologie". Engelmann, Leipzig.
- NOORDEN, G. K. VON, and LIPSUS, R. M. C. (1964). *Amer. J. Ophthalm.*, **58**, 41.
- PRIESTLEY, B. S. (1961). *Int. Ophthalm. Clin.*, **1**, no. 4, p. 787.
- SORSBY, A., BENJAMIN, B., DAVEY, J. B., SHERIDAN, M., and TANNER, J. M. (1957). "Emmetropia and its Aberrations", *Med. Res. Coun. spec. Rep. Ser.*, No. 293. H.M.S.O., London.
- VEREECKEN, E., and FLYNN, J. T. (1967). *J. pediat. Ophthalm.*, **4**, 43.