THE ASSOCIATION BETWEEN ANISOMETROPIA, AMBLYOPIA, AND BINOCULARITY IN THE ABSENCE OF STRABISMUS

By David R. Weakley, MD

ABSTRACT

Purpose: First, to determine if thresholds exist for the development of amblyopia and subnormal binocularity with various types of anisometropia and to confirm or refute existing guidelines for its treatment or observation. Second, to delineate any association between the degree or type of anisometropia and the depth of amblyopia and severity of binocular sensory abnormalities.

Methods: Four hundred eleven (411) patients with various levels of anisometropia, no previous therapy, and no other ocular pathology were evaluated. The effect of anisometropia (both corrected and uncorrected) on monocular acuity and binocular function was examined.

Results: Spherical myopic anisometropia (SMA) of >2 diopters (D) or spherical hypermetropic anisometropia (SHA) of >1 D results in a *statistically* significant increase in the incidence of amblyopia and decrease in binocular function when compared to non anisometropic patients. Increasing levels of SMA and SHA beyond these thresholds were also associated with increasing depth (and in the case of SHA, incidence as well) of amblyopia.

Cylindrical myopic anisometropia (CMA) or cylindrical hyperopic anisometropia (CHA) of >1.5 D results in a *statistically* significant increase in amblyopia and decrease in binocular function. A *clinically* significant increase in amblyopia occurs with >1 D of CMA or CHA. Increasing levels of CMA and CHA beyond >1 D were also associated with an increased incidence (and in the case of SMA, depth as well) of amblyopia.

Conclusions: This study provides guidelines for the treatment or observation

*From Department of Ophthalmology, The Universtity of Texas Southwestern Medical Center, Dallas, Texas.

of anisometropia and confirms and characterizes the association between the type and degree of anisometropia and the incidence and severity of amblyopia and subnormal binocularity.

INTRODUCTION

Anisometropia, a relative difference in the refractive state of the 2 eyes, is well known to be associated with amblyopia both in the presence and absence of strabismus. A considerable volume of literature supports the supposition that anisometropia (even in the absence of strabismus) is a significant risk factor for the development of amblyopia.[1-11] The term "anisometropic amblyopia"[12] is widely accepted to describe amblyopia presumed to be caused by anisometropia alone.

A great deal of information has been published during the past half-century regarding the prevalence, natural history, diagnosis, and treatment of anisometropia and associated strabismus and amblyopia. Nevertheless, critical questions regarding this relatively common clinical entity remain and are the focus of this study.

First, disagreement exists in the published literature as to the nature of, or even existence of, an association between anisometropia and the incidence or severity of amblyopia.[5,7,11,13-23] A majority of investigators acknowledge such an association, yet no study to date has clearly delineated it. The risk of developing amblyopia and/or subnormal binocular vision for a given degree or type of anisometropia has not previously been quantified. Furthermore, when amblyopia develops in association with anisometropia, it remains uncertain if the severity of amblyopia is directly related to the degree or type of anisometropia. The current study attempts to evaluate and define this association.

Second, although it is generally agreed that anisometropia (unassociated with strabismus) with associated amblyopia does require treatment, it has not been established what degree of anisometropia should be corrected when amblyopia is either absent (in order to prevent its development) or cannot be confirmed (eg, preverbal patients). The American Academy of Ophthalmology Preferred Practice Pattern (AAO-PPP) for amblyopia recommends levels at which various types of anisometropia should be treated or monitored to prevent the development of amblyopia.[4] However, these guidelines are based on clinical impression and not supported by published data. The current study attempts to confirm or refute these guidelines.

Third, despite a clear association between increasing anisometropia and decreasing stereoacuity and binocular function having been established experimentally in normal subjects,[24-33] considerably less attention has been devoted to the sensory findings in anisometropic patients.[26,34] The

effect of naturally occurring anisometropia on binocular sensory function has not been adequately investigated. The current study attempts to further examine this.

PATIENTS AND METHODS

All new patients presenting to the Children's Medical Center ophthalmology department during a period of 42 months (January 1, 1995 through June 30, 1998) were considered for inclusion in this study. Criteria were established to include all patients with pure refractive error (no other ocular pathology) and no previous ocular treatment of any kind.

Patients were excluded from the study for any 1 or more of the following:

1. History of glasses wear.
2. History of occlusion or penalization therapy.
3. Previous ocular surgery.
4. Any ocular pathology (including any strabismus*) noted on complete initial ophthalmic examination.
5. Incomplete records or inadequate follow-up to evaluate best-corrected visual status if spectacles were prescribed.
6. An age too young to obtain reliable visual acuity and/or sensory data.

Since patients were also excluded from this study if significant strabismus secondary to anisometropia was present (beyond that of microtropia or monofixational range), the results of this study likely underestimate the true overall morbidity of anisometropia. The incidence of patients with amblyopia and subnormal binocularity for a given level of anisometropia would certainly be higher if these patients were included in the analysis. However, exclusion was necessary since the separate effects of strabismus and anisometropia on the development of amblyopia and subnormal binocularity could not be distinguished. For this reason, the conclusions derived in this study are meant to apply to non strabismic anisometropic patients and are not necessarily representative of the anisometropic population as a whole.

The fact that previously treated patients were excluded should also be

*Patients with "microtropia" or manifest deviations within the monofixation syndrome range (up to 8 prism dipters of horizontal tropia) were also excluded. Such small deviations (with a foveal scotoma and eccentric fixation) do frequently occur secondarily to anisometropia and could reinforce or worsen any existing amblyopia. Since this study by design includes groups of patients with little or no anisometropia, inclusion of small-angle strabismus patients without anisometropia possibly would bias, in a negative way, the acuity data in these groups. Monofixation syndrome or microtropia patients may alone, without anisometropia, manifest amblyopia in the nonpreferred eye

taken into consideration when interpreting the findings of this study. Patients thus excluded might, in fact, represent a subset of patients that are more severely affected than the patients studied, as detection at an earlier age may result from more severe or easily detectable visual disability. However, exclusion of these patients was also necessary, since the original (pretreatment) levels of amblyopia could not be accurately determined. If amblyopia therapy had been successful, even partially, the effect of anisometropia would be underestimated by including these patients. Thus, the actual impact of anisometropia (in the absence of strabismus) on the development of amblyopia may, in fact, be more significant than that determined by this study.

Inclusion of younger patients would also have been desirable; however, preferential looking acuities were not considered acceptable for this study because of concerns of overestimation of acuity in amblyopic eyes and the inability to obtain reliable binocularity data in these patients.[35,36]

Patients included in the study underwent a complete initial ophthalmologic examination. The following data were obtained:

1. Unaided visual acuity in each eye.
2. Stereo-acuity with the Titmus stereo test.
3. Presence or absence of a monofixation response (with the 4-diopter base-out prism test at distance or distance fusion of the Worth 4-dot test).
4. Cycloplegic refraction with 1% or 2% cyclopentolate.
5. Funduscopic examination.

Visual acuity was again recorded with best correction after cycloplegic refraction. If equal, stereoacuity, with best correction and a +3.00 add, and distance monofixation response, with best correction, were retested if they were subnormal prior to cycloplegic refraction. No further follow-up data were required.

All patients with unequal best-corrected visual acuity at the initial visit were prescribed spectacles. Visual acuity and binocularity were reassessed at a subsequent visit and amblyopia therapy then instituted if indicated.

For the purpose of analysis, patients with anisometropia were divided into 4 types: spherical hyperopic anisometropia (SHA), spherical myopic anisometropia (SMA), astigmatic or cylindrical hyperopic anisometropia (CHA), and astigmatic or cylindrical myopic anisometropia (CMA). Patients with no anisometropia (NA) were analyzed separately and used as a control group. Patients with "mixed" anisometropia (1 eye hyperopic, the fellow eye being myopic) were too few in number (27/412) for further classification based on severity and meaningful analysis as a specific type of anisometropia. Therefore, these patients were classified as either hyper-

metropic or myopic based on the more ametropic eye. For example, a patient with the refraction OD = +1.50 and OS = -.50 was classified as a patient with 2 diopters (D) hyperopic spherical anisometropia (SHA).

The best means of analysis of patients with combined spherical and cylindrical errors has frequently confounded other investigators reporting on this subject. The most commonly used methods for analysis include either calculating the degree of anisometropia based on the spherical equivalent of the refractive error alone, ignoring astigmatic error, or calculating anisometropia based on the largest difference at any 1 meridian, ignoring the spherical equivalent. Each of these methods has merits but also limitations. Use of spherical equivalents alone can mask the effect of astigmatic anisometropia. For example, a patient with the refraction OD = plano + 4.00 x 90 and OS = +2.00 would have no calculated anisometropia, potentially increasing the amblyopia incidence in patients classified as "nonanisometropic."

Contrarily, use of the largest difference in any one meridian to calculate anisometropia does not distinguish spherical and cylindrical anisometropia and may mask large differences between patients. For example, the refraction OD = plano + 4.00 x 90 and OS = +2.00 sphere has the same degree of calculated anisometropia (+2 D in the largest meridian) as a patient with the refraction of OD = plano and OS = + 2.00 sphere. This method of analysis ignores the fact that not only is there a 2 D difference in spherical equivalent of anisometropia, but also a 4 D difference in cylindrical anisometropia between these 2 patients.

Other methods, attempting to calculate the combined effect of cylindrical and spherical errors in a compound refraction, have also been used to study anisometropia. These methods, however, are mathematically complex, difficult to apply in clinical situations, and often no more predictive of amblyopia than use of spherical equivalents alone.[23]

To avoid these pitfalls, patients with significant cylindrical anisometropia were analyzed separately from patients with significant spherical anisometropia. Patients with 1 D or less of cylindrical anisometropia were analyzed based on spherical equivalents alone and included in the myopic or hyperopic spherical groups. Patients with more than 1 D of astigmatic (cylindrical) anisometropia were analyzed separately as "cylindrical" aniso-metropes (if the overall spherical equivalent of anisometropia was 1 diopter or less).

Astigmatic or cylindrical anisometropia was calculated as the difference of the astigmatic error of the 2 eyes. All patients with significant astigmatic error had cylindrical axes that were within 10° of each other, or within 10° of symmetry (eg, 45° OD and 135° OS), and therefore axis of astigmatism was not considered in calculating the degree of astigmatic ani-

sometropia. The non anisometropic patients had zero spherical or cylindrical anisometropia.

The 4 aforementioned types of anisometropia were further broken down according to degree of anisometropia (Table I). Each group was limited to the first of 50 subjects, for statistical analysis. The initial plan was to analyze each type of anisometropia in one-half diopter groups (eg, 0 to .5, >.5 to 1); however, the smaller numbers of patients with >1 D of spherical anisometropia required larger intervals of 1 D to perform meaningful statistical analysis.

Each group was analyzed for the following information after converting Snellen fractions to the logMAR scale:[23,37,38]

1. Mean acuity better eye.
2. Mean acuity worse eye.
3. Interocular acuity difference (IOAD) (mean of difference in logMAR acuity of better versus worse eye).
4. Mean acuity amblyopic eye (corrected patients only).
5. Number of amblyopic patients in each group (corrected patients only).
6. Rate of monofixation response of the total group.
7. Degree of near stereoacuity.

For statistical analysis, patients with no stereopsis were assigned the worst measurable value (3000 sec/arc) by the Titmus stereo test.

The incidence and severity of amblyopia was determined with best correction and defined as 1 full Snellen line or greater of acuity difference between the 2 eyes.

RESULTS

Patients included in the study are summarized in Table I. Patients were divided into 5 types:

1. No anisometropia, or controls (NA, n = 50).
2. Spherical myopic anisometropia (SMA, n = 138).
3. Spherical hyperopic anisometropia (SHA, n = 139).
4. Cylindrical myopic anisometropia (CMA, n = 44).
5. Cylindrical hyperopic anisometropia (CHA, n = 40).

The 4 types of anisometropia were further broken down according to the amount of anisometropia. The patients were grouped in this fashion to determine the threshold at which each type of anisometropia is associated with increased amblyopia and decreased binocular function. In analyzing results, the subgroups in each type of anisometropia were compared to the

TABLE I. SUMMARY OF PATIENTS IN STUDY (N=411)

1.	No spherical or cylindrical anisometropia (controls subtotal (n = 50)	
2.	Spherical myopic anisometropia (in diopters)	
	>10	(n = 9)
	>4 to 10	(n = 13)
	>3 to 4	(n = 6)
	>2 to 3	(n = 6)
	>1 to 2	(n = 15)
	>.5 to 1	(n = 39)
	0 to .5	(n = 50)
	Subtotal	(n = 138)
3.	Cylindrical myopic anisometropia (in diopters)	
	> 2	(n = 8)
	>1.5 to 2	(n = 8)
	>1 to 1.5	(n = 13)
	.5 to 1	(n = 15)
	Subtotal	(n = 44)
4.	Spherical hypermetropic anisometropia (in diopters)	
	>4 to 10	(n = 13)
	>3 to 4	(n = 12)
	>2 to 3	(n = 13)
	>1 to 2	(n = 26)
	>.5 to 1	(n = 25)
	0 to .5	(n = 50)
	Subtotal	(n = 139)
5.	Cylindrical hyperopic anisometropia (in diopters)	
	>2	(n = 8)
	>1.5 to 2	(n = 6)
	>1 to 1.5	(n = 11)
	.5 to 1	(n = 15)
	Subtotal	(n = 40)

non anisometropic "controls" as well as to one another. The mean age of all patients was 105 months (8.75 years) (range, 37-174 months).

RESULTS IN UNCORRECTED ANISOMETROPIA

Monocular acuity data and binocular sensory data in uncorrected patients are summarized in Tables II through V. The group of 50 patients with no spherical or cylindrical anisometropia (NA) is represented in the first column of each table for comparison.

First, trend analysis reveals a significant trend for increasing interocular acuity difference (IOAD), worsening acuity in the "worse" eye, and

decreasing stereopsis (all P=.001 by Jonckheere-Terpstra Test) and an increasing rate of monofixation (P=.001 by Cochran-Armitage Trend Test) in all 4 types of anisometropia (SMA, SHA, CMA, CHA) as anisometropia increases across the subgroups defined above.

Second, group (interval) analysis using the Ryan-Einot-Gabriel-Welsch Multiple Range Test (REGWQ) was performed on the same variables in each type of uncorrected anisometropia to detect any significant differences in IOAD and stereopsis among the subgroups for each type of anisometropia. Differences in the incidence of monofixation among groups was also analyzed (Tukey type comparison of multiple proportions at P=.05). Better and worse acuities were not analyzed in uncorrected patients, since the overall degree of refractive error can mask the effect of the anisometropia.

A value with a significant difference from the nonanisometropic "controls" is indicated by (°), while a value that is significantly different from the adjacent (less anisometropic) group is signified by an asterisk (†) next to the value in each of the tables. For example, in Table II, patients with uncorrected spherical myopic anisometropia developed a significant increase in IOAD in the group where anisometropia was >-2 to –3 D when compared to the less anisometropic groups. The group with >-3 to –4D of anisometropia also differed significantly from these less anisometropic groups, but not from the >-2 to -3 group. The IOAD of the >-4 to-10 D group likewise differed significantly from the first 4 groups, but also from the >-2 to -3D and >-3 to -4D groups. The IOAD of the >-10D group was significantly worse than the >-4 to -10D group and all previous groups.

When analyzing stereopsis, a significant decrease was first noted in the group with >-3 to -4D of anisometropia as compared to the >-2 to -3D group and all groups with less anisometropia. The >-4 to -10D group had significantly worse stereopsis than the >-3 to -4 group (all by REGWQ multiple comparison). In terms of monofixation, all groups beginning with the group with > -1 to -2D of anisometropia had significantly higher rates of monofixation than the non-anisometropic patients, although they did not differ significantly from one another (Tukey type multiple comparison of proportions at P=.05)

The significant levels of change in IOAD, near stereopsis, and monofixation incidence in the uncorrected spherical hypermetropic anisometropia are summarized in Table III. Notably, IOAD increased significantly first in the >1 to 2D anisometropia group and again in the >3 to 4D anisometropia group. Stereopsis first deteriorated significantly in the >2 to 3D anisometropia group and again in the >3 to 4 diopter group (REGWQ multiple comparison). The monofixation rate increased first in the >1 to 2D group and increased again in the >2 to 3D group (Turkey-

TABLE II: ACUITY AND BINOCULARITY DATA IN UNCORRECTED SPHERICAL MYOPIC ANISOMETROPIA

	SPHERICAL MYOPIC ANISOMETROPIA (IN DIOPTERS)							
	0 (CONTROL GROUP)	**>0 TO-.5 MEAN = -.3**	**>-.5 TO -1 MEAN = -.75**	**>-1 TO -2 MEAN = -1.3**	**>-2 TO -3 MEAN = -2.7**	**>-3 TO -4 MEAN =-3.4**	**>-4 TO -10 MEAN = -6.8**	**>-10 MEAN = -13.5**
No. patient	50	50	39	15	6	6	13	9
Mean age (mo)	115	117	111	116	108	94	97	104
Mean acuity Snellen/logMAR (better eye)	20/39 .2918	20/61 .4809	20/39 .2912	20/39 .295	20/38 .2832	20/29 .1544	20/37 .2663	20/22 .043
Mean acuity Snellen/logMAR (worse eye)	20/41 .3117	20/71 .5523	20/54 .4285	20/72 .5548	20/118 .7735	20/92 .66141	20/274 .1371	20/800 .602
Interocular acuity difference (IOAD) (logMAR)	.0199	.0714	.1373	.2598	**.4903°†**	**.507°**	**.8714°†**	**1.559°†**
Mean near stereopsis (sec/arc)	55	70	227	462	683	**1650°†**	**2388°†**	**3000°**
Monofixation rate	6%	10%	23%	**53%°†**	**100%°**	**100%°**	**100%°**	**100%°**

° Value is significantly different from nonanisometropic controls.
† Significant difference between adjacent groups (REGWQ or Turkey type multiple comparison).

TABLE III. ACUITY AND BINOCULARITY DATA IN UNCORRECTED HYPERMETROPIC SPHERICAL ANISOMETROPIA

	SPHERICAL HYPEROPIC ANISOMETROPIA (DIOPTERS)						
	0 (CONTROL GROUP)	**>0 TO .5 MEAN = +.34**	**>.5 TO 1 MEAN =+.85**	**>1 TO 2 MEAN = +1.52**	**>2 TO 3 MEAN = +2.48**	**>3 TO 4 MEAN =+3.5**	**>4 TO 10 MEAN = +4.84**
Patient no.	50	50	25	26	13	12	13
Mean age (mo)	115	109	100	93	96	97	87
Mean acuity Snellen/logMAR (better eye)	20/39 .2918	20/27 .1272	20/25 .1076	20/23 .0585	20/23 .0673	20/22 .0396	20/21 .0285
Mean acuity Snellen/logMAR (worse eye)	20/41 .3117	20/28 .147	20/30 .171	20/45 .3545	20/59 .4729	20/139 .8432	20/186 .9694
Interocular Acuity Difference (logMAR)	.0199	.0198	.0634	**.296°†**	**.4056°**	**.8034°†**	**.9409°**
Mean near stereopsis (sec/arc)	55	61	198	365	**1014°†**	**1873°†**	**2384°**
Monofixation rate	6%	12%	20%	**69%°†**	**100%°**	**100%°**	**100%°**

° Value is significantly different than nonanisometropic controls.

† Significant difference between adjacent groups (REGWQ or Turkey type multiple comparison).

Type multiple comparison).

The results for the uncorrected cylindrical anisometropic patients were similar for both the hypermetropic and myopic varieties (Tables IV and V). A significant increase in IOAD occurred in both types when cylindrical anisometropia reached the >1 to 1.5 D level as compared to the control and the >.5 to 1D groups. The monofixation rate also increased significantly at the >1 to 1.5 D level in both the hypermetropic and myopic types. However, a significant decrease in stereopsis was noted only in the >2D groups for both CMA and CHA.

In summary, in uncorrected patients, binocularity as measured by monofixation versus bifixation, worsened significantly at relatively low levels of uncorrected anisometropia, regardless of type, while stereo-acuity did not decrease significantly until higher levels of anisometropia. On the other hand, IOAD increased significantly at >-2D in spherical myopic, >1D in spherical hypermetropic anisometropia, and >1D in either hypermetropic or myopic cylindrical anisometropia.

Limited conclusions should be drawn from the uncorrected acuity and binocularity data. It is unclear how much uncorrected refractive errors negatively affect binocularity test results, and corrected data must be considered in establishing any treatment guidelines. Furthermore, it is impossible to separate decreased vision caused by uncorrected refractive error from decreased vision caused by amblyopia. It is interesting to note, however, that the levels of anisometropia at which IOAD first increased significantly are the same levels in the uncorrected and corrected SMA and SHA patients. In CMA and CHA, uncorrected patients developed a statistically significant increase in IOAD at a slightly lower level than the corrected patients. However, as will be noted, a clinically (but not statistically) significant increase in IOAD did occur in the corrected CMA and CHA patients at the >1D level, the same level as in the uncorrected patients.

RESULTS IN CORRECTED ANISOMETROPIA

The best-corrected acuity and binocularity data were obtained from patients with equal corrected acuity at the time of the initial evaluation. Patients with unequal corrected acuity were prescribed spectacle correction at the time of the initial visit. These patients were allowed time to wear the correction (mean, 14.8 weeks from the initial visit) before obtaining best-corrected data at the next visit. Spectacle correction alone, in anisometropia, has been reported to improve acuity (and presumably anisometropic amblyopia) over time.[39,40] Therefore, the follow-up data were obtained from the second office visit, allowing for adjustment to the glasses, but soon enough to have minimal effect on improving any existing amblyopia.

TABLE IV. ACUITY AND BINOCULARITY DATA IN UNCORRECTED CYLINDRICAL MYOPIC ANISOMETROPIA

	CYLINDRICAL MYOPIC ANISOMETROPIA				
	0 (CONTROL GROUP)	**.5 TO –1** MEAN = -0.7	**>-1 TO -1.5** MEAN = -1.38	**>-1.5 TO -2** MEAN = -1.84	**>-2** MEAN = -3.4
Patient no.	50	15	13	8	8
Mean age (months)	115	115	119	97	116
Mean acuity Snellen/logMAR (better eye)	20/39 .2918	20/58 .4616	20/30 .1682	20/36 .259	20/24 .0718
Mean acuity Snellen/logMAR (worse eye)	20/41 .3117	20/77 .5856	20/55 .4396	20/69 .5403	20/75 .5759
Interocular acuity difference (log/MAR)	.0199	.124	**.2714°**	**.2813°**	**.5041°†**
Mean near stereopsis (sec/arc)	55	63	97	123	**500°†**
Monofixation rate	6%	13%	**46%°**	**75%°**	**75%°**

° Value is significantly different than nonanisometropic controls.

† Significant difference between adjacent groups (REGWQ or Turkey type multiple comparison).

TABLE V. ACUITY AND BINOCULARITY DATA IN UNCORRECTED CYLINDRICAL HYPEROPIC ANISOMETROPIA

	CYLINDRICAL HYPEROPIC ANISOMETROPIA				
	0 (CONTROL GROUP)	**.5 TO 1** MEAN = +.66	**>1 TO 1.5** MEAN = +1.38	**>1.5 TO 2** MEAN = +1.86	**>2** MEAN = +3.56
Patient no.	50	15	11	7	8
Mean age (mo)	115	108	111	96	102
Mean acuity Snellen/logMAR (better eye)	20/39 .2918	20/35 .2488	20/28 .1447	20/26 .1072	20/29 .1645
Mean acuity Snellen/logMAR (worse eye)	20/41 .3117	20/39 .2889	20/44 .3461	20/53 .4372	20/69 .5385
Mean interocular acuity difference (log/MAR)	.0199	.0401	**.2014°†**	**.33°†**	**.375°**
Mean near stereopsis (sec/arc)	55	63	121	121	**157°†**
Monofixation rate	6%	33%	**81%°**	**71%°**	**88%°**

° Value is significantly different than nonanisometropic controls.

† Significant difference between adjacent groups (REGWQ or Turkey type multiple comparison).

Tables VI through IX summarize the best-corrected monocular acuity and binocular sensory results. Mean acuity data are shown for each group of patients and were calculated in the same fashion as the uncorrected acuity data. Mean acuity data were recorded for the better eye and the worse eye. In any group with patients having unequal best-corrected "better" or "worse" eyes, mean acuity was also recorded for the amblyopic eyes. Mean interocular acuity difference for each group was also recorded as logMAR (.10 equals approximately 1 Snellen line of acuity difference). Thus, severity of amblyopia could be analyzed 3 ways:

1. By evaluating the mean acuity of only the amblyopic eyes in each group.
2. By evaluating the mean interocular acuity difference of each group.
3. By evaluating the mean acuity of the "worse" eye in each group.

Each of these methods yielded essentially identical results except where noted.

Mean acuities of the better, worse, and amblyopic eyes were recorded both as logMAR and the Snellen equivalent.

Groups with no amblyopic patients had mean acuity data that were the same for the better eyes and the worse eyes with no data for amblyopic eyes. Contrarily, groups in which all patients were amblyopic had mean acuity data that were the same for the worse eyes and the amblyopic eyes. Groups in which some but not all patients are amblyopic had mean acuity data that are better in the "worse" eyes than the "amblyopic" eyes, since the "worse" eyes included both normal and amblyopic eyes.

Incidence of amblyopia was evaluated by comparing the number of amblyopic patients in each group. Stereopsis was again measured with the Titmus stereo test. The presence or absence of the monofixation response was again determined with the distance Worth 4-dot and/or 4-diopter base-out prism test.

In Tables VI through IX, the first column in each table again includes the data for the patients with no spherical or cylindrical anisometropia (NA) for comparison. The mean visual acuities in the better eye (20/20) and the worse eye (20/21) in this group provide a means for comparison to the anisometropic patients (both spherical and cylindrical). The mean near stereoacuity in these patients was 53 sec/arc, with 2 of 50 (4%) having a difference in visual acuity between the 2 eyes (amblyopia) and the same 2 patients (4%) also having a positive monofixation response. While these 50 patients were entered into the study in the same fashion as the anisometropic patients, they were considered "controls," to which the acuity and binocularity of other groups were compared.

A significant trend was again noted in all 4 types of anisometropia

TABLE VI: ACUITY AND BINOCULARITY DATA IN CORRECTED MYOPIC SPHERICAL ANISOMETROPIA

	SPHERICAL MYOPIC ANISOMETROPIA (DIOPTERS)							
	0 CONTROL GROUP	**>0 TO -.5** MEAN = -.3	**>-.5 TO -1** MEAN = -.75	**>-1 TO -2** MEAN = -1.34	**>-2 TO -3** MEAN = -2.70	**>-3 TO -4** MEAN = -3.43	**>-4 TO -10** MEAN = -6.75	**>-10** MEAN =-13.5
Patient no.	50	50	39	15	6	6	13	9
Mean acuity (better eye) Snellen/logMAR	20/20 .0069	20/20 .0024	20/20 .0099	20/22 .0407	20/23 .0587	20/22 .0502	20/26 .1105	20/20 0
Mean acuity (worse eye)	20/21 0.148	20/20 .0024	20/20 .0099	20/22 .0407	**20/40°†** **.3049°†**	**20/60°†** **.4813°†**	**20/104°†** **.7174°†**	**20/432°†** **1.335°†**
Interocular acuity difference (log/MAR)	.0079	0	0	0	**.2462°†**	**.4311°†**	**.7174°†**	**1.335°†**
Mean acuity amblyopic eyes	20/32 .183	NONE	NONE	NONE	**20/40°†** **.3049°†**	**20/60°†** **.4813°†**	**20/104°†** **.7174°†**	**20/432°†** **1.335°†**
No. (%) amblyopic eyes	2/50 (4%)	0/50 (0%)	0/39 (0%)	0/15 (0%)	**6/6°†** **(100%)°†**	**6/6°** **(100%)°**	**13/13°** **(100%)°**	**9/9°** **(100%)°**
Mean near stereopsis	54	47	47	61.3	**680°†**	**1110°**	**3000°†**	**3000°**
Monofixation rate	2/50 (4%)	0/50 (0%)	0/39 (0%)	2/15 (13%)	**6/6°†** **(100%)°†**	**6/6°** **(100%)°**	**13/13°** **(100%)°**	**9/9°** **(100%)°**

° Significant diference from nonanisometropic controls.
† Significant difference from previous interval (group).

TABLE VII. ACUITY AND BINOCULARITY DATA IN CORRECTED SPHERICAL HYPERMETROPIC ANISOMETROPIA

	SPHERICAL HYPEROPIC ANISOMETROPIA (DIOPTERS)						
	0 CONTROL GROUP	>0 TO .5 MEAN =+.34	>.5 TO 1 MEAN =+ .85	>1 TO 2 MEAN = +1.52	>2 TO 3 MEAN = +2.48	>3 TO 4 MEAN = +3.5	>4 TO 10 MEAN = +4.84
Patient no.	50	50	25	26	13	12	13
Mean acuity (better eye)	20/20 .0069	20/21 .03	20/21 .0116	20/22 .0316	20/21 .0149	20/21 .0147	20/20 .0075
Mean acuity (worse eye)	20/21 .0148	20/21 .03	20/21 .0227	**20/27°† .1372°†**	**20/39°† .291°†**	**20/66°† .5174°†**	**20/81° .6052°**
Interocular acuity difference (log/MAR)	.0079	0	.0111	**.1046°†**	**.2761°†**	**.5027°†**	**.5977°**
Mean acuity amblyopic eye	20/32 .183	NONE	20/27 .1362	**20/36°† .2547°†**	**20/42° .3153°**	**20/66°† .5174°†**	**20/81° .6052°**
Number(%) amblyopic eyes	2/50 (4%)	0/50 (0%)	2/25 (8%)	**11/26° (42%)°**	**12/13°† (92%)°†**	**12/12° (100%)°**	**13/13° (100%)°**
Mean near stereopsis (seconds/arc)	54	54	60	**210°†**	**344°†**	**1312°†**	**1510**
Monofixation rate(number/%)	2/50 (4%)	0/50 (0%)	3/25 (12%)	**14/26°† (54%)°†**	**12/13° (92%)°**	**12/12° (100%)°**	**13/13° (100%)°**

° Significant difference from nonanisometropic controls.

† Significant difference from previous interval (group).

TABLE VIII. ACUITY AND BINOCULARITY DATA IN CORRECTED CYLINDRICAL MYOPIC ANISOMETROPIA

	CYLINDRICAL MYOPIC ANISOMETROPIA (DIOPTERS)				
	0 CONTROL GROUP	**-.5 TO -1** MEAN = -.7	**>-1 TO -1.5** MEAN = -1.38	**>-1.5 TO –2** MEAN = -1.84	**>-2** MEAN = -3.4
Patient no.	50	15	13	8	8
Mean acuity (better eye)	20/20 .0069	20/21 .015	20/22 .042	20/24 .074	20/20 0
Mean acuity (worse eye)	20/21 .0148	20/21 .015	20/23 .0556	**20/32°†** **.2003**	**20/39°** **.2905**
Mean interocular acuity difference (log/MAR)	.0079	0	.0136	**.1263°†**	**.2905°†**
Mean acuity (amblyopic eye)	20/32 .183	NONE	20/27 .1365	**20/42°†** **.3204**	**20/56°†** **.4455**
No. amblyopic eyes	2/50 (4%)	0/15 (0%)	2/13 (15%)	**5/8°†** **(62.5%)**	**5/8°** **(62.5%)**
Mean near stereopsis	54	45	56	77	**84°**
Monofixation rate	2/50 (4%)	0/15 (0%)	2/13 (15%)	**5/8°** **(62.5%)**	**5/8°** **(62.5%)**

° Significant difference from nonanisometropic controls.
† Significant difference from previous interval (group)

TABLE IX: ACUITY AND BINOCULARITY DATA IN CORRECTED CYLINDRICAL HYPERMETROPIC ANISOMETROPIA

	CYLINDRICAL HYPEROPIC ANISOMETROPIA				
	0 CONTROL GROUP	**5 TO 1** MEAN =+.66	**>1 TO 1.5** MEAN = +1.38	**>1.5 TO 2** MEAN = +1.86	**>2** MEAN = +3.56
Patient no.	50	15	11	6	8
Mean acuity (better eye)	20/20 .0069	20/22 .0588	20/23 .0573	20/22 .0277	20/21 .0242
Mean acuity (worse eye)	20/21 .0148	20/22 .0558	20/25 .1018	**20/26°†** **.121°†**	**20/32°†** **.213°†**
Interocular acuity difference (log/MAR)	.0079	0	.0445	**.0933°†**	**.1888°†**
Mean acuity (amblyopic eye)	20/32 .183	NONE	20/33 .2177	20/33 .2177	20/35 .2423
No. amblyopic eyes	2/50 (4%)	0/15 (0%)	**3/11‡** **(27%)**	**4/6°** **(66%)°**	**7/8°** **(87%)°**
Mean near stereopsis	54	50	73	**111°†**	75
Monofixation rate	2/50 (4%)	0/15 (0%)	**4/11‡** **(36%)**	**4/6°†** **(66%)°†**	**6/8°** **(75%)°**

° Significant difference from nonanisometropic controls.

† Significant difference from previous interval (group).

‡ Incidence of amblyopia and monofixation in >1 to 1.5D group was not statistically different from control group (which includes 2 affected individuals), but incidence is significantly greater than zero (P=.05).

(SMA, SHA, CMA, CHA) for each variable studied. These variables included worsening stereoacuity and worsening visual acuity in worse eye (P=.001 by Jonckheere-Terpstra Test in all cases, except stereo versus cylindrical hypermetropia (P=.012), and stereo versus cylindrical myopia (P=.010)). Increasing IOAD and an increasing incidence of monofixation response were likewise significant as levels of anisometropia increased in each of the 4 types (all P=.001 by Cochran-Armitage Trend Test).

Table VI summarizes the monocular acuity and binocular sensory data in patients with spherical myopic anisometropia (SMA). REGWQ multiple comparison of the groups demonstrated a significant increase in IOAD (also decrease in mean acuity worse eye and amblyopic eye) when anisometropia reached the >-2 to -3D level. Each group with increasing anisometropia beyond this level was also significantly worse than each previous group by all 3 measures of amblyopia severity. Stereoacuity (also REGWQ multiple-comparison test) monofixation incidence, and amblyopia incidence (Tukey type multiple comparison test) all first showed significant changes at the >-2 to –3D level as well. Since the monofixation and amblyopia rates both equaled 100% in the first group to have a significant increase (>-2 to-3D), an increased incidence in these variables did not occur in the other groups with increasing anisometropia. These data demonstrate both a threshold for the development of amblyopia (at the >-2 to -3 diopter level) and a significant increase in its severity (as measured by IOAD and mean acuity in worse and amblyopic eyes) as anisometropia increased beyond >-2 to -3 D in SMA.

Table VII summarizes the data for spherical hypermetropic anisometropia (SHA). The visual acuity data indicate a similar, though less sharply demarcated, relationship between the degree of anisometropia and both the incidence and severity of amblyopia. Patients in the >1 to 2D group of anisometropia were the first to show a statistically significant increase in the IOAD (and a decrease in the mean acuity of the worse eyes and amblyopic eyes) as compared to nonanisometropic patients. The IOAD also increased (and mean acuity worse eye decreased) significantly with each group with increasing anisometropia beyond the >1 to 2D level. The mean amblyopic acuity in the >1 to 2D and >2 to 3D groups did not differ significantly; however, both groups had significantly better amblyopic acuity than the >3 to 4D and >4 to 10D groups. Stereoacuity followed a similar pattern.

The incidence of amblyopia and positive monofixation responses also increased significantly first in the group of patients with >1 to 2 diopters of SHA. The incidence of amblyopia increased significantly in 2 groups (>1 to 2D and >2 to 3D), after which it leveled off at 100%. Again the data supported a threshold for the development of amblyopia (>1 to 2 D of

SHA) as well as an increase in its severity and incidence with increasing anisometropia.

The level at which patients with SHA began to demonstrate amblyopia and subnormal binocularity was both lower and less sharply delineated than in the patients with SMA.

The >1 to 2 D group of SHA was further analyzed to assess if any patients within the group were more likely to be amblyopic. Within the group there was no significant difference between amblyopic and nonamblyopic patients with regard to age, overall degree of anisometropia (within the >1-2D range), or overall degree of ametropia.

The corrected acuity and binocularity data for the cylindrical myopic and hyperopic anisometropic patients are summarized in tables VIII and IX. In cylindrical myopic anisometropia (CMA), IOAD, mean acuity in the worse eyes, and mean acuity amblyopic eyes showed statistically significant worsening in the >-1.5 to -2D group. A statistically significant increase in the incidence of amblyopia and monofixation also occurred in the >1.5 to 2D group. A significant decrease in stereopsis occurred only in the >2D group.

In cylindrical hyperopic anisometropia (CHA), IOAD and mean visual acuity of the worse eye both showed a statistically significant increase in the >1.5 to 2D group, although the mean acuity of the amblyopic eyes did not change significantly among the groups. A statistically significant increase in frequency of amblyopia and monofixation rate also occurred in this group (>1.5 to 2D) and also in the >2 D group. Stereopsis worsened significantly only in the >1.5 to 2D group.

Patient numbers were more limited than with spherical anisometropic patients, and differences among groups were less drastic, making statistical analysis somewhat more limited. In both types of astigmatic or cylindrical anisometropia, a statistically significant deterioration of monocular and binocular function was first noted in the >1.5 to 2D groups. The CMA and CHA data support a statistical threshold for the development of amblyopia at the >1.5D level of anisometropia. However, there was a notable increase in the frequency of amblyopia, especially with CHA, but also with CMA patients in the >1 to 1.5D group, although this was not statistically significant. However, one might argue that >1D of cylindrical anisometropia more fairly represents the *clinically* significant threshold for an increase in the incidence of amblyopia in these patients. In CMA, the incidence of amblyopia went from 0% to 15%, and in CHA from 0% to 27% at this level. As noted previously, the uncorrected acuity data also supported this to be the first level of statistically significant increase in IOAD.

Severity of amblyopia (as measured by IOAD and mean acuity amblyopic eye) increased further when cylindrical anisometropia

increased to >2D. While there was also a trend for increased incidence of amblyopia in CHA patients with >2D anisometropia, this was not statistically significant. Binocularity as measured by stereopsis and frequency of monofixation worsened significantly for CMA and CHA at either the >1.5D or >2D levels. The correlation between increasing anisometropia and IOAD was weaker in the cylindrical than the spherical anisometropia patients (Figs 1 and 2). Unlike the findings with spherical anisometropia patients, there appeared to be no significant difference in the effect of myopic versus hyperopic cylindrical anisometropia, the threshold for the development of amblyopia. This was not surprising when one considers that these patients had no significant spherical equivalent difference between the 2 eyes; hence the retinal blur caused by hyperopic cylindrical anisometropia would be expected to be the same as myopic cylindrical anisometropia of the same magnitude.

Figures 1 through 4 demonstrate some of these results graphically. The degree of correlation between the interocular acuity difference and the degree of anisometropia in corrected patients (both spherical and cylindrical) is characterized in Figures 1 and 2. The threshold for the development of amblyopia with each type of anisometropia is also apparent from these figures.

In Figures 3 and 4, the association between the degree of anisometropia and the incidence of monofixation, amblyopia, and subnormal stereopsis is characterized. Each of these outcomes is represented as a percentage of patients affected in each anisometropia group. Since stereoacuity was much better in the patients with cylindrical anisometropia than spherical anisometropia, different definitions of subnormal stereoacuity were used in these 2 figures (>200 sec/arc for spherical and > 60 sec/arc for cylindrical anisometropia).

DISCUSSION

ANISOMETROPIA AND AMBLYOPIA

Copps[14] in 1944, was the first to attempt to confirm an association between "pure anisometropia" (anisometropia in the absence of strabismus) and amblyopia in 44 patients with 1 D or more of anisometropia (spherical equivalent). Although this study was without the benefit of statistical analysis, he nevertheless concluded that the initial degree of amblyopia was proportionate to the degree of anisometropia. Copps further noted amblyopia to be more likely in hypermetropic than myopic anisometropia.

These findings were later confirmed by Jampolsky and associates in 1955.[17] These investigators also demonstrated decreasing "best" acuities in the worse eye of patients with increasing amounts of anisometropia. This

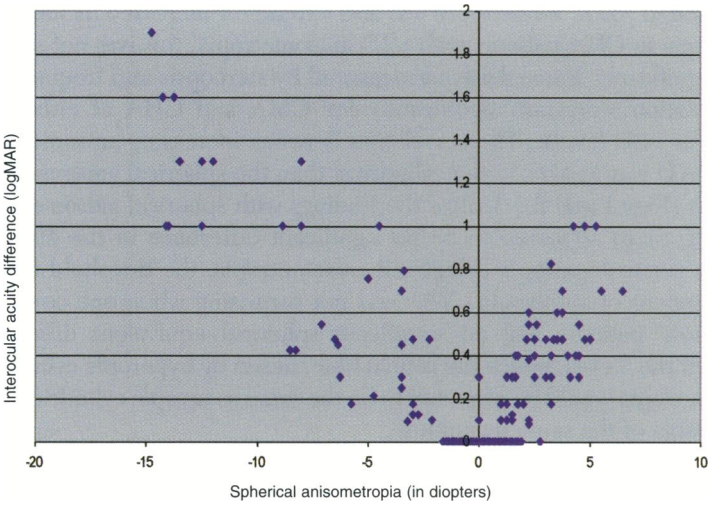

FIGURE 1

Degree of spherical anisometropia versus interocular acuity difference (IOAD). Correlation was highest in spherical myopic anisometropia (r = .86, $P < .0001$), but also highly significant in spherical hyperopic anisometropia as well (r = .73, $P < .0001$).

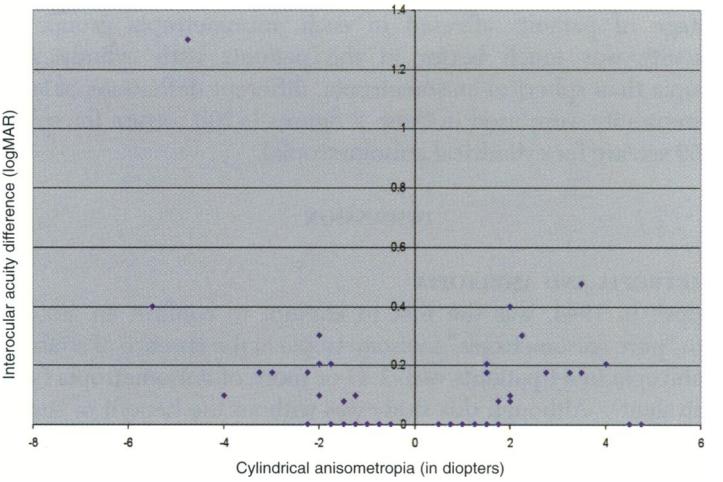

FIGURE 2

Degree of cylindrical anisometropia and interocular acuity difference (IOAD). While the threshold for development of amblyopia (>1D) was well demonstrated, correlation between severity of amblyopia and IOAD was weaker than in spherical patients for CMA (r = .47; $P = .0012$) with CHA there was no correlation (r = .23, p = .16).

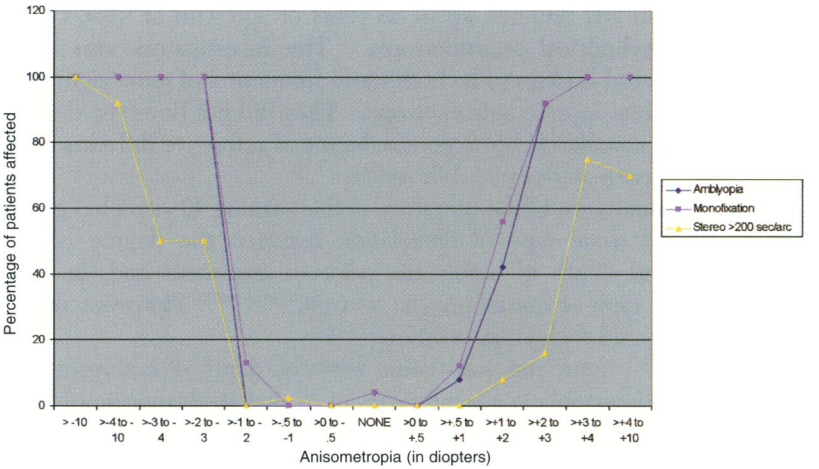

FIGURE 3

Spherical anisometropia versus amblyopia, monofixation, and subnormal stereopsis. The anisometropic groups with significant deterioration of stereopsis and an increase in the incidence of monofixation and amblyopia (SMA >-2 to -3) and (SHA >1 to 2D) were readily apparent.

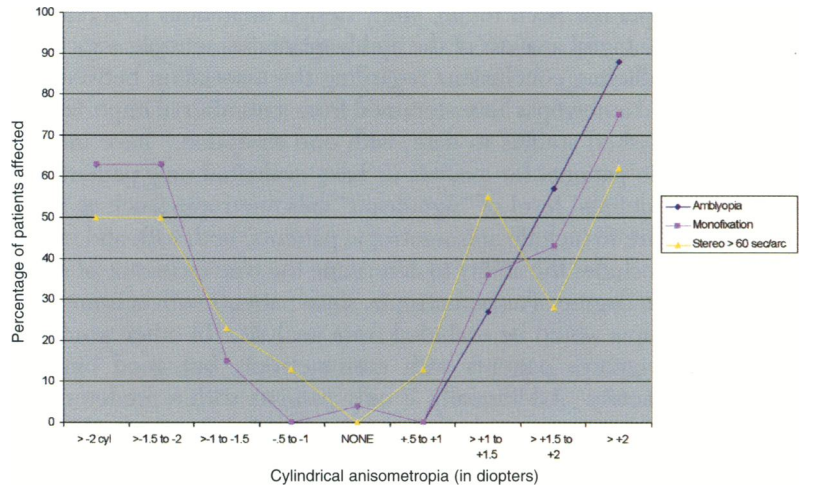

FIGURE 4

Cylindrical anisometropia versus amblyopia, monofixation, and subnormal stereopsis. Significant deterioration of stereopsis and an increase in the incidence of monofixation and amblyopia are noted in the >1D groups for both CMA and CHA.

study evaluated 207 patients up to 55 years of age with at least 1 D of spherical or cylindrical anisometropia. The investigators also noted unequal corrected acuities to be both more frequent and more significant in hyperopic than myopic anisometropia. They did not however, demonstrate a strong correlation between the degree of refractive difference and the degree of corrected acuity difference.

The predominance of the literature in the ensuing 40 years has generally supported some type of correlation between the degree of anisometropia and depth of amblyopia prior to treatment and, in some instances, the type of anisometropia as well.[5,7,15,18,20,23,41] However, not all studies have found such an association.[13,16,19]

Helveston[16] refuted any association between depth of amblyopia and degree of anisometropia in a small series of 37 non strabismic amblyopes. Kutschke and associates[19] likewise found no association between initial visual acuity and the degree of anisometropia in 75 non strabismic amblyopes. Bhatia and Pratap[13] found no true association between anisometropia and amblyopia in 61 non strabismic amblyopes, and DeVries[5] noted only that of 17 patients with anisometropia, more had amblyopia than 15 patients without anisometropia.

On the other hand, Hardman,[15] Ingram,[7] Kivlin,[18] MacDiarmid,[20] Sen, [22] Tanlamai,[41] and Townshend[23] all found varying associations between initial acuity or amblyopia and the degree of anisometropia. However, even in studies where an association between severity of amblyopia and the degree of anisometropia has been found, study design limitations generally preclude any meaningful analysis of the amblyopia/anisometropia association.

These conflicting conclusions regarding the association between anisometropia and amblyopia have stemmed from a number of important factors. All published studies to date, with one exception,[41] have included only amblyopic patients for analysis or have evaluated only patients with an arbitrarily defined level of "significant" anisometropia (such as >1 D), or both. Failure to include anisometropic patients, both with and without amblyopia, precludes the ability to determine the true incidence of amblyopia for a given degree of anisometropia, since patients with anisometropia but no amblyopia would be excluded from analysis. In other words, this methodology ignores patients with anisometropia but good binocular function and acuity. Additionally, if only patients with a predetermined degree of anisometropia are studied, the threshold or degree at which anisometropia truly becomes "significant" cannot be determined. Additional confusion has resulted from the differing definitions of both amblyopia and anisometropia among the various investigators. Most analyses have also suffered from 1 or more additional shortcomings, such as examination of only adults, use of noncycloplegic or autorefractions, failure to exclude

patients with previous treatment for amblyopia, strabismus or refractive error,[41] and failure to separate types of anisometropia.

This study has attempted to avoid these pitfalls by including patients with and without amblyopia and has not predefined a specific level of "significant" anisometropia. The data in this series of patients demonstrate a convincing association between both the degree and type of anisometropia and the incidence and depth of amblyopia. In this study, the incidence of patients developing amblyopia and subnormal binocularity increased in a statistically significant fashion once anisometropia reached a certain level in all 4 types of anisometropia defined in this study. This relatively sharp demarcation, especially in spherical anisometropia, allowed for the development of useful guidelines for careful monitoring or treatment of at-risk patients. These findings closely parallel the recent guidelines[4] previously supported only by clinical impression and experience. This study confirmed that >2 D of spherical myopic anisometropia (SMA), >1 D of spherical hyperopic anisometropia (SHA), and >1.5 D of cylindrical myopic or hyperopic anisometropia (CMA or CHA) should alert the clinician to the high likelihood of developing amblyopia and subnormal binocularity if the anisometropia persists.

As mentioned, in the case of the cylindrical anisometropia patients (CMA and CHA), lower levels of anisometropia (>1D) may also be a cause for concern. In the cylindrical anisometropia groups, while a statistically significant increase in amblyopia from the control groups was not noted until the level of anisometropia reaches >1.5 D, there was clearly a trend for an increase in the amblyopia incidence with less anisometropia. In CMA a 15% incidence of amblyopia was noted in the >1 to 1.5 group and in CHA, a 27% incidence of amblyopia is noted at this level. This increased incidence in CHA of >1 to 1.5 is statistically significant when compared to zero ($P = .05$) but not when compared to the control group. It is likely that larger numbers of patients with astigmatic anisometropia would have resulted in a statistically significant increase in amblyopia incidence from the control group at the >1D level. Furthermore, the IOAD data in the uncorrected CMA and CHA patients supports the lesser amount of anisometropia as resulting in a statistically significant increase in IOAD.

While comparison of best or worst acuities among groups is not useful with uncorrected refractive error, the IOAD would still be expected to be a useful outcome to compare (Tables IV and V). In light of these findings, it seems appropriate to define the "threshold" for the development of amblyopia to be the lower level (>1D) in both CMA and CHA patients. With uncorrected spherical myopic and hyperopic anisometropia, a significant increase in IOAD occurred at the same threshold level as in the corrected patients (>1 to 2 D in SHA and >-2 to -3 D in SMA) (Tables II and III).

In comparing the findings of this study to the guidelines of the American Academy of Ophthalmology Preferred Practice Pattern (AAO-PPP)[4] similar but slightly lower levels of anisometropia were of concern.* In this study, SMA >-2 D (eg, -2.25 or more) of myopic anisometropia was .75 D less than the AAO-PPP guidelines (≥ 3 D). SHA of >1 D (eg, +1.25 or more) was .25 D less than the AAO-PPP guideline, and in CMA and CHA in this study, >1D (eg, ± 1.25D or more) was also .25 D less than the AAO-PPP guidelines.

In addition to examining thresholds for the development of amblyopia, this study was also designed to confirm any association between the degree and type of anisometropia and an increased incidence and/or severity of amblyopia. The incidence of amblyopia in patients with spherical myopic anisometropia (SMA) was 100% in the first group with any significant degree of amblyopia and remained at that level for all groups with increasing anisometropia. Thus, for SMA, there was no significant increase in the *incidence* of amblyopia with increasing anisometropia beyond the >-2 to –3D threshold. However, the *severity* of amblyopia, as measured by IOAD ($r = .86$, $P < .0001$) and amblyopic acuity ($r = .86$, $P < .0001$) was strongly associated with the degree of SMA (see Table VI). In spherical hyperopic anisometropia (SHA), both the *incidence* and *severity* of amblyopia increased significantly as SHA increased. The incidence of amblyopia increased first in the >1 to 2D group and again in the >2 to 3D group, after which the incidence remained at 100%. The severity, as measured by IOAD and amblyopic acuity, increased significantly in the >1 to 2D group and again in the > 3 to 4D group. The overall level of correlation between SHA and IOAD ($r = .73$, $P < .0001$) and amblyopic acuity ($r = .63$, $P < .0001$) was also significant (Table VII).

The association between the degree of cylindrical anisometropia and the incidence and severity of amblyopia was less clear in this study, again possibly because of fewer patients. In both cylindrical myopic anisometropia (CMA) and cylindrical hyperopic anisometropia (CHA), there was only 1 group of patients (>2D) with a greater degree of anisometropia than the first group (>1.5 to 2D) to have a statistically significant increase

* The method of grouping within each type of anisometropia in this study defines the lower level of a group as greater than(>), not greater than or equal to ≥. Thus, the group > 1 to 2D of SHA does not include patients with 1D of SHA; these patients are in the previous group. Thus, in general, except in rare cases where mathematical calculations leads to a patient with 1.125 D of anisometropia, this group generally includes patients with 1.25 to 2 D of anisometropia. The same is true for the other groups as well. This should be noted when comparing to the AAO-PPP guidelines, which classify cut-off levels of anisometropia as greater than or equal to ≥.

in the incidence of amblyopia. The incidence of amblyopia did not increase between these 2 groups for either CMA or CHA; however, the severity did. In CMA, the amblyopic acuity, mean acuity worse eye, and IOAD worsened significantly between these groups. In CHA, the IOAD and mean acuity worse eye (but not amblyopic acuity) worsened significantly between the groups. Furthermore, if the lower level of >1D was taken to define the threshold of a clinically significant increase in amblyopia incidence in CMA and CHA patients, then increased severity of amblyopia was noted across all 3 groups (>1 to 1.5D, >1.5 to 2D, and >2D) as measured by IOAD and mean acuity of the worse eye.

In summary, these data support a strong correlation between increasing degrees of anisometropia (all 4 types) and an increasing severity of amblyopia. There was also an association between the degree of anisometropia and the incidence of amblyopia, at least in terms of a threshold for its development.

In most,[12,14,17,19,21] but not all,[18] previous publications, in which the issue has been addressed, findings have suggested that the amblyopia associated with hypermetropic anisometropia is more severe or more frequent than that associated with myopic anisometropia. The data in this study confirmed the tendency for the development of amblyopia at lower levels of hyperopic (SHA) (>1 to 2D) than myopic (SMA) (>-2 to -3D) anisometropia ie, a higher incidence and increased severity of amblyopia in the >1 to 2 D SHA group than the >-1 to -2 SMA group. However, in the patients with equal levels of SMA and SHA beyond > 2 D, both the incidence and the severity of amblyopia were remarkably similar (Tables VI and VII).

ANISOMETROPIA AND BINOCULARITY

Considerably less attention has been paid to the association between anisometropia and binocularity than to the association between anisometropia and monocular acuity or amblyopia. Studies examining the effects of naturally occurring anisometropia rarely address the issue of binocularity. While it is tempting to assume the levels at which anisometropia effects monocular acuity and binocular function are similar, this has not previously been substantiated in the literature.

A significant amount of literature has addressed the effects of *artificially induced* anisometropia on the binocularity of normal subjects. Brooks and associates[24] have shown a foveal scotoma to occur and stereoacuity to decrease in proportion to experimentally induced anisometropia in adults. As little as 1 D of hyperopic, myopic, or cylindrical anisometropia resulted in significant deterioration of binocular function in this study. Simpson[31] likewise has documented the "suppression" effect with development of a facultative foveal scotoma in simulated

anisometropia. A number of other investigators have previously demonstrated similar findings with regard to stereoacuity and experimentally induced anisometropia.[25-28,30,32,33,42]

Much less is known with regard to the effects of *naturally occurring* anisometropia on binocularity. The studies previously referenced make little or no mention of the effects of naturally occurring anisometropia (both treated and untreated) on binocularity. Hardman and associates[43] have in fact, argued that increasing anisometropia does not affect the loss or absence of bifoveal fusion. No studies to date have attempted to ascertain the level of anisometropia at which binocularity deteriorates significantly from normal, a question that has been addressed in this manuscript.

It is well known that anisometropia of sufficient severity will result in abnormal binocular vision and subnormal stereopsis. In Parks' initial description of the "monofixation syndrome"[44] 6 of the 100 patients in the study were anisometropic without strabismus. Helveston and von Noorden[45] also noted anisometropia to be a causative factor in a number of patients with "microtropia." Furthermore, it has also been documented that in some anisometropic patients this abnormal binocular state, whether one prefers the term "microtropia" or "monofixation," can be reversed with appropriate treatment.[44,46,47*]

Deterioration of binocular function, as measured by the rate of monofixation and decreased stereoacuity, did in fact parallel the development of amblyopia quite closely in all types of anisometropia in this study. Patients with corrected SMA and SHA developed a significant decrease in stereopsis and increase in monofixation when anisometropia reached > -2 diopters (SMA) and >1 diopters (SHA), the same levels at which amblyopia increased significantly (Tables VI and VII).

*Differing terminology to describe subnormal binocularity in patients without detectable strabismus (or very small angle strabismus) has led to some confusion in the literature. The term "microtropia"[45] includes patients with or without small angle strabismus on cover testing. The more recent term "microtropia with identity" has been coined to describe a subset of these patients with no deviation with cover testing yet who are felt to have a small angle strabismus and extrafoveal fixation.[43] Patients with "monofixation syndrome"[44] likewise may or may not have a small angle deviation (up to 8 prism diopters) on cover testing. These patients also have a foveal scotoma and extrafoveal fixation.

Thus, microtropia with or without "identity" and monofixation patients are clinically identical. However, patients described as "microtropia" or "microtropia with identity" are felt (by those who prefer this terminology) to have anomalous retinal correspondence (ARC). Contrarily, those patients described as having "monofixation syndrome" are felt by those preferring this terminology to have normal retinal correspondence (NRC).

For the purpose of evaluating patients in this series, we have adhered to the concept of monofixation as initially described by Parks. [44]

Patients with corrected CMA developed a statistically significant increase in monofixation with >-1.5D of anisometropia and decreased stereopsis with >-2D of anisometropia. Patients with corrected CHA developed a statistically significant decrease in stereopsis and an increase in the monofixation rate with > -1.5D of anisometropia (Tables VIII and IX). Again, because of fewer patients in the cylindrical groups, reliance only on statistically significant changes ignores findings that are not statistically significant, but may well be clinically significant. In CMA patients, the monofixation rate increased from 0% to 15% when anisometropia increased to >1D and stereoacuity decreased from 56 to 77 sec/arc when anisometropia increased to >1.5D. In CHA patients, monofixation increased from 0% to 36% when anisometropia increased to >1D and stereoacuity decreased from 50 to 73 sec/arc at the same level. Again, these levels closely correlated with the levels at which amblyopia increased significantly.

Binocularity data for patients with uncorrected anisometropia yield slightly different results. A significant increase in monofixation rate generally occurred at the same level as a significant increase in IOAD (all types except SMA, where monofixation increased at a lower level than IOAD); however, a significant decrease in stereopsis occurred at higher levels of anisometropia. However, as mentioned previously, the monocular acuities and binocularity results must be interpreted cautiously with significant uncorrected refractive error.

VARIABILITY OF ANISOMETROPIA

The prevalence of anisometropia in population-based studies varies widely, ranging from 1% to 8.1% in toddlers and young children to as high as 25% in newborns or infants.[1,5,48-55] Certainly much of this variation can be attributed to different definitions of anisometropia as well as the different ages and types of populations studied (eg, a hospital population versus a school population). Nevertheless, regardless of the true prevalence of anisometropia (which clearly does vary among groups studied), it remains a significant factor in the development of amblyopia and a significant public health concern.[4]

While longitudinal studies of anisometropia generally show little change in its prevalence over time, many of these studies have confirmed a considerable variability in its presence or severity among individuals followed over time. This seems particularly true of young children 1 to 4 years of age. On the other hand, some studies have demonstrated relative stability in an individual's anisometropia over time.

Abrahamsson and associates[1-3,56] in a cohort of patients followed for up

to 9 years, have reported that while the overall prevalence of anisometropia is relatively stable, individual patients develop, lose, or have changes in the magnitude of their anisometropia when followed longitudinally. A number of other studies have supported this general rule of a relatively consistent overall prevalence of anisometropia with considerable variability among individuals.[8-10,49,50,52] Other investigators have disputed this, arguing for a more consistent natural history of anisometropia over time.[5,15,51] DeVries[5] reported relative consistency in anisometropia over time with two thirds of patients unchanged over 2 to 8 years (mean, 4 years). Hardman and colleagues[15] likewise noted little change in anisometropia over a 3-year period. Hirsch[51] noted 8 of 9 patients with anisometropia at age 5 to 7 to still have it 12 years later.

Nevertheless, there is clearly a potential for variation of anisometropia in individuals over time, making it impossible to know the duration or constancy of anisometropia in newly diagnosed patients. Thus, if amblyopia is present in association with anisometropia, it is likely a function of not only the magnitude of anisometropia, but also its duration and consistency over time. A different "history" of anisometropia (duration, consistency), unknown to the examiner, may well account for the fact that 2 different patients with the same degree of anisometropia can have significantly different levels of amblyopia or subnormal binocularity. However, in young patients whose anisometropia persists or increases, the case for an increased risk for the development of amblyopia is convincing.[1-3,7-10,56]

The inability to determine the past history of anisometropia of the patients in this study was unavoidable with the study design (examination only of new patients with no previous treatment). Therefore, application of guidelines for treatment of anisometropia derived from this study should be applied cautiously to younger patients in whom anisometropia may be changing. Nevertheless, the association between a given degree and type of anisometropia and amblyopia is both clear and consistent in this study, and the thresholds established herein should be a valuable guide to the clinician.

TREATMENT OF ANISOMETROPIC AMBLYOPIA

This manuscript has not addressed the issue of the treatment of anisometropic amblyopia, but instead has focused on refining guidelines to aid in its early detection and prevention. One frequently agreed upon conclusion in the literature regarding the treatment of anisometropic amblyopia is that the severity of the amblyopia at the onset of treatment is the factor most predictive of outcome. Age at presentation, amount of anisometropia, compliance with or duration of occlusion therapy, and other factors much less consistently predict ultimate visual outcomes.

[5,15,18,19,21,22,34,57-60] Alternatively stated, early detection and treatment of anisometropia before or early in the development of amblyopia is likely to yield better visual outcomes than current treatment.

With the advent of newer technologies, such as photoscreening or photorefraction,[61,62] it is likely that anisometropia will be identified in increasing numbers of patients at younger ages. However, the decision to observe or treat patients with significant anisometropia but without evidence of amblyopia can be problematic. It is unclear whether, or at what age, spectacle correction negatively influences the emmetropization process. While some investigators have suggested that spectacle correction can inhibit emmetropization, at least in monkeys,[63] others[64] have refuted this interpretation. Ingram and associates[65] and Dobson and colleagues[39] have shown that early correction for hypermetropia, while reducing the incidence of refractive esotropia, also slows the loss of hypermetropic refractive error. Abrahamsson and Sjostrand[3] have noted, however, that significant anisometropic refractive errors often increase in spite of spectacle correction. Certainly the age at which anisometropia is identified must be taken into consideration before prescribing spectacles, as it seems to become more stable beyond infancy.[5]

While there is clearly a great deal still to learn about the natural history and effects of anisometropia on the developing visual system, it is hoped that the conclusions derived from this study can aid in its management. It seems most appropriate to use the guidelines developed in this study as levels of anisometropia that warrant careful observation and, depending on patient age and the physician's level of concern, spectacle correction when indicated.

SUMMARY

A number of conclusions regarding the nature of the effect of anisometropia (corrected and uncorrected) on the visual system can be drawn from the evaluation of the patients in this study.

1. The incidence and severity of amblyopia and subnormal binocularity were related to both the degree and type of anisometropia.
2. A trend for worsening acuity in the worse eye, increased interocular acuity difference, worsening amblyopia, worsening stereoacuity, and an increasing rate of monofixation became apparent as anisometropia (both corrected and uncorrected) increased in each type of anisometropia defined in this study.
3. Spherical hyperopic anisometropia (SHA) resulted in a statistically significant increase in amblyopia at lower levels than cylindrical hyper-

opic (CHA), cylindrical myopic (CMA), or spherical myopic anisometropia (SMA). SMA was the best-tolerated anisometropia, with CMA and CHA falling between the 2 spherical varieties in terms of tendency to cause amblyopia.

4. While SHA resulted in amblyopia at lower levels than SMA, the incidence and severity of amblyopia were similar for both types with equal anisometropia of >2 D.
5. The threshold amount of anisometropia beyond which the incidence of amblyopia first demonstrated a statistically significant increase from the nonanisometropic patients was as follows: (SMA = >-2D, SHA = > 1D, CMA = >-1.5D, and CHA = >1.5D). In astigmatic patients, a "clinically" significant increase in amblyopia occurred at the next lowest level defined in this study (> 1 diopter of CMA or CHA). These thresholds can be used as a guide for the need to correct or observe nonstrabismic anisometropic patients.
6. The severity of amblyopia increased relative to the magnitude of anisometropia beyond these thresholds in each type of anisometropia defined in this study except CHA.
7. The incidence of amblyopia increased relative to the magnitude of anisometropia beyond these thresholds except in patients with CMA, where the incidence was 100% in the first affected group.
8. Deterioration of stereopsis and an increase in the rate of monofixation closely paralleled the development of amblyopia in each type of anisometropia defined in this study.

REFERENCES

1. Abrahamsson M, Fabian G, Sjostrand J. A longitudinal study of a population based sample of astigmatic children. II. The changeability of anisometropia. *Acta Ophthalmol* 1990;68:435-440.
2. Abrahamsson M, Fabian G, Anderson AK, et al. A longitudinal study of a population based sample of astigmatic children. I. Refraction and amblyopia. *Acta Ophthalmol* 1990 (Copenh); 68:428-434.
3. Abrahamsson M, Sjostrand J. Natural history of infantile anisometropia. *Br J Ophthalmol* 1996;80:860-863.
4. American Academy of Ophthalmology; Amblyopia Preferred Practice Pattern. San Francisco: 1997;5-6.
5. De Vries J. Anisometropia in children: Analysis of a hospital population. *Br J Ophthalmol* 1985;69:504-507.
6. Flom MC, Bedell HE. Identifying amblyopia using associated conditions, acuity, and nonacuity features. *Am J Optom Physiol Opt* 1985;62:1543.
7. Ingram RM. Refraction as a basis for screening children for squint and amblyopia. *Br J Ophthalmol* 1977;61:8-15.
8. Ingram RM, Traynar MJ, Walker C, et al. Screening for refractive errors at age 1 year: A pilot study. *Br J Ophthalmol* 1979;63:243-250.

9. Ingram RM, Walker C. Refraction as a means of predicting squint or amblyopia in preschool siblings of children known to have these defects. *Br J Ophthalmol* 1979;63:238-242.
10. Sjostrand J, Abrahamsson M. Risk factors in amblyopia. *Eye* 1990;4:787-793.
11. Vital-Durand F, Ayzac L. Tackling amblyopia in human infants. *Eye* 1996;10:239-244.
12. Phillips CL. Strabismus, anisometropia, and amblyopia. *Br J Ophthalmol* 1959;43:449-460.
13. Bhatia M, Pratap VB. Anisometropic amblyopia. *Ind J Ophthalmol* 1976;24 (III): 10-13.
14. Copps LA. Vision in anisometropia. *Am J Ophthalmol* 1944;27:641-644
15. Hardman Lea SJ, Loades J, Rubinstein MP. The sensitive period for anisometropia amblyopia. *Eye* 1989;3:783-790
16. Helveston EM. Relationship between degree of anisometropia and depth of amblyopia. *Am J Ophthalmol* 1966;62:757-759.
17. Jampolsky A, Flom BC, Weymouth FW, et al. Unequal corrected visual acuity as related to anisometropia. *Arch Ophthalmol* 1955;54:893-905.
18. Kivlin JD, Flynn JT. Therapy of anisometropic amblyopia. *J Pediatr Ophthalmol Strabismus* 1981;18:47-56.
19. Kutschke PJ, Scott WE, Keech RV. Anisometropic amblyopia. *Ophthalmology* 1991; 98:258-263.
20. MacDiarmid JD, Waterhouse PF. Amblyopia associated with anisometropic hypermetropia. *Trans Ophthalmol Soc N Z* 1974;26:39-42.
21. Sen DK. Anisometropic amblyopia. *J Pediatr Ophthalmol Strabismus* 1980;17:180-184.
22. Sen DK. Results of treatment of anisohypermetropic amblyopia without strabismus. *B J Ophthalmol* 1982;66:680-684.
23. Townshend AM, Holmes JM, Evans LS. Depth of anisometropic amblyopia in difference in refraction. *Am J Ophthalmol* 1993;116:431-436.
24. Brooks SE, Johnson D, Fischer N. Anisometropia and binocularity. *Ophthalmology* 1996;103,7:1139-1143.
25. Donzis PB, Rappazzo JA, Burde RM, et al. Effect of binocular variations of Snellen's visual acuity on Titmus stereoacuity. *Arch Ophthalmol* 1983;101:930-932.
26. Goodwin RT, Romano PE. Stereoacuity degradation by experimental and real monocular and binocular amblyopia. *Invest Ophthalmol Vis Sci* 1985;26;917-923.
27. Larson WL, Lachance A. Stereoscopic acuity with induced refractive errors. *Am J Optom* 1983;60:509-513.
28. Lovasik JV, Szymkiw M. Effects of aniseikonia, anisometropia, accommodation, retinal illuminance, and pupil size of stereopsis. *Invest Ophthalmol Vis Sci* 1985;26:741-750.
29. Ong J, Burley Jr WS. Effect of induced anisometropia on depth perception. *Am J Optom* 1972;49:436-438.
30. Peters HB. The influence of anisometropia on stereosensitivity. *Am J Optom* 1969; 46:120-123.
31. Simpson T. The suppression effect of simulated anisometropia. *Ophthalmic Physiol Opt* 1991;11:350-358.
32. Westheimer G, McKee SP. Stereoscopic acuity with defocused and spatially filtered retinal images. *J Opt Soc Am* 1980;70:772-778.
33. Wood ICJ. Stereopsis with spatially-degraded images. *Ophthalmic Physiol Opt* 1983; 3:337-340.
34. Sanfilippo S, Muchnick RS, Schlossman A. Visual acuity and binocularity in unilateral high myopia. *Am J Ophthalmol* 1980;90:553-557.
35. Friendly DS, Jaafar MS, Morillo DL. A comparative study of grating and recognition visual acuity testing in children with anisometropic amblyopia without strabismus. *Am*

J Ophthalmol 1990;110:293-299.
36. Kushner BJ, Lucchese NJ, Morton GV. Grating visual acuity with Teller cards compared with Snellen visual acuity in literate patients. *Arch Ophthalmol* 1995;13:485-493.
37. Holladay JT, Prager TC. Mean visual acuity. *Am J Ophthalmol* 1991;111:372-374.
38. Westheimer G. Scaling of visual acuity measurements. *Arch Ophthalmol.* 1979;97:327-330.
39. Dobson V, Sebris SL, Carlson MR. Do glasses prevent emmetropization in strabismic infants? *Invest Ophthalmol Vis Sci* 1986;27(ARVO suppl):2.
40. Mosley MJ, Irwin M, Jones HS, et al. Effect of spectacle wear and minimal occlusion therapy on the vision of amblyopic children. *Invest Ophthalmol Vis Sci* 1996;37:S941.
41. Tanlamai T, Goss D. Prevalence of monocular amblyopia among anisometropes. *Am J Optom Physiol Optics* 1979;56:704-715.
42. Levy NS, Glick EB. Stereoscopic perception and Snellen visual acuity. *Am J Ophthalmol* 1974;78:722-724.
43. Hardman Lea SJ, Snead MP, Loades J, et al. Microtropia versus bifoveal fixation in anisometropic amblyopia. *Eye* 1991;5:576-584.
44. Parks MM. The monofixation syndrome. *Trans Am Ophthalmol Soc* 1969;69:609-657.
45. Helveston EM, von Noorden GK. Microtropia: A newly defined entity. *Arch Ophthalmol* 1967;78:272.
46. Cleary M, Houston CA, McFadzean RM, et al. Recovery in microtropia: Implications for aetiology and neurophysiology. *Br J Ophthalmol* 1998;82:225-231.
47. Houston CA, Cleary M, Dutton GN, et al. Clinical characteristics of microtropia–Is microtropia a fixed phenomenon? *Br J Ophthalmol* 1998;82:219-224.
48. Abolfotouh MA, Badawi I, Faheem Y. Prevalence of amblyopia among schoolboys in Abha city, Asir Region, Saudi Arabia. *J Egypt Public Health Assoc* 1994;69:19-30.
49. Almeder LM, Peck LB, Howland HC. Prevalence of anisometropia in volunteer laboratory and school screening populations. *Invest Ophthalmol Vis Sci* 1990;31:2448-2455.
50. Blum HL, Peters HP, Bettman JW. Vision Screening for Elementary Schools: The Orinda Study. Berkeley, California, University of California Press; 1959;103-104.
51. Hirsch MJ. Anisometropia: A preliminary report of the Ojai Longitudinal Study. *Am J Optom Arch Am Acad Optom* 1967;44;581-585.
52. Ingram RM, Traynar MJ, Walker C, et al. Screening for refractive errors at age 1 year: A pilot study. *Br J Ophthalmol* 1979;63:243-50.
53. Laatikainen L, Erkkila H. Refractive errors and ocular findings in school children. *Acta Ophthalmol* (Kbh) 1980;58:129-135.
54. Phelps WL, Muir V. Anisometropia and strabismus. *Am Orthopt J* 1977;27:131-133.
55. Saunders KJ. Early refractive development in humans. *Sur Ophthalmol* 1995;40:207-216.
56. Abrahamsson M, Fabian G, Sjostrand J. Changes in astigmatism between the ages of 1 and 4 years: A longitudinal study. *Br J Ophthalmol* 1988;7:145-152.
57. Latvala ML, Paloheimo M, Karma A. Screening of amblyopic children and long-term follow-up. *Acta Ophthalmol Scand* 1996;74:488-492.
58. Lithander J, Sjostrand J. Anisometropic and strabismic amblyopia in the age group 2 years and above: A prospective study of the results of treatment. *Br J Ophthalmol* 1991;75:111-116.
59. Sen DK. Results of treatment in amblyopia associated with unilateral high myopia without strabismus. *Br J Ophthalmol* 1984;68:681-685.
60. Wick B, Wingard M, Cotter S, et al. Anisometropic amblyopia: Is the patient ever too old to treat? *Optom Vis Sci* 1992;69:866-878.
61. Morgan KS, Kennemer JC. Off-axis photorefractive eye screening in children. *J*

Cataract Refract Surg 1997;23:423-428.
62. Ottar WL, Scott WE, Holgado SI. Photoscreening for amblyogenic factors. *J Pediatr Ophthalmol Strabismus* 1995;32:289-295.
63. Hung LF, Crawford MLJ, Smith EL. Spectacle lenses alter eye growth and the refractive status of young monkeys. *Nature Med* 1995;1:761-765.
64. Stone RA, Laties AM, Fernandes A, et al. Spectacles and young eyes. *Nature Med* 1996; 2:610-611.
65. Ingram RM, Arnold PE, Dally S, Lucas J. Emmetropisation, squint, and reduced visual acuity after treatment. *Br J Ophthalmol* 1991;75:414-416.