Results of a Monozygotic Cotwin Control Study on a Treatment for Myopia

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This is a report on the outcome of a therapeutic trial on myopia originally described at the First International Congress on Twin Studies as an example of an ongoing prospective investigation employing monozygotic (MZ) cotwin controls. Descriptions of the study design and methods used were published in the proceedings of that congress [23]; accordingly, the current introduction will be limited as needed to place the findings and discussion in perspective.

Myopia is often classified into two main categories. The most common “simple” type is characterized as having an uncomplicated course showing progress during the growing years which stabilizes upon reaching maturity. Spectacle-corrected visual acuity remains normal. The other main category progresses through high levels of myopia, shows degenerative changes having potentially blinding complications, and is sometimes called degenerative or pathologic myopia. Although both the causes and management of myopia have excited immense interest over the past century, the extent to which either category represents an “etiologically pure” entity remains unsettled, as does the extent to which myopia is determined by hereditary and/or environmental factors.

Among environmental factors of suggested etiologic importance in simple myopia, one widely held theme, recurrent through the literature, relates progression of this common myopia to prolonged use of the eyes for reading or other close work. This is sometimes called the “use-abuse” theory. Some more widely employed attempts at the prophylaxis or retardation of myopia have been directed toward limiting or relaxing accommodation of the eye through the aid of bifocal spectacles or the use of cycloplegic medications. The latter is a category of pharmacologic agents that induces relaxation of the ciliary muscles of accommodation.

When this investigation was planned, promising prospective data were available [4, 5] in support of at least a temporary retardation of myopia by extended full-time cycloplegia attained through the use of atropine, a deep-acting and
long-lasting cycloplegic agent. Earlier reports on the use of cycloplegic agents and/or bifocal spectacles [1, 2, 6-14, 19-22, 26-30] were generally based on retrospective observations drawn from clinical records. There were no other findings from long-term, prospective, randomized, single-masked, well-matched control studies on the prophylaxis or management of myopia.

This study was undertaken to test the effectiveness of a treatment that would induce relaxation of accommodation in an amount less than that which might interfere with daytime ocular function or appearance. Such a regimen, if effective, would seem readily acceptable to both patients and clinicians. The treatment regimen consisted of a combination of two drops of 1% tropicamide, a short-acting cycloplegic ophthalmic solution applied to each eye at bedtime, and the daytime use of bifocal spectacles having a reading addition of +1.25 diopters. The control twins received a standard single vision spectacle correction for myopia. The use of tropicamide had been reported [1, 2]; the combination with bifocals had not.

We set out to examine the general hypothesis that among the specially treated sample of twins, the average progression of myopia after 3 years would be less than their cotwin controls. From published descriptions of the rate of increase of myopia, an average expected increase during childhood and adolescence was estimated to be 0.58 diopters per year, and on this basis the present study was designed to detect a treatment benefit of 1 diopter in 3 years. Based on this and other considerations, the calculated number of required pairs was 22. (References, parameters, and calculations are given in the original article.)

To enter the study, the MZ twin pairs were required to be similarly myopic age 7-13 (one pair age 14), well within the age range of expected myopic progression. Treatment or control status was randomly assigned only after the twin pair and the parents expressed willingness to accept the rigorous requirements and the desire to participate. During the prospective observation period, the cohort was reexamined at approximately 6-month intervals at which time cycloplegic refractions were made under 1% cyclogel. All refractions were performed by the author, who was unaware of the treatment or control status of the examinees.

Each treated twin maintained a nightly record of medication adherence, generally with parental assistance. One parent, usually the mother, maintained general surveillance of the spectacle wearing patterns of each twin. Both of these monitored activities were reported and carefully reviewed at the 6-month visits.

RESULTS

Of the 26 pairs entered in the study, 25 participated through the full observation period, which was extended to 3½ years. Average entering age was 11.2 years; there were 13 male and 12 female pairs. Tabular distributions by age and sex were given in the original report.

A two-way summary of reported compliance to the regimen of drops and bifocal wear by treated members of the twinships is given in Table 1, which is oriented to show better compliance toward the lower left. Upon considering
that 20 missed drops are equivalent to only 11% of the prescribed regimen, the overall medication compliance seems satisfactory. The twins were encouraged to wear their spectacles during school, study, and other close work, but a full-time spectacle wearing schedule was not required. Indeed, there is a scattering of mediocre performances for wearing time. For both activities, the need for accuracy in reporting was repeatedly stressed in preference to exemplary performance. Spectacle wearing history for the cotwin controls is not indicated in the table; however, within-pair wearing patterns were highly concordant.

Figure 1 shows the frequency distributions of spherical equivalent cycloplegic refraction (eyes averaged) for the treatment and control twin samples upon entry into the study. It might be mentioned that the existence of larger amounts

![Graph showing frequency distribution of cycloplegic refractions.]

Fig. 1. Frequency distribution of cycloplegic refractions at baseline examination for 25 treated twins (crosshatch bars) and 25 control twins (solid bars). Each twin represented by average refraction for both eyes.

<table>
<thead>
<tr>
<th>TABLE 1. Compliance With Treatment Regimen by 25 Treated Twins</th>
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<td>Average hours of daily use of glasses</td>
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<td></td>
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<td>&lt;12</td>
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<td>Total</td>
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of myopia in young children is generally regarded as a predictor of greater progression. No lower limit was established for entrance into the study, and there were a number of instances of low grade or marginal myopia. The average beginning refraction for the treated twins was \(-2.33\) diopters and for the controls \(-2.22\) diopters.

Figure 2 shows the average refraction at the baseline and successive follow-up examinations for the treated and control twin subsets. The dotted line portrays the anticipated trend increase for myopia, based on the literature. Clearly, neither twin subset achieved this amount of progression. It is also seen that the overall difference between the treated and control groups was small. To examine more effectively this main issue of relative progression, the differences exhibited between twin pairs are reflected in Figure 3. In preparing this graph, the change in refraction following the baseline observation was determined for each successive visit. The differences between treated and control members of each twin pair were determined and averaged, and are represented by the solid line. The dotted straight line was fitted to the same data using the

![Graph](image_url)

Fig. 2. Average cycloplegic refraction (spheric equivalent) at successive examinations for 25 treated and 25 control twins.
method of least squares assuming a zero baseline value. The sign convention for intrapair differences was selected to portray a treatment benefit as positive on the ordinate scale. (Intrapair difference = [−Diopters Myopic Progress of Treated Twin] − [−Diopters Myopic Progress of Control Twin].) The observed trend was directionally consistent with a treatment benefit, i.e., there was on the average, less myopic progression among the specially treated members of the twin pairs. To lend a quantitative perspective to the amount of intrapair difference between treated and control members, however, a dashed line is shown which represents average successive refractions for all twins when superimposed using the same dioptic ordinate scale. The difference between treated and control twins was not statistically significant (paired “t-test” of the mean and sign test) and, by estimate based on the linear fit, it amounted to about 13% of the average myopic progression for the sample.

Because the total twin sample showed less overall myopic progression than anticipated, the data were reexamined for only those twin pairs in which at least one member, either the treated or control, progressed by ½ diopter or more during the period of observation. This truncation was an attempt toward elimination of those twinships destined to show little change with or without treatment.

The solid line in Figure 4 shows the average intrapair difference in refraction for the subset of 15 twinships exhibiting progression of ½ diopter or more. A dashed line representing average myopic progression for this sample of 15 is

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Fig. 3. Average intrapair differences (treated minus control) in myopic progression from baseline at successive examinations for 25 total pairs. Average sphoric equivalent refraction for total sample is shown for comparison.
again superimposed for perspective. A directional trend favoring treatment is evident as before, but the difference is not statistically significant. The average difference between treated and control members is equivalent to approximately 16% of the average myopic progress for this subset.

**DISCUSSION**

**The Clinical Issue**

This study was designed to detect an average treatment benefit of 1 diopter, based on an expected overall rate of myopic progression substantially higher than observed among the twin study sample. If the differences between treated and control twins observed here were universally representative, about twice the present sample size would be required in order to demonstrate statistical significance. In view of the evident nonrepresentativeness of the present sample with respect to overall myopic progression, the author is reluctant to reject the hypothesis of a treatment effect on the basis of the present findings. On balance, the findings might be viewed as supportive of a more vigorous definitive clinical trial among singletons, studying, perhaps, a somewhat stronger yet still acceptable clinical regimen.

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**Fig. 4.** Average intrapair differences (treated minus control) in myopic progression from baseline at successive examinations for 15 subset pairs. Average spheric equivalent refraction of subset is shown for comparison.
Reports on the therapeutic use of cycloplegic agents available prior to this investigation were cited earlier [23]. Since this study was undertaken, an additional prospective trial of bifocal wear among singletons has appeared [18]. Using overall reading addition power comparable to that employed here, the authors reported a substantially lower annual rate of myopic progression among the bifocal wearers. The report indicates that the treated and comparison groups of subjects were similar for beginning refraction, sex and beginning age, but their treatment and nontreatment status were neither obscured from the examiner nor randomly assigned. Ending ages for some of the study groups were not the same suggesting also a disparity in duration of follow-up. A study based on the exacting design considerations required for a definitive answer to this question still does not appear to be available.

Twin Study Considerations

The usual presentation of detailed study critique seems superfluous to this report since the findings are already limited by the fundamental problem of relatively low myopic progression among the study sample and the relatively small numbers of pairs studied, given the finding of low progression. However, one potential criticism seems worthy of mention at this congress because it may point up a potential flaw in the cotwin control design of studies. Brief mention of selected aspects of our understanding of myopia will provide background for the use of myopia as the theoretical example for this potential flaw.

Figure 5 presents a list of most of the measurable ocular dimensions that contribute to the ocular refraction. The existence of substantial biologic variation of the individual components of refraction has been recognized for well over a century. In myopia, the combined configuration of the components of refraction is such that the net light-converging power of the curved refracting surfaces is too great in relation to length of the eye, causing parallel rays of light to come to a focus in front of the retina and a blurred image to fall upon the retina. A variety of possible component configurations can lead to the same myopic refractive error. For example, as shown to the right in diagram B, the net converging power of the corneal and/or lenticular configurations can produce excess convergence of light in an eye of ordinary length, a situation sometimes called curvature myopia. Conversely, as seen in diagram C, overall refractive power of an ordinary amount can coexist with myopia in an eye that is too long, a condition sometimes called axial myopia.

Since ultrasound measurement techniques were introduced, two major studies have been undertaken on inheritance of components of ocular refraction using twin heritability study methods [15–17, 24, 25]. Both investigators found an inconsistent pattern of heritability among the batteries of individual components they studied. It is also of paranthetical interest that, although both investigators found high heritability for refractive error and for total axial length of the eye, their heritability findings were in direct opposition with respect to anterior lens curvature, lens thickness, and anterior chamber depth.

To return to the potential flaw in the cotwin control design of studies, the points to be emphasized from the foregoing are that the myopic refraction can be subclassified according to a variety of underlying causal configurations, ie,
the myopia observed clinically is actually a "common pathway" expression of a variety of component configurations. Suppose for this discussion that the relative roles of inheritance and environment differ among the various causal configurations of myopia, a supposition not inconsistent, perhaps, with the reports just cited [15–17, 24, 25], of dissimilar patterns of inheritance among the component elements of refraction. Given these conditions, a monozygotic cotwin control study requiring concordant pairs would favor entry of those twin pairs exhibiting the gene sensitive moiety(ies) and would be biased accordingly. If the inherited and environmentally determined forms were to have different responsiveness to the particular treatment under investigation, the generalizability of findings of the cotwin control study would be limited. Such potential source of bias might warrant consideration in other chronic disease ap-

Fig. 5. Components of refraction and example of diagrams of component configurations in myopia.
plications of the MZ cotwin control design of studies. It could be assessed by including discordant pairs in the study to see if they respond to treatment as do the concordant pairs.

Much information needed for the understanding of myopia and its clinical management is potentially available through further applications of twin study methods. To mention a few immediate needs, a comparison of intrapair differences in refraction between MZ pairs reared apart and those reared together could greatly assist the interpretation of existing twin heritability data on myopia with respect to the "twin environmental assumption" [3] discussed at the first congress [23]. Furthermore, twin heritability studies on components of refraction warrant careful repetition using newly improved examination techniques (adequately pretested for validity and reliability), preferably based on relatively "representative" twin samples. In addition to new information on the existing disparate findings on heritability of the individual components and, perhaps, the more prevalent patterns of component configuration, such restudy would also permit the comparison of component elements and configurations between concordant and discordant MZ twin pairs to aid further in identifying and/or confirming those relatively heritable or nonheritable forms that might exist. With respect to future therapeutic trials among twin or singletons, the inclusion of adequate measurements of components of refraction could serve to identify myopic configurations that might be amenable to therapy by comparing components among those who respond to therapy with those who do not.

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REFERENCES