A MONOZYGOTIC COTWIN CONTROL STUDY OF A TREATMENT FOR MYOPIA

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Myopia is the world's most common cause of defective vision. The role of controlled accommodation on the progress of myopia is unsettled. This cotwin control study is designed to provide a careful appraisal of the effectiveness of a clinically acceptable method of controlling accommodation. There are no previous reports of similar prospective studies among MZ twins. Expansion of such studies would be aided by collaboration among interested investigators.

This outline of a myopia treatment study is presented as a current example of an ongoing prospective study employing cotwin controls. The essential advantage of working with MZ twins in this ongoing investigation lies in the complete match on genetic constitution for the treated twin and his control. Key variables, age, sex, and national origin, are also matched, as are factors such as maternal age and parity, gestation, maternal health, family history, and, to some extent, intrauterine environment and companion sociocultural postuterine experiences.

BACKGROUND

Myopia is the world's most common cause of defective vision. Prevalence is commonly placed between 15 and 30% among Western populations with higher estimates reported among Chinese and Japanese (Duke-Elder 1949). As a public health problem, the impact of myopia is compounded when weighed in terms of person-years of involvement since myopia commonly begins in young children, progresses through late adolescence and remains for life.

Although the cause(s) and management of myopia have excited immense interest over the past century, both issues remain controversial. A review of the literature on this subject will not be attempted here, but present uncertainty regarding etiology is attested by contrasting general conclusions in two of the major position papers presented at a workshop on refractive anomalies reported by the National Institute of Neurological Diseases and Blindness in 1967. Dr. Sorsby (1967) presented a summary of his extensive data on components of refraction collected among MZ and DZ twins and among general population groups. He suggested that emmetropia, correlation ametropia and component ametropia are, in large part, genetically determined. He believes additional emphasis on environmental factors finds no support in the detailed studies of today. Twin heritability studies by Drs. Nakajima et al. (1966) and Otsuka (1976) are consistent with those of Dr. Sorsby in supporting a large genetic contribution to overall refractive status, but there is lack of agreement among twin studies with respect to inheritance of specific components of the ocular refraction.

Dr. Young (1967), reporting at the same workshop, took the position that environmental stress explains the mechanism of shift to most myopic refractive errors up to approwimately eight diopters. His interesting findings are based mainly on laboratory experiments on primates and on examinations of refractive error among remotely located communities made some years after the resident populations were introduced to the ocular stress of formal schooling.

It is reasonable to consider that an individual's refractive status may be determined by a combination of environmental influence and genetic predisposition, a concept which has been well-summarized by Otsuka (1967). Many potentially causal environmental factors have been suggested, but one

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widely held theme, recurrent throughout the literature, relates the progression of myopia to prolonged use of the eyes for the task of seeing at near. Most authors implicate the act of accommodation and/or convergence as the causitive element(s) linking near work with myopia. Accordingly, methods of treatment have been directed toward relaxing the mechanism of accomodation and reducing the amount of accomodation required for near tasks. More widely tried therapeutic measures have been the instillation of topical cycloplegic eye medications (Donders 1864, Parsons 1924, Leudde 1932, Eggers 1953, Lancaster 1953, Toki 1960, Gostin 1962, Abraham 1964 and 1966, Tokano 1964, Tokaro and Kabe 1964, Otsuka 1967) and/or the use of bifocal spectacles (Betz 1949, Gamble 1949 Tait 1951, Pascal 1952, Warren 1955, Miles 1957 and 1962, Parker 1958). Evaluations of therapeutic effectiveness have been in disagreement and have generally been based on clinical impressions, case reports, and retrospective comparisons of office records. More recently, prospective studies using opthalmic atropine medication, a long- and deep-acting cycloplegic agent, have begun to appear in the literature. These studies have employed fellow-eye controls and suggest that atropine cycloplegia, when maintained continuously over a one- or two-year period can materially retard the progression of myopia (Bedrossian 1971).

It may be of interest to note at this Congress that if environmental factors such as use of the eyes for near tasks do intensify the progression of myopia, then we are faced with an intriguing problem in interpreting twin heritability data on refractive errors since postnatal environmental influences can theoretically introduce bias leading to an overestimate of genetic effects (Schwartz and Feinleib 1974). For rxample, it has been observed that MZ and DZ twin pairs tend, in general, to subject themselves and to be subjected to different environmental opportunities, and that such differences tend to result in greater intrapair environmental dissimilarity among DZ pairs (Stocks 1930-31, Wilson 1934). In studies on refractive errors, this source of bias can be further complicated by different patterns of within pair psychosocial structuring which tend to develop within the two classes of twins. Some authors have described a higher degree of personal attachment and the desire for conformity within MZ pairs, but an opposite tendency toward competition and polarization within DZ pairs (von Bracken 1934, Husen 1959). If zygosity-related psychosocial structuring within pairs can give rise to bias with regard to within-pair patterns of environmental exposures, such forces would be expected to be operative during periods of shared domicile, i.e., during youth when the ocular refraction is maturing. If MZ twins, by virtue of constitutional predisposition, external influence, or evolving psychosocial intrapair relationships, are more likely than DZ twins to develop common behavioral patterns for near work (e.g., study habits, hobbies or reading for pleasure), then such environmental factors themselves could lead to greater MZ concordance for refractive error and could result in exaggerated estimates of heritability when based on the usual twin study methods. (This is a specific example of a potential violation of what Dr. Gordon Allen termed " the twin environmental assumption " in this morning's program. This particular example regarding myopia is especially interesting in that it deals with a *behavioral environmental* bias influencing the study of a *physical* characteristic ather than the study of cognitive or *behavioral* traits.)

PRESENT THERAPEUTIC TRIAL

The present twin study was undertaken to assess the influence of an unobtrusive, clinically acceptable treatment in retarding the progression of myopia in children. The study sample consists of young MZ twins who are similarly myopic. One cotwin receives a standard spectacle correction as the control; the other is managed using a combined treatment comprising especially prescribed bifocal spectacles and topical short-acting cycloplegic eye drops.

Specifically, the special treatment regimen consists of two drops of 1% tropicamide ophthalmic solution applied to each eye nightly, combined with the daytime use of a reading addition of 1.25 diopters applied to the spectacle correction as a wide-segment flat-top bifocal. As part of the special treatment regimen the full cycloplegic correction is sometimes reduced up to 1/2 diopter, providing such reduction dces not impair subject's vision below 20/20. This combined treatment was intended to approach the strongest regimen which would not interfere with visual acuity, daytime accommodation, binocular coperation and cosmetic appearance. Accordingly, if found to be effective in retarding the regression of myopia, it is expected that this type of in

regimen would offer a readily acceptable clinical treatment. In all cases, the control subject is provided with his full cycloplegic correction in single vision lenses. This latter is a standard method of managing myopia. We set out to examine the general hypothesis that among the specially treated sample of cotwins the progression of myopia over a three-year period would be less than among the cotwin controls by an amount ≥ 1.00 diopter. From published descriptions regarding the increase in myopia over time we estimated an average myopic increase for a period of three years during childhood and adolescence to be 1.743 diopters, SD = 1.145 diopters. For $\alpha = 0.05, \beta = 0.20$, the required number of pairs was estimated at 22, using the formula (Cochran and Cox 1950): 2 (coefficient of variation/per cent true difference)^2 $(t_a + t_b)^2$.

Requirements for participation in this study are given in Table 1. All twinships were drawn from a Twin Registry for Eye Examinations developed in the Washington, D.C., Metropolitan Area, which was described at the First International Symposium on Twin Studies (Schwartz 1971). It is of interest that although our twin register contains approximately 700 pairs of twins residing in the Washington area, less than 30 pairs qualified with respect to the requirements of Table 1. Even so, it was necessary to compromise some of the strict refractive requirements which are shown in Table 1. This problem of identifying appropriate twins for study reaffirms the desirability of wide national and international collaboration if such studies are to be expanded (Schwartz 1970).

The assignment of special treatment or control status to members of each twinship was based on a strict randomization protocol after the original base line examinations were completed and after qualifying twins agreed to participate. When refractions are performed at follow-up examinations, adequate measures are undertaken to insure that the examiner is unaware of the treatment or control status of the twins. The possibility of incorporating sham measures to obscure from the patient his own treatment status was considered in the design but rejected as impractical.

Table 1. *Requirements for twin participation*

(1) MZ as determined by blood grouping, anthropometry
(2) Age 7-13 (one pair age 14)
(3) Shared domicile
(4) Good general health
(5) Vision correctable to 20/20 or better
(6) Third degree fusion
(7) Absence of other significant ocular abnormality
(8) Both twins reside in local area
(9) Refraction requirements:
  (*a*) Individual twins
    1. Bilateral myopia
    2. Astigmatism of 1.00 diopter or less in each eye
    3. Anisometropia* of 1.00 diopter or less
  (*b*) Twinships
    1. Difference in refraction* between cotwins of 1.50 diopters or less in the more advanced eye

* For these requirements, amplitude of myopia is considered in terms of total spheric equivalent at cycloplegic examination.

Table 2. *Description of participating MZ twin pairs by sex and age at entry into the prospective study*

	Age									
Sex	6	7	8	9	10	11	12	13	14	Total
Male	1	0	0	2	2	1	3	4	0	13
Female	0	1	0	1	2	0	3	4	1	12
Total	1	1	0	3	4	1	6	8	1	25

A detailed description of the contents of our history and physical examination is not appropriate to this discussion. Essential base line examinations include a manifest refraction and two separate cycloplegic refractions, one following instillation of 1% cyclogel, the other following use of 1% atropine ointment three times daily for three days. In addition, components of refraction are measured using keratometry, phacometry and A-scan ultrasonography. Patients are reexamined at six-month intervals at which time manifest refraction and a cycloplegic refraction using 1% cyclogel are repeated and the spectacle prescriptions updated. Six-month interval histories are obtained and participants are carefully interviewed regarding their spectacle wearing time and with respect to a daily medication record which is maintained by the cotwin receiving this treatment. Ocular motility, ocular pressure, facility of aqueous outflow, slit lamp examination, accommodation, ophthalmoscopy, and external ocular examinations are monitored at each six-month follow-up.

A description of the present study sample of 25 pairs by sex and age at entry into the study is given in Table 2.

All are Caucasian. One additional pair entered the study, but was asked to withdraw at one year because of unsatisfactory adherence to the protocol. Otherwise, patient cooperation has been excellent. The medication protocol has been highly acceptable and well adhered to. Daytime spectacle wearing time by some twin pairs has been inconstant, but the wearing patterns within pairs tend to be highly uniform. We have not attempted to impose a full-time spectacle wearing schedule.
All examinations, medications and spectacles are provided free of charge. There is no additional honorarium. The data collection phase of this study is in its final year.

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