OCULAR FINDINGS IN DOWN'S SYNDROME*

BY *Edward A. Jaeger,* MD

HISTORICAL BACKGROUND

LANGDON DOWN IN 1866, ATTEMPTING TO CATEGORIZE MENTALLY RETARDED PERsons according to their ethnic background, first ascribed the term "mongolism" to those with short stature, mental deficiency and Mongolian features.[1] However, Down himself was puzzled by the fact that a "Kalmuc physiognomy" could be present in those of other racial backgrounds and considered this a disease that was able to break down ethnic barriers. Gradually this group became recognized as a distinct entity. Beach[2] established the difference between those with mental deficiency, many of whom were mongols, and those with emotional disturbances and suggested these groups be separated. Shuttleworth[3] considered mongols "unfinished children." In the half century following Down's paper, numerous small and large group studies emphasizing the clinical characteristics of this syndrome appeared in the world literature. Bourneville[4] and Comby[5] discussed pathologic autopsy findings and supported the prevailing opinion that mongolism was in some way related to thyroid abnormalities. Understandably, mongolism was confused with cretinism by many early workers and this thinking prevailed well into the twentieth century. However, Caldecott,[6] in a remarkably succinct discussion of a 1909 paper by Shuttleworth, stated that mongols rarely lived beyond 20 years, died of tuberculosis, their characteristics lessened with age, and thyroid therapy was useless. Oliver,[7] in 1891, was one of the first to document the ocular findings. Subsequently, emphasis was placed on the incidence of individual characteristics as well as the epidemiologic, psychologic and social aspects of Down's syndrome. Brushfield[8] in 1924 detailed the incidence of the various physical findings and van der Scheer[9] also noted that there was marked group similarity in the young but less so in adults. Comprehensive reviews of Down's syndrome were provided by Brousseau in 1928[10] and by Øster in 1953.[11]

Unveiling of the true etiology of mongolism advanced with the monumental work of Tjio and Levan[12] in 1956 who established the normal

*From the Elywn Institute, Elywn, PA.

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diploid chromosome number of 46. This paved the way for the discovery by Lejeune, et al in 1959 that those with Down's syndrome had 47 chromosomes.[13,14] The chronology of mongolism has been concisely documented by Smith and Berg.[15]

The discovery that Down's syndrome was due to a chromosome abnormality has reduced the diagnostic significance of the clinical characteristics. However, it is paramount for the clinician to recognize that there is as wide a variation in the mental, social and physical status of mongols as there is in a cross-section of the normal populace.

Epidemiologic studies have shown Down's syndrome to occur once in every 600-700 live births.[16,17] However, as the mortality rate has decreased the number of mongoloid persons in relation to the total population has increased. The number of 10-year-old Down's children in 1960 was 1 per 1,000 as compared with 1 per 4,000 in 1929. The influence of advanced maternal age in mongoloid births was first emphasized by Shuttleworth in 1909[18] and has been confirmed by many subsequent studies.[19,20] Smith and Berg[15] in a world wide statistical compilation of 9,441 Down's and 9,441 control births showed the average maternal age to be 34.43 years in the Down's group and of controls 28.17 years. While increased maternal age appears to be related to non-disjunction of the chromosomes, the exact reason for this remains speculative.

CHROMOSOME STUDIES

Down's syndrome was the first multi-system disease syndrome to be related to abnormal chromosome numbers.[13] Three abnormal chromosome patterns have been associated with mongolism. The most common is a tripling of chromosome 21 found in 95% of those with Down's syndrome. This extra chromosome is the result of a non-disjunction of the two paired homologue number 21 chromosomes early in meiosis.[21,22] The ovum then contains 24 chromosomes instead of 23 which when combined with 23 from the sperm at fertilization results in a zygote with 47 chromosomes. All cells in the resulting individual will contain 47 chromosomes, a complete Trisomy 21. However, a second pattern occurs if the failure of chromosome separation takes place in a cell division after fertilization. In this case some of the cells will contain the normal 46 chromosomes while the others will have 47. This pattern termed "mosaicism" was first described by Clarke, et al in 1969.[23] The mosaic Down's children tend to be of higher intelligence but still display typical mongoloid features. A third pattern, termed translocation, occurs when the extra chromosome 21 becomes attached to another chromosome, usually chromosome 15. In this case the total number of chromosomes will be the normal 46. Although translocations tend to

occur in younger mothers, little difference has been found clinically between standard Trisomy 21 and the translocation variety.

STUDY METHODS

Seventy-five institutionalized persons with chromosomally documented Trisomy 21 served as the basis of this study. Chromosome number was determined in most cases by leukocyte culture. Seventy-two were of the standard 47 chromosome Trisomy 21 type, one was considered mosaic, one a translocation and one questionable translocation but clinically a typical Down's syndrome. Because of the small number of mosaic and translocation types, these individuals were not considered separately. The control group consisted of eighty-eight institutionalized patients with mental retardation secondary to a wide variety of both known and nonspecific etiologies. These patients were drawn consecutively from those seen for routine two year eye examinations but also who fell within the approximate age and IQ range of the Down's group. Some selection occurred in that those with severe physical limitations or uncontrollable mental status could not undergo sufficient ocular examination.

Areas of study were: external ocular appearance, refractive error, strabismus, iris, lens and retinal vascular pattern. All phases of the study could not be completed on every patient. Several additional study groups were utilized for comparative interest. In the areas of refractive error and the lens, comparisons were made with eighty-eight consecutive office patients. Eleven persons of oriental descent with epicanthus were examined to determine the nature of their epicanthal folds.

The Down's group consisted of 46 males and 29 females and the control group 50 males and 28 females (Table I). The average age and IQ of the Down's group was 35.1 years and 32.6 IQ respectively, while that of the control group was 32.1 years and 43.3 IQ. The IQ was determined by the

Table I: General statistical comparison of Down's and control groups.

	Total	Sex	Age	Age range	IQ	IQ range
Down's	75	46M 29F	35.1yrs	15-64	32.6	15-68
Control	88	50M 38F	32.1yrs	13-63	43.3	15-62

Institutional Psychology Department using a variety of tests depending upon patient capability. Those with an IQ below the limits of testing were assigned a figure of 15 for statistical purposes.

EXTERNAL OCULAR PROFILE

The external ocular findings in mongolism are the features most widely associated with this syndrome. Epicanthus, narrowed interpupillary distance and oblique upward and outward slanting palpebral fissures are generally recognized characteristics of the mongoloid facies and were investigated in this study.

Considerable variation in the incidence of these findings has been reported in previous studies. Eissler and Longnecker[24] found epicanthal folds in 38.3% and oblique slanting fissures in 43.2% of 396 Down's individuals. Gaynon and Schimek[25] reported epicanthus in 53% and oblique fissures in 73% of 30 mongols. Much of the statistical variation may be the result of differences in the definition of epicanthus and the age range of the subjects. Skeller and Øster[26] and Benda[27] emphasized the difference between a Mongolian (oriental) fold and true epicanthus. They observed the Mongolian fold to arise from the margin of the tarsal fold of the upper lid and extend in curvilinear fashion to the skin below the inner canthus. True epicanthus, they felt, arises above the margin of the tarsal fold, from the orbital portion of the lid, and attaches inferiorly to the lower lid. Skeller and Øster found true epicanthus in 15 of 70 (21%) of mongols. Gifford,[28] however, believed the fold in Down's syndrome to extend from the skin of the upper lid to the side of the nose bridge without curving downward and again outward as in epicanthus. Lowe[29] observed epicanthus to be more common in the younger age mongols and rarely present in the adult. Solomons et al,[30] found epicanthus in 60% of those with Down's syndrome below the age of 10 years and in only 9% of those over 10 years. They observed that this may be true of epicanthus in general.

The interpupillary distance (IPD) in mongols has been variously described as wider,[31,32] the same as,[33] and narrower than normals.[29] Most studies involving actual measurements have shown a narrower interpupillary distance in Down's syndrome. Kerwood et al,[34] found this to be true in Down's syndrome, even in relation to cranial diameter.

In this study the Down's and control groups were examined for the presence and type of epicanthus. Epicanthus was used in the broad sense to mean any skin fold partially covering the medial canthus. Patients were examined both in straightforward gaze and on looking downward. The type of epicanthus was judged according to the origin of the fold in downward

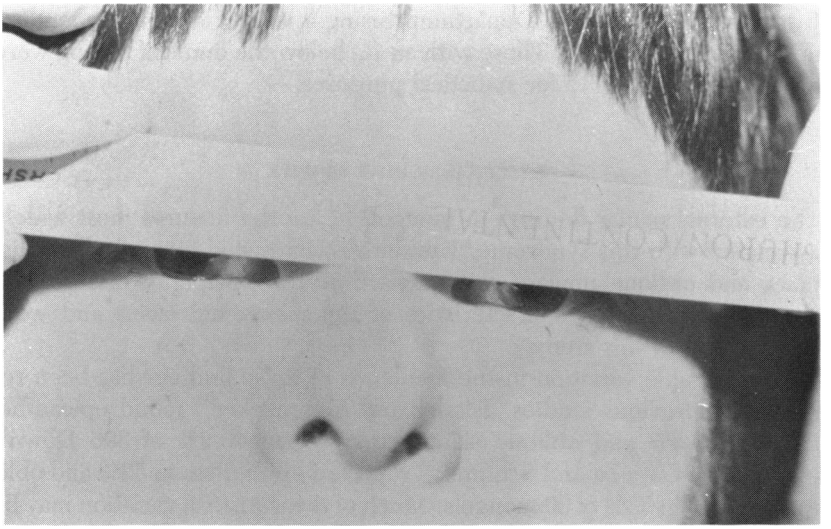

FIGURE 1
Millimeter rule aligned with outer canthi showing upward and outward slant of palpebral fissures in Down's syndrome.

gaze. The interpupillary distance was measured in 50 mongols and 50 control patients with equal sex distribution. The interpupillary distance was measured at near and 3 mm was added to this figure. A true distance interpupillary distance was felt to be less reliable in many instances. Some cases with strabismus were eliminated because of measuring difficulties. The slant of the palpebral fissures was measured by aligning a millimeter rule with the edge of each lateral canthus (Fig 1). The position of the medial canthus in relation to the rule, below, even with or above, was noted. A general external and slit lamp examination of the eyes were also performed and abnormal findings recorded.

Epicanthus was present in one or both eyes in 17.3% (13 of 75) mongols as compared with 3.6% (3 of 88) controls (Table II). The average age of those

Table II: Presence of epicanthal folds in Down's and control groups.

	No.	Epicanthus	Percent	Average Age
Down's	75	13	17.3	25.1 years
Control	88	3	3.6	14.6 years

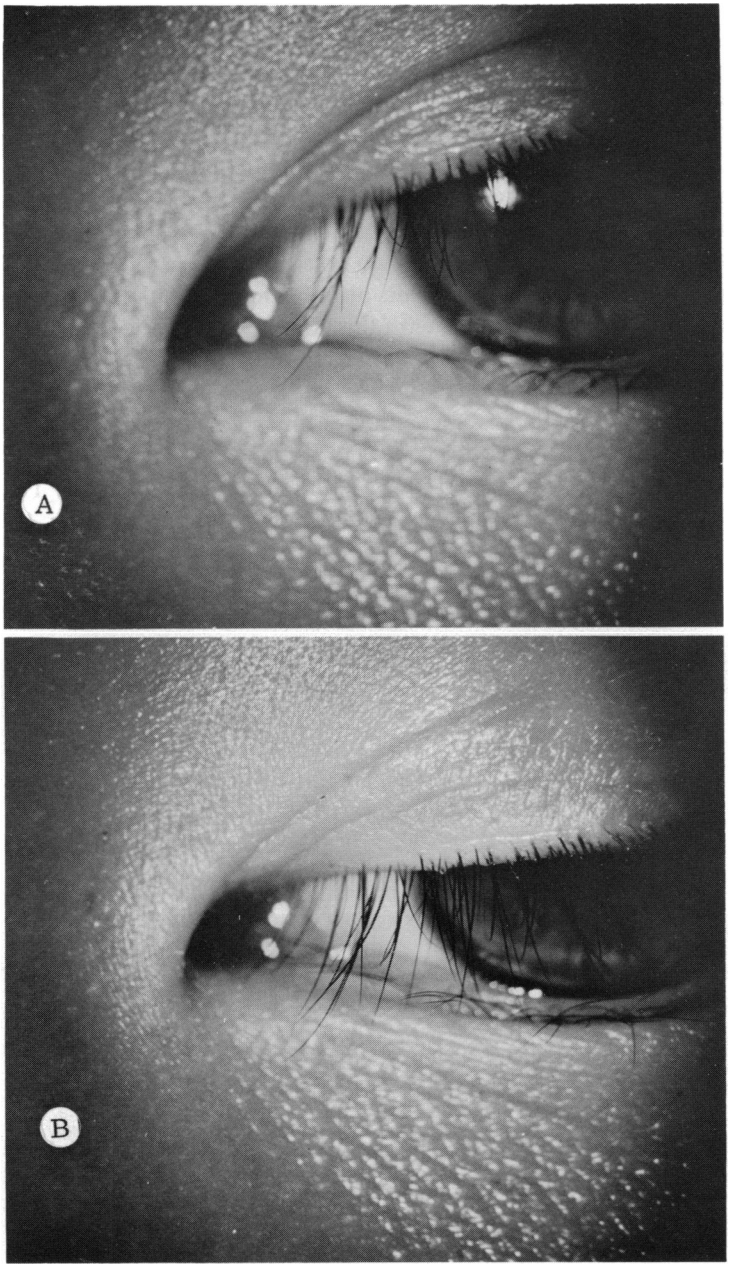

FIGURE 2
Typical oriental type epicanthus. A: Straight forward gaze; B: Downward gaze. The epicanthus remains continuous with the tarsal lid fold.

mongols with epicanthus was 25.1 years while those in the control group averaged 14.6 years. Those exhibiting epicanthus had a younger average age than those of their respective total groups, although the control group number was too small to permit significant comparison.

The type of epicanthus was analyzed in these two groups along with 11 individuals of oriental extraction with epicanthus. In most persons with epicanthus, the skin fold appeared to be continuous with the tarsal fold in straightforward gaze. In the true oriental fold, the epicanthal portion generally remains continuous with the lid fold on downward gaze (Fig 2). However, in non-orientals downward gaze often reveals the fold to actually arise from the orbital portion of the lid, the "true" epicanthus of Skeller and Øster (Fig 3). In rarer instances the fold may actually arise from the lid margin but may also arise from the tarsal fold.

All those with Down's syndrome exhibited similar type folds. The epicanthus began superiorly in the orbital portion of the lid (Fig 4). This

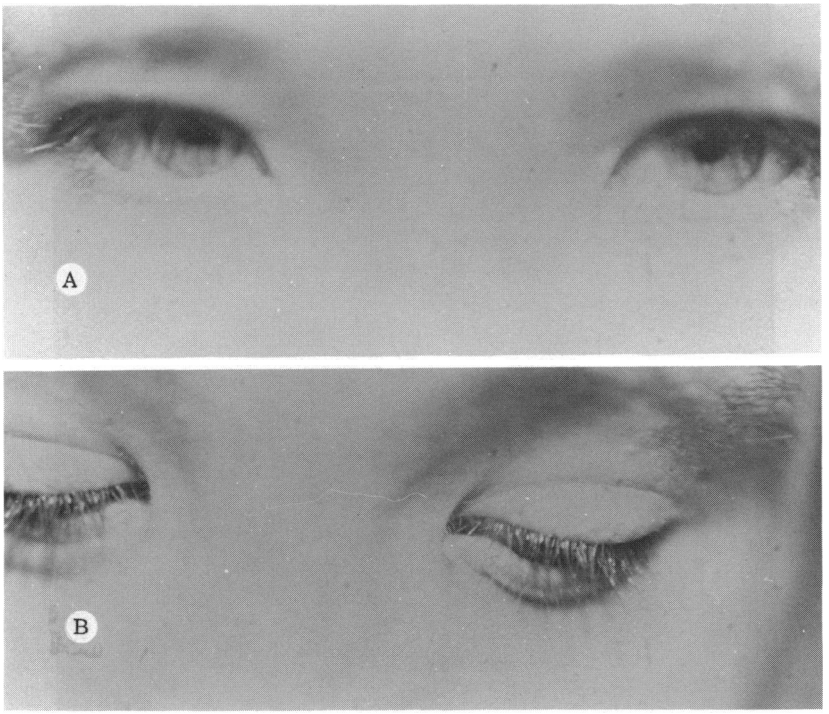

FIGURE 3
Epicanthus in Down's syndrome. A: Straight forward gaze appearing continuous with the lid fold; B: Downward gaze shown to actually originate from the orbital portion of the lid.

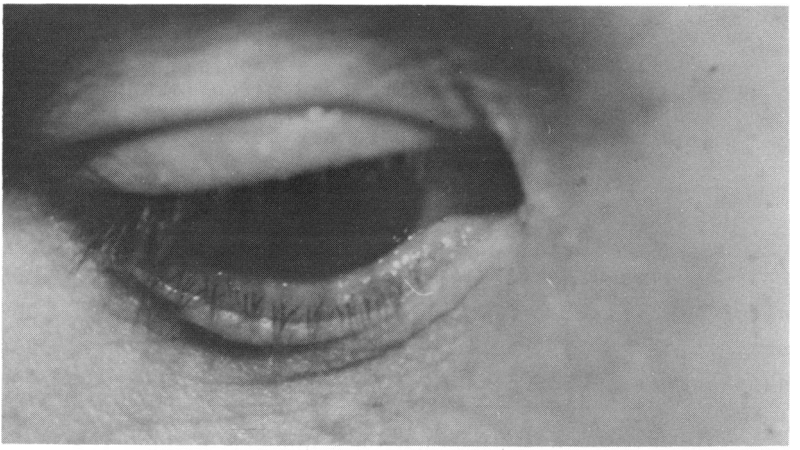

FIGURE 4
Forty-nine year old mongol with typical epicanthus originating from the orbital portion of the lid.

feature could be seen in a few cases in straightforward gaze but in most could only be distinguished in the downward gaze position. The fold extended in various degrees of curvature to the base of the nose at the level of the inner canthus or to blend into the lower lid below the canthus. The three individuals in the control group displayed a variety of fold types, one originating from the superior lid margin, one from the lid fold and one from the orbital portion of the lid. The epicanthus in 9 of 11 orientals was continuous superiorly with the tarsal fold and generally exhibited a more sharply curved course inferiorly. Two oriental folds originated at the upper lid margin.

The average interpupillary distance for Down's syndrome females was 57.4 mm and for control females 60.0 mm as compared with the Down's males of 58.6 mm and control males 61.4 mm (Table III). The interpupillary distance values between female Down's and female controls as well as male Down's and male controls were significantly different to a P level of .05. However, when these values were related to head circumference (IPD/HC ratio) there was found to be no significant difference between the female or male groups.

Oblique palpebral fissures, slanting upward and outward were found in 83% of those with Down's syndrome as compared with 36% of controls (Table IV).

Additional external ocular abnormalities found to be frequent in Down's syndrome were blepharitis, nystagmus, lacrimal obstruction and keratoconus (Table V). These findings are similar to those noted in many previous

Table III: Comparison of interpupillary distances (IPD) between the various male and female groups and the head circumference (HC)/ interpupillary distance ratio. Standard deviations (S.D.) are included.

	No.	Mean IPD	S.D.	Mean Head Cir.	IPD/HC	S.D.
Down's Females	25	57.4mm	2.47	51.58cm	.112	.005
Control Females	25	60.0mm	4.56	52.31cm	.115	.009
Down's males	25	58.6mm	2.00	53.39cm	.110	.004
Control males	25	61.4mm	3.91	54.38cm	.113	.006

studies. Tear testing was attempted on a number of subjects but was thought to be inaccurate. One mongol had slit lamp evidence of keratitis sicca.

The outward and upward slanting of the palpebral fissures present in 83% of mongols is the primary ocular feature responsible for the facial appearance in Down's syndrome. Epicanthus was present in only 17.3%. While epicanthus in Down's syndrome may not be singularly characteristic, it does appear to be distinctly different from the Mongolian (oriental) fold originally described by Langdon Down. A narrowed interpupillary distance is present in Down's syndrome but this appears to be related to smaller head circumference.

REFRACTIVE ERROR

The refractive error in 71 mongols was compared with 88 individuals in the control group. No persons in the study groups were institutionalized specifically because of visual problems. Cyclopentolate hydrochloride 1% or tropicamide 1% was used for cycloplegia in all cases and the refractive

Table IV: Comparison of palpebral fissure slanting in Down's and control groups.

	No.	Upward Slant	Straight	Downward Slant
Down's	67	83% (56)	12% (8)	4% (3)
Control	75	36% (31)	41% (31)	23% (17)

Table v: Additional external ocular findings in 75 Down's patients and 88 controls.

	Downs	Control
Blepharitis	10	1
Nystagmus	8	4
Lacrimal obstruction	8	0
Keratoconus	2	0
Pterygium	1	1
Keratitis sicca	1	1

error was based on the retinoscopic findings using sphero-minus cylinder combinations. In addition, for comparison the refractive error was recorded in 88 consecutive office patients seen for a general ophthalmologic examination and ranging in age between 12 and 60 years. A cycloplegic refraction was also done in these cases.

A visual acuity was attempted in all mongols and in control strabismus patients prior to cycloplegia. Glass or known trial frame correction was used. Acuity testing was difficult, especially at distance. However, a rough best corrected acuity was obtained in 45 of the mongoloid group. Most visual estimates were obtained with the use of pictures at near, several with picture cards at distance and rarely a Snellen distance acuity. Eight of the 45 were found to have vision of 20/30 to 20/50 in the better eye while the majority were in the 20/50 to 20/70 range.

The degree of deviation from emmetropia was evaluated at two levels. Refractive error at Level I was considered as equal to, or greater than ± 4.00 diopters of sphere or −2.50 diopters of cylinder. Level II was equal to or greater than ± 8.00 diopters of sphere or −5.00 diopters of cylinder. The eye in each patient with the greatest refractive error was used for comparison. In those cases in which both the sphere and cylinder were abnormal, only the spherical error was used for compilation purposes.

Table VI: Comparison of refractive error in Down's, control and office patient groups.

	Level I ≥ ± 4.00,-2.50cyl		Level II ≥ ± 8.00,-5.00cyl	
Down's	38 of 71	53.5%	12 of 71	16.9%
Control	21 of 88	23.9%	3 of 88	3.4%
Office	11 of 88	12.5%	1 of 88	1.1%

Refractive error at Level I (≥ ± 4.00 sphere, −2.50 cyl) was found in 38 of 71 mongols (53.5%) as compared with 21 of 88 (23.9%) in the control group and 11 of 88 (12.5%) office patients (Table VI). Comparison of these groups at Level II (≥ ± 8.00 sphere, −5.00 cyl) revealed 16.9% of mongoloid persons exhibited at least this degree of refractive error as compared with 3.4% of controls and 1.1% of office patients.

The refractive status of these patients was analyzed as to the type of error. It can be seen that at Level I there is a fairly even distribution of myopia, hyperopia and astigmatism within each group with the exception of a slight predominance of myopia among office patients as might be expected (Table VII). However, at Level II myopia in the Down's group was the predominant finding with nine persons having at least −8.00 diopters of refractive error and 2 additional persons with at least −5.00 diopters of cylinder (Table VIII).

Excessive deviation from emmetropia has been previously associated with Down's syndrome. However, each study utilized different criteria

Table VII: Comparison of the type of refractive error at Level I in Down's, control and office groups.

	Myopia	Hyperopia	Astigmatism	Total
Down's	14	13	11	38
Control	6	8	7	21
Office	7	2	2	11

making comparisons difficult. Brousseau[10] found a high degree of hypermetropia to be present while Lowe[29] reported 13 of 35 mongols to have −8.00 diopters or greater of myopia. At the higher level of refractive error (≥ ± 8.00 D, −5.00 cyl) this study confirms the increased incidence of myopia in Down's syndrome. At the lower level of refractive error (≥ ± 4.00 D, −250 cyl) a more even distribution in the type of error was found. However, this degree of error was present in more than twice the percentage in those with Down's syndrome (53.9%) as compared with the controls (23.9%) and four times that of the office patient group (12.5%).

There can be little doubt from the study that high degrees of refractive error in general are commonly found in Down's syndrome. The glass correction of these refractive problems must be based on the judgment of the examiner. Sometimes the correction of a large refractive error will result in significant functional improvement while in other cases little discernable change is noted. Early childhood correction of large refractive errors did seem to lead to better spectacle acceptance by the child and improved function. However, there are no statistics to substantiate this generalization. Interestingly, higher degrees of refractive error would appear to be more frequent in nonspecific mentally retarded patients than the general population as reflected in an office practice. Although these persons were not institutionalized because of visual problems, this could be an unrecognized subtle factor in these statistics. There is no obvious explanation for the increased incidence of refractive error in Down's syndrome or mentally retarded patients.

STRABISMUS

A standard corneal light reflex test and alternate cover test were performed on each subject using a pen light a 33 cm. Distance muscle testing was

Table VIII: Comparison of the type of refractive error at Level II in Down's, control and office groups.

	Myopia	Hyperopia	Astigmatism	Total
Down's	9	1	2	12
Control	2	0	1	3
Office	0	0	1	1

difficult and exact measurement was inaccurate. Vision was attempted at near or far with spectacle or trial frame correction where indicated.

Strabismus was found to be a common feature of Down's syndrome, occurring in 31 of 75 or 41.3% of patients as compared with 14 of 88 or 15.9% of those in the control group (Table IX). Esotropia was by far the predominant muscle deviation in both groups. Accurate measurement was difficult and was especially variable in degre in those with Down's syndrome. The average IQ of those mongols demonstrating strabismus was 30.8, compared with the group IQ of 32.6. The control strabismus group had an average IQ of 45.6 compared to the total group IQ of 43.3. However, 21 of the 31 Down's strabismus cases had an IQ of 32 or below while only 3 of 14 non-Down's strabismus patients fell below the average control group IQ of 43.3.

Those individuals with muscle deviations in both groups were further compared with regard to vision and refractive error. Admittedly, vision testing was difficult and inaccurate in many cases. In the Down's group, visual acuities were obtainable in 23 of 31 strabismus cases and 10 of 14 in the control group. Vision (near or distance) in each case was evaluated for the presence of amblyopia. The diagnosis of amblyopia was made if there was a difference of 3 or more standard lines (near or distance) between the two eyes. Twenty of the 23 testable mongoloid strabismus cases had vision with less than three lines difference between each eye while 7 of 10 in the control group had a similar visual status (Table X). Three of 23 mongols and 3 of 10 controls were diagnosed as having significant amblyopia by these criteria. Actually only one of this group, an esotropic control demonstrated a deep amblyopia of 20/400 in the right eye and 20/30 in the left eye.

Those cases with esotropia were further analyzed with regard to their refractive error. Twenty-four of 28 esotropic Down's and 10 of 10 esotropic

Table IX: Strabismus in Down's Syndrome

	Down's		Control	
Esotropia	28/75	37.3%	10/88	11.3%
Exotropia	2/75	2.7%	4/88	4.5%
Hypertropia	1/75	1.3%	0/88%	
Total	31/75	41.3%	14/88	15.9%

Table X: Evaluation of the vision between the two eyes in strabismus cases.

	No. of cases	Three or more lines difference	Less than three lines difference
Down's	23	3	20
Controls	10	3	7

controls were refracted. Four mongols could not be evaluated because of cataracts. Five of 24 refractable Down's esotropes were found to have a hypermetropia greater than 3 diopters compared with 2 of 10 control esotropic patients (Table XI). Seven of the Down's group and 3 of the control group demonstrated myopia greater than −3.00 diopters. Five of the esotropic Down's individuals had a myopia greater than −6.00 diopters.

Strabismus, particularly esotropia, has been commonly associated with Down's syndrome. Brushfield,[8] in an early series, thought that convergent strabismus was present in all mongoloid patients. Other studies have indicated strabismus to be present in 30% to 50% of those with Down's syndrome.[24,26,29] Strabismus is thought to occur in 3% to 5% of the general population.[35-37] Ocular muscle deviations have also been noted to be more common in those with mental retardation and neurologic dysfunction.[38,39] However, the frequency of strabismus in Down's syndrome in this series (41.3%) is 2½ times that of the control group (15.9%) and 8 times that of the general population.

Several features of this group are of interest. Amblyopia by the stated criteria was found to be uncommon, occurring in only 3 of 24 testable

Table XI: Evaluation of refraction in patients with esotropia.

	Patients with esotropia	>+3.00	-3.00 to -6.00	>-6.00
Down's	24	5	2	5
Controls	10	2	3	1

strabismic mongols. In those 3, the amblyopia visual deficiency was comparatively moderate. (OD 20/200, OS 20/50; OD 20/50, OS 20/100; OD 20/50, OS 20/100). This data would tend to indicate that attempts at occlusive therapy for amblyopia are generally unwarranted in this group. No explanation for the surprisingly low percentage of amblyopia in mongolism is apparent. Possibly the tropic condition does not become constant until later in childhood. It is also plausible that the visual system in some Down's patients is not capable of fully developed acuity, or the acuity demands do not provide stimuli sufficient to provoke the full time use of one eye alone in infancy. A decreased fusional capacity may also be present in Down's syndrome.

It would also appear that strabismus in Down's syndrome does not have the usual association with hypermetropia. In fact, high myopia (> -6.00 D) occurred as frequently as hypermetropia. An intermittent bilateral convergent strabismus was noted in several of these high myopes. Lowe[29] postulated that vision in these patients was restricted to near objects and secondary muscle changes developed. However, no abduction weakness was noted in this study. Surgical correction of the muscle deviations in Down's syndrome is rarely indicated.

There has been no explanation for the prevalence of strabismus in Down's syndrome. Possibly a combination of factors such as decreased fusional capacity, decreased visual resolution capacity and a failure to develop an adequate accommodative convergence mechanism may be responsible.

THE IRIS

The irides of 74 mongoloid and 88 control patients were examined with direct illumination and with the slit lamp for evidence of peripheral speckling and thinning of the iris stroma.

BRUSHFIELD SPOTS

Speckling of the iris was actually first described in normals by Wolflin in 1902[40] and later associated with Down's syndrome by Brushfield[8] in 1924. Brushfield spots are white to yellow, slightly raised, discrete pinpoint to pinhead sized areas in the iris periphery. Sometimes the spots may appear confluent. Generally, they form an even concentric ring but may also occupy only a portion of the iris periphery or may be scattered irregularly in the mid and peripheral zones of the iris (Fig 5). Past studies have shown the incidence of Brushfield spots in Down's syndrome to vary widely from 50% to 90% and to be more common in blue and hazel colored eyes than brown

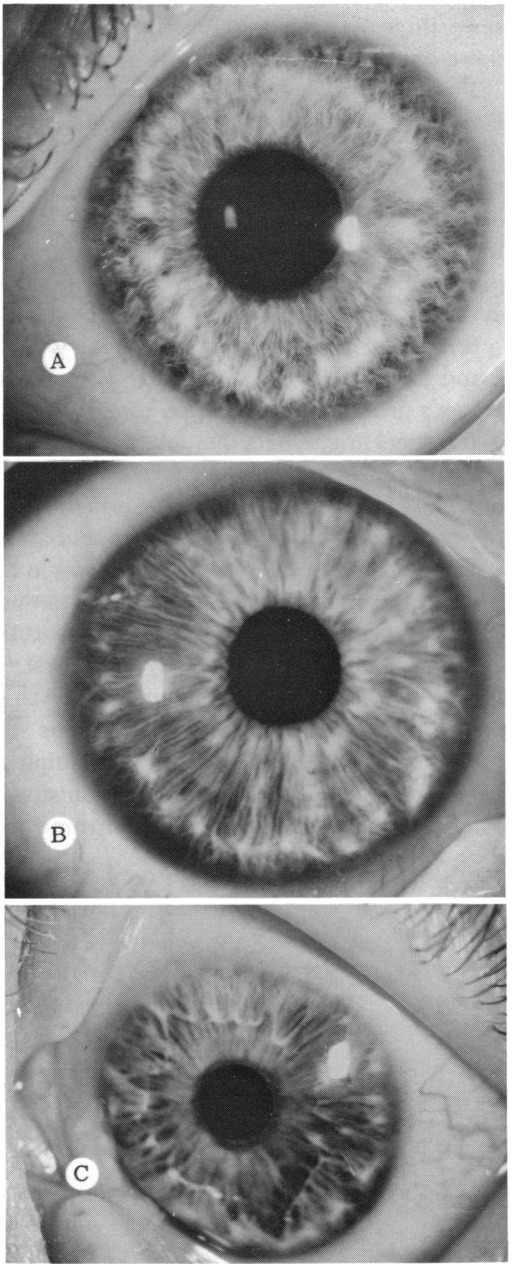

FIGURE 5
A: Brushfield spots in mid zone of iris in blue eyed mongol. B: Irregular iris speckling; discrete and confluent spots, located in peripheral one-third of iris in Down's syndrome. C: Speckling scattered in mid and peripheral zones of iris in Down's syndrome.

eyes.[25,29,41,42] Wallis[41] felt that all Down's newborns had Brushfield spots since their eyes were blue. The spots subsequently became invisible in those eyes that acquired brown pigmentation.

In this study a patient was considered positive for the finding of Brushfield spots if the speckling formed a partial (at least 90°) or complete ring in one or both eyes. Brushfield spots were present in 44 of 74 or 59% of mongols and 9 of 88 or 10% of controls (Table XII). Speckling was found to be more common in blue and hazel eyes in both groups, less common in irregularly brown pigmented eyes and never found in deeply and evenly pigmented brown eyes. In irregularly pigmented brown eyes and in hazel eyes, the spots tend to be less prominent and yellow white in color (Fig 6).

Strikingly, 95% of Down's persons with blue eyes in this study were found to have Brushfield's spots. The occurrence of iris speckling in the Down's group had no relation to age, IQ or sex predilection.

Iris speckling was further analyzed as to the position of the spots on the iris surface. The spots were located in the peripheral one-third or mixed mid and peripheral zones of the iris in 38 of 44 Down's patients (86%) while the remainder were located in the mid-zone.

All speckling in the control group was in the peripheral one-third of the iris and the spots tended to be less prominent (Fig 7).

Two mongols connected with this institutional population died and the eyes were obtained at autopsy. The first, a 54-year-old highly myopic female died of congestive failure. She was part of the 10 year follow-up group but died prior to the onset of this study. She was blue-eyed with prominent Brushfield spots, iris thinning and cataracts. A comparison between the clinical appearance and histopathology was possible (Fig 8). Microscopic examination of trichrome stained sections showed the

Table XII: Incidence of the speckled iris phenomena in Down's and control groups in relation to eye color.

	Down's	Control
Blue	33 of 35 95%	7 of 35 30%
Hazel	6 of 9 67%	2 of 14 14%
Brown	5 of 30 17%	0 of 39 0%
Total	44 of 75 59%	9 of 88 10%

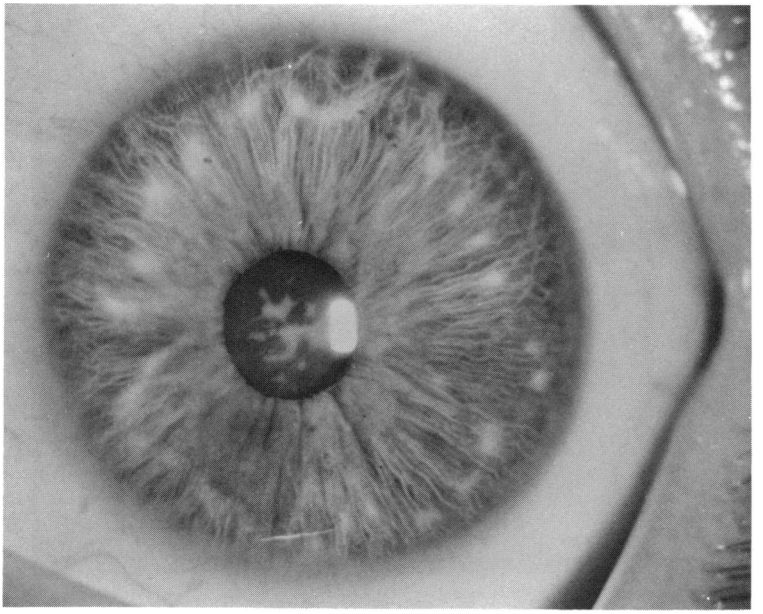

FIGURE 6
White and yellow spots in irregularly brown pigmented mongol iris.

Brushfield spots to be a condensation of collagenous tissue in the iris stroma. Thinning of the peripheral iris stroma was also apparent. These findings are similar to previous histopathology reports.[42,43]

The second patient was a 56-year-old female who died of pulmonary emboli complicating a viral pneumonia. The patient died after the completion of this study. The irides were also blue and cataracts and iris stromal thinning were diagnosed clinically. Microscopic examination again revealed a condensation of collagenous tissue in the iris stroma corresponding to the area of the Brushfield spots (Fig 9). Thinning of the iris stroma was not apparent.

These specimens dramatize the minimal histopathology findings in the iris compared to the clinically apparent Brushfield spots.

The most definitive study of Brushfield spots was done by Donaldson[42] using photography and ten power magnification. Donaldson found iris speckling in 85% of mongoloids and 24% of normals, an increased frequency in both groups as compared with this study. Donaldson's study found Brushfield spots to be more common in the mid-zone of the iris in Down's syndrome while in this study they were found to be more common in the

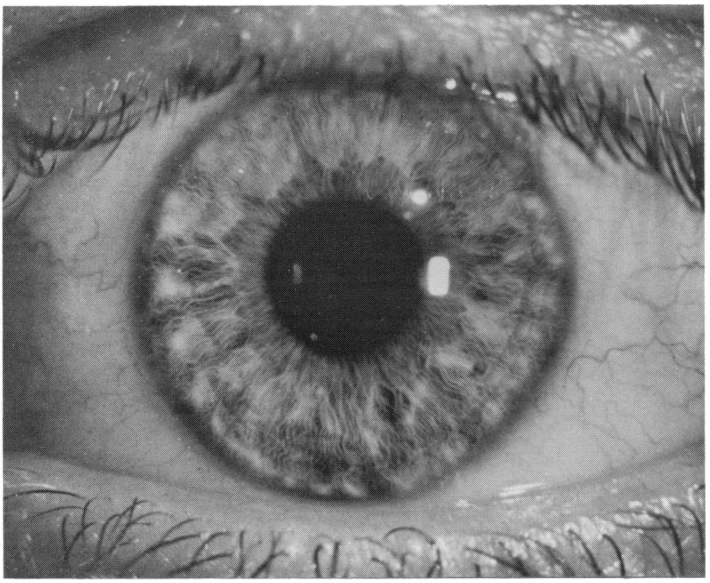

FIGURE 7
Less prominent peripheral iris speckling in normal individual.

peripheral one-third. The differences between these studies can be attributed to Donaldson's use of magnification and photography and the requirement of this study that the spots appear in at least a partial concentric ring. Exact zonal location tended to be difficult as many of the spots appeared to be at the junction of the middle and peripheral thirds of the iris. Those in the junctional area were counted as being in the peripheral portion. Slit lamp examination actually appeared to confuse rather than help the classification of patients as being positive or negative for Brushfield spots.

The etiology of Brushfield spots remains unknown. The advent of chromosomal studies confirming the presence of Down's syndrome has reduced the clinical importance of Brushfield spots as a diagnostic aid.

IRIS THINNING

A paucity or hypoplasia of the iris stroma was first described by Lowe[29] and thought by him to be even more characteristic of Down's syndrome than iris speckling. Thinning of the iris is a difficult feature to evaluate clinically. Characteristically, there is a decrease in the fine interconnecting stromal

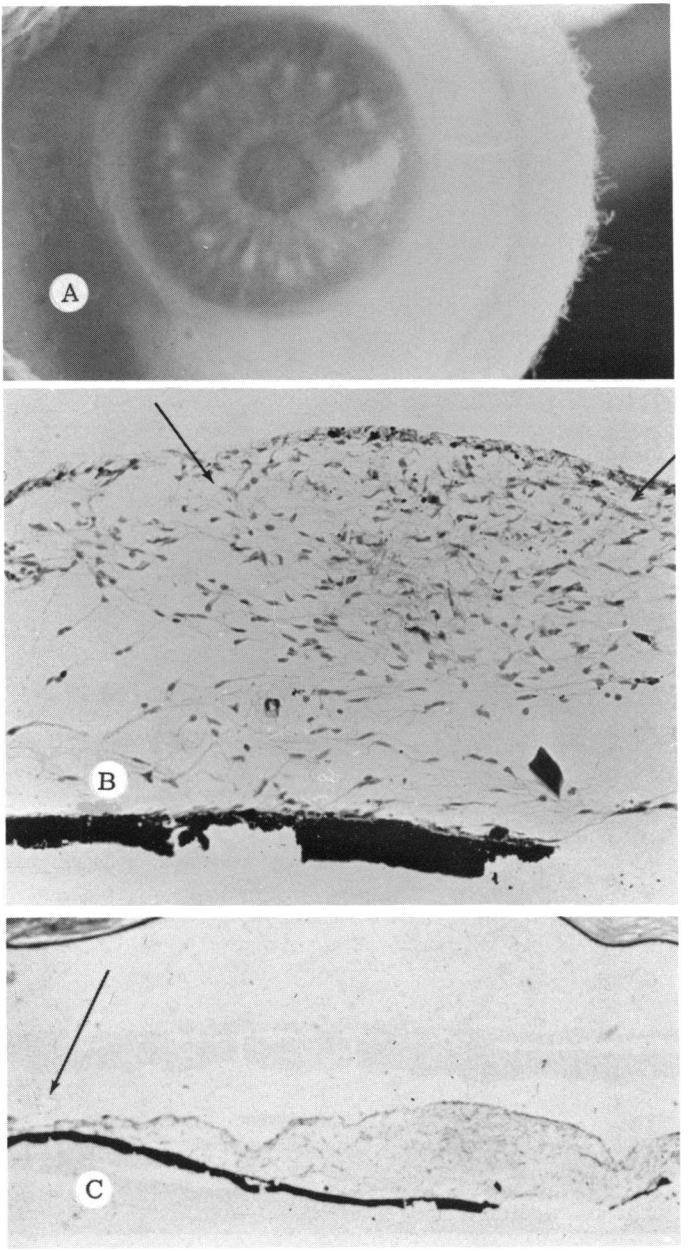

FIGURE 8

A: Mid iris speckling in post-mortem eye removed from 54-year-old mongol. B: Histopathology of iris using trichrome stain showing condensation of collagenous fibers in iris stroma corresponding to area of Brushfield spot (arrows). C: Thinning of iris toward periphery (arrow).

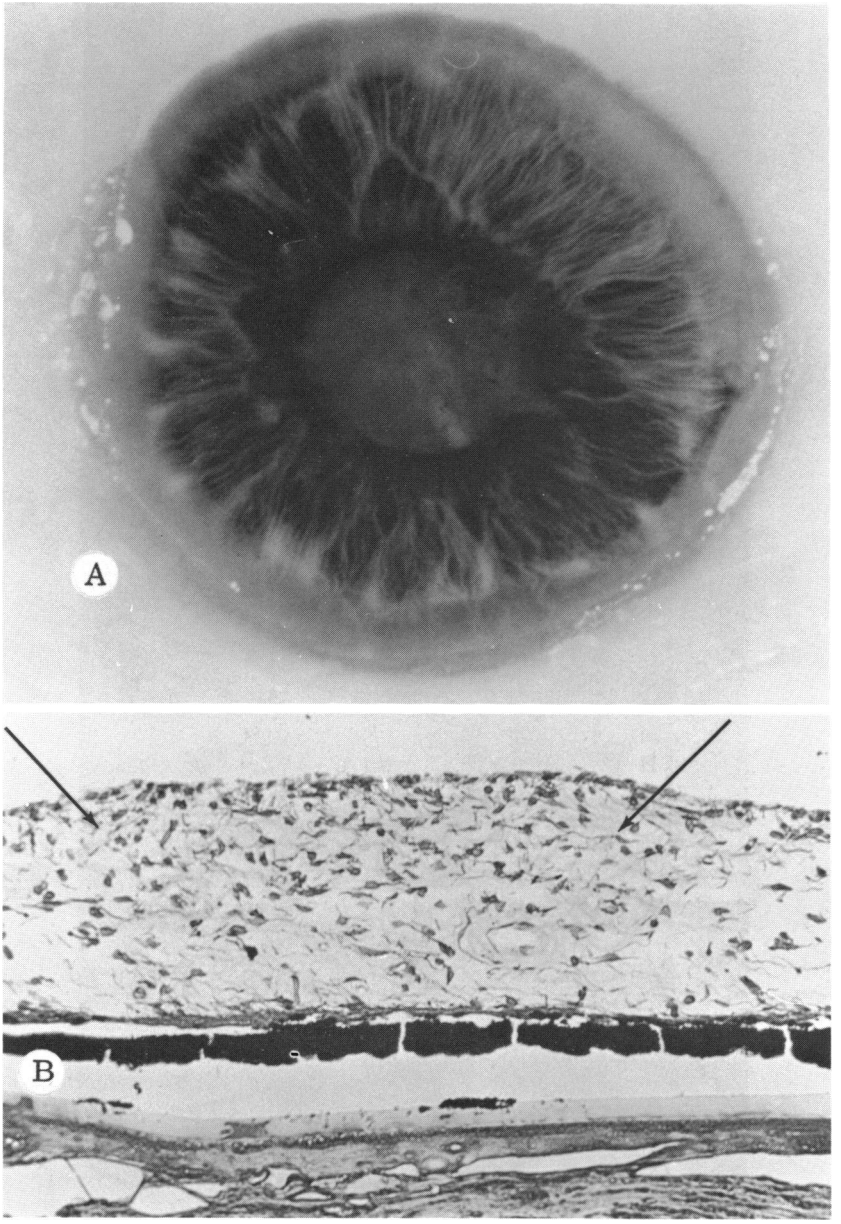

FIGURE 9

External appearance A: Left eye of 56-year-old blue eyed female mongol with peripheral Brushfield spots. B: Histopathology using trichrome stain showing condensation of collagenous tissue in iris stroma (arows). Although iris thinning was seen clinically none was apparent histopathologically.

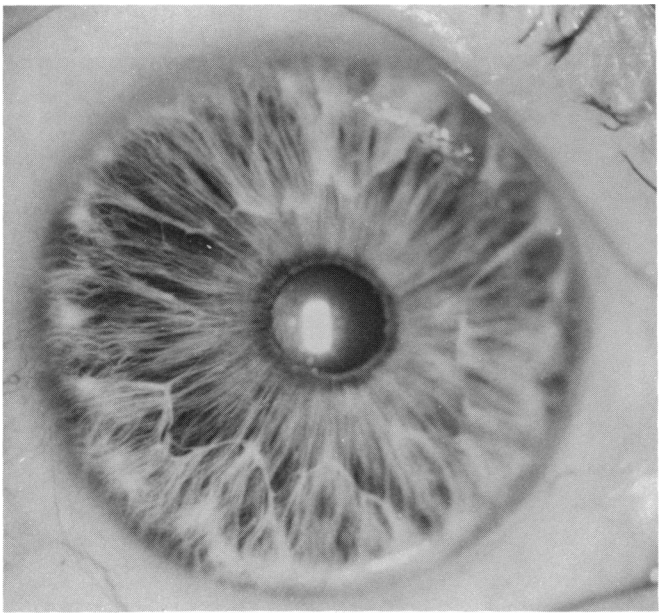

FIGURE 10
Iris thinning with loss of fine interconnecting stroma but with preservation of the radial strands and thicker superficial strands. The pigment epithelium could be seen beneath the radial strands on slit lamp examination.

strands, decreased stromal pigment in brown eyes and increased visibility of the underlying pigment epithelium. These findings are more prominent in the mid zone of the iris and tend to be diffuse in blue eyes and patchy in hazel and light brown eyes (Fig 10). Brushfield spots may be seen in the patchy areas of thinning in brown eyes, giving credence to the theory that speckling is less in brown eyes simply because the spots are not visible due to covering pigmentation (Fig 11). A decrease in the fine iris stroma may also occur in the very peripheral portion of the iris, and when this exists in combination with Brushfield spots, a prominent dark peripheral ring stands out in contrast to the speckling. However, this ring phenomena may frequently be seen in blue eyes of normal individuals. Occasionally, there is flattening of the iris sphincter ridge and loss of fine stroma in the central iris zone (Fig 12). The sphincter muscle itself may be prominently seen especially with indirect lighting.

Iris stromal thinning was present in 25 of 74 (34%) of mongols examined with the slit lamp as compared with 7 of 88 (8%) of controls (Table XIII). The average age of the Down's patients exhibiting thinning was 35 years and that of the control group 47 years. Iris stromal thinning was found much more commonly in blue eyes in the Down's group and was not present in

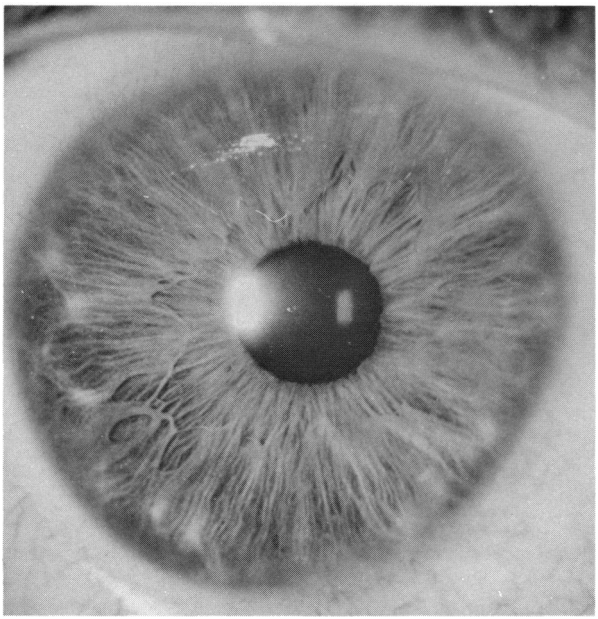

FIGURE 11
Sector loss of pigment and superficial stroma in brown eyed mongol. Brushfield spots can be seen in area of pigment loss.

dark brown eyes. No defects in the iris pigment epithelium were noted in either the Down's or control groups.

Iris thinning in Down's syndrome resembles that seen with aging in normals and this is susbstantiated somewhat by the age differential of those exhibiting thinning between the Down's (average age 35 years) and the control (47 years) groups.

The reason for the increased incidence of iris stromal thinning remains uncertain. Hypoplasia of the iris vascular system has been postulated but definitive proof of this is lacking.[26,27] Possibly, iris thinning may be a part of an early aging process that seems to affect some individuals with Down's syndrome. Iris stromal thinning does not appear to have any clinical significance.

LENS

The first association of lens opacities and Down's syndrome is attributed to Pearce, Rankine and Ormond in 1910[44] while the first slit lamp observation was reported by Koby in 1924.[45] Numerous studies have emphasized the frequency of lens opacities in mongoloid patients, most recording an inci-

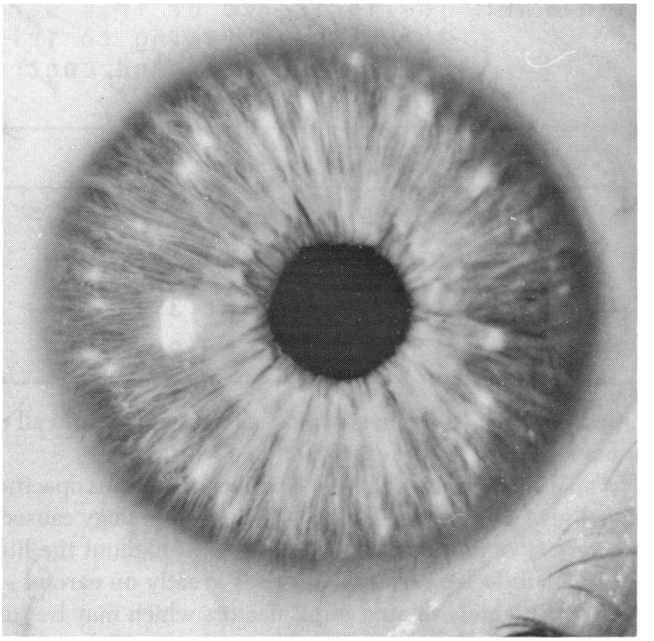

FIGURE 12
Marked loss of iris stroma, flattening of sphincter ridge with prominent visibility of sphincter muscle. Discrete Brushfield spots scattered in mid and peripheral zones of iris in Down's syndrome.

dence in the range of 25% to 60% or greater.[24,46-48] Apple[49] reported an incidence of 60% to 85% with lens opacities. All reports emphasize the acquired nature of the cataracts, opacities being rare in children and increasing dramatically in frequency after puberty.[50] Two detailed studies bear specific mention. Lowe[29] in 1949 described the lens findings in 52 mongols, 31 examined by slit lamp. He reported the frequency of four specific types of opacities which he considered characteristic of Down's syndrome. Lowe found arcuate lens opacities to be present in 8 of 52 patients, sutural in 14 of 52 patients, flake (smoke gray minute nuclear flecks) in 45 of 52 patients and congenital opacities in 3 of 52 mongols. Lowe considered the arcuate type in the fetal nucleus to be the most characteristic of Down's syndrome. Ingersheim[51] took exception to this and in his examination of 125 mongoloids described five categories of lens opacities: punctate, cerulean, sutural, various combinations and dense cataracts possibly of congenital origin. However, some cataracts of the senile type were eliminated from Ingersheim's study. The punctate (cortical and ceru-

Table XIII: The incidence of iris stromal thinning according to iris color in Down's and control groups.

	Down's	Control
Blue	21 of 35 (60%)	5 of 35 (14%)
Hazel	1 of 9 (11%)	0 of 14 (0%)
Brown	3 of 30 (10%)	2 of 39 (5%)
Total	25 of 74 (34%)	7 of 88 (8%)

lean) opacities were felt to be most typical. Ingersheim found all mongols over 21 to have some form of lens opacity.

Studies comparing the incidence and classification of lens opacities suffer several difficulties. There is some confusion in terminology caused in part by the large variety of lens opacities described throughout the literature. The finding of a subtle lens opacity depends greatly on careful slit lamp examination with a widely dilated pupil, factors which may be somewhat variable, particularly in this patient study population. The quantitation of findings is extremely difficult. In addition, large variations have been reported in attempting to document the incidence of lens opacities in the normal population.[52]

The lenses of 74 Down's, 88 control and 88 consecutive office patients were examined with the slit lamp after cycloplegic pupil dilation. Lens

Table XIV: Miscellaneous lens opacities in Down's, office and control groups. These changes were found without other flake-like or senile types of opacities being present.

	DOWN'S	CONTROL	OFFICE
Arcuate	1	1	
Anterior Polar	1		
Sutural	1	1	2
Fine Nuclear Flakes	2		1
Post. Cortical Plague			1

opacities were classified into two basic categories for comparison. The first group was termed flake-like opacities and included discrete or coalescent opacifications in sufficient quantity to be prominent throughout a specific lens area. Cerulean and coronary cataract types were included in this category. The second group was the senile type of opacities including cortical spicules, nuclear sclerosis and posterior subcapsular opacities. Other opacities within the lens including arcuate, sutural, isolated vacuoles, various singular punctate spots and the commonly encountered dust-like opacities were not included in the main grouping because of the variability in the adequacy of slit lamp examination in this study population, lack of visual interference and the unlikeliness of progression in these types. The incidence of these lens changes was not significantly different between the Down's, control and office groups (Table XIV).

Forty-one of the 74 (55.4%) patients with Down's syndrome demonstrated some form of lens opacity (Table XV). Twenty-seven of 74 mongols (36.5%) were found to have multiple large discrete or coalescent flake-like lens opacities (Fig 13). Those with additional senile lens changes were not counted in this group. This compared with 5 of 88 (5.7%) of the control group and 3 of 88 (3.4%) of office patients. The average age of those demonstrating flake opacities was 36 years in the Down's group, 36 years in the control group and 59 years in the office patient group. Flake opacities were most commonly demonstrated in the peripheral cortex but were often present in the anterior and posterior polar areas and, when coalescent, formed a star (Fig 14). In the latter areas, they tended to occur in the deeper portion of the cortex, near the cortex-nucleus junction. Occasionally, a discrete flake was present in the superficial nuclear area.

Fourteen of 74 (18.9%) Down's patients were found to have significant senile cataracts in one or both eyes (Table XV) (Fig 15). This compares with 8 of 88 (10%) control and 5 of 88 (5.7%) office patients. The average age of those mongols with senile cataracts was 48 years while that of the control group 50 years and the office patient 54 years.

Table XV: Comparison of lens opacities in Down's, control and office patient groups.

	Flake Opacities	Average Age	Senile Opacities	Average Age
Down's	27/74 (36.5%)	36	14/74 (18.9%)	48
Control	5/88 (5.7%)	36	8/88 (10%)	50
Office	3/88 (3.4%)	59	5/88 (5.7%)	54

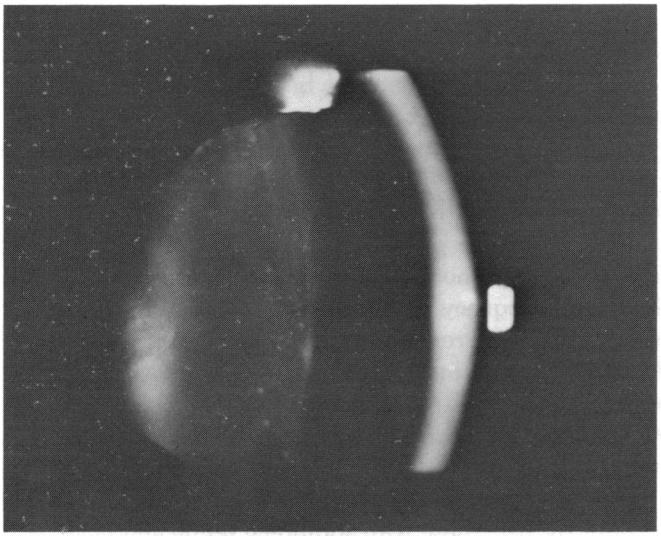

FIGURE 13
Discrete deep cortical flake opacities in right lens of 42-year-old mongol. Lens noted to be clear 11 years previously.

The incidence of lens opacities in younger Down's persons was low. Flake-like opacities occurred in only 2 of 20 mongols ranging in age from 15-22 years (13%) while 9 of 20 in the 36-50 age group (45%) had flake-like or senile type opacities (Fig 16). This incidence increased to 21 of 30 (70%) of mongols ages 36-50 and dropped slightly to 6 of 9 (67%) in the 51-65 year group.

This study indicates that lens changes in Down's syndrome are frequent but by no means distinctive in type. Flake-like opacities are the most common. Senile cataracts occur more frequently at a younger age in this group. Ten of 14 mongols demonstrated senile opacities in their 4th decade. This is most likely another manifestation of the early aging process that is apparent clinically in some mongols. However, several of the Down's group in the 40-50 year age range exhibited perfectly clear lenses. This is in contradiction to several previous studies.

Cataract surgery in mongols has been risky because of the difficulties encountered in controlling postoperative activity. One study reported cataract surgical complications as the leading cause of blindness in Down's syndrome.[53] The decision to perform surgery in this group should especially be based on functional impairment. Many mongols appear to go about their daily routines despite considerable lens opacification. However when

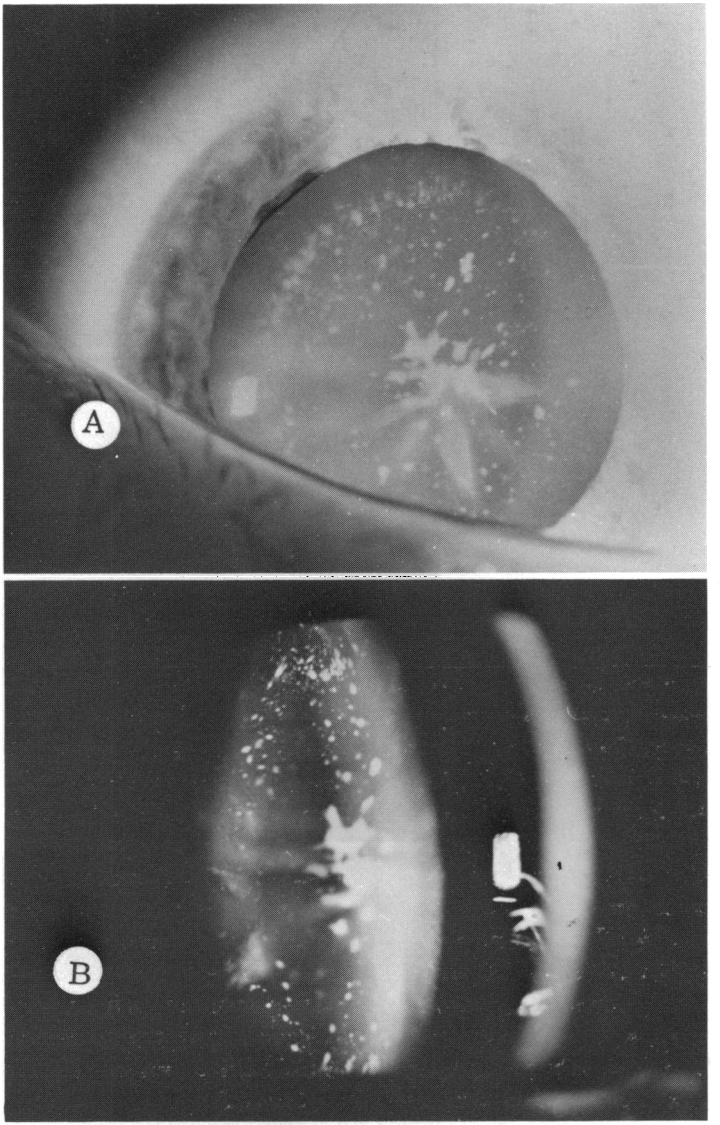

FIGURE 14
Discrete flakes in cortex of 26-year-old Down's male and incomplete cortical scar shaped opacity A: full illumination, B: slit photo showing clear nucleus.

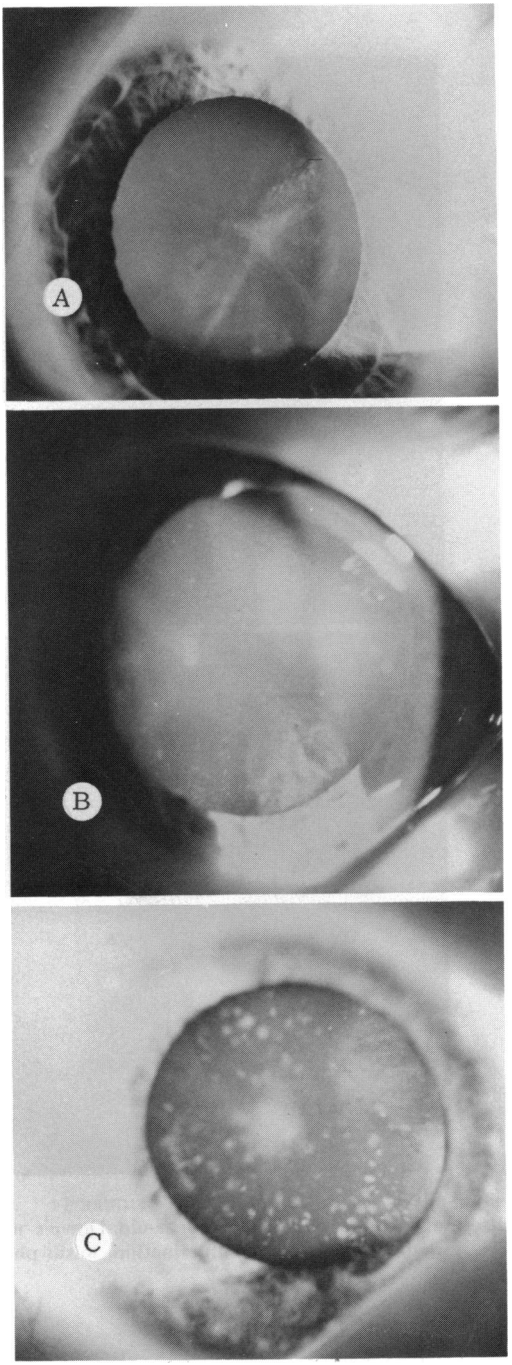

FIGURE 15
Senile lens changes in Down's syndrome. Cortical opacification in A: 46-year-old mongol without significant flake opacities. B: Cortical and nuclear opacities in left lens of patient in Fig 13. Lens noted to be clear 11 years previously. C: Cortical and flake opacities in 47-year-old Down's female with dense cataract in opposite eye. Progression noted OU over 10 year period.

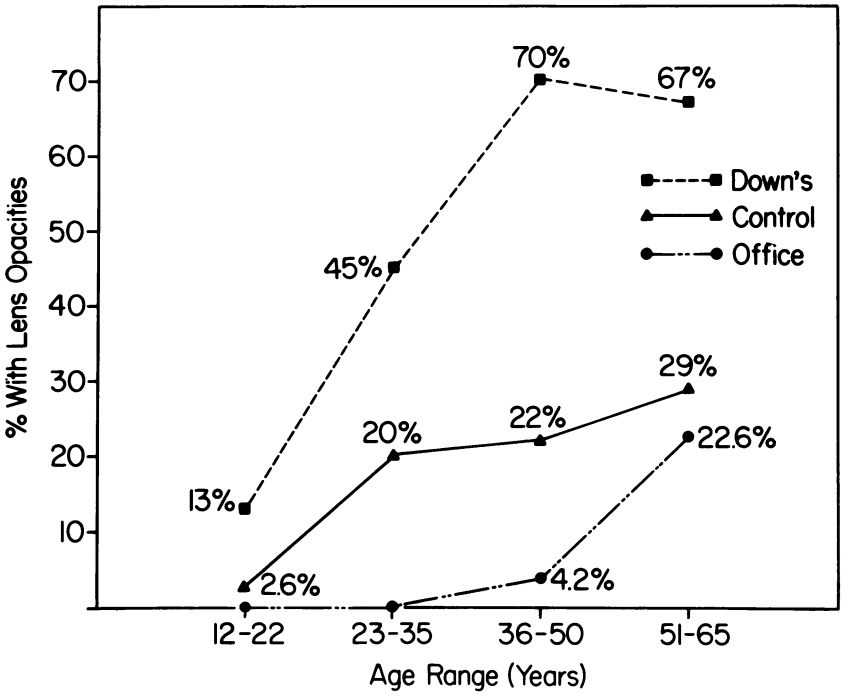

FIGURE 16
Comparison of the incidence of lens opacities (flake and senile combined) by age group in Down's, control and office patient groups.

the cataracts become sufficiently dense that the patient can no longer perform routine daily functions, surgery is indicated.

Two mongols (age 46, 64) in this study developed bilateral mature cataracts and cataract surgery was performed in one eye of each patient. The surgery was done on an out-patient basis under general anesthesia and with a familiar attendant standing by in the immediate pre- and postoperative periods. Both did well and returned to their daily routines (stealing food, TV, etc) despite their refusal to wear an aphakic correction. Typical cataractous changes were present on histopathologic examination of the lenses.

TEN YEAR FOLLOW-UP

Fifty of the 75 persons in this study with Down's syndrome had a complete ocular examination, including slit lamp observation with dilated pupils, ten or more years ago by the author. The average age of this group at the time of the present study was 40.2 years and the average follow-up period was 11.3

Table XVI: Patient population data in ten year follow-up study of lens opacities in 50 mongols.

	Total	Sex	Mean Age	Age Range	Mean Follow up	Follow-up Range
Down's	50	20F 30M	40.2yrs	18-64	11.3yrs	10-14yrs

years (Table XVI). Twenty-six of these 50 mongols had prominent lens opacities of either the "flake" or the senile varieties at the time of initial examination and were included in the previous portion of this study. Two persons with previously clear lenses were found to have developed opacities during the follow-up period. One, age 46, showed marked cortical type cataracts in each eye and the other, age 42, developed significant flake-like opacities throughout the lens cortex OU.

Fourteen of the 26 Down's persons with previous lens opacities appeared to have progressed in the density of their opacities over the follow-up period. Three mongols progressed to a bilateral "no red reflex" status, and a successul cataract extraction was performed in two of these patients and surgery in the third is anticipated. Three additional mongols progressed to a "no red reflex" condition in one eye with moderate changes in the other eye but with no observable functional impairment. The average age of these six patients was 47.8 years.

Although this follow-up study is not control matched, it would appear that those with Down's syndrome tend to develop lens opacities at an earlier age and these opacities tend to be progressive.

RETINAL VESSELS IN DOWN'S SYNDROME

Williams et al[54] first called attention to the fact that persons with Down's syndrome appeared to have more retinal vessels crossing the disc margin than normals. These investigators found an average of 17.7 vessels crossing the disc margin and extending for at least one disc diameter in Down's syndrome as compared with 13.4 vessels in normals. In addition, mongols appeared to have a spoke-like distribution of the vessels radiating from the papilla. This work had not been repeated prior to this study.

Fifty-five mongols and fifty-five control patients had fundus photographs of sufficient clarity to evaluate the number of vessels crossing the disc margin. A hand-held Kowa camera was used for retinal photography. No effort was made to match sex distribution. Only vessels extending for more

than one disc diameter beyond the disc margin were counted. As in the William's study, vessels branching at the disc margin were counted as two vessels. Those cases with congenital heart disease or significant cardiovascular disease were eliminated from this portion of the study. Disc vessels were not as easily counted as might be imagined. Overlapping of vessels at branching sites and indistinctness of the distal portion of small vessels presented the investigator with some degree of interpretation. Fundus slides of both Down's and control groups were mixed randomly in double blind fashion. The vessels were counted on two separate occasions by two observers. If three of these four recordings matched, the figure was recorded as the final vessel number. In those remaining slides a fifth count was taken which resulted in matching at least three of the five counts in all cases. The code was then broken.

The number of vessels in the Down's group ranged from 13 to 25 while the controls ranged from 10-19 vessels. The mean for the Down's group was 17.9 vessels compared with 14.2 for control (Table XVII) (Fig 17). The difference in the vessel number between the two groups is significant to the P level of .05 and is very similar to the results in the William's study. Distribution curves showed a wider spread in mongols with peaks at 17 and 19 vessels while the control group displayed a sharp peak at 14 vessels (Fig 18). In the Down's group, 54.5% had 18 or more vessels crossing the disc margin while only 5% of controls displayed such a picture.

The reason for increased retinal vessels crossing the disc margin in mongols is unclear. Many of the mongoloid fundi appeared to have a spoke-like pattern of vessels radiating from the disc although this was not numerically evaluated (Fig 19). There was no correlation between IQ and the number of disc vessels in mongols. Those with 17 or less vessels had an average IQ of 32.8, and those with 18 or more, an IQ of 34.4, both comparable to the average of the entire Down's group IQ of 32.6. Fundus

Table XVII: Data comparing the number of retinal vessels crossing the disc margin and extending for one disc diameter in Down's and control groups.

	Total	Sex	Mean Vessels Crossing Disc	S.D.	Level of Significance
Down's	55	32M 22F	17.9	2.76	P .05
Control	55	29M 26F	14.2	2.27	P .05

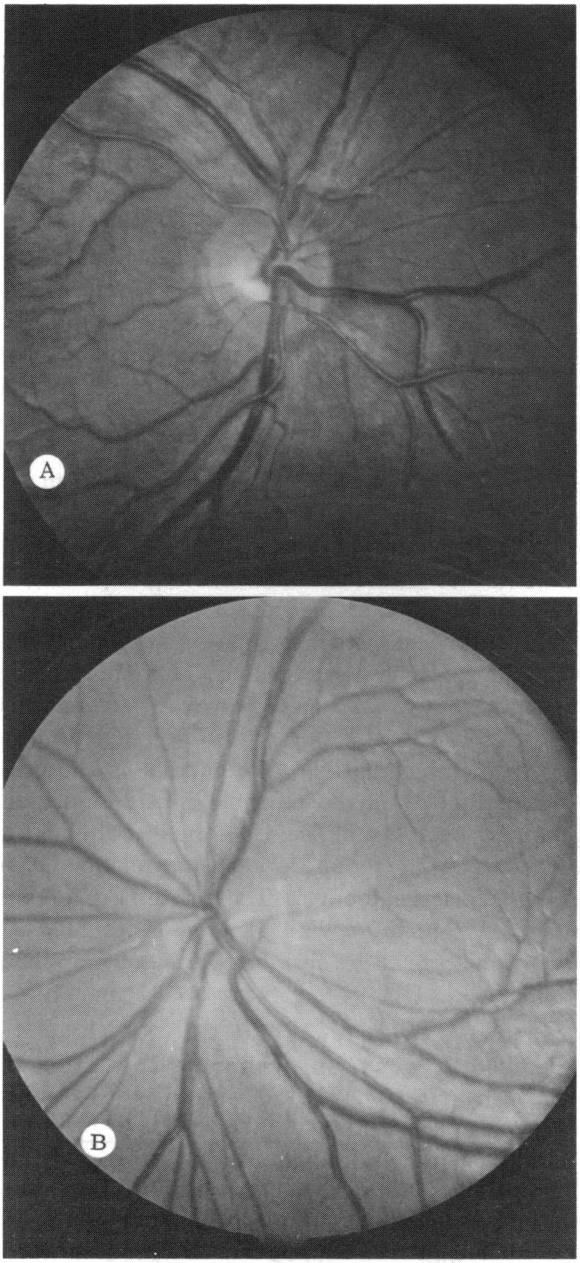

FIGURE 17

A: Control group fundus displaying 14 vessels crossing disc margin and extending for 1 disc diameter. B: Down's fundus displaying 18 vessel pattern.

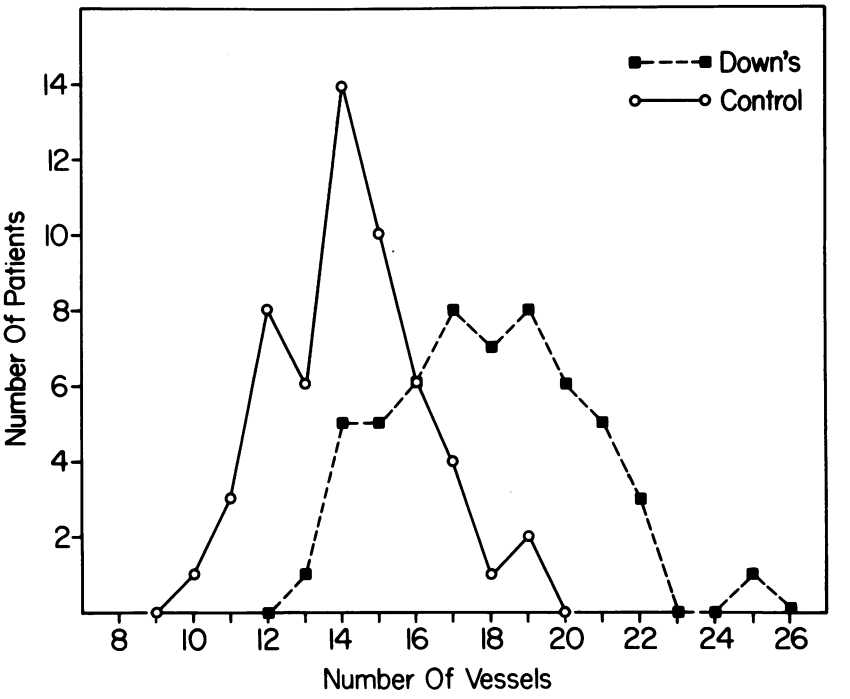

FIGURE 18
Graphic comparison of retinal vessels in control (solid line) and Down's (dotted line) groups.

photographs of several in the Down's group with lower IQ's could not be included in the retinal study because of poor quality of the slides. The cup-disc ratio appeared less in the Down's group and the central vessels branched deeper within the papilla, but these observations were difficult to document. No instances of glaucomatous cupping were seen.

There is no apparent clinical significance to the increased number of retinal vessels crossing the disc margin in those with Down's syndrome.

SUMMARY

The ocular findings in 75 institutionalized persons with Down's syndrome were compared with 88 mentally retarded individuals. Ocular parameters evalued were: external ocular profile, refractive error, strabismus, iris, lens and retinal vessels. In the area of refractive error and the lens these groups were compared with 88 office patients.

A 10 year follow-up documenting lens changes was done on 50 mongols.

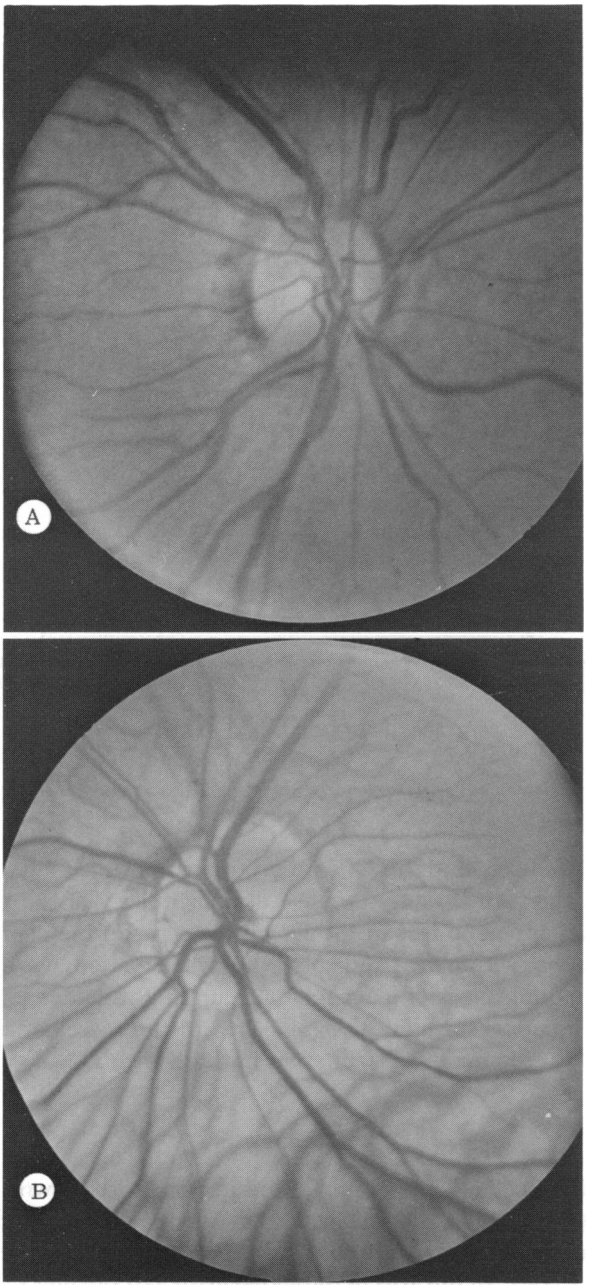

FIGURE 19
Spoke-like distributions of retinal vessels in Down's syndrome. A: 21 vessel pattern fundus, B: 25 vessel pattern in highly myopic mongol.

Epicanthal folds, long associated with Down's syndrome, were present in only 17.3% as compared with 3.6% in the control group. The characteristics of the fold in mongols appears to be distinctly different from those found in persons of oriental heritage. Obliquely upper and outward slanting palpebral fissures were present in 83% of the Down's group and is the feature most responsible for the facial appearance in Down's syndrome. The interpupillary distance was narrower in mongols but when this was considered in relation to the head circumference (interpupillary distance/head circumference ratio) there was no significant difference between the two groups. Blepharitis, nystagmus, lacrimal obstruction and keratoconus were found more commonly in the Down's group.

Those with Down's syndrome were found to have much greater degrees of refractive error, particularly high myopia, than those in the control group or in the office patient group.

Strabismus was present in 41.3% of those with Down's syndrome compared with 15.9% in the control group. All but one mongol with strabismus had esotropia. However, there did not appear to be the usual relationship between the esotropia and hypermetropia. Significant amblyopia was present in only 3 of 23 testable strabismic mongols.

Brushfield spots of the iris were present in 59% of mongols and 10% of controls while iris stromal thinning was noted in 34% of mongols and 8% of controls. These associated features of Down's irides are interesting but of little clinical significance.

Cataractous lens changes were found to occur much more frequently in Down's syndrome. However, while no specific type of opacity appeared to be singularly characteristic, flake-like opacities in the deep cortex, especially in the periphery of the lens were the most common findings. Mongols appeared to develop senile cataracts at an earlier age than those in the control group.

A ten year follow-up study of 50 individuals with Down's syndrome was reported. Definite progression of lens opacities was found in 14 of 26 mongols with previously existing lens changes. A total of eight eyes in six mongols progressed to a "no red reflex" lens status. Two additional persons with initially clear lenses developed opacities. Two patients underwent successful cataract extraction. Cataract surgery should be delayed until significant impairment of routine daily function is observed.

More retinal vessels were observed crossing the optic disc margin in Down's syndrome than in the control group. This created a spoke-like vessel appearance. No instance of glaucomatous cupping was observed.

Although many of these ocular characteristics may be found in non-mongoloid persons, the frequency of occurrence and the unique combinations remain distinctive of Down's syndrome.

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