APLASIA OF THE OPTIC NERVE

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APLASIA OF THE OPTIC NERVE (AON) IS A RARE OCULAR ABNORMALITY. Approximately 33 cases have been reported in the literature.[1-16] Following are the clinical and laboratory findings in another patient.

CASE REPORT

A girl, born 2 weeks after term following an uneventful pregnancy, had a birth weight of 8 lb 3oz. At birth her right eye was noted to be small and turned nasally. Family history was negative for ocular or other birth defects. The mother had been exposed to acetone at work during pregnancy. Eye examination at age 2 months documented right microcornea, right esohypotropia, and an absent right optic disc and retinal vessels. The left eye appeared normal. Surgery was performed to correct strabismus at age 4 years and was repeated at age 18 years.

At follow-up examination at age 23 (Fig 1), the patient was noted to be intelligent and in good health, she was not taking any medications and had no known drug allergy. Physical examination was unremarkable. On eye examination, symmetric bilateral eyelid ptosis was evident. Right abduction was restricted. The right pupil did not react to direct light stimulation but constricted sluggishly when the left eye was stimulated by light. The left pupil reacted normally to direct stimulation but showed no response to light stimulation of the right eye.

Both corneas were clear: the right horizontal diameter was 10.5 mm and the left 12.0 mm. Anterior chambers were deep and clear, both irides were normal, and lenses were clear and of normal shape. Gonioscopic examination

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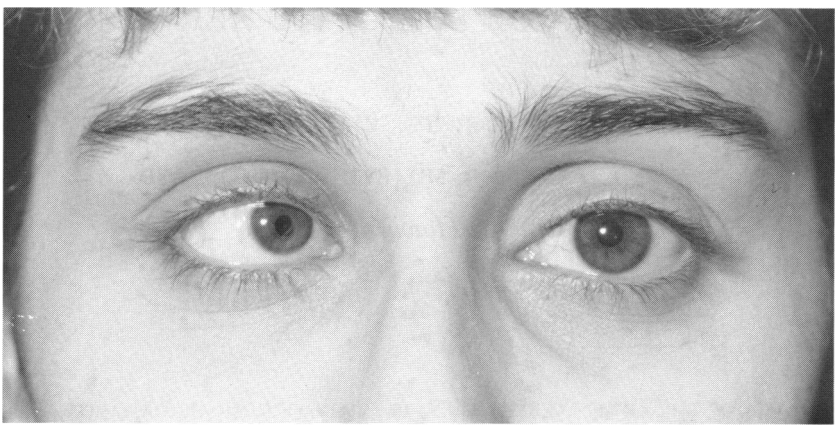

FIGURE 1
Right microcornea and esotropia in 23-year-old patient.

showed that iridocorneal angles were open and normal.

Right visual acuity was no light perception; left vision was 20/20 at near and distance, with +1.75 sphere correction. The intraocular pressure was 16 mm Hg OU. The right vitreous was clear, however a vitreous strand passed from the posterior pole toward the superior periphery. The strand did not attach to the posterior lens surface. No right optic nerve or retinal vessels were present (Fig 2). Only bare sclera was present in the region where the optic nerve should be located. Geographic areas of increased and decreased retinal pigment epithelium (RPE) pigmentation were present. Choroidal vessels were prominent in areas of decreased RPE. The left vitreous was clear. The left disc was small, with a C/D of 0.0. The left macula, vessels, and periphery were normal.

Results of a Giemsa banded chromosome study were normal: 46, XX. The left peripheral visual field was normal. There was no defect to suggest an abnormality in the chiasm.

The B-scan ultrasound showed no right optic nerve shadow. The external wall of the globe was round, and there was no deformity suggesting a staphyloma. On A-scan ultrasound, the mean axial length was 24.70 mm OD and 22.72 mm OS.

The electroretinogram (ERG) in the right eye was flat under photopic and scotopic conditions. The left ERG was normal under photopic and scotopic conditions. The oscillatory potentials and flicker fusion response were absent OD and normal OS.

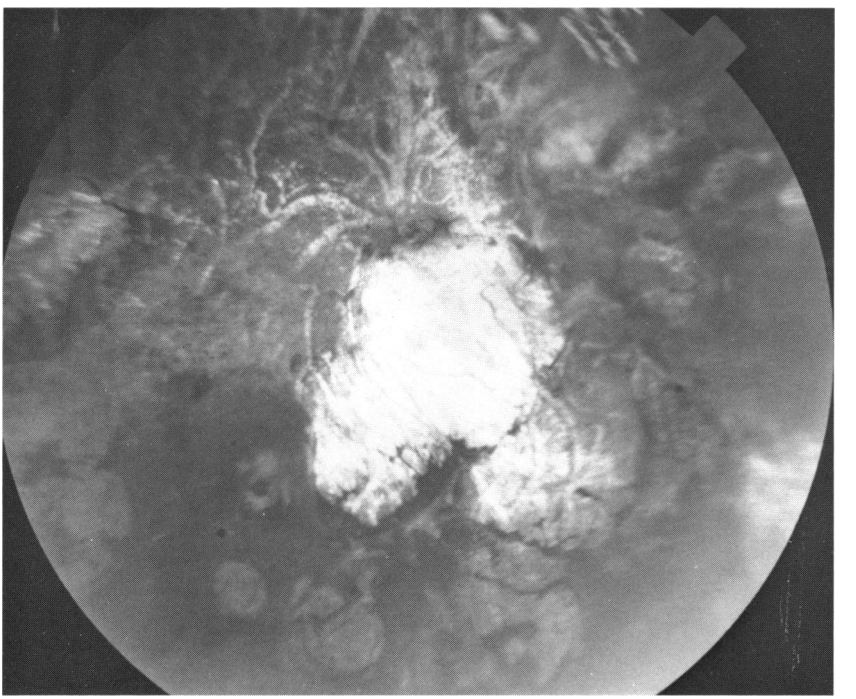

FIGURE 2
Fundus photograph of retina OD demonstrating lack of retinal vessels and optic nerve. RPE pigmentation is irregular.

The right electro-oculogram had an Arden ratio of 1.0 OD (abnormal) and 3.41 OS (normal).

On magnetic resonance imaging, no recognizable right optic nerve was demonstrated (Figs 3 and 4). The right globe was normal in appearance. The left globe and optic nerve were normal. The remaining ocular and cerebral structures were normal.

COMMENT

Aplasia of the optic nerve is characterized by an afferent pupillary defect, vision of no light perception, absent optic disc, absent optic nerve and absent retinal vessels. According to these criteria, 33 case reports accurately describe aplasia. Numerous case reports in the ophthalmic literature misidentify aplasia and really describe hypoplasia instead.[7]

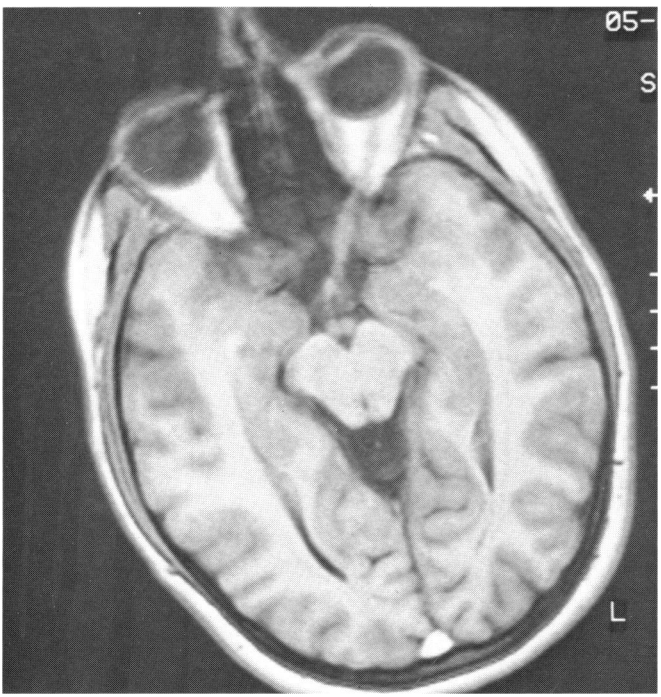

FIGURE 3
Magnetic resonance imaging, axial section demonstrating intact left optic nerve and absent right optic nerve.

Family history is not consistent with mendelian inheritance, and results of chromosome examinations are normal (as in this case).[11,12] Males and females are similarly affected (ratio, 11:16). Pregnancies are described as normal, but environmental factors might be a consideration since clinical histories from case reports mention exposure to a viral-like episode during the first trimester,[11] acetone exposure (as in this case), or smoking during pregnancy.[13] Since aplasia may be produced experimentally, environmental factors may contribute to AON.

Unilateral or bilateral aplasia[3,8,9,12,13] occurs in white, black, and Oriental persons. Microphthalmos[11] or anophthalmos may occur in the fellow eye.

Published reports have described a spectrum of eye abnormalities on the affected side. Frequently, these eyes are microphthalmic and enophthalmic, and the eyelid may be ptotic. Esotropia of the affected eye is com-

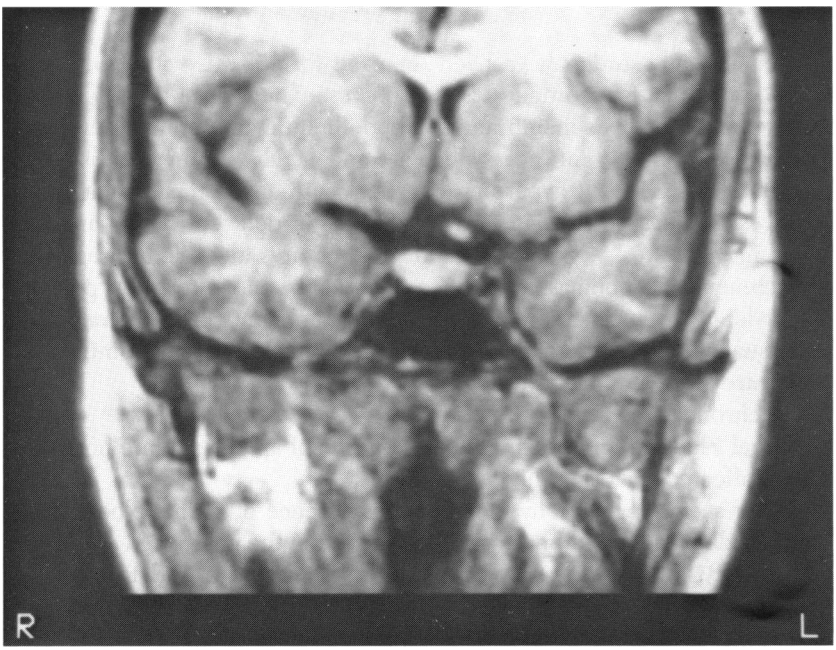

FIGURE 4
Magnetic resonance imaging, coronal section showing left optic nerve superior to pituitary. Right optic nerve is absent.

mon. The corneal diameter is usually small (5 to 10.5 mm). Corneal sensation may be present (as in this case).[7] An immature iridocorneal angle may be present.[8,9] Iris hypoplasia,[8] iris coloboma,[13] or aniridia[11] may occur. The lens may be clear or cataractous.[8,11] The vitreous is usually clear, but a fibrovascular strand may extend from a choroidal vessel toward the lens, representing primary hyperplastic primary vitreous.[8] The retina is avascular. No definite optic nerve is present. The RPE may be grossly abnormal, with geographic areas of hyperplasia, hypoplasia, or normal pigmentation. The choroidal vasculature is easily seen in regions of deficient RPE. No light perception is present in the affected eye, and light stimulation of the eye with aplasia elicits no direct or consensual pupillary response. Light stimulation of the normal eye results in direct and consensual pupillary responses.

Significant extraocular abnormalities are described, resulting in early death in at least six persons.[9-13]

LABORATORY STUDIES

Histopathologic studies have been reported for 25 eyes with AON.[8-11,13] Microphthalmia is recorded in 20 of 25 eyes. The cornea has scleral-type collagen. Descemet's membrane and endothelium are absent. Embryonic iridocorneal angles, anterior synechiae, and patchy iris hypoplasia occur commonly. Persistent hyperplastic primary vitreous, retinal displasia, and rosettes—especially associated with abnormal or deficient RPE—are identified in most eyes. Cystoid retinal degeneration is identified in regions of detachment. Colobomas, anterior to the equator and anterior or posterior staphylomas occur in the majority of eyes. Remnants of the dural sheath are usually identified. Absent or diminished ganglion cells with intraocular axons are observed in all eyes.

All chromosome reports are normal.[11,12]

Visual Fields are not recordable on the side of aplasia and are normal on the unaffected eye (as in this case).

Fluorescein Angiography demonstrates absence of retinal blood vessels on the side of aplasia but normal retinal vessels in the unaffected eye.[7,14, 15]

The ERG wave form may be flat; if present, the A and B waves are diminished.[7,14,15] Electro-oculograms show the Arden ratio is abnormal on the side of aplasia (as in this case).

With A-scan ultrasound the globe is usually small. With B-scan ultrasound a detached retina may be observed,[12] but no optic nerve shadow is visualized in the AON eye.

Plain X-ray can demonstrate a small optic foramen on the side of aplasia.[7] A CAT scan may show the globe and bony orbit to be smaller than normal.[16] Magnetic resonance imaging can document the absent optic nerve on the affected side. The chiasm and lateral geniculate may appear small (as in this case).[16]

Following pattern stimulation of one eye, the amplitude of electrical recording from each of two occipital skin electrodes can permit an estimate of nerve fibers crossing at the chiasm. In one patient with AON, such recordings suggest abnormal crossing with greater-than-normal contralateral fiber projections of the one "normal" nerve, similar to the findings in the albino.[16]

ANIMAL MODELS OF APLASIA OF THE OPTIC NERVE

AON occurs spontaneously in multiple animals species and can be produced by exposing pregnant animals to different environmental factors. Spontaneous AON is reported in blind cats,[17,18] unilaterally in F344 rats,[19] and in Slc Wistar rats.[20]

AON can be induced by treating pregnant rabbits with hypoglycemic sulfonamides[21,22]; by creating folic acid deficiency in pregnant rats[13]; by exposing mice and rat fetuses to x-ray radiation[24,25]; and by treating rabbits at the time of fertilization with actinomycin D.[26]

THEORIES OF AON DEVELOPMENT

True AON is a congenital, nonhereditary anomaly whose origin is still poorly understood. Family histories are not compatible with a pattern of mendelian inheritance, and chromosome studies are normal.

In early reports, retinal and optic nerve dysgenesis is attributed to failure of the mesoderm to enter the fetal fissure and provide vascularization of the retina and nerve tissue.[1,7] Weiter and associates[8] doubt that mesodermal development is defective, because the dural sheath (a mesodermal derivative) is present in most of their cases. They suggest that ventral invagination of the optic vesicle causes nerve fiber misdirection and secondary atrophy. Yanoff and colleagues[9] postulate a primary failure of ganglion cells to develop and send out axons. This results in a lack of induction of mesodermal ingrowth including a lack of retinal blood vessel development. Hotchkiss and Green[10] agree that failure of mesodermal induction secondary to a neuronal defect in the ganglion cell layer is probably responsible for the development of aplasia. They also state that an insult to normal ganglion cell development would cause the same result, and they place the time of insult between the sixth week and fourth month of gestation.

An absent or depressed ERG in eyes with aplasia indicates a more profound retinal dysfunction that merely reduced ganglion cells and axons. Clearly, there must be defects in the RPE, photoreceptor, and bipolar layers to explain diminished A and B waves. A defect in the development of all retinal cells, both functionally and anatomically seems to occur in aplasia of the optic nerve.

The multiple ocular abnormalities accompanying aplasia exhibit one common theme: loss of cells. This is demonstrated by loss of ganglion cells, RPE, and corneal endothelium and by retinal colobomas, iris hypoplasia, and reduced cellularity of the entire eye (ie, microphthalmia).

Over 100 genes are required for normal eye development in the genetic organism *Drosophila melanogaster*.[27,28] The complete absence of a neural connection between the human eye and brain seen in AON patients resembles the *Drosophila* eyes absent (*eya*) mutants.[29] Mutations in the *eya* gene cause a disruption of normal programmed cell death in *D melanogaster* eye development.

The occurrence of massive cell death during otogeny is a phenomenon that has evolved as a part of the normal development of many types of

cells, tissues, and organs.[30] For example, a significant number of neurons in a given population (eg, 20% to 80%) often die normally at a relatively late stage of maturation, with the remaining cells undergoing differentiation and survival. This programmed cell death typically occurs in conjunction with critical differentiation events.

The *eya* gene has been described in *D melanogaster*, where it is required for normal development of the compound eye; it is not ubiquitous. According to Ready and associates,[27] "During the third larval instar, progenitor cells commense differentiation to generate the various cell types. Differentiation is marked by a morphogenic furrow that moves from posterior to anterior across the field of progenetor cells in the eye portion of the eye-antennal imaginal disc." The *eya* gene modulates the differentiation-death decision as the progenitor cells mature. Mutants of *eya* undergo excessive cell death anterior to the morphogenic furrow, rather than proceeding into the pathway of retinal differentiation. *Eya* mutation produces a loss of the external eye morphology and ommatidia; in the brain, the first optic ganglion (lamina) is lost, the second optic ganglion (medulla) is reduced in size, and the lobule and lobular plate show some dis-organization.[29] Reintroduction of a normal eya gene into a mutant individual during the larval stage restores normal eye structure, and reduces death of progenitor cells to normal levels.[29] Function of the *eya* gene appears to be restricted to the eye, but it should be noted that some homozygous mutants of *eya* are lethal. Therefore a function in addition to eye development can be inferred for this gene.

The defects caused by *eya* gene mutation in the *D melanogaster* eye resemble those observed in the human eye with AON: excessive loss of visual cells and their connection to the central nervous system. The *eya* gene is not reported in the literature for mammalian species. However, if *eya* function is conserved between insects and mammals, total or partial absence of ganglion cells and axons in AON could arise from excessive cell death at the time of differentiation caused by an *eya* mutation. If excessive cellular programmed death in mammals were to occur in ocular tissues other that the ganglion cells, other defects, such as hypoplasia of the iris, colobomas of the retina, and reduced corneal endothelium, might occur as a result of an *eya* mutation.

A recently characterized mammalian gene (*sey*) is required for normal eye development but does not appear to be involved in AON.[31] Although *sey* mutations cause lens pit abnormalities, none have resulted in AON. Studies suggest that the *sey* gene is homologous to the human aniridia gene AN2.[32]

We suggest that mutation or inactivation of the *eya* gene offers a possible explanation for the development of AON. Because experimental models that produce AON are known, this hypothesis can be tested. If this interpretation is correct, one could imagine an eya mutant that would have reduced ganglion cells, as in optic nerve hypoplasia.

It is also likely that cases of AON are underreported. Since this patient was evaluated, another young girl with AON has been identified in our community.

ADDENDUM

An animal model in the mouse identified as the ocular retardation mutation, has been characterized by aplasia of the optic nerve, cataract, progressive retinal degeneration, and microphthalmia.[33,34] In this model, some ganglion cells with axons develop but do not leave the globe. During the development a burst of cell death in the retina occurs coincident with optic fissure closure and is followed by progressive retinal degeneration. The increased cell death demonstrated in the mouse model is similar to the increased programmed cell death noted in the *eya* mutation. The ocular retardation mutation may represent a mammalian homologue of *eya* and would be worthwhile investigating.

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DISCUSSION

DR MYRON YANOFF. It is indeed a pleasure to discuss the interesting paper by Dr Howard and associates on unilateral, true aplasia of the optic nerve (AON). IN the patient described, it seems that the only abnormalities found when she was examined at age 23 were bilateral ptosis and anomalies of the right eye, most

strikingly absence of the optic nerve and retinal vessels. Systemically, she appeared to be normal. It makes sense that on magnetic resonance imaging no recognizable right optic nerve was demonstrated and that the optic chiasm and right optic tract appeared diminished in caliber. The authors do not specifically mention the left optic tract, which I suspect also was diminished; can they comment on this? Also, the authors mention that the patient's mother was exposed to acetone during pregnancy. Do the authors know at what stage during pregnancy and in what dose the exposure took place?

Despite the fact that AON was described almost 140 years ago by von Graefe (*Arch Ophthalmol* 1941; 26:61-70), the cause still is poorly understood. One can look at optic nerve aplasia as either a failure of the mesoderm to enter the fetal fissure and provide vascularization of the retina and optic nerve, or as a failure of retinal ganglion cell development and subsequent lack of mesodermal induction because of the absence of retinal ganglion cell axons. We favor the latter theory.

In the case reported in 1978 by my colleagues and me (*Arch Ophthalmol* 1978; 96:97-101), autopsy at 3 days of age showed—in addition to multiple other central nervous system and systemic abnormalities—bilateral aplasia of the optic nerves, chiasm, and tracts. Yet the infant had relatively normal eyes except for the lack of optic nerves and retinal vessels. Interestingly, electron microscopy showed ganglion cells that were rather undifferentiated and had not elaborated any axons or dendrites, therefore leading to an absence of the retinal nerve fiber layer. Embryologically, the future optic nerves and retinal vasculature do not develop until after the retinal ganglion cell axons have grown into the optic stalk. It seems reasonable, therefore, to assume that the failure of the retinal ganglion cells to develop axons and dendrites is the primary defect in optic nerve aplasia. Why the ganglion cells fail to differentiate is unknown. As the authors state, this anomaly may be caused by environmental factors that somehow induce a mutation or inactivation of the *eya* gene.

I would like to emphasize one last point that the authors have made. In reviewing the literature, numerous cases reported as aplasia truly are hypoplasia, a different entity. In fact, one of the seminal papers on AON, reported by Scheie and Adler in 1941, contains a superb, scholarly discussion of optic nerve aplasia but actually describes a child who had bilateral hypoplasia, not aplasia, of the optic discs. The case described by Dr Howard and associates does represent true unilateral AON.

DR THOMAS P. KEARNS. Dr Howard, this was a fine presentation of a most interesting subject. Rufus, you may be justifiably proud of your daughter. I would like to ask one question. Did you consider any treatment of this blind microphthalmic right eye? There is treatment and I wonder if you are aware of it. I noted that the normal left eye had a refractive error of +1.75. If you will prescribe the appropriate correction for the left eye and put a +3.00 to +5.00 sphere over the blind right eye there will be a dramatic cosmetic improvement. This will not correct the esotropia but the magnification will correct the microphthalmic appearance of the right eye.

DR IRENE H. MAUMENEE. The following patient is presented to elaborate on the obvious: the significance of a history of systemic disease in patients with optic nerve head anomalies.

At age 12 the patient sustained bilateral loss of vision. The vision slowly recovered in both eyes. There were at least two more such episodes over the years. He was evaluated by multiple ophthalmologists and the diagnoses varied from open-angle glaucoma to retinal dystrophy. He was treated for many years with pilocarpine and also argon laser trabeculoplasty because of progressive field loss and several readings of pressures in the 20s.

He has had a lifelong history of renal insufficiency with proteinuria of 780 mg in 24 hours in 1985. An ultrasound showed bilateral loss of parenchyma. He did not have a renal biopsy. The family history is positive for an uncle with tunnel vision. On ocular evaluation at age 62 his visual acuities were 20/40 and finger counting. His tensions were 15 and 14 mm Hg. He had grade II open angles without periodic acid-Schiff. Visual field loss was asymmetrical with a ring scotoma on the right and a persistent temporal island on the left. The optic nerve heads were asymmetrical with the left being larger than e right. Bilaterally there was a pit in the optic nerve head. The general appearance of the nerve head was white and the cribiform plate could not be seen. There was no evidence for the glial tuft and grey ring typically seen in the morning glory disc, a unilateral disease. Fluorescein angiography was compatible with previous serous detachments.

A diagnosis of bilateral coloboma of the optic nerve with bilateral renal involvement was made, a well known association, which was previously discussed at this meeting by Maumenee and colleagues. If this diagnosis had been made earlier the patient could have been spared decades of glaucoma therapy.

DR JORAM PIATIGORSKY. I would be particularly interesting if the human genetic disorder described here is related to the *eya* gene of *Drosophilia* since the disease is unilaterally expressed. Since Benzer's laboratory has cloned the *eya* cDNA have you considered looking for a homologue in human?

DR RICHARD FORSTER. I would like to congratulate the authors on this paper. Dr Kearns, because of his seniority, beat me to the punch on management of this disorder. I recall a case in a young girl of true aplasia or absence of the optic disc when I was a resident that we reported in the proceedings of the *Neurophthalmology Symposium* in Miami in 1970, edited by Dr Lawton Smith. What I was impressed with in that young lady was that with a +6 lens over the eye with microcornea an excellent cosmetic appearance was achieved. Perhaps this is something that all of us can do with our abandoned aphakic lenses! I was encouraged by this technique, particularly from the point of view of insuring that such patients have protective glasses as well as improvement in cosmetic appearance.

DR RICHARD ROBB. I very much enjoyed hearing this account of the patient with optic nerve aplasia. A number of years ago I spent a good deal of time investigating a mouse model of what turned out to be something similar to optic nerve aplasia. It is called ocular retardation in the mouse. It occurs in an inbred strain of mice and those animals have a bilateral abnormality of eye formation in which the ganglion cells of the retina fail to connect. That leads to a rather major malformation of the eye in subsequent development, an outcome that is not surprising because there are many tissue interactions in the development of the eye that can lead to abnormalities beyond the initial or primary defect. I think the striking thing about optic nerve hypoplasia, which we see much more frequently than aplasia in humans, is that it is characterized by a very selective loss of ganglion cells in an otherwise apparently intact eye. That is quite different from the animal model in mice. The ocular retardation mutants in mice have a deficiency of programmed cell death in the optic nerve rudiment. The cells at the site of the optic nerve leaving the eye fail to degenerate and the axons of retinal ganglion cells cannot exit from the eye. The *Drosophila* mutation mentioned by Dr Howard seems to represent an abnormality of too much embryonic cell death rather than too little, a different but perhaps related abnormality.

DR THOMAS FRANCE. I would like to thank the authors for giving us an opportunity to look at a very unusual case which brings up some interesting aspects of what we know, or hope we know, about eye development. One of the things that I was struck by in your presentation was that I did not hear the refraction of the right eye. I did see an axial length. It looked to me as though it was 2 mm longer than the normal eye. Did I read that correctly? This was obviously a microcornea eye, at least, and one that I would not expect to be quite as long. As most of you know there has been interest in animals with deprivation amblyopia where lid suturing has been done. These animals develop a significant myopia with axial length increased. This was recorded some years ago and we have been looking to try to determine why such eyes get longer. There has been the question of is it one of the causes of school myopia, which I guess I don't believe. A few years ago we did look at patients with hypoplastic optic nerves and they turned out to be myopic as well. This is, as Dr Robb has pointed out, due to ganglion cell abnormalities and is quite different than patients with Leber's amaurosis who are born without rods and cones but do have ganglion cells. In the latter case the eyes are short and are very hypermetropic. So obviously the absence of ganglion cells has something to do with why these eyes enlarge in terms of axial length. If your case, as I suspect, was significantly myopic without any ganglion cells (or anything else for that matter) then this case may also contribute to the theory that ganglion cells are a factor in this elongation.

DR ROBERT YEE. Congratulations on an excellent paper. An even more unusual or rare disorder is aplasia of the optic chiasm. This year at ARVO, Dr P. Apkarian and

colleagues described the first two humans with the condition (*IOVS* [Suppl] 1993, p 711). A strain of sheep dogs that have no optic chiasm was also described by Dr R. Williams and Dr L. Del'Osso (*IOVS* [Suppl] 1993, p 1125). The patients' magnetic resonance imaging examination showed absence of the optic chiasm and VEP's showed no crossing from either eye. Both the patients and the dogs had a nystagmus that had some features of congenital nystagmus and also some vertical component that looked like see-saw nystagmus. Did your patient show any type of nystagmus and what was your evidence for the abnormal increased crossing of the optic nerve axons in the chiasm?

DR MARTHA HOWARD. I would like to thank Dr Yanoff for his excellent discussion of this paper. We do not know when the acetone exposure occurred during the course of pregnancy in the case we report today: whether it was during the first trimester or throughout the pregnancy. The report of the magnetic resonance imaging stated that there is a decrease in the size of the right optic tract, but when we reviewed it with the radiologist he felt that the study was not sensitive enough to distinguish any difference in size between the left and right tracts. A case of greater than normal crossing-over from the normal optic nerve has been determined by VEP studies in one reported case with AON. We did not evaluate our patient with a VEP.

Dr Kearns and Dr Forster, your suggestion for improving the microphthalmic appearance of the right eye with hyperopic correction is certainly one that could benefit the patient, and we will offer it to her.

I appreciate Dr Maumenee's discussion of the systemic abnormalities that have been seen in patients with optic nerve hypoplasia, as they are important in AON as well. In fact, significant systemic abnormalities have been described resulting in death during infancy in six individuals with AON. These cases represent more severe developmental defects. In the AON model presented, some homozygous mutants of *eya* are lethal, suggesting a function extending beyond eye development.

Dr Piatagorsky inquired about the availability of a human homologue for the *D melanogaster* gene. At this time Dr Bonini of Cal Tech is pursuing a search for a mammalian homologue of the *eya* gene. Once identified, it would be interesting to check the DNA in patients with AON to determine if they have a mutation in an *eya* homologue that could suggest that the genetic mutation plays a role in this disorder.

Dr Robb introduced a very important mouse model of a genetic defect, the ocular retardation mutation, in which ganglion cells fail to differentiate and optic nerve aplasia results. It would be of great interest to determine if the ocular retardation gene resembles the *eya* gene in structure or function in addition to the apparent similar effects on development.

The association of loss of ganglion cells with myopia as discussed by Dr France brings up an interesting point. In patients with AON, microphthalmia is reported in 20 out of 25 eyes studied by pathology. The mechanism to explain these opposing observations is unclear.

In response to Dr Yee's question regarding the optic nerve chiasm, the MRI showed that it was smaller than normal. The patient presented did not have nystagmus.

I would like to thank you all for your thoughtful comments.