British Journal of Ophthalmology, 1988, **72**, 176–182

Localising patterns of optic nerve hypoplasia—retina to occipital lobe

P NOVAKOVIC,[1] D S I TAYLOR,[1] AND W F HOYT[2]

From the [1]Department of Ophthalmology, the Hospital for Sick Children, Great Ormond Street, London WC1N 3BG, and the [2]Neuro-Ophthalmology Unit, University of California San Francisco, San Francisco, California 94143, USA

SUMMARY Six cases are presented which provide clinical evidence that optic nerve hypoplasia can occur as a result of a lesion at any site in the developing visual system. The mechanisms of hypoplasia are discussed in the light of recent understanding of optic nerve development.

Optic nerve hypoplasia (ONH) results from damage at any site in the developing visual pathway.

The development of the anterior visual pathways is intimately linked with that of the globes, which begin as evaginations from the neural ridges, first seen as small pits at the 2·6 mm stage. By 4 mm the evaginations have grown rapidly, containing the hollow optic vesicles, which are connected to the developing prosencephalon by optic stalks.[1] The wall of the vesicle, which ultimately forms among other structures the retina, including the ganglion cells, is neuroectodermal and is several layers thick by this stage.[1]

At the 5 mm stage the optic vesicles become invaginated, forming the optic cups. During this process an inferiorly located groove remains open, forming the embryonic or fetal fissure, containing paraxial mesoderm.[1] Fusion of this fissure begins at 10 mm and is completed by the 17 mm stage.

The first optic nerve elements are seen at the 13–14 mm stage in the form of dendriform fibrils emerging from the retinal ganglion cells proceeding towards the primitive epithelial papilla, the forerunner of the neuroectodermal optic disc.[1]

The fibres fill the optic stalk as they travel towards the future chiasm. By 22–30 mm the chiasm is formed, and the entire stalk is filled by fibres, cutting off the open communication between the optic vesicle and forebrain.

Decussating fibres appear first (22 mm), with the uncrossed fibres not appearing until much later at the 59 mm stage.[2] The optic tract is formed by 48 mm.

Mesodermal elements give rise to the vascular and septal system of the optic nerve and its dural sheath.

Correspondence to D Taylor, FRCS.

Recent evidence concerning retinal ganglion cells has shed a new light on their embryology, which in its early part is characterised by a massive overproduction of axons.[3] There is a very ordered growth pattern[4,5] along extracellular conduits,[6,7] but by 33 weeks of gestation there has been a 70% loss (known as 'apoptosis') of these axons.

ONH represents the stable result of diverse abnormal developmental processes affecting the visual system. It has aroused interest for over a century,[8] initially because of its alleged rarity[9] and more recently because of the numerous associated central nervous system (CNS),[10–19] endocrine,[13–17,19–21] ocular,[2,22–26] and neuropsychiatric[27] conditions.

Paralleling the clinical interest have been the embryological speculations, which have grappled with the diversity of ONH itself and of its numerous associations, in an attempt to produce an all-encompassing theory of the condition's pathogenesis. Embryological clues have been derived from the clinical associations[23,28] and from the ocular histopathology.[29–33] For instance, the association of ONH with either ocular, anterior visual pathway, or cerebral lesions may reveal something of the site of the destructive in-utero event, and the constant finding of absent retinal ganglion cells in severe ONH suggests an early in-utero event. Central to any embryological explanation of a defect are two factors: the timing and the localisation of the defect producing events.

The weight of published evidence favours a very early damaging event, from the sixth week of gestational life onwards[13,22,29,31,34] until the fourth month.[22] Others[27,35] imply that events up to the time of birth may result in ONH, albeit of a lesser severity. In

isolated ONH a primary ganglion cell failure,[29] occurring before the 17 mm stage (seven weeks gestation) has been implicated. This failure is most dramatically seen in optic nerve aplasia, which is believed to occur very early in the first trimester of development.[22]

Whether primarily or secondarily involved, retinal and CNS ganglion cell failure may result from events occurring very early in gestational life, producing diverse CNS defects and ONH.[20 36] Some congenitally anomalous discs represent lesser degrees of severity of ONH, and events up to and including the perinatal period may result in ONH.[27 35] Margalith *et al.*[27] described ONH coexisting with optic nerve atrophy in cases where defect-producing insults are assumed to have acted before or after visual pathway maturation.

The localisation of the defect is less clear than its timing. Scheie and Adler's[29] frequently quoted paper implicates a primary mesodermal[37] or ganglion cell failure. Others have argued for a primary CNS locus of insult.[20 34 38] The absence of ganglion cells in the presence of normal outer retinal layers on histopathological examinations[22 29 30 32 33] has led to the acceptance of primary retinal ganglion cell failure as being a causative event in ONH,[30 39] especially in isolated unilateral cases.[10] The amacrine and horizontal cells which arise from the same line are normal in these cases.[33] Causes of the primary failure may be impaired induction of differentiation,[9 22 30 33] unexplained[33] and possibly genetic,[40 41] though nearly all cases described are thought to be sporadic. Noxious and other environmental influences[16 27 42–47] have been implicated. In optic nerve aplasia there may be a complete failure of ganglion cells to send out axons.[48]

Mesodermal failure in optic nerve aplasia is made unlikely owing to the presence of other normal mesodermal derivatives.[3]

In the setting of an enormous normal axonal loss any abnormal influences would enhance such a loss either directly or by interfering with their trajectory to central synapses.[2] Such an influence at any site could result in a hypoplastic nerve. Environmental influences may be important in this sensitive stage of ganglion cell development.[5] One may speculate that such influences could alter the intrauterine environment sufficiently, at the critical point in time and location, to result in ONH and CNS defects.

Developmental abnormalities in the CNS may result in secondary retrograde optic nerve axon degeneration either directly or transsynaptically. Retrograde degeneration of optic nerve axons is not a new concept.[49–52] Encephaloclastic processes which result in major defects, such as porencephaly,[36] hydranencephaly,[33 36] and anencephaly,[9 53] have been associated with ONH. Hoyt *et al.*[38] linked ONH with cerebral abnormalities, and many published cases implicate the CNS at various levels.[18 19 24 35 36 54] ONH may also develop in association with early onset cerebral tumours.[13]

Central lesions may act via several mechanisms. A chiasmal or third ventricular lesion could obstruct[36] outgrowing axons or deflect them, preventing them from securing central connections, which are necessary for their survival.[3 12] This would result in an axonal degeneration and may be accompanied by a midline CNS defect and an endocrinopathy. Similar axonal effects may be seen in more posterior lesions. Hemispheric abnormalities could produce a retrograde axonal degeneration transsynaptically.[33] A developing CNS could also stretch the ganglion cell axons, resulting in their secondary degeneration.[20] Thus ONH could result from a multitude of influences acting early in embryonic life and at several points along the visual pathway.

In this paper we shall present six cases which provide clinical evidence that ONH occurs as a result of lesions at several sites in the visual pathway from the retina to the occipital lobe.

Case reports

CASE 1

This 4-year-old boy, who was deaf, presented with a right sided squint. It was not possible to measure his acuity, but he fixed well with the left eye. The right eye had a larger macular coloboma than the left, with evidence of sector hypoplasia in the part of each optic

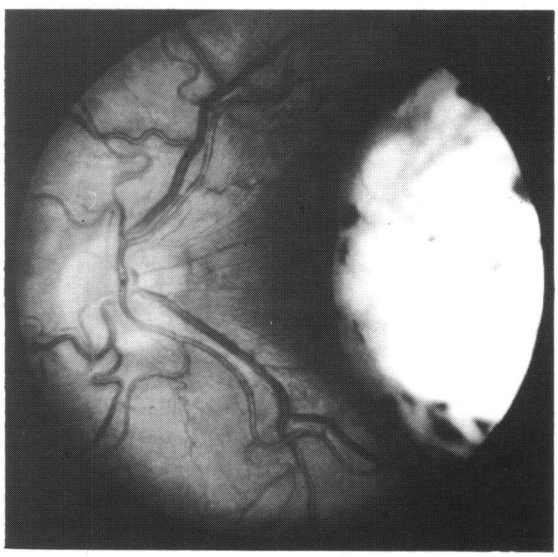

Fig. 1 *Case 1. Left eye showing a nerve fibre layer defect related to a temporal segment of hypoplasia in the optic disc.*

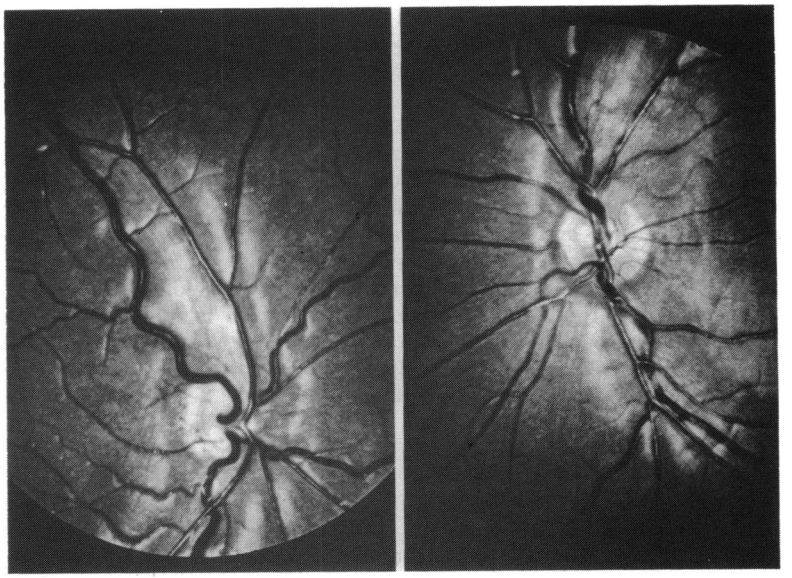

Fig. 2 *Case 2. The right eye has a profoundly hypoplastic optic disc, while the left is normal.*

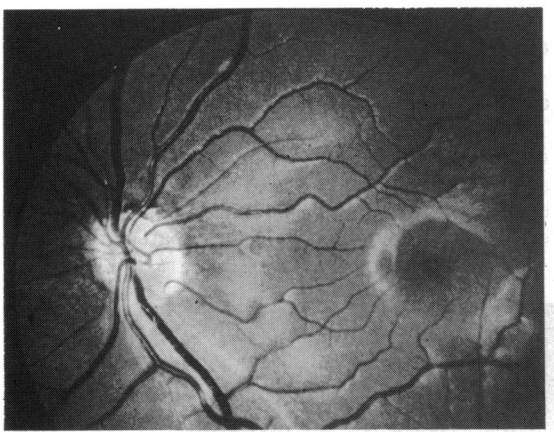

Fig. 3A

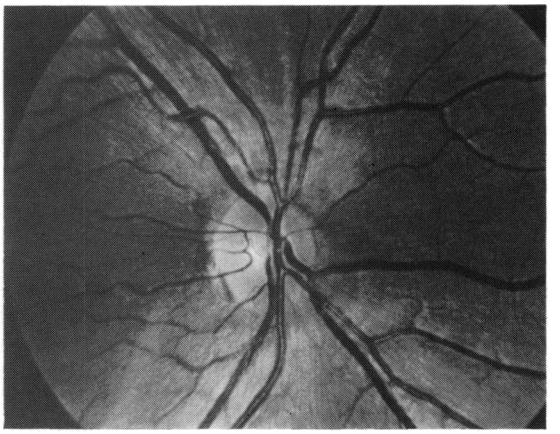

Fig. 3C

Fig. 3 *Case 3.* A: *The left optic disc has a hypoplastic upper half associated,* B: *with a total inferior altitudinal field defect.* C: *The right eye was normal.*

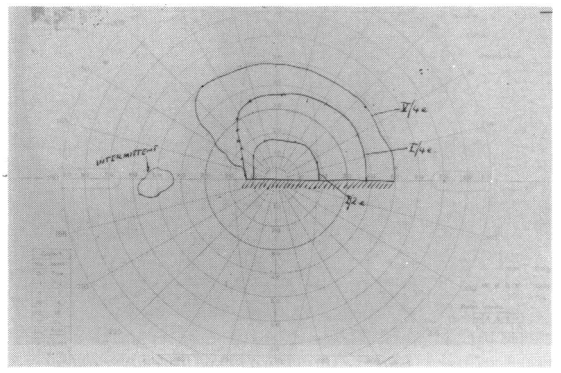

Fig. 3B

disc corresponding to the papillomacular bundle (Fig. 1).

CASE 2

This 6-month old boy presented with a squint and was found to have a relative afferent pupil defect in the right eye associated with a profoundly hypoplastic optic disc (Fig. 2). The left eye was unequivocally normal on examination. The visual evoked response (VER) and electroretinogram (ERG) were normal on the left.

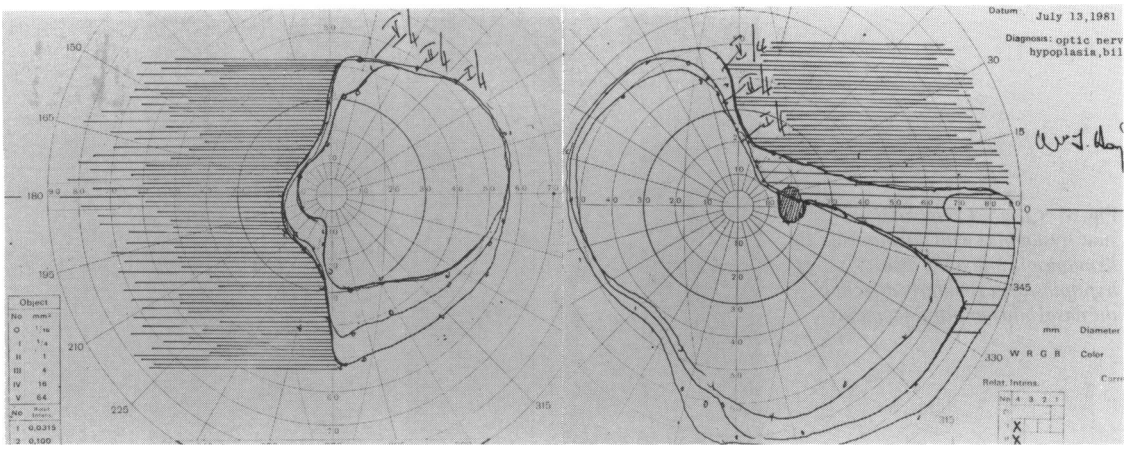

Fig. 4A

CASE 3

This 16-year-old girl presented because of non-specific headache. The visual acuity was 20/15 in each eye. Visual field examination revealed an absolute inferior altitudinal defect in the left eye (Fig. 3A) and there was a left relative afferent pupil defect. The left optic disc showed a markedly hypoplastic upper half with a marked retinal nerve fibre layer defect superiorly (Fig 3B). The right eye was normal (Fig 3C). A CT scan was normal.

CASE 4

This 17-year-old girl had had a fine rotary and horizontal nystagmus from early life. The visual acuity was 20/25 in the right eye and 20/100 in the left eye. She had normal colour vision in both eyes and normal pupil reflexes. There was a bitemporal visual field loss, with normal visual thresholds along the vertical meridian (Fig. 4A). Bilateral optic nerve hypoplasia in particular affecting the nasal and temporal segments of both optic discs, with relative preservation of the superior and inferior nerve fibre layer, was found on fundus examination (Fig 4B). Neuro-radiological investigations were all normal.

CASE 5

This 20-year-old Korean girl had had unsteady eyes from early childhood. She was found to have an

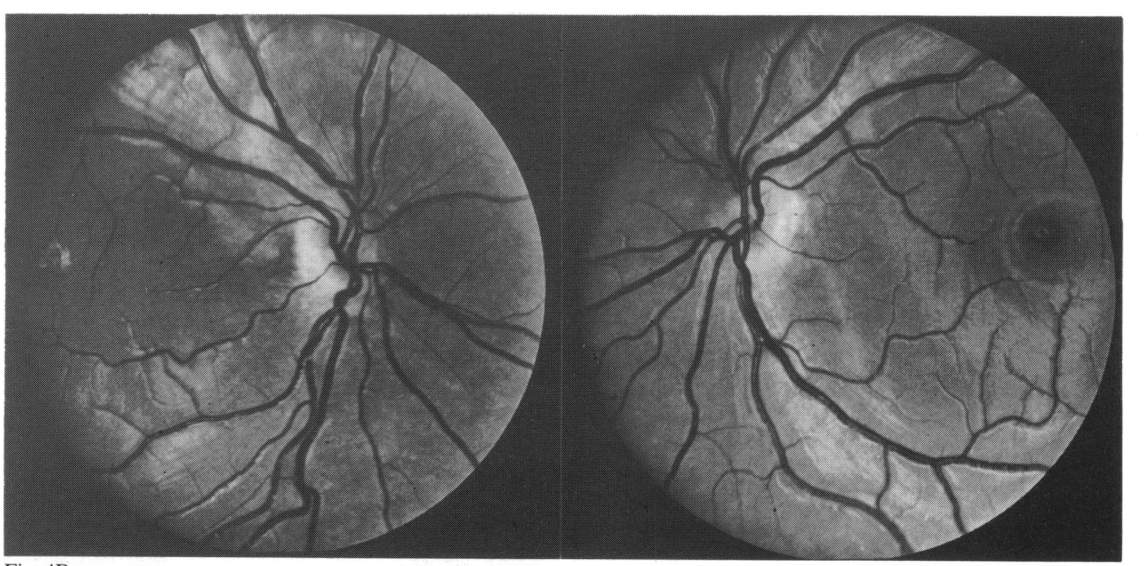

Fig. 4B

Fig. 4 *Case 4.* A: *Congenital bitemporal hemianopia associated, B, with optic nerve hypoplasia particularly affecting the nasal and temporal segments of the optic discs.*

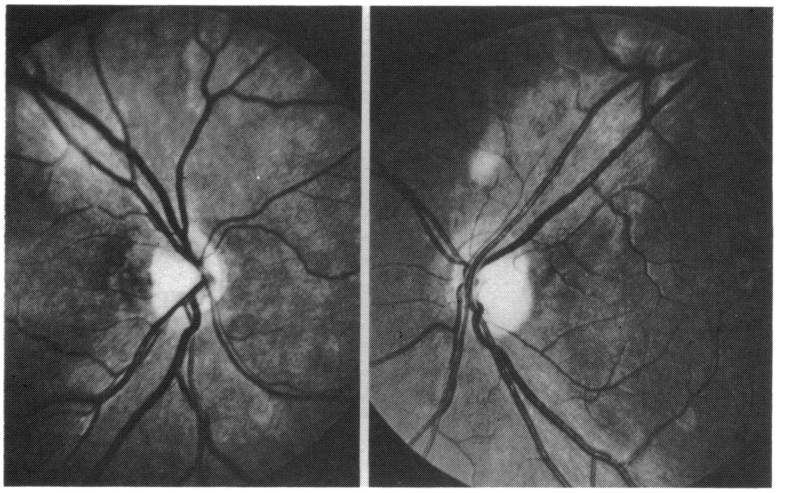

Fig. 5 *Case 5. Congenital 'see-saw' nystagmus with bitemporal hemianopia and optic disc hypoplasia, particularly affecting the nasal and temporal segments.*

acuity of 20/30 in the right eye and 20/100 in the left eye with an asymmetrical nystagmus with a see-saw component, with the left eye having a more or less vertical nystagmus with some rotary component, while the right had a purely horizontal nystagmus (Fig. 5). A bitemporal hemianopia was noted. There was bilateral optic nerve hypoplasia, in particular affecting the nasal and temporal segments of the optic disc. Pneumoencephalography demonstrated an absent septum pellucidum.

CASE 6

This 20-year-old girl was found to have a left homonymous hemianopia when she was examined for the investigation of headaches. Both optic discs were found to be small and the left showed a relative loss of disc substance and the associated nerve fibre layer in the nasal and temporal segments. The right optic disc was diffusely small (Fig. 6A). A CT scan (Fig. 6B) revealed a porencephalic cyst in the right occipital pole.

Discussion

Our cases provide clear evidence that there is no one site for the lesion responsible for ONH. The large congenital macular colobomas in case 1 have commensurate deficiencies in retinal ganglion cell axons in hypoplasia of a segment of the optic nerve, which demonstrates a primary ocular embryological insult causing ONH.

A well demarcated unilateral altitudinal field defect and the relative afferent pupil defect, with the other eye being normal (case 2), implicate the distal end of the optic nerve or the retina. The purely unilateral case 3 implies a site anterior to the optic nerve chiasmal junction.

Bitemporal hemianopic field defects in cases 4 and 5 are associated with chiasmal lesions, and see-saw nystagmus, as seen in case 5, is usually associated with supraseller lesions with bitemporal hemianopia.

Neurological investigations in case 4 were unrewarding, whereas in case 5 an absent septum

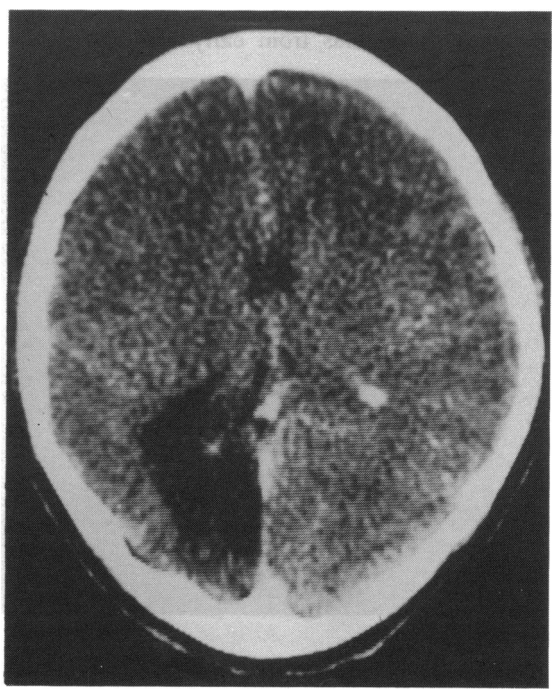

Fig. 6A

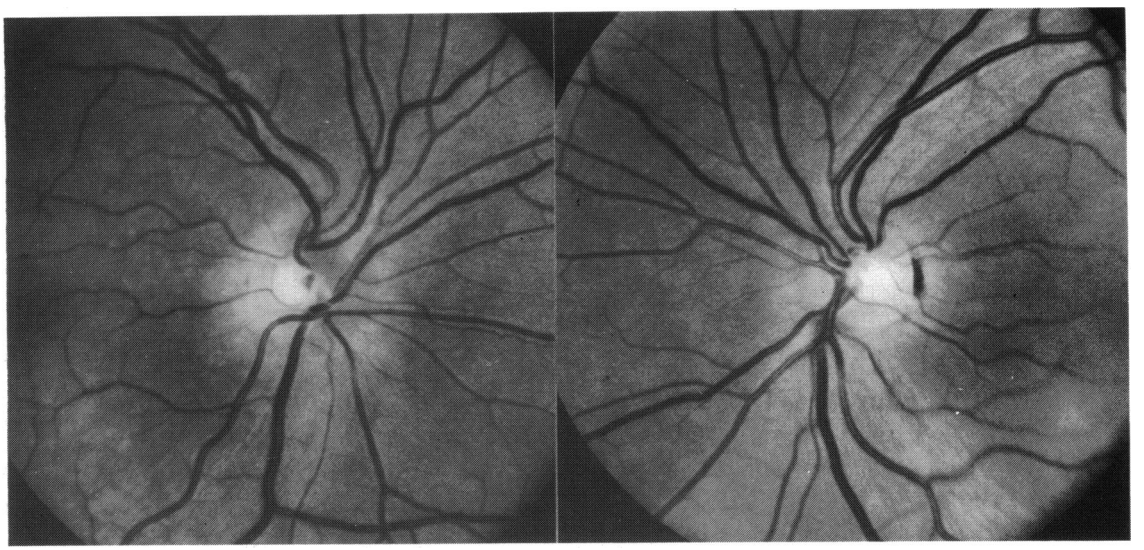

Fig. 6B

Fig. 6 *Case 6.* A: *Incidental finding of a left homonymous hemianopia led to a porencephalic cyst of the right occipital lobe.* B: *Both optic discs are hypoplastic, the left (associated with the temporal hemianopia) showing a relative loss of disc substance and associated peripapillary nerve fibre layer nasally and temporally.*

pellucidum was demonstrated, implicating destructive influences not confined to the visual system.

The 'bow-tie' or 'figure of 8' optic disc appearance in the eye opposite the occipital lobe dysplasia, with optic nerve hypoplasia in the other eye, seen in case 6 points specifically to a cerebral locus of in-utero damage, affecting the optic nerves transsynaptically. Hoyt *et al.*[38] described the characteristic retinal appearances in congenital cerebral hemisphere lesions, which may act primarily on the optic tract or transsynaptically. The resultant homonymous retrograde axonal degeneration causes hemiretinal ganglion cell loss with an asymmetrical appearance of the discs known as homonymous hemioptic hypoplasia. The contralateral disc to the lesion demonstrates the horizontal band of hypoplasia, while the ipsilateral disc may vary from a normal appearance to frankly hypoplastic.

The cases presented provide collective evidence that ONH may result from lesions occurring at any level of the visual pathway.

Professor Philip Aitken, of Burlington, Vermont, kindly allowed us to publish case 3.

References

1 Mann IC. *Development of the human eye.* 3rd ed. London: British Medical Association, 1964.
2 Miller NR. *Walsh and Hoyt's clinical neuro-ophthalmology.* 4th ed. Baltimore: Williams and Wilkins, 1982; **1:** 344–8.
3 Weiter JJ, McLean IW, Zimmerman LE. Aplasia of the optic nerve and disc. *Am J Ophthalmol* 1977; **83:** 569–76.
4 Holt CE. The topography of the initial retinotectal projection. *Prog Brain Res* 1983; **58:** 339–44.
5 Rager G. Structural analysis of fiber organization during development. *Prog Brain Res* 1983; **58:** 313–9.
6 Silver J, Sidman RC. A mechanism for the guidance and topographic patterning of retinal ganglion cell axons. *J Comp Neurol* 1980; **189:** 101–11.
7 Silver J. Studies on the factors that govern directionality of axonal growth in the embryonic optic nerve and at the chiasm of mice. *J Comp Neurol* 1984; **223:** 238–51.
8 Magnus H. Zur Casuistik der angeborenen sehnerven Missbildungen. *Klin Monatsbl Augenheilkd* 1884; **2:** 85–7.
9 Edwards WC, Layden WE. Optic nerve hypoplasia. *Am J Ophthalmol* 1970; **70:** 950–9.
10 Acers TE. Optic nerve hypoplasia. *Trans Am Ophthalmol Soc* 1981; **79:** 425–57.
11 Hoyt WF, Kaplan SL, Grumbach MM, Galser J. Septo-optic dysplasia and pituitary dwarfism. *Lancet* 1970; ii: 893–4.
12 Skarf B, Hoyt CS. Optic nerve hypoplasia in children. *Arch Ophthalmol* 1984; **102:** 62–8.
13 Taylor D. Congenital tumours in the anterior visual system with dysplasia of the optic discs. *Br J Ophthalmol* 1982; **66:** 455–63.
14 Brook GD, Sanders MD, Hoare RD. Septo-optic dysplasia. *Br Med J* 1982; iii: 811–3.
15 Harris SS, Haas L. Septo-optic dysplasia with growth hormone deficiency (de Morsier syndrome). *Arch Dis Child* 1972; **47:** 973–6.
16 Patel H, Tze WJ, Critchton JU, McCormick AQ, Robinson GC, Dolman CL. Optic nerve hypoplasia with hypopituitarism. *Am J Dis Child* 1975; **29:** 175–80.
17 Krause-Brucker W, Gardner DW. Optic nerve hypoplasia associated with absent septum pellucidum and hypopituitarism. *Am J Ophthalmol* 1980; **89:** 113–20.
18 Rogers GL, Brown D, Gray I, *et al.* Bilateral optic nerve hypoplasia associated with cerebral atrophy. *J Pediatr Ophthalmol Strabismus* 1981; **18:** 18–22.
19 Billson F, Hopkins IJ. Optic nerve hypoplasia and hypopituitarism. *Lancet* 1972; i: 905.

20 Keltner JL. The disc that really isn't (hypoplastic disc syndrome). *Surv Ophthalmol* 1985; **29:** 349–54.
21 Ellenberger C, Runyan TE. Holoprosencephaly with hypoplasia of the optic nerves, dwarfism and agenesis of the septum pellucidum. *Am J Ophthalmol* 1970; **70:** 960–7.
22 Hotchkiss ML, Green WR. Optic nerve aplasia and hypoplasia *J Pediatr Ophthalmol* 1979; **16:** 225–40.
23 Brown GC. Optic nerve hypoplasia and colobomatous defects. *J Pediatr Ophthalmol Strabismus* 1982; **19:** 90–3.
24 Layman PR, Anderson DR, Flynn JT. Frequent occurrence of hypoplastic optic discs in patients with aniridia. *Am J Ophthalmol* 1974; **77:** 513–6.
25 Lloyd L, Buncic JR. Hypoplasia of the optic nerve and disc. In: Smith JL, ed. *Neuro-ophthalmology focus*. New York: Masson, 1980: 85–96.
26 Brown GC, Tasman WS. Congenital anomalies of the optic disc. New York: Grune and Stratton, 1983: 17–23.
27 Margalith D, Jan JE, McCormick AQ, *et al.* Clinical spectrum of congenital optic nerve hypoplasia: review of 51 patients. *Dev Med Child Neurol* 1984; **26:** 311–22.
28 Jensen PE, Kalina RE. Congenital anomalies of the optic disc. *Am J Ophthalmol* 1976; **82:** 27–31.
29 Scheie HG, Adler FH. Aplasia of the optic nerve. *Arch Ophthalmol* 1941; **26:** 61–70.
30 Ewald RA. Unilateral hypoplasia of the optic nerve. *Am J Ophthalmol* 1967; **63:** 763–7.
31 Whinery RD, Blodi FC. Hypoplasia of the optic nerve: a clinical and histopathologic correlation. *Ophthalmology* 1963; **67:** 733–8.
32 Young SE, Walsh FB, Knox DL. The tilted disc syndrome. *Am J Ophthalmol* 1976; **82:** 16–23.
33 Mosier MA, Lieberman MF, Green WR, *et al.* Hypoplasia of the optic nerve. *Arch Ophthalmol* 1978; **96:** 1437–42.
34 Jerome B, Forster JW. Congenital hypoplasia (partial aplasia) of the optic nerve. *Arch Ophthalmol* 1948; **39:** 669–72.
35 Frisen L, Holmegaard L. Spectrum of optic nerve hypoplasia. *Br J Ophthalmol* 1978; **62:** 7–15.
36 Greenfield PS, Wilcox LM, Weiter JJ, Adelman L. Hypoplasia of the optic nerve in association with porencephaly. *J Pediatr Ophthalmol Strabismus* 1980; **17:** 75–80.
37 Little LE, Witmac PV, Wells TW. Aplasia of the optic nerve. *J Pediatr Ophthalmol Strabismus* 1976; **13:** 84–8.
38 Hoyt WF, Rios-Montenegro EN, Behrens MM, Eckelhoff RJ. Homonymous hemioptic hypoplasia. Funduscopic features in standard and red-free illumination in three patients with congenital hemiplegia. *Br J Ophthalmol* 1972; **56:** 537–45.
39 Macoul KL, Dellaporta A, Miller LC. Hypoplasia of the optic nerve. *Br J Ophthalmol* 1969; **53:** 496–7.
40 Kytila J, Miettinen P. On bilateral aplasia of the optic nerve. *Acta Ophthalmol (Kbh)* 1961; **39:** 416–9.
41 Hackenbruch Y, Meerhoff E, Besio R, Cardoso H. Familial bilateral optic nerve hypoplasia. *Am J Ophthalmol* 1975; **79:** 314–20.
42 Hittner HM, Desmond MM, Montgomery JR. Optic nerve manifestations of cytomegalovirus infection. *Am J Ophthalmol* 1976; **81:** 661–5.
43 McKinna AJ. Quinine induced hypoplasia of the optic nerve. *Can J Ophthalmol* 1966; **1:** 261–5.
44 Hoyt CS, Billson FA. Maternal anticonvulsants and optic nerve hypoplasia. *Br J Ophthalmol* 1978; **62:** 3–6.
45 Peterson RA, Walton DS. Optic nerve hypoplasia with good acuity and visual field defects: a study of children of diabetic mothers. *Arch Ophthalmol* 1977; **95:** 254–8.
46 Van Dyk HJL, Morgan KS. Optic nerve hypoplasia and young maternal age. *Am J Ophthalmol* 1980; **89:** 879.
47 Walton DS, Robb RM. Optic nerve hypoplasia—a report of 20 cases. *Arch Ophthalmol* 1970; **84:** 572–8.
48 Yanoff M, Rorke LB, Allman MI. Bilateral optic system aplasia with relatively normal eyes. *Arch Ophthalmol* 1978; **96:** 97–101.
49 Kupfer C. Retinal ganglion cell degeneration following chiasmal lesions in man. *Arch Ophthalmol* 1963; **70:** 256–60.
50 Kurz GH, Ogata J, Gross EM. Traumatic optic pathway degeneration: antegrade and retrograde. *Br J Ophthalmol* 1971; **55:** 233–42.
51 Gills JP, Wadsworth JAC. Retrograde transsynaptic degeneration of the inner nuclear layer of the retina. *Invest Ophthalmol Vis Sci* 1967; **6:** 437–47.
52 Quigley HA, Davis EB, Anderson DR. Descending optic nerve degeneration in primates. *Invest Ophthalmol Vis Sci* 1977; **16:** 841–4.
53 Boniuk V, Ho PK. Ocular findings in anencephaly. *Am J Ophthalmol* 1979; **88:** 613–7.
54 Seeley RL, Smith JL. Visual field defects in optic nerve hypoplasia. *Am J Ophthalmol* 1972; **73:** 882–9.

Accepted for publication 22 December 1986.