Optic disc changes in glaucoma

SOHAN SINGH HAYREH

Department of Ophthalmology, University of Edinburgh

Sir William Mackenzie (1835) was the first to describe raised intraocular pressure (IOP) in glaucoma. Following the introduction of the ophthalmoscope, the presence of glaucomatous cupping was soon recognized (Jacobson, 1853; Jaeger, 1854; von Graefe, 1854; Weber, 1855; and others) and was confirmed histopathologically by Müller (1856). Mackenzie (1854) described flattened and atrophic nerves in glaucomatous eyes. Nerve fibre bundle defects were first described by Landesberg (1869) and later by Bjerrum (1889). Cavernous degeneration of the optic nerve in glaucoma was noted by Schnabel (1892). Although the association of optic disc and optic nerve changes and visual field defects with glaucoma has been well-established for over a century, much controversy has centred in the pathogenesis of these lesions in glaucoma. The syndrome described by von Graefe (1857a), in which cupping of the optic disc and field defects occur with no rise in IOP, has added to the confusion. Recent studies, briefly discussed below, have helped somewhat to clarify these problems (Hayreh, 1969a,b, 1970; Hayreh and Perkins, 1968, 1969; Hayreh, Revie, and Edwards, 1970).

Structure of the optic nerve head

This is described in detail elsewhere (Hayreh and Vrabec, 1966). From behind forwards the nerve head (Fig. 1, overleaf) consists of:

(*a*) *The lamina cribrosa*

This is composed of dense compact connective tissue, continuous with the sclera, with many openings for the transmission of the nerve fibre bundles (Fig. 1*a*, *b*). The connective tissue trabeculae contain numerous capillaries.

(*b*) *The prelaminar region*

Here the compact connective tissue of (*a*) is replaced almost entirely by loose glial tissue, attached peripherally to the choroid and Bruch's membrane (Fig. 1*a*, *c*). There are many capillaries in the glial septa.

(*c*) *The surface nerve fibre layer*

This is the most superficial layer, consisting of compact nerve fibres continuous with the nerve fibre layer of the retina, covered by inner limiting membrane.

(*d*) *The retrolaminar part of the optic nerve*

Here the connective tissue septa are attached to the pia on the surface (Fig. 1*a*,*d*). The blood vessels lie in the septa.

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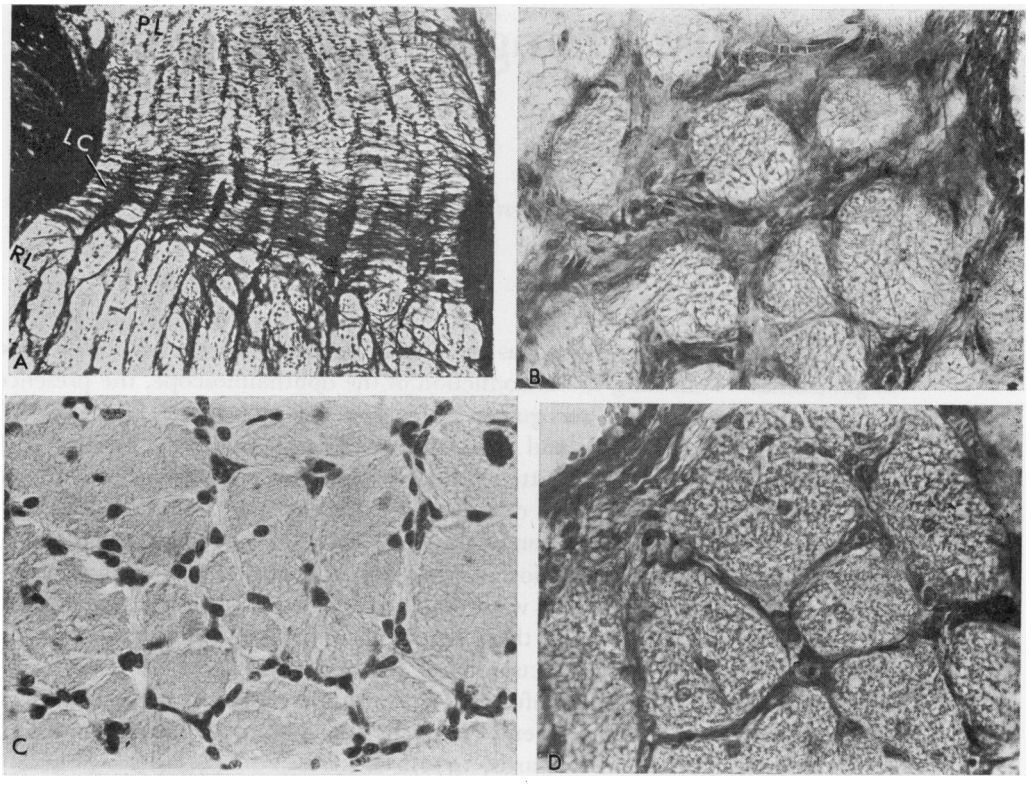

FIG. 1 *Histological section of the optic nerve head and adjacent retrolaminar optic nerve in rhesus monkeys:*

(*a*) Longitudinal section (LC = Lamina cribrosa; PL = Prelaminar region; RL = Retrolaminar region)

(*b*), (*c*), (*d*): Transverse sections in lamina cribrosa (*b*), prelaminar (*c*), and retrolaminar (*d*) regions

Blood supply of the optic nerve head

This is also given in detail elsewhere (Hayreh, 1969a, 1970, 1972; Hayreh and Perkins, 1968, 1969).

ARTERIAL SUPPLY (Fig. 2, opposite)

(*a*) *The lamina cribrosa* is supplied by centripetal branches from the short posterior ciliary arteries, either by direct branches or, less frequently, through the so-called arterial circle of Zinn.

(*b*) *The prelaminar region* is supplied mainly by centripetal branches from the adjacent peripapillary choroid (Fig. 3) and also possibly from (*a*). The part containing the papillo-macular bundle is much more vascular than the rest.

(*c*) *The surface nerve fibre layer* of the disc is supplied by the retinal arterioles; sometimes the temporal sector of this layer receives a contribution from (*b*).

(*d*) *The retrolaminar optic nerve* is mainly supplied by centripetal branches from pial vessels, which are mostly the recurrent pial branches from the peripapillary choroid and the circle of Zinn (or its substitute) (Hayreh, 1963). In about three-quarters of the nerves, the central retinal artery may supply the central part of this region by centrifugal branches.

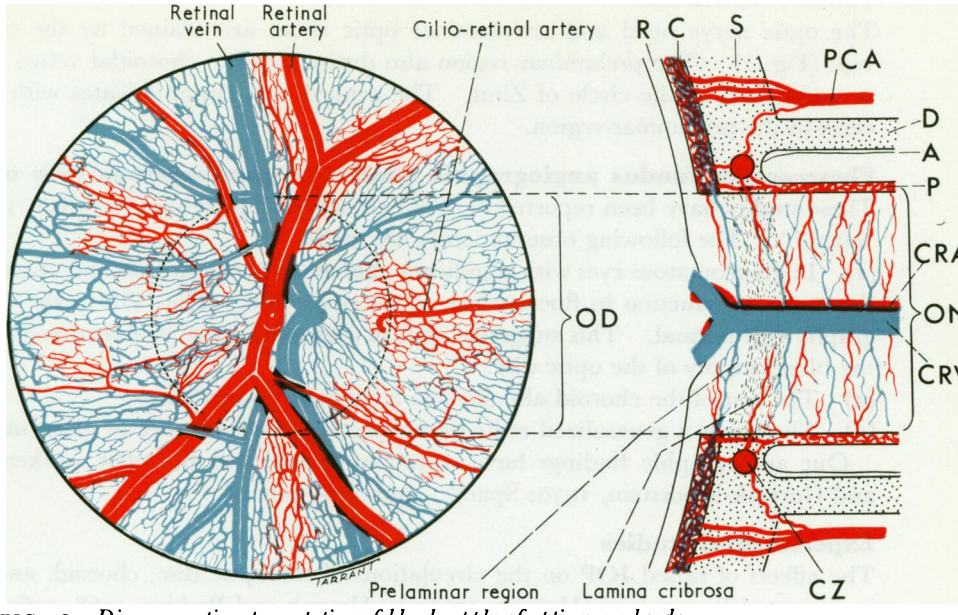

FIG. 2 *Diagrammatic representation of blood supply of optic nerve head:*

A	= arachnoid	CZ	= circle of Zinn and Haller	P	= pia
C	= choroid	D	= dura	PCA	= posterior ciliary arteries
CRA	= central retinal artery	OD	= optic disc	R	= retina
CRV	= central retinal vein	ON	= optic nerve	S	= sclera

Thus, the ciliary circulation is the only source of blood supply to (*a*) and (*b*) and the main source to (*d*), and it may supply the temporal part of (*c*). The posterior ciliary arteries have a segmental distribution, with the main artery supplying the nasal or temporal half (Fig. 3*a*), or the superior or inferior half (Fig. 3*b*) of the choroid and optic nerve head (Hayreh, 1970). The smaller short posterior ciliary arteries supply smaller sectors.

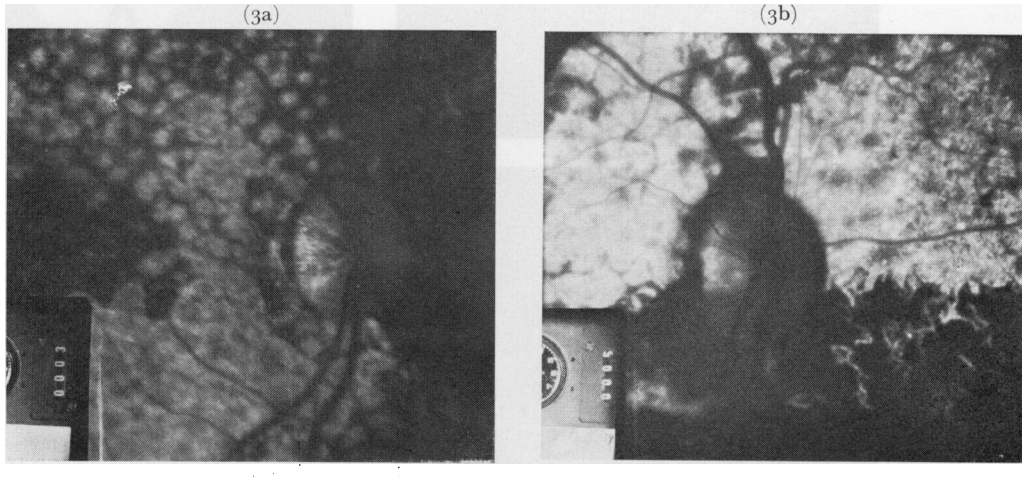

FIG. 3 *Fluorescence fundus angiograms of a cynomolgus monkey during the pre-retinal-arterial phase, showing a well-demarcated filling of* (*a*) *temporal half and* (*b*) *upper half of choroid and optic disc.*

VENOUS DRAINAGE

The optic nerve head and retrolaminar optic nerve are drained by the central retinal vein (Fig. 2). The prelaminar region also drains into the choroidal veins, with no veins to correspond to the circle of Zinn. The central vein communicates with the choroidal veins in the prelaminar region.

Fluorescence fundus angiographic studies in glaucomatous eyes of patients

These studies have been reported in detail elsewhere (Hayreh and Walker, 1967; Hayreh, 1969a,b). The following observations were made.

(1) In glaucomatous eyes with significant changes at the optic disc and visual field defects, there was a reduction in flucrescence of the optic disc. The IOP at the time of angiography was normal. This suggested that in glaucoma there is a permanent reduction in the blood supply of the optic disc.

(2) The rest of the choroid also showed a reduced fluorescence.

(3) There was a generalized reduction of the capillary network in glaucomatous eyes.

Our angiographic findings have since been confirmed by other workers (Oosterhuis and Gortzak-Moorstein, 1970; Spaeth, 1971; and others).

Experimental studies

The effects of raised IOP on the circulations of the optic disc, choroid, and retina were investigated in monkeys (Hayreh, 1969a,b; Hayreh and Perkins, 1968, 1969; Hayreh and others, 1970). These showed that under raised IOP:

(1) The vessels in *the prelaminar part of the optic disc* are most susceptible to obliteration (Figs 4, 5, 6).

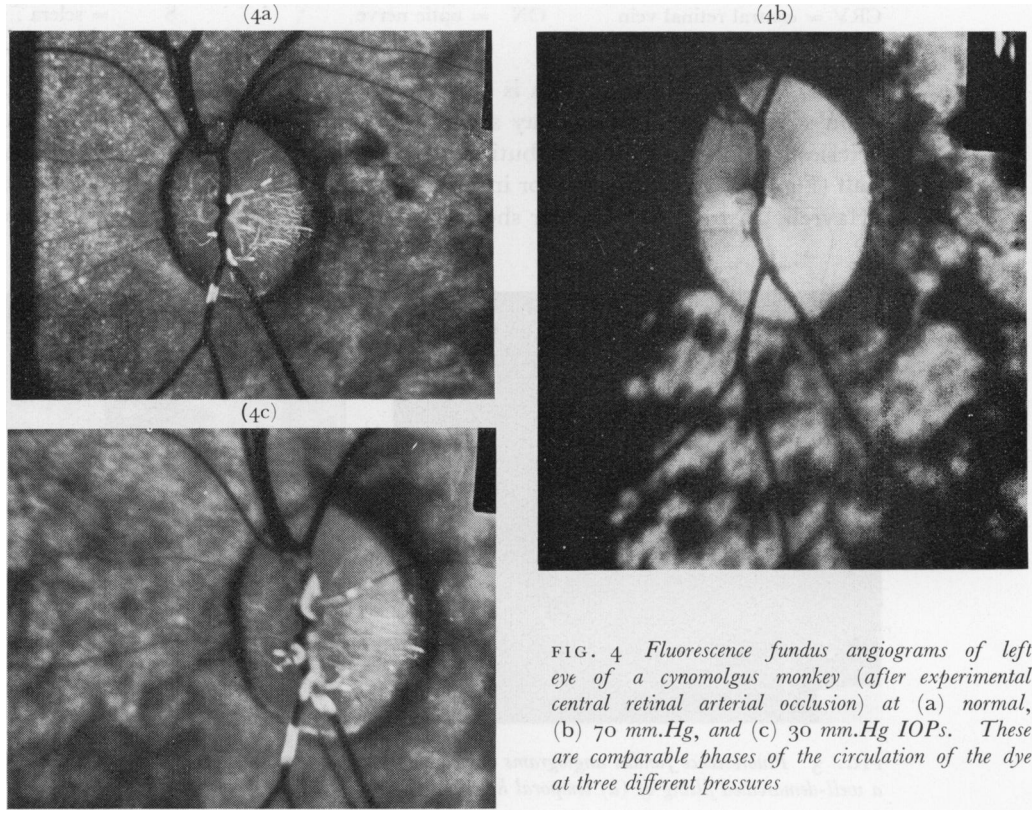

FIG. 4 *Fluorescence fundus angiograms of left eye of a cynomolgus monkey (after experimental central retinal arterial occlusion) at* (a) *normal,* (b) 70 *mm.Hg, and* (c) 30 *mm.Hg IOPs. These are comparable phases of the circulation of the dye at three different pressures*

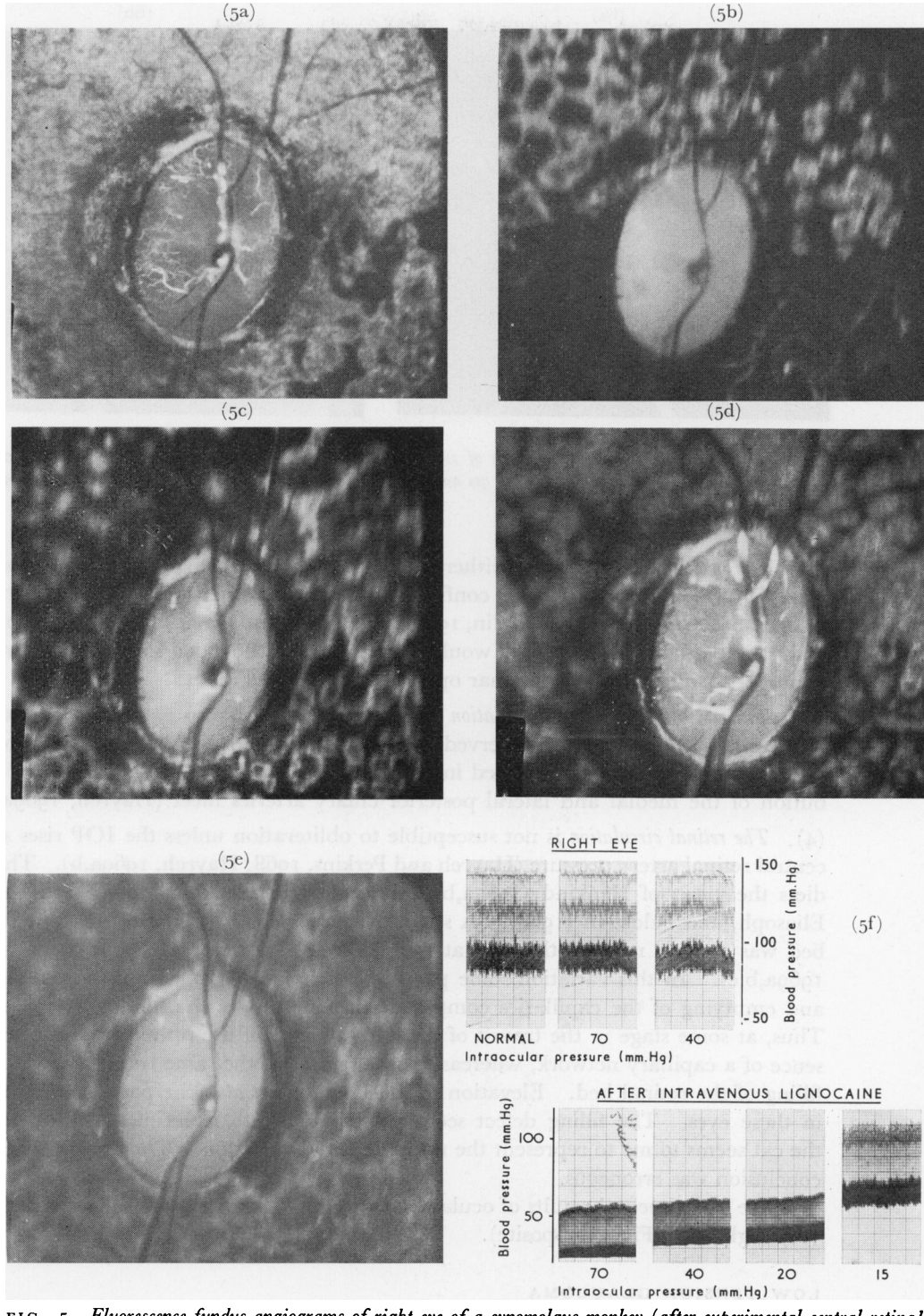

FIG. 5 *Fluorescence fundus angiograms of right eye of a cynomolgus monkey (after experimental central retinal arterial occlusion) at* (a) *normal,* (b, c) 70 *mm.Hg,* (d) 40 *mm.Hg, and* (e) 20 *mm.Hg IOPs.*

FIG. 5 (f) *Tracings of BP at the four pressures:* 140/80 *mm.Hg at* (a), (b), *and* (c); 140/75 *mm.Hg at* (d); 62/35 mm.Hg at (e)

(a), (c), (d), *and* (e) *represent comparable phases of circulation at the various pressures. Choroidal pigment deposit at disc margins obscures underlying fluorescence in some areas*

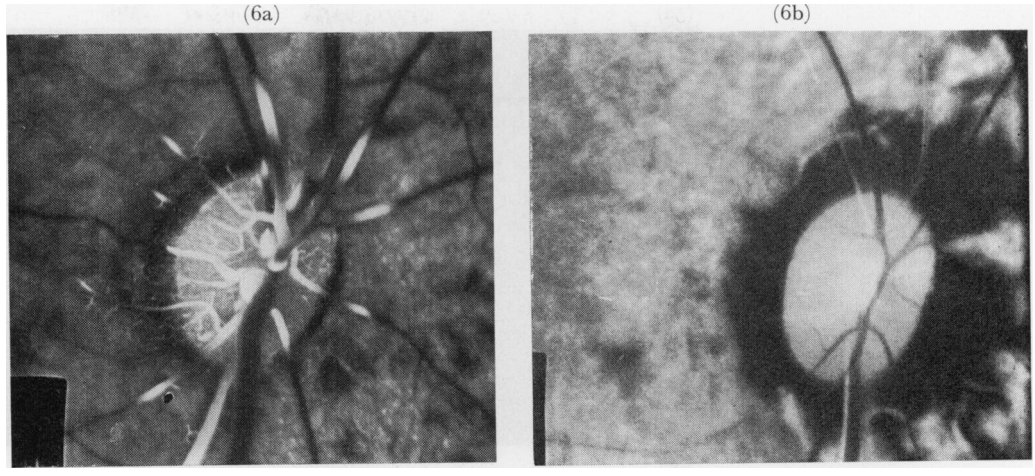

FIG. 6 *Fluorescence fundus angiograms of right eye of cynomolgus monkey (after experimental central retinal arterial occlusion) at* (a) *normal and* (b) 70 *mm.Hg IOPs. Choroidal pigment deposit at disc margins obscures underlying fluorescence in some parts*

(2) *The peripapillary choroid* is either equally or slightly less susceptible to obliteration (Fig. 6*b*). This has also been confirmed by other workers (Ernest and Potts, 1968; Blumenthal, Gitter, Best, and Galin, 1970; Swietliczko and David, 1970). The obliteration of the peripapillary choroid itself would in turn involve the blood supply to the prelaminar region of the disc and retrolaminar optic nerve as well (Fig. 2).

(3) *The rest of the choroidal circulation* is also very susceptible to obliteration, although less so (Figs 4, 5). This was also observed by Dollery, Henkind, Kohner, and Paterson (1968). In the choroid it was most marked in the watershed areas where the territories of distribution of the medial and lateral posterior ciliary arteries meet (Hayreh, 1969a,b).

(4) *The retinal circulation* is not susceptible to obliteration unless the IOP rises above the central retinal artery pressure (Hayreh and Perkins, 1968; Hayreh, 1969a,b). This contradicts the views of Henkind (1967a,b), Alterman and Henkind (1968), and Kornzweig, Eliasoph, and Feldstein (1968). A spatial variation in the filling of the retinal vascular bed was seen in most of the eyes at normal IOP (Hayreh and Perkins, 1968; Hayreh, 1969a,b,c). In this variation some parts of the retinal vascular bed showed early filling and emptying of the capillaries compared with the rest of the fundus (Fig. 7, opposite). Thus, at some stage in the transit of the dye, a sector of the retina showed complete absence of a capillary network, whereas another phase of the same transit showed complete filling of the retinal bed. Elevation of the IOP *did not alter* the pattern of retinal filling in these eyes. The filling defect seen by Henkind with experimentally raised IOP in the cat seems to me to represent the normal spatial variation. Therefore I think that his conclusion was erroneous.

These experimental results of ocular hypertension have been confirmed in patients with very high IOP (Fig. 8, opposite).

LOW TENSION GLAUCOMA

Considerable controversy has centred in this subject. Our studies have helped to clarify this and are reported in detail elsewhere (Hayreh and others, 1970). In these studies on monkeys, the effect of raised IOP on the circulations of the optic disc, choroid, and retina

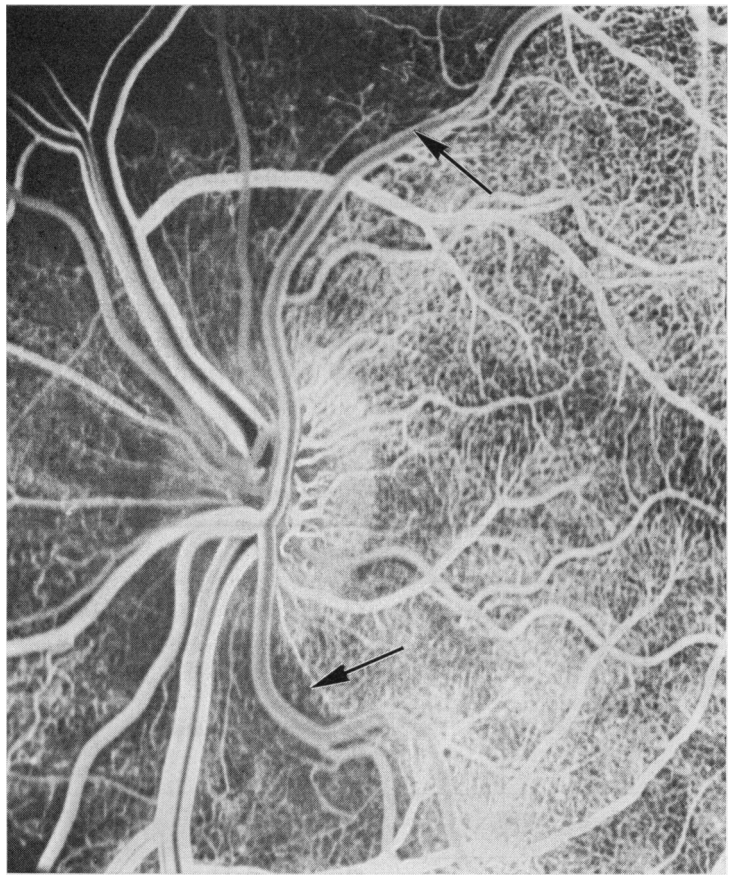

FIG. 7 *Fluorescence fundus angiogram of cynomolgus monkey, showing spatial variation in filling of retinal capillaries. Capillaries nasal to temporal retinal arterioles (arrows) filled first and emptied earlier; capillaries temporal to arterioles filled and emptied later.*

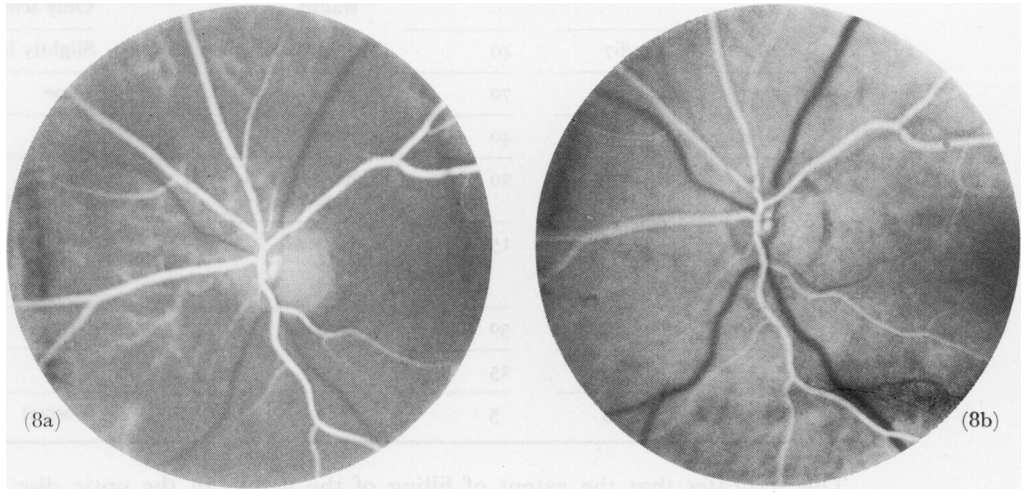

FIG. 8 *Fluorescence fundus angiograms of left eye of a 47-year-old woman with chronic simple glaucoma and deeply-cupped optic disc*

(*a*) AT 60 MM.HG Retinal arteries fill without choroidal filling. Normally the choroid fills before the retinal arterial system

(*b*) AT 20 MM.HG 2 DAYS LATER Retinal arterial and choroidal filling seen

The disc fluorescence seen in (*a*) and (*b*) is due to a preliminary test dose of fluorescein and not to disc filling

was first observed at normal systemic arterial blood pressure (BP). Later on in the same eyes, the effects of lowering the BP were studied in the same ocular circulations at different IOPs. The ophthalmic artery pressure (OAP) can be estimated from the BP by the following formula (Hayreh and Edwards, 1971):

Systolic opthalmic artery pressure = 0·80 × systolic BP − 8·63 mm. Hg ± 3·8
Diastolic opthalmic artery pressure = 0·80 × diastolic BP + 6·95 mm. Hg ± 3·4

The Table summarizes the filling pattern of the circulation in the choroid and optic disc at different IOPs and OAPs (Fig. 5). These results suggest that, when the difference between the diastolic BP and IOP is about 10 mm.Hg or less, there is very poor filling of the vessels in the optic disc, seen only in the temporal sector. When the diastolic BP is lower than the IOP, there is no filling of the vessels in the optic disc or choroid. The exact role of the systolic BP is not clear.

Table *Pattern of filling of vessels of choroid and optic disc in three eyes of two cynomolgus monkeys (Nos 1 and 2 from one animal) at different intraocular pressures and systemic arterial blood pressures.*

Eye no.	*Pressures (mm.Hg)*			*Filling of:*	
	Systemic arterial	*Ophthalmic arterial*	*Intraocular*	*Choroidal vessels*	*Optic disc vessels*
1	150/85	113/75	70	Slow with prolonged transit	Less than normal Temporal > nasal
	150/85	113/75	85	Still slower with more prolonged transit	Very poor Some vessels filled in temporal part only
	150/85	113/75	30	Normal filling and transit	Normal
2	140/80	103/71	70	Slow with prolonged transit	Poor Only temporal side filled
	140/75	103/67	40	Slightly less than normal	Slightly less than normal
	57/25	37/22	70	None	None
	60/32	39/29	40	None	None
	62/35	41/31	20	Slow with delayed transit	Poor Only temporal side filled
	110/60	79/55	15	Normal	Difficult to assess owing to marked fluorescence of optic disc
3	35/15	25/13	50	None	None
	35/15	25/13	25	None	None
	35/15	25/13	5	Normal	Normal

This indicates that the extent of filling of the vessels in the optic disc, peripapillary choroid, and the remaining choroid depends upon the difference between the perfusion pressure in the ciliary circulation (PP) and the IOP—the greater the difference the better the filling, and *vice versa*. A somewhat similar mechanism has been suggested by a number of clinical studies (Lauber, 1936; Reese and McGavic, 1942; Duke-Elder, 1955, 1962; Gafner and Goldmann, 1955; McLean, 1957; Harrington, 1959, 1964; Lobstein, 1959;

Drance, Wheeler, and Pattullo, 1968; Spaeth, 1971). However, almost all these workers attributed this to interference by the raised IOP with the retinal circulation instead of the choroidal circulation. Drance and others (1968) found a low diastolic BP in all patients who showed marked damage to the optic nerve head or visual field defects. Thus, "low tension glaucoma" represents a group experiencing a fall in PP without a rise in IOP, resulting in a vascular insufficiency similar to that caused by a rise in IOP with normal PP ("glaucoma"). Thus "glaucoma" and "low tension glaucoma" are identical processes producing ischaemia of the optic disc and peripapillary choroid. The low PP may result from arteriosclerotic narrowing of the posterior ciliary, ophthalmic, or internal carotid arteries, or from systemic arterial hypotension.

Effects of chronic choroidal ischaemia

Vascular insufficiency produced by the disturbed balance between the PP and IOP results in ischaemia of the following:

(*a*) *Optic disc*

The vessels in the prelaminar region of the optic disc become sandwiched between the raised IOP and the rigid fibrous lamina cribrosa (Figs 1 and 2), resulting in obliteration or reduced perfusion of the vessels in that region. Obliteration of the vessels in the peripapillary choroid (Fig. 6) would also interfere with the blood supply to the prelaminar part of the disc. This leads to atrophic changes in this region. Shaffer and Hetherington (1969) suggested that atrophy of astroglial elements came first, followed by permanent damage to the nerve fibres. The obliteration of the vessels in the prelaminar region causing atrophy of the tissues leads to cupping of the disc and field defects. In some eyes, a few days after lowering the IOP from a very high level to normal, I have observed a reduction in cupping of the optic disc. This would suggest that the cupping in such cases may be partly due to compression of the loose prelaminar tissue by the raised IOP. A lowering of the pressure could perhaps reduce the cupping, first because it allows the tissue to return into the loose prelaminar tissue, and later because the glial tissue may regenerate; the latter would give a pale appearance to the disc.

Since the arrangement of blood vessels in the prelaminar part of the optic disc is segmental (Fig. 3), obliteration of these, or of the adjacent peripapillary choroid from which they arise, could produce nerve fibre bundle defects (Hayreh, 1970). Obliteration of the vessels in some discs, instead of being chronic, may be acute and segmental, producing segmental ischaemic optic neuropathy (Begg, Drance, and Sweeney, 1971) and thus resulting in sectoral cupping and field defects.

Two to three posterior ciliary arteries, arising independently from the ophthalmic artery, account for the entire ciliary supply (Hayreh, 1962, 1970). These have no significant intercommunication and it is possible that the different arteries may not have identical PP. The area supplied by the artery with lower PP may, therefore, be involved in glaucoma earlier than that supplied by the others (Fig. 4*b*, 5*b*). This would produce altitudinal (Fig. 4*b*) or vertical (Fig. 5*b*) hemianopic field defects in the affected eye.

In acute congestive glaucoma, the disc shows oedema. This is presumably due to a sudden compression of the vessels in the prelaminar region, producing anoxia which, in turn, would lead to oedema (Hayreh, 1969a,b).

(*b*) *Peripapillary choroid*

Chronic obliteration of this region results in peripapillary choroidal atrophy (Hayreh,

1969a,b). This view is confirmed by the fact that peripapillary choroidal atrophy is much more common in glaucoma than in normal eyes. This would produce an enlarged blind spot. Since the prelaminar region is supplied mainly by the peripapillary choroid, the atrophic changes in the latter would involve the former.

(*c*) *Retrolaminar optic nerve*

The problem of association of cavernous degeneration of the retrolaminar optic nerve in glaucoma posed a baffling problem. Our studies seem to provide an explanation (Hayreh, 1969a,b). The centripetal vascular system of this part of the nerve is mainly derived from the peripapillary choroid *via* the pial branches (see above) (Fig. 2). Involvement of the peripapillary choroid by raised IOP (see above) (Fig. 6) would produce ischaemia of the peripheral part or the whole thickness of the retrolaminar optic nerve. This results in cavernous degeneration of this part of the optic nerve, accompanied by peripheral constriction of visual fields (Hayreh, 1969a,b, 1970)*.

Conclusions

Our studies have shown that:

(1) Ciliary circulation is the main source of blood supply to the prelaminar, laminar, and retrolaminar parts of the optic nerve.

(2) When the IOP is raised, the susceptibility of vessels to obliteration is as follows:

(*a*) Maximum in the prelaminar region;

(*b*) Next in the peripapillary choroid;

(*c*) Much less in the rest of the choroid;

(*d*) None at all in the retinal circulation.

(3) The presence of normal spatial variation in the filling of the retinal circulation can lead to an erroneous impression of localized capillary obliteration on angiography.

(4) The amount of filling of the ciliary vessels in the optic disc, peripapillary choroid, and the remainder of the choroid depends upon the difference between the PP and the IOP. A rise in the IOP has the same effect as a fall in the PP. The former is seen in "glaucoma" and the latter in "low-tension glaucoma". Both produce ischaemia of the tissues involved.

(5) Fluorescence fundus angiography has revealed reduced fluorescence of the optic disc in patients with significant changes at the optic disc and visual field defects.

(6) Ischaemia produces the following lesions:

(*a*) *In the optic disc* Cupping of the disc and nerve fibre degeneration, associated with visual field defects.

(*b*) *In the peripapillary choroid* Atrophy of the choroid and enlargement of the blind spot.

(*c*) *In the retrolaminar optic nerve* Cavernous degeneration and peripheral constriction of fields.

(7) Investigations in the assessment of patients with glaucoma:

(*a*) Estimation of IOP is done routinely by everyone.

(*b*) Determination of PP is equally important, particularly when the IOP is not

* See Commentary on p. 157

elevated, *i.e.* in "low-tension glaucoma". No satisfactory method yet exists for this (Hayreh and others, 1970).

(*c*) Visual field defects and optic disc changes reflect the end result of (*a*) and (*b*)—hence it is very important to look for them.

(*d*) Fluorescence fundus angiography as a routine procedure has no place in glaucoma because of its numerous drawbacks.

On the basis of our studies, we have defined glaucoma as *a disease wherein the normal balance between the intraocular pressure and the blood pressure in the choroidal vessels supplying the optic disc and retrolaminar part of the optic nerve is disturbed, resulting in vascular insufficiency in the optic disc and the retrolaminar part of the optic nerve, and hence in visual field defects and pathological changes in the optic disc and optic nerve.*

COMMENTARY

(1) AETIOLOGY OF DISC CHANGES IN GLAUCOMA

There are two hypotheses concerning the aetiology of the glaucomatous change in the disc in simple glaucoma. The first is a circulatory one, postulating a change in the capillary circulation of the prelaminal choroidal vascular network in the optic nerve head. In the early stages it is possible that this is a reversible process, as the disc had been observed to be bowed backwards and cupped when the intraocular pressure was very high and a few days later the cup was very much shallower, the pressure having been controlled. This had been observed in both angle-closure and open-angle glaucoma. However, when the capillary circulation becomes irreversibly damaged, the neural and glial elements in the prelaminal region begin to disappear, allowing the lamina cribrosa to bow backwards. The collagen fibres are not as sensitive to the loss of vascular tissue as nerve fibres.

The second hypothesis is that the hypertension itself changes the status of the axon. Dr. Hansson of the University of Göteborg discusssed axonal flow in nerve fibres. There is a continuous flow of proteins and other substances from the retinal ganglion cells to the lateral geniculate body of the opposite side and the superior colliculus. This has been shown by injecting radioactive amino acid of fucose incorporated into proteins of the ganglion cells. He found that these proteins were moved from the retinal ganglion cells to the lateral geniculate body and the superior colliculus at several speeds. The highest was 150 mm. per day, some were intermediate, and some at slow speeds of 2 to 3 mm. per day. There was also a retrograde flow, so that when a tracer was injected into the superior colliculus there was a flow back at a high speed into the retinal ganglion cells. When the intraocular pressure of rabbits was increased, a blockage occurred in the region of the lamina cribrosa so that there was an accumulation of tracer in the region of the lamina and the axons beyond the lamina became collapsed. The process is initially reversible so that when the pressure is relieved the axonal volume returns to normal. It is likely, therefore, that the axonal flow may have an important bearing on optic nerve damage in glaucoma, for if the blockage at the optic disc remains for a long time there will be disappearance of the axon, damage to the ganglion cells, gliosis, and secondary changes. These degenerative changes will be hastened if there is also relative hypoxaemia caused by circulatory changes in the optic nerve head.

(2) CHANGES IN THE DISC IN CAROTID OCCLUSION

Although glaucomatous cupping has been described in carotid occlusion, this change is extremely rare, probably because there is a low perfusion pressure in the disc. The circulation at the disc may be embarrassed but is often compensated by a good collateral circulation arising from the external carotid. If the blood pressure in the ophthalmic artery, and hence the optic disc, is maintained at a normal level during gradual occlusion, no cupping of the disc occurs. However, if the carotid occlusion leads to a sudden fall in the perfusion pressure of the disc, infarction occurs. If, therefore, glaucomatous cupping does develop after carotid occlusion, it occurs very rapidly over a period of 3 to 6 months.