Optic Atrophy in Compression of the Chiasm

A Funduscopic Study of the Human Retinal Nerve Fibre Layer

By
Mats Lundström

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This thesis is based on the following papers, which will be referred to in the text by their Roman numerals:

I. Lundström M. & Frisén L. (1975) Evolution of descending optic atrophy. A case report. Acta Ophthalmol. (Kbh.) 53: 738-746.

II. Lundström M. & Frisén L. (1976) Atrophy of optic nerve fibres in compression of the chiasm. Degree and distribution of ophthalmoscopic changes. Acta Ophthalmol. (Kbh.) 54: 623-640.

III. Lundström M. & Frisén L. (1977) Atrophy of optic nerve fibres in compression of the chiasm. Prognostic implications. Acta Ophthalmol. (Kbh.) 55 (in press).

IV. Lundström M. (1977) Atrophy of optic nerve fibres in compression of the chiasm. Observer variation in assessment of atrophy. Acta Ophthalmol. (Kbh.) 55 (in press).

CONTENTS

INTRODUCTION

Optic atrophy signifies irreversible wasting of optic nerve axons. Optic atrophy is not a disease but a morphologic sequel of disease. It may be caused by lesions affecting the eye, the optic nerves, the optic chiasm, the optic tracts, the lateral geniculate bodies, and sometimes also the suprageniculate visual pathways. Clinical signs of optic atrophy are ophthalmoscopic abnormalities of colour and structure of the optic nerve head as well as permanently defective function of the eye. Objective diagnosis of optic atrophy is largely based on pallor of the optic disc. Important diagnostic and prognostic considerations very often must be based on the appearance of the optic disc. However, the evaluation of optic disc colour by ophthalmoscopy is notoriously difficult.

It has been known for more than 60 years that it is possible to observe bundles of nerve fibres in the retina by ophthalmoscopy in red-free light (Vogt, 1913). Because of the convergence of nerve fibres towards the optic disc, prominence of nerve fibre bundles increases centripetally in the fundus, and is maximal in the peripapillary area. Recently, it has been shown that loss of axons can be more accurately evaluated from the ophthalmoscopic appearance of the peripapillary nerve fibre layer than from the appearance of the optic disc. These defects in the peripapillary retinal nerve fibre layer have been described in several diseases, e.g. glaucoma (Hoyt et al., 1973) and multiple sclerosis (Frisén & Hoyt, 1974).

Chiasmal lesions may be associated with optic disc pallor due to descending degeneration of optic nerve fibres. In patients with compression of the chiasm due to chromophobe adenoma, for instance, the incidence of disc pallor ranges between 49 and 72 per cent, according to the literature. It is reasonable to assume that changes in the retinal nerve fibre layer also occur in these patients. Very little is known in this regard. It is possible that the retinal nerve fibre layer may convey more accurate information about anatomical damage than the optic disc. If so, the possibilities to predict visual recovery after surgical decompression may be improved.

AIMS OF THE PRESENT STUDY

1. To investigate the occurrence and appearance of retinal nerve fibre layer defects in patients with varying degrees of chiasmal compression due to chromophobe adenoma.

2. To analyse the relationship between the functional defect and a visible nerve fibre layer defect in patients with partial recovery from chiasmal lesions.

3. To analyse possible prognostic implications in preoperative patients with active chiasmal compression.

SURVEY OF THE LITERATURE

OPTIC ATROPHY

General considerations.

Optic atrophy indicates irreversible wasting of the optic nerve. The histopathologic characteristics are loss of axons and shrinkage of supporting tissue. These pathological changes of the optic nerve reflect degeneration of nerve fibres in the anterior visual system (the retino-geniculate pathway). On rare occasions, such a degeneration also occurs in cases with suprageniculate lesions, so-called trans-synaptic degeneration (van Buren, 1963a). Optic atrophy is not a disease but a morphologic sequel of a spectrum of diseases and sites of lesions (Walsh & Hoyt, 1969).

Optic atrophy may be caused by any process that is capable of destroying axons. Once initiated, degeneration comprises the entire axon, its geniculate connections, and its ganglion cell body in the retina. Thus, an interruption of axons in the optic chiasm will produce a descending (retrograde) degeneration including the ganglion cell bodies, and an ascending (wallerian) degeneration including the synaptic terminals in the lateral geniculate body.

In ascending degeneration, the nerve fibres distal to the lesion disintegrate and disappear at a rate proportional to their diameter. This has been clearly shown in experimental studies in squirrel monkeys by Anderson (1973). Retinal nerve fibres were destroyed by photocoagulation in a ring surrounding the optic disc. In large optic nerve fibres signs of ascending degeneration were seen already after four days. After two weeks signs of degeneration were seen also in nerve fibres of small diameters. The axonal breakdown was followed by a collapse of glial tissue and myelin sheaths.

Descending degeneration started between four and five weeks after an experimental lesion of the squirrel monkey optic nerve at the apex of the orbit (Anderson, 1973). Six weeks after injury, degeneration comprised almost all axons in the optic nerve. The mitochondria of the axons were condensed and aggregated together with crinkled lipoprotein membranes. By eight weeks, most of the axons with myelin sheaths were entirely disintegrated. Later, a slowly decreasing amount of myelin debris was found. The optic nerve decreased in diameter. Longitudinal columns of astrocytes replaced the axon bundles. In the optic disc, astrocytes invaded the spaces previously occupied by bundles of nerve fibres. Spielmeyer (1906) is credited with the discovery of this type of astrocyte proliferation in optic atrophy. It is usually called columnar gliosis or columnar atrophy. Another kind of optic atrophy, cavernous atrophy, lacks the glial proliferation. Instead a mucoid degeneration of glial tissue occurs, and clear pools of watery material are formed within the spaces previously occupied by axons. Cavernous atrophy is common in cases with a longstanding optic nerve ischemia. It was first described in glaucoma (Schnabel, 1892).

Clinical signs of optic atrophy.

Clinical signs of optic atrophy include (1) ophthalmoscopic abnormalities of colour and structure of the optic nerve head, and (2) permanently defective function of the eye (Walsh & Hoyt, 1969).

Ophthalmoscopic diagnosis of optic atrophy is largely based on pallor of the optic disc. It is generally believed that pallor derives from glial proliferation, and/or from reduced blood flow. The functional consequences of atrophy form a wide spectrum as exemplified by reduced visual acuity, colour vision defects, and visual field defects.

Every ophthalmologist now and then sees a patient with an obviously pale optic disc but seemingly normal function. According to Mooney (1964), this may be explained by a scattered distribution of damaged axons, which

is extraordinarily difficult to record with presently available clinical tools. It has also been suggested that a pale optic disc is compatible with a normal optic nerve (Duke-Elder, 1971), but histopathological confirmation is scarce. Conversely, funduscopy in patients with irreversibly defective function of long standing may disclose a completely normal disc colour.

Evaluation of optic disc colour is notoriously difficult. The difficulties comprise evaluation, recording, and longitudinal study of disc colour. Mooney (1964) suggested three grades of pallor where

(1) the pallor is slight but definite,

(2) pallor is more marked but not absolute, and

(3) the disc is pure white.

Other graduations have also been proposed, but will not be discussed here. Walsh & Hoyt (1969) considered funduscopic grading of pallor as a measure of atrophy of little practical value.

The optic disc colour has also been evaluated by photographic methods (Schwartz et al., 1973) and by colorimetric measurements (Berkowitz & Balter, 1970). The value of such methods is limited by the fact that the disc rarely has a uniform colour.

The optic disc colour is not the only factor that has been used to assess atrophy. Kestenbaum (1946) introduced a capillary counting test. According to him, the average number of small vessels passing over the disc margin in normal eyes is about ten. In descending optic atrophy the number of small vessels is reduced to seven or six or even less (Kestenbaum, 1946).

Optic disc pallor in compression of the chiasm.

Pallor of the optic disc is a common sign in compression of the chiasm. The term compression implies primarily mechanical displacement and deformation of the chiasm. The ultimate cause of anatomical damage is not known and several alternative explanations are conceivable. The effects of mechanical deformation and compression on intraneural microcirculation, axonal flow, myelin sheaths, and supporting tissue are incompletely known (Frisén et al., 1976). Some authors favour the tension hypothesis, which implies that traction in the nerve fibres is the actual cause of axonal death (Fisher, 1913; Fleischer, 1914; O'Connell, 1973). According to O'Connell (1973) the non-crossing fibres in the chiasm are lax compared with the crossing fibres. Therefore, the tension will be greatest in the crossing fibres in the median plane of the chiasm in spite of variations in the exact size, shape and position of the tumour dome.

Pressure combined with tension and strangulation of the crossing fibres has also been proposed (Walker & Cushing, 1918). Another possible cause is ischemia due to strangulation of the supplying vessels (Hughes, 1958; Dawson, 1958). The fact that the central portion of the chiasm derives its blood supply solely from an inferior group of vessels from the circle of Willis has made the ischemia theory attractive (Bergland & Ray, 1969). François et al. (1958), however, believe that ischemia arises at a capillary level within the tissue due to compression from the outside and not from pressure on individual vessels. Irrespective of the actual cause of damage, a considerable displacement and deformation of the optic chiasm usually occurs with pituitary tumours. Therefore, the term compression will be used in this study.

The incidence of optic disc pallor in patients with pituitary tumours is indeed varying in the literature (Table I).

Table I.

Incidence of optic disc pallor in pituitary tumours as reported in the literature.

Author(s)	Diagnosis	No. of cases	Disc pallor, per cent of cases
Hirsch 1921	Pituitary tumour	45	89
Braunstein 1925	Pituitary tumour	73	56
Fischer 1935	Pituitary tumour	59	89
Hartmann & Guillaumat 1938	Pituitary adenoma	50	54
Bakay 1950	Chromophobe adenoma	232	72
Chamlin et al. 1955	Chromophobe adenoma	109	61.5
Lyle & Clover 1961	Pituitary adenoma	100	56
Nover 1962	Pituitary adenoma	100	54
Clarke et al. 1963	Chromophobe adenoma	75	49
Wilson & Falconer 1968	Chromophobe adenoma	50	56
Hollenhorst & Younge 1976	Pituitary adenoma	1000	34

Examination methods and surgical techniques have changed considerably since the earliest report, and therefore only reports published in 1920 or later have been included. Excellent surveys of the earlier literature have been given by Wilbrand & Saenger (1915) and von Hippel (1923).

The variations in incidence is not surprising with regard to the difficulties in evaluating the optic disc colour as detailed above. Chamlin et al. (1955) reported a great variation in assessment of atrophy between different experienced observers. Thus, in several cases, some observers were quite sure that the appearance of the disc represented optic atrophy, while other observers thought that the colour of the discs was within normal limits. Other factors than observer variation also influence the incidence of atrophy. An early diagnosis, for instance, will result in a low incidence.

Some authors have claimed that there are characteristic features in optic atrophy due to compression by tumour. Such features are a pronounced temporal pallor (Behr, 1931; Vogelsang, 1933; Hirsch, 1949), a yellowish tint of the disc colour (Holloway, 1931) or an excavated optic disc (Gutmann, 1929; Thiel, 1933). Huber (1971) stated that a uniform pallor of the entire disc is the most frequent variant.

De Martel et al. (1931) suggested that the early pallor in chiasmal compression may be caused by vascular compression instead of degeneration. Another hypothesis was presented by Schreiber (1933), who suggested that early pallor was due to axonal swelling. Schreiber thought that this could explain the reversible pallor sometimes reported in chiasmal compression. None of these ideas have been supported by objective evidence.

Optic disc pallor becomes increasingly frequent the longer the history of visual failure, but it may be present also in cases with a short history (Wilson & Falconer, 1968). In cases with unknown duration of visual failure a marked degree of disc pallor indicates a longstanding process (Chamlin et al., 1955).

Disc pallor is a sign of poor prognosis with regard to visual function (Kayan & Earl, 1975). However, after a successful surgical decompression the visual function may improve also in cases with disc pallor (Hirsch, 1930). Paradoxically, a considerable postoperative recovery of vision may occur even in patients with increasing disc pallor (Hirsch & Hamlin, 1954; Kayan & Earl, 1975).

Concluding remarks.

Previously described ophthalmoscopic signs of optic nerve fibre atrophy in patients with chiasmal compression have largely been limited to various grades of optic disc pallor. However, for several reasons disc pallor is an unreliable sign of optic atrophy. The paleness is probably not directly due to loss of axons. Circulatory changes in the optic disc or a reorganization of the glial matrix have been suggested to explain the paleness. The time interval between axonal damage and debut of disc pallor is also incompletely known. Disc colour is notoriously difficult to evaluate by ophthalmoscopy. A considerable observer variation has been reported. Epipapillary membranes (Foos & Roth, 1972; Jerndal, 1976) as well as variations in optic disc topography influence evaluation of the colour. Furthermore, nuclear sclerosis and poor illumination tend to give a false impression of "normal" colour. In patients with compression of the chiasm due to pituitary adenoma, several reports describe simultaneous evolution of disc pallor and recovery of visual function.

Recently, changes in the retinal nerve fibre pattern have been described in various diseases affecting the anterior visual pathways. These ophthalmoscopically visible defects in the nerve fibre layer have been correlated to visual field defects. Such nerve fibre layer changes may be more sensitive and more reliable indicators of nerve fibre atrophy than disc pallor in patients with optic atrophy due to chiasmal compression. A review of the present knowledge of the retinal nerve fibre layer is therefore motivated.

ANATOMY OF THE HUMAN RETINAL NERVE FIBRE LAYER

Microscopy.

History. The retinal nerve fibres are the axons of the retinal ganglion cells. These axons converge towards the optic disc and form the nerve fibre layer, which occupies the most vitreal layer of the retina.
The radial arrangement of the retinal nerve fibres was first described in 1836 by Wallace, who also described the arcuate course of nerve fibres above and below the macula. These observations were later confirmed by others (Michaelis, 1842; Bowman, 1849; Kölliker, 1854). Michaelis (1842) found that the nerve fibres between the optic disc and the macula had a straight course and formed a very thin layer. Michaelis also observed that the arcuate fibres outside the macula ended in a line of demarcation (the so-called raphe) which they never crossed. More temporally the raphe

disappeared, permitting partial intermingling of the upper and lower arcuate fibres. Still more temporally the fibres had a radial course. Kölliker (1854) found that the nerve fibres were arranged in bundles and that there was an exchange of nerve fibres between adjacent bundles. Michel (1874) managed to separate the nerve fibre layer from the rest of the retina by careful dissection and showed that there were spaces between the nerve fibre bundles. These spaces were broader in the periphery, and Schwalbe (1874) pointed out that these interspaces were occupied by processes from a special type of glial cells (Müller cells).
Dogiel (1891) stained the nerve fibre layer with methylene blue and found thin nerve fibres in the macular region and also some arcuate fibres overlapping the raphe.
These early observations were corroborated by others during the following period. Additional important contributions to our knowledge of the anatomy of the retinal nerve fibre layer have not been made until the last two or three decades, however. These modern contributions will be reviewed below.

Topography of the nerve fibre layer. Close to the disc border, the axons are arranged in a radial direction. Also in the nasal peripapillary retina the axons have an approximately radial course (Fig. 1). In the temporal peripapillary retina only axons from the nasal edge of the macula run directly to the disc. Fibres from other parts of the macula take an arcuate course. Thus, all macular fibres occupy an oval area, forming the papillomacular bundle. Hoyt & Tudor (1963) showed with degeneration studies in primates that axons arising from the retina between the macula and the optic disc passed directly to the disc on its temporal side. All other nerve fibres from areas situated temporally to the optic disc have an arcuate course. These arcuate fibres are especially prominent around the large temporal vessels where they form an upper and a lower arcuate bundle (Fig. 1).

The temporal raphe is about three to four mm long (Vrabec, 1966). The raphe is not a true anatomical dividing line between upper and lower arcuate fibres (Michel, 1874; Dogiel, 1891; Ballantyne, 1946; Vrabec, 1966). Vrabec (1966) stated that there is a horizontal overlapping of fibres for a distance of about 200 - 400 µm. Temporally to the raphe, the nerve fibres have an approximately parallel course without horizontal overlapping (Honrubia, 1976).

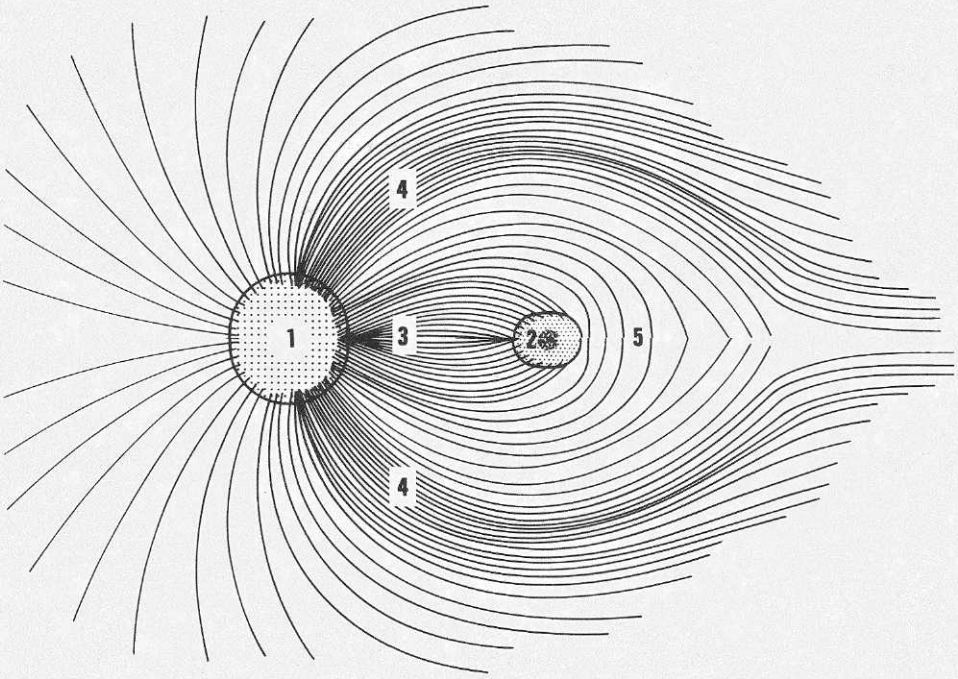

Fig. 1. Schematic drawing of the human retinal nerve fibre layer. 1. Optic disc. 2. Macula. 3. Papillomacular bundle. 4. Arcuate bundle. 5. Temporal raphe.

The position occupied by the retinal nerve fibres at the optic nerve head has been discussed extensively in the literature. The excellent degeneration studies in the rabbit and the monkey by Wolff & Penman (1950), and in the monkey by Hoyt (1962) have shown that in these species the peripheral retinal nerve fibres are situated peripherally at the nerve head. The retinal nerve fibres from the central ganglion cell bodies are found near the central core of the optic nerve. These findings agree with the opinions of several earlier investigators (Leber, 1877; Dean & Usher, 1896; Seidel, 1919; Brouwer & Zeeman, 1926). It is generally accepted that this organization is valid also for the human optic disc (Duke-Elder, 1971).

As to the topographic organization in depth of nerve fibres in the retina there are still conflicting views. There are three possibilities (Fig. 2). Nerve fibres from the peripheral retina may run deep in the nerve fibre layer, and fibres from central parts superficially (Fig. 2A). This topography was found in rabbits by Sjaaff & Zeeman (1924) and by Wolff & Penman (1950). Wolff & Penman considered the evidence overwhelmingly

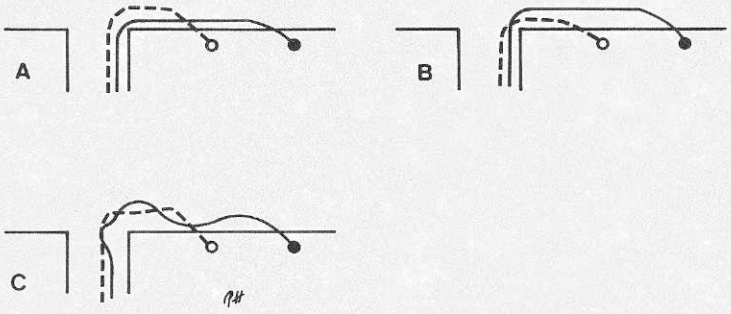

Fig. 2. Schematic drawing of possible topographic organizations in depth of retinal nerve fibres. A. Fibres from peripheral ganglion cell bodies deep, fibres from central ganglion cell bodies superficial. B. "Peripheral" fibres superficial, "central" fibres deep. C. "Peripheral" and "central" fibres intermingled.

in favour of the peripheral retinal nerve fibres lying deep in the nerve fibre layer in man as in rabbit. Copper (1955) was of the opinion that this is compatible with clinical findings in choroiditis.

Polyak (1957) suggested that the peripheral fibres may start superficially and gradually sink deeper as they approach the optic disc. Goldberg & Coulombre (1972) showed that in the chick retina the peripheral nerve fibres were situated in the most vitreal portion of the nerve fibre layer (Fig. 2B). Recently, Hoyt and co-workers in funduscopic nerve fibre studies found that in cases with atrophy of nerve fibres from the nasal hemiretina, the remaining fibres from the distant temporal retina seemed to have a superficial course (Hoyt & Kommerell, 1973; Hoyt et al., 1973).

The possibility of intermingling of nerve fibres in the retina was suggested by Traquair (1949). This theory was also supported by Ogden (1974), who showed by autoradiography that nerve fibres of Rhesus monkeys intermingle freely along the intraretinal course of an arcuate bundle (Fig. 2C). Positive proofs of the topographic organization of the human retinal nerve fibre layer are still lacking.

So-called accessory nerve fibre bundles and axons situated between the nerve fibre layer and the ganglion cell layer in the arcuate areas were described by Vrabec (1966). These fibres had not an arcuate but a radial course. According to Vrabec, they were probably primordial axons from ganglion cells differentiating at the same time as the axons of the central area or later.

Bundles of axons have been found in the tunica media of large blood vessels in the human nerve fibre layer (Wakui et al., 1968). In different animal eyes (rabbit, dog, cat, sheep and monkey) axons have been found terminating with peculiar end-bulb formations on the vessel walls (Iyoda, 1969; Matsuyama, 1973). It has been suggested that these fibres may be centrifugal nerve fibres. There is some evidence for such fibres in the dog and the cat (Hascke, 1963; Brooke et al., 1965). Noback & Mettler (1973) have shown in the Rhesus monkey that there may exist centrifugal nerve fibres from the colliculus superior to the retina. Wolter (1956a) has suggested that single apparently normal nerve fibres in the human optic nerve, found several years after enucleation, may be centrifugal nerve fibres. In man, the existence of such centrifugal nerve fibres has not been confirmed, however.

Microstructure of the nerve fibre layer. The nerve fibre layer of the human retina contains ganglion cell axons, glial cells, Müller cell processes and a well developed vascular system (Hogan et al., 1971). The nerve fibre layer is thickest around the margins of the optic nerve head. At the upper and lower nasal margins it is about 20 - 30 µm thick, but at the temporal margin only about 10 µm (Wolff, 1961). In the retinal periphery single axons together with single ganglion cell bodies constitute one thin layer (van Buren, 1963b). The axons are usually unmyelinated and have a diameter between 0.6 and 2 µm (Villegas, 1964). Sometimes some intraretinal nerve fibres may be medullated. The incidence ranges between 0.1 and 0.7 per cent (Kölliker, 1885; Wollenberg, 1889; Mayerweg, 1903; Terwelp, 1905; Lorentzen, 1963).
In the aged human retina axonal enlargements have sometimes been found. They probably represent a non-specific nerve fibre reaction (Vrabec, 1965a; Vrabec, 1965b; Wolter, 1968).

Most of the nerve fibres are arranged in bundles (Kölliker, 1854). Glial processes from astrocytes and Müller cells penetrate the bundles and surround the axons. Some parts of the axons may have a close membrane contact with neighbouring axons (Villegas, 1964). This close contact has also been found in the monkey retina, but the distance that a pair of con-

tiguous axons remain approximated is still unknown (Cohen, 1961). Cohen suggests that clusters of axons may be functional units of some sort. There is a tendency for fibres emerging from any territory of the retina to preserve their relative position with respect to other fibres (Polyak, 1941). There is also an exchange of axons between adjacent bundles (Kölliker, 1854; Polyak, 1941).

Adjacent bundles are separated by processes from the Müller cells (Schwalbe, 1874). The Müller cell processes form foot-plates in their vitreal part. Each process is on this level about 4 - 5 /um in diameter and they are arranged in bundles of about 20 - 25 /um in diameter (Uga, 1974). These bundles of Müller cell processes enclose the nerve fibre bundles (Fig. 3). Sometimes a bundle of Müller cell processes may diverge in the middle of the nerve fibre layer and so enclose a bundle of axons (Uga, 1974).

The astrocytes of the nerve fibre layer are as a rule bipolar. They are sometimes called lemnocytes (Wolter, 1955; Hogan et al., 1971). Towards the optic disc the ordinary astrocytes become frequent (Anderson, 1970), and transition forms are also numerous (Hogan et al., 1971). Other specialized glial cells found in the nerve fibre layer are the perivascular glial cells around the retinal capillaries (Wolter, 1959), and the microglial cells (Hogan et al., 1971).

The capillaries in the nerve fibre layer are surrounded by processes from Müller cells and other glial cells. These processes and their cells are also in close contact with the axons (Villegas, 1964). Besides the ordinary capillaries there are special capillaries occupying the superficial portion of the nerve fibre layer in the peripapillary retina, the so-called radial peripapillary capillaries (Henkind, 1967; Wise et al., 1971). Recently, Ueno (1976) by scanning electron microscopy has shown that these capillaries are extremely numerous close to the optic disc.

The vitreal surface of the nerve fibre layer is formed by the foot-plates of the Müller cells and special "endothelium-like" astrocytes (Wolter, 1956 b; Gärtner, 1962). The astrocytes are numerous close to the optic disc, and on the optic disc the surface is solely formed by astrocytes (Anderson, 1970). Vitreal to the glial cells and intimately attached to these cells is a basement membrane (Fine & Zimmerman, 1962; Gärtner, 1962). Vitreal to the basement membrane is another layer with fibrils. The basement membrane and the fibril layer constitute the internal limiting membrane, 2 - 3 /um in thickness (Gärtner, 1962).

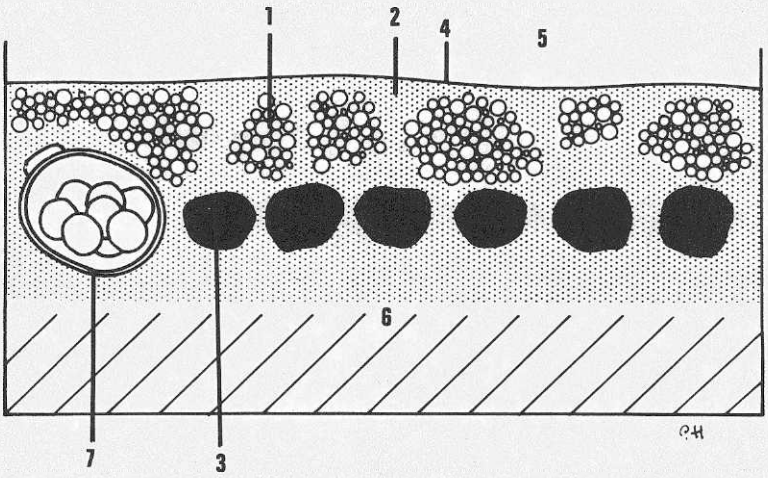

Fig. 3. Schematic drawing of relationship between nerve fibre bundles and bundles of Müller cell processes. 1. Nerve fibre bundle. 2. Bundle of Müller cell processes. 3. Ganglion cell layer. 4. Internal limiting membrane. 5. Vitreous body. 6. Deeper parts of the retina. 7. Blood vessel.

Funduscopic appearance of the normal retinal nerve fibre layer.

During the early ophthalmoscopy era technical limitations made visualization of the retinal nerve fibre layer difficult (Liebreich, 1869). In 1913 Vogt, during studies of the macular pigment in vivo, noticed that the nerve fibre pattern was enhanced by red-free light in ophthalmoscopy. Vogt reported that the nerve fibre layer appeared as light and dark linear reflexes sometimes interweaving with each other. The nerve fibre pattern was visible in patients of all ages. Nerve fibres perpendicular to a small vessel could be seen as fine lines superficial to the vessel. In this early report, Vogt simply stated that the nerve fibres had the same direction as the retinal vessels. Vogt's original report was followed by more extensive studies with red-free ophthalmoscopy of the retinal nerve fibre layer in normal and pathological conditions (Vogt, 1917; Affolter, 1917; Vogt, 1921; Vogt, 1925). According to these reports, the normal nerve fibre pattern was best seen in young individuals and in darkly pigmented eyes. Sometimes reflexes from the internal limiting membrane were disturbing, especially in young persons. These superficial reflexes had been thoroughly studied by Dimmer (1891). Vogt noted that these reflexes were more

glossy than the nerve fibre reflexes and that they changed position when the angle of ophthalmoscopic illumination was changed. The striated pattern was due to the nerve fibre bundles and the interspaces between them. The striations started at the border of the optic disc. The striations were coarse in the peripapillary region and more delicate in the periphery. The most prominent bundles were seen in the peripapillary sectors. In the papillomacular bundle the nerve fibre bundles were thin and formed a faintly visible striated pattern. The large retinal vessels were usually superficial to the nerve fibre layer, but the small vessels were embedded and overcrossed by nerve fibre bundles. Vogt reported that there was a certain degree of variation in bundle size between different individuals. He also stated that the nerve fibre reflexes temporal to the macula showed a considerable over-crossing of the raphe. Red-free ophthalmoscopy was performed by others of that period but little of importance was added to the above description of the normal nerve fibre layer (Heine, 1918; van der Heydt, 1919; Dobson, 1928). Recently, however, new contributions to this field have been made by Hoyt and co-workers (Hoyt et al., 1973), particularly in the field of acquired defects of the retinal nerve fibre layer (see below).

Concluding remarks.

Research upon the human retinal nerve fibre layer has been concentrated on cross-sectional microscopic studies. Very little is known about the three-dimensional topography. Although it is known that most fibre bundles follow curvilinear paths in the retinal nerve fibre layer, much remains to be learned about the areas of origin for those bundles that can be seen ophthalmoscopically in the peripapillary area. There appears to be a considerable variation between individuals. Better knowledge of the nerve fibre topography and the histologic correlates of the funduscopic appearance might be obtained by three-dimensional study technique like microdissection or serial sectioning.

The functional significance of the peculiar exchange of nerve fibres between adjacent fibre bundles is not known. The close membrane-to-membrane relation of single axons is also incompletely understood. This points to the need of functional studies.
Single axons from retinal ganglion cells fall below the resolution limits of the ophthalmoscope (Frisén, 1973a). Bundles of axons have better visibility. The relationship between visibility and bundle size is not known. There is an obvious variation in nerve fibre visibility between different individuals and sometimes the visualization of the nerve fibre layer may

be difficult.

METHODS IN CLINICAL EXAMINATION OF THE RETINAL NERVE FIBRE LAYER

Ophthalmoscopy.

Vogt, in his classical studies on the nerve fibre layer, used a fluid filter composed of two solutions to obtain red-free light: an aqueous solution of copper sulphate, and an aqueous solution of erioviridin B, an aniline dye. Such a filter transmits light in the 420 to 600 nm wavelength interval. A carbon arc lamp was used for illumination. Both filter and light source were of course difficult to handle, and this certainly limited the use of red-free ophthalmoscopy. Dobson (1928) used a green celluloid filter to obtain red-free light and considered it equivalent to a fluid filter. Nowadays most ophthalmoscopes are provided with a yellow-green absorption glass filter. This kind of filter is not red-free, because a truly red-free filter absorbs too much light (Ballantyne, 1937). A common compromise is a yellow-green filter resembling Kodak Wratten Gelatin Filter No. 61 (Table II) that transmits light between 490 and 605 nm.

When a modern ophthalmoscope that provides a bright green illumination is used, the nerve fibre layer appears slightly opaque. The nerve fibre bundles are visible at least two to three disc diameters outside the optic disc. Small vessels are obscured by nerve fibre bundles and probably by superficial capillaries too (Hoyt, 1976), and therefore have a blurred, cross-hatched appearance.

Vogt (1913) stated that the retina appears less transparent to light of short wavelengths. Light of longer wavelengths penetrates the retinal pigment layer and the major part of the reflected proportion comes from the choroid and the sclera (Vogt, 1913). Ballantyne (1937) and Behrendt & Wilson (1965) made the same conclusions.

Light of short wavelengths is to a considerable part absorbed in the lens (Vogt, 1917). This is especially the case with patients with pigmentation of the lens, as the aged. On the other hand, the disturbing glossy reflexes from the internal limiting membrane decrease with age, possibly due to a changed relation between the refractive indices of the superficial retinal layer and the vitreous body (Dimmer, 1891; Goodside, 1956). Red-free light shows the nerve fibre pattern most clearly in young patients with darkly pigmented fundi.

Table II.

Transmission peaks and luminous transmittance in some gelatin absorption filters used to obtain "red-free" light.

Filter	Transmission peak (nm)	Luminous transmittance per cent
Kodak Wratten No. 40	513.4	33.6
- " - 44 A	491.9	15.2
- " - 58	538.2	19.8
- " - 61	533.8	16.8
- " - 65	501.3	6.6
- " - 65 A	497.3	6.2

Fundus photography.

Many early investigators (eg. Pavia, 1931; Kugelberg, 1934) studied fundus details by photography with restricted spectrum light. However, the technical limitations of that time made demonstration of fine fundus details extremely difficult. By using interference filters and a Zeiss Oberkochen fundus camera, Behrendt & Wilson (1965) demonstrated that the nerve fibre layer could be photographed on black-and-white film. They used narrow-band interference filters (half-width[x] 10 nm) and reported that the nerve fibre bundles were seen when filters with transmission peaks in the interval from 431 nm to 577 nm were used. The nerve fibre bundles were best seen at 477 nm (Behrendt & Wilson, 1965; Behrendt & Duane, 1966).

In more recent reports on red-free fundus photography different Kodak Wratten absorption filters have been used. Transmission peaks and luminous transmittance for commonly used filters are detailed in Table II.

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x/ Half-width denotes the wavelength interval within which 50 per cent of the transmitted luminous energy is contained.

Table III.

Combinations of fundus camera, film and filter described in some recent reports on red-free fundus photography.

Authors	Camera	Film	Filter (Kodak Wratten)
Mizuno et al. (1968)	Olympus	Kodak Tri-X Pan	No. 65 A
Hoyt et al. (1973)	Zeiss Oberkochen	Kodak Plus-X Pan	No. 65
Sharp & Sanders (1975)	Zeiss Oberkochen	Ilford FP_4	No. 65
Iwata et al. (1975 a)	Olympus	Kodak Tri-X Pan	No. 44 A

Different fundus cameras and photographic films have been used (Table III). Usually the exposures were made on black-and-white negative film. Hoyt and co-workers (1973) reported, however, that they sometimes recorded the fundus on Kodachrome II film. The colour transparencies were then copied on black-and-white film by use of a Kodak Wratten filter No. 65. Fundus photography without a filter but with an orthochromatic black-and-white film will also result in a visible nerve fibre pattern (Craandijk & Aan de Kerk, 1969).

Irrespective of filters, however, the recording of fundus details of low contrast will be limited by other technical factors, such as the resolving powers of the eye, the camera and the photographic emulsion. According to Frisén (1973 a) the most important resolution-limiting factor in fundus photography is the fundus camera. For improved results the focal length/stop ratio of the camera must be decreased. The resolution is critically dependent on precision of focusing. Recently Laing & Danisch (1975) described a method which makes it possible to focus the fundus camera objectively. However, sharpness of an image has no fixed relation to the limit of resolution of an optical system (Stulz & Zweig, 1962). The clarity with which details are reproduced in a photographic image is influenced principally by four factors: sharpness, resolution, graininess and tonal reproduction (Brainard & Ornstein, 1965). It is sometimes possible to enhance the visibility of small details. The sharpness of details, for instance,

can be improved by the use of an unsharp mask (Yule, 1945). Unsharp masking in fundus photography has proved to be particularly valuable in studies of the retinal nerve fibre layer (Frisén & Hoyt, 1973). Also Iwata et al. (1975 a) applied a subtraction technique to the fundus photographs in their nerve fibre layer studies. It is also possible to make an objective assessment of density variation in negatives obtained by red-free fundus photography (Lundström & Eklund, 1977).

Concluding remarks.

The most important factor in fundus photography is precise focusing of the camera. Visibility of nerve fibre patterns is drastically reduced in blurred negatives due to poor focusing. A most desirable improvement, therefore, concerns objective focusing of the fundus camera. A better resolution of the fundus camera is also needed. This requires a larger aperture of the camera system. Many different filters have been used to obtain red-free light in fundus photography. A broad-band filter with a high luminous transmittance makes it easy to obtain normally exposed negatives. Conversely, when narrow-band filters with a low luminous transmittance are used, the amount of reflected light is small and the negatives tend to be underexposed. The density is a critical factor for the reproduction of small details such as nerve fibre bundles. Therefore, a broad-band filter with a high luminous transmittance usually will be the filter of choice.

According to Behrendt & Wilson (1965), even small opacities in the vitreous obscured the nerve fibre pattern when filters in the 431 to 477 nm wavelength interval were used. Such filters are therefore of little value when small details like the nerve fibre bundles are studied. Filters with peak transmission within the limits 504-549 nm are less sensitive to opacities, and therefore preferable.

If negatives of normal density are desired, a high-speed film (125-400 ASA) is usually necessary. There are films available with a better resolving power at low contrast (Frisén, 1973 a) but a wide use of these films is not possible without an improvement of the light source.

FUNDUSCOPIC APPEARANCE OF NERVE FIBRE ABNORMALITIES

Excessive prominence of the nerve fibre layer.

Already in 1869 Liebreich pointed out that the nerve fibre pattern was enhanced in "neuritis". Vogt (1921) found that during the acute phase of "neuroretinitis luetica" and central vein thrombosis a coarsening of the nerve fibre pattern occurred. The nerve fibre bundles were thicker and sometimes less distinct and the interweaving was more prominent. Vogt suggested that the coarsening of nerve fibre bundles was due to swelling of the axons. These changes were most prominent in the arcuate bundles.

Vogt's description of "nerve fibre swelling" somehow escaped attention until Ito et al. (1969) and Mizuno et al. (1971) reported similar changes of the nerve fibre appearance in early stages of retrobulbar neuritis. They suggested that the changes were due to edema between the nerve fibres.

More recently, Hoyt and co-workers have described in detail nerve fibre changes in several acute optic neuropathies. They have stated that coarseness of nerve fibre striations and increased opacity of the nerve fibre layer is characteristic of acute stages of retrobulbar neuritis, Leber's optic neuropathy, constrictive optic neuropathies, and ischemic optic neuropathy (Smith et al., 1973; Hoyt, 1976). It has been suggested that the greyish blurring of nerve fibre tissue in early papilloedema and in acute elevation of the intraocular pressure is due to swelling caused by a blocked axonal transport at the optic disc. (Hoyt & Knight, 1973; Hoyt, 1976).

Atrophy of the nerve fibre layer.

Vogt described total atrophy of nerve fibres in widespread areas of the retina. According to him the nerve fibre striation was lost and replaced by a "Marmorierung" of the retina (Vogt, 1913). A more detailed knowledge of the nerve fibre abnormalities has been obtained through modern studies.

Defects in the nerve fibre layer may be focal and/or widespread in the fundus. Focal defects appear as dark slits or grooves in the peripapillary arcuate areas (Hoyt & Newman, 1972; Hoyt et al., 1973). They are probably due to a focal loss of adjacent axons or bundles of axons. These slit-like gaps are best seen in the arcuate bundles, one or two disc diameters away from the optic disc. Such small defects are often hidden by other nerve fibre bundles near the optic disc because of the convergence

of the remaining nerve fibres. If atrophy involves several adjacent nerve fibre bundles the resulting defect has a wedge-shaped appearance (Hoyt et al., 1972 a). A wedge-shaped defect can be traced from the disc margin at least one or two disc diameters away, before it fades from view. In white light, such a defect appears redder than the adjacent nerve fibre layer and it appears darker when red-free light is used. Within the wedge-shaped area no vessels are obscured by nerve fibre bundles. A focal loss of axons may be seen as a dark streak in areas with medullated nerve fibres (Sharp & Sanders, 1975).

Wedge-shaped defects have been produced in Rhesus monkeys by argon laser photocoagulation (Frisch et al., 1974). The defects were documented by fundus photography. Examination of histopathological sections confirmed the presence of alterations corresponding to the defects. There was an obvious loss of nerve fibres.

A widespread atrophy of nerve fibres is usually best seen in the peripapillary area. If the atrophy is incomplete there will only be a diffuse thinning of the nerve fibre layer. The signs of such a defect include a decreased nerve fibre opacity, especially in the arcuate areas, less prominent striations, and sometimes a decrease in vessel diameter. In total atrophy, there is a complete loss of nerve fibre opacity and nerve fibre striation. Large vessels appear narrow and with a sheathing close to the disc. Vessels of medium size and small vessels are no longer obscured by nerve bundles. Small vessels are difficult to visualize. The retina often acquires a granular appearance (retinal mottling). (Hoyt et al., 1973)

Extensive nerve fibre defects are associated with changes of the optic disc. A wedge-shaped defect may be accompanied by a notch in the optic disc rim. If nerve fibre atrophy is widespread and total, the corresponding disc sector is pale and contains a reduced number of visible small vessels.

Occurrence of nerve fibre defects in various diseases.

Nerve fibre defects have been reported in many diseases affecting the anterior visual pathways on various levels (Table IV).

In the immature human brain a suprageniculate lesion may be followed by a retinal nerve fibre layer defect due to retrograde trans-synaptic degeneration. Such defects in suprageniculate lesions have been reported by Hoyt et al. (1972 b), Hoyt & Kommerell (1973), Hoyt (1976), Manor &

Korczyn (1976) and Frisén & Holmegaard (1977).

In adults with acquired homonymous hemianopia the site of the lesion determines whether retinal nerve fibre changes occur or not (Lauber, 1927). Lesions of the optic radiation are not followed by retinal nerve fibre atrophy, but lesions of the optic tract will result in typical changes in both fundi. In the ipsilateral eye the nerve fibres from the temporal retinal half will be missing and the normal difference between the prominent arcuate bundles and the nasal bundles will be decreased. In the contralateral eye, the nerve fibres from the nasal hemi-retina are missing and therefore the peripapillary nasal and temporal areas lack nerve fibre opacity and striations. The arcuate bundles have a normal appearance. The optic disc of the ipsilateral eye sometimes shows a mild temporal pallor. In the contralateral eye there may be a horizontal band-shaped pallor and the nasal and temporal disc borders are sharply defined. Such nerve fibre defects in optic tract lesions have been reported by Lauber (1927), Hoyt et al. (1972 b), Hoyt & Kommerell (1973), Lundström (1974), and Hoyt (1976).

When trans-synaptic degeneration occurs, suprageniculate lesions produce the same nerve fibre defects as optic tract lesions.
In lesions of the lateral geniculate nucleus, hemiretinal nerve fibre defects have been found (Hoyt, 1975).

Lesions of the optic chiasm also produce retinal nerve fibre defects. Acquired chiasmal lesions will be discussed in a following chapter. Nerve fibre defects due to congenital chiasmal defects have been reported by Davies & Shock (1975) and Hoyt (1976) in septo-optic dysplasia. The nerve fibre defects in both eyes were similar to those described in the contralateral eye in optic tract lesions. However, the optic discs were hypoplastic in their nasal halves with a white scleral halo around the disc.

Several disorders affecting the optic nerve may produce nerve fibre defects. Hoyt (1976) described nerve fibre defects in patients with congenital optic nerve hypoplasia. Frisén & Holmegaard (1977) observed subtle nerve fibre defects also in cases with hypoplasia of such small degree that disc involvement was equivocal only. Nerve fibre defects due to bullet injury have been reported by Vogt (1921). Vogt reported loss of nerve fibre reflexes six weeks after the injury.
Compression of the optic nerve due to extrinsic and intrinsic tumours may also cause nerve fibre defects (Johansson & Enoksson, 1976).

Table IV.

Survey of nerve fibre layer defects reported in the literature.

I.	Suprageniculate pathways		Hoyt et al. 1972 b; Hoyt & Kommerell 1973; Hoyt 1976; Manor & Korczyn 1976; Frisén & Holmegaard 1977.
II.	Lateral geniculate body		Hoyt 1975.
III.	Optic tract		Lauber 1927; Hoyt & Kommerell 1973; Lundström 1974; Hoyt 1976.
IV.	Optic chiasm	congenital defect	Davies & Shock 1975; Hoyt 1976.
		compression	Vogt 1925; Fischer 1935.
V.	Optic nerve	congenital optic nerve hypoplasia	Hoyt 1976; Frisén & Holmegaard 1977.
		tumour (intrinsic and compression)	Johansson & Enoksson 1976.
		trauma	Vogt 1921.
		optic neuritis	Vogt 1921; Frisén & Hoyt 1974; Lundström 1974; Hoyt 1976; Sharp & Sanders 1975.
		tobacco-alcohol amblyopia	Vogt 1921.
VI.	Optic disc	glaucoma	Vogt 1925; Hoyt et al. 1973; Iwata et al. 1975 b.
		low tension glaucoma	Lundström 1974; Hoyt 1976.
		ischemic optic neuropathy	Lundström 1974; Hoyt 1976.
VII.	Retina	"diffuse retinitis"	Affolter 1917.
		"neuroretinitis luetica"	Vogt 1921.
		retinitis pigmentosa	Vogt 1925.
		retinal vascular disease	Vogt 1921; Hoyt et al. 1972 a; Lundström 1974.

In retrobulbar neuritis retinal nerve fibre defects have been reported by Vogt (1921) and Hoyt (1976). Vogt told that in several cases with retrobulbar neuritis leading to permanent scotomas, the nerve fibre striations between the optic disc and the macula (the papillomacular bundle) were replaced by "Marmorierung". In optic neuritis due to demyelinating disease a typical pattern of nerve fibre defects has been reported by Frisén & Hoyt (1974) and confirmed by others (Lundström, 1974; Sharp & Sanders, 1975). In these cases multiple slit-like defects occurred in the peripapillary nerve fibre layer.
In some cases slit-like defects were found also in asymptomatic eyes, indicating a subclinical scattered attrition of axon bundles. In cases with so-called tobacco-alcohol amblyopia Vogt (1921) reported that atrophy of papillomacular nerve fibres might occur.

Several lesions, usually classified as optic disc lesions, cause defects in the nerve fibre pattern. It was obvious already to Vogt (1921) that advanced glaucoma would be associated with extensive nerve fibre atrophy. Early and moderate lesions due to glaucoma also produce nerve fibre defects (Hoyt & Newman, 1972; Hoyt et al., 1973; Iwata et al., 1975 b). These defects include slit-like and wedge-like gaps in the arcuate bundles and they are probably early signs. As the atrophy increases, these focal defects become less distinct due to the diffuse thinning of all surrounding nerve fibre tissue. Such early defects have also been found in patients with so-called ocular hypertension (Hoyt & Newman, 1972).

In low tension glaucoma, on the other hand, a somewhat different spectrum of defects has been reported (Lundström, 1974; Hoyt, 1976). These defects comprise broad wedges or total sectors of the retina with corresponding deeply excavated disc sectors. The surrounding nerve fibre layer usually has a normal appearance. Extensive nerve fibre defects are also reported in ischemic optic neuropathy together with a corresponding pale flat sector of the optic disc (Lundström, 1974; Hoyt, 1976).

Other lesions such as optic disc drusen and optic pit are commonly associated with defects in the nerve fibre layer (Frisén, personal communication). These defects are usually focal, but in cases with advanced drusen extensive nerve fibre defects are common.

Retinal lesions may produce an ascending degeneration and therefore also nerve fibre defects. Such defects have been found in patients with "diffuse retinitis" (Affolter, 1917), "neuroretinitis" (Vogt, 1921), retinitis

pigmentosa (Vogt, 1925), retinal arterial occlusion (Vogt, 1921), and central vein thrombosis (Vogt, 1925). Usually the defects are widespread and total. In arterial hypertension wedge-shaped defects have been observed following resolution of exudates (Hoyt et al., 1972 a; Lundström, 1974). Wedge-shaped defects are also common following retinochoroiditis. In juxtapapillary lesions the defects sometimes engage large sectors of the retina (personal observations).

If papilloedema develops in an eye with nerve fibre defects it will be restricted to those sectors of the disc and the peripapillary retina that contain nerve fibres. This was first shown in patients with optic tract atrophy by Paul & Hoyt (1976).

Correlation with visual field defects.

All modern reports on red-free funduscopy claim a close correspondence between nerve fibre defects and visual field defects. In patients with large defects comprising one half of the retina a correspondence has been shown by Hoyt and co-workers (Hoyt et al., 1972b; Hoyt & Kommerell, 1973). Such a relationship has also been shown in patients with sector-shaped defects due to vascular disorders (Lundström, 1974). With narrow wedge-shaped or slit-like defects the corresponding field defect may be more difficult to demonstrate. The corresponding scotomas are best revealed at the tangent screen (Hoyt et al., 1973; Frisén & Hoyt, 1974).

Concluding remarks.

Any disease that causes cross-sectional damage anywhere along the axon of a retinal ganglion cell, produces axonal degeneration both above and below the lesion. Logically, such damage will always be followed by a defect in the retinal nerve fibre layer. Such a defect should be visible ophthalmoscopically, provided that the number of adjacent axons that have been destroyed is sufficiently large.
Many authors have stated that changes of the retinal nerve fibre layer are easier to detect than the corresponding changes of the optic disc. Certainly, the most detailed information about the anatomical damage will be obtained by a simultaneous evaluation of both the nerve fibre layer and the optic disc.

Our present state of knowledge is valid only for static abnormalities in the retinal nerve fibre layer. No information is available about the dynamic evolution of nerve fibre defects. Longitudinal studies of the ret-

inal nerve fibre layer in glaucoma and other diseases must be considered as important.

The relationship between position in the retina and position in the visual field is incompletely known (Frisén & Schöldström, 1977). An accurate correlation between field defects and nerve fibre defects requires knowledge of the individual retinal distribution of ganglion cell bodies. A formidable histopathologic project!

NERVE FIBRE ABNORMALITIES IN COMPRESSION OF THE CHIASM

Previous reports.

In patients with chiasmal compression due to pituitary adenoma, funduscopic observations have been largely confined to optic disc pallor. Reports on retinal nerve fibre changes have been rare and in no case documented by fundus photography.

Vogt (1921) described a total loss of nerve fibre striations in a case with bilateral amaurosis due to a pituitary tumour. The vessels were prominent and normal in size. Fischer (1935), in a report on optic atrophy in pituitary tumours, made some observations on nerve fibre layer in red-free light. In one patient with a normal optic disc, there were signs of attrition of the nerve fibres from the temporal retina. In another patient with tumour recurrence and a pale optic disc, an obvious wasting of nerve fibres all around the optic disc was seen. Furthermore, Fischer reported that in patients without advanced damage, a loss of nerve fibre bundles temporal and nasal to the optic disc was seen. The nerve fibre bundles above and below the disc appeared normal. Gartner (1951), in a case with a malignant pituitary tumour, observed a subtle change of colour and sheen of the nasal retina suggesting degeneration. Histopathologic examination confirmed atrophy of nerve fibres and ganglion cell bodies.

Concluding remarks.

Very little is known about the incidence and distribution of nerve fibre layer changes in patients with chiasmal compression. The observations contributed by Vogt and Gartner concerned total atrophy. Fischer (1935) mentioned a few instances of partial atrophy. The wide spectrum of visual field defects in patients with chiasmal compression suggests that there must be a great variation in degree and distribution of nerve fibre atrophy.

A clinical study of the retinal nerve fibre layer and of the optic disc may

well reveal a higher incidence of anatomical damage than a study of the optic disc alone.

VISUAL FIELD DEFECTS IN COMPRESSION OF THE CHIASM

General considerations.

Defects in the visual fields due to compression of the chiasm have been extensively documented in the literature (e.g. Cushing & Walker, 1915; Henderson, 1939; Chamlin et al., 1955; Verriest, 1975). Defective visual function has also been shown with objective methods as exemplified by visual evoked response (Halliday et al., 1976; Wildberger et al., 1976).

Bitemporal field defects are typical in chiasmal compression. Such defects were first described by Mackenzie in 1835. The anatomical-pathological basis of bitemporal defects is interference with fibres coming from the nasal halves of the retina. These fibres cross in the optic chiasm to reach the contralateral optic tract. The existence of a semi-decussation was suggested already in 1704 by Newton, and confirmed later by others (von Gudden, 1874; Cajal, 1899). A highly readable review of the early theories on a semi-decussation of the optic nerves has been given by Rucker (1958).

Many investigators have tried to clarify the exact retinotopic organization of the optic chiasm (Rönne, 1914; Brouwer & Zeeman, 1926; Hoyt, 1962; Hoyt & Luis, 1963). Knowledge of the nerve fibre course in the chiasm could facilitate a precise localization of the lesion by examining the visual field defect. Such a precise localizing value of visual fields has been maintained by several authors (e.g. Knapp, 1940; Adler et al., 1948; Timmerman, 1966). However, the intrinsic nerve fibre organization of the human optic chiasm is still incompletely understood, and topical interpretation of visual field defects on this basis requires care (Huber, 1971). Furthermore, the localization of the optic chiasm is variable (de Schweinitz, 1923; Hughes, 1954). Sometimes compression by adjacent structures (e.g. anterior communicating artery, anterior cerebral artery) is superposed on tumour compression (Türck, 1852; Henderson, 1939; Rucker & Kernohan, 1954; Hirsch, 1965).

Spectrum of field defects in compression of the chiasm.

Bitemporal field defects have been reported in 52 to 96 per cent of patients with pituitary adenomas (Bakay, 1950; Chamlin et al., 1955; Nover, 1962). The variation in incidence may reflect differencies in (a) character of the tumour, (b) definition of a bitemporal field defect, and (c) visual field examination techniques. Some materials are composed solely of chromophobe adenomas (Bakay, 1950; Chamlin et al., 1955), others of both chromophobe and eosinophil adenomas (Lyle & Clover, 1961). In some materials the figure for bitemporal field defects also includes unitemporal field defects (Hirsch & Hamlin, 1954). In others amaurosis in one eye and a temporal defect in the other eye are included as well (Henderson, 1939). Visual field defects of different severity were recognized as stages in a progressive condition already in 1903 by Josefsson. Also Cushing & Walker (1915) claimed that there are typical stages of field defects in chiasmal compression, and they described no less than eight stages. The early stages include depressions in the superior temporal quadrants. In later stages, the field defects progress to the inferior temporal quadrants, leading to absolute bitemporal defects. Thereafter, a breakdown of the nasal field follows, usually beginning with the inferior quadrants; the superior nasal quadrants frequently are the most resistant (Lauber, 1944; Enoksson, 1965; Huber, 1971). Cushing & Walker (1915) claimed that the defects rarely advance symmetrically in both eyes. This has been contested by Huber (1971).

Bitemporal field defects are the most frequent defects according to the literature, but almost all existing combinations of field defects may occur. There are reports on homonymous hemianopsia (Henderson, 1939; Hirsch & Hamlin, 1954), central scotoma (Schlezinger & Thompson, 1967; Sugita et al., 1975), temporal scotoma (Lyle & Clover, 1961; Wilson & Falconer, 1968), arcuate defects (Kearns & Rucker, 1958; Enoksson, 1965), altitudinal defects (Enoksson, 1965), and binasal defects (Huber, 1971).

Visual field examination techniques.

Visual fields have usually been examined in the perimeter, at the tangent screen or by a combination of both methods.
The earliest changes in chiasmal interference are found in the 1/2000 isopter according to Chamlin & Davidoff (1950). They stated that the 1/2000 field also is the last to recover. A serious disadvantage with the

tangent screen is that the test objects have a variable visual angle and that they are difficult to standardize (Cushing & Walker, 1915; Frisén, 1974). These problems are avoided in modern perimeters, which also allow a more sophisticated analysis. Verriest (1975) has advocated kinetic perimetry with several test objects to obtain an accurate picture of both the central and the peripheral field.

Coloured test objects have been widely used earlier, but a carefully performed visual field examination with achromatic test objects is nowadays held to be equally sensitive (Chamlin & Davidoff, 1950; Dubois-Poulsen, 1952; Enoksson, 1953; Huber, 1971). However, coloured test objects have recently been used with advantage in examinations built on supraliminal colour saturation (Frisén, 1973 b; Enoksson & Fristrom, 1975).

Static perimetry has also been used (Harms, 1954; Aulhorn, 1972). Harms (1954) advocated a combination of kinetic and static perimetry in order to obtain maximal information. In most modern reports on chiasmal compression, the visual field examinations have been performed by kinetic perimetry with achromatic test objects only.

Concluding remarks.

According to the literature, compression of the chiasm may be associated with an almost infinite variety of field defects. Unfortunately, it is difficult to evaluate the incidence of various field defects reported in the literature because of varying definitions. The term bitemporal hemianopsia, for instance, ought to be preserved for absolute bilateral defects in both temporal quadrants. Furthermore, the examination techniques are rarely described in detail. Varying examination techniques may explain the variation in occurrence of temporal scotomas and temporal depressions respectively, found in the literature.

Most authors agree about the importance of a central field examination in cases with chiasmal disturbances. Therefore, when a series of patients are examined by perimetry, the test objects must be selected individually in order to obtain adequate sensitivity. Kinetic perimetry combined with an examination of defective areas by static perimetry seems to be an optimal strategy.

PRESENT INVESTIGATION

Compression of the chiasm often causes irreversible visual field defects. Signs of irreversible anatomical damage, as reflected by pallor of the optic disc, are not equally frequently found according to the literature. A direct inspection of the nerve fibre bundles in the peripapillary area may reveal abnormalities consistent with the functional defecit. Although the appearance of such nerve fibre abnormalities can be predicted from present knowledge of anatomy, such defects have not yet been documented by objective methods. Similarly, there should be a close relationship between the severity of visual deficit and the degree of anatomical damage, at least in patients in a postoperative steady state. This possibility merits investigation. If such a relationship can be defined, it should also be possible to predict prognosis for improvement in patients with active lesions: obviously, any improvement is limited by the degree of irreversible damage.

The syndrome of chiasmal compression may be due to a variety of lesions although chromophobe adenomas probably are the most common cause. These tumours do not infiltrate into the chiasm. In our hospital, they are usually treated by transcranial surgery alone, and rarely irradiated. Patients with chiasmal compression from chromophobe adenomas therefore constitute an ideal group for analysis of nerve fibre atrophy due to chiasmal compression.

PATIENTS

The evolution of optic atrophy was studied in one patient with a traumatic lesion of the intracranial part of one optic nerve (I). This was a 35-year-old man with no previous history of eye disease. A bullet injury resulted in immediate and permanent amaurosis of the right eye and an upper temporal field cut in the left eye. Neither x-ray examination nor surgical exploration could reveal the exact site of damage. The visual field defect of the left eye suggested a lesion of the right anterior knee of the optic chiasm.

The appearance of the retinal nerve fibre layer was studied in a series of 12 patients who previously had undergone transcranial surgery for chromophobe adenoma (II). At the time of examination, all these patients were

in a steady state since at least six months. Patients who had been given irradiation treatment were not included because of difficulties in evaluating a possible effect of irradiation upon optic nerve fibres and retina (Harrington, 1958; Harris & Levens, 1976).
Only patients without postoperative impairment of the visual function were selected in order to avoid visual defects caused by surgical trauma. Patients that could not co-operate in visual field examination were not included. Twenty-two eyes were examined in this group of 12 patients. Two eyes were excluded because of eye disease. The ages of the patients ranged between 28 and 69 years. There were five females and seven males.

The possibility to predict the postoperative recovery of visual function from funduscopic signs of anatomical damage was studied in six consecutive patients with suspected chromophobe adenoma (III). They were examined before and after uncomplicated transcranial surgery. The diagnosis chromophobe adenoma was ascertained by microscopic examination in all cases. There were three males and three females. Their ages ranged between 30 and 70 years. The follow-up period after surgery ranged between three and twelve months. The visual fields were considered to be in a steady state after this time interval. Most of the postoperative visual recovery occurs within the first two weeks after surgery according to Bakay (1950) and Kayan & Earl (1975).

METHODS

Photography. All fundus photographs were taken by the author with one and the same fundus camera provided with built-in "red-free" filters. An interference filter, similar to the filters advocated by Behrendt & Wilson (1965) for photographic documentation of the retinal nerve fibre layer, was used only in the first study (I), where the patient was young and had perfectly clear ocular media. This filter proved impractical in some other patients. Therefore, a broad-band, low-density green absorption filter was selected when patients with different severity of chiasmal lesion were examined (II, III). With this filter it was possible to obtain negatives of equivalent quality from fundi of all ages. The light transmitted through this filter was not truly red-free, and the pictures contained more details from deep structures (choroidal vessels, pigment) than the pictures obtained with the interference filter. However, nerve fibre visibility was nearly equivalent in negatives obtained with both filters.

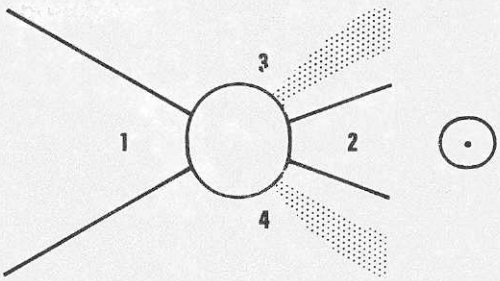

Fig. 4. Schematic drawing of the four peripapillary areas, evaluated separately. 1. Nasal sector. 2. Temporal sector containing the central part of the papillomacular bundle. 3. Upper sector containing the upper arcuate bundle (dotted area). 4. Lower sector containing the lower arcuate bundle (dotted area).

Evaluation of the nerve fibre layer. The nerve fibre appearance was evaluated by red-free ophthalmoscopy and in magnified (40 X) black-and-white photographic prints (consult II for further details).

A system for regional grading of the nerve fibre appearance was devised to ensure uniform assessment of the nerve fibre appearance in all examined eyes and to facilitate comparison between different eyes.

A mid-chiasmal lesion will primarily involve optic nerve fibres from ganglion cell bodies in the nasal hemi-retina. These fibres course towards the optic disc from all directions. They mingle with non-crossing fibres in all areas except for parts of the nasal and temporal peripapillary areas, where they can be seen in isolation. The exact borders of these areas are not known, and they probably vary between different individuals. In this study a nasal peripapillary sector of 60 degrees and a temporal sector of 40 degrees were considered to be occupied by fibres from the nasal hemi-retina only, and therefore these sectors were evaluated separately (Fig. 4). The horisontal parts of these sectors were considered most important when the nerve fibre appearance was evaluated.

In the sectors above and below the optic disc, fibres from the nasal hemi-retina intermingle with fibres from ganglion cell bodies in the temporal hemi-retina. These sectors were also evaluated separately. The appearance of the arcuate bundles was considered most important for the grading. The nerve fibre appearance was scored 0-2 separately in each sector. The characteristic features of each score are detailed in II. An improved version is given in IV. The definitions of score 0 and score 2 were based on findings described in paper I. The intermediary stage (partial atrophy - score 1) was based on previously published reports on diffuse partial atrophy of the nerve fibre layer (Hoyt et al., 1973; Lundström, 1974).

The optic disc was evaluated separately. The scoring 0-2 was based primarily on the definition of the optic disc borders in order to avoid the well-known difficulties in evaluating different degrees of disc pallor.

Functional tests. In all eyes the visual acuity and the visual field were tested by the author. The corrected visual acuity was determined by using a Monoyer-Granström letter chart at 5 m.

The visual fields were examined by kinetic perimetry (consult II for details). Though many kinds of visual field defects have been reported in chiasmal compression due to chromophobe adenoma, temporal field defects are by far the most common. In this study, therefore, test targets were individually selected on the basis of sensitivity in the nasal field. Thus, targets that gave isopters with approximately 10, 30 and 50 degrees of radius in the horizontal nasal meridian were preferred. The central isopter was plotted with a target speed of 1 degree per second. The intermediary (30^{o}) and peripheral (50^{o}) isopters were plotted with 2 and 5 degrees per second, respectively. Targets were usually moved from the periphery towards the point of fixation along meridians with an interspace of 15 degrees. Two additional meridians were examined between the 15-degree-meridians on each side of the upper and lower vertical midlines. The borders of defects were plotted by targets moving in perpendicular directions.

Static perimetry was also performed in order to analyse the kinetic field defects. The same perimeter was used (Haag-Streit Perimeter 940 ST) with its static perimetry attachment. Static perimetry was performed along one or two meridians going through the most defective parts of the kinetic field out to 20 degrees of radius.

A meaningful comparison between functional defects and signs of anato-

mical damage requires grading of the visual field defects. The scoring of field defects was built upon an increasing number of affected quadrants in the visual field (consult II for details). Central scotomas could not be included in this scoring system, but such defects were not found in the present study. It has to be pointed out that none of the scoring systems contains equidistant steps.

RESULTS AND DISCUSSION

Evolution of nerve fibre damage. After a total optic nerve lesion close to the chiasm a dramatic change of the nerve fibre appearance was observed (I). The striated pattern of the nerve fibre layer was totally lost. The nerve fibre opacity, especially prominent in the arcuate bundles, was also totally lost, and the retina acquired a granular appearance ("retinal mottling"). The obscuration of small and medium-sized vessels by overlying nerve fibre bundles disappeared completely. The medium-sized vessels became prominent. Some of the small vessels were no longer seen by ophthalmoscopy. The large vessels, especially the arteries, became narrow and appeared sheathed close to the disc. The appearance of the optic disc also changed. The disc borders became distinct, disc pallor appeared and a slight increase of the central excavation was noted.

The dynamic changes documented here justify the following conclusions. Signs of total atrophy of retinal nerve fibres include loss of nerve fibre striations, loss of nerve fibre opacity, exposure of vessels, a slight decrease in diameter of large vessels, vascular sheathing, a mottled appearance of the retina, disc pallor, and exposure of the disc borders. Conversely, signs of a normal nerve fibre layer include nerve fibre striations, nerve fibre opacity, obscuration of small vessels, normal disc colour and slightly blurred disc borders.

The signs of atrophy documented here agree with the observations by Hoyt and co-workers of static abnormalities in focal nerve fibre defects (Hoyt et al., 1973). Therefore it is reasonable to assume that a similar evolution of atrophy is possible also within restricted areas of the retina. It has to be pointed out, however, that none of the stages seen during the evolution of atrophy in this case, can be considered as typical for partial atrophy, as all the nerve fibres were damaged simultaneously here.

The nerve fibre layer began to change about 30 days after the injury and was completely lost after 60 days. This finding is in accordance with Vogt's (1921) report on loss of nerve fibres six weeks after bullet injury

to the optic nerve. In squirrel monkeys there seemed to be a more rapid wasting of nerve fibres, perhaps reflecting a species difference (Anderson, 1973).

Disc pallor was later in appearance and was not suspected until day 60. Pallor was maximal first around day 85. Disc pallor obviously cannot be ascribed solely to a disappearance of retinal nerve fibres (page 7). The retinal mottling was also late in appearance and not maximal until day 85. The cause of the granular appearance is not known.

Assessment of nerve fibre damage. The signs detailed above were used in a system for regional grading of nerve fibre atrophy described in paper II. The efficiency of such a grading system depends on the examiner's ability to observe relevant signs and his ability to apply his observations to the grading system. Therefore, in a separate investigation (IV), different observers' assessments of atrophy according to the grading system were analysed. Five ophthalmologists without formal training in ophthalmoscopic evaluation of the retinal nerve fibre layer partook as observers. They were provided with a written instruction identical to the section "Grading of ophthalmoscopic signs of atrophy" in II. The appearance of the nerve fibre layer was evaluated in 12 magnified black-and-white fundus photographs. Six fundus photographs were selected from a series of patients with compression of the chiasm due to chromophobe adenoma (Figs. 2-7 in II). Another six photographs were obtained from individuals without any known disease. Further details about the method are given in IV. Three of the six pictures from normal individuals were easily recognized as being normal. The other three pictures were judged by some observers to be normal, by others to show partial atrophy in some sectors. None of these pictures was considered to show total atrophy in any peripapillary sector. The remaining six pictures were considered to show partial or total atrophy by the author (II). These pictures were never considered to show a normal nerve fibre layer by the observers. Thus, pictures showing atrophy were easily recognized by all examiners.

One examiner had greater difficulty than the others in recognizing a normal nerve fibre layer and overrated atrophy in all pictures.

Shaffer et al. (1975) have studied various observers' numerical assessment of cup/disc ratio. They reported that there was a tendency for individual subjects to be consistently over- or underestimators. An improvement of the estimating ability by training has been claimed by Shaffer et al. (1975). In the present investigation the results from the second grading also suggested a positive effect.

Variations within and between examiners were most obvious in peripapillary sectors showing partial atrophy. Therefore, an attempt to improve the definitions of partial atrophy has been made (IV).

This study (IV) shows that the appearance of the retinal nerve fibre layer was accessible to meaningful evaluation to most of the examiners and that they achieved a reasonably uniform assessment of atrophy by use of the grading system.

Nerve fibre damage in chiasmal lesion. Steady state patients with visual defects of various severity showed a conspicuous variation in degree and distribution of signs of nerve fibre damage (II).
Partial atrophy of nerve fibres in the nasal and temporal sectors occurred in eyes with a slight depression in the upper temporal field, In eyes with an absolute temporal field defect, total atrophy in the nasal and temporal sectors was found. The disc borders were exposed in the same areas, and there was some pallor in the corresponding sectors, sometimes suggesting a pale band across the disc. In eyes with additional thinning of the arcuate bundles only a contracted nasal visual field was left. These eyes also showed a marked and uniform disc pallor and sharply defined disc borders.

The degree and distribution of nerve fibre damage in the eyes with absolute temporal field defects correspond with findings reported by Davies & Shock (1975) in a patient with a congenital chiasmal lesion. It is also in accordance with nerve fibre changes in the contralateral eye in optic tract lesion as reported by Lauber (1927) and Hoyt & Kommerell (1973). After the present study was completed, Vannas et al. (1977) have reported on nerve fibre changes in patients with temporal field defects. In spite of technical difficulties, these authors also found a correspondence between absolute temporal field defects and nerve fibre changes.

Several eyes in the present study had a visual field defect only in the upper temporal field, but showed the same degree of nerve fibre damage in both the upper and the lower parts of fundus. This discrepancy can not be explained at present. Conversely, when there were defects in the lower nasal field, a corresponding and pronounced atrophy in the upper temporal area was found.
Some of the eyes showed a pronounced thinning of the arcuate bundles in addition to total atrophy of the horizontal sectors. This indicates damage to both crossing and non-crossing fibres. Two of these eyes lacked nasal field defects. This seems to indicate that a diffuse loss of axons must not

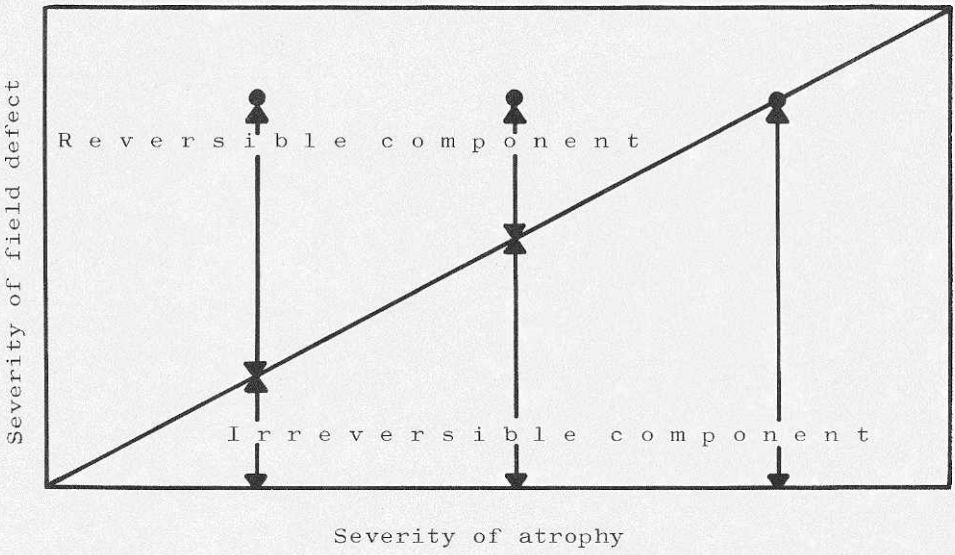

Fig. 5. An idealized relationship (diagonal line) between severity of field defect and severity of atrophy in steady state patients. Patients with active lesions may have visual defects that are excessive in relation to the degree of atrophy (dots), due to a combination of reversible conduction failure (upper arrows) and irreversible loss of axons (lower arrows). The latter limits recovery.

necessarily affect visual function as tested in ordinary perimetry.

In the series of steady state patients all the eyes showed some degree of nerve fibre damage. This selected material does not allow any conclusions about the incidence of nerve fibre defects in chiasmal compression. However, it is worthy of note that only eight out of 22 eyes showed indisputable disc pallor.

A close relationship was found between the visual field scores and the atrophy scores in patients in a postoperative steady state (Fig. 5). It is important to point out, however, that the scoring systems apply primarily to fairly symmetrical chiasmal lesions. Because of the peculiar anatomy of the nerve fibre layer, a complete loss of fibres from the temporal hemi-retina will result in a lower atrophy score than a corresponding damage in the nasal hemi-retina. A uniform rise in atrophy and field scores will only occur when damage proceeds from crossing to non-crossing fibres.

In patients with active chiasmal compression, the functional deficit may

be due to a combination of reversible conduction failure and irreversible anatomical damage. In such cases, the functional defect should be excessive in relation to the degree of atrophy (Fig. 5).

Six preoperative patients with active chiasmal compression were studied in this regard (III). In five out of 12 eyes the field defect was proportionately too large according to the steady state scheme outlined above. A certain degree of visual recovery was expected following surgical decompression in these cases, provided that the degree of atrophy remained stable.

As predicted, the visual field defects regressed to a level corresponding to the degree of atrophy in these five eyes. In one eye the degree of atrophy increased after surgery, and therefore the field defect improved to a lesser degree than initially expected. In this case there was a history of very recent visual impairment before surgery. As demonstrated in I, the time delay between axonal damage and debut of atrophy is at least four weeks. Therefore, interruption of axons within a few weeks before surgery cannot be diagnosed until some weeks later.

In the remaining seven eyes the relationship between atrophy and visual field defect before surgery was comparable with findings in the postoperative steady state patients. Therefore, none or only marginal visual recovery was expected in these eyes. These predictions turned out to be correct.

In this study (III) three eyes showed a marked pallor of the optic disc. The visual function did not improve in any of these eyes after surgery. This agrees with previous reports on disc pallor as a sign of poor prognosis (Kayan & Earl, 1975). Also in eyes with a lesser degree of anatomical damage it is possible to predict the surgical outcome of visual function as showed by this study: 11 out of 12 predictions were correct. The grading system must be used with certain qualifications, however. Obviously, a great deal of caution is necessary when trying to predict recovery in cases where deterioration of function occurs within a few weeks prior to surgery. Furthermore, variation in observer assessment is unavoidable. Therefore, when small discrepancies between functional defect and atrophy are found, the prediction must be made cautiously. Nevertheless evaluation of nerve fibre atrophy allows a more accurate assessment of the degree of anatomical damage than has been possible previously.

GENERAL SUMMARY

Optic atrophy indicates irreversible wasting of optic nerve axons. Previously described objective signs of optic atrophy in patients with chiasmal compression have been largely limited to various degrees of optic disc pallor. Unfortunately disc pallor is a notoriously unreliable sign of optic atrophy.

Recently, changes in the retinal nerve fibre pattern have been described in various diseases affecting the anterior visual pathways. These changes in the nerve fibre layer have been correlated to visual field defects. All previous reports have concerned static abnormalities.

In the present study dynamic changes in the nerve fibre pattern were documented in a patient who had injured one optic nerve close to the optic chiasm. A total loss of nerve fibre striation, nerve fibre opacity and vascular obscuration occurred. The optic disc became pale with sharply defined disc borders. The nerve fibre layer began to disappear 30 days after the injury and was completely lost around day 60. Disc pallor was still later in appearance.

These signs of nerve fibre atrophy were used in a system for regional grading of retinal nerve fibre atrophy in patients with chiasmal compression. Different observers' assessments of atrophy according to this grading system were analysed. Fundus photographs showing atrophy were easily recognized by the observers. Most fundus photographs showing a normal nerve fibre layer were recognized as being normal. Although some overratings were made, it can be concluded that the appearance of the retinal nerve fibre layer was accessible to meaningful evaluation for most of the observers, and that these achieved a reasonably uniform assessment of atrophy.

The degree and distribution of nerve fibre atrophy were studied in 12 patients with different degrees of chiasmal damage. They had previously undergone transcranial surgery for chromophobe adenoma and were in steady state. All eyes showed some degree of nerve fibre damage. Only eight out of 22 examined eyes showed disc pallor. Partial atrophy of nerve fibres in the nasal and temporal peripapillary areas occurred in eyes with mild degrees of upper temporal field defects. An absolute temporal field defect was associated with total atrophy in the nasal and temporal peripapillary areas with corresponding sharp disc borders. In eyes with more advanced nerve fibre changes, including thinning of the arcuate bundles and sharply defined optic disc borders, only a part of the nasal field was left.

A close relationship between visual function and degree of anatomical damage was found in steady-state patients. These findings show that the state of the retinal nerve fibre layer can be used as an objective indicator of the occurrence and severity of anatomical, chiasmal damage.

However, the close relationship between the degree of atrophy and visual field defect does not apply in all patients with untreated lesions: visual impairment is often more pronounced than could be expected from the amount of axonal wasting. The prognostic implications of this discrepancy were studied in six patients with compression of the chiasm due to chromophobe adenoma. Eyes showing a field defect that was excessive in relation to the degree of atrophy improved their field defects postoperatively to a level corresponding to the degree of atrophy. The visual field defects remained unchanged in eyes with a close correspondence between atrophy and visual field defect already before surgery. Provided that atrophy does not increase after surgery, simultaneous evaluation of retinal nerve fibre atrophy and visual field defects allow an accurate preoperative prediction of improvement.

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