REVIEW OF LITERATURE
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GLAUCOMA:

Glaucoma embraces a composite congeries of pathological conditions which have the common feature that their clinical manifestations are to a great or less extent dominated by the height of the intra-ocular pressure and its consequences.

The word 'Glaucoma' first appears in Hippocrates (420 B.C.). 'Glaukoma' is an ancient Greek word meaning 'glaze' such as silveryness of sky or dull sheen of an eye, which has lost its brightness. Glaucoma is no definite morbid entity but merely the off colour, lack luster appearance of the eye turned blind.

The general concept prevailed that primary glaucoma of all types was due to an obstruction to the drainage of aqueous humour, a new thought, however, suggested by Erich Seidel (1920) and was elaborated by Curran (1920), who advocated the idea of blockage of pupil as the cause of glaucoma.

According to Duke-elder and Jay (1969) glaucoma does not imply a disease entity but embraces a composite congeries of pathological conditions which comprise any raised intraocular pressure which the tissues of the particular eye are unable to stand without damage to their
structure or impairment of normal physiological function and with a diurnal variation of more than 5 mm. of Hg.

Hayreh (1972) by fluorescein angiography showed that increase intraocular pressure probably damages the tissue by influencing the circulation of blood in papilla.

With the aid of gonioscope, it was pointed out that in some glaucomatous eyes the angle of the anterior chamber was closed while in others it was open.

CLASSIFICATION:

Most commonly used classification based upon three different factors —

1. Etiology of the glaucoma;
2. Anatomic configuration of the eye; and
3. Age of onset of the disease.

On the basis of anatomic configuration, the glaucoma can be divided into open angle and angle closure glaucoma. These two groups are then subdivided by etiology into primary and secondary glaucoma. The primary glaucomas are those in which the cause of the glaucoma is considered idiopathic or unknown. The
secondary glaucomas are those that are secondary to some other ocular conditions or specific anatomic variation that is quite early evident. There is a third group of glaucoma - the congenital glaucoma. It includes both open angle and close angle varieties.

The clinical states of raised tension can be divided into two classes:

1. **Primary glaucoma** - The cause of which is still obscure.

2. **Secondary glaucoma** - The causes of which are known and obvious.

Two well-defined types of primary glaucoma exist which differ from each other in the type of patient affected, their clinical course and symptomatology, and in their prognosis and treatment.

**Closed angle and open angle glaucoma**:

The first type is characterised by sudden episodic subacute attack of raised tension, diminution of vision and the subjective appearance of halos caused by corneal oedema. The second type, develops slowly, quietly and insidiously over many years with a characteristic trial symptoms - Raised tension, Typical field defects and cupping and pallor of the disc. Except these the two rarely conditions -
Congenital Glaucoma - Which is usually due to failure in development of the tissue in the region of the angle of the anterior chamber and rarely another;
Low tension glaucoma - Which is, not glaucoma in true sense, here the intraocular pressure remains either normal or subnormal but in both cases the cupping of the disc is present.

In the absolute stage of glaucoma the eye become intensely hard, all vision is lost and disc develops a deep atrophic cup.

Among various forms of glaucoma, chronic simple glaucoma still remains one of the principal cause of the blindness throughout the world.

**OPHTHALMOSCOPY AND PHOTOGRAPHY**

After the introduction of ophthalmoscopy by Helmholtz in 1850, fundus photography is one of the fascinating development in ophthalmology. Engelbert stated that the first photograph of the human eye was made in 1886 by Howe & by Jackman & Webster.

Zeiss fundus camera developed by Littmann in 1955.

Fundus angiography has made available new data on anatomy, physiology and Pathology of the fundus. Its most important impact has been to convert diagnosis of
fundus disorders from a subjective approach to an objective and more scientific type of appraisal. It gives information regarding retinal circulation, retina, supporting choroid and optic nerve head. It helps in better understanding of retinal circulatory disorder and early diagnosis of problems and more information on prognosis and to monitor therapy.

The search for clinical signs that precede the development of visual field loss in glaucoma has emphasized the evaluation of optic disc. Optic disc can be described by signs of cupping and pallor (Schwartz, 1973). Schwartz (1976) defined cupping as three dimensional depression of the optic disc relative to the retinal surface. Pallor is the area of maximum colour contrast or the area lacking in small blood vessels. The amount of pallor is correlated with the degree of visual field loss. According to Cogan (1966) optic nerve head pallor, is a well recognized clinical manifestation of tissue atrophy in the infrageniculate visual pathway. It has been suggested that the disc pallor may reflect a decreased vascularity in the optic nerve head. Pallor of the optic nerve head seems to result from alternations in the tissue reflectance and translucency following axonal loss and glial reorganization rather than from a decreased micro-vascular bed.
Significance of fluorescein angiography in glaucoma:

Fluorescein angiography of the fundus is a newer technique in ophthalmology to study the dynamic vascular aspect of choroid, retina and optic disc. McLean and Maumenee (1960) examine the fundus first time by injection of 5% sodium fluorescein intravenously with slit lamp and indirect ophthalmoscopy.

Novotny and Alvis (1961) take the first photograph of passage of dye through retinal vessels with modified fundus camera. Since then the fluorescein angiography has been used as a very important diagnostic investigation in various fundus lesions. A lot of experimental work has been done on monkeys to know the physiological anatomy of the choroidal and retinal vasculature and their pathological entities (Hayreh, 1969, 1970, 1973, 1975; Hayreh and Baines, 1972, 1973; Oosterhuis and Boen-Tan, 1971 and Hyvarinen et al, 1969).

Usually fluorescein fundus angiography of one eye is done in one time but binocular fluorescein angiography of both eyes simultaneously can also be done as described by (Hisatomi and Suzuki, 1974; Kooijman, 1972; Laux, 1976).

Most of the workers prefer to take fluorescein angiograms in black and white, while some workers have also tried to take coloured photographs (Shikano and Shimizu, 1968; Hendrixson et al, 1970).
Usually with the conventional equipment angiography of the central fundus can be taken successfully but for the photographs of equator and beyond it, is also possible with the introduction of 100° Camera (Pomerantzeff and Govingson, 1971) and equator plus Camera (Pomerantzeff, 1975), with the conventional equipment.

DYE:

Chemical properties and biochemical interactions of fluorescein:

Number of chemical dyes has been used for the purpose of fluorescein angiography but the sodium fluorescein dye is the best for fundus angiography. It was synthesized by Von Beyer (1871) and was used in ophthalmology by Paul Ehrlich (1881). Fluorescein, chemically related to phenolphthalein, is synthesized from the interaction of phthalic acid anhydride and resorcinol, which in an alkaline sodium salt solution, form sodium fluorescein \( (C_{20}H_{10}O_5Na_2) \). It is highly soluble in water. The high solubility and low molecular weight (367.27) of it allow rapid diffusion through the body fluids. The yellow-green fluorescence is visible in aqueous solutions of sodium fluorescein in concentrations as low as 1 : 100,000. Improved slit lamp ophthalmoscopy can demonstrate fluorescence in dilutions as low as one
in one billion. It gives a maximum fluorescence at the 

pH of 7.4. Intravascular fluorescein is bound to a 
large extent by plasma albumin (40.85%) (Longe & Boyd 
(1944)), globulins bind a minor amount. The protein bound 
dye has a decreased intensity of emitted fluorescence 
which has been shown experimentally and clinically.

About 15-17%, of the total fluorescein concentration, 
of the dye molecule also binds to blood cells, predominantly 
deposited on the surface of the erythrocytes.

Fluorescein injected into whole blood loses part of 
its fluorescence since part of the exciting and emitted 
light is absorbed by hemoglobin (Dollery, Hodge & Engel, 
(1962)).

It has no firm bond with the vital tissues of the 
body and is, therefore, excreted in about 24-36 hours after 
intravenous injection but it stains skin and mucous membrane 
yellow for about 3-4 hours and causes yellowish discoloration 
of the urine for 1-2 days.

The dye has got remarkable fluorescent properties. 
The conversion of absorbed light to fluorescent light is 
almost 100%. Fluorescein absorbs light maximally between 
480 and 510 nm with a sharp drop in the absorptive curve 
on the side of longer wave-lengths between 510 and 530 nm 
and an extinction point at 530 nm. The emission spectrum
has an initial steep range from onset at 500 nm to a maximum at 530 nm. Other weaker absorption and emission ranges have been demonstrated at wave lengths longer than these, but they are clinically insignificant (Hodge & Clemett, 1966).

**Permeability of Ocular tissues to fluorescein**

Angiographic-histologic correlation of dye-protein-tissue-complexes using lissamine rhodamine (RB 220) (Mechemer, 1970) and microscopic localization of fluorescein dye within the eye have demonstrated the sites of blood tissue barriers (Grayson & Laties, 1971). Fluorescein is mainly contained in extracellular spaces or is loosely bound to cells that bind protein but some evidence has been presented for intracellular transport of fluorescein.

It diffuses freely in the eye through chorio-capillaris, bruch's membrane, optic nerve and sclera but not through the healthy retinal vessels, retinal epithelium and larger choroidal vessels. The compact retinal pigment epithelial cells and endo-thelial cells of the retinal vessels acts as a barrier to the passage of fluorescein (Schatz et al, 1978).
Fluorescein Preparations:

Most ophthalmic photographic departments use smaller volumes of more concentrated, commercially available solutions. Depending upon one's personal choice and experience, various concentrations and dosage schedules have been advised.

1. 5 ml. of 5% (Charamis, 1966); (Novotny and Alvis, 1961).
2. 10 ml. of 5% (Allen et al, 1966).
3. 5 ml. of 20% (Oosterhuis and Lammen, 1965).
4. 3 ml. of 25% (Archer, 1972).
5. Rosen (1969) prefers to give it in doses of 10 mg/kg body weight.

The smaller the bolus, the less the complication of nausea at the time of injection.

The sodium fluorescein dye has been given in catheterization into the big veins in experimental animals (Hayreh, 1968; Dollery et al, 1962). But the dye is conventionally given by intravenous route into the Antecubital vein in human beings. The smaller the bolus, the less the complication of nausea at the time of injection.

As the blood circulation in the antecubital vein is very slow and the dye undergoes dilution of about 600
times before reaching the ocular vessels, the use of
5-15 ml. of normal saline immediately after it, has been
advised by flower (1973).

Toxic reactions to fluorescein:

Fluorescein dye is much safer but nausea and
occasionally vomiting occur in 5 to 10% patients. It
is important only in so far as it disturbs photographic
quality (Hayreh, 1974). It may occur on first injection
even with a dilute test dose. On repeated injections of
fluorescein no nausea or vomiting occurs (Hayreh, 1968).
Therefore, nausea or vomiting on first injection is no
contra-indication for subsequent injection.

Stein and Parke (1971) analysed the side effects
in 55 cases and main side effects summerized as follows:

<table>
<thead>
<tr>
<th>Side effects</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Urticaria and allergic skin reactions</td>
<td>36</td>
</tr>
<tr>
<td>2. Respiratory allergic reactions eg. wheezing, laryngeal oedema etc.</td>
<td>05</td>
</tr>
<tr>
<td>3. Hypotension/Shock</td>
<td>10</td>
</tr>
<tr>
<td>4. Cardiac -</td>
<td></td>
</tr>
<tr>
<td>- Fatal myocardial infarction</td>
<td>01</td>
</tr>
<tr>
<td>- Cardiac arrest</td>
<td>02</td>
</tr>
<tr>
<td>5. Basilar artery sclerosis</td>
<td>01</td>
</tr>
<tr>
<td>6. Pyrexia</td>
<td>06</td>
</tr>
</tbody>
</table>
Other rare side effects like achromatopsia (Archer, 1972) and Hemiplegia (Mathews et al, 1979) have also been described. Extensive extravasation of the dye during injection given immediate intense yellow staining of the arm as well as severe pain. There may be protracted peripheral neuritis or rarely, slough off the overlying skin occur. Justice and Sever (1965) have described a case of thrombophlebitis from paravenous injection.

In addition to sodium fluorescein dye, another new dye named Indocyanine green (I.C.G.), A tricarbocya- nine compound, has also been used for the better understanding of choroidal vasculature (Kogure & Chromukos (1969), Kogure et al, (1970) and Flower, (1972, 1973).

**Fluorescence:**

In blood, the fluorescein is bound to plasma albumin to a large extent and to globulin to a lesser extent. The importance of protein binding is that only the free dye in plasma can diffuse across cell membrane. Fluorescein albumin conjugate shows only about 50% of fluorescence of dye in aqueous solution because of reduced absorption of light at the peak excitation wave length of 490-495 nm. A concentration 20% greater than
in saline being required to achieve a comparable fluorescent emission (Dollery et al, 1962). The visualization of fluorescein in the intra vascular or extracellular spaces is known as fluorescence. The physiological changes can modify the duration and intensity of fluorescence in retinal vessels. The oxyhaemoglobin molecule has absorption peak at 445 nm. and 577 nm. and reduced haemoglobin at 555 nm. so that appreciable absorption takes place at the frequencies between 500-560 nm. at which fluorescent light is emitted (Wessing, 1969). In patients who are anemic and diabetics who have renal disease and uremic bone marrow depression the emitted fluorescence is greater and necessary film exposure is less.

Fluorescein Clearance:

Fluorescein rapidly diffuses into all extracellular spaces, except for the potential extracellular space of the central nervous system and retina after the injection. Plasma concentration of the fluorescein dye, ten minutes after intravenous injection, remains only 1/4th that of radio-iodine labelled albumin, which had been mixed in the syringe (Dollery, Hodge & Engel, 1962).
PHOTOGRAPHIC METHODS:

Filters:

To check the pseudofluorescence or false fluorescence various types of filters are used in fluorescein angiography. Pseudofluorescence is a term that is used for nonfluorescent light that passes through a dual filter system and results in artificial fluorescence (Schatz et al., 1978). Usually exciter filter and barrier filter are used. Exciter filters must transmit enough energy without overlapping the transmission of barrier filter. Exciter filter should have a maximum transmission of between 485 and 500 nm, where fluorescein has its maximum light absorption. The ideal exciter filter is that which removes all the wavelength from the incident light except in the range of 480-510 nm, which is the absorption peak of fluorescein excitation. Exciter filter is incorporated before the flash source of fundus camera.

Barrier filter must screen out all light except that emitted by fluorescein and is incorporated in the camera back, just before the film plane. The barrier filter should have peak where the fluorescein emission is at a maximum i.e. between 525 and 530 nm.
The first filter system which minimizes the pseudofluorescence was reported by Hodge & Clemett, (1966). Later on Baird atomic interference filter B₄ & B₅ (Haining and Lancaster, 1968). B₄ in conjunction with kodak wratten 12 (Machemer et al, 1970). Broad band filter system (Frazier and Allen, 1972). Spectrotech SE₁₄ and SE₁₅ interference filters (Zondiros, 1974) and Delori filter system (Delori and Ben-Sira, 1975) were described. These are well proven good quality filter combinations.

**Film:**

Wessing (1969) has described detail about proper film, correct developer, proper temperature and time, to ensure best contrast with least grain. Black & White angiography is standard. The majority being done with Tri-X pan film. 125 A.S.A. are generally recommended. A fast film like 400 A.S.A. is better for very rapid sequence photography. Colour fluorescein fundus angiograms are likewise attractive but unnecessary for routine diagnostic evaluation or even therapeutic-localization.

**STEREO-ANGIOGRAPHY:**

Allen et al (1966) introduced the concept of stereoscopic angiography. A three dimensional photographs
of the fundus are taken consecutively in this procedure. For this purpose, Donaldson (1964) devised a special fundus camera which had many advantages like higher magnification, acute focussing mechanism and reflex mirror system. Introduction of Allen's stereo separator and other technical advancements have helped in getting rapid sequence stereo-angiographs (Allen et al, 1966; Farel et al, 1968; Crock, 1970; Haining and Lancaster, 1968).

Fluorescein - cine - angiography:

Fluorescein-cine-angiography first introduced by Hart et al (1963) and further modified by Oberhoff et al. (1965) is another advancement in the field of fluorescein angiography.

Television Ophthalmoscopy and Video-tape recording:

Another milestone in the field of angiography is the television fluorescein angiography. It was first invented in 1968 by Van-Heuven et al, (1971).

The method consisted of utilizing an image orthicon television camera, a videotape recorder and zeiss fundus camera. It is helpful in permanent documentation and accurate reproduction of dynamic aspect of retinal vascular flow. Videotape recording has advantage of playback possibilities.
Various modifications were made in the field of fluorescein angiography in this decade, utilizing a number of camera tubes secondary electron condition, silicon matrix and silicon intensifier target types. Yuhastz et al. (1973) introduced the videotape recording system for the teaching purposes. Later on stereoscopic T.V. angiography was developed (Van-Heuven and Schaffer, 1973; Van-Heuven and Schaffer, 1974). Shimizu (1976) introduced a new T.V. guided camera in which the infrared light was used and this is used in dark room in undilated pupils. This technique is very useful in the fluorescein angiography of the Glaucoma patients in which there is the problem of dilatation of the pupil is dangerous and in those cases of glaucoma in which dilatation of the pupil can precipitate the angle closure glaucoma.

**DIGITAL FLUORESCINE TELE-ANGIOGRAPHY:**

A new computer - based digital image system has been developed that allows telephone transmission, image enhancement and hard disk storage of fluorescein angiograms (Edward & Feldman, 1987).
Fluorescein angiography of the fundus and its related anatomy:

Fluorescein angiography is a technique for better understanding of normal and abnormal haemodynamics of the choroidal and retinal circulations and associated disorders and also the disorders of optic disc and retina in various ocular diseases.

As soon as the dye is injected into the antecubital vein it reaches the fundus very quickly in about 8 - 12 seconds (Archer, 1972). The time taken for the dye to reach the central retinal artery in the disc area is known as arm to retina circulation time which depends largely upon the concentration of the dye and its route of administration. Physiologic factors such as cardiac output, blood volume, blood viscosity and caliber of carotid vessels may alter this value.

The dye further passes through the retinal arteries, arterioles, capillaris, venules and then return to the central vein. The flow in the vein is first laminar and later the veins are completely filled up. After some time the recirculation of dye occurs and the fluorescence gradually diminishes till the whole of the dye has been washed up from the circulation. It has been shown that the flow of choroid is earlier than the retinal vessels. The dye appears within the arteries at the disc within 0.5 to 1.0 second later (Evans et al, 1973; Shimizu et al, 1974).
The results of fluorescein angiography largely depend upon the different spectrum distribution factors like an emission flash tube, transmittance of the excitor and barrier filters, activation spectrum, fluorescence spectrum of the fluorescein in the blood plasma, reflectivity of the retina and the film speed. However, from time to time modification in the procedure and use of dye have been undertaken for better results of the angiograms and retinal and choroidal haemodynamics.

OPTIC DISC CIRCULATION:

Optic disc circulation has been studied in detail by (Hayreh, 1969, 1972, 1974) and Ernest and Archer (1973). Hayreh (1969, 1972) has divided the optic nerve head into four parts depending upon its vascular supply as observed after fluorescein fundus angiography.

(1) Lamina cribrosa: It is a dense compact connective tissue, which is continuous with the sclera with many opening in it for the transmission of the nerve fibre bundles. It is supplied by centripetal branches from the short posterior ciliary arteries either directly or through the arterial circle of zinn.
(II) The prelaminar region: The part of the disc infront of the lamina-cribrosa is known as the prelaminar region. Here the connective tissue of the lamina cribrosa is replaced by loose glial tissue. This is attached peripherally to the choroid and bruch's membrane. This region is mainly supplied by the centripetal branches from the surrounding peripapillary choroidal vessels. Possibly this part may also get some branches from the short posterior ciliary arteries central retinal artery does not usually contribute to the vascular supply of this part.

(III) Surface nerve fibre layer: It is the most superficial layer consisting of compact nerve fibres. This is continuous with the nerve fibre of the retina and is covered by internal limiting membrane. This region is supplied by the branches of the central artery and some times the temporal part of this layer receives a contribution from the peripapillary choroid.

(IV) Retrolaminar region: This part is supplied mainly by the centripetal branches from the pial-vessels, which are mostly the branches of peripapillary choroid and circle of zinn. Three quarters of the nerve may be supplied by the centrifugal branches of the central retinal artery.
O'Day et al (1967) confirmed that there are two vascular networks in the optic nerve head. A deep plexus which provides the deep disc glow seen on the angiography, fills simultaneously with the choroidal circulation. In addition a superficial vascular network of radiate vessels fills during the earliest retinal arterial phase. These vessels are larger than capillaries and they are functionally and anatomically the first retinal vascular system.

VENOUS DRAINAGE:

The optic nerve head and the retrolaminar part of the optic nerve are drained by the central retinal vein. The prelaminal region is drained into the choroidal veins. There are no venous channels corresponding to the circle of zinn.

There is a communication between the central retinal vein and the choroidal circulation in the prelaminal region which has been confirmed after a complete retinal vein occlusion behind the lamina cribrosa.

NORMAL OPTIC DISC FLUORESCENCE:

Fluorescein filling characteristics has shown that the filling of the disc occurs prior to the dye reaches the central-retinal artery which confirms that the main vascular supply of the disc is through the ciliary vessels.
Furthermore, the filling of the disc occurs earlier on the temporal side which shows that this part is more vascular than the nasal part. Though the disc appear comparatively pallor on ophthalmoscopic examination (Hayreh, 1969; 1972; 1974).

The characteristics of the optic disc fluorescence can be categorised by a rather constant temporal sequence in the following stages.

1. Deep Hazy Fluorescence: Deep hazy fluorescence occurs during the choroidal phase or concomitant with the arrival of dye at the optic disc. The dye appears at the disc margins first in the centripetal branches from the posterior ciliary arteries (Hayreh, 1971) supplying the region of the lamina cribrosa and prelaminar region. This deep postlaminar capillary plexus is not influenced by intraocular pressure. It fluorescing even when the intraocular pressure is above the central retinal artery systolic pressure (Krill, 1972).

The fluorescence reaches a maximum in a few seconds is homogenous in nature, filling the entire optic disc, and outlines the still empty major retinal vessels by retrofluorescence. The fluorescence of this plexus is best seen when a deep physiologic cup is present.
(2) **Prelaminar capillary fluorescence**

It involves prelaminar capillaries. These are clearly visible during the choroidal and early retinal arterial phase, when a cilio-retinal vessel is present, this originates from the annulus of zinn and enters the fundus at the temporal disc margin with a sharp bend, and fills simultaneously with this plexus. In view of their origin from the posterior ciliary arteries, they are indicators of choroidal circulation (Wessing, 1969). Filling of the cilio-retinal artery precedes filling of central retinal artery (Archer et al, 1970; Hayreh, 1974). The incidence of cilio-retinal artery has been found to be 4.9% (Justice et al, 1976). There is dispute as to whether these vessels are primarily of choroidal origin (Wans, 1971) or arise from branches of peripapillary retinal arterioles (Hayreh, 1971; O'Day et al, 1967; Hill, 1966).

The filling of these vessels depends on intraocular pressure. They do not fill, when the intraocular pressure exceeds systolic retinal artery pressure (Krill, 1972). Although the fluorescence of this capillary bed is homogenous, individual capillaries can be differentiated. The fluorescence is separated from the adjacent choroidal vasculature by a non fluorescent zone.
3) **Epipapillary capillary fluorescence**:  

Epipapillary fluorescence is the filling of retinal epipapillary capillaris. This can be best observed when disc vessels are congested. These capillaris are densely found on the temporal side of the papilla. These temporal capillaris fills first on the nasal side. These vessels drain directly into the central retinal vein in the optic nerve head (Evans, 1971).

4) **Late fluorescence**:  

Late fluorescence of the disc is multifactorial in origin. Late fluorescence contributes from the deep capillary plexus of the disc, extra-vasation from chorio capillaris at the disc margin and scleral fluorescence in the lamina cribrosa.

Fluorescein angiography has been used in recent years as a diagnostic and investigative procedure in a variety of fundus lesions. It is generally believed that in glaucoma the changes at the optic disc and possibly a change in visual fields are the result of the interference with the blood supply of the optic nerve and optic disc.

Hayreh (1969df, 1972 d) by fluorescein angiography has revealed that in a normal optic disc, redness & pallor seen ophthalmoscopically are not true guides to its
vascularity because the temporal part of the disc, in spite of its pallor appearance is usually more vascular than nasal part. It also provides a dynamic tool for the further investigation of ischemia in glaucoma.

The bulk of recent evidence favours ischemia as the mechanism in the pathogenesis of visual field defects in glaucoma (Duane & Jaeger, 1971; Phelps, 1972).


Schwarz et al (1980) by the technique of fluorescein angiography offers the opportunity to study the circulation of the eye in glaucoma. Hayreh et al (1987) have used techniques varying from qualitative interpretation of
fluorescein angiograms to measurement of the appearance and circulation times of fluorescein in the retinal and choroidal circulations.

Rosen & Boyd (1970), Forofonova & Supsun (1974) by densitometric measurements have been made of the choroid and retinal vessels to determine inter-relationships between choroidal & retinal circulations in glaucoma.

From the densitometric and time curves of fluorescein angiograms of matched groups of normal, ocular hypertensive, and glaucomatous eyes, the time and rate of filling of retinal arteries and veins, optic disc, and peripapillary choroid was measured. In the whole population of eyes, with increasing age there was a decreased rate of filling of the retinal arteries, optic disc and peripapillary choroid with increased diastolic blood pressure, increased time was needed to fill the peripapillary choroid. Increased ocular pressures and decreased tonographic out flow facility were particularly correlated with the decreased filling of the retinal veins and the disc. Significant differences of circulatory changes in the retinal arteries and veins were obtained between normal ocular hypertensive, and glaucomatous eyes. Further, evaluation of these circulatory events could be clinically useful, especially in differentiating normal from ocular
hypertensive eyes in relation to the effect of ocular pressure on the retinal and disc circulations.

According to Hamaski (1970) various histopathologic studies of optic disc vascularity indicates that at elevated levels of intraocular pressure, the capillaris of the prelamina cibrose portion of the optic nerve fill poorly.

Fluorescein angiographic studies confirm this finding and furthermore, have shown that, even at normal levels of intraocular pressure, disc vascularity may be decreased in many glaucoma patients.

Dollery et al (1970) found that flow rate was reduced by experimentally raised intraocular pressure in both retinal and choroidal circulations.

Blumenthal et al (1973) found more markedly reduced blood flow in choroid than the retina.

Cristini, Zimmerman; De Vanecia, Hamaski & Lampert (1970); Vogel and Zimmerman (1970) found that the blood supply of the retrolaminar part of the nerve involves the choroidal circulation.

When ischemia of the optic disc is of gradual and of a chronic nature, it produces the changes described in glaucoma and low tension glaucoma. A rise in intraocular pressure (as in glaucoma) or a fall in perfusion pressure
(as in low tension glaucoma) produces an imbalance resulting in vascular insufficiency and ischemia of the optic disc, peripapillary choroid and retrolaminar optic nerve. This leads to cupping of the optic disc, cavernous degeneration of optic nerve and visual field defects.

These pointers to choroidal ischemia as the cause of optic nerve damage in glaucoma raise the question as to whether lesions in optic nerve, rather than in the disc or in the retinal nerve fibre layer, can cause typical glaucomatous field defect and there is no doubt that they can.

Optic nerve head disease in chronic simple glaucoma may only be the result of a direct mechanical effect of elevated intraocular pressure on the neurons or glial cells (Fuchs, 1916; Smith, 1965; Emery et al, 1974; and Anderson, 1975).

In contrast it may be possible that the glaucomatous optic nerve may reflect primary vascular or haematological disease principally affecting the optic nerve head (Drance, 1972) in a manner similar to those examples of acute anterior ischemic optic neuropathy, which are followed by an increase in volume of the optic cup (Hayreh, 1970).

The glaucomatous optic nerve may be a result of vascular disease of the optic nerve secondary to an elevated intraocular pressure (Hayreh, 1970).
Low tension glaucoma shows focal sector hypoperfusion of the optic nerve, so there is only sector type of hypofluorescence present, while chronic simple glaucoma patient demonstrates a wide range of optic nerve fluorescence all three type sector, Patchy and extensive hypofluorescence suggesting both focal and diffuse optic nerve head hypoperfusion.

Spaeth (1975) done fluorescein angiography on 42' patients with open angle glaucoma and photographs compared with normal patients. Persistent hypoperfusion of the optic disc was highly characteristic finding in subject with glaucoma. This was particularly apparent in cases with low tension glaucoma, in whom lasting hypofunction of the inferotemporal area of the optic disc was almost invariably present. Persistent hypofunction was significantly correlated with visual field loss. Transient hypofunction of the disc was not correlated with disease or with visual field loss. Staining of the optic nerve by fluorescein occurred in 30% of cases of glaucoma and appeared to be unrelated to IOP. As a result of these studies, the author feels that there are probably different mechanisms for development of optic nerve damage and open angle glaucoma. In some subject, the damage to the neuron is direct consequence of the IOP, while in others it is the result of ischemia associated with high IOP and in some cases without elevation of IOP.
Hayreh & Walker (1967); Ernest & Potts (1968) investigated 33 patients of glaucoma with fluorescein angiography, they concluded that there was a decrease in fluorescence of the optic disc in some glaucoma patients. They assumed that the arterial phase fluorescein angiograms is an index of disc vascularity. If this is true and since at the time of the angiogram, the patients all had normal intraocular pressure, then it may be evidence that there is a decrease in disc vascularity in glaucoma.

**Fluorescein filling patterns:**

Vessels that could not visible on colour photograph can be readily apparent on angiogram. Earliest phases of the angiogram showed fluorescein within the choroid and optic disc simultaneously. Usually the optic disc showed a small vascular fluorescent network of vessels appearing deep within its substance. Choroid did not fill uniformly but Areas of it filled segmentally, indicating different circulation times for separate areas of choroid. The nasal choroid generally filled first.

The deep disc circulation appeared to be related specifically within the choroid.
Similar to choroid the disc showed a segmental pattern of filling with fluorescein. This is observed as difference in fluorescein filling or a hypofluorescence generally detected as a difference of fluorescein intensity in various areas of the disc. Filling defect classified as—
(1) Sector; (2) Patchy; (3) Extensive hypofluorescence or in another way it may be classified as follows.

(1) **Absolute** - The defect in an area of the disc that demonstrates total hypofluorescence or non-filling throughout all phases of the fluorescein angiogram. This defect is particularly observed in early arterial phase and the late venous phase. This type of defect usually correspond the areas of severe pallor seen in the colour photograph. It often occurs in the deepest part of the cup where the grayish dots associated with the presence of lamina cribrosa are more readily seen.

(2) **The relative** - filling defect refers to an area of the disc that either fill more slowly (time delay) than other areas of the disc or never achieves total fluorescence (intensity) compared to other areas of the disc.

The relative intensity defect is observed when at full arterio-venous phase, areas of the disc are not seen with the same amount of fluorescence as other areas. These defects are commonly seen in the nasal rim of the disc.
The hypofluorescence may be in the central area of the disc or nasal rim or both. In the central area defects are usually relative but many times small circumscribed absolute filling defect can be seen in the depth of the cup corresponding to the area of greatest pallor. Fluorescein angiography of optic disc was performed by Schwartz (1977) on normal, ocular hypertensive and glaucomatous patients. In the normal eye, it is difficult to classify defects in the central area as absolute or relative.

In ocular hypertensive eye, the disc shows some type of relative defect, generally more on the nasal rim and the central areas of the disc has more small absolute defects and larger areas of relative defects.

In glaucomatous eye large number of absolute defects are seen in the floor of the cup, the relative defects are rarely seen.

The number of absolute filling defects much increased with degree of visual field loss, was greater in glaucomatous than in ocular hypertensive or normal eyes. Similarly ocular hypertensive eye showed a larger number of discs with filling defects than normal eyes. Therefore, it is postulated that relative defects changes to absolute filling defects, which is an indication of impending loss of visual fields.
Topography & extent of fluorescein – Filling defects of optic disc in glaucoma:


Begg et al (1972) specifically related a fluorescein defect of the disc to an arcuate defect in the visual field.

Topography and extent of localized areas of hypofluorescence of the optic discs of glaucomatous patients correlated positively with the loss of visual field. Filling defects tended to cluster at the inferior and superior poles of the optic disc margin than to the center. The location of the defects corresponded with the expected site of visual field loss respectively (Fishbein & Schwartz, 1977).

There was a positive correlation between the percent area of the filling defects and the degree of visual field loss. These observations support the concept that fluorescein filling defects of the optic disc in glaucoma represent areas of ischemia that are highly correlated with loss of visual field (Fishbein & Schwartz, 1977).
Loebl & Schwartz (1977) studied 23 normal & 29 ocular hypertensive eyes, found that there were also significant correlations of the areas of filling defects with age & systolic blood pressure in the ocular hypertensive eyes that were not present in the normals. These observations support the concept that fluorescein angiography of the optic disc demonstrates localized areas of impaired circulation that increases with ocular pressure, age and systolic blood pressure. This technique may be useful in separating normal from the ocular hypertensive patients who shows changes in the circulation of the optic disc with increased ocular pressure.

Halasa (1972) did fluorescein angiography of the optic disc on ten ocular hypertensive patients, but did not show any abnormalities of their fluorescein angiographic pattern.

Specificity of fluorescein angiographic defects of optic disc in Glaucoma:

Fluorescein angiography of the optic disc performed (Talusan & Schwartz, 1977) on normal subjects, patients with non-myopic open-angle glaucoma and myopic open angle glaucoma, normal myopes, patients with optic atrophy due to chiasmal pituitary tumours, and patients with sectorial ischemic optic neuropathy due to vascular hypotension.
The normal myopes, those with optic atrophy secondary to pituitary tumour, and the ischemic optic neuropathy group had optic discs similar in appearance to those with open angle glaucoma. Absolute fluorescein filling defects occurred only in patients with open angle glaucoma and sectorial ischemic optic neuropathy. The filling defects in open-angle glaucoma appear to be specific, indicating that the blood supply to the anterior portion of the optic nerve involved, as in ischemic optic neuropathy. Fluorescein angiography of the optic disc may be useful to differentiate open angle glaucoma from other entities that have similar optic discs.

Talusan & Schwartz (1977) show that except for those patients who has diagnosis of ischemic optic neuropathy due to vascular hypotension, the absolute fluorescein filling defects seen in glaucoma were not seen in myopic eyes in eyes of patients with pituitary tumours primarily confined to the chiasm. These latter patients had disc changes similar to those seen in glaucomatous eyes, but visual field changes characteristic of a chiasmal lesion. Typical absolute filling defects, as noted in glaucoma were seen only in those patients, who had definite ischemic optic neuropathy due to systemic vascular hypotension and optic disc and visual field
changes similar to those seen in glaucoma. These observations point to the specificity of the vascular lesion in glaucoma and in sectorial ischemic optic neuropathy, where the anterior nerve head is involved. A similar basis of the vascular lesions in these entities has been postulated by Hayreh (1975) who with Foulds (1968) has shown localized filling defects in sectorial ischemic optic atrophy.

Goldmann (1956) and Diaz – Dominiguez (1961) have pointed out the high incidence of glaucoma in myopic eyes and the difficulty in distinguishing the myopic disc from the glaucomatous disc. Fluorescein angiography would be useful where an adequate visual field could not be obtained or where one suspects that the disc is responding to the ocular pressure in the myopic eyes.

A comparison of two or more disc fluorescein angiograms performed on separate occasions was done on 60 eyes of normal subjects and patients with ocular hypertension, primary open angle glaucoma and low tension glaucoma. Clinically stable patients did not show any change in their disc angiographic filling patterns. Eyes that developed new visual field defects with increased disc cupping & pallor correspondingly showed new absolute filling defects or areas of hypofluorescence.
In those with established field defects, however, further changes in the visual field occurred without obvious changes in the disc fluorescein filling defects. Surgical lowering of intraocular pressure with or without decrease in disc cupping and pallor did not result in visible improvement of the disc angiographic pattern. Thus, the development of new visual-field defects is associated with changes of the circulation of the optic disc.

Adam et al. (1980) studied 171 optic fluorescein angiograms of glaucomatous, ocular hypertensive and normal patients, were studied for the hypo-fluorescence in the rim, wall and floor of the optic cup using disc stereo-photographs compared with the fluorescein angiograms. The wall of the cup has a greater percentage of filling defects in subjects with glaucoma than in ocular hypertensive or in normal subject. The floor of the cup has more filling defects in normal subjects than in those with glaucoma. The involvement of the wall of the cup increases with the degree of visual field loss in glaucoma. The effect of ocular pressure is greater on the wall of the cup than on the floor of the cup.
Hitchings & Spaeth (1976 & 1977) have noted that fluorescein filling defects have a strong predilection for the rim in glaucoma with moderate and advanced visual field loss. Difference in location of the absolute defects in normal and glaucomatous eye may be due to the differential effect of ocular pressure on the circulation in the wall and floor of the cup or to a change in the blood supply not related to pressure.

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