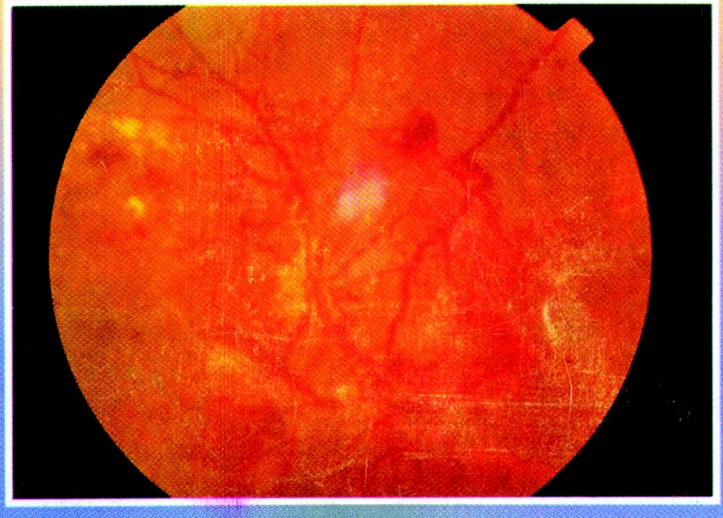
CME SERIES (No. 3)

1999

MANAGEMENT OF DIABETIC RETINOPATHY



ALL INDIA OPHTHALMOLOGICAL SOCIETY

By
Dr. P.N. Nagpal
Dr. Kamal Nagpal
Dr. Manish Nagpal

Published by :

ALL INDIA OPHTHALMOLOGICAL SOCIETY
Dr. Rajendra Prasad Centre for Ophthalmic Sciences,
All India Institute of Medical Sciences,
Ansari Nagar, New Delhi - 110 029

(as a part of the CME Programme)

THIS CME MATERIAL HAS BEEN SUPPORTED BY THE FUNDS OF THE AIOS, BUT THE VIEWS EXPRESSED THEREIN DO NOT REFLECT THE OFFICIAL OPINION OF THE AIOS.

For any suggestions, please write to :
Dr. H.K. Tewari
Hony. General Secretary

ALL INDIA OPHTHALMOLOGICAL SOCIETY
Dr. Rajendra Prasad Centre for Ophthalmic Sciences,
A. I. I. M. S, Ansari Nagar, New Delhi - 110 029
Phone :6568327

Ref. No. : F - 215/AIOS/ *Dated : June 3, 1999*

Dear Colleagues,

All India Ophthalmological Society has been publishing CME MATERIAL for the propagation of latest Technique and Development in the field of Ophthalmic Sciences. We have already published 2 such CME Materials, one on "PAEDIATRIC CATARACT" and the other on "EALES' DISEASE". Copies of the same have already been sent to you.

Now the 3rd CME Monogram on "MANAGEMENT OF DIABETIC RETINOPATHY" written by Dr. P.N. Nagpal, Dr. Kamal Nagpal and Dr. Manish Nagpal has been published and a copy of the same is being sent to you. You are requested kindly to read this material carefully and critically. We need inputs from your side. It may, however, be mentioned here that this CME MATERIAL HAS BEEN SUPPORTED BY THE FUNDS OF THE AIOS BUT THE VIEWS EXPRESSED THEREIN DO NOT REFLECT THE OFFICIAL OPINION OF THE ALL INDIA OPHTHALMOLOGICAL SOCIETY.

Dr. P.N. Nagpal has also made available to us "IFOS/ICO NEWS LETTER" Published by International Council of Ophthalmological on behalf of International Federation of Ophthalmological Societies. A copy of the same is also enclosed for your information.

The next "SAARC Conference" is being held at Kathmandu (19-21 November 1999). For further details please contact Dr. Shashank Koirala, *Organizing Chairman* or Dr. Dev N. Shah, *Organizing Secretary*, VI Ophthalmoligical Congress of SAARC Countries, B.P. Koirala Lions Center for Ophthalmic Studies, P.O. Box 8750, Maharajgunj, Kathmandu, Nepal. Fax : +977-1-420142. E-mail : bpklcos@healthnet.org.np

Looking forward to your support and guidance.

With best wishes,

Yours Sincerely,

(Prof. H.K. Tewari)

All Members
All India Ophthalmological Society

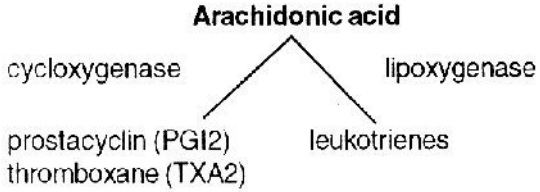
Pathogenesis of diabetic retinopathy

Hypoxia plays the major role as far as development and pro of diabetic eye disease is concered. On molecular level, it is expl the basis of decreased 2,3 diphoshoglycerate (2,3 DPG) in the eyt Since 2,3 DPG influences the oxygen dissociation curve of bloc is a diminished oxygen release to the tissues. Simultaneously, in level of glycosylated haemoglobin (10-15%) in diabetics as again in healthy persons is seen. Glycohaemglobins have greater oxygen capacity, and also cause blockage of oxygen release to the tissu

Polyol pathway of glucose metabolism, an alternative route be activated due to excessive glucose within the tissues, resul intracellular accumulation of sorbitol and fructose. This leads to inc osmotic pressure within the cells, creating celluar oedema. Also, i impedance of oxygen diffusion into cells results, exacerbating the h state.

Impaired glucose metabolism promotes the release of growth hor which in turn increases fibrinogen and α-2 globulin synthesis by the These large plasma proteins promote hyperaggregation of erythro and platelets, giving rise to sludging and resistance to blood flow. Willebrand factor VIII and anti-hemophilic factor (which are involv platelet adhesion and aggregation) are also known to have an incre activity in diabetics in general and especially so in those with retinop

Prostaglandins are also known to cause vascular insult. Arachic acid released from the cell membrane phospholipids by the actio enzyme phospholipase A2 further goes along the following routes:



PGI 2 is a potent platelet aggregation inhibitor and vasodilator, where TXA 2 is a platelet degranulation and aggregation promoter a vasoconstrictor. The leukotrienes inhibit PGI 2 release, promote the relea of TXA 2 and increase vascular permeability. A disparity between PGI and TXA 2 is likely to play a role in pathogenesis of diabet microangiopathy.

The factors summarized above act in conjunction with each other ar

ALL INDIA OPHTHALMOLOGICAL SOCIETY
Dr. Rajendra Prasad Centre for Ophthalmic Sciences,
A. I. I. M. S, Ansari Nagar, New Delhi - 110 029
Phone :6568327

Ref. No. : F - 215/AIOS/ *Dated : June 3, 1999*

Dear Colleagues,

All India Ophthalmological Society has been publishing CME MATERIAL for the propagation of latest Technique and Development in the field of Ophthalmic Sciences. We have already published 2 such CME Materials, one on "PAEDIATRIC CATARACT" and the other on "EALES' DISEASE". Copies of the same have already been sent to you.

Now the 3rd CME Monogram on "MANAGEMENT OF DIABETIC RETINOPATHY" written by Dr. P.N. Nagpal, Dr. Kamal Nagpal and Dr. Manish Nagpal has been published and a copy of the same is being sent to you. You are requested kindly to read this material carefully and critically. We need inputs from your side. It may, however, be mentioned here that this CME MATERIAL HAS BEEN SUPPORTED BY THE FUNDS OF THE AIOS BUT THE VIEWS EXPRESSED THEREIN DO NOT REFLECT THE OFFICIAL OPINION OF THE ALL INDIA OPHTHALMOLOGICAL SOCIETY.

Dr. P.N. Nagpal has also made available to us "IFOS/ICO NEWS LETTER" Published by International Council of Ophthalmological on behalf of International Federation of Ophthalmological Societies. A copy of the same is also enclosed for your information.

The next "SAARC Conference" is being held at Kathmandu (19-21 November 1999). For further details please contact Dr. Shashank Koirala, *Organizing Chairman* or Dr. Dev N. Shah, *Organizing Secretary,* VI Ophthalmoligical Congress of SAARC Countries, B.P. Koirala Lions Center for Ophthalmic Studies, P.O. Box 8750, Maharajgunj, Kathmandu, Nepal. Fax : +977-1-420142. E-mail : bpklcos@healthnet.org.np

Looking forward to your support and guidance.

With best wishes,

Yours Sincerely,

(Prof. H.K. Tewari)

All Members
All India Ophthalmological Society

Intravascular factors

Rheological factors that contribute to retinopathy are as follows :

* Decreased RBC wall deformability, impairing blood flow through capillaries.
* Enhanced platelet aggregation and adhesion and decreased platelet life span.
* Impaired Fibrinolysis and prolonged clot lysis time.
* Increased plasma fibrinogen and hyperlipidemia contributing to the increased plasma blood viscosity.

Vessel closure

Widespread pericyte and endothelial damage results in structural and functional alterations of the capillaries. Loss of endothelial cells and pericytes leaves behind a non-functional scaffold of cellular basement membrane tubes without any blood flow. This is seen on fluorescein angiography as capillary fallout areas, most easily demonstrated in the perifoveal capillary network. Dilatation of the adjacent capillary bed often occurs in response. Capillaries are the earliest vessels to close, followed by arterioles in more advanced cases.

Cotton wool spots

The pathophysiology of the cotton wool spots was classically described by Mcleod D in 1975. It was stated to be due to an interruption of antegrade and retrograde axoplasmic flow in the nerve fiber layer, thereby causing a gross,localized axonal distention. Any disorder which causes an acute arteriolar microvascular occlusion can give rise to these spots, such as diabetes, hypertension, retinal vein occlusion, retinal vasculitis, anemia, leukemia etc. Usually the precapillary arterioles are the first ones to occlude, followed by larger arterioles. Cotton wool spots commonly occur where the nerve fiber layer is the thickest - around the disc and along the temporal arcades. Pathologically they are characterized by presence of cytoid bodies and button like swelling of disrupted axonal ends. Once the cotton wool spot resolves, the nerve fiber and ganglion cells at that spot atrophy, giving rise to 'depression sign.'

The term "soft exudates " by which it was popularly known is a misnomer,because cotton wool spots are not exudates at all, but an accumulation of intracellular fluid and organelles as a result of local ischemia.

Neovascularization

In the normal eye there is a balance between vasoinhibitor and vasoproliferative factors in the retina & vitreous which results in a stable microvascular bed. Widspread ischemia results in a shift in this balance towards vasoproliferation with the development of fragile new vessels from the retinal venous microcirculation. These may bleed, giving rise to blinding complications. In the anterior segment, rubeosis, extension of new vessels into the angle and subsequent fibrosis leads to glaucoma.

Epidemiology

Diabetes remains a leading cause of legal blindness between the ages of 25-65 years in the western world. It acquires great economic significance, because majority of those affected fall in the 'working age'. 14 million Americans are estimated to be suffering from diabetes. In UK, the incidence of type 2 diabetes is 1% and that of type 1 is 1 per 1000. True statistics are not available in our country, though the emerging trends show that it is soon likely to become a major public health menace.

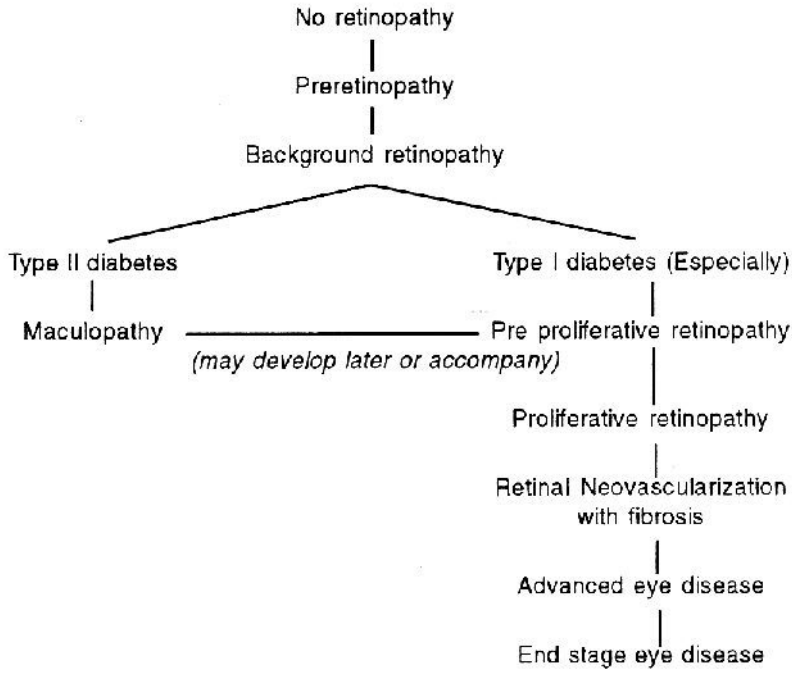
In type 1 diabetes, the incidence of retinopathy is 4% in the 0-9 years age group and 83% in 33-40 years age group. However, retinopathy is less clearly related to the age of the patient than the duration of diabetes. After 20 years, nearly all type 1 and about 60% of type 2 diabetes manifest some degree of retinopathy. There is a greater risk of development of proliferative retinopathy in males suffering from type 1 disease than females. The incidence of type 2 diabetes is higher in females as compared to males (3:2), though the rates of development of retinopathy do not differ. Diabetic retinopathy is primarily a direct long term consequence of sustained hyperglycemia, modified to a variable extent by genetic & acquired systemic factors. Therefore, a tight long term diabetic control along with control of hypertension, proteinuria and smoking can prevent or retard it's development. Patients with type 1 diabetes, (especially males) have a greater incidence of proliferative retinopathy, maculopathy being less common as opposed to those with type 2 who have a higher incidence of maculopathy.

Clinical classification : According to DRS and ETDRS

- Background retinopathy (Non-Proliferative Retinopathy)
- Maculopathy
  * Focal
  * Diffuse
  * Ischemic
  * Mixed

- Preproliferative diabetic retinopathy (severe NPDR)
- Proliferative diabetic retinopathy
- Advanced diabetic disease
  - Persistent new vessels
  - Tractional Retinal Detachment
  - Neovascular glaucoma
- End stage diabetic eye disease

Progression



Background retinopathy

The earliest manifestation of diabetes on the retina is in the form of background diabetic retinoathy (BDR). The patient is usually asymptomatic until macular oedema occurs, which causes a fall in vision. Ophthalmic signs are :

* **Microaneurysms :** Microaneurysms are focal saccular dilations of

the capillary bed, ranging from 20-100 microns in size and are ophthalmoscopically visible (better on red free illumination) if larger than 30 microns. Smaller ones can be visualized on angiography as tiny fluorescent dots. They are often present at the center of a hard exudate, an accumulation of lipoproteins leaked from the microaneurysm itself. They may also bleed producing intra-retinal haemorrhages. Microaneurysms have been reported to be maximum in number in the supero-temporal quadrant, and their counts using stereoscopic color fundus photographs are important indicators for the measure of the progression of retinopathy.

* **Retinal haemorrhages :** They may be small & round (dot & blot) or flame shaped depending on their depth within the retinal layers. Larger haemorrhages (>1/2 DD), especially if they are multiple are of prognostic significance because they indicate a preproliferative sign. Retinal haemorrhage spreads along the line of least resistance, constrained by the local anatomy of the particular layer from which it arises. Therefore a superficial bleed will track parallel to the nerve fiber layer resulting in a longitudinal spread - becoming flame shaped. However deeper in the retina, since the layers are vertically oriented it results in circumscribed, round haemorrhages, dot and blot (with fuzzier borders). They could originate either from fragile capillaries or microaneurysms.

* **Hard exudates :** Hard exudates are morphological signs of blood retinal barrier breakdown. Biochemically, they are composed of lipoproteins of plasma origin. They are deposited in the inner and outer plexiform layers and are exuded from microaneurysms. Areas of hard exudates are surrounded by an accumulation of macrophages. When arranged in dense conglomerates, they may cause localized scotomata.

* **Retinal oedema :** Diffuse retinal oedema represents a diffuse leakage from a dilated capillary bed at the posterior retina. Therefore, it can be considered a generalized breakdown of the blood retinal barrier, which allows passage of smaller molecules such as water instead of lipoproteins as seen in focal oedema. It is often accompanied with cystoid macular changes. In diffuse retinal oedema systemic factors other than diabetes such as hypertension and renal impairment also play a contributing role. Therefore their correction such as a control of blood pressure and diuresis are helpful in reducing the oedema. It is best assessed stereoscopically, by slit lamp biomicroscopy or indirect ophthalmoloscopy. Loss of macular reflex may be a useful sign in the young.

At the background stage, progression to more serious retinopathy may occur though it is not inevitable. The Diabetes Control and Complication Trial (DCCT) confirms that a tight blood sugar control retards the development and progression of retinopathy. Simultaneously control of other systemic abnormalities such as hypertension, renal disorder, anemia, etc. are of benefit in retarding the onset of more serious stages of retinopathy.

Diabetic maculopathy

Diabetes can affect macula in several ways, macular oedema being the most frequent. It is also the most frequent cause of visual loss in the background stage.

* **Diabetic Macular Oedema :** It is defined as a collection of interstitial fluid within the macula with or without lipid exudates and with or without cystoid changes. Clinically, macular oedema is retinal thickening within two disc diameters of the center of the macula (not fluorescein leakage without thickening). Retinal thickening or hard exudates with adjacent retinal thickening that threatens or involves the center of the macula is considered to be clinically significant macular oedema (CSMO)

CSMO as defined by the ETDRS includes any one of these lesions :

* Retinal thickening at or within 500 micron of the center of the macula.
* Hard exudates at or within 500 micron of the center of the macula, if there is thickening of the adjacent retina.
* An area or areas of retinal thickening at least 1 disc area in size, at least part of which is within 1 disc diameter of the center of the macula.

Macular edema may be focal, diffuse, ischemic or a mixed variety. It results mainly from breakdown of the inner blood retinal barrier, though the outer barrier (pigment epithelium) has also been suggested by some. It may be present during any stage of retinopathy, though, the percentage of patients with macular oedema increases with increasing severity of retinopathy. Other factors influencing the development of macular oedema are the age at onset, type and the duration of diabetes. According to the Wisconsin Epidemiologic Study of Diabetic Retinopathy, the prevalence rate of macular oedema is 10% in the diabetic population as a whole. It is seen earlier after the discovery of diabetes in the older onset patients and even in this group it is higher in those that are being treated with insulin (5% may already have macular oedema at the time of diagnosis).

* **Focal :** As the name suggests, this is a localized leak from a microaneurysm giving rise to a hard exudate, deposited at the junction of the normal and abnormal retina. Laser photocoagulation is often very successful in preventing or retarding visual loss and may even result in the visual improvement. However if the exudates are too far advanced, their resorption does occur following the laser treatment but retinal function may already have been destroyed due to which visual improvement may become impossible. Macular plaque is a long standing continued damage due to leakage into the macula.

* **Diffuse :** It is characterized by a wide spread leakage of fluid from retinal capillaries, IRMAs & microaneurysms, leading to a diffuse macular oedema and a reduction in vision. Clinically, there is retinal thickening, loss of macular reflex and at a later stage development of cystoid macular oedema due to a break down of the intervening normal retinal tissue. It may also present as scattered exudates in a non-circinate pattern. Without laser treatment in such cases, there is a continued fluid accumulation and destruction of the foveal architecture. Laser photocoagulation aims at limiting this destruction of macular structure and function.

* **Ischemic :** This type of maculopathy occurs as a result of non perfusion of parafoveal capillaries with or without intraretinal fluid accumulation. It usually coexists with the other types, but in its pure form is the least easy to recognize and diagnose. Ophthalmoscopically one may find a dull appearance to the macula. However an FA is necessary to confirm the diagnosis. It is essentially untreatable. Improvement of a poor diabetic control may retard the progression, but too rapid an implementation can also lead to a transient worsening of retinal ischemia. Preproliferative and proliferative changes should be actively looked for in such cases and treated early because it will help reduce the risk of further visual loss from extra-macular complications.

* **Mixed :** Diabetic maculopathies rarely exist isolated and most commonlly have two or more of the components listed above. Management is the treatment of remediable elements after assessing their respective contributions by FA.

Other mechanisms in which macula is affected in diabetes are as follows:

* Traction on the macula by fibrous tissue proliferation causing a drag of the retinal tissue, surface wrinkling or detachment of the macula.

* Intraretinal or preretinal (subhyaloid) haemorrhage on the macula.
* Lamellar or full-thickness macular hole formation.
* Any combination of the preceding.

Preproliferative retinopathy

BDR progresses to the preproliferative stage (PPDR), indicating enhanced retinal ischemia, hence an increased risk for neovascular proliferations. Major signs are :

* **Cotton wool spots** (See Page 4)
* **Large blot haemorrhages** (>1/2 disc diameter) especially if multiple and dark are suggestive of arteriolar blockage and therefore increasing ischemia. They are seen typically temporal to the macula, this area being more susceptible because it represents a watershed zone between the superior and inferior temporal vascular arcades.
* **Intra retinal microvascular abnormalities (IRMA) :** These are also termed as intra retinal neovascularization by some. They may develop in non proliferative or proliferative stage. Typically they originate from and drain into venules at sites of non perfusion and develop slowly over a period of many months. They have also been regarded as shunt vessels. Although some believe that they are leaky, others have stressed that they have a minimum tendency of leakage and are not associated with haemorrhages. Because of their timely association with retinal neovascularization, they are considered important in the diagnosis of the preproliferative stage.
* **White retinal arterioles :** Represent arteriolar closure (see above) and signify retinal ischemia.
* **Venous changes :** These are striking features of the pre-proliferative retinopathy. Venous beading and looping is a powerful predictor of development of new vessels. It may be caused by a paradoxical increase in blood flow in larger retinal veins due to shunting of blood across arterio-venous anastomosis as a result of capillary shut down. Further changes in the form of dilatation, omega looping, beading, sausaging and reduplication of veins can be seen.

Proliferative retinopathy

Proliferative diabetic retinopathy (PDR) is characterised by developrnent of new vessels on the disc or elsewhere in the retina, extending

along their inner surfaces or into the vitreous cavity. Eyes that have already developed the preproliferative changes are at a great risk of progressing into this stage. However, neovascularization is rarely also observed in retinas not showing these features. This is explained by the fact that these lesions are often transient, gradually disappearing despite an increasing ischemic state and producing a featureless retina. While new vessels can be observed any where on the retina, most commonly they are encountered within about 45 degrees from the optic disc.

Neovascularization occurs because of a loss of equilibrium between the ocular vaso-inhibiting and growth factors. Important endothelial growth factors that have been discovered include - insulin like growth factor, platelet derived growth factor, nerve growth factor and fibroblast growth factor. These are all angiogenic peptides. Under their influence, neovascularization proceeds through the following series of steps. In the beginning, there is desruction of the basement membrane, which is followed by extension of cytoplasmic buds from endothelial cells towards the chemotactic factors. Migration and division of the endothelial cels takes place to form tube like structures, which then unite to form capillaries. These vessels initially start off as small flat fronds on the retinal surface gradually growing through the ILM into the vitreous. To begin with, they are bare, but later on are accompanied with proliferative fibrous tissue. Thereafter, they proceed through a phase of total or partial regression, followed by a replacement by fibrous tissue. New vessels are in themselves asymptomatic. Therefore they may be detected on the routine examination of an asymptomatic patient which signifies the importance of screening. On the other hand, the patient may present with an intraocular bleed. Haemorrhage from the new vessels may occur without any previous warning. However, occasionally small bleeds (experienced as a brief phase of blurring vision or an episode of floaters) may precede the development of a large haemorrhage. These should not be ignored.

Risk of bleeding from the new vessels depend upon :

* Location : Neovascularization of the disc (NVD) > Neovascularization elsewhere (NVE)
* Support : elevated > flat
* Vitreous attachment

If the neovascular fronds acquire an attachment to the vitreous they are subject to dynamic traction due to vitreous movement during ocular movements if posterior vitreous detachment (PVD) has not taken place.

This results in traction at areas where vitreous is still attached such as at ora or at sites of neovascularization and adhesions to vitreous base. If neovascular fronds develop in presence of a PVD small raspberry like vascular complexes develop called abortive neovascular outgrowths (ANVO) which are relatively benign as the name suggests. Bleeding may occur into the vitreous or in the subhyaloid space. In the latter it appears like a "boat" or "swallows nest" outlining the attachment of the incomplete PVD.

The contraction of an extensive fibrovascular sheet can also give rise to traction to the macula, producing distortion or dragging, tractional detachment of the retina or a hole formation giving rise to rhegmatogenous detachment. In the end, proliferative retinopathy enters an involutional or burnt out stage, with a regression of all the signs of the disease and a limited visual potential.

Role of Fluorescein Angiography (FA) in diabetic retinopathy

Background Diabetic Retinopathy

- Baseline
- Maculopathy - unexplained visual loss

Clinically Significant Macular Oedema

- Ischemia
- Extent
- Location

Preproliferative Diabetic Retinopathy

- Extent of retinal ischemia : Capillary non perfusion areas
- Detect NVE, NVD which are not clinically evident
- IRMAs
- Maculopathy

Proliferative Diabetic Retinopathy

- Confirm clinical findings
- Residual or recurrent proliferations after laser treatment

Angiographic risk factors for progression of NPDR to PDR have been identified. Analysis of data from the untreated eyes in the ETDRS indicates that the followings lesions are independently related to outcome :(1) Fluorescein leakage (2) Capillary loss on FA (3)Capillary dilatation on FA (4) Color fundus photographic risk factors : IRMAs, venous beading, haemorrhages and micoaneurysms. Hard and soft exudates have an

inverse relationship to progression. It is widely accepted that capillary loss as documented on FA is a risk factor for progression of NPDR to PDR. Although the FA abnormalities provide additional prognostic information, the color fundus photographic gradings of retinopathy levels of both eyes give the same prognostic results. Therefore, the increase in power to predict progression from NPDR to PDR by FA is "not of significant clinical importance to warrant routine FA."

Laser Management of Diabetic Retinopathy

The pioneer in the management of diabetic retinopathy is Meyer-Schwickerath, who developed the Xenon photocoagulator, although treatment of diabetic retinopathy was not his initial goal. In 1945, there was a solar eclipse seen in Northern Germany. Many peopple developed solar retinopathy giving Meyer-Schwikerath the idea for photocoagulation. His early attempts used the sun as a light source (treating patients on the roof of the hospital), but this proved to be unsatisfactory. Shortly thereafter, the xenon bulb was deveioped and a practical photocoagulator was soon available to the world. It was in 1955 that he treated his first five patients of diabetic retinopathy with photocoagulation. He also emphasized upon the value of fundus photography and clinical investigation, because of which, he was able to document the changes that occurred in both treated and untreated eyes. Later, photographic documentation became an integral part of the various collaborative studies on diabetic retinopathy.

Clinical Trials

Three major randomized clinical trials have largely determined the strategies for appropriate clinical management of patients with diabetic retinopathy, namely the DRS, ETDRS and DRVS. Therefore a brief insight into these will help in better understanding the current protocol of management.

Diabetic Retinopathy study (DRS) :

The DRS conclusively demonstrated that scatter (panretinal) photocoagulation significantly reduces the risk of severe visual loss (SVL) from PDR, particularly when high-risk PDR is present.

Major Eligibility Criteria

1. Visual acuity$\geq$ 20/100 (6/36) in each eye.
2. PDR in at least one eye or severe NPDR in both.
3. Both eyes suitable for photocoagulation.

Major Design Features

One eye of each patient was assigned randomly to photocoagulation - scatter (panretinal), local (direct confluent treatment of surface vessels), and focal (for macular oedema) as appropriate. The other eye was assigned to follow-up without photocoagulation.

Major Conclusions

1. Photocoagulation reduced the risk of severe visual loss by 50% or more. (SVL = VA < 5/200 (5/60) at two consecutively completed 4-month follow-up visits).
2. Modest risks of decrease in visual acuity(usually only one line) and visual field (risks greater with xenon than argon photocoagulation).
3. Treatment benefit outweighs risks for eye with high-risk PDR (50% 5-year rate of SVL in such eyes without treatment was reduced to 20% by treatment).

Early treatment diabetic retinopathy study (ETDRS) :

Major Eligibility Criteria

1. Visual acuity ≥ 20/40 (6/12) (20/400 (60/120) *if reduction caused by macular oedema).*
2. Mild NPDR to non-high risk PDR,with or without macular oedema.
3. Both eyes suitable for photocoagulation.

Major design features

1. One eye of each patient assigned randomly to early photocoagulation and the other to deferral (careful follow-up and photocoagulation if high-risk PDR develops).
2. Patients assigned randomly to aspirin or placebo.

Major conclusions

1. Focal photocoagulation (direct laser for focal leaks and grid laser for diffuse leaks) reduced the risk of moderate visual loss (doubling of the visual angle) by 50% or more and increased the chance of a small improvement in visual acuity.
2. Both early scatter with or without focal photocoagulation and deferral were followed by low rates of severe visual loss (5-yr rates in deferral subgroups were 2-10%; in early photocoagulation groups these rates were 2-6%)

3. Focal photocoagulation should be considered for eyes with CSME.
4. Scatter photocoagulation is not indicated for mild to moderate NPDR but should be considered as retinopathy approaches the high-risk stage and usually should not be delayed when the high-risk stage is present.

Thus, the ETDRS provided valuable information concering the timing of scatter (panretinal) laser surgery for advancing diabetic retinopathy and conclusively demonstrated that focal photocoagulation for CSMO reduces the risk of MVL by 50% or more. Furthermore, it demonstrated that both early scatter (panretinal) laser photocoagulation (before the onset of high-risk PDR) and deferral of treatment "until and as soon as high-risk PDR developed are effective in reducing the risk of SVL." Scatter laser surgery, therefore, should be considered as an eye approaches the high-risk stage and "usually should not be delayed if the eye has reached the high-risk proliferative stage".

Diabetic retinopathy vitrectomy study (DRVS) :

The DRVS provided guidelines for the most opportune time to consider vitrectomy surgery for patients with type I and type II diabetes mellitus and vitreous hemorrhage or severe PDR in eyes with useful vision.

Group H - Recent Severe Vitreous Hemorrhage

Major eligibility criteria

1. Visual acuity $\leq$ 5/200 (5/60).
2. Vitreous haemorrhage consistent with visual acuity, duration 1-6 months.
3. Macula attached by ultrasound.

Major Design Features

1. In most patients, only one eye was eligible.
2. Eligible eye or eyes assigned randomly to early vitrectomy or conventional management (vitrectomy if center of macula detaches or if vitreous haemorrhage persists for 1 year, photocoagulation as needed and as possible).

Major conclusions

Chance of recovery of VA $\geq$ 10/20 (3/6) increased by early vitrectomy, at least in patients with type I diabetes, who were younger and had more severe PDR (in most severe PDR group, $\geq$ 10/20 (3/6) at 4 years in 50% of early vitrectomy group versus 12% in conventional management group)

Group NR - Very Severe PDR With Useful Vision

Major Eligibility Criteria

1. VA $\geq$ 10/200 (3/60).
2. Center of macula attached.
3. Extensive, active, neovascular, or fibrovascular proliferations.

Major Design Features

Same as group H (except conventional management included vitrectomy after a 6 months waiting period in eyes that developed severe VH).

Major Conclusions

Chance of VA $\geq$ 10/20 (3/6) increased by early vitrectomy, at least for eyes with very severe new vessels.

Early vitrectomy for eyes with recent severe vitreous hemorrhage and visual acuity less than 5/200 (5/60) was beneficial, especially for patients with type I diabetes mellitus. Furthermore, the chances of achieving visual acuity of 10/20 (3/6) or better increased when early vitrectomy was performed in eyes with severe new vessels. again especially for patients with type I diabetes mellitus.

Treatment Guidelines

Since diabetic blindness is emerging strongly on our horizon, certain guidelines need to be followed by the ophthalmic and non ophthalmic medical community in order to combat it. It has to be stressed upon the patient that a timely intervention can go a long way in preventing significant visual disabilities and therefore qualitative and quantitative salvation of lifestyle. Although, there is a presymptomatic stage of this disease, reliable detection methods are available and effective treatment is not only possible, it is also cost effective. Thus, the most important aspect of management is to emphasize the importance of a periodic follow up.

* All patients with diabetes should be informed that sight threatening eye disease is a common complication of diabetes. Diabetic eye disease can be present with good vision, and early detection and treatment improves the prognosis.

* Patients with juvenile onset diabetes should have a complete ophthalmic examination including history of visual

symptoms,measurement of visual acuity and intraocular pressure, and ophthalmoscopic examination through dilated pupils.

- Individuals with older onset diabetes should have the preceding ophthalmic examination at the time of diagnosis of the diabetes.
- After the initial ophthalmic examination, patients with diabetes should be examined yearly, unless more frequent examinations are indicated by their eye disease.
- Any woman with diabetes who becomes pregnant should be examined for retinopathy early in the first trimester and thereafter as indicated by any abnormality.
- Any woman with diabetes planning a pregnancy should be examined and followed for retinopathy.
- Patients should be under the care of a retina specialist or ophthalmologist experienced in the care of diabetic retinopathy when their eye findings indicate severe background retinopathy, proliferative retinopathy, or macular oedema.
- Patients with functionally decreased vision should undergo low vision evaluation and appropriate visual, vocational and psycho-social rehabilitation.

Eye examination schedule

Age at onset of diabetes	Recommended time of first examination	Routine minimum follow up (in absence of abnormal findings)
0-30 years	5 years after onset of DM	Every year
31 yrs and older	At the time of diagnosis of DM	Every Year
During pregnancy	In the first trimester	3 monthly and for first year following birth

Diabetic status of retina	Follow up (*months*)
Normal or minimal BDR	12
BDR without macular edema	6-12
BDR with non clinically significant macular oedema	4-6

BDR with CSMO	3-4
PPDR	3-4

Background diabetic retinopathy

Regular clinical checkup is mandatory to look for the development of the following :

* Maculopathy
* Preproliferative changes
* New vessels on the disc or elsewhere

Clinically Significant Macular Oedema

Focal laser treatment for CSMO consists of direct laser treatment, grid laser treatment, or a combination of the two. Based on previously mentioned randomised clinical trials for treatment of diabetic macular oedema, following guidelines are recommended.

* Eyes with macular oedema that is not clinically significant should generally be watched without treatment.
* Eyes with CSMO with center involvement should be considered for immediate laser treatment.
* Eyes with CSMO without center involvement should also be considered for immediate laser treatment, if the visual acuity is good.

In general, the following lesions are considered treatable :

* focal leaks > 500 microns from center of macula causing thickening or exudation.
* focal leaks 300 - 500 microns from center of macula, if the treatment is not likely to destroy the remaining perifoveal capillary network.
* ares of diffuse leakage not treated previously
* avascular zones other than the normal foveal avascular zone, not previously treated.

Factors favoring treatment include the evidence of advancing oedema and that the treatable lesions causing the oedema are located more than 500 microns from the center of fovea.

Technique : Usually a FA is done prior to deciding the treatable lesions. In the ETDRS protocol these treatable lesions were as follows:

1. Discrete points of retinal hyperfluorescence or focal leakage, that were 500 micron or more from the centre of the macula causing hard exudates and / or retinal thickening.

2. Focal leaks 300-500 microns from the centre of the macula thought to be causing retinal thickening and /or hard exudates.

3. Areas of diffuse leakage within the retina (IRMA or diffusely leaking capillary bed).

4. Thickened retinal avascular zones (except for normal FAZ).

The treatment techniques could be (a) **focal photocoagulation** or (b) **grid treatment**

Focal photocoagulation : Spot size from 50 to 200 microns of 0.1 seconds duration can be used to directly treat all the focal fluorescein leaks, which could include the microaneurysms, IRMAs or short capillary segments. The goal of treatment is to obtain closure or obliteration of the leak. The end point is a whitening or darkening of the microaneurysms.

Grid photocoagulation : This is applied to areas of thickened retina showing diffuse fluorescein leakage and/or capillary drop out. Burns of light intensity are placed in this area using 50 to 200 microns spots of 0.1 sec or 0.5 sec duration. Grid is not placed within 500 micron of center of the macula or within 500 micron of the disc margin,but can be placed in the papillomacular bundle. Peripherally, it can be placed in all directions upto 2 disc diameter from the center of the macula, or to the border of the PRP treatment. The main aim of grid treatment is to 'tickle' the retinal pigment epithelial cells and stimulate the retino-choroidal pump to hasten the absorption of fluid and not to the destroy the region.

Follow-up treatment : At 4 weeks after treatment the patients are reviewed. If some obvious treatable lesions are missed at the initial session, they are treated four months after the initial treatment confirming this with FA. Follow up should be done at 4 monthly intervals. The patients should be explained in detail that laser treatment of diabetic macular oedema is effective mainly in preventing further visual loss rather than restoring the vision already lost.

Preproliferative diabetic retinopathy

Preproliferative phase is variable in its speed of evolution and may or may not give rise to neovascularization. The mainstay of management is close observation at two or three monthly intervals with photographic documentation and angiography whenever essential. Laser treatment

should be considered on the development of new vessels. Laser treatment in this stage per se, is recommended and justifiable in selected circumstances in which a regular follow up is doubtful. Some also recommend laser treatment in presence of severe ischemia even in absence of neovascularization. An improvement in diabetic control can regress the preproliferative changes to an extent.

Proliferative diabetic retinopathy

On the basis of various studies including DRS and ETDRS the following are the guidelines for photocoagulation therapy in PDR :

* Treatment should be promptly carried out in eyes with PDR that have well established NVD and/or vitreous or preretinal haemorrhage. Treatment is particularly urgent in case of localised fresh haemorrhage, due to the risk of its dispersion, making any further laser treatment impossible.
* Whenever high risk characteristics are definitely present, PRP should be carried out inspite of presence of fibrous proliferation or tractional detachment (TRD). Areas of fibrous proliferation and TRD should be avoided, and treatment should be mild to moderate as there is a risk of extension of the localised TRD into the macula. A combination of vitrectomy and photocoagulation may be required in some patients.
* Whenever neovascularization is seen in the anterior chamber angle or in the iris, prompt PRP should be done, irrespective of the presence of or absence of high risk characteristics.
* Eyes with changes of severe ischemia, i.e. extensive retinal haemorrhages, capillary non perfusion, severe beading of veins prominent and multiple cotton wool spots also need early photocoagulation as there is a risk of anterior segment neovascularisation.
* The criteria for treating severe PPDR or eyes with NVE only without vitreous or preretinal haemorraghes is less clearly defined. In cases of NVE if active networks are growing along upper temporal arcade or there is extensive areas of PPDR, probably these eyes should also receive treatment.
* Eyes with "burnt out" retinopathy or showing regression of PDR should not be treated with photocoagulation. Small areas of NVE without associated haemorrahges also need not be treated and can be kept under observation only.
* In eyes with PDR and macular oedema, either focal or grid treatment

of macular oedema, can be done first followed about 4-6 weeks later by PRP.

- If delay in treatment is undesirable, the ETDRS protocol can be used combining focal treatment for macular oedema with PRP in the nasal quadrant at the first sitting and adding PRP in other quadrants in the subsequent sittings.
- Consideration of systemic factors may influence the decision to initiate treatment in patients with severe PPDR or PDR without high risk characteristics. For exemple,since PPDR/PDR is known to worsen in pregnancy or after renal transplant it would be better to initiate photocoagulation.

Pan Retinal Photocoagulation (PRP)

In eyes without cataract, argon blue green or argon green laser is used. In case of cataract or vitreous haemorrhage obscuring the view and hampering the passage of the above wavelengths diode red can be used.

Technique :The burns are usually placed 2 to 3 disc diameters away from the macula, i.e. usually outside the arcades and extended peripherally upto the equator. Typical initial settings are a 500 micron spot size, a 0.1 sec. exposure time and 250-270 mW power. The power is gradually increased till a whitish 500 micron lesion is obtained. Usually, first a row of laser marks is placed around the macula to help in avoiding any unintentional macular burns. Treatment is continued out at the far periphery. The lesions are placed one burn width apart. A total of 1600-2000 burns are placed, though it is not known as to how many burns an eye requires to induce regression of neovascularization. In the ETDRS, argon laser burns of 200-1000 micron spot size and 0.1-0.5 seconds duration were used. Strong burns applications increases the risk of haemorrhage during treatment and large scars produced during treatment can lead to noticeable scotoma or nerve fibre bundle defects. The ETDRS protocol allowed scattered treatment alone as an alternative to local treatment within 2DD of the centre of the macula and wherever local treatment would produce a scar larger than 2 DD in diameter. It is also recommended that local treatment should not be applied over major retinal veins, preretinal haemorrhages, darkly pigmented chorioretinal scars or within 1 DD of the centre of the macula.

Burns along the long ciliary nerve are often painful. Using only topical anaesthesia, most patients have little or no discomfort until the treatment approaches the equator. Alternatively one can use 200 micron burns to coagulate the same area. Another alternative is to use a 0.5 second

exposure time. A final alternative is to give retrobulbar anaesthesia.

The number of sessions used to carry out the treatment varies between one to four depending on the physician and the patient cooperation. We at Retina Foundation prefer to do it in two sessions, the first session covering the inferior sectors. The inferior sector should be preferably done first so that if a haemorrhage occurs, it would tend to settle inferiorly and one could still do the superior PRP. Multiple sittings help to avoid retrobulbar anaesthesia and also may decrease the incidence of angle closure glaucoma secondary to serous ciliochoroidal detachment.

In about 25% of eyes who undergo complete initial PRP for DRS - High risk characteristic, enough new vessels persist or recur to justify additional photocoagulation. The ETDRS guidelines for follow-up treatment after initial PRP includes consideration of the following factors.

1. Change in new vessels since the last treatment.
2. Appearance of the new vessels (caliber, degree of network formation, extent of accompanying fibrous tissue.)
3. Frequency and extent of vitreous haemorrhage
4. Status of vitreous detachment
5. Extent of photocoagulation scars
6. Extent of tractional retinal detachment and fibrous proliferation.

Additional photocoagulation is considered,

a) If new vessels appear active as suggested by presence of tight networks of fibrous tissue and increase in size since the last visit.

b) If the extent of new vessels is "substantially" greater than it was at the time of initial treatment.

c) If recurrent vitreous or preretinal haemorrhages occur, especially without any coincidental posterior vitreous detachment.

d) If the previous photocoagulation scars are widely spaced or there are "skip areas".

Additional photocoagulation may be less urgent if,

a) The caliber of new vessels has decreased and fibrous proliferations are developing

b) There is a single episode of vitreous haemorrhage coincident with a posterior vitreous detachment and no recurrent haemorrhage thereafter.

c) There is extensive or almost complete posterior vitreous detachment.

Additional treatment can be done by either placing the burns in between old treatment scars, anterior to them and/or in the posterior pole sparing the area within 500 micron of the center of the macula. Sites of preferential treatment are the quadrants with active new vessels, skip areas, the posterior pole and the areas temporal to the center of the macula. If scars are already closely placed and any additional treatment would require overlapping of treatment scars, clear indications are necessary before additional treatment is given as it can lead to extensive visual field loss. In some cases vitrectomy may be a better alternative.

Peripheral Cryoablation for Proliferative Diabetic Retinopathy

Since the advent of diode laser the role of peripheral cryoablation has decreased as the infrared wavelength is able to bypass media opacities such as cataracts and minimal vitreous haemorrhages. The main indications of peripheral cryoablation today include media too hazy to allow diode PRP and repeated vitreous haemorrhages despite a complete PRP has failed to regress the NVD.

Reported benefits include accelerated resorption of long standing vitreous haemorrhage and regression of neovascularization. The inflammation created is known to hasten the absorption process. The main complication is development of accelerated tractional retinal detachment, reported in 25% to 33% of treated eyes. This treatment can be considered before vitrectomy but should be avoided in patients with tractional retinal detachment or areas of strong vitreoretinal adhesions.

Technique : The cryoapplication is usually done transconjunctivally or after a limbal peritomy. In transconjunctival treatment, two rows of three to four applications are placed in each quadrant at 12mm and 16 mm from the limbus. In case of limbal peritomy, about 20 spots in four rows are placed in each quadrant, usually in two treatment sessions one week apart. The applications are generally monitored with indirect opthalmolscopy to see for area of whitening. At least the superior half should be done under direct visualisation and then same can be carried out for the inferior half which is usually covered with vitreous haemorrhage. Otherwise the application can be -60° C for 10-15 seconds. A prior careful B-scan ultrasonography should be done in such cases to avoid treating eyes with tractional retinal detachment.

Vitrectomy

Indications for vitrectomy in PDR are mainly for marked visual loss caused by vitreous haemorrhage and/or structural changes damaging the retina when the abnormalities are not likely to improve spontaneously and when they cannot be treated successfully by alternative methods.

Current indications for vitrectomy in diabetic eye disease include :

1. Severe non clearing vitreous haemorrhage
   * > 3 months (TYPE I)
   * > 6 months (TYPEII)
2. Tractional retinal detachment recently involving macula
3. Combined TRD and Rhegmatogenous RD
4. Severe progressive fibrovascular proliferation
5. Anterior segment neovascularisation with posterior segment opacity
6. Dense premacular haemorrhage
7. Ghost cell glaucoma
8. Macular oedema associated with premacular traction
9. Cataract preventing treatment of severe PDR

Aims of vitrectomy :

* Removal of all vitreous opacities, except those in the peripheral anterior vitreous and thus removing the scaffold along which fibrovascular tissue proliferates.
* Division of all membranes and strands extending between the vitreous base and the optic disc or other areas of vitreo-retinal attachment and treat any other retinal breaks.
* Division of elevated retino-vitreo-retinal sheets or bands and separation of epiretinal membranes from the retinal and segmentation of those remaining into separate islands.
* To do endophotocoagulation on table which otherwise is delayed leading to more severe proliferation and recurrent vitreous haemorrhage.

Benefits :

Vitrectomy prevents or delays :

- Persistent Intragel Haemorrhage
- Retinal Detachment
- Opaque Membranes
- Rubeosis
- Burnt Out Stage?

Risks :

- Progressive rubeosis iridis
- Cataract
- Glaucoma
- Recurrent vitreous haemorrhage
- Retinal detachment

Poor prognostic factors :

- Age > 40 years
- Preoperative iris neovascularisation
- Cataract
- Visual acuity <5/200 (5/60)
- Retinal detachment
- No previous photocoagulation

Practical Conclusions

The four major modes by which visual loss can occur in diabetic retinopathy bringing the patient to the ophthalmologist and brief management of these clinical presentations at a glance is as under.:

1.	Maculopathy	Fluorescein Angiography Control Diabetes Grid/Focal laser Vitrectomy (not totally accepted)
2.	Vitreous Haemorrhage	PRP after spontaneous clearing of haemorrhage or after vitrectomy
3.	PDR with TRD involving or threatening macula	Vitrectomy with PRP
4.	Involuted Diabetic Retinopathy	Leave it alone

Medical Management of Diabetes

The DCCT resolved the issue concerning the benefit of a tight long term blood-glucose control on the progression of retinopathy. The ophthalmologist should in this regard work along with the physician or endocrinologist to highlight the significance of a fastidious blood glucose control. This will not only retard or prevent the onset of sight threatening complications, but also improve the over all well being of the patient. A good medical management of the diabetic state includes :

* Control of blood sugar level
* Dietary planning
* Development of an exercise schedule
* Blood glucose monitoring
* Education about diabetes and its complications
* Psychological counseling of the patient and family

Besides a meticulous diabetic control, emphasis should also be laid on the control of other systemic and metabolic disorders such as hypertension, renal disorder, hyperlipemia etc. These factors upset the bodily homeostasis even further, thus exerting a detrimental influence on the patient's health in general and retinopathy in particular.

A special mention about the role of ophthalmologist in management of diabetes in pregnancy must be made. Pregnancy creates a state of insulin resistance, requiring close blood glucose monitoring **Recommendations for the Management of diabetes in pregnancy** as laid down by the American Diabetes Association are as follows :

Previously diagnosed diabetic	Baseline dialated fundus examination within 12 months of a planned pregnacy, comprehensive eye examination in the first trimester, frequency of follow-up examinations based on severity of retinopathy, patients should be counselled on the risk of development or progression of diabetic retinopathy

Women with insulin-dependent diabetes of <5 years, no retinopathy, nephropathy, or hypertension.	Perform ophthalmolscopy at least once between weeks 20 and 30 of gestation
Women with insulin-dependent diabetes of >5 years. no retinopathy, nephropathy, or hypertension.	Dilated fundus examination at least once per trimester
Women with mild nonproliferative retinopathy, nephropathy or hypertension.	Dilated fundus examination at least once per month.
Women with moderate or severe nonproliferative retinopathy, significant nephropathy, and proteinuria	Patient to be educated before or early in pregnancy regarding the potential risk to the eyes; dilated fundus examination at least monthly.
Women with active proliferative retinopathy, especially with high risk characteristics as defined by the Diabetic Retinopathy study.	Panretinal scatter photocoagulation.
Women who develop severe optic disc neovascularization in the first trimester that responds very poorly to aggressive laser photocoagulation.	Therapeutic abortion may be recommended.
Women who develop gestational diabetes mellitus.	No increased risk of the development of diabetic retinopathy,previous guidelines for monitoring do not apply in such cases.

Acknowledgements and further reading

1. LEO UPDATE : American Academy of Ophthalmology Retina, vitreous and posterior segment trauma 1996.
2. Preferred Practice Patterns Diabetic Retinopathy American Academy of Ophthalmolygy.
3. Jalali S and Das TP. Diabetic Retinopathy. In Modern Ophthalmology edited by LC Dutta, 1994:610 - 628.
4. Aiello LM, Miller JW and D' amico DJ : Diagnosis, management and treatment of NPDR and macular edema and PDR-Principles and practice of ophthalmology. Volume 2. edited by Albert and Jakobiec. 1994.
5. Swamura M : Effects of pregnancy on diabetes. Pregnancy. Ocular manifestations of systemic disease, edited by Bernard H Blaustein, 1994:189-191.
6. Peter Hodges Morse. Practical management of diabetic retinopathy, ACC, 1985.
7. Frank NR, Bresnik GH, Davis MD : Etiologic mechanisms in DR, BDR, PDR Retina Volume two. Editor-in-chief Stephen J Ryan, 1989 : 301 - 402.
8. Towler HMA, Patterson JA, Lightman S : Diabetes and the eye, CD ROM, BMJ publishing group, 1996.

AIOS
CME SERIES

No. 1	**Paediatric Cataract**	*Dr. Daljit Singh*
No. 2	**Eales' Disease**	*Dr. B. Patnaik*
No. 3	**Management of Diabetic Retinopathy**	*Dr. P.N. Nagpal*

Next Issue (No. 4)
Oculoplasty — by Chairman, ARC
(Dr. A. K. Grover)

Published by :

ALL INDIA OPHTHALMOLOGICAL SOCIETY
Dr. Rajendra Prasad Centre for Ophthalmic Sciences,
All India Institute of Medical Sciences,
Ansari Nagar, New Delhi - 110 029

Printed at : Neelkanth Graphics, Ph. : 4649183, 4692139