MEDICINE GRAND ROUNDS

# DIABETIC RETINOPATHY

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Diabetic retinopathy is a serious complication of diabetes. It is one of the leading causes of blindness and visual impairment in the United States. Its cost, in terms of health care fees and time lost from work, has been judged to be approximately 75 million dollars annually (1).

There are two types of diabetic retinopathy; a) background or non-proliferative and b) proliferative. Table 1 lists the characteristic findings in non-proliferative or background retinopathy.

TABLE 1

NON-PROLIFERATIVE DIABETIC RETINOPATHY

- Microaneurysms
- Capillary Non-perfusion
- Leakage
  - blood
  - exudates (edema)

Microaneurysms are the earliest findings in diabetic retinopathy. With the ophthalmoscope they appear as small circular red dots that vary in size from 20-200 microns. Pathologically, they are outpouches of the retinal capillaries. They usually first appear in areas of retinal capillary closure. Microaneurysms may also be found in eyes of non-diabetic individuals with sickle cell anemia, branch vein occlusion, carotid artery disease or severe hypertension(2). Microaneurysms often leak lipoprotein material which results in the appearance of hard exudates. Hard exudates are yellow, variable in size, and sharply defined. They appear in scattered, aggregated or ring-like configuration. When exudative material collects in the posterior part of the retina it can lead to macular edema which can result in loss of visual acuity. The diagnosis of clinically significant macular edema can be made either by steroscopic color fundus photographs or by clinical means that include ophthalmoscopy and contact lens biomicroscopy. Agreement occured 81% of the time when these two methods of detection were compared in the ETDRS study (3). Macular edema is a common finding in diabetes and recently a successful treatment has been found. This will be discussed subsequently. Clinically significant macular edema has been defined as shown in Table 2 (4).

TABLE 2

CLINICALLY SIGNIFICANT MACULAR EDEMA

- Thickening of the retina at or within 500 microns of the center of the macula
- Hard exudates at or within 500 microns of the center of the macula, if associated with thickening of adjacent retina
- A zone or zones of retinal thickening 1 disc area or larger, any part of which is within 1 disc diameter of the center of the macula

If there is closure of retinal capillaries and arterioles then retinal ischemia develops. Retinal ischemia often causes the development of cotton-wool spots. Cotton-wool spots or soft exudates are whitish or grayish areas that appear on the retina. Intraretinal microvascular abnormalities (IRMA) may also be found in areas of capillary non-perfusion. These dilated capillaries develop as a compensatory response to retinal hypoxia. Retinal ischemia and hypoxia can be associated with the appearance of venous beading and duplication as well as large dark intraretinal hemorrhages. The combination of IRMA, venous beading, intraretinal hemorrhages has been labelled "preproliferative retinopathy" (Table 3). This constellation of retinal findings suggests the impending growth of abnormal new retinal blood vessels, thus the name preproliferative retinopathy.

TABLE 3

PREPROLIFERATIVE DIABETIC RETINOPATHY

- Intraretinal Microvascular Abnormalities (IRMA)
- Intraretinal Hemorrhages
- Cotton Wool Spots
- Venous Beading

Proliferative diabetic retinopathy (PDR) (TABLE 4) begins with the appearance of abnormal retinal blood vessels (neovascularization). These abnormal vessels are usually found on or near the optic nerve head or in the vicinity of other normal retinal vessels. These new blood vessels usually appear as fine tufts on the surface of the retina and their growth is confined to the outer most layer of the retina. Because these blood vessels are abnormal they often hemorrhage into the vitreous, often as a result of vitreous contracture. Fibrous tissue is often associated with the development of new retinal blood vessels. If the fibrovascular tissue contracts, traction or dragging of the sensory retina, especially in the area of the macula, it may result in loss of vision. Further contraction can lead to retinal detachment. Late in the course of proliferative retinopathy, if the new blood vessels regress, the fibrous tissue may remain as the only sign of proliferative retinopathy.

TABLE 4

PROLIFERATIVE DIABETIC RETINOPATHY

- New Vessels (neovascularization)
- Fibrous Tissue
- Vitreous Hemorrhage
- Traction retinal detachment

Pathogenesis of Diabetic Retinopathy

The pathogenesis of diabetic retinopathy is unknown (5). However, most people think that in some way in susceptable individuals with diabetes that the retinopathy (and the other microvascular complications) is a consequence of chronic hyperglycemia (6). The idea that hyperglycemia is important in the pathogenesis of diabetic retinopathy has been supported by several retrospective studies such as those done by Johnsson in Malmo, Sweden (7) and Pirart in Belgium (8). The Pirart study was monumental, perhaps the largest of its kind. He followed 4,400 patients with diabetes from 1947, of whom a cohort of 2,745 patients were followed since the initial diagnosis of their diabetes. Despite the limitations of this study, that of the inability to accurately assess long term diabetes control, Pirart's data suggests a strong relationship between the level of long-term diabetes control and the development of diabetic retinopathy.

There are also data relating hyperglycemia to the development of retinopathy that are available from studies done in animal models of diabetes. Engerman, et al (9) in a classic study, randomly assigned alloxan-induced diabetic dogs to two groups according to the level of diabetic control. One group had chronic hyperglycemia with a mean plasma glucose level that averaged between 250-400 mg/dl. The other group received twice daily insulin injections and their plasma glucose levels averaged 90-180 mg/dl. By the end of five years of followup, differences between the 2 groups of dogs were striking. The hyperglycemic group's retinae showed sacular microaneurysms, pericyte ghosts, and retinal hemorrhages. The near normoglycemic animals had retinae that were similar to those of non-diabetic dogs (Table 5).

TABLE 5

**EFFECT OF GLYCEMIC CONTROL ON RETINOPATHY IN ALLOXAN-INDUCED DIABETES IN DOGS**

| | Capillary aneurysms per eye | Acellular capillaries per 10 mm. | Pericyte ghosts per 100 cells |
|---|---|---|---|
| Nondiabetic | 1 ± 1 | 39 ± 12 | 1.5 ± 0.4 |
| Poor control | 25 ± 6 | 171 ± 19 | 4.6 ± 0.9 |
| Good control | 2 ± 1 | 49 ± 10 | 1.4 ± 0.3 |

(Diabetes 26:760,1977)

Engerman and Kern (10) did an additional interesting experiment with alloxan-induced diabetic dogs. They randomized dogs into three groups according to levels of glycemic The first group had chronic hyperglycemia for the study period of 5 years. Another group had near-normoglycemia for 5 years. The third group had hyperglycemia for the first 2½ years and were made near-normoglycemic for the next 2½ years. Retinal capillary aneurysms and other lesions developed during 5 years of hyperglycemia and these lesions were not found if normoglycemia was instituted within 2 months of the induction of the diabetes and continued for the 5 year study period. After 2½ years of poor diabetic control retinopathy was absent but surprisingly developed over the subsequent 2½ years despite good glycemic control (Table 6).

TABLE 6

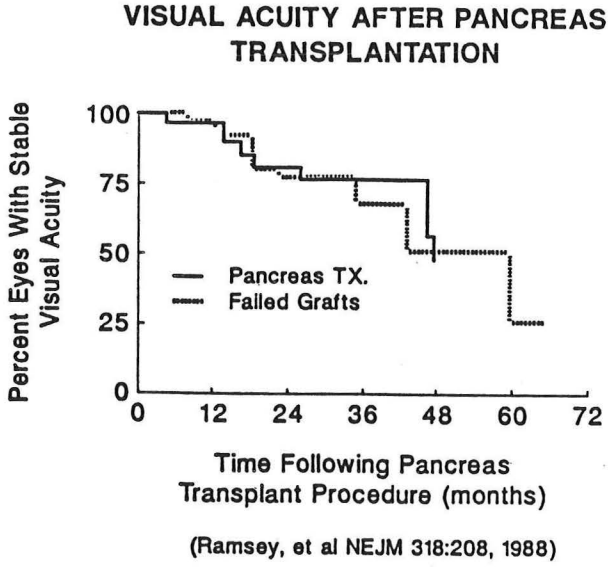
**DEVELOPMENT OF RETINOPATHY IN DIABETIC DOGS ACCORDING TO DEGREE AND HISTORY OF GLYCEMIC CONTROL**

| | Duration (yr.) | RETINOPATHY | | |
|---|---|---|---|---|
| | | Capillary aneurysms per eye | Acellular capillaries (per 11 mm$^2$). | Capillary basal lamina width (nm) |
| Normal | 5 | 1 ± 0.2 | 39 ± 6 | 168 ± 8 |
| Poor control | 5 | 42 ± 10 | 264 ± 25 | 319 ± 25 |
| Good control | 5 | 2 ± 1.3 | 80 ± 20 | 186 ± 14 |
| Poor control ↓ Good control | 2.5 + 2.5 = 5 | 0 ± 0<br>29 ± 16 | 48 ± 8<br>224 ± 29 | 164 ± 12<br>227 ± 29 |

(Engerman, Diabetes 36:808, 1987)

Ramsey et al, (11) studied the effect of successful pancreas transplant and consequent normoglycemia on the rate of progression of diabetic retinopathy. They compared retinopathy scores in 22 diabetic patients who had a successful pancreas transplant to those in 16 patients in whom the pancreas transplant did not succeed. After a mean followup of 24 months there were no differences between the groups and the rate of progression of retinopathy (Fig. 1). Thus, pancreas transplantation and subsequent normoglycemia neither reverses nor prevents the progression of diabetic retinopathy.

FIGURE 1



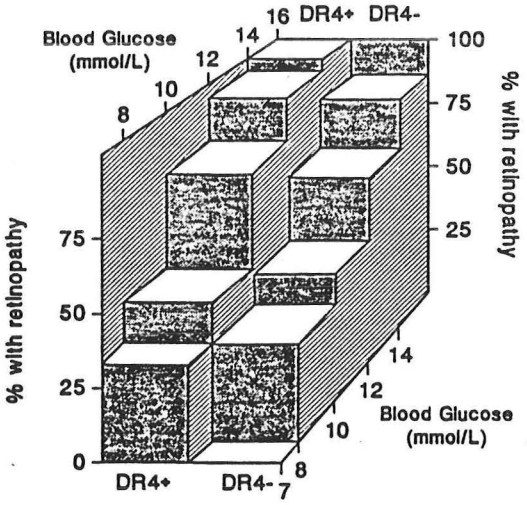

(Ramsey, et al NEJM 318:208, 1988)

If hyperglycemia is important in a cause and effect way to the development of diabetic retinopathy one of the proposed mechanisms by which hyperglycemia results in tissue damage is via the polyol pathway (12,13), the first reaction of which is catalyzed by the enzyme, aldose reductase. According to this theory, hyperglycemia causes the accumulation of sugar alcohols (sorbitol, galactitol). This accumulation of sugar alcohols has been shown to result in selective changes and degeneration of retinal pericytes, cause alterations in retinal pericyte myoinositol metabolism, and finally, retinal capillary basement membrane thickening and closure of retinal capillaries (14,15,16). Recent studies have shown that retinal microaneurysms can be produced in galactosemic dogs and that the thickening of retinal capillary basement membranes in this and other animal models can be prevented by the administration of aldose reductase inhibitors (17–24). Kador et al, (25) recently have described the prevention of characteristic changes of diabetic retinopathy such as the formation of microaneurysms, pericyte degeneration, vessel dilation and the formation of acellular capillaries after 36 months of treatment with two different aldose reductase inhibitor drugs, sorbinil and M–79175, in galactose fed dogs. Finally, studies have demonstrated that aldose reductase is present in the retinal pigment epithelium in 87.5% of eyes from diabetic patients with proliferative diabetic retinopathy and 55% of eyes from patients with background diabetic retinopathy. It was not found in retinal pigment epithelium in eyes of non–diabetic individuals. (20)

It is clear that hyperglycemia is not the only etiological factor in the development of diabetic retinopathy, some genetic factors must also be involved (6). Dornan, et al (26) showed that subjects who had the HLA–DR4 haplotype had a much greater chance of developing diabetic retinopathy than those diabetic patients who did not have HLA–DR4. The combination of poor diabetes control and HLA–DR4 increased the risk of developing diabetic retinopathy to 33.3 (Figure 2).

FIGURE 2

**RELATIONSHIP OF HLA-DR4 TO DIABETES RETINOPATHY**



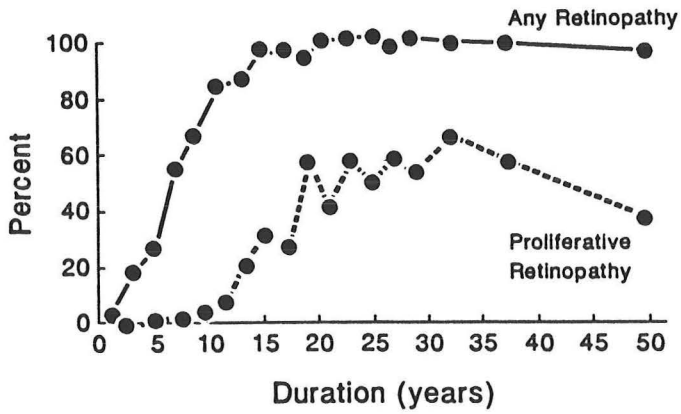

(Dornan, et al Diabetes 31: 226, 1982)

## EPIDEMIOLOGY OF DIABETIC RETINOPATHY

The best data on the epidemiology of diabetic retinopathy comes from the elegant and archival works of Ronald Klein and his associates from the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR). This is a large, ongoing epidemiological study of a very large number of diabetic patients in an 11 county area of southwestern Wisconsin. Younger-onset (age of diagnosis less than 30 years), insulin requiring persons have a much higher frequency of diabetic reteinopathy (any type) than do persons who develop diabetes after the age of 30 whether or not they require insulin (27,28). Perhaps the most important risk factor for the development of diabetic retinopathy is the duration of diabetes. In the WESDR the prevalence of any diabetic retinopathy (using stereoscopic fundus photographs) ranged from 2% in those who developed diabetes under the age of 30 with less than two years of diabetes to 98% in persons with 15 years or more of diabetes (29) Figure 3).

FIGURE 3

**FREQUENCY OF RETINOPATHY**
**IDDM**

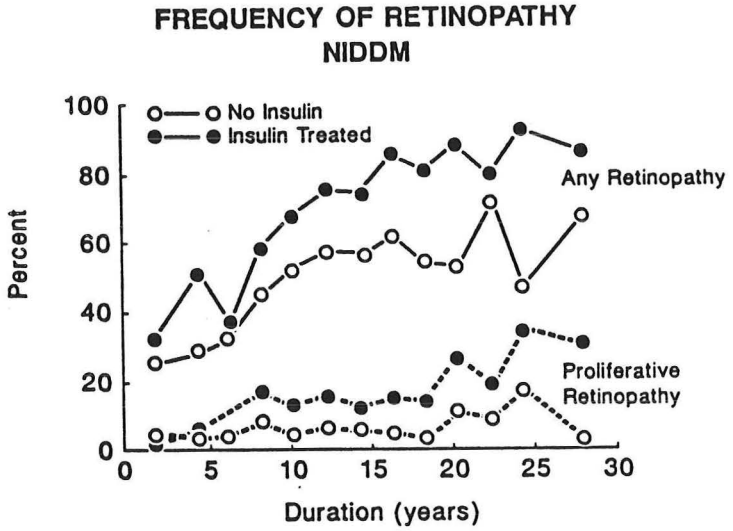



(Klein, et al Arch Ophthalmol 102:520, 1984)

The severity of diabetic retinopathy is also related to the duration of the disease. Proliferative diabetic retinopathy was found to vary from 0% in younger onset patients with diabetes for less than 5 years to 56% when the diabetes had been present for 20 or more years. Macular edema rarely was found during the first 9 years after the diagnosis of diabetes. After 20 years of diabetes, 21% of younger onset patients were found to have macular edema (28).

In patients who developed diabetes after the age of 30 (older-onset) there is a different picture. Those patients are much more likely to have retinopathy present at the time the diagnosis of diabetes is made. In the Klein study (28), the frequency of retinopathy during the first few years of diabetes was 24% in older onset diabetic patients taking insulin and after 20 years of diabetes it was 60%. After 20 years for those not taking insulin the prevalence was 84% (Figure 4).

FIGURE 4




(Klein, et al Arch Ophthalmol 102:527, 1984)

Proliferative diabetic retinopathy and macular edema may also be found shortly after the diagnosis of diabetes in older onset patients. After 15 or more years of diabetes the prevalence of proliferative retinopathy (Figure 4) was found to be 20% in those taking insulin and 4% in those who did not. Older onset patients have more macular edema than younger onset patients, especially during the first few years of diabetes (28). The four year incidence of clinically significant macular edema is 4.3% in younger onset patients and 2.9% in older onset patients. (30)

In recent studies, Klein and his associates evaluated the development of diabetic retinopathy over a 4 year period of time in those diabetic patients who originally participated in the WESDR study. Of the 271 patients whose diabetes developed before the age of 30 and who were free of diabetic retinopathy when initially seen, 59% had developed retinopathy by the time they were re-examined 4 years later. Of the 713 patients free of prolifera-

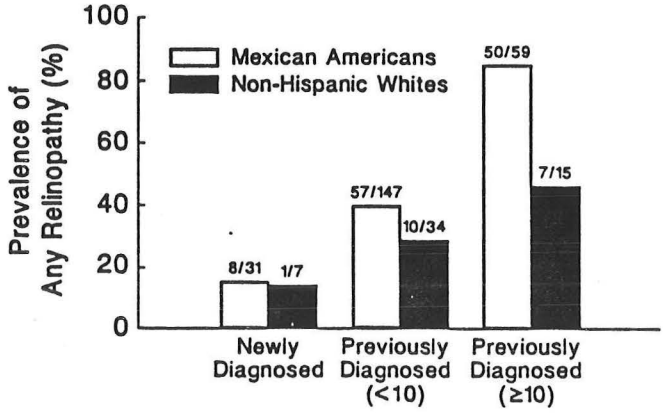
tive diabetic retinopathy on initial examination, 11% had developed proliferative retinopathy 4 years later. Overall worsening of diabetic retinopathy occurred in 41% of the population and improvement occurred in only 7% (31). In those diabetic patients who developed diabetes after the age of 30 they found that in those who used insulin, 47% of the 154 patients who had no retinopathy on initial examination developed it over the 4 year interval and 7% of those 418 patients free of proliferative retinopathy initially developed it during the four year interval (32). Worsening of retinopathy occurred in a total of 34% of the patients.

For non-insulin users 34% of the 320 patients free of retinopathy at the first visit developed it but only 2% of the 486 patients free of proliferative retinopathy developed it over the 4 year period. Overall, 25% of this population had a worsening of diabetic retinopathy. The greatest risk of developing retinopathy in younger onset persons occurs 4 to 7 years after the diagnosis and the risk remained appreciable (approximately 70%) after 10 or more years of diabetes. The highest incidence of proliferative retinopathy occurs after 9-15 years of diabetes. Thereafter the incidence is constant (31,32). Similar data have been reported from the Joslin Clinic (33).

Of interest is the fact that the prevalence of diabetic retinopathy is considerably higher in Mexican Americans with diabetes than it is in other non-Hispanic whites with diabetes. Mexican Americans have an approximately three-fold greater prevalence of non-insulin dependent diabetes than non-Hispanic whites (34). The increased prevalence of diabetes in Mexican Americans is thought to be related to mixture of the gene pool with Native Americans (35). Haffner, et al (36) studied stereoscopic retinal photographs in 257 Mexican American subjects and 56 non-Hispanic whites with non-insulin dependent diabetes mellitus. The Mexican Americans had a significantly increased risk of retinopathy relative to the non-Hispanic whites (Figure 5). The risk of severe retinopathy (proliferative or preproliferative) relative to background or no retinopathy was significantly greater in Mexican Americans than in non-Hispanic whites (Figure 6). Severe retinopathy was related to duration of disease, hyperglycemia and insulin therapy in both ethnic groups.

FIGURE 5

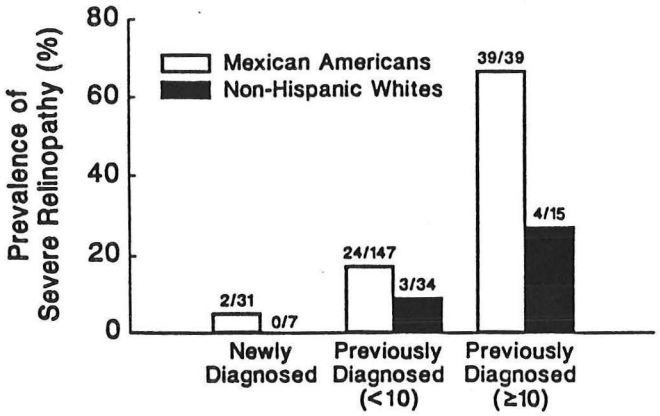
**PREVALENCE OF DIABETIC RETINOPATHY IN MEXICAN AMERICANS AND NON-HISPANIC WHITES**




(Haffner, et al Diabetes 37:878, 1988)

FIGURE 6

PREVALENCE OF DIABETIC RETINOPATHY IN MEXICAN AMERICANS AND NON-HISPANIC WHITES




(Haffner, et al Diabetes 37:878, 1988)

## OTHER RISK FACTORS FOR DIABETIC RETINOPATHY

There are other risk factors in addition to the duration of diabetes for the development of diabetic retinopathy. They are listed in Table 7.

TABLE 7

RISK FACTORS FOR DIABETIC RETINOPATHY

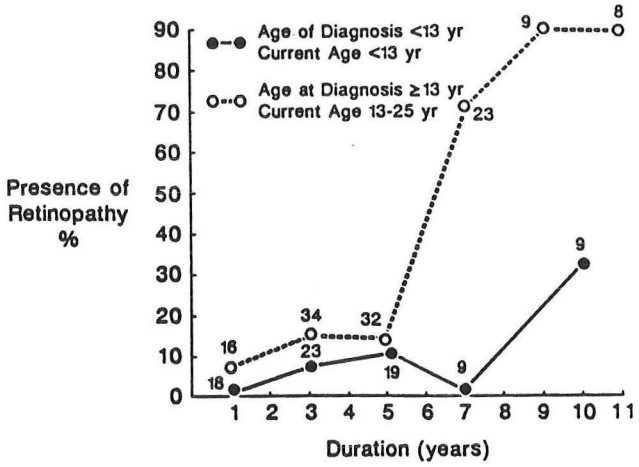
- Duration of Diabetes
- Hyperglycemia
- Genetic Factors
- Puberty
- Blood Pressure
- Nephropathy
- Smoking
- Pregnancy

### Puberty

Diabetic retinopathy occurs infrequently in children with diabetes prior to the onset of puberty (37,38). Figure 7 shows Klein's (37) data on this issue. It is clear that retinopathy is rare in children before the onset of puberty irrespective of the duration of diabetes, whereas the frequency of retinopathy after puberty is appreciable. Figure 8 shows the data of Cerutti, et al showing the decreased frequency of diabetic retinopathy in prepubertal children with diabetes (39).

FIGURE 7

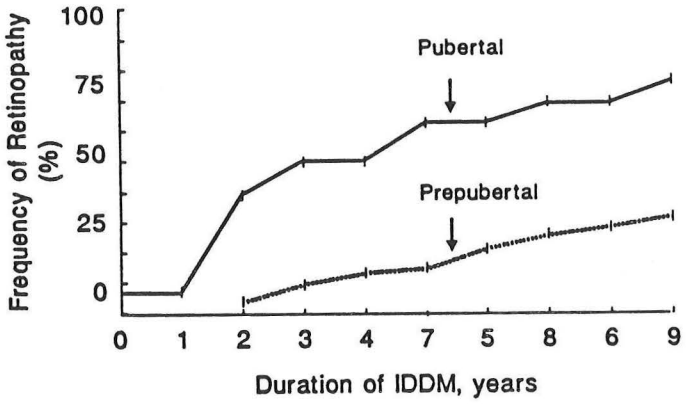
FREQUENCY OF RETINOPATHY IN RELATIONSHIP TO DURATION OF DIABETES




(Klein, et al Diabetes Care 8:311, 1985)

FIGURE 8

PUBERTY AND DIABETIC RETINOPATHY




(Cerutti, et al Ophthal 198:116, 1989)

## Genetic Factors

The possibility that some as yet unknown genetic factors influence the development of diabetic retinopathy has been discussed above. Dornan and his colleagues (26) were able to demonstrate a higher frequency of retinopathy in diabetic patients who had HLA-DR4 than those who did not have this haplotype. Conversely, Rand, et al (40) reported that insulin-dependent diabetic patients with a long duration of diabetes and minimal retinopathy were more likely to have a higher frequency of HLA-DR3 and DR4 and myopia than persons with diabetes for the same period of time who had proliferative retinopathy. Other investigators have been unsuccessful in their attempts to relate HLA-DR4 to an increased susceptability to diabetic retinopathy (41,42,43).

Smoking

There is no clear evidence that cigarette smoking increases the frequency and/or severity of diabetic retinopathy (44).

Blood Pressure

There is no question that the presence of hypertension is an important risk for the development of diabetic retinopathy. In fact, other than possibly hyperglycemia, it may be the most important. Klein et al, found in WESDR that the presence and severity of retinopathy were independently associated with diastolic blood pressure in younger onset diabetic individuals (32) and with systolic blood pressure in older onset persons (27). Janka et al, found in their Joslin Clinic Study (45) that the risk of progression from background diabetic retionpathy to more severe retinopathy was low in patients who had a diastolic blood pressure less than 70 mmHg (Table 8). The odds of the progression to severe retinopathy increases to 14 in patients whose diastolic blood pressure was greater than 70 mmHg. In a Swiss Study of 534 diabetic men and women aged 35–45 years diabetic retinopathy, among other things, was independently associated with systolic blood pressure (Figure 9). Lower rates of retinopathy development were observed during the followup period in the diabetic patients on antihypertensive therapy suggesting not only lower systolic blood pressure levels but also blood pressure therapy itself decreases the incidence of retinopathy (46). There is also evidence from studies in the Pima Indians that there is an increased incidence of diabetic retinopathy in those subjects with elevated systolic blood pressure (Figure 10)(47). Others have also shown a relationship between elevated blood pressure levels and diabetic retinopathy (48,49). In fact, in a group of 249 subjects studied by Chase et al (50) with insulin dependent diabetes mellitus the presence of a "high normal" level of blood pressure (i.e. systolic or diastolic blood pressure above the 90% percentile for age but less than 141/90 mmHg) increased the risk of the presence of retinopathy on initial examination as well as the progression of pre-existing retinopathy after 2.3 years of followup.

TABLE 8

PROGRESSION TO SEVERE RETINOPATHY
AND DIASTOLIC BLOOD PRESSURE IN IDDM

| Diastolic Blood Blood Pressure mm/Hg | Progression to Severe Retinopathy % |
|---|---|
| $\leq$ 70 | 3.7 |
| 71–79 | 35.0 |
| $\geq$ 80 | 31.6 |

(From Janka, et al Diabetes 38:460, 1989)

FIGURE 9

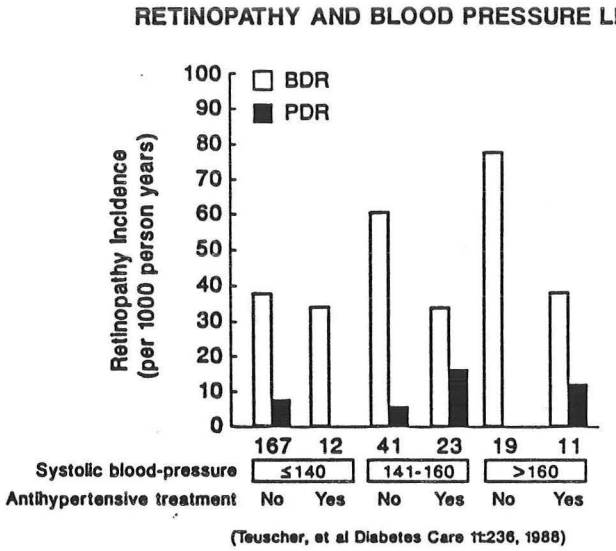
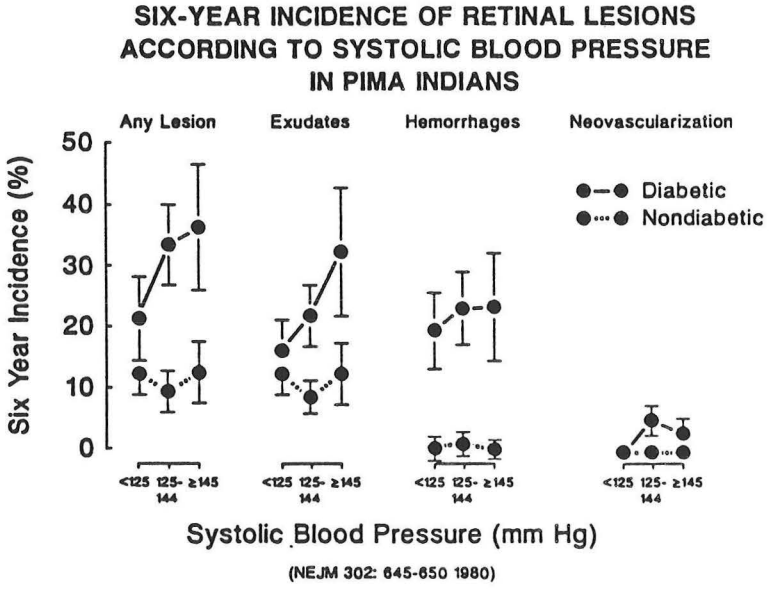



FIGURE 10



Nephropathy

Patients who have diabetic retinopathy are more likely to have diabetic nephropathy and vice versa. In Klein's Wisconsin studies, (51,52) proteinuria was strongly associated with the presence of diabetic retinopathy and macular edema. Proliferative retinopathy was found three times more often in insulin taking younger-onset persons with proteinuria than in those without proteinuria. Similarly, in older onset persons not taking insulin, proliferative retinopathy was 2-7 times as frequent in the presence of proteinuria as in its absence (51,52). Norgaard found that children with microalbuminuria were more likely to have background diabetic retinopathy than those children with diabetes who were normoalbuminuric (53).

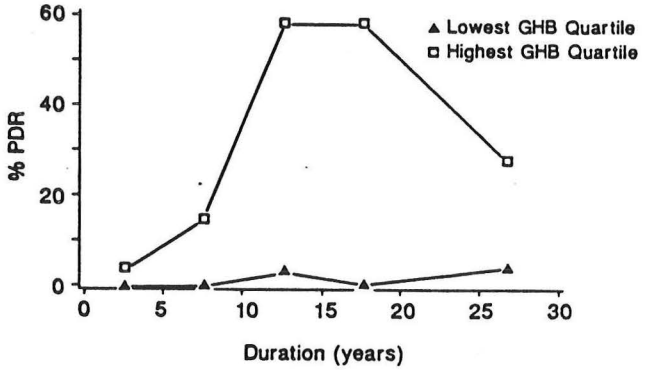
Hyperglycemia

Although far from a proven fact, there are considerable data to suggest that long term chronic hyperglycemia is a risk factor for the development of diabetic retinopathy. From the animal studies mentioned above by Engerman and his colleagues (9,10), it is clear that typical retinal changes occur in experimental diabetes in dogs and that these changes can be prevented by meticulous blood glucose control. It is important to note that diabetic control in Dr. Engerman's dogs had to be instituted almost immediately after the induction of diabetes. If it was delayed for 2½ years typical diabetic changes occurred despite ongoing good diabetes control (10).

From a clinical perspective, there are many studies suggesting hyperglycemia as a risk factor for diabetic retinopathy in addition to the early large studies of Johnsson (7) and Pirart (8) mentioned above. In the WESDR (54) younger-onset insulin taking patients whose glycosylated hemoglobin levels were in the highest quartile were far more likely to develop proliferative diabetic retinopathy over a four year period (odds ratio 21.8) than were those patients whose diabetes was of the same duration whose glycosylated hemoglobin levels were in the lowest quartile (Figure 11). For the older onset patients who did not take insulin a similar relationship is seen when comparing the highest and the lowest quartiles of glycosylated hemoglobin. (Figure 12).

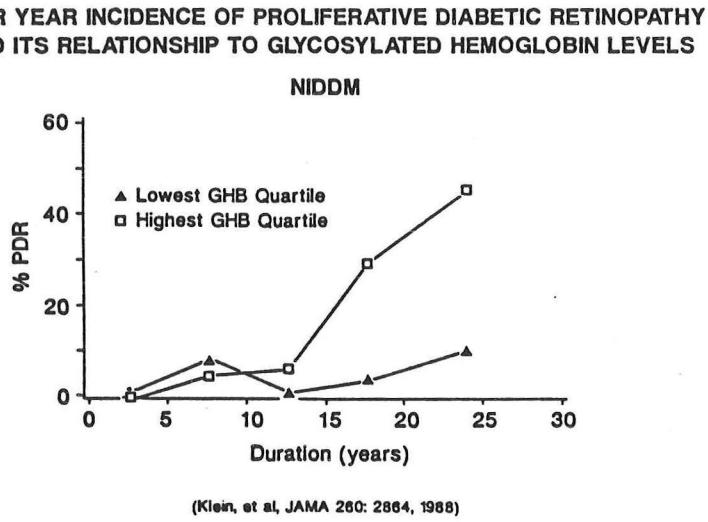
FIGURE 11

**FOUR YEAR INCIDENCE OF PROLIFERATIVE DIABETIC RETINOPATHY AND ITS RELATIONSHIP TO GLYCOSYLATED HEMOGLOBIN LEVELS IDDM**



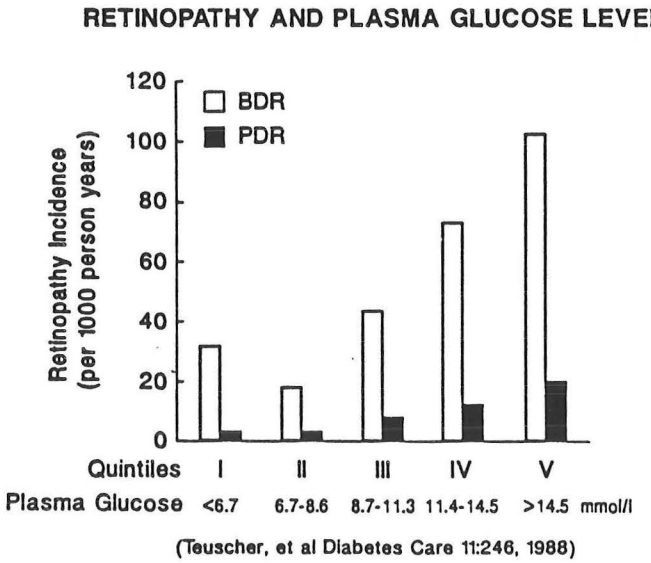

(Klein, et al, JAMA 260: 2864, 1988)

FIGURE 12




Other studies such as those by Janka et al (45) and Teuscher et al, (46) (Figure 13) also show that hyperglycemia is an important risk factor for the development of diabetic retinopathy.

FIGURE 13



Pregnancy

The relationship of pregnancy to diabetic retinopathy is unclear (55). It is recommended that pregnant women with diabetes see the ophthalmologist once during each trimester. These recommendations may be excessive relative to the data, however. In 1979, Rodman et al, (56) reviewed the literature on the relationship between pregnancy and diabetic retinopathy. They found 8% of 201 pregnant women with diabetes had progression of retinopathy during their pregnancy. This progression occurred both in women with and without background retinopathy. Only 2% of the entire group developed proliferative retinopathy during the course of their pregnancy. Of those 127 women who had proliferative retinopathy when their pregnancy was discovered, 25% experienced some progression throughout the course of the pregnancy. There are other studies in the literature that report varying results (57,58,59). Klein et al (60) also recently studied the effect of pregnancy on diabetic retinopathy. They compared seven field stereoscopic fundus photographs done in a group of pregnant diabetic women during the first half of the pregnancy and again at 10 weeks post-partum. Similar measurements were made in non-pregnant diabetic women. They found that pregnancy was significantly associated with progression of retinopathy as was the level of glycemia. Diastolic blood pressure had a lesser effect on the progression of retinopathy (Table 9).

TABLE 9

EFFECT OF PREGNANCY ON THE PROGRESSION OF DIABETIC RETINOPATHY

| | Pregnant % | Non-Pregnant % |
|---|---|---|
| Better | 9 | 17 |
| Stable | 47 | 43 |
| Worse | 44 | 39 |

(adapted from Klein, et al. Diabetes Care (3:34, 1990)

## TREATMENT OF DIABETIC RETINOPATHY

Table 10 lists the options for the treatment of diabetic retinopathy. The potential medical management of diabetic retinopathy consists of the theoretical beneficial effects of long term glycemic control, the possibility that the progression of diabetic retinopathy may be slowed by the use of aspirin and dipyridamole, and finally the potential use of aldose reductase inhibitor drugs. The aldose reductase inhibitor drugs are, of course, still experimental.

TABLE 10

TREATMENT OF DIABETIC RETINOPATHY

- Medical Management
  - Glycemic control
  - Aspirin and dipyridamole
  - Aldose reductase inhibitor drugs
- Surgical Management
  - Photocoagulation
  - Vitrectomy

## MEDICAL MANAGEMENT

There have been many studies that have attemped to look at the effect of improved glycemic control on the progression and/or reversability of early diabetic retinopathy. Among those prospective clinical studies the Steno (61,62), Oslo (63,64,65,66), Kroc (67,68) and Dallas (69,70) studies are the best known. Despite all the work that has been done there is very little evidence to suggest that once early background diabetic retinopathy is present that near-normoglycemia for periods of time up to 3 years has any impact on the slowing of the diabetic retinopathy. I have summarized the data from all four of these clinical trials in Table 11.

TABLE 11 DIABETIC RETINOPATHY AND PROSPECTIVE CONTROLLED CLINICAL TRIALS

| | | STENO (61,62) | | OSLO (63,64,65,66) | | | KROC (67,68) | | DALLAS (69,70) |
|---|---|---|---|---|---|---|---|---|---|
| NUMBER OF SUBJECTS | INTENSIVE RX* | 15 | | 30 | | | 35 | | 30 |
| | CONVENTIONAL RX | 15 | | 15 | | | 35 | | 24 |
| DIFFERENCE IN GLYCOHEMOGLOBIN (%) | | 1.6 | | 1.5 | | | 2.0 | | 2.4 |
| FOLLOWUP (MONTHS) | | 12 | 24 | 3-6 | 12 | 41 | 8 | 24 | 30 |
| NUMBER INTENSIVE PROGRESSION | | 10/15 | 6/15 | 15/28 | 4/28 | 15/28 | 14/32 | 4/29 | 3/30 |
| NUMBER CONVENTIONAL PROGRESSION | | 5/15 | 10/15 | 0/12 | 0/12 | 12/15 | 8/33 | 7/31 | 6/24 |

*EITHER MDI OR CSII

Of all the studies, only the one from Dallas showed a statistically significant impact of near-normoglycemia and slowing the progression of diabetic retinopathy. In the Dallas Diabetes Prospective Trial (69,70) after almost 3 years of followup, those patients with early diabetic retinopathy who were treated with an intensive treatment program (insulin pump) had significantly less progression of their retinopathy as assessed by stereoscopic fundus photographs and fluorescien angiograms, than did patients who were treated with a more conventional treatment plan that resulted in a stable but elevated levels of glycosylated hemoglobin (Table 12). None of the other studies were able to show any advantage of near normoglycemia on the progression of diabetic retinopathy. The data from the Kroc Study is shown in Figure 14. Of interest, many of these studies showed an initial worsening of retinopathy thought to be the result of a rapid normalization of the blood glucose levels. This deterioration was transient and the was result of the development of cotton wool spots (Figure 15).

TABLE 12

**EFFECT OF DIABETES CONTROL ON PROGRESSION OF RETINOPATHY**

| | Modified Treatment Diabetic Retinopathy Study | | Macular Microaneurysm Count | |
|---|---|---|---|---|
| | Experimental* Treatment | Conventional Treatment | Experimental* Treatment | Conventional Treatment |
| Better | 4 | 0 | 1 | 0 |
| Stable | 23 | 18 | 28 | 19 |
| Worse | 3 | 6 | 1 | 5 |

*p<0.05, experimental treatment versus conventional treatment (log-likelihood chi-square)

(AMER J. MED 81:1012, 1986)

FIGURE 14

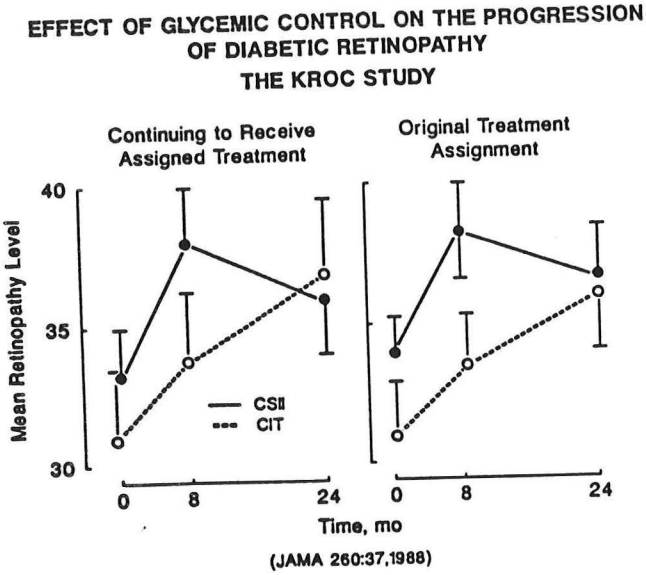
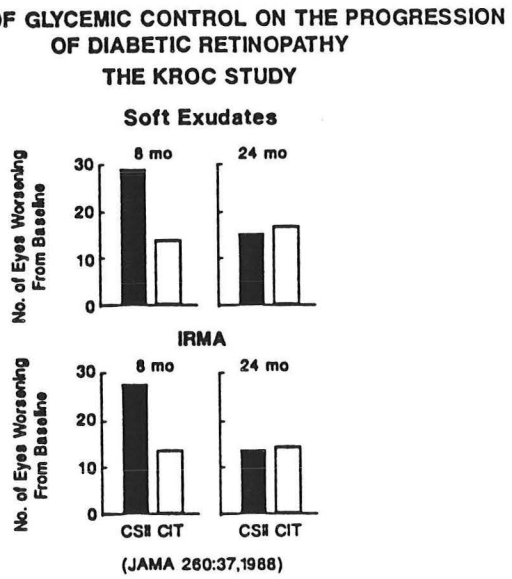



FIGURE 15




All the necessary data on the effect of glycemic control on the prevention or progression of diabetic retinopathy is not yet available. First of all, none of the above studies even addressed the issue of prevention. For data on the effect of glycemic control on the prevention of retinopathy we must await the results of the ongoing Diabetes Control and Complications Trial (DCCT) (71). This multicenter trial consists of 29 clinical centers, 26 in the United States and 3 in Canada. They are following two large groups of patients with insulin dependent diabetes for 7 to 10 years. In excess of 1400 patients (700 with no diabetic retinopathy [Primary Prevention Group] and 700 with early background diabetic retinopathy [Secondary

Prevention Group]) have been recruited and randomly assigned to two specific treatment regimens. One group is receiving conventional treatment and the other, an intensive treatment designed to achieve euglycemia. The major endpoint of the DCCT will be the development of early diabetic retinopathy in the primary intervention trial (patients without retinopathy at entry) and the rate of progression of the retinal lesions will be assessed in the secondary intervention trial.

Recently the report of the results of a double masked randomized clinical trial done in 2 French and 2 British Centers on the effect of aspirin and dipyridamole on the progression of diabetic retinopathy have been published (72). They studied the effects of aspirin alone (330 mg tid) or in combination with dipyridamole (75 mg tid) as compared to placebo administered to 475 patients with early diabetic retinopathy. The assessment of retinopathy was based on the change in the number of microaneurysms in the macular field as seen on fluorescien angiograms over a 3 year period. There were no differences in the yearly increase in the number of microaneurysms between the aspirin or the aspirin plus dipyridamole groups, but both of these groups seemed to develop less microaneurysms per year than did the placebo treated group (Table 13) The authors concluded that the use of aspirin alone or aspirin plus dipyridamole significantly slows the progression of early diabetic retinopathy. Care must be taken in the interpretation of these data. What impact on the progression of retinopathy reducing the number of microaneurysms that appear over three years has on the final outcome of diabetic retinopathy is not entirely clear. In defense of the paper, they were also able to show that an increase in the number of microaneurysms was correlated with a deterioration in other ophthalmological findings. Moreover, Klein et al, (73) recently studied the utility of retinal microaneurysm counts in evaluating the four-year progression of early diabetic retinopathy in their Wisconsin population. They found that the number of microaneurysms present at baseline was an independent predictor of progression of diabetic retinopathy. They concluded that microaneurysm counts may prove to be a useful endpoint in clinical trials of diabetic neuropathy.

TABLE 13

EFFECT OF ASPIRIN AND DIPYRIDAMOLE ON THE PROGRESSION OF EARLY DIABETIC RETINOPATHY

| TREATMENT | MEAN YEARLY INCREASE IN MICROANEURYSMS |
|---|---|
| Placebo | 1.44 |
| Aspirin | 0.69* |
| Aspirin and dipyridamole | 0.34* |

*=$p < 0.02$ vs placebo

(Diabetes 38:491, 1989)

Finally, there remains the never ending hope that if and when a safe and effective aldose reductase inhibitor drug is developed that these agents might prove to be effective in delaying or preventing diabetic complications independent of blood glucose control. To date, there are very little data in humans that bear on this issue. What is available is disappointing. Hotta et al, (74) reported the results of a randomized clinical trial in thirteen Japanese centers comparing the effects of epalrestat (ONO-2235) to placebo over a 12 month treatment period. They studied 214 patients with either nonproliferative or pre-proliferative diabetic retinopathy. They concluded that deterioration of the retinopathy, as determined by fluorescein angiography, was significantly less in the epalrestat treated patients as compared to the placebo treated patients. Kohner et al (75) studied 92 diabetic patients with early background retinopathy (between 5-75 microaneurysms) comparing the effect of ponalrestat (Statil®) and placebo. After 2 years of treatment there were no differences between the two treatment groups in terms of the number of eyes that stayed the same or deteriorated. The total yearly increase in microaneurysms in the ponalrestat treated group was 0.72 and 1.0 in the placebo group. They concluded that ponalrestat at a dose of 600 mg/day had no beneficial effect on the progression of early diabetic retinopathy (Table 14).

TABLE 14

EFFECT OF PONALRESTAT ON THE PROGRESSION OF EARLY DIABETIC RETINOPATHY

| | Ponalrestat | Placebo |
|---|---|---|
| Better | 38% | 34% |
| Stable | 51% | 61% |
| Worse | 11% | 5% |

(Kohner at al Diabetes 39(Suppl 1):62A, 1990)

Finally, the long awaited results of the Sorbinil Retinopathy Trial have recently been published (76). In this multicentered trial, 497 patients aged 18 to 56 years old who had insulin dependent diabetes for 1 to 15 years were studied. These patients all had absent or very mild diabetic retinopathy (i.e. five or fewer microaneurysms in each eye and no other detectable retinal lesions). The patients were randomly assigned to either sorbinil treatment (250 mg daily) or placebo. They were followed for a median of 41 months. The percentage of patients whose retinopathy severity grade worsened by two or more levels (ETDRS scale) was not significantly different between the two treatment groups at the maximum followup visit (Figure 16). The number of microaneurysms increased at a slightly slower rate in the sorbinil group than in the placebo group with statistically significant differences at 21 and 30 months but not at the maximal followup visit (Figure 17). The Sorbinil Retinopathy Trial Research Group concluded that sorbinil at a dose of 250 mg per day for approximately 3 years did not have a clinically important effect on the course of early diabetic retinopathy. Unfortunately in this study, there were a great many patients who did not complete the entire 54 months of treatment. Only 72% of the patients in the sorbinil group and 80% of the placebo group completed the study. Seven percent of the sorbinil treated group had significant hypersensitivity reactions to the drug. The large patient drop out rate could have contributed to the negative outcome of this trial.

Other potential explanations for the failure of this trial to show a beneficial effect on the progression of diabetic retinopathy include that the treatment period was not long enough and, of course, that sorbinil in particular or aldose reductase inhibitor drugs in general are not effective in preventing or delaying diabetic retinopathy.

FIGURE 16

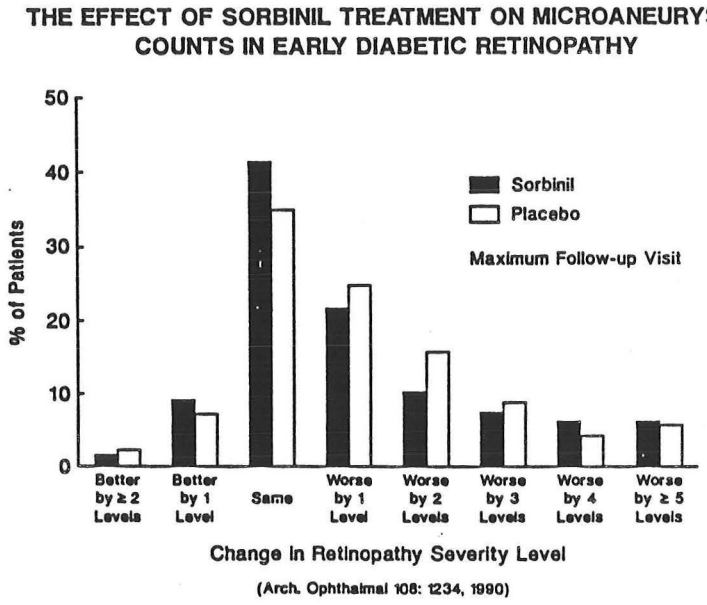
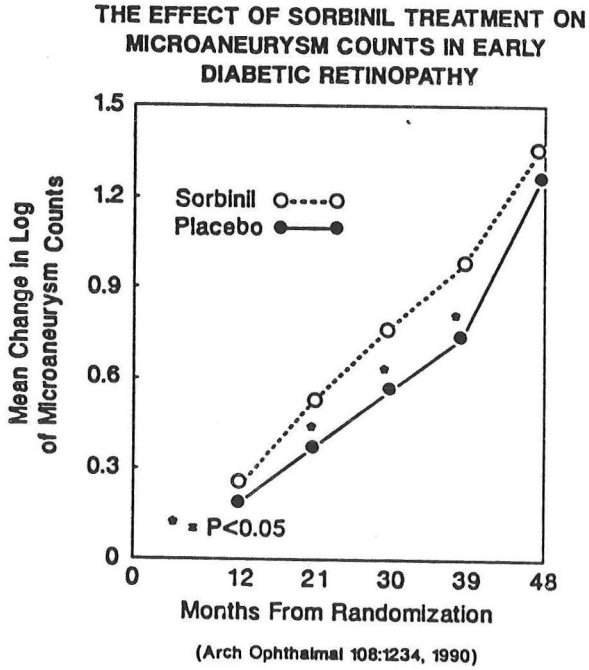



FIGURE 17

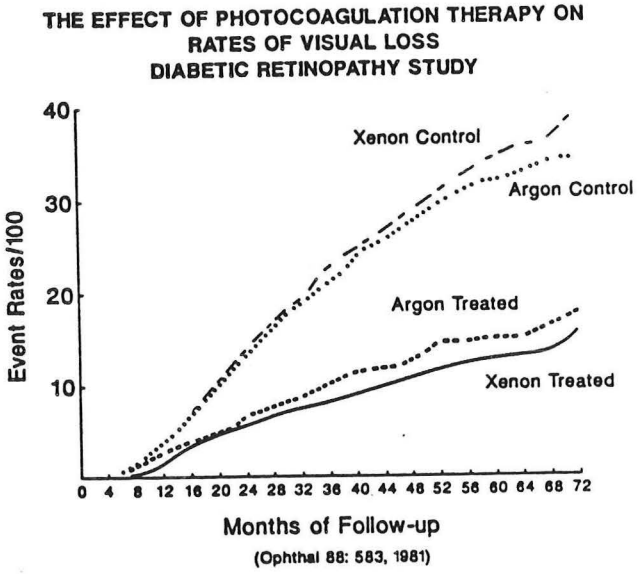


## SURGICAL MANAGEMENT

### Photocoagulation

There is no question that once significant proliferative diabetic retinopathy occurs laser photocoagulation is the treatment of choice. This was clearly shown in the Diabetic Retinopathy Study (77). This multicentered trial study conducted between 1972 and 1979 involved 1758 patients with proliferative diabetic retinopathy. One eye of each patient was randomly assigned to receive panretinal photocoagulation (the other eye serving as a control) using either a xenon photocoagulator or an argon laser. A major conclusion of this study was that the risk of severe visual loss (5/200 or worse) in treated eyes was approximately one-half of that found in untreated control eyes (Figure 18). During the six year study, visual loss occurred in 32% of the untreated and 16% of the treated eyes. They also found that in eyes with "high risk characteristics" the 2 year risk of severe visual loss was 25%. This risk could be reduced to 12% by photocoagulation treatment.

FIGURE 18




Panretinal photocoagulation is done as an outpatient procedure in one or more treatment sessions using a local anesthetic applied to the eye. In about two-thirds of the patients, complete regression of retinal new blood vessels is seen within 4 weeks (78). The mechanism by which photocoagulation causes a regression of retinal new blood vessels is unknown. Despite effective photocoagulation treatment some patients go on to suffer severe visual loss. The risk of visual loss increases with ongoing neovascularization, hemorrhage, retinal elevation, proteinuria and hyperglycemia. The risk of visual loss decreases with increasing "treatment density" (79).

Focal photocoagulation treatment has recently been shown to be effective in the treatment of clinically significant macular edema (4). In the Early Treatment Diabetic Retinopathy Study (ETDRS), eyes with clinically signficant macular edema were randomly assigned to either immediate focal photocoagulation or they deferred photocoagulation. Those eyes treated with focal photocoagulation immediately were half as likely to lose three or more lines of vision as compared to the control (untreated) eyes. Loss of three lines of vision occured in 24% of the untreated eyes as compared to only 12% of eyes treated with immediate photocoagulation. Of note, although the ETDRS recommended consideration of photocoagulation treatment for all eyes with clinically significant macular edema, it did not suggest that all such eyes be treated immediately. The decision to treat immediately or to follow carefully depends on individual findings in each patient.

Vitrectomy

Vitrectomy is the surgical procedure used to cut vitreous bands that cause traction of the retina or to remove vitreous hemorrhage. The two major objectives of vitreous surgery are to release mechanical traction on the retina and/or to clear to vitreous of opacities. Indications for vitrectomy include visual acuity of light perception or better, tractional macular detachment, documented progression of traction or traction retinal detachment, the failure of a vitreous hemorrhage to clear within 3 months in insulin dependent diabetic patients or 6 to 12 months in non-insulin dependent diabetic patients, lack of rebeosis or neovascular glaucoma and a lack of wide spread macular ischemia. Vitrectomy has been effective in causing an improvement of visual acuity to 20/20 or better in 50 to 66% of treated eyes (80, 81,82). However, vitrectomy is not a benign procedure having an overall complication rate of about 25%. Complications of vitrectomy include corneal edema, recurrent vitreous hemorrhage, iatrogenic retinal tears and development of rubeotic glaucoma (neovascularization of the iris and closure of the trabecular meshwork of the eye, leading to increased intraocular pressure). Recently a large study was done in an attempt to see if early vitrectomy would be helpful in severe proliferative diabetic retinopathy. No beneficial effects of early vitrectomy were seen (83).

## EYE CARE FOR DIABETIC INDIVIDUALS

Retinopathy is the only chronic complication of diabetes for which there are established treatments. Based on both the Diabetic Retinopathy Study and the Early Treatment Diabetic Retinopathy Study clear treatment recommendations have emerged. These treatment recommedations include:

1) Prompt panretinal photocoaguation for all eyes with High Risk Characteristics for severe visual loss.

2) For eyes with less severe proliferative retinopathy, either careful followup until High Risk Characteristics appear or prompt photocoagulation is appropriate.

3) Focal photocoagulation should be considered for eyes with clinically significant macular edema.

The National Diabetes Advisory Board has recommended ophthalmological consultation for individuals who have insulin dependent diabetes for more than 5 years and initially for all patients with non-insulin dependent diabetes. The need to refer diabetic individuals to the ophthalmologist certainly does not suggest that primary care physicians and diabetologists are relieved of their responsibility for examining the retinae of their patients. A careful funduscopic examination, preferably with dilated pupils should be done at least once a year in all diabetic patients. Often something will be found that requires the retinal specialist's immediate attention. However, special studies and training only available in ophthalmological offices are often required. These include the use of slit lamp biomicroscopy (to detect macular edema), color stereoscopic fundus photographs (to document presence, severity, and progression of diabetic retinopathy) and fluorescein angiography (to detect retinal leakage or ischemia).

In the Wisconsin Epidemiologic Study of Diabetic Retinopathy (29), Klein and his associates found that only 22% of younger-onset patients and 40% of the older onset patients would have met the suggested National Diabetes Advisory Board guidelines for ophthalmologic care. Those who did not meet the guidelines were more likely to be living in a rural area and be less well educated.

Followup care with the ophthalmologist must be individualized. For children and adolescents with diabetes and for adults without diabetic retinopathy an examination should be done annually. For those with non-proliferative retinopathy examinations should be done every 6 months. For patients with preproliferative diabetic retinopathy examinations should be done every 3 months, and for patients with proliferative retinopathy it should be individualized. Women with diabetes who are pregnant should be seen during each trimester of the pregnancy.

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