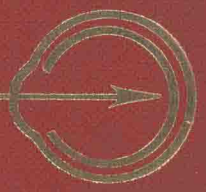
Management of Retinal Vascular and Macular Disorders



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MANAGEMENT OF RETINAL VASCULAR AND MACULAR DISORDERS

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Preface

The material in this book was presented in preliminary form in June, 1980, at Sun Valley, Idaho, at a meeting held to celebrate the tenth anniversary of the Wilmer Retinal Vascular Center (RVC) and to honor its founder, Dr. Arnall Patz. This brief introduction will chronicle the major activities of the RVC during the 1970s, with special attention to Dr. Patz's contributions.

The Retinal Vascular Center began in 1970 when Arnall Patz accepted a full-time faculty position at The Wilmer Institute and became the first Seeing Eye Research Professor of Ophthalmology. At that time, fluorescein angiography was still young, and laser photocoagulation was in its infancy. Maumenee first used intraocular fluorescein angioscopy in humans in 1955, and Novotny and Alvis published their photographic technique of fluorescein angiography in 1960. Arnall's pioneering contributions to the refinements of these techniques and to their clinical application have resulted in an enormous expansion in our ability to diagnose and treat medical retinal conditions. Among these advances, perhaps the single most important from the public health viewpoint was the demonstration that scatter photocoagulation could significantly reduce the risk of blindness in patients with proliferative diabetic retinopathy. The efficacy of this treatment was established by the Diabetic Retinopathy Study (DRS), a clinical trial supported by the National Eye Institute (NEI). Arnall's involvement in the DRS began when he participated as a member of the committee to develop the study protocol. Later he participated as a clinical investigator, as a member of the Executive Committee, and as a member of the Data Monitoring Committee.

The DRS was concerned with the treatment of proliferative retinopathy; however, the most frequent reason for visual loss among diabetic patients is macular edema, an observation reported by Arnall Patz and his colleagues in 1972. In a randomized trial, Patz and coworkers showed that photocoagulation could prevent progressive visual loss from macular edema in some of these patients. These observations provided some of the preliminary data that led to the development of the Early Treatment Diabetic Retinopathy Study (ETDRS), an NEI-supported clinical trial now in progress that is evaluating therapy for macular edema as well as for preproliferative retinopathy.

By the 1950s, retrolental fibroplasia (RLF) had become the leading cause of blindness in premature infants. Arnall's legendary contribution demonstrated, by means of a randomized trial, that high oxygen concentration in the infant's incubator contributed to the development of this disease. For this important work, he received the Albert Lasker Award in 1956. He continued his involvement in this area in the 1960s and 1970s by participating in another collaborative study to quantify the role of oxygen in the pathogenesis of RLF and by participating in a research team that included Robert Flower, Bernard Hochheimer, Daniel Finkelstein, and others.

Patz's pioneering work in angiography and photocoagulation established the framework for clinical studies on the natural history and possible therapeutic effects of laser photocoagulation for a number of macular disorders. Treatment for the neovascular complications of senile macular degeneration and ocular histoplasmosis, the two most important maculopathies from the public health viewpoint, is currently being evaluated in the NEI-supported Macular Photocoagulation Study (MPS).

Retinal angiogenesis research became prominent during the 1970s because of its relationship to the pathogenesis of the proliferative retinopathies. The research at Wilmer began after Folkman, working at Children's Hospital in Boston, identified a factor elaborated by solid tumors that promoted vascular growth toward the tumor. Folkman called this substance tumor angiogenesis factor (TAF). Patz and his collaborators were able to extend Folkman's observations on TAF to a study of angiogenesis in the ischemic retina. Drs. Bert Glaser, Alan Fenselau, Patricia D'Amore, Ron Michels, Gerald Lutty, Dan Finkelstein, Chung-Ho Chen, and others are trying to answer fundamental questions concerning the relationship between capillary closure, retinal ischemia, and retinal neovascularization in humans.

The 1970s were an enormously exciting time for all ophthalmologists and visual scientists concerned with retinal vascular and macular disease. It was particularly exciting to be at the Retinal Vascular Center where so much of the original work was being performed. More than 20 ophthalmologists completed a fellowship at the RVC during that decade, and most have continued to be productive in developing new information about natural history, pathogenesis, and better treatment for patients with retinal vascular and macular disorders.

To acknowledge the importance of those 10 years and to thank Arnall for being the inspiration to many of us, a symposium was organized at Sun Valley, Idaho. More than 125 ophthalmologists attended. Among the registrants were most of our former fellows, as well as several invited guests including Drs. Don Gass, Alan Bird, Dick Green, Steve Ryan, Lee Jampol, Jerry Shields, David Newsome, Ron Michels, Rick Ferris, and others who have authored one or more chapters of this book. I am grateful to the authors for their prodigious efforts in preparing manuscripts suitable for publication. I am also tremendously indebted to Sarah Owens, my associate editor,

for organizing and editing these manuscripts, and to my associate, Dr. Robert Murphy, for making many helpful suggestions during the editorial process. I am especially grateful to David Andrews for capable editorial review of all the proofs.

In 1979, Arnall Patz succeeded A. Edward Maumenee, also a pioneer in ophthalmology, as Director of The Wilmer Institute. At that time, I assumed the administrative responsibilities for the Retinal Vascular Center. It is my fondest wish that the 1980s will witness an even greater information explosion than the 1970s, both in understanding the pathogenesis of choroidopathies and retinopathies and in developing new and more rational treatments for choroidal and retinal disorders; and further, that the Retinal Vascular Center will continue to be at the forefront in contributing to a reduction in blindness from retinal and choroidal diseases.

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Baltimore, Maryland
March, 1982

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Contents

Section 1 RETINAL VASCULAR DISORDERS

CHAPTER 1

Retinal Branch Vein Occlusion Study

Daniel Finkelstein, M.D., Arnall Patz, M.D., Stuart L. Fine, M.D., and Thomas A. Rice, M.D.

The Branch Vein Occlusion Study (BVOS) is a multicenter randomized clinical trial supported by the National Eye Institute that has been recruiting patients for 2 years.

The goals of the study are limited to three:

1. Will laser photocoagulation prevent the development of neovascularization?
2. Will laser photocoagulation prevent the development of vitreous hemorrhage if neovascularization already exists?
3. Will laser photocoagulation stabilize or improve visual acuity that is affected by macular edema?

To accomplish these goals, there are three categories of eyes being studied. The first category is a major branch vein occlusion (over five disc diameters in diameter of retinal involvement) *without* neovascularization (Fig. 1.1). In this first category, half the patients will be treated with laser photocoagulation and half will be followed as controls without treatment. The second category is a major branch vein occlusion *with* neovascularization (Fig. 1.2); again, half the eyes will be treated with laser photocoagulation in the involved segment of the fundus and half will be followed without treatment to determine whether laser photocoagulation can prevent vitreous hemorrhage. The third category is macular edema with visual acuity of 20/40 or worse; these patients also are being randomized to laser treatment or no laser treatment to determine the efficacy of laser photocoagulation in the stabilizing or improvement of visual acuity.

There are five eye centers participating in this randomized clinical trial: Bascom Palmer Eye Institute in Miami, the Estelle Doheny Institute in Los Angeles, the Illinois Eye and Ear Infirmary with Ingalls Memorial Hospital in Chicago, the Retina Foundation in Boston, and the Wilmer Institute in Baltimore.

The data are monitored by a Data and Safety Monitoring Board. All the data from each clinical center are forwarded to a Coordinating Center at the Wilmer Institute; the study has been in progress since 1978. It is estimated that within 4 years significant data will be available regarding the management of these major complications of branch vein occlusion.

In the first 18 months, 300 patients were recruited. Recruitment will continue, with particular emphasis on patients with neovascularization and with macular edema and decreased vision.

Although it has never been proven that photocoagulation is of benefit for complications of branch vein occlusion, at the Wilmer Institute we have developed temporary recommendations until results become available from the Branch Vein Occlusion Study Randomized Clinical Trial. These recommendations are not based on data from the randomized clinical trial but simply represent our clinical impression from nonstudy patients examined and treated at the Wilmer Institute over the past decade.

We recommend that patients with major branch vein occlusion who exhibit capillary nonperfusion be followed closely (three or four times yearly) for the

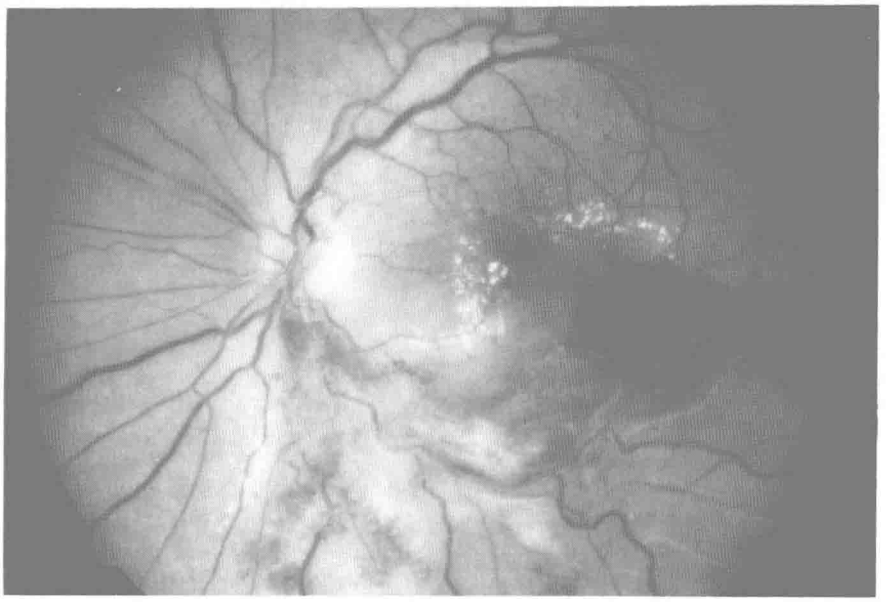

Figure 1.1. Inferotemporal branch vein occlusion with neovascularization of the disc.

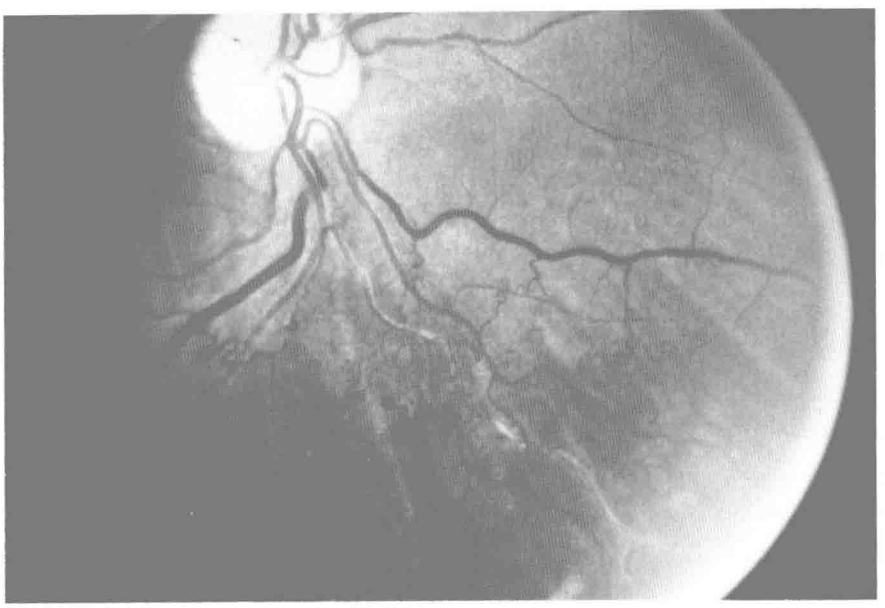

Figure 1.2. Inferior branch vein occlusion with neovascularization elsewhere.

development of disc or peripheral neovascularization. A fluorescein angiogram that includes a sweep of the periphery should be performed at the time of these examinations. Patients with major branch vein occlusion without capillary nonperfusion may be followed less frequently (twice yearly) because we believe their risk of developing neovascularization is lower. If disc or peripheral neovascularization does develop, we recommend scatter photocoagulation in the area of the fundus (Figs. 1.3 and 1.4) that is involved with the branch vein occlusion in an attempt to produce involution of the neovascularization and prevention of vitreous hemorrhage. We do not recommend focal treatment to the neovascularization itself. For eyes with macular edema as demonstrated by fluorescein angiography and vision of 20/40 or worse and not spontaneously improving, one may treat the leaking macular areas, avoiding shunts and collaterals. For all types of laser treatment for branch vein occlusion, it is particularly important to avoid treating over intraretinal hemorrhage because of the possibility of producing contraction of the internal limiting membrane.

DISCUSSION

Dr. Bergen: I have seen some literature on the subject, but it is still not clear in my mind why

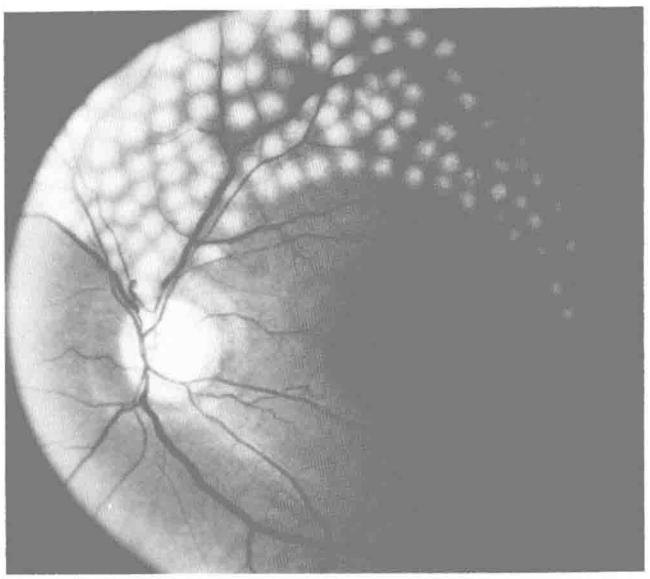

Figure 1.3. Quadrantic treatment for neovascularization elsewhere.

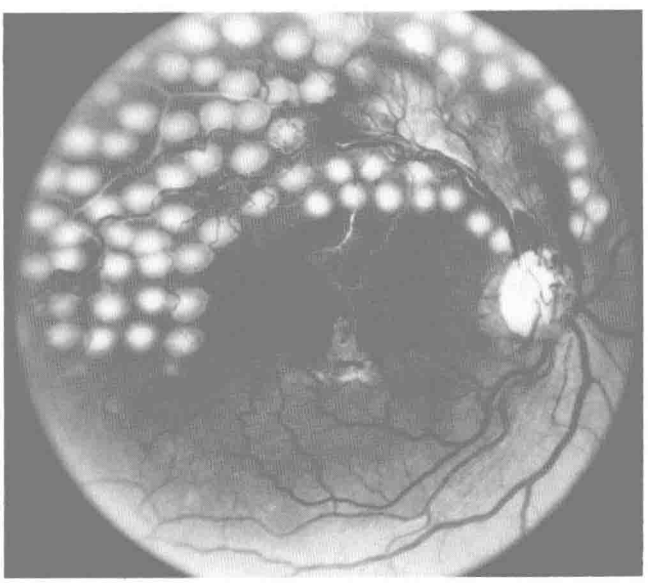

Figure 1.4. Quadrantic treatment for branch vein occlusion with neovascularization of the disc.

patients with central retinal vein occlusions develop retinal neovascularization much less frequently than patients with branch vein occlusions. Also, why do central retinal vein occlusion patients develop rubeosis much more frequently than patients with branch vein occlusions?

Dr. Finkelstein: That is a very good question, and we've been puzzled over that for a long time. As to why patients with central retinal vein occlusions develop rubeosis and not posterior segment neovascularization, there have been several suggestions. One is that the vessels in central retinal vein occlusion are damaged in such a way that they cannot respond. Another hypothesis might be that the angiogenesis material, if there is such a thing, diffuses in a different way in central vein occlusion. Of course, there can be much more capillary nonperfusion in central vein occlusion than in branch vein occlusion, and I think that explains why there is more rubeosis if we are thinking about the angiogenesis hypothesis.

Dr. Wells: First, is there any role for antiplatelet therapy in this entity, and second, why is it that some branch vein occlusion patients compensate well with shunt formation? Also, is there any way to predict those who will compensate?

Dr. Finkelstein: We don't know of any role for medical therapy; however, we have not ruled it out either. We really don't know why some patients with branch vein occlusion do better than others, why some compensate, why some develop edema, and why some develop nonperfusion; nor do we know whether shunts and collaterals are related to nonperfusion or edema. We haven't seen those kinds of correlations develop. You might think, for example, that if you see good collaterals, you would never see capillary nonperfusion, but that is not true. Also, if you do careful fluorescein sweeps in the periphery, you can be quite surprised at the mixtures of edema and capillary nonperfusion, seeing branch vein occlusion with a lot of edema in the posterior pole and very significant capillary nonperfusion in the periphery. We have seen patients with a double branch vein occlusion, one superior, one inferior; one is all edema, and one is capillary nonperfusion; so we can't answer your question.

Mr. Bird: I'd like to consider one or two points that I thought were very interesting. First, in terms of closure, when does closure occur? A study in London on monkeys with experimental branch vein occlusion implied that closure occurred and was totally defined within the first week. We really don't have an opportunity to observe disease in man during that period very often. When you see somebody with closure and bypass channels, you can't be sure that the bypass channels developed during the period when closure was occurring or afterward. If they had occurred afterward, then of course they couldn't have determined the natural outcome. It seemed to us that in monkeys there are several events that determine closure. We could see no reason why slow flow and progressive slowing of flow were not the cause of capillary nonperfusion. In man, a behavioral study undertaken by Kohner and others in London did suggest that in most patients the extent of closure was determined by the time the patient was first seen, and that would be in accord with the observations in the monkey. There were one or two patients who developed closure between the initial visit and 3 months, and of course we don't know what addi-

tional vascular event might have occurred in the retina to have caused that closure.

With respect to edema, John Schilling did some studies on macular edema and branch vein occlusion, and he came up with some very surprising data, mainly late recovery of vision. We have one patient who recovered acuity more than 3 years after the initial event. That really is something that we didn't expect from the information that we had before, and it emphasizes the need for controlled clinical trials. That visual recovery can occur so late really implies that any conclusion without a controlled trial really is not valid but is, rather, just an indication of what might be.

CHAPTER 2

Histopathologic Studies of Hypotensive Retinopathy, Branch Vein Occlusion, and Central Retinal Vein Occlusion

W. Richard Green, M.D.

HYPOTENSIVE RETINOPATHY

First, I would like to briefly review the features of what the Mayo Clinic group has called venous stasis retinopathy, what Dr. Knox has called ocular ischemic syndrome,[1] and what I think most people now refer to as hypotensive retinopathy. This is characterized by venous tortuosity, dilatation, and peripheral punctate hemorrhages and microaneurysms. In the case that Dr. Knox studied, there was also a predominance of inflammatory signs with keratic precipitates.

This patient presented with amaurosis fugax in the right eye. Venous dilatation and tortuosity and peripheral punctate hemorrhages were observed (Fig. 2.1*A*). The patient became blind in that eye and developed iris atrophy and cataract (Fig. 2.1*B*). Both eyes were obtained postmortem.[2] The appearance of the ischemic right eye was striking. There was extensive cobblestone degeneration (Fig. 2.1*C*) extending well posterior to the equator. In addition, the amount of proteinaceous material in the vitreous cavity was striking in the right eye and less striking in the left eye. No cobblestone degeneration was present in the left eye (Fig. 2.1*D*). The patient had experienced amaurosis fugax in the left eye on two occasions prior to death.

In Figure 2.1*E* is seen the cobblestone area—loss of RPE (retinal pigment epithelium) and all outer retinal layers including the outer aspect of the inner nuclear layer. The remaining inner aspect of the inner nuclear layer rests against Bruch's membrane. This is outer retinal ischemic atrophy. In other words, this eye with the hypotensive retinopathy suffers from a prejudiced blood supply to the entire eye, both inner and outer circulations.

The right eye also had extensive cataract formation. Figure 2.1*F* shows rubeosis iridis with closure of the angle from neovascularization and descemetization. Figure 2.1*G* shows marked flattening of the ciliary body. In addition, there was evidence of necrosis of the iris from prejudiced blood supply. There was only a bit of the sphincter muscle remaining (Fig. 2.1*H*). There is rounding up and dispersion of pigment from this process (Fig. 2.1*I*). The junction between the ischemic iris to the right and more normal iris to the left is also evident (Fig. 2.1*I*).

In the right eye, neovascularization at the disc (Fig. 2.1*J*) was also present in addition to the iris neovascularization. At the posterior pole were capillaries which had endothelium and pericytes, but outside the immediate area of the disc all the retinal vessels were totally acellular (Fig. 2.1*K*). This was associated with inner ischemic atrophy with loss of nerve fiber, ganglion cell and inner plexiform layers, and the inner aspect of the inner nuclear layer (Fig. 2.1*K*). In the macular area the RPE was intact, but the macula appeared to be acting as an end-organ of ischemia with thinning of the photoreceptor cells and also of all the inner retinal layers. There were only a minimal number of photoreceptor cells and a few bipolar cells remaining. The ganglion cells and most of the photoreceptor cells had undergone atrophy.

In the right eye the retina was subjected to trypsin digestion, but it almost totally disintegrated. In the few fragments that were remaining, the vessels were totally acellular.

The left eye, which had two episodes of amaurosis fugax, showed some interesting features. Recall that the patient had bilateral occlusion of the common carotids. In Figure 2.1*L* the capillary microaneurysms can be seen only in the periphery. The posterior pole had no aneurysms, but it was of interest to contrast the capillaries in the posterior pole, the mid-periphery, and the periphery. In the posterior pole there was a normal 1:1 ratio between the pericytes and the