Diabetic retinopathy (DR) is the leading cause of blindness among working-aged adults in the United States. It is estimated that more than 4 million Americans are affected by DR, and that number is expected to increase to 7.2 million by 2020. The availability of efficacious treatments for diabetic retinopathy will be a substantial public health concern in the coming years, of great interest to ophthalmologists and millions of their patients.

This article reviews some of the prospects for future developments in medical and surgical treatments for DR. It is useful to think of DR in terms of two critical abnormal processes in diabetic blood vessels: vascular incompetence and vascular occlusion. Vascular incompetence leads to leakage of blood and blood products into the retina, while vascular occlusion leads to patches of ischemia in the retinal capillary bed and to the eventual sequela of neovascularization.

The anatomic substrate for vascular incompetence is the appearance of microaneurysms. Intact retinal vessels rarely leak, but when they are complicated by microaneurysms they produce profuse leakage, the hallmark of nonproliferative macular edema (Figures 1-3). Microaneurysms have a life cycle, typically lasting...
approximately 3 months: They bloom, they grow, they fill with leukocytes and become autoinfarcted. This life cycle is often underemphasized; I have never been convinced that treating microaneurysms in the retina with laser does anything more than create incidental retinal damage on the way to the therapeutic RPE lesion.

ANTIINFLAMMATORY THERAPY
Vascular incompetence in DR leads secondarily to profound ischemia. The work of Joussen and colleagues suggests that antiinflammatory strategies may be important in the treatment of this component of the disease. Those researchers showed that the earliest sign of the development of DR in animals is the migration of leukocytes into the retinal capillary bed. They pointed out that vascular endothelial growth factor (VEGF) induces the expression of ICAM-1 and eNOS in the retina and initiates early diabetic retinal leukocyte adhesion in vivo, and they concluded that inhibition of VEGF may be useful in the treatment of early DR. The same may also be true for diabetic macular edema (DME).

The recent publication of a randomized trial comparing intravitreal injection of triamcinolone acetonide with grid laser cyclophotocoagulation in patients with DME, I believe, heralds the end of a period of intense interest in and use of intravitreal steroids as a treatment for this condition. Nevertheless, we may be able to learn something from the “Wow” effect seen immediately after steroid injection in many patients. Inflammation surely plays a role or roles in DR, and important antiinflammatory targets remain to be explored.

Steroids can have toxic effects in the retina. Kwak and D’Amico showed that dexamethasone caused increased staining and disorganization of Müller cells in the rabbit retina. Dexamethasone-induced alterations in retinal glutamate synthetase activity or glucose metabolism were proposed as mechanism for the interference in Müller cell function. Müller cells, also called Müller glia, are the metabolic supporting cells in the retina. There may be Müller-cell–related strategies that can be exploited in the future for DR therapy.

VEGF INHIBITION
Vascular endothelial growth factor is produced by ganglion and photoreceptor cells in the retina in response to ischemia. It induces profound leakage from existing vessels and the growth of new, immature vessels. It works in conjunction with multiple factors, including angiopeitin, erythropoetin, and others, to produce mature blood vessels. VEGF inhibition has been used successfully as a strategy in the treatment of retinal pathologies including, notably, age-related macular degeneration.

Trials of anti-VEGF agents in patients with DME have shown efficacy, with incidental regression of neovascularization. In an open-label study, Nguyen and colleagues demonstrated reduction in foveal thickness and improvement in visual acuity in 10 patients with DME after a series of injections of ranibizumab 0.5 mg (Lucentis, Genentech, Inc.). Visual acuity improved by a mean 12.3 letters from baseline.

While this is a promising result—and does, as the authors assert, demonstrate that VEGF is an important therapeutic target in DME—it suggests that more work is needed. With only 12.3 letters gained in a small nonrandomized series, it remains to be seen what the benefit would be in a randomized trial.

Even if these anti-VEGF drugs were shown to be efficacious against DME, the prospect of 7.2 million people lining up in retinal practices for monthly intravitreal injections is daunting. Platforms for extended drug delivery will surely be needed in order for this type of
therapy to balance the cost and benefits of treatment for this chronic life-long disease.

When I was a resident, we longed for the day we would have a magic drug that could undo neovascularization. In a sense, we now have it, with the advent of VEGF-blocking drugs. And yet we still treat proliferative DR (PDR) with panretinal photocoagulation. We have powerful pharmacologic tools that have been shown to regress rubeosis, surface neovascularization, and certainly retinal and subretinal neovascularization, but we cannot use them in many situations because of issues related to drug delivery, as well as concerns about applying anti-VEGF strategies to a severely ischemic retina. It is to be hoped that further research in this field will lead to wider utility for these agents.

ERYTHROPOEITIN

Other angiogenic factors in addition to VEGF are induced in the retina by ischemia. One of them, erythropoeitin (EPO), was shown by Watanabe and colleagues to be more strongly associated with the presence of PDR than is VEGF. The researchers concluded that EPO is a potent ischemia-induced angiogenic factor that acts independently of VEGF during retinal angiogenesis in PDR.

We evaluated the levels of VEGF and EPO in a nondiabetic patient who presented to our practice with a chronic rhegmatogenous retinal detachment with extensive retinal neovascularization. We compared the results of enzyme-linked immunosorbent assays of a sample of that patient’s vitreous with those of a small series of patients with other retinal conditions. His EPO level was higher than those of patients with PDR. His VEGF level was lower than those of patients with PDR but higher than those of patients without neovascularization. We concluded that vitreous concentrations of EPO and VEGF can be elevated in patients with neovascularization secondary to a rhegmatogenous retinal detachment of long duration.

If EPO inhibition is a potential target in the treatment of DR or DME, why do we not have anti-EPO drugs? Research is ongoing. EPO is complex; in addition to being an angiogenic factor, it is also a survival factor for photoreceptors. Simply blocking it may not be the best strategy. No doubt research into the potential of EPO as a target in diabetes-related ocular disease will continue.

VITREOUS SURGERY

Vitreous surgery has evolved to include less invasive transconjunctival modes, including 25-gauge and 23-gauge vitrectomy systems. These smaller-gauge instruments have offered surgeons a new subtlety and sophistication in the ability to handle tissues. Nevertheless, dissection of the thickened, taut, vascularized posterior hyaloid from the underlying ultradelicate, often sick and ischemic retina is still extremely challenging, one of the most difficult dissections in...
ophthalmology. I liken it to trying to pry bubble gum off wet tissue paper without tearing the tissue paper.

We have been exploring the application of erbium:YAG (Er:YAG) laser technology, which is currently used primarily for skin resurfacing, to perform retinal dissection for a number of years. These efforts have been temporarily suspended due to corporate rearrangements among the laser manufacturers, but we have the Er:YAG laser technology at Weill Cornell Medical Center and are building a new microsurgical area in which to explore it further.

With a high repetition rate, the Er:YAG laser can ablate very gradually with a precision approaching that of the excimer. With the laser connected to a sapphire fiber and set at pulse energies between 1.0 and 21.2 mJ and pulse repetition rates between 10 and 200 Hz, we documented clinically useful vitreous ablation rates that scaled linearly with high repetition rates. We believe this technology shows promise for removal of vitreous and other posterior segment tissues, including epiretinal membrane and posterior hyaloid, without damaging the retinal surface. The Er:YAG laser wavelength can be transmitted across perfluoro-octane as well as air. One can imagine a variety of strategies in contact and non-contact modes to use this tool.

I am convinced this technology will be used in the future, although currently it is impractical. We have no way to visualize the depth of a dissection, so we do not know when to stop. Also the laser technology must be combined with proper fluidics for intraocular use. Nevertheless, there is great potential for laser dissection of intraocular tissues.

RETINAL MICROVASCULAR SURGERY

We have investigated in animal eyes the feasibility of microvascular surgery to revascularize the retina.

In porcine eyes under an operating microscope, several classic microvascular maneuvers were possible, including vascular puncturing, catheterization, mobilization, and intravascular injections of retinal arteries and veins. Two remote retinal vessels were connected with a fine tube using a combination of these maneuvers. Instrumentation used included disposable 30-gauge needles, fine polyimide tubes, custom-made fine glass tubes, and the Er:YAG laser.

In the human the larger retinal vessels range from approximately 80 to 125 µm, and we can achieve catheterization, anastomoses, and other procedures, in the scale of the human hand. One can envision techniques by which an ischemic retina could be revascularized. This type of procedure has been successful in other parts of the body, so why not in the retina?

CONCLUSIONS

I noted above the two fundamental abnormal processes at work in diabetic blood vessels: vascular incompetence and vascular occlusion. The basic challenges in DR therapy flow from these critical vascular abnormalities. We must find therapies that prevent or reverse retinal vascular leakage, retinal ischemia and atrophy, and resulting neovascularization.

The future of DR therapy will be filled with innovation, both pharmacologic and surgical. Antiinflammatory approaches will be at the fore in pharmacology. Extended delivery vehicles will provide a foundation for multidrug multitreatment; an intracocular implant could potentially allow delivery of more than one drug to the retina. Laser technology holds promise for delicate, controlled ablation of tissues in the posterior segment, and true retinal vascular surgery may allow us to restore blood flow in ischemic tissues.

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