REVIEW ARTICLE

MEDICAL PROGRESS

Diabetic Retinopathy

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Diabetic retinopathy is the most severe of the several ocular complications of diabetes. Advances in treatment over the past 40 years have greatly reduced the risk of blindness from this disease, but because diabetes is so common (affecting approximately 6 percent of the U.S. population[1]), retinopathy remains an important problem.

Clinical and Histopathological Manifestations

The earliest clinical signs of diabetic retinopathy are microaneurysms, small outpouchings from retinal capillaries, and dot intraretinal hemorrhages. These signs are present in nearly all persons who have had type 1 diabetes for 20 years[2] and in nearly 80 percent of those with type 2 disease of this duration.[3] As the disease progresses, patients with preproliferative retinopathy have an increase in the number and size of intraretinal hemorrhages. This increase may be accompanied by cotton-wool spots; both of these signs indicate regional failure of the retinal microvascular circulation, which results in ischemia. On examination, retinal veins may appear dilated, tortuous, and irregular in caliber. Arteries may appear white on inspection with an ophthalmoscope and are nonperfused when examined with fluorescein angiography.

Proliferative diabetic retinopathy involves the formation of new blood vessels that develop from the retinal circulation. Untreated, the process carries an ominous prognosis for vision. New vessels can extend into the vitreous cavity of the eye and can hemorrhage into the vitreous, resulting in visual loss, and they can cause tractional retinal detachments from the accompanying contractile fibrous tissue. Late in the course of the disease, new blood vessels may form within the stroma of the iris and may extend, with accompanying fibrosis, into the structures that drain the anterior chamber angle of the eye. This development blocks the outflow of aqueous humor, causing neovascular glaucoma, with a devastating elevation of the intraocular pressure. Proliferative retinopathy may occur in up to 50 percent of patients with type 1 diabetes[2] and in about 10 percent of patients with type 2 diabetes[3] who have had the disease for 15 years. The prevalence of proliferative retinopathy is somewhat higher among those with type 2 diabetes who require insulin to control their disease and is lower among those who do not.

Another important change that can occur as diabetic retinopathy progresses is diabetic macular edema, which involves the breakdown of the blood–retinal barrier, with leakage of plasma from small blood vessels in the macula, the central portion of the retina that is responsible for the major part of visual function. This causes swelling of the central retina. Resorption of the fluid elements from plasma leads to the deposition of its lipid and lipoprotein components and the formation of hard exudates. Although diabetic macular edema does not cause total blindness, it frequently leads to severe loss of central vision. In a large population-based study, the incidence of macular edema over a period of 10 years was 20.1 percent in patients with type 1 diabetes, 25.4 percent in patients with type 2 diabetes who required insulin, and 13.9 percent in patients with type 2 diabetes who did not require insulin.[4] Some ophthalmologists who provide care for

large numbers of patients with diabetic retinopathy believe that the incidence of the condition and its progression to severe stages in which vision is threatened has decreased in recent years, perhaps because of the increased emphasis on tighter blood glucose control. However, actual data on this point are scarce. In a 14-year follow-up to the population-based Wisconsin Epidemiologic Study of Diabetic Retinopathy, the 20-year cumulative incidence of any retinopathy in persons with type 1 diabetes was 97 percent in 1998, as compared with a prevalence of almost 100 percent in this group in 1984.[2,5] Reports from the same long-term study indicated that the cumulative incidence of proliferative retinopathy over a period of 15 years in persons with type 1 diabetes was only 37 percent in 1998 as compared with a prevalence of 50 percent in 1984.[2,5]

The relatively selective loss of pericytes from the retinal capillaries is a characteristic lesion that occurs early in the histopathology of diabetic retinopathy.[6] Normal pericytes are thought to have a contractile function that helps to regulate capillary blood flow, a theory based on the observation that pericytes contain copious smooth-muscle actin and have multiple processes that are wrapped around the capillary endothelium. The loss of pericytes is followed by the loss of capillary endothelial cells. Apoptosis, or programmed cell death, is thought to account for the disappearance of both types of cells.[7] Since neurons in the retina have high metabolic requirements, the hypoxia that results from extensive retinal capillary cell death is a probable stimulus for the increased expression of molecules that enhance the breakdown of the blood–retinal barrier and lead to vascular proliferation (Fig. 1).[8,9]

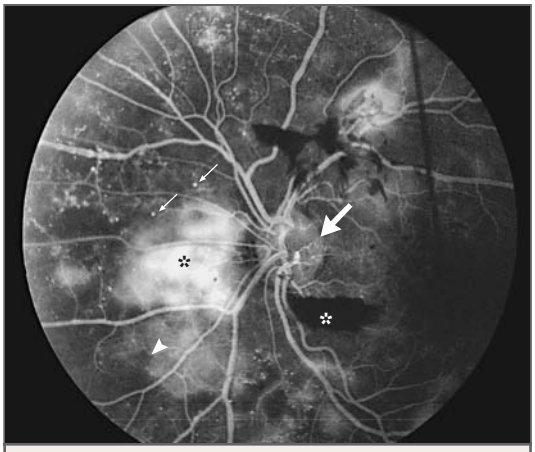

Figure 1. A Fluorescein Angiogram of the Left Eye in a Patient with Proliferative Diabetic Retinopathy.

The angiogram, which was obtained during the late arteriovenous phase (when both arteries and veins are filled), after injection of the dye into an antecubital vein, shows retinal neovascularization adjacent to areas of vascular nonperfusion, which results in retinal hypoxia. The multiple, tiny fluorescent dots (small arrows) are microaneurysms. The black asterisk indicates retinal neovascularization just nasal to (to the left of) the optic-nerve head (large arrow). The blood–retinal barrier breaks down in neovascular lesions, which therefore fluoresce brightly and appear blurred as the dye leaks from the vascular lumina. Another, smaller neovascular lesion is present along the superotemporal vascular arcade at the upper right of the image. The white asterisk indicates a preretinal hemorrhage, notable for its boat-shaped appearance, with a flat top and curved bottom. Its location in front of the retina is evident in that it partially blocks the retinal vessels. Another preretinal hemorrhage is located above the optic-nerve head. Extensive areas of capillary dropout appear as black zones at the left, inferior, and superior margins of the picture. The border of this region is indicated by the arrowhead. The dark, vertical bar at the upper right of the picture is a fixation target, used to keep the patient focused steadily in one direction during the photographic session.

CURRENT APPROACHES TO PREVENTION AND TREATMENT

Current methods for the prevention and treatment of diabetic retinopathy are listed in Table 1. Randomized, controlled clinical trials have shown that medical therapy that provides rigorous maintenance of blood glucose at near-normal levels significantly retards the development and progression of retinopathy in patients with either type 1 diabetes[10] or type 2 diabetes.[11] In addition, the control of blood pressure appears to delay the progression of retinopathy in patients with type 2 diabetes.[12] Two unexpected observations were reported in the Diabetes Control and Complications Trial among patients with type 1 diabetes. First, the differences in progression between the group with "tight" blood glucose control and the group with standard control did not appear until approximately two and a half years after the initiation of these regimens. Second, about 10 percent of the patients with preexisting retinopathy had a transient worsening of their retinopathy after the institution of tight blood glucose control.[10,13] However, this early worsening, which usually appeared as an increase in cotton-wool spots and blot hemorrhages, rarely progressed to retinal neovascularization. The cause of early worsening has not been defined, although the observations that increased

Table 1. Current Methods for the Prevention or Treatment of Diabetic Retinopathy.

- Control of blood glucose
- Control of blood pressure
- Ablation of pituitary by surgery or radiation (now largely abandoned)
- Retinal laser photocoagulation
  - Panretinal scatter photocoagulation for proliferative retinopathy or neovascular glaucoma
  - Focal photocoagulation for macular edema
- Vitrectomy for nonclearing vitreous hemorrhage or tractional detachment of retina

systemic levels of insulin-like growth factor 1[14] or increased levels of exogenous insulin[15] can up-regulate the mitogenic cytokine vascular endothelial growth factor (VEGF) have led to speculation that growth factors may be involved.

Argon-laser retinal photocoagulation therapy, introduced during the 1960s, has had an important effect on proliferative diabetic retinopathy and on diabetic macular edema, as demonstrated by two large randomized, controlled clinical trials — the Diabetic Retinopathy Study,[16-18] and the Early Treatment Diabetic Retinopathy Study.[19,20] Both trials demonstrated more than a 50 percent reduction in severe vision loss after laser treatment.

The Diabetic Retinopathy Study used panretinal, or scatter, laser treatment, in which multiple (1000 to 2000) large-diameter (approximately 500 μm), closely spaced laser burns are placed around the midperipheral retina. This treatment usually causes regression of the new vessels. It does not directly photocoagulate the new vessels, so the mechanism for the effect is unclear. It has been hypothesized that the destruction of presumably hypoxic regions of the peripheral retina produces a stimulus for neovascularization that is eliminated by the laser therapy.[8,9] Panretinal laser therapy causes surprisingly little contraction of the visual field.[20,21]

The Early Treatment Diabetic Retinopathy Study showed that focal laser treatment involving small laser burns (50 to 100 μm in diameter) in areas of vascular abnormality significantly reduced the progression of vision loss resulting from macular edema.[19,20] The mechanism underlying this beneficial effect is unclear.

Patients with symptoms of more advanced retinal disease such as nonclearing vitreous hemorrhages or tractional retinal detachments caused by fibrous bands that accompany retinal new-vessel formation may benefit from vitrectomy,[22] as suggested by the results of the Diabetic Retinopathy Vitrectomy Study.[23,24] These approaches to the treatment of diabetic retinopathy, including indications for their use, are described in detail elsewhere.[18,20,25,26] The remainder of this review focuses on research dealing with the pathogenesis of diabetic retinopathy from the 1960s to the present and on a discussion of new and experimental diagnostic methods, as well as new and experimental treatments that have been developed on the basis of putative pathogenic mechanisms.

PROPOSED PATHOGENIC MECHANISMS AND EXPERIMENTAL THERAPIES

Several biochemical mechanisms have been proposed as explanations for the development and progression of diabetic retinopathy (Table 2) and have led to exploration of possible treatments. However, except for the demonstration that chronic hyperglycemia contributes to retinopathy and other complications of diabetes, no mechanism can be regarded as established, and none have yet led to effective therapy. The failure in clinical trials of therapeutic agents based on these putative pathogenic mechanisms may not rule out the mechanisms as important to the development or progression of diabetic retinopathy. Rather, the drugs under evaluation may have been ineffective in blocking the metabolic pathways involved, or they may not have penetrated the blood–retinal barrier to reach target sites. Recently, Hammes and colleagues reported that benfotiamine, a thiamine derivative that blocks the hexosamine pathway, the increased formation of advanced glycation end products, the diacylglycerol–protein kinase C pathway, and the up-regulation of the transcription factor NF-κB, prevented lesions of early retinopathy in rats with streptozotocin-induced diabetes of nine months' duration.[83]

VEGF

The increased expression of VEGF has become a focal point of current research on the pathogenesis of diabetic retinopathy, as well as other retinal and choroidal vascular diseases. The VEGFs are a family of peptides produced from a single gene by alternative splicing. VEGF isoforms are specifically mitogenic for vascular endothelial cells and also increase permeability at blood–tissue barriers — hence the original name, vascular permeability factor. VEGF is es-

Table 2. Proposed Pathogenic Mechanisms for Diabetic Retinopathy.*

Proposed Mechanism	Putative Mode of Action	Proposed Therapy
Aldose reductase[27,28]	Increases production of sorbitol (sugar alcohol produced by reduction of glucose) and may cause osmotic or other cellular damage	Aldose reductase inhibitors (clinical trials in retinopathy and neuropathy thus far have been unsuccessful)
Inflammation[20,29-33]	Increases adherence of leukocytes to capillary endothelium, which may decrease blood flow and increase hypoxia; may also increase breakdown of blood–retinal barrier and enhance macular edema	Aspirin (ineffective in the Early Treatment Diabetic Retinopathy Study, but did not increase vitreous hemorrhage; therefore not contraindicated in patients with diabetes who require it for other reasons); corticosteroids (intravitreal injection or slow-release implants for macular edema now being tested)
Protein kinase C[34-37]	Protein kinase C up-regulates VEGF and also is active in "downstream" actions of VEGF following binding of the cytokine to its cellular receptor. Protein kinase C activity increased by diacylglycerol, which is accelerated by hyperglycemia	Clinical trials of a protein kinase C β isoform inhibitor in retinopathy have thus far been unsuccessful
Reactive oxygen species[38-41]	Oxidative damage to enzymes and to other key cellular components	Antioxidants (limited evaluation in clinical trials)
Nonenzymatic glycation of proteins; advanced glycation end products[31,42-46]	Inactivation of critical enzymes; alteration of key structural proteins	Aminoguanidine (clinical trial for nephropathy halted by sponsor)
Inducible form of nitric oxide synthase[43,46,47]	Enhances free-radical production; may up-regulate VEGF	Aminoguanidine
Altered expression of critical gene or genes[48]	May be caused by hyperglycemia in several poorly understood ways. May cause long-lived alteration of one or more critical cellular pathways	None at present
Apoptotic death of retinal capillary pericytes, endothelial cells[7]	Reduces blood flow to retina, which reduces function and increases hypoxia	None at present
VEGF[49-66]	Increased by retinal hypoxia and possibly other mechanisms; induces breakdown of blood–retinal barrier, leading to macular edema; induces proliferation of retinal capillary cells and neovascularization	Reduction of VEGF by extensive (panretinal) laser photocoagulation; several experimental medical therapies being tested
PEDF[67-75]	Protein normally released in retina inhibits neovascularization; reduction in diabetes may eliminate this inhibition	PEDF gene in nonreplicating adenovirus introduced into eye to induce PEDF formation in retina (phase 1 clinical trial ongoing)
Growth hormone and IGF-1[76-82]	Permissive role allows pathologic actions of VEGF; reduction in growth hormone or IGF-1 prevents neovascularization	Hypophysectomy (now abandoned); pegvisomant (growth hormone–receptor blocker; brief clinical trial failed); octreotide (somatostatin analogue, clinical trial now in progress)

* For all the proposed mechanisms, hyperglycemia accelerates the progression to diabetic retinopathy. VEGF denotes vascular endothelial growth factor, PEDF pigment-epithelium–derived factor, and IGF-1 insulin-like growth factor 1.

sential for the formation of the fetal vascular system; targeted disruption (knockout) of the VEGF gene in mice leads to impaired vasculogenesis and death in utero.[49] Normally, VEGF expression decreases substantially after birth, but some cells constitutively secrete picomolar amounts; cells in the neural retina secrete 15 to 20 pg per milligram of protein, and cells in the combined choroid and retinal pigment epithelium secrete 50 pg per milligram of protein.[50]

Constitutive VEGF secretion from the retinal pigment epithelium is asymmetric, occurring primarily from the basal surface of these cells,[51] and perhaps accounts in part for the richly vascular choriocapillaris, which lies opposite the basal surface of the retinal pigment epithelium (Fig. 2). The choriocapillary endothelium is itself asymmetrical, with a thin, fenestrated inner portion facing the retinal pigment epithelium and a thick, nonfenestrated outer portion facing the deeper layers of the choroid.[84] In vitro experimentation has shown that VEGF appears to induce endothelial fenestrations in cultured capillary endothelial cells that are derived from bo-

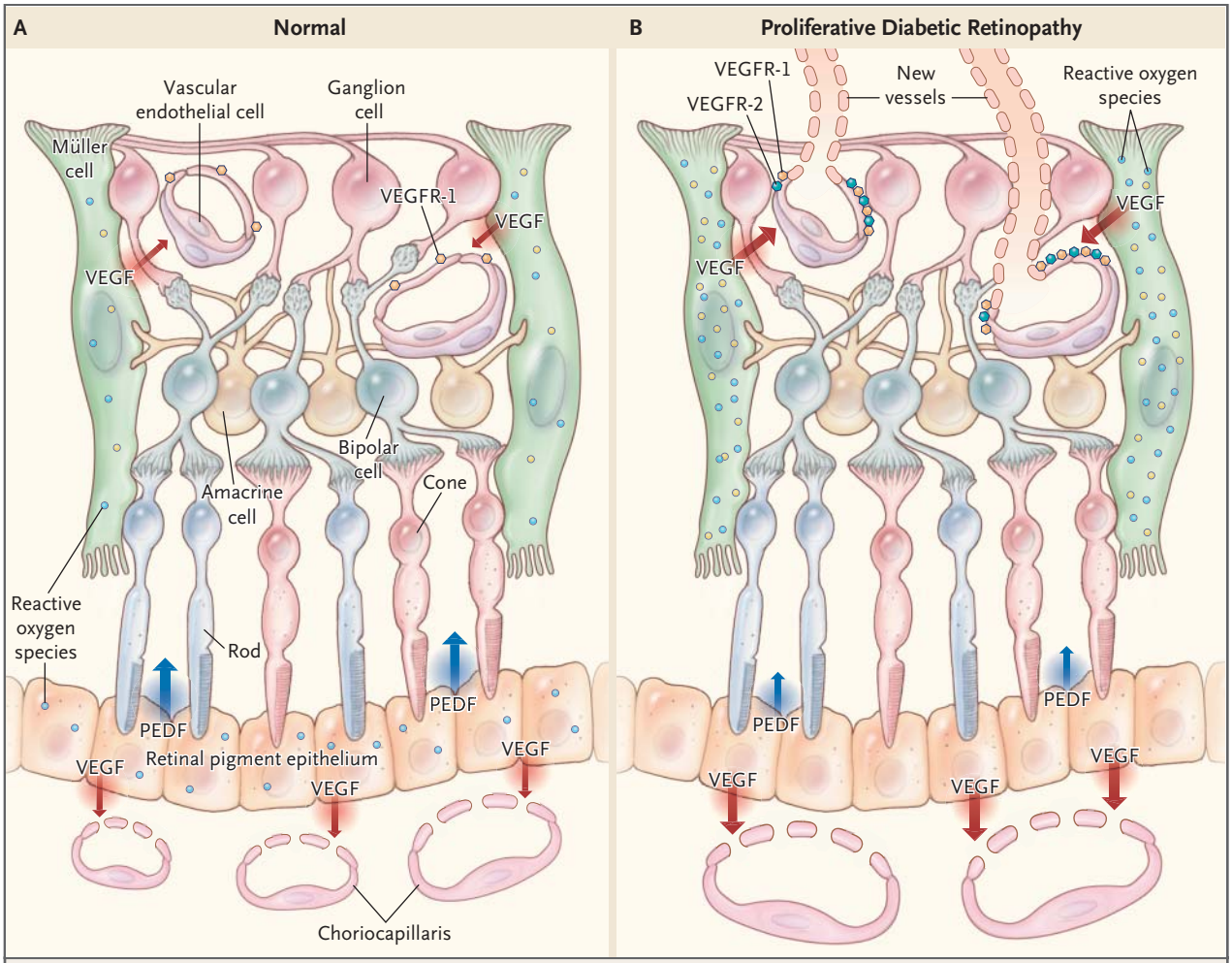

Figure 2. Retinal Anatomy and Mechanisms of Diabetic Retinopathy.

A normal retina is shown in Panel A, and a retina from a patient with proliferative diabetic retinopathy is shown in Panel B. Several polypeptide growth factors and their cell-membrane receptors have possible relevance to the pathogenesis of diabetic retinopathy, but vascular endothelial growth factor (VEGF) and its receptors, VEGFR-1 and VEGFR-2, and pigment-epithelium–derived factor (PEDF), for which no receptor has yet been identified, are currently undergoing the most intensive investigation. These two growth factors are both produced in the retinal pigment epithelium, where their constitutive secretion appears to be highly polarized.[51,73] Retinal neovascularization in diabetic retinopathy and other proliferative retinal vascular diseases nearly always occurs away from the retinal pigment epithelium and toward the vitreous space. There is evidence that both VEGF and PEDF are produced in retinal neurons and in glial cells,[52,53,69] such as the cells of Müller. In the normal retina, VEGFR-1 is the predominant VEGF receptor on the surface of retinal vascular endothelial cells, but in diabetes, VEGFR-2 appears on the endothelial-cell plasma membrane.[54]

vine adrenal cortex.[55] Endothelial fenestrations are thought to increase vascular permeability.

VEGF expression is enhanced by hypoxia,[56,57] which is a major stimulus for retinal neovascularization.[8,9] Reduced retinal blood flow and accompanying hypoxia may be present even before the early signs of retinopathy, such as loss of capillary pericytes and endothelial cells, are identified, and these changes are likely to be accompanied by an increase in the synthesis and secretion of VEGF.[36,52,53] Indeed, increased VEGF protein has been demonstrated by immunocytochemical analysis of nonvascular cells in the eyes of persons with diabetes even in the absence of retinopathy, supporting the hypothesis that diabetic retinopathy begins as a disease of retinal neurons and glia and only later involves the retinal vasculature.[52,53]

An increase in levels of VEGF by a factor of more

than 20, as measured by radioimmunoassay or radioreceptor assay, in the vitreous humor of patients undergoing vitrectomy in the presence of active retinal or iris neovascularization provided initial evidence that VEGF has a role in proliferative diabetic retinopathy.[58] Experimental data support this observation. Exogenous VEGF injected into the vitreous of the eyes of monkeys causes neovascularization of the iris[59] or retina.[60] In other animal models, interventions to block VEGF synthesis and intravitreal injection of anti-VEGF antibodies,[61] a chimeric fragment of a VEGF membrane receptor bound to an IgM fragment,[62] or antisense VEGF DNA[63] appear to prevent retinal neovascularization.

Strategies to block the formation of VEGF or to prevent its action in the human eye might be promising treatments for diabetic retinopathy. However, systemic anti-VEGF therapy would have potential clinical disadvantages.[64] Whereas neovascularization is harmful in several tissues of the eye, the formation of new blood vessels is beneficial in the coronary circulation and in the legs, which may be affected in patients with diabetic vasculopathy. Thus, direct intraocular administration of agents that block neovascularization may be preferable, despite the need for intravitreal injection, a potentially injurious procedure. Because laser therapy has been so effective in treating diabetic retinopathy, intravitreal injection has not generally been advised for the treatment of diabetic retinopathy. However, a VEGF aptamer consisting of a 28-base oligonucleotide that binds to VEGF protein is now undergoing a clinical trial for the treatment of exudative, age-related macular degeneration, which also involves neovascularization through the choroidal circulation.[65] The aptamer must be injected into the vitreous.

The blockade of specific VEGF receptors is another potentially useful therapeutic strategy. There are three known VEGF receptors; the expression of two of them, designated VEGFR-1 and VEGFR-2, is altered in the vascular endothelium in humans with diabetes.[54] A drug that blocks VEGFR-2 has undergone initial tests as an angiogenesis inhibitor for the treatment of cancer,[66] but it has not been tested as a treatment for diabetic retinopathy.

PIGMENT-EPITHELIUM–DERIVED FACTOR

First isolated from cultures of fetal retinal pigment epithelial cells,[67,68] pigment-epithelium–derived factor (PEDF) is also synthesized elsewhere in the eye[69] and throughout the body. The initial studies showed that PEDF promotes the differentiation of primitive cultured retinoblastoma cells into neuron-like structures. Subsequent work[70] showed that PEDF substantially inhibits neovascularization. Experimental studies indicated that systemic (intraperitoneal) administration of PEDF protein inhibits retinal neovascularization in the hyperoxygenated neonatal mouse, an accepted model of human retinopathy of prematurity.[71]

PEDF and VEGF appear to have a reciprocal relation in the eye. There is evidence that in proliferative diabetic retinopathy, levels of VEGF increase, whereas those of PEDF decrease.[72] VEGF is constitutively secreted from the basal surface of the retinal pigment epithelium, but the vascular anatomy of the neural retina, whose outer layers are avascular (Fig. 2), retinal pigment epithelium, and choroid suggests that PEDF is normally secreted from the apical surface of this cell layer, as was suggested by a preliminary report.[73]

The normal production and secretion of these two factors may be critical for maintaining the normal anatomy and function of the retinal and choroidal blood vessels, and PEDF may be important for maintaining the neural architecture of the retina. Abnormal production or secretion of VEGF and PEDF in retinal tissues may be a major effector of retinal disease. Both experimental retinal and choroidal neovascularization in the mouse can be inhibited after intravitreal injection of a replication-deficient adenovirus containing the PEDF gene[74] — suggesting that gene therapy with this agent in humans might be feasible. A phase 1 study of this approach in patients with very advanced neovascular age-related macular degeneration[75] is now under way.

INHIBITORS OF GROWTH HORMONE ACTION

The spontaneous resolution of proliferative diabetic retinopathy in a woman in whom acute panhypopituitarism[76] had developed stimulated interest in pituitary ablation as a treatment for vision-threatening retinopathy. Destruction of the pituitary by surgery or radiation was used before the introduction of photocoagulation, which is a more effective and far less hazardous therapy.[77] The earlier method has now largely been abandoned because of the high associated rates of morbidity and mortality. Because the beneficial effect of hypophysectomy might be due to the cessation of growth hormone secretion, therapies to block the actions of growth hormone were initiated. A three-month, open-label trial showed that pegvisomant, which blocks growth

hormone receptors,[78] did not cause regression of the new retinal vessels in patients with "non–high-risk"[18] proliferative diabetic retinopathy, although plasma levels of insulin-like growth factor 1 (IGF-1) decreased by 50 percent. A small-scale trial of octreotide, a somatostatin analogue, showed that at high doses, the agent prevented progression to the proliferative stage of diabetic retinopathy over a 15-month period.[79] A larger trial, involving 30 clinical centers, is in progress.

Growth hormone action is mediated primarily through stimulation of the production of the insulin-like growth factors.[80] Studies by Smith and her colleagues[81,82] have suggested that IGF-1 is not itself a vasoproliferative factor but, rather, is a permissive agent — that is, neovascularization cannot occur in its absence, but it must be accompanied by other molecules such as VEGF in order to stimulate new vessel growth. These experiments may explain why blocking IGF-1 secretion, either by destroying the pituitary or by more specific inhibition of IGF-1 production, appears to prevent retinal neovascularization.

GENETIC INFLUENCES ON DIABETIC RETINOPATHY

Although the importance of chronic hyperglycemia in the pathogenesis of retinopathy is now unquestioned, genetic factors appear to have important roles in determining whether diabetic retinopathy develops. Familial clustering of severe, vision-threatening forms of diabetic retinopathy was observed in the Diabetes Control and Complications Trial.[48] The continued progression of diabetic retinopathy after the institution of normoglycemia in human subjects and in laboratory animals[85,86] may be consistent with the altered expression of one or more critical genes induced by chronic hyperglycemia.

NEW DIAGNOSTIC METHODS

Several new, noninvasive techniques promise to improve diagnostic sensitivity and to enhance investigations into pathogenic mechanisms in diabetic retinopathy.

OPTICAL COHERENCE TOMOGRAPHY

One new technique is optical coherence tomography, which projects a pair of near-infrared beams from a diode through the pupil of the eye and then through the vitreous, retina, and choroid. The structures of the eye disrupt the coherence of the two beams, producing an interference pattern detected by the measuring system of the instrument and dependent on the optical reflectance and anatomical thickness of the retinal structures.[87] In the most commonly used protocol, the instrument produces a series of six radially oriented scans at equal intervals around a circumference of 360 degrees. The scans pass through the fixation point of the patient's eye (the center of the fovea). Each scan makes multiple measurements of retinal thickness; the most recent version of the instrument makes up to 768 measurements. The images produced appear to be good approximations of the cross-sectional anatomy of the retina.

Measurements of mean retinal thickness along these radii are plotted, along with a pseudocolor map of retinal thickness that enhances the visual interpretability of the images. Optical coherence tomography can therefore be used for the evaluation and follow-up of patients with diabetic macular edema (Fig. 3).[88] Because the method requires the projection of light onto the retina, it is subject to error in the presence of interfering opacities such as cataracts, corneal opacities, or vitreous hemorrhage. However, day-to-day variation in the same patient appears to be small.[89] In diabetic macular edema, optical coherence tomography can provide objective, quantitative measurements that are not possible with other methods. An advanced version of this device, involving a different optical system and a titanium–aluminum oxide laser, provides even more striking images, which display the cellular anatomy of the retinal layers in nearly the detail of a histologic section.[90]

MEASUREMENTS OF RETINAL BLOOD FLOW, VASCULAR LEAKAGE, AND OXYGENATION

Alterations in retinal blood flow that modify the supply of oxygen and other nutrients to the retina may be critical to the development of diabetic retinopathy. There are several methods for measuring retinal blood flow. The laser Doppler flowmeter,[91] which involves a laser beam projected at right angles to the blood column in a retinal vessel, quantitates Doppler shifts in the column of moving erythrocytes. The method can measure flow in only one vessel at a time, however, and only in the largest vessels close to the optic-nerve head. The scanning laser ophthalmoscope can be used to produce a video fluorescein angiogram,[92] from which the rate of flow of the plasma column in any blood vessel in the photo-

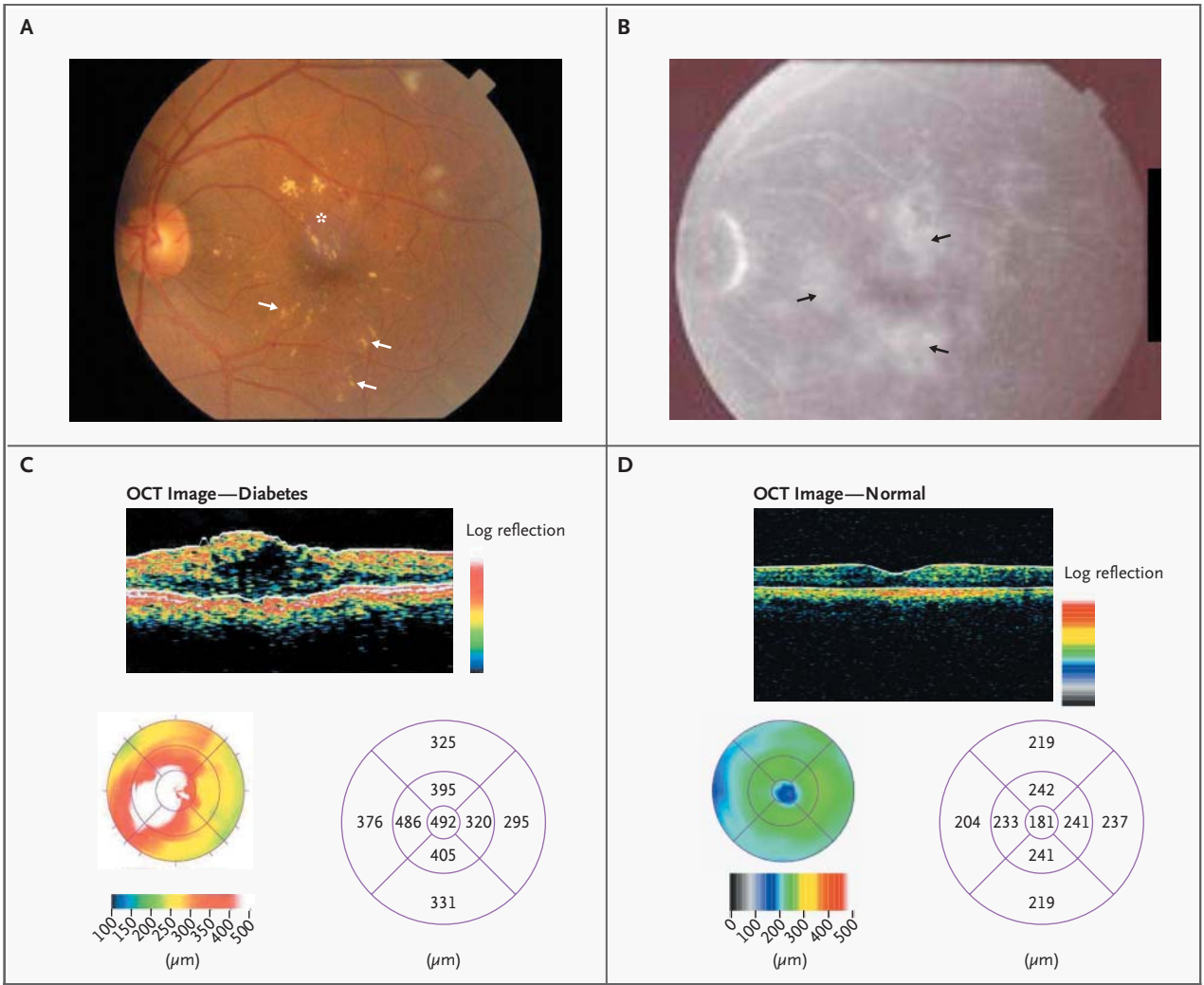

Figure 3. Diabetic Macular Edema and Optical Coherence Tomography.

A color photograph (Panel A) of the macular region of the retina of the left eye of a patient with diabetes shows a ring of hard lipid exudates (white asterisk) superior to the center of the macula, which is the dark circular zone near the center of the picture. Lipid rings often surround a zone of retinal thickening (edema). A frame from the fluorescein angiogram in this patient (Panel B) shows the leakage of dye (arrows) within the lipid ring and associated with the other lipid clusters (indicated by arrows in Panel A). A single, radial slice through the center of the macula from an optical coherence tomogram of the same eye (top image, Panel C) shows the tissue reflectance of the paired laser beams (labeled log reflection), with darker colors indicating lower reflectance. In the thickened retina, the normal depression at the center of the fovea is absent, and there is a partially vacant space, indicating edema, within the tissue. The approximately horizontal white boundary lines are arbitrarily drawn by the software to indicate the inner and outer borders of the neural retina. Measurements of retinal thickness are made by drawing perpendicular lines at intervals between these two horizontal lines. The colored circle at the lower left of Panel C is a pseudocolor map of central retinal thickness, with the color scale shown underneath. The region of greatest thickness corresponds to the zone of retinal edema denoted by the lipid ring in Panel A and the zone of dye leakage in Figure 1. In the diagram to the right of the pseudocolor map, this macular region is arbitrarily divided into nine sectors. The number in each sector is its mean thickness, in micrometers, averaged from the lengths of the perpendicular lines drawn by the software between the inner and outer boundaries of the retina. An optical coherence tomogram (OCT) of the macula in a normal subject (Panel D) is shown for comparison. The center of the macula is the thinnest region. The cross-sectional image at the top shows this thinned central zone, the so-called foveal pit. The images in Panel C and Panel D are from different models of the same instrument.

graphic field can be calculated from the movement of a point of fixed fluorescence intensity along the course of the vessel over time. The scanning laser ophthalmoscope produces a permanent electronic record that can be subjected to many forms of analysis, but it measures the movement of the plasma column, not the movement of the column of erythrocytes, which may be more physiologically relevant.

Retinal oxygenation has until recently been measurable only with intraretinal oxygen electrodes, an invasive technique that cannot be used in humans. A new, noninvasive method, functional magnetic resonance imaging (fMRI), does not measure retinal partial pressure of oxygen directly but, instead, calculates the change in oxygenation by comparing retinal oxygenation when the subject is breathing room air and when he or she is breathing 100 percent oxygen or a mixture of 95 percent oxygen and 5 percent carbon dioxide.[93] This technique can detect differences in the change in retinal oxygenation even in very small regions of the retina, a few hundred micrometers on a side. In rats that had been fed a high-galactose diet, which causes a diabetic-like retinopathy, fMRI studies showed that oxygenation decreases as soon as three months after the onset of the metabolic abnormality[94]; this finding is consistent with the early up-regulation of VEGF in the retina. Preliminary studies in humans[95] have demonstrated that functional MRI can provide accurate measurements of the change in retinal oxygenation, free of the eye movement and blinking artifacts that produced inaccuracies when this technique had initially been used in conscious human subjects. However, further development is required for clinical use.

CONCLUSIONS

Diabetic retinopathy, a major cause of blindness and visual disability in the United States, has been a focus of extensive basic and clinical research since the 1960s. The efficacy of retinal laser photocoagulation and vitrectomy for the treatment of this disease has been documented by large-scale randomized, controlled clinical trials. The value of blood glucose and blood-pressure control for the prevention of retinopathy in patients with type 1 or type 2 diabetes has been documented in similar trials. New techniques have enhanced the accuracy and sensitivity of diagnostic methods and may lead to a better understanding of pathogenic mechanisms. The identification of several such putative mechanisms has led to the development of new drugs, none of which have as yet proved effective in randomized, controlled clinical trials. Additional therapeutic approaches that are being developed or evaluated in clinical trials may ultimately improve the outcome for patients with diabetic retinopathy.

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