MAJOR REVIEW

Peripheral Proliferative Retinopathies: An Update on Angiogenesis, Etiologies and Management

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Abstract. Many clinical entities may be associated with the development of peripheral retinal neovascularization. In this paper, we review the mechanisms of normal and abnormal angiogenesis in the retina. Specific disease entities associated with peripheral proliferative retinopathies are discussed. These include vascular disease with ischemia, inflammatory diseases with possible ischemia and a variety of miscellaneous causes, including hereditary diseases and tumors. Basic principles for the clinical evaluation of patients with retinal neovascularization are described. Finally, the treatments for retinal neovascularization, including cryopexy and local and panretinal photocoagulation are reviewed, and techniques and possible mechanisms of the beneficial results of treatment are described **(Surv Ophthalmol 38:**519–540, 1994)

Key words. angiogenesis • cryopexy • diabetes • inflammatory disease • neovascularization • panretinal photocoagulation • proliferative retinopathies • retina • vascular disease

In 1980, we reviewed entities that result in midperipheral or peripheral retinal neovascularization.[106] At that time, much attention had been directed to neovascularization of the disk and posterior pole of the eye and the purpose of our review was to describe conditions that cause neovascularization in the midperiphery and periphery. Since that review, additional entities have been reported to cause peripheral retinal neovascularization. In addition, significant advances have occurred in our knowledge of retinal angiogenesis and the results and mechanisms of action of retinal photocoagulation. What follows is a brief summary of retinal angiogenesis, a characterization of recently discovered entities which cause peripheral neovascularization and an update of previously described causes of peripheral neovascularization. In addition, we will review what is known of the current therapy for these various conditions.

I. Definition

For this review, peripheral retinal neovascularization is defined as preretinal neovascularization arising from the retinal circulation, which is present predominantly or exclusively peripheral to the major arcades. The prototype of this neovascularization is sickle cell disease. Table 1 has been revised to include currently known entities that may result in peripheral retinal neovascularization. As in our original report, the majority of conditions resulting in this type of neovascularization are either retinal vascular diseases with ischemia or inflammatory diseases with possible ischemia. However, for a number of clinical entities (e.g., retinitis pigmentosa), the stimulus for

neovascularization remains uncertain.

II. Angiogenesis

A. MECHANISMS OF ANGIOGENESIS

A summary of the mechanisms of angiogenesis (the development of blood vessels from pre-existing blood vessels)[165] in the retina follows because it allows a rational approach to prevention and treatment of retinal neovascularization.

The retina becomes vascularized during embryonic development (vasculogenesis). A vanguard of mesenchymal cells sweeps from the optic nervehead into the retina from the hyaloid system at four months' gestation and proceeds to the periphery by the time of normal term.[4] This vascularization does not reach the temporal ora serrata until after birth. Behind the vanguard, mesenchyme remodels into capillaries, arteries, and veins.[66] Remodeling continues even after birth.

Healing is the body's effort to reconstruct the uninjured state. It depends upon the body's ability to sense tissue damage or dysfunction, signal the appropriate cells which carry out the repair, and terminate the process when its purpose is fulfilled.[95] Scarring, as part of the healing process, is the laying down and remodeling of collagenous tissue. If injury affects blood vessels, for example, if there is ischemia, angiogenesis is necessary for the scarring process.[95] During the scarring process, angiogenesis is stimulated by inflammation or ischemia. The angiogenic response is maintained in a constant state of readiness. On short notice, a vascular system that has been stable for years can rapidly grow new vessels. As the physiologic healing process matures, blood vessel growth slows and then stops. Angiogenesis can occur when it should not and may continue long after its useful purpose has ended. Sometimes it continues indefinitely.

Inflammation is also a prerequisite to healing. If there is no inflammation, healing does not occur. If there is too little inflammation, healing is slow. If too much inflammation occurs, excessive scar tissue may be produced.[95] Neovascularization is part of this inflammatory process, is preceded by an inflammatory cellular response, and is followed by fibroplasia.

Inflammation or ischemia working through inflammatory cells or tumor cells acting directly stimulate angiogenesis by the elaboration of angiogenic factors. There seems to be little or no biochemical difference between the angiogenic peptides expressed by tumors and those found normally in the tissue.[62]

Whether the stimulus for angiogenesis is a tumor, inflammation or ischemia, the sequence of events is the same.[61] These steps have been described by Folkman[61] and Ausprunk.[5] The response is modified in the eye because of its unique anatomic arrangements (Fig. 1).

Step #1: The venular ends of preexisting capillaries are activated to form new capillaries.[6,82] Frequently the affected vein dilates before the blood vessels form.[100]

Step #2: Endothelial cells, when stimulated, secrete collagenases and other proteolytic enzymes active against collagens 4 and 5, laminin, fibronectin and glycosaminoglycans in the basal lami-

TABLE 1

Peripheral Retinal Neovascularization

I. Vascular diseases with ischemia
   1. Sickling hemoglobinopathies:[32,149] SC,SS, SB thalassemia, SO Arab
   2. Other hemoglobinopathies: AC,[146] AS,[148] C Beta° thalassemia[48]
   3. Eales' disease[51,54,191]
   4. Small vessel hyalinosis[205]
   5. Diabetes mellitus
   6. Branch retinal vein occlusion[157]
   7. Branch retinal arteriolar occlusion[119]
   8. Retinal embolization (e.g., talc)[20,120,179]
   9. Retinopathy of prematurity[66,118,161]
   10. Familial exudative vitreoretinopathy
   11. Hyperviscosity syndromes (e.g. chronic myelogenous leukemia)[68,145]
   12. Aortic arch syndromes/ocular ischemic syndromes[19,98,158]
   13. Carotid-cavernous fistula[113]
   14. Multiple sclerosis[7,144,208]
   15. Toxemia of pregnancy[13]
   16. Encircling buckling operation[29]

II. Inflammatory diseases with possible ischemia
   1. Sarcoidosis[2,3,49,88]
   2. Retinal vasculitis: SLE,[115] arteriolitis with SS-A auto-antibody,[57] acute multifocal hemorrhagic vasculitis,[12] and vasculitis secondary to infection
   3. Uveitis including pars planitis[18]
   4. Birdshot retinochoroidopathy[8,168]
   5. Toxoplasmosis[73]
   6. Acute retinal necrosis[97,212]

III. Miscellaneous
   1. Incontinentia pigmenti[213]
   2. Familial telangiectasia, spondyloepiphyseal dysplasia, hypothyroidism, neovascularization, and tractional retinal detachment[124]
   3. Inherited retinal venous beading[139,193]
   4. Autosomal dominant vitreoretinochoroidopathy[11,114]
   5. Longstanding retinal detachment[59,202]
   6. Choroidal melanoma,[206] choroidal hemangioma[129]
   7. Retinitis pigmentosa[17,150,204]
   8. Retinoschisis[24,163]
   9. Cocaine abuse

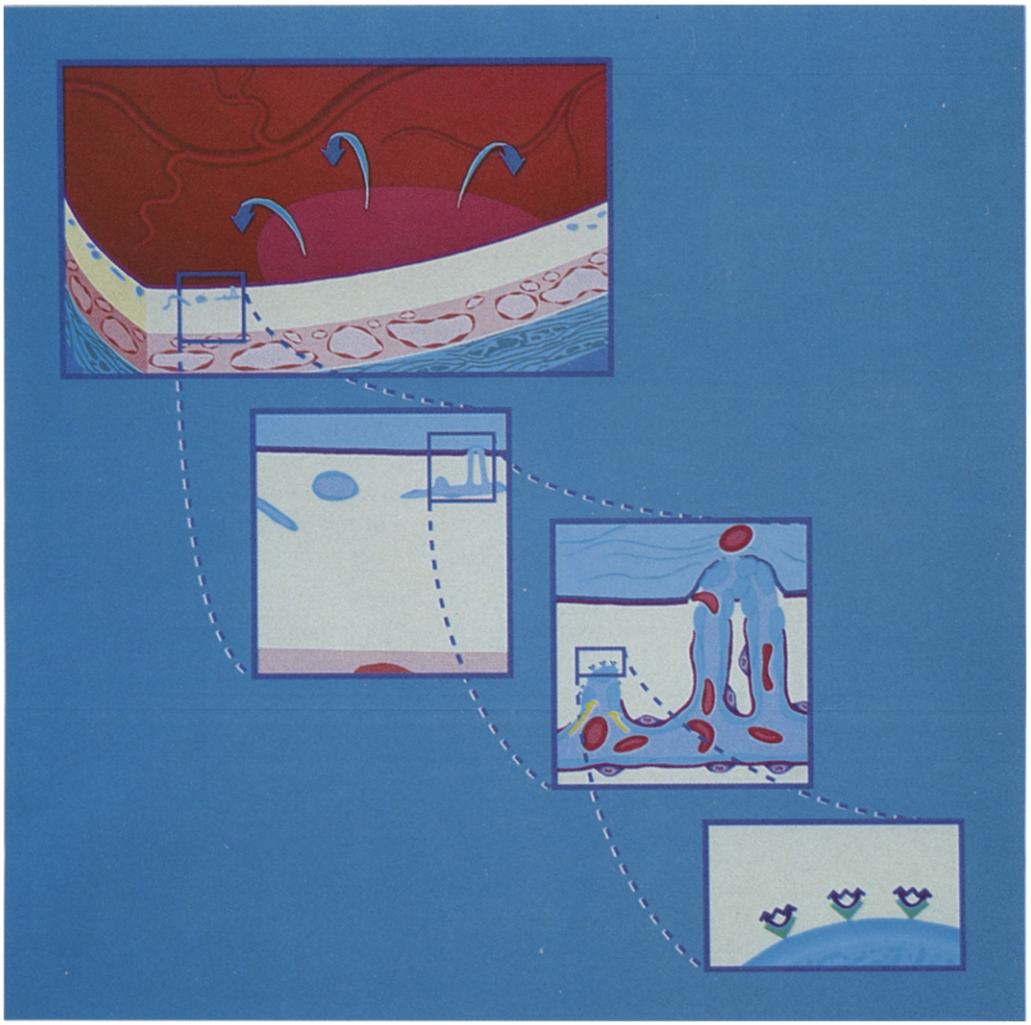

Fig. 1. Panel 1 (upper): Ischemic retina (light red) signals adjacent retinal venules to start neovascular process. The activated angiogenic factor may be in higher concentration in the vitreous just internal to the inner limiting lamina, attracting the neovascularization toward the vitreous cavity. Panel 2: A venule near the edge of the ischemic retina has a bud on the vitreous side of the vessel and a loop of neovascularization just penetrating the inner limiting lamina. Panel 3: The bud on the left is forming from the endothelial cells that have enzymatically lysed the basal lamina (purple) and have slid (yellow arrows) through the gap in the basal lamina. The loop on the right has formed from two cords of proliferating endothelial cells that have lumenized in the more mature part of the new vessel closer to the vessel of origin. The endothelial cells and pericytes in the more mature part are laying down a basal lamina. The growing tip, where the two new new vessels are anastamosing, does not have a fully formed lumen. The advancing endothelial cells have penetrated the internal limiting lamina of the retina (purple) and are adhering to the posterior vitreous face (blue). There are gaps between the endothelial cells in the immature part of the vessels that can leak erythrocytes, fluorescein, and large molecules of lipids and proteins. Panel 4: One proposed mechanism of activation of endothelial cells: bFGF (purple arc) has been released from heparan sulfate in the extracellular matrix by heparinase or collagenase. A piece of the heparin (blue zig-zag) occupies the site of bFGF that can bind heparin. The bFGF, unable to adhere to the extracellular matrix, can float to the receptor sites (green) on an endothelial cell (light blue) to activate the endothelial cell to start the neovascular process. (Artist: Ellen H. Mower, UCSD School of Medicine, Office of Learning Resources.)

na.[162] The stimulated endothelial cells also release plasminogen activator[91] which activates the latent collagenases. These secretions cause lysis of the basement membrane of the capillary on the side closest to the stimulus. The vessel wall bulges and then the basement membrane gapes.

Step #3: Endothelial cells lose their normal adhesion and migrate by sliding through the gap in the basement membrane toward the angiogenic stimulus. The preferential growth of new vessels in the retina toward the vitreous cavity suggests that angiogenic factors accumulate in the vitre-

ous, possibly binding to heparan sulfate in the vitreous body, just internal to the retina.

Step #4: The endothelial cells then slide out of the vessel to form a solid cord in the interstitial stroma.[28,180,181] Endothelial cells interact intimately with the stroma. Tissue culture of endothelial cells indicates a 3-dimensional matrix of extracellular tissue or fibrin is necessary for this step.[183] In the stroma, endothelial cells release enzymes active against collagen types 1, 3, and 5; fibronectin; elastin; and proteoglycans freeing FGF.[130,131,209] The stroma dissolves as the sprout advances, and the endothelial cells slide forward. Behind the advancing tip, the endothelial cells adhere to the remaining matrix through attachments to fibronectin. Growing capillaries may use collagen fibers or fibrin strands as a substrate for their growth. Not all extracellular matrix is penetrated by this activity. The extracellular matrix regulates the growth of neovascularization.[210] The internal limiting lamina of the retina does not offer a significant barrier to such lysis, but healthy intact Bruch's membrane generally does. The posterior vitreous face can be a substrate for vessel growth, but the healthy vitreous body usually inhibits vascularization into its substance, possibly through an inhibitory substance[166] or by mechanical resistance.[72]

Step #5: The endothelial cells curve in the matrix of tissue surrounding the parent vessel to form a tube. The endothelial cells at the tip of the blind tube have spaces between them, and it is likely that through these interendothelial spaces fluorescein, plasma, and fibrinogen leak.[6,100] Plasminogen activator assists in fibrin formation that in turn stimulates more endothelial cell migration and macrophage influx. Endothelial cells lay down a new basement membrane around the tube. Fluorescein angiography shows the new vessels budding from the parent retinal vessel.

Step #6: Endothelial cells just behind the tip divide to replace the cells that have migrated.

Step #7: Two adjacent tubes merge to form a tube which now becomes the parent vessel for further angiogenesis.[28,180,181]

Step #8: Flow is established in the loop. The optical system of the eye allows a magnificent view of these loops. In proliferative sickle cell retinopathy, we see these loops as an anastomosis at the border between avascular and vascular peripheral retina.[82]

Step #9: Pericytes appear around the bar of the loop.[4,28,38] Endothelial cells lay down a new basal lamina between the endothelial cells and the pericytes.[6,63,134] The pericytes in more mature vessels inhibit endothelial cell proliferation.[155,156] Absence of or reduction in pericytes is correlated with neovascularization (e.g., diabetes).

Step #10: The cycle repeats. Loss of growth factors results in cessation of angiogenesis.[5]

B. ANGIOGENIC FACTORS

The notion of factors inducing healing and neovascularization dates back at least to the wound hormones suggested by Loeb in 1893.[132] Isaac Michaelson proposed a soluble factor acting to produce growth in retinal blood vessels under conditions of ischemia.[142] The observation that the growth of tumors depended on angiogenesis led to the isolation of a diffusible angiogenic factor from tumors.[65,90] Since then a wide variety of agents involved in neovascularization have been found in different tissues.

The vascular system does not normally produce new vessels, yet, like the clotting system, it remains prepared to respond quickly to a stimulus. There may be more than one final pathway inducing neovascularization. It is likely that a cascade of events involving one or more angiogenic stimulants may induce new vessels.

Neovascularization is controlled by a balance of stimulating and inhibiting factors.[76] Angiogenic substances turn on or off the production and release of enzymes that digest the extracellular matrix, stimulate and attract the migration of endothelial cells, and activate the proliferation of endothelial cells.[62] Angiogenic substances fall into two classes — those that directly act on endothelial cells, causing migration or proliferation, and those that act indirectly through activation of macrophages, liberation of stored or sequestered direct-acting angiogenic material, or release of fibrinogen. The list of substances that affect angiogenesis is evolving, as is our understanding.

1. Factors That Act Directly on Endothelial Cells

a. Fibroblast Growth Factor (FGF)

Fibroblast growth factors comprise a group of structurally similar polypeptides. Two of these, basic fibroblast growth factor (bFGF) and acidic fibroblast growth factor (aFGF) have been well studied and appear to have a major role in angiogenesis. These two FGFs have a molecular weight of 18,000 daltons and consist of 154 amino acids with a 53% protein sequence homology.[74] Both aFGF and bFGF induce division of most cultured cells derived from embryonic mesoderm and neuroectoderm, stimulate mitogen-

esis of endothelial cells, and promote wound healing. The FGFs bind to heparin and heparin-like components of glycosaminoglycans. This property is useful in purifying the FGFs with affinity chromatography. In addition this binding may be the way that FGF is distributed in the extracellular matrix in an inactive form, yet in a state of readiness for action.[209]

Although the genetic control and distribution of aFGF and bFGF are different, it is unclear if these two substances have some differences in their actions or whether all functions are identical. Of major importance is that a number of tissue-derived angiogenic factors, such as eye-derived growth factor (EDGF),[35] retina-derived growth factor (RDGF),[36,41,78] and astroglial growth factor (AGF),[164] have now been recognized as FGFs.

Basic fibroblast growth factor is one of the first angiogenic substances to be isolated.[85] Basic FGF is active in embryonic and adult tissue. The gene for bFGF maps to chromosome 4.[140] bFGF induces endothelial cell migration and proliferation,[34,177] modulates endothelial cell collagenase and plasminogen activator,[91] induces neovascularization,[79] and brings about wound healing.[21] Basic FGF may also be responsible for pathological processes such as tumor growth.[175,187] Vascular endothelial cells synthesize bFGF, and they may incorporate it in the extracellular matrix they produce. The binding of bFGF to heparin and heparin-like extracellular matrix components sequesters bFGF from the receptors at potential sites of action.[209] With bFGF bound in extracellular matrix, endothelial cell proliferation remains quiescent until the FGF is liberated locally by heparinase released from platelets, mast cells, macrophages, neutrophils, or T-cells during sublethal cell damage, tissue injury, ischemia, or inflammation.[209] Plasminogen activator from endothelial cells may further stimulate FGF release from the extracellular matrix.

The role of bFGF in the eye is currently under investigation. The tendency for neovascularization in the retina to grow into the vitreous cavity implies a higher concentration of an angiogenic substance like FGF bound in the vitreous cavity, which is essentially extracellular matrix, than in the retina, which is mostly neural tissue. An alternative explanation might be lower concentrations of inhibitory substances in the vitreous. Basic FGF has been localized in the basement membrane of endothelial cells in normal retina, but it was not found in the basement membrane of active fronds in proliferative diabetic retinopathy.[94] Possible explanations are that active fronds are consuming the bFGF that would normally be found in the basement membranes of the endothelial cells or that another growth factor, such as aFGF, is responsible for the neovascularization.

Acidic fibroblast growth factor production maps to chromosome 5.[140] Endothelial cell growth factor (ECGF) is a precursor to aFGF.[22] There are differences in the conditions that will inactivate aFGF compared to bFGF. Most evidence points to affinity of aFGF and bFGF to the same receptors.

At least five other peptides with structural homology to aFGF and bFGF are aggregated into the FGF family: int-2 (DNA region of provirus integration site), hst/K-fgf (human stomach cancer transforming gene), FGF-5, FGF-6, and FGF-7. These peptides may be active during embryogenesis or may be oncongenes.

b. Transforming Growth Factor Type Alpha (TGF-α)

Transforming growth factors have the property of altering the phenotype of normal fibroblasts to transformed cells with malignant characteristics, including loss of density-dependent inhibition and having anchorage-independent growth.[173] They fall into two groups, TGF-α and TGF-β that, other than the transforming property, are unrelated in structure and action. TGF-α has a molecular weight of 6000 daltons and 50 amino acids with a 35% sequence homology with epidermal growth factor (EGF). It competes for the same receptors as EGF, and both substances have the same biological activity. Both are mitogenic for endothelial cells, but TGF-α is 3 to 10 times more potent.[184]

c. Platelet-Derived Endothelial Cell Growth Factor (PD – ECGF)

This growth factor isolated from human platelets has a molecular weight of 45,000 daltons.[143] PD-ECGF has no protein sequence similarity to known proteins. Its gene maps to chromosome 22. It is chemotactic and mitogenic to endothelial cells in vitro and induces angiogenesis in vivo. Like FGF, it appears not to be secreted in response to a signal peptide. It is retained intracellularly and may be released by cell lysis. It does not bind to heparin. Its role in the angiogenic pathways is not known.

d. Vascular Endothelial Growth Factor (VEGF)/ Vascular Permeability Factor (VPF)

VEGF and VPF are homologous basic peptides of molecular weight 46,000 to 48,000 dalton's.[200] The peptide sequences suggest member-

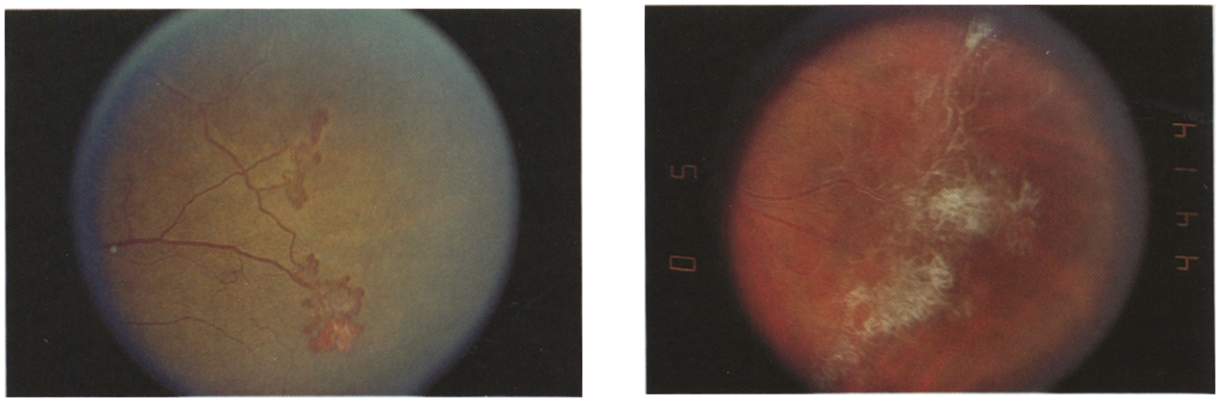

Fig. 2. Peripheral neovascularization in patients with hemoglobin SC (left) and incontinentia pigmenti (right).

ship in the family of platelet-derived growth factor (PDGF), which is mitogenic for smooth muscle cells but not endothelial cells. Their source includes tumor cells, retinal pigment epithelial cells, and pituitary cells.[1] They bind to heparin, but with less affinity than does FGF. They are strongly mitogenic for capillary endothelial cells, on which high-affinity receptors have been found.[103a] VEGF may be an important regulator of vasculogenesis in the embryo.[14a] VEGF/VPF also promote vascular leakage, presumably including fibrinogen, which could enhance the local environment for neovascularization. Monoclonal antibodies for VEGF/VPF inhibited angiogenesis in tumors.[116a]

e. Angiotropin

Angiotropin has been purified from macrophages. Though not a mitogen for vascular endothelial cells, it stimulates endothelial cell migration and organization into tubes.[101] It may induce angiogenesis through inflammation.

2. Factors that Act Indirectly on Endothelial Cells

a. Transforming Growth Factor-Beta (TGF-β)

TGF-β has a molecular weight of 25,000 daltons, with two equal monomers containing 112 amino acids each.[173] Platelets are a major storage site for TGF-β. All cells contain receptors for TGF-β.[201] TGF-β increases the number of macrophages, activates fibroblasts, and increases collagen synthesis.[125,174] It inhibits endothelial cell proliferation in vitro,[69] yet it stimulates angiogenesis in vivo, perhaps by generating inflammation and attracting macrophages. It promotes endothelial cell migration into tubes.[141] TGF-β is an important mediator of tissue repair.[173]

b. Tumor Necrosis Factor-Alpha (TNF-α)

TGF-α is an acidic peptide of 17,000-dalton molecular weight secreted by macrophages. It influences inflammation and stimulates the synthesis of granulocyte-macrophage-colony stimulating factor (GM-CSF).[10,147] TNF-α is angiogenic in vivo yet inhibits endothelial cell growth in vitro.[70] Like TGF-β, TNF-α encourages differentiation of endothelial cells into tubes.

c. Prostaglandins (PG)

Certain prostaglandins, e.g., PGE_1, and PGE_2, are angiogenic in vivo, possibly by activating macrophages.[9,67] This activity implies that antiprostaglandins could inhibit angiogenesis when prostaglandins are involved in the process.

3. Tumor Angiogenesis Factors

Tumor angiogenesis factor is mentioned because of its historical significance.[55] There seems to be little biochemical difference between angiogenic factors expressed by tumors and those found in normal tissues.[62] Angiogenin, initially isolated from human adenocarcinoma, is the first tumor angiogenesis factor to be isolated in pure form.[195] Though strongly angiogenic, it does not cause endothelial cell migration or proliferation. Tumor angiogenesis factors may be operative in eyes with intraocular tumors, such as melanoma and retinoblastoma. On the other hand, basic fibroblast growth factor has been proposed as an angiogenic substance[187] and a tumor supporting substance[175] in these tumors. VEGF has been identified as a principal angiogenic factor that directly affects endothelial cells.[74a]

4. Factors that Regulate Angiogenesis

a. Heparin

There are several useful observations about heparin, FGF, and angiogenesis. Heparin protects FGF from inactivation.[86] Basic FGF is stored in the extracellular matrix in a stable and inactive

complex with heparan sulfate in glycosaminoglycans. Mast cells, neutrophils, and platelets can express heparinase. Basic FGF is released from the extracellular matrix by degradation of the extracellular matrix by collagenase or by lysis of heparan sulfate by heparinase, which otherwise leaves the extracellular matrix intact while freeing the FGF.[209] The binding site for receptors on target cells differs from the binding site to heparan sulfate or heparin. Heparin inhibits angiogenesis in the presence of cortisone.[64] From these observations, the following hypotheses are offered: Heparin introduced into the system can bind to bFGF. The heparin-bound bFGF is able to diffuse through tissue until it reaches an endothelial target. Heparin bound to bFGF prevents it from being bound again to heparan sulfate in the extracellular matrix. Possibly cortisone reduces the amount of heparinase being released, and the added heparin uses up the small amount of heparinase left. Consequently, heparinase would not be available to release bFGF complexed in the extracellular matrix, thereby inactivating FGF-driven angiogenesis.

b. Copper

Copper ions appear to modulate the level of angiogenesis activity by an unknown mechanism. It has been proposed that copper and heparin interact to augment angiogenesis by improving the affinity of FGF for heparin.[194]

III. Diseases Associated with Peripheral Retinal Neovascularization

A. VASCULAR DISEASES WITH ISCHEMIA

1. Sickle Cell Hemoglobinopathies

Patients with sickle cell disease frequently develop peripheral retinal capillary nonperfusion and peripheral neovascularization, which takes the shape of a sea fan (Fig. 2, left) a type of coral.[149] For disease associated with retinal neovascularization, we use "proliferative *disease* (e.g., diabetic) retinopathy" as a name for the stage of neovascularization in that disease. Proliferative sickle cell retinopathy (PSR) was one of the first conditions described with peripheral neovascularization. Consequently, the designation of sea fan is commonly associated with PSR, but any neovascularization in the retinal periphery tends to have the shape of a sea fan. Neovascularization of the iris (NVI)[84] in patients with sickle cell retinopathy is rare, possibly because the vitreous in these young individuals is intact and provides a good anterior barrier to the angiogenic stimulus. The total area of ischemia may also be insufficient to induce NVI. The disk, which is far from the ischemic retina, uncommonly develops neovascularization.[154] The addition of outer retinal ischemia when the retina detaches in patients with PSR can induce NVI.

Sea fan neovascularization is most commonly seen with hemoglobin SC disease (Fig. 2, left), but may also be seen with hemoglobin SS and S-beta$^+$ or S-Beta$^\circ$ thalassemia. Rarely, patients with hemoglobin SO Arab may demonstrate peripheral neovascularization.[32] The reason for peripheral retinal nonperfusion in patients with hemoglobin SC is uncertain. The nearly normal hematocrit with a presumed elevated whole blood viscosity may slow the flow in the far peripheral capillaries. The slow flow may allow the high oxygen uptake by the retina to deoxygenate the blood in the capillaries to the point where intracapillary and perhaps precapillary arteriolar sickling occurs. It is possible that in the peripheral retina (but less often in other tissues) the oxygen desaturation and slow flow are sufficient to cause intravascular sickling, which may explain the high risk of eye disease but lower hazard of systemic disease. The mechanism of capillary occlusion in hemoglobin SS may be different.[214] Even though anemia reduces the viscosity of the blood compared to hemoglobin SC or normal hemoglobin AA, the percentage of irreversibly sickled cells is higher compared to hemoglobin SC. These rigid irreversibly sickled cells can occlude precapillary arterioles in the peripheral retina as well as elsewhere in the body.[122] Another theory of the higher prevalence of sea fans with SC compared to SS suggests that with hemoglobin SS, ischemia progresses rapidly to infarction; whereas, with hemoglobin SC, the progression is slower.[188,198] A prospective cohort study in Kingston, Jamaica, is following the peripheral retina in patients with various sickle hemoglobinopathies from birth. This longitudinal study seeks to uncover the reason for the disparity between the eye disease and the systemic manifestations in SC and SS hemoglobinopathies.[199]

In general, sickle cell trait, hemoglobin AS, does not cause systemic disease or retinal neovascularization. It has been suggested but not proven that sickle cell trait can potentiate the development of peripheral neovascularization in patients with other diseases that provoke retinal ischemia or neovascularization (e.g., diabetes mellitus).[148] It is unknown if sickle trait by itself can cause peripheral neovascularization.

Sickle cell sea fans can be occluded by laser occlusion of the feeding and draining vessels[30,51,52] (Section V. E) and cryopexy to envelop the sea fan.[41,67] Many sea fans regress after pe-

ripheral scatter photocoagulation.[56,93,172] Fewer complications following scatter photocoagulation led Jampol and coworkers to recommend this approach as the initial therapy.[105] Indications for vitrectomy in PSR include non-clearing vitreous hemorrhage, retinal traction, retinal detachment, and epiretinal membranes.[111]

2. Other Hemoglobinopathies

Occasional reports describe peripheral neovascularization in association with nonsickling hemoglobinopathies. These include hemoglobin AC,[146] and hemoglobin C-beta° thalassemia.[48] These associations may be coincidental. The origin of the neovascularization in these cases (if it is truly associated with the described hemoglobinopathy) remains uncertain. Successful therapy of the peripheral neovascularization in association with hemoglobin C-beta° thalassemia has been reported using peripheral sector panretinal photocoagulation.[48]

3. Eales' Disease

The eponym "Eales' disease" is sometimes used to describe patients with unexplained peripheral retinal vascular occlusion and neovascularization.[51,54,191] In most reported cases, the occlusive process predominantly involves the retinal venous circulation. In the United States, the term "Eales' disease" has been used for patients in whom no obvious systemic or ocular cause has been found for peripheral neovascularization. These patients have variable manifestations and may be a conglomeration of patients who have different origins for the final common pathway of peripheral neovascularization. In some countries, for example, India, the diagnosis of Eales' disease is applied to patients who appear to have a distinct entity with characteristic retinal changes; usually this disease affects young men, especially those 20–45 years old. Bilateral sheathing of retinal venules and arterioles is accompanied by peripheral capillary nonperfusion, particularly superior temporally. Neovascularization similar in shape to the sea fans in proliferative sickle cell retinopathy grows at the margin between the perfused and nonperfused retina. It is uncertain if ocular inflammation adds to the ischemic stimulus for neovascularization.[191] The retinal neovascularization may lead to vitreous hemorrhage, tractional retinal detachment, or rhegmatogenous retinal detachment. Rubeosis iridis, secondary glaucoma, and cataract may also ensue. The visual prognosis in most cases of Eales' disease is good. Either a scatter or feeder vessel type of photocoagulation therapy is useful to treat active proliferation.[136,192,215] Vitreous opacities and traction can be treated by vitrectomy.

4. Small Vessel Hyalinosis

A familial syndrome has been reported[205] characterized by progressive hyalinosis involving capillaries, arterioles, and venules that produces vascular lesions in the digestive tract, kidneys, skin, and brain. The apparent transmission is autosomal recessive, although an autosomal dominant pattern has not been completely excluded. The syndrome causes peripheral retinal ischemia and chorioretinal scars with the development of peripheral retinal neovascularization. The neovascularization responds to cryopexy or scatter laser photocoagulation.[205]

5. Diabetes Mellitus

In diabetes mellitus, the density of retinal nonperfusion tends to be highest in the midperiphery, with the posterior retina next in density. But even the far peripheral retina can be involved.[151] With the exception of neovascularization on the disk, neovascularization is apt to occur near large areas of ischemic retina. Consequently, in proliferative diabetic retinopathy, most neovascularization develops near the vascular arcades or on the disk. Occasionally, the neovascularization may develop in the periphery, either in the absence of much retinopathy in the posterior pole or in combination with posterior retinopathy. Panretinal scatter photocoagulation arrests or minimizes the adverse effects of proliferative diabetic retinopathy.[43,44,82,197] Peripheral neovascularization also responds to focal scatter photocoagulation of the nearby ischemic retina.[52] Vitrectomy can remove vitreous hemorrhage,[45] vitreoretinal traction, and proliferative tissue.[46] The Diabetes Control and Complications Trial (DCCT) has shown that tight control of blood sugar in insulin-dependent diabetic patients prevents or delays background diabetic retinopathy.[42] The institution of tight control in patients with background retinopathy (secondary intervention) also diminishes the percentage of patients developing proliferative or severe nonproliferative retinopathy and the percentage of patients requiring laser treatment.[42]

6. Branch Retinal Vein Occlusion

Depending on the location and extent of retinal ischemia secondary to branch retinal vein occlusion, neovascularization can occur posteri-

orly or in the periphery.[157] Scatter photocoagulation in the region of retinal ischemia can prevent or treat neovascularization and subsequent vitreous hemorrhage.[14] Tractional retinal detachment and epiretinal membrane are well handled by vitrectomy.

7. Branch Retinal Arteriolar Occlusion

Branch retinal arteriolar occlusion has occasionally been implicated in peripheral retinal neovascularization. These few reports, however, have not proven this association. Krausher and Brown described patients with non-insulin-dependent diabetes mellitus and such occlusions, who developed peripheral neovascularization in the absence of observable diabetic retinopathy.[119] The diabetes, or ocular ischemia, may have been a contributing factor to arteriolar obstruction. Branch (and central) retinal arteriolar occlusion rarely leads to neovascularization, probably because the inner retina undergoes infarction, which does not stimulate neovascularization. Ischemic retina is alive and capable of releasing angiogenic substance. Infarcted tissue is dead and is not.

8. Retinal Embolization

Peripheral retinal neovascularization develops in some intravenous drug abusers who crush and intravenously inject pills containing talc as a filler.[20,120,179] Several possible mechanisms may contribute to the development of talc retinopathy. Particles capable of occluding retinal blood vessels, which have a minimum diameter of 5μ, may pass through the lungs, where capillaries may be 15μ. Alternatively, collaterals that have formed to bypass talc occlusions of lung vessels may allow passage of larger talc particles that can reach the retinal circulation. Following intravenous injection of embolic material, foci of nonperfusion may occur posteriorly or in the peripheral retina of people or experimental animals.[20,120,179] We were unable to induce disk, retinal, or iris neovascularization in monkeys despite chronic talc embolization.[112] Nevertheless, when there is sufficient occlusion of the retinal circulation by the talc particles, retinal neovascularization occurs.[120] Scatter photocoagulation and cryopexy have been described as effective means to treat this peripheral neovascularization.[93,203]

Other types of embolization may also cause peripheral neovascularization. A patient with rheumatic cardiac valvular disease has been described with retinal vascular embolization and neovascularization.[116] Some patients with mitral valve prolapse chronically release platelet-fibrin emboli to the eyes,[211] which leads to retinal vascular occlusion and ischemia.[23] To date, however, this has not been associated with peripheral neovascularization.

9. Retinopathy of Prematurity

The natural history of retinopathy of prematurity (ROP) and the response of neovascularization in ROP to cryopexy of the avascular peripheral retina have been extensively studied in the Cryo-ROP study.[159] The normal vascularization of the retina starts at about four months' gestation and is not complete until about the time of delivery. The amount of peripheral retina without circulation depends on the gestational age. More than 50% of the retina may be avascular in a viable premature birth. Our present understanding is that the normal vasculogenesis process in the retina can be arrested by high levels of oxygen or other imbalances that can occur ex utero.[66,118,161] A theory has been proposed that insufficient gap junctions between spindle cells in the retina are the cause of the neovascularization.[121] Possibly the delay in normal vasculogenesis allows pathologic neovascularization to develop in response to the ischemic peripheral retina. It is not clear whether the peripheral immature and nonperfused retina in eyes with ROP is truly ischemic as compared to normal eyes or premature eyes without ROP. The extraretinal neovascularization seen with ROP differs considerably in its appearance from the other entities described in this review. It may differ considerably in its pathogenesis. If normal vasculogenesis resumes, and the peripheral retina is vascularized before the neovascularization is extensive, the process of neovascularization stops and cicatricial effects may be minimized. On the other hand, if the proliferation progresses to tractional retinal detachment, the pace of proliferation tends to pick up, possibly because outer retinal ischemia in the detached retina adds to the inner retinal ischemia in the nonvascularized retina. The neovascularization of ROP is often bilateral, but may be asymmetric. Although models of retinopathy of prematurity have been developed in dogs, cats, and other animals, none really matches the natural history of the human disease.

When the neovascularization reaches a threshold level while much of the peripheral retina is still nonperfused, cryopexy or scatter laser treatment of the avascular retina improves the likelihood of a favorable outcome (attachment of the macular region) from 50% to 70% or greater.

Timing of the treatment may be important, especially when neovascularization is active while the majority of the retina is still not vascularized. If tractional retinal detachment is incipient or present under those circumstances, treatment may not stop the proliferation.

10. Familial Exudative Vitreoretinopathy

In familial exudative vitreoretinopathy (FEVR), peripheral neovascularization may occur in young children of normal birthweight. Unlike ROP, there is often a family history of the same eye problem. Many pedigrees of this condition have been described,[25,37] usually with an autosomal dominant pattern, but very variable expressivity. The appearance of the ocular fundus resembles ROP. Normal vasculogenesis stops before the retina is completely vascularized. Apparently, the avascular retina continues to signal for new blood vessels, but the vessels at the margin of the avascular zone, where vasculogenesis should occur, do not respond to the stimulus. Developed vessels that can respond, either posterior to the nonresponsive vascular margin or in a meridian with more complete vascularization of the peripheral retina, may develop neovascularization and stimulate cicatricial changes, such as straightened arcade vessels, foveal ectopia, meridional folds, tractional retinal detachment, or traction-induced rhegmatogenous retinal detachment. Cryopexy ablation of the stimulating avascular retina can arrest active proliferation.[87] Recent experience indicates that panperipheral photocoagulation in the avascular retina is also effective. Early identification of avascular retina in newborns at risk may allow adequate follow-up and, where appropriate, ablation therapy to prevent neovascularization and cicatrization.

11. Hyperviscosity Syndromes

Abnormal increases in the cellular elements or proteins in the blood may increase the viscosity of the blood. White cells or erythrocytes may increase viscosity. Polycythemia infrequently leads to neovascularization.[110] The pronounced leukocytosis seen in patients with chronic leukemias, especially chronic myelogenous leukemia, can affect both the central nervous system[167] and the eye.[108] In the peripheral retina, perivenous sheathing and microaneurysm formations are accompanied by peripheral stagnation of blood flow and capillary nonperfusion.[108] The retinal venules are dilated, unlike the thin venules seen in other patients with ischemic retina and peripheral neovascularization. The sea fan neovascularization develops at the interface of perfused and nonperfused retina.[68,145] These patients usually have extremely elevated white blood cell counts, well above 100,000 cells per cubic millimeter.

One case report described peripheral retinal neovascularization in a patient with chronic myelogenous leukemia and diabetes mellitus.[128] This patient never had a white cell count greater than 37,600 cells per cubic millimeter, but had markedly elevated platelet counts, between 281,000 and 988,000 per cubic millimeter. It was hypothesized that the extremely high platelet count caused sludging of blood, with regions of ischemia of the peripheral retina resulting in neovascularization.[128] The diabetes mellitus and the moderately elevated white count may have contributed to the conditions for neovascularization.

Patients with dysproteinemias may also show stagnation of retinal blood flow, microaneurysms, and capillary nonperfusion. It takes a much greater elevation of smaller proteins, such as IgG, to raise the viscosity of blood than does elevation of larger proteins, such as IgM. Though peripheral neovascularization in patients with dysproteinemia seems possible, it has not been reported to occur.

12. Aortic Arch Syndromes, Ocular Ischemic Syndromes

Patients with occlusion of large arteries supplying the cerebral and ocular circulations (e.g., carotid insufficiency, aortic arch syndromes), may show peripheral retinal and disk neovascularization in response to generalized ocular ischemia.[19,98,158] These new vessels are a response to inner and possibly outer retinal ischemia. Causes include arteritis (e.g., Takayasu's disease), syphilis, and atherosclerosis. Because of the reduced choroidal perfusion and generalized ocular ischemia, ablation therapy is less effective; nevertheless, scatter photocoagulation or cryopexy have been reported to be effective in some cases of ocular ischemic syndrome.[27,50,53,176]

13. Carotid-Cavernous Fistula

Ocular ischemia induced by arteriovenous shunting of blood intracranially or intraorbitally can result in peripheral retinal ischemia and neovascularization. One case report described the development of peripheral retinal and disk neovascularization in a patient who was treated for a carotid-cavernous fistula.[113] It was uncertain if the neovascularization was related to shunting of blood or ischemia induced by carotid

occlusion surgically created to treat the fistula. In another report, panretinal scatter photocoagulation caused a regression of the neovascularization in a patient with carotid-cavernous fistula.[96]

14. Multiple Sclerosis

Patients with multiple sclerosis may develop retinal vasculitis, manifested by peripheral retinal vascular sheathing, particularly venous sheathing.[7] Occasionally, inflammatory changes in retinal veins may occlude the vessel, causing retinal ischemia. Several patients have now been reported in whom periphlebitis has led to peripheral retinal neovascularization.[144,208] Theoretically, antiinflammatory treatment for the phlebitis might prevent the occlusion. Once ischemia has developed, regional ablation of the ischemic area would be the treatment of choice to prevent or control peripheral neovascularization.

15. Toxemia of Pregnancy

Toxemia of pregnancy has been reported in association with peripheral proliferative retinopathy.[13] Toxemia is associated with fibrin-platelet deposition in capillary beds throughout the body, and this activation of the coagulation system in small blood vessels could account for capillary occlusion, ischemia, and the subsequent development of proliferative retinopathy. Regression of the neovascularization with scatter photocoagulation has been reported.[13]

16. Encircling Buckling Operation

An encircling buckling operation for retinal detachment, particularly a buckle with a tight encircling structure or high indentation, distorts the posterior ciliary arteries coursing forward through the choroid and puts pressure on the vortex veins as they pass obliquely through the sclera. The vortex veins carry almost all the blood from the choroid, ciliary body, and iris. Reduced circulation in the posterior ciliary arteries and elevated pressure in the vortex veins can cause anterior segment ischemia and congestion, with corneal decompensation, anterior segment inflammation, hyphema, shallowing of the anterior chamber, iris atrophy, rubeosis iridis, cataract, and either hypotony or secondary glaucoma. Peripheral retinal neovascularization has been reported following encircling buckles.[29] Presumably there was compromise of the retinal or choroidal blood flow. Alternatively, the peripheral retinal neovascularization seen with encircling buckles may have been associated with chronic retinal ischemia from chronic retinal detachment. The peripheral neovascularization was successfully treated by cryotherapy.[29] The ischemia and congestion can be relieved by loosening or cutting the encircling structure.

B. INFLAMMATORY DISEASES WITH POSSIBLE ISCHEMIA

Many inflammatory diseases may be associated with retinal, disk, and iris neovascularization. Since vascular involvement by inflammation may cause ischemia, it is often difficult to sort out the role of inflammatory cells verses ischemia in the development of neovascularization. Similarly, there is very little written on the treatment of retinal neovascularization in these entities with anti-inflammatory therapy, such as corticosteroids. If inflammation is the main angiogenic stimulus, early treatment before the development of ischemia or neovascularization may be effective. Treatment at a later time may be ineffectual.

1. Sarcoidosis

The uveitis in patients with sarcoidosis may be accompanied by posterior segment involvement with retinal periphlebitis.[127] The stimulus for neovascularization may be retinal ischemia following inflammatory blockage of one or more veins, or may be factors released by inflammatory cells. Peripheral retinal and posterior pole neovascularization may occur. The development of peripheral retinal neovascularization has been reported with sarcoidosis,[2,3,49,88] in one patient with sarcoidosis and sickle cell anemia,[135] and in one patient with sarcoidosis and thalassemia.[171] Scatter laser photocoagulation has been used successfully to treat peripheral proliferative sarcoid retinopathy.[49,88]

2. Retinal Vasculitis

Patients with retinal vasculitis affecting either arterioles or venules may develop peripheral retinal neovascularization. The retinal vasculitis may be associated with systemic vasculitis or with uveitis. The neovascularization may be a result of inflammation, ischemia, or a combination of the two. We have described retinal arteriolitis causing branch retinal arteriole occlusion with capillary nonperfusion and peripheral neovascularization.[109]

Systemic lupus erythermatosus (SLE) can cause thrombosis of capillaries and small-to-medium size arteries and veins, leading to proliferative retinopathy.[102,115,207] In patients with SLE, this thrombosis may be secondary to active vas-

culitis or to a nonvasculitic occlusion related to lupus anticoagulant or anticardiolipin antibody.[92] Proliferative lupus retinopathy may progress despite normal antinuclear antibody (ANA) titers and serum complement levels. There does not have to be serologic evidence of active SLE for neovascularization to develop, especially if retinal ischemia already is present. Regression of the neovascularization following panretinal scatter photocoagulation has been described.[102,207]

Patients with mild or presumptive SLE and autoantibodies to Sjogren's syndrome A-antigen (SS-A antigen) have been reported to develop peripheral retinal neovascularization.[57] It is interesting that SS-A antibodies are found in a high percentage of ANA-negative SLE patients and that these patients have a distinctive clinical appearance.[169] It appears that retinal vasculitis is seen more often in lupus-like illnesses if SS-A autoantibodies are present.[57]

Recently, a condition called acute multifocal hemorrhagic retinal vasculitis has been described, characterized by vision loss, retinal hemorrhage, posterior retinal infiltrates, vitritis and papillitis in otherwise healthy patients.[12] Retinal neovascularization occurs in these patients, presumably due to vasculitis and retinal inflammation or nonperfusion. Panretinal scatter photocoagulation has been shown to cause regression of this neovascularization.[12]

Patients with acute retinal necrosis (see below), retinal vasculitis accompanying posterior ocular infection, (e.g., viral infection) or infestation (e.g., toxoplasmosis) may show vascular occlusion, ischemia, and retinal neovascularization.

3. Uveitis

Patients with peripheral uveitis (pars planitis) and other forms of chronic uveitis may develop neovascularization of the disk.[189] In some patients, a fibrovascular membrane develops over the ora serrata, pars plana, and inferior retina, especially inferiorly.[18] Peripheral scatter treatment has been used to control the proliferation.[58]

4. Birdshot Retinopathy

Birdshot retinochoroidopathy is characterized by white patches at the level of the outer retina or retinal pigment epithelium, vitritis, and macular edema. Retinal neovascularization has been found adjacent to peripheral retinal nonperfusion.[8,168] Scatter photocoagulation in the region of retinal neovascularization and retinal nonperfusion has caused regression of the neovascularization.[8]

5. Toxoplasmosis

Foci of retinitis can result in obstruction of arteries and veins coursing through or near the retinitis. When toxoplasmosis causes interruption of the retinal vasculature, peripheral retinal neovascularization can occur.[73] Angiogenic factors released by inflammatory cells or ischemia may produce the neovascularization.

6. Acute Retinal Necrosis

Acute retinal necrosis syndrome (ARN) is characterized by an acute anterior uveitis, vitritis, necrotizing retinitis, and retinal vasculitis. Herpes simplex and herpes zoster have been associated with ARN. Previously infected retina can be reduced to a network of remnant blood vessels and a thin glial membrane that loses its adhesion to the choroid, resulting in retinal detachment. Patients with ARN may develop retinal neovascularization,[97,212] probably from angiogenic factors released by inflammatory cells or retinal ischemia. If there is retinal detachment, outer retinal ischemia may contribute to the stimulus for neovascularization. Wang et al described resolution of retinal neovascularization after vitrectomy.[212] The mechanism for this resolution could be removal of inflammatory cells, removal of extracellular matrix that holds an angiogenic factor close to the retina, or elimination of the supporting framework for the neovascularization.

C. MISCELLANEOUS CAUSES OF PERIPHERAL NEOVASCULARIZATION

1. Incontinentia Pigmenti

This rare disease has an x-linked dominant inheritance pattern. It is usually lethal in utero in males, where the affected gene is unaccompanied by a normal gene; hence, its occurrence almost exclusively in females. It is characterized by cutaneous, ocular, and dental abnormalities.[213] Extensive areas of the retinal periphery lose circulation. The pathogenesis of the loss of circulation is unknown. Peripheral neovascularization (Fig. 1, right) may lead to vitreous hemorrhage and retinal detachment. Cryotherapy effectively prevents or causes regression of the neovascularization.[152,170]

2. Telangiectasia, Spondyloepiphyseal Dysplasia

A syndrome has been described in two sisters who showed telangiectasia involving the face and

limbs, dwarfism from spondyloepiphyseal dysplasia, and hypothyroidism. Ocular manifestations include neovascularization from the retina, tractional retinal detachment, and iris neovascularization.[124]

Parafoveal retinal telangiectasis has also been reported in association with anterior retinal ischemia and iris and posterior segment neovascularization.[129a]

3. Inherited Retinal Venous Beading

Inherited "retinal venous beading" appears to be a distinct autosomal dominant disorder characterized by beading of the retinal veins.[139] Patients may also have retinal microaneurysms, retinal hemorrhages, exudates, neovascularization, and vitreous hemorrhage.[139,193] The cause of the venous beading is unknown, but it has been postulated that the neovascularization may be associated with retinal nonperfusion. The venous beading could be an exaggerated response of the vein to chronic angiogenic stimulation. This neovascularization may regress with panretinal scatter laser photocoagulation.[193]

4. Autosomal Dominant Vitreoretinochoroidopathy

In 1982, Kaufman et al described autosomal dominant vitreoretinochoroidopathy, a retinal dystrophy with abnormal peripheral chorioretinal pigmentation with a sharp posterior border near the equator.[114] Affected patients may also have leakage of the retinal vasculature, macular edema, punctate whitish retinal opacities, presenile cataracts, fibrillar condensation of the vitreous, narrowing and closure of the retinal arterioles, and retinal neovascularization.[11,114] Blair et al reported that hemorrhage from retinal neovascularization may contribute to visual loss.[11] Electroretinography is normal. Abnormal vitreous fluorophotometry confirms vascular leakage.

5. Longstanding Retinal Detachment

Retinal detachment of long duration may lead to the development of peripheral retinal neovascularization.[59,202] The neovascularization may be a response to the outer retinal ischemia due to separation of the outer retina from its nutritional supply in the choroid. It also may be due to inner retinal ischemia secondary to a disruption of the retinal circulation in the detached retina. Successful repair of rhegmatogenous retinal detachment usually leads to regression of the neovascularization, probably from reduction in retinal ischemia.[59] Cryotherapy, which may allow proteins holding subretinal fluid in exudative retinal detachment to escape to the choriocapillaris, can reduce associated neovascularization.[1]

6. Choroidal Melanoma and Hemangioma

Both disk and midperipheral retinal neovascularization have been described in a patient with choroidal melanoma.[206] This patient had an exudative retinal detachment in the area of neovascularization. Possible stimuli for neovascularization include a tumor angiogenic factor, outer retinal ischemia in the detached retina, and growth factors from inflammatory cells. We have seen a similar case where the neovascularization regressed following treatment of the melanoma by radioactive iodine plaque, possibly by reducing tumor angiogenesis or eliminating the retinal detachment. We have also seen a case of retinal neovascularization in an area of exudative retinal detachment over a choroidal hemangioma, and this has recently been described in the literature.[129]

7. Retinitis Pigmentosa

Patients with retinitis pigmentosa can develop disk or midperipheral neovascularization.[17,150,204] It has been postulated that the patients have developed this neovascularization as a consequence of peripheral retinal ischemia. A proposed sequence of events is that loss of photoreceptors leads to retinal thinning, increased oxygen tension, vasoconstriction, and neovascularization.[204] An alternative explanation is that the angiogenesis is mediated by inflammatory cells, which are seen in eyes with retinitis pigmentosa. The neovascularization has been successfully treated by cryopexy.[204] Depigmentation and death of the pigment epithelium can interfere with the production of photocoagulation lesions.

8. Retinoschisis

Neovascularization has been found with both x-linked (juvenile) retinoschisis and degenerative retinoschisis.[24,163] Degenerative retinoschisis may be accompanied by retinal vascular sheathing and vascular occlusion.[24] Similarly, in juvenile retinoschisis[89] and Goldmann-Favre retinoschisis,[60] white deposits in the walls of peripheral retinal blood vessels in a network or white bone spicule pattern (arborization) may occlude part of the peripheral retinal circulation. This ischemia may be the stimulus for neovascularization.

9. Cocaine Abuse

We have seen peripheral retinal neovascularization in a young woman who used nasal cocaine chronically. There were no other risk factors for retinal neovascularization. The basis of the neovascularization may be ischemia from repeated episodes of hypertension and retinal vasoconstriction. Scatter photocoagulation in the vicinity of the neovascularization produced partial regression of the neovascularization.

IV. Diagnostic Evaluation of Patients with Peripheral Retinal Neovascularization

Evaluation of a patient with peripheral retinal neovascularization should include ocular and systemic examinations seeking evidence of the entities described in this review (Table 1). Since peripheral retinal neovascularization is frequently found as a manifestation of systemic disease, an examination by an internist is often indicated. Depending on the clinical eye findings, and the systemic history and physical examination, one or more of the following tests may be useful to identify the etiology:

1) Hemoglobin electrophoresis to detect sickling hemoglobinopathies;

2) Complete blood count to detect polycythemia or leukemia;

3) Chest x-ray, serum lysozyme,[160] serum angiotensin converting enzyme,[196] and gadolinium scanning for sarcoidosis;

4) Serum protein electrophoresis to detect dysproteinemia;

5) Glucose tolerance test and hemoglobin A1C to detect diabetes mellitus;

6) Physical examination for cardiovascular disease, especially requesting evaluation for cardiac valvular disease, carotid artery disease, aortic arch syndromes, or carotid-cavernous fistula;

7) Sedimentation rate, and complement determination (C3) to detect vasculitis; antinuclear antibody; PTT and VDRL to screen for anticardiolipin antibodies, measurement of anticardiolipin antibodies; SS-A autoantibody for atypical lupus;

8) Family history of hereditary conditions such as familial exudative vitreoretinopathy and examination and counseling by physicians knowledgeable about genetic diseases;

9) Blood pressure and urine protein level in pregnancy to detect preeclampsia;

10) Other systemic examination and tests if other entities noted in Table 1 are suspected.

V. Treatment of Peripheral Retinal Neovascularization

Treatment can be aimed at prevention of the proliferative phase, inhibition of angiogenesis, induction of regression of neovascularization, elimination of the tissue framework (scaffolding) for neovascularization, removal of opacities such as hemorrhages or membranes, reduction of traction on the retina, or repair of a detached retina. Presently, we are learning about the pathways and mechanisms of the neovascular process. Since the process is complex, there may be several points where intervention can impede or arrest the course of events.

A. PREVENTION AND TREATMENT OF THE UNDERLYING CAUSE

Awareness of the factors in a disease that lead to neovascularization allows us to manage those factors. For example, tight control of blood sugar to produce a near-normal hemoglobin A1C in diabetes may delay or prevent occlusive diabetic vasculopathy that leads to many of the complications of diabetes, including proliferative diabetic retinopathy.[42] For prevention, the concept is often to try to diminish inflammation or prevent ischemia. However, once the retina is ischemic, control of the underlying disease may not reduce the stimulus for neovascularization. Though inflammatory cells are part of angiogenesis, it is difficult to predict the effect of anti-inflammatory therapy in preventing neovascularization. It appears that corticosteroid therapy of active periphlebitis from sarcoid may halt progression of the venous occlusion that precedes proliferative sarcoid retinopathy. Much more research is needed in this area. Removing or inactivating a tumor prevents or treats tumor-induced angiogenesis.

B. GROWTH FACTORS

Growth factors initiate and maintain neovascularization. It seems likely that normal mature blood vessels usually remain unchanged without angiogenic factors. (The alternative to this, that blood vessel homeostasis at all times requires a balance of angiogenic and inhibitory factors seems very unwieldy.) New blood vessels, however, often regress when the angiogenic stimulus is removed. Inhibition of angiogenesis can be accomplished by interfering with the production or action of growth factors. Theoretically heparin and corticosteroids could prevent vascular

proliferation or cause its regression by reducing unbound bFGF available for the endothelial cell receptors. One hypothesis for the effect of photocoagulation is that injury to the retinal pigment epithelium allows active growth factors to pass from the retina and vitreous through the regenerated retinal pigment epithelium to be carried away by the choroidal circulation, thus making it unavailable to the endothelial cells of the retinal vessels.

C. INHIBITORY FACTORS

Substances have been identified that inhibit some aspect of the neovascular process, but most have not been tested as clinical antiangiogenic treatments. TGF-β inhibits endothelial cell proliferation in vitro[69] and possibly in vivo.[99] TNF has several antiproliferative activities. It inhibits bFGF stimulated endothelial proliferation.[186] It may be toxic to stimulated endothelial cells, and blocks the migration of endothelial cells in response to a stimulus.[137] Retinal pigment epithelial cells can release an antiangiogenic factor, and it has been proposed that cryopexy or photocoagulation stimulates the release of this substance.[77] Some tissues naturally are not vascularized. Extracts of cartilage and vitreous inhibit neovascularization.[15,16] By an unknown mechanism, the interferons inhibit tumor and immunologically induced angiogenesis, probably independent of their antiproliferative effects.[190] Interferon is particularly effective in the treatment of vascular tumors, such as Kaposi's sarcoma and congenital hemangiomas. It seems unlikely that interferon alpha 2a is clinically effective in attenuating choroidal neovascularization, as reported by Fung,[71] since several groups have been unable to show a beneficial effect.[164a,199a] Through its cytotoxic effects and reduction of inflammatory cells, 5FU inhibits vascular and fibrous proliferation. Devices are being developed for the slow intraocular release of drugs such as 5FU.[178]

D. VITRECTOMY

Whereas the vitreous itself may inhibit the growth of blood vessels into the vitreous body, neovascularization can grow along the posterior vitreous face. Fibrosis that follows the neovascularization along the posterior vitreous face contracts, producing anteroposterior or tangential traction that may lead to tractional or rhegmatogenous retinal detachment. The indications for vitrectomy include the need for removal of vitreous hemorrhage or epiretinal membranes and reattachment of tractional or secondary rhegmatogenous retinal detachment. Vitrectomy removes the matrix necessary to support new blood vessel growth. After the vitreous is removed, new blood vessel growth stops or is greatly attenuated along the retinal surface. In addition to removing the matrix necessary for blood vessel growth, vitrectomy may also remove the matrix that holds the responsible growth factor in proximity to the retina.

E. PHOTOCOAGULATION AND CRYOPEXY

Photocoagulation can be applied directly to the feeding and draining vessels for direct closure of the neovascular circulation,[30,103,104,109,215] or it can be placed in a pattern in the nearby retina or over the entire retinal periphery for indirect regression of the neovascularization.[8,12,14,27,40,43,44,49,50,52,53,58,88,93,96,102,117,136,138,139,172,192,193,207] The wavelength is probably of minimal importance. The blue component of the blue-green laser may be toxic to the patients' or physicians' eyes and should be eliminated. The green laser produces lesions centered at the level of the pigment epithelium. Yellow laser at 576 nm is maximally absorbed by hemoglobin, a useful property for direct treatment of blood vessels. Red and infrared laser is absorbed partially by the pigment epithelium and partly by the pigment in the choroid. Consequently, to produce retinal coagulation, a larger amount of choroidal damage occurs. Since there is less absorption of red or infrared laser by hemoglobin or a yellow lens nucleus, mild vitreous hemorrhage or nuclear cataract is penetrated better with these wavelengths, and there is less heating of the red cell hazed vitreous.

Peripheral neovascularization is not well treated by focusing the laser energy on the elevated neovascular tips. The optimum spot size for scatter treatment or direct application to the feeding or draining vessels is 500μ.[80] An exposure time over 0.5 seconds creates a larger volume of treatment than a duration of 0.1 seconds. The white color in a fresh laser burn comes from denatured albumin in the retina. Since the lesion is centered in the choroid, red or infrared laser burns can exceed the vapor point in the choroid if an intense white lesion is attempted. Red or infrared lasers should be applied for a minimum duration of 0.3 to 0.5 seconds to reduce the risk of a vapor bubble.

Feeder vessel treatment to feeding arterioles and draining venules has been used to treat peripheral proliferative retinopathies, especially

sickle cell disease. Attempts are made to treat intensely on the arteriole until segmentation of the blood column occurs. The veins are then treated. The safest method of occluding feeding and draining vessels is to make mild to moderate lesions for several (500μ) lesion widths along the treated vessels, wait two weeks for hyperpigmentation of the RPE and thinning of the retina, and retreat over the previous treatment with 0.2 to 0.5 second spots of sufficient power to occlude the vessels.[83] Use of feeder vessel photocoagulation for proliferative sickle cell retinopathy with either laser or xenon arc was effective in preventing vitreous hemorrhage and vision loss from vitreous hemorrhage, and reduced vision loss from all causes.[30,103,104] Overly aggressive attempts to occlude feeding and draining blood vessels in the retina, especially with 100 or 200μ spots, can result in vapor bubble formation, bleeding from fractured choroidal capillaries, breaks in Bruch's membrane, and subsequent chorioretinal or choriovitreal neovascularization.[26,30,47,80,83,103,104] Feeder vessel technique has also been used to treat Eales' disease[215] and occasionally other causes of neovascularization.[109]

Scatter photocoagulation for peripheral neovascularization is generally applied with a mild-moderate intensity burn with a density of half to one lesion width separation to the ischemic retinal periphery (panperipheral photocoagulation). Small neovascular structures tend to regress with scatter photocoagulation of the ischemic retina or retinal periphery in the vicinity of the neovascularization (local scatter). This treatment did not produce serious side effects in patients with PSR.[56] However, careful, sensitive testing of retinal function, such as color vision testing, visual field measurements, and contrast sensitivity, were not performed in these patients. The apparent safety of this method recommends it as the initial type of photocoagulation.[105] Local scatter treatment has been effective in the treatment of sickle cell disease.[56,93,172] Studies in the sickle cell population showed that this technique reduces the incidence of vitreous hemorrhage and vision loss in patients with PSR. Local scatter photocoagulation has also been used in patients with branch retinal vein occlusion,[14] Eales' disease,[136,192] and retinopathy of prematurity.[123,138] For the last disease, local scatter photocoagulation compared to cryotherapy may lessen the amount of conjunctival scarring, scleral injury, and choroidal injury. Local scatter photocoagulation has also been shown to be useful in patients with neovascularization from sarcoidosis,[49,88] lupus erythematosus, pars planitis,[58] talc retinopathy,[93] and birdshot retinochoroidopathy.[8]

Panretinal scatter photocoagulation is firmly established as the treatment of choice for most cases of proliferative diabetic retinopathy.[43,44] Although panretinal photocoagulation can be associated with peripheral field loss, and some color vision and central visual loss, severe complications are rare. Other entities that have been treated with panretinal photocoagulation include lupus erythematosus,[207] proliferative talc retinopathy,[93,203] aortic arch syndrome,[27,50,53] carotid-cavernous fistula,[96] acute multifocal hemorrhagic vasculitis,[12] inherited retinal venous beading,[139,193] and sarcoidosis.[49]

Several hypotheses may explain the attenuation of the neovascularization from scatter photocoagulation. The laser scars may offer egress for growth factors from the retina and vitreous to the choroidal circulation (the hypothesis favored by one of the authors [MG]). Scatter photocoagulation destroys some of the ischemic retina. Necrosis of the outer retina brings the ischemic inner retina closer to the high oxygen level of the choriocapillaris. Death of photoreceptor cells, the major consumers of oxygen, allows more oxygen to reach the inner retina. The injured pigment epithelium may release an angioinhibitory factor. Whatever the reason, the method is effective.

In general, photocoagulation is preferred to cryopexy for the treatment of peripheral neovascularization. Cryopexy used to offer an advantage in treating the peripheral retina, but the indirect ophthalmoscope delivery system for lasers eliminates that advantage. The ease of this new laser delivery is making panperipheral photocoagulation the preferred method for scatter treatment of the avascular or far peripheral retina in ROP and other entities like PSR.

When media haze interferes with creation of laser lesions, cryopexy is an alternative.[39,81,87,93,126,152,153,159,170,176,204] It can be placed in a fashion similar to scatter photocoagulation for indirect attenuation of neovascularization. This technique has been used in patients with retinopathy of prematurity,[39,159] incontinentia pigmenti,[170] retinitis pigmentosa,[204] sickle cell disease,[93,126] familial exudative vitreoretinopathy,[87] longstanding retinal detachment, and ocular ischemic syndrome.[176]

Peripheral neovascularization can also be directly treated with an ice ball that is allowed to grow to envelop the neovascular structure as a single freeze-thaw application.[126] Multiple freeze-

thaw applications of cryopexy to the same spot causes more retinal necrosis than single applications.[81] If retinal traction exists, the necrotic retina can tear.

VI. Conclusions

A wide variety of diseases can cause peripheral retinal neovascularization. The process leading to retinovitreal neovascularization is complex. Underlying the list of diseases associated with retinal neovascularization are the common themes of inflammation, ischemia, and tumor angiogenesis, with the possibility that ischemia and tumor angiogenesis are partly mediated through inflammation. We have reviewed the process of angiogenesis in the eye and the clinical entities that are associated with peripheral retinal neovascularization. Knowledge of this list of diseases that can cause peripheral neovascularization aids in the clinical evaluation. We have combined these concepts to provide a broad picture of retinal neovascularization. We also have reviewed briefly methods of treatment. Understanding how intervention affects the angiogenic process allows us to make a rational plan for treatment.

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Outline

I. Definition
II. Angiogenesis
  A. Mechanisms of angiogenesis
  B. Angiogenic factors
    1. Factors that act directly on endothelial cells
    2. Factors that act indirectly on endothelial cells
    3. Tumor angiogenesis factors
    4. Factors that regulate angiogenesis
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    2. Other hemoglobinopathies
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    12. Aortic arch syndromes/ocular ischemic syndrome
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    15. Toxemia of pregnancy
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    1. Sarcoidosis
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V. Treatment of peripheral retinal neovascularization
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