Consensus Nomenclature for Reporting Neovascular Age-Related Macular Degeneration Data

AMERICAN ACADEMY OF OPHTHALMOLOGY®

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Consensus on Neovascular Age-Related Macular Degeneration Nomenclature Study Group

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Purpose: To establish a process to evaluate and standardize a state-of-the-art nomenclature for reporting neovascular age-related macular degeneration (AMD) data.

Design: Consensus meeting.

Participants: An international panel of retina specialists, imaging and image reading center experts, and ocular pathologists.

Methods: During several meetings organized under the auspices of the Macula Society, an international study group discussed and codified a set nomenclature framework for classifying the subtypes of neovascular AMD and associated lesion components.

Main Outcome Measures: A consensus classification of neovascular AMD.

Results: The study group created a standardized working definition of AMD. The components of neovascular AMD were defined and subclassified. Disease consequences of macular neovascularization were delineated.

Conclusions: The framework of a consensus nomenclature system, a definition of AMD, and a delineation of the subtypes of neovascular AMD were developed. Establishing a uniform set of definitions will facilitate comparison of diverse patient groups and different studies. The framework presented is modified and updated readily, processes that are anticipated to occur on a periodic basis. The study group suggests that the consensus standards outlined in this article be used in future reported studies of neovascular AMD and clinical practice. *Ophthalmology 2020;127:616-636 © 2019 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

Age-related macular degeneration (AMD) is a disease complex that is associated with a high risk of blinding complications. The manifestations are variable, and many have been discovered only recently. In 1967, Gass[1] provided the first description of many of the pathophysiologic features of neovascular AMD. A few years later, he showed a link between drusen and neovascular AMD.[2] In 1970, Gass,[3] in his first atlas, referred to geographic areas of atrophy, and in 1976, Blair[4] described geographic atrophy of the retinal pigment epithelium (RPE) that occurred in "senile macular degeneration," a former term for AMD. The diagnostic imaging tests at that time were limited to fundus photography and fluorescein angiography, which was a newly described method to evaluate macular disease. Over the 5 decades since Gass's 1967 article,[1] many studies have been performed based on imaging data from various imaging methods, new and old, and have yielded a wealth of information.

Each form of imaging is a source of data that may provide varying amounts of independent information about the structure or physiology of the macula in health and disease and that shapes the concurrent understanding of the underlying pathophysiologic characteristics. The terminology based on fluorescein angiography, used in most of the literature, does not

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Table 1. List of Terms and Definitions

Term	Definition
Age-related macular degeneration	A condition in patients, typically beyond 50 years of age, in which the structure and function of the macula deteriorates. A salient characteristic is the accumulation of extracellular deposits including subretinal drusenoid deposits, basal linear, and basal laminar deposit. These eyes may demonstrate neovascularization or atrophy.
Macular neovascularization	Denotes neovascular disease in the macula from many causes. In AMD, the neovascularization may start in the outer retina, and therefore, the term *choroidal neovascularization* is not appropriate for the class.
Type 1 MNV	Ingrowth of vessels initially from the choriocapillaris into and within the sub-RPE space. Leads to varying types of PEDs.
Polypoidal choroidal vasculopathy	A variant of type 1 MNV commonly seen in Asian persons. Indocyanine green angiography imaging shows a branching vascular network and aneurysmal dilations of varying number at the outer edge of the expanding lesion. The internal structure of the aneurysmal structures, often termed *polyps*, is controversial.
Type 2 MNV	Neovascularization that originates from the choroid that traverses Bruch's membrane and the RPE monolayer and then proliferates in the subretinal space.
Type 3 MNV	Neovascularization that originates from the retinal circulation, typically the deep capillary plexus, and grows toward the outer retina.
Retinal-choroidal anastomosis	Aberrant connection from the retinal to the choroidal circulation.
Leakage	Exudation of fluid and serum components from a lesion because of the breakdown of the blood–retinal barrier. Fluorescein angiography is a common way to detect leakage because in health, the blood–retinal barrier blocks the extravascular egress of fluorescein from vessels.
Intraretinal fluid	Leakage in excess of the local capability of removal leading to accumulation of the fluid in retinal thickening and formation of cystoid spaces. The fluid in the retina may come from retinal vessels or a subretinal source if the external limiting membrane is not intact.
Subretinal fluid	Leakage in excess of the local capability of removal leading to accumulation of the fluid under the retina. The fluid source generally is from underlying neovascularization in AMD in the context of an intact external limiting membrane.
Lipid (hard exudates)	Lipoprotein particles that precipitate in the retina related to chronic vascular leakage.
Subretinal hyperreflective material	Exudation into the subretinal space of material likely comprising serum, fibrin, and inflammatory cells.
Retinal pigment epithelial detachment	A clinically evident separation of the RPE monolayer from the underlying Bruch's membrane. This can occur from drusenoid material, serous fluid, neovascular infiltration, or blood. Collections of drusen material of more than 350 μm in diameter are called drusenoid PEDs. Serous PEDs are collections of fluid, but in AMD, serous PEDs typically are associated with neighboring MNV. Neovascular infiltration usually is associated with some element of fibrotic tissue and are called fibrovascular PEDs. Elevations with blood are called hemorrhagic PEDs.
Hemorrhage	Extravasation of blood from the neovascular complex located in the sub-RPE, subretinal, intraretinal, or occasionally, preretinal compartments.
Fibrosis	Buildup, in any layers of the retina, the subretinal space, the RPE monolayer, or the sub-RPE space, of tissue with significant collagen deposition.
Rip (or tear) of the retinal pigment epithelium	Disruption with scrolling and contracture of the RPE monolayer, usually occurring in association with a fibrovascular PED, but on rare occasions with a serous PED. For fibrovascular PEDs, the sub-RPE proliferation is thought to contract because of the angiofibrotic switch, and the tensile force created leads to the rip.
Outer retinal atrophy	Loss of the ellipsoid and interdigitation zones usually with corresponding loss of thickness of the outer nuclear layer. Outer retinal atrophy most commonly occurs after prolonged subretinal fluid accumulation, regression of field of subretinal drusenoid deposit, or over large collections of drusen material.
Retinal pigment epithelial and outer retinal atrophy	Atrophy refers to absence of a clinically normal RPE monolayer, usually by cell death. Therefore, it is not really atrophy, which implies a withering, but rather persistence of cells. In OCT imaging, RPE atrophy is characterized by a loss of the RPE band with associated choroidal hypertransmission. The loss of RPE cells usually is accompanied by concomitant loss of the outer retina. This combination forms RPE and outer retinal atrophy. If the zone of abnormalities is more than 250 μm in diameter, then the condition is termed complete RPE and outer retinal atrophy. If the zone of abnormalities is less than 250 μm, or if the hypertransmisssion is fragmentary, the eye is said to have incomplete RPE and outer retinal atrophy.

AMD = age-related macular degeneration; MNV = macular neovascularization; PED = pigment epithelial detachment; RPE = retinal pigment epithelium.

Table 2. New versus Old Terminology Correlates

Old Term	Multimodal Imaging Correlate	Old Term	Color Fundus and Fluorescein Imaging Findings
Type 1 MNV	Type 1 MNV represents areas of neovascular complexes arising from the choroid and imaged with OCT as an elevation of the RPE by material with heterogeneous reflectivity; vascular elements may be seen. OCT angiography shows vessels below the level of the RPE.	Occult CNV	Stippled hyperfluorescence over an area of elevated RPE, which expands to coalesce in the later phases of the angiography.
Polypoidal choroidal vasculopathy	OCT findings similar to type 1 MNV; however, in some patients, dilated vascular elements at the outer border of the lesion are apparent. Stippled hyperfluorescence over an area of elevated RPE, which expands to coalesce in the later phases of the angiography. The pattern of the RPE elevation may suggest nodules. Indocyanine green angiography shows a branching vascular network with aneurysmal dilations.	Polypoidal choroidal vasculopathy	Stippled hyperfluorescence over an area of elevated RPE that expands to coalesce in the later phases of the angiography. The pattern of the RPE elevation may suggest nodules. Indocyanine green angiography shows a branching vascular network with aneurysmal dilations.
Type 2 MNV	Neovascular complex located in the subretinal space, above the level of the RPE. May be associated with subretinal hyperreflective material and separation of the neurosensory retina from the RPE. OCT angiography demonstrates vascular elements above the level of the RPE.	Classic CNV	Early hyperfluorescence and late leakage that pools in the subretinal space. Neovascular elements may be detected in the very early phase of the angiogram.
Mixed type 1 and type 2 MNV	OCT findings of both type 1 and type 2 MNV together. OCT angiography demonstrates neovascularization in the sub-retinal pigment epithelial and subretinal compartments.	Minimally classic CNV	Early hyperfluorescence with late leakage and a larger surround of stippled hyperfluorescence that also shows leakage late in the fluorescein angiogram. Difficult to differentiate from type 3 neovascularization.
Type 3 MNV	Extension of hyperreflectivity from the middle retina toward to level of the RPE associated with intraretinal edema, hemorrhage, and telangiectasis. OCT angiography shows the downgrowth of new vessels toward or even penetrating the level of the RPE.	Retinal angiomatous proliferation	Focal hyperfluorescence associated with intraretinal staining. Often shows fluorescence from deeper layers suggestive of occult CNV. The neovascularization is not necessarily CNV.
Retinal-choroidal anastomosis	Aberrant connection from the retinal to the choroidal circulation. Course of vessel can be seen occasionally with OCT or OCT angiography. Although visible on fluorescein angiography, indocyanine green angiography often is better at demonstrating the anastomosis.	Retinal-choroidal anastomosis	Aberrant connection from the retinal to the choroidal circulation. Although visible on fluorescein angiography, indocyanine green angiography often is better at demonstrating the anastomosis.
Leakage	Breakdown of the blood—retinal barrier, typically demonstrated by fluorescein angiography.	Leakage	Breakdown of the blood— retinal barrier, typically demonstrated by fluorescein angiography.
Intraretinal fluid	Cystoid spaces in the retina typically associated with increased retinal thickening. Readily detected using OCT.	Cystoid edema	Thickening of the retina that may be difficult to detect and cystoid spaces that also may be difficult to detect by color photography. Fluorescein angiography shows pooling of dye in some of the cystoid spaces.
Subretinal fluid	Separation of the neurosensory retina from the RPE by fluid. Readily detected using OCT.	Subretinal fluid	Exaggerated accumulations in the macula may be detected with stereo color photography and also may be suggested by a loss of transparency of the detached retina.
Lipid (hard exudates)	Yellow-white globular material in or under the retina. OCT shows hyperreflective foci in the retina, some of which are not visible by ophthalmoscopy.	Lipid (hard exudates)	Yellow-white globular material in or under the retina.
Subretinal hyperreflective material	Exudation in the subretinal space of material that is hyperreflective as compared with fluid.	Not named before OCT era	In extreme cases, material is seen on color photography that is difficult to differentiate from fibrosis.

Table 2. (Continued.)

Old Term	Multimodal Imaging Correlate	Old Term	Color Fundus and Fluorescein Imaging Findings
Retinal PED	Several forms of elevation of the RPE monolayer from the underlying Bruch's membrane. This includes drusenoid, serous, and fibrovascular. Some forms of early type 1 neovascularization produce a relatively flat elevation. Many cases of serous PED show evidence of MNV. OCT angiography is particularly useful in detecting the presence of neovascularization.	Retinal PED	Several forms of elevation of the RPE monolayer from the underlying Bruch's membrane. These include drusenoid, serous, and fibrovascular. Accurately delineating serous and fibrovascular PEDs can be difficult. Early type 1 MNV with RPE elevation may not be detectable.
Hemorrhage	Blood in the retina, subretinal, or sub-RPE compartments. Exact location of blood apparent in OCT examination.	Hemorrhage	Blood in the retina, subretinal, or sub-RPE compartments. Location of blood can be inferred.
Fibrosis	White or yellow-white accumulation of material, usually in the subretinal or sub-RPE space. on OCT, the material is hyperreflective and may have a multilaminar appearance.	Fibrosis	White or yellow-white accumulation of material, usually in the subretinal or sub-RPE space.
Rip (or tear) of the RPE	Area of increased pigmentation from the scrolled RPE adjacent to a zone of decreased pigmentation. During fluorescein angiography, the increased pigmentation blocks the underlying fluorescence, whereas the area denuded of RPE is hyperfluorescent. OCT shows the anatomic configuration of the scrolled RPE and hypertransmission in the denuded zone.	Rip (or tear) of the RPE	Area of increased pigmentation from the scrolled RPE adjacent to a zone of decreased pigmentation. During fluorescein angiography, the increased pigmentation blocks the underlying fluorescence, whereas the area denuded of RPE is hyperfluorescent.
Outer retinal atrophy	On OCT imaging, loss of the ellipsoid and interdigitation zones associated with thinning of the outer nuclear layer.	Not named before OCT era	No color photograph or fluorescein angiography correlate.
RPE and outer retinal atrophy	OCT features of outer retinal atrophy and signs of RPE loss to include decrease or absence of the RPE monolayer and hypertransmission into the underlying neovascular lesion and choroid.	Roughly correlates to geographic atrophy	The color photographic definition of geographic atrophy includes a round or oval well-defined area in which the underlying choroidal vessels are seen more easily. In neovascular cases, there is no reason the RPE loss must be round or oval and well defined. The presence of underlying neovascular lesion may block visualization of the choroidal vessels in any case.

CNV = choroidal neovascularization; MNV = macular neovascularization; PED = pigment epithelial detachment; RPE = retinal pigment epithelium.

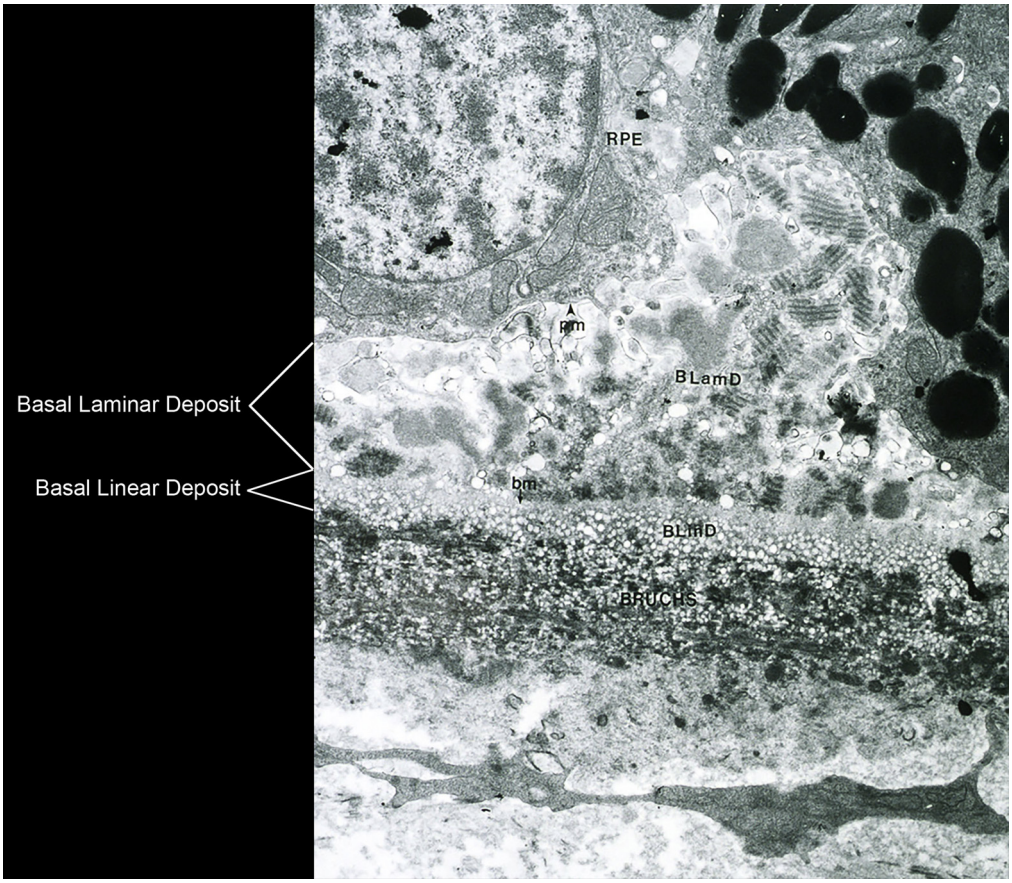

Figure 1. Electron microscopic image showing the retinal pigment epithelium (RPE) and Bruch's membrane (BRUCHS). The basal laminar deposit (BLamD) is located between the plasma membrane (pm) of the RPE and the basement membrane (bm). Between the basal lamina and the trilaminar Bruch's membrane is a collection of basal linear deposit (×1500).

apply to many aspects of the new data obtained by state-of-the-art imaging. Although using multiple imaging methods contributes different viewpoints on macular pathologic features,[5] this expanded capability can give rise to a fractured conceptualization of disease with the potential for varied terminology. Developing a standardized nomenclature system would improve clarity and accuracy of communication and enhance comparability of research results from different centers using diverse imaging methods. To develop a better nomenclature to describe disease, it is necessary to improve the clarity of concepts involved and evaluate these concepts regarding multimodal imaging and known histopathologic characteristics.

Nomenclature systems have been developed by hundreds of organizations and ad hoc working groups to describe disease and treatment, including standardized nomenclature of medicine for clinical terms,[6] bone density,[7] bipolar disorders,[8] radiation therapy,[9] nursing diagnoses,[10] and medical documentation.[11] In ophthalmology efforts have been undertaken to standardize the nomenclature of trauma,[12,13] uveitis,[14] and anatomic labeling of OCT.[15]

Age-related macular degeneration is a leading cause of irreversible visual impairment despite landmark advances, such as the injection of anti−vascular endothelial growth factor (VEGF) agents for macular neovascularization (MNV), a term recognizing that neovascularization does not necessarily originate from the choroid.[16–19] As the population continues to age, the incident cases of neovascular AMD are projected to rise. As in other fields, AMD could benefit from standardization of nomenclature that integrates concepts informed by recent advances in imaging technology. Given the rapid rate of change in AMD knowledge, any nomenclature system is likely to be a work in need of periodic revision. To work toward a consensus, a series of group meetings of experts were held under the auspices of the Macula Society. The participants were an international group of retinal specialists, imaging experts, and ocular pathologists.

Methods

Formation of the Classification of Macular Neovascularization Group

An international team of experts in AMD and AMD imaging research was assembled to address the definitions and classification of atrophy in the setting of AMD. The Classification of Atrophy Meetings group was selected by 3 chairs (S.R.S., G.S., and F.G.H.) using criteria that included a history of relevant publications, recent AMD and imaging research contributions, a track record of success in previous collaborative, consensus efforts, and availability to attend

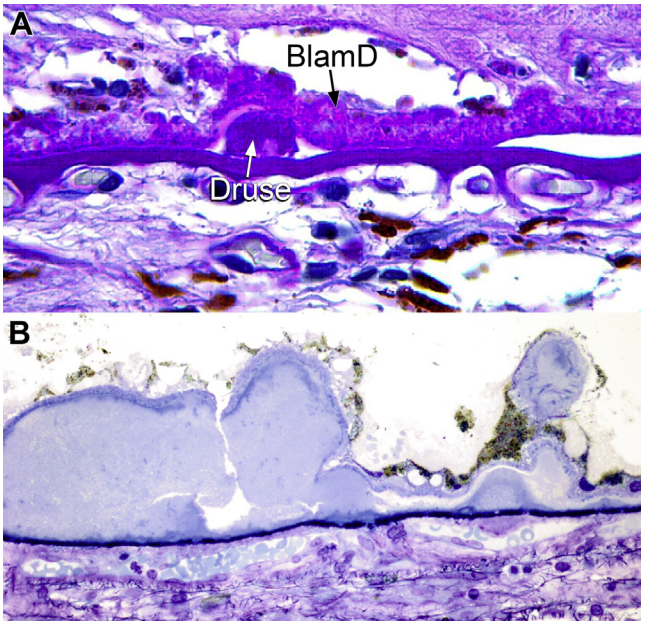

Figure 2. Light microscopy images showing drusen. **A**, A solitary druse and thick layer of basal laminar deposit (BLamD). Although drusenoid deposits are visible by ophthalmoscopy, BLamD is not typically recognized in the clinic. **B**, Confluent soft drusen, which are accumulations of BLamD, are clinically evident (toluidine blue, ×100).

the meetings.[20–22] An extension of this meeting addressing MNV was organized with the addition of 1 additional chair (R.F.S.) in conjunction with the Macula Society and the Federation France Macula. The study group, referred to as the Consensus on Neovascular AMD Nomenclature (CONAN) group, comprised an international panel of retina experts with an extensive publication history in neovascular AMD, representatives of retinal reading centers that have participated in major trials in AMD, and ocular pathologists with a considerable history of neovascular AMD publications.

To start the process, an international working group conducted several meetings to establish the range of concepts pertinent to OCT angiography, particularly the limitations of current imaging methods. The meetings were also attended by imaging scientists from the OCT industry (Heidelberg Engineering, Inc, Franklin, MA; Optovue Inc, Fremont, CA; Topcon Medical Systems, Inc, Oakland, NJ; and Carl Zeiss Meditec, Inc, Dublin, CA) who jointly served as a resource on imaging technologies and their limitations but did not have any influence on the outcome of the deliberations. For the present article, the group prepared preliminary definitions of various disease states before the meeting. Initially, these components were introduced in prepared presentations, which were followed by discussion. From those discussions, a series of schematic drawings of MNV were prepared and distributed for independent grading by the working group members. Initial examination of the responses from experts of this set of schematic images of MNV yielded nearly complete disagreement in terminology. Extensive group discussions were followed by the formation of small groups, each charged with developing definitions for a subset of entities. These definitions were then presented to the

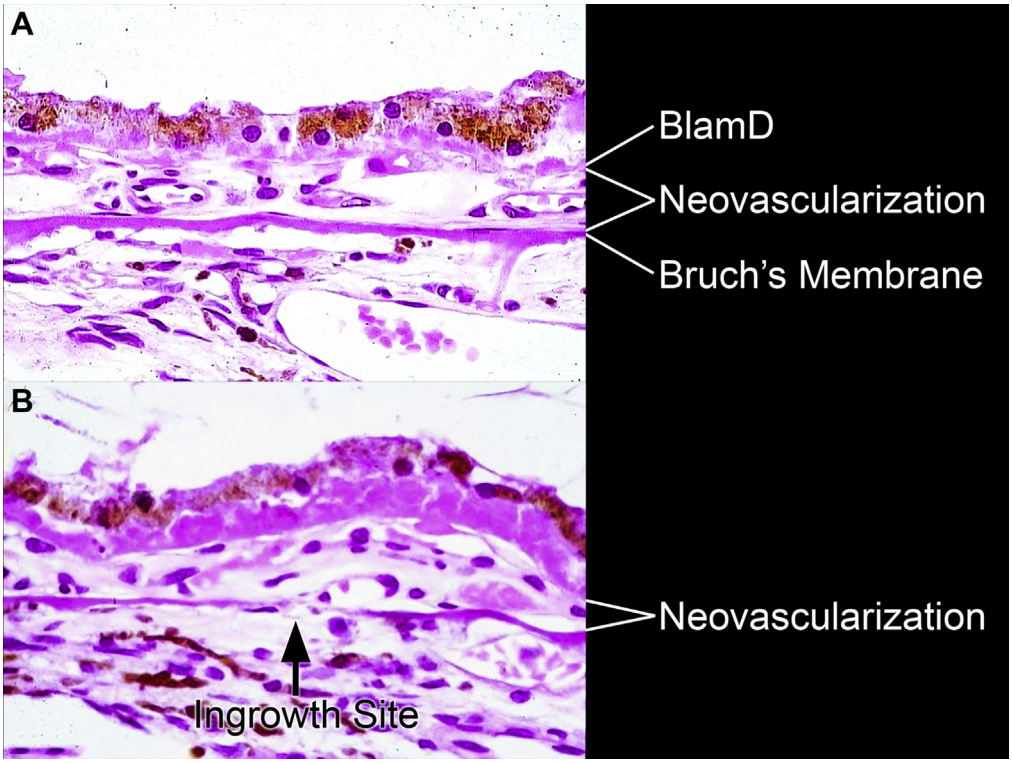

Figure 3. Light microscopy images showing neovascularization arising from the choroid. **A**, Neovascularization in this case proliferates in the potential space under the basal laminar deposit (BlamD) above the trilaminar Bruch's membrane. **B**, The ingrowth site is evident as a defect in Bruch's membrane (arrow) (hematoxylin and eosin, ×250).

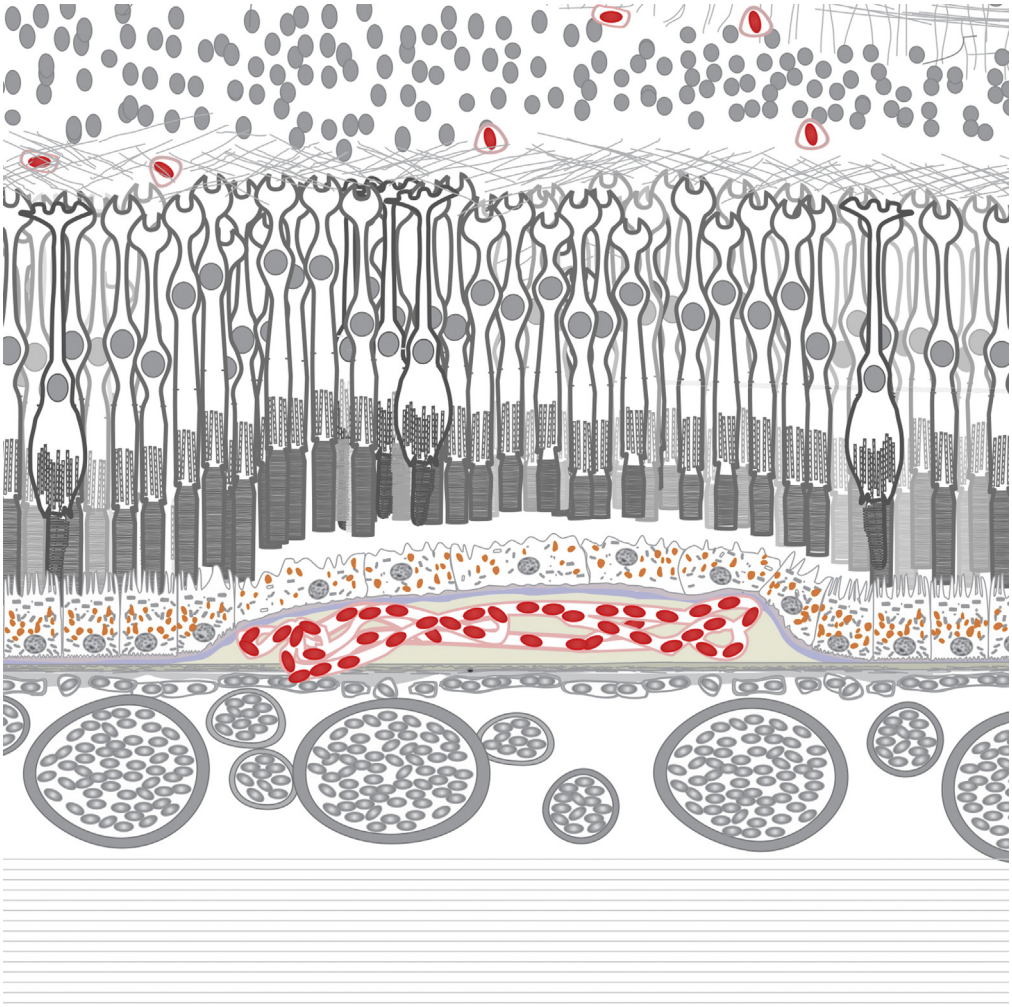

Figure 4. Diagram showing type 1 macular neovascularization. The ingrowth of vessels arises from the choriocapillaris and extends up to and under the retinal pigment epithelium.

larger group and then refined by the group at large until consensus was reached. Additional consultation was obtained from reading centers and authors outside of the meeting group. Definitions for atrophy in the context of neovascular AMD were developed because these lesions are common.

Results

Consensus Definitions

A list of definitions is shown in Table 1. A comparison of the new terms with older terms developed during the fluorescein angiography era is shown in Table 2. No direct porting of the new terms to the old ones and vice versa exists because newer imaging technologies, such as OCT and OCT angiography, have an ability to detect abnormalities not imaged by color fundus photography or fluorescein angiography and have greater precision for many entities that are imaged using these technologies. Using OCT and OCT angiography does not replace fluorescein angiography or color photography; rather, these additional forms of imaging augment those forms of imaging and provide additional data to improve classification possibilities.

Age-related macular degeneration is a process by which the structure and function of the macula deteriorates over time in association with distinguishing signs and symptoms that typically become evident clinically beyond 50 years of age and do not seem to be secondary to other processes such as pathologic myopia, central serous chorioretinopathy, monogenetic inherited retinal disease, chorioretinal uveitic syndromes or infections, or trauma. The salient characteristic of AMD is the accumulation of extracellular deposits within the macula. Basal laminar deposits are located between the RPE cell's plasma membrane and its basal lamina (Fig 1). Basal linear deposits are located external to the RPE basal lamina (also known as the *lamina densa*, as identified by electron microscopy). Both types of deposit occur internal to the inner collagenous layer of the trilaminar Bruch's membrane. Diffuse thickenings of these deposits may not be detectable by conventional ophthalmoscopy, but mounds of basal linear deposit appear as soft drusen (Fig 2).[23] Subretinal drusenoid deposits are accumulations of material located above the RPE and appear as pseudodrusen. Associated with the extracellular deposits are morphologic changes in the RPE visible by histopathologic analysis and, in more advanced stages, clinical imaging.

In the early phases of AMD, the visual performance may show minimal changes. With time, vitelliform deposit may accumulate, pigment may migrate into the retina, drusen size may increase, and

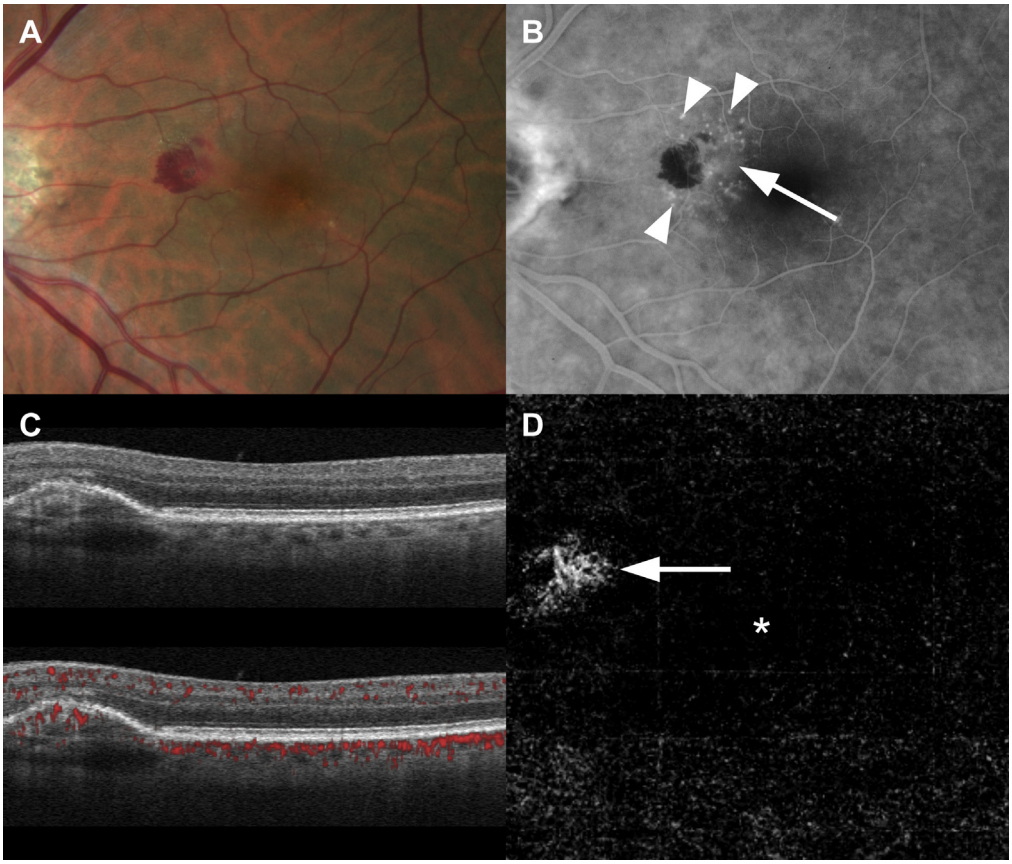

Figure 5. Images showing type 1 macular neovascularization. **A**, Fundus photograph from a 78-year-old with hemorrhage in the nasal macula. **B**, Fluorescein angiography image showing blocking defect caused by the hemorrhage, subtle diffuse leakage (arrow), and punctate leakage (arrowheads). **C**, OCT image (top) demonstrating heterogeneous reflectivity in a fibrovascular pigment epithelial detachment and (bottom) OCT angiographic overlay showing flow within the pigment epithelial elevation. **D**, En face OCT image showing the neovascular network (arrow) and the center of the fovea (asterisk).

hypopigmentation and hyperpigmentation of the RPE may develop. Late phases of the disease include atrophy of the outer retina, thinning and loss of the RPE, and MNV (Fig 3). Neovascular disease can lead to leakage, bleeding, and scarring as well as severe vision loss. Age-related macular degeneration can be asymmetrical; one eye may show manifestations, such as drusen, in the absence of fellow-eye abnormalities. The risk for progression in the eye without AMD stigmata is nearly zero, and accordingly, one should not diagnose AMD in an eye without visible abnormalities. This raises a conundrum: should AMD be diagnosed per eye or per patient? The group elected to consider AMD a disease diagnosed per patient given the use of vitamin supplements and other measures to reduce risk are deployed on a per patient basis.

Neovascularization Subtypes

Macular neovascularization is an invasion by vascular and associated tissues into the outer retina, subretinal space, or sub-RPE space in varying combinations. The ingrowth of neovascularization is generally considered to be pathologic but may have some beneficial secondary effects as well, in that the neovascularization may be an ocular protective response whereby the choriocapillaris is recapitulated to improve a deficient oxygen and nutrient supply.[24] The anatomic location of the neovascularization determined by OCT imaging is used to subclassify the vascular component of the disease process.

Type 1 Macular Neovascularization. Type 1 MNV is an ingrowth of vessels initially from the choriocapillaris into the sub-RPE space (Fig 4). With growth and expansion of the lesion, remodeling and enlargement of the feeding and draining vessels occurs within both the choroid and the lesion.[25] Accompanying the ingrowth is a varying amount of additional cellular elements including fibroblasts, myofibroblasts, and macrophages that seem to participate in the disease process and can lead to formation of fibrotic tissue. With fluorescein angiography, type 1 MNV commonly displays ill-defined regions of multipunctate leakage that correspond topographically to a region of elevated RPE (i.e., stippled hyperfluorescence) and thus was termed *occult* neovascularization (Fig 5). Indocyanine green angiography may help to visualize some of the vascular structure but often shows just late staining of the lesion, referred to as a plaque.[26] OCT angiography may aid in the visualization of these lesions. Leakage from vessels, hemorrhage, or associated proliferation of fibrotic tissue can cause expansion of a fibrovascular pigment epithelial detachment (PED). The relative role of the induced curvature of the pigment epithelium and other biological alterations on the outer blood–retinal barrier is not yet fully understood. However, in many eyes, increased intralesional hydrostatic pressure coupled with breakdown of the outer blood–retinal barrier leads to exudation into the subretinal space. Intraretinal fluid accumulation may occur in conjunction with breakdown of the external limiting membrane, or VEGF expression may induce intraretinal leakage independently.[27]

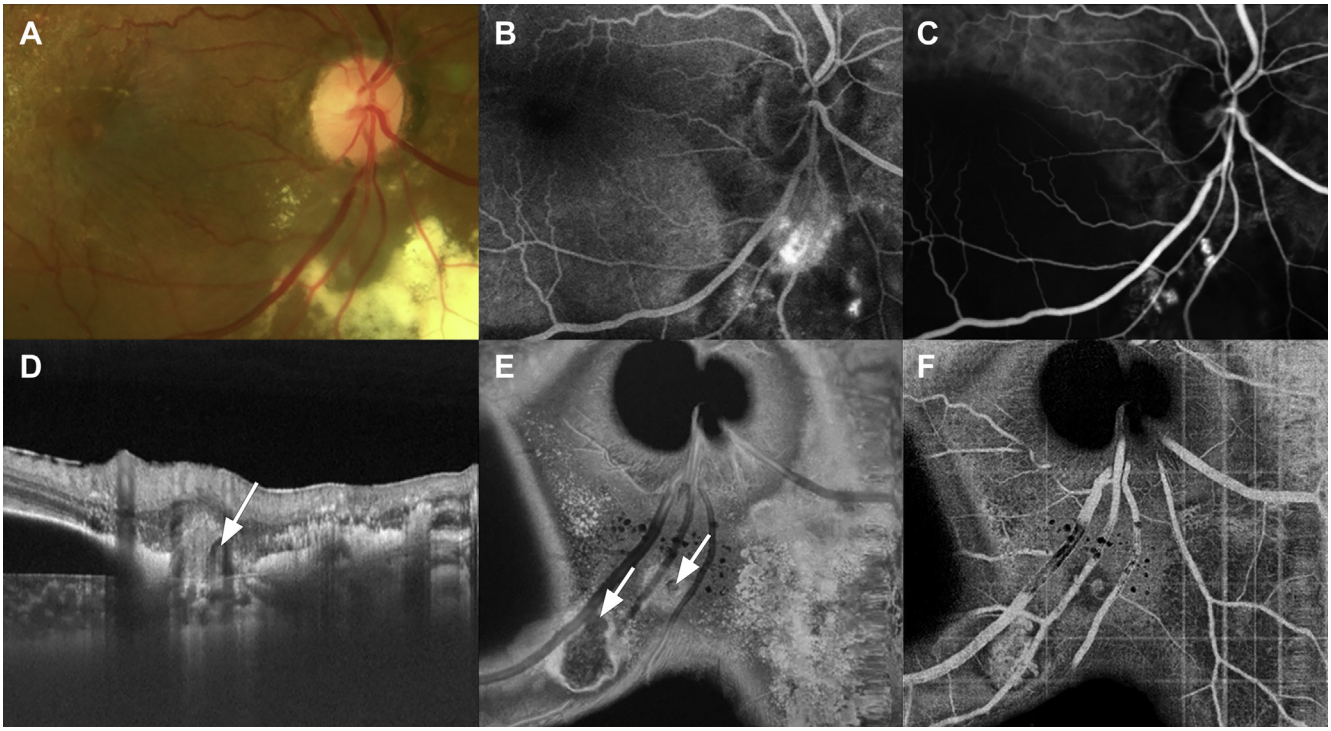

Figure 6. Images showing polypoidal choroidal vasculopathy (also known as aneurysmal type 1 macular neovascularization). **A**, Color photograph showing extensive exudation with subretinal lipid and an epiretinal membrane. **B**, Fluorescein angiogram showing hyperfluorescence in the region of neovascularization and adjacent dye pooling within a pigment epithelial detachment. **C**, Indocyanine green angiogram showing hyperfluorescent dilations, which are interconnected by a branching vascular network, some of which are seen. **D**, Structural OCT showing a nodular vascular structure (arrow) buried in hyperreflective exudative material and an adjacent detachment of the pigment epithelium. **E**, En face slab structural OCT showing the elevations caused by aneurysmal aggregates (arrows). **F**, OCT angiogram showing flow within the RPE elevations with some suggestion of the aneurysmal dilations, but there are internal details present that suggest tightly entangled vascular elements. RPE = retinal pigment epithelium.

In 1973, Sarks[28] reported histopathologic results of eyes with what is now known as type 1 MNV. These patients showed no clinical signs of neovascularization. In 1987, Gass[29] proposed that patients can demonstrate an occult stage of disease (not the same as occult type of neovascularization) in which "the patient is asymptomatic and the new vessels may not be apparent either ophthalmoscopically or angiographically." With the development of indocyanine green angiography, neovascular plaques with no signs of exudative disease were discovered in fellow eyes harboring soft drusen.[30] Patients with these nonexudative neovascular plaques had a much higher risk of progressing to exudative manifestations than eyes without nonexudative plaques. In 2012, Amissah-Arthur et al[31] found OCT evidence of neovascularization in 88% of eyes before the development of exudation, with conversion occurring up to 35.5 months after initial entry in the study. After this report, Querques et al[32] in 2013 reported cases of neovascularization without exudation in separate examinations separated by 6 months or more and called this form *quiescent neovascularization*. In 2018, de Oliveira Dias et al[33] reported eyes with nonexudative MNV in swept-source OCT angiographic imaging had a much higher risk of progressing to exudative manifestations than those without manifestations of nonexudative MNV. The CONAN group recognizes nonexudative MNV and that this form of neovascularization could be identified more commonly with advances in imaging technology. The group could not come to a consensus that the designation *quiescent* was a needed term.

Polypoidal Choroidal Vasculopathy. Polypoidal choroidal vasculopathy[34] is an important subtype of neovascularization defined by a branching vascular network and nodular vascular agglomerations (Fig 6), also called polyps. Although a minority subtype in white populations, it accounts for approximately half of MNV seen in Asia.[35,36] In polypoidal choroidal vasculopathy, the branching vascular network may have ophthalmologically visible large vessels (Fig 7), some that can be as large as the retinal arcade vessels. At the outer border of the vascular lesion, nodular vascular elements can be present that suggest the appearance of aneurysms. The morphologic features of the vascular lesion is imaged best with indocyanine green angiography[37] and OCT angiography. In the earlier phases of the indocyanine green angiographic sequence, the branching vascular network fills, and next, the dilatations are imaged. Over time, the dye is removed from the circulation and late staining of tissue around the dilatations occurs. Polypoidal choroidal vasculopathy expands slowly in the sub-RPE space over time and may grow to considerable size before having any meaningful impact on vision. The polyps may be pulsatile and are particularly prone to bleed. In OCT angiographic imaging, the aneurysmal dilations may not be imaged, suggesting the flow in these lesions is less than the detection limit for this method of imaging, but the branching vascular network is otherwise imaged. In Asian persons, the typical presentation comprises isolated macular involvement, unilateral, and male preponderance, whereas in white persons, bilateral involvement, female preponderance, and the neovascular lesion originating from the peripapillary region are more common.[38] Because of the slow perfusion dynamics, most polyps remain undetected by OCT angiography.

When polypoidal choroidal vasculopathy was named, the lesion was thought to be a distribution of abnormally dilated choroidal vessels bordered by enlargements called polyps. Shortly thereafter, separate histopathologic reports established that the lesion was the growth of cavernous thin-walled vessels immediately external to

the RPE,[39–41] above Bruch's membrane. The word *polyp* ordinarily refers to either a sedentary aquatic invertebrate or a solid growth of tissue from a mucous membrane, and not a vascular abnormality. Thus, every word of the term *polypoidal choroidal vasculopathy* is incorrect. An alternate term, *aneurysmal type 1 neovascularization*, has been proposed, but consensus could not be reached regarding whether polyps were simple aneurysms or more complicated vascular structures.[42]

Type 2 Macular Neovascularization. Type 2 MNV refers to the proliferation of new vessels arising from the choroid into the subretinal space (Fig 8). Although these vessels traverse the sub-RPE space, the disease process in type 2 neovascularization is dominated by the subretinal portion (Fig 9). These lesion types are associated with exudation or hemorrhage directly into the subretinal space. Type 2 neovascularization may be a component of a larger process including other forms of neovascularization in varying amounts. Type 2 lesions have the fluorescein angiographic characteristics of early, typically well-defined hyperfluorescence with late leakage. OCT angiography shows a neovascular network above the level of the RPE. Type 2 MNV occurs in conditions other than AMD that affect the RPE, such as angioid streaks, lacquer cracks, and chorioretinitis.

Type 3 Macular Neovascularization. Type 3 MNV refers to a downgrowth of vessels from the retinal circulation toward the outer retina. Thus, the term *choroidal neovascularization* is not accurate for type 3 neovascularization. The vascular proliferation is suspected to start from the deep capillary plexus in the retina with the vector of growth extending toward the outer retina. Increasing blood flow within the angiomatous proliferation is supplied by the retinal vessels, which seem to remodel over time to handle the flow requirements (Figs 10 and 11). Scattered flecks of intraretinal hemorrhage (always outside the foveal avascular zone) and cystoid spaces are present, both of which may appear before the neovascularization. The neovascularization has the potential to leak and bleed. Fluorescein angiography demonstrates intraretinal leakage of fluorescein with potential for cystoid macular edema, which can be substantial (Figs 12 and 13). Indocyanine green angiography shows a small hyperfluorescent lesion, which likely represents descending vessels viewed axially. OCT shows varying amounts of intraretinal edema, which in some eyes can be widespread compared with any neovascularization present. OCT angiography shows proliferation of vessels into the deeper portions of the retina; although these vessels seem to originate from the deep vascular plexus, with increasing proliferation and flow, remodeling of the vessels supplying and draining the neovascularization occurs. The eyes may also show subretinal fluid and exudation, subsidence of the retina, and development of a PED, findings highlighted by available histopathologic results (Fig 14).

Proliferation to the level of the RPE and eventual breakthrough of this layer can lead to sub-RPE neovascularization with potential for anastomosis to deeper layers. Although both type 2 and type 3 neovascularization lead to new vessels in the subretinal space, type 3 neovascularization originates from the retinal microvasculature, whereas types 2 and 1 develop from the choroid. Earlier descriptions of this form of neovascularization varied in content and used terms including *retinal vascular anomalous complexes*,[43] *retinal angiomatous proliferation* (also known as RAP),[44] and *occult retinal choroidal anastomosis*.[45]

Retinal-Choroidal Anastomosis. An anastomosis is a vascular communication between channels that are not ordinarily connected by means of vessels typically larger than a capillary. These vessels are a conduit for blood flow through neovascular networks that allows blood flow either from the retina to the choroid or the opposite, depending on relative pressure differences. The CONAN group recommends that the lesion should be named *retinal-choroidal anastomosis*, consistent with a retina-to-choroid hierarchical naming strategy that does not refer to the directionality of blood flow. Retinal-choroidal anastomoses are detected commonly using dye-based angiography, although OCT and OCT angiography may prove sufficient.

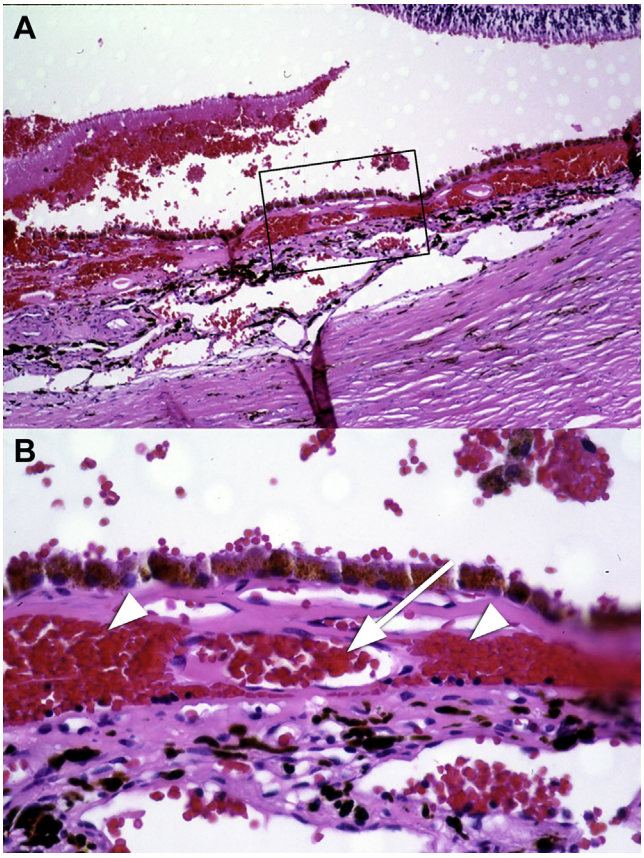

Figure 7. Light microscopy images showing polypoidal choroidal vasculopathy. **A**, A large lesion with subretinal and sub–retinal pigment epithelium hemorrhage (hematoxylin and eosin, ×100). **B**, Area shown in the bounding box in (**A**). Note the large thin-walled neovascular vessel (arrow) flanked by intralesional hemorrhage (arrowheads) (hematoxylin and eosin, ×200).

Neovascular Lesion Nomenclature. Based on the foregoing descriptions, the CONAN group proposes that the following terms should be used. *Type 3 neovascularization* is to be used when the vascular complex originates in the retina. *Type 1 neovascularization* is applied when the vessels originate from the choroid and remain under the RPE. *Type 2 neovascularization* is denoted if neovascularization that originates in the choroid breaks through the RPE to reach the subretinal space. The term *type 2* is derived from the anatomic location of the proliferating neovascular frond, although blood flow has to transverse the sub-RPE space to reach the subretinal space. If prominent neovascularization is present in the subretinal and sub-RPE compartments, the term *mixed type 1 and type 2 neovascularization* can be applied (Fig 15). Comparison of the histopathologic features of type 2 versus a mixed type 1 and 2 lesion is shown in Figure 16. Patients with mixed type 1 and type 2 lesions can show apparent regression of the type 2 component after initiation of treatment.[46] An eye with type 3 disease that has penetrated the RPE monolayer without making an anastomosis with the choroidal circulation is said to have extension of the type 3 disease into the sub-RPE space. Although the extension is under the RPE, it may not have the same long-term consequences as does type 1. Some evidence exists that

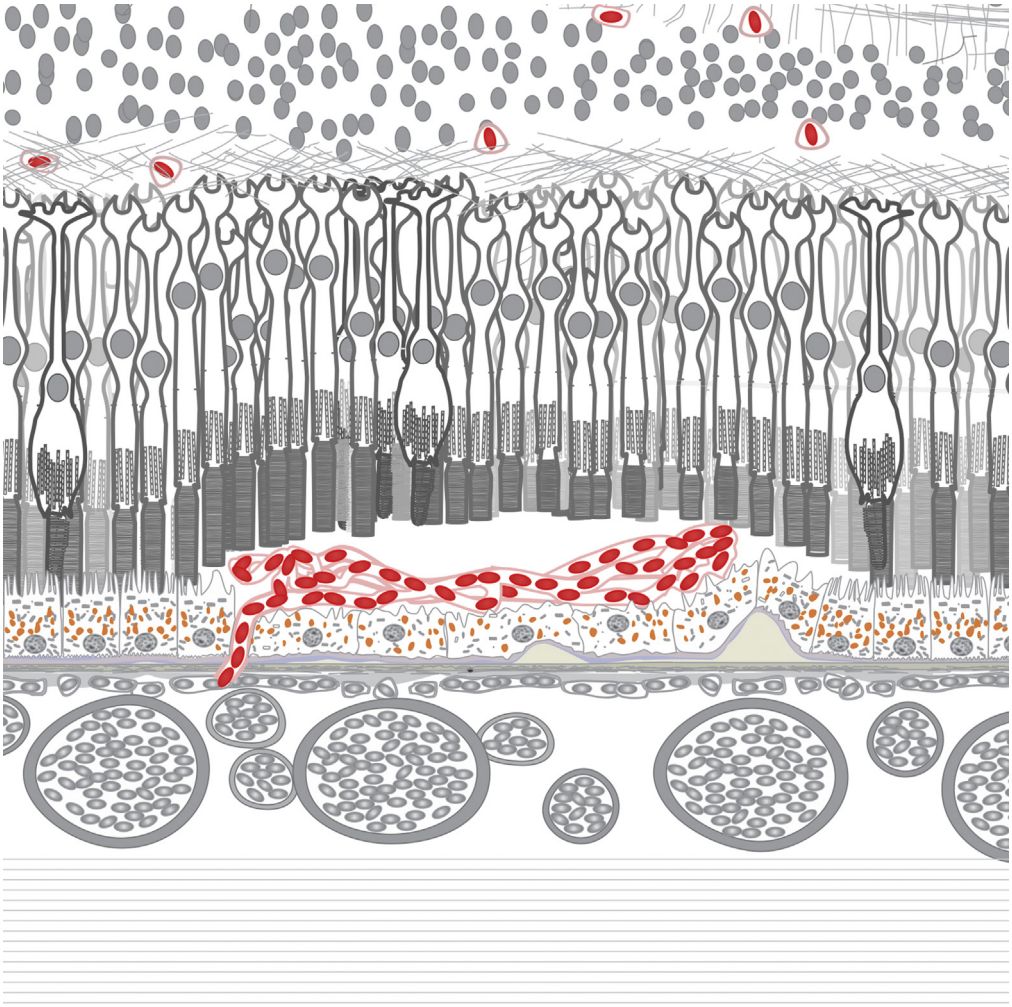

Figure 8. Diagram showing type 2 macular neovascularization. The ingrowth of vessels arises from the choriocapillaris and extends up through the retinal pigment epithelium (RPE) monolayer to proliferate in the subretinal space. To arrive in the subretinal space, the blood flow must traverse the sub-RPE space to reach the plane of neovascularization.

eyes with type 1 disease may be less likely to demonstrate RPE atrophy[47] than other forms of MNV, even with anti-VEGF treatment. Some eyes may show type 3 neovascularization and a separate unconnected region of another form of neovascularization, for example type 1 neovascularization. This situation may be summarized as *type 3/1 neovascularization*, in which the "/" is interpreted as meaning "and" in an independent sense.

Exudative Features of Macular Neovascularization

Exudation is a common feature of MNV and can manifest in 4 basic forms: leakage, subretinal fluid, lipid, and subretinal hyperreflective exudative material (SHRM).

Leakage. Leakage is the release of excess fluid and serum components as the result of the breakdown of the blood–ocular barrier. Leakage is typically detected with fluorescein angiography, in which hyperfluorescence outside of vascular confines is seen to expand in area over the course of the angiographic sequence. The dye may accumulate in tissue, a process called *staining*, or into fluid filled spaces, termed *pooling*. The appearance of hyperfluorescence does not necessarily mean that edema is present. It is possible that alteration in tissue function associated with local leakage could be present without overt signs of edema.

Intraretinal and Subretinal Fluid. Intraretinal and subretinal fluid accumulate if the leakage is in excess of local capability to remove the fluid. Intraretinal fluid may accumulate from retinal vasculature leakage or intraretinal neovascularization or diffusion of fluid through the outer retina related to abnormalities of the external limiting membrane and associated structures. The accumulation of subretinal fluid is dependent on removal rates; for example, disturbances in the RPE pump function may contribute to the buildup of subretinal fluid.

Lipid (or Hard Exudates). Lipid (or hard exudates) are lipoprotein precipitates related to chronic vascular leakage. The aqueous component of the leakage may be reabsorbed by different mechanisms that do not remove associated lipoprotein molecules directly. As such, the concentration of lipoprotein molecules may exceed their solubility, resulting in tissue deposition.

Subretinal Hyperreflective Material. Subretinal hyperreflective material is the exudation into or under the retina of material excluding red blood cells, as would be detected by color fundus photography. The material is detected by OCT and appears as regions of featureless accumulations of relatively uniform increased reflectivity. The material may include an admixture of serum, fibrin, and inflammatory

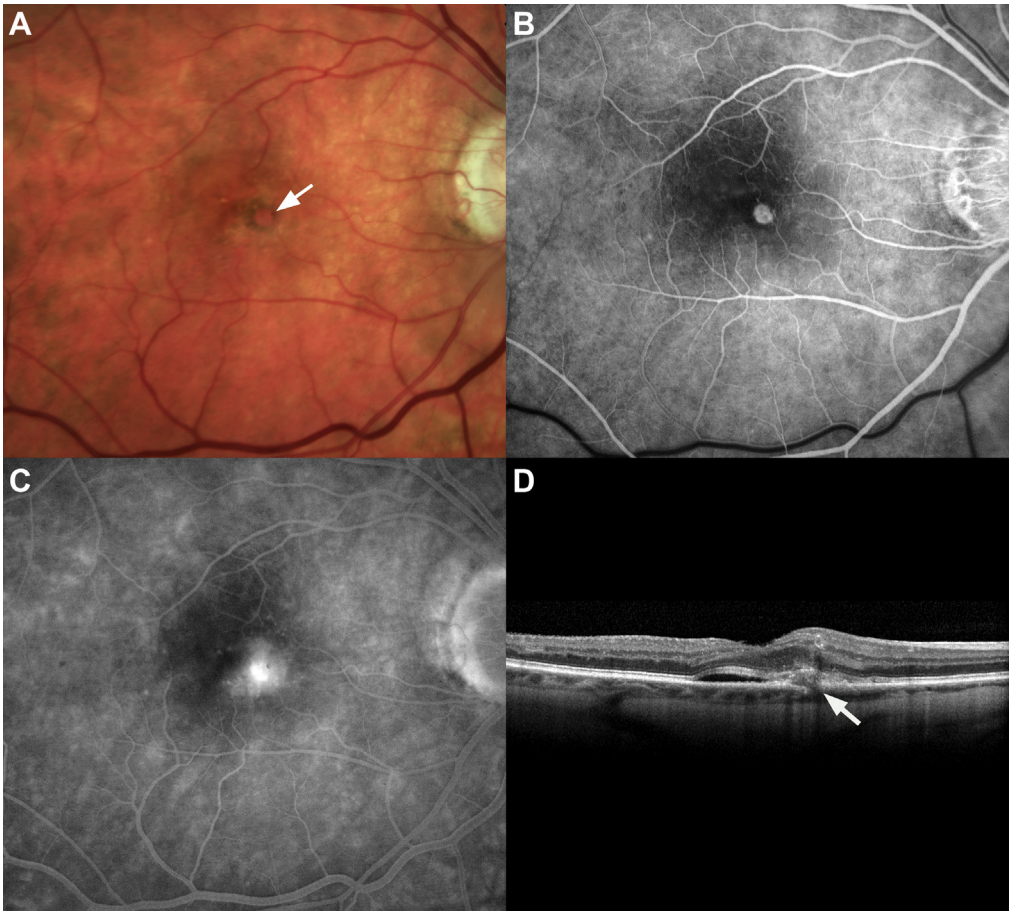

Figure 9. Images showing type 2 neovascularization. **A**, Fundus photograph from a 74-year-old showing a hyperpigmented ring in the fovea (arrow). **B**, **C**, Early-phase fluorescein angiogram showing (**B**) a well-defined lesion with late leakage and (**C**) obscuration of the borders of the neovascular lesion. **D**, B-scan OCT showing the outer retinal lesion with extension of subretinal fluid under the fovea. The ingrowth site through the retinal pigment epithelium is evident (arrow).

cells. Subretinal hyperreflective material is not hyperautofluorescent, as opposed to vitelliform material, which is hyperautofluorescent. Subretinal hyperreflective material can resolve, but fibrosis can occur in its wake.[48,49] The presence of SHRM is associated with poorer visual outcomes.[48] Patients with type 2 neovascularization demonstrate exudation directly into the subretinal space. Clues to the presence of type 2 neovascularization in the context of SHRM include a classic pattern on fluorescein angiography, disruption of the external limiting membrane, and intraretinal fluid. Reappearance of SHRM is a sign of recurrent exudative activity resulting from neovascularization.[50]

Lesion Components in Addition to Macular Neovascularization

Classification of the neovascularization concentrates on the topologic features of the new vessel growth but does not describe the resultant lesion. Additional terms are needed to describe the associated lesion components. The separation of lesion features from lesion components is somewhat arbitrary, but historically, exudation such as lipid or SHRM does not inhibit measurement of lesion size when imaged using fluorescein angiography. Lesion components can prevent the proper appreciation of the size of the neovascular lesion as assessed by fluorescein angiography, and so were considered to be part of the larger lesion. With the advent of modern imaging techniques such as OCT angiography, some of these considerations were obviated.

Retinal Pigment Epithelial Detachment. In AMD, RPE detachments are caused by an elevation of the RPE monolayer and its basement membrane from the inner collagenous layer of Bruch's membrane by sub-RPE fluid, blood, or fibrovascular material. Serous PEDs may occur in the context of nonneovascular AMD, but indocyanine green angiography has shown the large majority in eyes with AMD occur because of neovascularization.[51] The RPE may be elevated by fluid released from the neovascularization, and this may occur eccentric to the neovascular tissue, producing a notched PED where the neovascularization is in the notch. More commonly, the neovascularization is seen adherent to the undersurface of the RPE and its basal lamina. The structure of a fibrovascular PED is dominated by vessels and fibrotic tissue in a complex arrangement, although serous fluid may also be present. OCT and OCT angiography can be used to detect the internal anatomic structure of the PED, and OCT angiography can be particularly effective to image the associated vascular network, particularly if the PED is shallow. A special class of PED, drusenoid PED, is a large druse or a confluence of drusen, with a size at least 350 μm as defined by the Age-Related Eye Disease Study or at least 433 μm as defined in the Age-Related Eye Disease Study 2.[52,53] Because measurements are typically performed digitally now, instead of using a standard circular

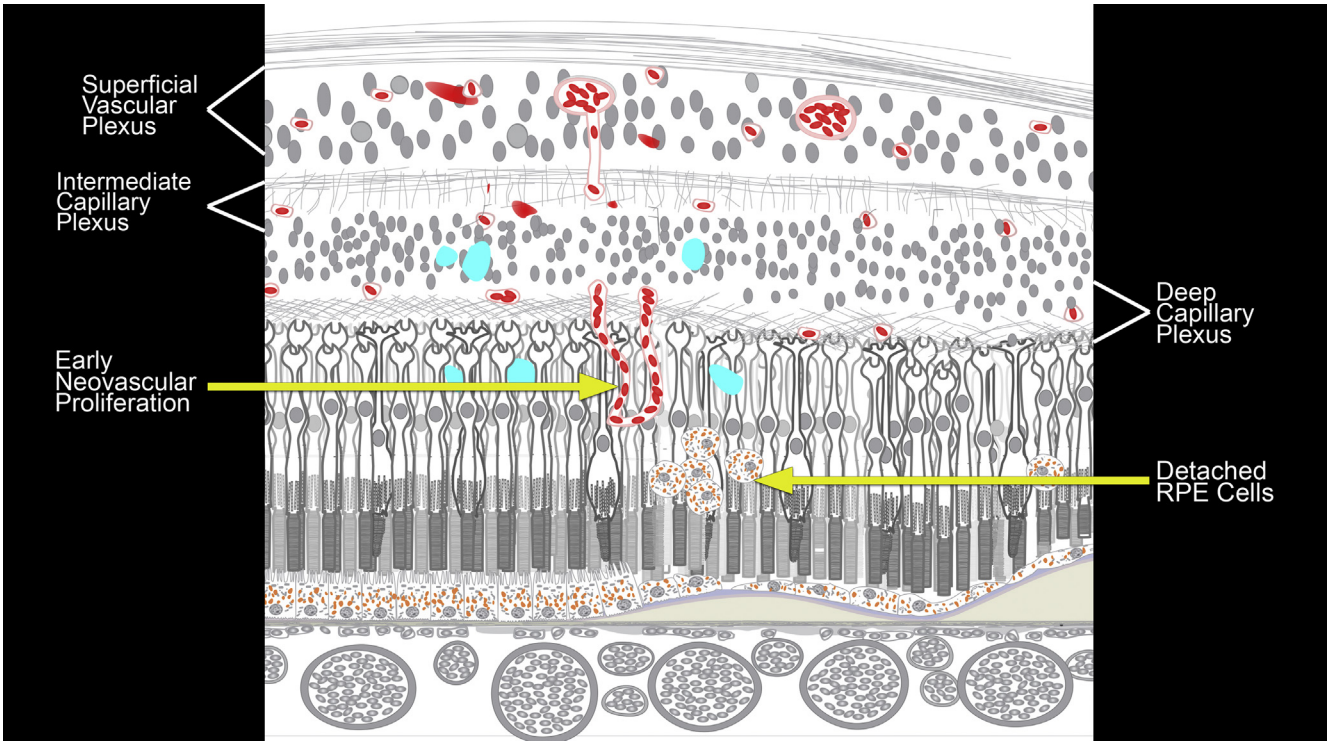

Figure 10. Diagram showing initiation of type 3 neovascularization. When the regional proangiogenic–antiangiogenic balances shift in favor of neovascularization, proliferation of vessels occurs along a vector along the vascular endothelial growth factor concentration gradient. The new vessels originate from and invade into tissues below the plane of the deep capillary plexus. Elevated cytokines, particularly vascular endothelial growth factor levels, can induce vascular leakage and intraretinal hemorrhage in addition to stimulating angiogenesis. RPE = retinal pigment epithelium.

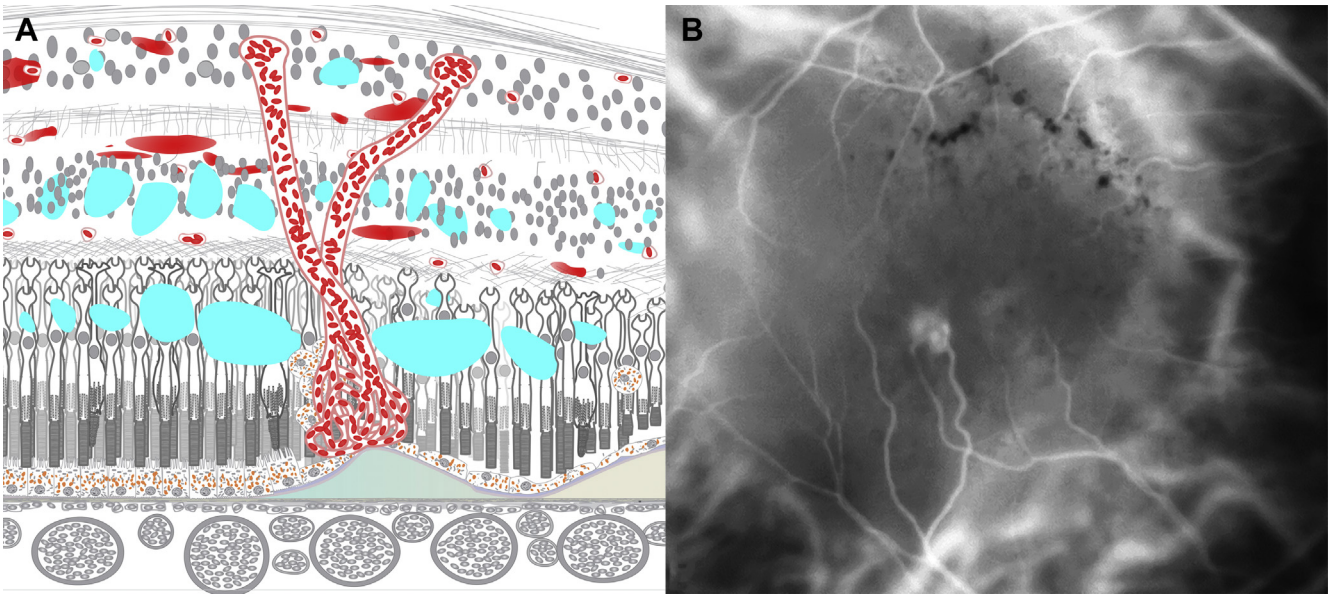

Figure 11. Images showing type 3 neovascularization. **A**, Diagram showing proliferation of vessels posteriorly with formation of what has been called an angiomatous lesion. The vessels supplying the blood flow to the angiomatous proliferation remodel into larger feeding and draining vessels. The edema and hemorrhage in the retina are from both the neovascularization and to increased local tissue levels of vascular endothelial growth factor. Some evidence is present that the retinal pigment epithelium monolayer may not be intact, even before penetration of new vessels into the basal laminar or basal linear material. **B**, Comparative indocyanine green angiographic image of a patient with an established type 3 neovascular lesion.

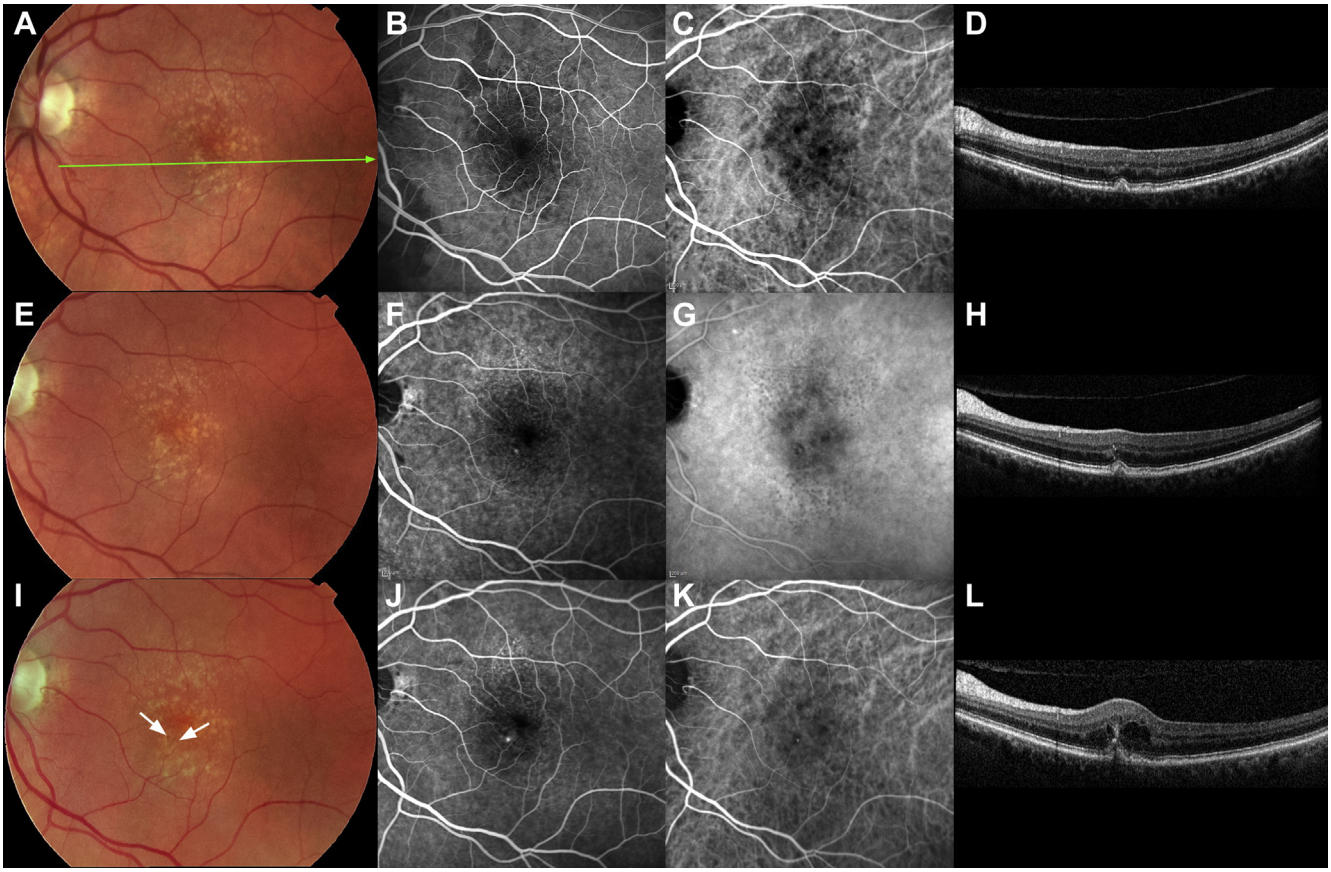

Figure 12. Images showing development of early type 3 macular neovascularization. **A**, Fundus photograph obtained at baseline showing drusen in the macular region. The green arrow indicates the location for future B-scan OCT images. **B**, Early-phase fluorescein angiogram showing decreased early fluorescence of the central macula. **C**, Early indocyanine green angiogram showing the decreased early fluorescence of the central macula seen in (**B**). **D**, OCT image showing drusen of varying sizes. **E**, Fundus photograph obtained 8 months later showing that the patient continued to harbor drusen. **F**, Fluorescein angiogram showing a very small dot of hyperfluorescence (arrow). **G**, Indocyanine green angiogram in which the very small dot of hyperfluorescence seen in (**F**) is barely visible. **H**, OCT image showing increased reflectivity in Henle's fiber layer above the solitary larger druse. **I**, Fundus photograph obtained 9 months later showing that the patient harbored small hemorrhages (arrows). **J**, Fluorescein angiogram in which the hyperfluorescence is more evident. **K**, Indocyanine green angiogram in which the spot seen in (**J**) also is more evident. **L**, OCT image showing cystoid spaces within the retina adjacent to the neovascularization descending to the druse.

measurement, 350 μm would be more convenient.[52] Pigment epithelial detachments can occur in the context of type 1 or type 3 MNV. The association with type 1 may be related to the sub-RPE location of the vessels and potential exudation. The association with type 3 is harder to explain with current knowledge. Although outer retinal exudation from the descending neovascularization may overwhelm the fluid diffusion abilities through Bruch's membrane, why similar PEDs do not form in the context of type 2 MNV is not known.

Hemorrhage. Hemorrhage is an extravasation of blood from the neovascular complex and can be located in the sub-RPE, subretinal, intraretinal, and occasionally preretinal compartments. Fresh blood is red and hypoautofluorescent. As blood ages, it becomes yellow, does not stain during fluorescein angiography, and also is hyperautofluorescent, in contradistinction to fibrosis, which is not hyperautofluorescent.

Fibrosis. The clinical definition of fibrosis is based on color photography and fluorescein angiography and refers to the apparent build-up of tissue in any layers of the retina, including the subretinal space, RPE monolayer, or sub-RPE space, of tissue suspected of harboring significant collagen deposition. The fibrotic region typically stains on fluorescein angiography and is not hyperautofluorescent in autofluorescence imaging. Fibrosis as imaged by color photography or fluorescein angiography has an uncertain OCT correlate at present.[54] Fibrotic tissue as seen by histopathologic examination has not been correlated closely with the clinical imaging but in histologic specimens contains type 4 collagen deposited by fibroblasts, myofibroblasts, and potentially transdifferentiated RPE cells and may be a lesion component in its own right but may be admixed with neovascular tissue. Fibrosis is a part of the wound-healing response[55] that results from numerous cytokines and factors such as transforming growth factor β1, pigment epithelial growth factor, and connective tissue growth factor.[56] Fibrotic tissue is associated with lesion contraction; it has been proposed that a balance between VEGF and connective tissue growth factor may control the behavior of fibrovascular tissue. Higher levels of VEGF in relation to connective tissue growth factor may promote vascular growth, whereas decreases in the ratio may lead to increased fibrosis, scarring, and contracture of that tissue.[56]

Rip. Rip (or tear) of the RPE is caused by a tractional dehiscence of the RPE monolayer. It is theorized that contracture of the

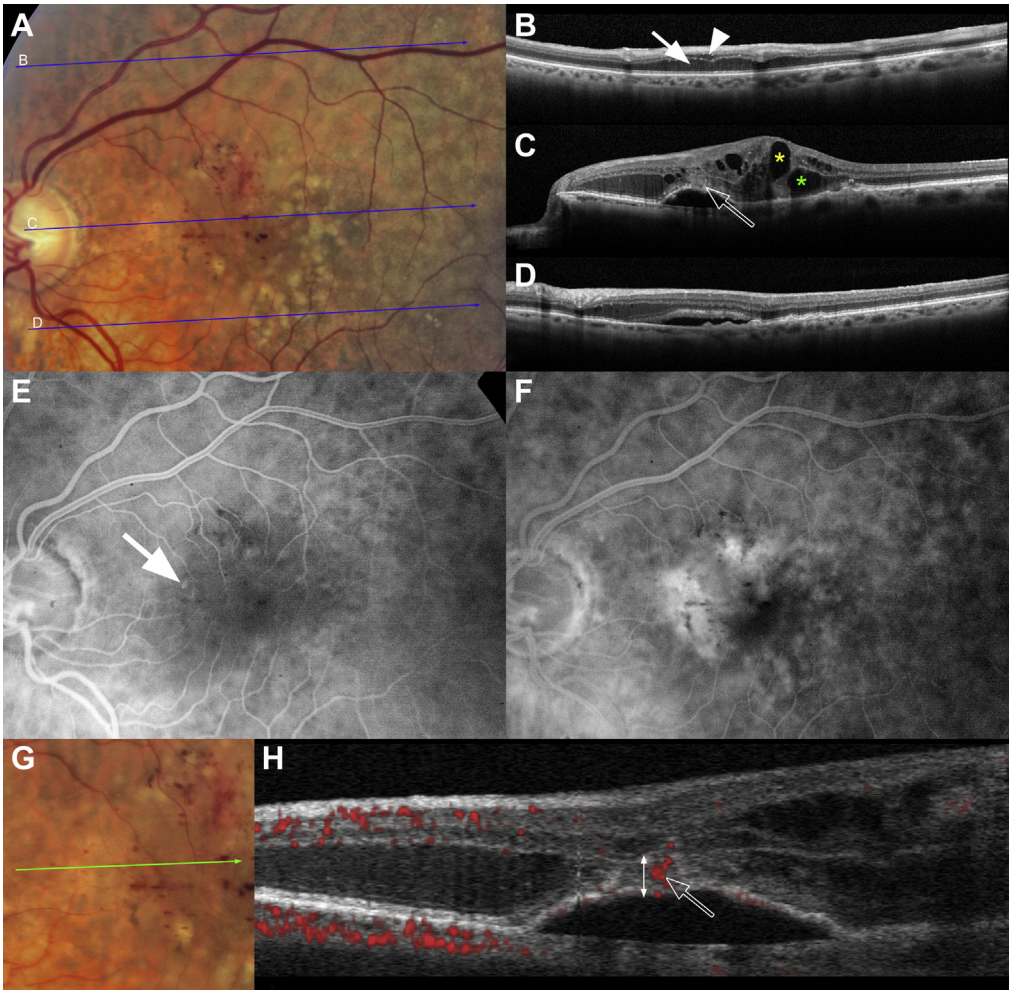

Figure 13. Images showing type 3 neovascularization with prominent edema and hemorrhage. **A**, Fundus photograph from an 87-year-old showing dozens of small fleck hemorrhages in the superior and nasal macula. The blue arrows show the location of the structural OCT scans. **B**, OCT scan of the section through the superior arcade showing expansion of the inner nuclear layer (arrowhead) and Henle's fiber layer from edema fluid (arrow). **C**, OCT scan of the section through the superior parafovea revealing edema of inner nuclear layer and Henle's fiber layer with cystoid spaces (yellow and green asterisks, respectively). Hyperreflectivity within the retina overlying the apex of the retinal pigment epithelial detachment (arrow) is evident. Note the edema nasal and temporal to the area of neovascularization is greater than that immediately surrounding the new vessels. **D**, OCT scan of the inferior macula showing edematous thickening of the retina and subretinal fluid. **E**, Fluorescein angiogram showing a small area of hyperfluorescence corresponding to the hyperreflective area in (**C**). **F**, Later fluorescein angiogram showing pooling of dye in cystoid spaces as well as diffuse staining well away from the area highlighted by the arrow in (**E**). **G**, Fundus photograph of magnification of the central portion of the involved macula showing the numerous isolated hemorrhages, many of which were in the inner retina. The green arrow shows the section captured by the OCT angiogram in (**H**). **H**, OCT angiogram showing the small focus neovascularization found within the outer retina (open arrow). The vertical double arrow is 150 μm. Note that the hemorrhages do not colocalize with the neovascularization.

sub-RPE fibrovascular tissue leads to sub-RPE traction across the inner chord diameter of the RPE detachment.[57,58] Tensile forces greater than the structural strength of the RPE monolayer can lead to a tear. The contracture of the fibrovascular tissue may be related to the angiofibrotic switch.[59] The dehisced RPE monolayer retracts to a varying extent, producing a heaped-up region adjacent to a zone of absent RPE tissue. The retracted RPE monolayer causes decreased transmission to the deeper layer. This causes decreased fluorescence during fluorescein angiography and choroidal hypotransmission with OCT. It is hyperautofluorescent because of the increased light path through fluorophores. In contrast, the area denuded RPE shows hyperfluorescence in fluorescein and indocyanine green angiography and hypertransmission to the choroid on OCT. With absence of the RPE, and likely atrophy of the choriocapillaris, flow signal can be obtained from deeper choroidal vessels in OCT angiography.

Components of Atrophic Age-Related Macular Degeneration in the Context of Macular Neovascularization

The main causes of vision loss in neovascular AMD include those directly related to the new vessels such as leakage, hemorrhage, and fibrosis. Another important cause of vision loss, particularly in treated cases, is atrophy.[60] The definition used in studies of geographic atrophy, a sharply defined round or oval area of decreased pigmentation in which the underlying choroidal

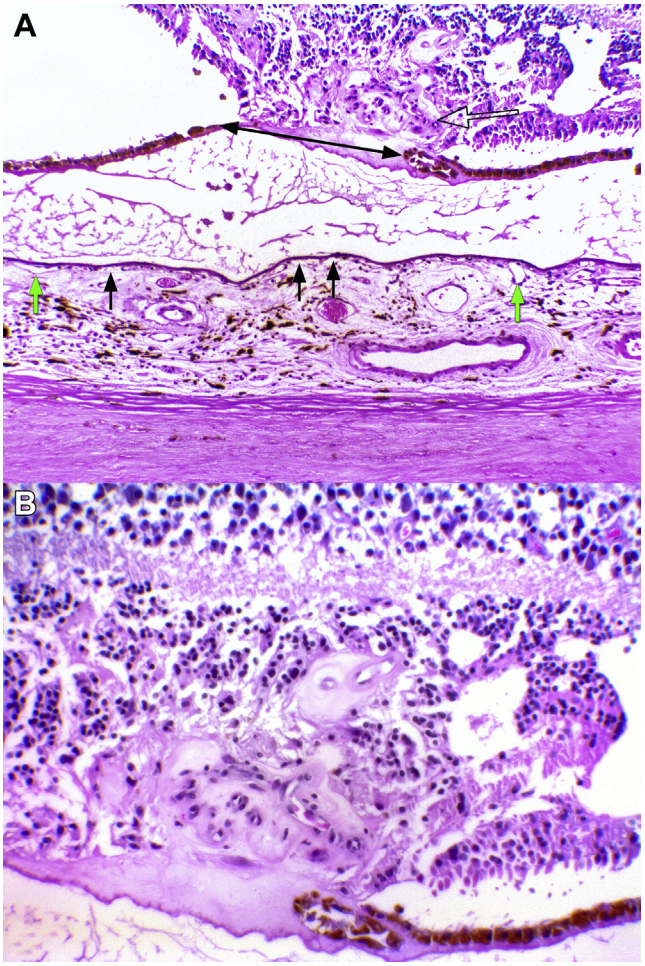

Figure 14. Light microscopy images showing histopathologic analysis of type 3 neovascularization. **A**, Entanglement of capillaries in a neovascular frond extending down through the outer nuclear layer (open arrow) to a retinal pigment epithelium (RPE) defect. Note the gap in the RPE layer at the region of contact (double arrow). The choriocapillaris bears numerous areas absent of vessels, some of which are shown by the black arrows, and the green arrows highlight deeper vessels that have been enfaced to the choriocapillaris level (hematoxylin and eosin, ×100). **B**, Higher magnification of the neovascularization (hematoxylin and eosin, ×200).

vessels were more easily seen,[61] does not translate well to neovascular lesions. No foundational reason exists to expect that the atrophic areas in the context of MNV would be round or oval well-defined lesions. Because intervening neovascular tissue is present, the underlying choroidal vessels may not be seen at all. In the Age-Related Eye Disease Study 2, 40% of patients demonstrating MNV also showed atrophy at baseline.[62] These data illustrate how late AMD is not an either-or phenomenon. Therefore, the CONAN group followed the lead of the Classification of Atrophy Meetings group[20] and adapted their definitions for nonneovascular AMD to describe atrophy in the context of neovascular disease.

Outer Retinal Atrophy. Outer retinal atrophy refers to observable architectural thinning of the outer nuclear layer with loss of visualization and intensity of reflection from outer retinal bands, particularly the ellipsoid zone as imaged by OCT.[63] There are no correlates visible by color fundus photography because this imaging method merely provides en face information, unlike OCT, which allows the architecture of the retinal layers to be visualized. Outer retinal atrophy can be seen in areas overlying large drusen, after regression of SDD, over areas of neovascularization, over areas of fibrosis, and in regions affected by subretinal fluid. Histologic evaluation has shown loss of photoreceptor outer segments, retraction and widening of the inner segments, and loss of the number of nuclei in the outer nuclear layer.[64] In complete outer retinal atrophy (cORA), the ellipsoid zone and the interdigitation zone are not visible, the external limiting membrane may not be discernable, and the outer nuclear layer becomes thinner. In incomplete ORA, a discontinuous loss of the ellipsoid zone has occurred, and the interdigitation zone is typically not visible.[20]

Retinal Pigment Epithelial and Outer Retinal Atrophy. In complete RPE and outer retinal atrophy,[20] an absence of the RPE is present, as manifested in OCT imaging by a loss of the RPE band with associated choroidal hypertransmission in OCT imaging, together with the findings of cORA in a zone of at least 250 μm (Fig 17). Incomplete RPE and outer retinal atrophy is defined in OCT imaging by heterogeneous hypertransmission and associated fragmentary attenuation or loss in the reflectivity from the RPE band with overlying photoreceptor degeneration in a zone less than 250 μm. In patients with MNV with exudation or in treated patients, the extent of RPE loss can be difficult to determine from OCT scans, because it may be difficult to identify with certainty the RPE band when adjacent exudation or fibrosis decreases local contrast. Autofluorescence imaging is very helpful; a region with decreased or absent autofluorescence in the absence of overlying hemorrhage implies a loss of functional RPE cells.

Varying amounts of atrophy are often present in eyes with MNV. Loss of more central macular tissue leads to the use parafoveal areas for fixation at a cost of decreased visual acuity. Visual acuity is related to the health and proximity that the new retinal locus of fixation has to the macular center. If parafoveal and perifoveal atrophy are present, the patient may retain relatively good visual acuity because the central fovea is intact. Subsequent involvement of the fovea with neovascularization would compromise foveal function, but then the nearest intact area of the retina to establish eccentric fixation may be outside of the anatomic confines of the macula. In these cases, a small area of neovascularization may cause a large loss of visual acuity.

Discussion

Advances in diagnostic imaging and learnings from therapeutic outcomes have substantially changed the understanding of neovascular AMD as a morphologic disease entity. The substitution of largely angiographic definitions by OCT-based feature identification, the insight into the origins of neovascular development including both the retina and choroid, and the differentiation of neovascular and atrophic pathways including their concomitant occurrence are prominent examples of evolution of disease conceptualization and the need for adjustment in AMD terminology. The OCT and OCT angiography findings, both noninvasive methods of imaging MNV, do not correspond directly to the older fluorescein angiographic categories such as classic, occult, or mixed. Over a period of 3 years, the CONAN study group held 3 two-day meetings to achieve consensus on many aspects of AMD. Consultation with outside experts and reading centers was obtained to help harmonize the definitions. The proposed classification has been propelled by advances in imaging technology,

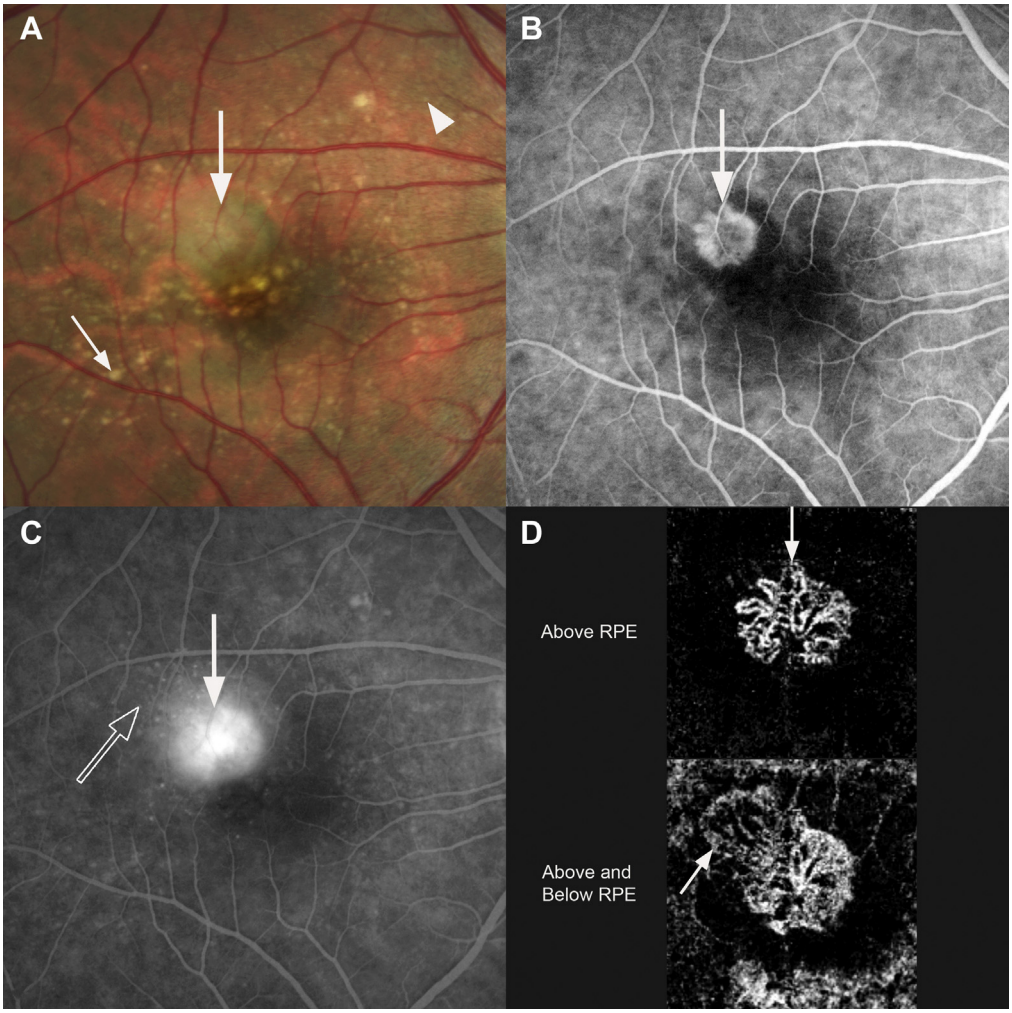

Figure 15. Images showing mixed type 1 and type 2 macular neovascularization. **A**, Fundus photograph from 62-year-old showing a region of yellowish exudation (larger arrow). Note the drusen (smaller arrow) and pseudodrusen (arrowhead). **B**, Early-phase fluorescein angiogram showing a well-defined area of neovascularization (vertical arrow). **C**, Later-phase fluorescein angiogram showing pronounced leakage from the well-defined neovascularization and some punctate leakage from and adjacent area (open arrow). **D**, En face OCT angiogram showing 2 perspectives: (**Top**) above the level of the retinal pigment epithelium (RPE), the well-defined lesion seen in the fluorescein angiogram is evident (vertical arrow); (**Bottom**) the slab section was deepened to include visualization of neovascularization below the RPE. The neovascularization above the RPE, seen as the well-defined lesion, is type 2, and the deeper proliferation, below the RPE, is type 2 macular neovascularization.

particularly OCT and OCT angiography, which have provided detailed 3-dimensional analysis of the vascular anatomic and topographic characteristics within neovascular AMD lesions. Use of accepted classification and terminology will improve standardization of investigation and reporting of AMD. Better precision in terminology will enhance reporting and comparability of AMD studies. The CONAN group recommends that the consensus standards outlined in this article should be used in future reported studies of neovascular AMD.

A plethora of terms exist in the literature to describe the lesions seen in neovascular AMD, and many of these continue to appear in the current literature. Many of these terms are based on older imaging technologies. For example, the term *occult* neovascularization is a fluorescein angiographic term describing MNV in which the vessels are not visualized directly but are rather presumed to be present based on certain fluorescein leakage characteristics.[65] This fluorescein angiographic appearance was used to infer that a subtype of neovascularization was present.[66] These fluorescein angiographic imaging characteristics are the result of discernable fluorescence within and in tissue around vessels but are influenced by many associated nonvascular factors, including vessel location, pigmentation, permeability of overlying RPE, and associated hemorrhage and exudation. OCT and OCT angiography techniques afford direct imaging of the anatomic features with precision in evaluating each component, neovascular or not.

Limitations and Challenges for the Future

The classification system is based on current knowledge of neovascularization imaged with contemporaneous imaging capabilities. Producing the most robust models of visual

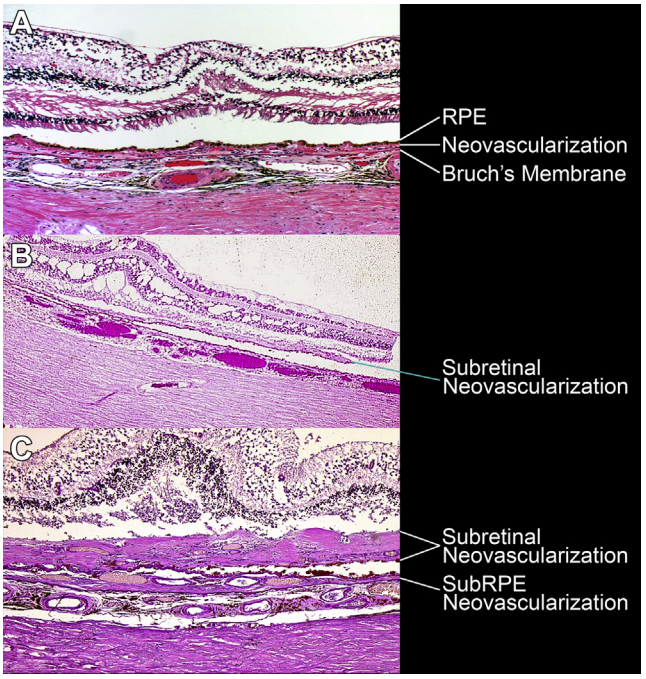

Figure 16. Light microscopy images showing variations on neovascularization arising from the choroid. **A**, The proliferation can occur directly under the retinal pigment epithelium (RPE). Note that the RPE and photoreceptors are intact. **B**, Neovascularization may grow in a purely subretinal location. The RPE is disrupted, the photoreceptors are atrophic, and cystoid edema is present. **C**, A mixed pattern of neovascular proliferation manifesting as both sub-PRE and subretinal growth. The neovascularization is collagenized; this may be considered a disciform scar (hematoxylin and eosin, ×100).

function, disease severity, and prediction for future vision loss will require additional information from multimodal imaging and cross-correlation with functional data. New research will be required to reach these goals. Over time, knowledge about neovascularization will increase and associated concepts will be refined. Concurrently, imaging will improve, and additional biomarkers may be realized. The current classification provides a method to categorize neovascularization and other lesion components in neovascular AMD and should help to improve standardization and communication among researchers, clinicians, and patients. This new classification should help future studies to be more rigorous and generalizable. It should also help in harmonizing definitions among both reading centers and clinical investigators. The general framework of this classification allows its refinement with the addition of future data, including analysis of accuracy and repeatability of the definitions.

With a classification system in place, a method of grading neovascular AMD disease severity would be possible. Currently, AMD is typically classified into stages, such as early, intermediate, or late.[66] The risk of progression from an earlier stage to late disease was analyzed extensively from data obtained in the Age-Related Eye Disease Study and used to create the Beckman

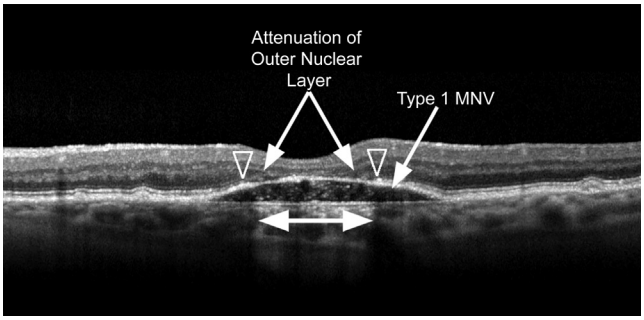

Figure 17. Complete retinal pigment epithelial and outer retinal atrophy in an eye with type 1 macular neovascularization (MNV) (arrow). Loss of the outer retina over the fibrovascular pigment epithelial detachment is present. The ellipsoid termination is demarcated by the arrowheads. Central to this is a tapering discontinuance of the outer nuclear layer (angled double arrow). Absence of the underlying retinal pigment epithelium with hypertransmission into the choroid (horizontal double arrow) is present.

classification.[67] Late AMD was defined as either geographic atrophy or choroidal neovascularization. Substituting more modern terms, late AMD would be complete RPE and outer retinal atrophy,[20] an OCT-defined entity that corresponds roughly to geographic atrophy or MNV. Criticisms of this approach are that complete RPE and outer retinal atrophy and MNV are different conditions with dissimilar pathophysiologies, and therefore, they should not be lumped together. The basis of this staging system was from an era when late AMD implied an extraordinary risk for severe vision impairment. Detecting a neovascular lesion by fluorescein angiography, for instance, generally meant the patient harbored an extreme risk for profound vision loss. The goal was to predict the likelihood of progressing to late disease, not to predict visual function. With modern treatment, stabilization or improvement of visual acuity is likely in patients with MNV, leading to the need to grade disease severity, which is an assessment of the total effect of disease on an organ, both reversible and irreversible. The CONAN group envisions that an extension of proposed terminology to describe disease severity in neovascular AMD and its relationship to visual function will be developed.

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Abbreviations and Acronyms:
AMD = age-related macular degeneration; **CONAN** = Consensus on Neovascular AMD Nomenclature; **cORA** = complete outer retinal atrophy; **MNV** = macular neovascularization; **PED** = pigment epithelial detachment; **RPE** = retinal pigment epithelium; **SHRM** = subretinal hyperreflective exudative material; **VEGF** = vascular endothelial growth factor.

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