SURVEY OF OPHTHALMOLOGY VOLUME 42 • NUMBER 3 • NOVEMBER–DECEMBER 1997

ELSEVIER

MAJOR REVIEW

Pathophysiology and Management of Subretinal Hemorrhage

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Abstract. Subretinal hemorrhage can arise from the retinal and/or choroidal circulation. Significant subretinal hemorrhage occurs in several conditions, but most commonly is associated with age-related macular degeneration, presumed ocular histoplasmosis, high myopia, retinal arterial macroaneurysm, and trauma. Released toxins, outer retinal shear forces, and a diffusion barrier created by subretinal hemorrhage all contribute to photoreceptor damage and visual loss. The use of tissue plasminogen activator and improvements in surgical instrumentation have facilitated surgical drainage and have made it a useful option in the management of selected cases. Mechanisms of subretinal hemorrhage formation, underlying etiologies, diagnostic evaluation, and the histopathology of damage are summarized. Published surgical series are reviewed and surgical advances are summarized. The value of surgically removing subretinal hemorrhages to improve visual outcome remains unestablished, because definitive studies have not been performed. Guidelines for selecting candidates for surgical intervention are proposed. (**Surv Ophthalmol 42**:195–213, 1997. © 1997 by Elsevier Science Inc. All rights reserved.)

Key words. age-related macular degeneration • choroidal neovascularization • retinal arterial macroaneurysm • retinal surgery • subretinal hemorrhage • tissue plasminogen activator

Subretinal hemorrhage refers to blood located between the neurosensory retina and the retinal pigment epithelium (RPE). Blood in this potential space can arise from the choroidal and/or the retinal circulation. Subretinal hemorrhage of choroidal origin may arise directly from choroidal neovascular membranes (CNVs) that have grown through breaks in Bruch's membrane, or subretinal hemorrhage may arise simply from choriocapillaris hemorrhage through discontinuities in Bruch's membrane. To understand why subretinal hemorrhage occurs, we will review several proposed pathophysiologic mechanisms of its formation.

I. Sources of Subretinal Hemorrhage

A. CHOROIDAL CIRCULATION

1. Choroidal Neovascular Membranes

Subretinal hemorrhage is often secondary to an antecedent CNV. As in other forms of neovascularization (e.g., diabetic retinal neovascularization), angiogenic factors, endothelial cells, and a scaffold for growth are necessary for CNV formation. Diseased or ischemic neurosensory retina (possibly Müller cells) and RPE are postulated to provide angiogenic factors;[71,72,78,86,88,96,102] the choriocapillaris provides endothelial cells, and the RPE/Bruch's membrane complex provides the scaffold for growth. Retinal pigment epithelium cells can produce basic fibroblast growth factor (bFGF) and other vascular mitogens, e.g., vascular endothelial growth factor (VEGF), which can promote choroidal microvessel endothelial proliferation.[72,86,102] The new vessels grow through Bruch's membrane and, in some cases, through the RPE into the subretinal space.[42]

Neovascular membranes are prone to bleed. The nonfenestrated retinal endothelial cell walls with tight junctions between adjacent retinal vascular endothelial cells comprise the inner blood-retinal bar-

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0039-6257/97/$17.00
PII S0039-6257(97)00089-1

rier. In contrast, the capillary beds of CNVs are fenestrated. This structure permits exudation and, potentially, hemorrhage into the subretinal space. However, the fenestrae normally do not permit red blood cell egress from the lumen. This fact implicates an additional mechanism.

Perhaps more important in promoting vascular leakage than the mere presence of fenestrae in neovascular tissues is the effect of VEGF on these blood vessels. Vascular endothelial growth factor, also known as vascular permeability factor (VPF), is a potent hyperpermeability agent. This hyperpermeability has been hypothesized to occur secondary to the opening of fenestrae, which allows vesicular-vacuolar organelles to facilitate macromolecular extravasation from the blood vessels.[29,57,79] Vascular endothelial growth factor and other mitogens (e.g., bFGF) have been identified in human CNV specimens.[33,68] This feature may differentiate CNV from the normal choroidal and retinal circulation in terms of susceptibility to hemorrhage.

There are several other predisposing factors which, especially in combination with the fenestrated endothelium of CNV and the hyperpermeability secondary to VEGF, make the CNV prone to hemorrhage. Hypertension possibly enhances leakage caused by raised internal pressure within the neovascular lumen. Microtrauma might facilitate leakage through fenestrated cell junctions, resulting in subretinal hemorrhage. Another proposed risk factor for formation of subretinal hemorrhage secondary to CNV is prolonged bleeding time due to anticoagulant use.[30]

In age-related macular degeneration (AMD), CNVs most commonly occur in the macula.[7] Diseased Bruch's membrane and RPE may predispose the macular area to develop CNV through several mechanisms. For example, RPE damage may be the greatest in the macula. Indeed, it is necessary to have some compromise of the RPE in choroid-derived subretinal hemorrhage. This compromise is necessary because the tight junctions between RPE cells, which comprise the outer blood-retinal barrier, must be penetrated to permit subretinal hemorrhage formation from the choroid. In AMD, RPE residual bodies are most abundant in the macular region,[104] and drusen and RPE degeneration (as well as CNVs) are found predominantly in the macula.[104] Thickened Bruch's membrane may be a barrier to the adequate transfer of metabolites between the choriocapillaris and the RPE and outer retina.[40] The resulting metabolic abnormalities, including ischemia, may predispose to neovascularization. In addition, the choriocapillaris and/or the RPE may lose some inherent function, such as the ability to suppress production of neovascular growth factors.[40] Also, the rate of choroidal blood flow and concentration of short ciliary arteries are greatest in the macula.[36] Because CNV has a predilection for the macula, this is a common site for subretinal hemorrhage.

2. Clinically Evident Discontinuities in Bruch's Membrane

Choroid-derived subretinal hemorrhage can arise from a break in the Bruch's membrane/RPE complex. Known as "choroidal rupture" when secondary to trauma and as "lacquer cracks" in the setting of high myopia, this condition predisposes to hemorrhage in the subretinal space.[4] At the time of initial bleeding, CNVs are not present in these cases, although CNVs can arise later at the site of the break in the Bruch's membrane/RPE complex. The break creates an access route from the choroidal circulation (choriocapillaris) through the compromised outer blood-retinal barrier to the subretinal space. Angioid streaks also predispose to the development of subretinal hemorrhage, as they represent discrete breaks in thickened calcified Bruch's membrane.[20,27,85] In this condition, Bruch's membrane is brittle, and choroidal rupture can occur with minor trauma.

B. RETINAL CIRCULATION

Subretinal hemorrhage can arise from the retinal circulation. As with choroidal sources of subretinal hemorrhage, a breakdown of the blood-retinal barrier is necessary, in this case in the inner blood-retinal barrier. The retinal vessels bleed, with resultant dissection into the subretinal space, forming subretinal hemorrhage and, at times, intraretinal hemorrhage. Thus, any retinal vascular abnormality or retinal trauma that causes retinal endothelial compromise (inner blood-retinal barrier) will predispose to formation of subretinal hemorrhage. Indeed, it is likely that some of the risk factors for subretinal hemorrhage derived from the choroidal circulation are also risk factors for hemorrhage derived from the retinal circulation—hypertension, microtrauma, and anticoagulant use.

II. Underlying Etiologies

In all cases, the choroidal and/or retinal circulations are the source of subretinal hemorrhage. There are specific ocular diseases that are commonly associated with subretinal hemorrhage. These conditions can produce either CNV, discontinuities in Bruch's membrane, or retinal circulation leakage.

A. AGE-RELATED MACULAR DEGENERATION

The most common disease associated with subretinal hemorrhage is AMD. A choroidal neovascular membrane is the usual source of bleeding in these cases. Pathological changes of AMD include attenua-

tion of the RPE, accumulation of vesicular granular material between the RPE plasmalemma and RPE basement membrane (basal laminar deposit), and accumulation of vesicular granular material external to the RPE basement membrane and within the collagenous layer of Bruch's membrane (basal linear deposit).[12]

Choroidal neovascular membranes predispose to subretinal hemorrhage as well as to disciform scarring. Histopathologic studies indicate that photoreceptor atrophy commonly accompanies CNV both in the early and later stages (i.e., disciform scarring) with or without associated subretinal hemorrhage.[35] Thus, the visual acuity prognosis in AMD-related subretinal hemorrhage is guarded, regardless of whether the hemorrhage spontaneously clears or is removed surgically.[6,8,30,65,90,102] In a series of 39 patients with subretinal hemorrhage and AMD, Ibanez et al found a mean final visual acuity of approximately 20/400 even after surgical removal of the hemorrhage.[52] This was not a significant change from the preoperative visual acuity. (Visual acuity prior to the subretinal hemorrhage was not reported.)

Nasrallah et al have described a subgroup of patients with subretinal hemorrhage and AMD that had no evidence of CNV.[73] In eight patients with hemorrhages in areas of the RPE and choriocapillaris atrophy without evidence of CNV, small subretinal hemorrhages resolved spontaneously. In six of eight patients, the hemorrhage was less than one-half a disk diameter in size. The hemorrhages spontaneously cleared without complications (no CNV) over 1–15 months, but the visual acuity remained unchanged (poor) because of the pre-existing retinal atrophy. Other authors have also recognized this subgroup.[52,63] The second mechanism described before may best explain the formation of these subretinal hemorrhages (i.e., temporary direct communication of choriocapillaris with the subretinal space).

B. PRESUMED OCULAR HISTOPLASMOSIS SYNDROME

Choroidal neovascular membranes associated with the presumed ocular histoplasmosis syndrome (POHS) may cause subretinal hemorrhage. Subretinal hemorrhage has been seen evolving during the course of fluorescein angiography, originating from a CNV secondary to POHS.[2]

Despite similar mechanisms of formation, the subretinal hemorrhage of AMD and that of POHS have markedly different visual prognoses, with or without surgery. Age-related macular degeneration and POHS both have subretinal hemorrhage secondary to CNVs. Age-related macular degeneration has the worst final acuity of all etiologies, whereas POHS-related subretinal hemorrhage may resolve to 20/30 vision.[6,31] This difference may be attributed to several factors.

First, there is a difference in patient age. Age-related macular degeneration is most common in patients over 60 years in age, whereas POHS most frequently affects the 20–50-year-old age group. The younger POHS patients may have better RPE function and, thus, a greater ability to limit CNV growth, promote CNV involution, and clear subretinal hemorrhage more efficiently and quickly through the endogenous release of plasminogen activator and the phagocytosis of erythrocytes.[16,17,39,51,58,60]

Second, in POHS the CNVs and resultant disciform scars are smaller than in AMD, which might favorably influence the final visual acuity.[37,51] This better acuity may be due to a preferred eccentric fixation locus closer to the fovea in POHS.[51]

Third, in AMD the blood from the CNV may be located in the sub-RPE space as well as the subretinal space.[35] Hemorrhage from POHS more often occurs principally in the subretinal space.[35a] Perhaps this occurs because a component of the CNV often underlies the RPE in AMD (classified by Gass as type 1 CNV), whereas in POHS, the CNV is relatively more often located anterior to the RPE (type 2 CNV).[37,42,92] Generally, sub-RPE hemorrhage has a worse visual prognosis than subretinal hemorrhage without sub-RPE hemorrhage. This is probably because the RPE is separated from the choroid by sub-RPE hemorrhage, thereby compromising metabolic exchange between the RPE and subjacent choriocapillaris. Also, thick subretinal hemorrhage, which portends a poor visual outcome (see next paragraph), is probably more common in AMD than in POHS.

Fourth, in AMD the RPE and Bruch's membrane are diffusely diseased (e.g., accumulation of lipofuscin in RPE, basal laminar deposit between RPE and its basement membrane, and thickening of Bruch's membrane with basal linear deposit), and this fact may in some way underlie the better prognosis of subretinal hemorrhage in POHS than in AMD, with or without surgery.

C. RETINAL ARTERIAL MACROANEURYSM

Another ocular disease associated with subretinal hemorrhage is retinal arterial macroaneurysm, a focal, acquired dilatation of a retinal arteriole. The pathogenesis of arterial macroaneurysm is postulated to be secondary to focal arteriolar wall disease causing increased susceptibility to dilatation by intralumenal pressure.[80] Predisposing factors, including increasing age (usually greater than 60 years old), hypertension, and atherosclerosis, may cause arteriolar wall damage and increase the propensity to macroaneurysm formation.[80] The condition is more prevalent in women and is most often found along

the temporal arcades. The most common causes of visual loss are macular exudate and hemorrhage from the macroaneurysm. The visual prognosis in these cases is relatively good, with or without surgery.[1,10,66,75] A rupture of the macroaneurysm may lead to dissection from the retinal circulation into the subretinal space, causing subretinal hemorrhage. This is usually accompanied by intraretinal and/or preretinal hemorrhage.[80] Consequently, the macroaneurysm may be difficult to detect clinically in cases with subretinal hemorrhage. Fluorescein angiography and identification of hard exudates and other signs of hypertension and atherosclerosis are helpful in establishing the diagnosis.

D. HIGH MYOPIA

High myopia (pathologic, degenerative), defined as myopia greater than −6 diopters, also is associated with subretinal hemorrhage.[4,87] Thinned choroidal and RPE layers in the area centralis along with lacquer cracks (breaks in Bruch's membrane) allow CNVs to grow into the sub-RPE and subretinal spaces, causing subretinal hemorrhage.[50] Continued CNV growth may lead to recurrent subretinal hemorrhage and eventual disciform scarring. The prognosis is better when the hemorrhage occurs through lacquer cracks without evidence of CNV; this type is more common in the younger population (less than 50 years old) with pathologic myopia.[47]

E. TRAUMA

A choroidal rupture secondary to blunt trauma may cause an immediate subretinal hemorrhage through direct communication of the subretinal space and the choroid. Hemorrhage can also occur months or years later as a result of CNV growth through the traumatic break in Bruch's membrane.[14]

Penetrating trauma can cause subretinal hemorrhage, sometimes massive in extent.[45] The visual prognosis is more guarded in these cases because of the large size of the subretinal hemorrhage and because of other complications of penetrating trauma (e.g., vitreous hemorrhage, infection, intraocular foreign body-induced damage, and neurosensory retinal trauma). Although CNVs do not play a role in the initial subretinal hemorrhage, CNVs can occur as early as 2 weeks after traumatic subretinal hemorrhage, making the treatment more complex and the prognosis worse.[14]

There is a subgroup of patients who have a good visual prognosis despite massive subretinal hemorrhage.[81] These are patients whose hemorrhages occur as complications of scleral buckle operations or other vitreo-retinal procedures. Three particular complications have been reported to cause massive subretinal hemorrhage: a deep scleral suture pass, hemorrhage at the internal drainage site, and perforation of the globe with a scleral depressor.[81] The subretinal hemorrhage is usually discovered intraoperatively, and it can be surgically drained, in many cases within an hour of formation.[81]

F. OTHER CAUSES

Other conditions associated with subretinal hemorrhage include angioid streaks (sometimes present in patients with pseudoxanthoma elasticum, Ehlers-Danlos syndrome, Paget's disease of the bone, and sickle cell disease), tumors (melanomas, choroidal metastases, choroidal osteomas, and retinal cavernous hemangiomas), other causes of CNVs, iatrogenic causes (laser procedures, surgery), retinal tears, Terson's syndrome, diabetic retinopathy, Valsalva retinopathy, central retinal vein occlusion, idiopathic central serous choroidopathy, and coagulopathies.[8,9,28,85]

III. Diagnosis of Subretinal Hemorrhage

A. SYMPTOMS/SIGNS

The usual initial symptoms of subretinal hemorrhage include sudden onset of blurred vision, scotoma, and/or metamorphopsia. However, in eyes with subfoveal disciform scarring (often AMD-related) or in eyes with penetrating trauma, the hemorrhage may not be as obvious to the patient because of concurrent visually limiting disease processes. If the subretinal hemorrhage is extrafoveal, it may be minimally symptomatic, with preserved central vision.

Subretinal hemorrhage causes elevation of the overlying neurosensory retina, as seen on fundus examination (Fig. 1). The color varies from bright red to dark red to green (in cases of very thick subretinal hemorrhage). Once the hemorrhage is dehemoglobinized, it can appear yellow or tan in color. Folds in the overlying retina may be present. The borders of the hemorrhage are generally scalloped with somewhat irregular margins. When the subretinal clot undergoes liquefaction, layering can be seen, with the liquefied blood appearing thickest centrally or inferiorly. Gravity-induced layering of the liquefied hemorrhage can give the appearance of a pseudohypopyon (Fig. 1). A large subretinal hemorrhage with a green appearance and moundlike elevation can be confused with a choroidal melanoma (Fig. 2). Unnecessary enucleations have resulted due to this diagnostic confusion.[9,35]

B. ASSOCIATED FINDINGS

A sub-RPE hemorrhage can appear as a dark green/brown bulla, deep to the subretinal hemorrhage. When visible, the borders of sub-RPE hemorrhage appear smooth and well demarcated. As discussed earlier, vision tends to be worse in these

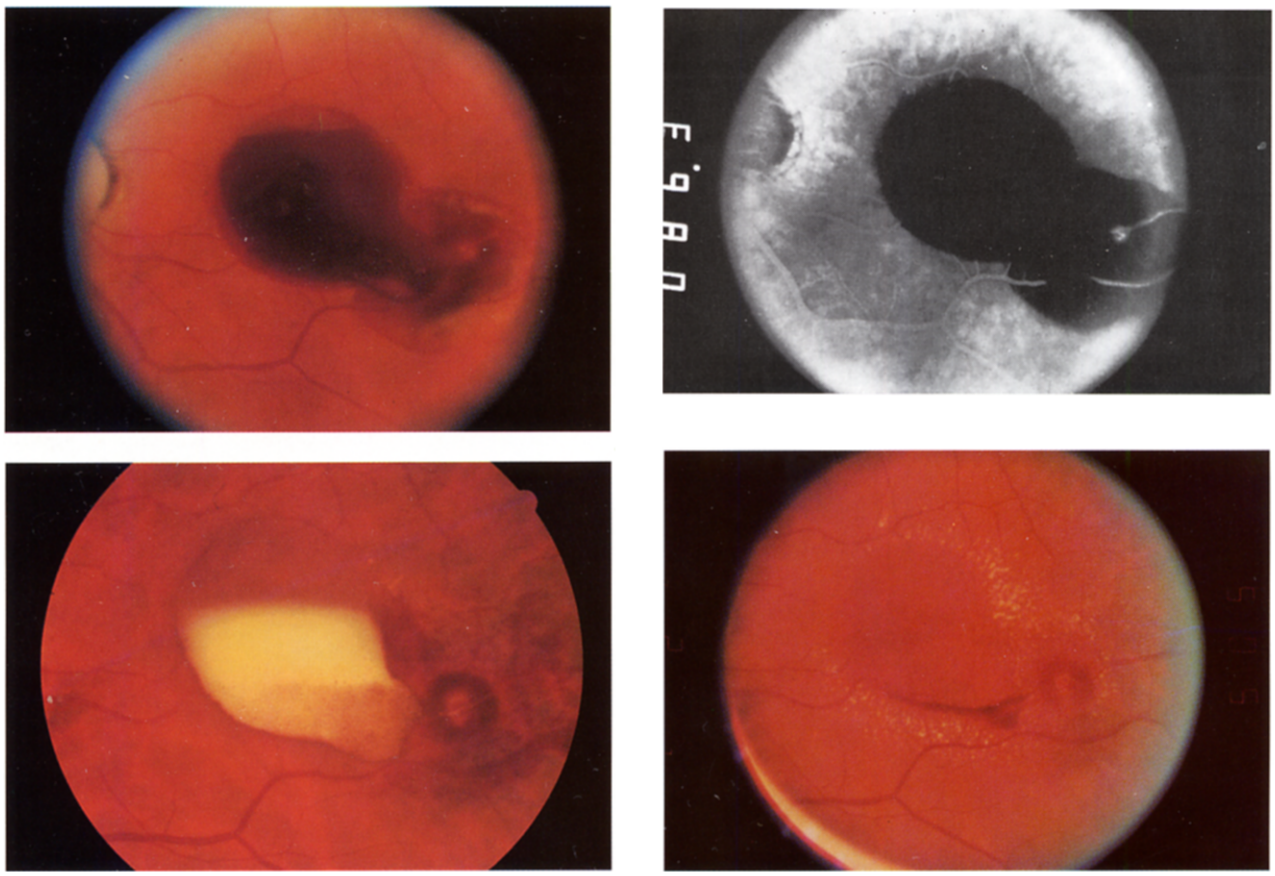

Fig. 1. Subretinal hemorrhage secondary to arterial macroaneurysm in a 65-year-old man with a history of hypertension controlled with medication. *Top left:* On presentation, the visual acuity was 2/200. The fundus photograph reveals boat-shaped subhyaloid hemorrhage over the macula. Inferotemporal to and contiguous with the subhyaloid hemorrhage is subretinal hemorrhage, some of which is dehemoglobinized (yellow). The arterial macroaneurysm giving rise to the hemorrhage appears yellow-white. *Top right:* Fluorescein angiogram shows the hyperfluorescent macroaneurysm. The subhyaloid hemorrhage blocks the fluorescent retinal vessels in contrast to the subretinal hemorrhage which blocks only the choroidal fluorescence. *Bottom left:* Fundus photograph taken 2 months later. The dehemoglobinized blood has layered, creating a boat-shaped subhyaloid pseudohypopyon. The subretinal hemorrhage has cleared substantially. *Bottom right:* Fundus photograph taken 6 months after presentation. The visual acuity is 20/25.

cases, as both the RPE and photoreceptors experience ischemic atrophy. Differentiating sub-RPE hemorrhage from subretinal hemorrhage can be challenging, as thick subretinal hemorrhage sometimes appears green (Fig. 2). With sub-RPE hemorrhage, surface details such as foci of RPE hyperplasia and drusen are visible. In contrast, such detail is usually obscured by subretinal hemorrhage.

Choroidal melanoma, retinal cavernous hemangioma, retinal arterial macroaneurysm, chorioretinal scars, signs of AMD, and evidence of CNV may also be associated findings. Choroidal neovascular membrane, however, may not be visible, either by ophthalmoscopy or fluorescein angiography. On fundus examination, clues to the presence of CNV, which may be only partially obscured by blood, include associated disciform scarring, RPE detachment, serous subretinal fluid and lipid, and, occasionally, a gray-green pigmentary ring at the level of RPE.[17] Fundus findings in the fellow eye (e.g., drusen, disciform scar, hypertensive retinopathy) also may give helpful clues to the etiology of subretinal hemorrhage in the involved eye (Fig. 2).

C. DIAGNOSTIC STUDIES

Fluorescein angiography, digital indocyanine green videoangiography (ICG), and echography are useful tools for identifying and examining subretinal hemorrhage.

1. Fluorescein Angiography

On fluorescein angiography, subretinal hemorrhage blocks choroidal fluorescence. Overlying retinal vessels may fill normally and may reveal a retinal arterial macroaneurysm (Fig. 1). If there is an associated CNV, a patch of irregular choroidal hyperfluorescence may be seen in the early phase. In its classic form, this appears as a cartwheel pattern of fine ves-

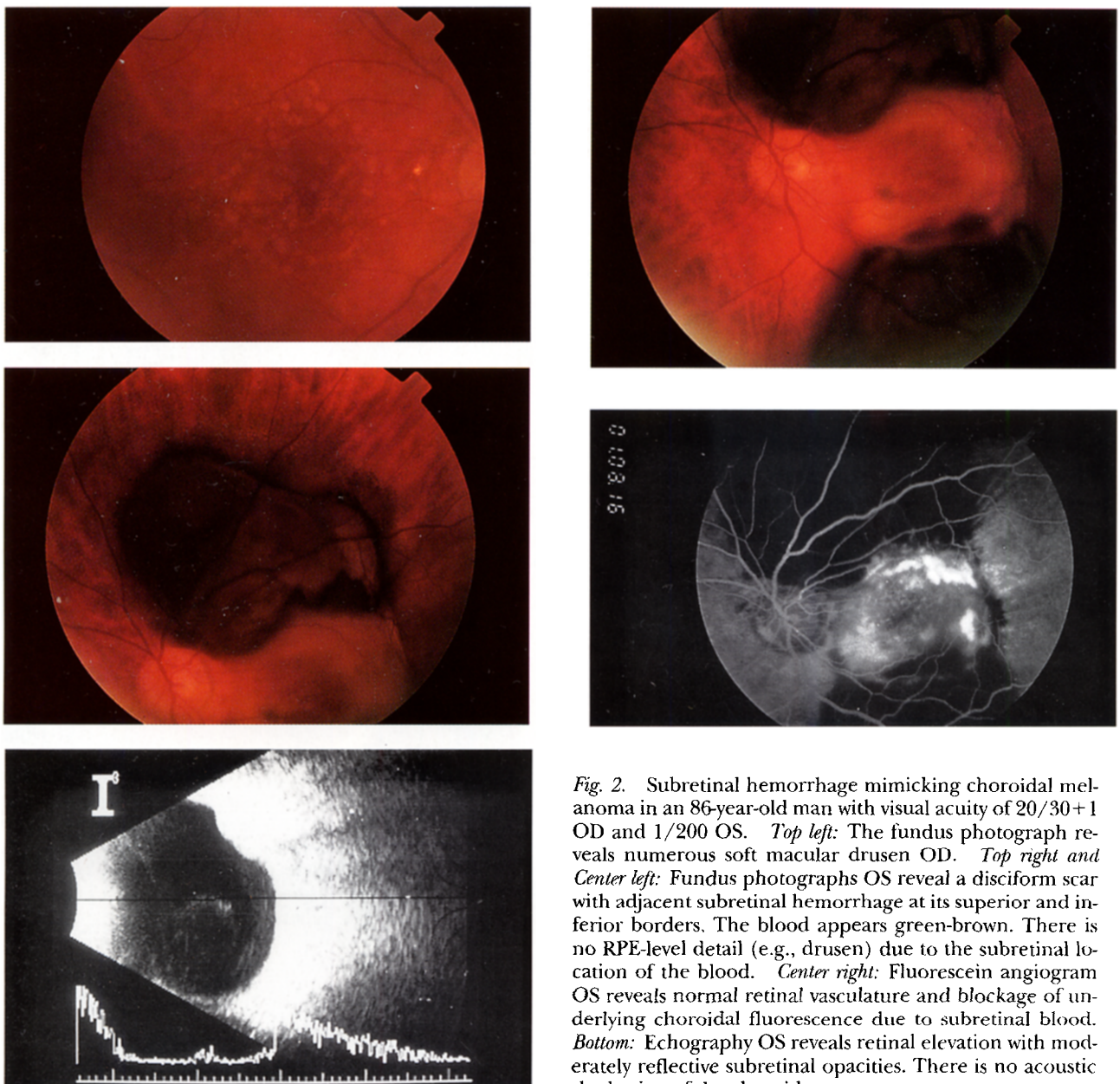

Fig. 2. Subretinal hemorrhage mimicking choroidal melanoma in an 86-year-old man with visual acuity of 20/30+1 OD and 1/200 OS. *Top left:* The fundus photograph reveals numerous soft macular drusen OD. *Top right and Center left:* Fundus photographs OS reveal a disciform scar with adjacent subretinal hemorrhage at its superior and inferior borders. The blood appears green-brown. There is no RPE-level detail (e.g., drusen) due to the subretinal location of the blood. *Center right:* Fluorescein angiogram OS reveals normal retinal vasculature and blockage of underlying choroidal fluorescence due to subretinal blood. *Bottom:* Echography OS reveals retinal elevation with moderately reflective subretinal opacities. There is no acoustic shadowing of the choroid.

sels. Of course, CNV will be seen only if it is located at the edge of subretinal hemorrhage or under very thin subretinal hemorrhage. Dye leakage into the subretinal space may be seen in the late venous phase of the angiogram, often with late staining of adjacent tissues.

2. Digital Indocyanine Green Videoangiography

Indocyanine green videoangiography may be useful in defining CNV in cases where it cannot be detected clinically or by fluorescein angiography (poorly defined, or occult CNV).[26] Indocyanine green absorbs light of long wavelength (790–805 nm) and also fluoresces in the near-infrared range (835 nm peak), which permits better penetration of overlying blood than fluorescein (which absorbs at 465–490 nm and emits 520–530 nm light).[44,83] Thus, in cases with thick, overlying subretinal hemorrhage, ICG may be able to define CNV (including occult CNV) better than fluorescein angiography can (Fig. 3).[44a] With ICG, in the late phase an increasingly hyperfluorescent spot or plaquelike area corresponds to CNV.[44a] Clinicopathologic correlation of occult CNV detected by ICG has been described.[18]

3. Echography

Echography is especially useful in the evaluation of massive subretinal hemorrhage. On B-scan, clotted

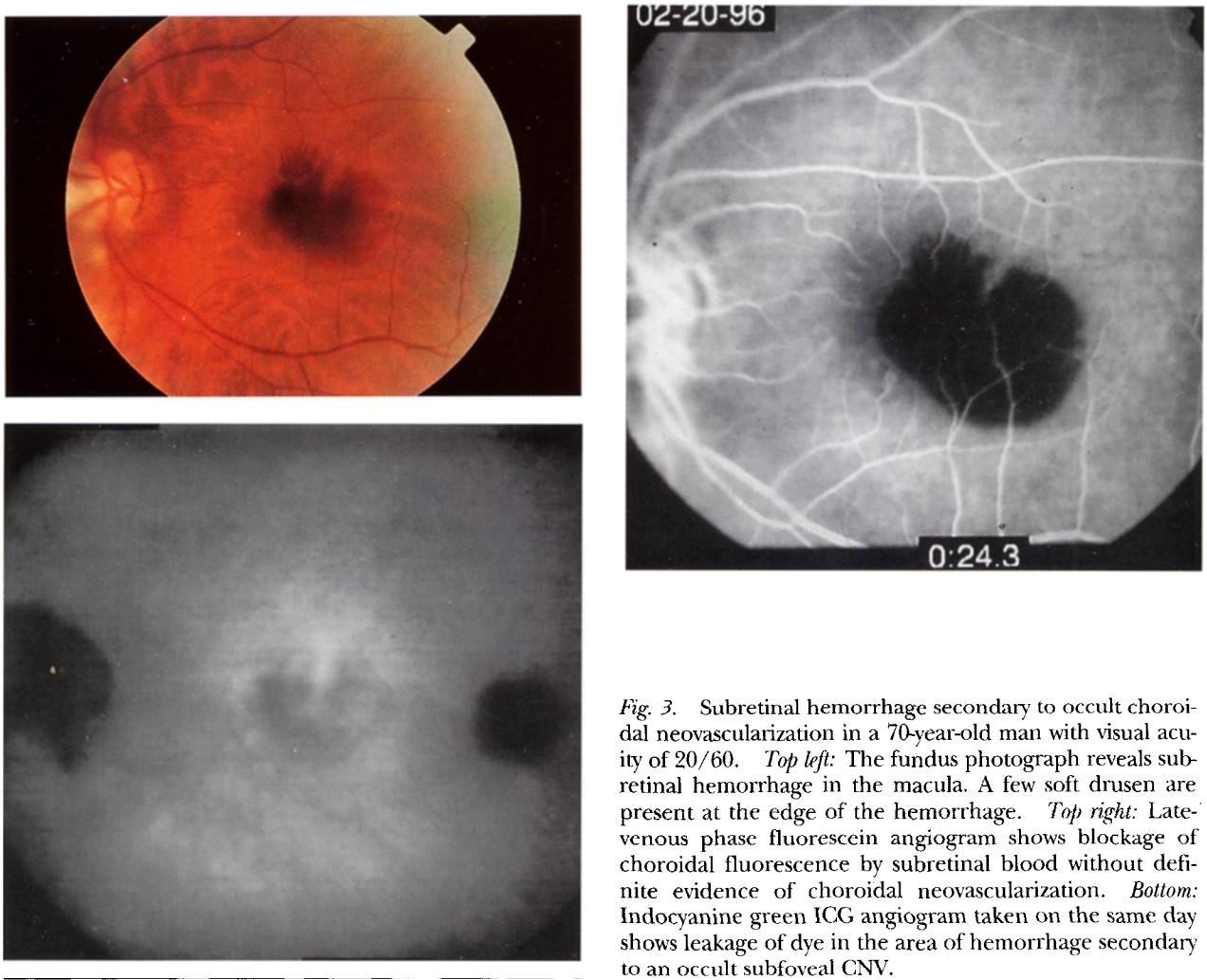

Fig. 3. Subretinal hemorrhage secondary to occult choroidal neovascularization in a 70-year-old man with visual acuity of 20/60. *Top left:* The fundus photograph reveals subretinal hemorrhage in the macula. A few soft drusen are present at the edge of the hemorrhage. *Top right:* Late-venous phase fluorescein angiogram shows blockage of choroidal fluorescence by subretinal blood without definite evidence of choroidal neovascularization. *Bottom:* Indocyanine green ICG angiogram taken on the same day shows leakage of dye in the area of hemorrhage secondary to an occult subfoveal CNV.

subretinal hemorrhage creates a nonmobile retinal elevation with moderately reflective subretinal opacities. When a funnel retinal detachment is present, the funnel apex may appear echolucent if surrounded by dense subretinal hemorrhage. With B-scan, layering of the subretinal hemorrhage might be seen after clot lysis. With A-scan, subretinal hemorrhage appears behind the high spike of the detached retina as low-reflective echoes, unless there is a dense clot of blood (uncommon), which would appear highly reflective.[35a]

IV. Histopathology and Pathogenesis of Visual Loss

Although diagnosis of subretinal hemorrhage can be made with funduscopy, the vision-impairing cellular changes that occur with it can be seen only with the aid of light and electron microscopy. Animal research has been invaluable in elucidating these histopathological changes, as well as the efficacy and mechanisms of various treatment strategies. The two animal models studied most commonly have been the cat and the rabbit. The cat retina is holangiotic (i.e., fully vascularized with a choroidal and retinal circulation), whereas the rabbit retina is merangiotic (i.e., only partially vascularized with choroidal circulation only, except at the medullary ray). Neither are perfect facsimiles of the human retina, but both models have provided background information that has been applied to human studies. Subretinal hemorrhage has been shown to cause retinal damage through three mechanisms: chemical toxicity, mechanical traction on the photoreceptor outer segments, and establishment of a diffusion barrier. These mechanisms were originally postulated by Glatt and Machemer in 1982.[40]

A. TOXIC EFFECT

The toxic effect of subretinal hemorrhage is caused by several different substances. Iron, in the form of ferritin, is produced during the absorption of subretinal hemorrhage. Erythrocytes are phagocytosed by macrophages and to a lesser extent by RPE, Müller cells, and giant cells.[58–60] As the engulfed erythrocytes are metabolized, hemosiderin is converted to ferritin. The released iron is toxic to the choriocapillaris and retinal circulation.[59,82] Iron in-

duces destruction of the photoreceptor layer and RPE.[54] The outer retina overlying the hemorrhage atrophies over months, in part due to iron toxicity. Iron toxicity appears to be time- and dose-dependent.[82] Subretinal hemorrhage also contains substances that are mitogenic for RPE cells and which may stimulate the development of CNV, as discussed earlier. Subretinal hemorrhage contains chemoattractants for macrophages and fibroblasts that predispose to fibrocellular scar formation.[15,35,101]

B. TRACTION EFFECT

Fibrin is produced by subretinal hemorrhage and is the blood product responsible for retinal traction during clot retraction. In the cat model, Toth et al found histopathologic evidence that 25 minutes after injection of blood into the subretinal space, fibrin strands directly attached to the subretinal hemorrhage clot interdigitated with photoreceptor outer segments.[95] At 1 hour, photoreceptor outer segments were torn in sheets from the retina in these areas of interdigitation.[54,95] By day 7 of subretinal hemorrhage, there was significant retinal degeneration involving both the inner and outer retinal layers, as well as the RPE.[54,95] In the rabbit model, Glatt and Machemer found fibrin attachments to the retina with the earliest signs of retinal changes at 24 hours, and significant degeneration of the retina between 3 and 7 days.[40]

C. BARRIER EFFECT

The third mechanism of retinal damage is the barrier effect of subretinal hemorrhage. Among the essential functions of the RPE is the transfer of nutrients (e.g., oxygen, retinoids) from the choriocapillaris to the outer retina and the transfer of metabolites (e.g., water, ions, and other metabolic byproducts of the RPE and retina) from the outer retina to the choroidal circulation.[48] The solid blood clot constitutes a diffusion barrier that interferes with these events. In humans, the thickness of the subretinal hemorrhage has been inversely correlated with the visual prognosis.[6]

V. Natural History and Prognostic Factors

A. NATURAL HISTORY

It is essential to establish the natural history of subretinal hemorrhage in order to evaluate treatments.

Bennett et al[6] retrospectively reviewed 29 cases of subretinal hemorrhage of at least one-disk diameter in size causing visual loss. These patients were studied for an average of 3 years (minimum of 6 months). This series was nonconsecutive, as only previously photographed eyes were included. Non-AMD eyes showed significantly improved mean visual acuity from 20/650 to 20/200 (N = 17). Age-related macular degeneration eyes showed no improvement (final average vision of 20/1700; N = 12). Eyes with choroidal rupture had the best final visual acuity (mean 20/35; N = 5). Thick subretinal hemorrhage had a worse prognosis (see next paragraph), and the size (area) of the subretinal hemorrhage was significantly associated with final visual acuity.

A retrospective study by Hayasaka et al of 24 eyes with pathologic myopia and subretinal hemorrhage showed that in 15 eyes without CNV the subretinal hemorrhage spontaneously resorbed within 1 year, and visual acuity improved or remained unchanged. In nine eyes with CNV, but without AMD, vision was unchanged or worsened.[49]

Berrocal et al, in a nonconsecutive retrospective study, found that eyes without subfoveal CNV experienced spontaneous improvement in visual acuity as subretinal hemorrhage resorbed.[8] Among eyes without subfoveal CNV, 6/6 (100%) with AMD-related subretinal hemorrhage and 4/5 (80%) with non-AMD-related subretinal hemorrhage showed spontaneous improvement in visual acuity (to better than 20/50 in four cases) over periods ranging from 3 to 56 months. In eyes with subfoveal CNV and subretinal hemorrhage, improvement in visual acuity was minimal as the subretinal hemorrhage resolved, except for two eyes that improved from approximately 5/200 to 20/400.

A retrospective study by Avery et al reported on 41 eyes with AMD-related subretinal hemorrhage and concurrent CNV.[3] The subretinal hemorrhage constituted greater than 50% of the lesion, so these eyes were not eligible for laser photocoagulation. Most eyes lost visual acuity. At 3 years follow-up, a mean of 3.5 Snellen lines (best corrected) had been lost, and only 3/16 (21%) of the eyes showed improvement of three lines or more. The thickness as well as the surface area of hemorrhage were predictive of worse visual outcome.

According to these retrospective reports, the natural history of subretinal hemorrhage is variable. Even though the data are limited, all studies support several conclusions. First, subretinal hemorrhage associated with CNV and thicker subretinal hemorrhage have a poor visual prognosis. Second, subretinal hemorrhage without CNV may have a good visual prognosis. The studies are limited because they are retrospective series, some are nonconsecutive series of patients, and refractions were not performed according to a standard protocol.

B. DURATION

The proposed mechanisms of retinal damage secondary to subretinal hemorrhage are time-dependent and species-specific in terms of the extent of in-

duced retinal pathology.[54] In humans, it is likely that all three mechanisms—the toxic effect, the fibrin-traction effect, and the barrier effect—play a role.[38] Generally, the extent of retinal degeneration and visual outcome worsen with increasing duration of subretinal hemorrhage. Several human studies have shown that the length of time between formation of subretinal hemorrhage and treatment is significantly correlated with final visual acuity, with longer time periods having poorer results.[3,63,97] However, enough exceptions have been reported to preclude definite conclusions regarding duration of subretinal hemorrhage and visual prognosis.[8,19,25,38,47]

C. THICKNESS

In addition to duration of subretinal hemorrhage, the thickness of subretinal hemorrhage is a prognostic factor in the final visual acuity. The average final visual acuity of thick subretinal hemorrhage in Bennett's retrospective series was 20/1300, whereas thin subretinal hemorrhage resolved to 20/240.[6] In that study, thick hemorrhage was defined as subretinal hemorrhage causing an obvious elevation of the retina. Thick subretinal hemorrhage may pose a more severe barrier to oxygen diffusion between the photoreceptors and choriocapillaris and may also have a greater toxic effect on the photoreceptors. In contrast to thickness, Bennett found no relationship between the surface area of the hemorrhage and visual prognosis (excluding the worse prognosis associated with subfoveal involvement). In contrast, Avery et al found that a larger surface area was correlated with a worse visual prognosis.[3]

D. UNDERLYING DISEASE

Underlying disease is one of the more significant prognostic factors related to final visual acuity. Many studies have found that AMD has the worst visual prognosis, whereas other etiologies, such as choroidal rupture and retinal arterial macroaneurysm, have the best prognosis. These differences can be explained by the different mechanisms of subretinal hemorrhage formation (subfoveal CNV versus other causes),[8,47] the age of the patients, the pre-existing damage to the photoreceptors and RPE, the anatomic distribution of blood (i.e., subretinal versus sub-RPE and subretinal), and the amount of hemorrhage.

VI. Surgical Removal of Subretinal Hemorrhage

Because of the time-dependent progression of retinal damage in animal models, researchers have studied the effect of prompt surgical removal of the subretinal hemorrhage in an attempt to improve final visual acuity.[40,95] Two additional areas of research to improve surgical results involve the use of novel drugs and instruments. First, recombinant human tissue plasminogen activator (TPA) has been used to lyse clotted subretinal hemorrhage and fibrin strands. Second, 25- to 36-gauge subretinal instruments have been developed to minimize tissue damage during TPA delivery to the subretinal space and during removal of subretinal hemorrhage.

A. PRETISSUE PLASMINOGEN ACTIVATOR STUDIES

Tissue plasminogen activator has been used in human vitreoretinal surgery for only the past 6 years. Prior to 1988, there were only isolated reports of drainage of subretinal hemorrhage without TPA.[23-25,48] In 1983, Dellaporta reported a case of massive subretinal hemorrhage drained using an endodiathermy needle placed through the sclera, choroid, and retina to improve vision from 3/200 to 20/20.[24,25] This case was significant for several reasons. First, this was the first published successful report of using a transbulbar endodiathermy needle to drain subretinal hemorrhage. Second, the patient, a healthy 29-year-old, was able to regain 20/20 vision despite an extended period of subretinal hemorrhage involving the macula (secondary to trauma). The endodiathermy was performed 30 days after the trauma, and the macula was exposed to visible subretinal hemorrhage for 3.5 months after the trauma (1 month after trauma with residual blood remaining for an additional 2.5 months). In an otherwise young, healthy eye with subretinal hemorrhage, this case report suggests that intervention can be useful, even after a 1–3-month time interval. Other anecdotal reports support this finding.[19]

In 1987 Hanscom and Diddie described performing vitrectomy and internal retinotomy with aspiration of the subretinal blood clot on two patients.[46] A 77-year-old AMD patient with previous 20/40 vision improved from count fingers to 20/400, and an 83-year-old patient with a retinal arterial macroaneurysm improved from hand motions to 20/80.

Wade et al reported a series of 14 cases of subretinal hemorrhage involving the macula.[98] Indications for surgery were subretinal hemorrhage greater than 5 disk diameters in size and the surgeon's judgment that the hemorrhage would not resolve spontaneously and would cause significant macular dysfunction. All eyes underwent pars plana vitrectomy and internal drainage with use of either a standard extrusion needle or a cannulated extrusion needle, with or without intraocular forceps. Fluid-gas exchange and endolaser treatment were used. Five of five eyes with AMD had postoperative visual acuity between no light perception and 5/200, whereas eight of nine non-AMD eyes with subretinal hemorrhage (89%) had postoperative visual acuity between 20/

40 and 20/200. The timing of drainage was between 1 hour and 4 weeks after formation of subretinal hemorrhage, and the trend was toward better postoperative acuity in AMD and non-AMD eyes when hemorrhage was evacuated within 2 weeks.

Han et al published a series of 19 patients with traumatic subretinal hemorrhage who were managed surgically.[47] The surgical techniques for removal of the hemorrhage were similar, i.e., a tapered extrusion cannula for internal drainage with or without forceps-assisted clot removal, fluid-gas exchange, and endolaser treatment around the drainage retinotomy. Indications for evacuation of subretinal hemorrhage included hemorrhagically elevated retinal breaks, massive hemorrhagic retinal detachment involving the posterior pole, and bullous detachment of the retina. Sixteen of 19 cases (84%) met these criteria. The remaining three were localized extramacular hemorrhagic retinal detachments, and the subretinal hemorrhage was not drained. These three patients underwent only vitrectomy, lensectomy, and scleral buckling. Thirteen of 19 cases (68%) had retinal reattachment, and 6 of 19 (32%) had vision better than 5/200 (4/16 [25%] with subretinal hemorrhage drainage). The eyes in this study needed vitrectomy to manage penetrating posterior segment trauma anyway; thus, the internal drainage according to the previously described inclusion criteria was felt to be worthwhile, as there was little additional risk of surgical morbidity. Clotted blood remained after operations performed within 10 days of injury, whereas clotted subretinal hemorrhage did not remain after surgery performed later than that.

Vander et al published a series of 11 surgically managed cases of subretinal hemorrhage secondary to AMD.[97] Surgery was performed in a fashion similar to that in the previously described papers. No specific inclusion criteria were given, but all eyes had hemorrhagic macular detachment that reduced visual acuity to 20/400 or worse. Final visual acuity varied from light perception to 20/200. Only 4 of 11 cases (36%) had any improvement in visual acuity. All four of these cases were operated within 1 week of visual loss (the time of presumed subretinal hemorrhage formation), while five of the eyes with no improvement in visual acuity had surgery after more than 2 months of visual loss.

There are several recurrent themes in the previously mentioned series of Wade, Han, and Vander. First, the major postoperative complications were CNV and proliferative vitreoretinopathy, with resultant disciform scarring and retinal detachment, respectively. Second, early surgical intervention showed a trend toward better postoperative visual acuity. Third, there was a sense among the authors that extraction of subretinal hemorrhage was probably traumatic, due to the large retinotomy and to the actual forceps-assisted clot extraction.

B. TISSUE PLASMINOGEN ACTIVATOR

1. Background

Tissue plasminogen activator was introduced in 1990 for intraocular use in humans, and it has greatly facilitated the surgical evacuation of subretinal hemorrhage. Tissue plasminogen activator is a naturally occurring endogenous serine protease with a molecular weight of 70,000. Endothelial cells release pre-TPA when stimulated by trauma or unknown stimulating factors.[20] Pre-TPA is then cleaved to the fibrin-specific, and therefore clot-selective, nonantigenic thrombolytic agent, TPA, for which specific inhibitors exist.[20] Tissue plasminogen activator then forms a complex with fibrin to activate plasminogen into plasmin, which, in turn, lyses fibrin and other procoagulant proteins into soluble degradation products, thus dissolving the blood clot.[20,49] Other thrombolytic agents, such as urokinase and streptokinase, do not have the same fibrin specificity (thus, clot specificity) as TPA. They are known to cause a large inflammatory response in the eye when used to treat experimental vitreous hemorrhage and hyphema.[61] Purified human TPA produced by recombinant DNA technology is now available for use in patients.[76]

2. Rationale for Use of TPA

Through dissolution of fibrin, TPA can reduce fibrin-mediated photoreceptor damage. The inherently traumatic surgical removal of the fibrinous clot can be minimized by use of TPA. Without TPA, a clot normally can adhere to the retina, RPE, or choroid, and shearing damage can result from surgical removal of the clot, especially with intraocular forceps.[64] Tissue plasminogen activator can reduce this iatrogenic damage by dissolving fibrin clot and by liquefying the subretinal hemorrhage, thus minimizing potentially damaging adhesions to surrounding photoreceptors and RPE. Because TPA lyses the clot sooner than would occur naturally, removal can be undertaken safely shortly after the hemorrhage occurs. Earlier subretinal hemorrhage removal should decrease toxin- and barrier-mediated damage.[64]

There are limitations to the efficacy of TPA. First, irreversible retinal damage (fibrin-mediated, toxin-mediated, or barrier-mediated) may have occurred prior to TPA injection. This limitation underscores the importance of timely therapy to achieve functional recovery.

Second, there are several theoretical limitations to efficacy of TPA in dissolving the clot. As described

above, plasminogen is necessary for the production of plasmin by TPA. As clotted subretinal hemorrhage is not in direct contact with the intravascular space, perhaps the surrounding liquid hemorrhage and clotted hemorrhage contain a limited, and thus, limiting, amount of plasminogen. This may explain why clot lysis with TPA is often incomplete, especially with massive subretinal hemorrhage. *In vitro* experimentation has shown that ideal TPA and plasminogen concentrations exist for maximal clot lysis.[74] Tissue plasminogen activator does not significantly deplete plasminogen, as it is clot specific, but the plasminogen contained in the clot alone is not enough for maximal clot lysis.[74] Fibrinolysis by TPA exposes new plasminogen binding sites in the clot matrix, and additional plasminogen is necessary for continued fibrinolysis for TPA.[89] An *in vitro* study using normal plasma showed that addition of plasminogen did not affect TPA-induced lysis rates.[99] To the best of our knowledge, the amount of plasminogen in the liquid plasma component of subretinal hemorrhage surrounding the subretinal clot has never been quantified.

A third theoretical limitation to TPA efficacy in dissolving the clot is the concentration of various fibrinolytic inhibitors. Plasminogen-activator-inhibitor 1 (PAI-1) and α2 plasmin inhibitor (α2-PI) inhibit TPA and plasmin, respectively.[93] α2-PI binds and cross-links the fibrin molecule, changing the tertiary configuration and making fibrin more resistant to lysis by plasmin.[93] Similarly, PAI-1 binds fibrin and can directly inhibit TPA.[93] Exogenous therapeutic concentrations of TPA, however, may easily overcome the effect of PAI-1.[12] The efficacy of TPA and plasmin are also reduced when the aging clot has completed more cross-linking reactions, decreasing the surface area for TPA, plasminogen, and plasmin binding.[93] Although these limitations are probably overcome by exogenous therapeutic doses of TPA, in cases of massive or old subretinal hemorrhage, they may not be.

A fourth factor in the efficacy of TPA is its ability to gain access to the center of the clot. Even with maximal plasminogen and TPA concentrations, repeat lavage is often required for maximal TPA-induced clot lysis, as the more central portions of the clot require direct contact with TPA for fibrinolysis.

C. TISSUE PLASMINOGEN ACTIVATOR STUDIES

1. Animal Studies

Several animal studies have been undertaken to assess the safety and efficacy of TPA. In the rabbit model, subretinal injections of TPA showed no signs of toxicity between 25 and 50 μg.[64] At doses greater than 50 μg, large necrotic retinal holes, bullous retinal detachment, and marked retinal vessel attenuation occurred.[53]

Twenty-four hours after experimental subretinal hemorrhage formation with autologous blood (not anticoagulated) in the rabbit, nontoxic doses of TPA were injected into the same subretinal space as the subretinal hemorrhage. The subretinal hemorrhage was found to clear faster than it did in a group that received a BSS injection or in a control group (no injection).[64] The thickness of the subretinal hemorrhage was also decreased with TPA, as compared to the BSS group and the control group.[54] Tissue plasminogen activator was presumed to decrease the toxic and barrier effects of subretinal hemorrhage as well, because TPA injections resulted in less retinal damage than occurred in the control group.[64] Tissue plasminogen activator-treated eyes showed the same amount of damage as the BSS group. This finding can be explained by the irreversible retinal damage that takes place in the merangiotic rabbit retina within 24 hours (before TPA was injected), as mentioned previously. On the other hand, both the TPA and the BSS group showed less damage than the control group. This outcome may be secondary to a dilution effect of toxic factors and a reduction of metabolic barriers by the TPA and BSS injections.

In contrast, the holangiotic cat retina was spared from retinal degeneration and toxicity when 0.5–5.0 μg of TPA was injected into the subretinal space. In fact, a dose of 0.3–1.4 μg given on day 7, followed by subretinal hemorrhage aspiration, was sufficient to prevent severe outer retinal degeneration in a cat model.[5]

2. Human Studies

The first case of intraocular TPA-assisted evacuation of subretinal hemorrhage in a patient was reported in 1991. Peyman et al treated two patients with arterial macroaneurysms, using micropipette application of TPA (6.25 μg) through a small retinotomy. After evacuation of subretinal hemorrhage, visual acuity improved from count fingers to 20/50 and 20/70.[77] In three AMD eyes with subretinal hemorrhage treated in the same manner, preoperative visual acuity ranged between count fingers and 20/400, and postoperative visual acuity was 20/400.

In 1994, Lewis published a prospective series of 24 AMD eyes with subretinal hemorrhage that were less than 14 days old.[63] The patients were all treated surgically with TPA-aided drainage of subretinal hemorrhage. There were four inclusion criteria: visual acuity of 20/50 or better before subretinal hemorrhage formation; duration of subretinal hemorrhage of less than 14 days; subretinal hemorrhage greater than 3 disk diameters in size and greater than 500 μ in thickness; and visual acuity of count fingers or worse.

Between 12 and 48 μg of recombinant TPA were injected into the subretinal blood clot through a 33-gauge access retinotomy. All eyes were followed for at least 6 months (mean = 14 months). Twenty eyes (83%) had improved visual acuity, and those eyes seen within 7 days of onset had the best visual outcome. Eight of 16 eyes (50%) treated within 7 days improved to acuity of 20/200 or better. No eyes treated after 7 days' duration of subretinal hemorrhage had vision of 20/200 or better. This study supports the notions that early surgical intervention is correlated with good visual outcome and that TPA appears to be a useful adjunct to drainage of subretinal hemorrhage.

Ibanez et al published a retrospective series of 47 consecutive surgical cases of subretinal hemorrhage drainage.[54] Twenty-three were treated prior to 1992 without TPA with a mean follow-up of 40 weeks, and 24 were treated with recombinant TPA-assisted drainage between 1991 and 1993 with a mean follow-up of 24 weeks. The method of TPA administration was similar to Lewis's method in that a total of 10–50 μg was injected subretinally into the clot.

The results were similar for both cohorts, with AMD eyes attaining a mean visual acuity of 20/200 without TPA and 20/480 with TPA (no significant difference). Age-related macular degeneration eyes comprised 39 of the 47 eyes (83%) and were evenly divided between the two study groups. Age-related macular degeneration eyes had improved postoperative visual acuity, but TPA use did not show significantly better results than simple surgical drainage. Ibanez et al noted that final visual acuities of both the TPA-assisted and non-TPA-assisted AMD groups compared favorably to the natural history (no surgical intervention) AMD group in the study of Bennett et al (final visual acuity of 20/1700).[6]

Lim et al in 1995 reported a retrospective series of 18 cases of TPA-assisted surgical removal of subretinal hemorrhage, of which 16 (89%) were AMD-related.[67] The median follow-up time was 33 weeks. Inclusion criteria included surgery within 14 days of onset, visual acuity of 20/200 or worse, size greater than four-disk areas, and absence of sub-RPE blood. Six to 36 μg of TPA was injected into each subretinal hemorrhage. Final visual acuity improved two or more lines in five eyes (28%) and decreased two or more lines in seven eyes (39%).

In 1996, Kamei et al reported a prospective series of 22 AMD eyes that underwent TPA-assisted surgical removal of subretinal hemorrhage.[56] Exclusion criteria included subretinal hemorrhage not covering the macula, subretinal hemorrhage thin enough to allow visualization of the underlying choroidal vascular pattern, hemorrhage mainly beneath the RPE, and completely organized (clotted) subretinal hemorrhage. The mean postoperative follow-up time was 15 months. Because perfluorocarbon liquid was used to squeeze the liquid subretinal hemorrhage into the vitreous, there was minimal manipulation of the retina and RPE. Thus, an extra retinotomy was avoided, and suction was not applied to the retina and underlying RPE. After fibrinolysis, organized fibrin material was left behind. Only residual subretinal fibrin degradation products were gently removed with use of limited balanced salt solution lavage combined with perfluorocarbon-induced expression of liquid from the subretinal space. The TPA dose was similar to that used in previous studies (12–50 μg).

The visual outcomes in Kamei's study were excellent. Nineteen of 22 eyes (86%) gained two or more lines of visual acuity (best postoperative), while the remaining 3 eyes were unchanged. Eighteen eyes (82%) had final visual acuity better than the preoperative vision, and only one eye had worse final vision. Poor visual acuity was correlated with surgery after 30 days of onset of subretinal hemorrhage and the presence of subfoveal CNV.

There are several shortcomings of the four studies, which render their results less meaningful and, perhaps, compatible. Lewis' study had strict inclusion criteria and was prospective; however, there was no control group. This means that although there were favorable results with TPA, there was no comparison with a group of patients meeting the same criteria that were either observed or had subretinal hemorrhage drainage without TPA.

The study by Ibanez et al was limited in that the series was retrospective. In addition, there were no inclusion criteria. There was no comparison with a nonoperated group, and there was inadequate documentation of the time between subretinal hemorrhage formation and surgery. The only mention of duration of hemorrhage was that the majority of eyes were treated within 10 days, and the visual outcome was no different than in those treated after 10 days.

The study by Lim et al was retrospective as well. Three of 16 AMD patients (19%) were followed 3 months or less after surgery. With a longer follow-up period, the best postoperative acuity, as well as the final visual acuity, may have been better than the reported visual acuity after subretinal hemorrhage removal in these patients.

Kamei et al's series was prospective, but there was no control group. Two patients were young (in their 40s) and had final visual acuities of 20/25 and 20/40, and seven patients showed no evidence of CNV on fluorescein angiography. These patients may have done well with no treatment. Nevertheless, the results of this series are better than the other series. As the authors claim, this may be due to improved surgical technique.

There were minor differences in the surgical technique used in the first three studies. The studies used similar amounts and concentrations of TPA. Ibanez waited 20–40 minutes after TPA injection before aspirating the liquefied blood, whereas Lewis and Lim waited 45 minutes. The indications for and technique of residual subretinal clot removal varied. Ibanez et al, in some cases, removed the subretinal clot with a forceps if it could be reached through the original retinotomy. Lewis, on the other hand, identified two specific residual clot removal criteria: less than 30% of the original clot liquefied and a large remaining subfoveal blood clot. This was the case in 7 of 24 (28%) patients; in 4 of these (57%) patients, a large anterior circumferential retinectomy was required to remove the clot. Neither study detailed postoperative results of this mechanical clot extraction subgroup. Lim et al did not perform any mechanical clot removal.

Kamei et al added the use of perfluorocarbon liquid in order to minimize retinal and subretinal manipulation. Residual clot was left behind. This technique may account for the improved visual acuity results.

The question of efficacy of TPA-assisted drainage remains debatable. Certainly, Lewis and Kamei had favorable results while using strict inclusion criteria. Three eyes with drainage without TPA (all AMD) and four eyes with TPA (two with AMD) from the series of Ibanez et al fit Lewis' inclusion criteria. In the former group, visual acuity worsened in two eyes and improved in one. In the latter group, in the AMD eyes, one remained stable and one improved. Eight of 16 (50%) of Lim et al's AMD patients fit Lewis' inclusion criteria. Of these, two improved and two worsened. The data are too limited to draw more meaningful conclusions.

Thus, the value of submacular surgery for subretinal hemorrhage drainage is unclear at this time. Two pilot studies had favorable results,[56,63] but these good outcomes were not reproduced in the other pilot studies.[52,67] Furthermore, the natural history of subretinal hemorrhage has not been thoroughly established. At present, the Submacular Surgery Trials are underway. One arm of this multicentered, randomized, prospective study compares surgery to observation for hemorrhagic subfoveal CNV lesions secondary to AMD in which more than 50% of the entire lesion is occupied by hemorrhage.[13] As far as we know, no study is systematically attempting to assess the value of TPA-assisted subretinal hemorrhage removal in other conditions associated with subretinal hemorrhage.

D. OTHER SURGICAL TECHNIQUES

Surgical techniques for evacuation of subretinal hemorrhage are not limited to vitrectomy and internal drainage, with or without subretinal TPA injection, and lavage. Dellaporta, over the past 18 years, has reported success in three cases, using either penetrating endodiathermy coagulation or argon laser retinal perforation.[22]

In 1983 and 1994, Dellaporta described success in draining a traumatic subretinal hemorrhage using endodiathermy (described earlier) in one case.[22,23] The endodiathermy needle enters the globe through the pars plana, and the endodiathermy tip penetrates the retina, subretinal hemorrhage, choroid, and sclera, creating a hole, which makes drainage into the vitreous and through the penetrated sclera possible.

Dellaporta also described the use of argon laser (two cases) to enable subretinal hemorrhage to drain into the vitreous. Citing the success of such drainage in an AMD eye (with visual acuity improvement from 4/200 to 20/60), he recommended this technique for fresh (nonclotted) subretinal hemorrhage.[22] The treatment is performed at high energy in short bursts (4.5–5.0 W, 50 μ, 0.2 seconds) and is aimed at areas of the highest extramacular retinal elevation. Visualization of subretinal hemorrhage escaping into the vitreous denotes adequate retinal perforation.

The advantage of the endodiathermy and the argon laser treatment of subretinal hemorrhage is that they are technically simple compared to vitrectomy and internal drainage. They may also be relatively cost- and time-effective. Some of the complications of subretinal surgery are avoided with argon laser-mediated drainage.

Some problems exist with these techniques. The subretinal hemorrhage may not drain completely; residual subretinal hemorrhage resorbtion is slow, resulting in a longer contact period with the retina; and the blood remains in the eye (vitreous). Vitreous hemorrhage may obscure vision until it resorbs weeks to months later.

Intravitreal injection of TPA may also be useful in the management of subretinal hemorrhage. In animal studies, intravitreal TPA injection induced partial subretinal clot lysis.[11,21] At a Vitreoretinal Frontiers Meeting (Chicago, 1996) Wilson Heriot presented results of a pilot study using intravitreal TPA and C_3F_8 gas to inferiorly displace the subretinal hemorrhage from the fovea. Of 10 patients, 9 (90%) had foveal subretinal hemorrhage clearance and 7 (70%) had some improvement in visual acuity. Final visual acuity was limited by AMD-related CNV in 8 (80%) patients. Our own experience with this technique, though limited, has also been quite favorable.

As is the case for submacular subretinal hemorrhage drainage with vitrectomy, the results of these alternative methods of clearing subretinal hemorrhage have not been proven to be superior to obser-

vation. Currently, the data supporting the use of these alternative techniques are limited to several case reports and an unpublished pilot study. In view of the apparent limitations of submacular subretinal hemorrhage removal via vitrectomy, however, these alternative techniques of drainage deserve more thorough evaluation in the context of well-controlled studies.

E. ADVANCES IN SURGICAL TECHNIQUE

Advances in surgical technique have been developed which reduce iatrogenic retinal trauma. In all cases prior to 1991, a 20- to 30-gauge cannula was used to remove the subretinal hemorrhage, with or without intraocular forceps to extract the clot. With the resultant tissue trauma caused by relatively bulky instruments, the risk of CNV (through mechanical damage to Bruch's membrane) and redetachment at the retinotomy site increased.[70] Also, the need to make large retinotomies to remove clotted subretinal hemorrhage probably increased the risk of proliferative vitreoretinopathy.[70]

Using an ultramicrosurgical machine (a stereotactic micromanipulator) to direct a micropipette into the subretinal space, TPA can be infused and subretinal hemorrhage aspirated through a retinotomy under 300 μ in diameter.[94] Such small retinotomies are self-sealing and thus do not require retinopexy and tamponade. In addition, better control of fluid flow is achieved, resulting in less RPE and retinal damage. Certainly, there is less damage to photoreceptors during TPA-assisted clot removal compared to the tissue damage during forceps removal. Less RPE damage might result in less CNV formation and better photoreceptor recovery. Histopathology shows no permanent retinal damage when TPA is used within 7 days in an ultramicrosurgical model.[94] In addition, the present availability of 33-gauge cannulas, subretinal horizontal and vertical scissors and forceps, and 36-gauge picks probably renders subretinal surgery less traumatic.[91]

During internal drainage surgery, it was also found that repeated lavage and aspiration of TPA was much more effective in rapid clot dissolution than either lavage and aspiration with BSS or a single injection of TPA.[55] Labeling TPA with fluorescein recently has been recommended as a method of monitoring drug penetration and spread intraoperatively.[84]

F. INDICATIONS FOR REMOVAL OF SUBRETINAL HEMORRHAGE

The surgical techniques presently available should probably be used only in selected cases of subretinal hemorrhage (Fig. 4). Cases that seem especially unlikely to benefit from surgery include those with 1) poor visual acuity in the affected eye before the subretinal hemorrhage occurred; 2)thin subretinal hemorrhage (i.e., no obscuration of underlying choroidal detail and no clinically evident retinal elevation by the subretinal hemorrhage seen by biomicroscopy; 3)massive subretinal hemorrhage with diseased/atrophic underlying RPE and overlying retina (e.g., a long-standing subretinal hemorrhage extending from the posterior pole to the equator, associated with a previous disciform scar); 4)extrafoveal location of the subretinal hemorrhage; 5)presence of a large subfoveal sub-RPE hemorrhage (if this can be determined.

Based on review of previous studies, we propose several guidelines for the selection of surgical candidates

1. The affected eye had good (useful) visual acuity before the subretinal hemorrhage occurred.
2. The duration of subretinal hemorrhage is less than 30 days, preferably less than 7 days.
3. The subretinal hemorrhage is thick, creating clinically evident foveal elevation of 500 μ or more with complete obscuration of underlying RPE and choroidal detail.
4. The underlying RPE and overlying retina are healthy (e.g., non–AMD-related subretinal hemorrhage).
5. The subretinal hemorrhage is causing significant visual impairment.

Although TPA is useful as a biochemical tool to remove subretinal hemorrhage relatively atraumatically in some circumstances, the value of hemorrhage removal as a means to improve visual outcome (via any technique) remains unestablished, because definitive studies to answer this question have not been performed. Therefore, surgeons must make decisions based on the facts of the individual case. All of the guidelines mentioned above are supported in the literature and are qualitative. Not all criteria are necessary to obtain a successful surgical and functional result.[19] Limitations in the quality of natural history data, however, make it difficult to be certain that patients with a good surgical prognosis would not do equally well with observation alone.

The surgical technique we usually recommend is vitrectomy with internal subretinal hemorrhage drainage, using subretinal recombinant TPA-assisted clot lysis. After pars plana vitrectomy and removal of the posterior vitreous cortex, a small (33-gauge) access retinotomy is created adjacent to the subretinal hemorrhage; the superotemporal (right eye) or superonasal (left eye) retina should be avoided to preserve a useful postoperative eccentric fixation locus.[44] Tissue plasminogen activator is then injected

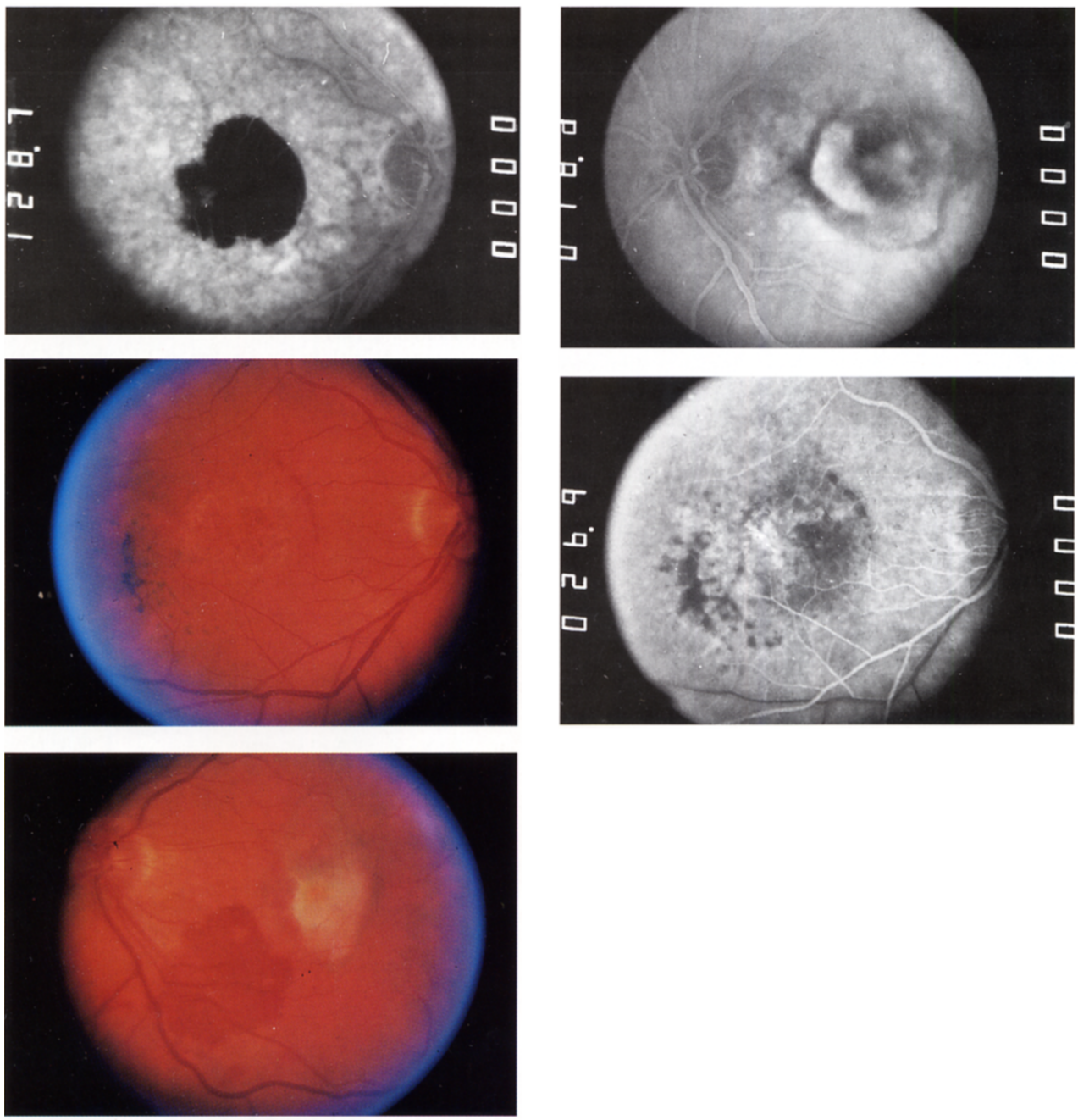

Fig. 4. Tissue plasminogen activator-assisted removal of subretinal hemorrhage secondary to CNV in a 69-year-old man with AMD. *Top left:* Preoperative recirculation-phase fluorescein angiogram demonstrates blockage of choroidal fluorescence by subretinal blood as well as dye leakage at the temporal margin of the blood secondary to occult CNV. Visual acuity was 20/240. *Top right:* Recirculation-phase fluorescein angiogram of the fellow eye demonstrates a large subfoveal CNV. Visual acuity was 20/400. *Center left:* Fundus photograph 2 months after TPA-assisted evacuation of subretinal hemorrhage and excision of the CNV. Visual acuity was 20/400. Temporal RPE hyperplasia marks the location of laser photocoagulation to the retinotomy. Trace subretinal hemorrhage remains at the nasal edge of the macula. *Center right:* Early venous filling-phase angiogram shows absence of CNV. *Bottom:* Fundus photograph taken at the same time as center figures above. A disciform scar has developed, and the visual acuity was 2/200. The efficacy of surgical excision of the CNV in this case is unproved. The worse outcome in the fellow eye does not prove that surgery is better than observation in such cases generally. The value of TPA in this case, however, is that it facilitated atraumatic removal of the subretinal hemorrhage (which was approximately 500 μ thick centrally), thus improving visualization of the subretinal space and facilitating dissection of the subfoveal CNV, which was as large in diameter as the subretinal hemorrhage itself.

directly into the clot. The concentration of TPA is 10 μg/0.1 mL, injected 0.1 mL at a time. A small air bubble can temporarily seal the retinotomy site to limit TPA diffusion into the vitreous cavity.[63] A 45-minute waiting period is allotted to maximize enzyme-assisted clot lysis. Based upon the amount of clot liquefaction, TPA injection can be repeated up to a total dose of 50 μg. If available, perfluorocarbon fluid can be used to displace the liquefied blood into the vitreous. Otherwise, subretinal irrigation/aspiration with minimal tissue manipulation is used to remove the liquefied blood. Any extrafoveal clot remaining should not be removed mechanically. A subretinal balanced salt solution lavage is then used to wash out remaining fibrin degradation products. To close, a fluid/air exchange is performed without endophotocoagulation to the small retinotomy site. If the retinotomy site has enlarged to greater than 500 μ in diameter (e.g., secondary to mechanical clot extraction), a row of endolaser treatment is applied at the margins, sparing the macula.

Published results and our own experience do not support aggressive mechanical removal of residual extrafoveal clots. Mechanical clot extraction alone has had unimpressive results, especially with AMD-related subretinal hemorrhage (which comprises 90% of all subretinal hemorrhage in the four large TPA-assisted surgical series). Other surgical techniques, such as penetrating endodiathermy coagulation or argon laser retinal perforation, and intravitreal TPA-assisted gas displacement of subretinal hemorrhage, may be appropriate in very carefully selected cases. Although case reports suggest that the relative ease and apparent efficacy of these techniques make them seem quite promising, further testing is warranted before a stronger endorsement can be given.

VII. Future Therapy

Despite encouraging data from animal studies, human studies have not shown a clearcut benefit with TPA use in the removal of subretinal hemorrhages, and additional approaches to management should be sought.[71] Research using growth factors to limit CNV growth[34] and to promote retinal survival after subretinal hemorrhage is in its early stages and may hold promise for the management of patients with subretinal hemorrhage.[32,62,88,96,100] Randomized, prospective studies such as the Submacular Surgery Trials will provide needed reliable data regarding the efficacy of surgical removal of subretinal hemorrhage in the setting of AMD and subfoveal CNV. Such studies should also be undertaken to clarify the role of surgery in patients with non-AMD-related subretinal hemorrhage.

Methods of Literature Search

The Medline database was searched using the search term, "subretinal hemorrhage." Abstracts were reviewed to identify articles that focused on etiology and management, and these articles were obtained. Additional papers cited in those articles were also obtained, as were articles that came to our attention through miscellaneous sources.

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Outline

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Supported in part by Research to Prevent Blindness, Inc.

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