

Comparison of Indocyanine Green and Fluorescein Angiography of Choroidal Neovascularization

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Abstract: We compared indocyanine green (ICG) and fluorescein angiography for evaluation of choroidal neovascularization (CNV). Cast preparations of CNV induced in monkey eyes by laser photocoagulation were correlated with ICG and fluorescein angiographies of the same CNV formations. Fluorescein angiography was more effective, in general, than ICG angiography in detecting CNV; however, CNVs with subretinal hemorrhage (2 of 35 sites) were visible only with ICG angiography. In early phase ICG angiography, CNV formations that casts showed to be dense or composed of thick vessels were seen, but less dense areas were not visible. Lesions that ICG angiography revealed as leaking were not differentiated morphologically from non-leaking areas by the CNV casts. This study confirms that only ICG angiography can identify CNV hidden by subretinal hemorrhage, although fluorescein angiography is otherwise superior. Indocyanine green angiography is indicated as a valuable complement to fluorescein angiography for evaluation of CNV. **Jpn J Ophthalmol 1997; 41:284-296** © 1997 Japanese Ophthalmological Society

Key Words: Age-related macular degeneration, choroidal neovascularization, fluorescein angiography, indocyanine green angiography, macular degeneration.

Introduction

Choroidal neovascularization (CNV) is seen in a number of fundus conditions including exudative age-related macular degeneration (ARMD), presumed histoplasmosis syndrome, and myopic fundus.¹ Fluorescein angiography has proven its value in the accurate identification and localization of CNV and is especially useful in the laser photocoagulation of CNV in exudative ARMD.^{2,3} The Macular Photocoagulation Study Group⁴⁻⁶ has described laser therapy for extra-, juxta-, and subfoveal well-defined CNV of ARMD as beneficial in prevention of severe visual loss. However, as many as 87% of patients with symptoms of exudative ARMD may be ineligible for laser treatment, according to the criteria of the Group,⁷ because they have poorly defined, or occult, CNV.

Such situations have brought increased interest in the use of indocyanine green (ICG) angiography to overcome the limitations of fluorescein angiography.⁸⁻¹⁷ There are two biophysical characteristics of ICG dye that provide potential advantages over fluorescein dye. First, peak absorption (805 nm) and fluorescence (835 nm) wavelengths of ICG are in the near-infrared, not visible, light spectrum; the longer wavelengths give better penetration through overlying pigment.¹⁸⁻²⁰ Second, ICG is highly protein-bound (98%) and, therefore, has relatively slower and more limited leakage from normal and abnormal choroidal vessels than fluorescein.^{20,21}

Several investigators have shown that ICG angiography can not only confirm, but better delineate, CNV in ARMD that is poorly defined or occult with fluorescein angiography. Slakter et al²² Sorenson et al²³ and Guyer et al²⁴ have recently reported pilot study data on CNV treatment, based on ICG angiography. Slakter et al²² noted that 23% of eyes with occult CNV had localized and definable lesions potentially amenable to laser photocoagulation therapy; Sorenson et al²³ noted that 44% of eyes with recur-

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rent CNV were eligible for laser treatment; and Guyer et al²⁴ found that 34% of eyes with occult CNV, without pigment epithelial detachment, and 42% with vascularized pigment epithelial detachment, were potentially treatable with laser photocoagulation—based on the additional information provided by ICG angiography.

Chang et al²⁵ reported the first clinicopathologic correlation of CNV by ICG angiography. The histopathologic features of occult CNV in ARMD indicate that hyperfluorescent leakage in ICG angiography occurs in the neovascular tissue. However, this has not yet been adequately documented. In the present study, therefore, we compared ICG and fluorescein angiography with visualization by vascular casts of experimentally-induced CNV.

Materials and Methods

Induction and Observation of Choroidal Neovascularization

Choroidal neovascularization was induced in 13 eyes of nine rhesus monkeys with laser photocoagulation, as described by Itagaki.²⁶ The monkeys were sedated with intramuscular ketamine hydrochloride (25 mg/kg) and the pupils were dilated with topical 10% phenylephrine hydrochloride. A total of 209 laser burns were placed in grid patterns in 13 eyes with a radiation krypton laser (System-910, Coherent, Palo Alto, CA, USA): spot size, 100 μ m; power, 200 mW; duration, 0.1 seconds. Fundus examination, fluorescein angiography, and ICG angiography were then done weekly with a TRC-501A (Topcon, Tokyo). For fluorescein angiography, 1 mL 10% sodium fluorescein was injected into the greater saphenous vein; ICG angiography was done with an intravenous injection of 2.5% ICG (5 mg/kg), using a view angle of 20° or 50°.

Animals were sacrificed with an overdose of sodium pentobarbital at intervals between 1 week and 1 year after laser photocoagulation. Vascular casts of the choroidal vessels were prepared following Uyama's method.²⁷ The skin was incised at the mid-clavicular line, teflon cannulas were placed in both common carotid arteries (with the cardiac end ligated) for perfusion with 1000 mL physiologic saline containing 10 000 units of heparin. Mercor resin (CL-2R-5, Dainippon Ink, Tokyo) was then perfused at 120 mm Hg pressure. After hardening of the resin, the eyes were enucleated and immersed in 15% KOH (J.T. Baker, Phillipsburg, NJ, USA) for 3 weeks. The resulting casts were rinsed, air-dried, and the entire posterior pole isolated under a dissecting

microscope. The casts were mounted on scanning electron microscope stubs, coated with 30 nm of gold-palladium, and examined with a scanning electron microscope (T200, JEOL, Tokyo).

Comparison of Angiography Findings With Vascular Casts

An image processing system (IMAGENet, Topcon, Tokyo) was used to compare CMV morphology revealed by the three techniques from electron photomicrographs of the vascular casts and the fluorescein and ICG angiograms. Region mapping software (Topcon, Tokyo) was used to match the coagulation sites in the three processes; reduction and inclination of the angiograms were adjusted to the cast photomicrographs. Angiograms of each site were evaluated for their ability to reveal the neovascularization shown by vascular casting.

Results

ICG Angiography

Choroidal neovascularization developed within 1–2 weeks after photocoagulation. In the early phase of the angiograms, typical CNV was visible as a network of new vessels. During the middle to late phases, extravascular leakage gradually appeared. As ICG was eliminated from the blood, in the late phase, the periphery and circumference of the CNV became hyperfluorescent while the root was hypofluorescent.

Three weeks after photocoagulation, the CNV began to regress. Although the neovascular network was still visible in the early and middle phases of angiography, the extravascular leakage decreased and appeared later. When the CNV had completely regressed, the neovascular network was visible during the early and middle phases, but there was no dye leakage or CNV seen in the late phase.

The CNV viability was categorized according to the visibility of the neovascular network in the early phase and the time required for dye leakage to appear and the amount of leakage:

- Type 1. Typical neovascularization at the coagulation site with a reticular or nodular network in the early phase and dye leakage in the late phase.
- Type 2. Atypical neovascularization, without the characteristics of type 1 lesions, was divided into two groups: (a) with no CNV visible in early and middle phases, but weak leakage in the late phase; and (b) with reticular and nodular CNV in the early and middle phases, but no leakage in the late phase.

- Type 3. No neovascular network visible during the entire angiographic sequence.

Fluorescein Angiography

- Type 1. Typical neovascularization at the coagulation site with reticular or nodular hyperfluorescence in the early phase and dye leakage in the late phase.
- Type 2. Atypical neovascularization with reticular or nodular hyperfluorescence in the early phase but no leakage in the late phase.
- Type 3. No hyperfluorescence during the entire procedure; CNV was obscured.

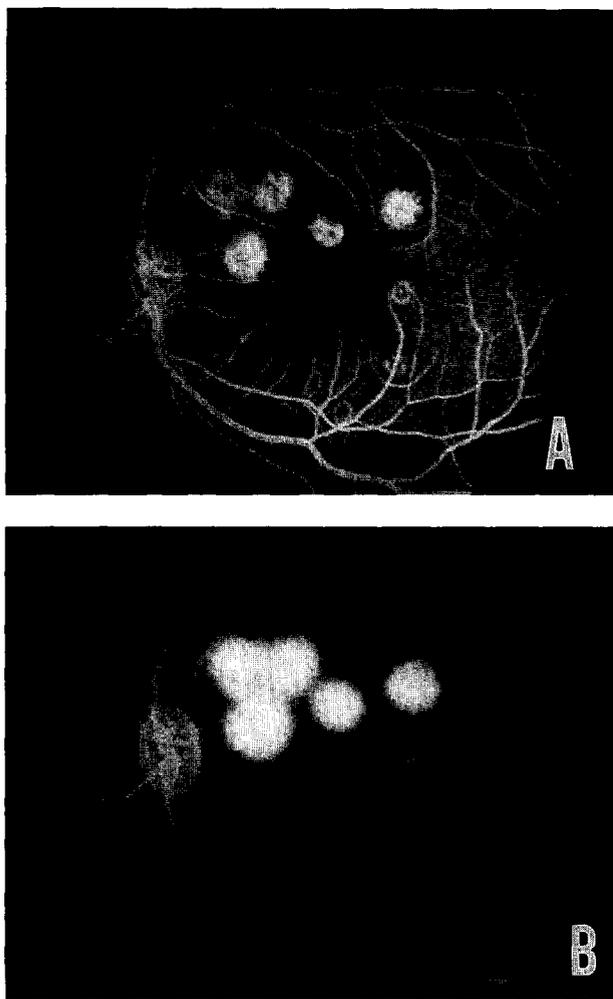


Figure 1. Fluorescein angiograms: early stage CNV (2 weeks after laser photocoagulation). (A) Early phase, after 11 seconds; reticular neovascular network visible in early phase (arrow). (B) Late phase, after 252 seconds; active leakage of network (arrow).

Development and Detection of CNV

Our observations of the developmental course of CNV are similar to other reports.^{21,22,24,27,28} Fluorescein angiography revealed CNV types 1 and 2 at 81

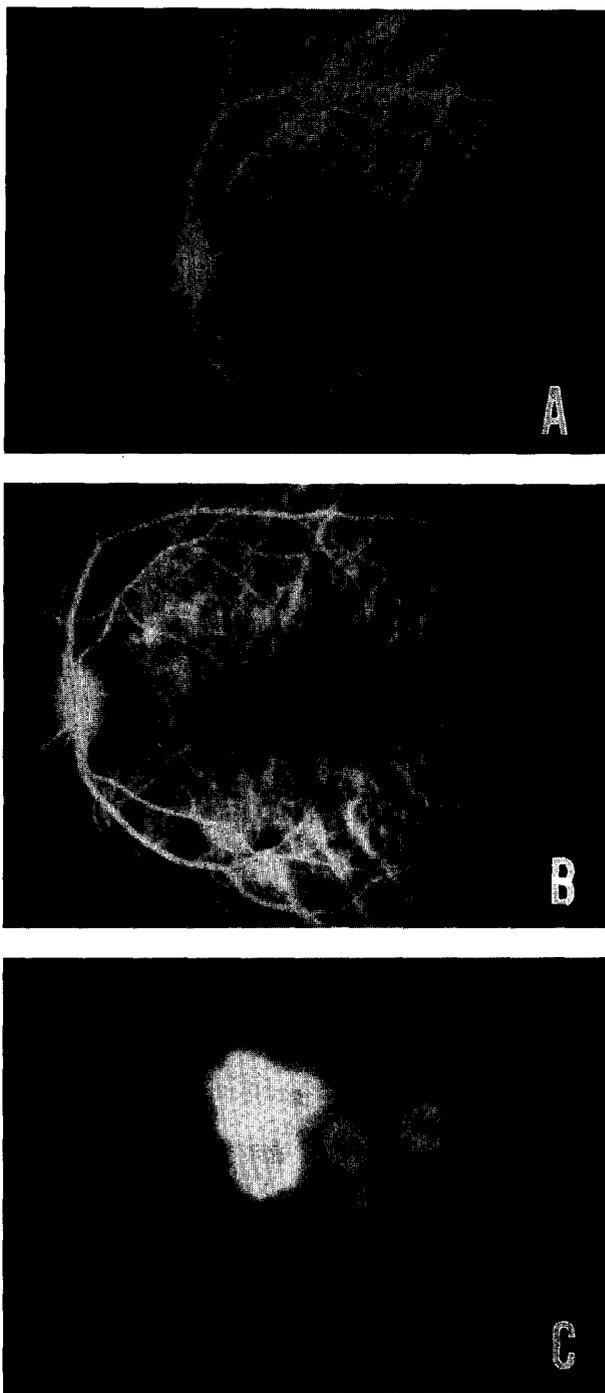


Figure 2. Indocyanine green angiograms: same eye as Figure 1. (A) Early phase, after 26 seconds. (B) Middle phase, after 107 seconds. (C) Late phase, after 31 seconds; periphery and circumference of CNV is hyperfluorescent; root is hypofluorescent (arrow).

of 209 sites; ICG angiography found CNV at 69 of 209 sites. The vascular casts showed CNV at 108 of the 209 sites; these were then evaluated according to their developmental stage.

Initial CNV stage. Both fluorescein and ICG angiography revealed typical CNVs of type 1 in early phase angiography within 1–2 weeks of photocoagulation. Early phase fluorescein angiography showed a reticular neovascular network; late phase angiography showed active leakage. Morphology visualization was clearest in the early angiogram phase (Figure 1).

Indocyanine green angiography showed reticular neovascular networks in the early and middle phases, and dye leakage in the late phase. The clearest CNV morphology appeared about 1 minute after the procedure began. In the late phase, the CNV periphery and circumference were hyperfluorescent while the root was hypofluorescent (Figure 2).

The vascular casts showed the radial extent of the new vessels in the subretinal space. Vascular lumina were irregular in size; vessels had abruptly ending rounded tips. These rounded structures seemed to be artifactual, perhaps due to the rupture of vessels at weak points under pressure of the resin injection. Extravascular dye leakage occurs through similar vessel weak points. The CNV root, with minimal leakage, had a thick afferent artery and efferent vein; the entire neovascular network was loosely arranged (Figure 3).

During neovascular development, vascular casts revealed 35 CNV sites; 29 (83%) of these were also visible on fluorescein angiography. Type 1 lesions occurred at 26 sites (74%); type 2 at three sites (9%); and type 3 at six sites (17%). Indocyanine green angiography identified 29 (83%) sites: type 1 at 19 sites (54%); type 2a at seven sites (20%); type 2b at three sites (9%); and type 3 at six sites (17%). There was

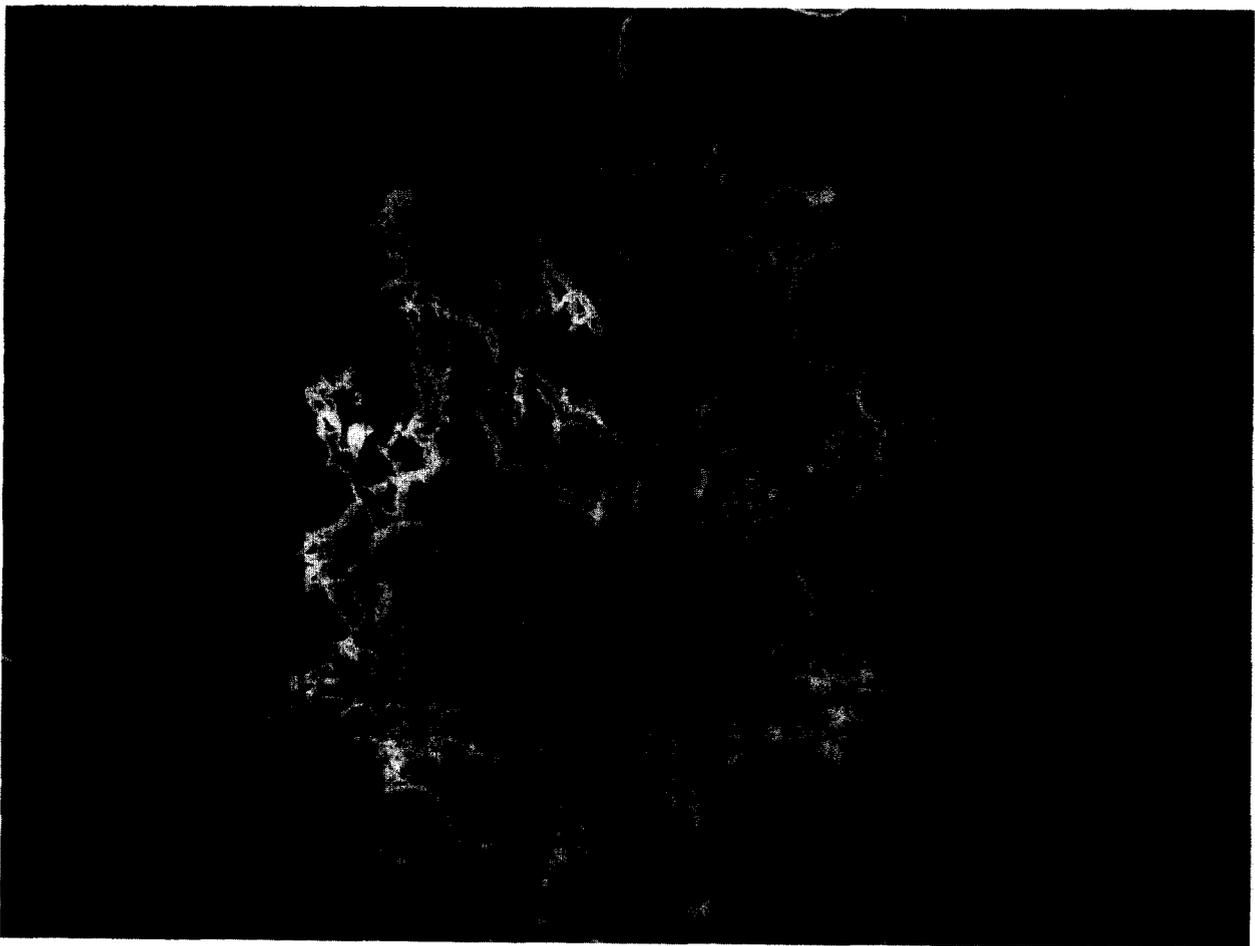


Figure 3. Scanning electron microscopic photo. Cast of CNV shown with arrows in Figures 1 and 2. Vascular cast reveals new vessels in subretinal space; vascular lumina are irregular in size; leading edge of formation is fusiform (arrowheads) or rounded (arrows); CNV root has thick afferent artery and efferent vein.

no difference in the detection rates of the two angiography methods, but fluorescein angiograms were more distinct than ICG angiograms. Two CNV formations were detected only by ICG, but not by fluorescein angiography; both were associated with subretinal hemorrhage (Figures 4, 5). Two other CNV formations were detected by fluorescein but not by ICG angiography; both had very few new vessels and were not associated with subretinal hemorrhage.

Established and regressive CNV stages. CNV began to regress naturally 3 weeks after photocoagulation. Early phase fluorescein angiograms showed hyperfluorescence with leakage in the late phase diminished (Figure 6).

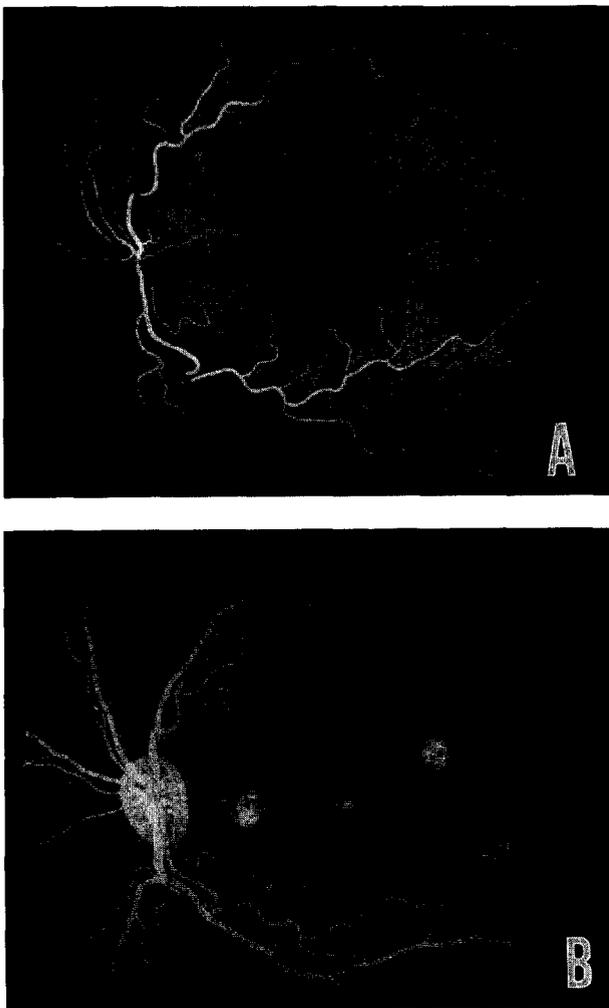


Figure 4. Fluorescein angiograms: CNV covered by subretinal hemorrhage. (A) Early phase, after 9 seconds; Hypofluorescence at subretinal hemorrhage (arrow). (B) Late phase, after 359 seconds; minimal dye leakage (arrow). CNV was not detected.

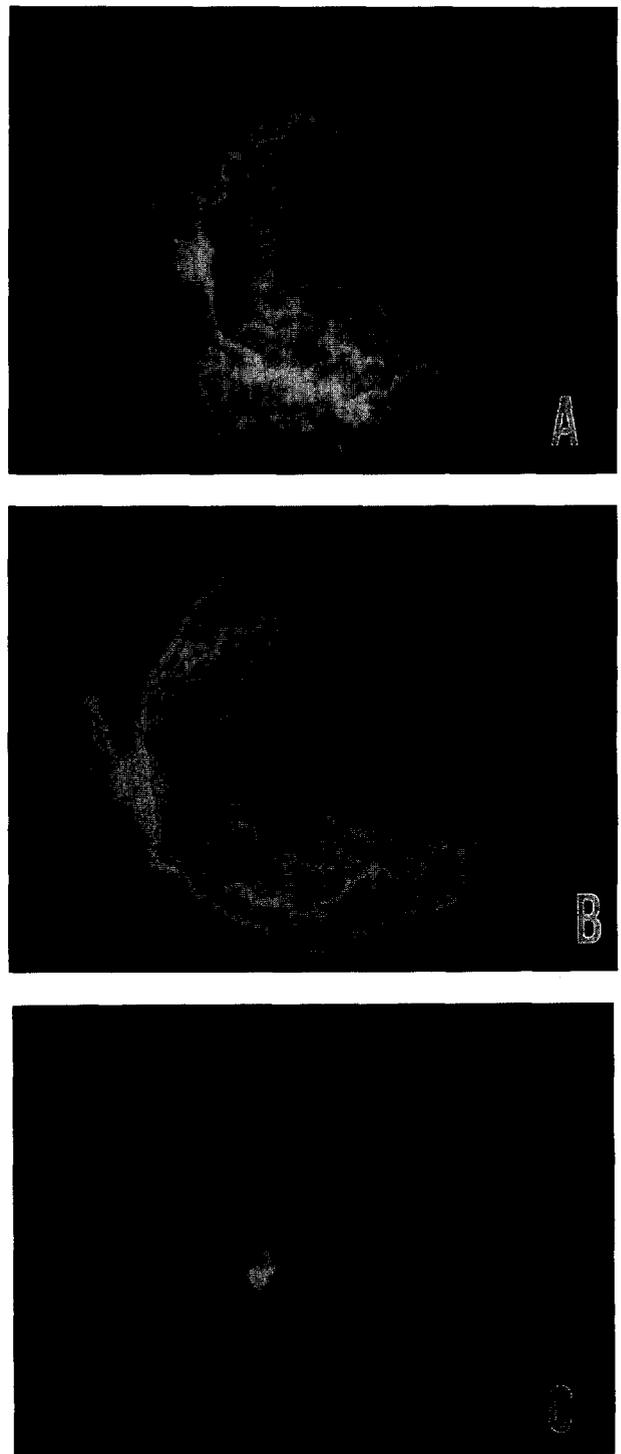


Figure 5. Indocyanine green angiograms of same eye as Figure 4. (A) Early phase, after 9 seconds; no CNV in laser site (arrows). (B) Middle phase, after 173 seconds; no CNV in laser site (arrows). (C) Late stage, after 31 minutes; CNV dye leakage associated with subretinal hemorrhage (arrow).

Early and middle phase ICG angiograms revealed reticular neovascular networks, but extravascular leakage was slower and minimal in the late phase. New vessel morphology was not clear in early phase angiograms, but became clear in the middle and late phases (Figure 7).

Vascular casts showed new vessels extending radially into the subretinal space; these vessels had uniformly sized lumina and a smooth surface (Figure 8).

When the CNV had completely regressed, there was hyperfluorescence in the early phase fluorescein angiogram, but no leakage in the late phase (Figure 9). The CNVs were visible in the early and middle phases of ICG angiograms, but not in the late phase, due to extravascular elimination of ICG (Figure 10).

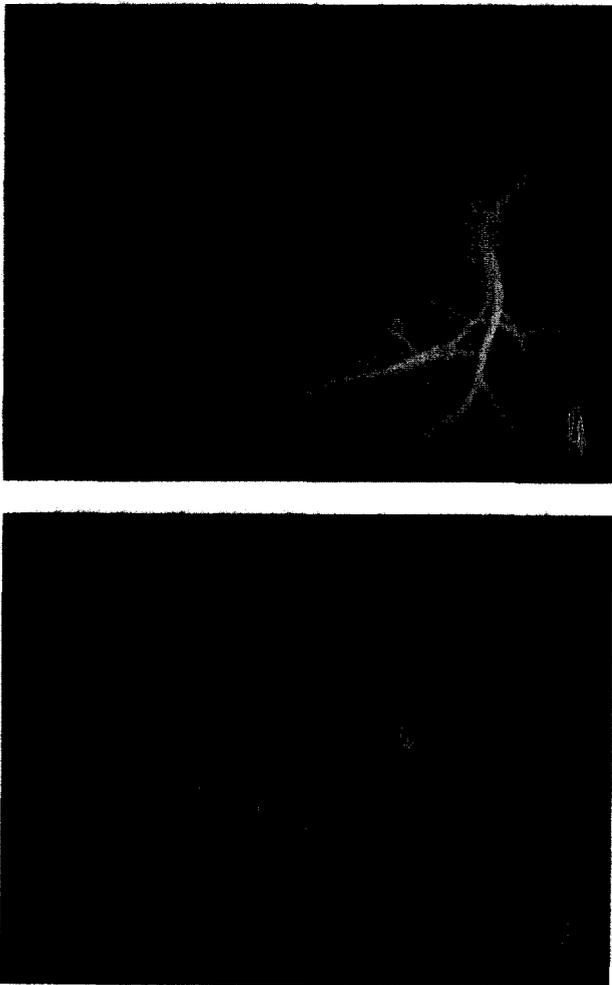


Figure 6. Fluorescein angiogram: 8 weeks after laser photocoagulation. (A) Early phase, after 13 seconds; ring of hyperfluorescence (arrow). (B) Late phase, after 200 seconds; mild dye leakage suggests CNV has begun to regress (arrow).

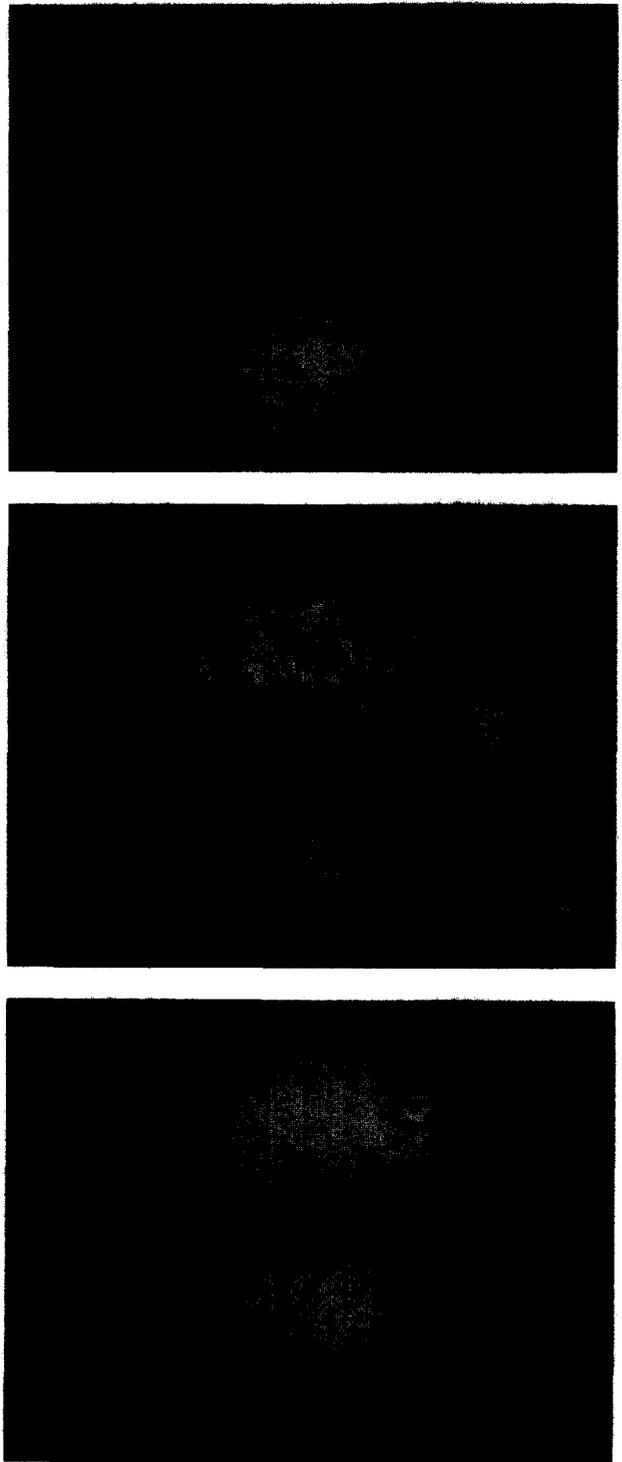


Figure 7. Indocyanine green angiogram of same eye and lesion (arrow) as Figure 6. (A) Early phase, after 23 seconds; round-shaped hyperfluorescence. (B) Middle phase, after 196 seconds; mild dye leakage. (C) Late phase, after 30 minutes; broad ring of hyperfluorescence; time delay of extravascular leakage became prolonged with minimal leakage.



Figure 8. Scanning electron micrograph: cast of CNV indicated in Figures 6 and 7. Formation of CNV extends radially in subretinal space; vessels have lumina of uniform size and smooth surface.

Vascular casts showed the uniform lumina of these vessels (Figure 11).

From the established stage to the regressive stage, 73 CNV sites were identified by vascular casting. Fluorescein angiography found 52 of these (71%): 34 (45%) were type 1; 18 (25%), type 2; and 21 (29%), type 3. Indocyanine green angiography found 40 (55%): 29 (40%), type 1; two (3%) type 2a; nine (12%) type 2b; and 33 (45%) type 3. No CNV was found only by ICG angiography. Fluorescein angiography had a higher CNV detection rate and clearer images than ICG angiography.

Comparison of angiographic and vascular cast findings. Vascular casts revealed more vessels and finer details than either angiography method (Figures 12-14). Indocyanine green angiography (Figure 13) found new vessels if they were densely grouped and had large lumina, as in the afferent and efferent vessels illustrated by vascular casting in Figure 14. If the vessels were loosely grouped, ICG angiography did not detect them or differentiate them from the background choriocapillaries vessels (Figure 13). The new vessels found by fluorescein angiography were in the superficial layer under the retina in the vascular casts. Vessels at the CNV root were better visualized with ICG angiography than fluorescein angiography (Figure 12). Fluorescein angiography was better able to contrast CNV and the choriocapillaris in the periphery; however, when the retinal pigment epithelium (RPE) partially atrophied at the

CNV periphery, fluorescein hyperfluorescence visible through a window defect was difficult to distinguish from the CNV hyperfluorescence. There was no hyperfluorescence from RPE atrophy with ICG angiography and the CNV was clearly visible.

Discussion

The natural progression of choroidal neovascularization visualized with fluorescein angiography in our study is similar to that reported in the articles of Miki et al.²⁸ Ryan,²⁹ Ohkuma and Ryan,³⁰ and Miller et al.³¹ The amount of leakage from the CNV indicated its viability. With ICG angiography, leakage was most obvious during the early developmental stage, diminishing when the CNV regressed. There was no leakage after complete regression. The CNV viability can also be evaluated by the elapsed time before leakage begins and by the extent of this leakage.

Other comparisons of observations during the two procedures were made. In the early phases, fluorescein angiography showed intense CNV hyperfluorescence that contrasted with the background, clearly revealing the neovascular networks. Early phase ICG angiography did not have comparable hyperfluorescence, and the nodular and reticular CNVs were not as clearly seen. The RPE acts as a curtain blocking the fluorescence of fluorescein and visualization of choroidal vessels, and permitting the subretinal space CNV to be seen as distinct hyperfluorescence above the RPE curtain. Indocyanine green angiography

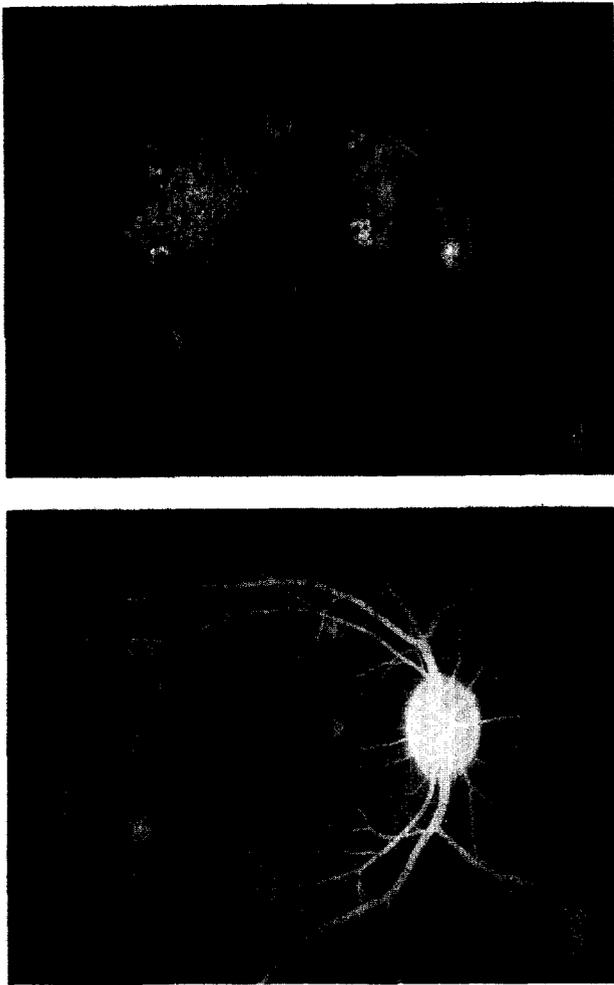


Figure 9. Fluorescein angiogram: 22 weeks after laser photocoagulation. (A) Early phase, after 10 seconds; hyperfluorescence (arrow). (B) Late phase, after 191 seconds; no leakage (arrow).

easily penetrates the RPE^{20,21} and CNVs in the subretinal space are detectable only as abnormal choroidal vessels that have courses that differ from the ordinary choroidal vessels.

Miki et al²⁸ reported that the architecture of CNV revealed by vascular castings is more complex than is visualized by fluorescein angiography: What appeared as a single vessel in an angiogram was found in the cast preparation to be an intricate complex of fine vessels. In the present study, the vascular casts revealed that CNVs seen by ICG angiography were formations of densely distributed small vessels having broad-lumen vessels at the root of the neovascularization. In formations with loosely grouped new vessels, or where the CNV was closely associated with choroidal vessels, the neovascularization could

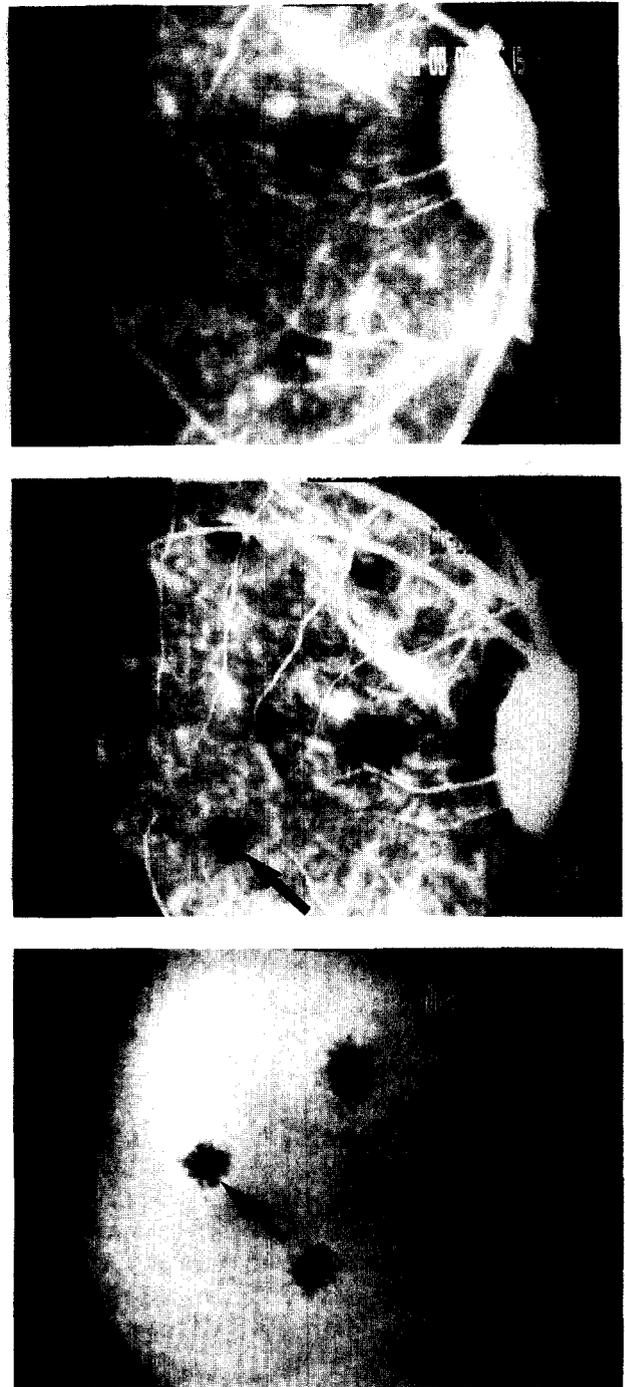


Figure 10. Indocyanine green angiogram of same eye as Figure 9. (A) Early phase, after 14 seconds; "C" shaped CNV (arrow). (B) Middle phase, after 15 minutes; "C" shaped CNV (arrow). (C) Late phase, after 41 minutes; no CNV visible in the laser site (arrow) because of extravascular elimination of ICG.

not be distinguished from the background choriocapillaris (Figures 13, 14). Flower³² has suggested that ICG fluorescence has a cumulative effect: When CNVs are densely packed, the fluorescence intensity

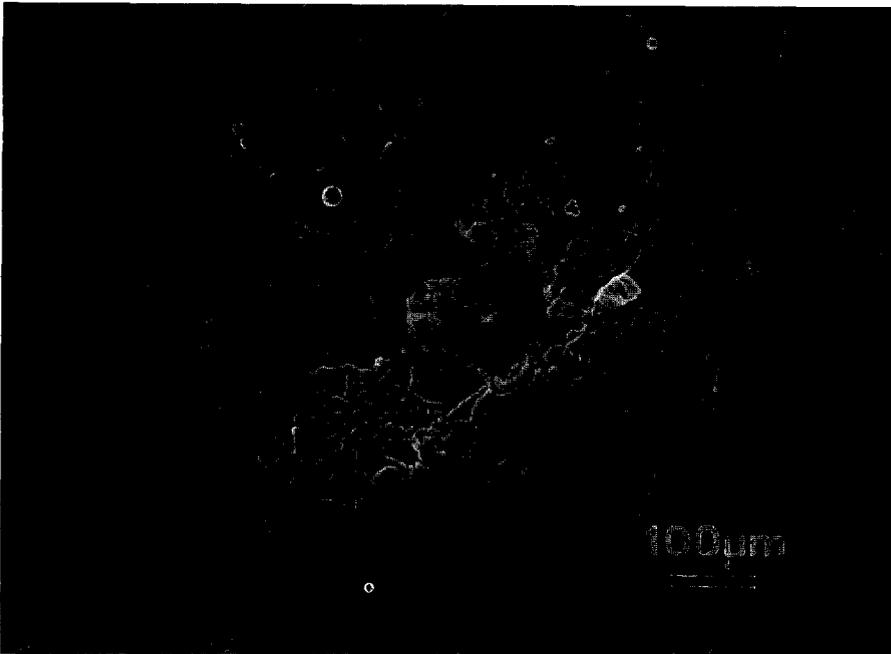


Figure 11. Scanning electron micrograph: cast of CNV in Figures 9 and 10. Vascular lumina are narrow; regression was previously documented by angiography.

is high, increasing CNV detection probability; when the vessels are loosely distributed, the fluorescence of the choroidal background is intense and CNV detection probability is low.

Indocyanine green angiography is superior to fluorescein angiography if CNVs are covered by a subretinal hemorrhage (Figures 4, 5) and have a window defect around them.¹⁴ When the CNV is covered by subretinal hemorrhage, the blood has less blocking effect with ICG angiography than with fluorescein angiography. If there is a window defect around the CNV, fluorescein angiography hyperfluorescence is visible in the early phase at the defect. In the late phase, however, stained tissue is also seen at the defect and the distinction between neovascularization and the window defect is blurred. Indocyanine green angiography shows no hyperfluorescence at the window defect and no stained tissue is visible; therefore, this type of CNV is more easily identified by ICG angiography (Figures 12-14).

Sheider et al³³ reported a dark rim visible at the periphery of the CNV with ICG angiography, providing additional confirmation. As noted above, the margin of the CNV is not clear in the early phase of ICG angiograms; however, if the dark rim proves to be an indication of CNV, defining its margin, the rate of CNV diagnosis by ICG angiography will improve. Hypofluorescence at the CNV periphery may result from choroidal circulatory disorders or blocking of the background fluorescence. We are investigating the dark rim by histological examination.

The clearest morphological features of CNV were seen in the middle phases of ICG angiograms. The ICG dye accumulated within the CNV produced an intense fluorescence that allowed clear visualization of the CNV. Similar clear visualization occurred in the early phase of fluorescein angiography.

In late phase fluorescein angiography, there was active leakage from the CNV and the entire neovascularization was intensely hyperfluorescent. This contrasts with ICG angiography in which the central part remained hypofluorescent even with leakage and hyperfluorescence at the edge of the formation. A few CNV formations showed no leakage of ICG, but did have fluorescein leakage. With fluorescein angiography, CNV leakage appears to result from several conditions: immaturity of the vascular endothelium, incomplete intercellular junctions, or influence of the environment around CNV such as the hyperplastic RPE enclosing it and the serous retinal detachment covering it.^{30,31,34,35} When active leakage was observed in ICG angiography, the tip of the CNV was fine-lumened with weak areas from which resin oozed, assuming the rounded shape seen in the vascular castings. Leakage also occurred from neovascularizations that did not have this morphology (Figures 7, 8). ICG leakage from a CNV indicates not only a change in the neovascularization itself, but the effect of the environment. We believe histologic investigation of leakage during the late phase of ICG angiography is significant and will describe our results in a future article.

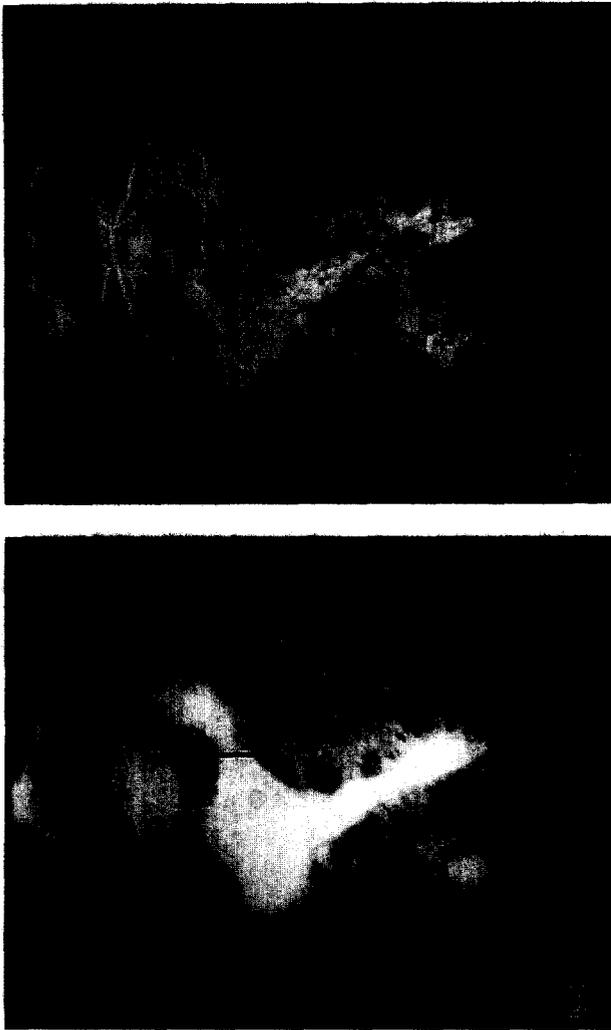


Figure 12. Fluorescein angiogram: 1 year after laser photocoagulation. (A) Early phase, after 8 seconds; edge of CNV formation is distinct. (B) Late phase, after 196 seconds; details of CNV formation are indistinct due to window defect.

The results of ICG angiography and the corresponding morphology can be summarized as follows. Type 1, the typical CNV: the neovascular network was comparatively large and dense; leakage indicated high activity and viability. Type 2a: occurred in two forms—some CNVs were small, with high activity and visible leakage; others were comparatively large, but with a loose network and slow leakage. Type 2b: neovascularization was comparatively large, with a dense network, but tended to regress and had no leakage. Type 3: included both small neovascularizations with no visible leakage and comparatively large forms with a loose network, low activity, and no leakage. Vascular casts proved that the formations



Figure 13. Indocyanine green angiogram: same eye as Figure 12, higher magnification. No hyperfluorescence visible because of window defect. (A) Early phase, after 8 seconds; although edge of CNV formation is seen, connecting vessel between edge of CNV and afferent (arrowheads) and efferent vessel is not seen. (B) Middle phase, after 47 seconds; mild dye leakage. (C) Late phase, after 33 minutes; mild dye leakage.

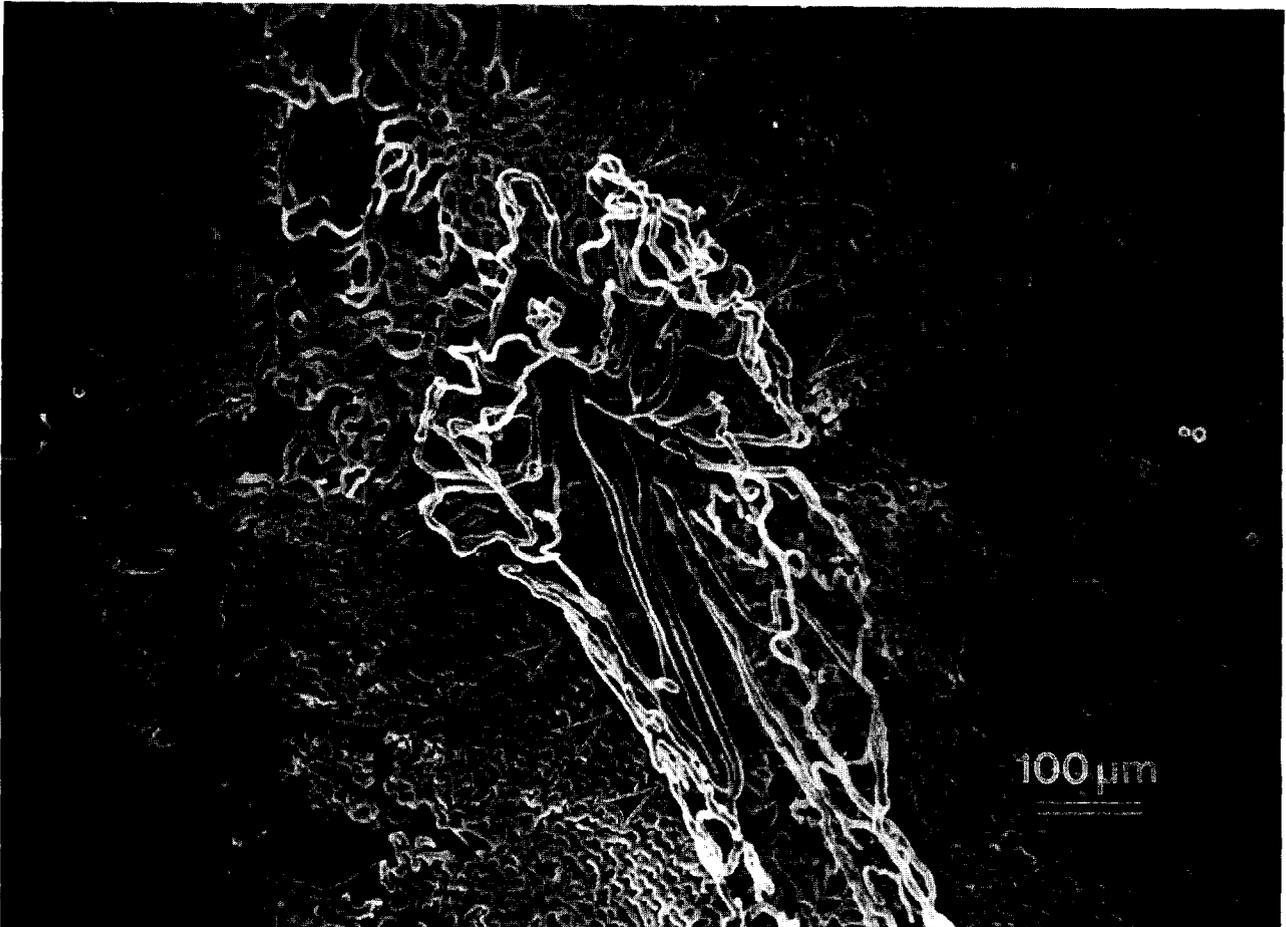


Figure 14. Scanning electron micrograph: cast of CNV in Figures 12 and 13 (framed area). Afferent (short, thick arrow) and efferent vessels (open arrow) extend from lower part of CNV formation. Cast clearly showed high density of CNV vessels (arrowheads) and afferent and efferent vessels detected by ICG angiography. Loosely arranged vessels were not visible with ICG angiography.

were not completely eliminated with clinical regression and the absence of leakage. While there is a possibility that resin did not fill all the CNV vessels, all vessels seen on ICG angiography were also identified in the vascular casts.

In this study, the neovascularization detection rate was lower with ICG angiography than with fluorescein angiography. In clinical practice, however, ICG angiography detects more CNV than fluorescein angiography.^{10,11} Experimentally induced neovascularization has neither large subretinal hemorrhages nor RPE detachment resembling the early stage of ARMD. In an animal model, the detection rate for fluorescein angiography is greater than for ICG angiography. When CNV was associated with subretinal hemorrhage or a window defect surrounding it, ICG angiography was more useful than fluorescein. These techniques have complementary advantages

that make them both valuable in detecting and describing the different forms of CNV.

From our results with ICG angiography, we discovered that CNV appeared as abnormal choroidal vessels in the early phase, leakage occurred in the middle and late phases, and the leakage was hyperfluorescent in the late phase. When CNV approached the regression phase, leakage decreased. When regression was complete, CNV appeared as choroidal vessels in the early and middle phases, but there was no leakage in the late phase. Indocyanine green visualization of CNV corresponded with the vascular castings. Neovascular activity was indicated by the time required for the appearance of dye leakage, and by the degree of leakage in the late phase angiography. New vessels observed were either densely distributed capillary networks or thick vessels in the root of the neovascularization. At sites with only a few loosely

organized blood vessels, it was not possible to distinguish between new and choroidal vessels.

In detection of experimental neovascularization, ICG angiography is less effective than fluorescein angiography. However, when CNV is associated with subretinal hemorrhage, or in the presence of a window defect in the perimeter of the neovascularization, detection is possible only by ICG angiography.

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