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Von Hippel-Lindau Disease: Clinical Considerations and the Use of Fluorescein-Potentiated Argon Laser Therapy for Treatment of Retinal Angiomas

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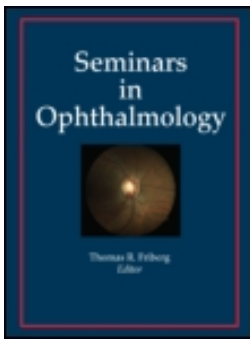
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## Von Hippel-Lindau Disease: Clinical Considerations and the Use of Fluorescein-Potentiated Argon Laser Therapy for Treatment of Retinal Angiomas

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# Von Hippel-Lindau Disease: Clinical Considerations and the Use of Fluorescein-Potentiated Argon Laser Therapy for Treatment of Retinal Angiomas

Michael B. Gorin

**S**INCE THE FIRST case report in 1886<sup>1</sup> and the classical monographs of Von Hippel<sup>2</sup> and Lindau,<sup>3</sup> angiomatosis retinae has been recognized as the ophthalmic expression of a familial disease that is characterized by (1) vascular hamartomas of the central nervous system, (2) renal cell carcinoma, (3) pancreatic islet cell tumors and adenocarcinoma, (4) renal, pancreatic, and epididymal cysts, and (5) pheochromocytoma. Seventy percent of patients with Von Hippel-Lindau (VHL) disease have retinal angiomas,<sup>4-8</sup> and the ocular lesions often precede the development of central nervous system and visceral lesions. The ophthalmologist plays a major role in the detection and management of these patients.<sup>9</sup>

## EVALUATION OF THE PATIENT WITH VHL DISEASE

The ophthalmologist is confronted by VHL from three different perspectives. First, there is the detection and diagnosis in individuals who have retinal angiomas. These individuals are initially recognized from their having ocular findings and/or symptoms. The physician must not only identify clinically significant lesions that require treatment, but also insure that the patient receives the appropriate systemic, central nervous system workup, and genetic counseling. The diagnostic criteria and workup are summarized by Glenn et al<sup>10</sup> and shown in Tables 1 and 2. The fundus examination, which consists of a meticulous dilated examination with indirect ophthalmoscopy and slit-lamp

biomicroscopy, is the same as that which would be used for an individual who is known to have VHL by nonocular criteria. Annual fluorescein angiography or angiography has been recommended by Maher et al,<sup>11</sup> but this is probably not necessary in most cases. Because of the onset of new lesions and the rapid expansion of even small angiomas, biannual examinations are advisable. It is essential that ongoing, life-long surveillance for angiomas be maintained.<sup>11</sup> During follow-up evaluations ranging from 6 months to 2 years of patients originally evaluated at the National Eye Institute (NEI) for VHL, new lesions were found in a number of individuals whether or not they had previous retinal angiomas. These individuals ranged in age from their 20s to mid 50s. In this series of 71 VHL patients, 15 individuals were known to have retinal angiomas that had been treated by laser or cryotherapy or observed before their evaluation at the National Institutes of Health (NIH). All of these patients had either persistent leakage from their treated tumors or new angiomas that had not been previously recognized or treated. Five of these individuals had peripapillary hemangiomas that had been followed for up to 16 years. In every case, untreated peripheral angiomas were identified in these individuals during their initial NEI evaluation. The ophthalmologist must have a systematic approach for evaluating the retina that is independent of previous examinations and known lesions.

## EVALUATION OF THE PATIENT AT RISK FOR VHL DISEASE

### Screening of Adults

The second ophthalmic perspective is the screening of those VHL family members who are at risk for the disease. The goal of the ophthalmologist is quite different for these patients than for those for whom the disease has been clinically established. The screening examination must be more rigorous and sensitive than the routine fundus examination because

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**Table 1. Guidelines for the Diagnosis of VHL Disease**

With VHL Disease Family History
Diagnostic lesions (one or more for diagnosis):
Central nervous system hemangioblastoma
Renal cell carcinoma, multifocal
Pheochromocytoma
Retinal angioma
Pancreatic islet cell tumor
Pancreatic cysts
Epididymal cystadenoma
Without VHL Disease Family History
Central nervous system hemangioblastoma and/or retinal angioma
If just one of above, then one of either:
Renal cell carcinoma
Pheochromocytoma
Epididymal cystadenomas
Pancreatic cysts and/or tumors

Adapted from Glenn et al.<sup>10</sup>

the implications for future medical evaluations, treatment, and counseling are critical, even if the angiomas are so small as to not pose any immediate threat to the eye or sight. In a prospective series of over 200 VHL family members, indirect ophthalmoscopy and slit-lamp biomicroscopy with a 90-diopter lens were combined with fluorescein angiography to evaluate all individuals. Ten of the 71 individuals who were clinically recognized to have VHL had retinal angiomas as the only diagnostic finding despite extensive imaging studies of the abdomen and central nervous system. In this series, 109 angiomas were identified in 57 eyes of 40 individuals. Twenty percent of all angiomas were 200  $\mu\text{m}$  or smaller in diameter, 37% were 500  $\mu\text{m}$  or less in diameter, and 20% of lesions were present anterior to the equator. There were 13 instances in which fluorescein angiography played a primary role in the detection of incipient angiomas which might have otherwise been overlooked by slit-lamp or indirect ophthalmoscopy.

Fluorescein angiography readily detects peripheral angiomas as well as early peripapillary lesions that are not evident by clinical examination. Although angiography alone does not provide a photographic record, it can be coordinated with angiography when documentation is required. It is preferable over angiography because one can insure complete coverage of the fundus, especially the areas anterior to the equator, and the ophthalmologist can readily

correlate potential fluorescein abnormalities with the standard fundoscopic examination. Fluorescein angiography can be very effective in young children who will not tolerate a careful

**Table 2. Current Recommendations for Clinical Evaluation for VHL**

Ophthalmic screening of patients with known VHL
Slit-lamp biomicroscopy of the fundus (with indirect lens or contact lens) especially anterior retina
Indirect ophthalmoscopy (often better tolerated by the patients when a red-free filter is used)
Examinations every 6 months
Ophthalmic screening of patient at risk for VHL
Slit-lamp biomicroscopy of the fundus (with indirect lens or contact lens)
Indirect ophthalmoscopy
Fluorescein angiography (use only instruments with interference filters) on first visit
Repeat examinations annually (fluorescein angiography is optional)
Ophthalmic screening of pediatric patients
Indirect ophthalmoscopy (red-free filter is often helpful)
Slit-lamp biomicroscopy, as tolerated
Fluorescein angiography under special circumstances to insure a complete examination
Examinations should begin the first year and continue at least annually
Systemic workup*
Complete physical and neurological examination including blood pressure, urinalysis, and palpation for scrotal mass (recommended annually)
Magnetic resonance imaging of brain and spinal cord with gadolinium (separate studies)
Computed tomography scan of kidney, adrenal glands, pancreas, liver, and spleen
24-hour urinary catecholamines, vanillylmandelic acid (VMA), and metanephrine
Ultrasound of scrotum
Ultrasound of the abdomen (annually with abdominal computed tomography every 3 years, according to Maher et al <sup>11</sup> )
Repeat systemic screening every 2-3 years (every 3 years according to Maher et al <sup>11</sup> )
More frequently if suspicious but nondiagnostic lesions are identified
Genetic counseling
Assessment of individual risk for the diagnosis of VHL
Identification of other family members who are at risk
Information regarding current and potential systemic, central nervous system, and ocular complications
Family counseling, aspects of inheritance, and risk to future children
Molecular genetic testing (when available)

\*Systemic workup data from Glenn et al.<sup>10</sup>

†Computed tomography scan precontrast and postcontrast of the abdomen for all persons age 20 and older; less than age 20, ultrasound of the abdominal viscera in lieu of computed tomography scan.

slit-lamp fundus examination. The combination of slit-lamp biomicroscopy, indirect ophthalmoscopy, and fluorescein angiography prolonged the examination, yet the additional discomfort to the patients was minimal and well-tolerated. The methods were complementary, and occasionally, lesions were noted in one part of the examination that had been overlooked by the other modalities. The 90-D lens is particularly helpful because of the excellent visualization of the anterior retina. Optimal corneal clarity can be preserved for examination with the indirect ophthalmoscope and fundus photography. A three-mirror contact lens examination is certainly a reasonable alternative to the evaluation with 90-D lens and can provide better visualization under some circumstances.

#### *Screening of Children*

The youngest patient found to have retinal angiomas in the NEI study was 11 years old at the time of examination. Retinal angiomas have been found in children less than 4 years of age<sup>7,11</sup> and the risk of retinal angiomas has been reported as less than 1% for children less than 5 years of age and 5% for children less than 10 years of age.<sup>11</sup> However, these values are not adjusted for the age distribution of the screened population and may represent significant underestimates of the likelihood of detecting retinal angiomas in the pediatric population. For this reason, the screening of infants and young children at risk should begin after the first year rather than after age 5 as proposed by others.<sup>11</sup> An annual examination using indirect ophthalmoscopy should be performed until such time as a definitive diagnosis is made by ophthalmic or other clinical criteria or by genetic testing. Maher et al<sup>11</sup> recommend that children receive annual fluorescein angiography or angiography from the age of 10. The goal of the ophthalmologist, in the pediatric years, is to detect clinically significant retinal angiomas that are a threat to the eye and require immediate treatment. The ocular lesions of VHL are the major threat to health in the young, whereas the systemic and central nervous system lesions are rarely symptomatic in children. Thus, if the child is asymptomatic, a complete fundus examination using indirect ophthalmoscopy is usually sufficient as long as the clinician is confident that the entire

retina has been examined. Fluorescein angiography may be helpful in selected instances because the blue light is well-tolerated by children and small angiomas are readily and rapidly seen even when cooperation is less than optimal. Molecular genetic tests will soon provide the capability of disease ascertainment regardless of the patient's age or clinical status.<sup>12-14</sup>

#### FOCAL TREATMENT OF RETINAL ANGIOMAS

The third perspective for the ophthalmologist is the treatment of retinal angiomas and the management of the complications of these lesions. The treatment of VHL-associated retinal angiomas has received a great deal of attention. It is clear that the most significant indicator for successful treatment is the size of the tumor at the time of treatment. Retinal angiomas (excluding peripapillary tumors) should be treated as soon as they are identified, when treatment is minimal and optimally effective.<sup>15,16</sup> Diathermy,<sup>17,18</sup> irradiation,<sup>19,20</sup> and xenon photocoagulation,<sup>21,22</sup> have all played a role in the earlier therapies for angiomas. However, current efforts have focused on the use of laser photocoagulation and cryotherapy.<sup>21,22</sup> Cryotherapy, with two or three freeze-thaw cycles and multiple applications, has been promoted as the most effective means of controlling large angiomas.<sup>21,22</sup> The complications of both forms of treatment are well-recognized, including tumor exudation and retinal detachment, subretinal and intravitreal hemorrhage, and progressive fibrovascular proliferation resulting in tractional detachments. Cryotherapy generally causes a large area of retinal destruction in the course of treatment, whereas laser photocoagulation can trigger significant hemorrhage and exudation. Surgical intervention has been advocated for large angiomas that are unresponsive to laser or cryotherapy and that are associated with significant ocular morbidity and complications.<sup>23</sup>

Laser photocoagulation of small angiomas is the preferred form of therapy.<sup>15,24-26</sup> The efficacy of laser photocoagulation for small angiomas under 0.8 disc diameters is well-established, but clinical reports and histological studies<sup>21,22</sup> have highlighted the difficulties of laser therapy at achieving tumor closure for large angiomas and those associated with retinal detachment. Lane

et al<sup>26</sup> reported the use of fluorescein to increase the effectiveness of laser phototherapy of angiomas. Fluorescein staining and permeation of angiomatous retinal vessels are almost universal features of these tumors.<sup>15</sup> Fluorescein angiography and angiography, when used in conjunction with laser therapy, provide an ongoing assessment of tumor response and aid in the detection of new retinal angiomas. The use of dyes to potentiate the effects of phototherapy is well-established. Hematophorphyrins have been used with laser photocoagulation for tumor ablation<sup>27,28</sup> and vessel closure.<sup>29,30</sup> Isothiocyanine<sup>31,32</sup> and rose bengal<sup>33,34</sup> have been used as light-activated free radical sources to close retinal vessels in laboratory animals.

Fifty-five retinal angiomas in 25 eyes of 17 individuals with lesions varying in size from 50  $\mu\text{m}$  to 4.0 mm in diameter were treated with fluorescein-potentiated argon laser (FPAL) therapy. The majority of the angiomas were small, in large part, because of the selection bias towards asymptomatic individuals in our VHL series. Peripapillary lesions were excluded from treatment because of the relatively stable vision (20/20 to 20/50) in 5 of the 6 affected eyes and the reports of complications arising from the treatment of peripapillary angiomas.<sup>21,22,35,36</sup>

### Method

After the patients were counseled and informed consent was obtained, both eyes were dilated with 1% tropicamide and 2.5% phenylephrine. The treated eye received topical proparacaine immediately before treatment. Photocoagulation was carried out with a Coherent (Palo Alto, CA) argon blue-green laser using either a three-mirror Goldmann lens or a Rodenstock panfundoscopic lens (Ocular Instruments, Bellvue, VA). In selected cases, scleral depression was used during the treatment session so that the anterior edge of a tumor adjacent to the ora could be completely treated. Photocoagulation was initiated within 5 minutes after injection of 3 to 5 mL of 10% fluorescein into an antecubital vein. For untreated lesions that showed a large amount of intravitreal fluorescein leakage during diagnostic angiography, the initial laser treatment was started within the 1 minute after injection to minimize energy uptake dispersion by fluorescein leakage into the vitreous. This

rapid postfluorescein laser application was only necessary during the primary treatment of these lesions and later treatment sessions were carried out with a time delay to allow transit of the dye from the retinal vasculature. If a treated area showed evidence of persistent staining or leakage, additional laser therapy was applied.

Laser photocoagulation was applied with 200  $\mu\text{m}$  spot size and a duration of 0.1 to 0.5 seconds. Longer-duration burns were applied to the body of larger angiomas for which heat penetration was problematic. Shorter applications were used for feeder vessel treatment. Energies ranged from 200 mW to 500 mW, with the majority of burns being between 200 to 300 mW. Burn duration in conjunction with burn intensity was adjusted to achieve adequate uptake. An intense white burn was considered the desired endpoint. Blood vessel spasm was also used as an indicator of effective laser application, particularly for lesions with a fibrous component. For the largest angiomas (greater than 1.5 disc diameter), the retina around the angioma was pretreated with standard argon laser 2 weeks before direct treatment of the angioma in order to create chorioretinal adhesions and minimize the risk of retinal detachment and spread of subretinal transudation. For small or flat angiomas, the entire lesion was confluent treated in a single session. Larger angiomas with well-defined feeder vessels were treated first with a confluent set of burns over the body of the angioma, followed by treatment of the feeder arteriole, then treatment of the feeder venule, and retreatment of the angioma if there was significant vasodilation after spasm of the venule. This treatment pattern was effective at sequentially decreasing blood flow through the angioma during the treatment session and appeared to minimize the risk of significant hemorrhage. Final treatment success was evaluated on the basis of attenuation of feeder vessels, resorption of subretinal fluid, and/or the elimination of tumor leakage as detected with fluorescein angiography. The treatment parameters are summarized in Table 3.

### Results

Ninety-six percent of lesions showed complete closure with fluorescein angiography/angiography within five sessions, whereas one

**Table 3. Treatment Parameters for FPAL Therapy**

<p><b>Large angiomas without significant serous detachment</b>          Pretreat around the lesion with argon green 2 weeks before directly treating the tumor 200-500 <math>\mu\text{m}</math> spots, standard intensity and duration for treatment of retinal tears.</p> <p><b>Angiomas with serous detachment, large angiomas with significant leakage</b>          Begin photocoagulation within 1-2 minutes of intravenous injection of 3 mL of 10% fluorescein. Minimize total treatment time to avoid uptake into vitreous.          Use 200 <math>\mu\text{m}</math> spot, 0.1 second 200-500 mW settings. Treat:</p> <ol style="list-style-type: none"> <li>(1) Body of tumor—endpoint is whitening of lesion and/or vessel spasm, confluent burns.</li> <li>(2) Feeder arteriole—treat along vessel, can use 100 <math>\mu\text{m}</math> spot but smaller spot size can punch a hole in the vessel. Endpoint is vessel spasm.</li> <li>(3) Feeder venule—treat along vessel, can use 100 <math>\mu\text{m}</math> spot but smaller spot size can punch a hole in the vessel. Endpoint is vessel spasm.</li> <li>(4) (Optional) Retreat the body of the tumor if vasodilation is apparent after venule spasm.</li> </ol> <p><b>Angiomas with reduced leakage and those with significant fibrosis</b>          Same as for large angiomas except that the onset of photocoagulation is delayed to 3-5 minutes after intravenous injection. Burn duration for the tumor body is usually increased to 0.2 to 0.5 seconds to achieve greater heat penetration.</p> <p><b>Small or flat angiomas, with or without feeder vessels</b>          Confluent treatment over the lesion—endpoint is whitening of the lesion and vasospasm. After treatment, vessel dilation may occur secondarily.</p>
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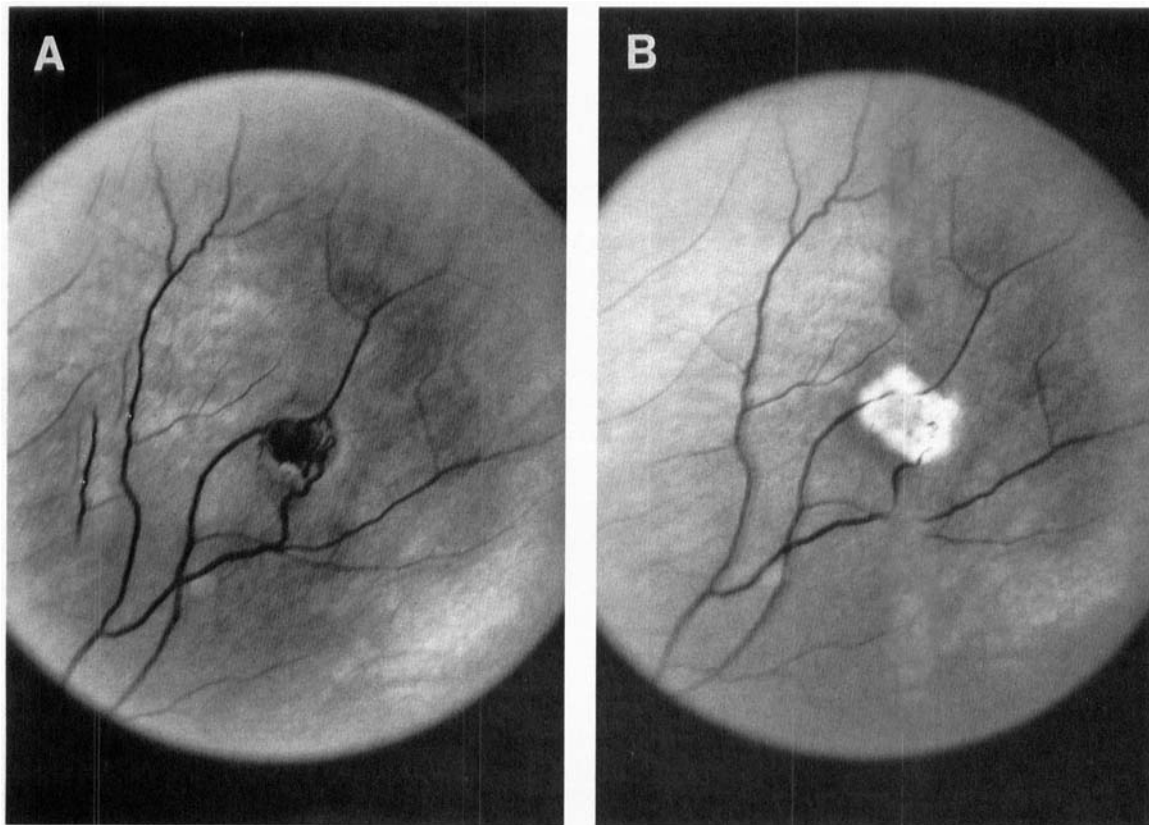
large angioma (4 mm) required a total of eight sessions to achieve complete regression and feeder vessel attenuation. Larger tumors required multiple sessions and a larger number of laser applications to achieve regression. Flat tumors usually required only one or two sessions with fewer applications than raised or elevated lesions. All tumors showed significant regression as determined by reduction in fluorescein leakage and attenuation of feeder vessels. No serious long-term complications of therapy were observed. Focal hemorrhage at the time of treatment or present during subsequent evaluations was common. There was a single instance of vitreous hemorrhage with visual impairment that occurred within 12 hours of a treatment session. Subretinal hemorrhage was observed in three instances with extension up to 1 disc diameter from the treated angioma. One patient experienced asymptomatic serous retinal detachments after each of three treatment ses-

sions for the same angioma. The shallow inferior detachments spontaneously resolved within 2 to 3 weeks and later treatment sessions were completed without complications.

The intensity of the burns applied to a small angioma (approximately 1000  $\mu\text{m}$  diameter) is shown in Fig 1. The posttreatment appearance of this lesion is representative of the intensity of photocoagulation used throughout this study. For this lesion, which was treated using a 3-mirror Goldmann lens, the laser was set at a 200  $\mu\text{m}$  spot size with 200 mW power and a burn duration of 0.1 second. The angioma was completely obliterated by a single-treatment session.

Two cases illustrate the time course and effectiveness of FPAL therapy for the treatment of moderate to large angiomas. The first example shown in Fig 2 illustrates the regression of a large, 3500  $\mu\text{m}$  angioma treated in a 9-year-old male. Six months before treatment the patient experienced an acute exudative episode from this angioma resulting in dense exudative deposits and a macular star. Figure 2A illustrates the angioma 2 weeks after treatment of the surrounding retina with a ring of laser application to minimize retinal detachment. At this time there was a considerable amount of subretinal fluid under the lesion. Treatment of this angioma was alternated with treatment of an additional 2,000  $\mu\text{m}$  angioma in the same eye and 10 smaller angiomas in the other eye. Figure 2B shows the appearance of the lesion after the second direct application of FPAL to the tumor 5 weeks after the first photograph. Figure 2C shows the angioma 5 months after the initiation of treatment, 4 weeks after the fifth and final application of FPAL. A total of 438 laser spots were applied to this angioma. Visual acuity improved from 20/200 to 20/50 at the time of final evaluation. Note the marked regression of the tumor, the lack of subretinal fluid, and the attenuation of the feeder vessels. The tumor showed staining with fluorescein, but minimal leakage of dye. All lesions in both eyes responded to FPAL treatment and have remained stable for at least 10 months after treatment.

The second case reflects the treatment progression of a 2,500  $\mu\text{m}$  angioma in an 11-year-old girl, who received treatment for two addi-



**Fig 1.** A flat, red angioma in the left eye of a 36-year-old man with a similar angioma in the right eye and a peripapillary tumor in the left eye. (A) Appearance of lesion before treatment. (B) Appearance of the lesion immediately after laser treatment with 27 applications of 0.1-second duration, 200 mW, 200- $\mu$ m spot size with a 3-mirror Goldmann lens. This single treatment resulted in complete ablation of the tumor.

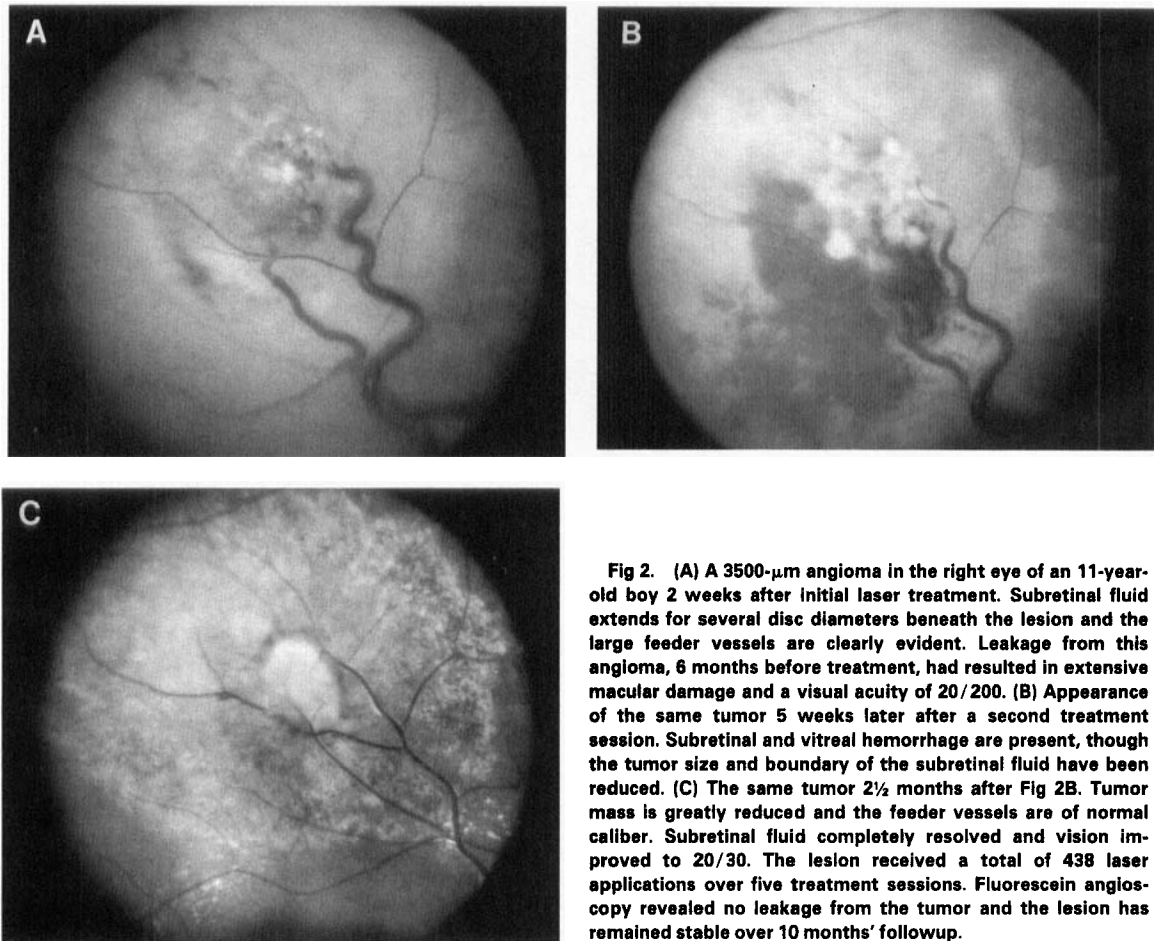
tional angiomas, 1,200 and 3,500  $\mu$ m in diameter, and four angiomas that were less than 200  $\mu$ m in diameter (Fig 3). Figure 3A shows the elevated, globular angioma with large feeder vessels before treatment. Figure 3B shows the appearance of the angioma after four laser sessions. There are white burns over the feeder arteriole and focal hemorrhage near the efferent feeder vessel. During the 2 month time interval between taking the photographs (Figs 3B and 3C), three laser sessions comprising a total of 115 spots were applied. At this stage, regression of the tumor and feeder vessel attenuation are clearly evident. Two months after the photograph (Fig 3C) was taken, the lesion was treated with an additional 35 laser spots. The angioma continued to involute after the final treatment. The appearance of the lesion 5 months after the preceding photograph (Fig 3C) was taken is

shown in Fig 3D. There is continuing feeder vessel attenuation, tumor regression, and minimal fluorescein leakage. This angioma received a total of 610 burn applications over eight treatment sessions.

#### *Discussion*

The rationale for fluorescein-potentiated argon laser treatment is straightforward. Laser photocoagulation destroys tissue and can be precisely controlled and titrated for tumors of varying sizes. The argon blue-green laser is readily available as compared with variable wavelength dye lasers. Fluorescein is routinely used for diagnostic purposes and strongly absorbs the blue light emitted by the laser. Because fluorescein readily stains the walls of angiomatous blood vessels, it provides a selective target for the laser energy. The strong





**Fig 2.** (A) A 3500- $\mu\text{m}$  angioma in the right eye of an 11-year-old boy 2 weeks after initial laser treatment. Subretinal fluid extends for several disc diameters beneath the lesion and the large feeder vessels are clearly evident. Leakage from this angioma, 6 months before treatment, had resulted in extensive macular damage and a visual acuity of 20/200. (B) Appearance of the same tumor 5 weeks later after a second treatment session. Subretinal and vitreal hemorrhage are present, though the tumor size and boundary of the subretinal fluid have been reduced. (C) The same tumor 2½ months after Fig 2B. Tumor mass is greatly reduced and the feeder vessels are of normal caliber. Subretinal fluid completely resolved and vision improved to 20/30. The lesion received a total of 438 laser applications over five treatment sessions. Fluorescein angiography revealed no leakage from the tumor and the lesion has remained stable over 10 months' followup.

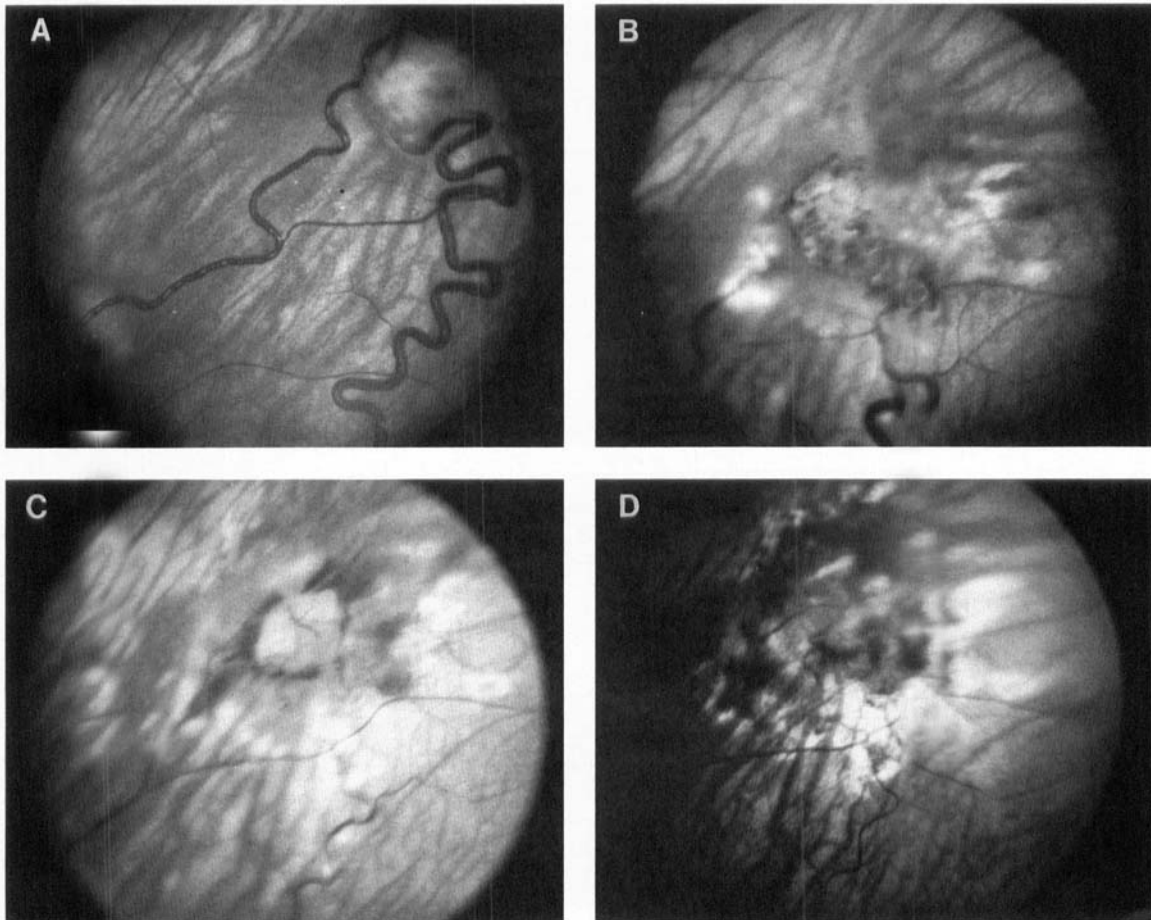
selective absorption of blue wavelengths by fluorescein considerably reduces the overall amount of light energy necessary for tumor vessel closure compared with argon green. This efficiency of energy uptake justifies the use of this wavelength.

Some ophthalmologists have raised concerns because of the absorption of blue by the macular pigments. In this series, no treated lesions were located within the macula. One can use laser energies that are comparable with those for a light burn as used in panretinal photocoagulation and yet obtain heavy energy uptake into the vessel walls of the tumor. The combination of low laser energies and the focal application of treatment minimizes the potential for blue-light induced visual damage. Unlike yellow-dye laser therapy, which has been advocated for the treatment of vascular lesions,<sup>21,22</sup> the combination of fluorescein and argon blue-green pro-

vides specificity for the vessels of the angioma while sparing normal retinal vasculature.

We have observed the emergence of new angiomas adjacent to tumors that have received laser and/or cryotherapy. It is desirable to minimize the potential for vascular damage to surrounding retinal vessels from laser scatter that might contribute to angioma formation. Though we lack a sufficient population to compare the effects of FPAL and the dye laser on new angioma formation, there is a theoretical justification for advocating tumor vessel specificity. Both FPAL and the yellow dye laser can achieve significant energy uptake in angiomas associated with retinal detachments because neither rely on the melanin pigment for energy absorption.

An advantage of the FPAL with respect to the yellow wavelength laser is that the leakage of fluorescein into the tumor can allow for



**Fig 3.** (A) A 2500- $\mu\text{m}$  angioma in the right eye of an 11-year-old girl with large feeder vessels and a highly vascularized globular tumor. This patient had multiple angiomas in both eyes ranging from 27 to 3500  $\mu\text{m}$  in diameter. (B) The appearance of the tumor after four laser sessions during a 6-week period. White burns over the feeder vessels and focal spasm are present. The view is slightly impaired by a small amount of vitreous hemorrhage. (C) The tumor 2 months after the treatment session shown in Fig 3B. The lesion has received three additional laser sessions totaling 115 burns. The feeder vessels are considerably attenuated and the tumor mass is reduced. A small amount of fluorescein leakage was noted and the tumor was treated with an additional 35 laser spots. (D) The same tumor 5 months after the final treatment. There has been ongoing involution of the tumor mass and further attenuation of the feeder vessels. Fluorescein leakage is no longer evident, though there is staining of the lesion (not shown). The angioma received a total of 610 laser applications over 8 sessions.

effective energy uptake into angiomas with fibrotic components that would otherwise obscure the tumor vascularity. This leakage is a potential disadvantage when dye leakage into the vitreous causes excessive energy uptake into the vitreous. This problem is minimized by carefully timing the application of laser therapy in relation to the time of fluorescein injection. In every instance, fluorescein leakage was sufficiently attenuated after the first course of treatment that such precautions were not necessary in later therapy sessions.

FPAL treatment can be integrated into the

diagnostic angioscopic examination of the retina so that tumor leakage can be readily assessed, treatment response can be monitored, and new lesions can be detected early. Leakage was identified in 12 of the 27 angiomas that had been treated before the entry of the patients in the NEI study. Leakage could be detected in some of the larger angiomas, even when the feeder vessels were markedly attenuated. For large angiomas, there was no correlation between the appearance of the angioma and the presence or absence of fluorescein staining and leakage. Resorption of subretinal fluid and

retinal flattening were indicators that leakage had qualitatively decreased. Because ongoing perivascular leakage may be responsible for cellular and membrane proliferation and contribute to the morbidity of this disease,<sup>37,38</sup> surveillance for fluorescein leakage in treated lesions may aid in long-term management.

Fluorescein has been widely used in ophthalmology, and the complications associated with its use have been very low.<sup>39</sup> These complications include transient nausea, bruising, dye extravasation, allergic responses, and very rarely, anaphylactic reactions including death. We observed no complications from fluorescein administration in these patients, including the three children less than 12 years of age. The added risk of using intravenous fluorescein is offset by the efficacy of the laser therapy for large angiomas, the improved ability to assess the effectiveness of tumor closure, and the detection of new angiomas. It is possible that other dyes and selected laser wavelengths can be developed which will offer comparable efficacy to FPAL as

well as eliminate any adverse risk associated with blue light exposure.

The limitations of FPAL on treating large angiomas or peripapillary tumors have not been established. Our findings and treatment experience are in agreement with previous studies of VHL and are consistent with the treatment outcomes reported by Lane et al.<sup>26</sup> The role for combined laser and cryotherapy in controlling angioma growth and damage has not been examined. There are clearly tumors of such size that laser therapy (of any modality) will be incapable of fully penetrating the tumor and achieving vessel closure. However, the use of FPAL to reduce the vascularity of the tumor and reduce exudation could play a valuable role in improving our success with cryotherapy and intraocular surgery. FPAL is a powerful adjunct to our current armamentarium of laser therapies and has potential in the treatment of other vascular disorders of the retina in which vascular specificity and preservation of surrounding tissues is of critical concern.

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