# TRANSPUPILLARY THERMOTHERAPY: A DEVELOPING APPROACH IN THE TREATMENT OF OCCULT SUBFOVEAL CHOROIDAL MEMBRANES DURING AGE-RELATED MACULAR DEGENERATION

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**Abstract**
Transpupillary thermotherapy (TTT) of choroidal neovascularization is a developing treatment modality. It uses large spot size, low irradiance and long exposure times with infrared laser to deliver hyperthermia to the choroid and retinal pigment epithelium.

TTT has been originally used in the treatment of ocular tumors such as choroidal melanoma and choroidal hemangioma. Histologic studies showed secondary vascular sclerosis of irradiated vessels. Most of treatments of choroidal neovascularization have been conducted in eyes with symptomatic subfoveal occult lesions. The rationale for the treatment of choroidal neovascularization is to induce moderate hyperthermia sufficient to produce CNV thrombosis without major collateral retinal damages. Preliminary results from a number of pilot studies showed that TTT can safely reduce the risk of vision loss in patients with occult CNV secondary to AMD. A placebo-controlled, multi-center trial (TTT4CNV) evaluating the long-term efficacy and visual implications of TTT in occult CNV is underway. The basic principle of TTT and the results of the initial studies are described in this review.

**Introduction**
Choroidal neovascularization is a leading cause of blindness in the western world. It causes 90% of the visual loss in age-related macular degeneration (AMD).[1] It also occurs during pathologic myopia (PM), which is the seventh leading cause of blindness in the United States,[2] ocular histoplasmosis syndrome, angioid streaks, or idiopathic causes. Laser photocoagulation treatment can reduce the incidence of severe visual loss in cases of classic extrafoveal and juxtafoveal CNV. However laser photocoagulation damages the overlying neural retina and results in immediate visual loss when the CNV is subfoveal.[3] There is also a high recurrence rate after laser photocoagulation.[4] Additionally only 13% of cases of neovascular AMD are eligible for laser treatment under the present guidelines, because the CNV is occult, or subfoveal and large.[5] Currently, there are no indications for the treatment of occult subfoveal CNV. Therefore, there is a need for alternative treatment modalities for CNV. Recently, photodynamic therapy (PDT) has shown promising results in the treatment of classic subfoveal CNV.[6] Photodynamic therapy has also shown modest benefits in the treatment of a subgroup of occult CNVs with smaller lesions (4 disc areas or less) or lower levels of visual acuity (approximate Snellen equivalent of 20/50 or less).[4] A number of other new treatments (radiotherapy, systemic thalidomide and other antiangiogenic agents, macular translocation, submacular membrane excision) are under investigation. Preliminary experiences have shown the benefit of TTT for the treatment of subfoveal CNV. Reichel et al.[7] and Newsom et al.[8] demonstrated a high closure rate and resolution of the neovacular membranes in patients with AMD without deleterious side effects.

**Principle and modality of application of transpupillary termotherapy**
Transpupillary therapy offers a potentially selective treatment for CNV secondary to AMD and other diseases. TTT is a low retinal irradiance, large spot size, long-pulse infrared diode laser photocoagulation treatment. The near infrared wavelength is absorbed by melanin contained into RPE cells and choroidal melanocytes. The aim of the treatment is to induce leakage reduction and exudate resorption. In this event fovea flattens and, potentially, vision stabilizes or improves.
Whereas PDT and hyperthermia use exposures of one minute or longer, standard laser photocoagulation is applied with exposures of less than 100 times. Standard laser photocoagulation uses irradiances more than 10 times higher than TTT. Retinal irradiance is less than 1W per square centimeter in PDT and more than 10 times higher with hyperthermia. With PDT there is no temperature increase at the retina, while standard laser photocoagulation gives a temperature rise of about 45° with complete protein denaturation. Conversely to suprathreshold standard laser irradiation, the endpoint of TTT is not tissue coagulation but a controlled gradual maximal temperature raise of 10° C at the level of the lesion.[10] In general no retinal color change should be obtained during laser exposure.
Usual setting for a 60-second exposure on occult lesion is a power/diameter ratio of about 250 mW per mm. A spot size of 3 mm micron requires a power of 800 mW with a Goldmann lens. The Goldmann type lens magnification factor is 0.93X, so the actual laser spot at the retina is obtained

dividing the diameter in air for the lens magnification (table 1).

**Table 1. TTT indications for initial laser power setting**

| 60 second laser exposure time | | | |
|---|---|---|---|
| Spot diameter in air (mm) | Power mW | Irradiance (W/cm2) | Power/Diameter Ratio (mW/mm) |
| 0.5 | 128 | 61 | 247 |
| 0.8 | 200 | 39 | 247 |
| 1.2 | 320 | 24 | 247 |
| 2.0 | 530 | 15 | 247 |
| 3.0 | 800 | 10 | 247 |

Before treatment, an accurate measurement of the lesion on fluorescein and indocyanine angiogram should be obtained in order to avoid irradiation of healthy tissue. The large laser spot is set to extend at least 100 micron beyond its margins.

For the purpose of producing and maintaining the same level of hypertermia with different spot diameters (ie. constant power/diameter ratio), TTT of smaller lesions need higher irradiances due to the faster heat dissipation. This is an apparent paradox according to the constant irradiance or power/area ratio normally used in conventional photocoagulation. Infact, for any given pigmentation, temperature rise depends on both laser irradiance and spot size. The spot size, however, determines the thermally affected volume of tissue irradiated. Irradiance is directly proportional to the cooling rate and inversely proportional to the thermally affected volume.

Transpupillary thermotherapy is a laser procedure but ophthalmoscopic and angiographic features differ significantly from the typical features of conventional laser theraphy. [12]

The challenge of TTT is also related to the proper selection of laser power levels that are not too low nor excessive but are sufficient to alter the natural history of the lesions and trigger the pathophysiologic response resulting in a therapeutical beneficial effect. The absence of a visible endpoint during TTT leaves the physician with no tangible sign of achieved proper threshold for a positive outcome.

### Angiographic characteristics

Although histologic studies of TTT-treated choroidal melanomas demonstrated extensive thrombosis of tumor vessels after treatment,[9,11] the mechanisms of TTT-induced vascular damage and occlusion of CNV are not yet fully understood.

Fluorescein and indocyanine green angiography are valuable tools to document the direct effect of TTT on the vascular integrity of CNV and collateral choroid. The changes that occur in the first weeks after TTT may provide some useful information to explain, predict and compare the effects in treated patients. Early angiographic images immediately after treatment might provide the treating ophthalmologist with a proof of a non-sham, and hopefully beneficial treatment.

Recently we examined initial morphological alteration of CNV after treatment of occult and classic lesions. [13]

Digital fluorescein angiography (FA)and indocyanine green angiography (ICGA) were performed at baseline and after TTT within 1 hour, and at 1 week.

Within 1 hour after TTT of CNV, 67% of observed eyes showed a hyperfluorescent area correspondent to the laser spot (fig. 1). Increased leakage activity was evident originating from CNV and collateral choroid included into the treatment spot. Similar angiographic findings can be appreciated after PDT of CNV. [14] The treatment with PDT is followed by early intensive increase in vascular permeability consistent with a loss of barrier function.

In 54% of cases observed, follow-up at 1 week after TTT of CNV demonstrated homogeneous choroidal hypofluorescence covering the entire size of the laser spot with absence of angiographic leakage (fig. 2). Hypofluorescence by ICGA angiography was not as deep as seen by fluorescein angiography, with larger choroidal vessels still seen. Late phases of ICGA angiography demonstrated reperfusion of the choroid with a ring-shaped hyperfluorescence of the collateral choroid included into the irradiated area. The retinal vessels were intact and physiologically perfused in all cases except the one that showed retinal whitening during treatment. Similarly to TTT, hypofluorescence of the light-exposed area has been described at one week after photodynamic therapy of CNV. [14]

Our results clearly showed that vascular damage and remodelling are consequences of TTT of CNV. The observation of hyperfluorescence and hypofluorescence after TTT derives from a combination of damage within the microvasculature and the stimulated responses.

### OCT imaging of CNV treated with TTT

TTT induces a dynamic sequence on CNV during the early post-operative period. Many of the biomicroscopic and angiographic signs of exudative AMD can be visualized and quantified with OCT. [21-23] OCT may be also of aid in understanding the rapid response to treatment in the research and clinical setting. [24]

Subfoveal CNV can be identified as a highly or moderately reflective mass that protrudes through

the RPE. The reflective band correspondent to the RPE and choriocapillaris is thickened in a fusiform manner and disrupted directly beneath the fovea (fig. 4, top). [25] Alternatively CNV is seen as generally enhanced choroidal reflectivity at the level of the fovea (fig. 3, top). In the case of fibrovascular pigment epithelial detachment, OCT shows an elevation of the RPE above a backscattering area corresponding to fibrovascular proliferation. CNV is usually accompanied by subretinal fluid, retinal edema and eventually retinal cysts that appear as non-homogeneous hypo-reflective areas. However OCT is most useful in assessing intraretinal and subretinal fluid and monitoring their changes after treatment. [26]

Minimal subretinal fluid appears as a nonreflective space between the RPE and neuroretina, while retinal edema is visualized as increased retinal thickness and a diffuse decrease in retinal reflectivity. Serous detachment of the RPE is characterized by elevation of the hyper-reflective layer corresponding to the RPE.

TTT of CNV is followed by an acute macular thickening within the treatment spot due to the inflammatory response to hyperthermia and endothelial damage with subsequent increased dye leakage (fig. 3, bottom). Extravasated fluid accumulates into the retina and in the subretinal space. OCT shows the resolution or improvement of fluid after 1 week. OCT taken within few hours and 1 week after photodynamic therapy of CNV shows similar patterns.[27] In some cases, homogeneously increased reflectivity of the neurosensory retina with improvement of edema is detected on OCT 1 week after TTT (fig. 4, middle). This pattern might represent either the sequelae of the inflammatory response to hyperthermia or the effect of a treatment not completely selective. During follow-up, OCT can also document progression to retinal atrophy with reduced retinal thickness due to an excessive treatment (fig. 4, bottom). In conclusion, the sequential imaging with OCT of CNV treated with TTT provides new insight into the patterns of acute tissue response by cross-sectional layer

## Pathophysiology of TTT effects on CNV

The early changes after TTT of CNV are similar to those observed after PDT of CNV. [18] Therefore TTT and PDT might share common mechanisms of action.

A hypothesis for the mechanisms leading to vessel closure begins with perturbation and damage to endothelial cells during hyperthermia to target tissues. Endothelial cells damage leads to the establishment of thrombogenic sites within the vessel lumen and this initiates a physiological cascade of responses including platelet aggregation, the release of vasoactive molecules, leukocyte adhesion, proliferation of RPE cells and increase in vascular permeability.

Histopathologic evaluations of excised CNVs after PDT, clearly show endothelial cell damage with subsequent thrombus formation and vascular occlusion of neovascularization. [14] Studies on tumor vessel damage following laser-induced hyperthermia demonstrated an increased vessel permeability and extreme edema of vascular endothelial cells.[15] As near-infrared wavelength is not absorbed by hemoglobin, vascular damage is likely to occur by heat transmission from the pigmented targets of the radiation (RPE cells and choroidal melanocytes).[16] Therefore the absorption centre lies outside the vessel lumen and the vascular endothelium is damaged by heat radiating from melanin granules towards the vessel wall. The amount of energy transmitted to hemoglobin within the vessel lumen is small and the temperature rise attained here is not sufficient to cause either protein or cell extensive damage. Most of red blood cells and platelets are not disrupted, and plasma protein (particularly fibrinogen) are not denaturated. Thus, platelets have ready access to damaged endothelium, promoting blood flow stasis through the normal hemostatic mechanism.

It is also known from experiments on tumors, that the blood flow in microcirculation during TTT is a bimodal function of temperature. At approximately 40-43°C the blood flow rate increases with temperature, while above 43°C it decreases with temperature. Recent *in vivo* studies on the effect of TTT on ocular perfusion after irradiation of occult subfoveal CNV during AMD, confirmed that hyperthermia is associated with transiently decreased volumetric blood flow in the retinal circulation at 24 hours post treatment. [17] Flow resistance in the choriocapillaris and in the CNV lesion might also be increased by interstitial pressure and edema due to extravasated fluid following TTT. [15] Early hyperfluorescence after TTT might be due not only to increased vascular leakage but also to impaired transport by the targeted RPE cells. Therefore normal fluid would not pumped out by the RPE.

Early hypofluorescence after 1 week might be interpreted as a hypoperfusion of the neovascular complex and choriocapillaris. It could also result from masking by protein-rich exudate originating from vascular or RPE breakdown within the treated area. Histologic studies on the application of TTT on choroidal melanomas show extensive thrombosis of tumor vessels.[9] Similarly hypertermic treatment of CNV could induce the progressive closure of the neovascular net through transient changes in perfusion dynamics.

A number of other factors may have an influence

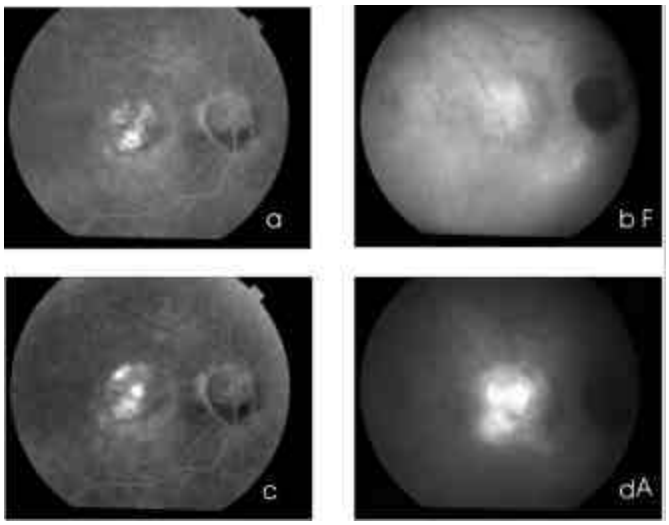



Fig. 1: FA (a) and ICGA (b) before and 1 hour after (c,d respectively) TTT of an occult CNV due to AMD. Both FA and ICGA show increased leakage activity. The margins of the treated area corresponding to the laser spot are well delineated by ICGA after treatment.

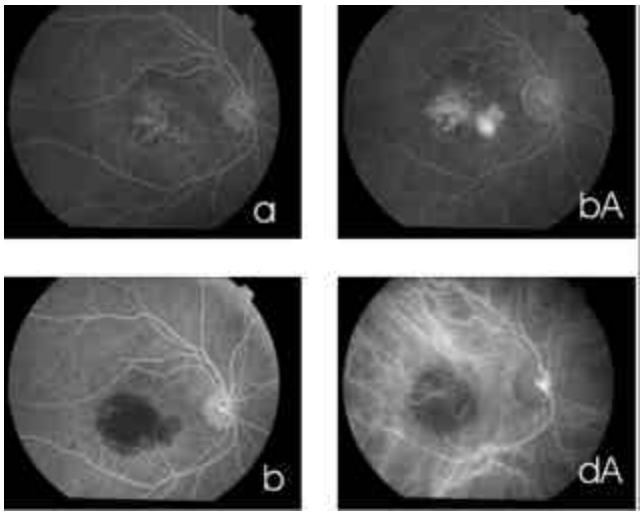



Fig. 2: FA early (a) and late (b) phases before and FA (c) and ICGA (d) 1 week after TTT of an occult CNV due to AMD. Both FA and ICGA show the exact contour of the treated area that appears homogeneously hypofluorescent with FA. Large choroidal vessels within the dark spot can be seen with ICGA.

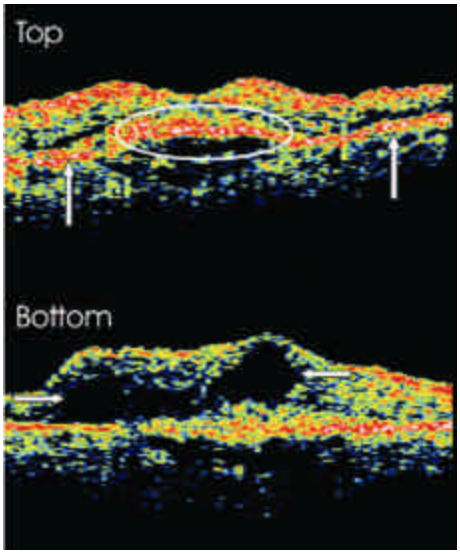
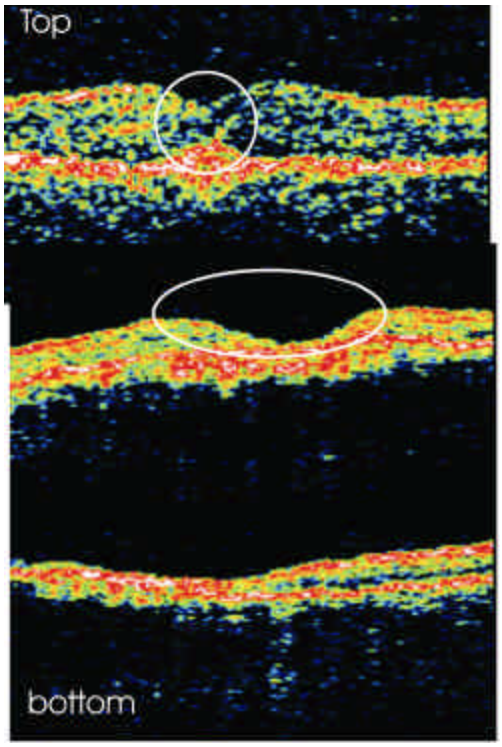



Fig. 3: OCT before (top) and 1 hour after (bottom) TTT of CNV. Before treatment, CNV appears beneath the fovea as a discrete thickening of the RPE-choriocapillaris layer (oval). Subretinal and intraretinal fluid is associated to the lesion (arrows). Immediately after treatment, OCT shows elevation of the inner retinal surface with increased fluid (arrows).

Fig. 4: OCT before (top), 1 week after (middle) and 3 months after (bottom) TTT of CNV. A fusiform thickening of the hyper-reflective band corresponds to the CNV (circle). One week after treatment, fluid has completely resolved. Note the increased reflectivity of the neurosensory retina (oval). Three months after TTT, the lesion has progressed to chorioretinal atrophy. OCT shows a significant decrease in retinal thickness with a hyper-reflective region corresponding to the area treated.



on vascular response to TTT. There is evidence that pH may decrease during hyperthermia, causing increased membrane rigidity of red blood cells which has an impact on the viscosity of blood. Lower pH also renders the endothelial cells more sensitive to heat. The resulting swelling of the endothelial cells reduces the effective diameter of the blood vessels with a flow reduction. The inflammatory reaction to thermal injury may induce the white blood cells to stick to the vessel walls and decrease their functional diameter. Recently, Mainster and Reichel have explored the role of heat shock proteins and apoptosis.[10] Finally, the beneficial effect of factors derived from a targeted RPE should be considered.[19,20]

**Study results**

Previous studies have shown that TTT may positively alter the natural course of ocular tumors. Recently, TTT has been proposed for the treatment of CNV. A number of pilot studies on transpupillary thermotherapy of subfoveal choroidal neovascularization have been conducted which show an average improvement of visual acuity in 15% of cases, stabilization in 57% of cases and worsening in 27%. [28-34] On average the avoidance of visual loss of three or more lines was obtained in 76% of cases treated. Most of authors report a high closure rate of newvessels, decreased exudation and relief of symptoms after treatment. Reichel et al.[7] and Newsom et al.[8] demonstrated a high closure rate and resolution of the membranes in patients with occult subfoveal CNV secondary to AMD. Reichel et al.[7] retrospectively evaluated 16 eyes with occult subfoveal CNV secondary to AMD that had received TTT. Three eyes (19%) showed > 2 lines improvement in visual acuity over a period of 6 to 25 months (mean 13 months). Visual acuity remained stable (no change or one-line improvement) in nine treated eyes (56%). The remaining four eyes (25%) showed a decline ($\geq$ 1 line worsened) in visual acuity. During follow-up, 10 eyes over 16 treated received FA which showed decreased exudation and no evidence of damage to the overlying retina. At the end of follow-up, most of eyes showed reduction of subretinal fluid and exudation with restoration of the retinal anatomy on OCT and/or clinical examination.

Newsom et al.[8] recently reported positive results in the use of TTT in the treatment of 42 eyes with classic and occult CNVs due to AMD. CNV resolved in 31 (74%) of eyes, remained persistent in 8 (19%) and recurred in 3 (7%). The vision was stabilized (+/- 2 lines) in 26 (62%) of eyes, a mild lost (3-5 lines) occurred in 15 (36%), and severe visual loss (6 or more lines) only in one eye (2%). In the subgroup of 22 eyes with occult subfoveal CNV the lesion was resolved in 16 (71%), remained persistent in 5 (23%), and recurred in 1 (5%). The vision was stabilized (+/- 2 lines) in 19 (86%) of eyes, a mild lost (3-5 lines) occurred in 3 (14%), without severe visual loss. The CNV disappearance was confirmed by fluorescein angiography during the average follow-up of 6.5 months.

In summary, initial results of TTT for the treatment of CNV in AMD demonstrate maintenance of visual acuity in both classic and occult membranes. Long-term results of randomized study-control trials are awaited.

Guidelines for transpupillary termotherapy

According to Reichel's protocol,[7] TTT is delivered with a large spot diameter and with very low irradiance to create a localized mild hyperthermia with no visible endpoint at the time of laser application and possible subtle color change of the lesion after treatment. Thermal application is delivered through a slit lamp using an 810 nm diode laser with an adjustable beam width of 0.8, 1.2, 2.0, and 3.0 mm. A three-mirror Goldmann fundus laser lens or similares are recommended. Treatment is conducted with 60 seconds' exposure time and a power/diameter ratio of 247 mW per mm in the case of occult CNV, such that no visible color change is detectable at the end or during irradiation. Power is reduced by one third for classic CNV and by one half in the case of CNV due to myopia or angioid streaks.

Treatment parameters are to be adapted depending on pigmentation, exudation, type of CNV and experience.

The use of multiple adjacent spots increases the risk of overtreatment.

Slit lamp illumination should be set to green and the aiming beam should be minimally visible to check better for any minimal color change during irradiation. Treatment should be abandoned in case of retinal whitening.

Laser treatments of eyes with cataract should be possible using the 810 nm infrared wavelength, thanks to its relatively better transmission and lower scatter in opacified lens than visible wavelengths. Obviously, the treatment is limited by fundus visibility and more importantly, by the ability to observe any subtle fundus change. Moreover, treatment parameters may require adjustment depending on the density of the cataract.

**Post-operative follow-up and re-treatments**

The success of TTT is typically measured by the resorption of exudation and collapse of PEDs on slit-lamp biomicroscopy and OCT measures of retinal thickness. FA and ICGA angiography per-

formed after one month can be useful in assessing reduction in leakage, although interpretation of leakage in association with occult CNV can be difficult. Stabilization and/or improvement of visual acuity is another useful parameter to follow. Improvement usually occurs over two to four months.

Re-treatments can be considered no earlier than 12 weeks if there appears to be minimal to no response to treatment. Clinical characteristics for re-treatments include: less than 50% reduction in fluorescein leakage; no flattening of PED's; no resolution of intraretinal and/or subretinal fluid; no change in the elevation of the RPE.

**Safety issues**

Relative contra-indications of diode TTT include patients with predominantly serous PEDs (larger than 25% of the lesion), for the risks of rips of the RPE, and patients with large geographic atrophy within 500 µm of the fovea.

Although the original results of the pilot studies used a Goldmann type lens with 810 nm anti-reflective coating, other lenses can be used but with caution. First, the use of panfunduscopic lenses might render the treatment less predictable. The presence of multiple reflecting surfaces and possible tilting of the lens during treatment can influence power transmission to the retina. This can result in uneven distribution of the laser energy to the treated area. Power density can be increased in some areas of the large spot and result in visible over-treatment. Second, their negative image magnification may not provide enough details for accurate treatments because the lower axial magnification may make the observation of the neurosensory retina more difficult.

When treating pseudophakic eyes, general TTT parameters can be used but careful monitoring of fundus colour change becomes particularly important because the laser beam may have higher transmission and lower scattering in IOL's than in the aged lens of elderly patients.

In case of any retinal whitening the irradiation must be immediately stopped and abandoned. The biological effect of thermal retinal photocoagulation has been already reached.

**Complications following TTT**

Occurrence of mild central scotoma and of postoperative edema have been reported. In general, when this occurs it is temporary and does not seem to affect the final visual acuity.

Retinal burns, which can result in severe loss of vision, are typically due to over-treatment.

Retinal arteriolar occlusion has been reported in 2.2% of treated eyes [35] and appears to be associated with prior laser photocoagulation. It may result from retinal attenuation (thinning of the retina) and focal areas of pigment migration that were results of previous laser treatment.

Subretinal and/or intraretinal hemorrhage may occur during and after the treatment. Generally, when this occurs, the procedure can be completed (810 nm infrared is minimally absorbed by hemoglobin) and most of the hemorrhage will disappear in the next weeks.

TTT: Current Benefit and Perspectives

The exact role of TTT in the treatment of choroidal neovascularization has not yet been determined conclusively. The results are encouraging in the small number of patients treated with this modality so far. Closure of choroidal neovascularization has been observed in a majority of cases treated. Visual acuity remained as good as or better than pretreatment levels in more than 90% of treated patients, possibly because of preservation of normal retinal tissue. Longer follow-up and additional experience are necessary before TTT can be recommended as an effective therapy.

Studies using larger numbers of patients are currently in progress, and may ultimately determine the role of TTT in the treatment of choroidal neovascularization.

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They answered, as they took their fees,
"There is no cure for this disease."
Hilaire Belloc (1870-1953), French Born British Writer.
Cautionary Tales "Henry King."

Make it compulsory for a doctor using a brass plate to have inscribed on it, in addition to letters indicating his qualifications, the words "Remember that I too am mortal"
George Bernard Shaw (1856 - 1950), Irish Playwright.
*The Doctor's Dilemma* "Preface on doctors."

The deficits in the eyelashes are not apparent to the eye.
- Tamil Proverb