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MONTGOMERY LECTURE

Subretinal Neovascularisation in Senile Macular Degeneration

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First of all, I wish to thank you most sincerely for the great honour of inviting me to deliver the Montgomery Lecture. I appreciate this honour, which becomes even more distinctive upon reading the list of previous lecturers. Robert Montgomery was a man with many scientific interests in ophthalmology, and the institution of this lecture represents a continuing achievement for Irish ophthalmology. I am fully aware of my responsibility in accepting your kind invitation.

Before considering the topic of my lecture, it is probably appropriate to apologise for selecting a subject for which it is still not possible to present a new point of view, but only the experience of our team in Créteil on senile macular degeneration. I should be very happy if I succeed in contributing something to the elucidation of several questions still in dispute.

Until recently, choroidal neovascularisation was considered *little more than a pathological curiosity*. At the American Academy of Ophthalmology Symposium on Macular Diseases, in 1965, no mention was made about macular subretinal neovascularisation as a relevant factor in Senile Macular Degeneration (SMD). Two years later, Gass[1] first pointed out the importance of subretinal new vessel growth by means of stereoscopic fundus photography and *fluorescein* angiography. Since then, clinical studies by Teeters and Bird[2] and many others documented the morphology and the distribution of the capillaries within this neovascular tissue. *Histopathologic* studies by Sarks,[3] Green[4] and others have shown that the neovascular process may be initiated by senile degeneration of Bruch's membrane and/or of the retinal pigment epithelium (RPE).

The occurrence of subretinal neovascularisation corresponds to the 'turning point' in the natural history of SMD, causing severe and irreversible lesions, leaking fluid or blood or both under and into the macula. Until it becomes possible to prevent the development of subretinal neovascularisation, laser photocoagulation will likely remain the single and most effective treatment. Recent French,[5] English[6] and American[7] randomised trials reported that argon laser photocoagulation was effective in reducing the risk of severe visual loss in patients with a neovascular form of SMD.

Epidemiological approach

In all developed countries for which good epidemiological data are available, SMD is the neovascular maculopathy that occurs with greatest frequency. SMD is also the leading cause of registered blindness in England,[8] Canada[9] and the United States[10] among people over the age of 50 years. It should be noted that these data reflect only the patients who are registered as legally blind, and that the classification of the cause of blindness is

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Table I *Prevalence of SMD in 2,000 consecutive charts of new patients over 45 years of age with symptoms of decreased vision presented in 1975 and in 1980.*

Age (years)	1975	1980
45–64	6.7%	11.3%
65–74	7.0%	17.5%
Over 74	21.4%	25.8%
Total	10.3%	16.9%

Table II *Sex prevalence of SMD*

Age (years)	*Men*	*Women*
Framingham 45–64	1.2%	2%
Créteil 1975	3.8%	8.9%
Framingham 65–74	8.8%	12.6%
Créteil 1975	8.5%	4.5%
Framingham Over 74	24.4%	30.1%
Créteil 1975	10.8%	42.1%

not done in a standardised way.[11] Another American survey published by Ganley[12] provides useful data from which prevalence estimates of SMD can be made; SMD was found in 8.5 per cent of those examined who were between 65 and 74 years old. These data were quite similar to the 11 per cent ratio obtained for this age-group in the Framingham Eye Study[13] and in the Gisborne Study from New Zealand.[14]

In our department, we tried to assess the number of out-patients with SMD, at presentation, in the General Clinic (Table I). We analysed 2,000 consecutive new charts for 1975 and for 1980 of patients over 45 years of age with symptoms of decreased vision. The prevalence of SMD was found in a ratio similar to the other studies for those patients 65 to 74 years old. There was a dramatic increase after the age of 74 years, in which SMD reached an incidence of 21.4 per cent in 1975 and 25.8 per cent in 1980. Among them, one-third presented with subretinal neovascularisation. It is clear that the risk of SMD increases with age, especially after the fifth decade. As the average life expectancy increases, the incidence and prevalence of SMD will undoubtedly also increase unless successful means of prevention can be found.

Although most studies have shown equal frequency between men and women, the Framingham Eye Study noted that SMD is more prevalent in women. This is similar to our data, particularly for patients over 74 years of age (Table II). However, the re-analysis of the Framingham Eye Study by Sperduto and Seigel[15] showed no increase of SMD among women. Epidemiological data can at times be difficult to evaluate and it would appear that women do not have an excessive risk of developing SMD.

Many risk factors were screened for possible associations with SMD. The positive associations that have been found suggest that the development of SMD is mainly influenced by familial, genetic and personal characteristics, rather than by environmental factors. The Framingham Eye Study positively associated SMD with elevated diastolic blood pressure. But a case-control study of Hyman[16] showed positive association of SMD only with arteriosclerosis, strokes and transient ischaemic attacks. It is also possible that SMD is associated with some forms of chronic hypertensive diseases. These two studies identified different characteristics positively correlated with SMD, such as viral infections, smoking habits, short stature, hand-grip strength, clear iris and hypermetropia, whose aetiological role is not obvious.

Several clinical studies have assessed the risk of visual loss in the second eye due to subretinal new vessels growth in patients with unilateral disciform degeneration. This risk of visual loss in the second eye has been reported as high as 9 per cent to 15 per cent per year by several authors.[3,17,18,19,20]

All these studies suggest that a greater number and greater confluence of drusen may be a risk factor for the development of exudative lesions. But little is known of the prognosis of patients with bilateral drusen and of the precise ophthalmoscopic features that carry a poor prognosis. Two studies[17,21] evaluated the cumulative risk for exudative maculopathy at about 9 to 10 per cent over 5 years. But drusen are not always present clinically in eyes with SMD, and their role in the patho-

genesis of exudative maculopathy is still unclear.

Pathogenesis

The pathogenesis of SMD has not been definitively determined. The early studies of Verhoeff and Grossman[23] laid the ground work for the more recent histopathological studies of SMD, which have suggested that drusen, retinal pigment epithelial detachment or atrophy, subretinal haemorrhage and disciform scars are all manifestations of the same disease.[5] Three main questions remain unsolved:

(1) Which age-related changes are directly involved in the pathogenesis of SMD?
(2) What are the factors that induce new vessel growth?
(3) Why does the subretinal neovascularisation clinically occur, mostly at the posterior pole and especially on the perifoveolar edges?

Drusen are the most common clinical manifestations of ageing. They are visible in at least 70 per cent of the population after the age of 50 years and histopathologically are probably universal after that age.[24] However, drusen have different forms: pathologically, they may be classified, as proposed by Sarks,[25] as hard drusen, soft drusen, and calcified drusen. Soft and/or clinically confluent drusen were identified to be high risk lesions frequently associated with SRNV.[20,25] Studies have shown fairly conclusively that drusen are a product of the retinal pigment epithelium, for the most part as an excretion of substances from the cytoplasm.[24,26] But as drusen seem to predominate in the macular area and the area surrounding the vortex veins, it suggests that the choroid or the choriocappilaris is also involved.[27,28,29]

Age-related RPE changes are probably linked with the pathogenesis of SMD. A key function of the RPE is the continual phagocytosis and digestion of damaged and discarded photoreceptor outer segments.[30] A portion of the damaged photoreceptor membrane material is thought to be resistant to enzymatic digestion and to collect in the basal cytoplasm as granules of lipofucsin.[31] There is a progressive accumulation of this pigment in the RPE cells. Concurrently, the cells gradually lose these apical granules of melanin. Old RPE elaborates large quantities of extracellular material such as collagen and basement membrane. But these changes produce few symptoms.

The changes in *Bruch's membrane* consist of degeneration of collagen and elastic fibres, increasing PAS positive deposit formation with thickening and calcification. The frequency and the role of ruptures of Bruch's membrane are still controversial. A basal laminar deposit often elevates the atrophic and degenerated RPE off the surface of the thickened Bruch's membrane. Transmission electron microscopy indicates that this basal laminar deposit is composed of abnormal basement membrane. It is sufficient to interfere with movement of nutrient substances into the retina as well as of waste products (especially outer segment debris) back toward the choriocapillaris.

Although drusen, Bruch's membrane and RPE changes are linked with SMD, these alterations could only be age-related manifestations and do not seem to be able by themselves to produce neovascularisation.[4,24] It should be remembered that many eyes with drusen do not develop neovascular disciform lesions and that black[32] and asiatic people[33] rarely present with neovascular disciform degeneration.

Penetration of Bruch's membrane by *choroidal blood vessels* and proliferation of these vessels in the subpigment epithelial space is the essential change in disciform degeneration, as demonstrated by Gass.[1] The factors that precipitate growth of these blood vessels have not yet been identified. It was thought for a long time that it was the origin of the new vessels that was important. There is now progressively more information available which suggests that environmental control is important in the growth of blood vessels, as shown by Patz[34] and by Miller in experimentally induced new vessels and RPE cell proliferation.[35] Many other factors have been advocated: it has been suggested that closure of choroidal capillaries and intercapillary fibrosis may result in ischaemia of the outer retina and growth of new vessels.[23,29] Disease of the retinal vascular supply has also been implicated as the cause of SMD,[28] but the

experimental work by Archer[36] and Ryan[37] demonstrated that retinal vascular occlusion is a minor factor in occurrence of SRNV.

Some additional stimuli have been proposed for this vascular ingrowth. They include normal[38] or excessive[39] exposure to light in a retina that may be deficient in ascorbates;[29] photochemical damage to the membrane outer segments by free radicals that probably contributes to the accumulation of lipofuscin;[31] inflammatory cells from the choroid such as macrophages that are known to collect beneath the RPE;[40] and angiogenic factors.

It may also be possible that the neovascular response corresponds to a self defensive reaction of the retina or to an attempt to eliminate toxic or waste products. In summary, blood vessel growth appears to be determined by a balance between inhibiting and stimulating influences.

It is significant that although the penetration of Bruch's membrane by choroidal blood vessels is histologically a widespread phenomenon neovascular disciform lesion (as well as drusen and pigmentary changes) almost always occurs in the macular region. It is likely that production of disciform lesions is a peculiar property of the posterior fundus, dependent upon the unique anatomical and functional characteristics of that region: Firstly, there is little evidence to suggest that the choriocapillaris or Bruch's membrane is different centrally. Pigment epithelium certainly looks different in the fovea from elsewhere. Secondly, subretinal new vessels and recurrences occur mostly near the central avascular zone, at the border between vascular and avascular retina. Thirdly, it is the zone where luteal pigment is located in the inner layers of the retina. Finally, since the foveola is an all-cone retina and since the ganglion cell layer is much thicker at its border, the phagosome material or the debris that is deposited on the inner surface of Bruch's membrane may be different.

Clinical Features

If only little is known about the mechanism of neovascularisation, we all recognise, as clinicians, that the risk of disciform degeneration is growth of the neovascular tissue and loss of central visual acuity. Once abnormal vessels proliferate they result in a detachment, perpetuated by the constant transudation of plasma constituents, from the abnormal capillaries into the subpigment epithelial space. The senile changes in the RPE, Bruch's membrane and choroid allow widespread detachment of the retinal pigment epithelium and serous or sero-sanguineous detachment of the neuro-sensory retina.

Symptoms caused by subretinal macular new vessels are related to anterior displacement of the retina and to loss of retinal function. Anterior displacement of the retina causes blurred vision, distortion of lines, micropsia. Metamorphopsia which is best assessed by the Amsler grid is one of the earliest and most reliable symptoms and one of the most suggestive. Visual loss depends upon the location of new vessels, the extent of the retinal detachment and the degree of retinal degeneration. A paracentral lesion may produce a scotoma near fixation but a majority of patients will present with loss of central vision and particularly near vision. The speed of visual loss is variable. Though a few patients retain some macular function for a year or more, most progressively lose central vision within a year of onset of symptoms.

Clinical characteristics may indicate the presence of new vessels: namely, serous retinal detachment, haemorrhages and lipids.[1] The serous retinal detachment is best seen with fundus biomicroscopy. It is usually shallow and increases on follow-up examination. It may be associated with a localised pigment epithelium detachment whose fluid may be clear or turbid. Cystoid retinal oedema may be visible, usually associated with long-standing detachment.

The neovascular tissue can rarely be identified by biomicroscopy. Only large draining vessels may be visible in advanced lesions. But the capillary network is difficult to distinguish. It can be suspected by localised retinal changes in an area which appears greyish and thickened. A ring of subretinal blood is usually present along the outer edge of the neovascular membrane.[2] The most reliable indicator of a subretinal membrane is the presence of haemorrhage. The haemorrhage may be located beneath the pigment epi-

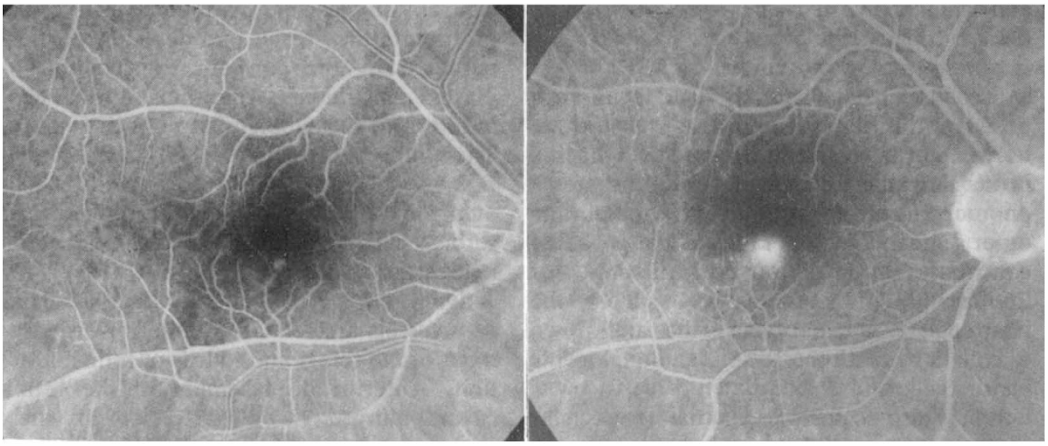

Fig. 1 (a and b). *Early manifestation as a subretinal neovascular membrane not clearly definable, because very small in size but appearing as an enlarging hyperfluorescent dot.*

thelium and gives the lesion a dark or brown appearance. The haemorrhage may lie beneath or within the sensory retina and may appear as brighter red blood. In some instances, the haemorrhage is very extensive and may collect in a dome-shaped haematoma or may acquire a tumour-like appearance. Rarely, the haemorrhage may break through the sensory retina to produce an intravitreal haemorrhage. Another sign is the presence of lipid hard exudates, which can accumulate in a carcinate ring or in a stellar or wing disposition. In a few cases, massive exudation has been recorded.[41]

Rapid-sequence stereoscopic fluorescein angiography is invaluable in detecting and outlining the precise location and size of the neovascular membrane in relationship to the fovea. Photographs should be taken in all phases of dye transit. The earliest manifestations of a subretinal neovascular membrane may not be clearly definable when it is small in size, and only appears as a small and enlarging hyperfluorescent dot (Figs 1, a and b).

Once new vessels have attained a sufficient size, a characteristic lacy pattern appears in the early phases of fluorescein angiography (Figs 2 a and b). This vascular pattern may be likened to a sea-fan or bicycle wheel, in that capillaries typically radiate outward from their point of entry through Bruch's membrane. Peripheral vascular arcades connecting

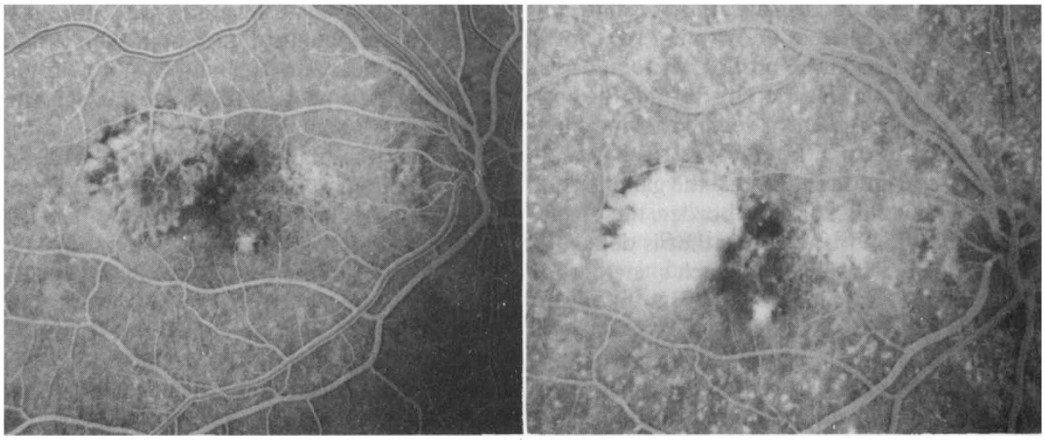

Fig. 2(a). *Characteristic lacy pattern in the early phase of the fluorescein angiography.*
(b). *Progressive leakage of the dye from the capillaries.*

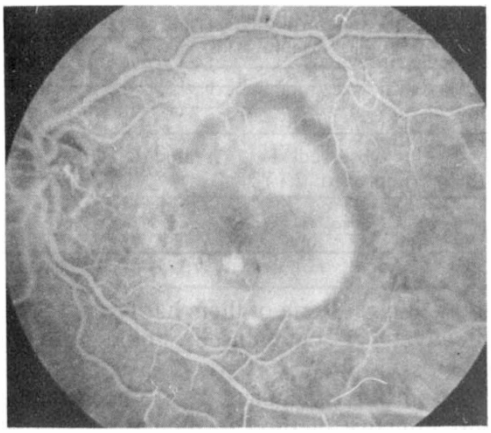

Fig. 3. *Retinal pigment epithelium detachment with 2 'hot-spots', that become brighter than the detachment itself and leak, suggestive of neovascularisation.*

these radial vessels are often more dilated than the radial vessels themselves. Angiographically, they are the most permeable to fluorescein and bleeding occurs initially from this peripheral vascular arcade. Progressive leakage of dye from the capillaries, into the fine connective tissue and the subpigment epithelial and subretinal spaces surrounding the new vessels, will appear during early recirculation phases of angiography. It will give rise to dense hyperfluorescence. In some instances, these details are partly obscured either by a cloudy subretinal exudate or by blood. This progressive leakage of fluorescein from the capillaries of the neovascular complex is a constant and the most reliable diagnostic feature.

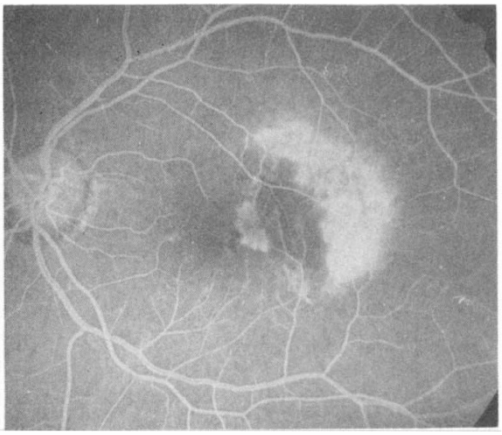

Fig. 4. *RPE detachment with retraction of the temporal edge, exposing the underlying Bruch's membrane, brightly hypofluorescent.*

Natural History

As the lesion develops, the new vessels progressively enlarge. The growth of the neovascular network may be rapid initially and associated with recurrent haemorrhages and fibrous tissue which is formed in the subretinal space. As the capillaries develop in the periphery of the lesion, the central capillaries often close. This results in a relative hypofluorescence centrally and a ring of hyperfluorescence at the edges of the lesion. The centre may be occupied only by large feeding and draining vessels. Significant leakage does not occur from such large vessels. They are often recognised as negative shadows. These clinically detectable and non-leaking vessels usually indicate an advanced disciform process. In a few cases, the process of capillary closure may continue to the point that the retina becomes flat but atrophic. The fibrovascular tissue may acquire a retinal arterial supply and retinal venous drainage.[42]

In most cases white and elevated fibrovascular tissue will develop in the subretinal space associated with varying amounts of serous or sero-sanguineous subretinal fluid. These are long-standing lesions. Fluorescein angiography shows diffuse staining of the fibrovascular tissue, often without any definite vascular pattern. The overlying retina shows cystoid changes. The visual acuity in these patients is uniformally less than 6/60.

In some cases, subretinal new vessels may not be identifiable. This can be due, in part, to the overlying pigment epithelium, and in part to subretinal fluid that may be turbid; blood, if present, may completely obstruct the view of the subretinal tissues. In about 10 per cent of cases, senile macular degeneration is associated with serous detachment of the pigment epithelium.

This retinal pigment epithelium detachment presents a 67 per cent risk of developing neovascularisation within one year.[3] Neovascularisation may be suspected when a fluid level of blood is seen inferiorly or when there are lipid exudates around the detachment; a hot spot that becomes brighter than the detachment itself and leaks as the angiogram

Table III *Results of randomised trials: changes in visual acuity*

	MPS Study		*Moorfield's Study*		*Créteil Study*	
	at 6 months		*at 6 months*		*at 24 months*	
VA	Treated	Observed	Treated	Observed	Treated	Observed
Improved or no change	57%	27%	35% (improved: 18%)	37% (improved: 7%)	72%	21%
Worse	43%	73%	65%	63%	28%	79%

progresses is also suggestive of neovascularisation (Fig. 3). The edge of this detachment may retract, exposing the underlying Bruch's membrane.[43] On fluorescein angiography, this rip in the pigment epithelium may mimic a neovascular lesion (Fig. 4). Although neovascularisation and pigment epithelial tearing are both seen in the elderly, they may not always be directly related.

Natural history studies of subretinal macular new vessels growth have shown that they are the most dangerous component of senile macular degeneration. Their rapid growth is the turning point of the disease. The risk of severe visual loss in patients with the neovascular form of SMD is about 70 per cent according to the control group in the recent randomised studies.[6,7,8] Among the different aetiologies, neovascularisation in SMD carries the most severe prognosis.[44,45]

Treatment

A variety of medications have been used to treat patients with SMD such as vasodilators and vitamins. None of them has proven to be effective yet randomised studies are in progress.

Laser photocoagulation is currently the only effective method to reduce the risk of severe visual loss in SMD. The early reports of photocoagulation in senile disciform macular degeneration showed poor visual results. With a better understanding of the disease process,[1,2,3] a more rational approach to photocoagulation has evolved. This has given rise to better functional results. The randomised studies have shown that argon laser photocoagulation was effective in reducing the risk of legal blindness by more than 60 per cent in patients with a neovascular form of SMD.

Concerning laser treatment, I would limit myself to giving our present answers to the three main questions: *Why? When?* and *How?*

(1) *Why?*

As already mentioned, the first question is answered: Laser treatment is useful and effi-

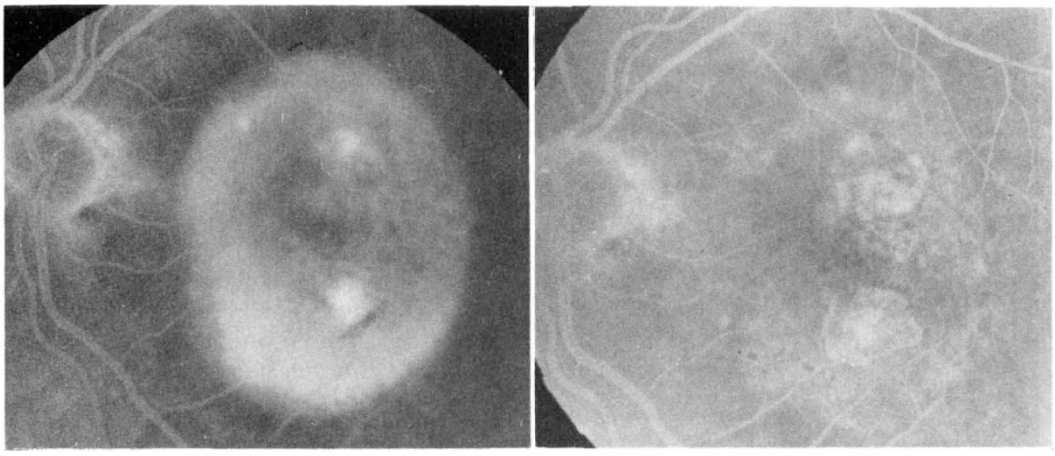

Fig. 5(a). *RPE detachment with two 'hot-spots' indicating faci of subretinal new vessels.*
(b). *Result of focal laser treatment directed to the 'hot-spots'.*

Table IV *1,000 new patients with SMD and SRNV (Créteil, 1977–83). Sex distribution*

	Treatable	*Non-treatable*
Men (413)	58% (240)	42% (173)
Women (587)	54% (317)	46% (270)
Patients (1,000)	(557)	(443)

Table V *1,000 new patients with SMD and SRNV (Créteil, 1977–83). Eye distribution*

	Treatable	*Non-treatable*	*Without SRNV*
RE (981)	30% (293)	49% (479)	21% (209)
LE (976)	31% (299)	43% (423)	26% (254)
Eyes (1,957)	(592)	(902)	(463)

cient. Treatment is useful because of the severe visual prognosis carried by the natural history of the disease. Subretinal new vessels are directly responsible for the loss of vision. Exudative maculopathy accounted for the visual loss in 88 per cent of the legally blind eyes from SMD. Treatment is efficient and randomised studies have shown that it is possible to destroy subretinal new vessels or to block further exudation and bleeding from them.

The Macular Photocoagulation Study showed that 45 per cent of untreated eyes compared to only 15 per cent of treated eyes progressed to severe visual loss after 6 months of follow-up. In the Moorfields Macular Study, the proportion of patients showing an improvement in visual acuity was consistently greater in the treated than in the untreated group.[7,8]

In the American Study, after 18 months of follow-up, 75 per cent of the treated eyes compared to 40 per cent of the untreated eyes retained useful central vision. This is similar to our data after 24 months of follow-up,[6] which showed that 72 per cent of the treated eyes compared to 21 per cent of the untreated eyes retained useful central vision (Table III).

Laser treatment must be directed to the subretinal new vessels and only to angiographically identified ones. Prophylactic treatment of drusen and other age-related changes was proposed,[18,46] but the site of subretinal new vessels is not histologically related to the site of the drusen. Their precise location is clinically unpredictable, and the results of prophylactic treatment of drusen showed no evidence of efficacy. Laser treatment of RPE detachment has not shown helpful functional results. In our experience, only 'hot-spots' are

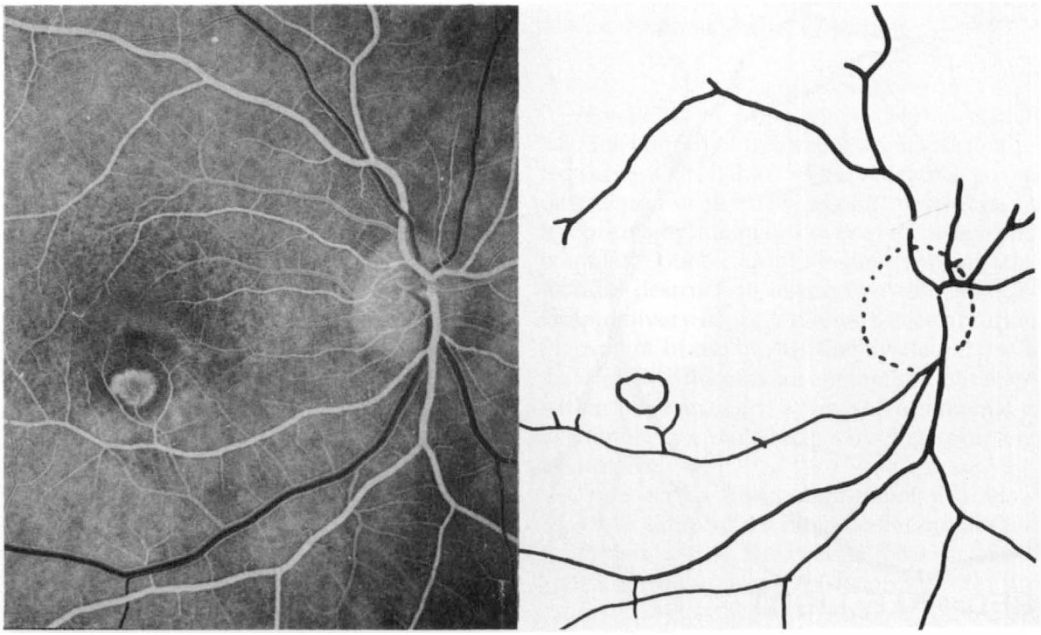

Fig. 6 (a). *The use of a transparent paper will allow the exact limits of the neovascular membrane to be delineated.*

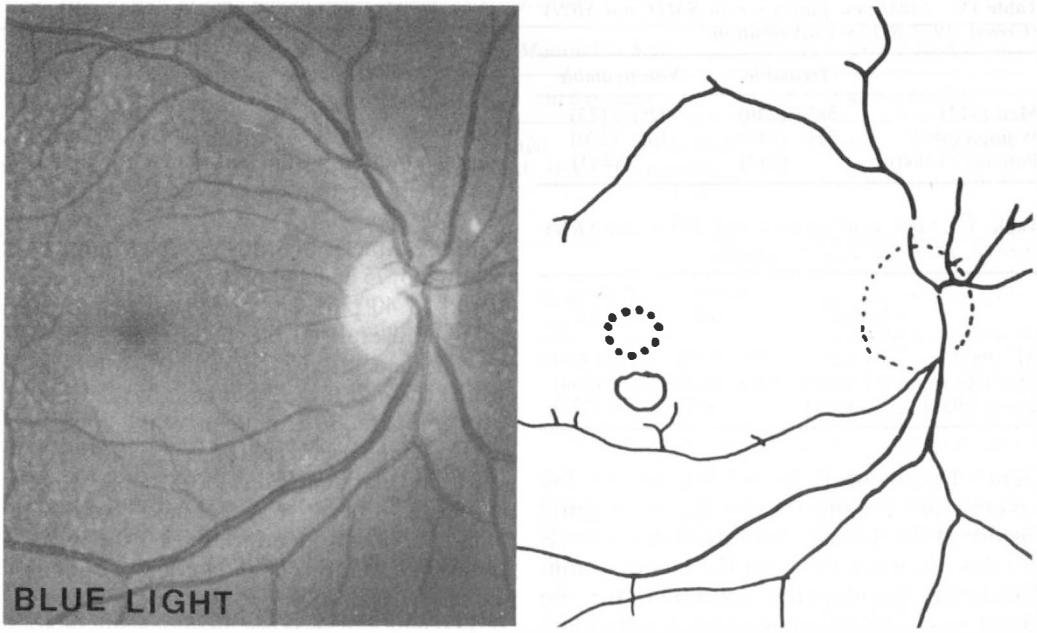

Fig. 6 (b). *The precise location of the xanthophyllic area can also be drawn using the same transparent paper.*

usefully amenable to treatment (Figs 5, a and b).

(2) *When?*

Patients with SMD and a symptomatic membrane sparing the foveola must be treated as promptly as possible.

Retrospective studies have been undertaken to identify clinical features of the lesions amenable to photocoagulation and to deter-

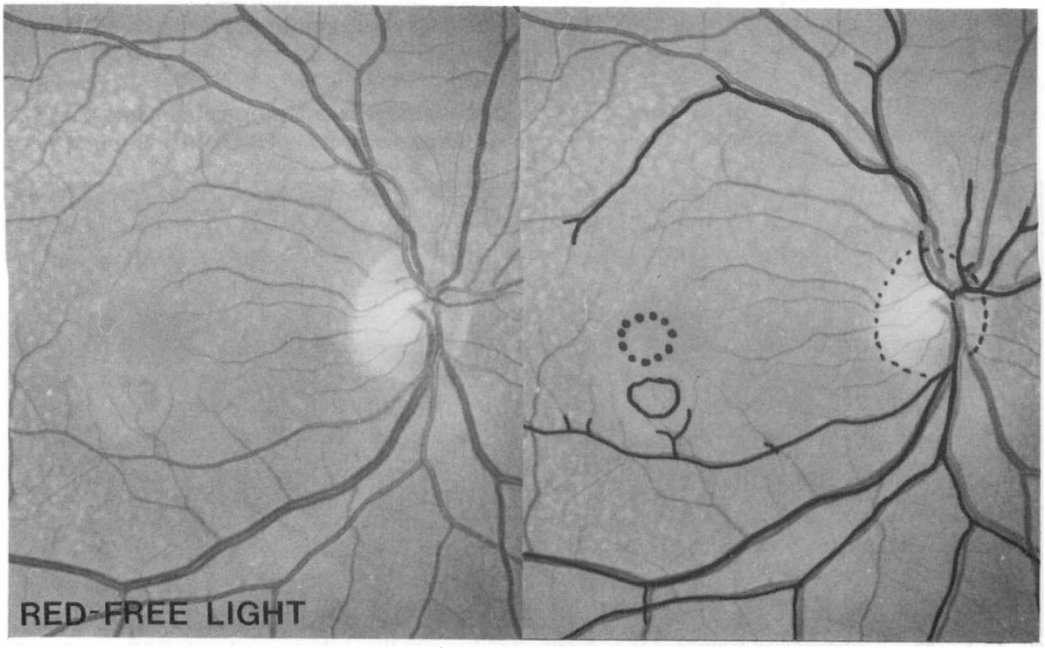

Fig. 6 (c). *Then it could be traced on the red-free or the colour print, finally to know the area to be treated and the area to be spared.*

Table VI *Age distribution. 1,000 new patients with SMD and SRNV (Créteil, 1977–83)*

Age	Eyes with SRNV		
	Number	Non-treatable	%
45–64	235	117	50
65–74	511	298	59
Over 75	748	487	66
Total	1,494	902	60

mine their percentage. In Grey, Bird and Chisholm's study[47] it has been shown that patients remain in the treatable stage for a relatively short period of time after the onset of symptoms: most patients are treatable when seen within the two first weeks; only 1 per cent of the lesions remain amenable to laser treatment after one year. The chance of a neovascular lesion being treatable may also be predicted from the visual acuity: the figure is 94 per cent when VA is 6/12 and becomes only 20 per cent when VA is 6/36 and 4 per cent when VA is 6/60.

In our Department in Créteil, we reviewd 1,000 fluorescein angiograms (1,957 eyes) of new patients with SMD and neovascularisation referred between 1977 and 1983. Among them, there were 413 men and 587 women, and there were 1,494 eyes with subretinal new vessels. These cases were further subdivided according to the possibility of laser treatment into treatable (592—40 per cent) and not treatable (902—60 per cent) lesions at the time of angiography. There was no statistical difference between men and women, nor predilection for the right or left eye between different groups of ages (Tables IV and V). But there was some increase of non-treatable eyes after the age of 74, particularly among women.

Treatable eyes are those in which the subretinal neovascular membrane can be clearly defined and in which there is a discernible gap between the edge of the neovascular tissue and the foveola, as shown by fluorescein angiography. Most of the randomised trials considered 2 or 3 groups according to the distance from the centre. Treatment was first considered only for a membrane not nearer than one-quarter disc-diameter, as suggested by Gass,[18] and then one-eighth disc-diameter by Bird[48] and even only to 100 microns (diameter of a major retinal vein at the disc.[6,8]

In the first group, the edge of the membrane is more than 400 microns from the centre of the fovea. Therefore it is outside the foveal avascular zone (FAZ) and mostly out of the xanthophyllic area. These patients are amenable to argon laser treatment with minor side effects.

The second group includes patients with membranes located between 200 and 400 microns from the centre. Thus, they extend into the foveal avascular zone and the xanthophyllic area. Blue-green argon laser is possible, but could cause unnecessary damage.

The third group includes the most difficult and hazardous cases because the treatment must be very close to the centre of the fovea. These eyes are still amenable to laser treatment, particularly using a monochromatic laser without blue wavelength.

Nevertheless, in the randomised argon laser trials, there were no significant differences in the visual outcome of treated patients according to the diameter or to the location of the neovascular complex. The results of all three subgroups were consistent with the findings in the total study population.

3. *How?*

The techniques of treatment are important to its success or failure. The objective is the destruction of the neovascular membrane in its entirety by adequate cover of the lesion and complete obliteration of the new vessels, without destruction of the foveola. The slit-lamp delivery of laser allows a very accurate placement of the burns. The availability of a good quality fluorescein angiogram, obtained within 48 hours of the time of treatment, is absolutely necesary for a safe and complete treatment.

The use of a transparent-paper will allow the exact limits of the neovascular membrane to be delineated. The precise location of the xanthophyllic area can also be drawn using the same transparent-paper and a blue-light print.[49,50]. Then it could be traced on the red-free or on the colour print, finally to know

very precisely the area to be treated and the area to be spared (Figs 6, a, b and c).

Treatment needs to be heavy and the photocoagulation lesions confluent or contiguous.[51] Intense and a relatively long duration application of laser burns over the entire extent of the membrane is required. Usually, treatment is performed with a 200 micron spot-size and 0.5 second duration. The intensity must be sufficient to produce a uniformly white lesion, according to the circumstances and transparency of the media. A topical anaesthesic only is used. Retrobulbar anaesthesia has been advocated to obtain better akinesia. But it does not avoid head movement and can cause unnecessary side-effects with persistant diplopia. We never use it.

The peripheral arcade must be treated initially, because bleeding could occur from this arcade. Test burns far from the centre will be useful to determine the correct level of intensity. Immediately after this the peripheral arcade close to the fovea will be treated to avoid bleeding. The entire periphery of the membrane is then photocoagulated, extending 100 microns beyond the edge of the neovascular complex. The central portion is treated with heavy overlapping burns. It is essential to treat the entire surface of the membrane to prevent post-operative bleeding and further extension of the membrane. If bleeding occurs during treatment, photocoagulation should be continued at the site of bleeding until it stops.

However, senile ocular media may induce difficulties for adequate treatment with conventional argon laser because there is increased scattering of blue wavelength. Thus to obtain the delivery of equal energies per unit of area at the RPE level, one requires about four times as much blue light as red light.[52]

Moreover, when new vessels are very near the centre of the fovea, there is considerable absorption of the blue wavelength at 488 nanometers by the xanthophyll pigment. In the human retina, macular luteal pigment can absorb more than 50 per cent of the argon blue light energy and can cause unnecessary damage in the inner layers of the retina. This intraretinal absorption creates a superficial white burn and will prevent delivery of energy to the subretinal tissues. It has been implicated as a potential cause of post-operative foveal denervation.[53] The whitening of the inner layers will also obscure residual or recrudescent new vessels and make early retreatment difficult.

Recently, these difficulties have been overcome by the development of monochromatic lasers. The efficiency of radiation depends on the transmission throughout ocular media and on the absorption by the target tissue. For parafoveolar photocoagulation, the ideal laser is one that emits a wavelength that is totally transmitted by ocular media, not absorbed by xanthophyll pigment and highly absorbed by melanine.

Several experimental and clinical studies with different lasers have been reported.[54-60] In our Department, we have evaluated the benefit of monochromatic green argon and red krypton lasers in clinical management.[59] Experiments were performed on eyes of adult baboons and histologic preparation for light and electron microscopy were obtained one hour and six weeks after applications of the burns.

Argon laser can be equipped with a filter to select only green wavelength (514.5 nm), with sufficient energy (Coherent 900). Histologic preparations after application of the burns showed sharply delimited lesions. Retinal pigment epithelial cells were destroyed, especially at the edges of the burns. The inner layers of the retina were quite intact.

The krypton laser we used (900 K from Coherent) emits 80 per cent red light at 647.1 nm and 17 per cent yellow light at 518.1 nm. The absorption of the red light by luteal pigment is about 1 per cent and the haemoglobin absorption is minimal. The histologic preparation showed very sharply delimited lesions extending from the choriocapillaris to the outer layer but the inner layers were intact. At six weeks, the choriocapillaris was entirely obliterated and RPE proliferation partially filled the area of outer segments.

These histopathologic observations suggest that krypton red and green argon laser photocoagulation are both effective in closing choroidal vessels. Green argon had its maximum effect at the level of the retinal pigment epithelium. The krypton laser had its maxi-

mum effect at the level of the choriocapillaris and the choroid. Krypton red photocoagulation near the fovea results in less destruction of inner retina than argon-green but these effects may also be energy-dose related.[61]

In our Department in Créteil, we studied the results of treatment of subretinal new vessels in senile macular degeneration performed in 45 patients with green argon radiation and in 85 patients with red krypton with at least one year of follow-up. We excluded from the study, 36 eyes treated for retrofoveolar new vessels growth. Patients were selected for treatment after meeting the following criteria: (1) visual acuity greater than or equal to 6/60 and (2) clinical and angiographic evidence of active subretinal neovascularisation located 50 to 400 microns from the centre of the fovea.

All patients had a complete ophthalmic examination and a close follow-up. A photograph in blue light was performed to locate the extent of the xanthophyll pigment. A photograph in red light was taken to evaluate the status of the retinal pigment epithelium. A stereoscopic angiogram was done precisely to locate the neovascular membrane and the extent of associated haemorrhages.

In this prospective non-randomised study, either krypton or green laser were selected for the following types of cases:

(1) a well-defined subretinal neovascular network extending into the foveal avascular zone;
(2) a recurrence of new vessels on the foveal edge of a lesion previously treated with conventional argon laser;
(3) a neovascular membrane located in the papillo-macular bundle.

In addition, argon green laser was selected for cases with neovascular membranes that were very near the centre and lying upon the RPE and easily recognisable.

The krypton-red laser was selected for:

(1) cases with subretinal new-vessels partially hidden by a turbid detachment of the RPE or the retina;
(2) cases with a yellow lens (because red light is well transmitted in cloudy media);
(3) neovascular membranes surrounded by a haemorrhagic border extending into the foveal avascular zone (red krypton radiation is not absorbed by haemoglobine).

Effective treatment was defined as the absence of angiographic evidence of active and leaking subretinal neovascularisation, with a flat retina. Since January 1981, 130 patients with SMD and SRNV have been treated and followed for more than one year.

In the green argon-treated group (45 cases), mean initial visual acuity was 0.37. Closure of the new-vessels was achieved in 30 cases (66.6 per cent). Visual acuity was stabilised or improved in 26 cases. In 15 cases (33.3 per cent), it was not possible to prevent extension of the neovascular membrane into the foveola because of failure of patients to return in time for scheduled follow-up and because of insufficient treatment.

In the red-krypton treated group of patients (85 cases), mean initial visual acuity was 0.38, closure of the new-vessels was achieved in 51 cases (60 per cent); visual acuity was stabilised or improved in 35 cases. In 34 cases (40 per cent, it was not possible to prevent extension of the neovascular membrane into the foveola.

Choroidal bleeding is more frequent with krypton than with argon laser but has not so far induced functional damage in our cases. Heavy laser burns, particularly with krypton, induce delayed filling of the choriocapillaris which is transient and without symptoms. Absorption of the green wavelength by haemoglobin can induce damage to the retinal capillaries overlying these heavy confluent treatment sites. With krypton laser, the macular retinal capillaries in front of the burns remain patent and not leaky even on immediate angiogram.

Red krypton and green argon laser offer a better alternative for treatment of neovascular membranes located near the foveola. The relative merits of the different lasers as therapeutic agents can be assessed only by the controlled clinical trials now in process.

To obtain optimal results all patients have to adhere to a close follow-up schedule every 10 days during the first month, therafter every month for three months and later on twice a year. Functional, biomicroscopic and angiographic assessments have to be performed at each visit: decrease in visual acuity, increase in metamorphopsia, and persistance or increase of retinal serous detachment are

indications for immediate fluorescein angiography. It is also important to examine the fellow eye at each visit. Even in patients who are well informed and aware of their condition, a rapid enlargement of a subretinal neovascular membrane may threaten or destroy central vision.

The main complication of laser photocoagulation is incomplete or inadequate treatment. Frequently, the vascular tissue is not completely obliterated by the initial laser session. Surviving capillaries may exist within the lesion. The appearance of a grey-green or yellow-pink coloured elevation at the margin of the treatment area means a recurrence of neovascularisation, easily visible on the angiogram.[51] If residual or recrudescent new-vessels are detected, additional laser treatment, if possible, will be performed until all blood vessels are obliterated, unless the foveola itself is involved.

Most of the recurrences occur at the edges of the treated area and particularly at the edge nearest the foveola. Close follow-up has shown that recurrences occur not only during the first weeks after treatment but also during the first year and even later on because photocoagulation does not modify the basic process.

Patients with new vessels under the centre of the fovea present a special problem: severe visual loss may result immediately from foveolar photocoagulation. While obliterating a small subfoveal lesion could facilitate the use of low-vision aid by preserving more of the parafoveal retina, considerable caution is advisable for two reasons: (1) subfoveal membranes do not have a uniformly poor prognosis; (2) there are at present no data to document any benefit for treating subfoveal new vessels membrane. Two studies, at least, are in progress at the moment: in the USA, the 'Subfoveolar Study', and in Créteil, the 'Perifoveolar Study' (laser destruction of all the macular subretinal new-vessels, sparing only the foveal avascular zone, has been able to give some useful results). Nevertheless, the use of photocoagulation in patients with extensive exudation and haemorrhagic lesions centred in the macular area in an effort to reduce the surrounding detachment and size of the central scotoma is of questionable value.[62]. But some of these patients may be helped by the use of appropriate low vision aids.

Laser treatment for subretinal neovascularisation in senile macular degeneration seems to be helpful and efficient, if it is an early and complete treatment: ophthalmologists have now increased responsibilities in the management of senile macular degeneration: firstly, to recognise and treat the treatable form of SMD, secondly, to reduce the delay of referral and initial ophthalmologic consultation. Recently, Bressler *et al.*[63] developed data to suggest that the majority of subfoveal membranes begin outside the centre and with time extend to a subfoveal position. Thus, it seems likely that earlier evaluation of patients with symptoms could enable us to identify a higher proportion of eyes with extrafoveolar neovascularisation that is amenable to treatment.

While photocoagulation is the only effective means of treatment, and improves the visual prognosis in respect of the original lesion, it is unlikely that it reduces the risk of other neovscular lesions arising in the same eye since SMD is a diffuse disease and neovascularisation is multifocal.

A significant number of recurrences occur each year. The long-term results of our randomised study on SMD, after five years,[64] have shown that 32 per cent of patients treated have had recurrences. After five years, 56 per cent of the treated eyes had retained useful central vision compared to only 7 per cent of the non-treated eyes.

Why neovascularisation and recurrences appear mostly in the macular area and particularly near the foveal avascular zone remains unknown. The answer to this question could help to find an aetiological or even a preventative treatment instead of destroying a part of the central retina to save a part of the central vision.

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