THE TREATMENT OF VITREORETINAL SCAR TISSUE

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SUMMARY

Methods of treating vitreoretinal scarring have been transformed by the introduction and development of closed intraocular microsurgery. Controlled access to the posterior segment of the eye, under excellent conditions for intraoperative viewing, have increased our understanding of the pathophysiology of epiretinal membranes. The ready ability to harvest tissue specimens for histopathological and immunochemical study, enabled by this type of surgery, has provided the stimulus for much basic research into the nature of fibrocellular (and fibrovascular) proliferative disease. Treatment of retinal conditions characterised by the proliferation of fibrocellular membranes has been improved, but the most important future advances are likely to be made in the fields of molecular biology and pharmacology.

BACKGROUND

When Jules Gonin first proposed that retinal detachment occurs as a result of breaks in the retina,¹ advanced surgical technology was not available. He and his successors in the field of retinal surgery had no way of treating the breaks directly, from within the eye, as they had no means of gaining access to them. They therefore had no choice other than to create an adhesion between the tissues surrounding the break(s), rather than attempt to repair the retinal defect(s) themselves.²⁻⁴

Remarkably, in spite of technological advances enabling access to the retina, especially during the past 20 years,^{5,6} as well as experimental work on glues^{7,8} and patches,⁹ there is still no satisfactory method of repairing breaks in the retina. Broadly speaking, the methods adopted by Gonin and his followers are still in use today. Thermocautery¹⁰ gave way to diathermy¹¹ and diathermy to cryotherapy,¹² sunlight¹³ has yielded to the laser tube^{14,15} and scleral resection,¹⁶ and the supramid suture¹⁷ has been superseded by silastic sponges¹⁸ and solid silicone explants,¹⁹ but the general principles of repair remain the same.

Considering that the retina is supported by a glial net-

work, and proliferation of retinal glia forms the basis of most epiretinal membranes,²⁰⁻²³ one might think that spontaneous repair of retinal breaks would occur as a matter of course. This is, however, not the case and spontaneous closure of breaks with consequent retinal reattachment, although by no means rare, is not a common event. Dehiscences in the retina do not usually heal over. Persistent traction on the torn retina, by the attached vitreous gel, commonly distorts and enlarges retinal tears, discouraging healing. Although successful attempts to induce healing in macular holes, by removing the vitreous and applying growth factor directly to the retina, have recently been reported,²⁴ this technique is not yet widely available or tested; nor is it necessarily applicable to peripheral tears. The mechanism employed by Gonin – bringing the retina into apposition with the underlying tissues and inducing a scar to form between them and the edges of the break – is, in consequence, still in use today.

Recent advances in our understanding and treatment of retinal detachment relate not only to the closure of breaks *per se*, but to the secondary effects generated by the healing process, in particular the stimulation of scar formation, inherent in the surgical method. Thus, modern techniques of closed intraocular microsurgery have focussed on the removal of epiretinal membranes and internal tamponade of retinal breaks in proliferative vitreoretinopathy (PVR), a condition which commonly results from overexuberance of the repair process and is often made worse by retinal reattachment surgery.

It is the ability to access intraocular structures, aided by microsurgical viewing, that has transformed our approach to difficult types of retinal detachment, rather than changes in the fundamental processes involved in repair. For the time being, at least, PVR remains the scourge of retinal surgeons and the predominant cause of failure in retinal reattachment surgery. Advances in laser technology and molecular-biological and pharmacological developments should, however, reduce the unwanted effects of excessive proliferation resulting from the healing process and thereby increase the success rate in surgical repair of retinal detachment.

The clinical appearances of advanced PVR are well known. Contraction of epiretinal membranes causes short-

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ening of the retina, leading to fold formation, while the effect of contraction on retinal breaks is to enlarge them, roll their edges and make them difficult to close. The retinal detachment becomes more extensive and bullous, retinal mobility decreases and the characteristic appearance of a more or less fixed funnel emerges. This is the picture of 'full-blown' PVR, associated with widespread, established epiretinal membranes. There is, however, a spectrum of disease, according to the stage and severity of the proliferative process. Initially, haziness of the vitreous occurs, followed by increasing cellularity, before decreased mobility and the development of fixed retinal folds becomes apparent. Even then, the process may be confined to one or two quadrants of the fundus and the retina may remain attached, and apparently unaffected, in others.

Foos²⁵ described a spectrum of non-vascular proliferative extraretinopathies (NPE), passing from simple membranes, composed exclusively of glia, in which the retinal topography remains undisturbed, through intermediate NPE (cellophane maculopathy, macular pucker, surface wrinkling retinopathy) to what is now termed PVR.

To follow the path along which our understanding of PVR has progressed, we need to retrace our steps to the pre-vitrectomy era of the 1950s and 1960s, when PVR was known as massive vitreous retraction (MVR).²⁶ Although the presence of membranes on the detached retina had long been recognised, the fundamental pathological process was considered to arise in the vitreous, contraction of which, it was thought, caused the retinal changes. It was therefore widely imagined that removal of the vitreous would lead to successful treatment of complicated retinal detachments. This optimistic belief was rudely shattered in the early 1970s, when the first results of closed vitrectomy in the management of retinal detachments complicated by MVR showed that removing the vitreous was not effective in achieving reattachment in these cases.²⁷

The advent of closed intraocular microsurgery,²⁸ permitting controlled access to the retinal surface, so that the disease process could be examined directly under the operating microscope, and the harvesting of tissue for histopathological study, was the stimulus to promote much essential research into the cellular mechanisms which cause PVR.²⁹⁻³² A huge leap forward in our understanding of why and how the disease develops has taken place during the past two decades.

Not only has our understanding of the mechanisms and underlying physical forces involved in retinal immobility and shortening been enhanced, but it has been possible to identify the parent cell types and to trace the differentiation of cell lines in the development of epiretinal membranes. It is clear that the simplest membranes are those derived from retinal glia and that these develop commonly, in the absence of true retinal breaks.³³ They are found in many normal eyes and often cause no clinical signs or symptoms. Glial cells do not have strong con-

tractile properties and so, as Foos noted, these simple membranes may cause no retinal distortion at all or only surface wrinkling.^{33,34} In more complex membranes, cells derived from the retinal pigment epithelium (RPE) are common and display strong contractile qualities, causing distortion of the retina, traction on retinal breaks and the formation of full-thickness retinal folds.³⁵⁻³⁷ Furthermore, RPE cells have been shown to develop into macrophages and to form fibroblasts, leading to the development of mature fibrous membranes containing collagen.³⁸ It has become clear that, in this way, RPE and glial cells gaining access to the retinal surface, as a result of macroscopic and microscopic breaks in the retina, can form widespread sheets of fibrocellular tissue capable of contracting and thereby shortening it.^{39,40} This process may occur in the attached or reattached retina, as for instance in macular pucker, causing distortion; or contracting membranes may, by opening or reopening retinal breaks, cause retinal detachment or redetachment.

RPE cells can also proliferate in the subretinal space and form membranes,⁴¹⁻⁴³ but contrary to what happens on the inner surface of the retina, these membranes do not form widespread attachments to the retina and display little capacity to cause retinal distortion or shortening. Only occasionally, when such subretinal bands cause a 'washing-line' or 'napkin-ring' effect,⁴⁴ do they grossly distort the retina or prevent its reattachment.

Classification of PVR

For clinical purposes, classification of PVR into its various stages or grades is of importance, because without some way of expressing the severity of the disease, it is difficult to evaluate and compare the results of treatment. For this reason, Machemer⁴¹ devised a classification based on his concept of its pathogenesis. He identified four stages, ranging from increased vitreous flare and cellularity, to total retinal detachment with a 'closed funnel' configuration. This classification proved unnecessarily complicated and cumbersome and in 1983 a further classification was produced⁴⁵ with four stages: A, B, C and D. A denotes increased vitreous activity, B the first indications of epiretinal membrane contraction, such as vessel tortuosity and rolled edges to breaks, C full-thickness fixed retinal folds and D fixed retinal folds in all quadrants causing a funnel configuration. Grade C was furthermore subdivided into 1, 2 or 3, according to how many quadrants were involved, and D similarly, according to whether the funnel was wide open, narrow or closed.

Both these classifications have been found to be useful in standardising the severity of PVR as identified in different centres, but less useful in providing indices for predicting the likely outcome of surgery. This is because they both fail to take into account the clinical significance of the surgical pathology, depending as it does on the distribution and direction of the tractional forces, rather than simply their extent.

In 1989, workers in Germany⁴⁶ and the United States⁴⁷ proposed new and similar classifications, leading to a bet-

ter scheme which acknowledges the surgical implications of PVR. This classification, updated in 1991,⁴⁸ distinguishes between peripheral and posterior, focal and diffuse and perpendicular, circumferential and anterior forms of contraction, enabling comparability of results from different centres.

TREATMENT

Retinal detachments complicated by PVR are difficult to treat, because the surface area of the retina is reduced, due to membrane contraction, so the retina cannot easily be reappplied to the underlying pigment epithelium, the surface area of which is unaltered. Retinal breaks, which are the cause of the detachment, cannot be closed by conventional means unless the breaks themselves are in an area of retina not involved by contracted membranes. In some instances this is the case and, in spite of PVR, the retina can be reattached by conventional surgery. Provided that all breaks are closed and remain closed, the retina will invariably reattach, although there may be gross distortion from epiretinal membrane contraction throughout the fundus elsewhere, causing areas of traction retinal detachment. As in all retinal reattachment surgery, the goal is to close the breaks and seal them.

Surgical Methods

Long before Machemer and Norton²⁷ demonstrated that removal of the vitreous was not sufficient, in itself, to cure retinal detachments complicated by PVR, Taylor Smith, Cibis and others had appreciated the significance of epiretinal membrane contraction and come to similar conclusions. Indeed, Taylor Smith,⁴⁹ writing in 1960, described their role in causing fixed retinal folds and recalled that, since the nineteenth century, many workers had noted the presence of epiretinal membranes on the surface of the detached retina, while Cibis⁵⁰ described how epiretinal membranes could be removed from the retinal surface, albeit without the degree of access provided by techniques available today. The use of silicone oil and intraocular instrumentation to dissect membranes and to tamponade breaks was used to good effect by Cibis,⁵¹ Scott⁵² and others,⁵³ prior to the introduction of closed intraocular microsurgery, up to 60% of such cases being successful.

The introduction of vitrectomy²⁸ led the way to more sophisticated methods of epiretinal membrane removal which, combined with internal tamponade of retinal breaks, opened up new avenues. While removal of the vitreous does not, in itself, relieve anything except direct vitreoretinal traction, the controlled access to and freedom of action within the preretinal space which it enables, has transformed the surgery of PVR.

It was soon apparent that the application of closed vitrectomy techniques could be combined with and enhance existing methods of treating retinal conditions characterised by the proliferation and contraction of fibrocellular (and fibrovascular) membranes.^{54–59} Bimanual manoeuvres, carried out under greatly improved condi-

tions of illumination and microscopy and with an ever-increasing range of sophisticated micro-instrumentation,^{60,61} brought the treatment of complicated cases of retinal detachment within the compass of many retinal surgeons, rather than the exceptional few. By direct removal of membranes responsible for retinal shortening, the retina can be mobilised and retinal breaks freed of traction, before filling the preretinal compartment with air, gas or silicone fluid. Moreover, it is no longer necessary to go through the coats of the globe to drain subretinal fluid, as this can be done safely, via a flute-needle passed through a break in the retina, using the operating microscope. Many of these considerations apply equally to fibrovascular as well as to fibrocellular membranes; however, only non-vascular disease will be discussed here.

Removal of the vitreous gel is the simplest part of surgery for retinal detachments complicated by PVR. Once the gel has been carefully removed, it is possible to gain access to all areas of the retina and it is important to remove the gel meticulously, up to its retinal attachment at the vitreous base. Mobilisation of the retina requires that all epiretinal membranes are stripped from its surface behind the base. This can be achieved using a 20 gauge needle, bent to form a pic; in PVR it is rarely necessary to use scissors, posterior to the vitreous base, because, unlike fibrovascular proliferations, fibrocellular membranes can be peeled and do not usually require segmentation or delamination.

The vitreous at the vitreous base itself cannot be removed from the retina and retinal shortening at or anterior to it must therefore be managed in different ways. If contraction is only mild or moderate, a scleral buckle will usually suffice to reappose the retina to the RPE, but if vitreous base shortening is severe, one of two methods must be adopted: (1) complete removal of all epiretinal tissue by meticulous dissection, including cutting the retina radially where necessary, followed by a deep, broad buckle and extensive laser photocoagulation,⁶² or (2) division of the retina, in a circumferential direction, immediately posterior to the shortened base,^{63,64} throughout at least 180° (separating the shortened anterior retina from the mobile retina posterior to the vitreous base), followed by laser photocoagulation to the cut edge of the posterior flap, after tamponade with gas or silicone oil.

Excellent results have been reported,⁶⁵ in anterior PVR, using the first of these two options, especially by those using gas rather than silicone oil tamponade, but the dissection can take 4–8 hours to accomplish. The second method is more practicable and good results have also been reported,^{66–68} removal of epiretinal membranes being limited to the posterior retina and care taken to excise the tissue anterior to the retinotomy to discourage the development of cyclitic membranes and rubeosis.

In cases where PVR is further complicated by the coexistence of a giant tear or giant retinotomy, causing destabilisation of the posterior flap, it is occasionally necessary to use retinal tacks to stabilise the retina. Tacks (introduced by Ando⁶⁹ in 1983) are used as an adjunct to tamponade.

nade and endolaser photocoagulation and not as a substitute.

More recently, liquid perfluorocarbons have been introduced by Chang and co-workers.^{70,71} These agents have a specific gravity greater than 1.5, low viscosity and moderate surface tension in aqueous fluids. Their density makes it possible to 'roll out' the detached retina posteriorly and displace the subretinal fluid laterally and anteriorly. Dissection of epiretinal membranes is facilitated and subretinal fluid can be displaced through anterior breaks into the preretinal space from where it can be removed easily.

Internal Tamponade

Internal tamponade with air has been used in the treatment of complicated retinal detachments for more than 80 years,⁷² while Rosengren⁷³ in 1938 reported a series of more than 300 cases treated in this way. The method became less popular with the introduction of scleral explants by Custodis,⁷⁴ and it was not until 1973 that Norton⁷⁵ popularised the use of air and less soluble, inert gases such as sulphur hexafluoride in the treatment of selected cases. In the early 1960s, Cibis⁵¹ began to use silicone oil for prolonged tamponade, the use of this material being popularised and developed by Scott,⁷⁶ Zivovnjovic⁷⁷ and others.^{44,78}

It has already been noted that vitrectomy enables the removal of epiretinal membranes and thereby facilitates retinal reattachment by internal fluid exchange through the retinal breaks. Air and gases are ideal materials for tamponading breaks, because of their high surface tension in aqueous fluids and their buoyancy. The duration of tamponade can be varied according to the type of gas chosen, the long-chain perfluorocarbon gases such as perfluoropropane remaining effective for up to 6 weeks. Nevertheless, as the gas is absorbed, the bubble gets smaller and tamponade becomes less reliable. By contrast, silicone oil has a lower surface tension in aqueous fluids and less buoyancy but remains in the eye indefinitely, so that its effect is constant. Arguments for and against the use of these agents centre largely around complications associated with their use,⁷⁹ while the results of recent studies suggest that there is no significant difference in efficacy between silicone oil and the longer-acting gases.^{80,81}

There is little doubt that the results of treating retinal detachments complicated by PVR have improved since the development of techniques combining vitrectomy with internal tamponade and that prolonged tamponade, whether by long-acting gases or silicone oil, conveys significant benefits. Furthermore, much of the resistance to the use of silicone oil has been overcome by the knowledge that it can be easily removed when tamponade is no longer needed,^{68,82-85} thus pre-empting development of long-term complications.

Prevention

It is now generally accepted that RPE cells and glia are the cells responsible for PVR^{86,87} and that agents such as fibronectin,⁸⁸⁻⁹² platelet-derived growth factor^{93,94} and transfor-

ming growth factor beta,⁹⁵⁻⁹⁷ stimulate and promote the proliferation, migration and contraction of these cells. The cells, in their turn, form extracellular matrix and finally collagen.⁹⁸ This chain of events is exacerbated by breakdown of the blood-ocular barrier.⁹⁹

Could the process be stopped at any point, it might be possible to prevent or arrest the development of epiretinal membranes causing complicated retinal detachments. To this end, efforts have been made to assess the influence of anti-inflammatory agents such as corticosteroids,¹⁰⁰⁻¹⁰² anti-proliferatives such as 5-fluorouracil^{103,104} and daunomycin,^{102,105} low-dose irradiation,^{106,107} and agents such as heparin¹⁰⁸ acting on the extracellular components, on the development of PVR. While experimental evidence suggests that they all influence the proliferative process¹⁰⁹ and their trial in animal models of PVR and even in human eyes has shown encouraging trends,¹¹⁰ no agent or combination of drugs has been demonstrated to be of incontrovertible benefit in clinical management. This may be because the development of PVR in the clinical arena is usually well established before the drugs are used, unlike the experimental situation where they may be delivered at the outset of the process.

CONCLUSION

Our understanding of the pathophysiology of PVR has been greatly enhanced as a result of closed microsurgical methods. Conversely, the development of modern surgical techniques has been influenced and guided by a better understanding of the underlying disease process. The development of PVR and its prevention depends on the quality of primary retinal reattachment surgery. Accurate identification of all retinal breaks, leading to their successful closure at the first attempt, would preclude the onset of PVR in the majority of cases, while improved techniques, causing less inflammation, reduced risk of haemorrhage and other stimuli to cellular proliferation, would contribute positively towards this end. Ultimately, however, the elimination or reduction of PVR is likely to result from advances in our understanding of molecular biology and pharmacology, rather than from changes in surgical method.

Key words: Epiretinal membranes, Proliferative vitreoretinopathy, Retina, Vitrectomy, Vitreoretinal.

REFERENCES

1. Gonin J. La pathogénie du décollement spontané de la rétine. *Ann d'Oculist* (Paris) 1904;132:30.
2. Gonin J. Le traitement du décollement rétinien. *Ann d'Oculist* (Paris) 1921;158:175.
3. Guist G. Eine neue Ablatiooperation. *Z Augenheilkd* 1931; 74:232.
4. Lindner K. Eine Beitrag zur Entstehung und Behandlung der idiopathischen und der traumatischen Netzhautabhebung. *Arch Ophthalmol* 1931;127:177.
5. Kasner D, Miller GR, Taylor WH, *et al.* Surgical treatment of amyloidosis of the vitreous. *Trans Am Acad Ophthalmol Otolaryngol* 1968;72:410.
6. Machemer R, Parel JM, Buettner H. A new concept for vitreous surgery. I. Instrumentation. *Am J Ophthalmol* 1972; 73:1.

7. McCuen BW, Hida T, Sheta SM, *et al.* Experimental trans-vitreous cyanoacrylate retinopexy. *Am J Ophthalmol* 1986; 102:199.
8. Gilbert CE. Adhesives in retinal detachment surgery. *Br J Ophthalmol* 1991;75:309.
9. Gilbert CE, Grierson I, McLeod D. Retinal patching: a new approach to the management of selected retinal breaks. *Eye* 1989;3:19.
10. Gonin J. Guérisons opératoires de décollement rétiniens. *Rev Gen Ophthalmol* 1923;337:37.
11. Pischell DK. Diathermy operation for retinal detachment: comparative results of different types of electrodes. *Trans Am Ophthalmol* 1944;42:543.
12. Lincoff HA, McLean JM, Nano H. Cryosurgical treatment of retinal detachment. *Trans Am Acad Ophthalmol Otolaryngol* 1964;68:412.
13. Meyer-Schwickerath G. Koagulation der Netzhaut mit Sonnenlicht. *Ber Dtsch Ophthalmol Ges* 1949;55:256.
14. L'Esperance FA. An ophthalmic argon photocoagulation laser system: design, construction, and laboratory investigations. *Trans Am Ophthalmol Soc* 1968;66:827.
15. Little HL, Zweng HC, Peabody RR. Argon laser slitlamp retinal photocoagulation. *Trans Am Acad Ophthalmol Otolaryngol* 1970;74:85.
16. Lindner K. Heilungsversuche bei prognostisch ungünstigen Fällen von Netzhautabhebung. *Z Augenheilkd* 1933; 81:227.
17. Arruga H. Le cerclage équatorial pour traiter le décollement rétiniens. *Bull Mem Soc Fr Ophthalmol* 1958;71:571.
18. Lincoff HA, Baras I, McLean J. Modifications to the Custodis procedure for retinal detachment. *Arch Ophthalmol* 1965;73:160.
19. Schepens CL, Okamura ID, Brockhurst RJ. The scleral buckling procedures. V. Synthetic sutures and silicone implants. *Arch Ophthalmol* 1960;64:868.
20. Laqua H, Machemer R. Glial cell proliferation in retinal detachment (massive periretinal proliferation). *Am J Ophthalmol* 1975;80:602.
21. Kenyon KR, Michels RG. Ultrastructure of epiretinal membrane removed by pars plana vitreoretinal surgery. *Am J Ophthalmol* 1977;83:815.
22. Hiscott PS, Grierson I, Trombetta CJ, *et al.* Retinal and epiretinal glia: an immunohistochemical study. *Br J Ophthalmol* 1984;68:698.
23. Van Horn DL, Aaberg TM, Machemer R *et al.* Glial cell proliferation in human retinal detachment with massive periretinal proliferation. *Am J Ophthalmol* 1977;84:383.
24. Glaser BM, Sjaarda RN, Kuppermann BD *et al.* Transforming growth factor-beta in the treatment of full thickness macular holes. *Ophthalmology* 1991;98(Suppl):145.
25. Foos RY. The spectrum of nonvascular proliferative extraretinopathies. In: Nicholson, editor. *Ocular pathology update*. Los Angeles, 1980:107.
26. Schepens CL. Retinal detachment and aphakia. *Arch Ophthalmol* 1951;45:1.
27. Machemer R, Norton EWD. A new concept for vitreous surgery. III. Indications and results. *Am J Ophthalmol* 1972;74:1034.
28. Machemer R, Buettner H, Norton EWD, Parel JM. Vitrectomy: a pars plana approach. *Trans Am Acad Ophthalmol Otolaryngol* 1971;75:813.
29. Smith RS, van Heuven WAJ, Streeten B. Vitreous membranes: a light and electron microscopic study. *Arch Ophthalmol* 1976;94:1556.
30. Clarkson JG, Green WR, Massof D. A histopathologic review of 168 cases of preretinal membrane. *Am J Ophthalmol* 1977;84:1.
31. Kampik A, Kenyon KR, Michels RG, Green WR, de la Cruz ZC. Epiretinal and vitreous membranes: comparative study of 56 cases. *Arch Ophthalmol* 1981;99:1445.
32. Grierson I, Rahi AHS. Structural basis of contraction in vitreal fibrous membranes. *Br J Ophthalmol* 1981;65:737.
33. Roth AM, Foos RY. Surface wrinkling retinopathy in eyes enucleated at autopsy. *Trans Am Acad Ophthalmol Otolaryngol* 1971;75:1047.
34. Foos RY. Surface wrinkling retinopathy. In: Freeman HM, Hirose T, Schepens CL, editors. *Vitreous surgery and advances in fundus diagnosis and treatment*. New York: Appleton Century Crofts, 1977:23.
35. Machemer R, Laqua H. Pigment epithelium proliferation in retinal detachment (massive periretinal proliferation). *Am J Ophthalmol* 1975;80:1.
36. Clarkson JG, Green WR, Massof D. A histopathological review of 168 cases of preretinal membrane. *Am J Ophthalmol* 1977;84:1.
37. Laqua H, Machemer R. Clinical-pathological correlation in massive periretinal proliferation. *Am J Ophthalmol* 1975;80:913.
38. Newsome DA, Rodrigues MM, Machemer R. Human massive periretinal proliferations: *in vitro* characteristics of cellular components. *Arch Ophthalmol* 1981;99:873.
39. Laqua H, Machemer R. Glial cell proliferation in retinal detachment (massive periretinal proliferation). *Am J Ophthalmol* 1975;80:602.
40. Algvere P, Kock E. Experimental epiretinal membranes induced by intravitreal carbon particles. *Am J Ophthalmol* 1983;96:345.
41. Machemer R. Pathogenesis and classification of massive periretinal proliferation. *Br J Ophthalmol* 1978;62:737.
42. Sternberg P, Machemer R. Subretinal proliferation. *Am J Ophthalmol* 1984;98:456.
43. Schwartz D, de la Cruz Z, Green WR, *et al.* Proliferative vitreoretinopathy: ultrastructural study of 20 retrolental membranes removed by vitreous surgery. *Retina* 1988;8: 275.
44. Charles S. *Vitreous microsurgery*, 1st ed. Baltimore: Williams and Wilkins, 1981.
45. The Retina Society Terminology Committee. The classification of retinal detachment with proliferative vitreoretinopathy. *Ophthalmology* 1983;90:121.
46. Heimann K, Wiedemann P. Cologne classification of proliferative vitreoretinopathy. In: Heimann K, Wiedemann P, editors. *Proliferative vitreoretinopathy*. Heidelberg: Kaden Verlag, 1989:148.
47. Irvine AR, Lean JS, Stern WH. Classification and photographic documentation of PVR. In: Heimann K, Wiedemann P, editors. *Proliferative vitreoretinopathy*. Heidelberg: Kaden Verlag, 1989:144.
48. Machemer R, Aaberg TM, Mackenzie Freeman H *et al.* An updated classification of retinal detachment with proliferative vitreoretinopathy. *Am J Ophthalmol* 1991;112:159.
49. Smith TR. Pathological findings after retina surgery. In: Schepens S, editor. *Importance of vitreal body in retinal surgery with special emphasis on reoperation*. St Louis: CV Mosby, 1960:61.
50. Cibis PA. *Vitreoretinal pathology and surgery in retinal detachment*. St Louis: CV Mosby, 1965.
51. Cibis PA. Recent methods in the surgical treatment of retinal detachment: intravitreal procedures. *Trans Ophthalmol Soc UK* 1965;85:111.
52. Scott JD. Treatment of the detached immobile retina. *Trans Ophthalmol Soc UK* 1972;92:351.
53. Grey RHB, Leaver PK. Silicone oil in the treatment of massive preretinal retraction. I. Results in 105 eyes. *Br J Ophthalmol* 1979;63:355.
54. Parel JM, Machemer R, Aumayr W. A new concept for vitreous surgery. IV. Improvements in instrumentation and illumination. *Am J Ophthalmol* 1974;77:6.
55. O'Malley C, Heintz RM. Vitrectomy with an alternative instrument system. *Ann Ophthalmol* 1975;7:585.

56. Charles S. Fluid-gas exchange in the vitreous cavity. *Ocutome/Fragmatome Newsletter* 1977;2:1.
57. Aaberg TM, Machemer R. Vitreous band surgery: instrumentation and technique. *Arch Ophthalmol* 1972;87:542.
58. Lean JS, Leaver PK, Cooling RJ *et al.* Management of complex retinal detachments by vitrectomy and fluid/silicone exchange. *Trans Ophthalmol Soc UK* 1982;102:203.
59. Machemer R. Surgical approaches to subretinal strands. *Am J Ophthalmol* 1980;90:81.
60. Michels RG, Rice TA, Ober RR. Vitreoretinal dissection instruments. *Am J Ophthalmol* 1979;87:836.
61. Courvillion GC. Vitreous surgery instrumentation. In: Freeman HM, Hirose T, Schepens CL, editors. *Vitreous surgery and advances in fundus diagnosis and treatment*. New York: Appleton Century Crofts, 1977:165.
62. Aaberg TM. Management of anterior and posterior proliferative vitreoretinopathy. XLV Edward Jackson Memorial Lecture. *Am J Ophthalmol* 1988;106:519.
63. Machemer R, McCuen BW, de Juan E. Relaxing retinotomies and retinectomies. *Am J Ophthalmol* 1986;102:7.
64. Jacobs PM, Cooling RJ, Leaver PK, McLeod D. Retinal relieving incisions. *Eye* 1987;1:500.
65. Lewis H, Aaberg TM, Abrams GW. Causes of failure after initial vitreoretinal surgery for severe proliferative vitreoretinopathy. *Am J Ophthalmol* 1991;111:8.
66. Reinking U, Lucke K, Bopp S, Laqua H. Results after retinotomy and retinectomy in the treatment of complicated retinal detachment. *Klin Monatsbl Augenheilkd* 1990;197:382.
67. Iverson DA, Ward TG, Blumenkranz MS. Indications and results of relaxing retinotomy. *Ophthalmology* 1990;97:1298.
68. Eckardt C, Behrendt S, Zwick A. Results of silicone oil removal from eyes treated with retinectomies. *German J Ophthalmol* 1991;1:2.
69. Ando F, Kondo J. A plastic tack for the treatment of retinal detachment with giant tear. *Am J Ophthalmol* 1983;95:260.
70. Chang S. Low viscosity liquid fluorochemicals in vitreous surgery. *Am J Ophthalmol* 1987;103:38.
71. Chang S, Ozmer E, Zimmerman NJ. Intraoperative perfluorocarbon liquids in the management of proliferative vitreoretinopathy. *Am J Ophthalmol* 1988;106:668.
72. Ohm J. Über die Behandlung der Netzhautablosung durch operative Entleerung der subretinalen Flüssigkeit und Einspritzung von Luft in der Glaskörper. *Arch Ophthalmol* 1911;79:442.
73. Rosengren B. Über die Behandlung der Netzhautablosung mittelst Diathermie und Luftinjektion in den Glaskörper. *Acta Ophthalmol (Copenh)* 1938;16:3.
74. Custodis E. Bedeutet die Plombenaufnahme auf die Sklera einen Fortschritt in der operativen Behandlung der Netzhautablosung? *Ber Dtsch Ophthalmol Ges* 1953;58:102.
75. Norton EWD. Intraocular gas in the management of selected retinal detachments. *Trans Am Acad Ophthalmol Otolaryngol* 1973;77:85.
76. Scott JD. The treatment of massive vitreous retraction. *Trans Ophthalmol Soc* 1973;93:417.
77. Zivojnovic R, Mertens DAE, Peperkamp E. Das flüssige Silikon in der Amotiochirurgie. II. Bericht über 280 fall-eweitere Entwicklung der Technik. *Klin Monatsbl Augenheilkd* 1982;181:444.
78. Lucke KH, Foerster MH, Laqua H. Long-term results of vitrectomy and silicone oil in 500 cases of complicated retinal detachments. *Am J Ophthalmol* 1987;104:624.
79. Leaver PK. Complications of intraocular silicone oil. In: Ryan SJ, editor. *Retina*, vol. 3. St Louis: CV Mosby, 1989:293.
80. Silicone Oil Study Report 1. Vitrectomy with silicone oil or sulphur hexafluoride gas in eyes with severe proliferative vitreoretinopathy. Results of a randomized clinical trial. *Arch Ophthalmol* 1992;110:770.
81. Silicone Oil Study Report 2. Vitrectomy with silicone oil or perfluoropropane gas in eyes with severe proliferative vitreoretinopathy. Results of a randomized clinical trial. *Arch Ophthalmol* 1992;110:780.
82. Gonvers M. Temporary silicone oil tamponade in the management of retinal detachment with proliferative vitreoretinopathy. *Am J Ophthalmol* 1985;100:239.
83. Casswell AG, Gregor ZG. Silicone oil removal. I. The effect on the complications of silicone oil. *Br J Ophthalmol* 1987;71:893.
84. Hoing C, Kampik A, Heidenkummer HP. Possibilities of silicone oil removal after complex vitreoretinal surgery. *Fortschr Ophthalmol* 1991;8:593.
85. Franks WA, Leaver PK. Removal of silicone oil: rewards and penalties. *Eye* 1991;5:333.
86. Hiscott PS, Grierson I, Hitchins CA *et al.* Epiretinal membranes *in vitro*. *Trans Ophthalmol Soc UK* 1983;103:89.
87. Hiscott PS, Grierson I, McLeod D. Natural history of fibrocellular epiretinal membranes: a quantitative, autoradiographic, and immunohistochemical study. *Br J Ophthalmol* 1985;69:810.
88. Weller M, Heimann K, Wiedemann P. Immunohistochemical findings in proliferative retinal diseases: on the significance of fibronectin, macrophages and transferrin. *Fortschr Ophthalmol* 1989;86:121.
89. Weller M, Wiedemann P, Bresgen M, Heimann K. Vitronectin: mediator of cell adhesion in proliferative vitreoretinopathy? *Fortschr Ophthalmol* 1990;87:221.
90. Hiscott P, Walker HA, Grierson I, *et al.* Local production of fibronectin by ectopic human retinal cells. *Cell Tissue Res* 1992;267:185.
91. Wilson-Holt N, Khaw P, Savage F, Grierson I. The chemoattractant activity of the vitreous to human scleral fibroblasts following retinal detachment and proliferative vitreoretinopathy. *Br J Ophthalmol* 1992;76:159.
92. Campochiaro PA, Jerdan JA, Glaser BM. Serum contains chemoattractants for human retinal pigment epithelial cells. *Arch Ophthalmol* 1984;102:1830.
93. Campochiaro PA, Glaser BM. Platelet-derived growth factor is chemotactic for human retinal pigment epithelial cells. *Arch Ophthalmol* 1985;103:576.
94. Pinon RM, Pastor JC, Saornil MA *et al.* Intravitreal and subretinal proliferation induced by platelet-rich plasma injection in rabbits. *Curr Eye Res* 1992;11:1047.
95. Connor TB, Roberts AB, Sporn MB *et al.* Correlation of fibrosis and transforming growth factor-beta type 2 levels in the eye. *J Clin Invest* 1989;83:1661.
96. Gaudric A, Glacet-Bernard A, Clement G *et al.* Transforming growth factor-beta in the vitreous of patients with epiretinal proliferation. *Ophtalmologie* 1990;4:51.
97. Wiedemann P. Growth factors in retinal disease: proliferative vitreoretinopathy, proliferative diabetic retinopathy, and retinal degeneration. *Surv Ophthalmol* 1992;35:373.
98. Campochiaro PA, Jerdan JA, Glaser BM. The extracellular matrix of human retinal pigment epithelial cells *in vivo* and its synthesis *in vitro*. *Invest Ophthalmol Vis Sci* 1986;27:1615.
99. Clausen R, Weller M, Hilgers RD *et al.* Quantitative determination of 5 vitreal proteins in the normal vitreous body and proliferative retinal diseases. *Fortschr Ophthalmol* 1990;87:283.
100. Tano Y, Chandler D, Machemer R. Treatment of intraocular proliferation with intravitreal injection of triamcinolone acetonide. *Am J Ophthalmol* 1980;90:810.
101. Chandler DB, Hida T, Sheta S *et al.* Improvement in efficacy of corticosteroid therapy in an animal model of proliferative vitreoretinopathy by pretreatment. *Graefes Arch Clin Exp Ophthalmol* 1987;225:259.

102. Hui YN, Liang HC, Cai YS *et al.* Corticosteroids and daunomycin in the prevention of experimental proliferative vitreoretinopathy induced by macrophages. *Graefes Arch Clin Exp Ophthalmol* 1993;231:109.
103. Blumenkranz MS, Ophir A, Clafin AJ *et al.* Fluorouracil for the treatment of massive periretinal proliferation. *Am J Ophthalmol* 1982;94:458.
104. Blumenkranz MS, Hernandez E, Ophir A *et al.* 5-Fluorouracil: new applications in complicated retinal detachment for an established antimetabolite. *Ophthalmology* 1984;91:122.
105. Wiedemann P, Lemmen K, Schmiedl R, Heimann K. Intraocular daunorubicin for the treatment and prophylaxis of traumatic proliferative vitreoretinopathy. *Am J Ophthalmol* 1987;104:10.
106. Binder S, Skorpik CH, Paroussis P *et al.* High-energy electrons used to inhibit experimental intraocular proliferation and detachment. *Ophthalmologica* 1987;195:128.
107. Kuriyama S, Ohuchi T, Yoshimura N, *et al.* Evaluation of radiation therapy for experimental proliferative vitreoretinopathy in rabbits. *Graefes Arch Clin Exp Ophthalmol* 1990;228:552.
108. Alvira G, Hartzler M, Blumenkranz MS. Heparin inhibits cell-mediated collagen gel contraction. *Invest Ophthalmol Vis Sci* 1986;27:305.
109. Blumenkranz MS, Clafin A, Hajek AS. Selection of therapeutic agents for intraocular proliferative disease: cell culture evaluation. *Arch Ophthalmol* 1984;102:598.
110. Radtke ND, Weinsieder AD, Ballou RJ. Pharmacological therapy for proliferative vitreoretinopathy. *Graefes Arch Clin Exp Ophthalmol* 1986;224:230.