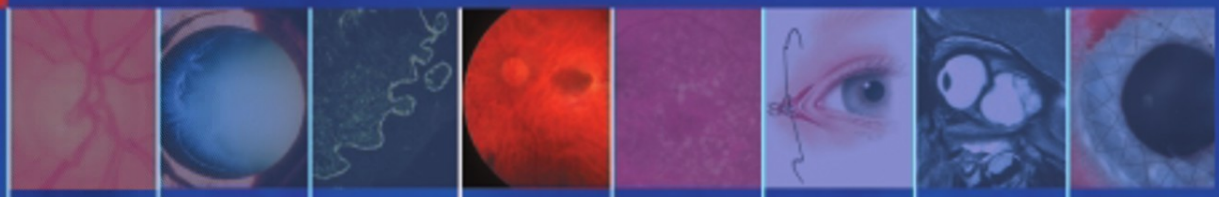
ESSENTIALS IN OPHTHALMOLOGY

G. K. KRIEGLSTEIN · R. N. WEINREB

Series Editors



Glaucoma | Cataract and Refractive Surgery | Uveitis and Immunological Disorders | **Vitreo-retinal Surgery** | Medical Retina | Oculoplastics and Orbit | Paediatric Ophthalmology, Neuro-ophthalmology, Genetics | Cornea and External Eye Disease

Vitreo-retinal Surgery

Edited by

B. KIRCHHOF

D. WONG

Springer

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Vitreo-retinal Surgery

With 79 Figures, Mostly in Colour,
and 16 Tables

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Foreword

Essentials in Ophthalmology is a new review series covering all of ophthalmology categorized in eight subspecialties. It will be published quarterly; thus each subspecialty will be reviewed biannually.

Given the multiplicity of medical publications already available, why is a new series needed? Consider that the half-life of medical knowledge is estimated to be around 5 years. Moreover, it can be as long as 8 years between the description of a medical innovation in a peer-reviewed scientific journal and publication in a medical textbook. A series that narrows this time span between journal and textbook would provide a more rapid and efficient transfer of medical knowledge into clinical practice, and enhance care of our patients.

For the series, each subspecialty volume comprises 10–20 chapters selected by two distinguished editors and written by internationally renowned specialists. The selection of these contributions is based more on recent and noteworthy advances in the subspecialty than on systematic completeness. Each article is structured in a standardized format and length, with citations for additional reading and an appropriate number of illustrations to enhance important points. Since every subspecialty volume is issued in a recurring sequence during the 2-year cycle, the reader has the opportunity to focus on the progress in a particular subspecialty or to be updated on the whole field. The clinical relevance of all material presented will be well established, so application to clinical practice can be made with confidence.

This new series will earn space on the bookshelves of those ophthalmologists who seek to maintain the timeliness and relevance of their clinical practice.

G. K. Krieglstein
R. N. Weinreb
Series Editors

Preface

This first issue of *Vitreoretinal Surgery,* in the series *Essentials in Ophthalmology,* has been written to update our knowledge on the large body of experimental research performed to date on the most urgent problems of vitreoretinal disease. Priority is given to the most important problems in terms of patient numbers – retinal degeneration, retinal oedema, and proliferative vitreoretinopathy.

Proliferative vitreoretinopathy (PVR) is the leading cause of blindness in retinal detachment (RD). Recent progress in surgical techniques, sophisticated surgical tools and new vitreous tamponades has reduced the number of enucleations, at least in Europe, but ultimately the risk of PVR has not been reduced, which is reported to be between 5% and 10% for idiopathic PVR, and between 10% and 45% for ocular trauma (the incidence being higher in cases of perforating and blunt injuries and lower with intraocular foreign bodies). Functional outcome of surgery for PVR is often disappointing despite attached retina. Carl Sheridan (Liverpool) reports on the cellular mechanisms of PVR. Adjunct pharmacotherapy reduces the number of reoperations in eyes with established PVR. Improvement of functional outcome requires that high-risk eyes are identified and selected, and that adjunct pharmacotherapy is applied prior to the establishment of PVR. The chapter by Chee Kon (London) elaborates the criteria for detecting eyes with increased risk of PVR, justifying a prophylactic dose of cytostatic drugs, and that by Martin Snead (Cambridge) portrays the "giant retina tear" as an example of a high-risk PVR situation. David Charteris (London) describes the pharmacological progress made in preventing PVR in eyes at risk, and David Wong (Liverpool) elaborates the rationale for heavier than water long-term vitreous substitutes in the prevention and treatment of PVR.

Retinal degeneration is common as a complication of age-related retinal pigment epithelial cell insufficiency (age-related macular degeneration), as a consequence of the inflammatory diabetic metabolism (diabetic macular oedema), and as a result of inherent outer retinal genetic disease (retinitis pigmentosa). Peter Walter (Aachen) reports on the latest progress on epiretinal implants for retinitis pigmentosa as research project results are turned into a commercially available medical device. The chapter by Antonia Joussen (Cologne) explains medical aids for macular oedema of different origins according to pathogenesis. Jan van Meurs (Rotterdam) reports the first experience with translocation of autologous whole grafts of choroids and retinal pigment epithelium under the macula, and Johann Roider (Kiel) questions the rationale of transpupillary thermotherapy in age-related macular degeneration.

Other chapters in the volume are by Silvia Bopp (Bremen), who discusses the latest surgical techniques for modulating macular oedema due to epiretinal membranes, and Tom Williamson (London), who describes the diagnostic and therapeutic value of vitrectomy in uveitis.

We hope that this review of the latest research in the field of vitreoretinal surgery will be of interest to practicing ophthalmologists and researchers alike.

Bernd Kirchhof
David Wong

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Retinal Implants

Peter Walter

1

Core Messages

- Retinal implants may restore vision in retinitis pigmentosa (RP) related blindness
- Retinal implants provide local electrical stimulation by an electrode array
- Electrode arrays can be placed onto or underneath the retina
- Animal experiments have shown promising results
- Clinical trials are in preparation or have just started

1.1 Introduction

Although considerable progress has been made in treating vitreoretinal disorders with modern surgical or pharmacological approaches, there are still some untreatable conditions which lead to blindness. One of the major causes of untreatable blindness is the manifestation of progressive retinal degeneration as in retinitis pigmentosa (RP) and RP-like dystrophies. It is estimated that worldwide 1.5 million individuals are affected by RP. It is further estimated that in Germany 15,000 subjects are legally blind as a result of RP [30].

A number of treatments have been tried, including immunostimulation [48], vitamin supplementation [6], oxygen therapy [41], scleral resection, and combinations of these techniques and others [5, 34]. All these approaches have failed to show a benefit for patients in terms of improvement of visual acuity or visual field. Because RP is caused by mutations in genes coding for key enzymes in the primary visual processes, gene therapy has been suggested as a therapeutic option. It has been shown that it is possible to transfer copies of these genes or growth factor encoding genes into retinal photoreceptors using different viral vectors [1, 3, 21, 31, 42]. These approaches have shown promising results but are also possibly associated with severe systemic complications [29]. Retinitis pigmentosa is caused by a variety of mutations so that the substitution of a single gene may not be effective in a large number of cases. Moreover, gene therapy may be useful in preventing the disease from progressing but may be less useful in very advanced cases of atrophy of the outer retinal layers.

In the late 1960s it was suggested that visual perception in blind subjects could be induced by electric stimulation of different levels of the visual system beyond the photoreceptors. Brindley and his group implanted early cortical stimulators with which he obtained visual sensations in subjects blind from RP [7, 8]. The visual cortex is the primary target in Dobelle's system, which is based on a small camera and an ultrasound detector. Information from both sensor systems is used in a visual processor, and stimulation pulses are provided to an electrode array positioned on the dura at the occipital cortex. A few patients were implanted with this system, and according to information from the company visual perception was achieved, allowing a blind subject to walk in unknown terrain [15, 16].

Considerable improvements in cortical prostheses have now been achieved by fabrication of new electrode arrays [33, 47]. Although the cor-

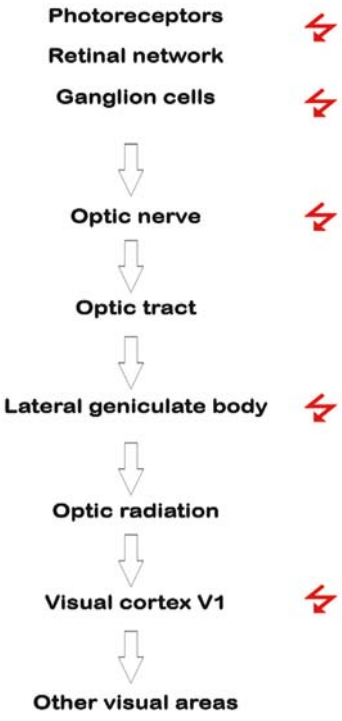

Fig. 1.1. Flow chart of the sensory input to the visual system and currently discussed targets for electrical stimulation as visual prostheses. *From top to bottom* subretinal retinal implant, epiretinal retinal implant, optic nerve cuff electrode, LGB stimulator, cortical prosthesis

tical prosthesis approach has been followed for some years, a retinal stimulator may be more useful with respect to topography (Fig. 1.1). Because many interneurons are involved in the processing of information between retinal photoreceptors and the visual cortex, a stimulation paradigm for realistic visual perception must be much more complex when the target for stimulation is central in the cortex when compared to peripheral stimulation in the retina. Cuff electrodes have been used for the stimulation of peripheral nerves [12]. A variation of such an electrode has also been considered for use as a stimulating electrode for the optic nerve. Experiments have already been performed in blind subjects. In these experiments localized phosphenes were elicited [14, 44]. Because the optic nerve fibers are very densely packed, a topographic correlation between the stimulation electrodes and visual perception was difficult to obtain. Several research groups have therefore decided to work on retinal stimulation.

Because in RP the degenerative process starts in the photoreceptors, the ideal approach would be to simply replace the abnormal photoreceptors by technical elements such as very small photodiodes, which can transform light energy into electrical power which can then be used to stimulate naturally the postsynaptic bipolar and horizontal cells in the retina. This idea was followed by Alan Chow and co-workers in the USA [9, 35] and by Eberhart Zrenner and his group in Germany [50]. The approach was published as the subretinal approach to a retinal prosthesis. Another concept for retinal implants comprises the fixation of a microelectrode array onto the retinal surface. In this epiretinal approach energy for the implant is provided by inductive or optoelectronic pathways. This method was described by Eugene deJuan and co-workers at Wilmers Eye Institute in Baltimore, by Joe Rizzo and his group at the MIT in Boston, and by Rolf Eckmiller and the German EPI-RET consortium, and was published as the epiretinal approach towards a retinal prosthesis [17, 26, 36].

1.2 Approaches for Retinal Implants

Electrical stimulation of the retina has been widely used in animal experiments to study the physiology of the retina with single electrodes [22, 24, 43]. Wolf and Dawson published experiments on therapeutic approaches using direct or indirect electrical retinal stimulation [13, 49]. Although these results were published 30 years ago, a device for application in blind humans was not fabricated. To obtain visual perception an array of very small microelectrodes has to be fabricated supplying stimulation pulses at various locations simultaneously and independently depending on the picture required. Therefore flexible and very thin microelectrode arrays for stimulation have been discussed which should be placed onto or underneath the retina (Fig. 1.2).

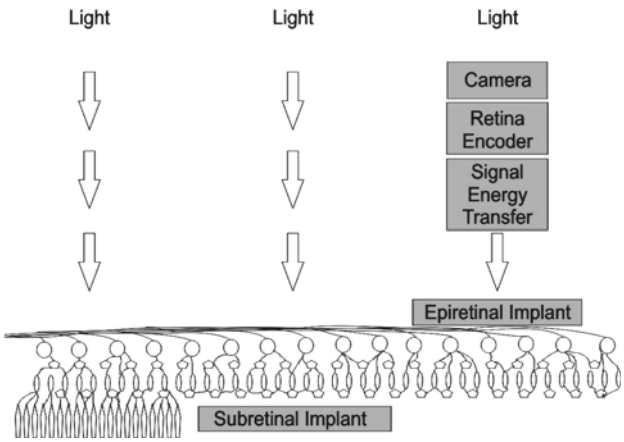

Fig. 1.2. Principal approaches for a retinal prosthesis. *Left* normal flow of light through the retina; *centre and left* receptor degeneration; *centre* subretinal approach: light activates microphotodiodes in the subretinal space inducing stimulation of postsynaptic neurons; *right* epiretinal approach: light is captured by a camera outside the eye. The signal is processed by simulation of receptive field properties. Energy and signal transfer is mediated by inductive or optoelectronic transponder systems

1.3 The Subretinal Approach

The idea of A. Chow and E. Zrenner was to use devices which could transform light energy into electrical energy and to insert a large number of these elements underneath the retina in the subretinal space. The basic concept of the subretinal approach was to replace the degenerated photoreceptors with technical elements with a similar function, i. e. the transformation of light to electrical energy. The charming advantage of this approach is that the topography of the incoming signal is more or less the original one. The postsynaptic cells in the retina, bipolar cells and horizontal cells are supplied with a local electrical input from the respective technical elements. No signal processing system is needed for this approach. The US and German groups working on the subretinal approach fabricated microphotodiode arrays as small discs or flexible foils which were inserted in the subretinal space. Animal experiments showed that the implantation of subretinal devices is possible and safe either through a transvitreal approach (ab interno) after vitrectomy and retinotomy or through a transchoroidal route (ab externo). The materials which were used for subretinal implants were clinically well tolerated; however, the material itself showed signs of oxidative or enzymatic damage of the metal layers. Therefore an adequate coating of subretinal devices is indispensable [40, 11, 28]. Chow had already implanted his device in seven humans suffering from end-stage RP. He described that the surgery was well tolerated by all patients and that no complication occurred. The patients reported visual perceptions. At present, it is still not clear whether this effect is a response to specific action of the device or if this effect is an unspecific response to the surgery itself. It could be speculated that vitrectomy and the opening of the subretinal space for insertion of the implant may lead to a release of neurotrophic factors, which could explain the results [10]. Another question arises from calculations demonstrating that the energy released by currently available microphotodiodes is not enough to generate electric power in a range sufficient to stimulate retinal neurons. Therefore, German researchers working on the subretinal prosthesis are developing a secondary system for amplification of the incoming signal to provide enough energy for neuronal stimulation. Figure 1.3 shows a prototype of an active subretinal implant.

Summary for the Clinician

- **In the subretinal approach the retinal stimulator is placed underneath the retina**
- **The stimulator consists of thousands of miniaturized photodiodes which transform light into electric power**
- **Postsynaptic cells in the retina are the target for stimulation**
- **Image processing equipment or a camera is not necessary**

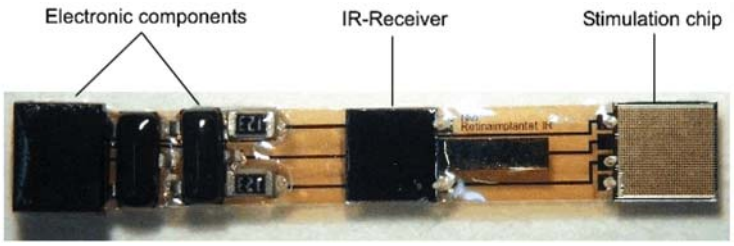

Fig. 1.3. Prototype of an active subretinal implant with a receiver for IR energy (*centre*), electronic components (*left*) and the subretinal stimulator (*right*)

1.4 The Epiretinal Approach

Electrical stimulation of the inner surface of the retina has been followed as a possible approach to retinal prostheses. The target cells for epiretinal electrical stimulation are the ganglion cells. Due to the natural processing of the visual input in the healthy retina by interneurons, ganglion cells do not efficiently respond to pulses directly derived from the visual input. Therefore the visual input in this approach has to be processed outside the retina in a neural network simulating functional properties of receptive fields with respect to contrast, colour, orientation, velocity, and other parameters. As a result of this signal, processing ganglion cells can be efficiently stimulated by series of short current pulses. In contrast to the subretinal approach, in the epiretinal approach the scene needs to be captured by a small camera and processed before the ganglion cells can be stimulated.

Cameras can be fabricated as CMOS systems characterized by low energy consumption, small size and efficient on-chip signal processing [27]. This camera module has to be integrated into the frame of normal spectacles. The output from the camera is further processed by the retina encoder simulating properties of the target cells. Because prior to implantation it is not known which electrode is in good contact with which ganglion cell, the signal processing should be adjustable depending on the visual sensations of the patient. The retina encoder calculates the pulse sequence and the parameters of each stimulation pulse at each electrode depending on the camera input. The number of pulses, amplitude and duration of each phase of each pulse have to be determined and then transmitted to the implant [17–19]. Not only the signal is transmitted to the implant but also the necessary energy to drive the electric circuits of the device. Currently an electromagnetic inductive coupling with a primary and a secondary coil is being fabricated. However, an optoelectronic solution which may provide higher data rates is also under construction. Figure 1.4 shows the general concept of an epiretinal prosthesis.

Summary for the Clinician

- **In the epiretinal approach the retinal stimulator is placed onto the retinal surface**
- **Ganglion cells are the target of epiretinal stimulation**
- **The image needs to be captured by an extraocular camera**
- **The camera signal is further processed by a retinal encoder simulating normal retinal signal processing based on receptive field properties**
- **The information on the pattern of electrode activity is transmitted via radiofrequency into the eye**
- **Energy to drive the implant is transmitted via radiofrequency into the eye**

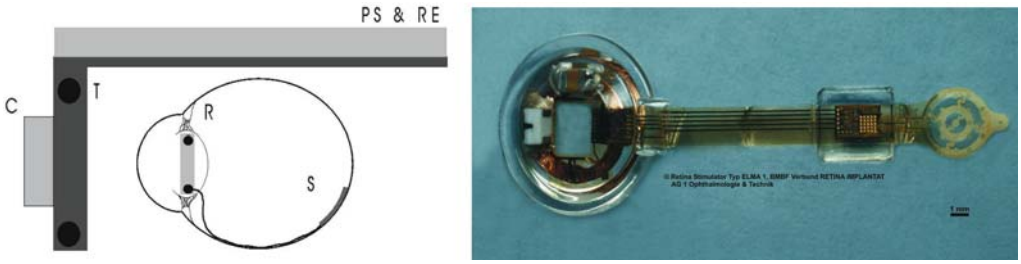

Fig. 1.4. *Left* General concept of an epiretinal prosthesis. The camera *C* captures visual data, the retina encoder *RE* processes the data according to the functional properties of receptive fields of the assumed target ganglion cells (*PS* power supply). The transponder system *T* transmits data and energy using inductive coupling into the implant consisting of the receiver *R* unit and the stimulator *S*, which is fixated onto the retinal surface. *Right* prototype of an epiretinal prosthesis (EPI-RET research group) with the receiver embedded into a silicone disc (*left part*), a polyimide-based microcable, and the microcontact array with 25 active electrodes independently driven by a stimulation microchip just left of the array

1.5 Experimental Studies

Early studies showed that in the cat cortical activation can be recorded as a result of stimulating indwelling electrodes [13]. Although in this study it was shown that cortical activation was achieved over a considerable follow-up of 6 months, this effort did not end up with a retinal prosthesis available for use in humans. In research initiatives in the USA and Germany, experimental data have been collected which show that retinal implants can restore visual perception in blind humans suffering from RP. The first studies concentrated on the biocompatibility of implanted materials and on surgical feasibility.

1.5.1 Biocompatibility of Implanted Materials

In a series of in vitro experiments, neural cells and connective tissue cells as well as retinal cell cultures were exposed to material specimens of implant and encapsulation components. The cells were also exposed to basic substances for electronic components such as silicon and gold [23]. It could be shown that some silicones were toxic to these cells whereas others were not. Polydimethylsiloxane (PDMS), which is also known as a standard material for the fabrication of intraocular lenses, proved to be non-toxic in these studies. Electrically inactive components of the devices were implanted into the eye of pigmented rabbits (Fig. 1.5). It was shown that the components were well tolerated even 6 months after implantation [2].

1.5.2 Surgical Feasibility

In rabbits and pigs it was demonstrated that subretinal implants can be inserted either after vitrectomy through a retinotomy in the subretinal space or by an external approach through an incision through the choroid (Fig. 1.6). Complications such as retinal detachments or choroidal bleeding were rarely reported. The retina overlying the implant could be preserved if the implant was very thin and perforated. With the subretinal position of the implant a specific fixation procedure was not necessary. The implant showed a stable position over a period of more than 1 year [40].

Chow's group did not report any complications occurring during or after the implantation of their subretinal device in patients.

The implantation of epiretinal devices is more complex because a fixation procedure has to be followed as well as a procedure for implantation of the receiver part of the implant. Walter and co-workers as well as Majji and deJuan's group independently applied tack fixation to stabilize the microelectrode array onto the reti-

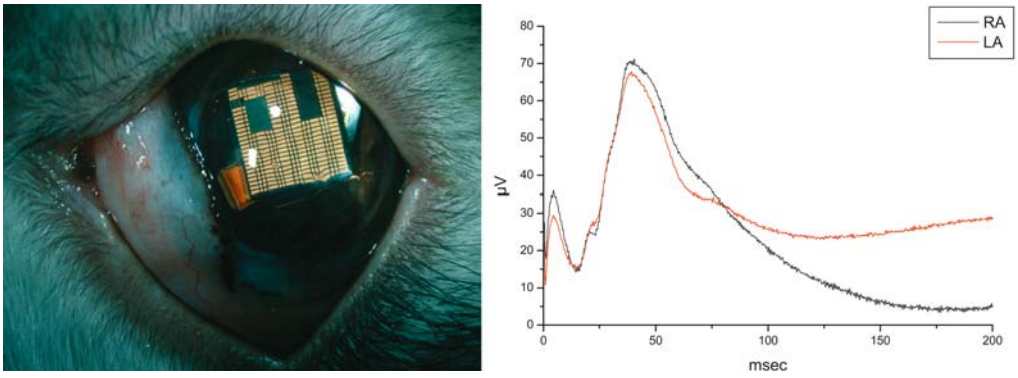

Fig. 1.5. *Left* Electrical passive silicon structure encapsulated in PDMS 6 months after implantation in the capsular bag of a rabbit. *Right* Same rabbit, 6 months after implantation. Electroretinogram: *red* left eye (control); *black* right eye (study eye after implantation)

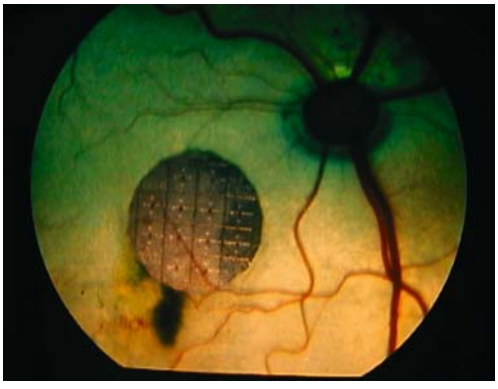

Fig. 1.6. Subretinal implant 12 months after transvitreal implantation in the subretinal space of a pig

nal surface. They found that with the use of retinal tacks (Fig. 1.7) a stable position of the implant could be achieved in over 6 months and that the complication rate was low [32, 46]. The complete removal of the vitreous in the rabbit is much more complex than in man. The adherence of the vitreous to the retina is stronger and therefore in our series we performed a two-step approach. In the first step a core vitrectomy with endolaser of the prospective fixation area was performed. Two weeks later in a second vitrectomy vitreous remnants were removed and the implant was inserted and tack fixated.

Alternatives to this approach use enzyme assisted vitrectomy. Plasmin or tPA was used in these procedures to separate the posterior vitreous from the retinal surface. It is mandatory in the epiretinal approach that the stimulating electrodes are placed as close as possible to the ganglion cell layer. Tissue or any material in between the stimulator and the target cells will reduce the effectivity of stimulation. Under such circumstances the resistance will increase and therefore much more energy is necessary for an effective stimulation. In terms of long-term biocompatibility the currents for stimulation should be as small as possible. Currently it is unknown if in chronic experiments tissue will grow in between the stimulator and the retinal surface. It could be expected that if the primary contact between the retina and the stimulator is very good, the ingrowth of fibrous tissue will be limited. Further experiments are necessary to demonstrate the behaviour of the interface between the implant and the retinal surface.

In a number of experiments it was demonstrated that tack fixated stimulators could also be explanted [4]. Explantation of microelectrode arrays could be less traumatic when biological fixation procedures are available. The explantation of tack fixated microelectrode arrays is comparable to trauma surgery and is characterized by the use of perfluorcarbon liquids, endolaser and silicone oil. Improvements in the design of retinal tacks are therefore desirable.

In 2003 the German EPI-RET consortium fabricated the first functional wireless epiretinal

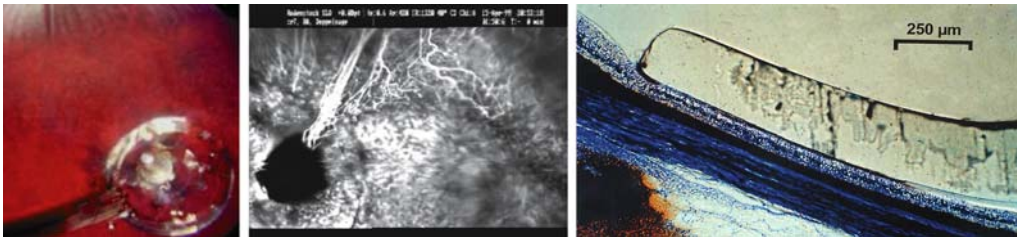

Fig. 1.7. *Left* Fundus photograph of a tack fixated microelectrode array onto the retinal surface of a rabbit 6 months after implantation; *centre* angiogram 6 months after implantation showing no neovascular elements only a slight deviation of a vessel towards the tack; *right* histology after tack fixation of an epiretinal contact array on the retinal surface. Grinding technique

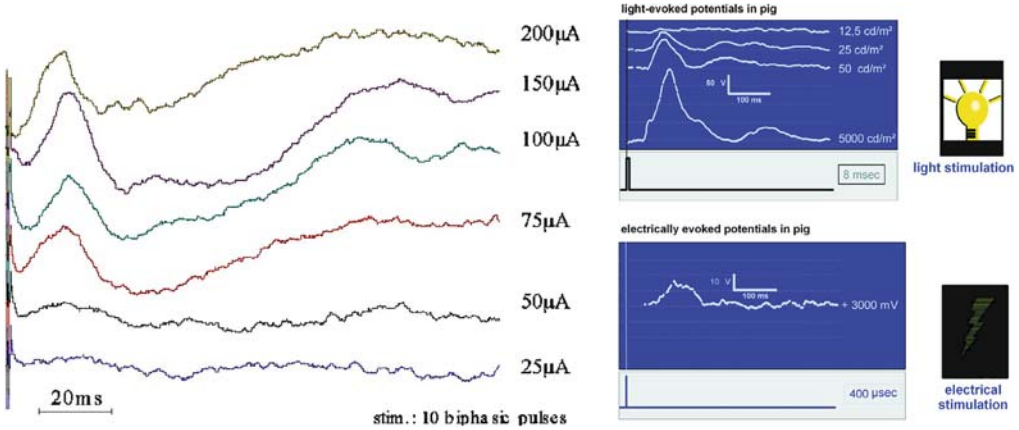

Fig. 1.8. *Left* Electrically evoked cortical potentials in the rabbit after pulse train stimulation of the inner retinal surface with repetitive short biphasic current pulses; *right* light evoked (*top*) and electrically evoked cortical potentials in the pig after subretinal electrical stimulation

prosthesis with 25 electrodes and a transponder system for data and energy. After developing procedures for the implantation of such complex prostheses in rabbits the system was implanted in cats and pigs to study cortical activation. The lens was removed with a standard phacoemulsification procedure. The vitreous was removed with vitrectomy, and the eye was filled with perfluordecalin. The posterior capsula was opened and the implant inserted through a corneal incision. The receiver was placed in the capsular bag, the stimulator was positioned on the decalin surface after pushing it through the posterior opening of the capsula and with removal of decalin it was placed on the retinal surface. Then with the use of a retinal tack it was fixed onto the retinal surface in or close to the area centralis.

1.5.3 Studies on Cortical Activation

Functional studies on cortical activation have been performed in rabbits, cats, pigs, but also in humans (Fig. 1.8). In early approaches acute experiments were performed in rabbits in which the cortical activation was demonstrated by recordings of evoked potentials (EPs) as a result of retinal stimulation achieved by electrode arrays directly connected to a stimulator device. Thresholds for the detection of EPs after epiretinal stimulation were found at 30 µA with repeated biphasic pulse trains of ten pulses (1 ms for each pulse) [45]. For subretinal stimulation, Zrenner and his group and Chow and co-work-