THE VALUE OF PREOPERATIVE TESTS IN THE SELECTION OF BLIND PATIENTS FOR A PERMANENT MICROELECTRONIC IMPLANT

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ABSTRACT

Purpose: To determine the best candidates (ie, those requiring lowest current levels delivered to the retina to elicit visual perceptions) for long-term implantation of a microelectronic retinal implant through a series of preoperative visual, psychophysical, and electrophysiological tests.

Methods: This study protocol was granted an investigational device exemption by the Food and Drug Administration and was approved by the institutional review board at the University of Southern California. After informed consent was obtained, all subjects underwent the following preoperative tests: dark-adapted bright flash and 30-Hz flicker electroretinograms, electrical evoked responses (EERs) using a Burian-Allen corneal electrode to stimulate the globe, and psychophysical tests to evaluate the light and electrically elicited visual perceptions. Intraocular stimulation (IOS) of the retina was performed by an array of electrodes positioned on the internal limiting lamina.

Results: Lower vision correlated with less sensitive psychophysical responses ($P<.0001$). Lower vision and less sensitive psychophysical tests correlated with higher EER values for stimulus pulse widths of 2 ms ($P<.0008$) and 4 ms ($P<.0002$). Lower IOS currents correlated with more sensitive psychophysical responses ($P<.02$) and lower EER values at 4 ms ($P<.04$).

Conclusions: Preoperative testing, especially psychophysical and electrophysiological tests to assess light and electrically driven visual responses, can help in evaluating patients for suitability for receiving a permanent microelectronic retinal implant. Further study is warranted.

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INTRODUCTION

Each year, thousands of people are afflicted with photoreceptor degenerative diseases that reduce vision to bare light perception or complete blindness.[1] A number of possible therapies have been proposed for the treatment of visual deficit due to photoreceptor loss in inherited retinal degenerations or age-related macular degeneration. One approach is to use implantable microelectronics.[2-8] A critical aspect in identifying the best candidates for a microelectronic implant is an accurate estimate of the amount of stimulating current required to elicit visual perceptions. In this study, we report our experience in using preoperative testing to help select patients for clinical trials of retinal stimulation devices.

The different methods currently being pursued to electrically stimulate the damaged visual system can be divided into extraocular and intraocular device implantation sites. Extraocular locations include the visual cortex, optic radiations, and optic nerve.[5-8] Intraocular sites include the epiretinal and subretinal surfaces.[2-4] This report focuses on work related to the intraocular epiretinal stimulator being developed by our group. We believe there are several advantages to this approach. First, our intraocular approach carries significantly less morbidity than the more invasive cortical and optic nerve surgical procedures. Also, an epiretinal approach is advantageous because stimulating electrodes can be in close contact with the retina while the remainder of the implanted device can be positioned in the vitreous cavity, keeping thermal sources away from the retina. Moreover, an

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epiretinal device can be relatively large and incorporate sophisticated powering and data transmission schemes. Although the subretinal implant has the theoretical advantage of being placed closer to the nearest layer of surviving neurons (ie, bipolar cells),[4] the size, and thus the capability, of the subretinal device is limited by the small subretinal space.

Both the subretinal and epiretinal implants are currently in early clinical trials under an investigational device exemption approved by the Food and Drug Administration (FDA).[9-12] Given that patient testing has started, an important aspect of this testing is the use of preoperative testing to help select suitable recipients for these retinal implants.

At Doheny Retina Institute, we have conducted a series of tests for each prospective candidate in clinical trials of epiretinal electrical stimulation with acute and chronic electrodes. These tests include visual acuity, psychophysical tests, and electrical evoked response (EER). The purpose of this study is to determine whether visual, psychophysical, and electrophysiological preoperative testing may predict the patients who will require lower levels of stimulating currents to elicit a visual perception. We believe this to be an important criterion in identifying the best candidates for long-term implantation of a microelectronic retinal implant.

METHODS

This study protocol was granted an investigational device exemption by the FDA and was approved by the institutional review board at University of Southern California.

PATIENT SELECTION AND TESTS

All the subjects had visual acuity of either light perception (LP) or no light perception (NLP) in the study eye as a result of retinitis pigmentosa. Seventeen eyes of nine subjects were analyzed. After informed consent was obtained, subjects underwent a series of preoperative tests that included the following: dark-adapted bright flash (BF) and 30-Hz flicker electroretinograms, visual evoked potentials, EERs, psychophysical tests with dark-adapted BF detection/discrimination, retinal fluorescein angiography, and color fundus photography. Intraocular stimulation (IOS) of the retina was performed with the use of an array of electrodes positioned on the internal limiting lamina of the retina.

ELECTRICAL EVOKED RESPONSE

The EER was recorded by passing current between a Burian-Allen corneal electrode and an ipsilateral retroauricular electrode. The subject was asked to report any light perception. False stimulus (ie, subject asked to report perception but no stimulus applied) was given during the tests as a false-positive control test. The stimuli currents ranged from 0 to 8 mA with a pulse width of either 2 ms or 4 ms. Threshold was defined as the current that elicited a visual perception in at least three-fourths of subjects in three to five trials.

PSYCHOPHYSICAL TEST: DARK-ADAPTED BRIGHT FLASH DETECTION

After pupil dilatation and 45 minutes of dark adaptation, BF detection was performed in all eyes. The test consisted of using a xenon flash with different filter intensities (from 4.8 to 0 dB) to evaluate the light-elicited visual perceptions. The subject was asked to report when there was any light perception. If the subject could not perceive the light, a professional photography flash replaced the xenon flash. With the photographic flash, the filters were varied from 2.6 (which has the same intensity as the xenon flash with 0-dB filter) to 0 dB. The final scale (BF standardized) used for analysis was standardized starting in 7.4 dB (xenon flash with 4.8-dB filter, most sensitive, dimmest light) and finishing in 0 dB (photography flash, 0-dB filter, brightest light). Subjects unable to perceive the brightest possible flash were designated as having no flash perception (NFP) for this test.

INTRAOCULAR STIMULATION OF THE RETINA

Five eyes underwent IOS of the retina. All eyes underwent pars plana vitrectomy with positioning and IOS of the electrode array on the internal limiting lamina in the macular region. All eyes were stimulated and tested using a 16-electrode array except eye 12, which was tested with a two-electrode probe.[9] In four subjects, IOS was performed during the surgery in the operating room using only topical anesthesia. In eye 8, IOS was performed 1 week after the implantation of a permanent microelectronic implant (Second Sight model 1, Second Sight, LLC, Sylmar, Calif). Threshold was defined as the lowest charge that elicited visual perception (flash of light; phosphene) in at least three or four trials. False-positive tests were conducted to determine the reproducibility of the phosphene. The false-positive test consisted of asking the subject if a phosphene was present in the absence of stimuli (the subject was not informed of the absence of stimuli).

Stimulus delivery was controlled by computer hardware and software. In eye 12, a 286 microprocessor (2402 Tekmate, Tektronix, Beaverton, Ore) coupled with an analyzer (2630 personal Fourier analyzer, Tektronix) was used to generate the waveforms and currents. In the other eyes, a Pentium 3 microprocessor (Vaio, Sony, New York, NY) with Second Sight VPU software version 1.0.6 (eye 8) or Second Sight PSP software version D (eyes 10, 15, and

16) was used to generate the waveforms and pulses. The stimulating pulse shapes and principles used were similar to what has been described by Humayun and coworkers.[13]

STATISTICAL ANALYSIS

Analysis of variance (ANOVA), *t* tests, and Pearson's tests were performed using JMP software version 4 (SAS, Inc).

RESULTS

All the study eyes had nonrecordable preoperative electroretinograms and visual evoked potentials. The fluorescein angiography and color fundus pictures confirmed no retinal pathologic changes other than those caused by retinitis pigmentosa.

PREOPERATIVE VISUAL ACUITY, PSYCHOPHYSICAL TESTS, AND EER

Ten eyes had LP and seven eyes had NLP when the brightest setting from an indirect ophthalmic headset was used as the light source (Table I). However, during the BF psychophysical testing, which used a brighter source after a period of dark adaptation, many of the subjects, even those diagnosed as having NLP by a clinical evaluation, could perceive the flashes of light.

The subjects' BF (standardized) detection levels ranged from 5 dB to NFP with a mean of 3.14 ± 1.53 (SD). In the LP group, the BF values were 4.22 ± 0.53 dB, while in the NLP group the BF values were 1.6 ± 1.06 dB. All of the eyes with LP presented BF detection higher than 3 dB (n = 10), and those with NLP had BF detection lower than 3 dB (n = 7). NLP correlated with less sensitive BF values (P<.0001, n = 17, *t* test, ANOVA).

In comparing the EERs at 2 ms, the LP eyes presented thresholds from 2 to 5mA (4.0 ± 0.87) and the NLP eyes presented thresholds from 5 to 8 mA (6.6 ± 1.34). At 4 ms, the LP eyes presented thresholds from 3 to 4 mA (3.2 ± 0.42) and the NLP eyes presented thresholds from 4 to 7 mA (5.5 ± 1.29). Thus, eyes with NLP (n = 14, *t* test, ANOVA) correlated with higher EER values for stimulus pulse widths of 2 ms (P<.0008) and 4 ms (P<.0002).

Less sensitive BF values (n = 14, Pearson's test) correlated with higher EER values for stimulus pulse widths of 2 ms (r = –0.613, P<.001) (Figure 1) and 4 ms (r = –0.662, P<.0099) (Figure 2).

PSYCHOPHYSICAL RESPONSES, EER, AND IOS

The IOS charges varied from 45.8×10^{-9} to $1{,}931.8 \times 10^{-9}$ coulomb (C) (Table II). Lower IOS charges correlate with more sensitive BF values (r = –0.945, P<.02, n = 5) (Figure 3) as well as lower EER values at 4 ms (r = 0.998, P<.04, n = 3) (Figure 4). EER at 2 ms showed a trend of correlating with IOS but was not statistically significant (r = 0.79, P<.22, n = 4).

DISCUSSION

Accurate methods to identify blind patients with retinal cells that are sensitive to lower levels of electrical current will improve the effectiveness of a microelectronic implant designed to restore useful vision to patients with

TABLE I: PREOPERATIVE TEST RESULTS

EYE	VISUAL ACUITY	BF STANDARDIZED (dB)	EER 2 MS (mA)	EER 4 MS (mA)
1	LP	5	4	3
2	LP	4.7	5	3
3	LP	4.5	5	4
4	LP	4.4		4
5	LP	4.4	4	3
6	LP	4.4	4	3
7	LP	4.1	4	3
8	LP	3.9	4	3
9	LP	3.6	4	3
10	LP	3.2	2	3
11	NLP	2.8	8	7
12	NLP	2.4	6	
13	NLP	1.4	5	4
14	NLP	1.4	6	5
15	NLP	NFP	8	6
16	NLP	2.6		
17	NLP	0.6		

BF, bright flash (dark-adapted); EER, electrical evoked response; LP, light perception; NFP, no flash perception (using brighter light sources); NLP, no light perception (during regular clinical evaluation with usual spotlight).

TABLE II: COMPARISON BETWEEN EYES THAT UNDERWENT INTRAOCULAR STIMULATION

EYE	BF STANDARDIZED (dB)	EER 2 MS (mA)	EER 4 MS (mA)	IOS (COULOMB)
8	3.9	4	3	45.8×10^{-9}
10	3.2	2	3	147.2×10^{-9}
12	2.4	6		192.0×10^{-9}
15	NFP	8	6	$1{,}931.8 \times 10^{-9}$
16	2.6			205.7×10^{-9}

BF, bright flash (dark-adapted); EER, electrical evoked response; IOS, intraocular stimulation; NFP, no flash perception (using brighter light sources).

outer retinal degenerations. Since conventional means of assessing vision are nearly impossible in eyes with bare light perception or NLP, we have tried to identify other means of testing that would help us select those who would require the lowest retinal stimulating currents. Our study showed that lower vision correlated with less sensitive psychophysical responses (BF detection) and that both lower vision and less sensitive psychophysical responses correlated with higher EER values for stimulus pulse widths of 2 ms and 4 ms. Lower IOS currents strongly correlated with more sensitive psychophysical responses and lower EER values at 4 ms.

The inadequacies of routine clinical testing for visual acuity became more apparent when a large number of eyes that were diagnosed as having NLP could detect a BF after dark adaptation. Moreover, comparable BF and EER findings demonstrate increased sensitivity as compared to the usual testing methods in the clinic (Table I) and were further supported by the IOS results (Figures 3 and 4) as an important predictive factor.

The BF results clearly indicate that there are remaining photoreceptors and therefore some intact retinal circuitry. Morphometric analysis of the retina has demonstrated preservation of ganglion cells and the inner nuclear layer in retinitis pigmentosa and age-related macular degeneration.[14-17] But more pertinent to our findings is the fact that in eyes with retinitis pigmentosa, preservation of the inner retina is greater in the macular than the extramacular region.[15-17] This is believed to be due in part to the fact that the macular photoreceptors are lost later. Thus the eyes that are more sensitive to BF have some remaining macular photoreceptors and therefore presumably more inner retinal preservation than eyes with no flash perception.

The EER has been shown to have its origin in the inner retinal layers.[18-20] In our patients with greater inner

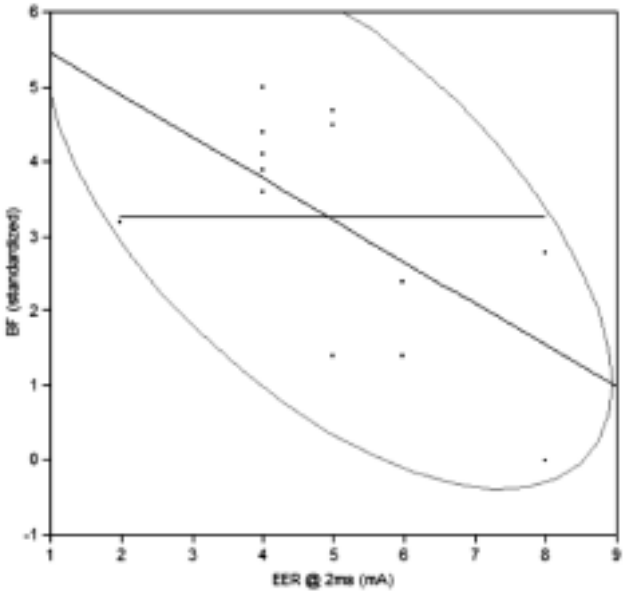

FIGURE 1

Bright flash (BF) versus electrical evoked response (EER) at 2 ms. Bivariate fit of BF (dB) by EER at 2 ms (mA); $r = -0.613$, $P<.001$, n = 14 (Pearson's). Higher BF values (more sensitive, dimmer stimulus) correspond to lower EER values at 2 ms (more sensitive, lower current).

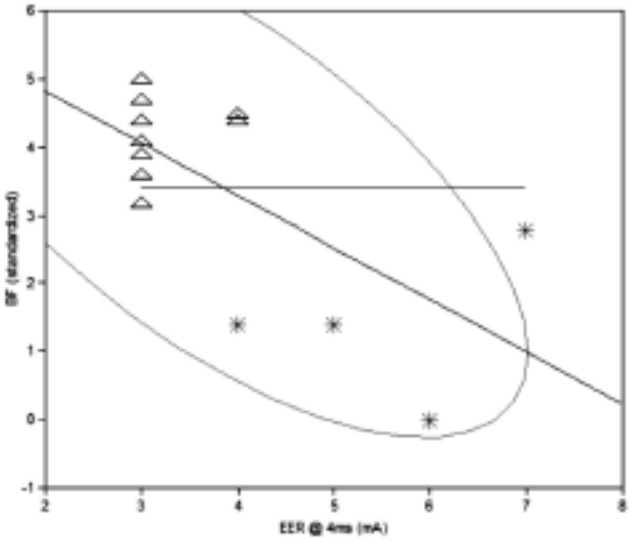

FIGURE 2

Bright flash (BF) versus electrical evoked response (EER) at 4 ms. Bivariate fit of BF (dB) by EER at 4 ms (mA); $r = -0.662$, $P<.0099$, n = 14 (Pearson's). Higher BF values (more sensitive, dimmer stimulus) correspond to lower EER values at 4 ms (more sensitive, lower current).

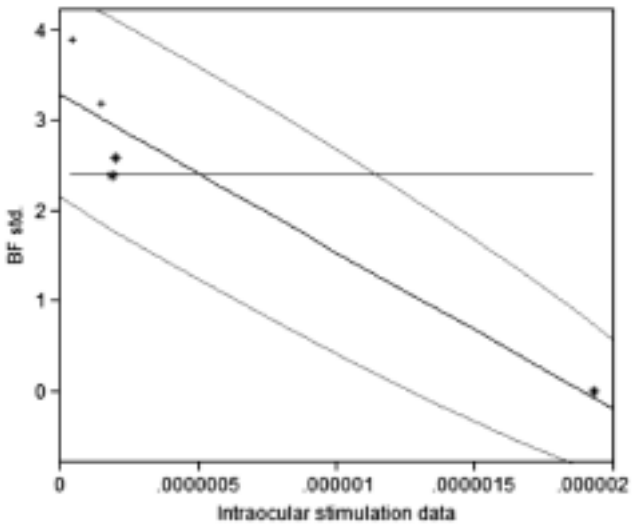

FIGURE 3
Intraocular stimulation (IOS) versus bright flash (BF) test. Bivariate fit of BF (dB) by IOS data (coulomb); $r = -0.945$, $P<.02$, n = 5. Higher BF values (more sensitive, dimmer stimulus) correspond to lower IOS charge (more sensitive).

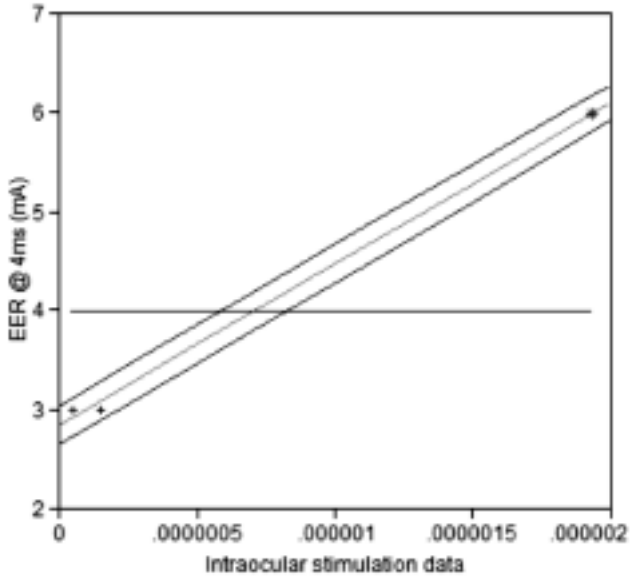

FIGURE 4
Intraocular stimulation (IOS) versus electrical evoked response (EER) at 4 ms. Bivariate fit of EER at 4 ms (mA) by IOS data (coulomb); $r = 0.998$, $P<.04$, n = 3. Lower EER values (more sensitive, lower current) correspond to lower IOS charge (more sensitive).

retinal preservation, we would thus expect lower threshold values for the EER testing to elicit a visual perception. This was shown by our data in patients with more sensitive BF results (ie, patients with less severe outer retinal degeneration), where the EER threshold values were indeed lower. The importance of EER testing as a screening tool for identifying patients for a microelectronic implant is also evident from our study. Lower EER thresholds correlated strongly with lower IOS thresholds.

Correlation of preoperative tests with IOS allows for predictions of the required stimulus current for each patient. Lower IOS thresholds correlate with less current needed to elicit a visual perception. A device with lower current requirements can use a large number of small electrodes, since the stimulus current requirement sets a minimum size for electrodes. Thus, a reliable estimate of these requirements can identify better candidates for long-term implants with a higher density of electrodes and potentially greater resolution.[3] Their preoperative determination may allow for improved sophistication of the next-generation implanted devices and, eventually, improved success of visual perception for the patients.

The IOS data is interesting and encouraging but must be considered cautiously, since so few data points are available. The small number of patients with IOS results reflects the necessary precaution in the subjects' selection. As the study continues, more data must confirm the current findings and make statistically significant those where just a trend is currently shown. While these tests will contribute to the selection process, other factors will also be considered. Some of the other important factors are the patient's overall health, which affects the ability to undergo surgery, and the patient's ability to grasp at a basic level the principle behind the retinal prosthesis.

CONCLUSIONS

Preoperative psychophysical and electrophysiological tests to assess light and electrically driven visual responses proved to be helpful in evaluating subjects for suitability for receiving a permanent microelectronic retinal implant. Microelectronic retinal prostheses have had encouraging results from early clinical trials. As we learn more about interfacing electronics with the retina, we hope to develop more meaningful means of stimulating the retinal neurons and communicating with the brain so that the patient can ultimately achieve vision that will be useful in activities of daily living.

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DISCUSSION

DR DONALD G. PURO. Approximately 100,000 Americans have no light perception. Certainly, we hope that knowledge gained by laboratory and clinical research, as well as improved access to high quality ophthalmologic care will decrease the incidence of severe vision loss. However, for the foreseeable future it seems likely that a significant number of people will lose all of their useful vision.

Yanai and his colleagues are addressing the challenge to restore vision after irreversible photoreceptor damage has led to bare light perception or no light perception. Their strategy is to develop a bioelectric visual prosthesis that can be positioned on the inner surface of a damaged retina. It is hoped that application of electrical current via an array of microelectrodes will activate retinal neurons in a sufficiently selective manner to simulate, at least in some ways, the actions of photoreceptors. Obviously, this endeavor has daunting challenges. Fortunately, there are a number of intrepid teams of scientists, engineers and ophthalmologists that are making serious attempts to develop a retinal prosthesis.

The aim of this study was to establish procedures to select from patients with bare LP or NLP vision those whose retinas can be stimulated by relatively small amounts of electrical current. This selection process is important because the lower the intensity of current needed to activate the retinal neurons, the closer the stimulating electrodes can be positioned, and the greater the density of stimulated sites, the greater the possible visual resolution.

Not unexpectedly, the authors found that lower vision correlated with less sensitive psychophysical responsiveness. Also, not surprisingly, they found that the greater the residual retinal function as assessed by psychophysical testing, the less the intensity of intraocular electrical stimulation needed to evoke crude visual sensations.

In other words, the better the retina, the easier it is to elicit a visual sensation.

Although the number of eyes in this study was small, only 5 were tested with intraocular stimulation, the fact that the results are very consistent with what would be expected makes a larger sample size seem unnecessary.

Based on this study, the bright flash test used after dark adaptation and the evoked response to stimulation by a corneal electrode are reasonable screening procedures to rank the degree of residual retinal function in patients who have bare light perception or no light perception.

Clearly, there is a long road ahead for the development of a useful retinal prosthesis. The authors should be congratulated for undertaking this formidable biological and technological quest.

DR CHARLES P. WILKINSON. Artificial vision is something that retina surgeons get asked about every day. Could give us some real life opinions about where you see this going versus direct cortical stimulation. Dr Dobell has done about 18 of these direct cortical stimulations in Portugal. He showed a tape of a patient driving a car around a parking lot with this artificial device. How do you see that sort of strategy where it will end up compared to your implant?

DR KENNETH W. WRIGHT. Have you seen a neurotropic effect of electrical stimulation on the retina? Electrical stimulation of the retinal can induce neural regeneration and at ARVO this year and last year there has been a lot of talk about that.

DR FRONCIE A. GUTMAN. The retinitis pigmentosa patients are desperate and want to know where they should go. Could you counsel us on what we should say to them and how you're accessing your patients?

DR DAVID L. KNOX. There's an Indian writer by the name of Ved Mehta who lost his vision at an early age from encephalitis and he wrote stories about how he would scamper across rooftops in India, using what he called facial sight. He said it was a perception in the face of bright light, and I wonder if this phenomenon or this sensitivity was incorporated in your responses to the very bright flash you use for light perception.

DR MARK S. HUMAYUN. Concerning Pat Wilkinson's question about how we look at the different approaches: this is an international effort worldwide including researchers in Germany and Japan. Bill Dobell has been in the field for quite some time with cortical stimulation. The areas that you can put these visual implants are at the visual cortical level, which is the longest standing approach and is what Bill Dobell uses. That probably addresses a larger population of blind people because you don't need an intact optic nerve. In Belgium they're placing a cuff electrode around the optic nerve and stimulating the nerve. It's difficult obviously because you lose your spatial correlation because there are 1.2 million fibers or some percentage of that left and it's hard to stimulate them in a retinotopic fashion when you're stimulating the cable. We've taken the retinal approach.

In the retina, there are two different types of devices. One is epiretinal and one is subretinal, so you can put either the device on the ganglion cell side or you can put it underneath the retina where the photoreceptors would be. I think the subretinal approach has been difficult to bring to fruition, simply because the space is very limited. If you could just put a solar cell that could stimulate electrodes and that had enough of the power budget to do the stimulation, then that would be an ideal place. It turns out, however, that it takes about three suns to power one of these photocells to give enough current. There's enough digital signal processing that a simple device like that will not work, and so the German effort in Tubingen has realized this and are trying to develop a more complicated device.

In terms of the optic nerve, it's showing that the patient that's been implanted can only see one pixel, because it's hard to stimulate all the nerves in the appropriate fashion. It is probably going to be limited in its resolution. The problem with the cortical approach has been that the visual cortex is primarily buried inside the calcarine fissure. Dobell has been in this business since the 70s, but it turns out that using surface electrode stimulation you really couldn't address the majority of the visual cortex. NIH and Utah and everyone else have gone away from surface stimulation and are developing penetrating electrodes into the cortex. These electrodes move and in the brain parenchyma cause a lot of damage. Many people believe the Bill Dobell approach doesn't work. He has revived his old effort and gone to Portugal where he has implanted ten or so patients at a significant charge for the surgery.

In terms of the neurotropic effect, the question is whether you could put a device in there that could actually rejuvenate or rescue the photoreceptors. At ARVO the session that I chaired and some of the posters subsequently showed that, if you transected the optic nerve and then put a contact lens on these rats, in the stimulated eye there was a greater preservation of ganglion cells in the stimulated eye versus the unstimulated eye. In the RCS rat, an inactivated implant was just as effective as the electrically active implant. Was this neurotropic effect more surgical effect and a foreign body effect? It seemed that way in the RCS rat, and we know that from some transplantation work as well. The neurotropic effect is still very hotly contested and really no one knows if electrical stimulation has an effect or not in the retina in that regard. Our group is conducting experimental studies in RCD1 dogs with chronic and intense electrical stimulation of the retina and may bring some answers in the future. In terms of Dr Gutman's question: What do you tell your patients? Certainly not everybody can fly out to Los Angeles to see us. Right now the FDA studies are for people with end-stage retinitis pigmentosa only. People with macular degeneration and disciform scars don't meet the criteria. If they fit the criteria of bare light perception or worse vision due to Retinitis Pigmentosa and do not have any other ocular pathology, we perform a lot of psychophysical testing and determine how good a candidate they are for these FDA tests. You could fax us the records of these

patients and then give you further determination.

As for Dr Knox's question, in order for the blind person to do the amazing feats he could do, he must have very sensitive thermal receptors in his face and has developed to use this to guide him in his physical feats. As for our testing protocol, we were very careful to make sure that there wasn't a thermal effect by keeping the flash pretty far away and using it indirectly. If you bring the flash very close in some of this testing, that can be a problem. You have to control for that.