PROTOCOL

SAFETY STUDY IN RETINAL TRANSPLANTATION FOR DRY AGE RELATED MACULAR DEGENERATION

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I. PURPOSE:

The aim of this clinical trial is to test the safety of transplanting human fetal neural retinal tissue and retinal pigment epithelium into the eyes of human patients with age-related macular degeneration. Vision in the eye to be operated on will be the poorer vision of both eyes and must be 20/200 or worse. “Retinal tissue”, the layers in the back of the eye, consists of neural retina and retinal pigment epithelium. “Neural retina” is the nerve cell layer that processes light into vision. The "photoreceptor cells" in the neural retina detect the light and transform it into electrical signals, which are then transferred to the brain by other retinal cells. "Retinal pigment epithelium" (RPE) is the layer behind the neural retina which helps both to nourish the cells of

the neural retina and also to get rid of waste products. The fetal tissues used in this study will be derived from dead fetuses in the first 9-16 weeks of pregnancy obtained from elective abortions (see XV. FETAL DONOR TISSUE).

Fetal retinal transplantation is highly experimental. The research will be conducted in accordance with the prohibitions regarding the use of human fetal tissue described in Public Law 103-43, section 498B. There will be no compensation for the donor. The research will be conducted in accordance with any applicable Federal, State and local laws.

First, the technical application of the implantation instrument and its safety in the transplantation will be demonstrated in patients with 20/200 vision in one eye or worse, with functional acuity in the contra lateral eye.

Secondly, the human fetal retinal tissue will be placed in the areas beneath the retina where presently the patient has atrophy of the retinal pigment epithelium and poor retinal function.

The specific goals of this study are to demonstrate that:

1. Safety of the procedure by testing with pre-operative and post-operative vision evaluation by ETDRS (Early Treatment Diabetic Retinopathy Study) and microperimetry in patients with age-related macular degeneration and a vision of 20/200 or worse in the operated eye. The level of anticipated visual acuity improvement is unknown, but none of the patients treated thus far have lost acuity in the treated eye to the extent that this can be assessed within the limits of the testing method.

2. To determine that the donor tissue transplanted into the subretinal space will not cause harm to the host eye, the health of the retina will be assessed by clinical examination, fluorescein angiography, and the fellow eye will be examined to rule out sympathetic ophthalmia. Immediately prior to the implantation, the fluid surrounding the donor tissue will be sampled and later tested for sterility, mycoplasma, and endotoxins.

3. To confirm that the donor tissue will not provoke a rejection response in the host. A rejection response will be identified by retinal leaking surrounding the graft with staining on fluorescein and the presence of inflammation in the area of the graft. Chronic rejection would be recognized on the clinical examination by scar tissue formation in the parenchyma of the transplant.

II. DESCRIPTION OF DEVICE

Sheets of human fetal neural retina with its retinal pigment epithelium will be placed beneath the retina with the implantation instrument.

Obviously, the device is the implantation instrument and the fetal donor tissue is a biological tissue and not a device. Because of fetal tissue transplantation being under FDA supervision, the device and fetal donor tissue will be considered under the same IND number, even though the tissue is not per se a device.

III. INTRODUCTION:

The long-term goal of this proposal is to show that retinal transplantation can help to prevent blindness and to restore eyesight.

"Fetal retinal cell transplantation" includes transplantation of fetal neural retina (that will develop photoreceptors) and/or fetal retinal pigment epithelium (RPE) cells. "Retinal pigment

cell transplantation" means only transplantation of RPE cells. RPE can be "cografted" with the neuronal retina. This means that the donor RPE and the retina are not separated.

A considerable part of the American population is afflicted with incurable retinal diseases (such as macular degeneration (ARMD) [3,65] . In this disease, blindness is due to specific degeneration of photoreceptors and/or RPE even though the neural retina that connects to the brain can still remain relatively intact [31,41]. If the diseased photoreceptors and/or RPE can be replaced and the new cells can connect to the functional part of the host retina, a degenerated retina might be repaired and eyesight restored. There is now clear evidence that transplanted fetal neurosensory retina can re-establish connections with the residual neural network [53]. Synapses between the transplant and host have been demonstrated, but the physiological function of these synapses is unknown [51]. Several publications indicate that the transplant takes part in the beneficial effects on vision [46,57,62]. In addition, the transplanted tissue might exert a positive rescue effect on the recipient's retina, as has been shown in animal experiments *in vitro* and *in vivo* [43].

Advantages of fetal donor tissue

There are many reasons why we have chosen to use fetal donor cells - and not adult donor cells - for this study. The fetal cells have a high capacity to sprout processes, and to produce trophic substances that will aid host and transplant cells to establish contacts. Fetal cells can multiply, so that the transplant can grow to cover a larger area. Fetal transplants of retinal aggregates in nude rats can grow larger the younger the donor age [4]. Fetal cells can overcome the trauma of transplantation much easier than adult cells because fetal retinal cells do not depend as heavily on oxygen as adult cells [61]. Fetal retinal tissue is likely less immunogenic than adult tissue because it contains less microglia than older tissue [11,44].

Retinal transplant immunology

The subretinal space is regarded as an immunological privileged site [56] so that there is a reduced probability of rejection of allografts of fetal tissue. The neural retina is non-immunogenic but the RPE and the microglial cells in the donor retina are immunogenic [39,63]. In spite of the potential for rejection based on the microglia in the donor retina, our hypothesis is that rejection will probably not happen because of the immunological privileged site of the subretinal space. So far, our hypothesis has been confirmed in our results with patients [46,47].

Most of the microglial cells are associated with blood vessels and migrate postnatally into the rat retina [11] and from 16 weeks gestation into the human retina [44]. The number of immunogenic microglial cells in fetal rat retina is much lower than in postnatal retina [11]. Therefore, it is likely that fetal retina is less immunogenic than postnatal retina because fetal retina still lacks inner retinal vessels. However, nobody has tested it. In our model, we have seen stable transplants in rats 6 to 10 months after surgery. This indicates that allogeneic retinal sheet transplants can be tolerated in the subretinal space of rats with retinal degeneration.

Summary of Prior Investigations

Retinal transplantation studies have involved either RPE cells (review: [37,38]) or cells of the neural retina (review: [5,7]).

Transplantation of RPE cells is aimed at delaying retinal degeneration. Several groups have shown that transplantation of healthy RPE cells can rescue photoreceptors – that would

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otherwise degenerate – in an animal model of RPE dystrophy [27,35,36]. The rescue effect is related to the age of the donor cells: only young RPE cells support long-term survival [54,55].

Relatively few research groups have investigated transplantation of neural retinal cells (including photoreceptors) to the retina (review: [7]).

Our group has focused on transplantation of intact sheets of fetal retina, in contrast to disrupted or dissociated retinal cells**.** Such transplants can develop layers as in a normal retina with photoreceptor outer segments in contact with the host pigment epithelium [51]. The transplant photoreceptors express several proteins that are important for the phototransduction process that transform light into electrical signals. Some of these phototransduction proteins migrate in the photoreceptors depending on whether it is light or dark. This also occurs in transplant photoreceptors indicating that they can function normally [52]. In RCS rats and transgenic rats with retinal degeneration, sheet transplants can restore light sensitivity in an area of the superior colliculus that topographically corresponds to the placement of the transplant in the retina [49,58,64]. Transplants can also delay the deterioration of visual acuity in retinal degenerate rats as shown by optokinetic testing [57].

We have also introduced the immunodeficient athymic rat for interspecies retinal transplantation, in which human retinal transplants are not rejected [4,6]. Human fetal retinal transplants in rats develop all cell types according to the normal human developmental time table.[4,9,50]. We are the only team that has systemically studied long-term transplants derived from human fetal retinas as a model of retinal development [6]. Retinal tissues from human embryos of 8-16 weeks gestational age have been routinely dissected and used for transplantation to nude rats [4,6,9,50].

In most retinal diseases, the patients need both photoreceptors and RPE. Therefore, we have developed a procedure to transplant both tissues together [6] which can develop to morphologically resemble a normal retina [6,8]. Such transplants have the potential to benefit retinal diseases with dysfunctional RPE and photoreceptors such as in age-related macular degeneration.

Fetal tissue transplanted in humans

A) Fetal neural tissue transplanted to the brain

This field of research has evolved so rapidly in the last years that it is impossible to give an approximate number of subjects involved. Human fetal tissue transplantation has been aimed at a wide range of disorders, e.g., diabetes (fetal pancreas transplants), hematopoietic disorders (fetal liver or thymus transplants), and neurological disorders (especially Parkinson's disease). In clinical trials with Parkinson patients, fetal dopaminergic transplants have been able to reduce the symptoms of this incurable disease (reviews: [21,48]).

B) Fetal tissue transplanted to the eye

Multiple authors have reported RPE-only transplants in humans with varying degrees of rejection (see below), but at this time, this issue is not resolved. It is very likely that donor and recipients are not matched in Class I and Class II major histocompatibility complex (MHC) antigens. In our clinical trials with cografts of fetal RPE sheets together with neural retina, no rejection has been observed. The donor tissue and the recipients are tissue typed for Class I and Class II MHCs. Recipient blood is tested for antibodies to the MHC antigens to test whether an immune response occurs.

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The success of RPE transplants in RCS rats (see previous section "Summary of Prior Investigations") has led to clinical trials in ARMD patients by a team in Sweden in collaboration with Columbia University, NY [2] and in the U.S. [62]. The results were mixed, rejection was observed depending on the status of retinal degeneration, the presence of an intact blood brain barrier, and immunosuppression [20]. RPE transplants have been done in two patients with RP. These patients experienced improved performance on visual field testing [30].

To overcome the rejection problems with allogeneic RPE, different groups have performed autologous transplants of adult RPE cells [15] and iris pigment epithelial (IPE) cells [1,59], mostly to patients with "wet" age-related macular degeneration (ARMD). Improvements in visual acuity (subjective) were reported.

When photoreceptors are irreversibly lost, transplantation of RPE cells cannot be of help because there is nothing to rescue (review: [5]). Fourteen RP patients in India [19], and eight patients with RP and one patient with ARMD in the U.S. received aggregate retinal transplants [26]. Ten patients received adult photoreceptor sheet transplants [13,29]. These experiments have shown no clinical signs of rejection, but also no improvement in vision. However, the presence of subclinically evident graft rejection cannot be excluded.

IV. EXPERIMENTAL DATA:

The uniqueness of our approach is to transplant intact sheets of human fetal retina alone or together with its RPE. In previous clinical trials with retina-only transplants to four RP patients performed by our group, transient functional improvement was observed as measured by mfERG in one patient who received an intact-sheet of fetal retina implanted into the subretinal space [45]. After FDA approval (BB-IND number #8354 about clinical retinal transplantation, Principal Investigator Norman D. Radtke), we have transplanted co-grafted sheets of fetal retina together with its RPE in 5 RP patients with light perception or no light perception [47]. No adverse effects but also no vision improvement was noted. After these 5 patients, the FDA was satisfied with the safety of the procedure, and allowed us to transplant patients with vision of 20/800 in one eye or worse.

An RP patient transplanted in February 2002 with pre-operative vision of 20/800 improved her vision to 20/160 at 1 year post-op and remained stable at 20/200 at 2 years post-op whereas the right non-surgery eye remained unchanged at 20/400. Improvements were also observed independently in another eye hospital by a scanning laser ophthalmoscope (SLO) test, from 20/270 at 9 months to 20/84 at 2 years and 3 months after surgery [46]. This means that the patient is now able to read and handle e-mail from a computer screen, using a magnification glass. After this patient, the FDA allowed us to use patients with 20/200 vision.

The fixation of this patient at 9 months was a bit unclear but became much more defined and significant after 1 and 2 years. The SLO testing at 9 months showed that fixation was unsteady and involved the nasal edge of the transplant as well as the retina nasal and immediately adjacent to the transplant. At 1 year 3 months, and 2 years 3 months, after transplantation the fixation was similar in both tests, and appeared to be concentrated over the nasal edge of the transplant. The rescue effect versus synaptic connection effect is not resolved. Fixation issues are a short coming with the SLO.

In addition, one ARMD patient (surgery March 2004) improved from 20/400 to 20/240 at 6 months. Further tests are pending. With SLO testing at 6 months, the fixation was over the pigmented transplant area. This means that the patient is using the transplant area.

The SLO at 6 months showed less scatter than preoperatively. These early findings are encouraging but we need confirmation from long term follow-up studies. Two other RP patients with transplant surgery in June 2003 and February 2004 remained unchanged.

V. PATHOGENESIS OF MACULAR DEGENERATION:

Our approach will mainly focus on dry age-related macular degeneration. In age related macular degeneration (ARMD), the etiology is basically unknown although evidence suggests certain forms are inherited [3,60,65]. Regardless of the cause, severe changes occur in the RPE cells and Bruch's membrane, eventually leading to local atrophy of the RPE layer and subsequent degeneration of the photoreceptors [18,22].

Symptoms of wet and dry macular degeneration include:

- A change in vision, usually a sudden blurring in one eye
- Distortion of vision, where straight lines appear crooked in the affected eye
- A blind spot appearing in the vision of the affected eye, where things seem to disappear when looked at centrally
- A change in the size of things, with objects appearing to be smaller or larger than with the other eye

"Dry macular degeneration": This form of macular degeneration consists of slow deterioration of the retina. Deposits form under the retinal pigment epithelium (RPE) called "drusen". Drusen may block nutrition from reaching the retina from a highly vascular layer under the retina called the "choriocapillaris". The choriocapillaris is a capillary network outside RPE that nourishes the outer layers of the retina while the inner retinal layers are supplied by retinal blood vessels coming from the optic disc. Over time, the RPE and the outer retina atrophy, or degenerate, over these areas of drusen, and a spotty loss of vision occurs. If more and more of these atrophic areas form and merge together, the macula can take on a moth-eaten appearance, with progressive loss of vision [23]. This usually occurs over a period of many years. Since macular degeneration affects the RPE cells which form the outer blood-retinal barrier, degeneration of RPE can lead to loss of the immune privilege of the subretinal space.

A subgroup of dry macular degeneration, central areolar choroidal and retinal pigment epithelial dystrophy, is a hereditary macular disease characterized by bilateral, symmetric, and well-circumscribed, solitary area in the macula with choroidal and retinal pigment epithelial atrophy [17]. There is a bilateral, usually symmetric, bull's-eye pattern of macular dystrophy with a sharp border of underlying large or middle choroidal vessels which are usually unassociated with any surrounding lesions. Fluorescein angiography reveals a transmission window defect due to retinal pigment epithelial atrophy with remaining choriocapillaris intermingled with a hypofluorescent area of choriocapillaris atrophy. Loss of visual acuity is caused by progressive atrophy of both the retinal pigment epithelium and choriocapillaris [17]. There also appears to be an ARG-142-TRP mutation in the peripherin-RDS gene [24]. The earliest degeneration here appears to affect the photoreceptors first and then later RPE and choriocapillaris.

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VI. THERAPEUTIC APPROACHES TO MACULAR DEGENERATION:

Dry age-related macular degeneration therapies have dealt with vitamin and antioxidant treatments. The National Eye Institute has sponsored the AREDS (The Age Related Eye Disease Study) to test the effect of antioxidants and zinc on the progression of age-related macular degeneration [10]. Experimental work on membrane differential filtration is available in Europe and test centers in the U.S.

Our approach will focus on dry age-related macular degeneration. Replacement of degenerating cells by retinal pigment epithelium together with neural retina may offer success in restoring the atrophying neural retina, the pigment epithelium and part of the choroid.

VII. HYPOTHESIS TO BE TESTED:

1. Retinal transplantation by co-grafting sheets of human fetal neural retina with RPE is a safe procedure and will not have any adverse effect on the host eyes when transplanted into the subretinal space.
2. The intact sheet of transplanted human fetal neural retina with its RPE will not provoke a rejection response in the host.

VIII. DESIGN OF THE STUDY:

The participating surgeon will be Dr. Norman D. Radtke. The participating persons obtaining fetal retinal and RPE tissues will be Dr. Robert B. Aramant and Dr. Magdalene J. Seiler. Diane J. Pidwell and Dr. Heywood Petry will participate as consultants during this project for immunology and electrophysiology testing respectively.

Before surgery, the recipient has to sign a statement that he/she is aware about the source of the donor tissue (see Research Subject Information and Consent Form), and a consent form (see Research Subject Information and Consent Form) in which the study is explained.

Ten patients with ARMD and a vision of 20/200 or worse in one eye will be selected for the study and will undergo an operation to implant fetal neural retina with RPE under the retina. Two complete examinations will be performed at least 30 days apart to confirm the visual acuity, and only one eye will be subject to surgery.

The donor tissue is taken up in a custom-made instrument with a flat, curved nozzle so that the tissue will be maintained in the correct orientation and polarity in the subretinal space of the patient's eye. (U.S. patents # 5,941,250: "Retinal tissue implantation method"; # 6,159,218: "Retinal tissue implantation tool"; # 6,156,042: "Retinal tissue implantation instrument")

A standard three-port vitrectomy is used prior to inserting the instrument into the eye and into the subretinal space. The implantation instrument with the double sheet of fetal neural retina with its retinal pigment epithelium is inserted into the eye beneath the retina. The tissue is then released from the instrument, placing it into the subretinal space, after which the instrument is withdrawn from the eye. In the treatment of patients with "dry" macular degeneration, the three-port vitrectomy will be performed. The vascular net will be removed and then the patient will receive the co-graft of fetal neural retina and retinal pigment epithelium.

For the first seven days postoperatively the patient will receive oxygen through a nasal cannula at 4 liters per minute from a portable tank. They will have a dosimeter to ensure oxygen saturation is at 90% or greater.

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The rationale for the oxygen treatment is as follows: Our most visually improved patient aspirated postoperatively and was on a ventilator for one week. Did oxygen play a role in her improved visual acuity? We will never know. The literature suggests oxygen therapy helps diabetes (Nguyen et al. 2004, Supplemental oxygen improves diabetic macular edema: a pilot study; IOVS 45:617-624). Further, it has been shown that oxygen treatment,- even with a delay - reduces the detrimental effects of retinal detachment, i.e. it prevented cone death, and reduces gliosis of Mueller cells (Sakai et al. 2001, The ability of hyperoxia to limit the effects of experimental detachment in cone-dominated retina, IOVS 42: 3264-73; Lewis et al., ARVO 2003; abstract 2952). This indicates that the recovery after surgical trauma is faster with oxygen treatment. - Because it is non invasive and can play a beneficial role, the FDA and IRB and Norton Healthcare Research Office has approved our postoperative use of oxygen.

Postoperatively, the patients will be evaluated at one week, one month, three months, six months, nine months and twelve months for follow-up (F/U).

1-wk F/U	1-mo F/U	3-mos F/U	6-mos F/U	9-mos F/U	1-yr F/U
2-15 days	16-60 days	61-120 days	121-270 days	271-364 days	365-455 days

The following tests will be performed:

1) Visual acuity will be measured using the ETDRS (Early Treatment Diabetic Retinopathy Study) visual acuity standard. Before surgery, complete examinations will be performed at least 30 days apart to confirm the visual acuity.
2) Parameters of visual function will be investigated by microperimetry testing of contrast sensitivity and the visual field (Goldmann) (e.g., [25,33,42]).

The preoperative and postoperative testing will be done on patients with the NIDEC MP1 microperimetry testing system and not the SLO. Microperimetry which is used to test light sensitivity is better for several reasons. First, the examiner can see the fixation point directly. A cluster of blue dots is seen where the patient is fixating. Second, it allows the examiner to do a separate fixation test which can be run in less than a minute. Minimizing patient fatigue during testing increases accuracy of the test. Third, the microperimetry has color photographs and actual fundus tracking which the SLO did not. Fourth, the microperimetry has automated perimetry which the SLO could not do. This increases the repeatability of patient to patient testing at any duration interval. All that is needed is a retinal landmark and the repeat testing spot can be obtained within 0.1 of one degree from the previous testing spot. In addition, there is a library of different types of testing patterns that can be used and, for low vision type situations, as it applies to our patients, there is a feedback training module to train patients to change the preferred retinal focus. The SLO is currently no longer produced. The SLO has poor reliability and is very expensive to maintain.

3) Intraocular pressure measurement.
4) Slit lamp biomicroscopy for (a) conjunctival reaction, (b) corneal clarity, (c) anterior chamber depth and clarity, (d) iris and pupillary appearance and lens evaluation, and (e) indirect ophthalmoscopy in examining the retinal fundus.
5) Fundus photographs and fluorescein angiography studies will be taken preoperatively and at each follow-up visit.

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The amount of time required for the follow-up visit will be ca. three hours at each visit postoperatively. It is expected that six postoperative visits in one year will be required.

The criteria for success will be:

1. The donor tissue does not provoke a rejection response in the host or cause an infection. A rejection response will be identified by leaking at the site of the graft with staining on the fluorescein and presence of inflammation in the area of the graft. The presence of inflammation is defined as seeing white edematous retina with fluid over the area of the transplant. This clinical picture would coincide with the hyperfluorescent areas seen as leakage on fluorescein. Scar tissue formation in the parenchyma of the transplant is defined as seeing fibrotic tissue in the retinal pigment epithelium and neurosensory retina in the area of the transplant.

Chronic rejection will be recognized in the clinical examination by scar tissue formation in the parenchyma of the transplant.

2. To determine that the implantation procedure will not have an adverse effect on the host eye. This is obtained by assessing the health of the retina by clinical examination, fluorescein angiography, and to rule out sympathetic ophthalmia in the fellow eye. Immediately prior to implantation, samples of the fluid surrounding the donor tissue will be taken and tested later for sterility, mycoplasma, and endotoxins.

IX. METHODS USED TO IDENTIFY, RECRUIT, AND SELECT SUBJECTS:

Sample size will be ten patients per year with Age Related Macular Degeneration (ARMD). Recruitment of subjects to undergo transplantation will be from the clinical vitreoretinal practice of Dr. N. D. Radtke. Randomization is not an issue in this study as only patients who meet the criteria for macular degeneration loss of vision will be used.

Criteria for selection of patients:

Inclusion Criteria:

- The subject must have decreased central visual acuity of 20/200 or worse in one eye by ETDRS vision testing for a duration of at least one year in the operated eye and have the diagnosis of age related macular degeneration; vision in the nonoperated eye must be better than the operated eye. Vision in the operated eye cannot be better than 20/200.
- Subject is older than 55 years of age
- Patient is willing to return for follow-up visits
- Patient has signed informed consent for retinal transplantation
- Patient has undergone microperimetry and Goldmann visual field testing.

Exclusion Criteria:

- Patient having a central visual acuity of better than 20/200 in one eye by ETDRS or vision worse than 20/200 in one eye by ETDRS for a duration of less than one year
- Unwilling to sign an informed consent
- Patient under 55 years of age
- Patient having medical problems that are contraindicatory for short-term anesthesia

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- Patient unwilling to return for follow-up visits
- The patient has been determined to be pregnant by patient history or by pregnancy testing in women of childbearing potential
- Features of any condition other than age-related macular degeneration in the study eye (such as pathologic myopia or presumed ocular histoplasmosis) associated with choroidal neovascularization
- Any significant ocular disease (other than choroidal neovascularization) that has compromised or could compromise vision in the study eye and confound analysis of the primary outcome.
- Inability to obtain photographs to document choroidal neovascularization, including difficulty with venous access
- History of choroidal neovascularization in the study eye
- Participating in another ophthalmic clinical trial or use of any other investigational new drugs within 12 weeks before the start of study treatment
- Prior photodynamic therapy or Macugen therapy for choroidal neovascularization
- Patient who has a history of uveitis, Coat's disease, diabetic retinopathy, glaucoma, or a cataract that prevents visualization of the posterior pole

X. POTENTIAL RISKS:

This research procedure might have unwanted side effects for different reasons.

The known and potential risks for this trial involve standard anesthesia hazards, general and/or local. The surgery would occur under retrobulbar and/or general anesthesia. Surgical complications could result in blindness and/or loss of the eye.

Adverse effects related to the "experimental pilot trial" surgery are: (1) retinal detachment, (2) vitreous hemorrhage, (3) subretinal hemorrhage and/or subretinal proliferative tissue, (4) endophthalmitis, (5) neovascular glaucoma, (6) corneal epithelial defects, (7) cataracts, (8) diplopia, (9) ptosis, (10) prephthisis or phthisis, or (11) possible complications from anesthesia, allergic reaction or side effects from certain medicines.

The adverse effects related to transplantation include (1) the knowledge that the tissue was obtained from an induced abortion may cause psychological stress. (2) There is a possible risk of transmission of viral infection, such as AIDS or hepatitis, from the transplanted tissue. However, blood of the woman having the abortion that has donated the fetal tissue will have been tested for the presence of antibodies against human immunodeficiency virus (HIV, the virus that causes **AIDS), hepatitis (Hepatitis B Surface Antigen, Hepatitis C Virus Antibody) and syphilis.** To reduce the risk for virus transmission, aborted tissue from women positive for the above mentioned viruses is excluded. In addition, any donors with any risk factors in their history, such as multiple sex partners, drug use, jail time etc. are excluded (see **Behavior and Risk Assessment Form in Donor Consent)**. (3) There is a low possibility of an immunological reaction to the donor tissue. The immunologic reaction to the donor tissue is to be studied. Because we feel there is a low probability of an immunological response to the donor tissue, immunosuppression, either systemic or local, will not be used. Therefore, there is a potential risk of immune rejection of the transplanted tissue.

Sympathetic ophthalmia is a possibility, but the prevalence of sympathetic ophthalmia is difficult to measure because it has always been a relatively rare disease; as a result of improvements in modern surgical and medical treatment it has become even more uncommon. Kilmartin et al. reported in 2000 that the incidence of sympathetic ophthalmia after vitrectomy has increased and is more than twice that of the previously reported 0.06% risk. (Kilmartin et al., Br J Ophthal 84:448, 2000) Vote et al reported in 2004 that after repeated vitreoretinal surgery the risk of sympathetic ophthalmia is approximately 1/800 (=0.125%). Prompt and effective management with systemic immunosuppressive agents permits good control of this disease with retention of good visual acuity (Vote et al., Clin Exp Ophthal 32(5):542, 2004).

The donors will not require an extra blood drawing procedure since the donor sample will come from the same blood sampling procedure that the Women's Surgical Center does for blood typing, antibody screens and complete blood cell count. The extra amount needed for the testing is 10 cc. This poses no additional risk for the donor because the blood drawing has already been done prior to the abortion procedure.

Pregnant and nursing women are excluded as recipients from the study. Pregnancy testing will be done in women of childbearing potential.

It is necessary to be aware that there are additional risks in this procedure that are currently unforeseeable.

XI. POTENTIAL RECIPIENT BENEFITS:

Potential benefits to the age related macular degeneration patients are that vision may be preserved or improved.

Subjects will be informed of any new findings that may influence their willingness to continue their participation in this study. This would apply to findings that have become available after they have signed the consent form but before transplantation.

XII. MONITORING UNANTICIPATED ADVERSE EVENTS:

The principal investigator will monitor the progress of the patients.

All adverse reactions, such as chronic elevation of pressure, intraocular infection and/or delayed wound healing, with or without wound leak sympathetic ophthalmia, will be reported within ten days to the local IRB.

XIII. COMPENSATION COSTS:

The subjects will not be compensated for participating in this surgical procedure. The responsibility for the costs of physician, surgery, and hospital will be covered by funds provided by our anonymous sponsor. Travel for follow-up visits will be at the patient's expense.

XIV. FUNDING:

Funding for this clinical trial has been covered by an anonymous sponsor and the Foundation Fighting Blindness is administering the funds. The latter organization is a non-profit 501-C3 health organization. Its purpose is to support retinal research. It has supported projects at the University of Louisville in the Departments of Anatomy and Ophthalmology since 1983.

XV. CONFIDENTIALITY:

All records regarding the individual patients involved will be maintained in a locked cabinet within the office of Dr. Norman D. Radtke, 240 Audubon Medical Plaza, Louisville, Kentucky. Routine medical confidentiality will apply to all trial records. Use and/or publication of trial results will not involve the use and/or release of patient identities. There is the possibility that the Food and Drug Administration and the Human Studies Committee at Norton Audubon Hospital may wish to inspect the records.

XVI. FETAL RETINAL TISSUE:

The research will be conducted in accordance with the prohibitions regarding the use of human fetal tissue described in Public Law 103-43, section 498B. There will be no compensation for the donor. The research will be conducted in accordance with any applicable State or local laws.

Persons engaged in the proposed studies will have no part in: (i) any decisions as to the timing, method, and procedures used to terminate the pregnancy, and (ii) determining the viability of the fetus at the termination of the pregnancy. The proposed studies will not introduce any procedural changes which may cause greater than minimal risk to the fetus or the pregnant woman into the procedure for terminating the pregnancy.

The fetal tissues used in this study will be derived from dead fetuses at the first 9-16 weeks of pregnancy obtained from elective abortions. The tissue will be harvested at the EMW Women's Surgical Center at Louisville.

After the woman seeking abortion has signed the formal papers for this procedure in the presence of an Attending Counselor, only then will she be asked to donate the aborted tissue and sign the consent form (see Donor Research Subject Information and Consent Form). The decision for an abortion and the signing of the consent form will remain completely independent of each other. The consent form is signed in the presence of an Attending Counselor, and not of the Attending Physician because the Attending Physician is only present for the actual abortion procedure. Before signing, the necessity to give a blood sample (see below) is also discussed. The cost for the blood test will be paid for by the investigator. The Medical History and Behavior Risk Assessment form is completed to assist in excluding different diseases (see Donor Research Subject Information and Consent Form).

Even after signing the consent form, the donor can retract her decision to donate the tissue any time. There will be no benefit to the donor, monetary or otherwise. The donor will remain anonymous to the investigators. There will be absolutely no change in the surgical procedure as a result of the participation in the project.

The attending physician will sign the consent form and will make the determination whether the fetus is dead. Suction abortion procedure will be used that macerates the fetal tissue. The attending counselor and the attending physician will have no connection with the proposed studies (see Donor Research Subject Information and Consent Form).

In the consent form, the donor is also asked to give a blood sample to determine that the tissue is safe for transplantation. The necessity to give a blood sample will be explained to the donor by the Attending Counselor at the same time as she is asked to donate the tissue.

Only tissues that are free from contamination will be considered. A blood sample of the donor will be tested for the presence of antibodies against human immunodeficiency virus (HIV) and hepatitis (HAV, HBV, HCV), HLA complete typing, RPR, and ABO testing. To reduce the

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risk for virus transmission, aborted tissue from women positive for the above mentioned viruses is excluded.

The donors will not require an extra blood drawing procedure since the donor sample will come from the same blood sampling procedure that the Women's Surgical Center does for blood typing, antibody screens and complete blood cell count. The extra amount needed for the testing is 10 cc. This poses no additional risk for the donor because the blood drawing has already been done prior to the abortion procedure.

In addition, blood- and tissue typing will be done with a sample of the fetal tissue and the recipient's blood to observe whether donor and recipient are matched in the MHC-antigens. We have done this for the last four patients and donors. No matching in any MHC antigens was observed. Even though there is no blood sample from the fetus, the tissue that was transplanted came from a large section, a piece of which was used for the tissue typing of the donor. The typing of this donor tissue was done by extracting the DNA from the fetal tissue using a QIAGEN DNA extraction kit (Pel Freeze, Brown Deer, Wisconsin) which is specific for tissue and different from the one used for blood typing. The kit allows us to identify specific sequences in the MHC DNA and that allows us to identify the donor tissue MHC sequences.

The following is the **procedure of handling fetal donor tissue**:
Sterile procedures are used at all times including the use of sterile surgical gloves, sterile containers, sterile filtered solutions and sterilized instruments. When possible, instruments, transfer tools, etc., are autoclaved before use. Instruments that cannot be autoclaved, such as the handle of the transfer tool, are sterilized by the Sterrad procedure. The sterilization with the Sterrad procedure consists of a sterilant hydrogen peroxide and gas plasma, at 10-40 degrees centigrade for 75 minutes. This is a standard common procedure at Norton Audubon Hospital. Gloves are changed regularly. Waste tissue is treated as biohazard waste.

1. The tissue is obtained by a sterile abortion procedure, placed into a sterile container and refrigerated. The tissue might have to stay in the refrigerator (4°C) for 1 hour depending on when our assistant, Mary Hilliard, can come and pick it up.
2. The tissue is transported in this container on ice to the Norton Audubon Hospital.
3. In a laminar flow hood in the lab, extraocular tissues are removed, the eyes are dissected from surrounding tissue, and are placed into a sterile plastic 6-well dish, containing cold sterile Hibernate E medium (Supplier Specialty media, Philipsburg, NY) with B-27 supplements (cat. # 17504-044) (Gibco BRL, Baltimore, MD).
   In the previous clinical trials, the time from step 1 (abortion) to step 4 (placement in hibernation medium) ranged between 30 and 90 minutes.
4. The retinal tissue is dissected aseptically in a sterile 35 mm dish on a metal cold plate (containing a small ice tray) under a dissection microscope with fiber optics. The blower of the laminar flow hood is constantly left on, and decontaminated with UV light when not in use.
5. Dissection starts at 1 to 2 hours after abortion. During dissection, the tissue is transferred several times into a fresh dish with Hibernate E medium. Two alternative procedures are used:
   a) *dissection of retina only:* The retina is dissected free from surrounding tissues (sclera, choroid, RPE, cornea, lens and blood vessel layer in vitreous). The dissection of retina only

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takes ca. 15-25 minutes.

b) *dissection of retina with RPE:* First, the back of the eye is dissected free from extraocular muscles and connective tissues. Then, the eye is incubated for 30 minutes in sterile dispase (Collaborative Biomedical Products, cat. # 354235) at 37°C in a humidified incubator. After 3 washes with hibernate E medium, the sclera is removed. The dissection of retina with RPE in the lab takes ca. 45-70 minutes, including the incubation time in dispase.

6. The tissue is transported to the surgery room and kept on ice in Hibernate E medium.
7. In the surgery room, in a sterile environment, a **second** dissection microscope with its fiber optics has been decontaminated and covered with sterile plastic covers according to standard surgery procedures.
8. The fine dissection of the RPE (removal of choroid) takes place in the surgery room. This dissection takes ca. 20 – 45 minutes, depending on the size of the eye. Rectangular pieces of retina with or without RPE (1.5 – 2 mm width, 2 – 3.5 mm length) are cut with sterile microscissors. Notes are made regarding the orientation and retinal quadrant from which the pieces are cut.
9. The piece is loaded into the implantation tool, together with a small spacer (same width, but only 0.2 – 0.4 mm length) close to the mandrel, and handed to the surgeon.
10. Fluid surrounding the tissue is sent for microbial testing at the hospital; mycoplasma and endotoxin testing will be done at Focus Technologies in Cypress, California.
    In the previous clinical trials, the time from abortion to implantation ranged between 3 and 30 hours.

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