

A Discussion With
Dr. Norman D. Radtke, M.D., P.S.C.

September 11-18, 2004

Topic: Retinal Transplantation Update

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Background

This background information is summarized from the web site of the Retina Vitreous Resource Center. For more details, visit www.rvrc.com.

The Research

A team of doctors led by Norman D. Radtke, M.D. (University of Louisville) has launched a new research program which involves the transplantation of intact sheets of both immature (fetal) neural retina cells and retinal pigment epithelial (RPE) cells in the sub-retinal space of patients with dry macular degeneration (AMD), retinitis pigmentosa (RP), and retinal dystrophies like Stargardt's disease.

Previous work on rodent models has shown excellent results from the transplantation of the neuroretina and the RPE cells, and it has shown a modicum of success in two patients with RP, who were transplanted with only one layer. The new experimentation (co-grafting of both layers) is now in Phase I and II with FDA supervision and the Human Studies Committee's approval.

There is currently no treatment available that can reverse the degenerative process and restore vision. There is, however, hope for patients who still have intact retinal ganglion [nerve] cells, and the research team can now replace degenerated photoreceptors and retinal pigment epithelial cells, which gives hope for restoration function.

According to Dr. Radtke, "By transplanting an intact sheet of neuroretina and retinal pigment epithelium, we can now repair an area of damaged retina resembling a normal retina. This retina functions like a normal piece of retina. It has connections to the brain in animals like a normal piece of retina would, and there has been some function seen by stimulating the blind retina in rats and recoding electric function in the brain. This holds tremendous potential for the future, and we are using benchmark research with parallel clinical trials to improve the results as new factors are uncovered from our basic research. These are the first steps, and we hope very successful ones, for patients who have RP and dry AMD."

Subjects are being sought for the trials. Under current restrictions, vision must be no better than 20/800 in one eye. For more information about enrolling in the trials, contact:

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Dr. Norman Radtke



Norman D. Radtke, M.D., P.S.C., is fully trained to care for all medical and surgical problems related to the retina and vitreous. He is certified by the American Board of Ophthalmology and is a Fellow of the American college of Surgeons. Dr. Radtke is internationally recognized for his research, teaching, and lecturing on vitreous surgery to ophthalmologists in the United States and abroad. He is a Clinical Professor in the Department of Ophthalmology at the University of Louisville, and he is a leading authority on diabetes of the eye. He is actively involved in clinical and basic science of diabetic research, with particular emphasis on problems relating to the eye.

(For more information about Dr. Radtke and to read a discussion with him from 2001, select [this link](#). Use your back button to return here.)

The Research Team and Sponsors

The team is led by Norman Radtke, M.D. Team members are Robert B. Aramant, Ph.D., Magdalene J. Seiler, Ph.D., Heywood M. Petry, Ph.D., and Diane Pidwell, Ph.D. The research is supported by The Murray Foundation, Inc., Vitreoretinal Research Foundation, Kentucky Lions Eye Foundation, Research to Prevent Blindness, and an anonymous donor. N. D. Radtke, M. J. Seiler, and R. B. Aramant have a proprietary interest in the implantation instrument and procedure.

Discussion

Cliff: I have several questions regarding retinal transplants:

1. Since your procedure uses fetal stem cells in the transplant process, would the regenerated tissue be immune from genetic defects found in the original retinal cells in those of us that have genetically diseased eyes?
2. I note that you've had fair success in candidates as outlined on your web site. It would seem to me that more complete recovery (to normal vision) might be possible for those who had this procedure done earlier rather than waiting till it got to the point of being 20/800. What is the prognosis for being able to perform a procedure like this for someone who was (a) diagnosed with a degenerative disease but (b) still in the early stages (say between 20/30 and 20/50)?
3. I've seen mention of multiple "layers" being involved in retinal transplantation. Can you please explain what this is and the significance of doing a multi layer transplant would be?

Thank you for your research. I have been looking for these developments for over 5 years now.

Dr. Radtke: This is an answer to your first question regarding whether or not the regenerated tissue would be immune to genetic defects found in the original retinal cells in people who have had a genetically diseased eye. The answer is that, at this point, we do not know. It would take some time for those to probably cause problems in the transplanted tissue, and at this point, we simply do not have an answer for your question; but it is an excellent one.

Your second question is one that we are continually trying to address, and we are doing the transplant in patients who have less severely affected eyes. We have gone from light perception in both eyes to 20/400 in one eye, and we hope to go to 20/200 in one eye. This depends upon the FDA's review of our study and their safety assessment and possible efficacy. At the present time, our patients will be 20/400, but we hope that very soon we will be able to have this done on patients that are 20/200. Whether or not we will be able to do the procedure in earlier stages, for instance between 20/30 and 20/50, is yet to be determined.

Regarding your third question about the layers, in the degeneration of retinitis pigmentosa and in macular degeneration the two layers that are regenerating are the photoreceptors and the retinal pigment epithelium. We are transplanting both layers, and we are the only ones who have been able to do this successfully, because we have an instrument that can put both the retinal pigment epithelium and the neural retinal together in the eye. Most places are just using

the pigment epithelium because it is too difficult to adhere the neural retina to the retinal pigment epithelium where the transplant is done. The significance of this is that we are replacing both layers that are degenerating, and these hook up to the layers that are presently in the eye but are functioning, such as the bipolar cells and probably the ganglion cells. We have shown in animals that the hookups do occur and that you can get connections, as well as having a rescue effect from the cells around them receiving some of the factors that are produced by the new transplanted cells.

Leigh: I have a few questions regarding this procedure:

1. What are the risks involved?
2. Are there any rejection issues with the transplant?
3. What is the approximate cost for one eye?
4. What are other health, age, or risk requirements for eligibility?

Dr. Radtke: The risks involved are that the patient could lose the eye completely or develop a retinal detachment and possibly develop other problems from the surgery, such as a droopy lid. At this point, we have not had any of these develop, and the patients have not had any adverse effects from the surgery.

About your question regarding the rejection of tissue with the transplant, at this point, we do not see rejection clinically. We have not been able to assess this histologically, because we have not had any eyes to examine histologically. There has been some criticism that this is occurring, but at this point, we cannot say whether or not it is or is not, because we do not have the histology to back up our position either way. We definitely are not seeing any rejection clinically, as this would involve seeing it on fluorescein leaking or in the eye itself with whiteness to the area of the transplant. This has not occurred clinically, so we know it does not occur clinically. It may, however, be occurring histologically.

The cost for transplant for one eye is, at this point, of no consequence for the patient, because it is experimental and is paid for by a benevolent benefactor. The entire expense, both pre-operative and post-operative testing and the surgery and the hospitalization are all covered at this time. However, the patient would have to enter into the protocol. It is not available for use outside of the protocol, and it is under FDA scrutiny.

Other health, age or risk requirements for eligibility is that the patient should not have diabetes or glaucoma. They must be 21 or older and cannot be pregnant. These are basically the high

points for eligibility, and should you be interested, we would be happy to send you the requirements, as it is quite long.

John (from Seattle): Dan has referred to your work in regard to dry MD and RP, but did not mention wet MD. Is it your hope to repair scarring damage resulting from neovascularization or the argon laser? Thanks and best of luck for continued success.

Dr. Radtke: We are doing work with dry macular degeneration and have not mentioned the wet macular degeneration, because at this time we are not conducting transplants in patients with wet macular degeneration. However, down the road, patients who have had membranes removed and are now dry may well benefit from having the pigment epithelium and a neural retinal transplanted. It is not our hope, at this time, to repair scarring damage resulting from neovascularization or Argon laser therapy.

Natalie: Will this not be helpful for those with wet AMD?

Dr. Radtke: This may be helpful for patients who have wet macular degeneration if the nets are removed and then they become dry, and we can transplant the pigment epithelium and neural retina, which is usually removed when the nets are removed in patients with wet macular degeneration. At this time, it is not part of the protocol, but this may be something that we would be doing in the future.

Marian: Thank you for your research into retinal transplants. It is very exciting. Do you have any time line as to when this treatment might be available to those of us who could benefit from it? Will it have to go through FDA trials? If so, how long might that take? Is the procedure patented, or will it be available to all doctors? Many thanks.

Dr. Radtke: The time line as to when this treatment might be available to patients who could benefit from it is probably in the range of five to ten years from now. At this point, we are still in FDA trials. The trials that we are conducting are Phase I and II and again, this is in the range of five to ten years before it becomes clinically acceptable for the general public. The procedure and equipment is patented, but it will be available to all doctors as soon as the FDA approves the procedure.

Maria: Regarding Mishiel, my 11 year old with Stargardt's:

1. Do you foresee this type of treatment as being beneficial to younger patients with Stargardt's in the future?
2. Will the defective genes continue to affect the transplanted cells, or would the transplanted cells essentially replace the defective cells?
3. How much of an improvement in vision is possible to hope for?

Dr. Radtke: We do foresee this type of treatment as being beneficial to younger patients with Stargardts in the future as pigment epithelium and photoreceptor destruction as well. At this point, it is not part of our protocol, but we do hope to include that in the future.

To answer your question about whether the degenerative genes continue to affect the transplanted cells or would the transplanted cells essentially replace the defective cells: We are trying to address this issue, but at this point we do not have the answer. We do not know whether or not the cells can withstand the other influence of the defective genetic cells, but even if they do, it could be re-transplanted in the future. At this point, we do not know the answer to your question. It is an excellent question, and we are addressing this with our research.

We cannot offer any hope for improvement in vision, as the procedure is still experimental. All we can do is relate to you the results of patients that we have had where one patient has gone from 20/800 to 20/250. We can let you read our paper, which is on our website at www.rvrc.com, and goes into detail as to what the improvement of vision has been achieved.

Larry: Do you plan large-scale human trials anytime soon? What are the challenges of large scale human trials?

Dr. Radtke: The challenges of large scale human trials is that, at the present time, we are not in the planning stage for large scale human trials, because we are trying to address the issues of what we would do for such a project. At this time, it is premature to enlist a large number of patients, and the challenges are too numerous to mention. We need to address what would be the best way to conduct this trial in a large number of patients, and, at this point, we are just accumulating that data.

Manish: 1. Does the retina transplant procedure also help to any extent in resolving MD, which damaged the original retina? If not, will this be like a temporary retina that one gets for say the next "n" years until MD damages this one as well? Or will the actual transplant treatment have to wait until a cure is found for MD?

2. Dr. Radtke, you say that your research is one of the first few steps of a very very long climb. Is it possible to summarize the major known problems that you think will be the most time consuming before we have a comprehensive treatment covering a large percentage of the patients? This information will help patients like me understand the importance of the various research studies and discoveries that we hear about these days.

Thanks and all the best for your research.

Dr. Radtke: The retinal transplantation procedure will not help to an extent in resolving dry macular degeneration, except in the area or immediately surrounding the area where the transplant is. We hope to increase the number of pieces that we can put in the eye and also increase the actual area by other techniques. At this time, we hope that actual transplant will replace the damaged retina, and we do not need to wait for a cure for macular degeneration.

The question is a very good one summarizing the major known problems that exist to have a comprehensive treatment covering a large percentage of patients, and this would be either transplanting a large sheet of retina or developing genetic engineering that can replace the damaged cells. At this point, these are all basic research areas, and, like stem cell research, will take a long time to see to fruition.

Anita: Where do you get the tissues for implantation?

Dr. Radtke: The question about where our tissue comes from is in transition. At this time we are using discarded fetuses and have shown that the tissue does work in humans. We are now attempting to obtain tissue from genetically cloned pigs that have no immunological rejection response in humans. This would allow us to obtain the needed tissue for transplantation in humans from animals that would show no rejection in humans. This work is now being pursued, but to date no results are available.

Mindy: 1. Can these same cells be found in the stem cells of stored cord blood of an unaffected sibling, and then be transplanted into other siblings that have Stargardts?

2. Can the stem cells replace degenerated photoreceptor and RPE cells in a 7 year old, and will it restore the vision he's already lost?

3. Can the stem cells be transplanted into the retina of a 4 year old who is positively diagnosed with Stargardts, via blood and DNA analysis, but doesn't show any clinical symptoms at this point?

Thanks so much for your work in this field.

Dr. Radtke: The retinal epithelial and neuroblastic that we are transplanting in patients with macular degeneration, dry macular degeneration and retinitis pigmentosa are fetal cells and are not the same cells that are found in stem cells with stored cord blood. The answer to your question regarding this being transplanted in other siblings that have Stargardt's is that it would not be possible.

At this point, stem cells will not replace degenerative photoreceptor and retinal pigment epithelium cells in a 7 year old, and it will not restore the vision that he has already lost. Stem cell research is still 10-15 years down the road for this kind of thing. Right now we can use these retinal pigment epithelium and neuroblastic cells from fetal tissue.

Stem cells, again, can not be transplanted into the retina of a 4 year old who is positively diagnosed with Stargardt's via blood and DNA analysis. Even though these patients do not show any clinical symptoms at this point and may develop Stargardt's in the future this type of research is very premature and is many, probably 10-15 maybe even 15-20 years down the road.

Shirley: As advised by Dan Roberts, I have read through the information from the web site covering your last question session in 2001. I have what is, I believe, junior MD. Is the Retina transplant programme suitable for this type of condition? I am not a resident of the US. Is your treatment going to be available in the UK at any time? If not, is it possible for a person from another country to visit you?

Thank you for taking my question.

Dr. Radtke: Retinal transplantation may be suitable if you do have macular degeneration. If you want to send us a copy of your medical records from your ophthalmologist regarding your vision and your diagnosis, we would be happy to let you know if you could be a candidate for the protocol.

Even though you are not a resident of the United States, and while our treatment is not available in the United Kingdom, we are doing patients from England, Pakistan and are evaluating a patient from Australia. It is definitely possible for a person from another country to visit us. The problem, however, is that there is a requirement that the patient gets preoperative testing both in San Francisco and in New Jersey, and then we follow the patient postoperatively at day 1, 1 week, 6 weeks, 3 months, 6 months, 9 months and 12 months. These postoperative visits are critical for your enrollment in the protocol, and the testing and must be agreed upon prior to enrollment that you would participate in this. Obviously, it would

be much more difficult for a person out of the country to maintain this commitment, but it is a requirement to do so for the completion of the study. If you would like further information, we would be happy to send you a protocol and consent form.

Paul: With the current patients, there appears to be some evidence of improvement in acuity. Is there any evidence that the field of vision has been impacted?

Dr. Radtke: The central visual acuity area is where the transplant was located, and because of the small size, at this time, there was no expectation for improvement of field of vision. In the future, we hope to put in multiple pieces so that this does occur; but at this time with the preliminary work, the main object is to see if the tissue we put in can essentially improve acuity. We have had one patient and two potential patients showing improvement in the central visual acuity.

Dan (moderator): Dr. Radtke, your participation in this Q&A has been informative, giving us all renewed hope for the future. Your research is important to all of us, and we will continue to follow your progress with great interest. Thank you very much for your time and caring.

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