

# Transcript of a chat session with Dr. Steve Goldberg 8/30/98

*(Edited for clarity and space.)*

**DAN:** Dr. Goldberg will speak on several topics relating to the Foundation Fighting Blindness Conference which was held in Chicago last weekend, and we will periodically open the floor for questions or comments. Steve, thank you for offering to make this presentation to us. The floor is yours.

**DR. GOLDBERG:** Thank you, Dan. I had the pleasure of attending the Foundation Fighting Blindness Conference in Chicago about a week and a half ago. It was my first time there and it was a tremendous experience, although I must say that we had more contact with hotel security than we would have liked. We checked in to the hotel Thursday afternoon and we weren't there more than thirty minutes before we got a call from hotel security asking if everything was alright. It turns out that my two-and-a-half year old was hitting the "emergency" button on the phone! Then at about four in the morning that night (Friday morning) there was a loud commotion just outside our door. It turns out that the people in the room just across the hall apparently were drunk and quite boisterous. The hotel security ended up kicking in the door and escorting them out, with the help of two uniformed Chicago policemen. I can tell you these details because my wife and I were spying through the peephole in the door! Anyway, by the time the conference began a few hours later, I was ready for a change of pace, and the speakers were very enthusiastic and invigorating.

There were approximately 800 attendees, almost all those either with retinal degenerative diseases, or families of those with such diseases. It was quite a sight - some people had on assisted-listening headphones, others were viewing the closed-caption TV monitors if they couldn't hear the speakers; and others were watching people who were presenting the speaker's information in sign language. We saw many white canes and many guide dogs (my little boy loved them!) I don't want to ramble on too much, but what I have planned is to try to combine information from several speakers into a few categories.

First is gene therapy, second is transplantation research, third is pharmaceutical work, and fourth is other therapies. After each section, I will stop for questions, although I am not averse to taking questions at any point if someone is afraid they might forget. I wanted to also add that the people attending spanned all age groups. I saw infants in mothers' arms and elderly folks and everyone in between. I don't think anyone felt out of place. Well, on to the information.

## Gene Therapy

Regarding gene therapy, there are two primary goals: either replace the defective gene with a "good" gene, or implant another gene to overcome the defect. Either way, new genes are implanted using what are called "vectors," which are modified viruses that are able to penetrate cells much better than human technology alone can do. Some problems here are that the vectors need to enter the desired cells, we need the good effect to be maintained for a long time, and we need to control the amount of gene product produced (proteins). We don't want too much or too little produced. In addition, we want to make sure that the virus itself does no harm.

Dr. Ted Dryja, from the Harvard Medical School spoke at length, and indicated that nearly one billion copies are available from a single tube of blood, and that the target gene can be replicated many times over within several hours, resulting in several billion copies of a desired gene fragment in short order. An interesting comment he made was "Most businesses ask for your money - I'm asking for your blood", indicating that this is how genetic research can be speeded up. He estimated that perhaps 100 genes are involved in various retinal degenerative diseases, and that approximately 30 have been identified so far. It is important to note, he added, that two patients with the same genetic defect can show vastly different signs and symptoms, showing that other factors are involved in modulating retinal degeneration (i.e. other genes, diet, or other unknown factors).

The past ten years have seen an explosion in genetic research - in fact, it was stated that retinal gene research is at the forefront of medical gene research in general. Dr. Richard Lewis of the Baylor College of Medicine in Houston also spoke. He is heavily involved in Stargardt's research. He said that, interestingly enough, the ABCR gene found to be defective in people with Stargardt's is only turned on in rod cells, not in cones. This is surprising since Stargardt's causes decreased central vision, just like age-related macular degeneration. and it is the cone cells, not the rods, which are responsible for good central vision.

He also spoke about some of the racial/ethnic differences which exist regarding AMD (age-related macular degeneration). For example, ARMD is uncommon in blacks, more common in Hispanics, very common in Caucasians, and virtually unknown among native Africans. As an aside, I know that other eye conditions also can follow racial/ethnic lines to some extent. For example, glaucoma in the U.S. occurs perhaps five times as much in black patients as in whites. We don't know quite why these things occur yet. The bottom line, according to Dr. Lewis, is that the defective gene must first be definitively identified before we can expect any realistic gene therapy. In his words : "You cannot repair the machinery if you don't have the instruction manual."

So where do we stand today in genetic research? A few scattered notes:

No genes have clearly been identified as being responsible for ARMD, although the ABCR gene has been shown to be responsible for at least some Stargardt's disease. Animal models are being developed for Stargardt's so that human clinical trials can follow. This is the general way this research goes on - first the defective gene is identified, then an animal model simulating the human condition is found. Then human clinical trials can occur if the animal testing shows promise.

The first gene for retinitis pigmentosa was only identified about ten years ago, and human clinical trials for gene therapy for RP are perhaps two to five years away yet. So these things take time, but the results to date appear to be encouraging with virtually every month yielding new, previously unknown information.

This covers a very brief summary of the topics covered regarding gene research. I am now open to questions about gene therapy.

**JOAN:** As one who has Stargardt's, for which the gene has been identified, can you tell me who wants my blood for research?

**DR. GOLDBERG:** There are various research centers around the country who would welcome your blood samples.

**JOAN:** I'm in Virginia. Any suggestions?

**DR. GOLDBERG:** If you'll hold on just a moment, I'll get the number of the Foundation Fighting Blindness.

**DAN:** I can look that up, Steve. You go ahead with questions.

**DR. GOLDBERG:** Thanks, Dan ... I thought I was prepared enough!

**DAN:** FFB Phone number: (800) 683-5555

**JOAN:** Thanks.

**DAN:** Steve, will gene therapy be a cure for existing conditions, or more of a preventative measure?

**DR. GOLDBERG:** I think that, initially, it will act to stabilize the degenerative condition, but if identified early enough, it is possible that genetic intervention might be a real cure. The problem is that we are early enough with this that we don't know the long-term effects. For example, will the positive changes be permanent or not.

**JOAN:** My daughter is going into this field. The duration of improvement is one caveat she has mentioned.

**DR. GOLDBERG:** That is an unknown at this point.

**DONNA:** Where can I send my blood? Call that same number?

**DR. GOLDBERG:** Yes, Donna, I would contact the FFB at the number Dan gave out for nearest research center.

**DONNA:** Thanks.

## **Transplantation Research**

**DR. GOLDBERG:** The next area I wanted to cover was transplantation research. There are two basic kinds of transplantation involved here. Either the photoreceptors can be transplanted, or the RPE (retinal pigment epithelium) cells can be transplanted. Either method involves rather difficult surgery with a number of problems to date. Although human clinical trials are underway for photoreceptor transplants, Dr. Gerry Chader at the conference indicated that this was premature and probably should not have taken place yet. It is not yet known whether this type of transplant can really work (no "proof of principle" yet) because there apparently are no good animal models for this yet.

One of the problems encountered is rejection, although this can be overcome to an extent by immune suppression. The problem here is that people over age 65 may not tolerate immune suppression very well. Another problem is that the implanted photoreceptor cells need to connect properly to the retinal neural network, and scientists apparently don't have the foggiest idea how to do this, although the photoreceptor cells themselves seem to be able to connect to some extent on their own! It is estimated in research thus far that perhaps 15% of implanted photoreceptor cells do connect to the neural network properly. It is unknown whether this is enough for clinically-improved vision.

It seems, however, that transplantation of RPE cells may offer a much brighter hope. These cells act as the "support" for the photoreceptor cells and indeed proof-of-principle has been demonstrated with this type of transplant. It may even be possible to transplant a person's own good RPE cells to the damaged area of the retina.

A couple of notes here:

Implanted RPE cells need to be "oriented" in the proper direction and this is difficult to accomplish surgically.

Previous surgical work (i.e. submacular surgery or laser surgery) causes damage to area RPE cells and may make this type of transplantation more difficult.

And it is unknown how long transplanted cells can live.

An interesting point with transplanted photoreceptor cells is that the transplanted cells seem to aid native cone cells (the person's own photoreceptors) quite a distance from the transplanted cells, through some unknown mechanism. Another interesting point brought up was that there are some fish species whose retinal tissue continually regenerates. Therefore it may be possible to learn how to make this happen in human retinas. If this can be done, macular degeneration may be a thing of the past. The speakers indicated that transplantation research is most likely to benefit those with macular degeneration, although there was some disagreement whether this is most likely for wet or dry AMD.

Though as you can see, many hurdles remain, the researchers were very enthusiastic about research efforts on-going and to be done in the near future. Any questions regarding transplantation work?

**DAN:** Has there been any significant improvement in sight in subjects who received this treatment during the last year at Washington University?

**DR. GOLDBERG:** Unfortunately, I don't believe so. However, this was pretty preliminary work, and as Dr. Chader remarked, it may have been a little premature.

**JOAN:** What I have read regarding transplant surgery indicates that improvement has been reported subjectively, though clinical measurements have not supported improvements.

**DR. GOLDBERG:** We have to be very careful about subjective reports. Many times patients may report that "things seem better" because they so desperately want it to be so.

**JOAN:** Point: There is a big difference between clinical measurements and subjective experiences in my case.

**DR. GOLDBERG:** But we must see repeatable, objective improvement in order to know that a given treatment really is helpful. Joan, it may be that different tests need to be done to objectively verify your subjective reports.

**DAN:** Steve, shall we move on to pharmaceutical work?

**DR. GOLDBERG:** Sounds fine, Dan.

## **Pharmaceutical Work**

**DR. GOLDBERG:** I know that this is an area of interest to many people and the topic of hot debate. The goal with pharmaceutical therapy is to keep photoreceptor cells alive (the drugs that do this are called "neuron-survival agents"). These may take the form of vitamins, minerals, or other drugs. If such therapy is successful, for example, transplantation work or gene therapy is unnecessary. Anti-oxidants have been the primary area of interest in recent years, and the jury is still out. A five-year study is on-going that should end relatively soon and give us more information. We still really don't know whether people should be taking multi-vitamins or not; although the consensus appears to be, as I stated in the chat channel discussion some months back, that these pills probably don't hurt (if taken as directed), and might possibly help. Though I heard Dr. Eliot Berson remarking to someone in a side discussion that some of these multi-vitamins might contain enough zinc and selenium to be harmful. So again, I advise everyone to speak with their eye doctors and their general physicians if they are taking or plan on taking this type of pill. As an aside, I saw a patient just a few days ago who was taking both Centrum pills and Ocuvite pills, both over-the-counter multi-vitamins. I advised him to discontinue one or the other so as not to get an overdose of the vitamins and minerals included in the pills. In the case of retinitis pigmentosa (RP), Dr. Berson has shown that approximately 15,000 IU of Vitamin A taken daily can help to slow down retinal cell degeneration, perhaps yielding several additional years of good vision. He also found, however, that excessive use of Vitamin E can actually speed up retinal degeneration. Now his research was with RP patients, not AMD patients, but certainly it is clear that we need to be careful with even over-the-counter medications.

Another type of neuron-survival agent that was discussed was axokine, which is an agent naturally produced by eye cells in four different animal models. Axokine has been shown to delay photoreceptor death in RP cases. Human clinical trials are now getting underway with axokine injections into the eye to see if these results can be duplicated in humans.

Another note about vitamin A therapy. Dr. Berson was very upbeat about this being a definitive treatment for RP, although he seemed to negate the possible liver damage that can occur with excessive vitamin A therapy. So again, more research is needed to know exactly what will work and what will not work, for each type of retinal degeneration. I am again open to questions.

**DAN:** Is their indication that zinc can aggravate retinal cells? I hadn't heard this before, and I take it often.

**DR. GOLDBERG:** I have heard for some time now that zinc can be harmful in high enough concentrations, but I don't know that anyone knows what exactly an ideal dose is. I think we'll have to wait for additional research, but I would be careful not to exceed what is contained in the over-the-counter pills. And again, it wouldn't hurt to speak to your doctors for their opinions.

**DAN:** Thank you, Steve. If there are no more questions, let's move on to the final topic.

## **Therapies**

**DR. GOLDBERG:** Thank you, Dan. Another interesting therapy that is not on the immediate horizon is that of the implantation of electrical devices (computer chips) in the retina. This is apparently within the realm of current technology with the recent tremendous advances in computer technology. In fact, this is currently being worked on in five labs around the world - two in Germany, and three in the U.S. The way this is envisioned is that a small camera mounted on glasses will send a signal to the implanted electronic photoreceptor cells. This is in the very early stage right now - the researchers are still attempting to demonstrate that all-important "proof-of-principle" which means that the treatment works in animals before proceeding to human trials. I'm not certain, but I believe that it was stated that this has produced light perception or "hand-motion" vision where no vision was present before. Remember that although the retina acts as the photographic plate, it is the visual cortex of the brain (at the back of the head) where we actually "see," so theoretically, it should be possible for a person without any eyes at all to see, as long as the neural network is still functioning. Not surprisingly, this work is many years away from being something we can really hope will work; but many millions of dollars are being invested in this and may yet yield fruitful results.

At the closing session on Sunday, I asked the researchers at the dais about photodynamic therapy. This is where a dye is injected and a low-level laser is applied to better target damaged blood vessels. It is presently in human clinical trials and acts as a treatment to preserve vision, not as a cure, and it does seem to require multiple treatments; but after the person at the microphone was done answering my question, Dr. Chader (who happened to be sitting next to me in the audience) leaned over and said that two different drug companies were "betting the bank" that this would be effective. So we'll see what comes of photodynamic therapy.

I and others also asked about microcurrent stimulation and Rheotherapy. Although

I'm not entirely familiar with either of these, I believe that microcurrent stimulation involves some type of combination of acupuncture and mild electrical stimulation, and rheotherapy involves a type of blood filtration. The problem with both of these, as the researchers stated, is that neither has any firm scientific data to stand on. This doesn't mean that both are "snake oil," as one questioner was asking, but it does mean that we just don't have the information available to allow us to recommend these type of treatments. Some of the researchers were very diplomatic about this, and others were very clear in their disdain for doctors who claim to offer some type of cure without making clear on what scientific basis the work rests. As one researcher stated, it is unethical to withhold such information if it exists.

A few other comments. Although the primary focus of the FFB in the past has been retinitis pigmentosa, the huge banner at the head of the convention hall stated that the goal of the FFB is "to cure RP, macular degeneration, Usher's Syndrome, and related degenerative diseases." It was my experience that most of the people attending the convention were RP patients, but a significant amount also were there because of macular degeneration, particularly Stargardt's macular degeneration. I met a family with three girls, ranging in age from about 13 to 20, all with Stargardt's, another fellow in his fourth year of medical school with Stargardt's, and a young lady who is a principal of a day school in New York, who was just diagnosed with Stargardt's a few months ago. There was also a woman whose 11-year-old son, active in sports, was just diagnosed a year ago with Stargardt's. There were many others who have age-related macular degeneration, or choroideremia, or cone dystrophy, or other forms of retinal degenerative disease. Every one of them was at the right place - I don't believe that anyone felt out of place, or that the conference was not directed toward them. There was a dinner/dance Saturday evening. At one point I was speaking with a teenage girl with Stargardt's who asked me if the people dancing wildly on the dance floor can even see what they are doing. And I answered that at the moment I didn't think it mattered - they were just having a great time.

The people that attended this convention did so at much personal discomfort in that they had to travel long distances, and left the comforts and safety of home; yet they were there for the common purpose of trying to keep up with the latest research information available and to be able to go home with renewed hope and courage that things may yet improve for them. I was very touched to be among them and left very upbeat and optimistic about the future.

The researchers that presented their information are some of the finest scientists around. I was quite impressed with what they had to say and with the fact that they are dedicating their entire professional lives to the cure of these devastating retinal diseases. As one researcher stated, "All the boats in the harbor rise with the tide." What he meant was that, although research is on-going in many different directions

(gene therapy, transplantation, pharmaceutical work, etc.), as one of these areas comes up with new and unexpected findings, they all benefit. And with a little luck, and with continued perseverance, it is very likely that the next ten years will show even more massive growth in our understanding of retinal disease than have the last ten years.

The convention booklet contained a quote that I thought was very appropriate: "Never doubt that a small group of thoughtful, committed people can change the world. Indeed, it is the only thing that ever has" (Margaret Mead). At this meeting I had the opportunity to meet many researchers, many people with retinal diseases. I had the chance to speak at length with Tom Hoglund of the FFB, who is very down-to-earth and very knowledgeable about current and past research. I hope to attend next years' conference in Los Angeles (date to be determined), and I hope to see some of you there. I told my wife that this was the best medical conference I have ever attended. Although there are many hurdles ahead, great progress has been made. Never doubt that there are dedicated people out there working day and night, trying to help each of you make your life a little brighter. Thank you for the opportunity to share my excitement from this convention.

**DAN:** Are there any further questions for Steve before we bring the session to a close?

**JOAN:** About drugs. I keep running into prescriptions for other conditions that may harm my vision. The prescribing docs have always been unaware of this. Any suggestions?

**DR. GOLDBERG:** Anything specific you care to mention?

**JOAN:** Many medications increase photophobia. Some are tricyclics and quadracyclic antidepressants.

**DR. GOLDBERG:** Joan, the best way to deal with this is to have your other doctors confer with your ophthalmologist or optometrist before prescribing these.

**JOAN:** None of them seem to know.

**DR. GOLDBERG:** If you become aware of unwanted side effects, let your prescribing doctor know, and he may be able to change the prescription, or find a way to lessen the effects. Proper communication among your doctors should help this.

**DONNA:** My doctor said the Tambocor I take can be affecting my eyes.....its for my heart arhythmia. Nice choice eh?..heart or eyes...geez.

**DR. GOLDBERG:** I am not familiar with that medication - again, I would advise speaking with your ophthalmologist or having your cardiologist speak with him.

**DONNA:** He is my cardiologist.

**DR. GOLDBERG:** I meant have your cardiologist speak with your ophthalmologist.

**DONNA:** k

**DAN:** Steve, on behalf of everyone on both the MDList and the RPList, I want to thank you for enlightening us once again. We greatly appreciate your time, your dedication, and your concern; and we look forward to future sessions with you.

**MARIE:** Thank you, Dr. Goldberg. You have given all of us a ray of hope.

**DR. GOLDBERG:** Dan, thank you for this opportunity, and thank you all for taking the time to listen in!