

# Transcript of a chat session with Dr. Gislin Dagnelie 6/6/98

*(Edited for clarity and length.)*

DAN: Gislin, please tell us a little about your work at Johns Hopkins.

GISLIN: My pleasure, Dan. I came to Hopkins 12 years ago after completing my training in Amsterdam. My specialty is medical physics. That is the application of physics and math to the field of medicine. I am working with RP and AMD patients, in part to develop more sensitive ways to measure their vision, and in part to assist medical doctors in the development of new techniques. Over the past 3 days I attended a conference on macular degeneration here at Hopkins. There was an outstanding list of speakers, both basic researchers and doctors, so I can say that I am well prepared for this session. (smile)

DAN: Thank you, Gislin, and welcome to the session. We appreciate your time. Anne, would you like to ask your question now? Thanks for waiting.

ANNE: Can you tell me about macular translocation please.

GISLIN: The macular translocation surgery is not new, but it has been perfected a lot since it was first tried by Dr. Machemer at Duke University, 15 years ago. One of Dr. Machemer's former students, Dr. Eugene de Juan, is the head of vitreoretinal surgery here at Hopkins. He has improved the technique of Dr. Machemer, and so has Dr. Claus Eckart in Frankfurt, who also spoke today at the conference. The idea of the surgery is that in AMD there is scar tissue-- or at least new blood vessels-- growing under the central macula that is threatening central vision. By moving the central retina away, you can not only keep it healthy by placing it over healthy pigment epithelium, but you can also treat the new vessels with laser without threatening central vision. You have to realize, though, that this procedure will not work if the vessels or scar are already very extended, and that you also can't guarantee that the vessels won't grow back. That means that we will have to wait several more years before we know the long-term success.

ANNE: Thank you. How long does the operation last?

GISLIN: The operation typically lasts about 1-2 hours under local anesthesia. This does not include any laser or other treatment of the new vessels or scar tissue, which is usually done in the outpatient clinic.

DAN: Gislin, I have a question. Someone asked yesterday about a new treatment called photo point procedure. Have you heard about that?

GISLIN: I have not, but it may have other names as well. Did they give you a description?

DAN: It was announced on KCAL News in LA. That's all I was told.

GISLIN: I'm afraid I don't know. There are a lot of "fringe" therapies. Even if they may have some merit, they're hard to keep track of. If anyone knows more, please speak up.

RUTH: My ophthalmologist told me that a great deal of research is happening on gene therapy for AMD, dry or wet. Can you elaborate on that? He said that even in my lifetime (I'm 77) it may likely happen.

GISLIN: Gene therapy is a very exciting field. One of the things I came away with at this conference is the very fine balance of nutrition and cell health in our retinas. Gene research is now finding some markers and mutations for several retinal diseases, and in animal models they are indeed successful in prolonging the life of photoreceptors and other cells that would normally degenerate early in the animal's life. With AMD, there is not yet a clear gene that is held responsible for many of the cases. In Stargardt's, the ABCR gene is a strong candidate, and some mutations have been found. This gene seems to be involved in some 4% of AMD patients as well.

Let me tell you about two ways gene therapy may work. The first one, in recessive disease, is that it may be possible to introduce just one good copy of the gene back into the retina, at a time early enough to prevent degeneration. After all, in recessive disease both copies of the gene are bad. In dominant disease it only takes one bad molecule to poison the cell, and the way gene therapy may work there is by breaking up the precursors of the bad molecule, so it never gets formed. AMD is more complicated, though, because there is this very slow process of build-up that makes the membrane under the retina harder and harder to penetrate for all the molecules that need to pass through. That's why it only develops in old people.

KATE: What about the above in application to 40 years olds, say with myopic MD?

GISLIN: Good question! Myopic MD, as far as we understand, is first of all caused by the mechanical stress on the retina. If you're a high myope, you very probably have an eye that is longer than usual, and this "stretches" the retina. Why, precisely, is not clear, but the risk of fluid and other debris building up under the retina is higher than in people with a normal size eye, and so the degeneration that in normal people starts in their 70s and 80s starts much earlier in myopic degeneration. Unfortunately, treatments like retinal translocation have a higher risk in these patients, because the retina has to reattach following the surgery.

KATE: Most retinal/submac surgeries all seem to indicate that high myopes are at much greater risk...because of the elongation of the eyeball, etc.

GISLIN: You're right. I can speculate a little bit. One thing Dr. de Juan does in this retinal translocation is to make a fold in the outside of the eye, in one place, to get the slack he needs to move the central retina away from the new vessels or scar. Theoretically, the same thing could be done in high myopes: as a prevention, the eyeball could be shortened by making such a fold. I don't think anyone has done that, and it would be hard to get that far back behind the eye, but I'm going to ask him what he thinks!

DAN: Thank you, Kate. Gislin, what do you have to say about the controversial rheotherapy in Florida?

GISLIN: Hmmm. Rheotherapy was not presented at this conference, and I think for good reason: First of all, what the procedure does, in my interpretation, is to clean out the vessels and improve the passage of small molecules through the vessel walls. In itself that is a useful idea, and there is a group in Germany that has quite a bit of success with a similar procedure in diabetics; not just for retinal problems, but for all sorts of complications of diabetes. My problem with rheotherapy is the for-profit aspect, and the fact that no good clinical studies have ever been done to support Occulogix's claims. Interesting tidbit: they were supposed to have a booth at the ARVO conference in Fort Lauderdale last month, but they didn't show. I guess they were a little apprehensive about meeting the guys who are not in it for the money, and who expose themselves to scientific scrutiny. Am I too harsh?

DAN: Does this mean you will not accept the \$1000 I was going to pay you for today?

ANNE: hahahaha

GISLIN: Can we take this to the other room? (smile)

DAN: lol.

GISLIN: Let me make one thing clear: I am not against any therapy, as long as there is a willingness to submit it to review by others, and as long as there are no signs of abuse of people in a vulnerable position.

RUTH: Back to translocation. Would a person with dry md, no bleeding, be a candidate for translocation?...could translocation help to prevent dry from becoming wet?

GISLIN: Another good question! Dry AMD doesn't always go on to become wet. My colleague here, Dr. Janet Sunness, has been following about 150 patients with dry AMD for up to 5 years, and only a small percentage have gone on to wet AMD. As long as the AMD is dry, translocation surgery will probably do more harm than good, because you are moving the central retina, which in dry AMD actually keeps vision for a number of years. In 2 or 3 years, though, the surgical technique may have improved to the point that it can be used in a much earlier stage, and thus prevent much of the vision loss in dry AMD.

RUTH: Thanks so much. You've answered my questions really well. Appreciate it. smile

DAN: Thank you, Gislin. Can you give us your thoughts on micro-current stimulation? Several of our listeners are considering it.

GISLIN: Another technique that was not represented at the conference. I am not as familiar with it, but I know similar approaches from the treatment of RP. My guess is that it can temporarily improve the permeability of membranes under the retina, and maybe even dislodge some of the "gunk". In other words, just like rheotherapy, it is something that needs to be repeated fairly frequently, at considerable cost (not necessarily, but that's how it is right now), so it's more a milk cow than a permanent solution for now. Don't get me wrong, though, I think therapies like these may play a useful role in prolonging vision. The problem is just that the people practicing it are not doing the research necessary to prove that.

DAN: There are clinical studies going on now in San Pablo CA. So far, there have been varied rates of success with it, so we are keeping a hopeful watch on it. As with rheotherapy, however, there is money being made. Kate, you have the floor.

KATE: Gislin, are PDT [photo dynamic treatment] and BPD [benzoporpharine derivative] in that category also?

GISLIN: PDT is a great idea. To close up the new vessels without destroying the retina overlying it is a very worthwhile goal. Actually, there is an even better approach around the corner, but it has only been done in animals until now. You package the BPD or other photoactivated substance in a fatty substance called liposomes, and free it up from there by warming it up just a little with a laser, then you give the retina two seconds to clear out the substance from all the healthy vessels; it stays behind in the new vessels since they don't have good circulation, and then you blast the BPD with the laser, ablating only the new vessels. Neat, eh?

KATE: Interesting--How to find more info on that?

GISLIN: Dr Ran Zeimer here at Wilmer is working on this. If you look at the Wilmer Web Page: [www.wilmer.jhu.edu](http://www.wilmer.jhu.edu), and go under Research, you'll probably find him there. I don't know how up to date the page is, but I imagine it's pretty good.

KATE: Thanks.

MILLIE: Is there anything for dry md?

GISLIN: The two topics we haven't touched upon: cell transplantation and the development of a retinal prosthesis. Which one do you want first?

MILLIE: Either.

GISLIN: OK. Let's look at cell transplantation. There are two types of cells that are hurt in AMD: photoreceptors and RPE cells. RPE cells are probably the more critical step in the process, and, for that reason, researchers have concentrated on RPE cell transplantation when talking about therapies for macular degeneration. The problem with RPE cells is that they are more easily rejected than photoreceptor cells, so you have to do a tissue match, just as in organ transplants, or you can try to take pigment epithelium cells from the patient's own eye. This can be from the peripheral retina, or from the iris. In animals, transplants from the peripheral retina seem to work fine, but the comparison is not fair, since they don't have sick RPE cells to begin with.

A group in Valencia, Spain, has done 5 transplants with iris pigment epithelium, but it's been very recent, so the results are unclear. In this country, animal experiments were done, as is the case in Germany; but again, in a healthy retina it's hard to draw conclusions. My guess is that it's mostly a matter of getting the surgical problems under control and getting approval for clinical trials. I wouldn't be surprised if it's a fairly common procedure in 5 years. The biggest question is, though, would you get more wet AMD or other complications following the surgery? Again, I think that's mostly a matter of getting the technique under control. There is one complication: people with dry AMD have fairly good central vision, and you don't want to do risky surgery in a good eye. But if you wait too long there will be nothing to rescue, so--until the technique becomes very good--it may not be a very helpful approach :-)

DAN: As of a couple of months ago they reported luck with non-rejection of transplanted RPE cells in human subjects, but there has not been significant improvement in vision noted as yet. Is this still the case?

GISLIN: There was no outright rejection, but the cells didn't survive for more than a few months. This is true for the transplants that were done in Europe as well as

those done here, in Chicago, Baltimore, and St Louis. I think the consensus is that the technique is not going to get better until they start to either match tissue or use autologous material (from the patient's own retina).

DAN: Thank you. Can you comment now on retinal prostheses?

GISLIN: Sure. The retinal prosthesis is a concept that is based on the cochlear prosthesis. As you probably know, this is a device that is implanted in the inner ear of patients whose haircells no longer transfer sound vibrations into neural impulses. Even with 4-8 electrodes, these patients can hear well enough to carry on phone conversations. About 10 years ago, Dr. de Juan and then medical student Mark Humayun at Duke University decided to try if this same principle might work in the eye. They found a late-stage RP patient willing to undergo an experimental procedure. First the outside of the eye was stimulated electrically, and the patient saw flashes of light, indicating that some retinal cells survived, even though he could barely tell day from night. They then went into the eye with a small probe, under local anesthesia, and stimulated the retina with very small currents. The patient saw a small dot of light, flashing at exactly the position corresponding with the retinal stimulation.

When Drs. de Juan and Humayun came to Hopkins, I joined the project, and we have now done similar experiments in 14 RP patients and 2 AMD patients. In all of them, it turns out that cells in secondary retinal layers are still functioning, a decade or more after the photoreceptors have died. The idea is now, to implant a "matrix" of electrodes over or under the retina, and stimulate the cells. The resulting image will be quite crude, but for an RP patient who is completely blind it will be good enough to move around without a cane, we think. In a later stage, I expect that the technique will improve enough that it can be safely applied to the blind central retina in MD patients. There are currently at least 5 groups working on these devices: 3 in the US (Chicago, Boston, Baltimore), and 2 in Germany, where the government is generously sponsoring this research. The image to be presented through these electrodes could come from an external camera, or in the subretinal variant. The electrodes would also contain "photo cells". The technical problems are still considerable, but I expect prototypes to be available in the next 5 years.

DAN: You have covered many topics this afternoon, and we have only about 20 minutes remaining.

RUTH: I am so impressed, I'm speechless.

MILLIE: Thank you. We do have hope for dry md in the future then.

DAN: Anne, you have the floor.

ANNE: May I revert back to the translocation surgery and ask how long it takes for the recovery time, and when you see results. Also, what % is there for rejection of retina re attaching?

GISLIN: As far as I understand, the results can be seen within a week; although I think they can continue to change for another 2-3 weeks after that. You can imagine that it's quite an attack on a non-suspecting retina. smile. As I was looking at the videotapes today I was impressed how much can be done with tissue that is not much stronger than wet tissue paper.

ANNE: Wow. Thanks.

DAN: Before we end the session, Gislin, can you touch on the success of submacular surgery, and the progress of beta blockers by cancer researchers?

GISLIN: OK. The biggest problem of submacular surgery, as I heard it today, is that there are a lot of recurrences. In other words, you can take out the membranes, but they start growing back pretty soon. Originally, it was thought that SS works best for histopolasmosis, because the scar tissue is not firmly attached to the overlying retina. Unfortunately, in myopic and other forms of MD, a lot of retinal tissue is torn out (literally) along with the membrane. Now, after a few years, it looks like the recurrence of membranes is a bigger problem, and it occurs in at least half of the cases, usually after 6 months or so.

This brings me to the other half of Dan's question: the new drugs that have become famous in the last few weeks, because by stopping new blood vessels from growing we may be able to stop tumors in their tracks. If we use surgery or laser to take out new vessel membranes, but cannot prevent following membranes from growing in, we're not going to solve the biggest complication of MD. The two drugs that have come into the news--and in fact quite a few others--may be able to stop the vessels from growing, and a small trial with thalidomide is already under way. The biggest problem is to localize the application, or to limit it in time in cancer, you may be able to apply the drugs for a few weeks, and then follow up with chemotherapy or surgery. In the eye, it's not yet clear that this will be enough. Researchers are looking at ways to slowly release these drugs inside the eye so you don't have to give them systemically.

DAN: Thank you, Gislin. We have about 10 minutes left. Are there any quick comments or questions from the floor?

KATE: Anything new on better policies re insurance coverage for low vision aids, etc?

GISLIN: Apart from research, I spend a lot of time working with Medicare, because I am also the director of our low vision clinic. I have a study proposal in with NIH to look at complications of vision loss so we can prove once and for all that people with low vision are exposed to a lot of other health risks: falls, problems taking care of themselves, medications, etc. I hope to be able to prove this by looking at millions of Medicare claims, concentrating on two groups of people. The case group will be elderly people with a diagnosis of AMD or open angle glaucoma, since we know they are at high risk of low vision. And the control group will be people who underwent cataract surgery, since they get good check-ups, so if they had another eye disease we would know, and they can be excluded. I look at all the claims from 1992 to get the case and control populations, and then follow their claims over the next 4-6 years to see what other medical problems they get into, from falls to nursing home admissions.

KATE: Thanks.

MILLIE: Is there anything that you recommend to do right now for dry md?

GISLIN: What we haven't talked about is nutrition. I think there is a lot to be said for a balanced diet: no smoking, little alcohol, dark green leafy vegetables. And if you want antioxidants and multivitamin additives, there is no hard proof, but certainly anecdotal evidence. Oh yes, and get sunglasses that cut out ultraviolet and blue light, since there is more and more evidence that those play a role.

DAN: Dr. Dagnelie, you have been a fantastic guest. Your knowledge seems unlimited, and we are lucky to have you out there working on our behalf. Thank you for spending time with us today, and please consider subscribing to our MDList. You would be a wonderful asset.

ANNE: It's been wonderfully informative. Thank you very much for your precious time.

GISLIN: I've enjoyed it a great deal.

MILLIE: Thank you so much!

KATE: Thank you very much for the time and info you've given us, Dr. Dagnelie. You're much appreciated, and I hope there are more like you!!!

TOM: A wonderful afternoon. Thanks a lot.

GISLIN: Gotta run now, or my wife won't be too happy with me.

RUTH: Dan, I'll play my Chopin Etude for you!

DAN: I will publish the transcript on the web site by Monday, and will spread the word to both the MD and RP Lists. Have a good time at the wedding, Gislin.

DAN: And now, Ruth will play us off with a little Chopin.

GISLIN: Thanks! Over and out.