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WILL NEW THERAPY FOR GENETIC DISEASE ALTER UNDERWRITING PRACTICES?

Robert Desnick, MD*

DR. LOWDEN: Our next speaker will discuss, "Will New Therapy for Genetic Disease Alter Underwriting Practices?" This presentation will be made by Dr. Robert Desnick. Dr. Desnick is the Arthur J. and Nellie Z. Cohen Professor of Medical and Molecular Genetics at the Mount Sinai School of Medicine. He received his B.A., Ph.D. and M.D. degrees from the University of Minnesota. His research areas include molecular, biochemical, somatic cell, and clinical genetics. He has contributed to more than 300 research publications and edited six books on topics in genetics. He is on the editorial board of several journals, including Journal of Clinical Investigation and Pediatrics, and I might say he looks like an awfully young man to have done all of this already. Please join me in welcoming Dr. Desnick. (applause)

DR. DESNICK: Well, thank you very much. I’m delighted to be here as one of the younger members of Sandy Lowden’s genetics mafia. Sandy called me up and said, "Well, will you talk about genetic therapy and what’s new in genetic therapy?" I said, "I’d be delighted to." He said, "Here’s your title, ‘Will New Therapy for Genetic Diseases Alter Underwriting Practices?’" Now I have to point out that my father was not in the insurance business and I can’t predict such a thing because I don’t know anything about underwriting practices. But there’s going to be a tremendous revolution in terms of therapy, but how that therapy will have an effect on underwriting practices, I can’t tell you. I’m sure it will. I’m sure it’s going to have a great impact in terms of health insurance, but those sands are shifting daily here, so I couldn’t predict that either. But what I thought I’d do with you today is talk about something I do know a bit about, and that is to tell you a little about the current modes of genetic therapy. Then I’d like to discuss what’s happening in terms of the application of recombinant DNA technology to genetic therapy, and I’m going to talk about two examples. I’m going to discuss the potential of recombinant protein replacement or protein replacement therapies. I’m also going to talk about the future for somatic gene therapy, because that’s a way of delivering the gene which will make the protein and actually provide continual therapy. These molecular therapeutics will be very expensive. But coupled with what you have heard about genetic diagnosis, or what I call prediction/prevention strategies, they will turn out to be cost-effective. And we’re going to talk about situations where you can actually effectively treat a disease, or actually cure a genetic disease. How you factor that into your underwriting policies is something you’ll have to think about as I illustrate these examples.

Now when we talk about genetic disease, you know that there’s chromosomal disease, the inborn errors of metabolism, and the multifactorial traits that we’ve talked about. For chromosomal disease, Down’s syndrome, for example, there’s no way you’re going to pluck out the extra twenty-first chromosome, so there we have only supportive treatment, no new therapies. For inborn errors, and there are hundreds of these different metabolic diseases, there are a variety of strategies which have been pursued. Some of these may be applicable to multifactorial traits once we understand what the primary or major gene is causing the disorder.

Let’s look at inherited metabolic diseases. Currently, we’re at the level of metabolic manipulation. You all know the story with phenylketonuria. It was discovered that if you could intervene early and deprive the patient of the toxic phenylalanine that impaired brain function and caused mental retardation, if you could simply give the patient a diet that was low in phenylalanine, the outcome would be that the child would have an IQ within five points of normal. Very effective, very cost-effective. It’s just dietary therapy, and what we’re doing is metabolic manipulation. We’re eliminating a toxic compound that cannot be metabolized. Another approach is product replacement, and you think of this for hemophilia or other disorders like a hormone deficiency, where they can’t metabolize compound A to compound B which is crucial for their normal growth and development, and we just provide them compound B, the product. This is metabolic manipulation. We’re eliminating a toxic compound that cannot be metabolized. Another approach is product replacement, and you think of this for hemophilia or other disorders like a hormone deficiency, where they can’t metabolize compound A to compound B which is crucial for their normal growth and development, and we just provide them compound B, the product. This is metabolic manipulation. There are a variety of strategies, and generally, they’re clinically beneficial. In fact, for many of these diseases they’re so beneficial that we ended up generating a newborn screening program to detect the disease in the newborn period, intervene very quickly, and change the outcome for that individual remarkably.

At the moment there’s much research going on at the level of the gene product. I think you know what’s

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happening in terms of transplantation, and there are a host of genetic diseases where you have a liver-specific enzyme or a bone marrow-specific enzyme. You do either a liver transplant or a bone marrow transplant, and you effectively cure the disease. On the other hand, we're going to talk about enzyme replacement therapy, because there's been a resurgence of interest in this particular area.

What I really want to focus on is gene therapy. Gene therapy is the application of recombinant DNA technology, this molecular revolution that we've just gone through, using the fruits of that information to produce human gene products, because we can now engineer cells to produce any human biological we want. Biotech companies are generating all kinds of expensive new drugs that have a really remarkable potential to treat and cure genetic disease. And then we are going to talk about gene replacement therapy, and I want to portend for you what the potential of this very important strategy is to cure genetic disease.

Let me give you an example of tying together the production of the human gene products using recombinant DNA technology and enzyme replacement or protein replacement therapy. And then the second example I'll give you is what's happening in gene therapy. Biotech companies are taking the developments in recombinant DNA technology, isolating the genes, and then using different kinds of expression systems to make human biologics. I think you know very well that the first one has turned out to be a very, very effective one, and that was to take the gene sequence for making the insulin A chain and the insulin B chain and put them into E coli. Eli Lilly in Indianapolis has a vat the size of Anheuser Busch's, and they're making recombinant insulin. It solved many of the problems of allergy that patients develop to bovine insulin that had three amino acid differences and hog insulin which had one amino acid difference. This is human insulin, and it works great, and it's reasonably inexpensive, and it's available at the drug store today. Some other products have been made by drug companies; in many cases they're orphan drugs, and in some cases, they're quite expensive. But they are really generating the whole era of recombinant human biologics: insulin, growth hormone, interferon, interleukins, tPA, alpha-1 antitrypsin, on and on and on. One is called beta-glucosidase. That enzyme is the one that's deficient in a disease called Gaucher's disease. This is a lysosomal storage disease. Individuals who are deficient in this enzyme, also known as glucocerebrosidase, cannot hydrolyze a normal glycolipid which is a component of all cell membranes. It's called glucosylceramide. The inability to release free glucose in the fatty portion results in the accumulation of this compound in patients with Gaucher's disease in target sites of pathology: reticuloendothelial disease in liver, Kupfer cells, bone marrow, spleen, and lymph nodes. There are three types of Gaucher's, and I only want to focus on Type I, which has its onset of symptoms in childhood or early adulthood. It's a progressive disease with massive hepatosplenomegaly, with hypersplenism, and all the hematologic complications of secondary hypersplenism. They have very low platelet counts, very low absolute neutrophile counts. They bleed easily, they bruise easily, they're susceptible to devastating infections because of their low absolute neutrophile count. The deposition in their bone marrow, of course, is bone crisis. They actually have infarcts in the bone, due to pressure on the vascular system, that leads to fractures. In bones that have very limited vascular supply, like the hip, they can end up with a vascular necrosis. This is a disease that has absolutely no neurologic aspects to it, in contrast to the other forms, and these people are perfectly functional individuals except for their Gaucher's disease. Unfortunately, due to this disease and its progressive nature, many of the patients expire in childhood or early adulthood.

Efforts were directed to treat these patients. You know, insulin for diabetes, why not enzyme for Gaucher's disease? Very early on Roscoe Brady at the NIH started purifying the enzyme and giving the enzyme to patients. For many years there was no proven clinical benefit. They were looking at biochemical endpoints, and one study showed one thing, another study by a different investigator showed another. It was very controversial until they started giving massive doses of the enzyme. They recently reported in the New England Journal that if they gave very high dose enzyme, and they changed the sugars on the enzyme, they could show that in rats and other species, the enzyme tailored in this way was targeted to the reticuloendothelial cell. That was the key, understanding the fact that you could tailor this enzyme and target it, and the effect was dramatic. Hemoglobin went up about a gram a percent a month. The platelet count increased. After six months of treatment, on the average, a 25 percent decrease in splenic volume occurred. As the patients were treated longer you could get up to 75 percent, but let's say it was an average of 50 percent after 18 months of treatment, rather dramatic. You could show that the hepatic volume in most of the patients, after 18 months of treatment, had decreased about 25 percent.

Who would have expected that giving an enzyme would have reversed the disease process? It's amazing! You're completely debunking a process that had gone on in these patients for years. When you looked at the
bone marrow pretreatment, their bone marrow was just full of Gaucher’s cells.

After treatment, in the young patients, in particular, there was remodeling, and only 15 percent instead of 85 percent of the marrow was filled with the Gaucher’s cell. A remarkable change!

There’s a debate about effective dose, and I’m not going to get into that. This is an expensive drug and the company that developed it started out taking human placenta and purifying it. Now there’s recombinant drug, and I think it will be more effective because it will be fresh enzyme. But the studies are ongoing now to determine the effectiveness of the recombinant, and to determine effective dose.

Our experience in this particular disease has taught us enzyme therapy works, and a little enzyme goes a long way. In the future, we’re going to detect these patients early on by genetic testing. We’re now going to be able to prevent the disease because we can give them a low dose or preventive therapy for a period of time, and maybe only have to treat them periodically. Maybe they only have to come in once a year to get rid of what they’ve accumulated in the past year, rather than starting in adulthood and trying to reverse many years of toxic accumulation.

You’re going to see this happen in other diseases. Protein replacement works. We’re coming out with recombinant drugs for a whole variety of diseases. Probably the next one on the market is going to be for hemophilia. These products don’t have the problems of natural biologics which are isolated from human blood or tissues, which bring with them all the viral possibilities. You know what’s happened in our hemophilia centers; they’ve been devastated by AIDS. Any hemophiliac who was born more than five years ago probably has AIDS. Only five years ago did we learn we could eliminate that particular complication.

I now want to turn to the 2nd example and teach you a little bit about gene therapy. If you were treating Gaucher’s now, by gene therapy, you’d go into every bone marrow stem cell and every liver and splenic cell, and you’d replace the defective gene with a normal gene. This is a “genetic surgeon.”

Actually, there are two kinds of gene therapy. There’s germ cell gene therapy and there’s somatic cell gene therapy. I want to differentiate the two for you. Germ cell gene therapy means you’re introducing into the germ line a new gene, which will then be inherited in successive generations. That is not permissible in the United States and in Western countries, for a whole lot of reasons. It’s discouraged or illegal in man, but it’s encouraged in mouse, and I’m going to show you how studies of germ line gene therapy in the mouse prove that gene therapy works.

Then we’re going to talk about somatic cell gene therapy. That’s taking the patient, like we do in medicine, and fixing the mutant gene in those cells in which the disease pathology is manifest. That’s what you’re reading about in today’s lay press, and shortly in the scientific literature. In the mouse we can take a female and male mouse, and we can ask them to copulate, and we can isolate the one-celled embryos. In the one-celled embryos we can see the pronuclei from the male and female contributions, and we can actually manipulate that one-celled embryo. We can inject into one of these pronuclei any gene we want from any source we like, and when the embryo divides, it will incorporate that gene. We can take the embryos and we can do ovaductal implantation in yet another mouse. A mouse who has mated with a vasectomized male and who is pseudopregnant has been hormonally conditioned to accept that embryo, and in fact, will take it to term. We can deliver the pups, and then we can take a little snap of the tail and see which one got the transgene, the gene you introduced. These are called transgenic mice, and they’re very important in terms of gene therapy.

This has been done in some mice that suffer from a growth hormone deficiency. These are called dwarf mice; they have a deletion of their growth hormone gene. We can take the rat growth hormone gene and introduce that into embryos that would have been dwarfed. Similarly, there is beta-thalassemia in the mouse, and it’s due to deletion of the gene. In this case, the human gene was introduced into mice that would have had thalassemia.

The approach of using growth hormone is being applied commercially, and there’s a company in Wisconsin which is introducing bovine growth hormone genes into cows, to make them as big as elephants, so that they’ll be able to ship these cow embryos around the world, and you’ll have lots of nutrition for underdeveloped regions.

Now what about somatic gene therapy? What we’re talking about here is taking a patient who’s got a genetic disease and fixing them. We have to get the normal gene into every one of the cells, across the cell membrane and across the nuclear membrane and then into the chromosome, where it’s stably integrated. Every time that cell divides, that gene will be copied and go into the daughter cells. That gene has to be placed in a position where
it will make its protein product or be expressed normally, so that it makes the right amount of the protein.

We’re using a retrovirus which is designed like HIV, except we modify it genetically. That virus enters the cell normally in its life cycle, absorbs under the membrane, gets into the nucleus, integrates into the host chromosome in a stable way and takes over and uses the host machinery to express its genes. We can do some genetic tricks to engineer the retroviral genome, and replace some of its important packaging genes with the human gene. And we can take the retroviral genome containing the human gene or the business portion of the human gene, the portion that encodes the protein, and package it up as a defective retrovirus. What’s a defective retrovirus? It doesn’t have the retroviral genes that are needed to maintain its life cycle, to go into a cell and, once it’s in there, to make the packaging proteins that are necessary so it can go and infect other cells in the body. In fact, this defective retrovirus will just go into the cell once and put the human gene into the host genome and that’s it. It can’t go on; it’s not infectious and that’s why we call it defective. So it can only get into that one cell and add the gene to the chromosome. We can take bone marrow from a patient, put it in culture, and infect it with the defective retrovirus. We can take liver cells, get them to divide in culture, or any other cell that you can get to divide in culture, and introduce the defective retrovirus into it, and then transplant back into the patient. And what’s the candidate disease? Well, there are two candidate diseases right now where gene therapy is being done. The first one is severe combined immunodeficiency disease. This disease is treated by bone marrow transplant. The technology at this point is just taking leukocytes from the patients, putting the gene into the white cells and giving them back. So it’s sort of a leukocyte infusion with the gene. But in the future they’re going to take the bone marrow from the patient, use the retrovirus to infect the bone marrow cells, and then ablate the patient’s own bone marrow, give him a transplant with his own marrow containing the gene, and that should cure the disease.

The other disorder that is being treated is homozygous familial hypercholesterolemia. I understand there’s one patient that’s been treated. This is a disease in which the LDL receptor is defective. Wilson, in Michigan, first demonstrated in an animal model, the rabbit, which has hypercholesterolemia due to the same genetic defect, that he could fix it by giving the gene to the rabbit hepatocytes which brought down the cholesterol levels. It was very effective. He got permission to do this in the human. The human trial is underway, and although it’s not been reported, I understand the results are very encouraging.

You’ll read about that in the very near future.

Another disease that is the target for gene therapy is cystic fibrosis. The gene’s been cloned, and people have put it into retroviral and other vectors. The vector that is being used by Crystal’s group is the adenovirus. The idea is that you’ll just inhale the adenovirus containing the normal gene and it will get to the cells in the lungs to provide what’s needed and correct the disease in that target site of pathology.

Some of you are interested in atherosclerosis. Surgeons have been interested in angioplasty. We might be able to do the angioplasty, and at the same time introduce the gene that will get rid of the plaque. So that’s one approach, directly administering the virus right to the site of pathology.

Another approach which people are working on is taking neurotropic viruses, like herpes-simplex, and putting genes in that might fix Alzheimer’s or genetic diseases where mental retardation is the major clinical manifestation. We’re talking about using that neurotropic virus, where you’d introduce that gene in either the spinal cord or directly into the brain, and it would eventually get to the neurons and correct the disease.

Well, everything I’ve told you about gene therapy so far has been add-a-gene. And it will only work for those diseases that are recessive traits where you can add the missing protein and get clinical benefit. For the dominant diseases where one good gene and one bad gene don’t make for normalcy, such as for Marfans and many of the other dominant diseases, this approach won’t work. What we’re really going to have to do is go right to where the gene is and fix the mutation. People are learning how to do homologous recombination, to actually fix genes in cell culture, and it won’t be long before this approach may be feasible in terms of gene therapy.

You can predict that the next decade will be the decade of molecular therapy for genetic diseases. We’re going to be able to treat many by protein replacement, and for an ever-increasing number of diseases in which the disease genes are identified, we’re going to have gene therapy. You can bet on it. Gene therapy is going to work, and we’re going to cure many of these diseases. Thank you. (applause)

DR. LAIRD JACKSON, Thomas Jefferson Medical College: If I could just offer a comment on your last topic. As you know, Darwin Procoff at our institution has been interested in the genes that are involved in matrix pro-
teins. He has some intriguing ideas, and apparently some initial results from in vitro and, perhaps, also from in vivo work with mice. If there is an abnormal dominant gene that's making protein pro-collagen chain which forms an abnormal collagen that won't then form its triple helix and a secure structural protein, by the introduction of antisense oligonucleotides he can convert an abnormal heterozygote into a normal hemizygote, apparently. That may lead to something that would work for the dominant diseases.

DR. DESNICK: I am familiar with that approach and his work. I think there's no end to the creativity that's going to be applied in this molecular revolution. Down the road, we're going to see a lot of these genetic defects fixed. (applause)

MODERATOR: I'd like to thank Dr. Desnick for his excellent presentation. I think if he ever needs a career change he can probably find a lot of underwriters looking to hire him. There is one more person I want to thank, and that's our chairman of our genetic issues committee, Dr. Sandy Lowden. He has brought this group together, and I don't think anybody in this room or in our industry could have done it as well. He has experience in genetics. He has the contacts. He has experience in insurance medicine, and he has a real commitment to making a difference. So please join me in giving a hand of thanks to Dr. Lowden.