Diabetes Management

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Defeating diabetes

DR JAY S SKYLER* SPEAKS TO NATASHA LEESON, COMMISSIONING EDITOR: Dr Skyler, MD, MACP, is currently a Professor of Medicine, Pediatrics and Psychology, in the Division of Endocrinology, Diabetes and Metabolism, Department of Medicine, University of Miami Miller School of Medicine (FL, USA). He is Deputy Director for Clinical Research and Academic Programs at the Diabetes Research Institute, University of Miami, and is Adjunct Professor of Pediatrics at the Barbara Davis Center for Childhood Diabetes, University of Colorado. A native of Philadelphia, Dr Skyler is a graduate of Pennsylvania State University and Jefferson Medical College, and did his postgraduate training in Internal Medicine and in Endocrinology and Metabolism at Duke University Medical Center. Dr Skyler's research interest focuses on immune intervention and β-cell expansion or replacement. Since 2001, he has been Chairman of the NIH (NIDDK)-sponsored Type 1 Diabetes TrialNet, an international network conducting clinical trials to prevent Type 1 diabetes or interdict the Type 1 diabetes disease process. Type 1 Diabetes TrialNet is the successor of the Diabetes Prevention Trial – Type 1 Diabetes Study Group, of which Dr Skyler served as Chairman throughout its existence from 1993 until it was replaced by TrialNet. Dr Skyler received the 1985 Achievement Award of the American Society of Contemporary Medicine and Surgery for "Distinguished Contributions to the Knowledge of Diabetes Mellitus". He received the 1992 Banting Medal for Service to the American Diabetes Association. In 2005, he was named a Master of the American College of Physicians (MACP). He received the 2014 Distinction in Endocrinology Award from the American College of Endocrinology. He has written over 450 articles, book chapters or editorials.

Q How did your career lead you to working in diabetes?

When I was a medical student, I did a research project where I was grading the degree of diabetic retinopathy from fundus photographs in a study in which my professors were destroying the pituitary gland; the neurosurgeons had developed a new technique, this goes back to 1960s so there wasn't much available, to stop rapidly progressing diabetic retinopathy. It had been previously shown that if you open the skull and took out the pituitary gland, via open craniotomy, that it could slow the progression of disease, but that was a rather huge procedure. So, they developed a new technique where you could go through the nose with a probe and, using radiofrequency, coagulate and destroy the pituitary gland. That technique made it easier to do the surgery, and so individuals who had rapidly progressive retinopathy that was threatening vision would come from all over the world in order to have the procedure done and they got fundus photographs of their eyes before and after. It turns out that the procedure did work approximately a third of the time in reversing things, a third of the time stopping progression and a third of the time it did not work at all. My job was to grade the fundus photographs, and I did not know if they were before photographs or after photographs. One time I asked if it was

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possible to go on rounds and see the patients who were participating in this, and when I went on rounds, I was flabbergasted to find that the patients were my own age. I was a very young medical student; I was probably only 20 years old. Most of the patients were late teens and early 20s. It really shocked me because these were very young people with Type 1 diabetes who were already going blind and progressing rapidly. It was already known by then, in animal models at least, that if you had excellent glucose control you could slow the progression of complications; although it was hotly debated, the following year – 1968 – saw the emergence of two papers claiming opposite sides as to whether microvascular disease – including retinopathy – was an independent genetic problem, or whether it was really related to glucose control. I looked at that and thought there had to be a way to make diabetes control better. So, I sort of differentiated into a diabetes specialist as a medical student in 1967. And I have stayed with it ever since. I have progressively seen the disease get better and better as we have developed, and I have been happy to participate in some of the developments, of ways to make the disease better and easier to manage.

Q Were there any particular colleagues that you worked with who really influenced the path your research has taken?

Yes, there have been many folks, but the two I will single out are the late Richard Field who was my mentor as a medical student, who got me interested in diabetes in the first place, and Harold Lebovitz, who I met when I was an intern and resident at Duke University (NC, USA) was chief of endocrinology there at the time, and with whom I did my fellowship. There were a lot of other people along the way who have influenced me and have clearly contributed to success. I guess two others I should mention. One was my godfather in the American Diabetes Association, the late Donnell Etzwiler. I first met Don when I was working at the National Institute of Health, and I had done a survey of diabetes summer camps, circa 1973. Don was organizing the first international congress on diabetes and camping, and he invited me to speak at that. It was the first time I had been an invited speaker at any event, and since I had done the survey I had all the data. Subsequently that led, within a year or so after that, to my becoming the chairman of the American Diabetes Association (ADA) Camping Committee, which got me involved in ADA. During that involvement, a couple of years later, Don was forming a committee to develop a new journal for the ADA, *Diabetes Care*, and asked me to be on that committee and it turns out the plan that I proposed for *Diabetes Care* was the one that the committee accepted, namely that it be a peer-reviewed journal that would focus on clinical contributions to diabetes. I was then asked to be the editor. Thus, I had the privilege to be the first editor of *Diabetes Care*, and Don was responsible for stimulating me to do that. My grandfather in the ADA, if you will, was the late Harold Rifkin from New York, who guided me into leadership positions at ADA, which resulted in my being president of ADA and vice-president of the International Diabetes Federation, all because of Harold pushing me in those directions. Those are the four people who mostly influenced my development. Subsequently, I was lucky enough to give the Etzwiler memorial lecture at the International Diabetes Center in Minneapolis (MN, USA), the Center that he founded; and the Rifkin memorial lecture at Albert Einstein (NY, USA). I feel privileged to have honored my mentors in that way.

Q What do you consider to be the biggest achievement in your career so far?

I have been involved in so many things over the years; it is difficult to dissect all that out. I would say that starting *Diabetes Care* was certainly a big achievement. Another was that I happened to be one of the first investigators to introduce patient self-monitoring of blood glucose. The late Thaddeus (Ted) Danowski – there's another person who influenced my life – had introduced me to the concept of having patients measure their own blood glucose. Ted had the first paper on that subject, although he doesn't always get credit for it. The paper happened to be in the inaugural issue of *Diabetes Care.* He had shown me about this approach. Thus, we were one for the first groups to have patients measure their blood glucose to manage their diabetes. And with that, we had to teach patients what to do with that information. We ended up developing algorithms for patients to use to adjust their insulin dose and manage their own disease. This was important, as you wanted to avoid hypoglycemia yet still maintain good glucose control. So those algorithms for dose adjustments became quite popular in the late 1970s and early 1980s after we published them. All the blood glucose monitoring companies were distributing them with their monitors for a while, someone called

them 'Skyler algorithms', giving me a lot of notoriety. I received an award for having developed the algorithms – the achievement award of the American Society of Contemporary Medicine and Surgery "for distinguished contributions to the knowledge of diabetes mellitus." Michael DeBakey presented me with the award, and it was a thrill to get to meet him. The algorithms were an important achievement that really began to change the course of the disease by letting individuals manage their disease, and we were one of several groups that were champions in that regard. Together with three of those other champions – David Schade from New Mexico, the late Julio Santiago from St Louis, and Bob Rizza from Mayo Clinic – we got together and wrote a book on how to achieve excellent glucose control that was published in 1983 called *Intensive Insulin Therapy*. That became the bible of how you do this and sort of became the methods section of the Diabetes Control and Complications Trial. Beginning in 1993, I was approached by the NIH to chair the Diabetes Prevention Trial for Type 1 diabetes and then subsequently to chair its successor beginning in 2001/2002 – Type 1 Diabetes TrialNet (the clinical trials network for Type 1 diabetes), which I am still involved in. I have now spent more than 20 years chairing the NIH networks to try to halt the progression of Type 1 diabetes, either by preventing it or preserving pancreatic beta-cell function, which we do mostly with immune intervention strategies. It's a lot of fun. The nice thing about it is that it has been really great to try and put these things together and try and make an impact.

Q You're the chairman of Type 1 Diabetes TrialNet. How did this network come about on the back of the Diabetes Prevention Trial?

We were approaching the end of the 8 years of funding for the Diabetes Prevention Trial. We proposed that instead of just doing single prevention trials like we had done, that the network we had constructed should be expanded to do several trials simultaneously. This would mean that we could look at different things, particularly in prevention, but also in terms of preserving beta-cell function in new-onset Type 1 diabetes. We were able to expand on the network from the Diabetes Prevention Trial and we've had quite a number of studies that we have completed, a couple of which have been successful in demonstrating potential preservation of beta-cell function in new-onset Type 1 diabetes. Some of our studies have also failed to demonstrate this, which was surprising to us on a couple of occasions. But, you never know when you start to do a trial how it will end; if you did you wouldn't need to do the trial. I have been called by some the 'master of the negative trial', as several of our trials have been negative, yet fortunately we still have been able to publish these. I consider myself a clinical trial-ist by trade, having done all these trials for all these years. One of the things that I have learned is that negative studies, as well as positive studies, ought to be published. When studies are well conducted, regardless of the outcome, there is something to be learned. I think that's a critically important issue. For example, there was a pilot study with glutamic acid decarboxylase (GAD) that suggested that a GAD vaccine may be effective in preserving beta-cell function. Yet, we noted that only appeared to be true in a tiny subgroup. Since we wanted to use GAD in a large prevention study, we decided first to do a large Phase II trial to determine whether or not there was sufficient evidence of an effect of GAD to warrant a prevention trial. However, our Phase II trial turned out to be negative, and we published it in *The Lancet*. Around the same time we were conducting that trial, the company that made the GAD vaccine went and did two large Phase III trials. These also turned out to be negative. Had they waited for our Phase II trial they might have saved themselves the trouble and money. On the other hand, we should not write GAD off altogether. Although the GAD vaccine did not work by itself, there are a lot of theoretical reasons that GAD might work in combination with other interventions. In general, I that negative studies still teach us lessons; there are often mechanistic studies associated with them that give important insights.

Q What are the aims of the network? What do you think have been the most promising results so far?

One of the studies was on a costimulation blocker, called abatacept, we demonstrated with that preservation of beta-cell function in new-onset Type 1 diabetes. We thought that was promising. We are now studying it in individuals who do not have diabetes as one of the prevention studies. Our main mission in TrialNet is to try and prevent the disease. If this does turn out to prevent the disease in this cohort, I think it will turn out to be a major contribution. Its effect

of preserving beta-cell function in new-onset diabetes was not a sufficiently robust effect to recommend it as a treatment modality by itself at this juncture, but the fact that it works to some extent allows us to conclude that this is something we should test further. We are currently doing this, and in the end I think we will learn a lot from it. One of the other things that another research group did was with anti-CD3 monoclonal antibodies; TrialNet wasn't the lead sponsor but a lot of our centers participated in that and we collaborated on some of that, and we're taking that into prevention as well. So we have a number of these things that have been studied in new-onset diabetes and show promise that we have been able to take into prevention studies. I think this is a direction we are going to see things moving in.

Q You've recently published a paper on the importance of considering autoantibodies in assessing the risk of Type 1 diabetes. Can you tell me a bit about this study? How do you propose this could be translated into the clinic?

One of the things we've learned from the combined DPT-TrialNet experience is that we can take a number of factors that are present and put them together to get an idea of who is at risk of the disease, which is particularly helpful if you are going to be doing prevention studies. It turns out we do our initial screening by measuring antibodies, whether or not people have them, and by collating all this information we are able to tell who with antibody levels are at what degree of risk. It's interesting because when we screen for antibodies, it turns out that 95% of individuals do not have them when we screen. So you get a 95% chance that we're not necessarily interested in you. If you're young (below 10 years of age) we want to screen you again every year just to be sure that you don't convert. But the conversion rate over 10 years of age is very low, and essentially nonexistent over the age of 20 years, so we continue to re-screen individuals yearly up to 10 years of age and every other year up to 20 years of age. However, the bulk of individuals we are going to find will be found on the first screening. But then we want to be able to subdivide them further, so we look at a number of parameters (genetic, antibodies, metabolic) to try to define what is their quantitative risk. One thing we've learned over the 20 years we've been doing this, is that we are pretty good at predicting who is going to develop the disease and over what general time frame. Therefore, we can categorize individuals for potential participation in future prevention studies. This is enormously helpful. As I've mentioned, we're doing a study with anti-CD3, we're doing a study with abatacept in prevention, and oral insulin in prevention. The oral insulin one is an interesting story because what we are trying to do is confirm a finding that we found in a *post-hoc* analysis in DPT1. In DPT1 we took people of certain characteristics and put them into a study of oral insulin. Statistically, it turned out that oral insulin did not delay or prevent the development of the disease in the group as a whole. But if we looked at a subgroup – which actually was about two-thirds of the patients who we enrolled – who had higher levels of insulin autoantibodies at baseline, the data suggested that oral insulin might delay the onset of diabetes by 4–5 years. If we looked at those who had the highest levels of insulin autoantibodies at baseline, oral insulin could be projected to delay diabetes for 10 years (I say projected as few participants were followed for that long). From this we were able to devise a new oral insulin trial to try to confirm or refute those findings. If we can delay the disease 5 or 10 years by taking one pill a day, we really want to do that. Unfortunately, the subgroup analysis showing benefits was retrospective and not prespecified, we need to do the second trial to answer the question.

Q Do you think in the future there could be one 'magic bullet' to prevent diabetes or do you think prevention will require a multifactorial approach?

I think there is enough heterogeneity in terms of the disease that I seriously doubt that there will be one single 'magic bullet'. I think we will need to be looking at a variety of different approaches that we might use at different times in people with different characteristics. I do think we will be successful in preventing the disease, but it will likely require a combination of several interventions. I also think we will be successful in preserving beta-cell function, and I think we will be successful in reversing the disease. That is one of the things that my colleagues here at the Diabetes Research Institute focus on, in terms of developing a platform that we call the BioHub, which will allow insulin replacement by cellular therapy. I think the field is moving well and I think some time in the future we will be able to prevent Type 1 diabetes, we will be able

to stabilize Type 1 diabetes and keep beta-cell function going for a protracted period of time, and we will be able to replace beta-cell function in people who have already lost it. I am highly enthusiastic in where the future is going!

Q How important do you think comorbid conditions, such as depression, are in medication nonadherence in individuals with Type 1 diabetes?

That's a tougher question to answer. People use the term depression because that is something that is identifiable. As I look at it, Type 1 diabetes comes in and in order to manage it you need to take injections several times a day, you need to be measuring your glucose levels, so you are always going to have to track what your blood sugars are doing. That will impact all your food choices and it will impact all of your exercise choices, and no matter how good we are at predicting, it is an imperfect science and this can be very frustrating for patients. I think it is a frustration as much it is as anything else. You can call it depression. I think managing diabetes is a major challenge and I think one has to appreciate that and recognize that these are struggles and even if you are doing everything well, it still may not turn out the way you like. That can be enormously frustrating. It is unsurprising that there are times when patients feel like they need to give up and stop. I'm not sure it's a real depression, I think it is the difficulty of dealing with a disease that is complex and one has to juggle an awful lot of balls in order to be successful. In terms of children with the disease, it becomes the whole focus for their parents. As a teenager, if you want to go out with your friends, you have to stop and think of other things first. Many patients decide they don't want to tell their friends they have diabetes; I think they should. For one thing, in case they get into some sort of difficulty their friends ought to know how to help them out. It is not something they should be ashamed of. I'm not sure I would call it depression; I think it is really a life struggle that brings with it its own unique factors, complications and stresses that can be difficult to manage, as opposed to a type of depression that is a brain chemical imbalance.

Q Where do you see the field of Type 1 diabetes research going in the next 5–10 years?

I think we have had some great practical research over the last several years. The introduction of continuous glucose monitoring has really allowed people, instead of just having a glimpse of what their blood sugar is four- or five-times a day, they can see what it is every 5 min continually, without needing to do a blood stick test. That is very important. If your blood sugar happens to be 10 mmol or 180 mg/dl, which is too high, but you know it is dropping because it was previously been at a peak which was 150% of that, and is dropping, that's different than if it is at the same level but it is rising. So looking at the pattern at what is going on is even more critical when you are close to your target. Because if you are sitting there at 5.5 mmol, which is 100 mg/dl, that is exactly where you want to be but if you are dropping rapidly, then that is different than if you are rising rapidly and that is different still if you are stable at that level. Patients who have access to this information are much more able to make an informed decision about their food, activity and insulin, so I think it has been an absolute tremendous advance in the field that can really change people's lives and I really think is the most exciting thing to happen over the last decade or so.

I have already mentioned over the next few years being able to prevent Type 1 diabetes, being able to stabilize beta-cell function, being able to reverse it with cellular therapy. The other thing is coupling the continuous glucose monitoring to appropriate algorithms to control insulin release, presumably by a pump, which would essentially be a bionic pancreas. There are approximately 19 or 20 research groups around the world that I can count who are working on the concept of a bionic or artificial pancreas. I think that will come to fruition over the next number of years and I really look forward to it.

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