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Q1 You have led or contributed to some of the most influential clinical trials in diabetes, and many of their findings have fundamentally changed practice. But there can be a gap between what a major trial demonstrates and what actually happens in the clinic. Where do you think we are still failing to translate the evidence we already have into better diabetes care, and what could we do to better bridge this gap?

The major studies I have participated in have all been collegial, collaborative efforts. I helped lead some of them, principally the long-term follow-up of the Diabetes Control and Complications Trial (DCCT) in Type 1 Diabetes (T1D), the Diabetes Prevention Programme (DPP), its follow-up, the DPP Outcomes Study (DPPOS), in Type 2 Diabetes (T2D), and the Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness (GRADE) study, which was a multicentre comparative effectiveness study of T2D therapies.

At the start of the DCCT, we had only old-fashioned insulins and pumps that were heavy, bulky, and difficult for patients to use. Industry took what the DCCT showed, specifically, that intensive therapy aiming for near-normal glycaemic control had multiplex benefits, and ran with it: finger-stick monitoring evolved into continuous glucose monitoring (CGM) and pumps became smaller, more programmable, and with built-in feedback control. All of the fundamental research was funded by the National Institutes of Health (NIH), particularly the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). Once the science was there, industry looked for a business model and developed new insulins, better monitoring, and automated pump technology; innovations that needed industry's capital to reach patients.

For T2D, I was fortunate to work with the late Joel Habener, the father of glucagon-like peptide-1s (GLP-1), at my institution. None of us ever anticipated these medications would come to dominate medical care and even economies worldwide. I had the good fortune to be among the first people to give a GLP-1 to a human being in our clinical research centre, and showed that it stimulated insulin and lowered glucose levels. In the first paper we wrote on GLP-1, around 35 years ago, I wrote that whether these chemicals would ever become effective medications remained to be seen; the understatement of a lifetime.

I can remember the first time that I should have realised that the GLP-1s might be good for weight loss. We were giving the purified hormone intravenously, and when I turned up the infusion rate on one occasion, the participant vomited, our first clue that it affected gastric motility, though we didn't appreciate its significance for weight loss at the time. Industry then developed the GLP-1s progressively from an intravenous infusion into twice-daily and then once-weekly

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injections, combined them with other active agents, and they have since become, among other things, the most effective weight-loss medications ever seen.

That pattern of drug and device development holds more broadly: federally sponsored scientists make the fundamental discoveries, and industry commercialises them. Once basic science and federally funded clinical studies pave the way, industry has generally done the right thing in advancing those discoveries into the public realm.

The remaining translational challenges are numerous, but I would highlight two. The challenge for T1D is ensuring that intensive therapy is affordable and available to all, and is modified, as needed, to be accessible and acceptable to younger people. For the prevention of T2D, we need to focus on implementing the lessons learned in DPP and DPPOS in a much broader swath of the at-risk population. The effective implementation of prevention strategies is especially needed in low- and middle-income parts of the world where barriers to diabetes prevention need to be systematically dismantled. When it comes to the treatment of T2D, we need to apply what we have learned and continue to learn about its heterogeneity more effectively, and stop treating all people with T2D as if they have the same disease.

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Q2 The DCCT and its long-term Epidemiology of Diabetes Interventions and Complications (EDIC) follow-up have shown that the benefits of good glycaemic control can persist for decades, including effects on complications and cardiovascular outcomes. With today's CGM, automated insulin delivery, and other technologies, is there anything you think clinicians lose sight of about the fundamental lessons of DCCT/EDIC, and what remains just as relevant today as it was 30 years ago?

As you've pointed out, the major lesson of the DCCT was that over a relatively short period (the study averaged 6.5 years of follow-up) in a lifelong disease, we achieved remarkable results. We were powered to detect smaller differences than we actually saw, and the study was stopped a year early as a result.

We found that intensive therapy, using what now look like prehistoric tools, reduced complications by 35–75%, and that this was entirely owing to the separation in HbA1c we achieved between the two groups. But these were early-stage complications; participants were young and close to the start of their disease, so almost no one had advanced complications such as losing their vision or having a heart attack. Once we had the initial DCCT results, we were ethically obliged to teach the conventional therapy group intensive therapy, and, at the same time, we planned a long-term follow-up, EDIC, to see whether these early results would translate into lasting benefit.

Since 99% of the benefit came from the separation in HbA1c, and we expected the two groups' HbA1c would converge once

everyone was on intensive therapy, we assumed that the differences in complications might disappear too. They didn't. A phenomenon we now call 'metabolic memory' meant the differences in outcomes continued to widen for a decade or more after the HbA1c levels in the original intervention groups converged. The original intensive therapy group went on to have less severe vision outcomes, kidney failure, heart attacks, and death.

The DCCT established the worldwide standard, since 1993, of an HbA1c target below 7%, the level where intensive therapy had near maximal benefit but with minimal risk of hypoglycaemia. What has changed since is that CGM and automated insulin delivery now let people lower their HbA1c further with relatively less risk for hypoglycaemia, meaning that, without needing further studies, we may now be able to safely push for lower targets (for example a 6% HbA1c), and reduce complications even more.

There is a downside with intensive therapy though, alongside the risk of hypoglycaemia. Intensive therapy, having effectively eliminated most glycosuria, provided more efficient utilisation of calories, leading to weight gain, and we are now seeing people with T1D becoming overweight or obese, something we did not anticipate having to combat. So, we have also created some problems we need to deal with.

Overall, the lessons from DCCT continue to underlie the modern-day therapy of T1D. By aiming for near-normal glycaemic levels, people with T1D can now look forward to healthy, normal lifespans with the long-term complications largely reduced if not eliminated.

Q3 One of the striking features of the GRADE study is that it asked a question clinicians actually face: not simply whether a drug works, but which effective treatment works best for which patient. You have also previously said that T2D is probably not one disease but contains a number of subgroups, yet we often treat all T2D similarly. How close are we to being able to use that heterogeneity to make genuinely personalised treatment decisions, rather than simply choosing from an increasingly large menu of effective drugs?

That question was the basis for starting GRADE, which we began planning almost 20 years ago. These large studies take a long time, and you have to think carefully about whether the questions will still be relevant by the time you finish. The GRADE investigators compared the effectiveness of four of the major glucose-lowering medication classes. Unfortunately, we didn't include sodium-glucose co-transporter 2 (SGLT2) inhibitors, for example, because they had not yet been approved during the planning stage of GRADE.

Even 20 years ago, it was clear that treating T2D as a single disease was a major public health problem in diabetes. T2D is now the world's most common chronic disease and is continuing to grow. So, the question is whether we are close to identifying subtypes and using that heterogeneity clinically.



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T1D genetics are relatively straightforward compared with the polygenic T2D. Most geneticists have concluded that sub-classifying T2D based solely on genotyping is aspirational. Aside from the monogenic forms of diabetes, which affect a tiny fraction of people and, once identified are treated specifically, the treatment of the vast majority of people with T2D would likely not benefit from understanding their genetic background.

Beyond genotyping people with T2D, phenotyping them to guide therapy also remains largely aspirational, because the needed studies simply haven't been done. We know we can separate patients into subtypes, for example based on relative insulin resistance or deficiency, but not whether they respond differently to therapy 'X' or 'Y' over time. Answering that question was, in part, why we designed GRADE, to compare major classes of medications, when added to metformin, and look at differences between them in their ability to maintain target levels of glycaemia. We are now doing secondary analyses looking, for example, at insulin resistance versus deficiency as a way of subtyping. I think that these insights will be a major scientific dividend from GRADE.

Notably, GRADE had no placebo group. It was a comparative effectiveness study, with active medications competing against one another, which was a new world for me. Industry was remarkably generous in contributing medications, including liraglutide, without which the study would not have been

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affordable. I hope that continues, because the cost of independently studying newer drugs, without a company's support, is now a real barrier to this kind of research.

Q4 The DPP showed that T2D could be delayed or prevented through lifestyle intervention and metformin, and its findings have subsequently been translated into large-scale prevention programmes. Given how strong that evidence is, why do you think diabetes prevention remains so difficult to deliver at population level, and what have we learned about making prevention interventions practical and sustainable rather than simply proving that they can work in a trial?

Let's start with metformin. It remains unapproved in the USA for diabetes prevention, despite a 31% reduction in progression to diabetes during DPP and long-term follow-up of the DPP showing that the original metformin group maintained a 17% lower risk of developing diabetes some 20 years after the study ended. Metformin is also cost-saving, not merely cost-effective, because of its low cost and the cases of diabetes it prevents downstream. Yet, it isn't approved in the USA, largely because metformin is generic and manufactured inexpensively by many companies; therefore, there is little profit to be made in requesting a new indication through the regulatory process, which is costly for the requesting manufacturer. I find the failure to request a new indication for metformin for prevention colossally short-sighted.

The lifestyle intervention, which was even more effective than metformin, has fared somewhat better. To the USA's government's credit, it is now covered by public funds through Medicare and Medicaid. So, why hasn't this dented the epidemic more? Likely, because implementing lifestyle changes to lose weight and increase physical activity is hard. The rise in obesity has paralleled the rise in the number of health clubs in this country. It isn't causal, but it illustrates how difficult behaviour change is when food is plentiful, calorie-dense, heavily advertised, and delicious, while daily life demands less physical activity than ever before. We seem, as a species, unable to resist temptation, despite knowing the consequences.

The benefits of a lifestyle intervention aren't unique to the DPP. The Da Qing study[1–4] and others have shown the same pattern of effective interventions that are hard to sustain at scale. Now, GLP-1s have been shown in short-term studies to be potentially more effective at producing weight

loss and preventing diabetes. However, the cost of using them population-wide would be enormous, and there is the major, separate question of long-term sustainability. This is one of my real disappointments: manufacturers have shown little interest in improving the longevity of use of these drugs. Their business model is to sell as much as possible now, even though roughly half of people stop within a year, weight regain follows, and diabetes returns. These drugs are not the cure-all they are sometimes presented as, and, in my opinion, companies have an ethical responsibility to find better, less expensive, more sustainable ways of using them long-term, something we are only beginning to grapple with as newer, more powerful combination drugs bring the same on-off pattern.

Q5 The burden of T1D has been transformed by advances in intensive insulin therapy, pumps, CGM, and closed-loop systems. Yet you have suggested that the really important frontier may now be whether we can alter or reverse the disease itself. If you look beyond the technologies that are improving management today, which developments in T1D do you think have the potential to genuinely change the trajectory of the disease?

This is also aspirational. I think of it as a pyramid: at the base is treating diabetes to prevent or delay complications, which we have achieved. Next is salvaging or replacing β cell function, and we are getting better at that with therapies like teplizumab, directed against the autoimmune, CD8/CD3-mediated process, and with new approaches to islet transplantation.

> **The DCCT gave one of the earliest demonstrations that preserving β cell function matters clinically**

The DCCT gave one of the earliest demonstrations that preserving β cell function matters clinically. In participants with limited disease duration who still had some insulin secretory capacity, intensive therapy preserved C-peptide secretion for about 2 years longer than conventional therapy. That group went on to have lower HbA1c, fewer complications, less insulin requirement, and fewer hypoglycaemic episodes, showing that preserving β cell function early in the disease has real clinical value, even without immune therapy.

Newer immune therapies can't prevent T1D yet, though that was the original goal, but they can slow its progression. Talking to parents of newly diagnosed children made me appreciate how much delay alone matters to families, pushing onset from age 7 years to 9 or 10 years, or from pre-pubertal to post-pubertal, means a great deal, even without full prevention.

To actually prevent T1D, we first need better, safer tools for immune modulation, which are coming. The practical problem is identifying who to treat. We can screen first-degree relatives who are at high risk for autoantibodies, but only around 10% of people who develop T1D have an affected relative; the other 90% develop diabetes *de novo*, without an affected first degree relative. We would therefore need to screen huge, unselected populations to catch most future cases, which is a major public health and affordability challenge we are still far from solving.

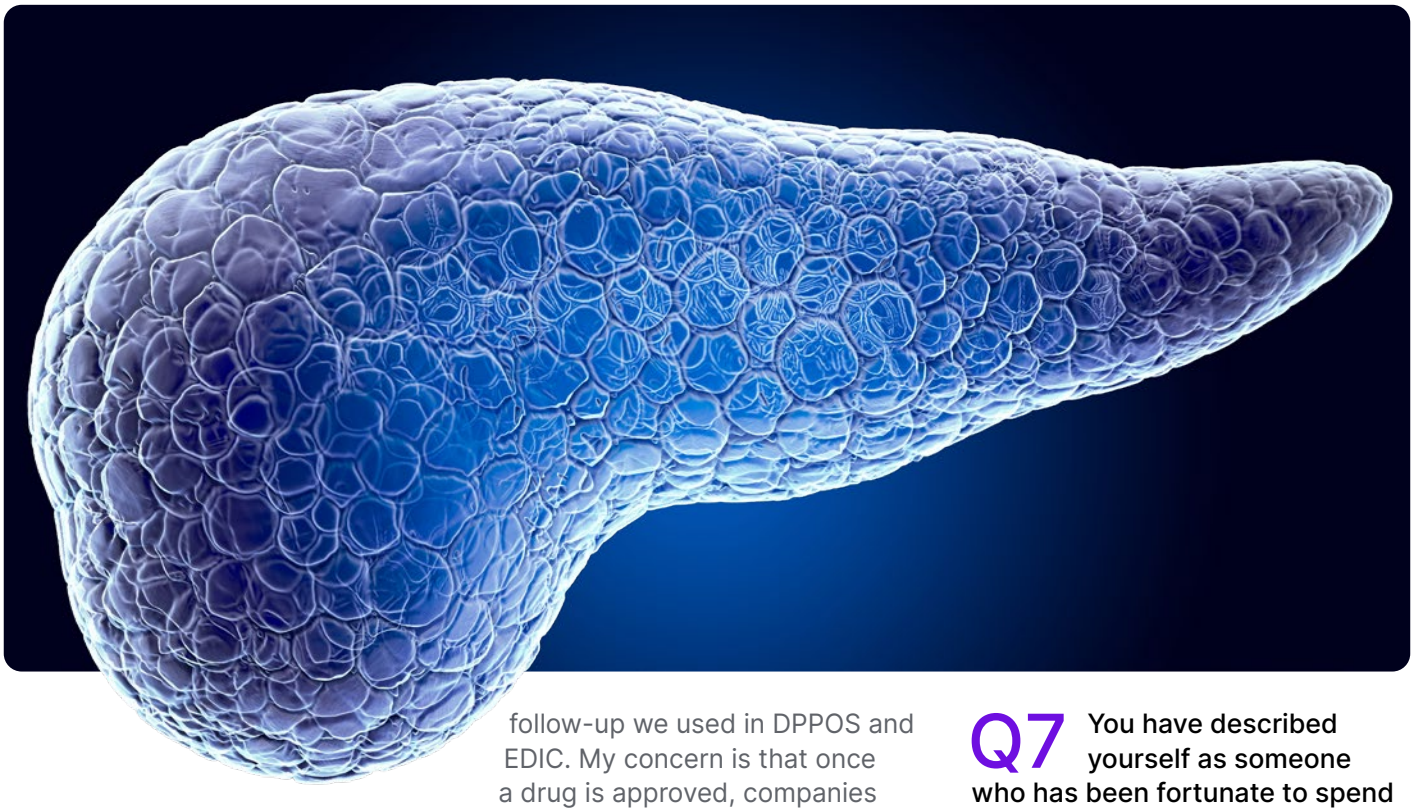
Slowing β cell destruction with intensive therapy is more achievable now, helped by smaller, easier CGM devices that can help "close the loop," providing more physiologic insulin delivery and glucose control. However, implementing intensive therapy in children and adolescents remains harder than in adults.

Q6 Looking across DCCT, EDIC, DPP, and GRADE, a common feature is that these were large, long-term studies designed to answer questions that could not be answered by smaller or commercially driven trials. If you were given the resources to launch one new landmark diabetes trial today, without worrying about whether it was commercially attractive, what question would you most want that trial to answer?

The major human and financial cost of diabetes lies in its complications, the kind we studied in the DCCT, though it wasn't until EDIC that we demonstrated the reductions in cardiovascular disease and mortality. I can now tell the parents of a newly diagnosed child with T1D that their child's prospects are utterly different from 30 years ago; we haven't eliminated complications, but we have reduced them substantially.

We shouldn't forget the UK Prospective Diabetes Study (UKPDS), led by the late Robert Turner and Rury R. Holman, University of Oxford, UK, which did equivalent work in T2D at

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the same time as the DCCT. The UKPDS established in T2D the myriad benefits of "tight control." Worldwide, T2D is the more 'popular' form of diabetes. They deserve more recognition than they have had.

The lesson for future trial design is that this is a chronic, lifelong disease, and even with excellent surrogates like HbA1c, we need studies long enough in duration to demonstrate benefits in long-term complications, not just short-term markers. The studies I have been involved in have run for 30 or 40 years, thanks to unwavering federal support by the NIH, and that is the timescale we need to keep in mind, even though few have the patience for such long-term studies.

If I could launch one new trial without worrying about commercial attractiveness, it would test whether today's dramatic short-term results, particularly with GLP-1s, actually translate into sustained long-term benefit, using the same kind of long-term, persistent follow-up we used in DPPOS and EDIC. My concern is that once a drug is approved, companies have little incentive to fund long-term follow-up, and it may become impossible to run proper epidemiological studies once medications, like the GLP-1s, are so widely used that no meaningful comparison groups remain. We know these medications work over 1 or 2 years on important acute outcomes, including cardiovascular events, and I don't dispute that. But we need to know whether people who stop taking them simply return to their original path towards serious complications. A benefit that vanishes soon after someone comes off a drug is not a benefit for public health.

> **That is where a genuinely personalised approach to treatment will make progress over the next decade**

Q7 You have described yourself as someone who has been fortunate to spend almost 50 years solving problems in diabetes research, and you continue to be interested in questions around individualised treatment and improving outcomes. What are you most curious about now? What would you like your research team to help us understand over the next 5–10 years, and what would success look like for patients and clinicians?

If I were a new investigator, I would be back in the laboratory looking at new tools. The tools of my early career, measuring acute and chronic glycaemia, pumps, and multiple daily injection regimens in T1D, have been used effectively by a whole community of researchers. Now, the question is how to move further up the pyramid I mentioned before, for both T1D and T2D, and address what remains a lifelong disease more fundamentally by investigating cures.

T2D can already be reversed in some people, first shown with weight-loss surgery, and our

own DPP showed that people who returned to normal glucose tolerance did best of all. If I were redirecting my own effort now, it would be towards developing new tools in molecular biology and genetics. I was fortunate to be in the right place with the right colleagues to work on the HbA1c assay, pumps, and multiple daily injection regimens, and later on the GLP-1 story, purely because I happened to be down the hallway from Joel Habener.

I think better genotyping and phenotyping of individuals with pre-diabetes and T2D will let us direct existing therapies more precisely and generate new ones aimed at a person's specific pathophysiology, rather than at the disease in general. That is where a genuinely personalised approach to treatment will make progress over the next decade. We are not there yet.

For T1D, the focus should be on prevention. For T2D, I think it is about sharpening our focus on the particular metabolic deficits driving disease in a given person, which we understand far better than we used to, so that we can determine which therapies will be most effective in a given subpopulation, rather than working through an ever-growing menu of drugs by trial and error.

Success, for patients and clinicians alike, would include testing a newly diagnosed person and knowing, with confidence, which treatment would work best for them, guided by their own biology rather than by where they happen to fall in a standard treatment algorithm. That is still some years off, but I think it is the direction in which the whole field is heading, and it is what I would want my own team's work to contribute to over the next 5–10 years.

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