On 13 June 1993, the results of the Diabetes Control and Complications Trial were announced during the annual scientific meeting of the American Diabetes Association in Las Vegas, Nevada. After more than a decade of careful planning, much hard work, and perseverance, the results were both clear and dramatic. Intensively managed 13- to 39-yr-old IDDM patients maintained (for 4–9 yr at ~50 mg/dl [2.8 mM]) lower mean blood glucose levels than fairly well controlled, conventionally treated patients and had a substantial reduction in the development or progression of retinopathy, nephropathy, and neuropathy as well as a likely reduction in macrovascular complications of diabetes. These benefits outweighed a threefold increase in the risk of severe hypoglycemia and modest excess weight gain observed in intensively managed patients.

As Dr. Oscar Crofford informed the patient volunteers several days before the public announcement of the main DCCT results, the early termination of the trial was only the “end of the beginning.” The study describing the main DCCT results has been published (1). More detailed results of the ocular, renal, neurological, and macrovascular aspects of the trial, and additional reports on treatment implementation, quality of life, neurobehavioral effects, pregnancy, adolescent control, and other issues are being prepared. Most importantly, soon after each of these results are published, the DCCT plans to make most of the data tapes available to qualified scientists for further analysis and discussion in the years to come. Furthermore, it is likely that much will be learned from an anticipated long-term follow-up of the DCCT patients during the next decade. The sera and immortalized lymphocytes and DNA from the DCCT volunteers and their first-degree relatives should prove to be an invaluable resource for further research. The DCCT may very well spawn more original, peer-reviewed scientific studies than any other experiment in the history of diabetes research and may do this before the end of this decade.

In this perspective I share a few of my own initial impressions of the DCCT results. Like other investigators participating in the DCCT, I have not had access to much more data than that presented publicly because the main study results remained masked to the investigators until shortly before they were released to the general public. Furthermore, it should be made clear that these are my own impressions and do not necessarily reflect the opinions of either the DCCT or the American Diabetes Association.

LESSONS IN RETINOPATHY
Before publication of the DCCT results it was known that two factors served as powerful predictors of subsequent retinopathy progression in patients with diabetes: duration of disease and glycosylated hemoglobin concentrations (2–4). After 15 yr of IDDM, almost everyone develops a mild form of background retinopathy. Among these, a minority progress to more severe forms of clinically significant macular edema or proliferative retinopathy that can impair or threaten vision. Although genetic and other factors, such as hypertension, may influence which patients do or do not develop more severe disease, one thing seems certain: a single measurement of glycosylated hemoglobin predicts the future 4 yr later.
The DCCT has taught us several important lessons about retinopathy. First, treatment that lowers previously stable mean blood glucose by \(-50\) mg/dl and median HbA\(_1c\) from \(-9\) to \(-7\%) will have no apparent beneficial effect on retinopathy for \(\approx3\) yr. A previously stable HbA\(_1c\) seems to have a potent imprinting effect that is hard to erase in \(<4\) yr. Indeed, the only significant short-term effect of glucose lowering is deterioration of retinopathy during the first year in \(-1\) in \(8\) patients with pre-existent background retinopathy and a somewhat smaller proportion of patients without retinopathy at baseline. In most of these patients, the deterioration is reversible after the first year. These findings confirm those reported earlier by others (5,6) and underscore the importance of careful ophthalmic monitoring during intensification of IDDM treatment. The mechanisms of this paradoxical short-term deterioration in retinopathy are unknown. Also unknown is whether a more gradual lowering of glycemia (e.g., over \(6\)–\(12\) rather than \(1\)–\(3\) mo) will prevent the deterioration and affect long-term outcome.

The second ophthalmic lesson learned from the DCCT is that currently available forms of intensive therapy will reduce but not totally prevent the eventual appearance of microaneurysms in most IDDM patients with a mean duration of diabetes of \(3\) yr at the onset of treatment. After \(3\)–\(4\) yr of intensive therapy, clinically significant, persistent progression from no apparent retinopathy to mild or moderate retinopathy is reduced substantially, increasing to \(-76\%) after \(8\)–\(9\) yr. These findings are new. No previous primary prevention trials had demonstrated a benefit from any form of treatment in patients with short-duration IDDM and no retinopathy at baseline before announcement of the results of the primary prevention arm of the DCCT.

The third lesson from the DCCT is that secondary intervention patients with pre-existent mild or moderate retinopathy whose mean blood glucose is lowered by \(-50\) mg/dl for \(>3\) yr are at a \(48\)–\(54\%) reduced risk for clinically significant progression to more severe, vision-threatening retinopathy resulting from either macular edema or proliferative retinopathy. The DCCT findings help explain why so many previous pilot studies and smaller clinical trials lasting \(<3\) yr demonstrated no convincing benefits in the reduction of clinically significant progression of pre-existent background retinopathy (7–9). The findings are also consistent with the beneficial effects of intensive therapy reported in the Stockholm Diabetes Intervention Study after 5 and 8 yr (10,11). The main clinical lesson from these data is that perseverance in maintaining lower mean blood glucose levels begins to pay off after \(-4\) yr and has incremental benefits at \(8\)–\(9\) yr. These benefits were obtained even by patients with pre-existent moderate retinopathy and \(10\)–\(20\) yr duration of IDDM. Unlike Engerman’s diabetic dogs (12), starting relatively late was still of benefit to these patients. Furthermore, the benefits of sustained lowering of mean blood glucose seem to be linear, i.e., lowering glucose from 250 to 200 mg/dl (13.9 to 11.1 mM) seems to have effects comparable to lowering it from 200 to 150 mg/dl (11.1 to 8.3 mM). For reasons that will be discussed below, mean glucose levels rather than HbA\(_1c\) values are given in these examples.

Lastly, although not all of the DCCT results may be reliably applied to patients with NIDDM, they are certainly highly encouraging. It is already known that for both insulin-treated and non-insulin-treated diabetic patients with onset of disease after \(30\) yr of age (most of whom presumably have NIDDM), a single HbA\(_1c\) predicts clinically significant progression of mild to moderate retinopathy \(4\) yr later in a fashion similar to that observed in patients with IDDM (2,4). Among these patients, it is the severity of hyperglycemia, rather than the type or treatment of diabetes, that best predicts clinically significant progression of background retinopathy. There is no reason to predict that lowering the mean level of glycemia from 200 to 150 mg/dl or less will not benefit hyperglycemic NIDDM patients. This is an important issue because among patients with known diabetes, the total number of NIDDM patients with mean blood glucose \(>200\) mg/dl is far greater than the total number of IDDM patients with this degree of hyperglycemia (2). Furthermore, lowering mean blood glucose from 200 to 150 mg/dl may be more readily achieved in NIDDM than in IDDM patients with currently available forms of treatment, such as oral hypoglycemic agents, insulin, or both.

**LESSONS IN NEPHROPATHY**

During the course of the DCCT, only a few patients progressed from supranormal or near-normal glomerular function to the characteristic triad seen in patients with advanced diabetic nephropathy: 1) clinical albuminuria, 2) a glomerular filtration rate \(<70\) ml \cdot min\(^{-1}\) \cdot 1.73 m\(^2\) surface area\(^{-1}\), and 3) hypertension. Nevertheless, the results of intensive therapy seen in the DCCT are highly encouraging in that maintaining lower blood glucose concentrations reduced the appearance of both persistent microalbuminuria (40–200 mg/day) and more severe albuminuria by \(35\) and \(56\)\% respectively, among patients treated for \(8\)–\(9\) yr. Both persistent microalbuminuria and gross proteinuria have been shown by others to predict more advanced long-term disease in IDDM (13).

The DCCT results confirm and extend the results of earlier clinical trials on reduction of albuminuria with reduction of hyperglycemia (10–14). Like other clinical trials, however, a substantially longer period of observation will be required to determine to what extent a sustained lowering of mean blood glucose by \(-50\) mg/dl will prevent or delay renal failure over 10, 15, or \(20\) yr. The 8-yr Stockholm data suggest that the benefits of intensive management of IDDM may be amplified for several years after patients cross over from \(3\)–\(5\) yr of conventional treatment (11). Also awaiting further analysis is the effect of intensive therapy on patients entering the DCCT with microalbuminuria at baseline. This is the largest group of patients ever to have undergone such a long-term trial. The DCCT data need to be analyzed carefully to clarify the clinical significance of sporadic episodes of microalbuminuria in single urine collections for those involved in day-to-day patient management. Many of these patients seem to revert to normalalbuminuria on follow-up sam-
ling a year later without any apparent interval change in glomerular function, blood pressure, or glucose control. Are these sporadic bouts of microalbuminuria manifestations of the inherent weakness of this type of functional testing in predicting what is really happening within the kidney? How many of these sporadic episodes of apparent microalbuminuria result from intercurrent febrile illness, contamination with blood or leukocytes, or short-term changes in diet, exercise, posture, or metabolic control? How often and over what period of time does one have to have persistent low-grade microalbuminuria before a normotensive IDDM patient is at a 25 or 50% risk for clinically significant nephropathy within 2, 5, or 10 yr?

It is likely that these and other issues will benefit from imaginative planning and careful follow-up of DCCT patients over the next decade. For example, it will be interesting to compare the metabolic imprinting phenomenon that seems to occur in the eye with a possible similar phenomenon in the kidney. Should these follow-up studies be undertaken without serial renal biopsies? Much needs to be considered and learned in this area.

LESSONS IN NEUROPATHY

During the DCCT, a rather simple set of measures was performed to assess clinical neuropathy. This set included a clinical examination by a neurologist, measures of sensory and motor nerve conduction velocity, measures of autonomic function that included measures of beat-to-beat variation of heart rate during paced breathing and the Valsalva maneuver, and blood pressure changes after standing. Clinical neuropathy was operationally defined by a neurologist's ascertainment of abnormal clinical findings supported by definite electro-physiological abnormalities in 2 or more large nerves or definite abnormalities in autonomic tests. The findings at 5 yr and at study end (some patients did not complete 5 yr, others completed 6–9 yr) showed a clear benefit from a mean glucose lowering of 50 mg/dl in patients without neuropathy at baseline.

The benefit of intensive therapy in preventing the appearance of clinical neuropathy was both new and highly encouraging. More detailed analyses are needed to determine the time course of this benefit, the effects of intensive therapy in patients with mild clinical or subclinical neuropathy at baseline, and the effects of intensification on specific outcome measures, such as ankle and autonomic reflexes and sensory versus motor nerve function. Whether specific abnormalities in sympathetic versus parasympathetic neuropathy uniquely predict sudden death in IDDM, as observed by the Stockholm group (15), also requires further analysis.

Because of funding limitations and other factors, the neurological testing used in the DCCT was less sophisticated than that available even at the time of the trial design in 1982. Lamenting this and other lost opportunities will do little good. However, the NIDDK and the National Institute of Neurologic Disorders and Stroke should convene major investigators and pharmaceutical firms, who collectively contemplate funding millions of dollars per year for clinical trials in diabetic neuropathy, to help design and fund a more comprehensive protocol for DCCT patients being followed for a long term. Such a battery could include, for example, yearly quantitative sensory testing as well as more sophisticated and extensive electrophysiological and autonomic testing. This collaborative effort would extend already existent NIDDK and industry-sponsored collaborative efforts in other areas such as diabetic retinopathy and nephropathy. More importantly, it would yield very important information elucidating the evolution of earlier phases of neuropathy progression in well-controlled IDDM patients. This will be of enormous value in the planning and interpretation of a wide range of intervention trials in neuropathy in IDDM and NIDDM.

LESSONS IN MACROVASCULAR DISEASE

One of the nagging fears of some of us designing long-term clinical trials in IDDM during the 1980s was that intensive management of IDDM might actually increase cardiovascular morbidity because of higher insulin levels, more hypoglycemia, or excessive weight gain. Fortunately, not a shred of evidence to fuel this anxiety emerged from analysis of the available data from the DCCT. Intensive management of IDDM over 9 yr did not increase mortality or morbidity from macrovascular disease over 9 yr. Indeed, the data suggest a possible benefit, and further studies of the DCCT patients will be required to assess the potential benefits of intensive therapy on the macrovascular complications of diabetes. Indeed, possible examination of carotid arteries with doppler techniques is currently being explored by the DCCT. Similar tests of blood flow to the lower extremities pre- and postexercise should be considered.

Clearly, more needs to be learned concerning the effects of intensive therapy for IDDM on macrovascular disease. Note, however, that the total amount of insulin given daily to intensively managed DCCT or Stockholm patients may not have been substantially greater, in the long term, than the insulin given twice daily to conventionally treated patients. Simply stated, no evidence suggests that giving insulin from a bottle in a more effective way increases the risk of macrovascular disease in IDDM. Furthermore, the relative hyperinsulinemia, hyperproinsulinemia, and dysinsulinemia seen in NIDDM may have only limited relevance to the typical IDDM patient.

LESSONS IN SEVERE HYPOGLYCEMIA

Two important new findings regarding severe hypoglycemia in intensively managed IDDM were reported at the Las Vegas meetings. First, intensively managed patients did not experience any evidence of long-term brain dysfunction even though, as a group, they did experience severe hypoglycemia 3 times more frequently than conventionally managed patients. This is similar to the results of the Stockholm Study at 3 and 8 yr (15,16). Second, none of the DCCT patients were judged to have died as a result of severe hypoglycemia. Nevertheless, the hypoglycemia-associated death of one non-DCCT patient.
participant as a result of hypoglycemia in a DCCT volunteer serves as a grim reminder of the potential hazards of severe hypoglycemia for all patients who are insulin treated. Actuaries may now have more of the hard data they need to explore and define more reliably the risks of intensive therapy in IDDM when this is supervised by experienced personnel and reliable ascertainment of adverse events has been made systematically over 9 yr.

Two problems described previously by the DCCT regarding severe hypoglycemia during intensive therapy still remain. Half of all severe hypoglycemic episodes occur during sleep and ~33% of daytime episodes occur without apparent warning (17). A substantial reduction in severe hypoglycemia that was observed after the first 3 yr of the DCCT may have been influenced by elimination during the screening process of a small number of potential DCCT patients more likely to develop hypoglycemia. However, this is not the entire explanation. Increased use of preventive measures, raising target glucose levels in individual patients with recurrent severe hypoglycemia or hypoglycemia unawareness, and more extensive use of blood monitoring are likely to have helped avoid a much higher rate of severe hypoglycemia. Remember, however, that these results were obtained in expertly monitored and managed DCCT patients. The benefit-to-risk ratio may not be as favorable if intensive therapy is attempted by poorly supervised patients or by inexperienced physicians.

Clearly, two immediate challenges are to develop means to reduce nocturnal hypoglycemia and daytime hypoglycemia unawareness. It seems appropriate to advise the technological wizards currently scrambling toward development of needle-type glucose electrodes and pulse-oximeter-equivalent bloodless polarographic glucose sensors to set their sights on devices that can reliably sense and warn against hypoglycemia. It would be a small sacrifice for an IDDM patient to spend a few minutes every night calibrating and securing an 8- to 10-h sensor onto or under the skin before going to sleep if this would substantially reduce the risk of severe hypoglycemia. Similarly, it would be rewarding if clinical researchers could find reliable ways to predict, reduce, prevent, or reverse daytime hypoglycemia unawareness in IDDM.

Severe hypoglycemia remains the single most important barrier in managing IDDM patients intensively to maintain mean blood glucose ≤150 mg/dl. This problem will remain until our still imperfect treatment of IDDM becomes more reliable.

TRANSLATING THE DCCT MESSAGE INTO THE COMMUNITY

During the design of the DCCT, investigators from 21 clinical centers, half a dozen or more supporting centers, the NIDDK, and a myriad of consultants locked themselves into closed rooms every 2 weeks for a year until they came up with a consensus protocol that worked. This consensus agreement did not include a detailed plan for translating the DCCT results to the general public. This remains the difficult challenge of others such as the NIDDK, the CDC, concerned lay and professional groups, health policy planners, and those who determine the funding and quality of medical care in North America. The ball is now in these many and varied hands rather than those of the DCCT investigators. Some Scandinavian and European countries have previously made the decision to offer more or less intensive treatment to all IDDM patients. This is carried out in government-funded specialty clinics. In these countries, the primary care physician still retains primary responsibility for most patients with NIDDM.

As suggested recently by a group of representatives from the NIDDK, the CDC, and the Diabetes Research and Training Centers, the core message to patients and health providers alike is simple: control matters. Delivering this core message should be centered on educating patients and health providers alike about the importance of knowing a given diabetic patient's current mean blood glucose. This program should inform the public that patients with mean blood glucose of 150 mg/dl have substantially reduced risks of long-term diabetic complications than those with mean blood glucose of 200, and that the latter is at a relative advantage over the patient with a mean glucose of 250 mg/dl. Because measuring mean blood glucose directly is not practical, one can do it with a single, simple test that costs <30 U.S. dollars. An HbA1c of ~7.0% corresponds to a mean blood glucose of 150 mg/dl and an HbA1c of 9.0% corresponds to a mean blood glucose of 210 mg/dl over the preceding 2 mo. This seems a simple enough message to remember, especially when patients and health providers alike are told that for any 1% long-term increase >6.0% in mean HbA1c, mean blood glucose goes up ~30 mg/dl (1.7 mM) and the risk for a given complication over 4 yr goes up by a given value, say 30–50% for retinopathy.

One major barrier to delivering such a simple message to patients and the physicians who care for them is that not all glycated protein assays are created equal. Most diabetologists know that differences exist, but most diabetic patients and their physicians do not. Instead, the average patient and health professional is posed with a dizzying array of HbA1c, total HbA1, total glycated hemoglobin, fructosamine, and other measurements. Each has its own normal range and correlations with mean blood glucose over different time periods. Some are expressed in hopelessly confusing measurements such as milli-moles of fructose released per some unit that even experts cannot remember. This mess is almost impossible to translate into a simple, coherent message directed toward the real-world patients and doctors who need to hear it.

Two recent examples come to mind that illustrate some of the problems. In July 1993, I was honored to present the preliminary DCCT results at medical grand rounds at two of the world's leading diabetes research centers: the University of Chicago (Chicago, IL) and Washington University (St. Louis, MO). In neither of these prestigious institutions was the HbA1c assay used in the DCCT offered routinely in clinical management. In one, a mini-column HbA1c assay developed in the late 1970s was used, and in the other, an affinity chromatography assay developed a decade later was used. I venture to guess
that less than 10% of the academic pediatric and internal medicine trainees and faculty at these two conferences understood that a blood sample with a 9.0% HbA1c (the median for conventional treatment in the DCCT) would have been measured as a 9.7% HbA1 in Chicago, as an 11.2% glycated hemoglobin in St. Louis, and as god knows what else by a physician in Peoria, Illinois. The attendees at these conferences were being asked to consider lowering mean glucose to ≤150 mg/dL, but I would have required a separate 50-min session to explain to them what this meant with 3 or 4 different glycated hemoglobin or protein assays or rationalize how we got into this mess at all.

The anecdote gets even more disconcerting when one knows that the assays used at Washington University have been changed 3 times in the last decade: from an HbA1c HPLC assay in the early 1980s to an HbA1 minicolumn assay in the mid 1980s to a glyco-hemoglobin assay by affinity chromatography in the late 1980s. Each switch had its rationale and appropriate assay validations, but each left in its wake confused patients and physicians. For example, does a current glyco-hemoglobin of 12% mean that a patient's control has deteriorated, remained stable, or improved from a decade ago when the HbA1c was 11% or 6 yr ago when the total HbA1 was 8%? To this date, neither the Chicago nor the St. Louis centers routinely inform physicians or patients what their assay reports mean in terms of mean blood glucose concentrations over the last 2 mo (Fig. 1).

The computer technology to provide these estimates with appropriate CIs is at hand and could be used in this manner. Something needs to be done to clean up our HbA1c mess before we try to move out in the real world with a coherent message such as "control matters" or "your HbA1c predicts the future."

One remedial option would be to force everyone to accept and use some common, gold standard assay. The logical nominee is the HbA1c assay. This is the assay used in the DCCT and by many major European centers. Such a solution may not be practical in our decentralized free enterprise system. A second option would be to relate a given assay's results to an accepted reference or gold standard, such as the HbA1c method. This option has been shown to be reliable and, with the collaboration of investigators at the University of Missouri, was used in St. Louis for a time during the transition from the last two assays (18,19). Parenthetically, this approach was abandoned when a cadre of advisors considered it too confusing. The third option would be to report the findings of a given assay in terms of an estimate of mean blood glucose with appropriate CIs. This option is complicated by the fact that few new assays have reliably correlated their results with frequently measured blood glucose levels. Indeed, inferences regarding mean blood glucose in some new glycated protein and hemoglobin assays are currently drawn indirectly by correlating the new assay's results with published DCCT results (20).

My own preference would be this last option if the assay used is practical for clinical use and can be calibrated against an HbA1c standard or some other standard available to the clinical laboratory.

I wish to take this opportunity before stepping down from my soap box to share one final personal impression that relates directly to the translation of the DCCT results to the real world. Although the design of the DCCT protocol was driven primarily by the trial's principal investigators, few would deny that most of the actual work was, in most centers, done by the patients themselves and nonphysician health professionals who taught, encouraged, and supervised them. It is unlikely that enough physicians or diabetes treatment teams have sufficient expertise in diabetes management to translate effectively the DCCT's results to the millions of diabetic patients. This is a problem everywhere in the world. The number of physician diabetologist trainees in the pipeline is small and their numbers may not grow substantially during the next decade. As we move toward systems of increased capitation arrangements and managed care, those who pay for and provide medical care should consider encouraging the implementation of teams of specialized professionals composed of nurses, dietitians, social workers, and others who would provide 90% or more of the essential, early patient training and long-term preventive management needed in both IDDM and NIDDM. These teams should, of course, include a physician. However, the role of this physician would change sub-
stantially to that of a team manager who could be replaced without dissolving the existent team. Indeed, the team could be organized so that it would serve the needs of many physicians, not just the manager, in a given community. There are many ways to encourage such systems. One would be to reward health-care providers for patient education, training, and preventive care up front so that we would not have to later pay really big bucks so that surgeons can saw off legs, ophthalmologists can perform photocoagulation, which takes minutes but costs thousands of dollars, and nephrologists can arrange for kidney transplants that will soon cost the U.S. taxpayer over $2 billion per year. Another would be to allow nurses, dietitians, and other health professionals who have received appropriate training and periodic recertification to make periodic health assessments and simple insulin, diet, exercise, and other lifestyle adjustments without having to track down a physician specialist for a signature intended to serve as an umbrella against a possible lawsuit. The professional pipeline is now full of these non-physician professionals who are ready, able, and eager to do a great job if only given the chance. We did it in the DCCT and it worked. I think we should try it in the real world.

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