Diabetes Research and Care Through the Ages

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As has been well established, the *Diabetes Care* journal's most visible signature event is the *Diabetes Care* Symposium held each year during the American Diabetes Association's Scientific Sessions. Held this past year on 10 June 2017 in San Diego, California, at the 77th Scientific Sessions, this event has become one of the most attended sessions during the Scientific Sessions. Each year, in order to continue to have the symposium generate interest, we revise the format and content of this event. For this past year, our 6th annual symposium, I felt it was time to provide a comprehensive overview of our efforts in diabetes care to determine, first and foremost, how we arrived at our current state of management. I also felt the narrative needed to include the current status of management, especially with a focus toward cardiovascular disease, and finally, we wanted to ask what the future holds. Toward this goal, I asked four of the most noted experts in the world to provide their opinion on this topic. The symposium started with a very thoughtful presentation by Dr. Jay Skyler entitled "A Look Back as to How We Got Here." That was followed by two lectures on current concepts by Dr. Bernard Zinman entitled "Current Treatment Paradigms Today—How Well Are We Doing?" and by Dr. Matthew Riddle entitled "Evolving Concepts and Future Directions for Cardiovascular Outcomes Trials." The final lecture for the symposium was delivered by Dr. Ele Ferrannini and was entitled "What Does the Future Hold?" As always, a well-attended and well-received symposium is now the norm for our signature event and our efforts were rewarded by the enthusiasm of the attendees. This narrative summarizes the lectures held at the symposium.

—William T. Cefalu

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I. A LOOK BACK AS TO HOW WE GOT HERE

A polyuric state, presumably diabetes, was described more than 3,500 years ago, being noted by the physician Hesy-Ra in an Egyptian papyrus (from approximately 1500 B.C.) found by George Ebers. The sweetness of urine was noted by the Hindu physicians Charaka and Sushruta around 400–500 B.C. (1). Apollonius of Memphis (around 250 B.C.) used the term "diabetes" (from the Greek for siphon), and Aretaeus of Cappadocia (A.D. 30–90) described what is likely type 1 diabetes (T1D) as a melting down of flesh into urine, with short survival (2). The sugary nature of the urine also was noted by Zhen Li-Yan in China in the 7th century A.D., by the Arabian Avicenna (A.D. 980–1037), and in detail by Thomas Willis in 1675, who labeled it the "pissing evil" (1,3). John Rollo in 1797 applied the descriptor "mellitus" (from the Latin for honey) (4,5).

Dietary Manipulations

As elegantly catalogued in the classic 1919 monograph "Total Dietary Regulation in the Treatment of Diabetes" (6), the treatment of diabetes for centuries was empiric and fundamentally one of dietary restrictions and manipulations, with the addition of various substances, some of which might be considered drugs. Aretaeus recommended a

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"non-irritating diet" of milk and carbohydrates and hiera, nardum, mastix, and theriak as drugs. Aëtius of Amida (A.D. 550) introduced bleeding, emetics, and narcotics, which were used long after. Avicenna used a treatment consisting of powders of fenugreek, lupin, and wormseed in dosages up to 45 g/day (6).

Thomas Willis said that "treatment should aim to thicken the blood and supply salts" and recommended "milk, rice, and starchy and gummy foods" (6). He limited patients to a diet of milk and barley water boiled with bread and thus became the author of the first carbohydrate or undernutrition care (6). He also initiated opium treatment (3).

Thomas Sydenham prescribed narcotics and theriak and said, "Let the patient eat food easy of digestion, such as veal, mutton, and the like, and abstain from all sorts of fruits and garden stuff" (6).

John Rollo began treatment with bleeding. He ordered "confinement . . . preferably to one room, with the utmost possible quiet and avoidance of exercise" (6). A diet of animal food, as rancid as possible, was also proposed. Drugs were chosen to produce anorexia and nausea, including ammonium sulfide, wine of antimony, tincture of opium, digitalis, and tobacco (4–6).

Apollinaire Bouchardat in France resurrected and transformed the Rollo treatment (7,8). Some consider him the father of diabetology. He was the first to insist on individualized treatment for patients. He disapproved the rancid character of the fats in the Rollo diet but substituted fat and alcohol for carbohydrate in the diet (6). He forbade milk because of its carbohydrate content, and he "urged that patients eat as little as possible, and masticate carefully" (6). He introduced fasting to control glycosuria and recommended green vegetables to provide "little sugar, a little protein and fat, but especially potassium, organic acids, and various salts" (6). He also first introduced the intelligent use of exercise in the treatment of diabetes and advocated daily urine testing "to keep track of the tolerance and to guard against a return of sugar without the patient's knowledge" (6). He prescribed sodium bicarbonate, chalk, magnesia, citrates, tartrates, and ammonium and potassium salts.

Sir Henry Marsh criticized the Rollo diet as "impossible to follow because of the indigestion and repugnance to food resulting," but he used the Bouchardat plan with the addition of vegetables and restriction of fluid intake as well as exercise, warm clothing, and baths (6).

Arnoldo Cantani established a new strict level of treatment (9). He isolated his patients "under lock and key, and allowed them absolutely no food but lean meat and various fats. In the less severe cases, eggs, liver, and shell-fish were permitted. For drink the patients received water, plain or carbonated, and dilute alcohol for those accustomed to liquors, the total fluid intake being limited to one and one-half to two and one-half liters per day" (6).

Bernhard Naunyn encouraged a strict carbohydrate-free diet (6,10). He locked patients in their rooms for 5 months when necessary for "sugar-freedom" (6). When sugar-freedom was not attained through the withdrawal of carbohydrate, protein was reduced as low as 40–50 g/day and the calories were also diminished. Occasional fast days were advised as necessary.

Karl von Noorden used 1 or 2 fast days, with the only food being alcohol (up to 200–250 mL cognac). As soon as glycosuria and acidosis were partially controlled, he quickly provided an "oat-cure" (6).

Frederick M. Allen of the hospital of The Rockefeller Institute for Medical Research was one of the first to appreciate that diabetes involves total metabolism rather than carbohydrate metabolism alone (6,11). He studied a detailed regimen that involved fasting 2–10 days to clear glycosuria, followed by a restricted-calorie diet that provided mainly fat and protein (especially eggs) with the smallest amount of carbohydrates (mostly vegetables) necessary to sustain life. If glycosuria appeared, fasting was resumed for 1–2 days. The regimen essentially starved people with severe diabetes in order to control the disease.

Elliot P. Joslin embraced the Allen approach but also used a treatment that began by withdrawing only fat (12).

Pre–Insulin Therapy

In addition to the various dietary manipulations described, other nonpharmacologic and pharmacologic approaches were proposed. In his 1892 textbook (13), William Osler recommended a dietary prescription 65% fat, 32% protein, and 3% carbohydrate, including abstaining from "all fruits and garden stuff." He also proposed to "avoid worry and lead an even, quiet life" in an equitable climate, use flannel or silk near the skin, take a cold bath daily and a Turkish bath occasionally, and get moderate exercise or massage. He noted that "no one drug has directly curative influence" but that "opium alone stands the test of experience as a remedy capable of limiting the progress of the disease." He wrote that other "effective" agents included potassium bromide, lactic acid, arsenicals, creosote, and lithium salts.

Insulin Era

In 1889, Josef von Mering and Oskar Minkowski reported that total pancreatectomy in dogs resulted in severe diabetes in the dog (14,15). In 1893, Gustave Edouard Laguesse (16) deduced that the pancreatic islands described by Paul Langerhans in 1869 (17) as a "little heap of cells" produced an internal secretion that regulated glucose metabolism. In 1901, Eugene L. Opie reported that degeneration of the "islets of Langerhans" was associated with diabetes (18,19). All of these events contributed to the search for the hypothetical hormone that Jean De Meyer in 1909 dubbed "insuline" (20). Edward Sharpey-Shafer in 1916 coined "insulin" as a single substance from the pancreas responsible for diabetes.

Meanwhile, multiple people (Table 1) around the world were attempting the extraction of insulin. These are chronicled in detail in Michael Bliss's book *The Discovery of Insulin* and will not be reviewed here (21).

It was in 1921 that Frederick Banting and Charles Best, working in the laboratory of J.J.R. Macleod at the University of Toronto, successfully extracted insulin. It was first used as treatment in January 1922 (22) and was a truly life-saving achievement. Unselfishly, the University of Toronto made their achievement available to companies around the world so that insulin could be widely used. Initial improvements in isolation and purification were made by J.B. (Bert) Collip and George H.A. Clowes.

Insulin launched a new era of diabetes management. Elliot P. Joslin noted, however, that "the disease . . . was far from solved by insulin. Insulin marked the end of one era in diabetes management, not the end of diabetes" (23).

The way that insulin was used differed widely. One U.K. specialist in 1924 asserted

Table 1—Attempts at insulin extraction

1892	Capparelli
1892	Comby
1892	Minkowski
1893	Bathistini
1893	White
1895	Vanni
1897	Hougounena and Doyou
1898	Blumenthal
1898	Hedon
1903–1907	Zuelzer
1905	Gley
1906	De Witt
1907	Rennie and Frazer
1908	Siorqvist
1909	Lepine
1910	Pratt
1911	Knowlton and Starling
1912	Massaglia and Zannini
1912	Scott
1913	Murlin and Krammer
1916	Clark
1919	Kleiner and Meltzer
1916–1921	Paulescu
1921–1922	Banting and Best

that "essential parts of the treatment with insulin were 'slowing the metabolism' by rest in bed for a month at least at the beginning of treatment, and careful eradication of septic foci" (24). In contrast, in 1923 in Cleveland an outpatient clinic was established that included individual and group education by a physician, a dietitian giving food demonstrations, and a social worker who made sure patients came, investigated home conditions, and kept records (24).

The initial preparations of insulin were extracted from beef and pork pancreata obtained at the slaughterhouse. The initial preparations contained 10 (U-10) or 20 (U-20) units of insulin per mL. The "unit" dosing was originally based on the dose required to induce hypoglycemic convulsions in laboratory rabbits.

The characteristics of insulin preparations include the purity of the preparation, the concentration of insulin, the species of origin, and the time course of action (onset, peak, duration) (25). From the 1930s to the early 1950s, one of the major efforts made was to develop an insulin with extended action (Table 2). Most preparations contained 40 (U-40) or 80 (U-80) units of insulin per mL, with U-10 and U-20 eliminated in the early 1940s. U-100 was introduced in 1973 and was meant to be a standard concentration, although U-500 had been available since the early 1950s for special circumstances. Preparations were either of mixed beef and pork origin, pure beef, or pure pork. There were progressive improvements in the purity of preparations as chemical techniques improved. Prior to 1972, conventional preparations contained 8% noninsulin proteins.

In the early 1980s, "human" insulins were introduced (26). These were made either by recombinant DNA technology in bacteria (*Escherichia coli*) or yeast (*Saccharomyces cerevisiae*) or by enzymatic conversion of pork insulin to human insulin, since pork differed by only one amino acid from human insulin.

The powerful nature of recombinant DNA technology also led to the development of insulin analogs designed for specific effects. These include rapid-acting insulin analogs and basal insulin analogs.

Oral Therapies

Biguanides

In medieval Europe, *Galega officinalis* (goat's rue or French lilac) was used as a treatment for diabetes (27). The active component of *G. officinalis* is guanidine. In 1926, in Germany, a biguanide derivative (synthalin) was introduced, but it was withdrawn because of toxicity. In the late 1950s, three other buguanides were developed—metformin, phenformin, and buformin. Phenformin was the only biguanide introduced in the U.S. Unfortunately, it was associated with induction of lactic acidosis, which often was fatal. Consequently, in 1977 the U.S. Food and Drug Administration (FDA), using the "clear and imminent danger" provision of the Food and Drug Act, ordered phenformin withdrawn from the U.S. market. This represents the only time the FDA has ever withdrawn a drug from the U.S. market. Many drugs have been withdrawn by manufacturers—usually with prodding by the FDA—but in the case of phenformin, the manufacturer declined to act. Meanwhile, metformin was widely used around the world. Unfortunately, however, its patent had expired by the time phenformin was withdrawn. Thus, there was not a pathway to license and commercialization of metformin until the Hatch-Waxman Act was passed by Congress in 1984. That law gave limited exclusivity in the market for new chemical entities approved by the FDA. Subsequently, metformin was studied, approved, and introduced in the U.S. in 1995.

Table 2—Insulins with extended action

Protamine insulinate, 1936
Protamine zinc insulin, 1936
Surfen insulin, 1938
Globin insulin, 1939
Phenylcarbamoyl insulin, 1944
Isophane (NPH) insulin, 1946
Lente insulins, 1951

Sulfonylureas

Celestino Ruiz of Argentina noted hypoglycemic action of some sulfonamides in 1930 (28). Subsequently, Auguste Loubatières of France discovered the hypoglycemic action of a prototype sulfonylurea in 1942 and worked extensively on understanding its mechanism of action (29). The first sulfonylurea, carbutamide, was introduced in 1955, followed by tolbutamide in 1957 and chlorpropamide in 1960. Subsequently, a variety of other sulfonylureas were introduced, including acetohexamide, tolazamide, glipizide, glyburide (glybenclamide), gliclazide, and glimiperide.

Until 1996, the only oral medications available were biguanides and sulfonylureas. Since that time, there has been an explosion of new classes of oral and parenteral preparations.

II. CURRENT TREATMENT PARADIGMS TODAY—HOW WELL ARE WE DOING?

The Current Management of Type 2 Diabetes

The management of type 2 diabetes (T2D) has undergone rapid change with the introduction of several new classes of glucose-lowering therapies. This increase in diabetes therapy options represents both an opportunity, with the expansion of the tool kit to optimize treatment, and the uncertainty as to deciding on the correct treatment interventions in a timely manner. In fact, the treatment guidelines are generally clear in the context of using metformin as the first oral medication for T2D and present a menu approach with respect to the second and third glucose-lowering medication (30–32). In order to facilitate this decision, the guidelines list the characteristics of each medication including side effects and cost, and the health care provider is expected to make a choice that would be most suited for patient comorbidities and health care

circumstances. This can be confusing and contributes to the clinical inertia characteristic of the usual management of T2D (33). Rather than revisiting this topic in this narrative, it is felt we can all agree that we are now in an era of diabetes therapy where the first choice of medications should provide effective glucose-lowering without weight gain or hypoglycemia. An expanded list of the desirable characteristics of glucose-lowering therapies is presented in Table 3. (34)

In addition to effective glucose lowering, low hypoglycemia risk, and no weight gain, the therapy should be able to be combined with other agents and provide a complementary mechanism of action, provide durable control, and possess a reasonable short- and long-term adverse effects profile. As added value, relevant to the day-to-day management of T2D, a medication that preserves β-cell function, which invariably decreases with longer diabetes duration, would be of particular interest. In addition, given the increased risk of cardiovascular (CV) morbidity and mortality in T2D, a medication associated with reduced CV events would be particularly noteworthy.

Clinical Inertia

Perhaps the most frustrating barrier to optimizing diabetes management is the frequent occurrence of clinical inertia (whenever the health care provider does not initiate or intensify therapy appropriately and in a timely fashion when therapeutic goals are not reached). More broadly, the failure to advance therapy in an appropriate manner can be traced to physician behaviors, patient factors, or elements of the health care system. The clinician-based issues that lead to clinical inertia are itemized in Table 4. Despite clear evidence from multiple studies, health care providers fail to fully appreciate that T2D is a progressive disease. T2D is associated with ongoing β-cell failure and, as a consequence, we can safely predict that for the majority of patients, glycemic control will deteriorate with time despite metformin therapy (35). Continued observation and reinforcement of the current therapeutic regimen is not likely to be effective. As an example of real-life clinical inertia for patients with T2D on monotherapy metformin and an HbA_{1c} of 7 to <8%, it took on the average 19 months before additional glucose-lowering therapy was introduced (36). The fear of hypoglycemia and weight gain are appropriate concerns for both patient and physician, but with newer therapies these undesirable effects are significantly diminished. In addition, health care providers must appreciate that achieving early and sustained glycemic control has been demonstrated to have long-term benefits, as demonstrated in both the Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) and the UK Prospective Diabetes Study (UKPDS) (metabolic memory), resulting in remarkable reduction in the risk of subsequent microvascular (retinopathy, nephropathy, and neuropathy) complications. Clinicians have been schooled in the notion of a stepwise approach to therapy and are reluctant to initiate combination therapy early in the course of T2D, even if the combination intervention is formulated as a fixed-dose combination.

Table 3—Desirable characteristics of glucose-lowering therapies

Effective glucose-lowering action
Low risk of hypoglycemia
No weight gain
Complementary mechanism of action with other therapies
Durability
Well tolerated
Long-term safety
Added value, e.g., β-cell function, CV, etc.

Table 4—Potential causes of clinical inertia in T2D

Failure of clinicians to fully appreciate the progressive nature of T2D consequent to β-cell failure
A clinician's lack of understanding about the frequent failure of monotherapy and that most patients will ultimately require combination therapy
A clinician's and/or patient's fear of hypoglycemia and weight gain when intensifying therapy, particularly with sulfonylureas or insulin
A clinician's lack of confidence, particularly when working in the primary care setting, in using insulin
Poor recognition, by clinicians, of the evidence that demonstrates the benefits of early glycemic control
A clinician's general reluctance to use combination therapy early after diagnosis

Rationale for Early/Initial Combination Therapy in T2D

The recognition that T2D is a disease with a complex underlying pathophysiology that includes components of increased insulin resistance, increased hepatic glucose production, β-cell failure, abnormalities in incretin action, enhanced renal sodium–glucose cotransporter 2 (SGLT2) activity, and abnormalities in glucagon physiology—to name a few—must be taken into account in determining an intervention strategy (37). In addition, the body generally has the ability to overcome a single-pathway intervention because of built-in redundancy. Thus, it is not surprising that monotherapy metformin failure rates with a starting HbA_{1c} >7% are ~20% per year (35).

Table 5 summarizes the rationale for early/initial combination therapy. With initial combination therapy, one can expect a more robust initial response and, since two medications are initiated, inertia is less of a problem. Although the reduction in β-cell glucose toxicity may have long-term beneficial effects on β-cell function, this remains to be documented. In addition, complementary mechanisms of action and the elimination of early hyperglycemia, which may have longer-term consequences, provide important benefits of early/initial combination therapy.

CV Risk in T2D and Its Relationship to the Treatment of T2D

As documented by the DCCT/EDIC and UKPDS, there is little question that the benefits of optimizing glucose control as it relates to microvascular complications is substantial for both T1D and T2D. Similarly, glycemic control, if initiated early in the course of diabetes and with long-term follow-up, can be shown to reduce CV outcomes.

However, as shown in Fig. 1, CV events, CV mortality, and heart failure were not positively affected by intensive versus less intensive glycemic control in rather short trials in T2D. In 2008, the FDA mandated that all new diabetes medications demonstrate CV safety in dedicated CV safety trials. The first four of these trials (Evaluation of Lixisenatide in Acute Coronary Syndrome [ELIXA], Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care [EXAMINE], Saxagliptin

Table 5—Rationale for initial combination therapy in T2D

Early robust lowering of HbA_{1c}
Avoidance of clinical inertia associated with a stepwise approach to therapy
Potential for early combination therapy to improve β-cell function
Initiation of therapeutic intervention with complementary mechanism of action
Potential to use less than maximal doses of individual agents to minimize side effects
Avoiding long-term consequences of metabolic memory

Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53 [SAVOR-TIMI 53], and Trial Evaluating Cardiovascular Outcomes With Sitagliptin [TECOS]) met this important safety requirement (38–41). Subsequently, the BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) and Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results—A Long Term Evaluation (LEADER) trials demonstrated not only safety but also a reduction in the primary MACE (CV death, nonfatal myocardial infarction [MI], nonfatal stroke) outcome and robust reductions in CV death and hospitalization for heart failure with empagliflozin (42,43). More recently, the Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes (SUSTAIN-6) also documented a reduction in MACE but not in CV death or heart failure (44). The Canagliflozin Cardiovascular Assessment Study (CANVAS) is the second SGLT2 trial to report a benefit in the primary MACE outcome and hospitalization for heart failure but failed to demonstrate a reduction in CV mortality. In addition, CANVAS reported an increase in lower-limb amputation (hazard ratio [HR] 1.97 [95% CI 1.41–2.75]) with canagliflozin compared with placebo (45).

These findings have changed the prescribing label and guideline recommendations for empagliflozin. Guidelines have also recognized the CV benefits of liraglutide. Semaglutide is not currently an approved medication, and the CANVAS results have only recently been reported.

An Approach to Diabetes Therapy

If we eliminate cost issues and drug plan restrictions, can we develop an approach to the management of T2D that better reflects modern therapy and current evidence? As previously indicated, the primary focus should be on therapies not associated with hypoglycemia or weight gain. Weight loss and evidence for a reduction in CV outcomes, even in a subset of patients with previous CV events, would be viewed positively.

In this context, initial combinations with metformin (i.e., metformin/dipeptidyl peptidase 4 [DPP-4] inhibitor, metformin/SGLT2 inhibitor, or DPP-4 inhibitor/SGLT2 inhibitor) seem like obvious choices. In the

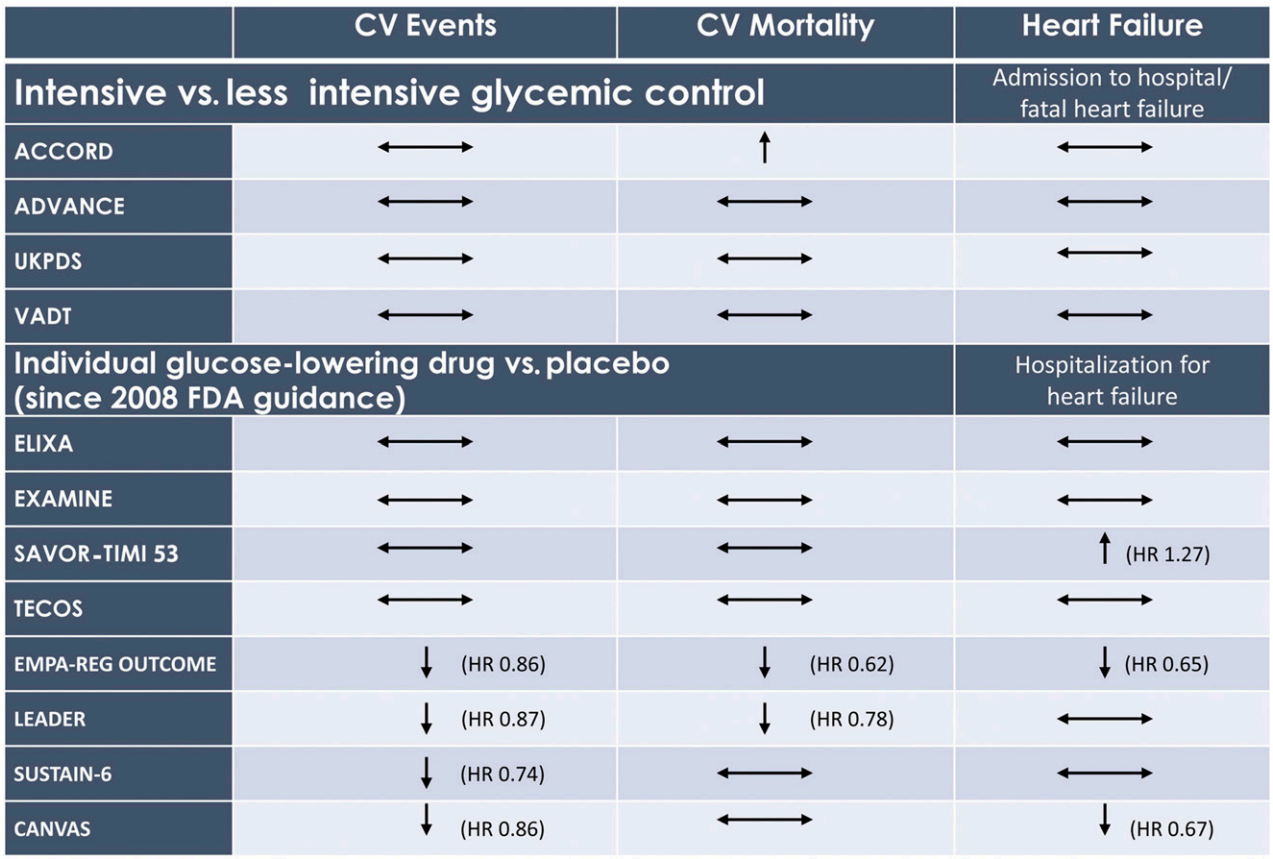

Figure 1—CV risk in T2D: summary of large randomized trials with respect to CV events (MACE), CV mortality, and heart failure.

context of individualizing therapy, a history of pancreatitis (avoid DPP-4 inhibitors), renal impairment, or recurrent genital infections (avoid SGLT2 inhibitors) and other circumstances may determine the specific combination. As another example, there are significant numbers of patients with gastrointestinal intolerance to metformin or reduced renal function contraindicating metformin use. The beneficial effects of glucagon-like peptide 1 (GLP-1) receptor agonists and their once-weekly formulations without weight gain or risk of hypoglycemia make them an additional valuable component of a combination approach. Although there is reasonable rationale for this approach, long-term studies documenting the beneficial effects of newer combinations versus stepped approaches with these newer medications will have to be documented.

To summarize the current status of T2D at this time, it should be clearly emphasized that, first and foremost, T2D is characterized by a progressive deterioration of glycemic control. A stepwise medication introduction approach results in clinical inertia and frequently fails to meet long-term treatment goals. Early/initial combination therapies that are not associated with hypoglycemia and/or weight gain have been shown to be safe and effective. The added value of reducing CV outcomes with some of these newer medications should elevate them to a more prominent place in the treatment paradigm.

III. EVOLVING CONCEPTS AND FUTURE DIRECTIONS FOR CV OUTCOMES TRIALS

Compared with the treatment of cancer and CV disease, management of diabetes has been guided by relatively few large clinical trials. Fortunately, recent evidence is closing this gap. As described in the previous section, we have a growing array of therapies for patients with diabetes and, as our understanding of the natural history of both microvascular and CV complications improves, we are learning how best to deploy these therapies.

Time Course of Microvascular and CV Disease in Diabetes

Epidemiologic analyses show that risks of microvascular disease and CV disease increase with duration of time since the onset of diabetes (46,47) and also with severity of hyperglycemia (48,49). Retinopathy often begins before the diagnosis of diabetes and progresses steadily in the first 10 years (50). CV disease may occur before the onset of diabetes, but more often it is not present at diagnosis. In the seminal Framingham Heart Study, mortality from coronary heart disease increased gradually with duration of observation over more than two decades (51). The rate of increase for men with diabetes was twice that of men without diabetes and fourfold higher for women, with the greater part of this differential after 10 years of diabetes. Typically, clinically evident CV disease appears more slowly than microvascular complications.

Short-term Glycemic Intervention in Early Diabetes: DCCT and UKPDS

Such evidence prompted testing whether improved glycemic control can reduce complications in people with newly diagnosed diabetes. Beginning in 1982, the DCCT enrolled patients with T1D with mean duration of ~6 years. From 1977 on, the UKPDS enrolled patients shortly after diagnosis of T2D. The main results of these trials were reported in 1993 and 1998, respectively.

The DCCT showed that 6.5 years of treatment causing an ~2% mean reduction of HbA_{1c} led to 63% less progression of retinopathy and 54% less macroalbuminuria (52). A corresponding primary analysis of the UKPDS, comparing insulin or sulfonylurea with conventional (lifestyle) therapy, showed that 10 years of ~1% mean reduction of HbA_{1c} caused a 25% reduction of combined microvascular end points (53). Both studies had relatively few CV events, and better glycemic control showed no significant effect on them. However, in a separate randomization in the UKPDS, participants treated with metformin had 36% lower all-cause mortality than those allocated to lifestyle therapy (n = 50 of 342 vs. 89 of 411).

Short-term Glycemic Intervention in Diabetes With CV Disease: ACCORD, VADT, and ADVANCE

Verification that improved glycemic control reduces microvascular complications had a profound effect on treatment guidelines, but the limited CV effects were disappointing. To determine whether failure of glucose lowering to improve CV outcomes was due to low statistical power in populations with low CV risk, further studies were designed to study patients with longer duration of diabetes who had established CV disease or were at very high risk. These were the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, the Veterans Affairs Diabetes Trial (VADT), and the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) study (54–56). All reported some microvascular benefits after ~5 years of randomized treatment, but despite including enough events, they again found no consistent reduction of CV risk. Most significantly, a 20% increase of all-cause and CV mortality occurred in the intensive arm of ACCORD (53). This too had a strong effect on clinical guidance. It is now commonly advised to avoid seeking HbA_{1c} levels <7% in "high-risk" patients.

Long-term Follow-up of DCCT/EDIC and UKPDS

While ACCORD, VADT, and ADVANCE were under way, long-term passive observation of the DCCT cohort (termed the EDIC study) and continued follow-up of participants in the UKPDS added important new information. Follow-up in EDIC showed that the risk of the original composite primary CV end point was 42% lower in the previously intensively treated group than after standard therapy in the DCCT, and a composite of nonfatal MI, stroke, or CV death was reduced 57% (57). When enough deaths had occurred to provide power for analysis in EDIC, all-cause mortality was reduced by 33% (58), and the investigators have provided evidence that adjusted mortality rates in the DCCT/EDIC intensive group are no different from that of the general population in the U.S. (59). Similarly, 10 years after the 10-year randomized treatment period of the UKPDS, the intensive group using insulin or sulfonylureas had significant reductions of combined microvascular end points (24%), MI (15%), and all-cause mortality (13%) (60). The smaller intensive group using metformin had 16% (not statistically significant), 33%, and 27% reductions of the same end points.

Although limited by problems always present in passive follow-up studies, these consistent long-term observations are highly provocative. They suggest what the investigators of these studies have

termed a "legacy effect" or "metabolic memory" of prior glycemic control. That is, a 6- to 10-year period of excellent glycemic control may leave a structural imprint on vascular and other tissues, leading to clinical benefits more than 10 years later. A corollary of this idea is that a harmful legacy effect may follow an early period of poor control, causing tissue injury that cannot be reversed by improved control later on. Measures of glycemic control during the entire period of follow-up in DCCT/EDIC correlate strongly with both microvascular and CV outcomes (61,62), a finding consistent with long-lasting effects of hyperglycemia during the early period of randomized treatment. Potential mechanisms for legacy effects are irreversible changes of collagen and other molecules in blood vessels by glycation or oxidative pathways (63). Furthermore, renal disease resulting from such mechanisms may itself become an important CV risk factor.

Short-term Benefits From Specific New Therapies: EMPA-REG OUTCOME, CANVAS, LEADER, and SUSTAIN-6

Prompted by concerns about increased CV risk attributed to treatment with rosiglitazone, the FDA advised in 2008 that when early studies of new drugs could not provide strong evidence of CV safety, adequately powered CV outcomes trials should be done. To limit the time and resources required for this purpose, subsequent trials of DPP-4 inhibitors, GLP-1 receptor agonists, and SGLT2 blockers have enrolled populations with very high CV risk (and an average duration of diabetes >10 years), thereby assuring high CV event rates. Of eight such trials reported to date, four had neutral results for their primary composite CV end points, but four showed significant benefit of the drug tested. The drugs shown to reduce CV risk were empagliflozin (13), canagliflozin (45), liraglutide (14), and semaglutide (15). The most dramatic benefits were seen with a median 3.2-year period of treatment with the SGLT2 blocker empagliflozin, during which risk of the CV composite was reduced 14%, CV mortality 38%, and all-cause mortality 32%. The mechanisms of these effects are not well understood, but two important principles have been proved: drugs in these three classes do not seem to have short-term CV risks, and some have favorable effects beyond what can be attributed to metabolic improvements alone, even in patients with established microvascular and CV complications of diabetes. These recent findings, added to the older ones, have implications for both clinical practice and future research.

Lessons for Clinical Practice

The concept of a positive legacy effect of initially good metabolic control demands consideration of early diagnosis of diabetes and strong efforts to obtain and maintain good control from the start. In addition to efforts to prevent diabetes,

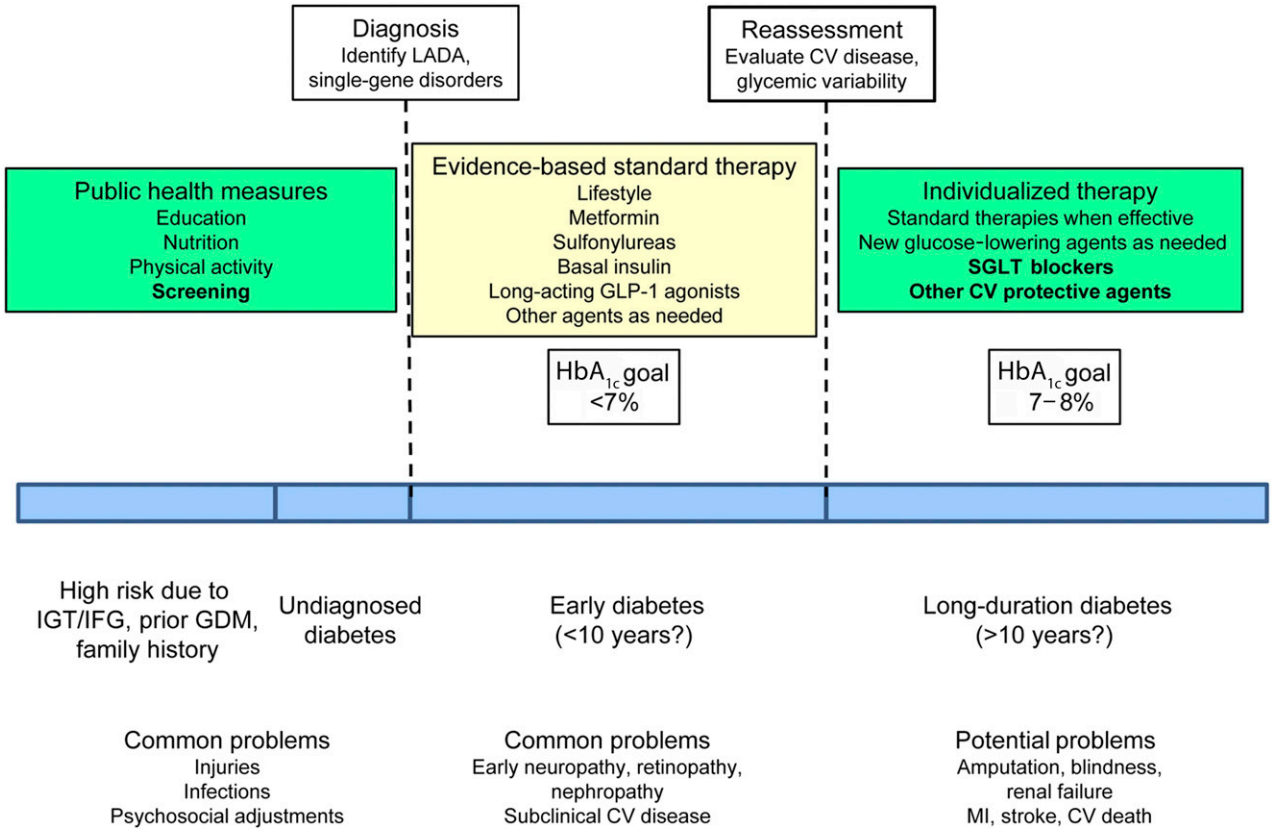

Figure 2—Schematic depiction of three stages of the natural history of T2D, noting several opportunities for improvement of management. During the period before diagnosis, risk factors for developing diabetes call for systematic screening to reduce the interval between onset and diagnosis, thereby reducing an untreated interval of hyperglycemia. At diagnosis, specific subtypes of diabetes may be identified. During the early stages of T2D, evidence-based standard treatment algorithms may be effective in controlling glucose and reducing later complications. At some point in each individual's experience, often close to 10 years after diagnosis, more individualized therapy is likely to be needed, including consideration of newer therapeutic agents with nonglycemic effects that reduce the risk of CV events. GDM, gestational diabetes mellitus; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; LADA, latent autoimmune diabetes in adults.

screening to identify it within a year of onset seems a good investment. If the emerging pattern of long-term outcomes in DCCT/EDIC and the UKPDS continues, marked reduction of the greater than twofold increase of CV risk accompanying diabetes may be within reach, provided excellent metabolic control, perhaps with HbA_{1c} <7.0%, is maintained in the first 10 years. At the other end of the natural history of diabetes, secondary intervention for established CV disease in diabetes should emphasize nonglycemic effects of drugs rather than glucose lowering alone. Thus, evidence from these trials now supports renewed clinical efforts before the current diagnosis of diabetes, in the first 10 years after diagnosis, and after more than 10 years. These opportunities at all stages of the natural history of T2D are illustrated in Fig. 2.

Lessons for Future Clinical Trials

The good news for pharmacologic research is that required safety studies of new agents can yield important new information on both short-term risks and short-term benefits. More problematic is the reminder that a few years of observation cannot predict the legacy effects of either metabolic changes or other effects of drugs that may emerge only decades later. Notably, the impressive short-term benefits of empagliflozin, and perhaps other drugs of its class, cannot be assumed to be free of later harms. Also, the results these studies of very high-risk patients cannot confidently be extrapolated to the entire range of patients seen in clinical practice. Finally, to limit costs, the study of both short-term and long-term outcomes must be made more efficient by new trial designs and statistical methods, prospective data collection, and perhaps embedding of research within health care systems.

IV. WHAT DOES THE FUTURE HOLD?

To tackle the question of what the future holds, one might take two routes: one deals with what is *reasonable* to expect given current trends; the other is about what would be *desirable* to see in the future.

To begin with the reasonable, Table 6 is a nonexhaustive list of research areas in T2D that are evolving toward disruptively new knowledge (indexed by a makeshift heuristic score of value and speed of scientific discovery). Genetics has been disappointing for clinical diabetes as it shifted from the early T2D candidate gene approach, which basically failed, to genome-wide association scanning and genomics, which showed that dozens of genes are involved in the predisposition to T2D (64–66). Furthermore, joint predisposition to T2D and comorbidities (principally, obesity [67], hypertension [68], and dyslipidemia [69]) has raised the task of identifying the genetic makeup of T2D to quasi-intractable levels of complexity. However, epigenetics and the "omics" (mainly metabolomics and proteomics) are providing increasingly more "physiological" profiles of diabetic subphenotypes by using integrated network methodology (70). Understanding which gene variant controls the transcription of which protein in which metabolic pathway, resulting in which distinct, measurable biochemical signature, currently appears to be a trajectory of slow but unrelenting progress (71,72).

At the tissue level, classical studies of β-cell function are being refueled by the increased availability of human islets. Thus, three-dimensional in situ and in vivo imaging has exposed the structure of the human islet at an unprecedented level of resolution, highlighting the relative (i.e., as compared with rodent islets) short total vessel network, the tight connection between α- and β-cells, and the presence of β-cell clusters within the islet (73). With regard to the latter feature, brilliant work has recently discovered "hubs" of β-cells that serve the function of synchronizing insulin discharge across the islet (74), a sort of specific conduction system analogous to that of the heart. The fundamental discovery of β-cell plasticity will add important details to the processes of dedifferentiation and redifferentiation of α- and β-cells (75–78). By way of example, an antimalarial drug class, the artemisinins, facilitate transdifferentiation of α- to β-cells in a pathway involved in active $GABA_A$ receptor signaling in neurons (79). These developments will not only provide insight into the behavior of this diffuse organ but also extract molecular targets for intervention, with the use of drugs or by engineering synthetic gene circuits with CRISPR technology (synthetic biology) (80). The gut is likely to yield much novel information both in the epithelial compartment (metabolic effects of substrate transporters [81], bile acids [82], microbiota and their products [83]) and in the sparse endocrine section (L and K cells and the panel of their interrelated hormonal products) (84).

Table 6—Putative development of major research areas

	Score*	
	Value	Speed
Genome level	6	4
Genes		
Epigenetics		
"omics"		
Tissue level	7	5
β-Cell plasticity		
Adipose tissue plasticity		
Gut factors (including the microbiome)		
Organ level	9	5
Heart		
Kidney		
Brain		
Environment	3	3
Diet and exercise		
Toxic factors		
Infections		
Pharmacology	6	7
New drugs		
Strategies		
Information technology	2	9
Sensors		
Electronic health records		
Big data		

*On an ascending scale of 1 to 10.

Thanks to ever more powerful in vivo imaging techniques (e.g., MRI and spectroscopy, positron emission tomography with multiple tracers), there is likely to be a reprise of whole-organ studies jointly of structure, metabolism, and function (85,86) (Fig. 3). Quantitation of regional uptake of substrates and perfusion in the liver (87), adipose tissue (88), and myocardial muscle (89) and tissue perfusion/metabolism matching (90) will enhance our understanding of tissue energetics and their derangements in diabetes. The heart and the kidney will be in the front line as ischemic heart disease, heart failure, and renal insufficiency continue to pose the major challenge to the survival of T2D patients. The brain will steadily generate information on the neural control of not just behavior but also metabolic functions (e.g., endogenous glucose production and insulin action [91,92]); even more impressively, the inherent links between T2D and Alzheimer disease along the aging process (93) will be elucidated, and attempts at intervening jointly on

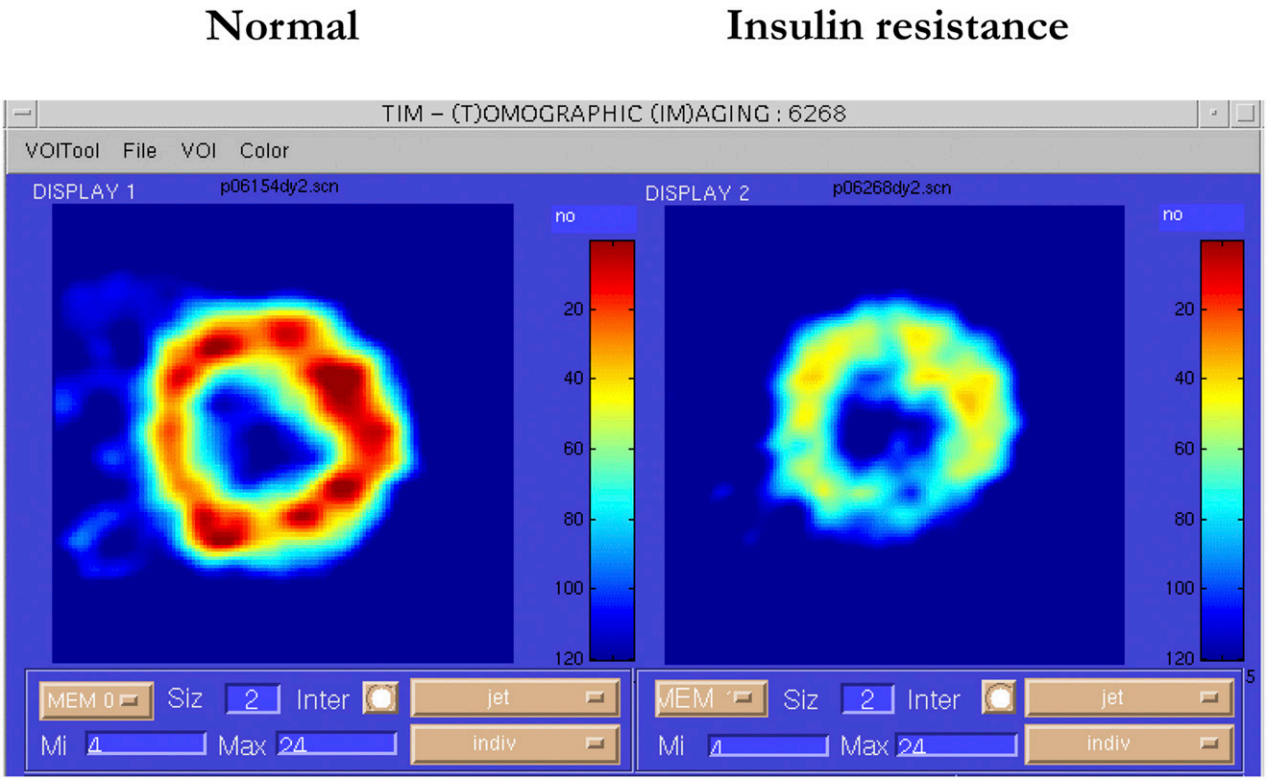

Figure 3—The use of a glucose analog (^{18}F-deoxyglucose) and positron emission tomography images of the left ventricular wall of the heart of a normal subjects (left). The diffuse pattern of tracer uptake documents the absence of perfusion defects; quantification of these images measures insulin-mediated glucose uptake. In the insulin-resistant subject (right), tracer uptake is also diffuse but uniformly reduced, thereby demonstrating myocardial insulin resistance.

metabolic control and cognitive function will proliferate (94).

Much is already known about the environmental factors that impact on the natural history of T2D: the roles of obesity, sedentariness (95), smoking, chemical pollution (96), occupational changes, and infections on glucose tolerance and its main determinants (β-cell function and insulin sensitivity) have been worked out well enough. Unfortunately, clinical experience with lifestyle modification typically is frustrating; in addition, randomized clinical trials have confirmed the limited efficacy and the resource intensity of lifestyle intervention (97). Concomitantly, several new classes of efficacious and safe agents have been introduced in rapid sequence, which may have decreased the drive toward lifestyle intervention. The search for novel therapeutic targets is very active (98), and the development of glucose-sensitive insulins (99), if successful, would be a game-changer as compared to the dual-hormone artificial pancreas (100). Moreover, early use of drug combinations is very likely to increase, especially with strategies based on complementary mechanisms of action or chemical hybridization (101). In particular, in the future, insulin may be mostly used in combinations with agents that reduce the associated risk of hypoglycemia and weight gain.

Application of information technology to health care is already galloping, and its rate of development may accelerate under heavy market pressure by corporate giants (Google, Facebook, etc.). Refined sensors acquire all sorts of data (glycemia, heart rate, etc.), which are relayed to smartphones/tablets/computers equipped with feedback algorithms capable of adjusting treatment (mobile health). Increasing adoption of electronic health records will facilitate planning bed occupancy and reduce in-hospital time. This, along with linking medical and administrative databases, can help prioritize resource allocation and cost assessment. The temptation, however, to mine the emerging humongous data pools to extract counterfeit clinical guidance (102) will be increasingly difficult to resist. Indeed, means and strategies will have to be deployed to deal with information flux because the relationship between information supply and information handling has long been known to have an inverted U shape (103): above a certain range of information load lie confusion and, worse, manipulation (Fig. 4). Additionally, some governance will have to be put in place to prevent fraudulent data hijacking and to protect the privacy of medical data.

Turning to what is desirable, the answer is straightforward (and nowadays "viral"): precision medicine. On the shoulders of outstanding progress in diabetes science, it should be possible to personalize diagnosis, prognosis, and treatment for the individual patient by using a battery of examinations (physical) and tests (in silico) as the patient first accesses the point of care. The patient would be classified into one of several subphenotypes (104,105), be given reliable quantitative risk scores for complications, and walk out with a tailored set of drug prescriptions (106), each complemented by a predicted rate of therapeutic response and side effects. Years later, epidemiologists and health care providers would proudly announce that the deadly gap in CV and cancer morbidity/mortality between the T2D segment and the background population was canceled. This rosy prospect

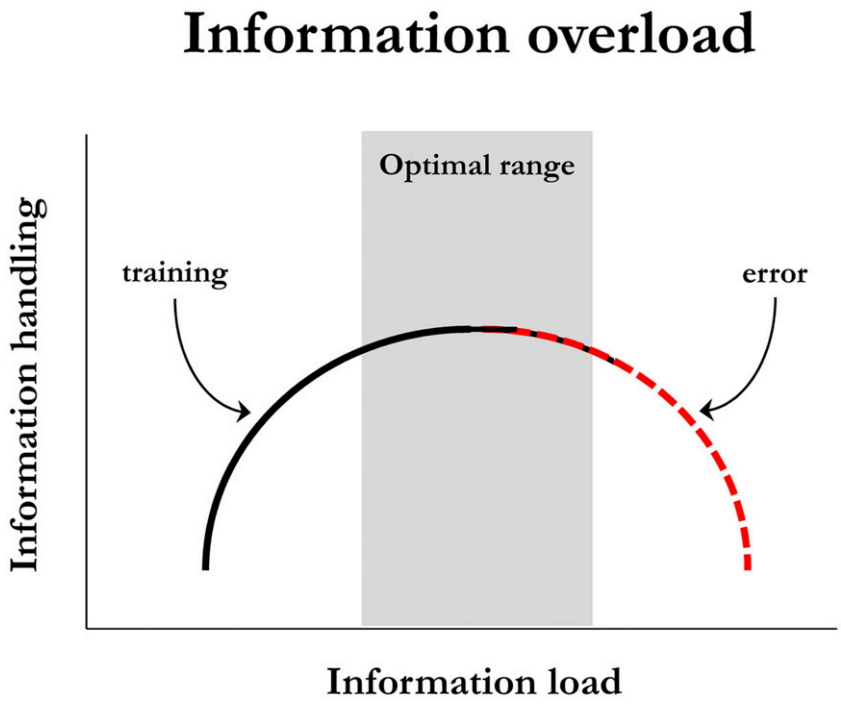

Figure 4—In learning machines and humans, the relationship between information load and information handling takes the shape of an inverted U (32).

would seem to be at hand, especially since the pathophysiology of diabetes is already known with enough detail to account for every milligram of circulating glucose. There are, however, major hurdles. First, the sheer number of patients with known or unknown T2D, which is climbing up to one-sixth of the general population (107), and the systemic nature of the disease once complications develop will pose a hefty levy on health care. Second, given the geographic and socioeconomic distribution of T2D (107), most of the "reasonably" expected benefit (Table 6) may go only to a fraction of the patients—those who have access to and can afford the progress. Even these happy few may experience a progressive erosion of physician contact as they become identification numbers in a mechanized, automated, digitalized path. But the underprivileged many will still be in environments that preclude detailed phenotyping, expensive drugs and devices, and connectivity. Finally, the explosion of diabetes care demand may enter into fierce competition with other resource-intensive diseases, e.g., cancer and Alzheimer disease.

At this juncture, a development that is both reasonable and desirable is in sight: prevention. The ongoing efforts to identify subjects strongly predisposed to T2D (108) will capitalize on selective screening (by age, family history, gestational diabetes mellitus, etc.) and powerful biomarker panels; treatment may exploit the safer new drugs. Intervention in prediabetes, however, must include obesity, which remains the most powerful known risk factor for dysglycemia at all latitudes. Bariatric surgery cogently demonstrates that, once stripped of weight excess, T2D (but also hypertension and dyslipidemia) undergoes prolonged remission or major improvement. Indeed, "lean" or postobese T2D is where genetic predisposition is strongest and easiest to identify. Although obesity, by nature and size, is also a social problem, science could contribute to its attenuation, if not solution, by building and testing a stepped approach using combinations of less invasive surgery (e.g., sleeve gastrectomy), drugs (e.g., GLP-1 receptor agonists, SGLT2 inhibitors), and "early" lifestyle counseling (i.e., in children and adolescents). This will remain an uphill trajectory—because of the body's attitude to strenuously defend achieved weight (109)—but one that goes straight to the root of the problem. The increasingly "social" dimension of diabetes—due to its systemic and comorbid nature and its high prevalence—is likely to expand the diabetologist's remit: from care to prevention, from single point-of-care to networks, from individual education to public advocacy, from science translation to lobbying. A formidable prospect, particularly in times of recurrent attacks on public health care, which still is a hallmark of civilization.

Duality of Interest. B.Z. has served as consultant for and has received honoraria from AstraZeneca, Boehringer Ingelheim, Eli Lilly and Company, Janssen, Merck Sharp & Dohme, Novo Nordisk, and Sanofi and has received grant support from Boehringer Ingelheim, Novo Nordisk, and AstraZeneca. J.S.S. has acted as an advisor to ADOCIA, AstraZeneca, BD Technologies, Boehringer Ingelheim, Dance Biopharm, Diavacs, Elcelyx Therapeutics, Eli Lilly and Company, Ideal Life, ImmunoMolecular Therapeutics, Intarcia Therapeutics, Intrexon, Merck Sharp & Dohme, Orgenesis, Sanofi, Servier, vTv Therapeutics, Valeritas, and Viacyte; has received research funding from Mesoblast and Viacyte; is a member of the board of directors of Dexcom, Moerae Matrix, and VasoPrep Surgical; and has equity in Dance Biopharm, Dexcom, Ideal Life, Intrexon, Moerae Matrix, and VasoPrep Surgical. M.C.R. has received honoraria for consulting from ADOCIA, Eleclyx, Sanofi, and Valeritas; for serving on a data safety monitoring committee for AstraZeneca and GlaxoSmithKline; for serving on a clinical trial steering committee for Eli Lilly and Company and Theracos; and for speaking at professional meetings for Sanofi and has received research support through his institution from AstraZeneca, Eli Lilly and Company, and Novo Nordisk. E.F. has been a speaker and consultant for AstraZeneca, Takeda, Novo Nordisk, Sanofi, Mitsubishi Tanabe, Eli Lilly and Company, Boehringer Ingelheim, and Merck Sharp & Dohme; has received research funds from Boehringer Ingelheim and Eli Lilly and Company; has done ad hoc consulting for Janssen and AstraZeneca; and is a member of the scientific advisory board of Boehringer Ingelheim/Eli Lilly and Company, Merck Sharp & Dohme, and Sanofi.

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