Insulin resistance and β-cell dysfunction are the core pathophysiological mechanisms of all hyperglycemic syndromes. Advances in in vivo investigative techniques have made it possible to quantify insulin resistance in multiple sites (skeletal and myocardial muscle, subcutaneous and visceral fat depots, liver, kidney, vascular tissues, brain and intestine), to clarify its consequences for tissue substrate selection, and to establish its relation to tissue perfusion. Physiological modeling of β-cell function has provided a uniform tool to measure β-cell glucose sensitivity and potentiation in response to a variety of secretory stimuli, thereby allowing us to establish feedbacks with insulin resistance, to delineate the biphasic time course of conversion to diabetes, to gauge incretin effects, and to identify primary insulin hypersecretion. As insulin resistance also characterizes several of the comorbidities of diabetes (e.g., obesity, hypertension, dyslipidemia), with shared genetic and acquired influences, the concept is put forward that diabetes is a systemic disease from the outset, actually from the prediabetic stage. In fact, early multifactorial therapy, particularly with newer antihyperglycemic agents, has shown that the burden of micro- and macrovascular complications can be favorably modified despite the rising pressure imposed by protracted obesity.

PREAMBLE

Over the past ~30 years, the number of people with diabetes has more than doubled worldwide; this trend is projected to continue (1) and the associated health expenditure to explode accordingly (2). Yet, since the 1980s mortality in people with diabetes has been declining more than in people without diabetes (at least in Europid populations) (3). The relationship between disease prevalence and mortality is complex, but at a simplistic level the disconnect between rising numbers of people with diabetes and decreasing deaths among them begs the question: has treatment of serious diabetes complications outperformed treatment and/or prevention of diabetic hyperglycemia? If so, can we trace the pathophysiological mechanisms that may underlie this outcome?

The following exposition is built around a central tenet: that type 2 diabetes is not a single-organ disease—the pancreatic β-cell—that ultimately results in multiple end-organ damage but, rather, an inherently multiorgan disease from the outset, indeed, from the prediabetes stage. As preliminaries, advances in insulin sensitivity and β-cell function, i.e., the proximal determinants of plasma glucose levels, will be described.

Insulin Resistance

Through the 1980s and 1990s, the clamp technique—using a feedback algorithm to fix plasma glucose concentration at any desired level—was established as the gold standard method to measure insulin sensitivity in vivo. Subsequently, the combination of the clamp technique with tracer glucose infusions, indirect calorimetry, artero-venous catheterization, and positron emission tomography (PET) has made it possible to construct dose-response curves of peripheral and hepatic insulin sensitivity and intracellular glucose partition and to discern organs/tissues participating in overall glucose disposal (4).

While glucose uptake during a standard euglycemic-hyperinsulinemic clamp occurs mostly (~70%) in skeletal muscle (4), PET studies—using a glucose analog...
mediated glucose uptake by the concomitant blood reported in humans (11). Thus, when normalizing insulin-visceral than in subcutaneous fat, a per unit mass is also reduced in adipose tissue, whether in subcutaneous or visceral depots (though an increased total fat mass may maintain or even increase the contribution of fat to whole-body glucose disposal) (5). Decreased adipocyte glucose utilization restrains the production of α-glycerophosphate necessary to reesterify free fatty acids (FFA), resulting in increased delivery of FFA to the circulation. Because FFA, unlike glucose, do not require insulin to enter cells, their augmented availability increases their oxidation at the expense of glucose oxidation (6), thereby closing an in vivo Randle cycle (7). A further downstream consequence of higher FFA oxidation is the stimulation of ketogenesis, principally in the liver but possibly also in the kidney, with the attendant release of ketones into the bloodstream (Fig. 1).

Of note in the PET studies (8), glucose uptake per unit mass is higher in visceral than in subcutaneous fat (Fig. 2A), despite strong evidence that the former carries independent cardiometabolic risk (9). More recent PET studies—combining [15O]FDG with labeled water ([18F]FDG-PET scanning) and defects thereof—are described in a vast number of in vitro and animal studies. In vivo studies in humans, however, are relatively few, due to the technical difficulty inherent to investigating renal perfusion and metabolism. Even just focusing on glucose and sodium, the kidney uses glucose as a fuel, makes glucose by gluconeogenesis, and reabsorbs filtered glucose through sodium-glucose cotransporters. The large load of filtered sodium is handled by a plethora of exchangers before final excretion (20). The bulk of current evidence indicates that renal gluconeogenesis may be upregulated in states of insulin resistance, especially in the postprandial state (21,22). More recently, the combined use of noninvasive technology—PET scanning of [15O]H2O and 14R(S)-[18F]fluoro-6-thia-heptadecanoate (an analog of short-chain FFA), computed tomography, and MRI—has made it possible to demonstrate higher FFA uptake in the cortical than in the medullary region and increased renal volume, blood flow, and FFA uptake in obese, insulin-resistant individuals (23). In insulin-resistant

Moreover, and more importantly, in either subcutaneous or visceral fat depots insulin-stimulated fractional glucose uptake is similar in insulin-resistant and insulin-sensitive individuals, indicating that uptake in this tissue is largely flow mediated. In contrast, muscle glucose uptake is markedly reduced in insulin-resistant subjects both in absolute and fractional terms; i.e., it is a predominantly cellular phenomenon (Fig. 1).

As myocardiocytes are richly endowed with insulin receptors, the human heart is exquisitely sensitive to insulin (13). With use of [18F]FDG-PET in patients with coronary heart disease, myocardial insulin resistance was found to be proportional to whole-body insulin resistance (14) (Supplementary Fig. 1A). Vascular cells (endothelium and smooth muscle) also carry insulin receptors, which are involved in the vasodilatation induced by endothelium-dependent (e.g., acetylcholine) and endothelium-independent (e.g., sodium nitroprusside) agonists. In patients with type 2 diabetes, the forearm vasodilatory responses to both acetylcholine and nitroprusside are reduced in proportion to the degree of clamp-based insulin resistance (15) (Supplementary Fig. 1B). In the hearts of patients with coronary heart disease, especially if hypertensive, myocardial architecture is often disarrayed, and the combination of tissue insulin resistance and impaired coronary vasodilatation may cause a mismatch between perfusion and metabolism, such that some muscle regions may be perfused but insulin unresponsive (16). It should be recalled that insulin, a phylogenetically ancient hormone, does have vasoactive properties (17), though at physiological concentrations these are weak compared with nitric oxide or angiotensin. However, insulin, among several other factors, is involved in the regulation of the microcirculation not only in the retina, kidneys, and peripheral nervous system but also in skin, brain, adipose tissue, and cardiac and skeletal muscle (18).

In the kidney, insulin receptors are expressed in several cell types, from podocytes to epithelial cells throughout the tubular nephron (19). Renal insulin actions—and defects thereof—are described in a vast number of in vitro and animal studies. In vivo studies in humans, however, are relatively few, due to the technical difficulty inherent to investigating renal perfusion and metabolism. Even just focusing on glucose and sodium, the kidney uses glucose as a fuel, makes glucose by gluconeogenesis, and reabsorbs filtered glucose through sodium-glucose cotransporters. The large load of filtered sodium is handled by a plethora of exchangers before final excretion. The bulk of current evidence indicates that renal gluconeogenesis may be upregulated in states of insulin resistance, especially in the postprandial state. More recently, the combined use of noninvasive technology—PET scanning of [15O]H2O and 14R(S)-[18F]fluoro-6-thia-heptadecanoate (an analog of short-chain FFA), computed tomography, and MRI—has made it possible to demonstrate higher FFA uptake in the cortical than in the medullary region and increased renal volume, blood flow, and FFA uptake in obese, insulin-resistant individuals. In insulin-resistant

**Figure 1**—Reciprocal relation of whole-body lipid oxidation to glucose oxidation (red line) and direct relation of lipid oxidation to fractional glucose uptake per unit mass (green line) during 5 h following a mixed meal. Plotted are mean data in subjects with type 2 diabetes (redrawn from Ferrannini et al. Shift to fatty substrate utilization in response to sodium chloride loading in patients with type 2 diabetes. Diabetes 2016;65:1190–1195). T2D, type 2 diabetes.
patients with type 2 diabetes, physiological hyperinsulinemia appears to reduce proximal tubular reabsorption of glucose and sodium (24).

Recent studies have provided in vivo evidence of insulin resistance in two other peripheral organs, namely, brain and intestine. With regard to the brain, insulin permeates the central nervous system by transcytosis as well as through gaps of the blood-brain barrier. Insulin receptors are widely distributed in the brain, and insulin action in the brain, especially in the hypothalamus, has been shown to regulate peripheral metabolic tissue activities, including suppression of hepatic glucose output and lipolysis in white adipose tissue and increased thermogenesis in brown adipose tissue (25). Shown by PET scanning, fasting brain glucose uptake is not affected by insulin resistance, but physiological hyperinsulinemia leads to brain glucose accumulation in obese, insulin-resistant subjects (26), a change that associates with enhanced endogenous glucose output (27). Higher glucose uptake appears to occur in astroglial cells rather than neurons and to be accentuated in certain areas of the encephalon. What exactly this apparent paradox means to synaptic activity and neuronal function is an area of intense investigation.

In the human duodenum and jejunum, insulin increases glucose uptake, an effect that is blunted in the obese and improved by bariatric surgery–induced weight loss (28). Mechanisms and physiological impact of insulin-sensitive jejunal glucose uptake in humans are still uncertain (29).

The liver is central to insulin action by virtue of its anatomical connection in series to the pancreas, while all other tissues are placed in parallel to systemic insulin delivery. In fact, the liver senses insulin at concentrations that are approximately threefold higher than the concomitant peripheral levels. Unlike rats and dogs, in man euglycemic hyperinsulinemia fails to stimulate splanchnic tissue glucose uptake above fasting levels (i.e., a rate of 0.6 mg · min⁻¹ · kg⁻¹ or ~3% of incoming glucose); this rate, however, increases with hyperglycemia (30). In contrast, endogenous glucose production is exquisitely sensitive to insulin, which suppresses it virtually completely at (calculated) prehepatic insulin concentrations of 400–500 pmol/L (30). Resistance of endogenous glucose production to insulin suppression is present in obesity and diabetes (Supplementary Fig. 2A); gluconeogenesis is the resistant pathway in both conditions, and glycogenolysis also fails to be normally suppressed in type 2 diabetes, resulting in fasting hyperglycemia (Supplementary Fig. 2B). Furthermore, the increased delivery of FFA resulting from adipose tissue insulin resistance (Fig. 1) has two consequences in the liver: it enhances lipid oxidation, which provides the energy for the enhanced gluconeogenesis (Supplementary Fig. 3), and it accelerates reesterification of FFA to triglycerides—which excess is exported as triglyceride-rich VLDL particles and piles up in hepatocytes as lipid droplets. Thus, typical diabetic dyslipidemia, i.e., high triglycerides and low HDL cholesterol, and hepatic steatosis are in large measure terminal outcomes of insulin resistance (31).

**β-Cell Function**

β-Cells must supply insulin to the body tissues in quantity and time dynamics apt to maintain plasma glucose within a very narrow concentration range on a minute-by-minute basis. In fact, insulin output must cope with acute challenges—i.e., size, composition, and rate of absorption of meals—as well as adapt to long-term settings, such as changes in target tissue sensitivity to insulin. As they execute such tasks, β-cells integrate multiple inputs, excitatory (glucose but also FFA, amino acids, incretins, etc.) as well as inhibitory (α-adrenergic outflow, somatostatin, etc.), and coordinate intraslet activation (32). It is therefore not surprising that there are different—sometimes mutually inconsistent—modes of insulin response depending on the stimulus that is applied (oral glucose or meal, intravenous glucose bolus, hyperglycemic clamp, etc.) and the
pathophysiological condition under study. For description of β-cell function comprehensively, mathematical models have been used since the late 1960s. We developed a model featuring the three main modes of β-cell response identified in a wealth of isolated perfused pancreas experiments: a dose-response function relating insulin secretion to concomitant plasma glucose concentrations (i.e., glucose sensitivity), an early response function (i.e., response to glucose rate of change or rate sensitivity), and a potentiation factor, accounting for upward modulation of the dose response by time-dependent potentiating stimuli (e.g., glucagon-like peptide 1 [GLP-1] and its receptor agonists) (33). When tested in collated data from multiple in vitro and in vivo experiments, the model has yielded good evidence for a defective amplifying pathway of β-cell secretory response to glucose in type 2 diabetes (34). With this model used on data from clinical cohorts, β-cell glucose sensitivity has been described as a continuous inverse function of 2-h postglucose glycemia, whereas absolute glucose-stimulated insulin secretion has reproduced the typical biphasic pattern, i.e., initial increase followed by slow, progressive decrease through to insulin deficiency (32). Thus, the increased insulin secretion that characterizes states of impaired glucose tolerance is compensatory—to the rising glucose levels—but maladaptive insofar as it amounts to further secretory stress on already dysfunctional β-cells (Fig. 3). Accordingly, in prospective studies of individuals with normal glucose tolerance, preserved glucose sensitivity is a strong protective factor against progression to dysglycemia—independent of clinical risk factors and insulin resistance—whereas absolute insulin secretion is a risk factor (35).

The model has also been able to consolidate two important notions. Firstly, in subjects with type 2 diabetes, glucose sensitivity is almost invariably compromised as compared with matched subjects without diabetes, whereas in postmortem specimens of human pancreas, β-cell mass widely overlaps between patients with diabetes and healthy control subjects and insulin stores are reduced by only one-third in the former as compared with the latter (36). Therefore, β-cell dysfunction cannot be solely attributed to actual demise of β-cells. Secondly, careful physiological phenotyping and follow-up of morbidly obese patients with type 2 diabetes has demonstrated that diabetes remission not only is associated with the marked improvement in insulin sensitivity that is expected to follow major weight loss but also is accompanied by a sizeable recovery of β-cell function (37). Strikingly, a definite improvement in glucose sensitivity can already be detected 15 days after the operation, when plasma glucose, insulin secretion rates, and insulin sensitivity are unchanged and no measurable weight loss has occurred (38) (Fig. 4). In fact, in larger series of patients, preoperative β-cell glucose sensitivity predicts extent and durability of diabetes remission almost regardless of the type of surgery, Roux-en-Y gastric bypass, biliopancreatic diversion, or sleeve gastrectomy. This result—seen even in patients with long-standing diabetes on insulin therapy—obviously implies that a fraction of the β-cell complement is functionally mute but not dead and can be brought back into function by intervention. It also speaks to the power of even short-term caloric restriction, such as prevails during the surgical recovery phase (~800 kcal/day), possibly aided by an early surge of GLP-1.

Measuring β-cell glucose sensitivity has introduced a new concept in type 1 diabetes. In the Diabetes Prevention Trial–Type 1 (DPT-1) of first-degree relatives of subjects with type 1 diabetes, the availability of sequential oral glucose tolerance tests made it possible to show that in
high-risk subjects who progress to type 1 diabetes, the time course of glyceremia is biphasic, with an essentially stable plateau followed by an abrupt surge into the diagnostic range. Moreover, the corresponding trajectory of glucose sensitivity displays a decline that anticipates the glycemic transition by \(0.7\) years, while insulin sensitivity starts to deteriorate only after hyperglycemia ensues (39) (Fig. 5).

The mechanisms responsible for the biphasic pattern of transition to overt diabetes have not been clarified, but it is intriguing that the same pattern has also been observed in cohorts of pre–type 2 diabetes (e.g., in the Mexico City Diabetes Study [40]) over longer follow-up periods than in type 1 diabetes (Supplementary Fig. 4A). While intense, prolonged stress is a possibility, the explanation may lie in a principle of physics known as phase transition: strongly homeostatic variables—such as plasma glucose concentration—that are controlled by multiple factors may be in a state of dynamic instability as a result of multiple defects and may be propelled into failure by a further small deterioration of a single etiologic factor (39).

With regard to potentiation, early perfused pancreas and animal experiments indicated that glucose-induced insulin secretion can be augmented by a number of potentiators, ranging from certain amino acids to sulfonylureas. Early studies in healthy volunteers did show a strong enhancement of the insulin response when oral glucose was superimposed on a hyperglycemic clamp while preventing changes in glyceremia (41). On the basis of these results, it was postulated that lack of a putative “gut factor” might partake of the hyperglycemia of type 2 diabetes (42). Subsequent work has firmly established the identity of gastrointestinal hormones (GLP-1, the main incretin, and gastric inhibitory peptide), quantified their role in insulin potentiation, and established a defective incretin effect as an inherent abnormality of type 2 diabetes (43). While the search for the origin and mechanism of such defect is ongoing, in vivo studies have indicated that glucose tolerance and obesity make independent contributions to the severity of the incretin defect, thereby implicating higher circulating FFA in the pathogenesis (44) (Fig. 6). Because circulating incretin concentrations are not consistently reduced in association with a functional incretin defect, the concept is emerging of incretin resistance. Because the incretin effect is operationally defined as the difference in stimulated insulin secretion between the oral and intravenous route of nutrient arrival, the corresponding incretin resistance would reside in the islet. In line with this notion, recent imaging studies using labeled exendin in murine and human islets show that periods of hyperglycemia significantly reduce GLP-1 receptor (GLP-1R) expression and that subsequent blood glucose normalization restores GLP-1R expression and halts the observed loss in islet volume (45). Also, incretin resistance could be a global \(\beta\)-cell problem occurring also with other nonglucose secretagogues.

It has long been known that glucagon secretion is paradoxically enhanced in type 2 diabetes, thereby exacerbating the effects of diminished insulin release and action on plasma glucose levels. More recently, estimates of the prehepatic insulin-to-glucagon molar concentration ratio have refined information about the bihormonal control of liver metabolism. In healthy subjects, the ratio averages 10 in the fasting state and rises to a peak of \(~30\) in response to a mixed meal, confirming the overall dominance of insulin over glucagon. In subjects with type 2 diabetes, the initial peak of the insulin-to-glucagon ratio is
beheaded, and it surpasses that of control subjects during the late phase of meal absorption (Supplementary Fig. 5A). Importantly, the time courses of the corresponding insulin secretion rates closely match those of the insulin-to-glucagon ratio (Supplementary Fig. 5B), confirming the tight control of the former by the latter (37). Also of note is that in these subjects with moderate hyperglycemia, the total amount of insulin released during the 5 h of meal absorption is very close to that of the lean control subjects (∼11 units/m²) despite the higher glycemia.

Interactions Between Insulin Resistance and β-Cell Dysfunction

It has long been known that the plasma insulin concentration is the fulcrum of a physiological feedback between insulin secretion and insulin action. In fact, insulin resistance begets hyperinsulinemia, principally through small increments in plasma glucose levels (but also FFA and certain amino acids). In turn, chronic hyperinsulinemia depresses insulin action via downregulation of insulin receptors in target tissues as well as by interfering with intracellular insulin signaling (46). By this paradigm, the hyperinsulinemia of insulin-resistant states has typically been regarded as the compensatory adaptation of the β-cell (47). However, animal studies and a few human observations have hypothesized that in some individuals an inappropriate increase of insulin secretion may occur independently of insulin resistance. Recent studies provided strong evidence of such primary insulin hypersecretion by using direct measurements of glucose-induced insulin secretion and of insulin sensitivity (by the clamp technique) and an unbiased criterion to define hypersecretion itself (48).

With use of this approach, in “hypersecretor” individuals glucose regulation was abnormal compared with in the normosecretors despite the hyperinsulinemia, and anticipated further dysglycemia at follow-up. Excessive endogenous glucose production could therefore be pinpointed as the source of the excess glycemia, and direct neural influences to the islet and the liver were postulated (Fig. 7).

With regard to glucose levels, insulin resistance and β-cell dysfunction are the basic mechanisms of any dysglycemic syndrome, to which they make variable quantitative contributions in different pathologic circumstances (paths 1 and 2 in Fig. 8). In turn, hyperglycemia feeds back to both insulin action and β-cell function through a series of mechanisms [advanced glycation end product, endothelial nitric oxide synthase, GAPDH, manganese superoxide dismutase, nuclear factor κB, poly(ADP-ribose) polymerase, protein kinase C, reactive oxygen species, superoxide dismutase, uncoupling protein] collectively indicated as glucose toxicity (comprehensively discussed in the 2005 Banting Lecture by Michael Brownlee [49]). In a nutshell, chronic hyperglycemia (and wider glycemic swings) worsen insulin secretory function (path 3 in Fig. 8) as well as the tissue response to insulin (path 4 in Fig. 8) (reviewed in 50). Of special interest is novel evidence demonstrating a direct feedback between islets and insulin sensitivity. Sick islets release signal molecules (e.g., citrate, glutamate, etc.) that might interfere with insulin action in target tissues (path 5 in Fig. 8); site and size of these effects remain to be elucidated. Conversely, the presence of insulin resistance in individuals without diabetes induces a generalized hyperplasia of the islet, with an expansion of both the β-cell and the α-cell area (path 6 in Fig. 8). These changes predispose to defective β-cell response and glucagon hypersecretion when the system is stressed (e.g., by partial pancreatectomy, weight gain, etc.) (51). Note that a direct consequence of the operation of multiple physiological feedbacks is the marked heterogeneity of the clinical phenotype at the population level.
A peculiar kind of islet response to stress that has received increasing attention in recent years is transdifferentiation. As originally discovered by Domenico Accili and discussed in his 2017 Banting Lecture (52), β-cells may dedifferentiate and go quiescent and can be revived by antihyperglycemic treatment. Moreover, by a transdifferentiation cycle α-cells may serve as a source of new β-cells in models of extreme β-cell loss (53). The specific impact of insulin resistance on these cell phenotype switches, and the underlying molecular mechanisms are an area of intense investigation, especially since they may represent novel therapeutic targets.

Genetic Influences
An ever-growing number of genetic loci are found to be associated with the risk of type 2 diabetes and its complications (54) or with plasma glucose as a continuous trait. The majority of them turn out to be common variants that connect to β-cell dysfunction, but some also associate with insulin resistance (55). More recently, the discovery of epigenetic modifications has added a further layer of transmissible influences to the picture. Importantly, acquired influences modulate not only insulin sensitivity—classically, sedentariness and obesity—but also β-cell function, through toxins present in food and packaging, the atmosphere, and several drugs (extensively discussed by Barbara Corkey in her 2011 Banting Lecture [56]).

Type 2 Diabetes as a Systemic Disease
Some degree of β-cell dysfunction can be demonstrated in each and all conditions of hyperglycemia, whether transient or permanent. On the other hand, while the vast majority of patients with type 2 diabetes—and many with prediabetes—are insulin resistant (57), the segment of the general population that manifests reduced (by some criterion) insulin sensitivity is much larger than the fraction with diabetes. Obesity (58), essential hypertension (59), dyslipidemia (60), and other pathologies are states of stable insulin resistance, whereas fasting, pregnancy, trauma, and infections are examples of transient insulin resistance. The fact that most patients with type 2 diabetes are overweight/obese, hypertensive, and dyslipidemic has led to the coinage of the term “insulin resistance syndrome” to indicate comorbidant, variable abnormalities of body weight and fat distribution, glucose, lipids, and blood pressure in the population (47). Thus, if the prevalence of type 2 diabetes is 5–10% in a population, the prevalence of the “syndrome” would be at least twice as high. Furthermore, each of the comorbidities is under the influence of genetic and acquired factors, which are partly superimposable on those of type 2 diabetes (e.g., overeating, sedentariness); each of them carries separate predisposition to, and antecedents, macro- and microcirculatory end-organ damage (Fig. 8). Importantly, the time trajectories of type 2 diabetes and comorbidities frequently cross each other. For example, in normoglycemic individuals the presence of essential hypertension is an independent predictor of incident diabetes and, conversely, in normotensive individuals the presence of diabetes is an independent predictor of incident hypertension (61). In fact, the insulin resistance syndrome can be traced back to childhood (62), and evidence of primary insulin hypersecretion has been described in youths, with characteristics similar to those in adults (48). On the other hand, there is evidence that prediabetes itself is a risk factor for cardiovascular disease (CVD) (63), which led, more than two decades ago, to the hypothesis of a “common soil” for the diabetes/CVD complex (64). The development of “omics” platforms (for gene variants, transcripts, proteins, metabolites, etc.) is making rapid progress toward the identification of biomarkers of such diabetes cluster (65). These “omics” searches almost invariably yield networks rather than single “hits,” just as clinical investigation conjures up clusters or syndromes. Intuitively, pulling a node in a web distorts neighboring nodes and branches in proportion to their strength of linkage. Therefore, descriptors such as syndrome, complex, and network in essence imply that diabetes—at all its stages—can be operationally regarded as a systemic disease, whose main features are high frequency and heterogeneity.

Treatment of type 2 diabetes, by contrast, has been rather uniform: lowering glycemia still is the cornerstone and HbA1c, its metric. Success is often modest, as normoglycemia is rarely achieved without paying the price of hypoglycemia and weight gain, and vascular complications remain more frequent than in populations without diabetes. The complex pathogenesis of hyperglycemia has been acknowledged by trials of drug combinations targeting both insulin (endogenous and exogenous) availability and insulin resistance (57); the broader diabetes/CVD complex has been addressed by multifactorial intervention (on glucose, LDL cholesterol, blood pressure, and smoking as in the Steno-2 Study [66]).

More recent pharmacology has capitalized on the biology of incretins by showing that incretin mimetics not only potentiate insulin secretion but also lower glucagon and GLP-1R agonists) can reduce hospitalization for heart failure, progression of renal impairment, and, to a lesser extent, atherosclerotic CVD (57). The mechanisms of these benefits appear to be little dependent on the drug glucose-lowering potency; otherwise, they are still incompletely understood though definitely different between sodium–glucose cotransporter 2 inhibitors and GLP-1R agonists (67) and GLP-1 agonists (68).

Thus, a plausible prospect for a not-too-distant future is that the systemic nature of diabetes will register in clinical practice in three main areas: optimization of comorbidity therapy, earlier intervention, and wider use of new anti-diabetes drugs. What then accounts for the hiatus between decreasing diabetes complications and mortality (3) and persistently insufficient glycemic control? It could be
argued that once a tight homeostasis is broken, full reversal is inherently unrealistic or even that tight glycemic control is not crucial for survival. However, another explanation calls on the role of obesity. Obesity is a prototypical state of insulin resistance and remains the major risk factor for type 2 diabetes (69). Less well appreciated is that long-term obesity—with the attendant chronic increase in lipid oxidation (70)—may cause a degree of β-cell “exhaustion” even in the absence of genetic risk (71), which may be the culprit for the relative refractoriness of glucose control. In fact, weight loss—by bariatric surgery (37) or very-low-calorie diet (72)—has powerful effects on glyce-
mia. However, ordinary lifestyle intervention on obesity is fraught with a high failure rate. It follows that more effort should be directed at preventing obesity, particularly in youths (73), both at the population and individual level.

Acknowledgments. The author is indebted to the many collaborators and fellows who have contributed to the work described in this article. Special thanks are due to Andrea Mari, at the Institute of Neuroscience of the National Research Council in Padua, Italy, for the development and implementation of the β-cell mathematical model, and to Ralph A. DeFronzo, at The University of Texas Health Science Center at San Antonio, for a constant exchange of ideas. The list of references is meant to summarize the author’s laboratory contributions rather than conveying a comprehensive account of the literature. The author regrets the omissions.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

References
1. Cho NH, Shaw JE, Karuranga S, et al. IDF Diabetes Atlas: global estimates of diabetes prevalence for 2017 and projections for 2045. Diabetes Res Clin Pract 2018;138:271–281
2. Williams R, Karuranga S, Malanda B, et al. Global and regional estimates and projections of diabetes-related health expenditure: results from the International Diabetes Federation Diabetes Atlas, 9th edition. Diabetes Res Clin Pract 2020;162:108072
3. Chen L, Islam RM, Wang J, et al. A systematic review of trends in all-cause mortality among people with diabetes. Diabetes Care 2020;43:1718–1735
4. Ferrannini E, Mari A. How to measure insulin sensitivity. J Hypertens 1998;16:895–906
5. Virtanen KA, Peltoniemi P, Marjamäki P, et al. Human adipose tissue glucose uptake determined using [(18)F]-fluoro-deoxy-glucose ([18F]FDG) and PET in combination with microdialysis. Diabetologia 2001;44:2171–2179
6. Felber JP, Ferrannini E, Golay A, et al. Role of lipid oxidation in pathogenesis of insulin resistance of obesity and type II diabetes. Diabetes 1983;32:1341–1350
7. Randle PJ, Garland PB, Hales CN, Newsholme EA. The glucose fatty-acid cycle. its role in insulin sensitivity and the metabolic disturbances of diabetes mellitus. Lancet 1963;1:785–789
8. Virtanen KA, Iozzo P, Hällsten K, et al. Increased fat mass compensates for insulin resistance in abdominal obesity and type 2 diabetes: a positron-emitting tomography study. Diabetes 2005;54:2720–2726
9. Neeland U, Ross R, Després JP, et al.; International Atherosclerosis Society; International Chair on Cardiometabolic Risk Working Group on Visceral Obesity. Visceral and ectopic fat, atherosclerosis, and cardiometabolic disease: a position statement. Lancet Diabetes Endocrinol 2019;7:715–725
10. Ferrannini E, Iozzo P, Virtanen KA, Honka MJ, Bucci M, Nuutila P. Adipose tissue and skeletal muscle insulin-mediated glucose uptake in insulin resistance: role of blood flow and diabetes. Am J Clin Nutr 2018;108:749–758
11. Thompson D, Karpe F, Lafontan M, Frayn K. Physical activity and exercise in the regulation of human adipose tissue physiology. Physiol Rev 2012;92:157–191
12. Tchernof A, Després JP. Pathophysiology of human visceral obesity: an update. Physiol Rev 2013;93:359–404
13. Ferrannini E, Santoro D, Bonadonna R, Natali A, Parodi O, Camici PG. Metabolic and hemodynamic effects of insulin on human hearts. Am J Physiol 1993;264:E308–E315
14. Paternostro G, Camici PG, Lammerstma AA, et al. Cardiac and skeletal muscle insulin resistance in patients with coronary heart disease. A study with positron emission tomography. J Clin Invest 1996;98:2094–2099
15. Natali A, Toschi E, Baldeweg S, et al. Clustering of insulin resistance with vascular dysfunction and low-grade inflammation in type 2 diabetes. Diabetes 2006;55:1133–1140
16. Iozzo P, Chareonthaitawee P, Rimoldi O, Betteridge DJ, Camici PG, Ferrannini E.Mismatch between insulin-mediated glucose uptake and blood flow in the heart of patients with type II diabetes. Diabetologia 2002;45:1404–1409
17. Baron AD. Hemodynamic actions of insulin. Am J Physiol 1994;267:E187–E202
18. Barrett EJ, Liu Z, Khamasi M, et al. Diabetic microvascular disease: an Endocrine Society scientific statement. J Clin Endocrinol Metab 2017;102:4343–4410
19. Artunc F, Schleicher E, Weigert C, Fritsche A, Stefan N, Häring HU. The impact of insulin resistance on the kidney and vasculature. Nat Rev Nephrol 2016;12:721–737
20. DeFronzo RA. The effect of insulin on renal sodium metabolism. A review with clinical implications. Diabetologia 1981;21:165–171
21. Meyer C, Dostou J, Nadkarni V, Gerich J. Effects of physiological hyper-
insulinemia on systemic, renal, and hepatic substrate metabolism. Am J Physiol 1996;275:F915–F921
22. Altschul M, Gerich JE. Renal glucose metabolism in normal physiological conditions and in diabetes. Diabetes Res Clin Pract 2017;133:1–9
23. Rebeles E, Dsdon P, Oikonen V, et al. Renal hemodynamics and fatty acid uptake: effects of obesity and weight loss. Am J Physiol Endocrinol Metab 2019;37:E871–E878
24. Ferrannini E, Pereira-Moreira R, Seghieri M, et al. Insulin enhances renal glucose excretion: relation to insulin sensitivity and sodium-glucose cotransport. BMJ Open Diabetes Res Care 2020;8:e001178
25. Kullmann S, Kleinridders A, Small DM, et al. Central nervous pathways of insulin action in the control of metabolism and food intake. Lancet Diabetes Endocrinol 2020;8:524–534
26. Tualari JJ, Karlsson HK, Hirvonen J, et al. Weight loss after bariatric surgery reverses insulin-induced increases in brain glucose metabolism of the morbity obese. Diabetes 2013;62:2747–2751
27. Rebeles E, Immonen H, Bucci M, et al. Brain glucose uptake is associated with endogenous glucose production in obese patients before and after bariatric surgery and predicts metabolic outcome at follow-up. Diabetes Obes Metab 2019;21:218–226
28. Mäkinen J, Hannukainen JC, Bucci M, et al. Influence of obesity and type 2 diabetes on glucose excretion: relation to insulin sensitivity and sodium-glucose cotransport. BMJ Open Diabetes Res Care 2020;8:e001178
33. Mari A, Schmitz O, Gastaldelli A, Oestergaard T, Nyholm B, Ferrannini E. Meal and oral glucose tests for assessment of beta-cell function: modeling analysis in normal subjects. Am J Physiol Endocrinol Metab 2002;283:E1159–E1166
34. Grespan E, Giorgino T, Arslanian S, Natali A, Ferrannini E, Mari A. Defective amplifying pathway of β-cell secretory response to glucose in type 2 diabetes: integrated modeling of in vitro and in vivo evidence. Diabetes 2018;67:496–506
35. Ferrannini E, Natali A, Muscelli E, et al.; RISC Investigators. Natural history and physiological determinants of changes in glucose tolerance in a non-diabetic population: the RISC Study. Diabetologia 2011;54:1507–1516
36. Henquin JC, Ibrahim MM, Rahier J. Insulin, glucagon and somatostatin stores in the pancreas of subjects with type-2 diabetes and their lean and obese non-diabetic controls. Sci Rep 2017;7:11015
37. Camasta S, Muscelli E, Gastaldelli A, et al. Long-term effects of bariatric surgery on meal disposal and β-cell function in diabetic and nondiabetic patients. Diabetes 2013;62:3709–3717
38. Nannipieri M, Mari A, Anselmino M, et al. The role of beta-cell function and insulin sensitivity in the remission of type 2 diabetes after gastric bypass surgery. J Clin Endocrinol Metab 2011;96:E1372–E1379
39. Ferrannini E, Mari A, Nofrato V, Sosenko JM, Skryer JS; DPT-1 Study Group. Progression to diabetes in relatives of type 1 diabetic patients: mechanisms and mode of onset. Diabetes 2010;59:679–685
40. Ferrannini E, Nannipieri M, Williams K, Gonzales C, Haffner SM, Stern MP. Mode of onset of type 2 diabetes from normal or impaired glucose tolerance. Diabetes 2004;53:160–165
41. DeFronzo RA, Ferrannini E, Hendler R, Wahren J, Felig P. Influence of hyperinsulinemia, hyperglycemia, and the route of glucose administration on splanchic glucose exchange. Proc Natl Acad Sci U S A 1978;75:5173–5177
42. DeFronzo F, Ferrannini E, Wahren J, Felig P. Lack of a gastrointestinal mediator of insulin action in maturity-onset diabetes. Lancet 1978;2:1077–1079
43. Nauck MA, Meier JJ. The incretin effect in healthy individuals and those with type 2 diabetes: physiology, pathophysiology, and response to therapeutic interventions. Lancet Diabetes Endocrinol 2016;4:525–536
44. Muscelli E, Mari A, Casolaro A, et al. Separate impact of obesity and glucose tolerance on the incretin effect in normal subjects and type 2 diabetic patients. Diabetes 2008;57:1340–1348
45. Bulitinga M, Cohrs CM, Eter WA, et al. Noninvasive monitoring of glycemia-induced regulation of GLP-1R expression in murine and human islets of Langherans. Diabetes 2020;69:2246–2252
46. Boucher J, Kleinridders A, Kahn CR. Insulin receptor signaling in normal and insulin-resistant states. Cold Spring Harb Perspect Biol 2014;6:a009191
47. Reaven GM. Banting Lecture 1988: Role of insulin resistance in human disease. Diabetes 1988;37:1595–1607
48. Tricò D, Natali A, Arslanian S, Mari A, Ferrannini E. Identification, pathophysiology, and clinical implications of primary insulin hypersecretion in non-diabetic adults and adolescents. JCI Insight 2018;3:e124912
49. Brownlee M. Banting Lecture 2005: The pathobiology of diabetic complications: a unifying mechanism. Diabetes 2005;54:1615–1625
50. Yki-Järvinen H. Glucose toxicity. Endocr Rev 1992;13:415–431
51. Mezza T, Cinti F, Cefalo CMA, Pontecorvi A, Kulkarni RN, Giaccari A. β-Cell fate in human insulin resistance and type 2 diabetes: a perspective on islet plasticity. Diabetes 2019;68:1121–1129
52. Accili D. Banting Lecture 2017: Insulin action research and the future of diabetes treatment. Diabetes 2018;67:1701–1709
53. Gromada J, Chabosseau P, Rutter GA. The α-cell in diabetes mellitus. Nat Rev Endocrinol 2018;14:694–704
54. Vujkovic M, Keaton JM, Lynch JA, et al.; HPAP Consortium; Regeneron Genetics Center; VA Million Veteran Program. Discovery of 318 new risk loci for type 2 diabetes and related vascular outcomes among 1.4 million participants in a multi-ancestry meta-analysis. Nat Genet 2020;52:680–691
55. Scott RA, Fall T, Pasko D, et al.; RISC Study Group; EPIC-InterAct Consortium. Common genetic variants highlight the role of insulin resistance and body fat distribution in type 2 diabetes, independent of obesity. Diabetes 2014;63:4376–4387
56. Corkey BE. Banting Lecture 2011: Hyperinsulinemia: cause or consequence? Diabetes 2012;61:4–13
57. DeFronzo RA, Ferrannini E, Group L, et al. Type 2 diabetes mellitus. Nat Rev Dis Primers 2015;1:15019
58. Kahn BB, Flier JS. Obesity and insulin resistance. J Clin Invest 2000;106:473–481
59. Ferrannini E, Buzzigoli G, Bonadonna R, et al. Insulin resistance in essential hypertension. N Engl J Med 1987;317:350–357
60. Ginsberg HN. Insulin resistance and cardiovascular disease. J Clin Invest 2000;106:453–458
61. Tsimihodimos V, Gonzalez-Villalpando C, Meigs JB, Ferrannini E. Hyper tension and diabetes mellitus: coprediction and time trajectories. Hypertension 2018;71:422–428
62. Berenson GS, Radhakrishnamurthy B, Bao W, Srinivasan SR. Does adult-onset diabetes mellitus begin in childhood?: the Bogalusa Heart Study. Am J Med Sci 1995;310(Suppl.):S77–S82
63. Kahn R, Robertson RM, Smith R, Eddy D. The impact of prevention on reducing the burden of cardiovascular disease. Diabetes Care 2008;31:1686–1696
64. Stern MP. Do non-insulin-dependent diabetes mellitus and cardiovascular disease share common antecedents? Ann Intern Med 1996;124:110–116
65. Laakso M. Biomarkers for type 2 diabetes. Mol Metab 2019;27S(Suppl.):S139–S146
66. Gaede P, Lund-Andersen H, Parving HH, Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. N Engl J Med 2008;358:580–591
67. Ferrannini E. Sodium-glucose co-transporters and their inhibition: clinical physiology. Cell Metab 2017;26:27–38
68. Drucker DJ. Mechanisms of action and therapeutic application of glucagon-like peptide-1. Cell Metab 2018;27:740–756
69. Hu FB, Manson JE, Stampfer MJ, et al. Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. N Engl J Med 2001;345:790–797
70. Felber JP, Golay A, Jüquer E, et al. The metabolic consequences of long-term human obesity. Int J Obes 1988;12:377–389
71. Luo J, Hodge A, Hendryx M, Byles JE. Age of obesity onset, cumulative obesity exposure over early adulthood and risk of type 2 diabetes. Diabetologia 2020;63:519–527
72. Lean ME, Leslie WS, Barnes AC, et al. Primary care-led weight management for remission of type 2 diabetes (DIRECT): an open-label, cluster-randomised trial. Lancet 2018;391:541–551
73. Hu T, Jacobs DR Jr., Sinaikor AR, et al. Childhood BMI and fasting glucose and insulin predict adult type 2 diabetes: the International Childhood Cardiovascular Cohort (i3C) Consortium. Diabetes Care 2020;43:2821–2829