A Journey in Diabetes: From Clinical Physiology to Novel Therapeutics: The 2020 Banting Medal for Scientific Achievement Lecture

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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

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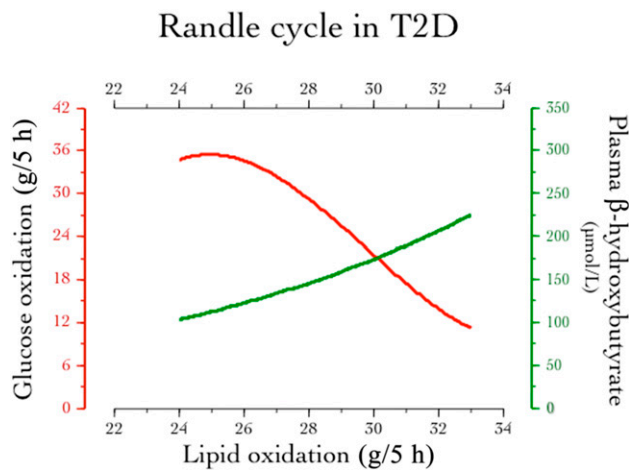
Randle cycle in T2D

Figure 1—Reciprocal relation of whole-body lipid oxidation to glucose oxidation (red line) and direct relation of lipid oxidation to ketone body production (indexed as plasma β-hydroxybutyrate levels [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–glucose cotransporter 2 inhibition in subjects without diabetes and patients with type 2 diabetes. Diabetes 2016;65:1190–1195). T2D, type 2 diabetes.

([^{18}F]deoxyglucose [FDG])—have conclusively demonstrated that in insulin-resistant individuals glucose uptake 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 [^{18}F]FDG with labeled water ([^{15}O]H$_2$O) to concomitantly measure glucose uptake and perfusion (10)—have shown that blood flow is higher in visceral than in subcutaneous fat, a finding not previously reported in humans (11). Thus, when normalizing insulin-mediated glucose uptake by the concomitant blood flow rate, fractional glucose uptake is twice as high in subcutaneous as in visceral fat (Fig. 2B). These quantitative perfusion/disposal relationships substantiate the differential biology of subcutaneous versus visceral adipose tissue, i.e., triglyceride storage versus rapid FFA turnover (12).

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 [^{18}F]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 (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 [^{15}O]H$_2$O and 14(R,S)-[^{18}F]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
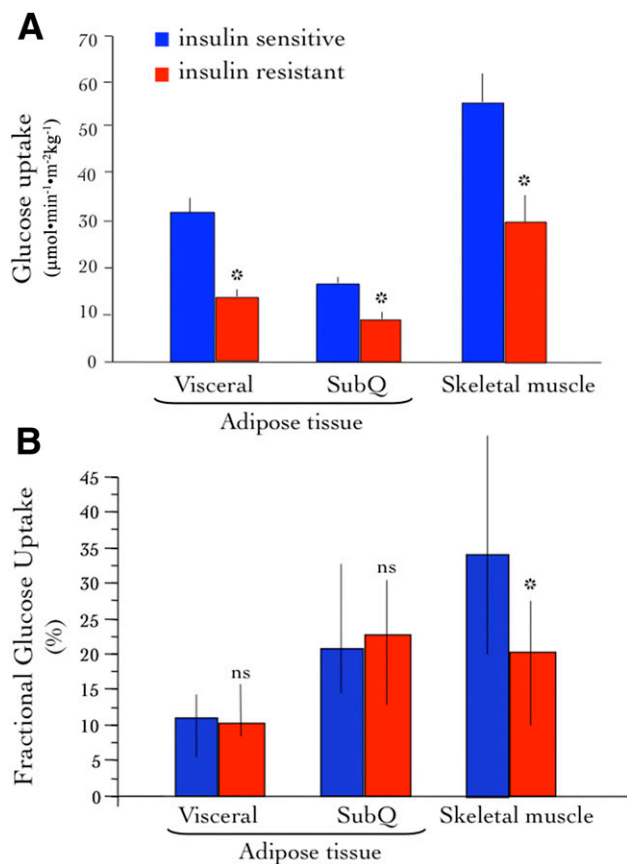
Figure 2—*A*: Glucose uptake by visceral and subcutaneous (SubQ) adipose tissue and skeletal muscle in insulin-sensitive and insulin-resistant individuals reconstructed from PET of [^{18}F]FDG uptake. Bars indicate mean ± SEM. Stars indicate between-group statistical significance ($P < 0.001$ for all). Redrawn from Virtanen et al. (8). *B*: Fractional glucose uptake (= uptake rate / blood flow rate) by visceral and subcutaneous adipose tissue and skeletal muscle in insulin-sensitive and insulin-resistant individuals (by [^{18}F]FDG and [^{15}O]H$_2$O PET). Bars indicate median and interquartile range. Redrawn from Ferrannini et al. (10). ns, not significant.

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 hyper-insulinemia 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 sees 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 $0.6 \, \text{mg} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ 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. 2*A*); 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. 2*B*). 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 intraislet 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
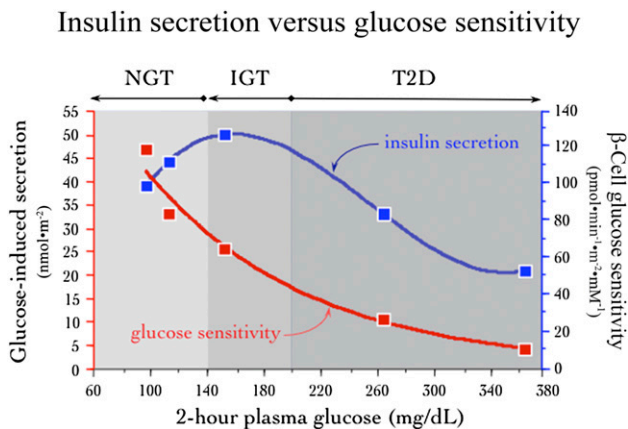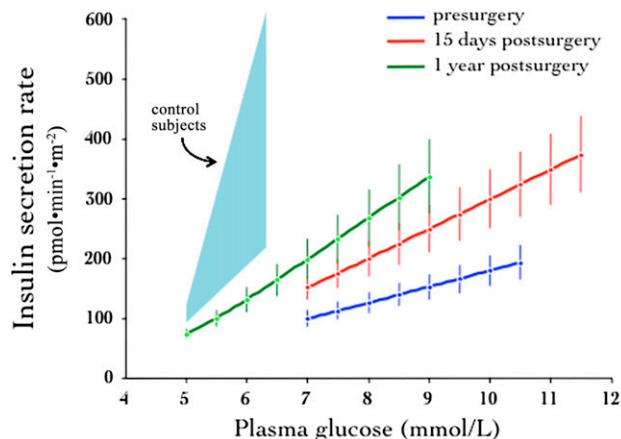

Figure 4—β-Cell sensitivity in morbidly obese patients with type 2 diabetes before, 14 days after, and 1 year after bariatric surgery (Roux-en-Y gastric bypass) as measured during a mixed-meal test. Plots are mean ± SEM over the observed plasma glucose ranges in the different groups. Redrawn from Nannipieri et al. (38).

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

Figure 3—Contrasting relation of absolute oral glucose–induced insulin secretion and β-cell glucose sensitivity to the 2-h plasma glucose concentration across stages of glucose tolerance. Redrawn from data in Ferrannini et al. (35). IGT, impaired glucose tolerance; NGT, normal glucose tolerance; T2D, type 2 diabetes.
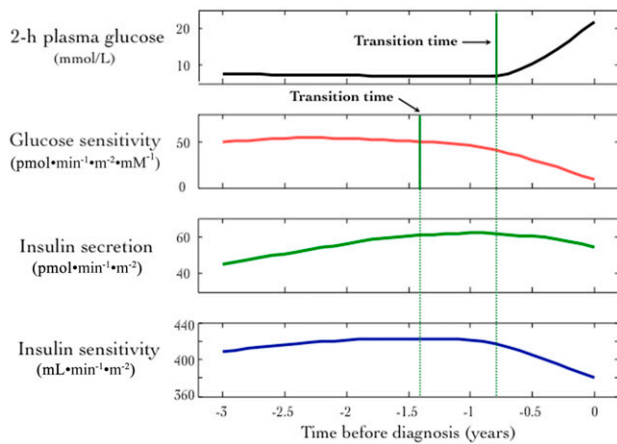
Mode of onset of type 1 diabetes

Figure 5—Time trajectories of 2-h plasma glucose concentrations, β-cell glucose sensitivity, postglucose insulin secretion, and insulin sensitivity in high-risk relatives of subjects with type 1 diabetes. Data synchronized on the time of diabetes diagnosis (time 0). Redrawn from Ferrannini et al. (39).

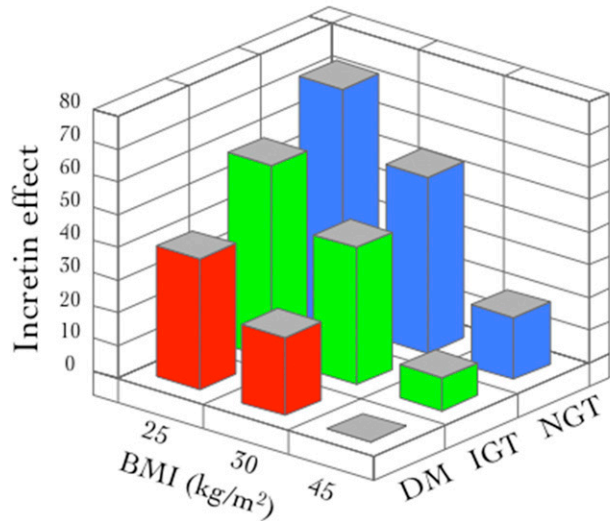## Determinants of the incretin effect

Figure 6—Dual impact of glucose tolerance and obesity, as the BMI, on the incretin effect. Redrawn from Muscelli et al. (44). DM, diabetes mellitus; IGT, impaired glucose tolerance; NGT, normal glucose tolerance.

high-risk subjects who progress to type 1 diabetes, the time course of glycemia 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 time 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 is 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 glycemia (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 β-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 ($\sim$11 units/m^2) 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).
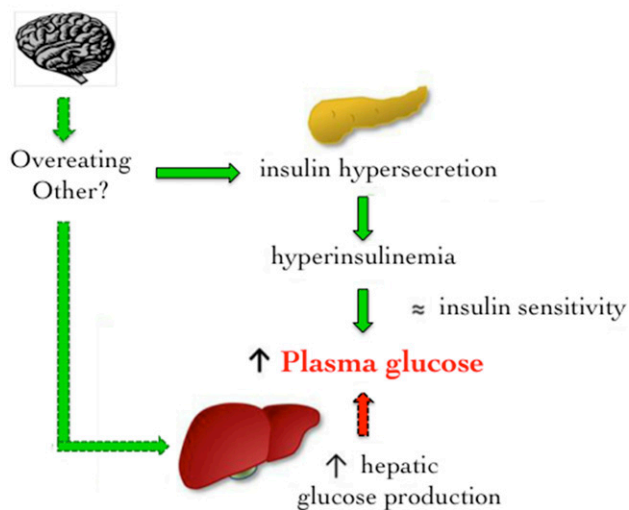

Figure 7—Insulin hypersecretion with normal insulin sensitivity is associated with increased rather than decreased plasma glucose concentrations due to increased endogenous (hepatic) glucose production. Neural influences to islets and liver are postulated. Modified from Reaven et al. (47).
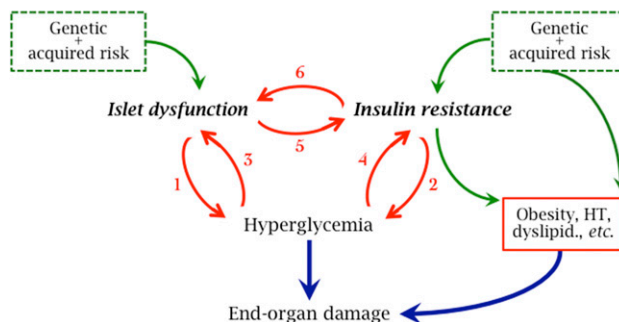

Figure 8—Main pathophysiological paths and influences in type 2 diabetes. Red lines and numbers refer to feedback cycles; associations are in green and paths to end-organ damage in blue. See text for further explanation.

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 concomitant, 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 antecedes, 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 HbA$_{1c}$ 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 levels and slow down gastric emptying (57). But the latest, and least expected, developments have zeroed in on CVD and renal disease by showing that the newer antihyperglycemic drugs (sodium–glucose cotransporter 2 inhibitors 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 (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 antidiabetes 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 glycemia. 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.

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