The hormone glucagon has long been dismissed as a minor contributor to metabolic disease. Here we propose that glucagon excess, rather than insulin deficiency, is the sine qua non of diabetes. We base this on the following evidence: (a) glucagon increases hepatic glucose and ketone production, catabolic features present in insulin deficiency; (b) hyperglucagonemia is present in every form of poorly controlled diabetes; (c) the glucagon suppressors leptin and somatostatin suppress all catabolic manifestations of diabetes during total insulin deficiency; (d) total β cell destruction in glucagon receptor–null mice does not cause diabetes; and (e) perfusion of normal pancreas with anti-insulin serum causes marked hyperglucagonemia. From this and other evidence, we conclude that glucose-responsive β cells normally regulate juxtaposed α cells and that without intraslet insulin, unregulated α cells hypersecrete glucagon, which directly causes the symptoms of diabetes. This indicates that glucagon suppression or inactivation may provide therapeutic advantages over insulin monotherapy.

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resulted in a rapid fall in glucose production (16), whereas a selective increase in the hormone caused a rapid rise in hepatic glucose production (17, 18). In fact, after an overnight fast, the basal glucagon level accounted for up to 70% of glucose production (16). In addition, a rise in plasma glucagon of only 100 pg/ml in the liver sinusoids tripled glucose production (19, 20). Thus, the control strength of glucagon is profound, with a dynamic range of approximately 5 mg/kg/min over the physiologic range of plasma glucagon concentrations (Figure 1 and refs. 21–26). Not only is the liver very sensitive to changes in plasma glucagon, it also responds rapidly, with a half-maximal activation time of only 8 minutes (27). Human studies, although less well controlled, confirmed that the observations made in the dog extend to man (22–25, 28–30). Thus, it is evident that after an overnight fast, basal levels of glucagon drive resting glucose production, thereby allowing insulin to link hepatic glucose output to the body’s need for glucose.

Whenever there is an increased demand for glucose (i.e., starvation, hypoglycemia, and exercise), insulin secretion falls, stimulating glucagon secretion. This removes insulin’s inhibitory action on the liver while augmenting glucagon’s stimulatory effect on fuel production. As a result, glucose production is increased to meet the needs of the organism. When glucose is abundant, as with an oral glucose load, the reverse occurs.

Glucagon also modulates hepatic glucose uptake (HGU) (28, 31, 32) and hepatic glycogen synthesis (33). A decrease in plasma glucagon has little effect on HGU in the presence of elevated insulin (31), but the effect can be quite marked when insulin is deficient (32), which has obvious implications for diabetes. Insulin is a key determinant of hepatic glucokinase (GK) expression, which is required for HGU. It is unclear whether, in the presence of complete insulin deficiency, glucagon suppression would increase liver glucose uptake, a possibility that still needs to be directly examined. On the other hand, it is clear that an increase in glucagon can interfere with the ability of a rise in plasma insulin to enhance glucose uptake by the liver (31). This suggests that glucagon and insulin jointly control hepatic production (in times of deficit) and storage (in times of plenty) of glucose. When glucose is scarce, as in starvation, lipolysis increases, as does the delivery of nonesterified fatty acids to the liver. It is also now clear that insulin and glucagon interact to govern hepatic fatty acid synthesis (34) and hepatic ketogenesis (4). Likewise, the two hormones oppose each other with regard to liver protein metabolism (35).

**Endocrine and paracrine credentials**

The demonstration that glucagon has powerful glycogenolytic activity exerted via the second messenger cAMP (7) provided strong biochemical evidence for it being a true hormone. In vivo evidence of its physiologic activity was provided by Foa’s elegant pancreatic-ic-femoral cross-circulation studies in dogs, which demonstrated that the pancreas was indeed the source of the hyperglycemic factor (36). Histochemical evidence reinforced the conclusion that glucagon came from pancreatic α-cells (37).

The development of highly specific RIAs for insulin (38) and glucagon (10, 11) demonstrated reciprocal behavior of the 2 hormones. Insulin levels fell during glucopenia and rose during glucose administration (Figure 2A and ref. 38), and glucagon levels rose during

![Figure 1](http://www.jci.org)  
**Figure 1**  
Relationship between hepatic sinusoidal glucagon and glucose production in vivo. A pancreatic clamp was used to keep plasma insulin basal and constant. The glucose production rate reflects the maximal effect of glucagon and was observed approximately 15 minutes after the change in the hormone level. In this way, the accompanying hyperglycemia was limited such that its inhibitory effect on glucose production was minimal. When glucagon was made deficient (i.e., 0 pg/ml), euglycemia was maintained by glucose infusion. The region shaded blue denotes the physiologic range of plasma glucagon. Figure adapted with permission from *Handbook of Physiology* (96).
Glucopenia and fell during glucose administration, fully consistent with its glycogenolytic and gluconeogenic actions (5–7). Glucagon was localized immunocytochemically to α cells of the pancreas (39), confirming the histochemical findings of Ferner (37). Nevertheless, the importance of its role continued to be debated, despite metabolic, physiologic, and anatomical clues suggesting a bihormonal homeostatic relationship between insulin and glucagon (12, 40, 41).

Another clue to the critical nature of this bihormonal relationship was the demonstration that when insulin rises after glucose feeding, the accompanying suppression of glucagon secretion is caused not by hyperglycemia, but by increased insulin levels (42), Indeed, if a rise in blood glucose is unaccompanied by insulin release, hyperglycemia stimulates glucagon secretion (Figure 2B and refs. 43, 44). This established insulin as a glucagon-suppressing hormone and, as detailed below, made it increasingly clear that the glucagon-suppressing action of insulin was largely a paracrine function (45), providing further support for the concept of bihormonal control of glucose homeostasis (Sidebar 1 and refs. 5, 6).

The reciprocal changes in insulin and glucagon secretion that occur in response to relatively minor perturbations in plasma glucose (Figure 2A and ref. 38) give further credence to the concept of bihormonal control at the level of the islets, as well as of the liver (46).

Anatomical credentials

Finally, anatomical clues suggested that paracrine insulin reaches the α cells before insulin reaches any other targets in the body in concentrations far above the endocrine levels delivered to peripheral insulin targets. In rodents, the first clue (47) was the “portal” microcirculation that carries insulin from the β cell core to the α cell mantle of the islet (48). In addition, the demonstration of gap junctions between α and β cells (49) raised the possibility that their activities are also coordinated via intracellular signals. In human islets, there is extensive juxtaposition of β cells and α cells that should permit insulin to reach α cells across their shared interstitium in a paracrine relationship. (Figure 2C and refs. 48, 50, 51). Interestingly, although the topographic arrangements of α and β cells differ in different species, they all appear to enable insulin to control glucagon secretion via some type of
The tightly coupled reciprocal nature of changes in the secretion of the two hormones (Figure 2A) was suggestive of coordinated relationships analogous to the reciprocal innervations of skeletal muscle contraction described in the Second Law of Sherrington, which states that whenever the biceps contracts, the triceps relaxes (52).

Powerful evidence that insulin controls the secretion of glucagon via a paracrine mechanism was obtained by perfusing the isolated pancreas of normal rats with a potent neutralizing anti-insulin serum. Whereas perfusion of nonimmune serum had no effect, perfusion of the anti-insulin serum caused a prompt and dramatic increase in glucagon secretion (Figure 2D and ref. 53). This demonstrates that insulin acts inside the islets to inhibit glucagon secretion.

Interestingly, recent reports suggest that insulin may also regulate glucagon secretion through an action in the ventromedial hypothalamus, as well as by an effect on the α cell directly (54, 55), a dual control system.

Glucagon, sine qua non of hyperglycemia in all forms of insulin deficiency

The similarity between the glycogenolytic, gluconeogenic, and ketogenic actions of glucagon (Sidebar 1) and the metabolic abnormalities of insulin deficiency suggested that the α cell hormone played a central pathogenic role in diabetes. Using the glucagon RIA, it was demonstrated that hyperglucagonemia is present in untreated T1DM in humans and animal models (40). Absolute proof that endogenous glucagon plays an essential role in the pathogenesis of diabetes requires that suppression of glucagon secretion or action reduces the metabolic manifestations of insulin deficiency. In 1974, Koerker et al. (56) reported that somatostatin (57) could suppress glucagon. Several groups quickly exploited this to test the effects of glucagon suppression on the metabolic manifestations of insulin deficiency. When somatostatin was infused into alloxan-diabetic dogs (Figure 3A and ref. 58) or in insulin-deprived humans with T1DM, as first shown by Gerich et al. (Figure 3B and refs. 59, 60), hyperglucagonemia was suppressed and hyperglycemia was markedly decreased, even though insulin had been reduced or discontinued. Notably, infusion of exogenous glucagon restored the hyperglycemia. Physiologic studies by Stevenson et al. (20), using the depancreatized dog, demonstrated that when insulin was replaced intraportally at a basal rate, the plasma glucagon level (3,500 MW glucagon produced by α cells in the gut) fell markedly. It was the fall in glucagon that was responsible for most of the insulin-driven improvement in glycemia, since it ceased when glucagon was replaced. These experiments provided the first concrete evidence that glucagon might be playing an essential pathogenic role in the hyperglycemia of insulin deficiency. They also called into question for the first time the dogma of insulinocentrism, suggesting that glucagon excess, rather than insulin deficiency, causes the catabolism of insulin deficiency.
The main opposition to this idea was based on the fact that total pancreatectomy causes diabetes. This argument was based on the false assumption that α cells are located only in the pancreatic islets (61). However, in the 1970s, several groups reported measurable glucagon levels in insulin-deprived, totally pancreatectomized humans and animals (62–65). The stomach was found to be an important source of the nonpancreatic hyperglucagonemia, and classical α cells were found in the gastric fundus and duodenum of animals and humans (66, 67). Gastric α cells were shown to oversecrete glucagon during insulin deficiency and to be more sensitive than pancreatic α cells to small amounts of insulin. Interestingly, immunoassayable glucagon was present in a totally depancreatized, totally gastrectomized human (68), which suggests that α cells are present in the digestive tract below the pylorus. The recent demonstration by Thorel et al. that ablation of 98% pancreatic α cells does not lower glucagon levels sufficiently to suppress streptozotocin-induced diabetes (69) may have a similar explanation.

These insights invalidated the only argument against an essential diabetogenic role for glucagon (67). Glucagonocentrism had become plausible.

**Glucagon and the glycemic volatility of T1DM?**

Glycemic volatility, a hallmark of insulin-treated T1DM, is its most challenging day-to-day clinical problem. T1DM patients must constantly monitor glucose levels in order to respond to and correct major glycemic deflections with supplemental insulin or glucose (70), profoundly reducing quality of life. Given that T1DM is the only condition in which such glucose volatility occurs and that T1DM is the only condition in which the islets are devoid of β cells, the possibility of a causal relationship between the volatility and the loss of paracrine control of glucagon secretion by insulin seems quite plausible.

For example, it is not widely appreciated that, when hyperglycemia is unaccompanied by an increase in insulin, it stimulates rather than suppresses glucagon secretion. This paradoxical increase in glucagon could be an important factor in the exaggerated postprandial hyperglycemia of T1DM. If β cells are not juxtaposed to α cells to provide a glucose-stimulated paracrine “squirt” of insulin, postprandial hyperglycemia will stimulate a paradoxical rise of glucagon secretion, rather than trigger suppression of its release (Figure 2B and refs. 43, 44). This adds an endogenous source of glucose to the exogenous glucose from the meal.

**Glucagon and the hypoglycemia of T1DM**

Another burden of T1DM is that hypoglycemia (precipitable by physical exertion or by delays in feeding) is unalleviated in the absence of the normal glucagon response. In this case, the circulating insulin derived from the injection does not decline when blood glucose levels fall, thus preventing the glucagon rise that would otherwise defend against hypoglycemia. In addition, the observation that high levels of insulin in the brain can inhibit glucagon secretion through a neural mechanism (54, 55) suggests that central insulin action may also contribute to high hypoglycemia incidence in patients with T1DM.

**Glucagonocentrism: insulin actions are mediated by glucagon**

Studies in glucagon receptor–null (Gcgr−/−) mice indicate that glucagon mediates the catabolic consequences of insulin lack (71). In these Gcgr−/− mice, which exhibit no response to glucagon at any concentration, total β cell destruction did not result in any of the diabetic abnormalities thought to be caused by insulin deficiency. Destruction of β cells in wild-type controls resulted in the familiar catabolic consequences of insulin deficiency, with death due to ketoacidosis within 6 weeks, whereas in the Gcgr−/− mice, none of the clinical or laboratory manifestations of insulin deficiency was detected (Figure 4). The insulin-deficient Gcgr−/− mice did not become hyperglycemic or hyperketonemic, and their livers exhibited no increase either in phospho–cAMP response element–binding protein (p-CREB; a mediator of glucagon action) (72) or in the gluconeogenic enzyme phosphoenolpyruvate carboxykinase, both of which are elevated in uncontrolled diabetes.

These findings agree with other work in which glucagon receptors were blocked with antibodies (73, 74) or with glucagon recep-
tor antagonists (75). Such maneuvers also improved the metabolic state in insulin deficiency (76–80). These results strongly suggest that the catabolic actions heretofore considered the direct consequences of insulin lack are actually mediated by a relative or absolute excess of glucagon to insulin.

By far the most surprising observation in the Gcgr−/− mice was the fact that oral or intraperitoneal glucose tolerance tests remained normal (Figure 4B), despite destruction of virtually all β cells and lack of an insulin response to glucose (Figure 4C). Since a normal glucose tolerance test excludes the diagnosis of diabetes, one must conclude that the diabetic state cannot be manifest without glucagon action — at least in the mouse. Therefore, the abnormalities of glucose and ketone metabolism associated with T1DM in the mouse are mediated by dysregulated glucagon secretion, rather than by insulin lack per se (Sidebar 1 and refs. 51, 71).

Gcgr−/− mice reportedly have very high plasma levels of the incretin hormone glucagon-like peptide 1, but this is not thought to account for their improved oral glucose tolerance, although the plasticity of the incretin system in this model is striking (81). If these rodent findings extend to humans, as suggested by the somatostatin studies of Gerich et al. (59) and Raskin and Unger (60), the excess of unsuppressed and unopposed glucagon, rather than the lack of insulin by itself, would be the direct cause of the catabolic cascade in insulin deficiency states (Sidebar 1). It should be stressed that, at present, there is no basis for questioning a direct role for insulin lack alone in the enhanced lipolysis seen in adipose tissue or in the increased proteolysis seen in muscle in individuals with uncontrolled T1DM (Sidebar 1). In fact, there are no known glucagon receptors in muscle (82). Therefore, why insulin deficiency in Gcgr−/− mice does not appear
decrease in glucose clearance and a consequent doubling of the use insulin in doses that meet the requirements of peripheral plasma glucose level. Thus, in large mammals, the effect of insulin required by various targets of the hormone. By virtue of their proximity to skeletal muscle (Figure 5A). In contrast, injected insulin provides a similar insulin concentration for all tissues (Figure 5B), which results either in underinsulization of α cells or in overinsulization of peripheral tissues. The obvious solution is to use insulin in doses that meet the requirements of peripheral tissues but are not high enough to suppress hyperglucagonemia and to reassign the duty of α cell suppression to a noninsulin agent, such as leptin (Figure 5B).

Noninsulin glucagon suppressors
In 1978, the first clinical trial of glucagon suppression in T1DM was reported (60). Patients were treated with somatostatin infusion after reduction of their insulin (Figure 3B and refs. 59, 60). When hyperglucagonemia was suppressed, hyperglycemia and glycosuria were markedly reduced. Unfortunately, side effects of somatostatin precluded its long-term use in T1DM, and more than 20 years passed before another glucagon suppressor was identified.

Amylin is a second glucoregulatory β cell hormone that is normally co-secreted with insulin in response to meals and is deficient in patients with T1DM (86). Preclinical studies have shown that amylin slows nutrient absorption, acts as a satiety factor, and decreases glucagon secretion (86). In clinical studies in which pramlintide (a commercially available amylin analog) was used as an adjunct to insulin therapy in patients with T1DM, there were decreases in plasma glucagon levels, glucose fluctuations, postprandial glucagon levels, and plasma triglyceride concentrations (86–89). As one might expect, the patients’ insulin dose had to be decreased in order to prevent hypoglycemia. To the extent that these effects relate to the reduction in plasma glucagon, the data support the therapeutic concept described above.

In 2008, 14 years after its discovery (90), leptin was shown to suppress glucagon hypersecretion in T1DM rodents at least as effectively as somatostatin and without undesirable side effects (Figure 5C and refs. 91–93). Should similar results be demonstrated in humans, glucagon suppression with leptin could become a new treatment strategy for T1DM.

In rodents, continuous glucagon suppression is required to maintain glycemia within the normal range throughout the day (92). This can be achieved by continuous subcutaneous infusion of leptin to suppress the hyperglucagonemia caused by the 90% reduction of the insulin dose to eliminate hypoglycemia; the glycemie profile produced by low insulin plus leptin infusion is virtually normal. (Figure 5C). The low insulin plus leptin regimen reduces the expression of transcription factors and enzymes involved in lipogenesis and cholesterologenesis (34), presumably by eliminating the iatrogenic hyperinsulinemia required in the absence of glucagon suppression by paracrine insulin action. All in all, it would seem that conventional monotherapy with insulin is incomplete because it can provide paracrine suppression of glucagon secretion only by seriously overdosing the extrapancreatic tissues.

The antidiabetic glucagon-suppressing effects of peripherally induced hyperleptinemia (Figure 6A and ref. 92) have been duplicated by leptin infusion into the intracerebral ventricle (Figure 6B and ref. 91). This provides evidence for both a leptin-responsive hypothalamic pathway for glucagon expression (94) and direct leptin-mediated suppression of α cells. However, leptin could also act directly on the α cell, in a model of dual control similar to that proposed for insulin secretion (Figure 6C and ref. 55).

Summary
It is understandable, but nevertheless troubling, that the historic dimensions of the discovery of insulin in 1922 have distorted scientific and clinical perspectives of hormonal dysregulation in
diabetes for so long. Even though nine decades of insulin mono-
therapy have taught us that insulin replacement alone cannot normalize glucose homeostasis in T1DM, while α cell research has repeatedly suggested the diabeticogenic role of glucagon, no intensive effort to reduce or block glucagon actions in diabetes has yet been undertaken. Failure to translate decades of favorable preclinical evidence to the management of human diabetes must reflect insulino-centric skepticism concerning the pathophysi-
ologic importance of diabetic hyperglucagonemia. Indeed, this is suggested in the title of the outstanding review by Gromada et al., “α-Cells of the endocrine pancreas: 35 years of research but the enigma remains” (95). It is hoped that this review will catalyze such efforts to determine whether this research can improve and extend life for diabetic patients.

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