

Diabetes as a Paracrinopathy of the Islets of Langerhans

Pierre Lefèbvre

Emeritus Professor of Medicine, Division of Diabetes, Nutrition and Metabolic Disorders, Department of Medicine, University of Liège

Abstract

The small clusters of cells scattered in the pancreas and discovered by Langerhans in 1869, currently known as the islets of Langerhans, are at the centre of the pathology of diabetes. Today they appear as sophisticated micro-organs in which various cell types function in a remarkably co-ordinated manner. Until recently, most of the interest has been centred on the β -cells, which synthesise, store and secrete insulin. Insulin deficiency is the hallmark of diabetes, with insulin resistance being associated with some forms of the disease. Although identified more than 40 years ago, a possible role of glucagon in the pathophysiology of diabetes has been largely neglected. Synthesised, stored and released by the α -cells of the islets of Langerhans, glucagon plays a key role in the main metabolic disturbances of diabetes that are hyperglycaemia and excessive lipolysis and ketogenesis. Suggested by Samols et al. decades ago, the possibility of close interactions between α - and β -cells within the islets of Langerhans has recently received considerable experimental support. Unger and Orci have proposed that such paracrine interactions within the pancreatic islets play a crucial role in a vital homeostatic domain and that disruption or dysfunction of these interactions has to be considered as a key component in the pathophysiology of diabetes. This brief article will present arguments supporting the view of diabetes as a paracrinopathy of the islets of Langerhans.

Keywords

Glucagon, insulin, islets of Langerhans, paracrinology, paracrinopathy

Disclosure: The author has no conflicts of interest to declare.

Received: 7 July 2011 **Accepted:** 28 July 2011 **Citation:** *European Endocrinology*, 2011;7(2):79–83 DOI:10.17925/EE.2011.07.02.79

Correspondence: Pierre Lefèbvre, Division of Diabetes, Nutrition and Metabolic Disorders, Department of Medicine, Liège University Hospital Centre, Sart Tilman, B-4000 Liège 1, Belgium. E: pierre.lefebvre@ulg.ac.be

A Thesis in Berlin in the 19th Century

On 18 February 1869 in Berlin, a 22-year-old student of the famous pathologist Rudolf Virchow presented his thesis for an MD degree at the Friedrich Wilhelms University entitled '*Beiträge zur mikroskopischen Anatomie der Bauchspeicheldrüse*' or 'Contributions to the microscopic anatomy of the pancreatic gland' (see *Figure 1*). The opponents to this thesis were G Loeillot de Mars, O Soltmann and Paul Ruge – their names have long been forgotten. That of the student, Paul Langerhans, has become famous. Maybe today faculty professors should remember this when listening to a student presenting and defending his/her thesis.

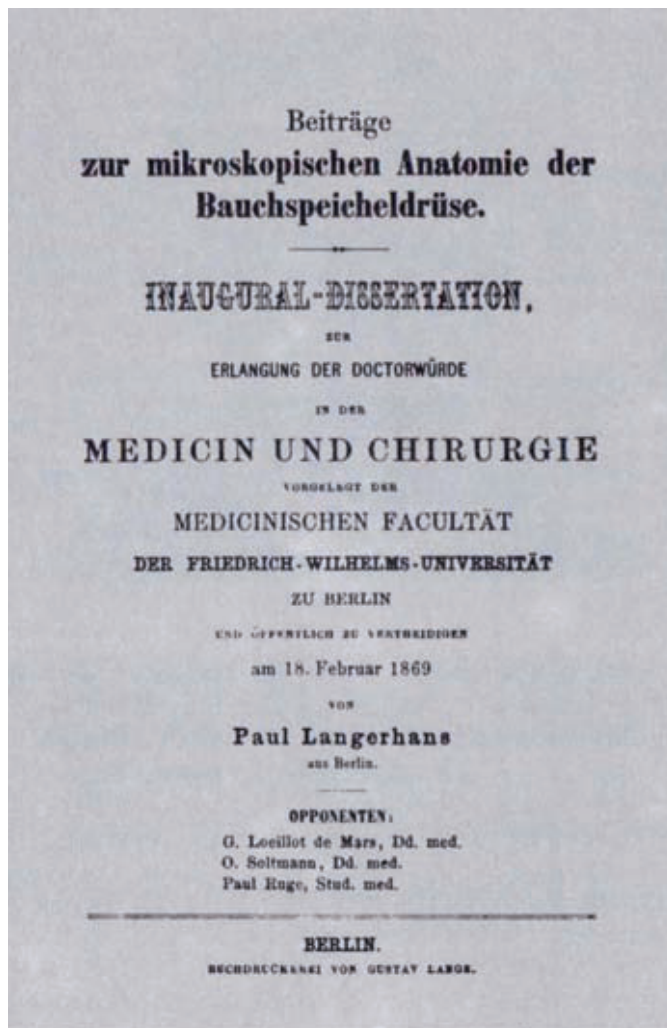
Langerhans mostly examined pancreatic glands from rabbits and attempted to describe the different cell types and structures. He produced preparations by injecting dyes into the pancreatic duct and found that some cell groups were not in connection with the ducts. He wrote: "These cells are placed in rather great numbers, close together and scattered in the parenchyme of the gland. After the pancreas had been placed for 2–3 days in the fluid of Müller, observation under slight magnification will reveal intensely coloured yellow spots, evenly distributed in the gland; these spots consist only of our cells." Quite genuinely, he wrote: "I admit frankly that I am not able to explain the nature and function of these cells." Thus were born the islets of Langerhans. Sadly, the life of Paul Langerhans was short. He became prosector at the University of Freiburg im Breisgau, contracted tuberculosis, migrated to Madeira for its climate and continued studies on the local natural fauna, but ultimately died in 1888 at the age of 41.

The Islets 142 Years after Langerhans

Initially described as clusters of cells homogeneous in nature and different from the surrounding exocrine cells, the islets of Langerhans appear today as remarkable micro-organs of extraordinary complexity. In the human adult, their mass is around 1,500 mg, they represent about 2 % of the pancreatic weight and their number per pancreas is around one million. The pancreatic islet is composed of five endocrine cell types: the β -cells that produce insulin, the α -cells that produce glucagon, the δ -cells that produce somatostatin, the pancreatic polypeptide (PP)-cells that produce the pancreatic polypeptide and the more recently identified and less numerous ϵ -cells that produce ghrelin. The most detailed studies on the structure of the islet of Langerhans have been performed by Lelio Orci in Geneva and summarised in his Banting lecture at the American Diabetes Association meeting in 1982.¹

The islets are innervated and vascularised. For obvious reasons, most studies on the islet as a micro-organ have been performed in rodents. In rodents, most β -cells are located in the centre of the islet while the other endocrine cells, mainly the α - and δ -cells, are located at the periphery. In these species, the microcirculation appears remarkable in its microanatomy and microphysiology.² The arteriolar blood enters the core of the islet where, potentially, the β -cells can enrich it with the highest concentration of insulin in the body as it flows to the mantle and reaches the α - and δ -cells (see *Figure 2*). Furthermore, the blood flow dynamics in the islet are affected by the level of glucose in the blood, with hyperglycaemia increasing and

Figure 1: Facsimile of Cover Page of Paul Langerhans's Thesis

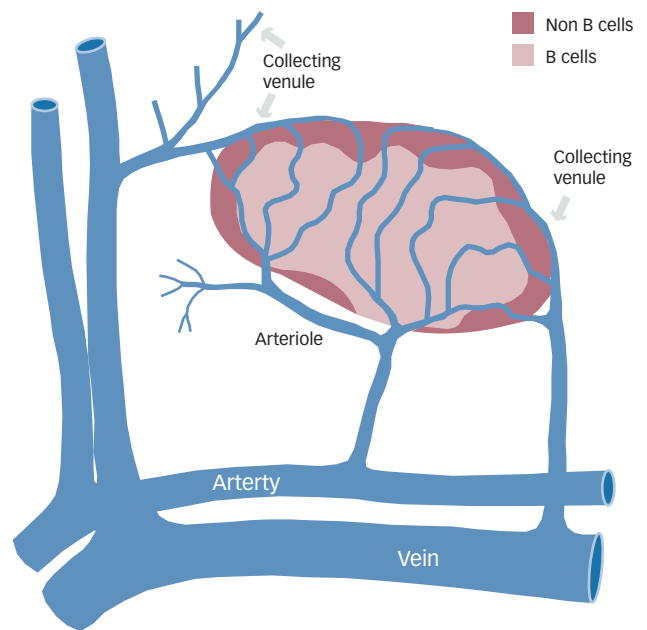


hypoglycaemia decreasing the flow respectively.^{3,4} With such a setting, a clear possibility exists for β -cell products, such as zinc, γ -aminobutyric acid (GABA) or, of course, insulin itself, to modulate α - and δ -cell function. As analysed in detail by Bosco et al.,⁵ the architecture of normal islets in humans differs from that in rodents. The β -cells form a lower percentage of the endocrine population than in rodent islets, but, as in rodent islets, they occupy a core position surrounded by mantles of α -cells in pseudo-lobular subdivisions, with blood vessels at their periphery. In human islets, more than 70 % of β -cells are in contact with non- β -cells. As discussed by Unger and Orci,⁶ if anything, the morphological difference in human islets compared with rodents would tend to increase the possibility of paracrine interactions.

The Strange Co-ordination of Islet Cell Secretion

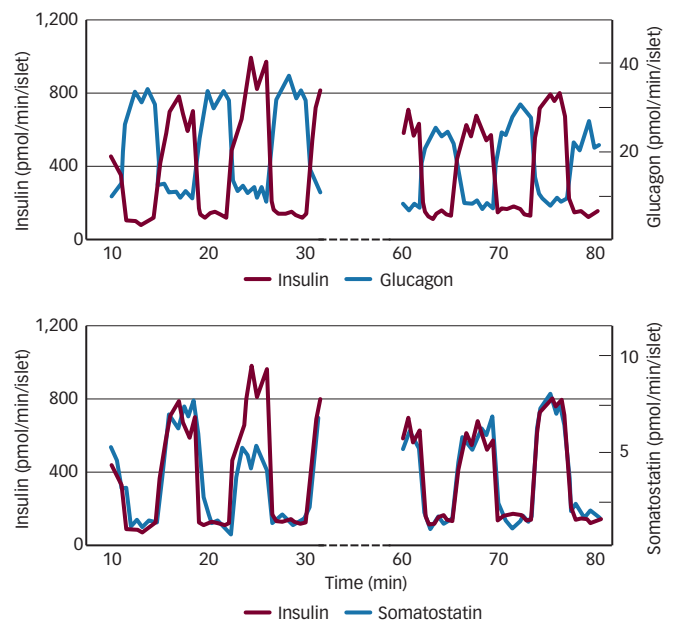
The development of sensitive and specific assays for polypeptide hormones has permitted investigation in depth of the mechanisms controlling the release of the products of the various endocrine cells of the islets of Langerhans. Studies were performed *in vivo* in numerous species, including man. *In vitro* studies were conducted mainly in isolated perfused pancreases and on isolated perfused islets of Langerhans. These studies have provided insight on the many factors – metabolites, hormones, neuronal signals – that control the

Figure 2: Bonner-Weir and Orci's Model of the Microcirculation in Rodent Islets



Source: Bonner-Weir and Orci, 1982.²

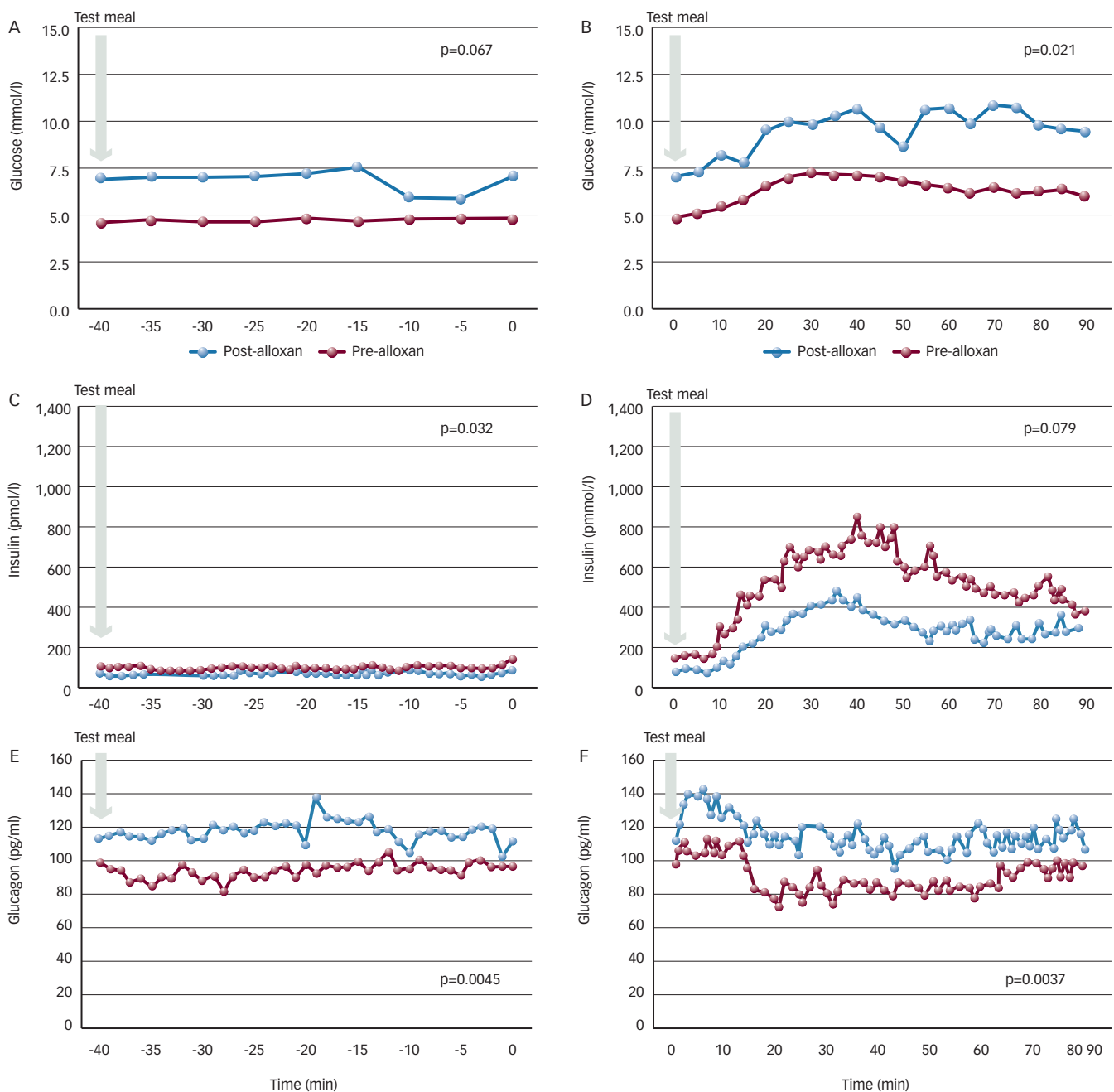
Figure 3: Temporal Relationships between Repetitive Hormone Pulses from Human Isolated Perfused Islets



Insulin and glucagon pulses are antisynchronous (upper panel) while insulin and somatostatin pulses coincide.

Source: Redrawn from Hellman B, Salehi A, Gylfe E, et al., Glucose generates coincident insulin and somatostatin pulses and anti-synchronous glucagon pulses from human pancreatic islets, *Endocrinology*, 2009;150:5334–40.⁸ © 2009, The Endocrine Society.

release of the products of the islet endocrine cells. For more than three decades, there have been indications that there is co-ordination in the releasing mechanisms and that this co-ordination exists within the islets themselves.⁷ The most impressive data on this issue recently came from the laboratory of Hellman et al. in Sweden.⁸ Using isolated perfused human islets, the authors have shown that glucose generates coincident insulin and somatostatin pulses and clear anti-synchronous glucagon pulses (see Figure 3). The periodicity of

Figure 4: Experimental Model of Type 2 Diabetes in the Minipig after ~60 % Destruction of the β -cell Mass by Alloxan

Left panel, in the fasting state: hyperglycaemia (A) and hyperglucagonaemia (E). Right panel, after a test meal: postprandial hyperglycaemia (B), reduced insulin secretion (D) and lack of glucagon suppression (F).

Source: Kjemis, et al., 2001.¹³

these pulses is seven to eight minutes. The fact that these pulses occur in isolated islets demonstrates that their origin is in the islets themselves and is independent of external metabolic, hormonal or neuronal signals. The nature of the intra-islet signal(s) co-ordinating the secretion of the various endocrine cells of the islets of Langerhans is still the subject of intense investigation.⁹

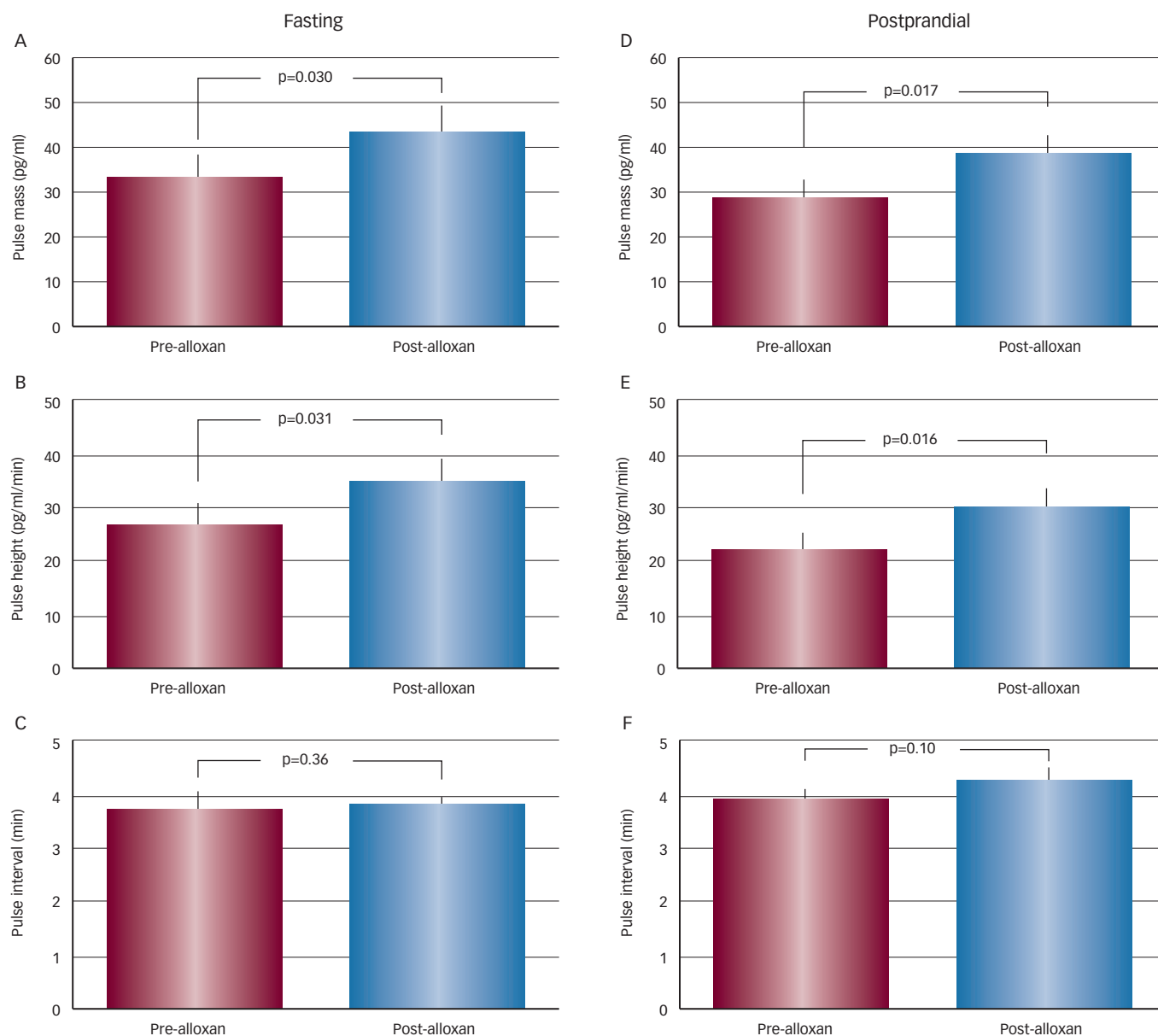
Insulin and Glucagon – A Harmonious Couple in the Islet House

It is now largely recognised that insulin and glucagon are the key hormonal factors regulating energy metabolism. Insulin, the anabolic hormone, promotes storage of glucose in the form of glycogen in liver and muscle and favours the synthesis of triglycerides in adipose tissue.

In contrast, glucagon, the catabolic hormone, inhibits liver glycogen synthesis and stimulates liver glycogenolysis, gluconeogenesis and ketogenesis; it also stimulates adipose tissue lipolysis, particularly when insulin is deficient. The relative levels of these two hormones determine whether energy is stored or mobilised. The control of the secretion of the two hormones involves metabolic, hormonal and neuronal factors that have been reviewed elsewhere.^{10,11} Interestingly, there are strong indications that some modulation/synchronisation of their respective secretions may occur within the islets.

We have seen above that insulin and glucagon are secreted out of phase in perfused islets of Langerhans. In this non-physiological setting, any effect of extra-islet signals is excluded. As insulin is a

Figure 5: Experimental Model of Type 2 Diabetes in the Minipig after ~60 % Reduction of the β -cell Mass by Alloxan



Glucagon pulses before and after alloxan in the fasting state (A–C) and after a test meal (D–F). Pulse mass and pulse heights are increased while pulse frequency is unchanged. Source: Meier, et al., 2006.¹⁴

powerful inhibitor of glucagon secretion, one can postulate that an intra-islet increase in insulin would suppress glucagon secretion and a decrease in intra-islet insulin would stimulate glucagon release. As we have seen, the microanatomy of the islets permits such interactions. One should not exclude the possibility of additional intra-islet mechanisms. Somatostatin, for instance, is another powerful inhibitor of glucagon secretion and, as demonstrated by Hellman et al.,⁸ its pulses in isolated perfused human islets are synchronised with insulin and could therefore participate in the overall intra-islet regulatory system.¹²

Disintegration of the Couple by the Disease or Death of One of the Partners

Selective destruction of the islet β -cells can be achieved by alloxan or streptozotocin. Such destruction universally results in diabetes and hyperglucagonaemia, further suggesting a key role of insulin in the control of glucagon secretion. In a study performed with Butler et al.

in California,^{13,14} we have reported that a 60 % selective reduction of the β -cell mass in the minipig results in a decrease in the amplitude of insulin pulses in the portal blood associated with a significant increase in the amplitude of the intraportal glucagon pulses (see Figures 4 and 5). In this model, mathematical analysis has suggested that, in normal animals, pulsatile insulin directly suppresses glucagon secretion, but that this association is lost after selective partial reduction in β -cell mass, thus supporting the concept of Unger and Orci⁶ that diabetes should be considered as a paracrinopathy. Interestingly, recently published observations of Menge et al.¹⁵ have reported almost identical findings in human type 2 diabetes.

Diabetes as a Paracrinopathy of the Islets of Langerhans

Since the experimental reproduction of diabetes by pancreatectomy in 1889 by von Mering and Minkowski and the discovery of insulin in pancreatic extracts by Banting and Best in 1921, diabetes has been

considered to be essentially a disease resulting from insulin deficiency. It has been recognised more recently that resistance to insulin may be a contributing factor, particularly for type 2 diabetes associated with excess weight or obesity.

The suggestion that glucagon may contribute to the pathophysiology of diabetes was made more than 40 years ago but has been poorly recognised.^{16,17} Renewal of interest in the role of glucagon in diabetes has been recently reinforced by studies showing that inhibiting glucagon secretion markedly improves experimental diabetes in rodents¹⁸ and that knock-out of the glucagon receptor makes insulin-deficient type 1 diabetic rodents thrive without insulin.¹⁹ Morphological studies have established that the main abnormality in the islet cell population of diabetes is a decrease in the number of β -cells without expansion of the α -cell mass.^{20,21}

The interest of the recent proposal of Unger and Orci⁶ to consider diabetes as a paracrinopathy has been to draw attention to delicate regulatory mechanisms occurring inside the islets of Langerhans. In this concept, the very high levels of insulin normally reached inside the stimulated islets exert a major inhibitory effect on glucagon secretion by the neighbouring α -cells. Conversely, a reduction in

intra-islet insulin concentrations would permit release of glucagon from the α -cells. Disruption of this mechanism appears as a key factor in the pathophysiology of diabetes.

In type 1 diabetes, " α -cells lack constant action of high insulin levels from juxtaposed β -cells. Replacement with exogenous insulin does not approach paracrine levels of secreted insulin except with high doses that 'overinsulinize' the peripheral insulin targets, thereby promoting glycaemic volatility."⁶ In type 2 diabetes, it has been proposed that the α -cell dysfunction results from failure of the juxtaposed β -cells to secrete the first phase of insulin.^{6,22} We proposed in 1991 that the loss of the normal intra-islet pulsatile secretion of insulin should be considered as a critical factor in the well-recognised hyperglucagonaemia of diabetes.^{23,24} This hypothesis is now supported by the above-mentioned observations made in experimental diabetes in minipigs^{13,14} and recently confirmed in human type 2 diabetes.¹⁵ Whatever the mechanisms involved, considering diabetes as a paracrinopathy of the islets of Langerhans paves the way to innovative approaches in the understanding, management and treatment of diabetes in which the α -cells of the islets and their product, glucagon, should not be forgotten. ■

- Orci L, Macro- and micro-domains in the endocrine pancreas, *Diabetes*, 1982;31:538–65.
- Bonner-Weir S, Orci L, New perspectives on the microvasculature of the islets of Langerhans, *Diabetes*, 1982;31:883–9.
- Iwase M, Tashiro K, Uchizono Y, et al., Pancreatic islet blood flow in conscious rats during hyperglycemia and hypoglycaemia, *Am J Physiol Regul Integr Comp Physiol*, 2001;280:R1601–5.
- Nyman LR, Ford E, Powers AC, et al., Glucose-dependent blood flow dynamics in murine pancreatic islets *in vivo*, *Am J Physiol Endocrinol Metab*, 2010;298:E807–14.
- Bosco D, Armanet M, Morel P, et al., Unique arrangement of α - and β -cells in human islets of Langerhans, *Diabetes*, 2010;59:1202–10.
- Unger RH, Orci L, Paracrinology of islets and the paracrinopathy of diabetes, *Proc Natl Acad Sci USA*, 2010;107:16009–12.
- Samols E, Weir GC, Bonner-Weir S, Intra-islet insulin-glucagon-somatostatin relationships. In: Lefèbvre PJ (ed.), *Glucagon II, Handbook of Experimental Pharmacology*, Berlin: Springer, 1983;133–73.
- Hellman B, Salehi A, Gylfe E, et al., Glucose generates coincident insulin and somatostatin pulses and anti-synchronous glucagon pulses from human pancreatic islets, *Endocrinology*, 2009;150:5334–40.
- Tian G, Sandler S, Gylfe E, Tengholm A, Glucose and hormone-induced cAMP oscillations in α - and β -cells within pancreatic islets, *Diabetes*, 2011;60:1535–43.
- Quesada I, Tuduri E, Ripoll C, et al., Physiology of the pancreatic alpha-cell and glucagon secretion: role in glucose homeostasis and diabetes, *J Endocrinol*, 2008;199:5–19.
- Powers AC, Stein RW, New insight of islet biology and the pathophysiology of type 2 diabetes, *Translational Endocrinology and Metabolism*, 2011;2:95–116.
- Rutter GA, Regulating glucagon secretion: Somatostatin in the spotlight, *Diabetes*, 2009;58:299–301.
- Kjems LL, Kirby BM, Welsh EM, et al., Decrease in β -cell mass leads to impaired pulsatile insulin secretion, reduced postprandial hepatic insulin clearance, and relative hyperglucagonemia in the minipig, *Diabetes*, 2001;50:2001–12.
- Meier JJ, Kjems LL, Veldhuis JD, et al., Postprandial suppression of glucagon secretion depends upon intact insulin pulsatile secretion: Further evidence for the intraislet insulin hypothesis, *Diabetes*, 2006;55:1051–6.
- Menge BA, Grüber L, Jorgensen SM, et al., Loss of inverse relationship between pulsatile insulin and glucagon secretion in patients with type 2 diabetes, *Diabetes*, 2011;60:2160–8.
- Unger RH, Aguilar-Parada E, Muller W, et al., Studies of pancreatic alpha-cell function in normal and diabetic subjects, *J Clin Invest*, 1970;49:837–48.
- Lefèbvre PJ, Luyckx AS, Glucagon and diabetes: A reappraisal, *Diabetologia*, 1979;16:347–54.
- Yu X, Park BH, Wang MY, et al., Making insulin-deficient type 1 diabetic rodents thrive without insulin, *Proc Natl Acad Sci USA*, 2008;105:14070–5.
- Lee Y, Wang MY, Du XG, et al., Glucagon receptor knock-out prevents insulin-deficient type 1 diabetes in mice, *Diabetes*, 2011;60:391–7.
- Meier JJ, Ueberberg S, Korbas S, et al., Diminished glucagon suppression after β -cell reduction is due to impaired β -cell function rather than an expansion of the alpha-cell mass, *Am J Physiol Endocrinol Metab*, 2011;300:E717–23.
- Henquin JC, Rahier J, Pancreatic alpha cell mass in European subjects with type 2 diabetes, *Diabetologia*, 2011;54:1720–5.
- Ward WK, Beard JC, Halter JB, et al., Pathophysiology of insulin secretion in diabetes mellitus, *Adv Exp Med Biol*, 1985;189:137–58.
- Lefèbvre PJ, Paolisso G, Scheen A, The role of glucagon in non-insulin-dependent (type 2) diabetes mellitus. In: Sakamoto N, Angel A, Hotta H (eds), *New directions in research and clinical works for obesity and diabetes mellitus*, Amsterdam: Elsevier Science, 1991;25–9.
- Paolisso G, Sgambato S, Passariello N, et al., Pulsatile insulin delivery is more efficient than continuous infusion in modulating islet-cell function in patients with type-1 diabetes, *J Clin Endocrinol Metab*, 1988;66:1220–6.