Type 2 diabetes mellitus has reached epidemic proportions leading Paul Zimmet to state that diabetes will be in the 21st century what HIV/AIDS has been in the last century... Time has come to attempt to have an integrated view on a condition affecting today some 200 million individuals in the world and many more in a short future.

For years, the debate on the pathophysiology of diabetes has been centred almost only on insulin with endless discussions about which is coming first of insulin resistance or insulin secretion defects. Consensus has emerged that insulin resistance certainly plays a role but that a failure of insulin secretion to compensate for is probably the crucial factor. Emphasis has been put on progressive disappearance of islet beta-cells, at least in part by an apoptotic process.

Type 2 diabetes has a strong genetic component and discussions are going on whether the genes involved affect insulin secretion, insulin sensitivity or both. Candidate gene approach and genome-wide searches have already permitted to identify about a dozen of genes probably acting in an almost infinite number of combinations. On the top of the list is the transcription factor TCF7L2 of which some polymorphisms are strongly associated with increased risk of type 2 diabetes.

Environmental factors are also involved, probably mainly through life-style induced changes in body weight mass and composition.

Interestingly, long-known factors have been left aside in the current analyses of the pathophysiology of type 2 diabetes. Glucagon is one, the incretin pathway another.

For almost 40 years was it known that glucagon, the second main hormone produced by the islets of Langerehans, has all the potentials to be part of the game. Glucagon circulating levels are elevated in all forms of diabetes, glucagon is not normally suppressed in diabetes, glucagon exerts effects on the main metabolic events associated with diabetes, including raising blood glucose and plasma free fatty acids levels and favouring liver ketogenesis. All this had been reviewed in details some 35 years ago already [1]. Surprisingly, and until very recently, glucagon was absent of most of the debates on diabetes pathophysiology and treatment.

Similarly, the role that the gut may play in diabetes has long been left aside.

The hypoglycaemia potential of duodenal extracts is known for more than a century, the incretin concept has been elaborated in the 1920’s by Zunz and Labarre, the evidence that for the same hyperglycaemia an oral dose of glucose is more efficient than an intravenous infusion in stimulating insulin secretion has been provided in 1964 by Mc Intyre et al and repeated a number of times, the richness of the incretin concept had been exposed in 1978 by Werner Creutzfeldt in a magistral Claude Bernard Lecture at the EASD Congress in Zagreb.

Time has come to attempt to integrate what has long been forgotten. In this issue of Diabetes & Metabolism the reader will find all the current informations permitting this integration including the defects, not only in insulin, but also in glucagon, the revisited physiology of the incretin pathway and its perturbation in type 2 diabetes mellitus, the potential of the main incretin, GLP-1, its analogues and the drugs inhibiting its degradation for innovative therapeutic approaches.

Let us dream for a moment. Most recent studies have indicated that the insulin response to GLP-1 is reduced in individuals with polymorphisms in the gene sequence of TCF7L2, polymorphisms strongly associated with the risk of type 2 dia-
The consequences of such reduced GLP-1 signalling potentially include reduced β-cell proliferation and regeneration, increased β-cell apoptosis (all leading to a reduction in the active β-cell mass) and reduced α-cell suppression (leading to excessive and inappropriate circulating glucagons levels)… Integration, who said integration?

References
