Storm over diabetes

Autopsy of a world epidemic

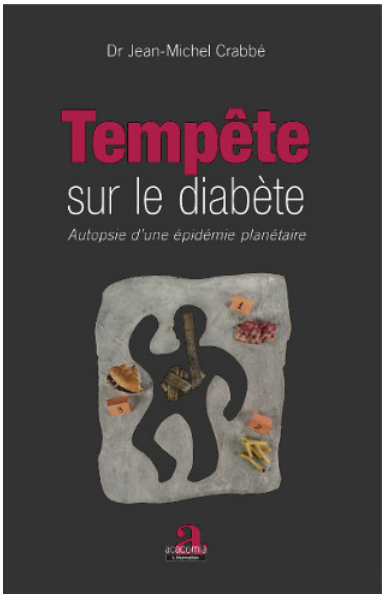
Éditions Académia/L'Harmattan
Dr Jean-Michel Crabbé

2014 october

"Team work may inhibit the primary initiation of something quite new..." Nobel Lecture, Flemming speech, dec 1945

Abstract « Storm over diabetes » is avaible in french or in english on `www.sitemed.fr/diabete` : Free download. Website certified by the Health On the Net (HON) Foundation.

Abstract : stress, glucagon and endogenous glucose are responsible for a global epidemic



We urgently need a New Biology for Diabete: « Glucagonocentric restructuring of diabetes: we propose that glucagon excess, rather than insulin deficiency, is the sine qua non of diabetes. » Pr. Roger Unger has been awarded the 2014 Rolf Luft Award from the Karolinska Institute, the prestigious medical university, home to the Nobel Assembly [18].

This document provides the reader with a new conception of type 1 diabetes. Thoroughly argued, it has received the support of Professor Roger Guillemin, recipient of the Nobel Prize in Medicine, Salk Institute, La Jolla CA [2].

Type 1 diabetes is characterized by an insufficient secretion of insulin, a hypoglycaemic hormone discovered in the 1920s. Without insulin, glucose is no longer used by peripheral tissue and accumulates in the blood. This rapidly fatal deficiency is triggered by a

progressive destruction of insulin producing β-cells in pancreatic islets. The destruction of these β-cells is now attributed to specific auto-antibodies. Type 1 diabetes is considered an autoimmune disease, which cause is unknown, fostered by genetic and environmental factors. The treatment consists in regularly injecting the patient with insulin they need while regularly monitoring their blood glucose level, their diet and physical activity. Usually, patients receive an educational therapy, which allows them to understand their illness and adapt their treatment. At first glance, type 1 diabetes with insulin deficiency seems easy to understand and treat [5].

> *"Out of the mountain came a mouse, as we say in French!"* The mountain = science, research and medicine.

This simple model of diabetes is challenged, however, by a series of epidemiological, experimental, clinical and therapeutic observations. A great victory of modern medicine, diabetes is now responsible for an uncontained and costly world epidemic [22]. This epidemic is all the more serious that it affects children at an increasingly younger age [13]. Yet, diabetes is not a contagious disease. Faced with this unexplained epidemic, the role of antibodies, genetic and environmental factors has not been proven.

Furthermore, the monitoring of diabetic patients shows that their blood glucose levels do not follow the rules of classical physiology [1]. The treatment becomes complicated, it demands close monitoring of blood glucose levels with regular changes in diet and insulin dosage. Even when carefully followed, this treatment gives no guaranty as to the stability of blood glucose levels. The patient must consult many specialists, and the complications of diabetes remain unavoidable [13].

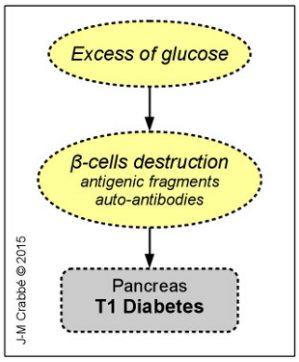


Figure 1: Experimental diabetes: *glucose overload, β-cells destruction, auto-antibodies and T1 diabetes [23].*

The classical model of type 1 diabetes, based on the elementary knowledge of the 1920s with the dogmas and simplifications of the period, has little evolved and ignores some recent discoveries. We are now in need of a new synthesis of the knowledge acquired over the past decades in the areas of physiology, histopathology, neurophysiology and epidemiology.

Firstly, experimental diabetes shows that an excess of glucose can destroy insulin-producing β-cells – *figure 1 on this page. With type 1 diabetics, the role of glucose* in the destruction of β-cells is confirmed by other observations. The examination of the diabetic pancreas under the microscope

shows abnormal proliferation of α-cells producing glucagon, a hyperglycemic hormone – *figure 2 on the current page* – H. Zöllinger, 1971 [23].

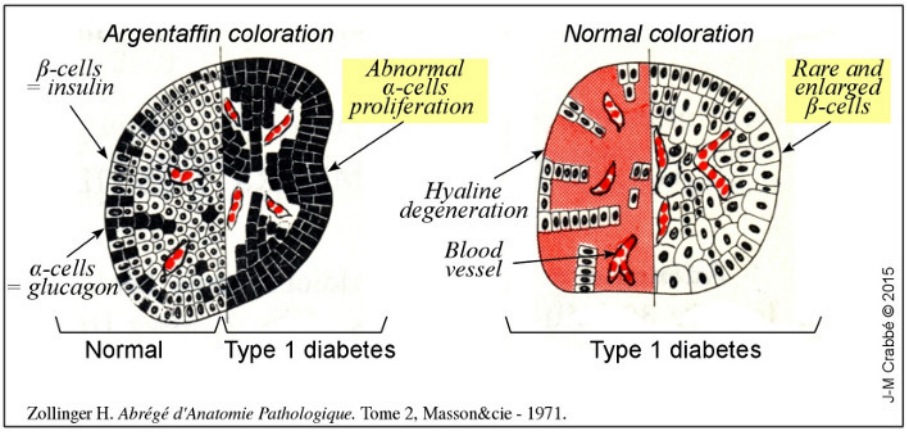


Figure 2: Pancreatic islet cells – *Abnormal proliferation of α-cells producing glucagon – Argentaffin coloration [23].*

« Glucagon is sine qua non condition of diabetes »: other studies confirm glucagon is playing an essential role in diabetes, see Roger Unger, Rolf Luft Award 2014:

> *« Diabetes is a bihormonal disease in which insufficiency of insulin is always associated with an excess of glucagon, which accounts for the hepatic overproduction of glucose and ketones in diabetes. Moreover in the absence of glucagon signaling, either due to somatostatin treatment or a glucagon receptor knockout, a complete deficiency of insulin production no longer causes hyperglycemia or ketosis. »* R. Unger, 2012 and 2014 [18].

The overproduction of glucagon and glucose can explain hyperglycemia, β-cells destruction, autoimmune reaction and other symptoms of diabetes.

Secondly, the central mechanisms capable of increasing the production of glucose have also been known since the discovery of cerebral neurohormones and the 1977 Nobel Prize [2]:

> *« Roger Guillemin, a distinguished professor, won the Nobel Prize in 1977 for discoveries that laid the foundation for brain hormone research. His work brought to light an entire new class of substances shown to be important for the regulation of growth, development, reproduction and responses to stress. The impact of Guillemin's studies has been profound for a variety of diseases and disorders, including thyroid diseases, problems of infertility, diabetes and several types of tumors. »*
> `www.salk.edu/faculty/guillemin.html`

In case of intense stress, the vegetative nervous system [14], the hormonal system and the neurotransmitters increase glucagon secretion and glucose production[2, 7, 10]. These systems decrease the peripheral use of glucose – insulin-resistance – they stimulate food intake and nutrient absorption. These complex interactions are diabetogenic and are in opposition to the homeostatic principle of equilibrium in glycaemia [1]. In case of intense stress, the main goal of these systems is to supply the central nervous system with enough glucose by increasing its production and by decreasing its peripheral use – *see Hans Selye, Stress and General Adaptation Syndrome [16].*

Finally, epidemiological studies have identified and ranked the environmental factors linked to the diabetes and obesity pandemic:
No infectious or toxic agent and no nutritional factor have been found to be responsible for this pandemic [4, 21]. However, the global changes in lifestyle are obviously linked to the spreading of these diseases. In adults, the disappearance of traditional communities, the breach of the ancestral link between man and earth and rural depopulation have all contributed to considerable stress in direct relation to diabetes and obesity [8, 9, 13, 22].

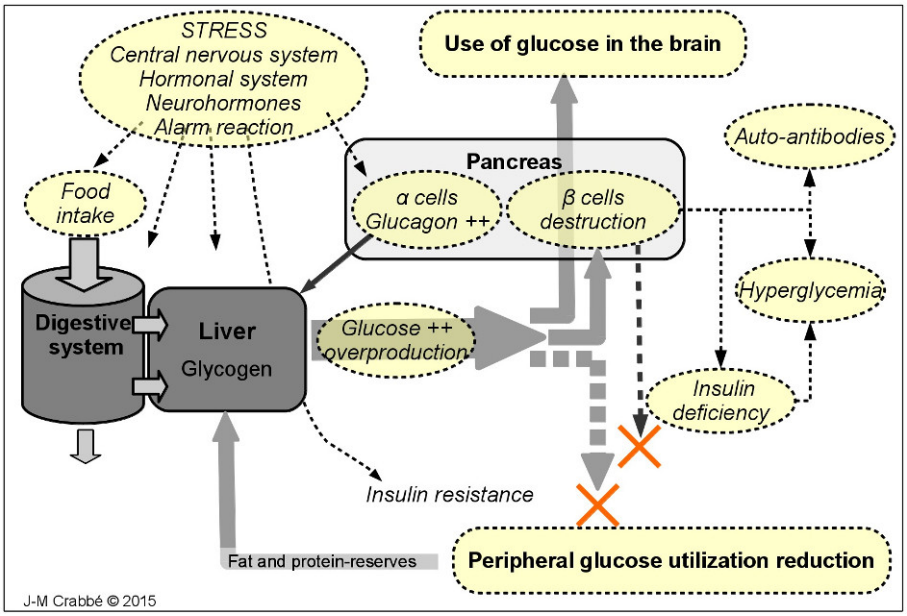


Figure 3: Stress and diabetes – *Alarm reaction, glucagon and glucose overload, β-cells destruction, auto-antibodies and T1 diabetes...*

In young children, premature weaning from breast-feeding and the breach in the mother-child relationship represent a vital stress comparable to the breach between man and Mother Earth [3, 17]. Independently of calorie

requirements, this stress develops in children neuroendocrine, immune and emotional conditions conducive to diabetes and other metabolic, infectious and tumor diseases or psychological disorders [20].
Then, other toxic or infectious dietary factors, the stress of an urban lifestyle, the chronic lack of sleep and the disruption in physiological rhythms all contribute to the decompensation of diabetes or destabilize diabetes under treatment [6, 15].

Using the previous observations, we can build a new and very coherent model of type 1 diabetes in which stress and glucose production play an essential role:
Some intense stress factors trigger a warning reaction resulting in a prolonged over-production of glucagon and glucose. During a short or extended first silent phase, glucose excess progressively destroys β-cells. This cellular necrosis induces the appearance of auto-antibodies – *figure 3 on the preceding page.*

Clinical diabetes appears when 90 % of the β-cells are destroyed. Stress is also responsible for glycemic instabilities, therapeutic difficulties and organic complications connected to type 1 diabetes [1]. Taking into account stress gives an explanation as to why diabetes took epidemic proportions at the end of the 20th century. We can thus imagine new preventive and therapeutic strategies.

Some usually accepted connections concerning diabetes must be reversed: glucose in excess destroys β-cells and not the opposite; cellular necrosis induces the appearance of auto-antibodies and not the opposite.

This new model of type 1 diabetes then adjusts itself to type 2 diabetes and to obesity, two diseases, which have become epidemic and also strike the old rural populations exposed to the stress of an industrialized and urbanized lifestyle.

In type 2 diabetes, the high production of glucose is linked to a resistance to insulin that diminishes the peripheral use of glucose in favor of the central nervous system. Resistance to insulin leads to hyperglycemia with organic complications and to an evolution towards type 1 diabetes through an excess of glucose in β-cells.

As far as obesity is concerned, a resistance to insulin that leads to type 2 diabetes limits the sometimes-disproportionate storage of glucose in excess later. Obesity usually precedes type 2 diabetes which itself precedes diabetes by insulin deficiency.

Type 1 and 2 diabetes and obesity have a profound common origin, overlooked by classical physiology, a complex neurohormonal reaction with an over-production of glucagon and glucose – *figure 4 on the current page.* This

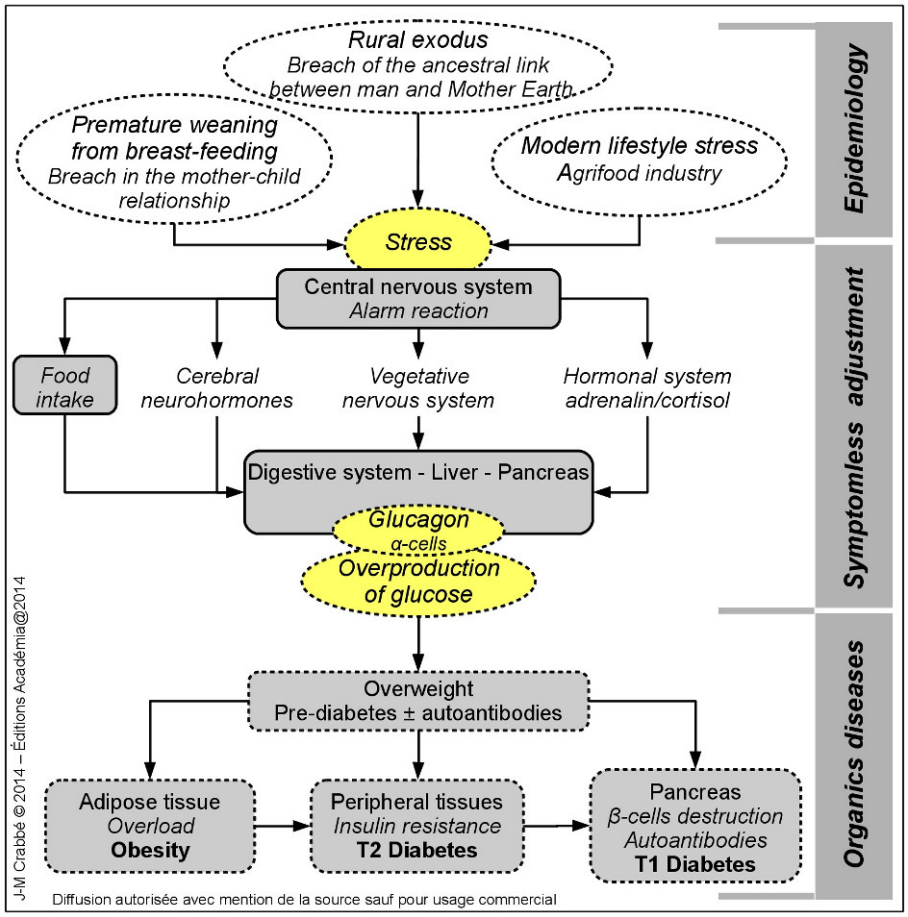


Figure 4: Stress and diabetes – *T1 diabetes, T2 diabetes and obesity have a profound common origin, overlooked by classical physiology, a complex neurohormonal alarm reaction with an over-production of glucagon and glucose.*

reaction is a consequence of the stress connected to the total disruption in the lifestyle of old rural populations [3, 8, 9, 11, 13, 17]. Then, the symptomatology varies depending on the genetic characteristics of the patient, their environment and other stress factors to which they are subjected [6, 16, 20]. The same phenomenon is occurring around the world; in China for instance, after a recent massive rural exodus, about 50 % of adults are prediabetic or overweight in 2013 [22].

In the modern world, various non-contagious diseases like diabetes and obesity spread on an epidemic scale, because they depend on the same lifestyle and stress factors. Thus, the epidemiology shows that resistance to insulin is, on a higher frequency, linked to cancers: the warning reaction triggered by intense stress affects glucose metabolism, immunity and carcinogenesis.

The example of diabetes highlights the new leads that research and medicine must explore: study the effects of stress, the psyche and the neurohormonal functions on physiological functions and organic diseases.

Dr J.-M. Crabbé - 2014-2015

Bibliography

The work of many researchers remains largely unimplemented, the academic medicine retaining a traditional conception of diabetes and obesity.

1. Froguel P. *La découverte des gènes du diabète.* Vidéo-conférence 2002 sur canal-u.tv:

> *« In diabetics, liver can sometimes release too much glucose, even though blood sugar is very high. »*
>
> A violation of the glucose homeostasis principle.

2. Guillemin R. *Peptides in the Brain. The New Endocrinology of the Neuron.* Nobel Prize in Physiology or Medicine 1977, Nobel Lectures.

3. Harder T. and all. *Duration of breastfeeding and risk of overweight: a meta-analysis.* Am. J. Epidemiol. 2006; 163(9): 870-2.

> *« Observational studies suggest a longer duration of breastfeeding to be associated dose dependently with a decrease in risk of overweight in later life... »*

4. Heini A. and al. *Divergent trends in obesity and fat intake patterns: The american paradox.* American Journal of Medicine, 1997:

> *« Reduced fat and calorie intake and frequent use of low-calorie food products have been associated with a paradoxical increase in the prevalence of obesity. »*

5. Inserm.fr. *Diabète T1, Diabète T2 et Obésité.* Dossiers d'information 2013.

6. Knutson K. and al. *The Metabolic Consequences of Sleep Deprivation.* Sleep Med Rev, juin 2007:

« The prevalence of diabetes and obesity is increasing at an alarming rate worldwide, and the causes of this pandemic are not fully understood. Chronic sleep curtailment is a behavior that has developed over the past 2-3 decades. Laboratory and epidemiological studies suggest that sleep loss may play a role in the increased prevalence of diabetes and/or obesity. »

7. Macleod J. *Nobel lecture.* The Nobel Prize in Physiology or Medicine 1923:

« [...] The hyperglycaemia in itself was not sufficient to prove that the fish had become diabetic as a result of the isletectomy, for it was found, in other fish that were exposed to air for a period equal to that required for the operation (about 15 minutes), that the blood sugar rose, sometimes almost as much as in the operated ones. This asphyxial hyperglycaemia, however, was found to disappear within four days, nor while it lasted was it so pronounced as in the isletectomized fish. »
Hypoxia → Alarm reaction → Glucagon → Glucose → Hyperglycemia.

8. Papoz L. Inserm. *« Le diabète de type 2 dans les Dom-Tom: un effet pervers de la modernité (Dom-Tom T2 diabetes, perverse effect of modernity). »* Institut de Veille Sanitaire, 20-21/2002.

9. Papoz L. *Type 2 diabetes in the French overseas Departments and Territories, the "syndrome of Nauru".* Diabetes Metab. 2002:

Diabetes epidemiae on Nauru island: *« En quelques décennies, la prévalence du diabète de type 2 a atteint 40 % chez les adultes alors que la maladie était inconnue auparavant (...the disease was once unknown). »*

10. Perlemuter L. *Diabète et maladies métaboliques.* Elsevier-Masson, 2003:

α cells: *« Pour certains auteurs, il existerait au cours du diabète sucré un dysfonctionnement primitif des cellules-α sécrétrices de glucagon. »*

11. Pettitt D.J. et coll. *Breastfeeding and incidence of non-insulindependent diabetes mellitus in Pima Indians.* The Lancet 1997:

Abstract: *« Early exposure to cow's milk has been implicated in the occurrence of insulin-dependent diabetes mellitus but there is little information about infant-feeding practices and subsequent non-insulin-dependent diabetes mellitus (NIDDM). We examined*

the association between breastfeeding and NIDDM in a population with a high prevalence of this disorder, the Pima Indians. [...] Exclusive breastfeeding for the first 2 months of life is associated with a significantly lower rate of NIDDM in Pima indians. The increase in prevalence of diabetes in some populations may be due to the concomitant decrease in breastfeeding. »

12. Ponvert C. et coll. *Immunologie fondamentale et immunopathologie.* Édition Marketing, 1998.

13. Public Health Agency of Canada editions. *Diabetes in Canada: Facts and figures from a public health perspective.* 2011-12-15, `www.publichealth.gc.ca`:

« From 1998/09 to 2008/09, the prevalence of diagnosed diabetes among Canadians increased by 70 %. The greatest relative increase in prevalence was seen in the 35 to 39 and 40 to 44 year age groups, where the proportion doubled.
The incidence of type 2 diabetes among Inuit, in whom the disease was once unknown, is also rising. For the Inuit, there is a much lower rate of diabetes and heart disease. However, their genetic profile does not appear to be more favourable than in other populations. The lower rates of heart disease may be attributable to protection from lifestyle factors, such as diet, that may override any genetic susceptibility.
Individuals with diabetes are over three times more likely to be hospitalized with cardiovascular disease than individuals without diabetes, 12 times more likely to be hospitalized with end-stage renal disease, and almost 20 times more likely to be hospitalized with non-traumatic lower limb amputations.
Diabetes is one of the most common chronic diseases among children and youth. Type 1 diabetes remains the main form of the disease in this population, but type 2 diabetes, historically viewed as an adult disease, has been on the rise globally in children and youth for the last two decades. An increase in type 1 diabetes has also been documented in different countries, but the reasons are not completely elucidated. Children and youth with type 1 diabetes are at a greater risk of life-threatening complications because they rely on daily doses of insulin. »

14. Razavi R. *Sensory Neurons Control β-Cell Stress and Islet Inflammation in Autoimmune Diabetes.* Cell 2006:

Abstract: *« In type 1 diabetes, T cell-mediated death of pancreatic beta cells produces insulin deficiency. However, what attracts or restricts broadly autoreactive lymphocyte pools to the*

pancreas remains unclear. We report that TRPV1(+) pancreatic sensory neurons control islet inflammation and insulin resistance. Eliminating these neurons in diabetes-prone NOD mice prevents insulitis and diabetes, despite systemic persistence of pathogenic T cell pools. Insulin resistance and beta cell stress of prediabetic NOD mice are prevented when TRPV1(+) neurons are eliminated [...]»

15. Reinberg A. *Chronobiologie et chronothérapeutique.* Flammarion 2003.

16. Selye H. *The Stress of Life, Le Stress de la Vie.* Gallimard, 1962, 1975.

17. Sguassero Y. *Optimal duration of exclusive breastfeeding: RHL commentary (last revised: 28 March 2008).* The WHO Reproductive Health Library; Geneva; World Health Organization.

This is not to prove and say that exclusive breastfeeding is a matter of life and death:

« [...] First, it has long been demonstrated that breastfed infants have different growth patterns compared with formula-fed infants. Secondly, recent research suggests that breastfeeding has positive long-term benefits, including possible protection against obesity and breast cancer.[...] According to the review findings, exclusive breastfeeding for six months and continued breastfeeding with safe, appropriate and adequate feeding is recommended as a global health policy in both developing and developed countries. »

« [...] For outcomes for which data are currently lacking, well-conducted randomized controlled trials are needed, except for 'infant mortality' because it would be very difficult to design ethically acceptable studies that include infant mortality as an outcome... » No comment!

« [...] Breastfeeding contributes to maternal health in the immediate postpartum period by helping the uterus to contract rapidly, thereby reducing blood loss. In the short term breastfeeding delays a woman's return to fertility, and in the long term it reduces the risk of cancers of the breast and ovary. » No comment!

18. Unger Roger H., Rolf Luft Award 2014. *Glucagonocentric restructuring of diabetes: a pathophysiologic and therapeutic makeover.* J. Clin. Invest., janvier 2012:

Abstract: *« 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;
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 intraislet 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. »

Rolf Luft Award 2014, Nobel Forum, Karolinska Institute, May 13th 2014. `http://ki.se/en/mmk/rolf-luft-award-2014`:

« Unger has studied the normal and abnormal physiology of the islets of Langerhans in an effort to understand the mechanisms that predispose to diabetes.
In 1959 he developed a radioimmunoassay (RIA) for glucagon and established that glucagon was a true hormone, that it originated in the pancreatic α-cells, and that it was released in coordinated fashion with insulin to maintain glycemic control within the very narrow normal range.
In fact, Unger developed the first RIA for measuring a hormone and these studies were completed prior to the publication of an insulin RIA by Berson and Yalow (though Unger acknowledged their primacy in developing the method and generously held up his publication until their work could be published). These and subsequent studies revealed that diabetes is a bihormonal disease in which insufficiency of insulin is always associated with an excess of glucagon, which accounts for the hepatic overproduction of glucose and ketones in diabetes. Moreover in the absence of glucagon signaling, either due to somatostatin treatment or a glucagon receptor knockout, a complete deficiency of insulin production no longer causes hyperglycemia or ketosis.
Recent studies have explored the effect of leptin on glucose metabolism and established that leptin can improve diabetes in both Type 1 and Type 2 diabetes. The data further suggest that leptin lowers

blood glucose by inhibiting glucagon action. Unger is a giant in endocrinology and metabolism and an extremely worthy recipient of the Luft Prize. »

19. Wilhelm J.-M. *Intérêt d'une approche chronobiologique du diabète de type 2.* Annales de Médecine Interne, mars 2002.

20. WHO editions. *Mental Health: new understanding, new ope.* World health report 2001:

« Mental and physical health are two vital strands of life that are closely interwoven and deeply interdependent. Advances in neuroscience and behavioural medicine have shown that, like many physical illnesses, mental and behavioural disorders are the result of a complex interaction between biological, psychological and social factors.
Meanwhile, scientific evidence from the field of behavioural medicine has demonstrated a fundamental connection between mental and physical health -for instance, that depression predicts the occurrence of heart disease. Research shows that there are two main pathways through which mental and physical health mutually influence each other.
Physiological systems, such as neuroendocrine and immune functioning, are one such pathway. Anxious and depressed moods, for example, initiate a cascade of adverse changes in endocrine and immune functioning, and create increased susceptibility to a range of physical illnesses. »

21. WHO editions. *Obesity and overweight.* 2013-2015:

« Facing a double burden of disease: Many low- and middle-income countries are now facing a "double burden" of disease. While they continue to deal with the problems of infectious disease and under-nutrition, they are experiencing a rapid upsurge in noncommunicable disease risk factors such as obesity and overweight, particularly in urban settings.
It is not uncommon to find under-nutrition and obesity existing side-by-side within the same country, the same community and the same household. »

22. Yu Xu, PhD1 and all. *Prevalence and Control of Diabetes in Chinese Adults.* JAMA 2013; 310(9): 948-958:

Conclusions and relevance: *« [...] The estimated prevalence of diabetes among a representative sample of Chinese adults was 11.6 % and the prevalence of prediabetes was 50.1 %. Projections*

based on sample weighting suggest this may represent up to 113.9 million Chinese adults with diabetes and 493.4 million with pre-diabetes. These findings indicate the importance of diabetes as a public health problem in China »

A dramatic epidemic after a recent massive rural exodus... Chinese medicine unable to fight this scourge.

23. Zollinger H. *Abrégé d'Anatomie Pathologique.* Tome 1 et 2, 1970-71:

    Glucose and experimental T1 diabetes: *« An excess of glucose can destroy insulin-producing β-cells and can lead to diabetes. »*

    Diabetes and α-cells: *« The examination of the diabetic pancreas under the microscope shows abnormal proliferation of α-cells producing glucagon, a hyperglycemic hormone, normally 12 à 15 α-cells/islet. This rule is valid even in cases where diabetes is treated. »*

24. Témoins anonymes. *Stress et diabète.* Forum internet:

    Un diabétique type 1: *« Le stress intervient-il à ce point sur la glycémie ? Cet après midi je me suis disputé avec une personne pour des bricoles. 30 minutes après j'ai commencé à me sentir très mal, j'ai pris ma glycémie et j'étais à plus de 3,30 g/l alors qu'une heure trente avant j'étais à 1,60. »*

    Un diabétique type 1: *« ... Je suis traité avec une pompe à insuline. En période de repos, vacances et weekends, mes bolus et besoins de base sont très faibles. Pendant la semaine au travail, mes glycémies sont anormalement très élevées. »*

    Une diabétique type 1: *« J'ai toujours été persuadée que mon diabète s'est déclenché à l'âge de dix ans parce que j'avais perdu ma mère dans un horrible accident qui m'a marquée à vie à l'âge de quatre ans. »*

Dr J.-M. Crabbé - Octobre 2014

« Tempête sur le diabète » is currently available:

`www.editions-academia.be` – Order Book - web link

`www.editions-harmattan.fr` – Order Book - web link

`www.amazon.fr` – Order Book - web link

Autographed book: Mail
Website: `www.sitemed.fr` – Approved by the Healt on the Net Foundation.

The licensor permits others to copy, distribute and display this work. May not use for commercial purposes unless the licensor's permission. In return, you must give the original author/publisher credit :
Tempête sur le diabète – ISBN : 978-2-8061-0194-5.
Dr J-M Crabbé – Besançon, France – `www.sitemed.fr`
Éditions Academia – Louvain-la-Neuve, Belgique – `www.editions-academia.be`