Diabetologia (2004) 47:581–589
DOI 10.1007/s00125-004-1336-4

Diabetologia

Decreased beta-cell mass in diabetes: significance, mechanisms and therapeutic implications

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Abstract

Increasing evidence indicates that decreased functional beta-cell mass is the hallmark of both Type 1 and Type 2 diabetes. This underlies the absolute or relative insulin insufficiency in both conditions. In this For Debate, we consider the possible mechanisms responsible for beta-cell death and impaired function and their relative contribution to insulin insufficiency in diabetes. Beta-cell apoptosis and impaired proliferation consequent to hyperglycaemia is one pathway that could be operating in all forms of diabetes. Autoimmunity and other routes to beta-cell death are also considered. Recognition of decreased functional beta-cell mass and its overlapping multifactorial aetiology in diabetic states, leads us to propose a unifying classification of diabetes. [Diabetologia (2004) 47:581–589]

Keywords Hyperglycaemia · Apoptosis · Proliferation · Cytokines · Insulin

Type 1 diabetes is recognised as a condition of absolute insulin deficiency due to destruction of beta cells. To the extent that this aetiology is not in dispute, it will not be a major focus of this For Debate. By contrast, Type 2 diabetes was for many years attributed solely to insulin resistance. Although altered insulin secretion in patients with Type 2 diabetes had already been demonstrated in the 1960's [1, 2, 3], it was not until the 1980's that the debate on the true aetiology of the disease became heated. Thus, once the reality of impaired beta-cell function in Type 2 diabetes was acknowledged even by the most fervent champions of insulin resistance [4], this debate focused in the first instance on the relative importance of these two components and their putative respective causality. There is now general agreement that all hypotheses were correct to a certain degree and that Type 2 diabetes is a complex pathophysiologic spectrum encompassing situations reflecting the combination of beta-cell failure or demise and insulin resistance to varying degrees. More recently, the debate has been complicated by equally heated discussion on the cause of impaired insulin secretion: is this due to reduced beta-cell mass or to an intrinsic defect in the secretory machinery of the beta-cells or both? Now that the significant reduction in beta-cell mass observed many years ago [5, 6] has been clearly established in Type 2 diabetes [7, 8, 9], studies must focus on whether such a reduction alone can account for impaired insulin secretion and on the molecular mechanism responsible for the decreased beta-cell mass.

Received: 18 September 2003 / Revised: 17 December 2003
Published online: 7 February 2004

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Insufficient insulin secretion in Type 2 diabetes

The defect in insulin secretion in Type 2 diabetes is the consequence of two confounding components: insulin deficiency and disturbed kinetics of secretion combined with impaired glucose stimulus-secretion coupling.

Insulin deficiency. It cannot be stressed enough that insulin deficiency in Type 2 diabetes is relative to the

prevailing hyperglycaemia and reflects the analytical methods used. The simple measurement of circulating concentrations of immunoreactive insulin at least at early stages of the disease, shows hyperinsulinaemia. Clearly, however, this level of immunoreactive insulin is insufficient to control the prevailing hyperglycaemia: hence "insulin deficiency". Most conventional assays detect both proinsulin and insulin indifferently. Yet, it has been known for some time that Type 2 diabetes is characterised by an increased ratio of proinsulin:insulin [10, 11] and that the biological activity of proinsulin is approximately 10% that of fully-processed insulin. Thus, in order to assess the hypoglycaemic potential of circulating insulin, one should in reality consider only the true insulin component rather than total immunoreactivity (reflecting all immunoreactive species including proinsulin and conversion intermediates). When this is done, the insulin deficiency becomes more evident. In addition, most measurements are done on a single fasting blood sample, yet it is under these conditions that the demand for insulin is at its lowest. Only after stimulation does the magnitude of the insulin deficiency become fully manifest. Leaving aside the specific defect in glucose stimulation, even a potent stimulus such as arginine elicits a markedly diminished insulin response in patients with Type 2 diabetes [12]. Thus, we have shown that after an i.v. arginine challenge, patients with Type 2 diabetes and with a high fasting concentration of immunoreactive insulin (163% of the control subjects) only released 62% as much immunoreactive insulin as the control subjects [11].

Beta-cell secretory defect. Insulin secretion from subjects with Type 2 diabetes is characterised by a relatively selective loss of glucose stimulation manifested by the lack of first phase of secretion and decreased second phase. Sensitivity to non-metabolisable stimuli such as arginine remains normal although the magnitude of the response may be attenuated. Baseline insulin secretion is normally pulsatile, with a periodicity of 5 to 10 min. Such pulsatility of insulin secretion, believed to be important for normal glucose homeostasis, is also perturbed in Type 2 diabetes as are the ultradian oscillations of insulin secretion [13, 14]. This could in addition, at least in part, account for some insulin resistance [15, 16, 17]. These defects in secretion, and particularly the lack of response towards glucose, act in concert with the insulin deficiency along with a disproportionate amount of proinsulin. Together, they compromise severely the ability of residual beta cells to provide sufficient insulin to achieve euglycaemia in the face of insulin resistance. When evaluated during an OGTT, these secretory defects can be observed shortly after glucose ingestion.

Decreased beta-cell mass in Type 2 diabetes

It was suggested many years ago that beta-cell mass is reduced in Type 2 diabetes ([18] and see [19] for a more recent review). This decrease in beta-cell mass has been confirmed by a series of convincing studies in which beta-cell mass was quantified morphometrically in a large series of pancreata from patients with Type 2 diabetes and appropriately matched control subjects [7, 8, 9]. Thus, and most importantly, obese patients with Type 2 diabetes have decreased beta-cell mass compared to obese individuals without diabetes. This suggests that in patients with Type 2 diabetes there is a loss of beta cells and/or impaired augmentation of beta-cell mass consequent to increased demand. By contrast, the beta-cell mass in non-obese control subjects was not significantly different to that of obese patients with Type 2 diabetes. This could explain the discrepancies in earlier studies. By definition, any change in beta-cell mass must reflect an altered balance between the rate of production (whether by neogenesis or replication of beta cells) and disappearance (cell death by necrosis or apoptosis). It is difficult to distinguish between the two mechanisms in human tissue sections mainly because dead cells are removed rapidly from the islet by macrophages and neighbouring cells, making it hard to quantify cell death. Although cell proliferation can be quantified in tissue sections using markers such as Ki-67, this only provides a single snapshot in time which probably does not reflect accurately the complex dynamic of the process. Nevertheless, one study in humans does indicate that increased apoptosis is of greater importance in the reduced beta-cell mass of Type 2 diabetes than impaired neogenesis and/or proliferation [8]. It is important to note that these studies in humans cannot be prospective in nature, given that they were done at autopsy. Most specifically, the beta-cell mass in these individuals before onset of the disease is not known. Thus individuals susceptible to diabetes possibly have limited beta-cell mass early in life, perhaps even at birth, due to genetic or environmental factors. If such were the case, the decrease in beta-cell mass seen in patients with Type 2 diabetes would not necessarily be the sole consequence of the disease itself.

Mechanism of beta-cell death in Type 2 diabetes

Major mechanisms proposed to lead to beta-cell death in Type 2 diabetes and discussed here include: increased circulating cell nutrients, ER-stress, signalling factors from the adipocyte, and iatrogenic mechanisms. This For Debate is obviously not all-inclusive. Without any prejudice towards the other mechanisms and their relative importance, as well as the valuable contributions of the respective authors, we focus primarily on the pro-apoptotic effect of hyperglycaemia

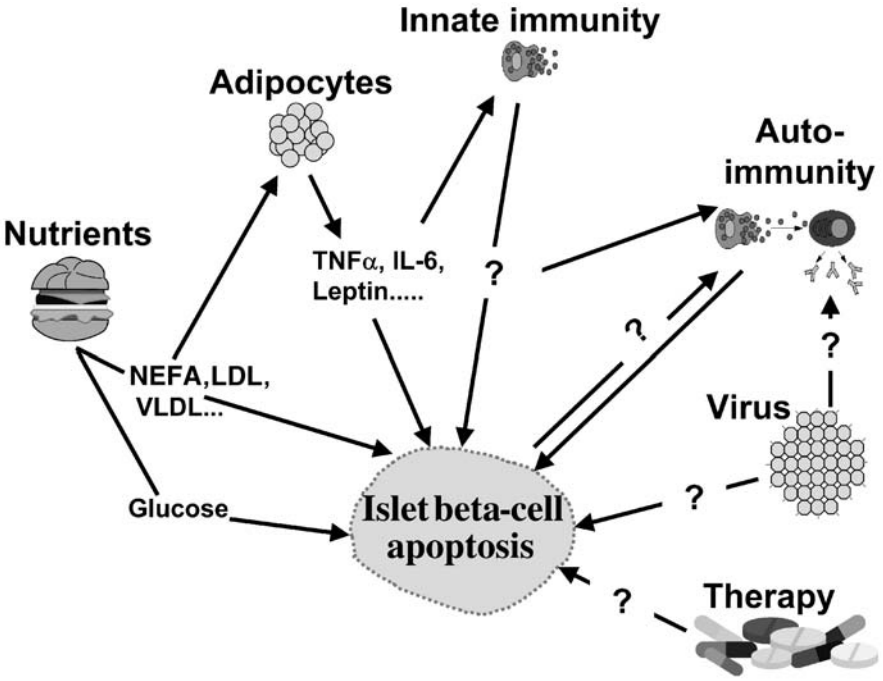

Fig. 1. Proposed model for the interplay between "aggressors" of the beta cell in the pathogenesis of diabetes. Factors possibly affecting beta-cell survival should be considered representative of the given pathway; the list is not intended to be comprehensive. Signalling pathways within the beta-cell leading to apoptosis are not included. Increased concentrations of glucose and lipids (NEFA, LDL, VLDL) are believed to have deleterious effects on beta cells. Lipids might affect the viability of beta cells directly or via obesity. Similarly, cytokines secreted by adipocytes (i.e. TNFα, IL-6 and leptin) could act directly on beta cells or activate the innate immune system. In turn, innate immunity could favour an acquired immune response in genetically predisposed individuals. Additional factors precipitating beta-cell demise in diabetic patients include viruses and drugs. The aetiology of the particular diabetic condition and in turn the precise role and respective importance of each pro-apoptotic pathway will vary from one patient to the next

and dyslipidaemia on beta cells and possible molecular pathways (Fig. 1). Significant omissions include the possible pro-apoptotic roles of IAPP [20, 21, 22, 23] and inflammatory factors [24, 25, 26].

From hyperglycaemia to beta-cell death. It is important to stress that glucose affects survival of human and rodent islets differently. This has led to a certain amount of confusion in the field. In brief, graded increases in glucose from 5.6 to 11.2 mmol/l and above induce apoptosis of human beta cells in vitro in a dose-related fashion [27, 28]. By contrast, studies on rat islets have shown that increasing glucose from a physiological concentration of 5.6 to 11.2 mmol/l decreases apoptosis [29]. A further increase above 11.2 mmol/l has been shown to be either pro- or anti-apoptotic depending on the study [29, 30]. However, islets from *psammomys obesus*, a gerbil, behave like human islets [31]. This small animal and humans both develop nutrient-dependent forms of diabetes, possibly reflecting the importance of glucose-mediated beta-cell loss in these two settings. In this context, it is important to consider the possible detrimental effect on beta-cell turnover of transient post-prandial glycaemic excursions early in the development of overt diabetes. This could perhaps underlie the decrease in beta-cell mass documented in patients with impaired fasting glucose, the earliest manifest stage of diabetes [8]. The situation is confounded by the fact that (in rodents) glucose can also stimulate proliferation [32] and neogenesis [33, 34] of beta cells: the relative impact on proliferation and apoptosis will thus dictate the outcome of decreased or increased beta-cell mass [19]. Furthermore, the mitogenic effects of glucose, at least in vitro, seem to be limited in time in human islets [28] but are long-lasting using rat islets. The mass of beta cells at any given time is thus the consequence of a complex algorithm reflecting glucose concentration, time, proliferation and apoptosis.

Given that glucose does induce apoptosis in beta cells what might be the mechanism? One clue may lie in the relative specificity of this toxicity towards the beta cell, but not other islet or most non-islet cell types. This cell is by design exquisitely sensitive to small changes in ambient glucose. When these changes are of short duration and in the physiological range as after a meal, they lead to insulin secretion. However, when of longer duration and more pronounced in magnitude, perhaps they are translated by the beta-cell glucose-sensing pathways into pro-apoptotic signals. One such signal might be increased ER-stress [35, 36, 37]. The increased demand on beta cells in terms of insulin output leads to increased secretion as well as increased proinsulin biosynthesis to replenish beta-

cell insulin stores [38]. The increase in proinsulin biosynthesis in turn causes an increased flux of protein through the RER. Flux through the RER of the beta cell is quite high compared with other cell types even under physiologic conditions and any further increase is expected to tilt the balance in favour of ER-stress-induced apoptosis. Chronic hyperglycaemia could also lead to long-term increases in cytosolic Ca^{++} [as opposed to the normal short-term increases arising from glucose-induced closure of ATP-dependent potassium channels (K_{ATP})] that could in turn be pro-apoptotic [39]. High glucose also leads to the generation of reactive oxygen species (ROS) [40, 41], believed to be particularly toxic to the beta cell. We have shown, using human islets, that high glucose in vitro activates an additional and unexpected apoptotic pathway involving beta-cell production of IL-1β, activation of NFκB and Fas signalling [42]. This was confirmed in beta cells in sections of pancreata from patients with Type 2 diabetes [42]. This last pathway may turn out to be a unifying mechanism for beta-cell death in disease. The situation is complicated by the fact that as mentioned above, glucose (at least in vitro) has a dual effect on human beta-cell turnover, promoting proliferation in the short-term and apoptosis in the longer term [28]. We have suggested a common factor, FLIP providing a switching mechanism between these two opposing effects [43].

From dyslipidaemia to beta-cell death. Diabetes is associated with dyslipidaemia characterised by increased circulating concentrations of NEFA and changes in lipoprotein profiles. Both have been shown to be pro-apoptotic in the beta cell [44, 45]. Intriguingly, saturated fatty acids such as palmitate are highly toxic to the beta cell whereas the mono-unsaturated fatty acids such as oleate are protective against both palmitate and glucose-induced apoptosis [46]. A similar balance between pro- and anti-apoptotic effects is found for lipoprotein action on beta-cell survival. VLDL and LDL are thus pro-apoptotic whereas HDL protects beta cells against these pro-apoptotic effects [45]. Fatty acid cytotoxicity is mediated by the ceramide-mitochondrial apoptotic pathway [47] whereas pro-apoptotic lipoproteins seem to act via c-Jun N-terminal kinase (JNK) [45]. Regardless of the importance of these pro-apoptotic pathways in some situations, dyslipidaemia is not common to all patients with Type 2 diabetes. Furthermore, toxicity of lipids towards beta cells may be influenced by or possibly dependent upon the prevailing glycaemia [48, 49].

The interplay and relative importance of beta-cell death caused by glucose or fatty acids/lipoproteins could thus vary from one patient to another. Additionally, other pathways may come into play. We have thus discovered that leptin, the protein hormone released by adipocytes, in addition to its established effect on insulin secretion [50, 51], induces apoptosis in human beta cells (Maedler et al; submitted for publication). This contradicts previous studies on rodent islets showing that leptin protects against NEFA-induced apoptosis [52]. Whether this reflects the use of rodent versus human islets or a truly selective protective effect remains to be investigated.

Is there a common pathway linking reduced beta-cell mass and impaired beta-cell function?

Clearly, loss of enough beta cells will lead to decreased insulin output from the pancreas. The interesting question is whether this is an "all-or-nothing" phenomenon, with a more or less direct relationship between beta-cell mass and function, or whether partial loss of beta-cell mass leads directly or indirectly to impaired secretion from the remaining cells. Before speculating on this, let us examine the known facts. In humans, before impaired glucose tolerance becomes apparent (the earliest manifestation of incipient diabetes) there may have been loss of as much as ~50% of beta-cell mass [8]. Surprisingly, as overt diabetes develops, further loss might be quite limited, amounting to no more than an additional 10% or so [8]. This certainly points to a secondary or parallel impairment of beta-cell function. Again in humans, hemi-pancreatectomy led to impaired beta-cell function [53] whereas in rats, partial pancreatectomy results in impaired insulin secretion resembling that encountered in Type 2 diabetes despite extensive regeneration of the remnant and only very modest increase in glycaemia at the time of study [54]. Taken together, one must conclude that decreased beta-cell mass can lead to impaired function but the mechanism is not apparent nor is it necessarily the sole answer.

Two mechanisms possibly account for such impaired beta-cell function consequent to decreased beta-cell mass: (i.) increased insulin demand on residual beta cells per se leads to changes in function (whether by ER-stress or other mechanisms), (ii.) hyperglycaemia consequent to decreased beta-cell mass drives the impairment in beta-cell function. Distinguishing between the two is complicated by the fact that decreasing beta-cell mass experimentally more often than not leads to a more or less prolonged period of hyperglycaemia [55, 56]. Moreover, in many instances there is a compensatory regeneration of beta cells. Newly formed beta cells might not be as well-differentiated as older, fully mature residents in the pancreas. Regardless, there is ample evidence from in vitro studies on islets (e.g. [57, 58]) as well as in vivo by glucose infusion (e.g. [59]), that high glucose for extended periods of time leads to impaired beta-cell secretory behaviour. Although we agree with Gordon Weir et al. that "excessive glucose stimulation of a reduced beta-cell mass leads to functional abnormalities of the beta cell" [60], this is surely just one factor.

Consequently we acknowledge that the initial events leading to the progressive increase in glycaemia seen in diabetes remain elusive. For example, a genetic component combined with excessive food intake may lead to clinically undetectable hyperglycaemic excursions that could have an effect at an early stage on beta-cell mass and/or function. Furthermore, glucose is just one factor influencing beta-cell mass. Finally, we stress the importance of the amplitude and duration of hyperglycaemia. It is thus known that shorter periods of increased glucose in humans in fact increase glucose sensitivity of insulin secretion [12, 62].

Whereas Type 2 diabetes in humans progresses over time, impaired beta-cell function appears to be reversible to a certain degree at all stages. Thus, if an individual with Type 2 diabetes, even with severe hyperglycaemia, is rendered euglycaemic by either pharmacological means or changes in life-style, beta-cell function, and in particular glucose-responsiveness, is restored [63, 64]. This is particularly true at early stages of the disease where the limiting threshold for reversibility of decreased beta-cell mass has perhaps not been passed. Rendering an individual with Type 2 diabetes euglycaemic interrupts the vicious cycle linking decreased beta-cell function with hyperglycaemia. This might not only restore insulin secretory patterns but also allow for some restoration of beta-cell mass. Although there are many reasons for believing that this may occur in humans as in animal models of reduced beta-cell mass, it has never been documented directly and it will be difficult to do so as long as beta-cell mass cannot be measured non-invasively.

Unravelling the pathways leading to beta-cell death and impaired function may provide the basis for innovative therapy of Type 2 diabetes. This is particularly true when one considers the reversibility of impaired beta-cell function and possibly beta-cell mass discussed above. One example might prove to be long-acting analogues of GLP-1 (or inhibitors of the enzyme DPP IV that degrades GLP-1) that will be in clinical use to enhance insulin-secretion but could have additional beneficial effects on beta-cell mass by stimulating proliferation and inhibiting apoptosis [65, 66]. Other examples for innovative therapy are K_{ATP} channel openers. Treatment with diazoxide not only of patients with Type 1 but also with Type 2 diabetes, partially restores insulin secretion [67, 68, 69]. While this beneficial effect may be due to inducing beta-cell "rest", it could also reflect in part the anti-apoptotic effect of such drugs [29]. We believe that IL-1β secretion by the beta cell might be a common pathway linking hyperglycaemia to both impaired beta-cell function and beta-cell apoptosis. Blocking IL-1β signalling could thus be useful in treating Type 2 diabetes. Use of the natural soluble IL-1 receptor antagonist, IL-1Ra, might serve this purpose and we are currently investigating the effect of this protein in a clinical trial in Type 2 diabetes.

Decreased beta-cell mass as a common denominator of Type 1 and Type 2 diabetes: clinical consequences and implications for the classification of diabetes

Current classification of diabetes distinguishes between Type 1 and Type 2 [70]. Type 1 diabetes is defined by beta-cell destruction and subdivided into immune-mediated and idiopathic. For Type 2 diabetes, no mention is made of possible beta-cell loss. Emerging theories from basic scientists and diabetologists alike, are tending towards a unifying hypothesis of diabetes. While it is probable that genetic predisposition is an important feature in all forms of diabetes, advances in the field do not yet allow for useful classification on this basis and indeed do not exclude the broad spectrum of diabetic conditions we propose. So what is the evidence for blurring and overlapping diabetic conditions? Immunological phenomena (e.g. anti-islet cell antibodies) typically associated with Type 1 diabetes are encountered in 10 to 20% of so-called Type 2 diabetic patients, which led to a separate classification of these patients in a subtype named "LADA" (latent autoimmune diabetes of adults). We now have paediatricians studying islet cell autoimmunity in elderly diabetic patients [71]. Consider also the intriguing theory that obesity could underlie the observed increase in Type 1 diabetes [72], a causal correlation which has been recently confirmed in two independent studies [73, 74]. Meanwhile, clinical research has shown that changes in inflammatory cytokines are not limited to classic autoimmune-type diabetes but are increased in Type 2 diabetes [75, 76] and could indeed be useful as markers of risk for developing the disease [77]. That being said, this is also the case in obesity, in turn suggesting an intrinsic beta-cell defect of some kind that renders individuals susceptible to progressing from obesity to diabetes. Clearly the time-course and extent of loss of beta cells, in association with varying degrees of insulin resistance, will affect the clinical manifestations of the disease. Autoimmune destruction of the majority of beta cells in young individuals will lead to a rapid onset of the disease and if treatment is delayed, ketoacidosis will occur. This is rarely seen in adults with Type 1 diabetes, therefore referred to as suffering from LADA. The situation is, however, complicated by anecdotal reports from paediatricians describing the dynamics of the regression of beta-cell function in young Type 2 diabetic patients as much more rapid than in adult counterparts. If this observation holds true, there will be obvious therapeutic implications.

Observations from the basic scientist are equally illuminating. Apoptosis in the presence of cytokines including IL-1β may lead to an autoimmune response [78]. Moreover, both beta-cell apoptosis [8] and an increase of locally produced IL-1β [42] are observed in Type 2 diabetes. Furthermore, signalling networks pre-

viously believed to be limited to islets of patients with Type 1 diabetes are detectable in islets from patients with Type 2 diabetes, e.g. Fas-FasL, IL-1β [28, 42, 43]. As mentioned above, apoptosis itself may induce an autoimmune response. Interestingly, apoptosis of beta cells precedes the emergence of insulitis in the NOD mouse [79] and lymphocyte infiltration is also observed consequent to apoptosis in islets of immune-competent *Pdx1*$^{+/-}$ mice [80]. Therefore beta-cell apoptosis, whether genetically programmed, or induced by a virus, IAPP, glucose or NEFA could prove to be a very early event. Depending on its magnitude and duration, secondary phenomena including insulitis may appear with different timing and severity, thus escaping notice. There has to our knowledge been no systematic attempt to detect insulitis in the pancreas of early-onset Type 2 diabetes. That being said, we do not ignore some morphological findings that appear to be specific to Type 2 diabetes, most specifically islet amyloid deposits, but they are not found in all cases of Type 2 diabetes just as insulitis has not been detected in all Type 1 cases examined. In both cases, we also recognise the importance of the timing of the events leading to such manifest morphological features; depending on this timing with respect to the age of the subject at autopsy and duration of the disease, these "morphological markers" may or may not be apparent. Certainly, it is not our intention to refute the existence of auto-immune diabetes. However, and as acknowledged by the Expert Committee on Diagnosis and Classification of Diabetes [70], beta-cell destruction in Type 1 diabetes can, in addition, arise by other mechanisms. Furthermore, as mentioned, immunological marker and inflammatory mediators are also detected in Type 2 diabetic patients. While we certainly do believe that autoimmune diabetes exists, the frontier between this form of diabetes and others is, to our mind, blurred.

Increasing evidence would now suggest that beta-cell death underlies most forms of diabetes. While the aetiology of beta-cell death may vary from one condition to the next, we reason that it will inevitably result in a state of insulin deficiency and impaired beta-cell function. We are not alone. According to his "Accelerator hypothesis", Wilkin states: "Clinically, there is little other than tempo to distinguish two types of diabetes" [81]. Therefore, we and others (e.g. [75, 81]) believe that the classification of diabetes should be revisited. The clinical definition of diabetes can continue to be that proposed by the American Diabetes Association and now generally accepted [70, 82]. In all instances, we now propose that individuals with these clinical features suffer from one of many conditions of relative or absolute insulin deficiency, that we propose calling simply "diabetes mellitus". The only subsidiary question is whether the patient has, in addition to insulin deficiency, insulin resistance. While an objective and ready index of insulin resistance does not exist in the absence of reliable and easily measurable surrogate markers, it may be sufficient in most cases to note whether the patient presents with obesity (and metabolic syndrome) and/or has a family history suggestive of insulin resistance. We propose the following subtypes in our classification: diabetes mellitus with or without insulin resistance, with or without autoantibodies.

So what is new? We already have just two major subtypes of diabetes: Types 1 and 2. Are we simply changing names? No. The fundamental difference is that our classification provides intrinsic guidelines for therapy since insulin resistance can be easily detected and indeed modulated. If present, insulin sensitivity should be targeted by lifestyle intervention, shown to be so effective in recent American, Chinese and European studies [83, 84, 85]. The earlier such intervention in the progression of the disease (i.e. patients with impaired glucose tolerance rather than overt diabetes) the better. This can be supplemented by insulin-sensitising agents. If these strategies fail or are insufficient, the next step could be to replace what is missing, i.e. insulin. We do recognise that insulin resistance is not peculiar to Type 2 diabetes. Indeed, patients with Type 1 diabetes can present with insulin resistance and/or obesity and this may be induced or exacerbated by intensive insulin therapy. The sub-classification "with or without autoantibodies", alas, has no impact on therapy today. Nevertheless, we include this as an incentive for further research leading towards targeted therapy and perhaps ultimately a means to prevent or slow down autoimmune destruction of beta cells.

What are the pitfalls? We do not underestimate the possibly negative effects of extensive use of insulin therapy: the menace of hypoglycaemia may be more of a concern than with other therapy. Moreover, it is generally accepted that patients, particularly the elderly, may be reluctant to treat themselves by injection. Insulin therapy does require greater support from health professionals and this could pose a problem. Finally, as we all recognise, exogenous insulin is not the perfect replacement for secretion from the beta cell. Many aspects of physiological insulin delivery are missing and this probably affects its efficacy. Certainly, we do not wish to promote irresponsible use of medication (whether insulin or other) when behavioural changes (moderate exercise and improved diet) can be efficacious. On the other hand, it is mandatory that patients with absolute insulin deficiency, as seen typically in younger lean individuals, receive insulin from the very beginning of the disease as currently practised by most diabetologists.

Given the rationale behind this approach to diabetes, namely that decreased beta-cell mass underlies all common forms of the disease, particular attention should be paid to the possible beta-cell toxic side-effects of any supplementary or alternative medication. For example, it is suggested from in vitro studies that sulphonylureas could have such effects both on rat

[29] and human islets [86]. Whether these studies turn out to be of clinical relevance remains to be seen but they are in line with an important recent prospective study comparing insulin and sulphonylurea treatment of Type 2 diabetes. This study shows that treatment with insulin preserved beta-cell function more effectively than glibenclamide [87]. It remains to be established whether it is the beneficial effects per se of insulin or possible beta-cell toxicity of glibenclamide that account for this observation. While a deterioration of insulin secretion was seen in patients treated with sulphonylurea in the UKPDS, those treated with insulin were not evaluated in this regard [60]. This should not, however, detract from use of what have been shown to be effective drugs particularly in the elderly in whom any possible acceleration in the decrease of beta-cell mass could be of less clinical relevance. At the other extreme, prolonged use of any drug that could negatively affect beta-cell mass in young patients is clearly not indicated. It is too early to know whether the new generation of oral secretagogues such as the glinides will negatively or positively affect beta-cell turnover with prolonged use.

Summary and conclusion

We present evidence in support of the hypothesis that diabetes is a spectrum of clinical conditions all of which arise from relative or absolute insulin deficiency that is caused by decreased functional beta-cell mass. Hyperglycaemia is suggested to be a major, but not the only, driving force for beta-cell death. This does not, of course, exclude the existence of autoimmune diabetes and neither does it diminish its importance. The same goes for the genetic predisposition to diabetes. Current classification of diabetes is inadequate. We propose a new classification focused on decreased functional beta-cell mass and consequent insulin deficiency with two subtypes based on the presence or absence of insulin resistance and/or autoimmunity.

Acknowledgements. The authors are greatly indebted to Drs. E. Cerasi (Jerusalem), S.E. Kahn (Seattle) and G.C. Weir (Boston) for critical review of the manuscript and their numerous constructive suggestions. The authors' research is supported by the Swiss National Science Foundation Grants 3200-067049.0, 3200B0-101902/1 and PP00B-68874/1, by a grant from the European Foundation for the Study of Diabetes/Johnson & Johnson Research Programme and by grant 4-1999-844 from the Juvenile Diabetes Research Foundation International.

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