The concept of pancreatic β-cell mass is fundamental to the understanding of normal metabolism, the pathogenesis of diabetes, and the transplantation of β-cell tissue. The amount of β-cell tissue present in the pancreas is a major determinant of the quantity of insulin that can be secreted, and its mass will vary according to the size of the individual and the degree of insulin resistance present. Not all insulin-producing cells are the same, and the dimensions of this heterogeneity remain to be defined. Pancreatic β-cell mass is markedly reduced in insulin-dependent diabetes mellitus and moderately reduced in non-insulin-dependent diabetes mellitus. In both forms of diabetes, there are qualitative and quantitative abnormalities of insulin secretion that cannot be explained entirely by changes in β-cell mass. The amount of β-cell tissue needed for successful transplantation has only been partially defined. Segmental (~50% of the pancreas) transplantation can normalize plasma glucose levels in humans. Difficulty obtaining sufficient amounts of β-cell tissue is expected to remain a barrier to successful islet transplantation for the immediate future. More should be learned about the function and fate of grafted islet cells. Diabetes 39:401–405, 1990

The release of insulin during meals is an exquisitely timed, highly sophisticated process orchestrated by nutrient, neural, and gut hormone signals. Even between meals, the precision with which insulin is delivered into the portal vein engenders great respect for the remarkable islet organ. The success of this system depends on the capacity of individual pancreatic β-cells to respond to diverse combinations of stimulatory factors and on the maintenance of the mass of this population of cells. The individual β-cells that make up this mass have often been thought to be a population of cells with identical characteristics, and we are only beginning to understand their complex heterogeneity. The mechanisms that control the mass of β-cell tissue are considerably more complicated than is generally appreciated. However, the concept of β-cell mass is of central importance in consideration of normal metabolism, diabetes, and pancreas and islet transplantation. The intent of this perspective is to highlight important unanswered questions concerning these two areas.

CONSIDERATION OF β-CELL HETEROGENEITY

Most of what is written and taught about β-cells suggests they are all identical, and this is understandable because almost all information about their physiology and biochemistry comes from work with large populations of cells. However, recent studies indicate that the threshold for glucose-induced insulin release and biosynthesis varies among β-cells (1,2). These findings immediately raise many questions. For instance, in addition to variation in threshold, there may also be variations in the amount released at maximal or submaximal stimulation. Furthermore, during meals, certain β-cells could have specific response characteristics to glucose, amino acids, or gut hormones.

Surely, there are differences in function that depend on the age of the β-cell. Cells that are about to divide or have just divided probably do not behave the same way as the rest of the population. Likewise, young, mature, elderly, and senescent cells might have their own characteristics. Unresponsiveness of fetal cells to glucose has been well documented (3). We do not know if adult islets contain a minority population of fetallike β-cells.

Differences in the local environment of a β-cell must account for some heterogeneity. Because of the large amount of blood flow in islets, β-cells probably have a particularly high requirement for oxygen, raising the question of whether some β-cells are more fortuitously placed next to vessels...
that deliver more oxygen (4). Considering islet innervation, would β-cells behave differently if they were next to a nerve terminal that was intermittently secreting norepinephrine, acetylcholine, or galanin? There has been considerable interest in groups of cells within islets that communicate via gap junctions that allow passage of chemical and electrical signals (5). There may therefore be considerable differences between or even within these domains of communication.

The concept of a cell that serves as an electrical or even a chemical pacemaker is still viable. What would be the difference between a "pacemaker" and a "paced" β-cell?

Another consideration is whether a β-cell is adjacent to the non-β-cell mantle or buried within the islet core (Fig. 1). Core β-cells appear to be more readily degranulated by glucose stimulation than those adjacent to the mantle (6).

The reason for this regional difference is unknown, but recent information about islet blood flow may provide some leads. Blood flows from the β-cell core to the non-β-cell mantle (7,8). This means that mantle products (glucagon, somatostatin, and pancreatic polypeptide [PP]) should not reach β-cells via local blood flow, although they may do so through interstitial fluid. The capacity for this should depend on rates of diffusion and interstitial fluid flow. However, it might be guessed that interstitial fluid would flow in the same general direction as blood, and this would minimize such a paracrine interaction. Perhaps the β-cells of small islets have greater exposure to mantle peptides. There has been considerable curiosity about whether β-cells in dorsal lobe islets (their mantle contains a-cells and few PP cells) are different than those of ventral lobe islets (their mantle has mainly PP cells and a few a-cells). Islets from the dorsal lobe appear to secrete more insulin than those from the ventral lobe, and this finding raises questions about paracrine effects of glucagon (9,10). This issue may not be merely academic, because the function of these different types of islets could be important for islet transplantation and subjects with partial pancreatectomies.

Pancreatic β-cells may vary in how they function during hypoglycemia or in diabetes. For instance, experimental chronic hypoglycemia or hyperglycemia have profound effects on secretion (11,12), and perhaps some β-cells adapt to these stresses differently than others. Surely, some β-cells are more susceptible to autoimmune destruction than others. Could this be related to the position of the cell within the islet, the relationship to blood vessels, the age of the cell, or some other factors? Why do some β-cells survive a dose of streptozocin or alloxan? Why do some β-cells fail before others as non-insulin-dependent diabetes mellitus (NIDDM) becomes more severe? Fetal β-cells have great capacity for growth, but what are the characteristics of the few adult cells that can be easily stimulated to divide? Are there some populations of β-cells that are supersecretors of insulin, and could this be exploited for transplantation?

CHANGE OF β-CELL MASS AS ADAPTIVE MECHANISM

Changes in the mass of pancreatic β-cells are certainly an important adaptation to changes in insulin resistance. For example, an increase in β-cell mass is present in the insulin-resistant state of obesity. During any given 24-h period, an obese individual will secrete considerably more insulin than a thin person (13). How much of this increase can be accounted for by an increase in β-cell mass, and how much can be accounted for by increased secretion from a given fixed mass? As suggested above, there could even be an increase of insulin output from a discrete subpopulation of β-cells. Nonetheless, changes in β-cell mass can occur rapidly. For example, when adult rats are infused with large amounts of glucose for 96 h, there is a 50% increase in β-cell mass (14). Some of this results from β-cell hypertrophy and some from cell division. There are probably impressive variations in β-cell mass during a lifetime, even during relatively short periods. A sedentary accountant who weighs 200 lb might become inspired, drop his weight to 160 lb, and become a marathoner. His insulin sensitivity would dramatically increase, plasma insulin levels might fall by 75% (15) and pancreatic β-cell mass might also fall by some unknown large factor. Even in more common situations, there might be meaningful changes in β-cell mass during a week of starvation or dietary overindulgence.

PANCREATIC β-CELL MASS IN DIABETES

Assessment of β-cell mass in human diabetes is limited to autopsy studies, which usually suffer from inadequate clinical information. There is agreement, however, that there is a marked reduction of β-cell mass once insulin-dependent diabetes mellitus (IDDM) is fully developed. It is not known, however, how much β-cell loss is required for diabetes to develop. There is a considerable amount of interest in the prediabetic phase of IDDM, and during this period, individuals may have islet cell antibodies, anti-insulin antibodies, and a loss of first-phase glucose-induced insulin secretion (16). This secretion defect is thought to develop shortly before frank hyperglycemia is found. How much β-cell mass remains at this stage is unknown, and it may be between 10 and 30% of normal, based on animal studies (17,18) and the results of partial pancreatectomy in humans (19,20).

NIDDM is a poorly understood process that is usually strongly influenced by genetic background. The genetic basis of NIDDM is not known, but current conjecture and debate centers on the relative contributions of inherited β-cell...
deficiency and insulin resistance (21,22). Certainly, the insulin resistance of obesity is the major factor that leads to the expression of hyperglycemia, and yet diabetes is found in only a minority of people who are overweight (23). No matter how much of a driving force insulin resistance is in the pathogenesis, frank diabetes will only be found when β-cell reserve is exceeded. Much of the limited capacity for insulin secretion must depend on inadequate β-cell mass.

Pancreatic β-cell mass has been measured in NIDDM in several autopsy studies and has been found to average ~60% of normal (24,25). It might be thought that this amount of insulin-secreting tissue should be enough to prevent diabetes, but there are some factors that may help explain this paradox. The quantity of insulin that is released by this mass of β-cells in response to even nonglucose stimulation is reduced. For example, maximal stimulation of secretion with arginine and glucose in NIDDM produced an insulin response that was only 15% of normal rather than the 60% that might have been expected (26). Another factor that might turn out to be important is the amyloid deposition often found in the islets of subjects with NIDDM. This amyloid has recently been found to be made up of the peptide amylin, which is synthesized in β-cells (27,28). Perhaps these amyloid deposits somehow limit insulin secretion. In any event, some of this reduced secretion is thought to be secondary to the adverse effects of chronic hyperglycemia (22), and improvement in secretion is seen when glucose levels are lowered by diet, sulfonylureas, or insulin (29–31).

There are also qualitative abnormalities of secretion that are presumably important. In both NIDDM and IDDM, the pancreatic β-cell fails to respond to an acute increase in the plasma glucose concentration, whereas secretory responses to various nonglucose secretagogues, e.g., arginine, isoproterenol, or glucagon, are at least somewhat intact (32,33). The capacity of glucose to potentiate the effects of nonglucose secretagogues is impaired (34). In addition, the proportion of proinsulin to insulin released by β-cells is increased (35). There is a considerable amount of work in animal-model systems suggesting that these abnormalities, which are partially reversible, are secondary to the effects of chronic hyperglycemia on the β-cell (12). Furthermore, in the nondiabetic state, there is a periodic oscillation of plasma insulin concentrations of 12–15 min, and these are lost in NIDDM (36). Some subjects receiving islet transplants in the future will have inadequate β-cell mass, and this deficiency may result in the same quantitative and qualitative defects of secretion as seen in NIDDM.

CONSIDERATION OF PARTIAL PANCREATECTOMY
It is often said that only 10% of the normal β-cell mass is needed to maintain euglycemia. This concept is based largely on surgical experience in humans and experimental animals in which a 90% pancreatectomy often does not cause diabetes (17,19). However, these surgical examples are misleading for at least three reasons. First, there can be considerable regeneration of β-cells; for instance, after a 90% pancreatectomy in rats, the mass of β-cells in the remnant increases to ~40% of normal in a few weeks (37). Second, removal of a large amount of pancreas leads to glucagon deficiency, which should make it easier for a marginal β-cell mass to keep glucose levels in a nondiabetic range (38). Third, loss of pancreatic exocrine secretion can lead to nutrition problems and weight loss, resulting in increased insulin sensitivity.

Further insight is obtained from subjects who have donated the distal half of their pancreas to a diabetic recipient. Follow-up of the graft donors reveals that many have glucose intolerance, and some develop frank diabetes (39). These findings must be interpreted cautiously. Virtually all of these donors were family members of recipients who had autoimmune IDDM. Perhaps some of the donors had incomplete subclinical autoimmune destruction, which resulted in diminished β-cell capacity. In addition, some members of this heterogeneous group of donors undoubtedly had insulin resistance with or without a genetic predisposition to NIDDM. These important lessons in humans make it clear that prospective donors for segmental pancreas transplants must be made aware of their increased risk of diabetes.

ISLET TRANSPLANTATION
A fundamental question about islet transplantation is how much β-cell mass is needed to produce normal glucose tolerance. This question is complicated by the fact that islet transplantation can theoretically be performed in countless ways. All of these will result in situations with abnormal anatomical and physiological relationships. There have been proposals that islets be placed into the liver, spleen, brain, testes, peritoneal cavity, kidney, muscle beds, and subcutaneous spaces; the amount of required β-cell mass may vary considerably between these sites. To make things even more complicated, the islets could be from fetuses or young or old cadaver donors. Furthermore, the implanted islets differ considerably depending on how they are prepared, having different sizes and amount of contamination with exocrine tissue. Islets from other species—pigs, cows, rodents, and even fish have been suggested—enclosed in immunobarrier devices such as capsules and hollow fibers might be transplanted (40,41). The question of how much β-cell mass is necessary is fundamental in all of these situations. A difficult problem centers on the immediate survival of the transplanted tissue. It is relatively easy to determine the amount of tissue that is implanted, but some amount will die, and the extent of this will depend on the form of the tissue, the technique of transplantation, and the site of implantation. For example, the laws of gas diffusion indicate the center of large islets or clumps of islet tissue will be vulnerable to anoxia. The amount of necrosis that takes place will depend on the number of large pieces grafted, the way they are implanted, and the rapidity with which vascularization occurs.

Little is known about growth of blood vessels in transplanted islets. Vessels appear to grow into islets from the recipient tissue bed, but the capacity of donor endothelial cells to contribute to this process is unknown (42). Extracellular growth and differentiation factors undoubtedly have profound effects on the implantation process. Sites in the liver, spleen, and peritoneum presumably have very different local environments, and the islets themselves no doubt bring their own paracrine and autocrine growth factors. In addition, fetal tissue grafting must be associated with a different but related array of interactions. Normal islets have a unique and highly specialized portal vascular system, but it is not known
if the same pattern will be recreated in transplanted islets (7). The delivery of insulin in high concentration to the islet mantle by intrasit blood flow is thought to be a critical determinant of glucagon secretion during changes in blood glucose levels (8,43). Neural influences on secretion in normal islets are important, and there is also the intriguing possibility that neural regulation of blood flow may affect islet function (44). How might these influences be altered during transplantation? The complexity of the normal islet is remarkable, and hopefully all of the important functions of islet tissue will be retained after transplantation.

To date, there have been no truly successful human islet transplants, and there has always been a question about whether enough islets have been used (45,46). A useful lesson has come from segmental pancreas transplants. The distal 50% of the pancreas can normalize plasma glucose levels in some recipients (47). Therefore, as a rough guide, 50% of the normal mass of β-cells, transplanted as isolated islets, should be successful. The β-cell mass of a normal pancreas from a human adult is ~700 mg. This mass is based on the assumption that the weight of the pancreas is 70 g and that the β-cell mass is 1% of the weight (48). Islet size is variable, but if all the islets were 150 μm in diameter—this being an average size—and if the β-cell mass of the islet were 70% of the whole, there would be ~600,000 islets per pancreas. Thus, the isolation of 250,000 islets of 150 μm diameter, or more islets with smaller diameters, would contain 40% of the β-cell mass of a normal pancreas and therefore be expected to come close to curing diabetes. Unfortunately, if some important percentage of the islets were lost to anoxia or some other process in the first few days after implantation, the amount of β-cell tissue would probably be inadequate. There has been concern that the presence of hyperglycemia during the immediate transplantation period could have an adverse effect on the success of the graft (49), but this problem should be preventable with insulin treatment. The effects of chronic hyperglycemia on an inadequate mass of β-cells pose a different set of problems. The hyperglycemia would be expected to cause a functional derangement in secretion, but it might also produce structural damage, which could lead to a further loss of mass (50). There are undoubtedly other nonimmune mechanisms that could contribute to the failure of a graft. Autotransplants in young dogs were found to be successful for only a short time; important questions about the reasons for the failure arise (51). At least one possibility is that the early success was caused by a mass of β-cells that was barely sufficient but did not have enough growth capacity to keep up with the gain of body weight as the dogs matured. It is comforting that islet transplants in rats can maintain near normoglycemia for substantial portions of the animals’ lifespan (52).

Immunological factors can be expected to have an important influence on the maintenance of islet mass and function during transplantation in humans. The mixed assaults of rejection and the original autoimmune (DDM process will be variably held in check by immunomodulation. The mechanisms of immune destruction are being rapidly clarified, and it is becoming apparent that the involved cytokines not only can kill islet cells but can adversely influence their secretory capacity (53). To make matters more problematic, it has been suggested that both glucocorticoids and cyclosporin have potential negative side effects on β-cells (54,55).

However, we should not become Cassandras because pancreas transplantation has enjoyed considerable success in the face of all of these insurmountable barriers. Transplantation of an apparent excess amount of β-cell tissue may be an eventual solution for the obligatory losses of cells that will presumably take place. This potential solution raises the question of autoregulation of β-cell mass. If excessive amounts of β-cell tissue are transplanted, there would be atrophy or some kind of functional downregulation of insulin secretion so that normoglycemia rather than hyperglycemia would occur. This assumption is based on the finding that insulinomas causing hypoglycemia are associated with atrophy of the β-cell portion of endogenous islets (11). It is unclear what would happen to the mass of α-, δ-, or PP cells, but there is some evidence that autoregulation of α-cell mass occurs (52). Nonetheless, implantation of an excessive amount of tissue has attractive features. The immediate loss of tissue that might occur could be withstood. There would be enough autoregulation of the β-cell mass to prevent hypoglycemia and maintain euglycemia. Finally, there might be enough regenerative capacity to allow long-term survival of the graft.

The lack of any successful human islet transplants has been very frustrating for participants and observers. There may be some immunological advantages to the use of pooled multiple donors (56), and it is now possible to freeze islets (57). Perhaps it is time to give some patients with diabetes a clearly excessive number of islets. There is much that could be learned from such an approach, and some success would energize a search for ways to find or make more islet tissue. Insufficient β-cell mass is clearly fundamental to the pathogenesis of both IDDM and NIDDM, and the quest for ways to restore this deficit is an endeavor of critical importance.

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