Pancreatic islet transplantation: studies on the technique and efficacy of islet isolation and transplantation

Burg, M.P.M. van der

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of islet isolation and transplantation

Michel P.M. van der Burg

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Dedicated to my parents
Sonja
Esther and Yorick

Cover — Isolated canine islets of Langerhans stained by dithizone, obtained using the University of Wisconsin solution during isolation and purification in Percoll gradients (illustration by the author).

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Preface

Pancreatic islet transplantation aims to prevent, postpone or ameliorate the long-term crippling complications of insulin-dependent diabetes mellitus (IDDM), which affects 0.2-0.4% of the population in industrialised countries. In these patients a high blood sugar level is the consequence of destruction of the ß-cells in the islets of Langerhans, which normally produce the insulin that is required to regulate the blood sugar level. The human pancreas contains roughly 1 million of these islets — which are up to 0.5 millimetre in diameter, and together weigh approximately 1 gramme. Conventional treatment with daily insulin injections in IDDM patients sustains the patient's life, but usually does not prevent a chronic high blood sugar level which after 20-30 years may cause serious damage to vital organs — and may lead to e.g. blindness, kidney failure requiring dialysis or a renal transplant, and lower limb amputations. The overall morbidity accounts for a one-third reduction of the life expectancy of IDDM patients. Considerable efforts are focused on the education of patients for self-control, and the development of new insulin injection or infusion devices to normalise blood sugar levels. The current insulin therapies, however, do not mimic the moment-to-moment control and adjustion of insulin secretion by the normal islets. At present pancreas transplantation is the only way to reach long-term normal blood sugar control in diabetic patients. With a well functioning graft, the progression of most complications is halted or reversed, and the patient's quality of life improves, primarily by eliminating the need for frequent insulin injections and blood sugar measurements. Because transplantation of the pancreas requires major surgery and life-long immunosuppressive therapy, this operation is, in general, only considered for the minority of IDDM patients who need a kidney transplant for renal failure. Since the pancreatic islets produce the insulin, and since the islets can be isolated from the pancreas in the laboratory, transplantation of only the islets appears a more rationale approach. Islet transplantation potentially offers many advantages over pancreas transplantation. Because of the small size and volume of the islets, implantation of isolated islets is simple and safe, consisting of little more than an injection of a few millilitres of a suspension. Further, the islets can be stored frozen in 'banks' or cultured allowing a host of manipulations in the laboratory prior to transplantation, to lower or eliminate the need for anti-rejection drugs. Since 1989 over 100 islet transplants in diabetic patients were attempted, and 15 % of these patients could stop insulin administration temporary. Thus, the feasibility of this approach has been established, but many problems need to be solved before wide-spread application of this technique in IDDM patients before the onset of the devastating complications will become available. It was this future prospect which initiated the studies presented in this thesis.

Contents