

*For debate***Pancreatic transplantation: why, when and who?*****P.J. Lefèbvre**

Division of Diabetes, Nutrition and Metabolic Disorders, Department of Medicine, University of Liège, Liège, Belgium

At the Third International Congress on Pancreatic and Islet Transplantation held in Lyon, France in June 1991, D. Sutherland who keeps the International Pancreas Transplant Registry stated that from December 1966 through 30 May 1991, 3207 pancreas transplants in diabetic patients had been reported. A detailed analysis of the world results of 2871 pancreas transplants performed at the cutoff date of 21 October 1990 has just been published [1]. Pancreas transplantation cases have been reported by 144 institutions to the Registry since 1966, including 80 in North America, 48 in Europe, and 16 elsewhere. While reporting to the Registry is mandatory in the United States, it is not elsewhere. Sutherland estimates that 60% of all transplantations performed in the United States, and 40% of all performed elsewhere have been reported to the Registry.

As reflected in the correspondence section of a leading medical journal [2–4], indications for performing pancreas transplantation in diabetic patients remain the matter of a passionate debate. Is it possible today to answer the crucial questions [5] of why and when pancreatic transplant should be performed, or may be considered, and in which patients it should be envisaged?

Pancreatic transplantation: why?

The answer to this question is probably different, at least conceptually, for the surgeon, for the internist and for the patient.

Over the last 30 years, surgery has entered an extraordinary new era. The often desperate surgery of amputation, mutilation and destruction has progressively been

transformed to a surgery of repair, reconstruction and replacement. Transplantation surgery is the latest example of this transition. Many patients, who were dying of end-stage heart failure or of fulminant hepatitis, are alive and well today thanks to a heart or liver transplant. Thanks to kidney transplant, numerous patients have recovered a quality of life they had forgotten during years of 3 days-a-week haemodialysis. Every transplantation surgeon who understands diabetes, who has realized the constraints that interfere with the everyday life of a young patient on multiple daily insulin injections, and who has seen the terrible outcome of the disease in many patients (blindness, amputations, kidney failure, coronary heart disease, stroke, to list only a few) must be tempted to see if he can do better [6].

Today, the internist (sometimes before him the paediatrician) is responsible for the care of the diabetic patients. This is a formidable task that requires a scientific mind, devotion and tenacity. Sometimes, the exercise looks like a lottery. The physician does his best for all his patients, he teaches them, trains them, monitors their therapy, uses the best insulins available, recommends multiple injections a day, tries a portable insulin pump and, finally has patients who have done their best and still present after 10, 15 or 20 years of diabetes with severe complications, while others, sometimes less compliant, and indeed not so well-controlled, are still healthy after 50 years or more of the disease [7]. Whilst there are epidemiological indications [8, 9] that good blood glucose control helps to reduce the incidence of microvascular complications, on an individual basis nobody at present can predict which patient will follow the first track, and which one the second [10]. The internist too is tempted to do better and thinks about, or dreams of, pancreas (or islet) transplantation as the ultimate achievement in substitution therapy. Finally the patient. Here, and this is probably the most difficult problem, patients ask for transplantation. The adolescent, who is told that he has diabetes because his/her pancreas does not produce insulin anymore and that insulin injections are now needed, almost inevitably asks why “a graft” is not possible. The adult diabetic patient, who fears hypoglycaemia, the discomfort of today, as hyperglycaemia,

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The section “For debate . . .” is open to contributions dealing with issues of a particularly debatable nature in diabetology. Contributions are published either standing by themselves or accompanied by invited comments. Other comments from the readership may be published as Letters to the Editor. Manuscripts intended for publication in this section of the journal are accepted at the discretion of the Editor-in-Chief and may be subject to a referee procedure.

the insidious danger of tomorrow, and who sees that, despite considerable efforts, he has to face both, the patient who has read about pancreas transplantation, will ask his physician if it is not intended for him. So to the question "Pancreas transplantation, why?", the answer is: for the surgeon because he can do it, for the internist because he is not always satisfied with what he achieves today, and, for the patient, because he has the hope that a pancreas transplantation will "cure" diabetes. In fact, all three are probably right in principle, but, in the reality of the early 1990's, all three are wrong [to a large extent]. Pancreas transplantation today is only for a minority of the diabetic patients, so the next two questions: when and who?

Pancreas transplantation: when?

The obvious answer is: not too early, not too late. Our knowledge of the aetiology of Type 1 (insulin-dependent) diabetes has greatly increased over the last few years. The disease is autoimmune in nature and occurs in genetically predisposed individuals [11, 12]. Protocols are under development to identify individuals at risk, and, to further identify the subjects in whom the disease is in progress at the subclinical level. Experts consider that tools will be available, probably before the end of this century, to prevent the occurrence of diabetes before the onset of the clinical manifestations of the disease [13]. When diabetes is manifest, a large percentage of the islet Beta-cell mass is already destroyed [14] and, despite promising early results [15, 16] immunotherapy at this stage is unable to prevent progression of the disease or even to reverse it [17]. If and when diabetes can effectively be prevented, then pancreas (or islet) transplantation should be considered only for those who have already developed diabetes and for those, hopefully few, who will escape prevention of the disease. If we exclude islet transplantation from the debate, we return to the "not too early, not too late" problem mentioned earlier. Let us consider "not too late" first. There is evidence today that a pancreas transplant will not reverse advanced retinal [18, 19] lesions. In contrast, there are some indications that progression of diabetic neuropathy [20] and nephropathy [21] may be halted through the restoration of a euglycaemic state by successful pancreatic transplantation. "Not too early" is not a matter of a given number of years: the time scale is probably not the same for all patients. As long as medical management is successful, that adequate metabolic control is achieved, that quality of life is good and that major complications do not occur, there is no indication at present for a pancreas transplant. Obviously, at this time, further considering the question "when", simultaneously requires considering the question "who".

Pancreas transplantation: who?

One may consider this question as ambiguous. Does "who?" mean "what patient?" or "what surgeon?"

Let us consider "what surgeon?" first. In this particular field, the responsibility of the physician towards the patient is great. The situation is very different from that of heart or liver transplantation where, on good indication, non-intervention indeed equals sentence to death. In the case of pancreatic transplantation the procedure carries a risk (for 1986–1990, the one-year patient survival rate was

89% and the one-year graft survival rate was 62%) [1], the immunosuppressive treatment carries a risk, and the life of the patient is not in immediate danger. Would it not be reasonable to agree that, in the early 1990's, 25 years after the pioneer case reported by Kelly et al. [22], pancreas transplantation should only be performed in specialized centres and by specialized surgeons working together with interested internists? The concerns of Tattersall [3], who wrote that "the situation threatens to arise in which surgeons in small units will perform the operation for unspecified indications in response to pressure from patients", are probably justified.

Next, the crucial question, "what patient?". The only answer is: for the patient who will benefit from it, in terms of longevity, morbidity and quality of life. There is so far evidence to suggest that, in some patients, pancreas transplantation may improve survival. For instance, it is usually accepted that diabetic patients with abnormalities in cardiorespiratory reflexes have increased frequency of sudden death and increased overall mortality rates [23]. Navarro et al. [24] have shown that the 84-month survival rate of patients with abnormal cardiorespiratory reflexes was significantly better after successful pancreas transplantation than when a pancreas graft had failed or transplantation was not performed. In terms of morbidity, several studies have shown improvement of diabetic neuropathy after successful pancreas (or pancreas plus kidney) transplantation [20, 25–27]. As far as retinopathy is concerned, the Minnesota group [18] reported that pancreas transplantation and subsequent normoglycaemia neither reversed nor prevented the progression of diabetic retinopathy, in addition the Munich group [19] recently reported that pancreas transplantation failed to improve late stage diabetic retinopathy in patients followed up for 3 years. Furthermore, they have emphasized that "periods of destabilisation that occur in some patients who experience multiple rejection episodes are a definite threat for retinopathy". Quality of life has been objectively and scientifically investigated by several groups. Improvements in quality of life after pancreas transplantation, often associated with kidney transplant, have been recently reported from Minneapolis [28], Stockholm [29], Munich [30] and Boston [31], with indications that quality of life was better after combined kidney-pancreas transplant than after kidney transplantation alone.

In view of these considerations is it possible to answer the question "who should be offered a pancreas transplant today?" It is obvious that the situation of the patient, who has reached end-stage diabetic nephropathy, is different from that of the patient who has not. Nathan et al. [31] have recently compared the outcome of 33 pancreas *and* kidney recipients to that of 18 diabetic recipients of kidney transplant alone, performed over the same time period. General quality of life improved significantly both in pancreas plus kidney and kidney alone recipients but quality of life specifically concerning diabetes-related problems improved only in the pancreas plus kidney recipient group. However, pancreas plus kidney recipients required hospitalization twice as long for transplant surgery and twice as many readmissions for a variety of complications. Overall mortality was similar in the two groups. From that [31], and from other studies [3], it is reasonable to suggest that pancreatic

transplantation should be considered when a kidney transplantation is decided for a Type 1 diabetic patient. However, such double transplants should only be performed [1] in patients whose general condition and cardiovascular status are satisfactory and [2], as mentioned above, by medico-surgical teams qualified for this type of operation. Another group is patients who have already successfully received a kidney transplant and in whom a pancreas transplantation is envisaged. In the International Pancreas Transplant Registry [1], 223 such patients (or 7.8% of the total) were included at the cutoff date of 21 October 1990. The major argument in favour of such a pancreas transplantation in such patients is that they are already receiving immunosuppressive therapy for their kidney transplant. Analysis of the registry figures shows that those patients have a lower pancreas graft function rate (45% at one year) vs those having simultaneously received pancreas and kidney (68%). The reasons for pancreas graft failure in these patients should be analysed in more depth and indications for adding a pancreas transplant to a patient who has already successfully received a kidney transplant should be defined more precisely.

The most difficult question is, however, that of the indications for solitary pancreatic transplantation before end-stage diabetic nephropathy [33–34]. Referring to the Registry [1], 221 such patients have had such transplants up to October 1990, representing some 10% of all the reported transplanted cases both in North America and in Europe. It is precisely for this category of patients that the great debate has been opened. To the question “is pancreatic transplantation, when used alone and prior to end-stage renal disease, (A) a safe and (B) an effective method of preventing progression of diabetic nephropathy”, a panel of 26 specialists (10 surgeons, 8 endocrinologists, 1 gastroenterologist and 7 nephrologists) recently considered that the procedure was investigational (13), doubtful (6), promising (5) and unacceptable (2). In fact, results of a completely successful pancreas transplantation are quite remarkable with a full normalization of blood glucose profiles and HbA_{1c} levels [36–39]. Such results are almost never achieved by insulin intensive therapy [40] using multiple insulin injections or insulin infusion pumps, a situation which is undoubtedly due to the fact that in most cases insulin is injected, or infused, in the wrong place, in wrong doses and at wrong times. The decision to undertake a pancreas transplantation in a diabetic patient who is not in end-stage renal failure is probably one of the most difficult to make. As a guideline, one may follow the University of Michigan Transplant Evaluation Committee [41] which has stated “candidates are selected who have predictors of future morbidity and mortality but who do not yet demonstrate irreversible neurovascular complications and an inexorable general course of deterioration”. Precise criteria to evaluate the candidates who meet these principles have been designed and published [41]. Candidates should have insulin-dependent diabetes, be aged 18–50 years, have a sufficient cardiac reserve and express a thorough understanding of the risks and benefits of the procedure. Inclusion criteria are one of the following: (1) established diabetic nephropathy with persistence of creatinine clearance above 60 ml/min; (2) proven autonomic neuropathy; and (3) labile diabetes/“failure of in-

sulin therapy” with repeated episodes of hypoglycaemia and/or diabetic ketoacidosis, requiring prolonged or repeated hospitalization. Interestingly, no form of diabetic retinopathy alone was considered as inclusion criteria. Exclusion criteria, one being sufficient are: advanced nephropathy, uncorrectable coronary artery disease, major psychiatric illness, ongoing substance abuse, active infection, active peptic ulcer disease or cancer, unless cured or without recurrence for more than 5 years. Such criteria are similar to those used by the University of Minnesota group [34], the leading centre in solitary pancreas transplantation [32, 33].

So to the question “What patient for a pancreas transplantation?” (12) one may consider answering:

1. In a patient with end-stage diabetic nephropathy, simultaneous kidney and pancreas transplantation *should* be envisaged; this is an *a priori* indication; a decision to perform the kidney transplant only should be essentially based upon the presence of contraindications for this type of major surgery;
2. In a patient who has already successfully received a kidney, pancreas transplantation *may* be considered but there is a great need to better define this indication;
3. In the patient who does not require a kidney transplant, pancreas transplantation should only be done on an investigational basis, in carefully selected individuals, by medico-surgical teams who continuously aim at improving their techniques, evaluating their results and confronting these with those obtained by their peers all over the world, like they did in Lyon in June 1991.

In conclusion, for the past 25 years the surgeons have joined the team of the internists to attempt to improve the results of the management of insulin-dependent diabetes mellitus. Pancreas transplantation has been performed, and the results carefully analysed in more than 3000 patients world wide. Over the last 3 years, the one-year patient survival rate is over 90% and more than two thirds of the patients have a functioning graft one year after surgery [1]. Pancreas transplantation resulted in increased longevity, lower morbidity and better quality of life in many patients [42]. In many others however, particularly in the early times, it resulted in peri- and post-operative death, in multiple rejection episodes requiring hospitalisation, in transplant failure and in a return to insulin injections, not to speak of the psychological, sociological and financial consequences of these events. Whole organ or segmental pancreas transplant has been an important step in diabetes management and one should acknowledge the efforts and tenacity of all those involved in this enterprise. The future goal with respect to Type 1 diabetes is prevention of the disease which may well be achieved before the year 2000 [13]. For those who have established insulin-dependent diabetes, the future is better replacement therapy, which will probably be best achieved by transplantation of isolated islets [43–45], Beta cell transplants [46] or bioartificial devices [47]. If this is confirmed, patients and physicians in 10, 15 or 20 years from now should respectfully remember those patients and physicians, who, in the last third of the twentieth century, have established this milestone in diabetes management that has been pancreas transplantation.

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Dr. P.J. Lefèbvre
Diabetes, Nutrition and Metabolic Disorders Unit
C. H. U. Sart Tilman (B 35)
B-4000 Liege 1
Belgium