PART XIX

GUEST LECTURE

Chairmen:   H Brynger
            J P Squifflet
KIDNEY AND PANCREAS TRANSPLANTATION IN MAN: THE CURRENT POSITION

P McMaster, W A Jurewicz, B K Gunson, L Angrisani, R M Kirby
Queen Elizabeth Hospital, University of Birmingham, Birmingham, United Kingdom

Introduction

Sixty years after the experimental work to produce a pancreatic extract to control hyperglycaemia, controversy continues as to the precise credence to be contributed to the individual workers involved [1]. While Banting and McCloud received the Nobel Prize for their developmental work and the introduction of insulin into clinical practice, each promptly shared his award with his co-worker Best and Collip. In addition many, especially Europeans, felt that the pioneering contributions by men such as Paulesco should more fully have been recognized.

That such controversy should continue even at this late stage attests to the medical importance attached to insulin’s introduction into clinical practice and the dramatic change it produced in what had been a lethal condition. Who at that time in the early 1920s would have foretold that within a decade it would become clear that although the immediate deaths due to ketoacidosis had been overcome, the misery of micro- and macroangiopathic complications would only ensue.

In spite of many therapeutic developments in the management of diabetes mellitus (type I) it continues to present a major health problem. In the United States of America there are some 5.5 million diabetic patients who account for a third of all hospital consultations and admissions and diabetes is a major factor in the increasing frequency of coronary artery bypass surgery and peripheral vascular disease [2].

Diabetes mellitus is a complex condition resulting in failure of multiple systems; blindness in 5,000 new patients a year in the States due to diabetes is estimated at a cost of approximately 45 million dollars. Nearly one in four dialysis patients in North America are diabetic, representing a 17-fold increased risk factor of renal failure when compared to non-diabetic patients at an annual estimated cost of some 500 million dollars.

In Europe diabetic patients in renal failure have received less attention and although the overall numbers treated has risen from two per cent of treated
uraemic cases in 1972 to seven per cent in 1983, in some countries who have continued to underfund their renal failure programme, diabetic treatment has been limited [3].

Treatment of diabetic patients in renal failure continues to be problematical because of the multiple system failure and patient survival is inferior to non-diabetic patients at three years on haemodialysis (39% versus 68%) and after transplantation (65% versus 80%) [4]. Even centres, such as the University of Minnesota, who by their outstanding contribution have played such a major part in establishing renal failure programmes specifically designed for diabetic patients, continued to find patient survival of diabetic patients at two years inferior after cadaveric renal transplantation (68% versus 75%) [5].

From the above introduction it must seem clear that there can be little grounds for complacency in treating diabetic renal failure.

The rationale for pancreas transplantation

Ideally, optimal therapy for a diabetic patient would be aimed at re-establishing normal carbohydrate control with the prevention of macro- and microangiopathic complications. Such a form of treatment does not exist.

Increasing evidence suggests that carbohydrate control plays an important role in determining the extent and rate of progression of diabetic complications. Continuous subcutaneous insulin infusion significantly improves carbohydrate control for many diabetic patients when compared to traditional insulin injection therapy and may improve both peripheral nerve conduction [6] and reduce albuminuria [7]. However, improvement in retinal damage is less clear. Other evidence that carbohydrate control is critical in the development of microangiopathic lesions comes from the observation that a kidney transplanted from a non-diabetic into a diabetic recipient within a few short years, develops clear diabetic sclerotic damage [8]. Here the inherited and genetic predisposition can clearly have no role.

While ultimately islet or direct beta cell transplantation may become a practical proposition, the formidable technical problems in harvesting an adequate number of viable islets compounded by their aggressive destruction in the host, must mean that significant developments in both technique and immunology will be needed before successful programmes can be established in man.

For the present, therefore, pancreatic transplantation is likely to be confined to solid organ replacement and may offer the prospect for the patient of not just the withdrawal of exogenous insulin injections, but an important improvement in quality of carbohydrate control and of life style (Table I). At the same

<table>
<thead>
<tr>
<th>Rationale</th>
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<tr>
<td>1. To resolve the clinical syndrome of diabetes and improve quality of life.</td>
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<tr>
<td>2. Normalize carbohydrate control; delay or prevent microvascular complications.</td>
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time the improved carbohydrate control may play a part in delaying the development or progression of microangiopathic complication. Clearly, if safe techniques could be developed to achieve these objectives combined with safe immunosuppression, then pancreatic replacement might form an integral part in the treatment of large numbers of diabetic patients.

**Kidney and pancreas transplantation**

Although the first attempts at pancreas transplantation in man were undertaken nearly 100 years ago, it was not until the late 1960s that the modern era of pancreas replacement began with the early combined kidney and pancreas transplants in Minnesota [9]. These early attempts at pancreas grafting resulted in few of these critically ill patients surviving 12 months after surgery.

However, at this time the procedure was clearly seen as experimental and so only those terminally ill uraemic diabetic patients were considered for the procedure. As a wider acceptance of treating diabetic patients was realized then ‘less ill’ diabetic patients have been considered for combined grafting and this clearly has resulted in the reduction of the unacceptably high mortality of the early procedures.

Nevertheless, it should at the outset be clearly admitted that pancreas transplantation is still very much in a developmental phase and requires significant improvement in both technique and immunosuppression before its wide application and introduction into clinical practice should be considered.

In the decade that followed the first pancreas transplant in 1966 60 pancreas grafts were performed and only two of these grafts functioned for longer than one year. Since 1977 over 500 pancreas transplants have been performed in man. In these patients a pancreas graft was implanted either simultaneously with a kidney graft (n=281) or subsequent to establishing a successful kidney transplantation (n=112). Such patients are exposed to the risk of both surgery and immunosuppression during kidney transplantation as part of their care of renal failure; clearly as techniques improve and transplantation of the pancreas becomes safer and more successful, more pancreatic implantation will be undertaken at a much earlier stage before ultimate renal destruction has occurred (n=106); however, at the present for the most part it has been undertaken in uraemic diabetic patients (n=393).

**Patient selection**

Table II shows the associated complications in diabetic patients at the University of Birmingham undergoing transplantation and simply serves to emphasize the extensive multisystem problem that these patients present. That coronary artery disease in diabetics is a fundamental problem has again recently been emphasized by Braun et al [10]. They noted that 21 per cent of their diabetic patients had over 70 per cent coronary artery occlusion and 42.9 per cent had greater than 50 per cent coronary artery disease! They clearly demonstrated in the long-term follow-up of diabetic patients that those who are not candidates
TABLE II. Diabetic complications
University of Birmingham: 17 diabetic patients 5–32 years

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage</th>
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<tr>
<td>Hypertension</td>
<td>93%</td>
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<tr>
<td>Myocardial</td>
<td>80%</td>
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<tr>
<td>Retinal</td>
<td>83%</td>
</tr>
<tr>
<td>Peripheral vascular</td>
<td>66%</td>
</tr>
<tr>
<td>Neuropathic</td>
<td>55%</td>
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<tr>
<td>Dialysis</td>
<td>100%</td>
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for coronary artery bypass and have extended coronary artery disease, are at major risk of having major myocardial infarction or death within 12 months of institution of renal failure therapy. The likelihood of progression to new infarction was nine times greater in those with over 70 per cent occlusive disease than those without, and often occurred soon after transplantation. Meticulous coordinated review and evaluation of patients presenting in uraemia is therefore clearly mandatory with progression to coronary artery studies in those showing severe left ventricular dysfunction on echocardiography or cardiac scans. In suitable patients coronary artery bypass should be considered and in those patients who are unsuitable minimal surgical therapy should be the objective in treating their renal failure. There would seem little benefit in undertaking relatively complex pancreatic transplants in those with major advanced cardiac disease.

Technical aspects

The successful establishment of pancreatic transplantation has been hindered by the formidable technical problems that need to be overcome and although there has been significant progress the results of pancreatic grafting remain inferior to other forms of transplantation. Undoubtedly one reason lies in the relatively high incidence of technical complications, the majority of which are associated with the exocrine secretion of the pancreas or vascular anastomosis and thrombosis. Initially pancreatic-duodenal grafts were used [9] but it was found that the duodenum itself could break down and cause complications and since these early studies a segmental pancreatic implant has been the most usually undertaken technique [11]. In this segmental graft the body and tail of the pancreas are removed using the splenic artery and vein as the vascular implantation vessels [12].

Controversy has surrounded the optimal technique for managing the pancreatic ductal exocrine secretion (Table III). Initial attempts involved drainage of the pancreatic duct into the intestine but were associated with a high incidence of major infective complications in an azathioprine high dose steroid regime [13]. In 1977 Dubenard et al described the technique of ductal injection using Neoprene [14] which produces occlusion of the ductal system and progressive atrophy and sclerosis of the acinar tissue. Although since that time other agents
TABLE III. Current techniques of exocrine management

1. **Ductal drainage:**
   A. Intestine
   B. Stomach
   C. Bladder/ureter

2. **Ductal occlusion:**
   Prolamine, neoprene or latex polymer

such as Prolamine and Polyisoprene have been used, the principle has remained the same in the majority of pancreatic transplants [15]. However, recent studies have suggested that ductal obliteration in the dog is ultimately associated with a substantial reduction in insulin producing capacity, probably associated with progressive sclerosis [16] and several centres have again been studying the technique of ductal drainage. Currently techniques exist for drainage of the pancreatic ductal system into either the bladder [17], small intestine [18] or stomach [19] to try to create a more physiological drainage system for the implanted pancreas. Recent analysis of the Pancreas and Islet Transplant Registry suggests that the three principal procedures afford approximately equal success as judged by one year actuarial graft survival; intestinal drainage \((n=155)\) gives a one year graft function of 41 per cent, urinary tract drainage \((n=47)\) 29 per cent and polymer injection \((n=260)\) 30 per cent [11]. Recent attempts at pancreatic drainage into the stomach have also afforded the opportunity to implant the pancreas directly onto the splenic artery and vein thus allowing a first phase pass of insulin directly into the portal system and liver [19]. The initial results appear encouraging with nine of 13 paratopically implanted grafts still functioning with an actuarial one year graft survival of over 50 per cent.

In an effort to increase the total islet cell mass implanted recently a further attempt at total pancreas implantation has been undertaken, with re-implantation of the duodenal segment [20]. As yet the number of patients transplanted with a total pancreas technique has been small \((n=79)\) and clear conclusions cannot as yet be made. One year graft survival is currently 33 per cent.

The incidence of pancreatic graft thrombosis has also been relatively high with nearly 15 per cent of implanted grafts failing within four weeks of implantation due to primary thrombosis. The relatively low perfusion characteristics of the implanted pancreas may lead to a low flow venous phase but both the introduction of anticoagulation in a distal splenic arteriovenous fistula failed to prevent this complication in all implanted grafts.

**Diagnosis of rejection**

The diagnosis of pancreatic rejection remains one of the fundamental problems facing implantation of a pancreatic graft. When pancreas and kidney are implanted
simultaneously the kidney may act as an excellent marker of immunological activity with the progressive rise of creatinine and reduction in urinary output acting as early 'markers' of immunological damage. At this time there is rarely a change in concomitant blood sugar concentrations and it is now clear that the development of hyperglycaemia comes in a late phase of immunological destruction of the pancreatic graft [21]. In such patients the monitoring of the graft can be undertaken by an estimation of C-peptide excretion from the graft, or, by direct biopsy or angiography although such techniques are both disturbing to the patient, invasive and are unlikely to be suitable for repeated screening. Initially encouraging results in the daily monitoring of pancreatic grafts using an injection of Indium labelled autologous platelets, in our own department, has proved a sensitive method of detecting early pancreatic allotransplantation [22]. The addition of gamma imaging also suggests a greater specificity of the test allowing differentiation between graft failure due to vascular thrombosis and early immunological damage.

In a number of series the true incidence of pancreatic destruction and rejection has proved difficult to assess because graft failure may occur for other technical reasons, and it will often do so insidiously without there being a clinical need for exploration (Table IV). The polymer injected graft may undergo progressive sclerosis and fibrosis resulting in graft failure and this is difficult clinically to differentiate from chronic progressive rejection.

<table>
<thead>
<tr>
<th>Diagnosis of graft rejection</th>
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<tbody>
<tr>
<td>1. Kidney as marker</td>
</tr>
<tr>
<td>2. Blood glucose ↑, C-peptide ↓</td>
</tr>
<tr>
<td>3. Angiography</td>
</tr>
<tr>
<td>4. 111I oxine platelet scan</td>
</tr>
<tr>
<td>5. Biopsy</td>
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Immunosuppressive protocols in the early pancreatic grafts with the need for administration of large doses of steroids represented a major drawback. Not only did the uraemic diabetic tolerate this poorly with a high incidence of infection, but frequently this produced profound carbohydrate disturbance making monitoring of the pancreatic graft extremely difficult. The majority of centres now undertaking pancreatic transplantation incorporate Cyclosporin A within their protocol and the pancreatic registry data (between 1977 and 1984) suggest that one year graft survival of technically successful grafts with Cyclosporin A may be superior to conventional immunosuppression with prednisolone and azathioprine (46% versus 26%, p<0.001) [11]. However, of course the conventionally treated patients fell in the earlier part of this series so that several developments may have occurred with the same time interval. Nevertheless the ability to prevent acute rejection of grafts without the need to administer significant quantities of prednisolone is clearly a major benefit, although preliminary
suggestions indicate that Cyclosporin A may block peripheral insulin receptors which may impair carbohydrate control [23]. For this reason and because of the difficulty in managing nephrotoxicity in the post-transplant phase one centre (Lyon) uses conventional treatment, prednisolone and azathioprine in the initial weeks after transplantation, only later to convert to Cyclosporin A.

**Overall results**

The clinical results of pancreatic transplantation remain disappointing although studies over the last 15 years have shown slow but progressive improvement in overall results. Patient survival rates for the period before 1977, between 1977 and 1983 and during 1983 alone are 39 per cent, 74 per cent and 77 per cent respectively. The overall corresponding graft survival rates for the same time intervals were 3 per cent, 20 per cent and 40 per cent respectively (Figure 1).

![Graph showing graft survival rates](image)

**Figure 1.** Functional graft survival for all pancreas transplant cases reported to the Registry by year of transplantation.

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In a recent survey we undertook of 11 European transplant centres engaged in pancreatic grafting, the overall one year patient survival was 83 per cent and the actuarial one year kidney graft survival 69.4 per cent. Overall pancreatic graft survival at one year was 33.8 per cent. However, if pancreas transplants only in those centres who have performed more than 10 transplants are considered the one year actuarial pancreatic graft survival approaches 50 per cent (Table V). At our own Institute one year patient survival is 82 per cent, kidney graft survival is 66 per cent and pancreas graft survival 44 per cent. A reduction in both patient survival in non-diabetic patients undergoing cadaveric grafts of 94 per cent and kidney survival of 79 per cent.

**TABLE V. Kidney and pancreas transplantation**

European Centres: one year per cent survival

<table>
<thead>
<tr>
<th></th>
<th>Patient</th>
<th>Pancreas graft</th>
</tr>
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<tbody>
<tr>
<td>Lyon (52)</td>
<td>64</td>
<td>40</td>
</tr>
<tr>
<td>Munich (41)</td>
<td>80</td>
<td>55</td>
</tr>
<tr>
<td>Stockholm (23)</td>
<td>84</td>
<td>58</td>
</tr>
<tr>
<td>Cambridge (23)</td>
<td>85</td>
<td>55</td>
</tr>
<tr>
<td>Birmingham (17)</td>
<td>82</td>
<td>44</td>
</tr>
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</table>

**Pancreatic complications and reasons for failure**

By far the most frequent cause of graft failure after pancreatic transplantation is rejection, followed by thrombosis, chronic graft failure probably associated with fibrosis and sclerosis in ductal injected grafts. However, in nearly one-quarter of patients graft failure is associated with infection or leakage associated with technical difficulties surrounding the exocrine secretion of the pancreas. While not infrequently this results in a relatively minor and clinically unimportant loss of fluid or wound infection, in some individuals a significant leakage can occur resulting in abscess formation requiring surgical intervention and drainage and graft removal (Table VI).

**TABLE VI. Pancreas transplantation**

<table>
<thead>
<tr>
<th>Reason for pancreas ‘failure’</th>
<th>41 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Rejection</td>
<td>41.5%</td>
</tr>
<tr>
<td>2. Death</td>
<td>36.4%</td>
</tr>
<tr>
<td>3. Thrombosis</td>
<td>19.5%</td>
</tr>
<tr>
<td>4. Infection</td>
<td>2.4%</td>
</tr>
</tbody>
</table>

Dubernard 1985
Carbohydrate control

Following pancreas transplantation the plasma glucose returns to normal quickly and all exogenous insulin administration can be discontinued. In all aspects the clinical syndrome of diabetes mellitus has been resolved with the absence of hyperglycaemia and glycosuria. Oral and intravenous glucose tolerance tests may be normal but in combined kidney and pancreas transplantation where a degree of renal impairment continues after grafting, a glucose tolerance test may resemble that of a maturity onset diabetic with delayed uptake of glucose and elimination [24]. Nevertheless in the presence of excellent renal function both oral and intravenous glucose tolerance tests are either normal or near normal [25], and satisfactory haemoglobin A1Cs and K values for glucose excretion in systemically draining pancreatic grafts is seen. Peripheral plasma insulin C-peptide may in fact be significantly elevated although hepatic glucose handling in such patients is normal.

As far as the question of whether the degree of carbohydrate control achieved by pancreatic transplantation will be sufficient to delay or prevent the progression of microangiopathic complications, only preliminary observations can be made. The number of pancreatic implants still remains relatively small and almost invariably they have been undertaken in those with advanced macroangiopathic complications, in whom it would be unlikely to see a rapid reversal of such extensive complications.

Retinal changes may be influenced by a number of factors including, of course, hypertension, a significant problem in the uraemic diabetic patient, and following implantation of both kidney and pancreas improvement in the retina or indeed nerve conduction studies which have been observed, may in a large part be associated with the resolution of the uraemia rather than in the improvement of carbohydrate control [26]. Perhaps more impressive has been the clear observation that kidneys implanted simultaneously with the pancreas do not develop the clear diabetic glomerular sclerotic changes seen invariably in normal kidneys implanted into diabetic recipients.

The future

It is now clear that increasing numbers of diabetic patients will enter renal failure programmes and improved dialysis and transplantation programmes must be developed. In experienced centres nearly half the pancreatic grafts will be functioning well at one year, although long-term survival has not yet been widely established. Nevertheless, a continued search and improved techniques of implantation associated with a modest improvement is needed before widespread introduction of pancreas grafting.

Already newer protocols are being studied in one or two institutions and may in part show the way forward. Recently in the University of Minnesota both the immunosuppressive protocol and the approach to pancreas transplantation has changed [27]. They have more recently been implanting pancreatic grafts into non-uraemic individuals and as might be expected, found them more immunologically competent than the uraemic individual. Twelve consecutive
non-uraemic, non-kidney transplant recipients of mismatched pancreatic allografts rejected the grafts quickly on a schedule of both Cyclosporin A and prednisolone. They are, therefore, now exploring combined immunosuppressive protocols incorporating both Cyclosporin A, azathioprine and prednisolone [27]. In those grafts technically successfully implanted, one year actuarial functional rate is now over 90 per cent on this triple therapy regime.

In addition they are now exploring the role of living related pancreatic donation to diabetic recipients. They have been able to establish that the body and tail of the pancreas may safely be removed from the donor leaving the spleen in place, from close relatives in whom the risk of development of diabetes is minimal because of a wide discordant period between the onset of diabetes in the recipient.

The outcome of these grafts from living related donors has been significantly higher than cadaveric grafts [27]. For HLA identical siblings donating a pancreatic graft the overall one year graft survival is 46 per cent although when only those technically successful grafts were considered, HLA identical graft success rate approached 75 per cent and from non-HLA matched siblings 43 per cent (Table VII).

| TABLE VII. Kidney and pancreas transplantation |
| University of Minnesota (1978–1984) |

<table>
<thead>
<tr>
<th></th>
<th>Patient One year per cent</th>
<th>Pancreas graft</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Overall results (83)</td>
<td>85</td>
<td>28</td>
</tr>
<tr>
<td>2. Cadaveric graft</td>
<td>77</td>
<td>20</td>
</tr>
<tr>
<td>Living related</td>
<td>95</td>
<td>46</td>
</tr>
<tr>
<td>3. Successful grafts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HLA—identical</td>
<td>–</td>
<td>75</td>
</tr>
<tr>
<td>Mismatched relatives</td>
<td>–</td>
<td>43</td>
</tr>
</tbody>
</table>

Nevertheless, with the triple therapy over 90 per cent of HLA mismatched technically successful transplants achieve one year functional survival.

Increasingly also they are turning to the non-uraemic patients whose diabetic complications are in a pre-morbid stage and who have not yet been subjected to dialysis or transplantation. Their current protocol incorporates the use of ductal drainage into the intestine to optimize physiological drainage, the administration of Cyclosporin A and prednisolone to HLA identical donor grafts, and Cyclosporin A, azathioprine and prednisolone to HLA mismatched recipients. In these non-uraemic immunologically competent recipients impressive survival is being achieved in those technically successful implanted grafts.
Conclusions

Results of pancreatic transplantation continue to be disappointing although significant improvements and developments over the last decade have resulted in the technique becoming safer and in part more successful. As greater numbers of diabetic patients are brought forward for transplantation improved techniques of kidney grafting will be required, combined with better immunosuppressive protocols and the quality of rehabilitation may be enhanced by pancreatic transplantation.

Only, however, when the techniques in immunosuppression reach an optimal stage will the use of pancreatic implantation in the non-uraemic patient, before extended diabetic complications occur, become a feasible reality.

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