LETTERS to the EDITOR

Pancreas transplantation or insulin?

SIR,—Your June 9 editorial half-heartedly endorses pancreas transplantation when combined with a kidney transplant for patients with type I diabetes and end-stage nephropathy. More enthusiasm is warranted. Transplantation of the pancreas simultaneously with a kidney is now so successful that it is a standard approach in the United States; more than seventy centres have had their programmes approved by the government-funded United Network for Organ Sharing, the organisation that coordinates all US transplant activity. Indeed, the latest Pancreas Transplant Registry report[1] shows the success rate to be even higher than that cited in your editorial. Of 237 pancreas/kidney transplants registered in the United States from Oct 1, 1987, to June 30, 1989, one-year patient survival and insulin-independent rates were 90% and 75%, respectively.

As pointed out in the editorial, end-stage diabetic nephropathy is best treated by a kidney transplant, obligating the recipient to immunosuppression; thus there is very little reason not to add the pancreas to achieve an insulin-dependent as well as a dialysis-free state. Your editorial gives prevention of secondary complications as the putative reason for pancreas transplantation, but that is a bonus; insulin independence and the attendant increase in quality of life is the main goal.[2,3] In diabetic patients with uraemia retinopathy and neuropathy are so advanced that a functioning pancreas may not help, even though recurrence of disease in the newly transplanted kidney is prevented.[4]

In non-uraemic diabetic patients it is another matter, and you ask the natural question—Why is pancreas transplantation so infrequently performed in this group?—giving low survival rates of functioning grafts in solitary pancreas transplants, and the side-effects of immunosuppression not otherwise required, as the reasons. Immunosuppression remains the main impediment, since the graft survival rates you cite are out of date. Once a procedure has been shown to work, it is only a matter of time before results improve and clinicians figure out how to make best use of it. This is the case with isolated pancreas transplants.[5] The registry of cases in the US (where almost all isolated pancreas transplants alone have been done) shows one-year patient survival and insulin-independence rates of 92% and 62%, respectively, in 63 non-uraemic recipients of solitary pancreas transplants from Oct 1, 1987, to June 30, 1989. Thus pancreas graft survival in non-uraemic recipients is currently double that referenced in your editorial. One reason for this improvement is the use of the bladder-anastomotic technique to drain the graft exocrine secretions, allowing enzyme activity to be directly measured in urine.[6] A decrease is an early marker of rejection and permits treatment and reversal before hyperglycaemia can occur.[7] Further improvement is likely, especially since the latest registry analysis shows that graft survival rates are significantly greater in recipients matched for both HLA-DR antigens with the donor.[1]

Disease recurrence is not a problem as long as the recipient is immunosuppressed, even with a living related donor graft. You are concerned about the metabolic effects of hemipancreatectomy in donors, but if the insulin response to a glucose challenge is above the lower thirtieth percentile of normal preoperatively, all the donors have remained within the normal range.[8] Furthermore, the changes in glucose tolerance are similar in magnitude to those seen in creatinine clearance after living related kidney donation,[9] and are probably not of any more consequence.

I agree that to apply pancreas transplants alone in non-uraemic patients there should be a benefit to secondary complications, but day-to-day quality of life should not be overlooked. Zehrer and Gross[10] studied 88 such patients, 44 whose grafts functioned for 1–10 years and 44 whose grafts had failed but were followed up for a comparable period of time. 93% of patients with successful grafts were generally happy while 61% of those who had reverted to the diabetic state because of a failed graft were unhappy. Of those with functioning grafts 93% felt they were more healthy than before the transplant, compared with only 22% of the other group. 62% of patients with functioning transplants felt that their diabetes had been more demanding of time and energy than the maintenance of the transplant; only 9% felt that the transplant and immunosuppression were more demanding than the diabetes had been. 95% of the patients whose grafts were functioning and 75% of those whose grafts had failed were comfortable with their decision to have a transplant. 71% of those with functioning grafts were certain that they would undergo a second transplant if the first failed, hesitation in the remainder stemming largely from uncertainty over whether their insurance would cover a second attempt.

I agree that for the non-uraemic diabetic patient with no known propensity for secondary complications and in whom insulin management is no problem, the substitution, via a pancreas transplant, is problematic. There is no assurance that the anti-rejection treatment will cause fewer complications than would evolve over time if the patient remained diabetic. There is, however, a subset of patients in whom the difficulties of being diabetic are such that a pancreas transplant should be an available option. Diabetics with problems today should not be denied today's treatments simply because there may be better treatments in future. Work with encapsulation of islet cells to prevent rejection without immunosuppression has been going on for 20 years, and one cannot tell a diabetic that success is just around the corner. The insulin gene is also not defective in most diabetics; for fibroblasts to take over from beta cells they will have to be manipulated for more than just the insulin gene.

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Small-bowel transplantation: European experience

SIR,—A case of successful small-bowel transplantation (combined with a liver graft) was recently described in *The Lancet*.[1] A few other encouraging reports have emerged over the past two years, notably from European centres. The Paris group, though they failed to

achieve graft survival in their first clinical case, were able to remove the rejected transplant without morbidity[2-4]—a major improvement on the fate of earlier recipients.[5]

The expansion in transplantation in terms both of organs used and recipient suitability has stimulated surgeons to reconsider small-bowel transplantation for patients permanently dependent on total parenteral nutrition (TPN), especially the few who have persistent complications such as catheter sepsis, major venous thrombosis, or parenchymal liver disease. Since March, 1987, fifteen small-bowel transplants have been done in 12 cases in Paris, Kiel, Innsbruck, and Uppsala. The patients ranged in age from 5 months to 49 years. Four grafts are currently functioning, and their recipients are entirely independent of parenteral nutrition, the first of these patients having been transplantated on Aug 9, 1988.[6] A recent graft (Dec 26, 1989) was part of a multiorgan transplantation of liver, stomach, pancreas, and 130 cm of small bowel in a patient who had had Whipple's operation for a carcinoma of the head of pancreas that encircled the superior mesenteric artery. Arterial replacement with a synthetic prosthesis had been followed by thrombosis. Two children aged 3 and 4 years were successfully transplanted in Paris, 15 and 4 months ago, respectively. Four patients with failed grafts remain alive on TPN; none has had significant intestinal adaptation to allow enteral feeding. Three patients have died—after cyclosporin-induced renal and hepatic failure, from pulmonary embolism more than 8 months after graft removal, and from graft rejection and fungal infection (a 14-month-old child).

All the patients were given cyclosporin and prednisolone prophylaxis against rejection and graft-versus-host reaction (GVHR), usually supplemented with azathioprine and antithymocyte or antilymphocyte globulin. Rejections have been successfully treated with intravenous methylprednisolone and antilymphocyte globulin. Opportunistic infection is often seen after such treatment and requires reduction in immunosuppression; on two occasions the intestinal graft has had to be removed because further immunosuppression would have resulted in overwhelming infection. Unlike Hoffman and colleagues[7] we feel that initial triple therapy, including cyclosporin, provides satisfactory immunosuppression; and in our opinion newer methods of reducing graft immunogenicity offer greater prospects for progress than switching to FK-506.

Two of the Kiel patients have received intestine from living relatives and two of the Paris paediatric patients have received bowel from anencephalic donors. The optimum length appears to be 120 cm of jejunoileum. Graft vessels were perfused with University of Wisconsin solution in most cases, the longest preservation being 10·5 hours. Every graft was in two stages (proximal anastomosis and distal enterostomy, or vice versa) and the graft mesenteric vein was drained systemically. Portal drainage has been inaccessible and is only suitable for patients undergoing multiorgan transplantation.

Graft monitoring has included daily multiple mucosal endoscopic biopsies during the early postoperative course, and thereafter twice weekly. The specimens have been subjected to routine histology, although immunohistochemical techniques will shortly replace this approach. Newer monoclonal antibodies are available which discriminate musocal lymphocyte subpopulations and brush border enzymes; the brush border is especially susceptible to immunological rejection.[8]

Technical difficulties accounted for many clinical failures in the early 1970s.[5] Two of the recent European transplants were too long for the very contracted peritoneal cavity and required segmental resection; thus donor and recipient size matching is important. There were no intestinal anastomotic leaks but a single case of anastomotic arterial rupture eventually led to graft removal. Serious cytomegalovirus infection was seen in two patients; this settled spontaneously in one and was treated by ganciclovir in the other. Rejection episodes, seen in every patient, were heralded by abdominal pain and fever. Two complications not previously recorded have been chronic acidosis (serum pH 7·1) in one patient and anaemia secondary to humoral GVHR in the long-term Kiel patient. Unforeseen practical problems have been encountered in children. The transplantation of neonatal intestine ideally requires a specialised diet of (breast) milk, not only to confer local and systemic immunity but also to permit normal mucosal maturation and adaptation in the first few weeks of life. The introduction of oral feeding in a child who has only known parenteral therapy requires psychological adjustment. Also one of the Paris children developed acute pancreatitis.

In February, 1989, the European Intestinal Transplantation Study Group had its inaugural meeting. The group promotes and coordinates experimental and clinical small-bowel transplantation and is developing a central registry of potential recipients. Careful selection and planning are vital if this treatment is not to fall once again into disrepute.

The president of the European Intestinal Transplantation Study Group is Prof E. Deltz, Department of General Surgery, Christian Albrecht's University, D-2300 Kiel, West Germany. The four centres responsible for the grafts reviewed here are: Kiel (Professor Deltz), Paris (Prof C. Ricour, Prof Y. Revillon, Hôpital Necker), Innsbruck (Prof R. Margreiter, University Hospital), and Uppsala (Dr G. Tufveson, University Hospital).

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Treatment of malaria with sulfadoxine/pyrimethamine: note of caution

SIR,—In the past decade, the use of a single dose of sulfadoxine and pyrimethamine ('Fansidar') alone in the curative treatment of uncomplicated malaria caused by *Plasmodium falciparum* has become widespread in Cameroon, where falciparum malaria is endemic and chloroquine resistance is well established.[1,2] Moreover, chloroquine is used indiscriminately and is sold without medical prescription. Indeed, fansidar is an attractive alternative treatment in view of its lack of side-effects, its low cost, and the simple dose regimen. We describe an 8-month-old infant living in Yaounde for the past 2 months and receiving regular weekly chloroquine antimalarial prophylaxis, who was referred for fever of 36 hours' duration.

The baby had a rectal temperature of 38·4°C but was playful, alert, and well nourished with no other pathological signs. He had 1500 *P falciparum* parasites per µl blood. A single dose of fansidar (sulfadoxine 25 mg/kg body weight) was given parenterally. 48 h after treatment a rapid deterioration in clinical status was noted with the appearance within 4 h of high fever (40·2°C), tachycardia (160/min), hypotension (50/30 mm Hg), severe chills, increasing pallor, jaundice, and splenomegaly. Intravenous fluids and quinine (10 mg/kg every 8 h) were started with progressive clinical improvement and the disappearance of parasites from blood after 24 hours. He had completely recovered and smears were consistently negative a week later.

This case illustrates an important pitfall in the treatment of uncomplicated *P falciparum* malaria with a slow-acting antimalarial drug such as fansidar, particularly in young vulnerable patients. It is noteworthy that the strict criteria for drug resistance to fansidar were not met in this patient.[3] Although well-documented cases of resistance to fansidar have not yet been described in Cameroon, the rapidly evolving resistance with the drug's widespread use in East Africa[4,5] suggests that its appearance is only a matter of time. In the