Intrahepatic islet transplantation and preserved insulin secretion

Transplantation of pancreatic islets, rather than whole pancreas, has been introduced as a treatment for diabetes mellitus. The authors studied five patients, ranging in age from 12 years to 37 years, who had severe chronic pancreatitis. All of them underwent total pancreatectomy followed by isolation and hepatic transplantation of their own islets.

All patients had remained insulin-independent for 1 year to 7.5 years after transplantation. The numbers of transplanted islets ranged from 110,000 to 412,000. Researchers assessed islet function by measuring the plasma insulin responses to intravenously administered glucose and arginine and the plasma glucagon responses to hypoglycemia and arginine. In one patient, islet function was studied during catheterization of the hepatic vein, portal vein, and splenic artery, and by analysis of a liver biopsy specimen.

After transplantation, the mean fasting plasma glucose concentration was 122 ± 47 mg/dL. The hemoglobin A_{1C} concentration was 6.0% ± 0.8% in the five patients. Most of the values were abnormal in the one patient who received only 110,000 islets. The acute plasma insulin responses to glucose and to arginine in the five patients were 23 ± 13 and 26 ± 10 μU/mL, respectively. Responses to glucose and arginine in control subjects were 58 ± 6 and 37 ± 8 μU/mL Peak plasma glucagon responses to insulin and arginine were 21 ± 4 and 65 ± 36 pg/mL, respectively, compared with 125 ± 28 and 156 ± 99 pg/mL in healthy subjects.

All five patients had plasma epinephrine but not pancreatic polypeptide responses to hypoglycemia. Results of the hepatic vein catheterization in one patient indicated that the transplanted islets released insulin and glucagon in response to arginine. Immunoperoxidase staining of this patient's liver biopsy specimen showed that the islets contained insulin, glucagon, and somatostatin but not pancreatic polypeptide.

Intrahepatic transplantation of as few as 265,000 islets can result in the release of insulin and glucagon at appropriate times and in prolonged periods of insulin independence, conclude the authors.

Pyzdrowski KL, Kendall DM, Halter JB, et al: Preserved insulin secretion and insulin independence in recipients of islet autografts. *N Engl J Med* 1992;327:220-226.

IV immunoglobulin: Prophylactic in HIV-infected children?

In this randomized, double-blind, placebo-controlled study, researchers compared the incidence of laboratory-proved and clinically diagnosed viral, opportunistic, and bacterial infections in 376 children infected with the human immunodeficiency virus (HIV). Of these children, 313 had entry $CD4^+$ lymphocyte counts of at least 0.20×10^9/L. Of these patients, 162 children received intravenous immunoglobulin every 28 days (400 mg/kg of body weight).

Viral infection and minor bacterial infections contributed more frequently to morbidity in children with entry $CD4^+$ counts of at least 0.20×10^9/L than did serious bacterial infection, the primary outcome of this trial. Opportunistic infections occurred at a rate similar to that of laboratory-proved serious bacterial infections.

In this group of children, the intravenous immunoglobulin therapy significantly decreased the rate of viral infections and minor bacterial infections per 100 patient-years. A decrease in the rate of serious bacterial infections per 100 patient-years also occurred. Researchers found no apparent difference in the rate of opportunistic infections between treatment arms.

These results indicate that intravenous immunoglobulin has a beneficial effect in multiple infectious outcome measures, particularly in serious and minor viral and bacterial infections in children with entry $CD4^+$ counts of at least 0.20×10^9/L.

Mofenson LM, Moye J Jr, Bethel J, et al: Prophylactic intravenous immunoglobulin in HIV-infected children with $CD4^+$ counts of 0.20×10^9/L or more: Effect on viral, opportunistic, and bacterial infections. *JAMA* 1992;268:483-488.

Efficacy of intravenous magnesium sulfate in preventing acute myocardial infarction

Magnesium has been reported to protect myocardial tissue in experimental models of ischemia and reperfusion. Although several small clinical trials in suspected acute myocardial infarction have suggested that early mortality can be

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reduced by intravenous infusion of magnesium salts in the acute phase, none has been large enough to be conclusive.

Therefore, the authors conducted a randomized, double-blind, placebo-controlled study in which 2316 patients were enrolled. Of these, 1159 patients were receiving intravenous magnesium sulfate, with the remaining subjects receiving physiologic saline solution.

The primary outcome measure was 28-day mortality, ascertained in 99.3% of the patients. Groups were well balanced for prognostic factors. Using intention-to-treat analysis, researchers found the mortality from all causes was 7.8% in the magnesium-treated group and 10.3% in the control group. These findings represent a 24% reduction. The incidence of left ventricular failure was reduced by 25% among patients in the magnesium-treated group. No significant difference was found between the groups in the incidence of heart block or the use of antiarrhythmic drugs, direct-current cardioversion, or temporary pacing. Myocardial infarction was confirmed in 65% of the patients in each group, with closely similar rises in cardiac enzymes.

Among the reported side effects in patients in the magnesium-treated group were transient flushing related to speed of injection of the loading dose and an increased incidence of sinus bradycardia. Exploratory subgroup analysis of 28-day mortality did not indicate any effect modification by thrombolysis or aspirin, or by previous treatment with β-blockers, calcium antagonists, or diuretics.

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Researchers conclude that intravenous magnesium sulfate is a simple, safe, and widely applicable treatment. Its efficacy in reducing early mortality associated with myocardial infarction is comparable to, but independent of, that found in thrombolytic or antiplatelet therapy.

Woods KL, Fletcher S, Roffe C, et al: Intravenous magnesium sulphate in suspected acute myocardial infarction: Results of the second Leicester Intravenous Magnesium Intervention Trial (LIMIT-2). *Lancet* 1992;339:1553-1558.

Transdermal estrogen as osteoporosis therapy inpostmenopausal women

Researchers set out to evaluate the tolerance and effectiveness of transdermal estrogen for women with diagnosed postmenopausal osteoporosis and vertebral fractures.

Seventy-five postmenopausal women, aged 47 years to 75 years, were enrolled in this double-blind, randomized, placebo-controlled clinical trial. All of the women had one or more vertebral fractures due to osteoporosis. Thirty-six women wore 17 β-estradiol patches (0.1 mg) for days 1 to 21. This same group received oral medroxyprogesterone acetate during days 11 to 21 of a 28-day cycle. The remaining 39 women received the placebo.

Researchers assessed bone turnover using biochemical markers and iliac bone histomorphometry; serial measurement of bone density and vertebral fracture rate was used to assess bone loss.

Compared with the placebo group, the median annual percentage change in bone mineral density in women in the estrogen-treated group reflected increased or steady-state bone mineral density at the lumbar spine, femoral trochanter, and midradius. However, no significant difference was found at the femoral neck. Estrogen treatment uniformly decreased bone turnover as assessed by several methods, including serum osteocalcin concentration. Histomorphometric evaluation of iliac biopsy samples confirmed estrogen's effect on bone formation rate per bone volume. Among the women in the treatment group, 7 women had a total of 8 new fractures, compared with 20 fractures in 12 women in the group receiving placebo.

Based on these findings, the transdermal estradiol treatment is effective in preventing further fractures in postmenopausal women with already diagnosed osteoporosis, conclude the researchers.

Lufkin EG, Wahner HW, O'Fallon WM, et al: Treatment of postmenopausal osteoporosis with transdermal estrogen. *Ann Intern Med* 1992;117:1-9.

Long-term benefits of cholestyramine in treating hypercholesterolemia

The Lipid Research Clinics Coronary Primary Prevention Trial included 3806 men, aged 35 years to 59 years, who had hypercholesterolemia but were asymptomatic. The trial was conducted between 1973 and 1983; follow-up occurred annually, from 1985 until 1989. The researchers did not provide posttrial treatment.

However, they did test 11 predefined hypotheses pertaining to the possible benefits and adverse effects of in-trial cholestyramine treatment in this population. They used standard statistical comparisons of the two original Coronary Primary Prevention Trial treatment groups (cholestyramine and placebo).

During the posttrial period, cholesterol-lowering drugs were used by a similar number of subjects in the treatment and control (placebo) groups. After 13.4 years of in-trial plus posttrial follow-up, 13 fewer deaths occurred among patients in the treatment group, compared with subjects receiving placebo. Although not statistically significant, the mortality hazard ratio was similar to that in other cholesterol-lowering trials.

This trend, a result of reduced coronary heart disease mortality, occurred despite a posttrial narrowing of the in-trial cholestyramine-placebo difference in coronary heart disease incidence from 32 to 16.

The cholestyramine-treated and control groups had similar 13.4-year mortality rates from cancer, other medical causes, and trauma and similar cancer incidence rates. However, incidence of benign colorectal tumors, cancer of the buccal cavity and pharynx, gallbladder disease, and gallbladder surgery were not significantly increased among patients receiving cholestyramine therapy during the 13.4 years of this trial and follow-up period.

Overall, 6 years of post–Coronary Primary Prevention Trial follow-up have not provided conclusive evidence of benefit or long-term toxicity associated with cholestyra-

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mine treatment beyond that found at the trial's end.

Lipid Research Clinics Investigators: The Lipid Research Clinics Coronary Primary Prevention Trial: Results of 6 years of post-trial follow-up. *Arch Intern Med* 1992;152:1399-1410.

Intracoronary dipyridamole infusion's effects on myocardial blood flow and intrinsic TI-201 washout in dogs with coronary stenosis

Intravenous dipyridamole (DP) infusion produces a significant endocardial-to-epicardial flow gradient distal to a critical coronary stenosis, resulting in diminished regional thallium-201 (TI-201) uptake and washout. Intravenous DP can also produce a significant decrease in arterial blood pressure and, therefore, in coronary perfusion pressure.

The authors sought to further clarify the mechanism of this transmural coronary "steal" using intracoronary DP administration to avoid systemic hypotension. Using dogs in this study, researchers found that intracoronary DP caused no significant drop in systemic arterial pressure in five of eight dogs with critical left anterior descending (LAD) stenosis. However, a rise in epicardial flow did occur, with a slight fall in subendocardial flow. Intracoronary DP did not prolong the intrinsic TI-201 washout rate.

In three dogs in which systemic hypotension developed after intracoronary DP, endocardial flow fell from 1.14 to 0.63 mL/min/g. Likewise, the epicardial/endocardial flow ratio fell to 0.35; TI-201 washout became more prolonged.

Thus, intracoronary DP in the setting of a critical LAD stenosis caused minimal endocardial-to-epicardial steal and had no effect on the intrinsic TI-201 washout rate unless it was accompanied by a fall in systemic arterial pressure.

The magnitude of the transmural steal was substantially less than that reported in the researchers' previous experiments, in which they used intravenous DP infusion. The current study provides further insight into the mechanism of DP-induced subendocardial ischemia. These results suggest that systemic hemodynamic alterations play an important role in the effects of the vasodilator on myocardial blood flow and TI-201 kinetics.

Beller GA, Granato JE, Cannon JM, et al: Effects of intracoronary dipyridamole infusion on regional myocardial blood flow and intrinsic thallium-201 washout in dogs with a critical coronary stenosis. *Am Heart J* 1992;124:56-64

Efficacy of β-adrenergic agonist ritodrine in treating preterm labor

Although treatment of preterm labor with β-adrenergic agonists can delay delivery by 24 hours to 48 hours, the potential risks and benefits to the mother and infant before and after delivery have not been adequately assessed.

To that end, investigators here assigned 708 women in preterm labor to receive an intravenous infusion of either the β-adrenergic agonist ritodrine (n = 352) or placebo (n = 356). The women were assigned with stratification according to four gestational age categories: 20 to 23 weeks, 24 to 27 weeks, 28 to 31 weeks, and 32 to 35 weeks. The researchers' primary objective was to assess the effect of ritodrine on perinatal mortality. Secondary objectives included the evaluation of the causes of perinatal death, specifically the extent to which delivery was delayed with ritodrine; and the effects this drug has on birth weight, maternal morbidity, neonatal morbidity, and infant morbidity at 18 months of postnatal age, corrected for preterm delivery.

Among the 771 infants born to women in this study, 23 deaths occurred in the ritodrine-treated group and 25 deaths occurred in the group that received placebo. No difference was noted between the groups in the extent of delivery delay, the incidence of delivery before 37 weeks' gestation, the proportion of infants weighing less than 2500 g, or measures of neonatal morbidity.

Maternal morbidity, such as chest pain and cardiac arrhythmias, occurred more frequently—but not exclusively—among women in the treatment group. One infant born to a woman in the ritodrine-treated group and five infants born to women in the control group had cerebral palsy. A slight—but not significant—trend toward an improved score on the Bayley Psychomotor Development Index was noted at 18 months of age among the infants of ritodrine-treated mothers.

Ritodrine has no significant benefit in the treatment of preterm labor, specifically on perinatal mortality, the frequency of prolongation of pregnancy to term, or birth weight, conclude the researchers.

Canadian Preterm Labor Investigators Group: Treatment of preterm labor with the beta-adrenergic agonist ritodrine. *N Engl J Med* 1992;327:308-312.

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Link between maternal prenatal nutrition supplementation, postnatal growth

Researchers conducted a controlled, randomized trial in Madura, East Java. In this trial, pregnant women received a high- or low-energy supplement during the third trimester that provided 465 kcal or 52 kcal, respectively. Researchers longitudinally assessed the children's growth for the first 5 years of the children's lives.

Mothers who complied for at least 90 days were included. Infants' growth was assessed at 4-week intervals from birth until 12 months. Thereafter, they were measured every 3 months.

Up to age 24 months, children who had received the high-energy supplementation diet prenatally were significantly heavier than children who received the low-energy diet. These same children were also taller than their low-energy diet counterparts throughout the first 5 years of life.Weight-for-height by age was similar in children in both groups, but stunting (height-for-age) was less prevalent in children who had received a high-energy diet prenatally.

Such suppplementation is beneficial, particularly among women characterized by chronic energy deficiency, conclude the authors.

Kusin JA, Kardjati S, Houtkooper JM, et al: Energy supplementation during pregnancy and postanal growth. *Lancet* 1992;340:623-626.

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