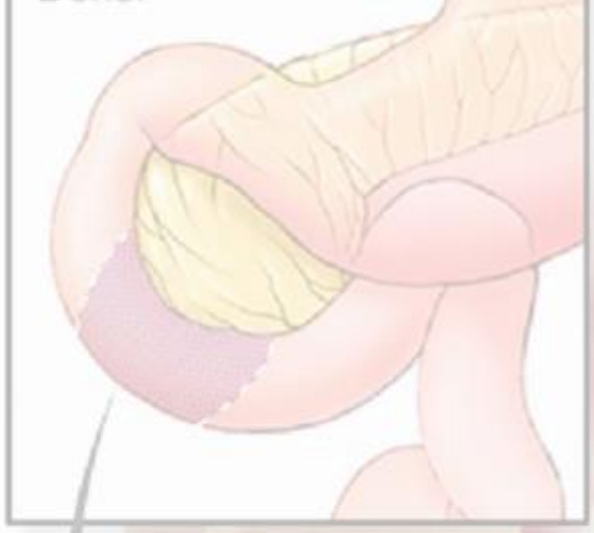


Recipient

Donor pancreas with portion of donor's small intestine

CURRENT CONCEPTS IN PANCREAS TRANSPLANT SURGERY

©2016

Contents

- History
- Introduction
- Criteria for transplantation
- Donor selection
- Contra-indications
- Evaluation
- Scope
- Surgical Aspect


INSULI
50 Units—5 C.C.
10 Units per C.
CONNAUGHT LABORATO
UNIVERSITY OF TORO


DHARMA
Diabetes & Metabolic Clinics
100
ENHANCED LIFESTYLE WITH
PANCREATIC ISLET TRANSPLANTATION
IN TYPE 1 DIABETIC

TABLE 82.1 Milestones in organ transplantation.	
1954	Joe Murray performed successful kidney transplantations between identical twins (Boston, MA, USA)
1962	Roy Calne demonstrated the efficacy of azathioprine in preventing rejection of kidney allografts (Boston, MA, USA)
1963	Tom Starzl performed the first human liver transplantation (Denver, CO, USA)
1966	Tom Starzl and colleagues used anti-lymphocyte globulin immunosuppression (Denver, CO, USA)
1966	Richard Lillehei and William Kelly performed first human whole organ pancreas transplantation (along with a kidney
1969	Geoff Collins developed Collins solution – a new kidney preservation solution
1974	David Sutherland and John Najarin performed the first human pancreatic islet transplantation (Minneapolis, MN, USA)
1978	Roy Calne introduced ciclosporin into clinical practice (Cambridge, UK)
1981	Bruce Reitz and Norman Shumway performed the first successful human heart–lung transplantation (Stanford, CA, USA)

On December 20, 1893, P. Watson Williams grafted three pieces of sheep pancreas into the subcutaneous tissues of a child with diabetes, who died 3 days later of unrelenting diabetic ketoacidosis

Bailey and Love 27th E, Pg:1533

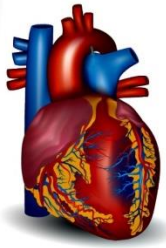
Introduction

- Insulin replacement can lead to acceptable control of blood glucose levels
- Secondary complications
- It also has been shown to lead to an increased number of ***dangerous hypoglycemic episodes***

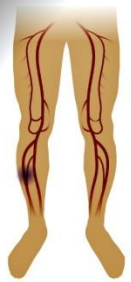
DIABETES COMPLICATIONS

STROKE

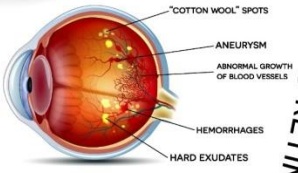
HEART ATTACK



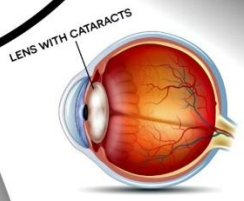
PERIPHERAL ARTERY DISEASE



DIABETIC RETINOPATHY

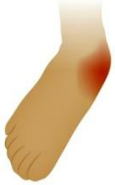


CATARACTS

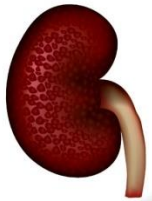


GLAUCOMA

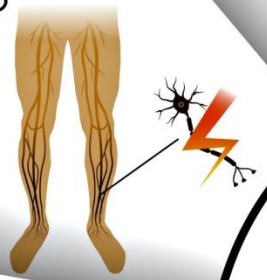
DIABETIC FOOT



DIABETIC NEPHROPATHY



PERIPHERAL NEUROPATHY



RESTORING NORMOGLYCEMIA

1. INTENSIVE INSULIN REGIMEN

2. INSULIN PUMP

3. TRANSPLANTATION OF INSULIN PRODUCING TISSUE- WHOLE PANCREATIC OR ISLET TRANSPLANTATION

- Neither pancreas nor islet transplantation is a life-saving intervention.
- The aim for both procedures is to prevent secondary diabetic complications and improve quality of life
- Therefore patient selection criteria are stricter than for other organ transplantation in order to protect patient safety and properly identify candidates who can benefit from the procedures

- Simultaneous Pancreas and Kidney (SPK)
- Pancreas After Kidney (PAK)
- Pancreatic Transplantation Alone (PTA)

- The American Diabetes Association (ADA) criteria for transplantation are as follows :

  ●**SPK or PAK** –

  – Patients with type 1 diabetes and end-stage kidney disease who have had or plan to have a kidney transplant are candidates for pancreas transplantation.

  – improve glycemia and improve kidney survival.

- **PTA** – in patients with serious progressive complications of diabetes in whom the quality of life is unacceptable. Such complications include:
  - A history of frequent, acute, severe metabolic complications (hypoglycemia, marked hyperglycemia, ketoacidosis)
  - Incapacitating clinical and emotional problems with exogenous insulin therapy
  - Consistent failure of insulin-based management to prevent acute complications

	SPK	PAK
Advantages	1.Single surgical procedure 2.Single cycle of induction immunosuppression 3.Better graft survival	1.Minimizes or avoids the need for dialysis (in LDKT) 2.Shorter surgical procedure 3.Avoids uremia-asociated complications 4.Time to pancreas transplantation usually shorter than for SPK
Disadvantages	1.Longer waiting-list time 2.Lower probability of receiving kidney transplant preemptively	1.Two surgical procedures 2.Two cycles of induction immunosuppression 3.Higher incidence of acute rejection 4.Inferior pancreas graft survival

Evaluation of candidates

- Patients with chronic kidney disease, referred to a pancreas transplant center as soon as glomerular filtration rate (GFR) falls below 25–30 ml/min
- Patient evaluation and clinical workup is similar to that performed for kidney transplantation, such as complete medical history, immunological study, uremic state, liver disease, cancer and infection screening, with some additional particularities related to diabetic disease: hormonal study, β cell autoantibodies, as well as study of the main diabetic complications

- Hormonal assessment: to determine whether or not the patient has endogenous insulin secretion. Fasting plasma levels of C-Peptide

- Autoantibodies: Quantification of β cell autoantibodies (IAA, GAD, ZnT8A, IA2) is to establish a baseline

- Diabetic retinopathy is present in up to 90% of all transplant candidates, with varying degrees of severity. It is not considered an exclusion criteria for transplantation

- Diabetic polyneuropathy
- Cardiovascular evaluation
- Vascular evaluation: an angio-computed tomography (CT) to rule out vascular lesions, mainly at the level of the iliac vessels and the celiac trunk that could hinder the implantation of the grafts
- Assessment by the transplant team: nephrologist, endocrinologist, anesthesiologist, and surgeons

- The cold ischemia tolerance of the pancreas is 20 hours preserved in the University of Wisconsin(UW) solution (Ideal < 12h)
- Pancreas retrieval operation –

- Flush the Duodenum with antiseptic using RT.

- Removal of the spleen and pancreatico-duodenal graft en bloc with the liver is the quickest and safest method.

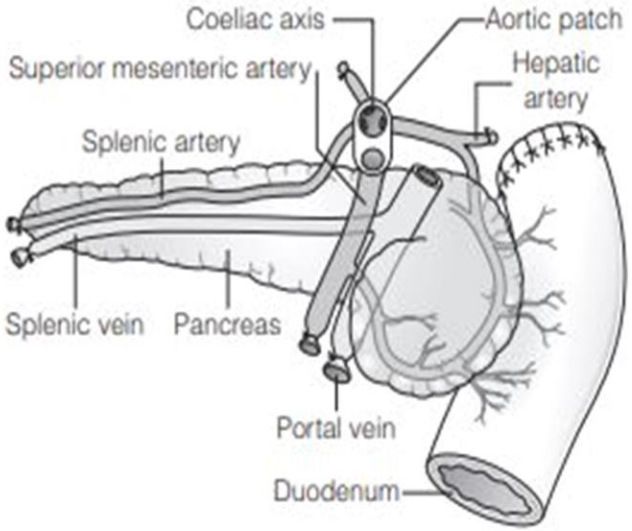
Pancreas transplant operation

- - The short stumps of gastroduodenal artery and the splenic artery are marked with prolene sutures.

- An iliac Y graft of donor origin is anastomosed to the SMA and splenic artery is the most common method od reconstruction for the graft arterial inflow.

- Aortic patch may also be utilised but iliac Y graft are better in diabetic pts as atherosclerotic changes are minimal.

Pancreatico-duodenal graft excised with an aortic patch



Reconstruction of arterial vessels

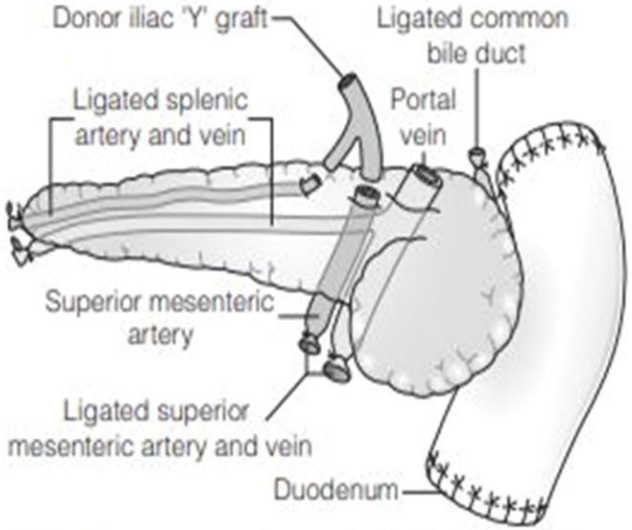
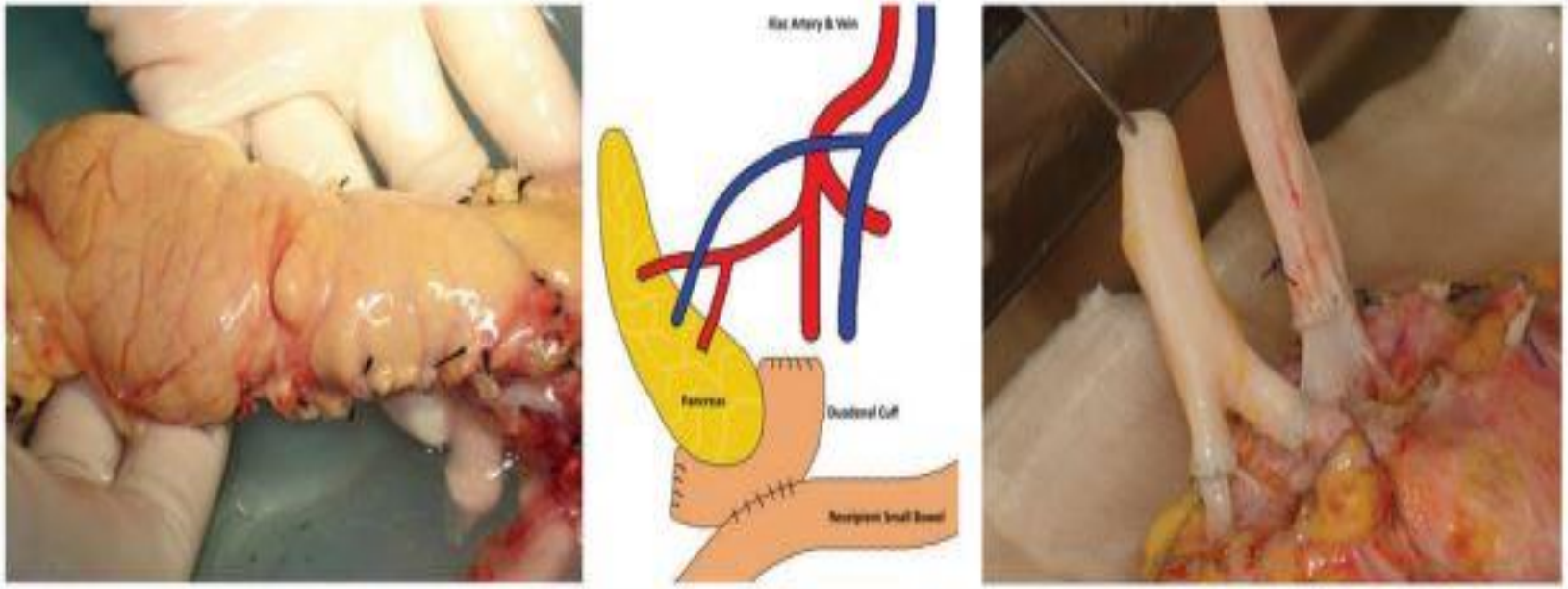


Figure 9.2 • In the absence of an aortic patch containing hepatic artery and the gastroduodenal artery, the pancreatic graft reconstruction requires a donor iliac 'Y' graft.

Figure 1. Solid organ pancreas with vessel extension and diagramatic representation of operation.



Pancreas transplant operation

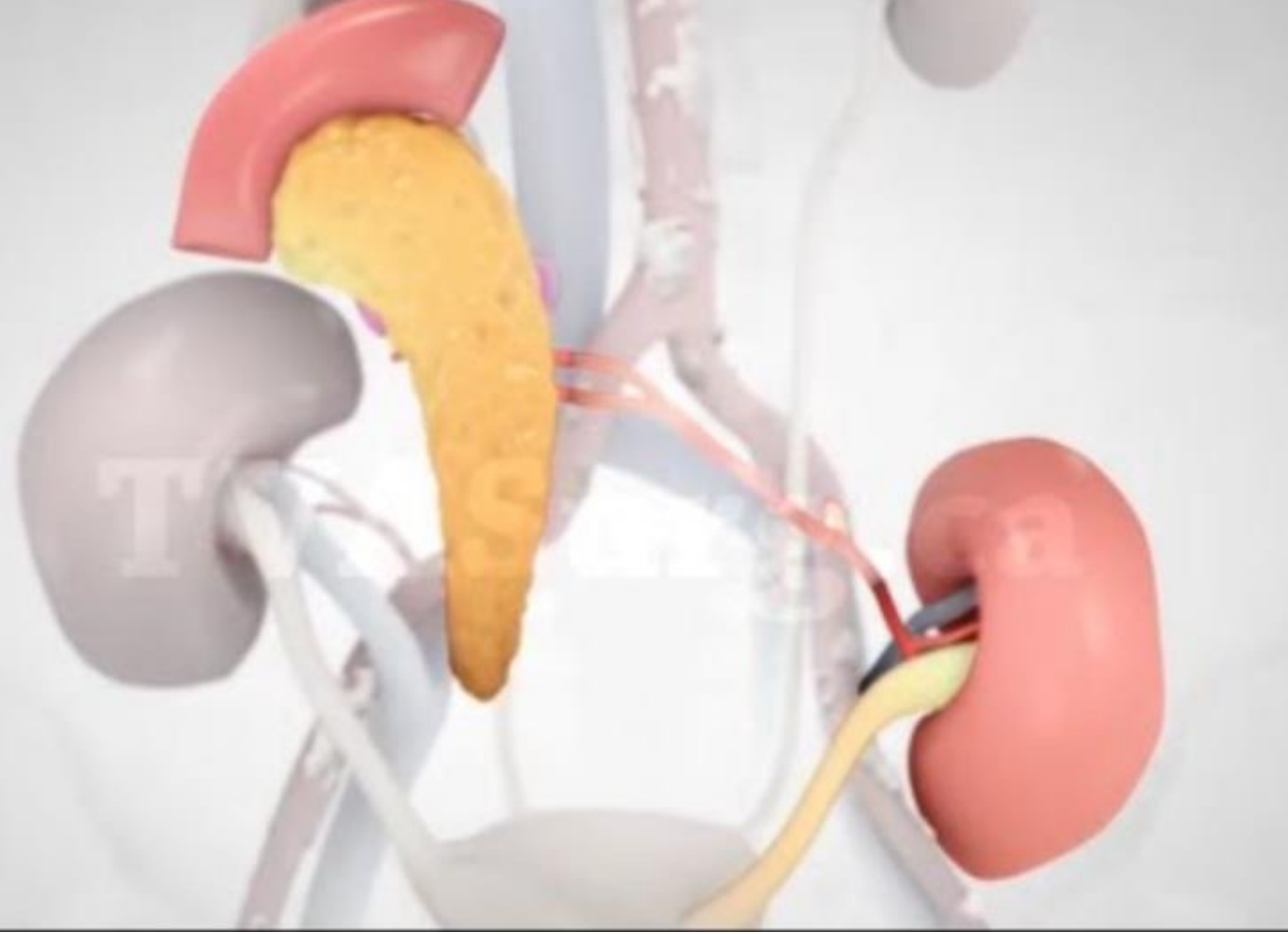
- In SPK transplantation, pancreas is usually implanted first i/v/o lower ischemia tolerance of the pancreas.
- It is easier to implant the pancreas on the right side.
- Management of the exocrine secretions is by drainage into the recipient's bladder / bowel.

Side – side enteric anastomosis is preferred more than Roux en Y.

No particular site is preferred.

Urinary complications are more in urinary diversion.

Urinary amylase monitoring is an advantage.



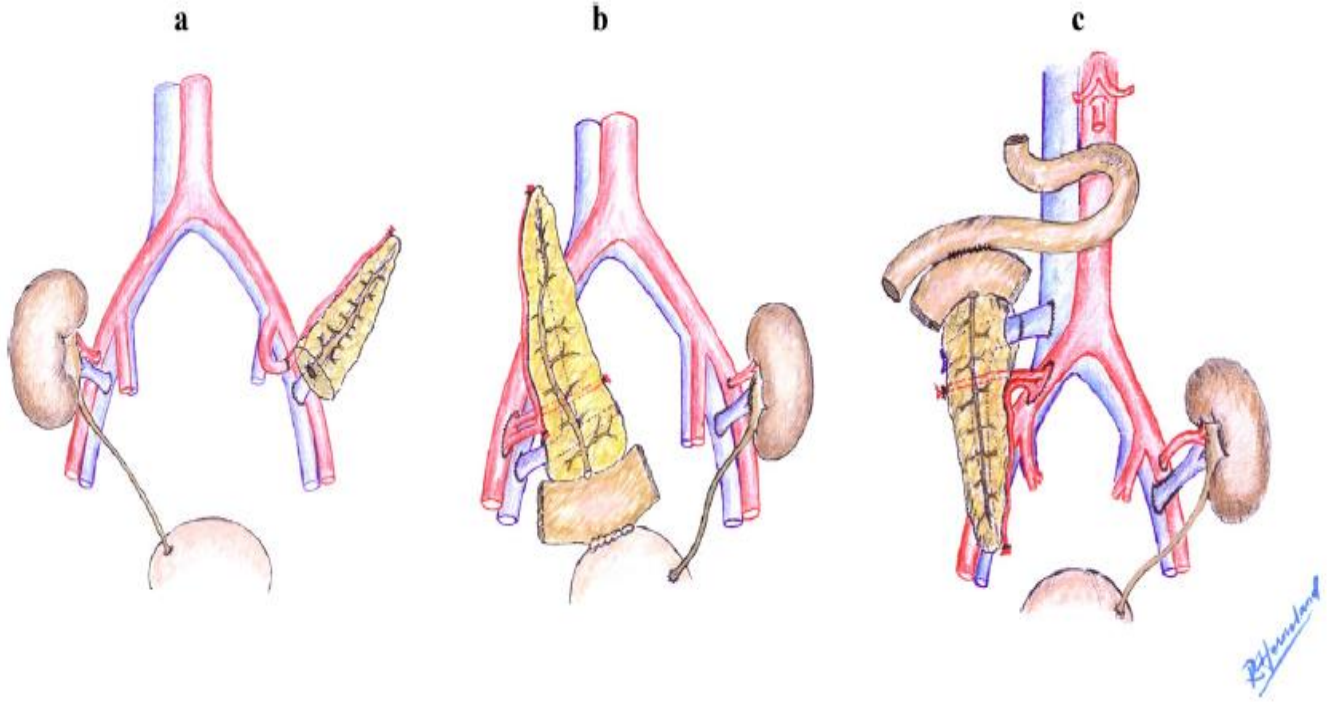
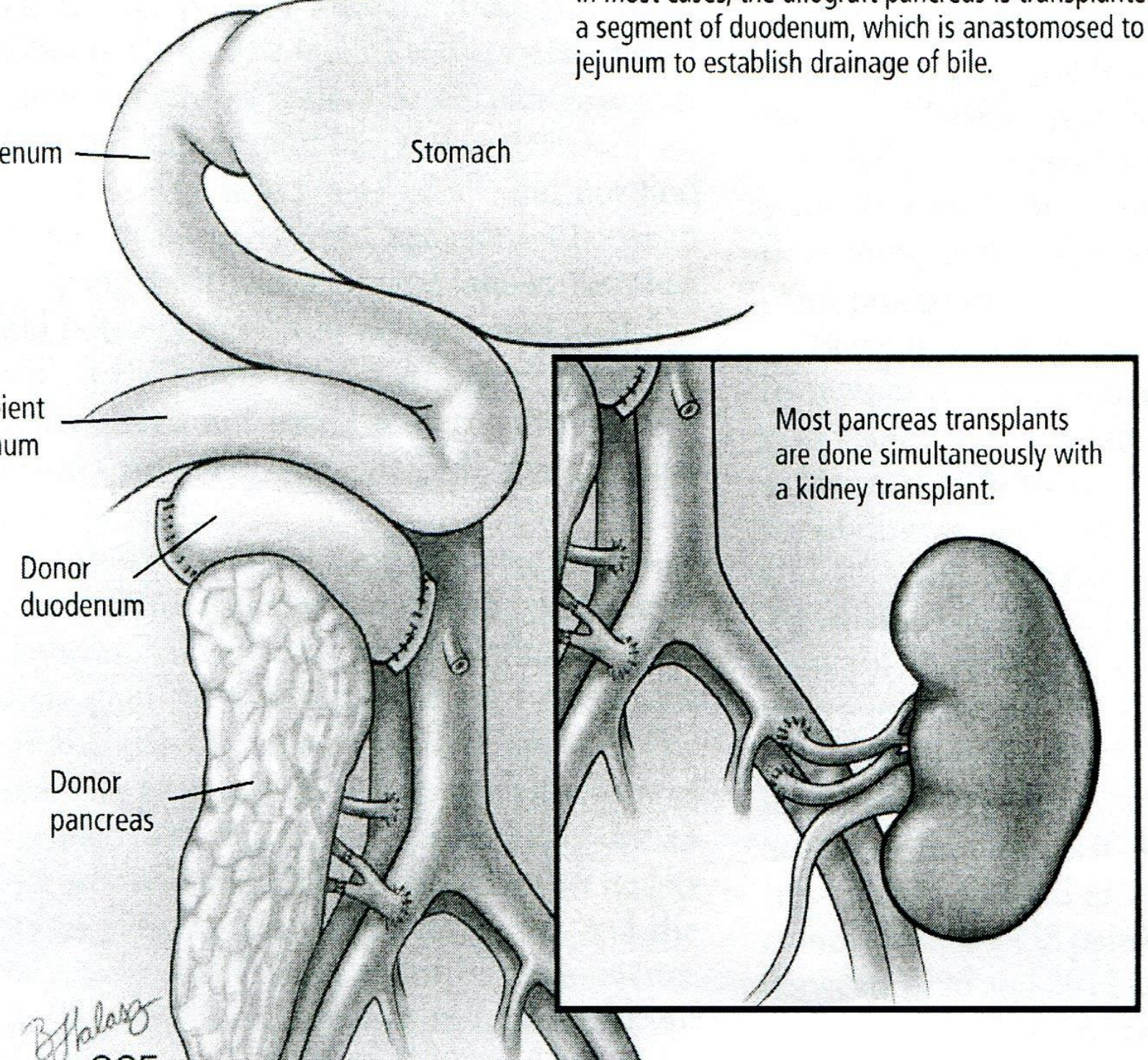


Fig. 1 – The initial technique of pancreas transplantation using the segmental pancreas transplantation and occluding the duct with neoprene (a). The whole pancreas transplant drained to the urinary bladder via a duodenal segment (b). The present technique of pancreas transplantation with intestinal drainage (c).
Illustration courtesy of Rune Horneland.

a segment of duodenum, which is anastomosed to the recipient's jejunum to establish drainage of bile.



Immunosuppression in Pancreas transplantation

- Tacrolimus has largely replaced ciclosporin and MMF has replaced azathioprine based on evidence from prospective RCT showing improved outcomes.

- There is no benefit in steroid avoidance or withdrawal.

- Induction therapy with biological agents is part of the immunosuppressive protocol in nearly all pancreas transplants.

Diagnosis and management of acute rejection following pancreas transplantation

- In SPK patients, early rejection is done by measuring serum creatinine and undertaking biopsy when indicated.

- Discordant rejection of pancreas alone occurs in only 5-10 % with pancreatic rejection.

- Acute rejection of pancreas affects the exocrine component first with s/o pain, fever and rise in amylase.

- Islets of Langerhans are scattered sparsely in the exocrine pancreas and beta cells have considerable functional reserve and hence rejection occurs very late.

- There are no specific signs of acute rejection however CT/MRI can be employed to check for lack of perfusion and intra abdominal collection.

- Detection of urinary amylase is a sensitive indicator of exocrine function. (> 25% redn. UA – acute rejection)

- Gold standard in dx – Pancreatic allograft biopsy (CT/USG guided) to detect donor specific antibodies (DSA).

- Treatment consists of high dose steroids.
- Recurrent rejection requires anti T cell agents.

- Rejection if diagnosed before hyperglycemia are mostly reversible.

Complications of pancreatic transplan

- Factors include higher level of immunosuppression in a high risk diabetic population with impaired infection resistance and poor healing.

Box 9.3 • Complications of pancreas transplantation

Vascular complications

- Thrombosis: allograft venous or arterial thrombosis
- Haemorrhage: early haemorrhage from allograft vessels and late haemorrhage (rupture of pseudoaneurysms)

Infective complications

- Systemic infection: opportunistic infections associated with immunosuppression
- Local infections: peritonitis, localised collections, enteric or pancreatic fistulas

Allograft pancreatitis

- Ischaemia–reperfusion injury or reflux pancreatitis (especially after bladder drainage)

Complications specific to bladder drainage

- Chronic dehydration, acidosis, recurrent urinary tract infections, haematuria, chemical cystitis, urethral strictures or urethral disruption

Vascular thrombosis

- Most common cause of early graft loss.
- Venous thrombosis is more common than arterial by 2:1 ratio.
- Treatment involves early laparotomy and graft pancreatectomy.

Hemorrhage

- Early hemorrhage

  - Leak of exocrine secretions into the thrombus sealed small vessels / vascular anastomoses.

- Late haemorrhage

  - Rupture of pseudoaneurysm / direct erosion of one of the anastomoses.

Infective complications

- CMV disease is more common after pancreas transplantation like any other transplantation.

- Hence immunosuppression is mandatory with all transplants.

Allograft pancreatitis

- Cold storage and ischemia reperfusion injury result in edema of the allograft.
- There is no universally agreed definition of allograft pancreatitis.
- Bladder drainage is more frequently associated with pancreatitis due to the reflux - catheter drainage of the bladder for 7-10 days is usually sufficient.

Islet tranplantation

- Initially attempted by Bristol as xenograft from sheep pancreas into the subcutaneous plane of a 15 year old DKA boy.

- In 2000 Edmonton group successfully did a series of seven consecutive pts and achieved insulin independence.

- Edmonton protocol – two islets from 2 different donors and immunosuppression achieved by tacrolimus, sirolimus and induction with daclizumab.

Indications

- Severely impaired awareness of hypoglycaemia (IAH)
- Patients with T-1 DM with a functioning kidney allograft who are unable to maintain their HbA1c < 7 %

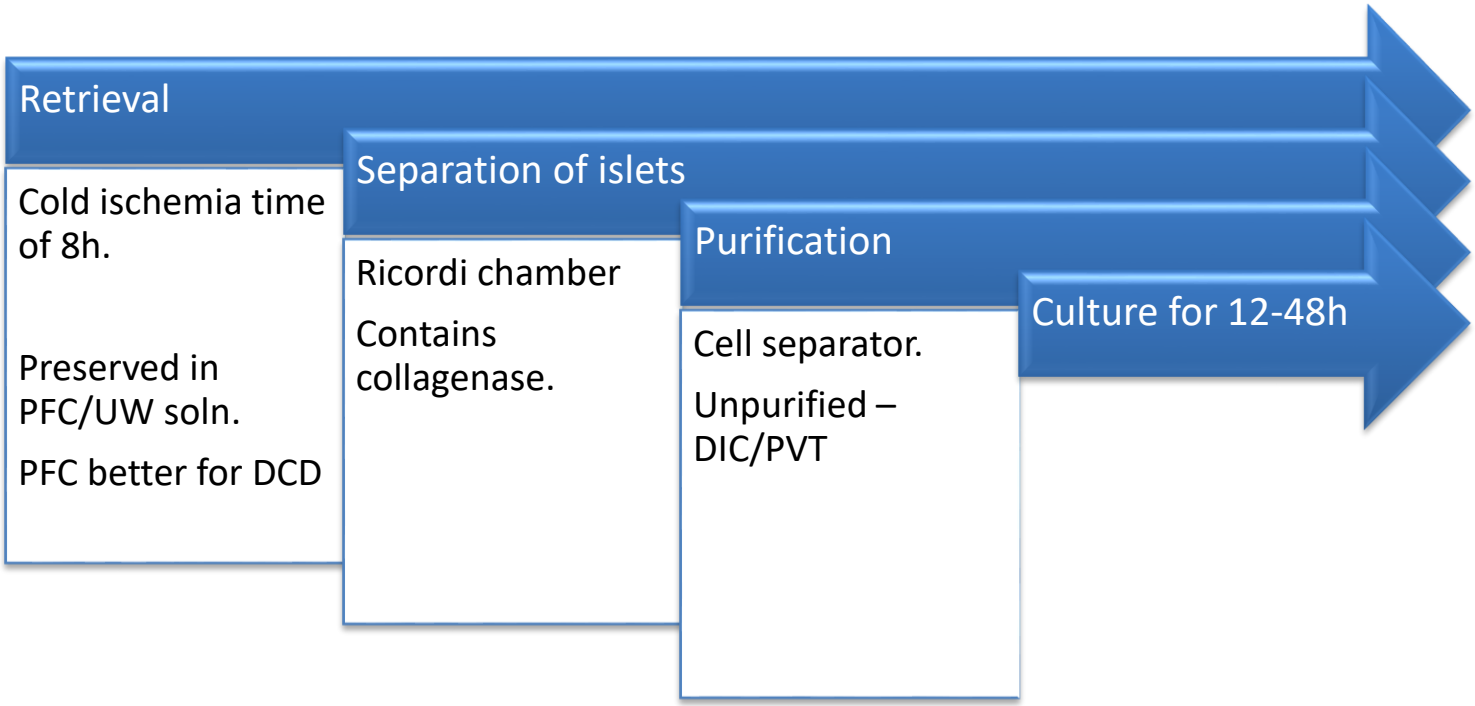
The number of islets is documented in terms of islet equivalents .

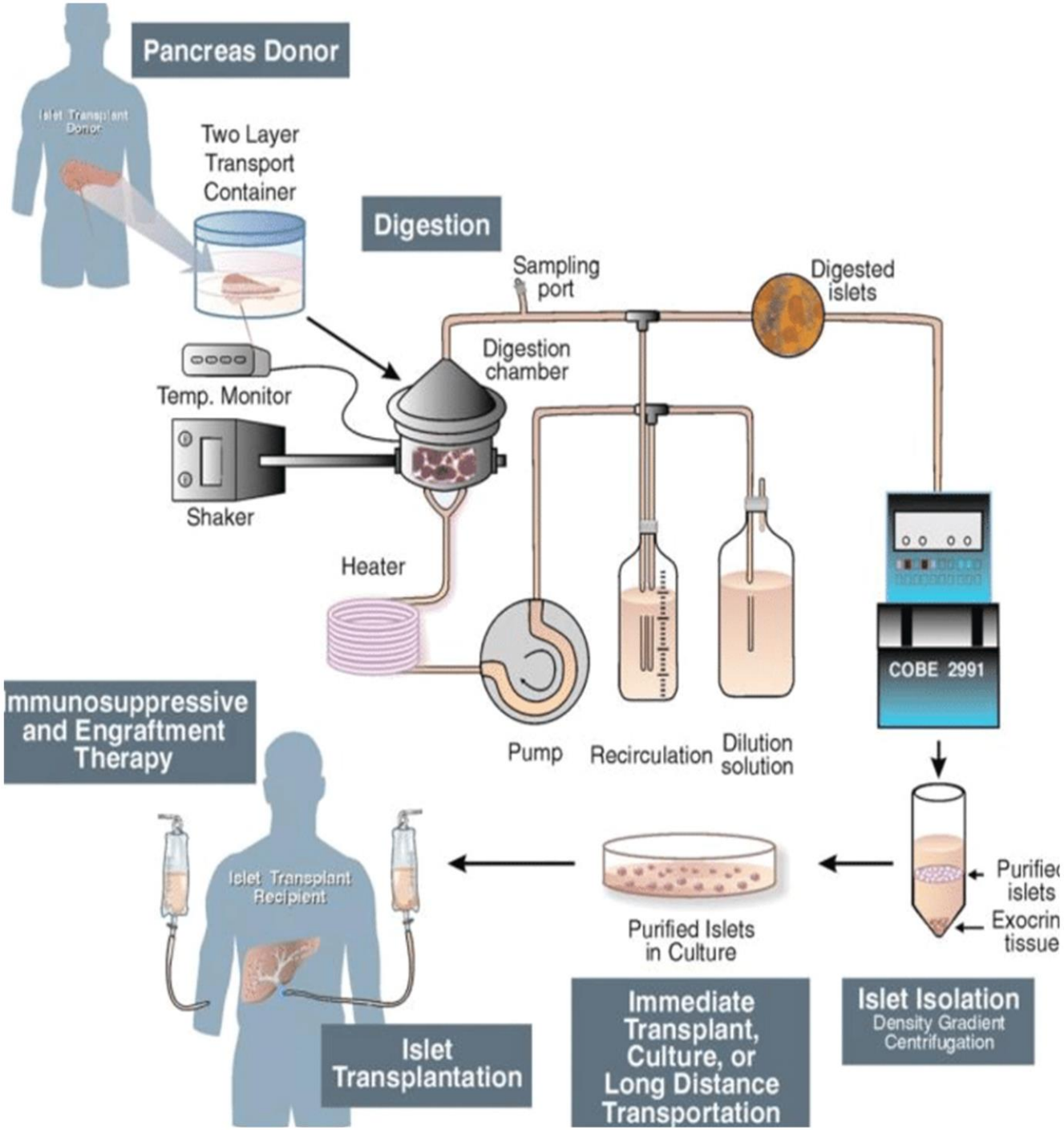
- Minimum release criteria for Islet transplantation are
- >200,000 IEQ
- >70% viability
- >30% purity
- Gram stain negative
- Endotoxin negative

ISLET ISOLATION

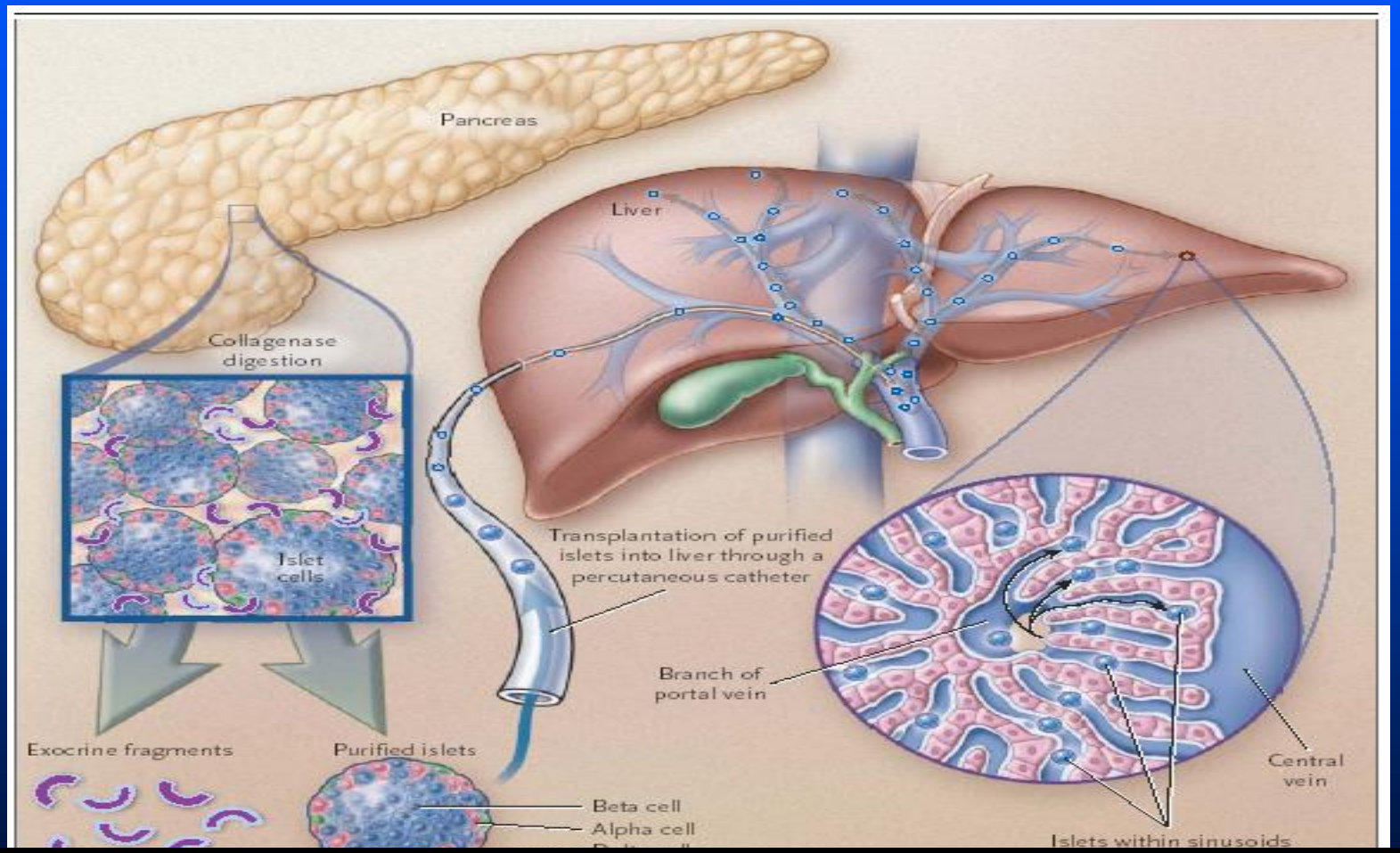
ISLET TRANSPLANT

- They are infused into the portal vein if the recipient under LA and sedation in the radiology suite.
- A 4 Fr cannula is introduced under USG guidance and videofluroscopy into the PV and islet preparation is infused under gravity feed over a period of 15-20 min.
- It is usually heparinised (35U/kg)
- Infusion can also be done using the umbilical vein or an omental vessel.
- Other techniques that are under research are encapsulation devices.


Retrieval
Cold ischemia time of 8h.
Preserved in PFC/UW soln.
PFC better for DCD
Separation of islets
Ricordi chamber
Contains collagenase.
Purification
Cell separator.
Unpurified – DIC/PVT
Culture for 12-48h


Pancreas Donor
Islet Transplant Donor
Two Layer Transport Container
Digestion
Sampling port
Digested islets
Digestion chamber
Temp. Monitor
Shaker
Heater
Pump
Recirculation
Dilution solution
COBE 2991
Immunosuppressive and Engraftment Therapy
Islet Transplant Recipient
Purified Islets in Culture
Purifie islets
Exocrin tissue
Islet Transplantation
Immediate Transplant, Culture, or Long Distance Transportation
Islet Isolation
Density Gradient Centrifugation

Pancreatic islets are transplanted into the liver by infusion into the portal vein



Robertson R.P. New Engl J of Med. 2004.

- After infusion they undergo a process of angiogenesis which takes 14-21 days.
- There will be reduced insulin need around 3-4 weeks post transplant.

Islet infusion into the portal vein

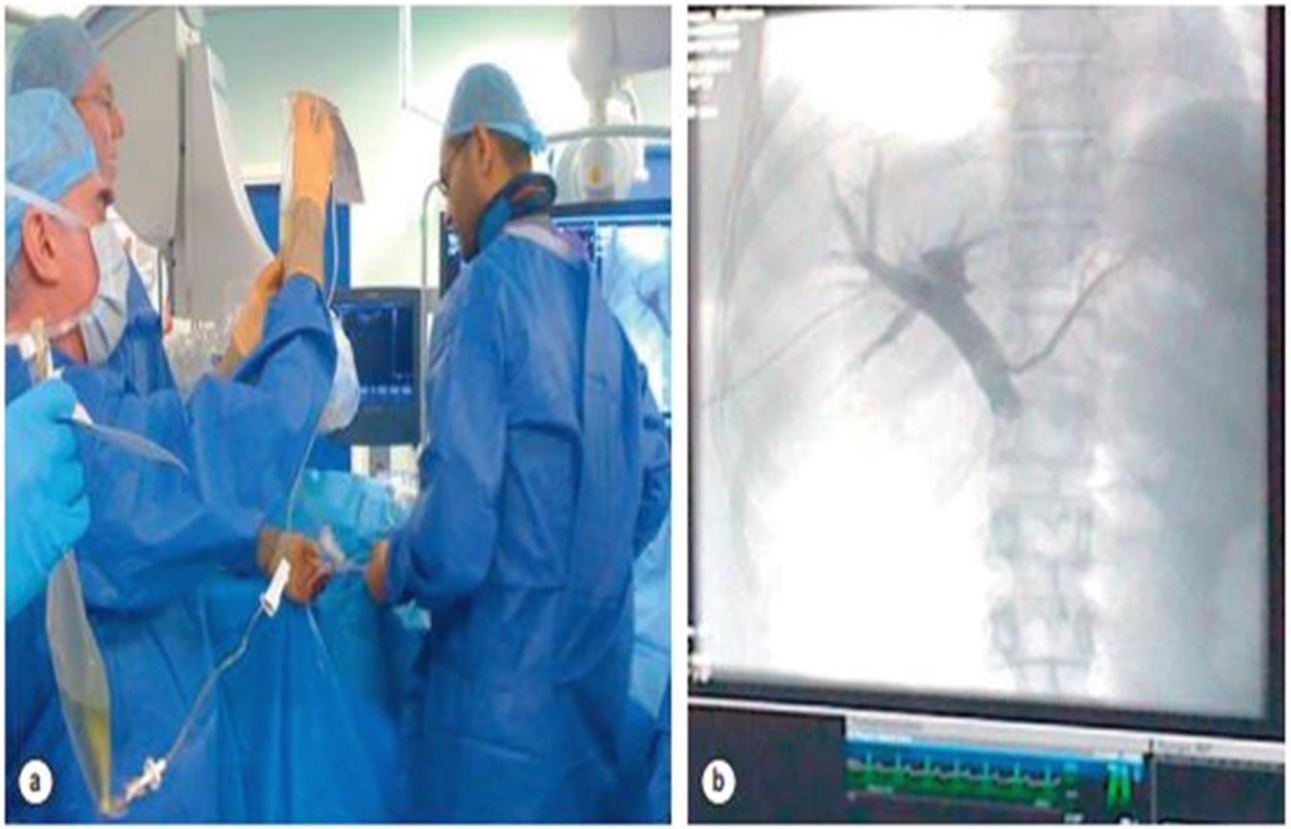


Figure 9.6 • Islet infusion into the portal vein.

Immunosuppression

- To improve long term outcomes.
- T cell depleting agents like ATG(antithmocyte globulin), anti CD3 and alemtuzumab – induction agents.
- MMF,TNF-antagonists, etanercept – maintenance agents.
- Studies show that insulin independence reaches upto 50% at 3 -5 years with these agents. (Edmonton was 10% at 5 years)

Future scope of islet transplantation

- Directed differentiation of the human embryonic stem cells (Hesc)
- Yamanaka and Takahashi – iPSC
- Transcription factors required for beta cell differentiation – Ngn3, Pdx1, MafA.

THANK YOU