

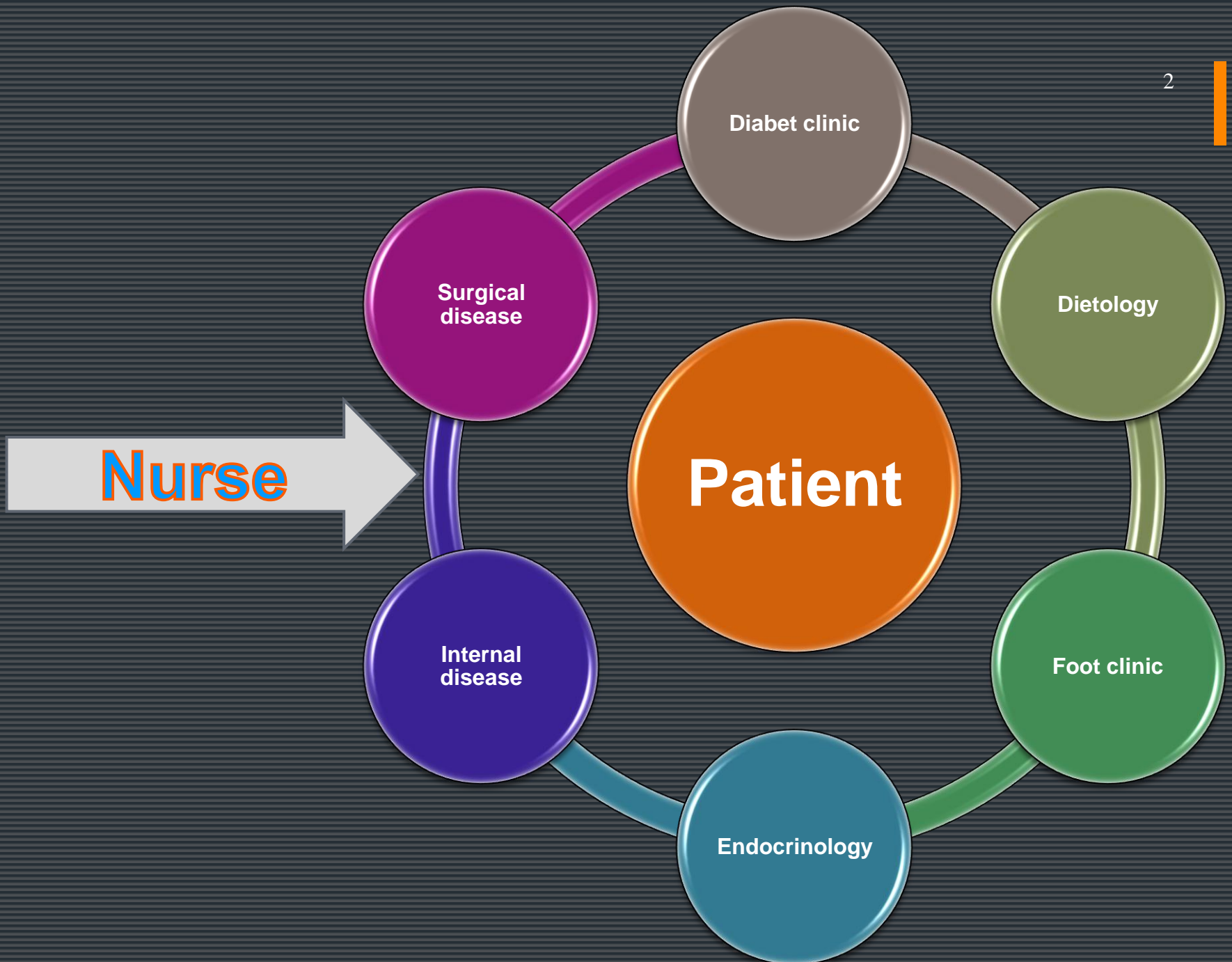
HUMAN ISLET TRANSPLANTATION

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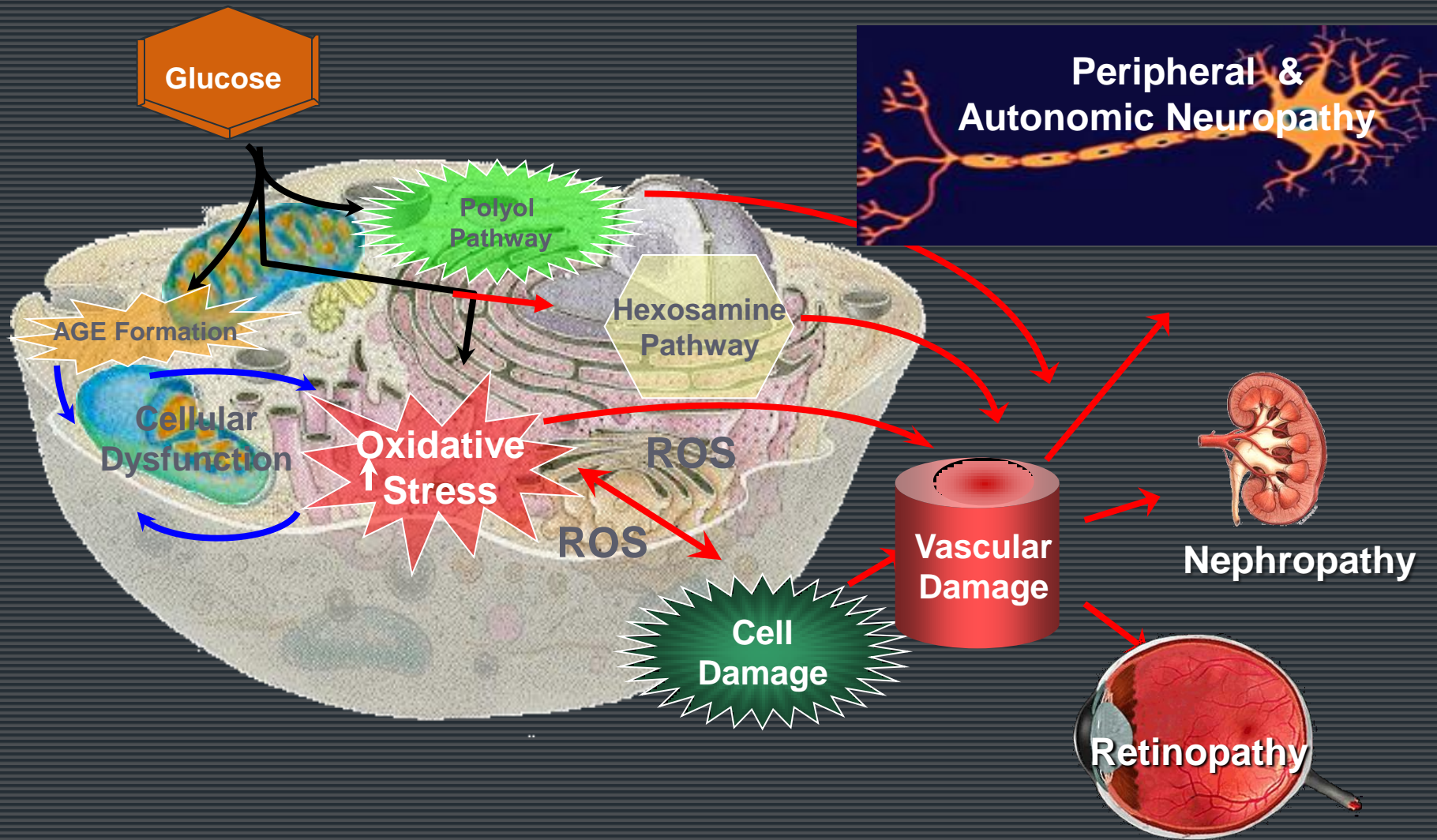
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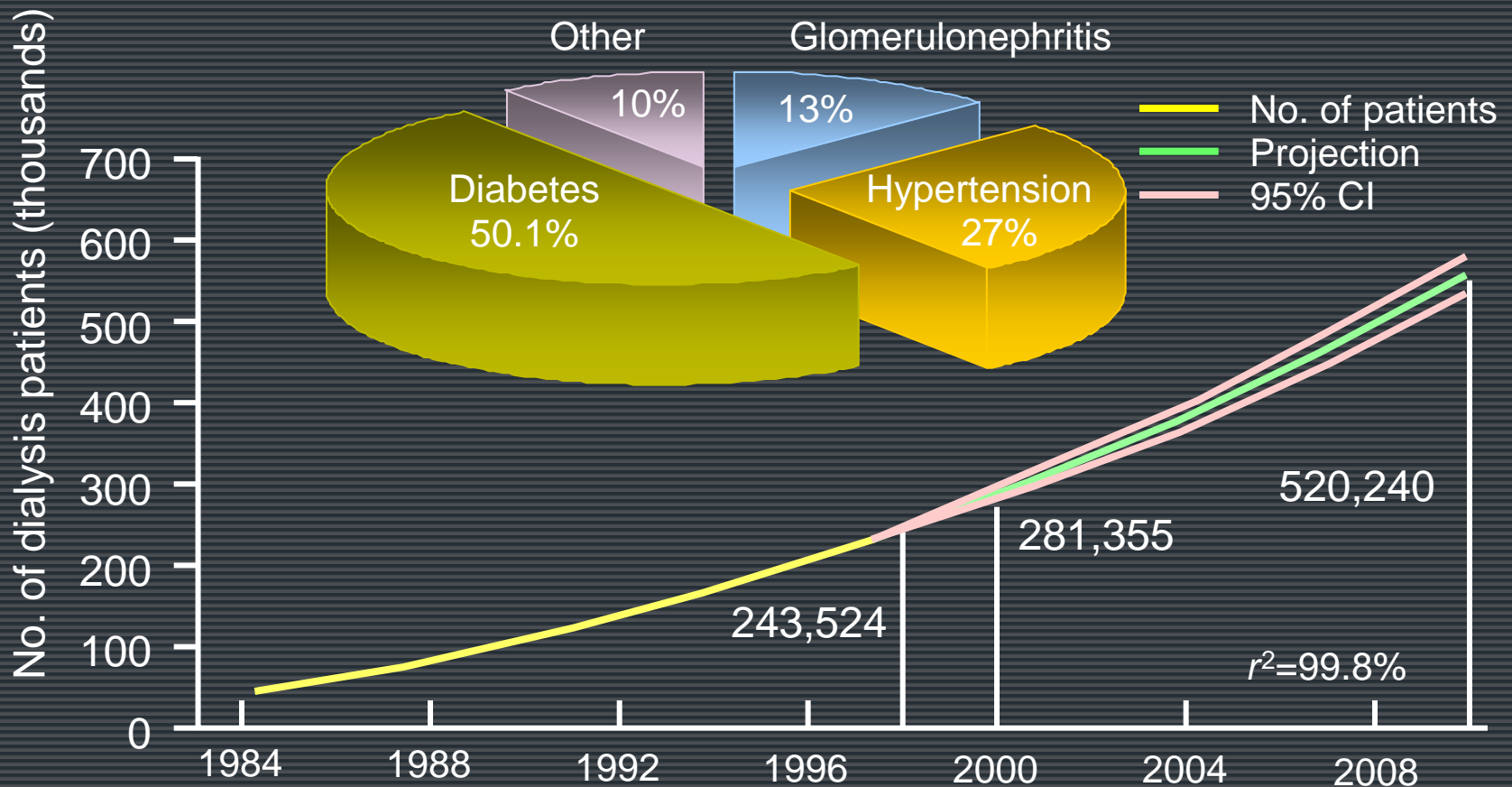




Common Pathways in DM Complications



DM in Renal Failure: A growing epidemic

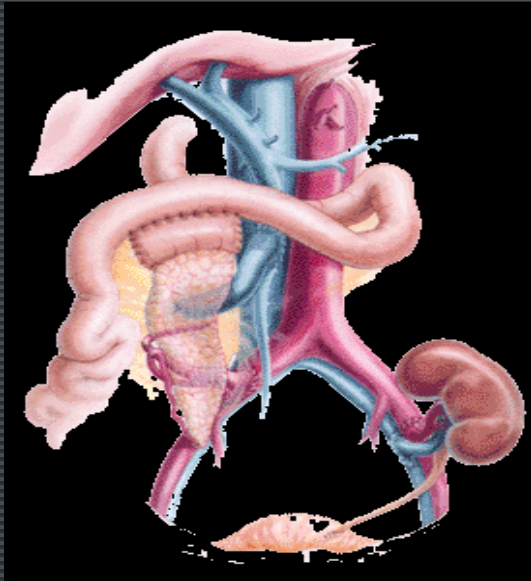


General Principle

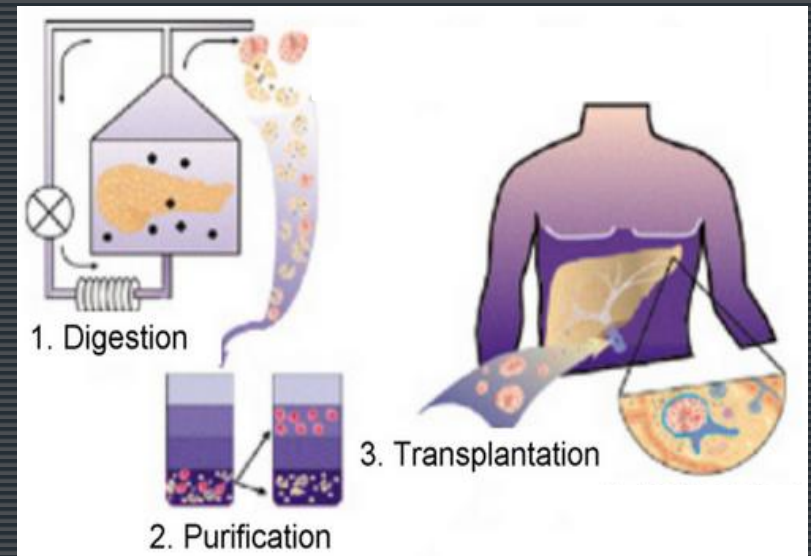


- **Normalization** of blood glucose (not merely control of blood glucose) will lead to improvements in:
 - Survival
 - Quality of life
 - Protection from heart disease, kidney disease, retinopathy, and nerve injury
- The only method that normalizes blood glucose in patients with diabetes is treatment with insulin-producing cells

2 types of transplants are offered to patients with complicated insulin dependent diabetes mellitus:



■ whole pancreas transplantation



■ pancreatic islet transplantation

Worldwide until 2009 a total of

29000 whole pancreas Tx  1500 islet Tx

Methods to treat with insulin-producing cells

Pancreas transplant

- Pancreas obtained from cadaver donors, transplanted surgically within 12 hours
- Surgical procedure involves general anesthesia, abdominal surgery, and a 10-20 day hospitalization
- Complications:
 - Thrombosis of pancreatic vessels
 - Pancreatic leak
 - Infection
 - PNF

Islet Cell Transplant

- Islet tissue obtained from cadaver organs by collagenase digestion of the pancreas and purification of islets via density gradients (CIT < 12hours)
- Islets injected into portal vein for liver implantation, performed by surgeon /interventional radiology, followed by a 1-2 day hospitalization
- Complications:
 - Bleeding
 - Thrombosis
 - PNF

Islets are better than insulin

A microscopic image showing a needle tip on the left, with a bright light reflecting off its point. The needle is positioned near a cluster of red, spherical cells, which are likely islets of Langerhans. The background is dark, and the cells are out of focus, creating a bokeh effect.

**Internal
secretion**

**Built-in
glucose
sensor**

**Built-in
power supply**

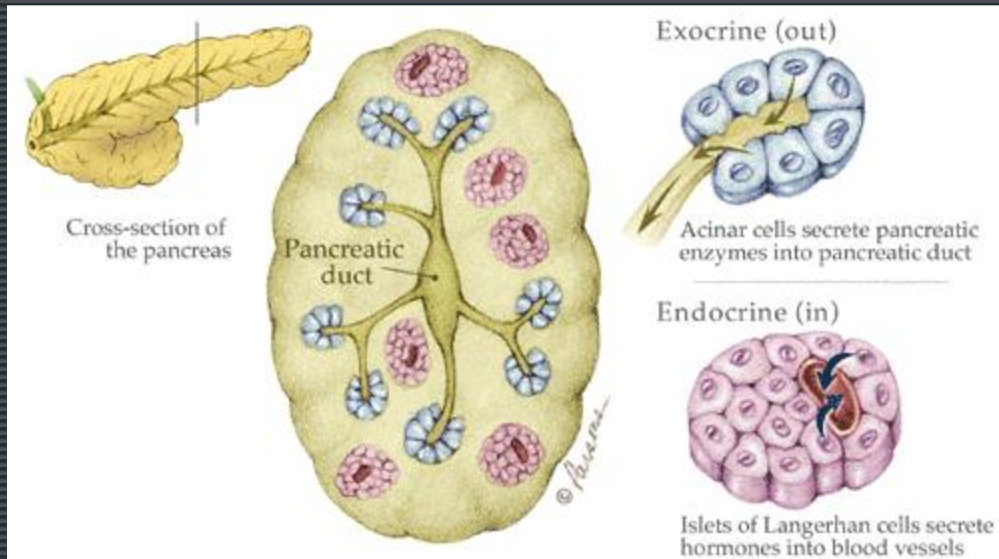
**Perfectly
timed
insulin
release**

**Keep
glucose
in normal
range**

Function for entire lifetime

Islet Transplant

has been a goal, for insulin replacement therapy, because islet respond to glucose immediately, and frequently, which eliminates the need for insulin injections & glucose monitoring.



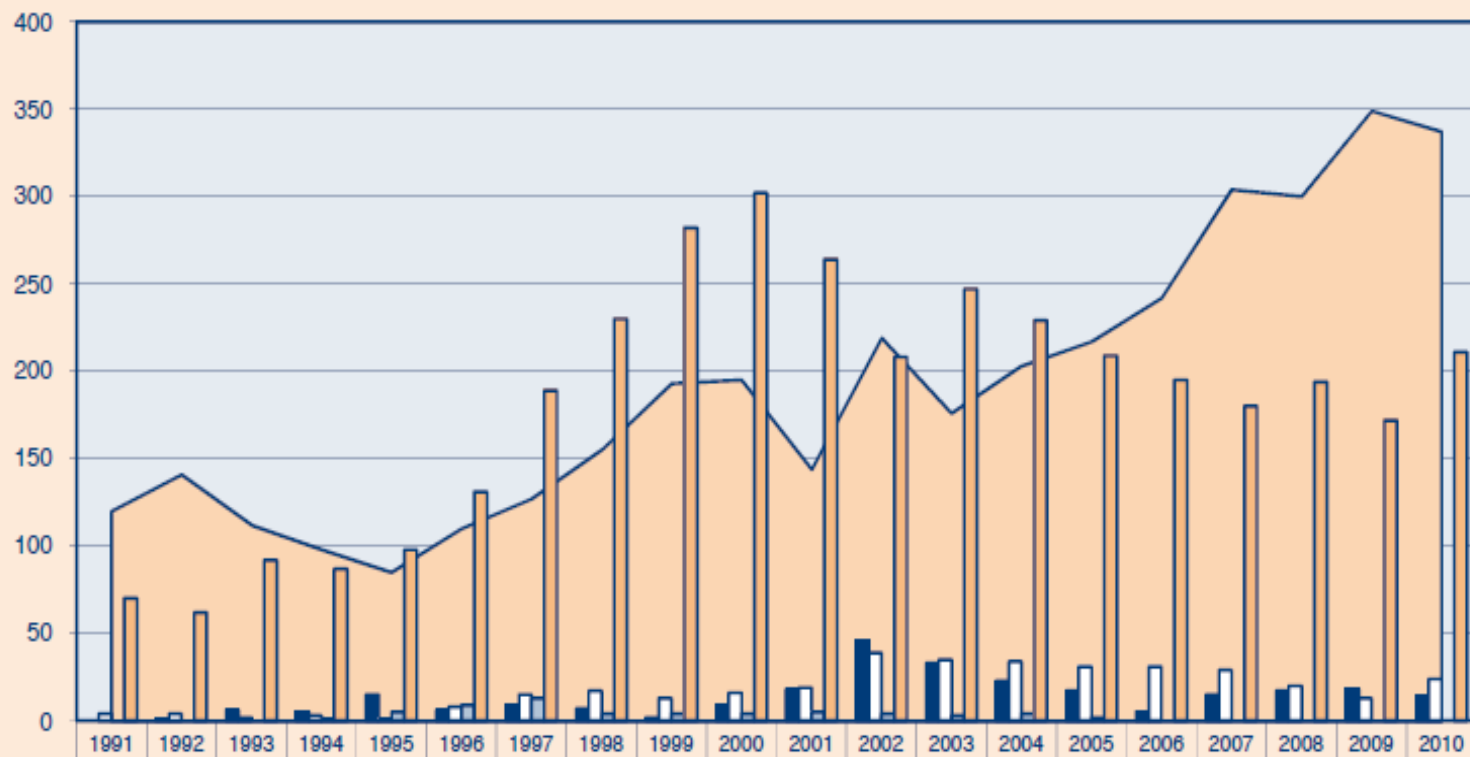
History of Islet Transplantation



Success of Islet Transplantation. has been elusive.

In 1999 International Islet Transplant Registry found fewer than 10% of the islet transplants recipients, were insulin independent

Figure 7.5 Dynamics of the Eurotransplant pancreas+kidney and islet+kidney waiting list, pancreas+kidney, islet+kidney, pancreas and islet-only transplants between 1991 and 2010



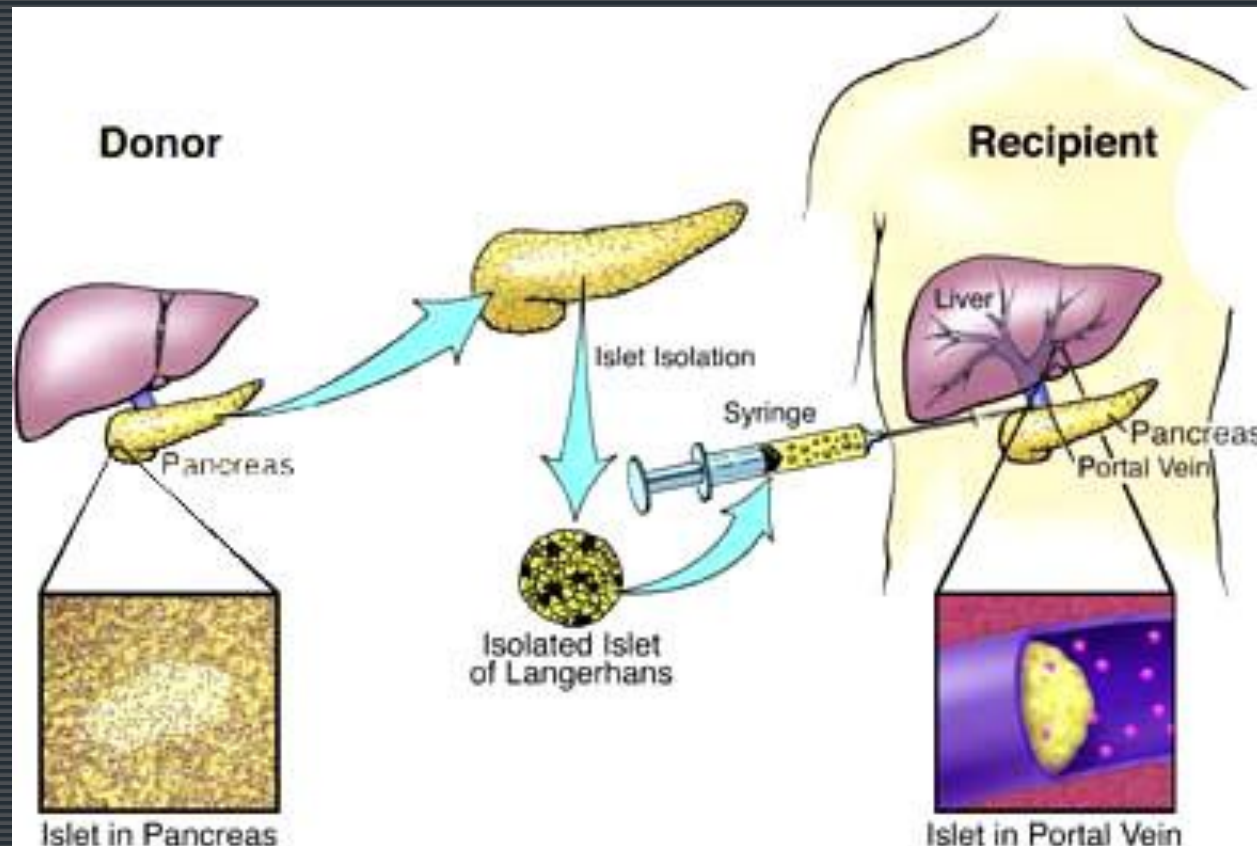
Islet+Kidney & Pancreas+Kidney waiting list	120	141	112	98	85	110	127	155	193	195	144	219	176	203	217	242	304	300	349	337
Islet transplants	0	1	6	5	15	6	9	7	2	9	18	46	33	23	17	5	15	17	18	14
Pancreas transplants	4	4	2	3	1	8	15	17	13	16	19	39	35	34	31	31	29	20	13	24
Islets+Kidney transplant	0	0	0	1	5	9	13	4	4	4	5	4	3	4	2	0	0	0	0	0
Pancreas+Kidney transplants	70	62	92	87	98	131	189	230	282	302	264	208	247	229	209	195	180	194	172	211

Components of an Islet Transplant Program

- **Laboratory:** (B-cell bank) cleanroom specifications, technical support (4-5 on call at all times), in-process environmental monitoring, post-isolation quality control testing, staining > 24 hrs
- **Clinical:** recipient eval and post-transplant follow-up, training/cooperation for organ allocation, transplant procedural coverage, inpatient care, immune/metabolic monitoring
- **Regulatory:** Federal law, annual reports, standard operating procedures for islet isolation/transplant, training documentation and equipment validation, certification and reporting
- **Finance:** INAMI, European Union (FP6 and FP7), Juvenile Diabetes Research Foundation (JDRF).

Transplantation of islets of Langerhans

consists of, implantation in the recipient's hepatic portal system, different quantities of purified endocrine pancreatic tissue, obtained from a deceased donor after its digestion.



The Steps

The islets are harvested, from the donor pancreas

Recipients immune system is suppressed, using a steroid free regimen of immunosuppressant drugs

Islets infused into portal vein

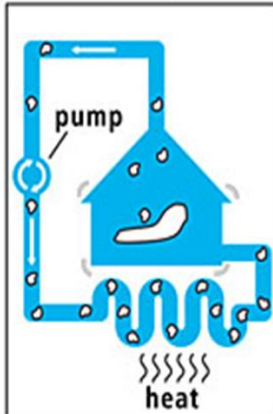
ISLET ISOLATION AND TRANSPLANT

PANCREAS DIGESTION



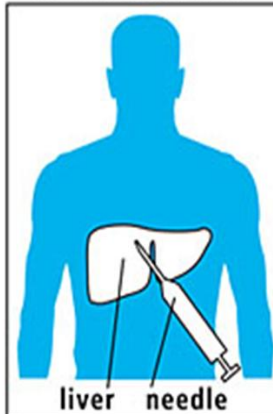
A donor pancreas is injected with digestive enzymes. A machine shakes and breaks the pancreas into pieces. One to three organs are needed for each transplant recipient.

ISLET ISOLATION

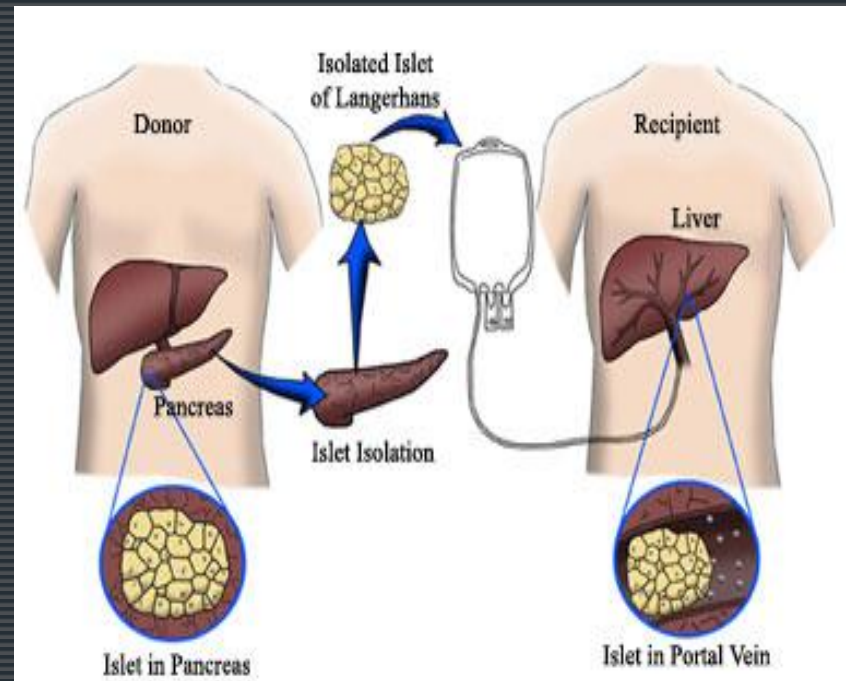


As chunks of the pancreas become smaller, they are pumped into a recirculating chamber. Heat helps to isolate the islets.

TRANSPLANTATION



A surgeon injects purified islets into the patient's liver within two days of cell isolation. Cells take up residence in the liver, but immunosuppressive drugs are needed for life to prevent rejection.



Islet isolation procedure

The pancreas is generally obtained en bloc from a HLA matched deceased donor along with a segment of the duodenum and the spleen

Before isolation the gland is freed from the surrounding tissue, paying attention to preserving the integrity of its capsule (a).

The pancreatic duct is cannulated and solution containing collagenase enzyme injected resulting in distension of the gland (b).

The gland is then cut into large pieces of equal size (c) and transferred with dissociation solution into the digestion chamber

The chamber (d) consists of a lower cylinder and an upper conical portion, separated by a removable stainless steel screen, and stainless steel marbles.

The tissue is then collected and centrifuged to remove the enzyme (f).

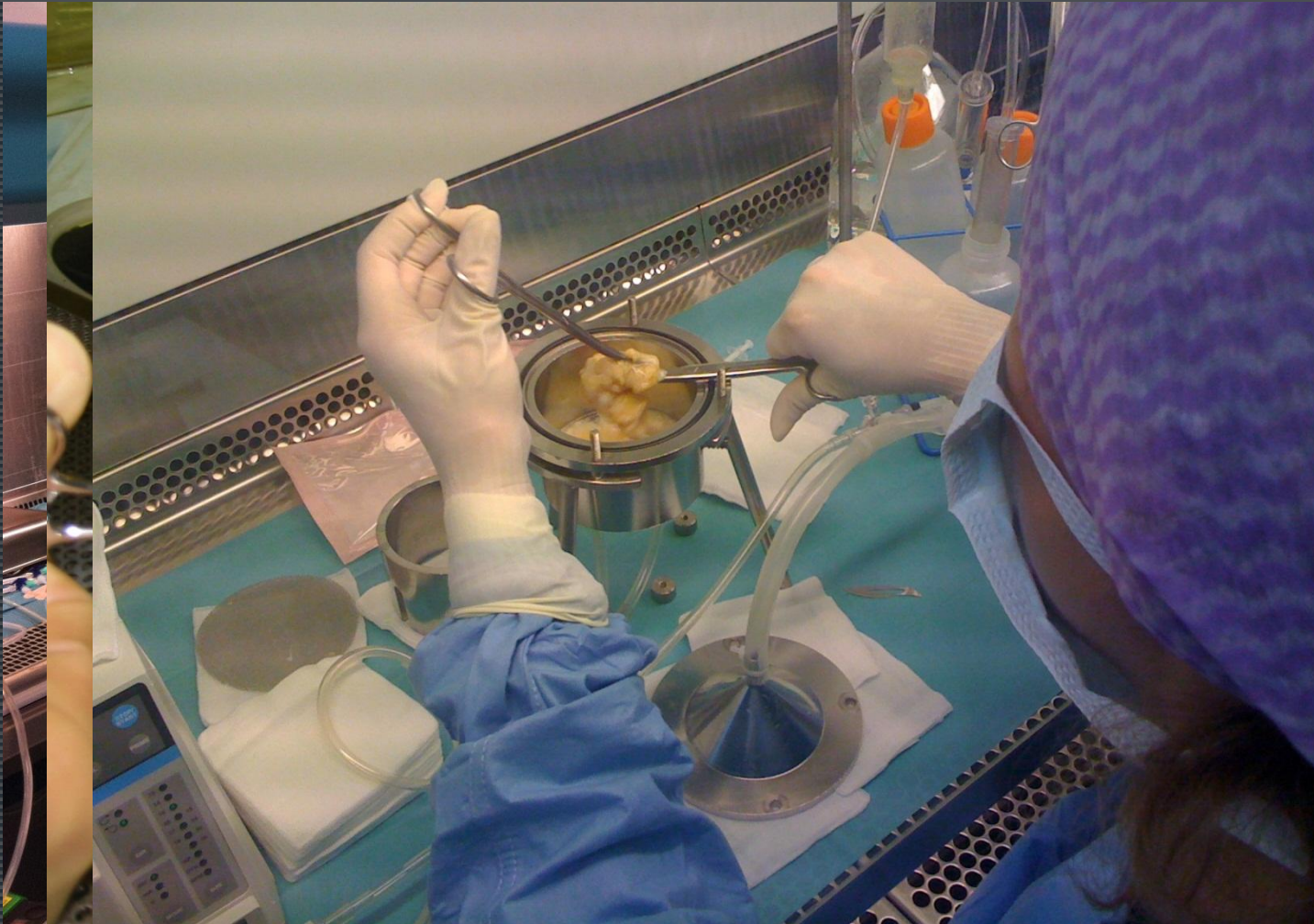
Combination of both enzymatic and mechanical actions allows release of particles from pancreas, which are continuously removed and preserved

Islets, which represent ~2% of the tissue, can be identified by dithizone staining, which confers a characteristic red pigment (g).

The purification step follows, where the tissue is separated according to differences in density, utilizing semi-automated computerized centrifuge (h).

After purification, different degrees of islet purity can be obtained (i).

B-cell Bank



Islet preparation for transplant

These islets. have been isolated and purified from a whole organ pancreas graft and now ready for transplantation. The stain is Dithizone and the size of islets range from 50-500um.



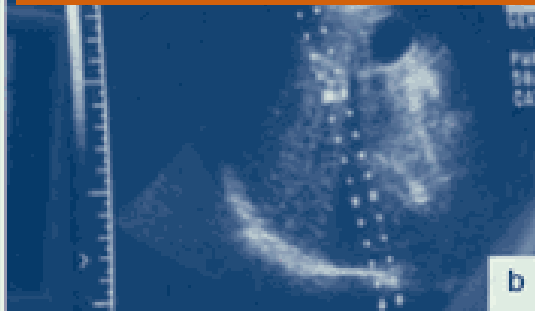
Islet transplantation procedure:

Isolated islets from the donor are infused in the portal system of the liver of recipient using a minimally invasive approach that can be performed as an outpatient procedure.

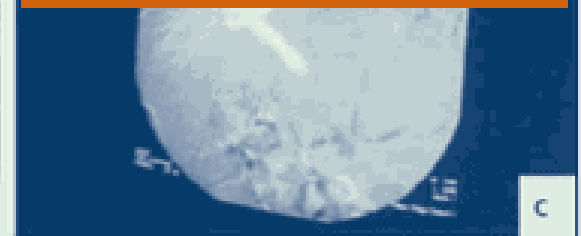
The patient is under light sedation and conscious throughout the session (a).



Under ultrasound (b) and



angiographic (c) guidance, the portal vein is cannulated



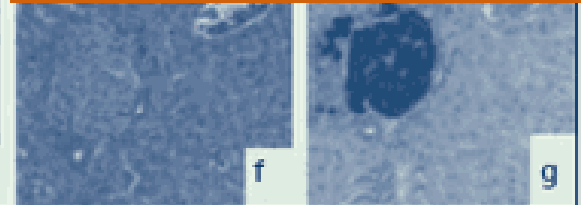
The islets are transferred into a transfusion bag in transplant media, which is connected to the implanted catheter and allowed to empty by gravity (d).



The portal pressure and the patient's heart rate are closely monitored during the infusion (e).



The implanted islets lodge into the recipient's hepatic sinusoids, and start secreting insulin.



Success rates: pancreas vs. islet transplantation

	One-year	Graft Survival:
■ <u>Transplant:</u>		
■ Kidney/Pancreas (SPK)	82%	86%
■ Pancreas after kidney (PAK)	74%	79%
■ Pancreas alone (PTA)	76%	76%
■ <u>Islet Transplant</u>		
■ Combined data	8%	58%*
■ *data from 12 participating centers, up to 3 infusions		

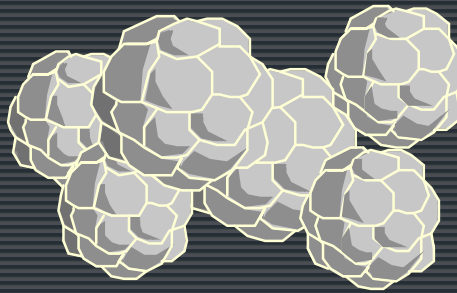
Source: SRTR and CITR

Possible Reasons for Islet Graft Failure

Insufficient islet mass

Poor quality of islets

Failure to engraft



Toxicity of anti-rejection drugs

Insulin resistance

Islets

Disease recurrence

Allograft rejection

Is islet transplantation safe?

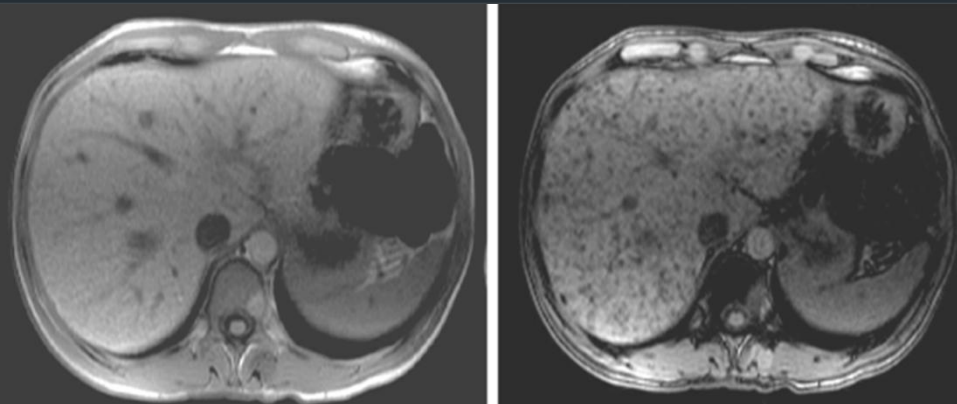
■ Acute complications:

- Bleeding ~10-15%
- Thrombosis ~5%
- Transaminitis ~50%

■ Long-term complications:

- Renal function
- Hypertension
- Hyperlipidemia
- Mouth ulcers
- Risk of sensitization
- Risk of infection (CMV)

Hepatic Steatosis following islet transplantation



IDEAL DONOR „??

Islets exclusion criteria

DM I and II (unless there is consent for research)

WIT > 10 min

Pancreas from NHBD Cat I; II; IV

Polytrauma with sign of pancreas damage

Cardiac arrest and / or prolonged hypotensive period >> AST; ALT

Amylase values > 600 U/L Lipase > 350 U/L

Pancreas fibrosis

Islets inclusion criteria

General donor inclusion criteria

Adequate in situ hypothermic perfusion

Max CIT 12 hours

No age limitation

Whole and large segmental (body and tail) pancreas

Pancreas from NHBD (Cat III) ventilation switch off and death < 30 min

DONOR for Islets graft

	OPTIMAL	SUB-OPTIMAL
CIT	< = 8 hrs	>8-12 hrs
Age	➤ 20	<20
BMI	➤ >23	<23
Hospitalisation	➤ < 8 days	➤ 8days
Glucose	➤ <200 mg/dL	➤ > 200 mg/dL
Amylase	➤ < 300 U/L	➤ >300-600 U/L
Lipase	➤ < 160 U/L	➤ 160-350 U/L
SGOT	➤ < 32 U/L	➤ <200U/L
SGPT	➤ <32 U/L	➤ <200U/L
γGT	<30 U/L	➤ <200U/L
	Whole pancreas	➤ Segment

OBSTACLES TO SUCCESSFUL ISLET TRANSPLANTATION:

Low engraftment of islets

- The transplanted β cell mass is ~50% of the mass present in a normal individual
- The engrafted β cell mass is ~30% of the transplanted β cell mass
- Islet engraftment takes weeks before revascularization is completed, rendering islets susceptible to:
 - Hypoxic injury
 - Nonspecific cell-mediated injury: “IBMIR”, cytokine release, reactive oxygen intermediates elaborated during postoperative healing/wound reaction



Disadvantage of Islet Transplant:

at present is that for a single recipient two or more cadaveric donor pancreas are required and in this era with deficiency of transplant material it is a very difficult task to obtain these.

Achieving Sufficient Islet Mass for Type 1 Diabetes



Pancreas Transplantation:



One is enough

Islet Transplantation:



+



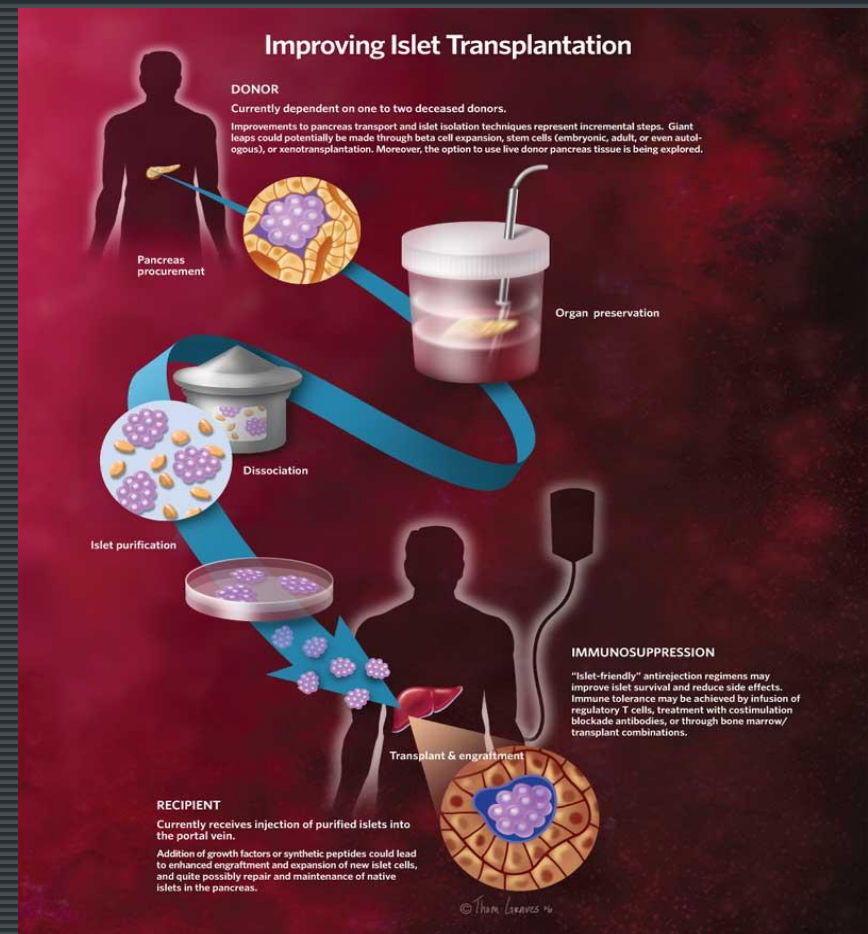
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Improving Islet Transplantation

Regarding donor, improvements
Preservation / preparation methods
Perfusion

Xenotransplantation
Stem cell derived islets
The option of live donor pancreas

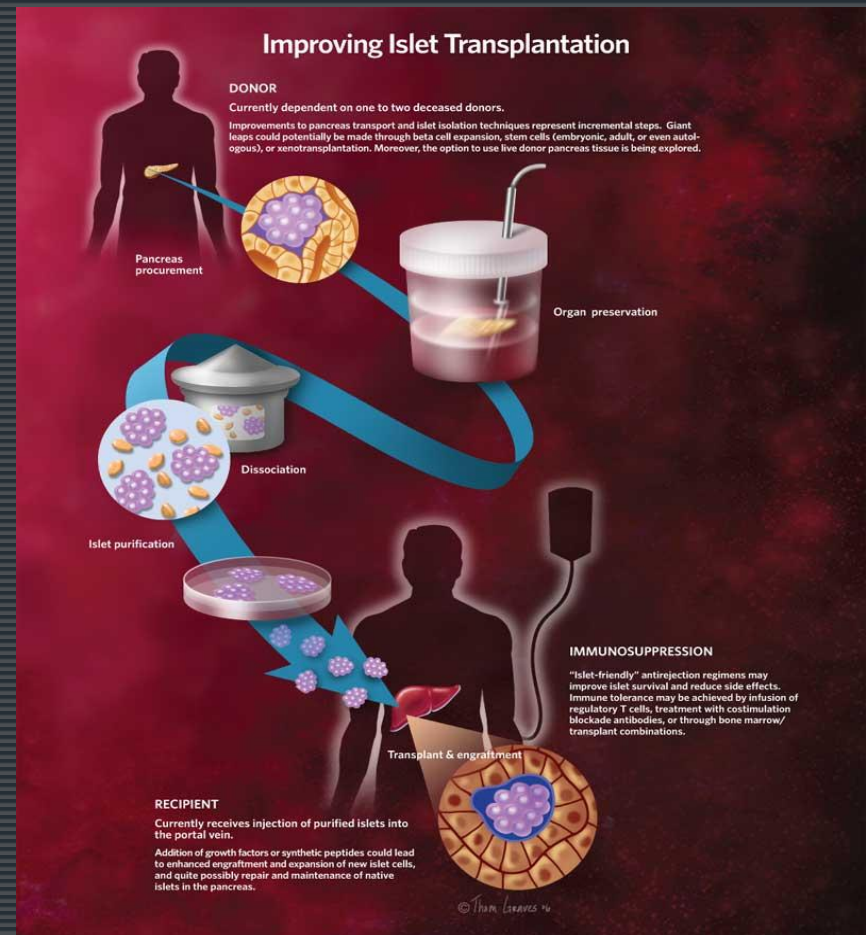
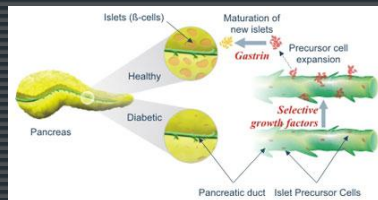
β cell expansion



Immunosuppression and Transplantation

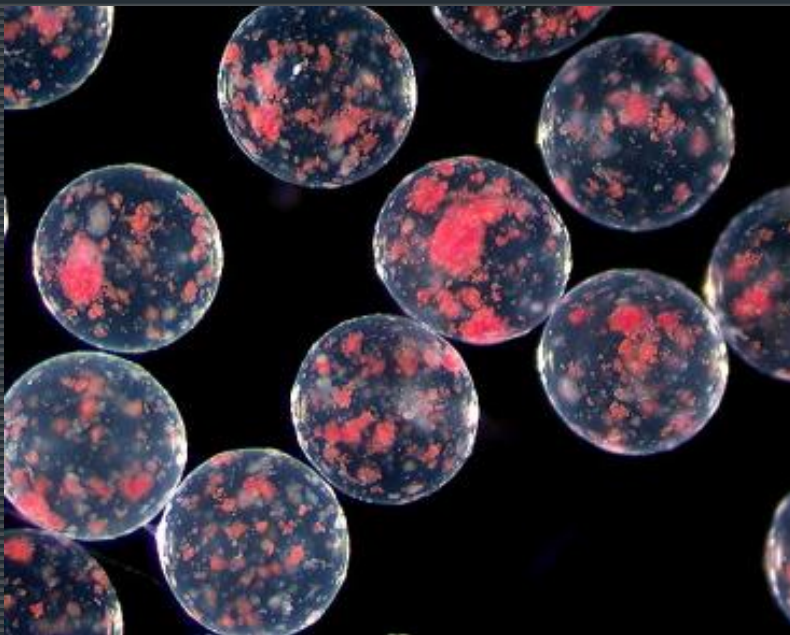
Islet friendly anti-rejection regimens may improve islet survival and reduce side effects.

Addition of growth factors or synthetic peptides could lead to enhanced engraftment.

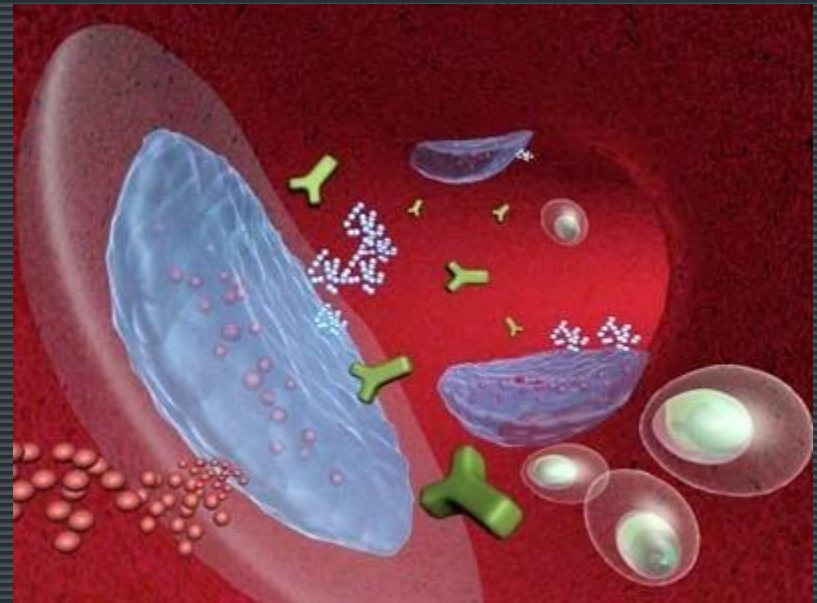


Encapsulated islet-cell graft:

The cells are generated in culture systems in the laboratory and protected by an electively permeable capsule. Islets will control the blood glucose levels in a physiological manner.



The capsule will protect against the assaults of immune cells and antibodies, but allow nutrients and insulin to pass.



CONCLUSIONS:

- Successful islet cell transplantation is now possible
 - Less invasive but less durable than pancreas transplants
 - Innovations in inhibiting early inflammation, reducing toxicity of meds needed
- Organ allocation, patient selection, and payment for islet transplantation will remain controversial topics of development of islet transplant programs