PANCREATIC TRANSPLANTATION

Essay submitted for partial fulfilment
of the master degree in general surgery

By

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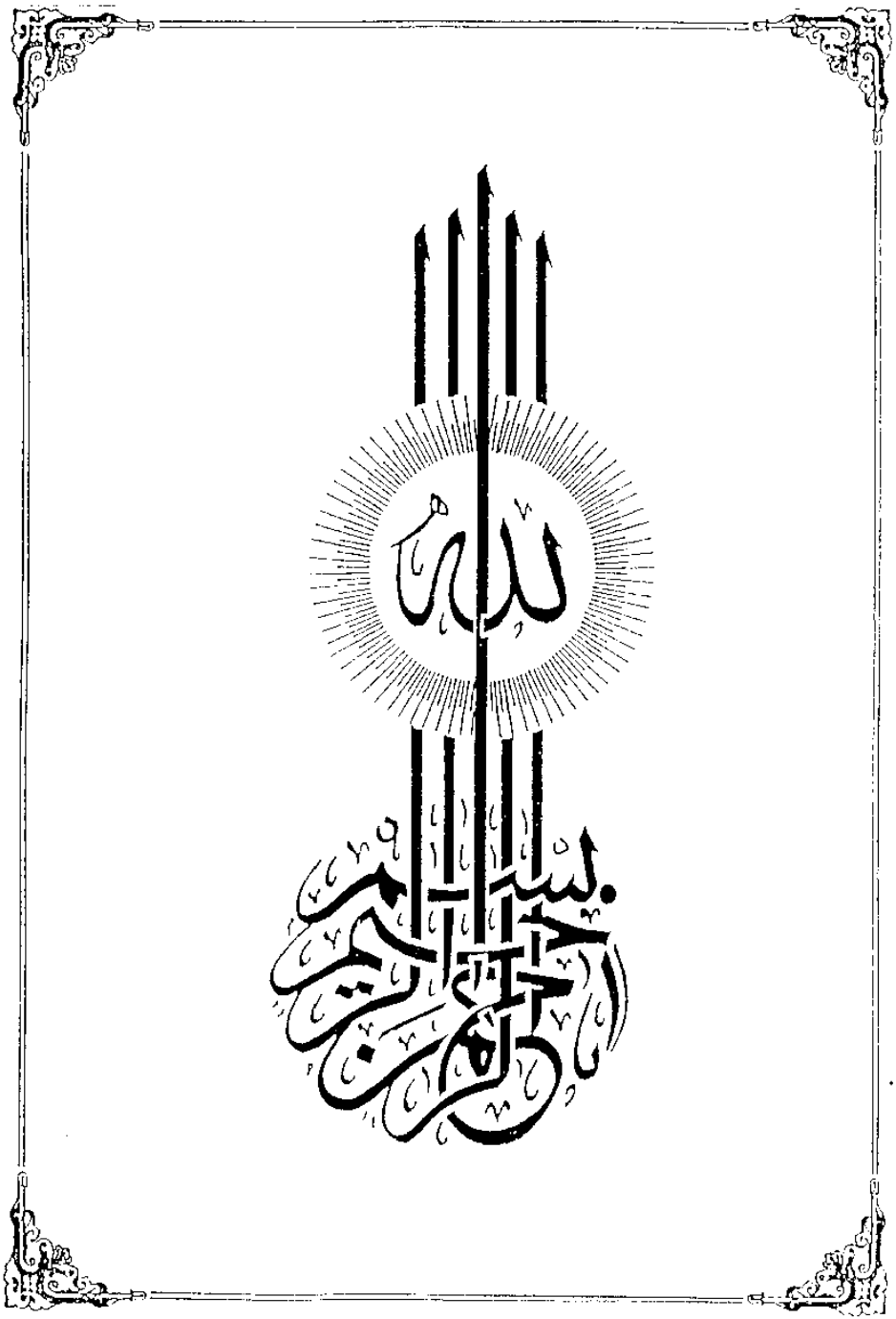
1995

ACKNOWLEDGEMENTS

Because the function of a review essay is to present concisely the basic information that forms an accepted body of knowledge, only the organization and presentation of those facts and concepts may be original. Therefore, I humbly acknowledge the numerous references from which the material presented herein has been derived. Even more humbly I acknowledge ***Prof. Abd El-Moguid El-Shinnawy****, his encouragement, advices and criticism were indispensable for the achievement of this work. To* ***Dr. Emad Abd El-Aziz Hussein****, I present my profound gratitude for his help, guidance and criticism.*

In addition, I acknowledge those uncounted and anonymous individuals who have contributed over the years to my fund of knowledge.



ABBREVIATIONS

ALG	: Antilymphocyte globulin
ATG	: Antithymocyte globulin
BD	: Bladder drainage
CAD	: Cadaver
Cr	: Creatinine
Cr Cl	: Creatinine clearance
DD	: Duplex Doppler
DD US	: Duplex Doppler ultrasound
EKG	: Electrocardiogram
EPS	: Exocrine pancreatic secretion
ESDN	: End stage diabetic nephropathy
HBAic	: Glycosylated haemoglobin
HDL	: High density lipoprotein
HFP	: Human fetal pancreas
IV	: Intravenous
KF	: Kidney function
KID	: Kidney
KT_X	: Kidney transplantation
LDL	: Low density lipoprotein
LRD	: Living related donor
PAK	: Pancreas after kidney
PD	: Pulsed doppler
PDC	: Pancreaticoduodenocystomy
PKT	: Pancreas & Kidney transplantation
PMP	: Per million population
PO	: Post operative
PTA	: Pancreas transplantation
PX	: Pancreas
SPK	: Simultaneous pancreas and kidney
TPC	: Total plasma cholesterol
TS	: Technically successful
Tx	: Transplant
UW	: University of Wisconsin
US	: United States

CONTENTS

INTRODUCTION

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Significance and need for pancreas transplantation:

"Insulin is not a cure for diabetes, but it is a potent preparation, alike for evil and for good" (Elliot Proctor Joslin, 1922)

The above sentence was stated in the year when the discovery of insulin by Banting and Best was published (Banting and Best, 1922) and when insulin preparations were introduced into therapy. E.P. Joslin was one of the pioneers of insulin therapy and founder of the Diabetes Center in Boston, USA. Unfortunately the statement is still true. Although the diabetic patients rarely die of acute complications of their disease or the insulin treatment, they suffer and finally die of secondary complications i.e. mainly macroangiopathy, microangiopathy (nephropathy, retinopathy) and neuropathy. These are predominantly caused by hyperglycaemia itself and thus, the failure of the combined efforts of doctors, nurses and patients to establish normoglycaemic blood glucose control. (Siegel & Creutz Feldt, 1989)

Prevention or amelioration of vascular and neurological complications are the main goals in modern diabetology. The most important prerequisite to achieve these aims is normalization of glucose metabolism. However long term normoglycoemia cannot be achieved in insulin dependent (Type 1) diabetes with all so far available sophisticated strategies of diabetes therapy. (Landgraf et al. 1989)

Diabetes mellitus is the most common endocrine disease and is a world wide public health problem, being the fourth leading cause of death by disease in Western countries.Estimates for insulin dependent diabetes (type 1) indicate a prevalence of 0.26 percent by age 20 in the United States. There is evidence that the incidence of this disease is

increasing in several world populations. Prolongation of life is achieved by current maintenance therapy with insulin but an increased number of diabetic patients are treated for complications including end stage renal failure now representing 10-40% of new patients on dialysis, Diabetes is also the leading cause of new cases of blindness in patients over the age of 20 (Ricordi et al., 1992).

In Sweden the incidence rate of type I diabetes has been estimated at approximately 100 newly diagnosed cases PMP/year. This is one of the highest incidences in the world. Ineeded some other Western countries have incidences as low as 20 PMP/year. Approximately 40% of all patients with type I diabetes have been reported to develop clinical diabetic nephropathy. However the incidence of end stage diabetic nephropathy in diabetic population in Sweden is only about 10% . The explanation of this marked discrepancy is the high mortality rate from cardiovascular disease in patients who have developed clinical diabetic nephropathy. Thus,three of four patients die before they become uremic. (Tyden et al., 1992A)

Pancreas transplantation is performed in insulin dependent diabetic patients to cure insulin dependence. This surgical procedure is generally associated with kidney transplantation in uremic diabetic patients. Results reported in the literature showed progressive improvement of patient and pancreas survival in recent years. Several studies have shown that successful pancreas transplantation leads to insulin independence with a near normalization of glucose metabolism although some minor metabolic abnormalities such as hyperinsulinemia and impaired glucose tolerance are still present after transplantation. The effect of pancreas transplantation on long term degenerative diabetic complications was investigated in several articles. These investigations

have shown that pancreas transplantations have a positive effect on diabetic neuropathy while diabetic retinopathy is not improved by successful pancreas transplantation. (Secchi et al., 1993)

HISTORY:

The basis for pancreas transplantation was set in 1889 when Von Mering and Minkowski showed that pancreatectomy produced diabetes mellitus in dogs. (Von Mering and Minkowski, 1889). In the years following this discovery treatment of diabetes by implantation or transplantation of pancreatic tissue was suggested and attempted by several investigators (Hedon, 1892; Minkowski, 1892; Scobolew, 1902; Williams, 1894). Series of experimental studies were initiated leading via the discovery of insulin (Banting and Best, 1922) to pancreas transplantation by vascular anastmosis (Gayet and Guillaumie, 1927) and pancreas transplantation in humans. The first series being started in 1966 (Kelly et al., 1967); (Brekke, 1988).

The first clinical pancreas transplant was performed by William D. Kelly and Richard C. Lillehei on 17th December 1966 at the University of Minnesota (Kelly et al., 1967). The body and tail segment of a cadaveric pancreas was transplanted and the pancreatic duct was ligated. The graft was placed in the left iliac fassa and a kidney was transplanted to the right iliac fassa. The recipient was a very sick, uraemic diabetic woman. The patient immediately became normoglycemic and insulin independent but she died at 2 months from a combination of rejection and sepsis. Lillehei and his associates (1976) then went on to perform a series of 13 more pancreas transplantations between the end of 1966 and 1973. The first ten transplantations were in uraemic diabetic patients of whom nine also received kidney transplants, while the last three were in non-uraemic diabetic patients. (Najarian, 1988)

Coincident with the arrival of immunosuppressive drugs, there were a number of segmental pancreatic homografts that were performed after the early Minnesota experience but the results were not good. Up to 1977 only 55 transplants had been done worldwide and graft survival was no more than 3% at 1 year. (Brooks, 1989)

There was resumption of segmental and whole organ pancreatic transplantation in 1978. Since that time there has been doubling of the number of grafts every other year. From 1966 to 1984, 501 whole organ or segmental organ transplants were performed (Brooks, 1989).

The history of clinical pancreas transplantation largely revolves around development and application of various surgical techniques for grafting. The first pancreas transplant was segmental with duct ligation. Lillehei and collegues (1976) however favored the whole pancreas transplant technique with anastmosis of the graft duodenum or a button of the papilla of Vater to the recipient bowel. Gliedman and associates (1973) introduced the novel technique of anastmosis of the duct of a segmental pancreas graft to the recipient ureter in uremic diabetic patients. A modification of urinary drainage was made by Sollinger and associates (1984) in which the pancreatic duct of segmental grafts or a portion of the duodenum of whole pancreas grafts was anastmosed directly to the recipient bladder. Groth and collegues (1976) applied segmental pancreas transplants with anastmosis to a Roux-en-Y limb of recipient bowel in the early 1970s. This group has continued to use this basic technique with certain refinements into the 1980s. In 1978 Dubernard and Co-workers reported on a new method of pancreas transplantation in which the duct was injected with a synthetic polymer . (Sutherlend et al., 1988a)

Today the three most popular techniques for management of the

graft pancreatic duct are polymer injection, enteric drainage and bladder drainage all of which have relative merits and all of which can succeed. (Sutherland et al., 1988a)

ANATOMY OF THE PANCREAS

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Development:

The pancreas develops from two endodermal buds (the dorsal and ventral pancreatic buds) at the junction of the foregut and midgut. The ventral bud is on the same side as and immediately below the hepatic diverticulum. Growth changes in the duodenal wall are such that hepatic and ventral pancreatic buds move round dorsally to lie below the opening of the dorsal pancreatic bud. The two pancreatic elements then fuse, the ventral portion becoming the uncinate process and adjacent part of the head, and the rest of the gland being derived from the dorsal part. The duct systems of the buds also fuse in such a way that the adult main duct represents (1) the duct of the ventral bud near and when entering the duodenum and (2) the duct of the dorsal bud and its anastmotic connection with the ventral bud duct in the rest of the gland. The adult accessory duct is the duodenal end of the duct of the dorsal bud. (Mc Minn & Hobdell, 1974)

Gross anatomy:

The pancreas is a solid viscus that lies transversely across the posterior abdominal wall at the level of L1 and L2. It lies deep within the epigastrium in a retroperitoneal position. The pancreas is quite firmly fixed in position with only slight superior and inferior range of movement. Because the mid portion of the body of the pancreas overlies the abdominal aorta, aortic pulsation may be transmitted to the gland. (Lindner, 1989)

The expanded head lies in the concavity of the of the duodenum, overlapping the descending and horizontal parts. The head is anterior to the inferior vena cava, to the bile duct which grooves its superolateral

part and to the aorta where its inferomedial extension (uncinate process) passes posterior to the superior mesenteric vessels. The head is crossed anteriorly by the transverse colon or its mesentery and superiorly by the first 2-3 cm of the duodenum and join the body anterior to the formation of the portal vein. (Romanes, 1992)

The body passes to the left across the aorta (anterior to the superior mesenteric artery), the left crus of the diaphragm, psoas major, the left renal vessels and kidney. It is posterior to the omental bursa and stomach but its tuber omental is in contact with the lesser omentum immediately inferior to the coeliac trunk. The splenic artery runs a sinuous course along its upper margin. The splenic vein lies on its posterior surface and is joined by the inferior and superior mesenteric veins. The blunt end of the body, the tail, lies in the lienorenal ligament and may touch the hilum of the spleen. (Romanes, 1992)

The average weight of the pancreas is 85 g and the usual length is 12-15 cm, the normal anteroposterior thickness of the head is less than 2.5 cm, the neck 1.5 cm, the body 2 cm and the tail 2.5 cm.

The pancreatic ducts drain pancreatic secretions into the duodenum and they comprise two separate systems:

* The major system is the duct of Wirsung, which empties into the ampulla of Vater in conjunction with the common bile duct.
* The minor system is the duct of Santorini, which empties into a minor papilla approximately 2 cm above the ampulla of Vater (Jarrell et al., 1986).

Pancreatic vasculature:

ARTERIES:

Arterial supply to the pancreas is from both the celiac and superior mesenteric distributions. The great pancreatic artery, caudal pancreatic arteries and an occasional dorsal pancreatic artery all arise from the splenic artery. The superior pancreaticoduodenal artery arising from the gastroduodenal artery, bifurcates into anterior and posterior branches which supply the head of the pancreas and the duodenum. The inferior pancreaticoduodenal artery arising from the superior mesenteric artery also bifurcates into anterior and posterior branches which anastomose with those from the superior pancreaticoduodenal artery (April, 1990).

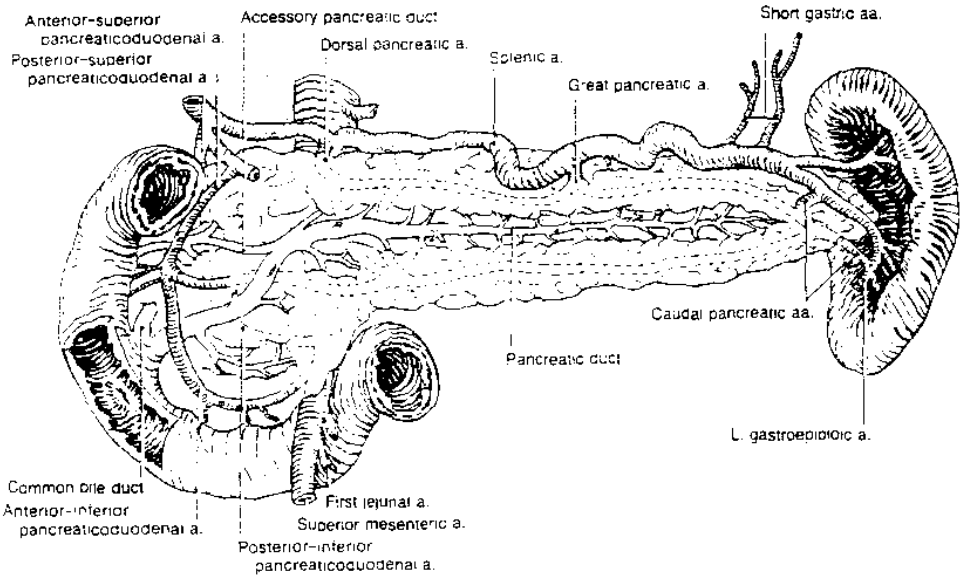

Fig. 1: Pancreas and spleen. The primary and secondary (if present) pancreatic ducts empty into the descending portion of the duodenum. The pancreas receives its blood supply from branches of the celiac and superior mesenteric arteries. The spleen receives a profuse blood supply from the splenic branch of the celiac artery. (April, 1990)