The Pancreas as an endocrine gland-
Exocrine and Endocrine functions exist!!

Below the stomach is the pancreas consisting of a head, body and a tail. It is considered an accessory gland in digestion due to its exocrine function.

The pancreas produces enzymes that break down all categories of food stuffs. These enzymes are then emptied into the small intestine along with bile from the liver. The exocrine product of the pancreas is called pancreatic juice and it passes to the small intestine via the pancreatic duct.

Pancreas has 2 portions:
1) Acinar cells – full of RER-containing digestive enzymes (proteins) and other juices. This represents the exocrine portion of the pancreas since the contents empty into a duct.
2) Islets of Langerhans – actually are the endocrine portion of the pancreas because they release hormones into the bloodstream without a duct.

Pancreatic juice contains enzymes for digesting all three major types of food: proteins, carbohydrates, and fats. It also contains large amounts of bicarbonate ions to neutralize the acid chyme emptied by the stomach into the duodenum.

1) Proteolytic enzymes – trypsin, chymotrypsin (both make smaller peptides), carboxypeptidase (breaks off amino acids from the carboxyl ends of peptides), ribonuclease; and deoxyribonuclease (breaks two split two types of nucleic acids – ribonucleic acid and deoxyribonucleic acid).
2) Carbohydrate digestive enzymes – pancreatic amylase (hydrolyzes starches, glycogen and most other carbs except cellulose).
3) Fat digestive enzymes – pancreatic lipase (hydrolyzes neutral fat into fatty acids and monoglycerides), cholesterol esterase (hydrolyzes cholesterol esters) and phospholipase (hydrolyzes fatty acids from phospholipids).

When each of these proteolytic enzymes are synthesized in pancreatic cells, they are found in inactive forms such as trypsinogen, chymotrypsinogen, and procarboxypolypeptidase. They only become activated after being secreted into the intestinal tract. Important not to become activated until these proteolytic enzymes have been secreted into the intestine for the trypsin and others would digest the pancreas itself. The same cells that make trypsin secrete another substance called trypsin inhibitor simultaneously. It prevents activation of trypsin both inside the secretory cells and in the acini and ducts of the pancreas. Trypsin activates most of these other enzymes so the TI prevents their activation until out of the pancreas.

Acute pancreatitis – seen commonly clinically. This is where the pancreas becomes severely damaged or a duct becomes blocked and large quantities of pancreatic secretion become pooled in the damaged areas of the pancreas. The TI is overwhelmed by the quantity and as a result the proteolytic enzymes become activated and literally digest the entire pancreas within a few hours and seen in the condition as acute pancreatitis. It is often lethal and if not, leads to a lifetime of pancreatic problems. Would see an increase in amylase to indicate problems with pancreas.

Exocrine portion acinar cells secrete digestive enzymes into the small intestine along with bicarbonate (HCO3-) which neutralizes the gastric acid produced by the stomach.

Two ducts: 1) Primary is the Duct of Worsung which unites with the common bile duct, and 2) secondary is the Duct of Santorini.

Regulation of these pancreatic juices is controlled by 2 hormones not released from the pancreas but released by the intestinal mucosa cells of the small intestine:
1) Secretin – released due to the presence of acid chyme in the small intestine. Chyme is partially digested food that leaves the stomach. Bicarbonate is released as a result of secretin trying to neutralize acid chyme.
2) Cholecystokinin – released due to presence of partially digested foods in S.I. It causes the gall bladder to contract.
And the sphincter of Oddi to relax. The sphincter of Oddi is the sphincter that separates the common bile duct and pancreatic duct from the small intestine. So by relaxing it, bile and pancreatic juices can be dumped into the small intestine.

That is the exocrine portion of the pancreas. Endocrine function of the pancreas -
Between exocrine cells are cluster of cells called the Islets of Langerhans that contain actually 4 types of cells:
1) Alpha cells – produce glucagon (hormone); 25% total cells
2) Beta cells – site of insulin synthesis and secretion; 60%
3) Delta cells – produce somatostatin (inhibits GH); 10%
4) PP cells – least common; secretes pancreatic polypeptide; <5%

Factors Regulating Insulin Secretion
1) Hi plasma glucose levels – insulin is secreted to return glucose levels back to normal. This is the biggest negative feedback to regulate insulin secretion! Insulin increases in 3 stages: a) 1st 5 minutes after the initial challenge is from preformed beta cell stores then decreases halfway back to normal; b) 20 min. from the initial challenge and lasts for 1 – 2 hours is newly synthesized insulin and is higher than the initial release of insulin; c) days from initial challenge is from hypertrophication of beta cells and could destroy them or burn them out.
2) Hi plasma amino acids – just after a hi protein meal, arginine and lysine stimulate the beta cells to increase insulin secretion. Amino acids and glucose together potentiate the effects on insulin. Increased insulin enhances entry of these amino acids into cells so lowers the amino acids and promotes protein synthesis.

Factors Influencing Insulin Secretion, cont.
3) Fatty acids and ketone bodies – increases insulin secretion
4) Hormones: a) GI hormones – gastrin, secretin, cholecystokinin, and gastric inhibitory peptide all cause a moderate increase in insulin. Released after eating a meal in “anticipation” of an increase in preparation for the glucose and amino acids to be absorbed from the meal. These also double the rate of insulin secretion following an average meal.
   b) Others – glucagon, GH, cortisol, to lesser extent progesterone and estrogen. These either increase insulin secretion or potentiate glucose stimulus for insulin secretion. Importance is that if any one of these has prolonged secretion in large quantities then the beta cells could be overworked and exhausted to eventually cause diabetes. Pharmacological doses of any of these could lead to diabetes especially if the person has a diabetic tendency.
Effect of Insulin on Carbohydrate Metabolism

1) Promotes glucose uptake into LIVER to be stored as glycogen. This occurs almost immediately after glucose is increased and insulin is released. This is for the times between meals when glucose levels fall and at that time, glycogen is then split back into glucose and released back into the blood to bring glucose levels back to normal.

2) Insulin stimulates an increase in glycogenesis especially in skeletal muscle and liver and glucose uptake by the liver cells all with the net effect of increasing the amount of glycogen stored in the liver.

3) Enhances conversion of excess liver glucose into fatty acids which are then transferred into adipose tissue and deposited as fat.

4) Insulin inhibits gluconeogenesis (in the liver).

5) Insulin inhibits glycogenolysis.

Summary: Lowers blood glucose; The only hormone to do so!!

Effect of Insulin on Fat Metabolism

Insulin increases the utilization of glucose by most of the body’s tissues which automatically decreases the use of fat so serves as a “fat sparer”. It promotes fatty acid synthesis within liver cells which are then transported to adipose cells for storage. Some fat synthesis occurs in fat cells themselves.

How does it spare fat:

a) Insulin increases the transport of glucose into liver cells. After glycogen formed, xs glucose is available to form fat.

b) Large amounts of fatty acids are used by the liver to form triglycerides, the storage form of fat. They eventually make their way through the blood to be stored in fat cells.

c) Insulin inhibits the action of hormone-sensitive lipase which breaks down fats.

d) Insulin promotes glucose transport into the fat cells.

Effects of Insulin on Protein Metabolism

Insulin’s overall effect on proteins is to cause proteins to be stored, not used for energy source. How does it do this?

Insulin:

1) Causes active transport of many amino acids into the cells, most especially valine, leucine, isoleucine, tryosine, and phenylalanine. So shares with GH the ability to increase uptake of amino acids into cells. However, not the same ones.

2) Increases the rate of translation of messenger RNA, thus forming new proteins.

3) Increases the rate of transcription of DNA in the nucleus to form increased quantities of RNA, ultimately forming new proteins.

Summary of Insulin on Metabolism:

1) Carbohydrates: ↑ glucose utilization, ↑ CHO storage, use of CHO for energy.

2) Fats: ↑ fat storage, not used for energy

3) Proteins: ↑ protein anabolism, ↓ protein catabolism

Insulin also has a synergistic effect with GH on growth. Each was tested alone and caused almost no growth. But a combination of the two does cause a dramatic effect, each promoting its specific function that is separate from the other.
Another pancreatic Hormone - Glucagon

Glucagon – a large polypeptide with a MW of 3485 and is composed of a chain of 29 amino acids. It is secreted by the alpha cells of the pancreas when blood glucose concentrations falls. It has several functions diametrically opposed to insulin. The most important is to increase blood glucose levels, exactly opposite to that of insulin. For this reason, it is also called “hyperglycemic factor”. Most of its action is at the liver, however, and therefore is not quite as potent.

Factors Regulating Glucagon Secretion

1) Low Plasma glucose concentration – when levels get to the hypoglycemic stage below 90 g/dl (normal fasting level), glucagon can increase several-fold as a result. This is the most potent factor controlling glucagon secretion. Likewise, increasing glucose to hyperglycemic levels will decrease plasma glucagon. Once glucagon released, it will mobilize glucose from the liver to correct the hypoglycemia.

2) Hi plasma amino acids - stimulate the release of glucagon as in after a protein meal, which is similar to the way insulin is released so it is not opposite here.

Factors Regulating Glucagon Secretion, cont.

The reason they both are released after protein meal is that while insulin is making glucose and amino acids enter the cells, decreasing their amount in the blood, glucagon is allowing the liver to bring more glucose into the bloodstream for cellular energy which is needed for protein synthesis.

3) Exercise – in exhausting exercise, glucagon increases as much as five-fold. However, blood glucose doesn’t really fall. So why? A) May be beneficial not to prevent glucose from falling to a low level when you need it most; B) Could increase glucagon due to increased circulating amino acids from exercise; C) Could increase due to nervous stimulation of Islet cells.

Factors Regulating Glucagon Secretion, cont.

Effects of Glucagon

Glucagon has two major effects:

1) Breakdown liver glycogen (↑ glycogenolysis) to increase blood glucose.

2) Increase gluconeogenesis in the liver.

Both of these enhance the availability of glucose for other organs.

Other activities:

3) Activates adipose cell lipase to make available increased amounts of fatty acids for energy source. It also inhibits the storage of triglycerides in the liver. Breaks down fats.

4) Causes breakdown (catabolism) of proteins in the liver only.

Insulin = hormone of feasting;
Glucagon = hormone of fasting.

Summary of Glucagon:

- Inhibits hepatic protein synthesis or causes hepatic protein catabolism +
- Stimulates liver gluconeogenesis +
- Stimulates lipolysis for energy +
- No effect on muscle proteins (no sig. chg. in blood amino acids) +
- Increase blood glucose for the brain but not for cellular energy +

Which is blood glucose regulation so important? It is the only nutrient that can be used by brain, retina and germinal epithelium of the gonads in sufficient quantities to supply them with their energy. Any small amounts made by liver between meals is used for metabolism of the brain only, otherwise, it would go to muscles and other tissues and leave the brain with no nutrition.

Hypoglycemic = lethargy, vision problems, acute, tired, dizzy
Hyperglycemic = (Chronic) systemic diuresis with cellular dehydration, loss of glucose in urine followed by fluid, depletes body electrolytes and fluid, dehydration in body.

Pathologies (Diabetes mellitus)

3rd leading cause of death in US; 2nd leading cause of blindness.

Two Major types: Juvenile onset and Maturity-onset diabetes

- Heredity plays an important role in each.
- Is caused by diminished rates of secretion of insulin by the beta cells of the islets of Langerhans.
- Juvenile is rapid in onset, usually early in life but not always and results from heredity and makes up 20% of all.
- Maturity-onset results from degeneration or suppression of beta cells and makes up 80% or more of all.
- Obesity predisposes to maturity-onset due to two reasons:
  1) In obesity, the beta cells become less responsive to stimulation by increased blood glucose. So, the surge of insulin secretion following a meal is less marked in obese people.
  2) Obesity also greatly decreases the number of insulin receptors in the insulin target cells throughout the body. So, larger quantities of insulin are required to have the same metabolic effects in obese as in the nonobese. Therefore, those who have obesity type can be treated simply by dietary control of the obesity itself.
Pathological physiology of Diabetes mellitus

Most of the pathology can be due to 1 of the three major effects of insulin lack:

1) A decreased utilization of glucose by the body cells, resulting in an increase of blood glucose to as high as 300 – 1200 mg/dl.

2) A markedly increased mobilization of fats from the fat storage areas, causing abnormal fat metabolism as well as deposits of lipids in vascular walls to cause atherosclerosis.

3) Depletion of protein in the tissues of the body.

Other problems not so readily apparent:

1) Loss of glucose in the urine, glycosuria, in a diabetic.
   If the blood glucose rises above 225 mg/dl at the kidney, a significant portion of glucose that is filtered will not be reabsorbed and will instead spill into the urine.

2) Dehydrating effect of Elevated blood glucose in diabetics.
   If blood glucose is 1200 mg/dl, 12x normal, there will be a significant dehydration of the tissue cells since water follows glucose osmotically which keeps glucose in extracellular fluid compartments. In addition to dehydrating cells, the glycosuria causes an osmotic diuresis. If too much intracellular and extracellular dehydration, the diabetic could go into circulatory shock – generalized inadequacy of blood flow through the body, to the extent that the tissues are damaged because of too little flow, esp. too little O2 and other nutrients. Even the CV system itself is damaged and begins to deteriorate as it becomes worse.

3) Acidosis in diabetics.
   The shift from CHO to fat metabolism increases in diabetics, the levels of acetoacetic acid, \( \beta \)-hydroxybutyric acid and ketones increases which leads to increase acid content of the blood. If these acids in an uncontrolled diabetic are high enough the condition could lead to acidic coma and death within hours. The individual is disoriented and smells of ketone bodies which has a fruity smell. Has been mistaken as a "wino" syndrome but was merely the 3 ketones causing it. Acetone is volatile and vaporized into expired air.

Other diabetic symptoms:

1) Polyuria (excess urine production)
2) Polydipsia (excess drinking of water)
3) Polyphagia (excessive eating)
4) Loss of weight
5) Asthenia (lack of energy)

Treatment of Diabetes Mellitus

Juvenile diabetes – Type I Diabetes
Insulin control, diet, weight control and exercise.

Mature-onset – Type II Diabetes
Diet, weight loss, and exercise to increase receptor responsiveness; and, sulfonylureas to increase number of receptors.