The Liver and Carbohydrates

Carbohydrates: Glucose and Fructose enter the liver via the hepatic portal vein.

What happens to fructose? Generally, it is used by the liver for immediate energy. Excess fructose is stores as triglycerides in the liver or shipped off to adipose tissue for long-term storage.

What happens to glucose? The liver uses what it needs immediately and lets some of it enter the blood to keep blood sugar stable. Excess is stored as glycogen in a process called **glycogenesis**; futher excess is stored as triglycerides in the liver (this process is called **lipogenesis**) or shipped off to adipose tissue.

Between meals **glycogenolysis** is the process of breaking glycogen back into glucose molecules to be released into the blood to maintain blood sugar.

Once glycogen stores are depleted, the liver can

- use fatty acids and amino acids to build glucose to maintain blood sugar. This process is called **gluconeogenesis**.
- use fatty acids to make ketone bodies, which can substitute for glucose as fuel. This process is known as **ketogenesis**. It appears that in some disease states, such as Parkinson's Disease epilepsy, autism, and Alzheimer's, the neurons of the brain need fuel and are not able to use glucose normally (due to insulin resistance?). In these cases, ketone bodies may be used as treatment and have seen some success. The liver can be stimulated to produce ketones by:
    - Fasting
    - Low-carb diet
    - Coconut oil
    - Butter

Chronically, an excess of calories in carbohydrate form may force the liver to become "fatty". Longer spacing between meals and/or a temporary fast can stimulate lipolysis of this stored fat.

If the liver becomes resistant to a hormone called insulin, it may continue to allow sugar to enter the bloodstream and blood sugar can become too high.

Key Idea: The liver is critical in the maintenance of stable blood sugar. If blood sugar dips too low, the liver breaks down glycogen and puts more glucose in the blood.

- **Insulin** (a hormone from the pancreas) signals the liver to **STORE** glucose as glycogen so that blood sugar does not go too high.
- **Cortisol** (a hormone from the adrenal glands) signals the liver to **MOBILIZE** glucose into the bloodstream to raise blood sugar and deal with potential stress.

The Liver, Part 2

The Liver and Ammonia – Without the Liver You'd be Angry and Confused!

- Ammonia (NH_3) is a nitrogenous waste produced by amino acid metabolism.
- The liver converts ammonia into the slightly less toxic substance urea.
- Urea is then excreted by the kidneys.
- Malfunctioning hepatocytes may allow ammonia to build up in the bloodstream, which can ultimately cause a patient with end-stage liver disease to have personality/behavior changes.

The Liver and Plasma Proteins—Without the Liver You'd have Low Blood Pressure and Bleed to Death!

- Makes clotting factors, including fibrinogen
- Makes albumin, which is critical to maintaining blood pressure. Albumin is a big protein that "pulls" water toward it; we call this osmotic pressure. Albumin provides osmotic pressure in the blood vessels to keep blood pressure adequate.

The Liver and Iron Metabolism –Without the Liver You'd be Anemic!

- Stores iron
- Makes transferrin, a transporter for iron in the blood
- Makes hepacidin, a molecule that blocks iron absorption from the gut when levels of iron are high enough in the body

The Liver and Bile – Without the Liver You'd Have Jaundice and be Unable to Digest Fat!

- The liver helps break down old RBCs. It takes the leftover yellowish pigment of red blood cells (**bilirubin**) and conjugates it so that it dissolves in bile and the blood.
    - Some of this **conjugated bilirubin** is then released back into the bloodstream, where it is excreted by kidneys in urine. This makes urine yellow. It is called **urochrome** when measured in urine.
- Conjugated bilirubin leaves the liver as a component of bile (bile also contains bile salts, cholesterol)
- Bile is released from the gall bladder and liver when fat enters the duodenum.
- Bile helps emulsify fats, then the salts and some of the cholesterol are reabsorbed and reused. The conjugated bilirubin is converted into stercobilin and exits the body in feces.
- Any problems (blocked bile duct or inadequately functioning hepatocytes) that cause bilirubin to build up in the blood result in jaundice. UV light is sometimes prescribed for infants with jaundice because the UV light breaks down bilirubin.

The Liver, Part 3

The Liver and Lipoproteins

- Approximately 80% of the cholesterol in your body is made by the liver. ~20% is from diet.
- Excess carbohydrates in a meal are stored as triglycerides and packaged, along with some cholesterol, into transport proteins called Very Low Density Lipoproteins (VLDL).
- The more lipid that is contained in a lipoprotein, the lower its density.
- The liver also produces LDLs and other lipoproteins that vary in how much lipid they contain. High density lipoproteins (HDL) carry small amounts of triglycerides and cholesterol.
- These lipoproteins circulate in the blood to carry cholesterol and triglycerides to body cells.
    - Structural uses (building more cells requires cholesterol)
    - Hormone production (testosterone, estrogen, and cortisol, for example)
    - Energy use (triglycerides are the favorite fuel of muscle cells, for example)
    - Long-term Storage (adipose tissue)
- Because cholesterol may be associated with increased risk for CV disease, statins have been VERY popular in recent years. These drugs inhibit the liver's ability to synthesize cholesterol.
    - Clinical trials show that these drugs may reduce risk of a second heart attack in some male patients. In patients without a previous heart attack, there is no significant evidence that statins prevent a heart attack. Statins increase the risk of diabetes and liver damage.

The Liver Protects Against Invaders and Toxins

- The liver detoxifies the blood from the intestines of possible toxins that were ingested.
- The liver modifies most drugs that are taken orally.
    - Drugs will be modified in their "first pass" through the liver, and must be designed to still be active despite modification.
    - Drug dosing is based on how many "passes" through the liver a drug can make before it is deactivated completely.
- Kuppfer cells are specialized macrophages that reside in the liver and prevent most pathogens from entering the bloodstream, even if they did manage to get into the submucosal blood vessels of the gut.
    - Well-known pathogens of the liver are the Hepatitis viruses
        - ✓ A: oral/fecal route
        - ✓ B: body fuids (sexually transmitted disease); blood-borne (tattooing, needle prick)
        - ✓ C: blood-borne (intravenous drug use or blood transfusions)

The Liver and Vitamin Storage

- The liver stores fat-soluble vitamins: A, D, E, K
- Eating liver is like taking a powerful multi-vitamin