Liver
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Structure [1]

- 2\textsuperscript{nd} largest organ
- 1\textsuperscript{st} largest gland
- Weighs 3 pounds
- Contains:
  - Hepatocytes
  - Bile Canaliculi
  - Hepatic sinusoids

Figure 1: The liver [1]
Hepatocytes [2]

- Hepatocytes are epithelial cells which make up about 80% of liver volume.
- They play a key role in metabolic, secretory and endocrine functions.
- These cells initiate formation and secretion of Bile, which is a yellow, brownish, or olive-green liquid.
- **Bile** is a detoxifying and digestive secretion liquid needed for the absorption of dietary fats
- Help maintain hemostasis by regulating blood levels of substances such as cholesterol and glucose.
Bile Canaliculi

- These are ducts located between hepatocytes.
- They collect bile, merge and form larger right and left hepatic ducts which unite and exit the liver as the common hepatic duct.
- The common hepatic duct joins the cystic duct from the gallbladder to form the common bile duct. Bile then enters the small intestines to participate in digestion.
Hepatic Sinusoids [2]

- Blood capillaries located between rows of hepatocytes.
- They are highly permeable.
- They receive oxygenated blood hepatic artery and deoxygenated blood from branches of the hepatic portal vein.
- Hepatic sinusoids converge and deliver blood to the central vein, then from the central vein the blood flows into the hepatic vein. This blood then drains into the inferior vena cava.
- Note: Bile flows opposite to the blood direction. Why?
- Contain Kuffer Cells, phagocytes which destroy damages white and red blood cells, bacteria and other foreign matter in the venous blood draining from the gastrointestinal tract.

Figure 2: Hepatic blood flow [2]
Structure

Histologically, the liver is composed of hepatocytes, bile canaliculi, and hepatic sinusoids.

Figure 3: Histology of the liver [2]
1. Carbohydrate metabolism:
   - Maintains normal blood glucose levels:
   - When blood glucose is low liver breaks down glycogen, amino acids and lactic acid and releases glucose into blood stream.
   - When blood glucose is high (after a meal) liver converts glucose to glycogen and triglycerides and stores them.

2. Lipid Metabolism:
   - Liver generates ATP by breaking down triglycerides and fatty acids
   - Synthesizes cholesterol and uses cholesterol to make bile salts.

3. Protein Metabolism:
   - Toxic ammonia (NH3) is converted into less toxic urea and excreted in urine, result of ammonium breakdown for ATP.
   - Synthesizes most plasma proteins such as albumin and protein for blood clotting.

4. Processing of Drugs and Hormones:
   - Detoxifies toxins such as alcohol and metabolizes then excretes drugs into bile such as penicillin.

5. Removes albumin bound toxins via degradation

6. Excretion of Bilirubin:
   - Is a derivative of aged red blood cell heme, absorbed by liver via blood and excreted into bile. Most of Bilirubin is metabolized in the small intestines.
Liver Failure [3]

- **Chronic Liver Failure:**
  - the patient becomes jaundiced, develops fluid retention and may develop kidney failure & ultimately coma & death.

- **Liver Cirrhosis:**
  - causes normal liver tissue to be replaced by scar tissue, which blocks the flow of blood though the liver and slows the processing of nutrients, hormones drugs and TOXINS. Also, slows liver protein production. Causes Liver Cancer.

- **Chronic (lasts longer then 6 months) Hepatitis B, C and D (deadliest):**
  - Inflammation of the liver due to viruses, drugs, alcohol abuse and chemicals destroying liver cells and presence of inflammatory cells in liver cause inflammation. [3] [4]
  - Produces cirrhosis and possibly cancer of liver.

Note: “According to the Natural Institute of Health Cirrhosis is the 12th leading cause of death by disease.” [3]
Liver Research

Liver research can be divided into 3 main categories:

- **non-biological** chemical processing plants:
- MARS (Molecular Adsorbents Recirculating System)
- Fractionated Plasma Separation and Absorption (FPSA)
- SPAD (Single Pass Albumin Dialysis)
  - bio-artificial organs using modified xenografts (other species) or allografts (same species)
- Bio-artificial Liver Support (BAL):
  - cells in bioreactor Hepatoblastoma-derived cell lines, human or porcine
- Liver sectioning (implanting only a section of liver)
  - tissue-engineered organs
- stem cell research: Articles: *World's First Artificial Human Liver Grown In Lab*
- stem cells and Lymph nodes
- Stem cells and potential to fix damaged liver tissue
Molecular Adsorbents Recirculating System (MARS)

**Figure 2.** MARS. It consists of two parallel circuits communicated by an intermediate circuit (albumin) with ion exchange resins are located (adsorption columns) and an activated charcoal column. (Author’s diagram.)
MARS Structure

- **Dialysate** is defined as a chemical substance that enables metabolite and toxin exchange and clearance.
- **MARS is made up of 3 main parts:**
  1. **Albumin hemodialyzer:** also called hemofilter acts as a dialysate through a hollow chamber which enables the removal protein bound toxins such as amino acids via absorption. During the process albumin is also dialyzed and filtered, then returned to the system free of toxins.
  2. **Activated charcoal interface:** this enables detoxification of organic anions by absorption of ionic elements.
  3. **Anion exchange resin interface:** It helps establish and maintain electro-neutrality and electrochemical balance, therefore homeostasis is maintained. [5]
How does MARS function?

MARS is like Kidney dialysis except it uses albumin dialysis to remove water-insoluble toxins whereas Kidney dialysis only removes water soluble insoluble toxins.

-MARS selectively removes the albumin bound substances from the blood.

- the blood is detoxified in the MARS FLUX filtering unit. Blood and human serum albumin flow past each other but separated by a membrane. There is never any contact between patient blood and the absorber columns. The albumin is freed from toxins, re-circulated and reused for blood detoxification. [6]

-Note: only a fixed amount of albumin (dialysate) is used for a cycle (600 ml of 20 % Hyman Albumin).

MARS has been shown to be effective at reducing blood levels of the following:

Among the toxins that MARS can remove are: [7]

- Bilirubin, bile acids
- Phenols
- Dioxin-like substances
- Tryptophan
- Ammonia
- Copper, iron

Reduction in the above resulted in a significant impact on the progression to hepatic encephalopathy in Acute Liver Failure and the reduction of its severity. MARS has been shown to facilitate hepatic “recovery.”
Elimination of Toxins

- Dialysate albumin
- Albumin related binding sites
- Toxic, albumin-associated compounds, e.g. bilirubin
- Free low molecular weight substances
- Other plasma and carrier proteins, e.g. TBG

Membrane

Plasma-albumin

Protein-layer

MARS MEMBRANE
Why use MARS?

• MARS is a temporary measure, which gives immediate reduction in the levels of toxins, but the benefits can be observed only for short period. After discontinuation of the therapy, the accumulation of toxins starts again. The patient therefore has to be on a continuous prolonged treatment.
• Due to high demand for livers and low cadaver/donor supply there is a long wait time.
• MARS is used to bridge this time.
• MARS is also used when the patient is not in good condition secondary to liver disease, to improve the patients condition to increase tolerance to surgery better. [7]
HepatAssist 2000 System
by Circe Biomedical

Bio- artificial Liver support (BAL): Using Porcine (Pig) Hepatocytes
This type of system was designed to support vital hepatic functions and became a bridge therapy that does not only adsorb toxic solutes but also plays a key role in metabolism and synthesis.

Note: bioreactors where plasma undergoes a process of ultrafiltration, metabolic exchange, oxygenation and allogenic plasma addition before entering the patient again

PROCESS STEPS used by HepatAssist
[9]
- Approximately six hours per treatment.
- The patient’s blood is first separated into plasma and cellular components in a plasmapheresis device.
- The cellular component remains in the plasmapheresis device, while the plasma goes through further processing in the bioreactor.

- The plasma first goes through two charcoal filters, which filter out of the plasma massive bacteria and other matter that the system’s hepatocytes might be unable to handle.
- The second round of detoxifying involves the plasma running through the hepatocyte-lined hollow fiber column.

- The cleaned plasma is then joined with the plasma component, which was stored in the plasmapheresis device and the whole blood is reinfused into the patient.

- During the process, a membrane oxygenator and heater are housed between the charcoal filters and hepatocyte bioreactor, with the purpose of keeping the plasma and the hepatocytes over which they flow at body temperature. The membrane oxygenator provides the porcine hepatocytes with the requisite oxygen for correct function.
**Figure 3.** Schematic configuration of the lines and safety devices for the Hepatassist® system. A femoral arterial line is used to introduce a double-lumen line connected to the plasmapheresis device which, in turn, pumps the blood through an activated charcoal column and an oxygenator. Afterwards, the blood passes through the internal bioreactor circuit where the hepatocyte lines play their detoxifying role through conventional cell processes. The final filtrate is delivered to a reservoir connected with the plasmapheresis device from which it is returned to the patient. Modified from [http://biomed.brown.edu/Courses/BI108/BI108_1999_Groups/Liver_Team/Liver.html](http://biomed.brown.edu/Courses/BI108/BI108_1999_Groups/Liver_Team/Liver.html)
Why are hepatocytes used?

1) They make the membrane more permeable
2) They allow blood detoxification
3) They allow blood detoxification, metabolism and synthesize proteins like bile.
Tissue engineering
World’s First Artificial Human Liver

• **What:** Colin McGuckin and Nico Forraz of the University of Newcastle in England gathered stem cells from umbilical cord blood which were treated with nutrients and growth factors that programmed them to become liver cells.

• **Result:** is a homogeneous blob of hepatocytes, the detoxifying, metabolizing cells that make up most of the liver’s mass.

• **mini livers aren’t real organs,** thus they don’t have the blood vessel structure or a red, plumped-up look of a full liver.

• **So Far:** They’re not developed enough to function as liver transplants, but the cell clusters do have important uses: [9]

  1) they can provide an intermediate step between pharmaceutical tests on animals and those on people.

  2) In a few years, dialysis machines with mini livers inside could be used to clean the blood of patients who have been poisoned or are waiting for a transplant.

  3) could someday lead to the development of full-size, implantable human livers.
If your liver fails, having 40 small livers scattered around your body might be the next best thing!

- A surprising new technique under development by University of Pittsburgh stem cell researcher Eric Lagasse [10]
- Lymph nodes are ideal bioreactors: blood supply, nutrients, hormone signals, and expansion capability.
- Liver cells from healthy donors and placing them inside the lymph nodes of patients suffering from liver disease.
- Successfully experimented in mice with end-stage liver disease which survived and were cured.
- Future testing on pigs then hopefully humans.
For people suffering from advanced liver disease, many patients, such as those with cirrhosis, the liver tends to become so clogged with scar tissue that healthy cells are choked off, preventing it from fulfilling its role of filtering toxins. The only cure is a liver transplant.

- 6,000 available organs for some 100,000 patients each year
- If you’re elderly or suffering from another disease, the chances are closer to zero.

Bridge Liver Transplant:
- MARS
- BAL using hepatocytes: human, porcine Hepatoblastoma-derived cell lines.
  - Porcine is the easiest to get and use, not any better than human because no plasma dialysate contact.
  - Hepatoblastoma-derived cell lines incorporate fear of potential transfusion of malignant cells to the patients

Liver Transplant:
- Adults: usually require whole or 60% liver.
- Children: usually require whole or 40% liver.

Stem Cell Research: no present day cures tested thoroughly
References:

6. MARS, November, 2012