Liver Support Systems

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Anatomy

- Located in the right hypochondriac region and part of the epigastric region of the abdominal cavity
- The heaviest gland in the body (~3 lbs on average)
- 2\textsuperscript{nd} largest organ in the body (next to the skin)
- Divided into a right and left lobe by an extension of the peritoneum (falciform ligament)
• The liver is made up of groups of cells arranged into six-sided lobules
• A central vein (hepatic venules) runs through the middle of each lobule
• The vein branches into capillaries known as sinusoids
• Each sinusoid is bordered by hepatocytes (liver cells)
• Each lobule has small bile canaliculi (canals) which drain bile produced by hepatocytes to a bile duct
• The sinusoids also contain phagocytes known as Kupffer cells
• These cells destroy old red blood cells, white cells and foreign matter contained in blood traveling from the digestive tract

Red Arrows: Sinusoid
Blue Arrows: Hepatocytes
Black Arrow: Kupffer Cell
Yellow Arrow: Bile Canaliculi
• Oxygenated blood is received from the heart through the hepatic artery
• Deoxygenated blood full of nutrients and compounds absorbed from the digestive tract is received through the hepatic portal vein
• Branches of the hepatic artery, portal vein and bile ducts are usually grouped together into groups known as portal triads which run between lobules
Bile

- Breakdown of Hemoglobin in red blood cells produces Bilirubin
- The liver removes Bilirubin from the blood and uses it to produce bile
- Bile is an excretory product and is sent to the intestines
- The liver also uses bile to produce bile salts, which aid in the digestion of lipids

The molecular structure of Bilirubin:

[4]
Functions

• The liver performs many functions
  – Production of bile and bile salts
  – Carbohydrate metabolism
  – Protein metabolism
  – Drug and hormone metabolism
  – Lipid metabolism
Carbohydrate Metabolism

- Glycogen is a large, multi-branched polymer of glucose
- It is used to store large amounts of energy in one molecule
- When needed, glycogen is broken down to glucose to provide energy to cells in the body
- The liver produces glycogen for storage, and breaks it down when glucose is needed
Protein and Lipid Metabolism

- The liver synthesizes cholesterol, lipoproteins and most of the proteins for blood plasma.
- Serum albumin (albumin) is one of the most abundant plasma proteins.
- Albumin is a large, negatively charged protein.
- Albumin is vital for maintaining osmotic pressure, and transporting drugs and other lipophilic (non-polar) molecules around the bloodstream.
- Prothrombin is a required protein for clotting of the blood.
- Amino acids can be deaminated so they can be broken down by other cells for energy.

\[ \text{NH}_3^+ \rightarrow \text{Urea} \quad (\text{enters bloodstream, eventually excreted}) \]

\[ \text{R} \quad \text{H} \quad \text{C} \quad \text{C} \quad \text{C} \quad \text{O} \quad \text{H} \]

\[ \text{R} \quad \text{H} \quad \text{C} \quad \text{C} \quad \text{OH} \]

\[ \text{R} \quad \text{H} \quad \text{C} \quad \text{C} \quad \text{OH} \]

\[ \text{R} \quad \text{H} \quad \text{C} \quad \text{C} \quad \text{OH} \]

\[ \text{R} \quad \text{H} \quad \text{C} \quad \text{C} \quad \text{OH} \]
Drug/Toxin Metabolism

- Drug metabolism refers to either the modification/activation or degradation/deactivation of drugs in the body.
- The liver is the main site for metabolism of drugs.
- Degradation/deactivation is used to eliminate toxins and drugs which have ‘run their course’.
- Many drugs are non-polar, and therefore are not easily excreted.
- The liver deactivates many of these drugs and converts them into polar forms for excretion by the kidneys.
- Others are added to bile, and excreted through the intestines.
Drug catabolism is often broken down into 2 phases
Phase I usually involves a family of enzymes known as Cytochrome p450
The p450s catalyze reactions which convert drugs into more polar forms
One important characteristic of the p450 enzymes is the presence of a heme (Iron) centre, which is important in oxidation reactions
Phase I reactions often involve the addition of hydroxyl (-OH) groups or carbonyl (=O) groups through oxidation

A p450 enzyme (example)

The structure of the heme centre
• Phase II is also referred to as the conjugation phase
• In phase II, other molecules are added to the drug to make it even more polar
• There is a huge supply of highly polar Glucuronic acid in the liver
• This acid is added to drugs through a process known as Glucuronidation
• This process is one of the many different types that can occur during phase II drug metabolism
• Other groups that can be added to drugs during phase II are Sulfate and Glutathione

Glucuronic Acid

Glutathione
Alcohol Metabolism

- A specific example of drug metabolism
- 90% of alcohol consumed is metabolized by the liver
- The other 10% is removed by the kidneys and the lungs
- The following reaction pathway is followed:

\[
\text{Ethanol} + \text{NAD}^+ \xrightarrow{\text{Alcohol Dehydrogenase}} \text{Acetaldehyde} + \text{NADH}, \text{H}_2\text{O} \xrightarrow{\text{Aldehyde Dehydrogenase}} \text{Acetate Ion}
\]

- The acetate ion can then be converted to Acetyl CoA, which is used for production of ATP during the Kreb’s Citric Acid Cycle of cellular respiration
- This is a type of phase I reaction
Liver Regeneration

- The liver is able to rapidly regenerate itself!
- Upon receiving damage, a response to regenerate is triggered within the hepatocytes
- The signals which trigger, maintain and end regeneration are, as of yet, unknown
- Most regeneration occurs within 72 hours after damage has occurred
- The following graph shows the recovery of the liver after ~60% of the volume has been surgically removed
Common Afflictions of the Liver

- Hepatitis
- Cirrhosis
- Ascites
- Fatty Liver
- Liver Cancer
- Acute Liver Failure

[13]
Hepatitis – 1st Type:

“Inflammation of the liver”

**Non-viral**

Cause: ingestion of either

(a) toxic/drug-induced [ex. Poison mushrooms, arsenic, oral contraceptives, acetaminophen]

(b) alcohol – “Alcohol Liver Disease”

which are liver toxins (or “hepatotoxins”)

Why is it so bad?

- When the liver is inflamed, it cannot clear bile and poisonous substances, provide energy, or make proteins.
- Ascites
- Fatty Liver
- Cirrhosis
- Neurological dysfunction
- Fluid accumulation
- Blood clots
- Bleeding in the esophagus
Hepatitis – 2nd Type:

Viral

**Hepatitis A**

Transmission: orofecal route - unclean hygiene practices

Symptoms:

“flu-like” meaning
  - fever
  - appetite loss
  - nausea
  - abdominal pain
  - jaundice (yellowish colour on the skin and eyeballs)

- not too severe, there are vaccines available
- lasts generally 3-6 weeks
**Hepatitis – 2\textsuperscript{nd} Type:**

**Viral**

*Hepatitis B*

Transmission: travels through pretty much all bodily fluids (ex. Blood, saliva)

What it does:
- more inflammation! More processes disrupted!
- like the influenza virus, it goes into the cells (in this case, liver cells) and gets its DNA replicated over and over and over…
- can become a carrier of the virus for life, infecting others
- cirrhosis
- liver cancer (chances increase 200x)
- It can live outside the body for up to 10 days!
- People die from this
- There is a vaccine, as well as medication for those that are infected
Hepatitis B
Hepatitis – 2nd Type:

Viral

Hepatitis C

Transmission: only blood transmission, ex. Tattooist needle

Duration: 6 months (acute phase)

indefinite (chronic phase)

Why is it so bad?

- no cure!!!!!
  -- therefore you are a carrier for life
  -- only treatment right now is chemotherapy

- chronic liver disease
- liver cancer
- no healing able to happen, eventually

need liver transplant
Hepatitis C
Cirrhosis

What it is: Severe scarring of the liver tissue

Why this is bad: As scar tissue increases, amount of functioning liver cells decrease and liver works less effectively. Liver can stop functioning. Cirrhosis can lead to end-stage liver disease.

Causes: some type of chronic liver damage/disease
- Males drinking in excess of 80 g and females in excess of 40 g of alcohol per day for 10 years are at a high risk of developing cirrhosis

Treatment: can’t get rid of the scarring, only stop the progression of more (ex. Stop drinking alcohol)
- liver transplant
Ascites

- Fluid builds up in between membranes lining the abdomen and abdominal organs
- Liver damage causes dysfunction and sends messages to the kidneys to retain sodium and water
- Portal vein tension keeps the excess fluid in the abdomen
- More common in cirrhosis from alcohol or alcohol hepatitis
- Diuretics combined with salt restrictions can get rid of it

[21]
Fatty Liver

What it is: accumulation of fat cells in the liver

Causes: obesity, diabetes, alcoholism, drugs, pregnancy, starvation, hepatitis

Symptoms: patients are often asymptotic!

What it does: fat can increase the amount of enzymes present in the liver, which can then cause inflammation and as we know, leads to scarring and cirrhosis

Treatment: depends on the main cause of each case of Fatty Liver

examples of possible treatment:
- exercise
- abstaining from alcohol
- dietary fat restriction
Liver Cancer

1. Heptoma:
   - Cancer of the hepatocytes
   - “Primary Liver Cancer”
   - Grows in the liver as a ball-like tumor, invading the normal tissue surrounding it

2. Cholangiocarcinoma
   - Cancer of the bile ducts
   - Often caused by infestation with the liver fluke Clonorchis (a parasite you can get from eating fish)
   - Grows along the bile ducts in sheets or lines & is hard to find on X-ray studies.

   [23]

   - Cirrhosis and chronic hepatitis are risk factors that may one day lead to cancer
   - Only treatment is normal cancer treatments such as chemotherapy/radiation therapy, or a liver transplant
Liver Failure

Generally,
- Uncommon
- High mortality
- Acute or Chronic types

What it is: The liver is so damaged and cannot function even close to normal, that encephalopathy (dementia, seizures, brain afflictions) due to fluid build up in the brain is observed.

Causes: anything that causes extensive damage to the liver, such as cirrhosis, hepatitis C

Treatment: not too much can be done at this point, trying to get rid of the underlying cause (if possible) might not really help. Liver transplant is needed.
Liver Transplants

- **Cadaveric:**
  - donor is someone with extensive & irreversible brain damage ("brain-dead")
  - Most common
  - Months – years on a waiting list
- **Living:**
  - portion of a liver is taken from someone who is alive, and this is implanted into the recipient
  - Donor between 18 and 60
  - Donor has the right lobe (accounting for 60% of liver mass) removed and implanted in recipient
  - Both donated and left behind livers reach full size in 6-8 weeks

Cons:
- 4000 donors a year, while 17000 people on waiting list
- For Living Liver Transplantations, there is a 19% chance of complications and up to a 1% chance of death for the donor
- Cost of liver transplant as well as the necessary medication, PRICEY!

Estimated First-Year Charge (1996): $314,600
Estimated Annual Follow-up Charge (1996): $21,900

Wouldn’t it just be easier if your own liver worked again???

Who is *not* given a liver:
- Active alcohol or substance abuse
- Cancers in locations other than just the liver weigh against a transplant.
- Advanced heart and lung disease: These conditions prevent a transplanted liver from surviving.
- Severe infection: Such infections are a threat to a successful procedure.
- Massive liver failure: This type of liver failure accompanied by associated brain injury from increased fluid in brain tissue rules against a liver transplant.
- HIV infection
Alternative to Liver Transplantation

• In some cases, devices called Liver Support Systems can be used as an alternative to liver transplantation
• These devices may be used to take strain off the liver and give it time to regenerate on its own (*bridging to regeneration*)
• In other cases, they may be used to keep a patient alive until a suitable donor can be found (*bridging to transplantation*)
• As well, to reduce effects of encephalopathy
• Liver support systems can be divided into two types: artificial and bioartificial devices
Artificial Liver Support Systems

- Artificial livers do not include any biological components (cells)
- They run with mechanical, chemical and electrical components
- Two of the artificial liver support systems available today are the MARS and Prometheus systems
- These devices can only remove toxic substances in the blood; they have no ability to take over for the other functions of the liver
Hemodialysis

- Hemodialysis is a process which is most commonly used to take over the functions of the kidneys
- Blood is taken out of the body, passed through the machine, and passed back into the body
- Blood passes through artificial capillaries surrounded by semi-permeable membranes inside a dialysis tube
- A mineral-rich dialysis fluid is also pumped through the tube
- Waste material in the blood diffuses through the membrane into the fluid
- Anticoagulants such as heparin are used to prevent clotting in the machine
- Often a fistula is made by tying an artery and a vein together to increase blood supply
The hemodialysis loop

A dialyzer, opened up to show capillaries

A dialyzer
Molecular Adsorbent Recirculation (MARS)

- Very similar to hemodialysis, but with 2 separate dialyzers
- Dialyzer 1 has blood flowing through capillaries, and albumin flowing through the tube
- Non-polar toxins pass through the membrane and are ‘picked up’ by the albumin
- Polar substances diffuse into the albumin solution due to electrochemical attractions
- Albumin passes through capillaries of a 2nd dialyzer containing sodium bicarbonate, which removes polar substances
- Albumin continues through active charcoal filters and anionic exchangers, which remove albumin-bound substances
Albumin solution contains both protein-bound polar and ‘free’ non-polar molecules.

Albumin contains protein bound non-polar molecules, and very few polar molecules.

Active charcoal filters and anionic exchangers

"Clean Albumin"
<table>
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<th>Age</th>
<th>Sex</th>
<th>Pathology</th>
<th>Indication</th>
<th>Cr  μmol/l</th>
<th>Bill μmol/l</th>
<th>HRS</th>
<th>HE</th>
<th>VB</th>
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</table>

M, male; F, female; ALF, acute liver failure; AoCLF, acute on chronic liver failure; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; PBC, primary biliary cirrhosis; HRS, hepatorenal syndrome; HE, hepatic encephalopathy; VB, variceal bleed; Cr, creatinine level before treatment; Bill, total bilirubin level before treatment.
Prometheus

- Blood is first passed through a fractionated plasma separation and adsorption (FPSA) system
- This separates the albumin from the rest of the blood
- The albumin is passed through a secondary circuit containing two columns known as prometh 01 and 02
- 01 contains a neutral resin, and 02 contains an anion exchange resin adsorber
- These two substances adsorb the toxins out of the albumin, and the albumin is passed into the blood again
- After rejoining with the albumin, the blood passes through a conventional hemodialysis machine to remove polar toxins
Albumin, and protein-bound toxins

Blood + polar toxins

“Clean” Albumin

“Clean Blood”
Prometheus vs. MARS

• A study was performed on 18 patients in Belgium suffering from different forms of liver disease

• 9 were put on MARS and 9 on Prometheus

• Prometheus was found to have a better clearance rate for most toxins, especially protein-bound (non-polar) toxins
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<td>PROM</td>
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<td>Support</td>
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<td>Support</td>
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<td>2</td>
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<td>Mean</td>
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<td>58.7</td>
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<td>26</td>
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BTP, bridge to transplantation; HE, hepatic encephalopathy; M, male; F, female; NA, not applicable.
HCV, hepatitis C virus.
HBV, hepatitis B virus.
### TABLE 2. Biochemical data at pretreatment and posttreatment

<table>
<thead>
<tr>
<th></th>
<th>Pretreatment</th>
<th>Posttreatment</th>
<th>RRt</th>
<th>Pretreatment</th>
<th>Posttreatment</th>
<th>RRt</th>
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<tr>
<td><strong>MARS</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>10.2 ± 0.4 (9)</td>
<td>8.8 ± 0.3 (9)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>NA</td>
<td>8.3 ± 0.4 (9)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>7.9 ± 0.4 (8)</td>
<td>NA</td>
</tr>
<tr>
<td>Platelets (thousands/μL)</td>
<td>132.3 ± 24.9 (9)</td>
<td>116.4 ± 24.7 (9)</td>
<td>NA</td>
<td>92.4 ± 18.8 (9)</td>
<td>64.0 ± 13.6 (8)</td>
<td>NA</td>
</tr>
<tr>
<td>Leukocytes (thousands/μL)</td>
<td>11.8 ± 1.3 (9)</td>
<td>13.6 ± 2.6 (9)</td>
<td>NA</td>
<td>13.6 ± 2.6 (9)</td>
<td>11.7 ± 2.6 (8)</td>
<td>NA</td>
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<tr>
<td>Prothrombin time (%)</td>
<td>36.5 ± 4.7 (6)</td>
<td>48.3 ± 5.4 (6)</td>
<td>NA</td>
<td>36.1 ± 3.8 (9)</td>
<td>26.8 ± 4.3 (9)&lt;sup&gt;*&lt;/sup&gt;</td>
<td>NA</td>
</tr>
<tr>
<td>Serum albumin (g/L)</td>
<td>31.3 ± 1.4 (9)</td>
<td>29.8 ± 1.4 (7)</td>
<td>NA</td>
<td>31.0 ± 1.4 (9)</td>
<td>27.6 ± 2.3 (7)</td>
<td>NA</td>
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<tr>
<td>ALAT (U/L)</td>
<td>214 ± 140 (8)</td>
<td>131 ± 75 (7)&lt;sup&gt;*&lt;/sup&gt;</td>
<td>NA</td>
<td>106 ± 48 (9)</td>
<td>42 ± 9 (8)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>NA</td>
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<tr>
<td>Lactate dehydrogenase (U/L)</td>
<td>489 ± 75 (8)</td>
<td>615 ± 142 (7)</td>
<td>NA</td>
<td>695 ± 163 (7)</td>
<td>426 ± 37 (6)</td>
<td>NA</td>
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<tr>
<td>Total bilirubin (mg/dL)</td>
<td>24.9 ± 4.2 (9)</td>
<td>18.4 ± 2.3 (9)&lt;sup&gt;*&lt;/sup&gt;</td>
<td>15.7 ± 10.7 (9)</td>
<td>33.3 ± 3.9 (9)</td>
<td>16.8 ± 1.3 (9)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>48.2 ± 5.0 (9)</td>
</tr>
<tr>
<td>Conjugated bilirubin (mg/dL)</td>
<td>17.6 ± 3.2 (9)</td>
<td>12.8 ± 2.1 (6)&lt;sup&gt;*&lt;/sup&gt;</td>
<td>25.0 ± 6.0 (6)</td>
<td>25.4 ± 3.1 (9)</td>
<td>12.3 ± 1.3 (9)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>52.5 ± 4.3 (9)</td>
</tr>
<tr>
<td>Bile acids (μmol/L)</td>
<td>149.9 ± 21.8 (9)</td>
<td>61.8 ± 9.6 (5)&lt;sup&gt;*&lt;/sup&gt;</td>
<td>65.7 ± 3.0 (5)</td>
<td>145.8 ± 32.9 (9)</td>
<td>29.0 ± 2.6 (6)&lt;sup&gt;*&lt;/sup&gt;</td>
<td>69.7 ± 5.3 (6)</td>
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<tr>
<td>Serum urea nitrogen (mg/dL)</td>
<td>96.7 ± 26.7 (9)</td>
<td>48.4 ± 11.3 (9)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>40.3 ± 8.3 (9)</td>
<td>108.3 ± 23.3 (9)</td>
<td>47.9 ± 15.3 (9)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>58.3 ± 7.6 (9)</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>2.03 ± 0.3 (9)</td>
<td>1.60 ± 0.20 (9)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>15.8 ± 6.2 (9)</td>
<td>2.50 ± 0.64 (9)</td>
<td>1.40 ± 0.30 (9)&lt;sup&gt;*&lt;/sup&gt;</td>
<td>39.1 ± 7.9 (9)</td>
</tr>
</tbody>
</table>

*P < 0.05; <sup>†</sup>P < 0.01 pre versus post; <sup>‡</sup>P < 0.05; <sup>§</sup>P < 0.01 PROM versus MARS.

<sup>*</sup>Number of data sets between brackets.

RRt, treatment phase reduction ratio; NA, not applicable.

ALAT, alanine aminotransferase.

---

**Toxin levels**
Bioartificial Livers (BALs)

- Still in clinical trials
- Extracorporeal
- Human hepatocytes get harvested from donor livers that were discarded because of steatosis, cirrhosis, fibrosis, or mechanical injury.
- Also use animal hepatocytes (mostly pig)
  - When using the animal hepatocytes, the designs include covering the cells with a collagen layer, and then a porous outer layer. This ensures that the blood never comes in contact with the pig hepatocytes, since they will start attacking them when this happens
Bioartificial Livers

HepatAssist
- Utilizes pig hepatocytes
- Can be used for 6-8 hours a day

Basic Design:
- Venous connection leads the plasma to the HepatAssist
- Cellular component of the plasma gets separated into by a “plasmapheresis” device
- Plasma goes into a hollow microfibre, which is surrounded by a micro porous membrane
  → Membrane pores are large enough for toxin molecules to pass through, but too small for the
  hepatocytes
  → Micro porous membrane pig hepatocytes
- The two are reunited and undergo heating and oxygenation together, and return to the body

Clinical Study:
• During one study of 171 patients (86 control and 85 bioartificial liver (BAL)), majority with hepatic
  failure but some with acute liver failure
• Survival for the entire patient population at 30 days was 71% for the BAL group versus 62% for
  the control group

Despite these results, the HepatAssist was not given FDA approval and is not on the market
Bioartificial Livers

**Extracorporeal Liver Assist Device (ELAD)**
- Outside of the body, these devices use liver cells to filter the blood that usually goes to your liver
- Liver cells are from a human liver
- To be used continuously for up to 10 days, then change the cartridges
- Also used for rehabilitation after receiving a liver transplant

**Basic Design:**
- Venous connection to the ELAD
- 2 chambers that have cartridges of liver cells
- Liver cells filter out the toxins via *dialysis*
  - Passes blood along one side of a semipermeable membrane, having some dialysis fluid and hepatocytes on the other side.
  - The toxins (ex. Urea) undergo diffusion and leave the blood for the fluid on the other side, and nutrients that the liver normally supplies diffuse into the blood
- Chamber then remixes the blood
- Blood is returned to the body
Modular Extracorporeal Liver Support (MELS)

- Integrated oxygenation
- Treatment up to 3 days
- Based on the “Cell Module”, a unit consisting of 3 interwoven capillary bundles in a polyurethane housing.
  - One of the bundles serves as decentralized oxygenation;
  - 2 bundles are used for perfusion with patient plasma. It is operated with primary porcine hepatocytes as well as human hepatocytes isolated from discarded donor organs.
- The modular design is based on a **parallel plate geometry**.
  - Rectangular cross-section flow channel formed by two polycarbonate plates.
  - The lower plate supports a semi-permeable membrane to which the liver cells are attached.
  - A parallel array of gas permeable hollow fibres are mounted on the upper plate.
  - Blood plasma from the patient flows along the channel and is therefore in direct contact with the liver cells.

[25]
Modular Extracorporeal Liver Support

- Cell Module
- Detox Module
- Dialysis Module
- Plasma Filter
- High Flux Dialysis Filter
- Dialysis Fluid
- HA Solution
- Waste
Future

• Stem cells [ex. embryonic, adult liver progenitors] are being considered for liver treatment
• Also, tissue engineering an actual liver with hepatocytes
• Stem cells would allow livers to be grown in a lab and transplanted into patients
  – **PROBLEM**: The liver has too many functions to be replaced with a machine
Image References

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PG: 1084-1091
YR: 2001
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AD: First Department of Surgery, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan; Department of Preventive Medicine, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan
DOI: 10.1046/j.0007-1323.2001.01832.x
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