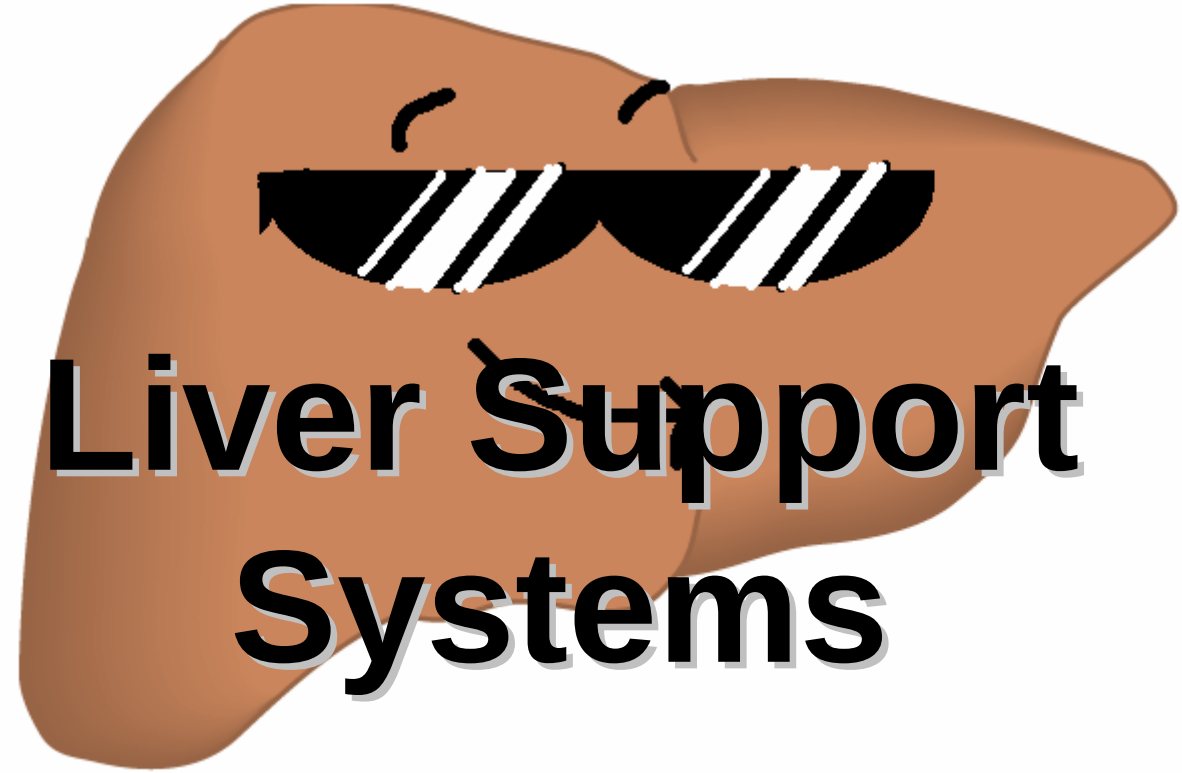
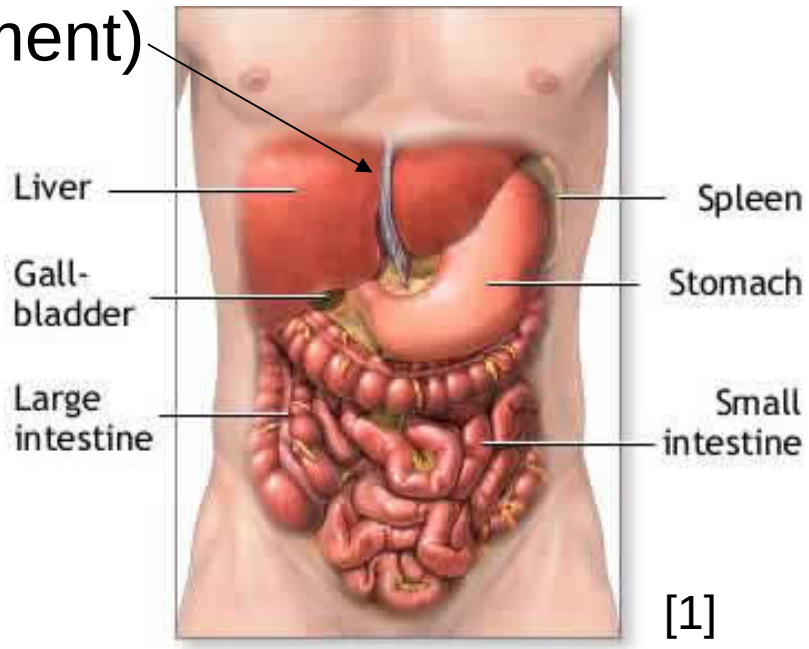


Liver Support Systems

By:
Derek Cappon 0465328
Erika Schimek 0444900

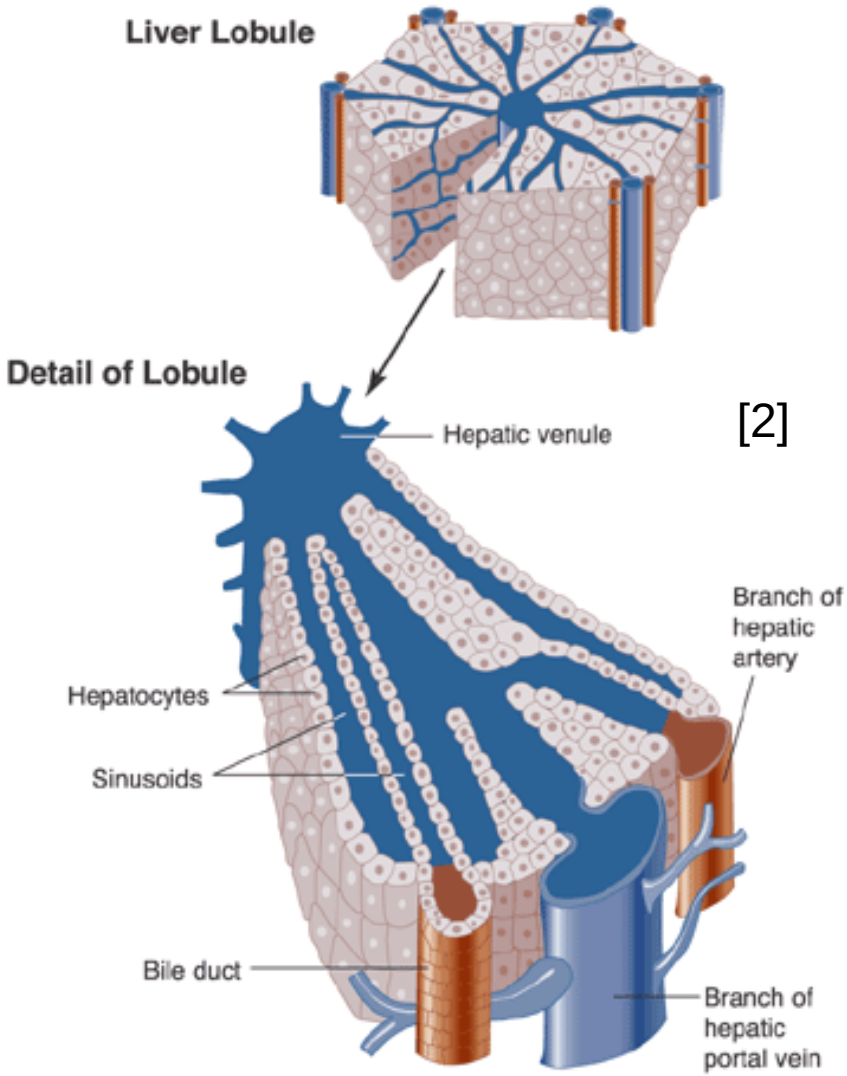
Anatomy

- 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)
- 2nd largest organ in the body (next to the skin)
- Divided into a right and left lobe by an extension of the peritoneum (falciform ligament)



[1]

- The liver is made up of groups of cells arranged into six-sided lobules
- A central vein (hepatic venule) 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



[2]

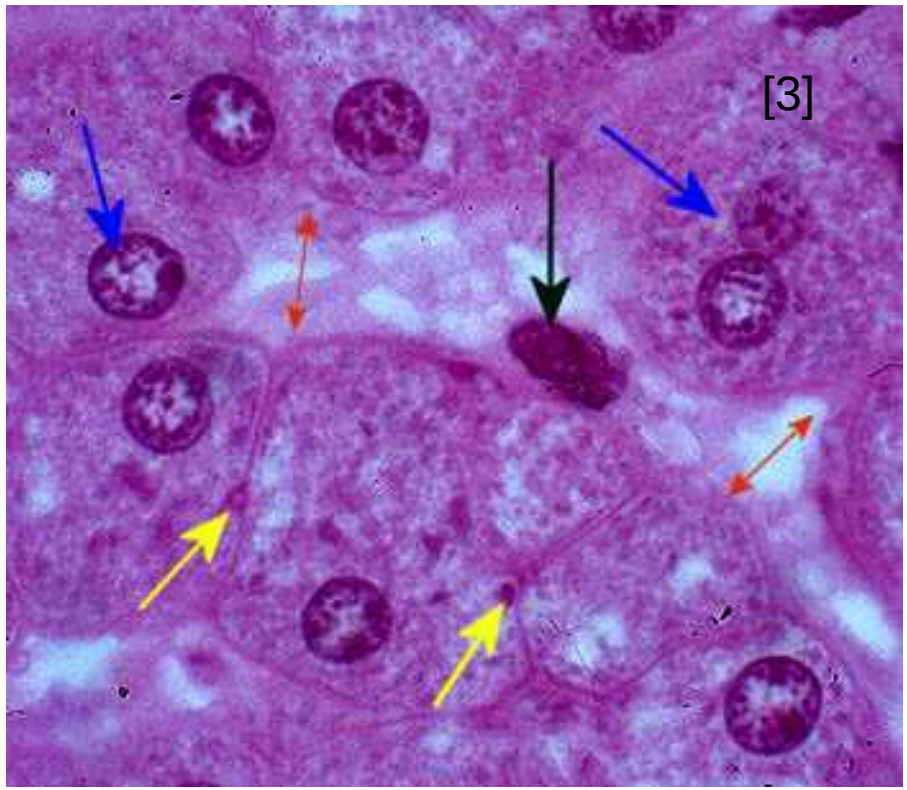
- The sinusoids also contain phagocytes known as Kupffer cells
- These cells destroy old red blood cells, white cells and foreign matter contained in blood traveling from the digestive tract

Red Arrows:
Sinusoid

Blue Arrows:
Hepatocytes

Black Arrow:
Kupffer Cell

Yellow Arrow:
Bile Canaliculi

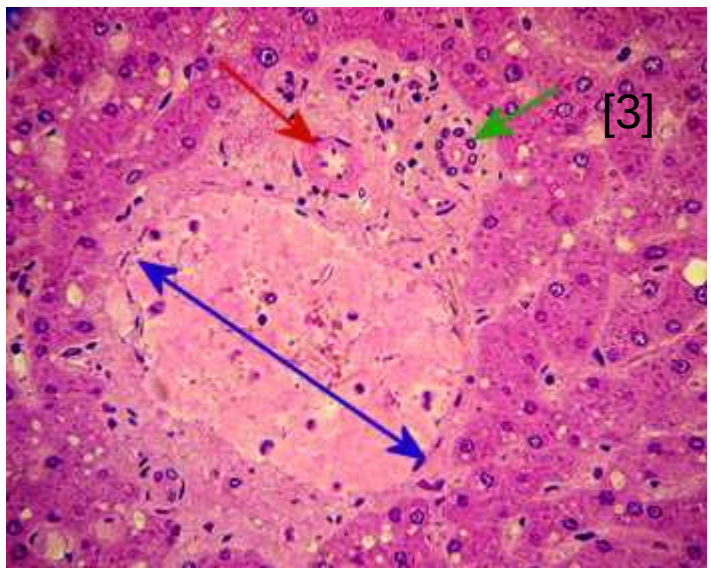


- Oxygenated blood is received from the heart through the hepatic artery
- Deoxygenated blood full of nutrients and compounds absorbed from the digestive tract is received through the hepatic portal vein
- Branches of the hepatic artery, portal vein and bile ducts are usually grouped together into groups known as portal triads which run between lobules

Blue Arrow
Portal Vein

Green Arrow
Bile Duct

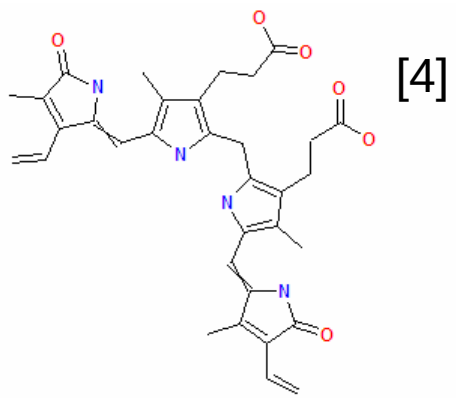
Red Arrow
Hepatic Artery


[3]

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:



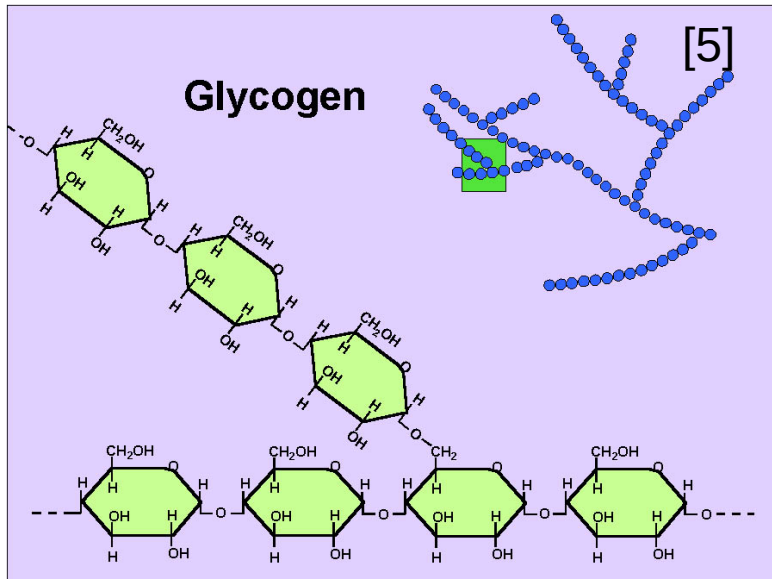
[4]

Functions

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

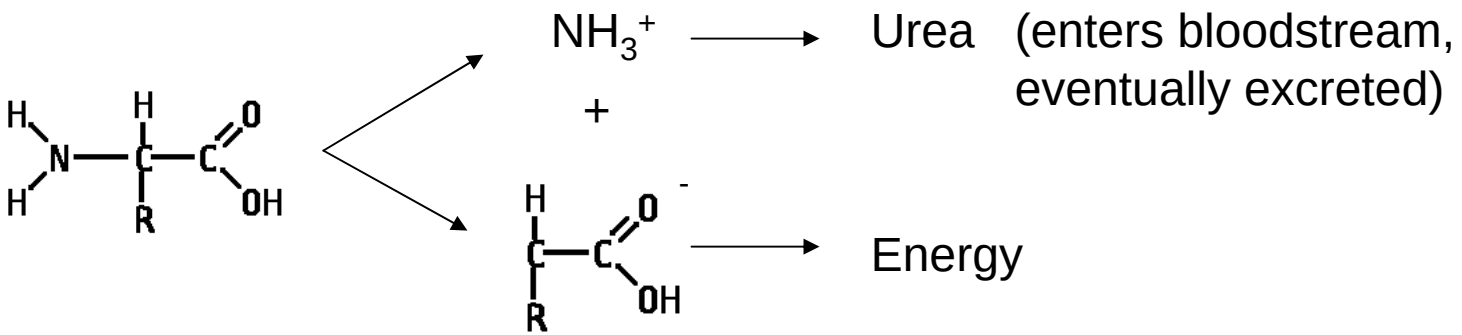
Carbohydrate Metabolism

- 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



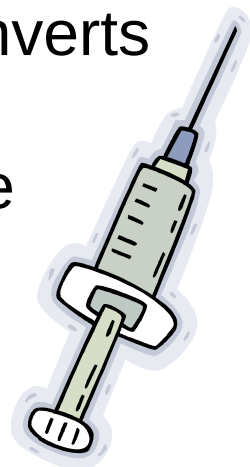
Protein and Lipid Metabolism

- 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

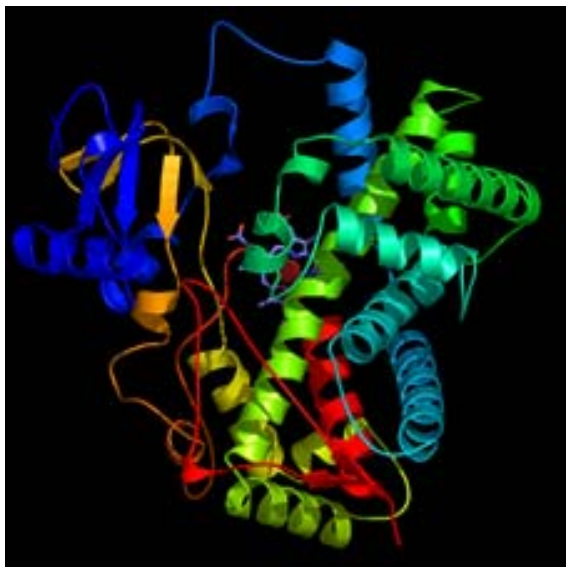


Drug/Toxin Metabolism

- 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

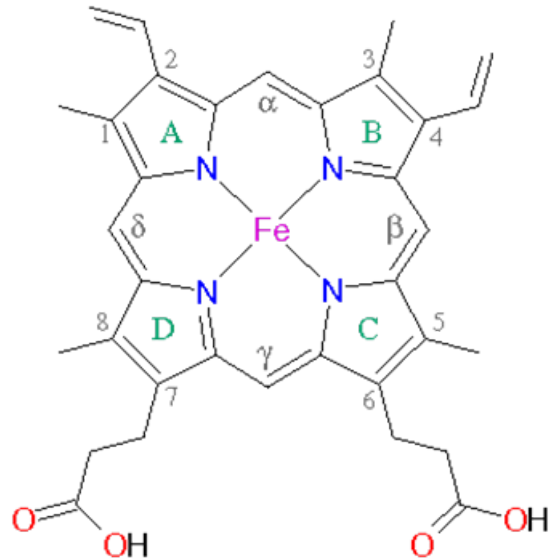


- Drug catabolism is often broken down into 2 phases
- Phase I usually involves a family of enzymes known as Cytochrome p450
- The p450s catalyze reactions which convert drugs into more polar forms
- One important characteristic of the p450 enzymes is the presence of a heme (Iron) centre, which is important in oxidation reactions
- Phase I reactions often involve the addition of hydroxyl (-OH) groups or carbonyl (=O) groups through oxidation



[6]

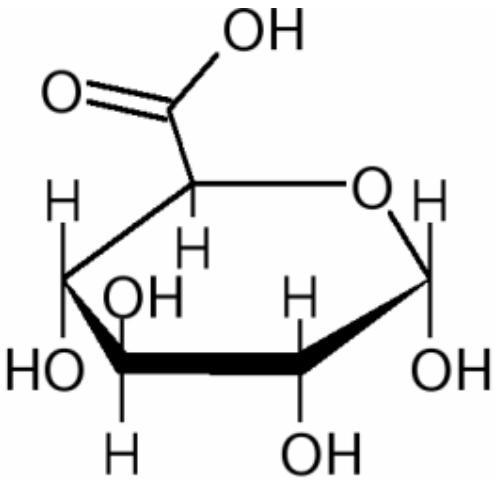
A p450 enzyme (example)



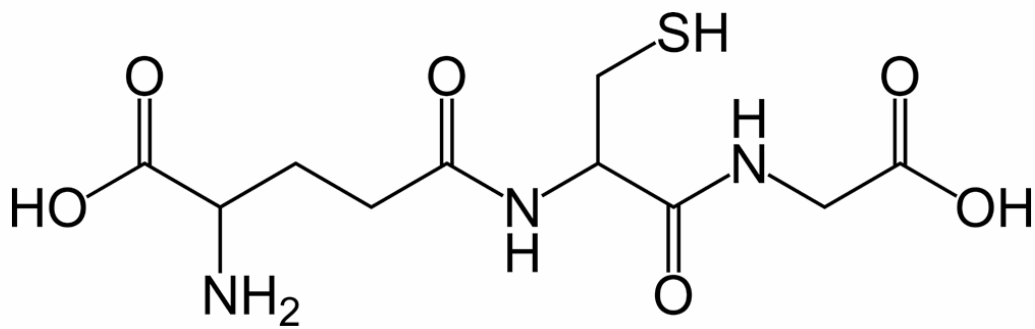
[7]

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



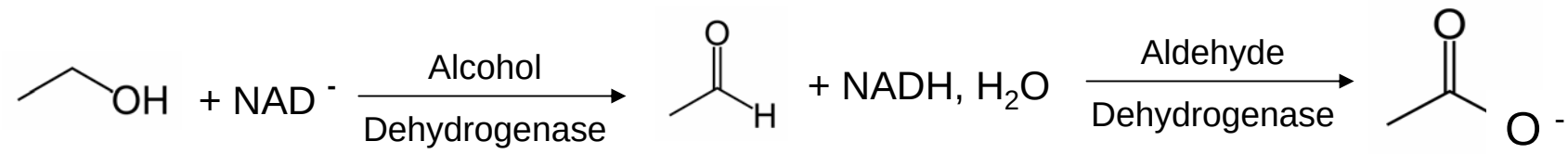
Glucuronic Acid



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:

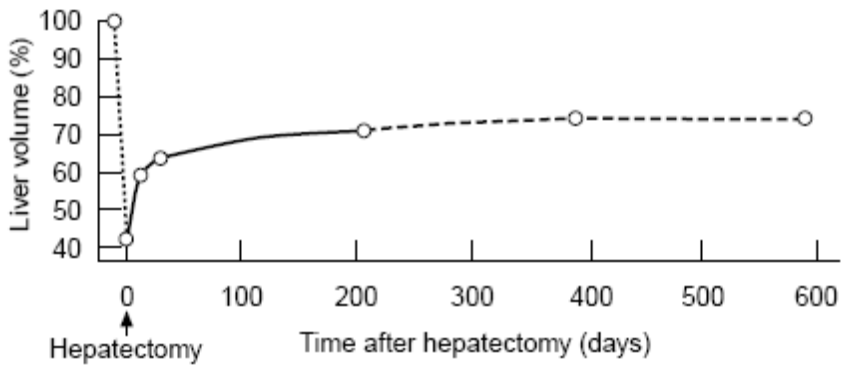


Ethanol Acetaldehyde Acetate Ion

- 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

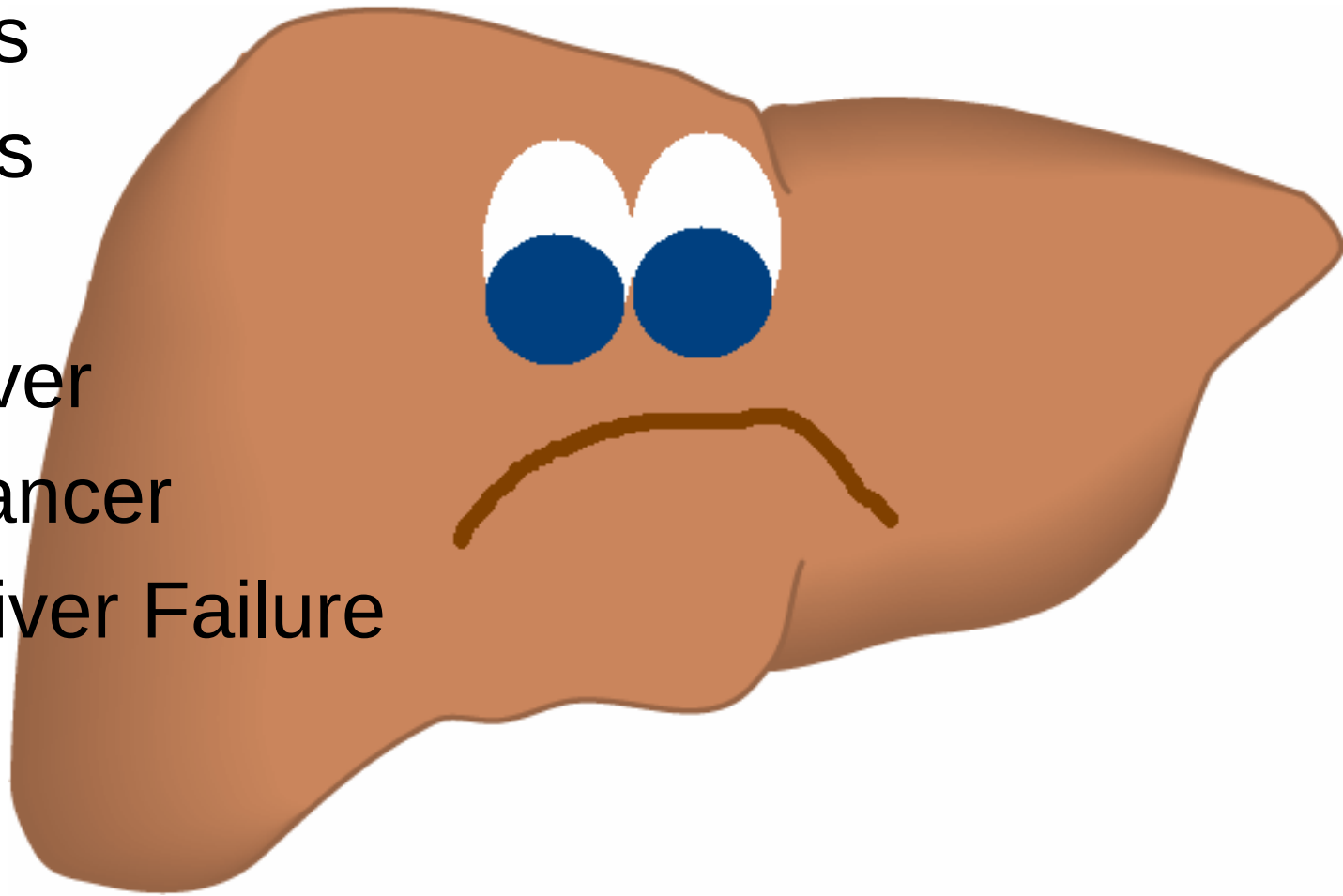
- The liver is able to rapidly regenerate itself!
- Upon receiving damage, a response to regenerate is triggered within the hepatocytes
- The signals which trigger, maintain and end regeneration are, as of yet, unknown
- Most regeneration occurs within 72 hours after damage has occurred
- The following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



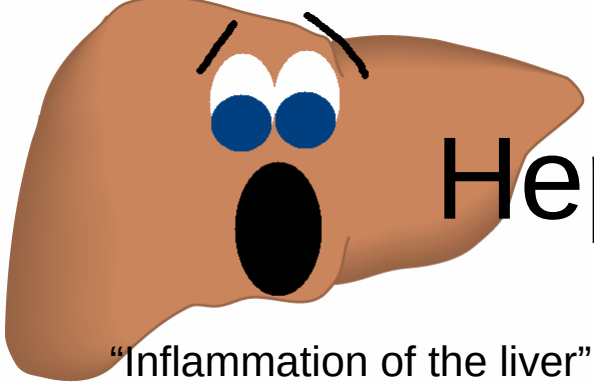
[8]

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

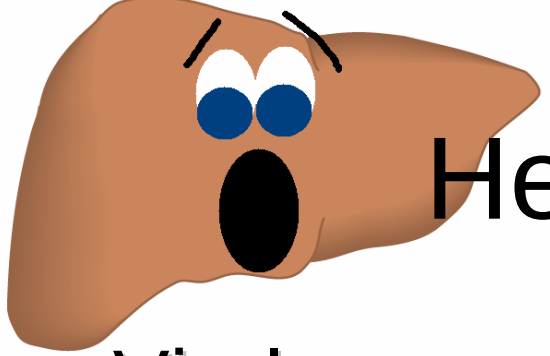
(a) toxic/drug-induced [ex. Poison mushrooms, arsenic, oral contraceptives, acetaminophen]

(b) alcohol – "Alcohol Liver Disease"

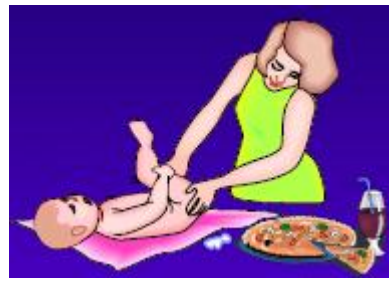
which are liver toxins (or "hepatotoxins")

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



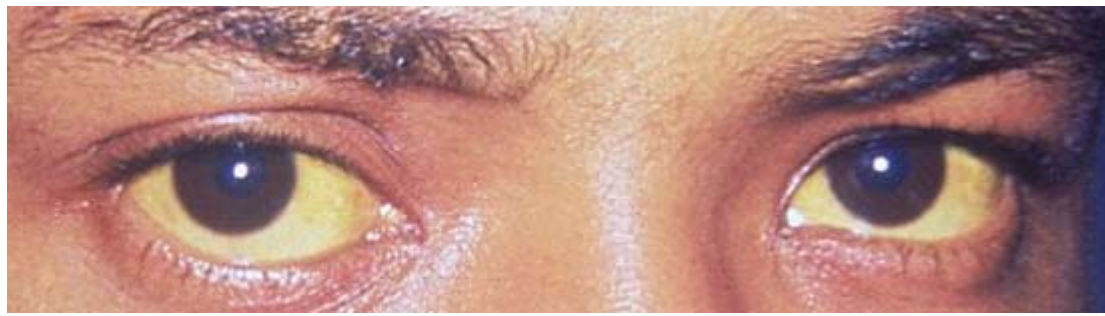
Hepatitis – 2nd Type:



Viral

Hepatitis A

Transmission: orofecal route - unclean hygiene practices [15]

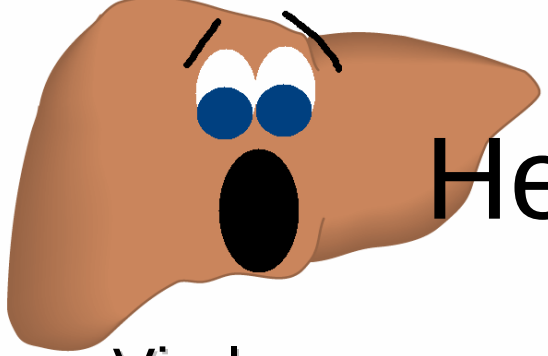


Symptoms:

"flu-like" meaning

- fever
- appetite loss
- nausea
- abdominal pain
- jaundice (yellowish colour on the skin and eyeballs) [14]

- not too severe, there are vaccines available
- lasts generally 3-6 weeks



Hepatitis – 2nd Type:

<u>Viral</u>

Hepatitis B

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

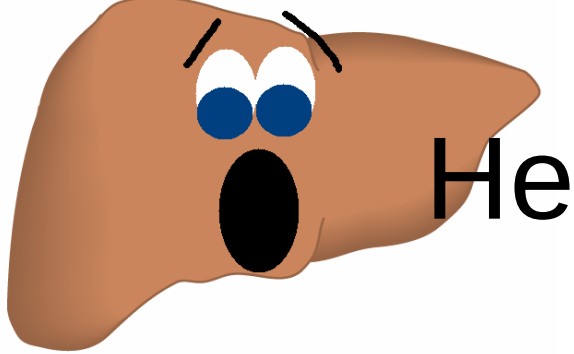
What it does:

- more inflammation! More processes disrupted!
- like the inlfuenza 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

[16]



Hepatitis – 2nd Type:

Viral

Hepatitis C

[17]

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

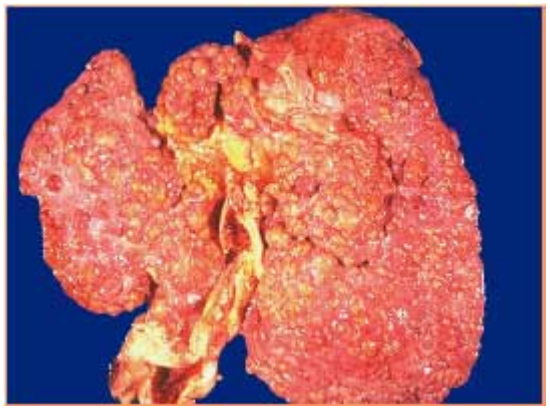
[18]

Hepatitis C

[19]

Cirrhosis

What it is: Severe scarring of the liver tissue



[20]

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

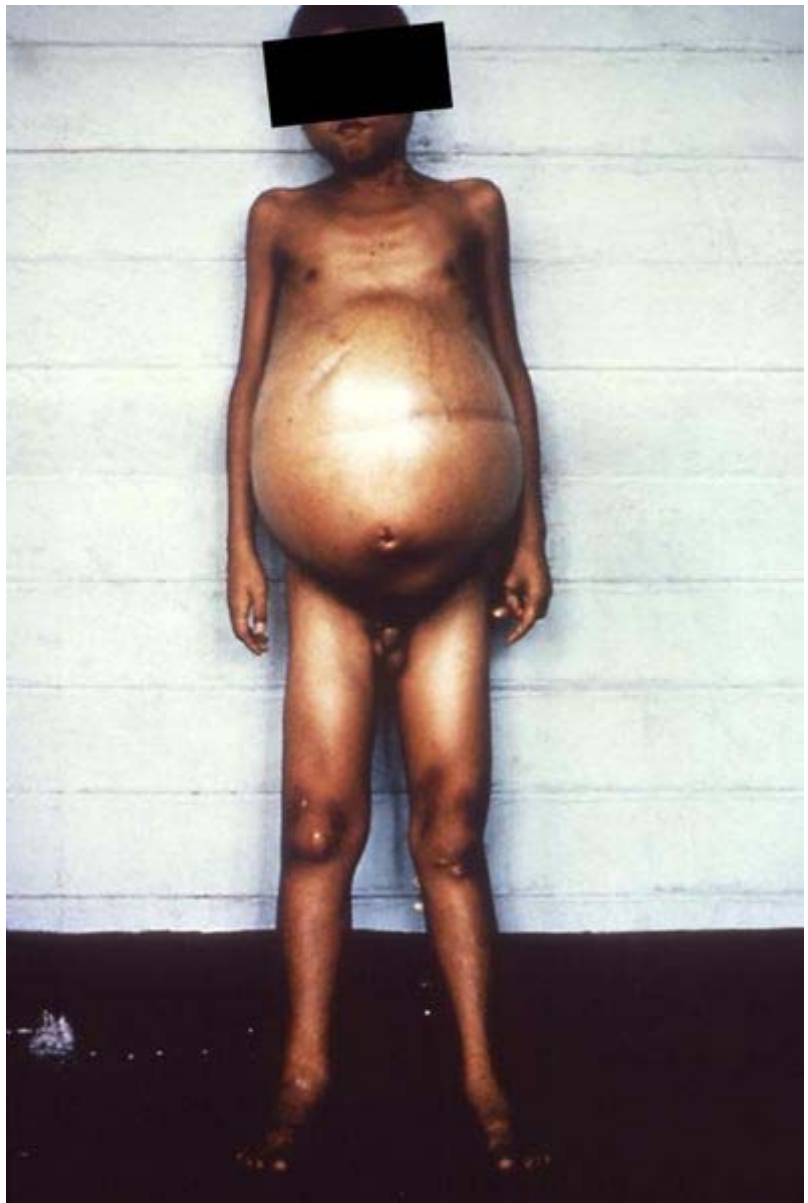
→Males drinking in excess of 80 g and females in excess of 40 g of alcohol per day for 10 years are at a high risk of developing cirrhosis

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



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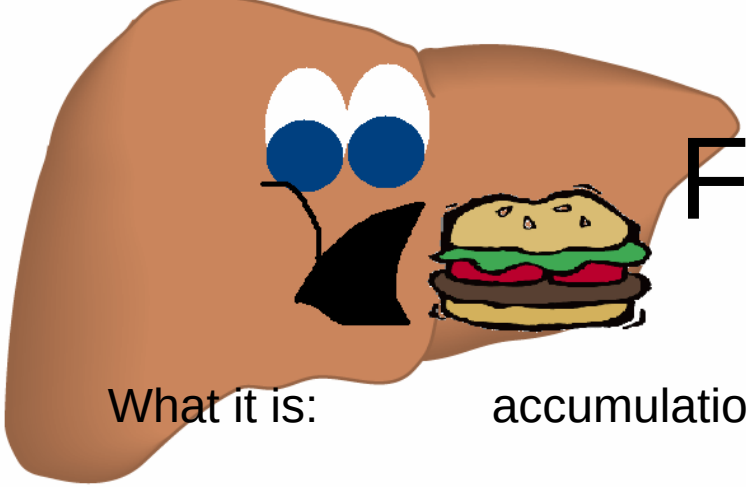
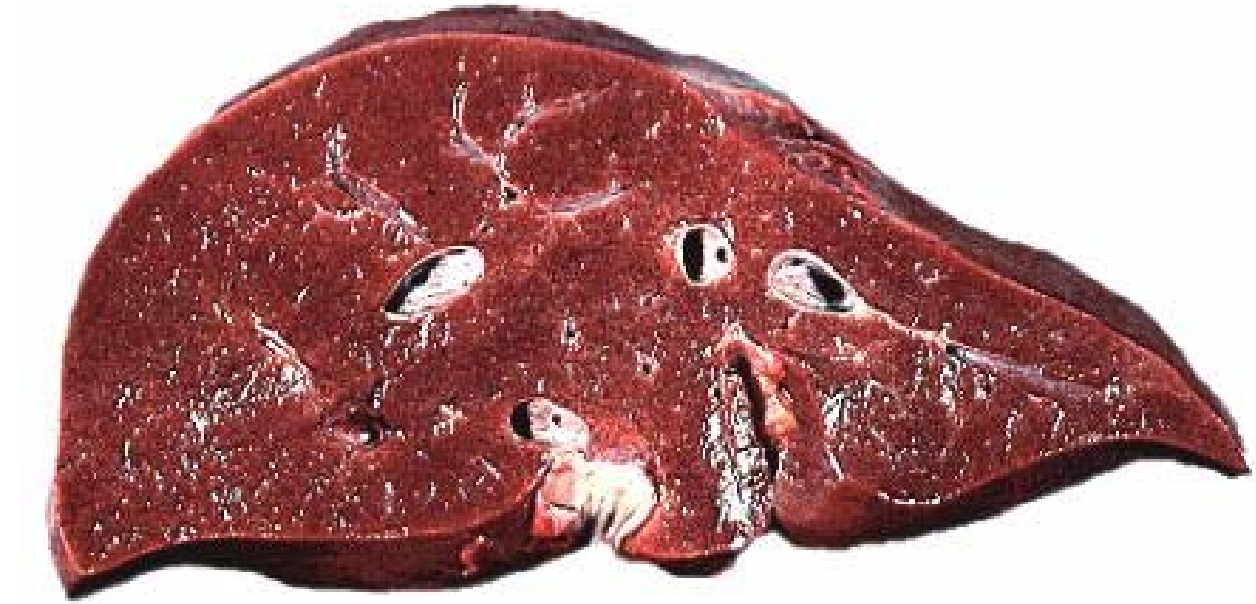
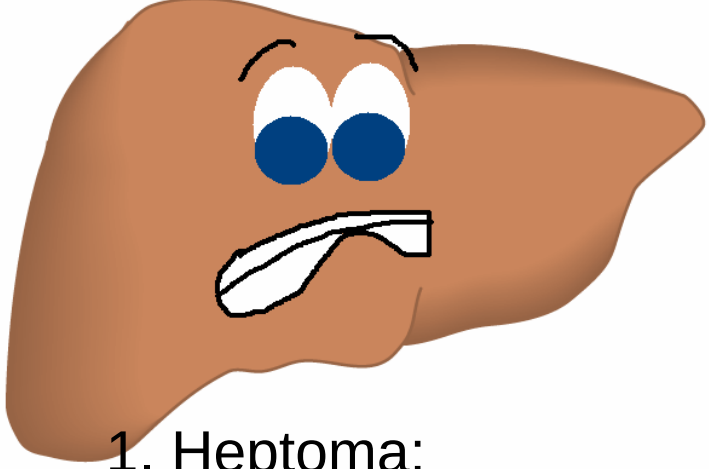


Fatty Liver

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

[22]

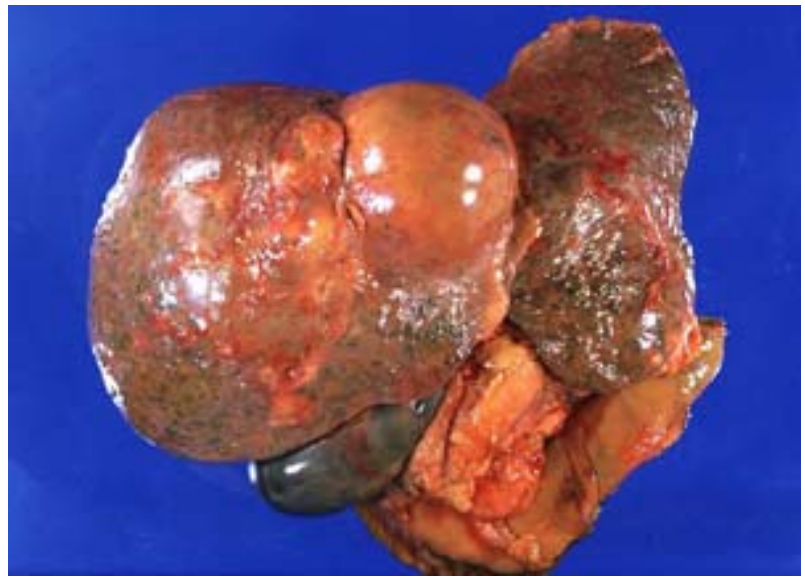




Liver Cancer

1. Heptoma:

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



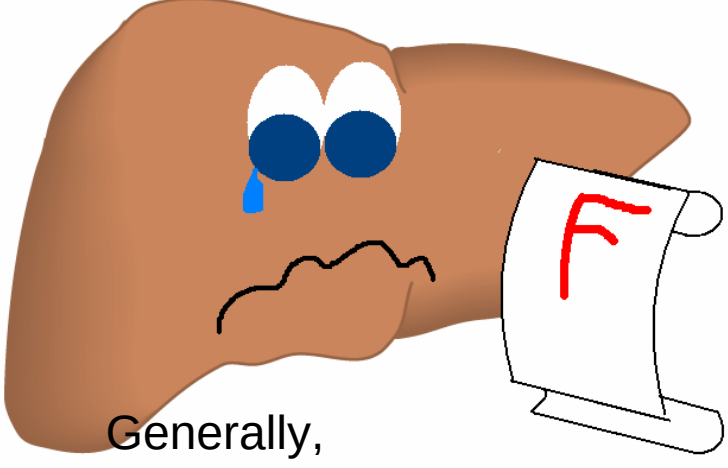
2. Cholangiocarcinoma

- 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!

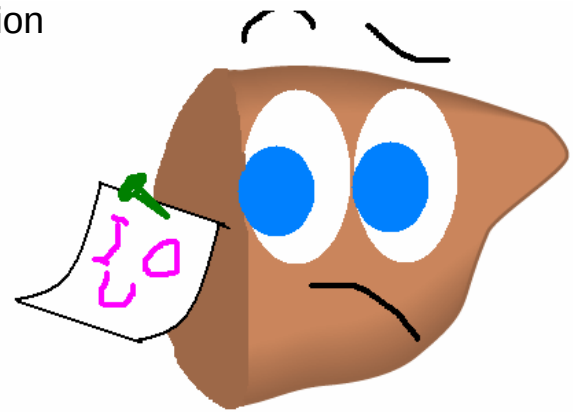
Estimated First-Year Charge (1996): $ 314,600

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

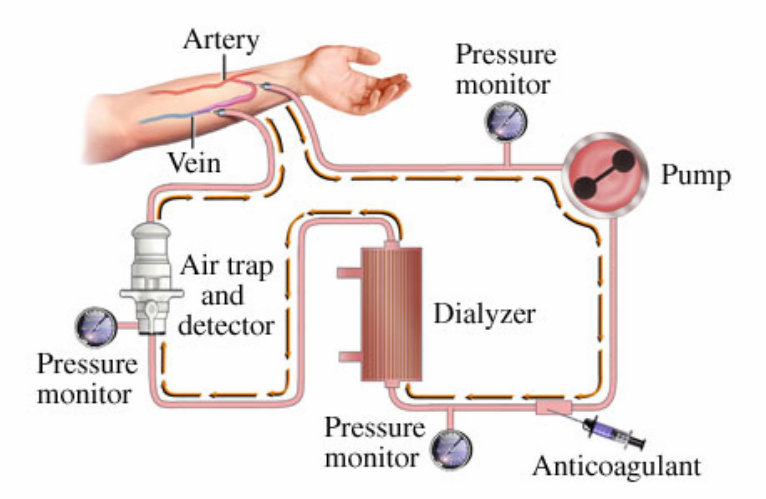
- In some cases, devices called Liver Support Systems can be used an as alternative to liver transplantation
- These devices may be used to take strain off the liver and give it time to regenerate on its own *(bridging to regeneration)*
- In other cases, they may be used to keep a patient alive until 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



[9]

The hemodialysis loop

[10]

A dialyzer, opened up to show capillaries

[11]

A dialyzer

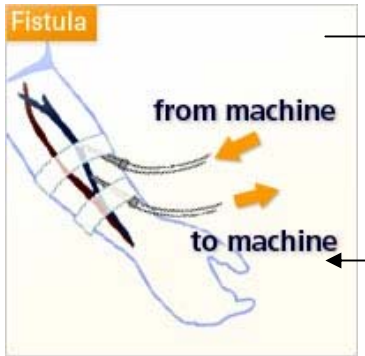
Molecular Adsorbent Recirculation (MARS)

- 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

Dialyzer 1

Dialyzer 2



Blood Loop

Albumin Loop

$NaHCO_3$ Loop

“Clean Albumin”

Active charcoal filters and anionic exchangers

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

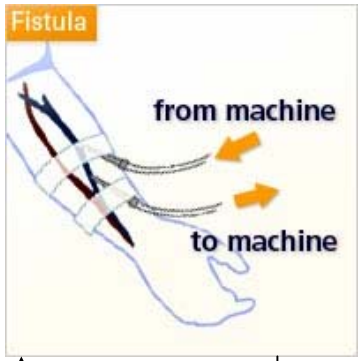
Table 1. Clinical features of 22 patients treated with MARS

Case	Age	Sex	Pathology	Indication	Cr μmol/l	Bili μmol/l	HRS	HE	VB	Sepsis	Total number of MARS	Outcome
1	59	F	HBV cirrhosis	AoCLF	210	520	–	+	–	–	1	Died
2	52	M	HBV cirrhosis	AoCLF	480	890	+	–	+	–	2	Died
3	62	M	HCC	Posthepatectomy	256	676	–	–	–	+	2	Died
4	42	M	Acute HBV hepatitis	ALF	86	512	–	+	–	–	1	Alive
5	33	M	HBV cirrhosis	AoCLF	250	798	+	+	–	–	1	Died
6	51	M	Wilson's disease	AoCLF	186	1029	+	–	+	–	3	Died
7	59	M	HBV cirrhosis	AoCLF	513	707	–	+	–	–	2	Died
8	56	F	PBC	AoCLF	100	578	+	+	–	–	2	Died
9	52	F	Posttransplant	Graft dysfunction	112	1030	–	–	–	–	2	Transplant, died
10	47	M	HCC	Posthepatectomy	589	167	–	–	–	–	3	Died
11	68	M	HCC	Posthepatectomy	319	83	–	–	–	–	2	Died
12	50	M	HBV cirrhosis	AoCLF	193	706	+	–	–	–	5	Transplant, alive
13	48	M	HBV cirrhosis	AoCLF	120	576	+	+	–	–	6	Transplant, died 12 months
14	47	M	Posttransplant	Graft dysfunction	56	956	–	–	–	–	2	Transplant, died 4 months
15	42	M	HBV cirrhosis	AoCLF	424	684	+	–	–	–	9	Died
16	34	M	Drug-induced ALF	ALF	75	811	–	+	–	–	2	Transplant, alive
17	57	M	Posttransplant	Graft dysfunction	594	702	–	+	–	+	6	Died
18	46	M	HBV cirrhosis	AoCLF	243	764	+	+	–	–	13	Died
19	55	M	HBV cirrhosis	AoCLF	190	652	–	+	–	+	3	Died
20	39	M	Posttransplant	Graft dysfunction	344	643	–	+	+	–	2	Died
21	66	M	Cholangiocarcinoma	Posthepatectomy	392	713	–	–	–	–	3	Died
22	54	M	HBV cirrhosis	AoCLF	464	355	+	+	–	–	2	Died

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; Bili, 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

FPSA (Albumin filter)

Prometh 01 Adsorber

Prometh 02 Adsorber

Blood + polar toxins

Hemodialysis Unit

Dialysis fluid

"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

[12]

TABLE 1. *Clinical characteristics of patients*

Device	n°	Age	Sex	Liver disease	LTX-candidate	Indications	Number of sessions	Duration of treatment (day)	HE	Child-Pugh	UNOS	APACHE II	MELD	SOFA	3-month outcome
PROM	1	38	M	ACLF: HCV	Yes	BTP	2	2	1	C11	2A	17	41	10	Alive
PROM	2	59	F	ACLF: alcohol	No	Support	3	3	1	C12	2B	21	26	7	Dead
PROM	3	64	F	ACLF: alcohol	Yes	Support	3	3	0	C11	2B	13	21	7	Dead
PROM	4	30	M	ACLF: alcohol	No	Support	3	3	2	C11	2A	12	28	8	Alive
PROM	5	63	F	ACLF: alcohol	No	Support	2	2	2	C13	2A	22	29	11	Dead
PROM	6	54	M	Failing-liver transplant, HCV	Yes	BTP	3	3	1	C12	2A	10	18	8	Alive
PROM	7	55	F	ACLF: alcohol	Yes	BTP	2	3	0	C12	2A	17	26	8	Alive
PROM	8	47	F	ACLF: alcohol	No	Support	3	3	1	C12	2B	8	29	7	Dead
PROM	9	53	F	ACLF: alcohol	No	Support	3	3	2	C13	2A	20	44	10	Dead
	Mean	51.4					2.7	2.8	1.1	C11.8		15.6	29.1	8.4	Survival: 44%
	SEM	3.8					0.2	0.2	0.3	0.3		1.7	2.8	0.5	
MARS	10	68	M	Acute HBV	No	Support	3	3	1	NA	2B	28	NA	10	Dead
MARS	11	62	M	ACLF: alcohol	No	Support	3	3	0	13	2B	12	17	6	Alive
MARS	12	57	M	ACLF: alcohol	No	Support	5	5	1	13	2A	22	27	7	Dead
MARS	13	77	M	Chronic cholestatic toxic syndrome	No	Support	3	3	0	NA	2B	8	NA	6	Alive
MARS	14	69	M	Chronic cholestatic toxic syndrome	No	Support	3	3	2	NA	2B	8	NA	6	Alive
MARS	15	46	M	ACLF: alcohol	No	Support	2	2	2	7	2A	19	30	12	Alive
MARS	16	52	M	ACLF: alcohol	No	Support	3	3	2	14	2A	13	25	8	Dead
MARS	17	43	M	ACLF: HBV	No	Support	3	3	3	13	2A	22	30	9	Dead
MARS	18	55	M	Primary graft dysfunction	No	Support	3	3	2	9	2 A	22	27	11	Alive
	Mean	58.7					3.1	3.1	1.4	C11.5		17.1	26	8.3	Survival: 56%
	SEM	3.7					0.3	0.3	0.3	1.1		2.4	2	0.8	

BTP, bridge to transplantation; HE, hepatic encepahlopathy; M, male; F, female; NA, not applicable.
HCV, hepatitis C virus.
HBV, hepatitis B virus.

[12]

TABLE 2. *Biochemical data at pretreatment and posttreatment*[¶]

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

*$P < 0.05$; [†]$P < 0.01$ pre versus post; [‡]$P < 0.05$; [§]$P < 0.01$ PROM versus MARS.
[¶]Number of data sets between brackets.
RRt, treatment phase reduction ratio; NA, not applicable.
ALAT, alanine aminotransferase.

Toxin levels

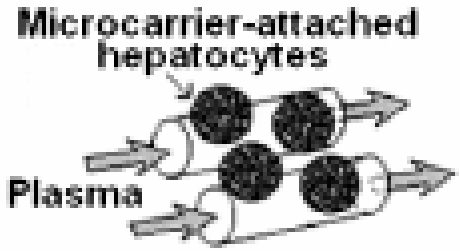
Bioartificial Livers (BALs)

- 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 [25]



Basic Design:

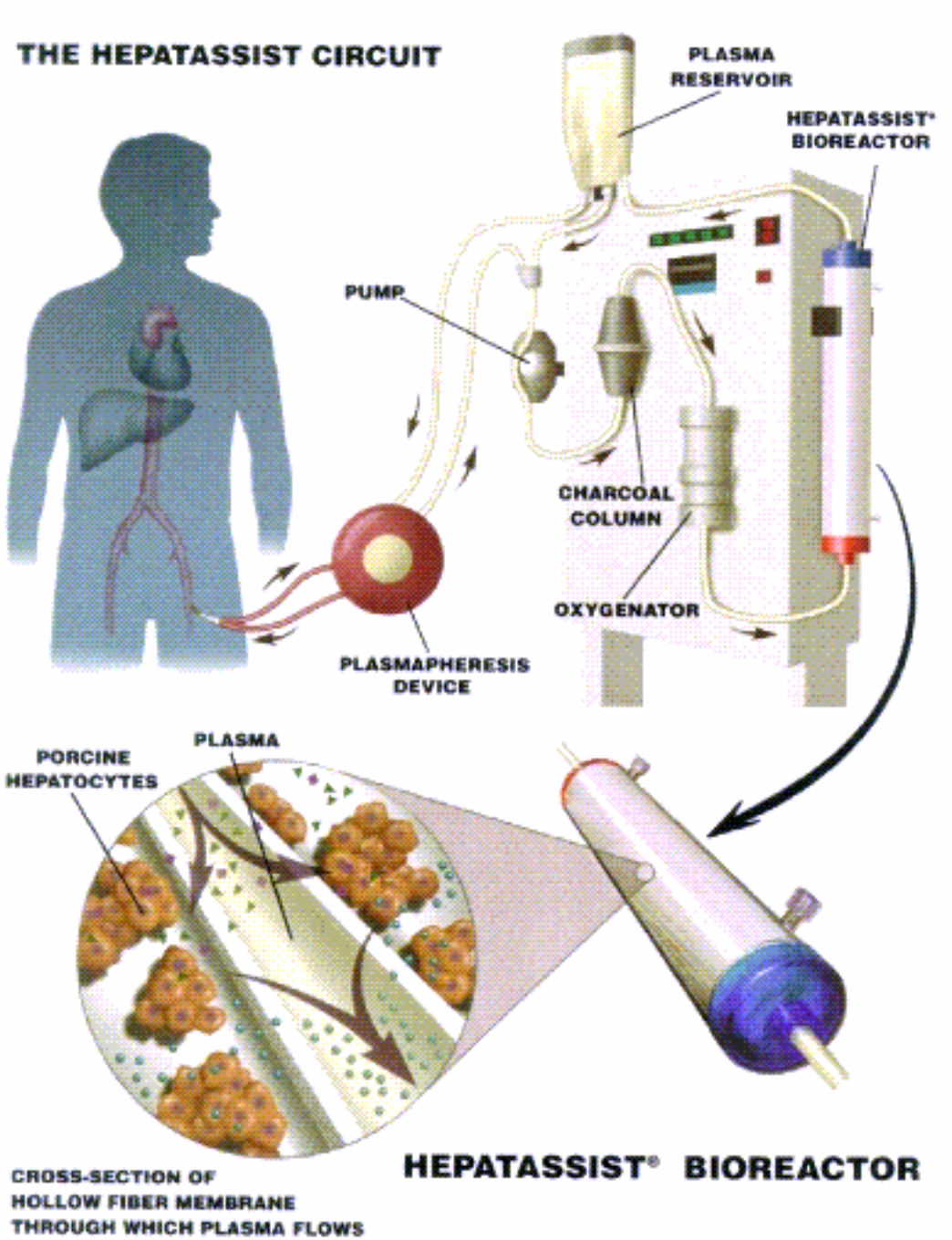
- Venous connection leads the plasma to the HepatAssist
- Cellular component of the plasma gets separated into by a “plasmapheresis” device
- Plasma goes into a hollow microfibre, which is surrounded by a micro porous membrane
  - → Membrane pores are large enough for toxin molecules to pass through, 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

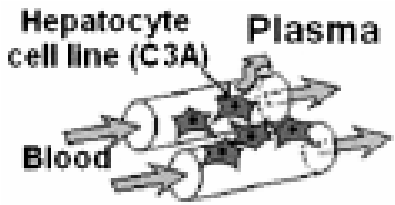
[24]


THE HEPATASSIST CIRCUIT
PLASMA RESERVOIR
HEPATASSIST® BIOREACTOR
PUMP
CHARCOAL COLUMN
OXYGENATOR
PLASMAPHERESIS DEVICE
PORCINE HEPATOCYTES
PLASMA
CROSS-SECTION OF HOLLOW FIBER MEMBRANE THROUGH WHICH PLASMA FLOWS
HEPATASSIST® BIOREACTOR

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



[25]

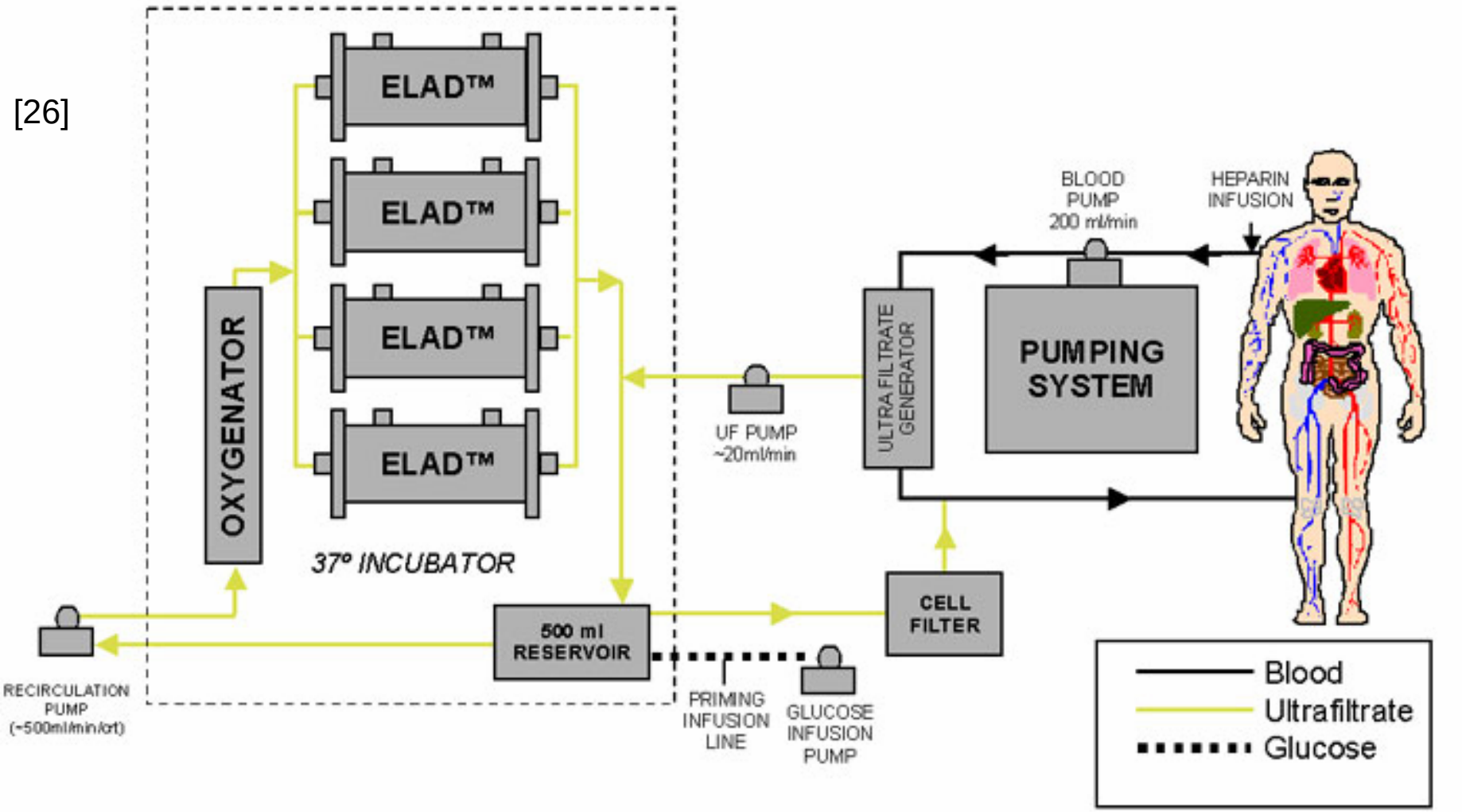
<u>Basic Design:</u>

- 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

[26]


ELAD™
ELAD™
ELAD™
ELAD™
OXYGENATOR
37° INCUBATOR
BLOOD PUMP 200 ml/min
HEPARIN INFUSION
ULTRA FILTRATE GENERATOR
PUMPING SYSTEM
UF PUMP ~20ml/min
CELL FILTER
500 ml RESERVOIR
RECIRCULATION PUMP (~500ml/min/crt)
PRIMING INFUSION LINE
GLUCOSE INFUSION PUMP
Blood
Ultrafiltrate
Glucose

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;

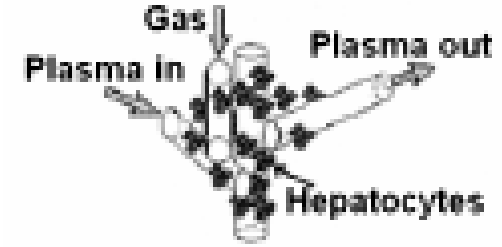
  →2 bundles are used for perfusion with patient plasma. It is operated with primary porcine hepatocytes as well as human hepatocytes isolated from discarded donor organs.
- The modular design is based on a **parallel plate geometry**.

  →Rectangular cross-section flow channel formed by two polycarbonate plates.

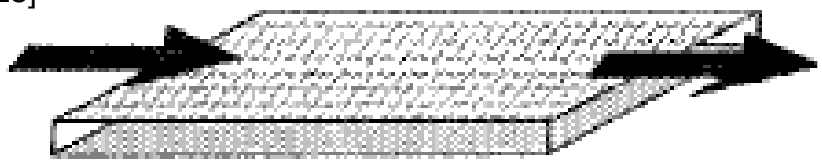
  →The lower plate supports a semi-permeable membrane to which the liver cells are attached.

  →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.

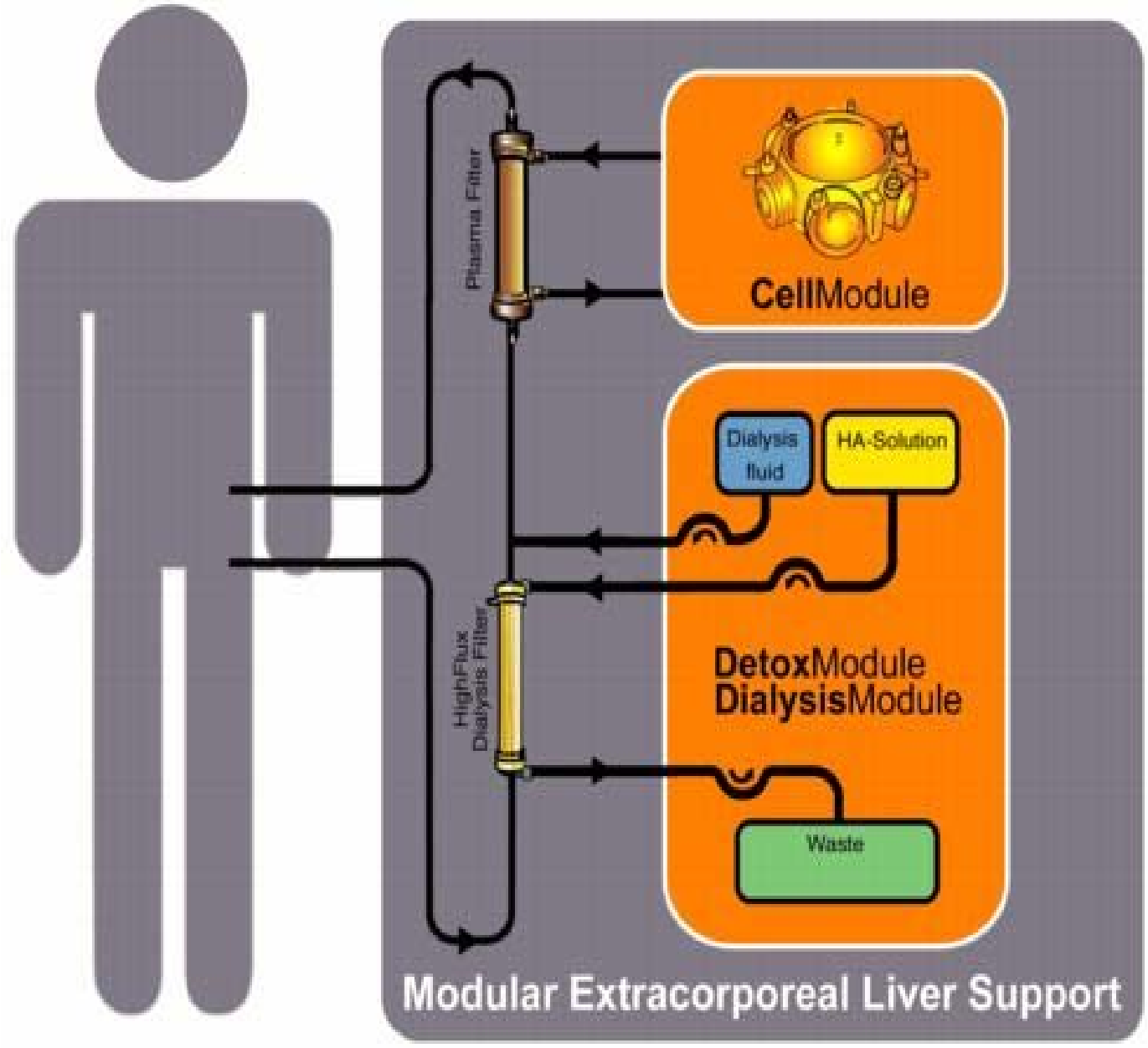


[25]



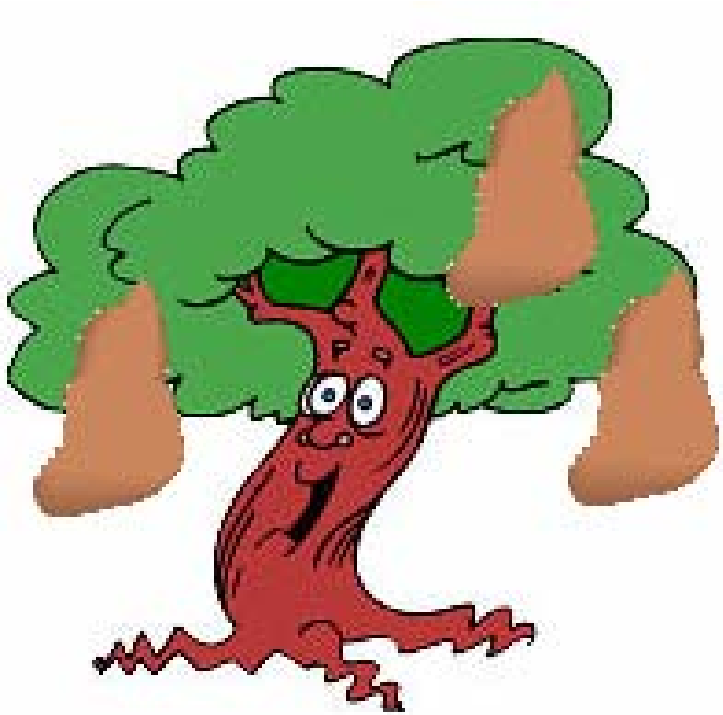
Flat Plate and Monolayer

[26]


Plasma Filter
CellModule
Dialysis fluid
HA-Solution
HighFlux Dialysis Filter
DetoxModule
DialysisModule
Waste
Modular Extracorporeal Liver Support

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



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SO: British Journal of Surgery
VL: 88
NO: 8
PG: 1084-1091
YR: 2001
CP: © 2001 British Journal of Surgery Society Ltd
ON: 1365-2168
PN: 0007-1323
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
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