

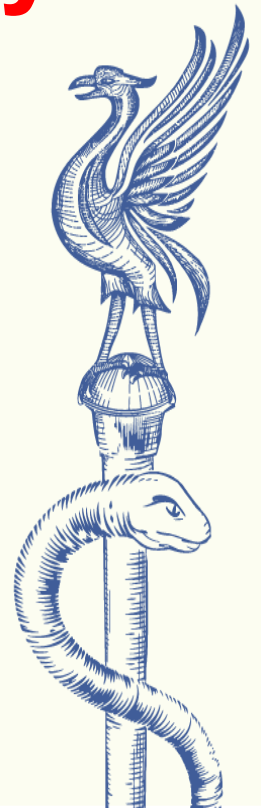
‘Metabolism of alcohol - Alcohol’s trip through the body’

Prof. Barry Campbell

Infection Biology & Microbiomes, IVES

bjcampbl@liverpool.ac.uk

<http://pcwww.liv.ac.uk/~bjcampbl/Alcohol.htm>



Learning objectives

- **L01** - Alcohol, measures and safe limits
- **L02** - Examine the absorption of alcohol from the GI tract to the tissues and organs of the body
- **L03** - Understanding the metabolic pathways used to breakdown alcohol
- **L04** - Tissue damage caused by excess alcohol (GI tract, Liver, pancreas and other tissues)
- **L05** - Discuss what causes fatty liver
- **L06** - Examine how damage to hepatocytes leads to fibrous scar tissue characteristic of the cirrhotic liver
- **L07** - Other biologic effects of alcohol intoxication

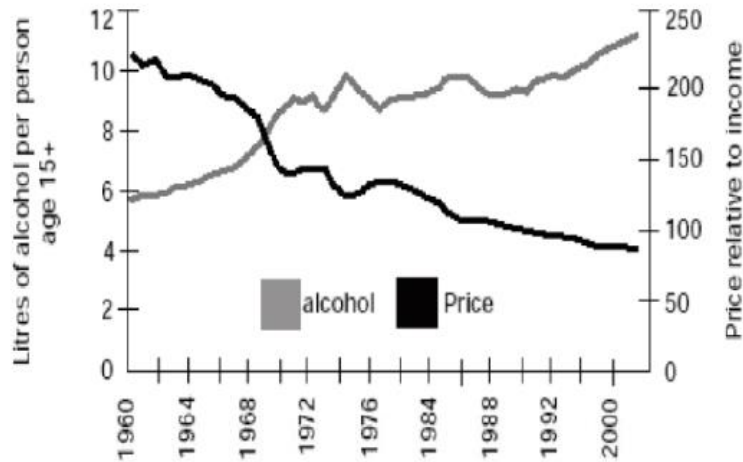
Alcohol-related deaths rising

- In England, there were 8,274 alcohol-specific deaths (deaths wholly due to alcohol) in 2023, which was an increase of 63.8% from 5,050 deaths in 2006; [Local alcohol profiles for England, 2024](#).
- Over 0.8 million estimated [admissions related to alcohol consumption](#) in 2020-2021. Down for the first time (due to COVID lockdowns) from ~1 million in 2019-2020 (which was third consecutive increase in the rate since 2016-2017).
 - Death rate from liver disease continues to rise.
 - Alcohol consumption is an important cause of liver disease. The mortality rate for chronic liver disease in England was 15.0 per 100,000 population in 2023 and was also the highest rate since the start of the data series in 2006 (12.6 per 100,000).
 - Hospital visits for alcohol poisoning have more than doubled in last 6 years with highest rate among females in their teens
- [Institute of Alcohol studies](#) in 2024 estimates alcohol misuse cost the UK economy between £34 to 40 billion
- [Minimum pricing set](#) (currently 65 p/U) in Scotland (2018) and Wales (2020), likely in NI (2025), but not in England!



LO1 As prices went down relative to income, alcohol consumption (between 1960-2002) went up.

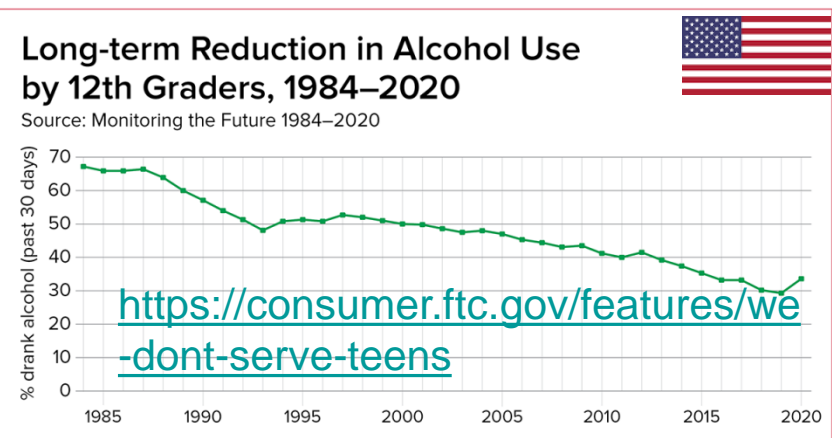
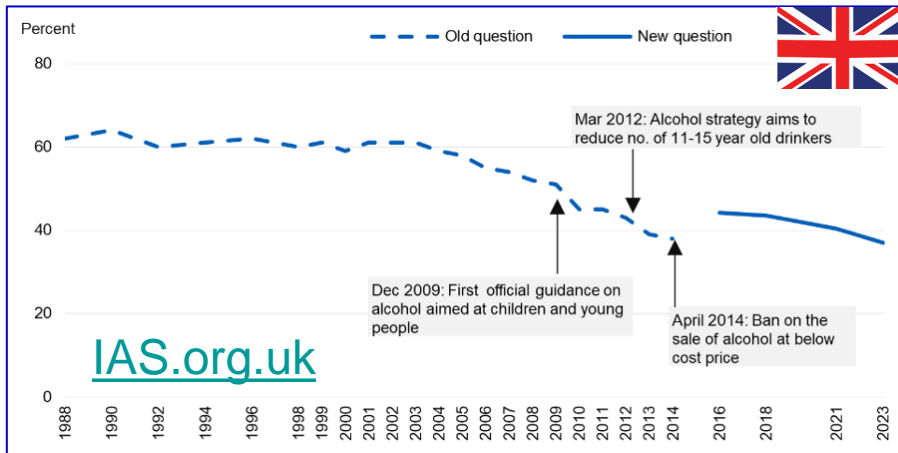
Institute of Alcohol Studies (2007)



Statistics on Alcohol, England 2017

- Higher earners were more likely to drink alcohol.
- 77% of those earning > £40K drank alcohol compared to 46% of those earning up to £10K.

Some good news - The proportion of 11-15 year-olds in UK who have ever had an alcoholic drink has been declining (37% in 2023 compared to 40% in 2021).



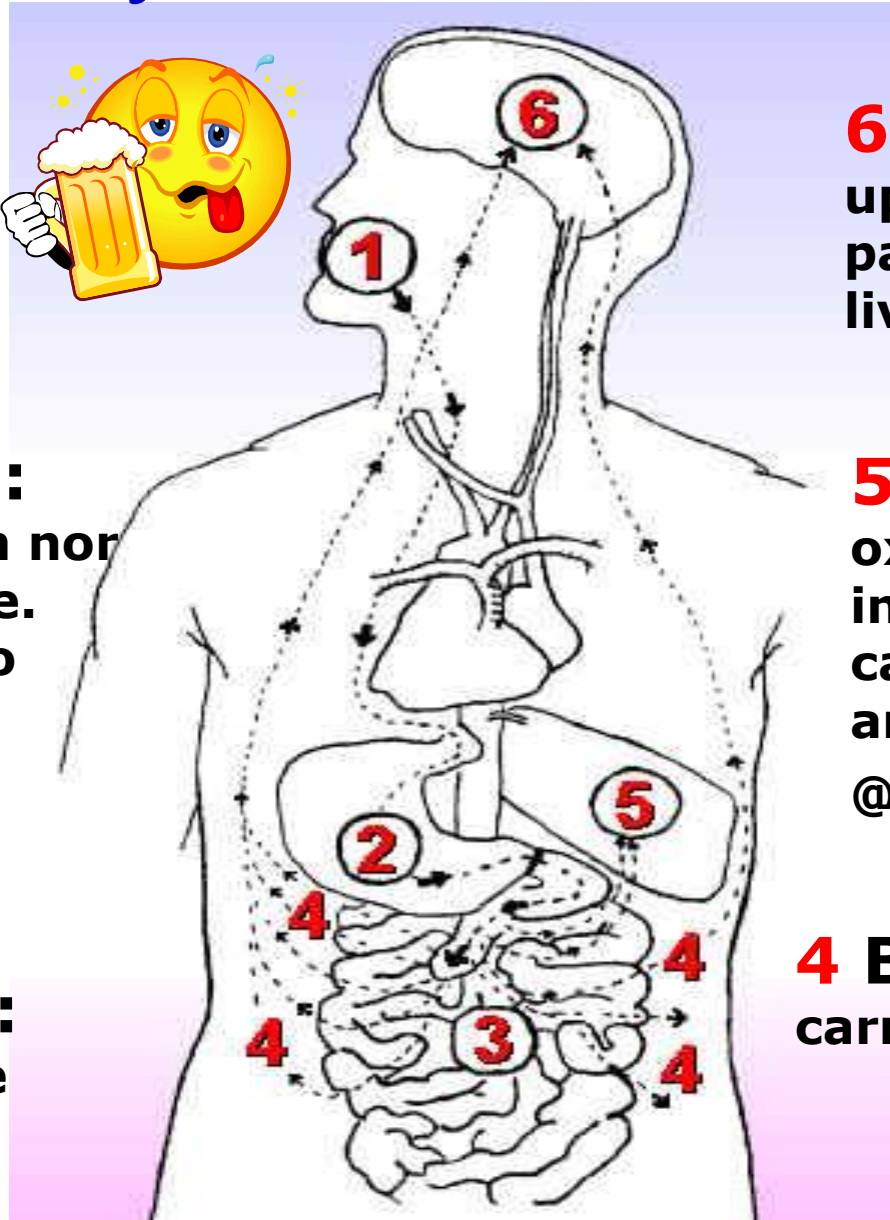
Fancy a nice cool beer?

1 MOUTH:
usual ingestion
route



2 STOMACH:
little absorption nor
breakdown here.
Most emptied to
small intestine

**3 SMALL
INTESTINE:**
uptake into the
bloodstream



6 BRAIN: rapid
uptake.. keeps
passing through until
liver breaks it down

5 LIVER:
oxidises alcohol
into water,
carbon dioxide,
and energy.
@0.015% /h.

4 BLOODSTREAM:
carries the alcohol

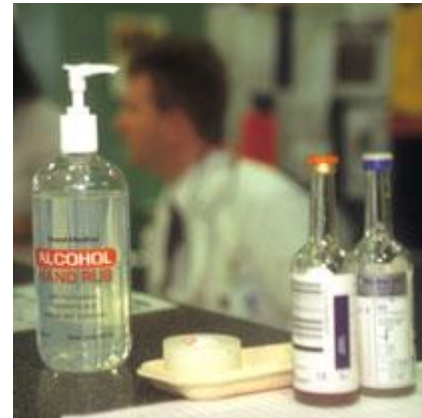
Alcohol – access to the body

Ingestion:

- slowly absorbed from the stomach
- rapidly absorbed from the small intestine

Other routes of entry:

- Skin
- Nasal passages
- Lungs



Alcohol – access to the body

Ingestion:

- slowly absorbed from the stomach
- rapidly absorbed from the small intestine

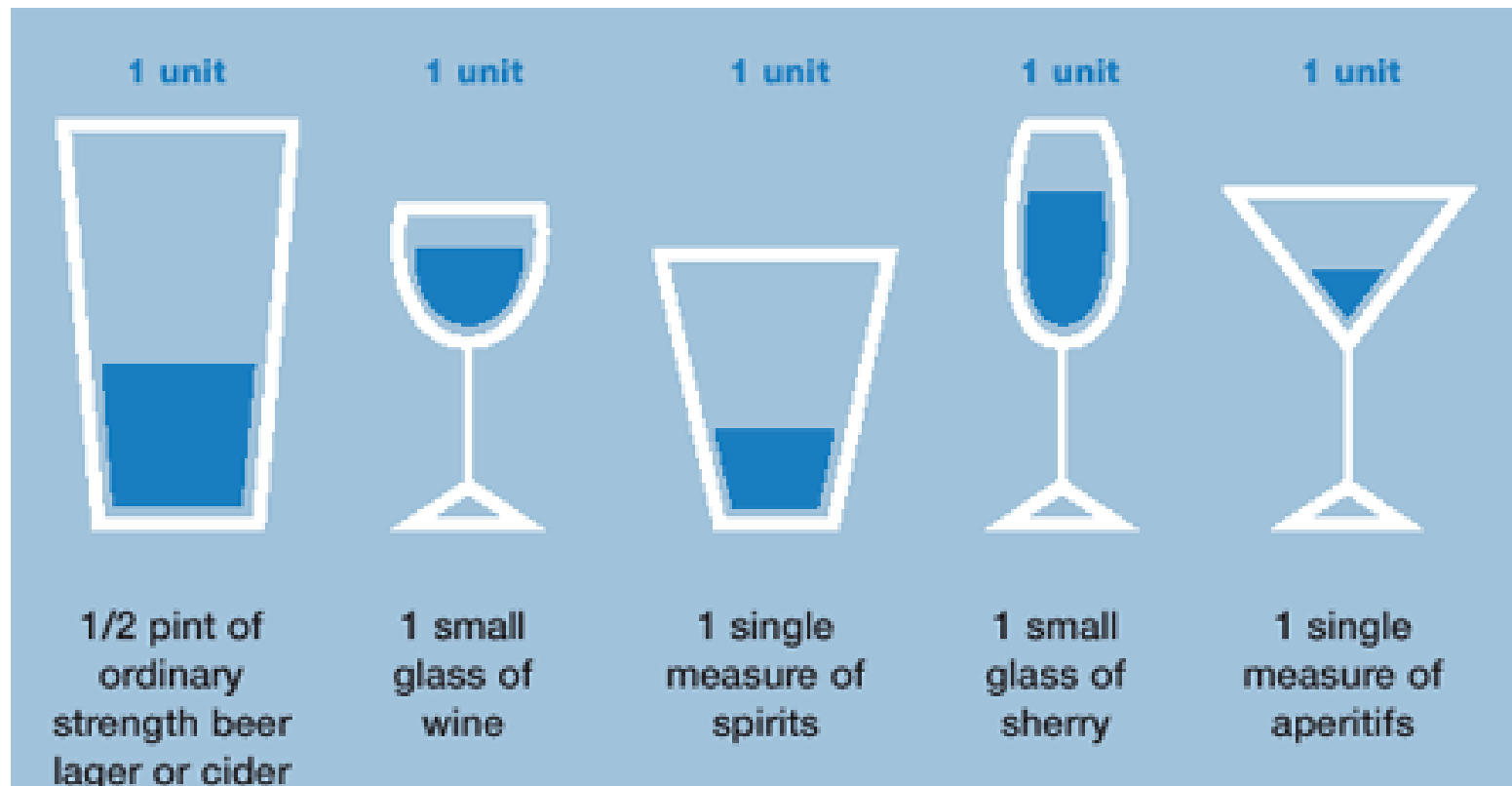
Other routes of entry:

- Skin
- Nasal passages
- Lungs
- **Other epithelia**

How to measure alcohol consumption?

Alcohol measures

- Units/grams
- 1 unit = 8 grams of alcohol



“Safe limit” for alcohol?

- Since 1995 Government advice, healthy men no more than 28 U/wk
- In healthy women no more than 21 U/wk
- **May be too much for some?**
Doctors advised 21U/wk and 14U/wk respectively
- **Estimated that 8% of men and 3% of women are "problem drinkers" in the UK**

UK Chief Medical Officers - 8 Jan 2016

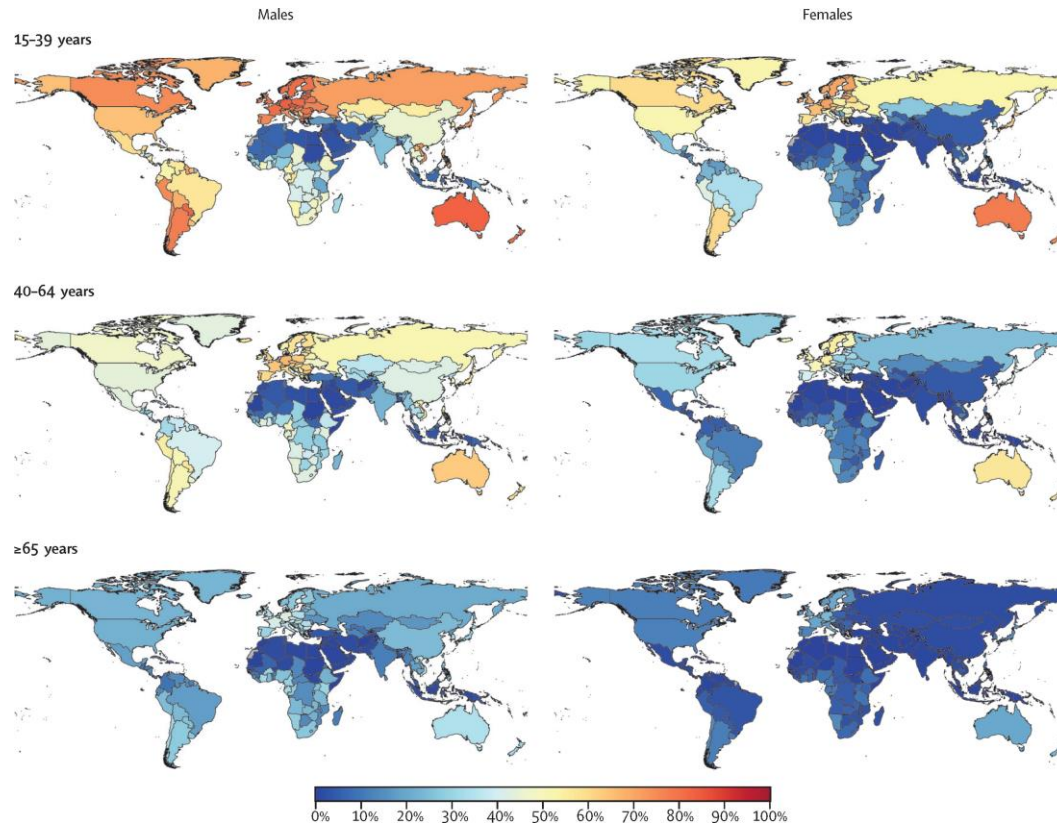
“No safe limit” for alcohol

- Both men and women are advised to drink no more than **14 U/week**, and to spread them over ≥ 3 days rather than consuming them all in one session
- Have several alcohol-free days per week
- Drinking more slowly, with food, and alternating between alcoholic and soft drinks
- Pregnant women should not consume alcohol at all
- Any alcohol consumption is associated with increased risk of some cancers & other diseases



The health risks associated with moderate alcohol intake continue to be debated

THE LANCET 2022: 400, Issue 10347; 185-235

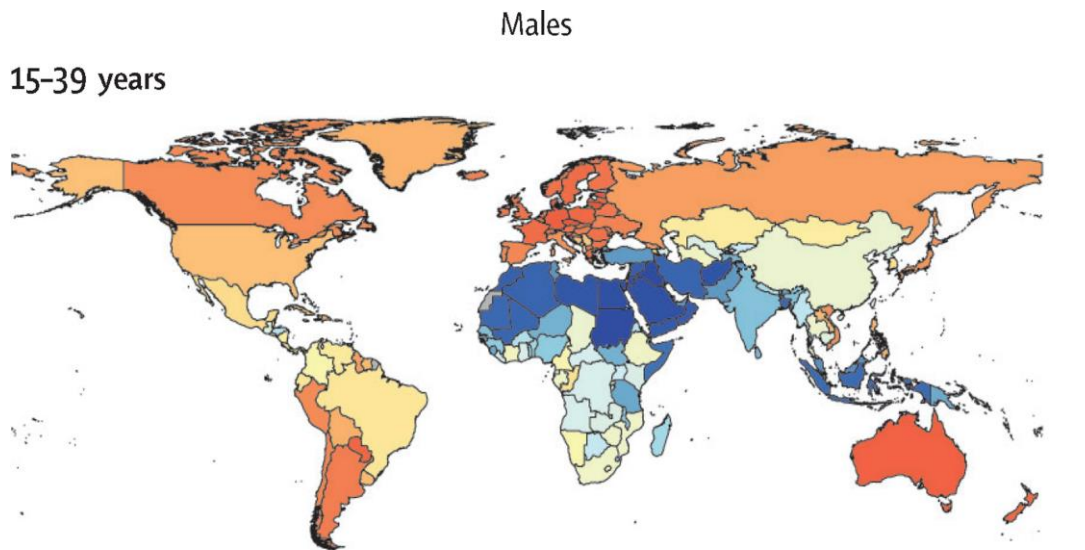


- alcohol advice should vary according to age and gender
- alcohol consumption is never beneficial for people < 40 years old
- Any amount of alcohol increases the risk of certain cancers, and that is at any age
- **Young males consuming most harmful amounts of alcohol**

Figure 4. Proportion of the population consuming harmful amounts of alcohol, in 2020

The health risks associated with moderate alcohol intake continue to be debated

THE LANCET 2022: 400, Issue 10347; 185-235



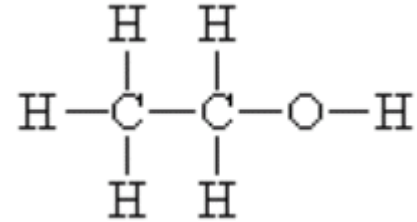
- alcohol advice should vary according to age and gender
- alcohol consumption is never beneficial for people < 40 years old
- Any amount of alcohol increases the risk of certain cancers, and that is at any age
- **Young males consuming most harmful amounts of alcohol**

Figure 4. Proportion of the population consuming harmful amounts of alcohol, in 2020

LO1

LO2

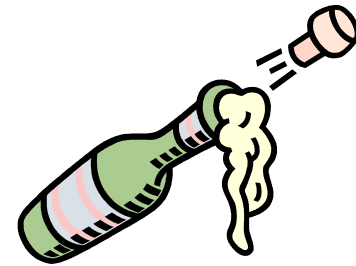
Ethanol (C₂H₅OH)



- provides 'empty' calories - no nutritional benefit
- 7 calories per gram - almost as high as fat in caloric content
- **water soluble** - does not enter fat.
- size and body build affect uptake
 - in general, women get drunk quicker than men.... higher body fat, smaller amount body water.

Absorption of alcohol

- rate dependant on alcohol type and concentration
(Sherry 20% > beer 3-8% > spirits 40%)
- peaks 1h after consumption
- faster with carbonated alcohol
- greater with an empty stomach
- increased by drugs enhancing gastric emptying and those drugs that inhibit gastric alcohol dehydrogenase
- retarded by food, esp. carbohydrate (as much as 75% compared to an empty stomach) – *Alcoholpops & energy drinks!*
- **caffeine counters alcohols soporific affects** ('The party's over'. *Nature* (25th Nov. 2010) 468, p475). FDA regulators now targeting makers of caffeinated alcohol.



Distribution of absorbed alcohol

- Distribution is throughout the water in the body
- Most tissues (e.g. heart, brain and muscles) are exposed to the same concentration of alcohol as the blood
- Exposure of the liver is greater because blood is received direct from the small bowel via the portal vein
- Alcohol diffuses rather slowly, except into organs with a rich blood supply such as the brain and lungs.

Physiological changes accompanying alcohol consumption

■ Sweating, flushing (dilation of blood vessels) and bruising

- acetaldehyde; Tyramine or histamine in fermented alcoholic beverages; suppression of endothelin 1 (vasoconstrictor); aberrant CNS control of vascular tone.

Body can suffer from heat loss and hypothermia

■ Tachycardia and increases in blood pressure

- stimulation of the hypothalamus and increased release of sympathomimetic amines and pituitary-adrenal hormones.

Can lead to increases in systolic & diastolic blood pressure, irregular pulse, enlarged heart and even stroke!

■ Kidneys secrete more urine (polydipsia)

- not only because of the fluid drunk but also because of the osmotic effect of alcohol and inhibition of secretion of anti-diuretic hormone.

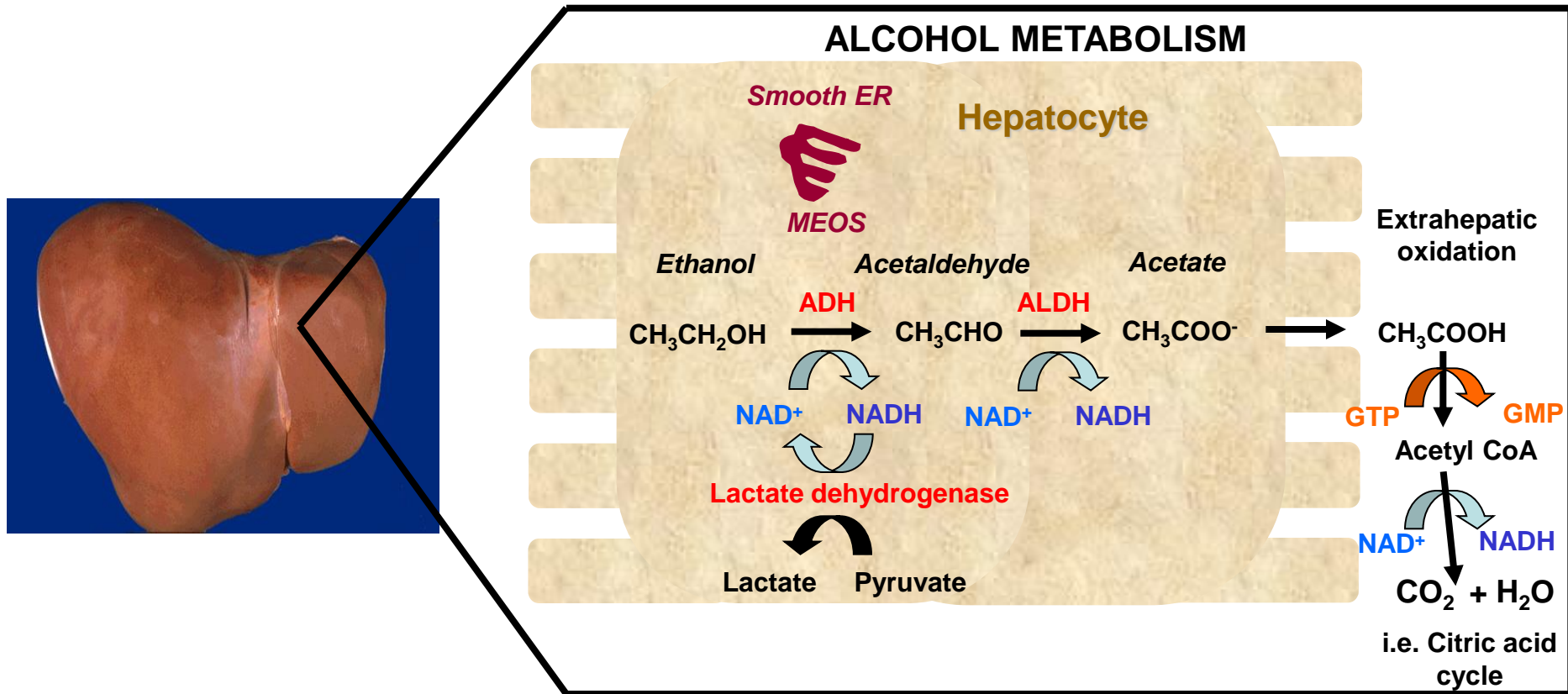
Can lead to severe dehydration

Elimination of absorbed alcohol

- **95% metabolised by the liver**
 - removed from the blood at a rate of about 3.3 mmol/h (15 mg/100 ml/h)
- **2-5% is excreted unchanged in urine, sweat, faeces, milk or breath**
 - in proportion to the concentration in the blood, alcohol transfers from the blood into the alveolar air sacs in the lungs then exhaled in breath as per CO₂

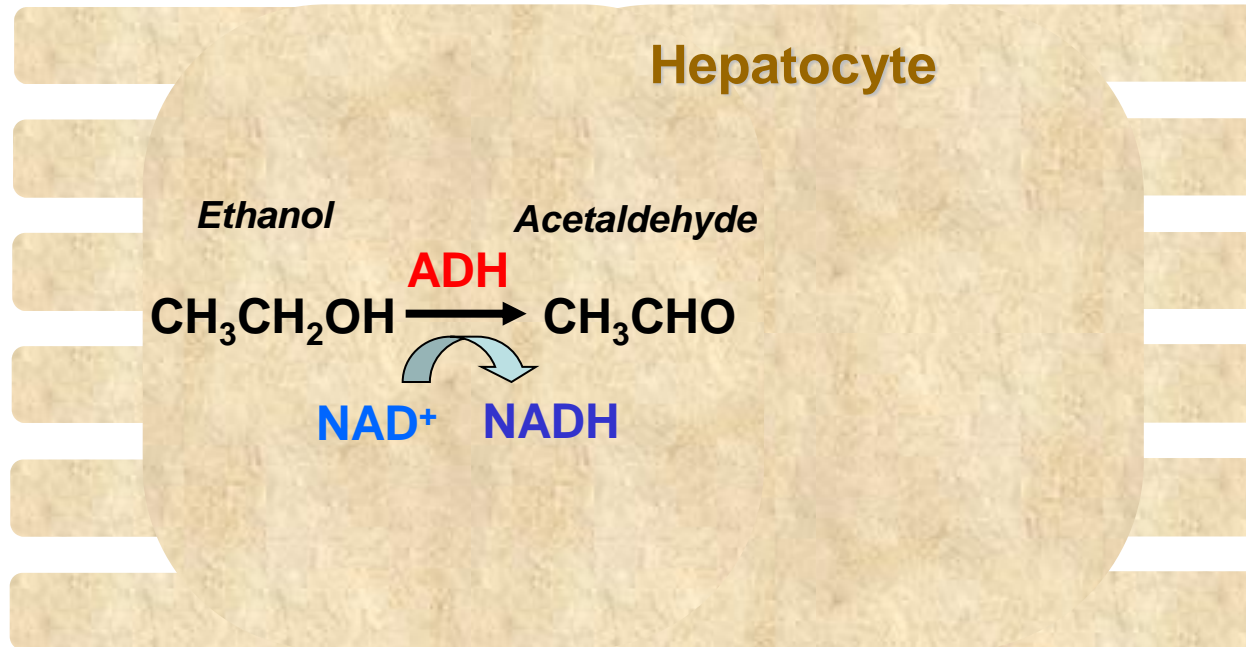
Alcohol breakdown in the liver

Alcohol dehydrogenase (ADH) and mitochondrial acetaldehyde dehydrogenase (ALDH) metabolise ethanol consumed



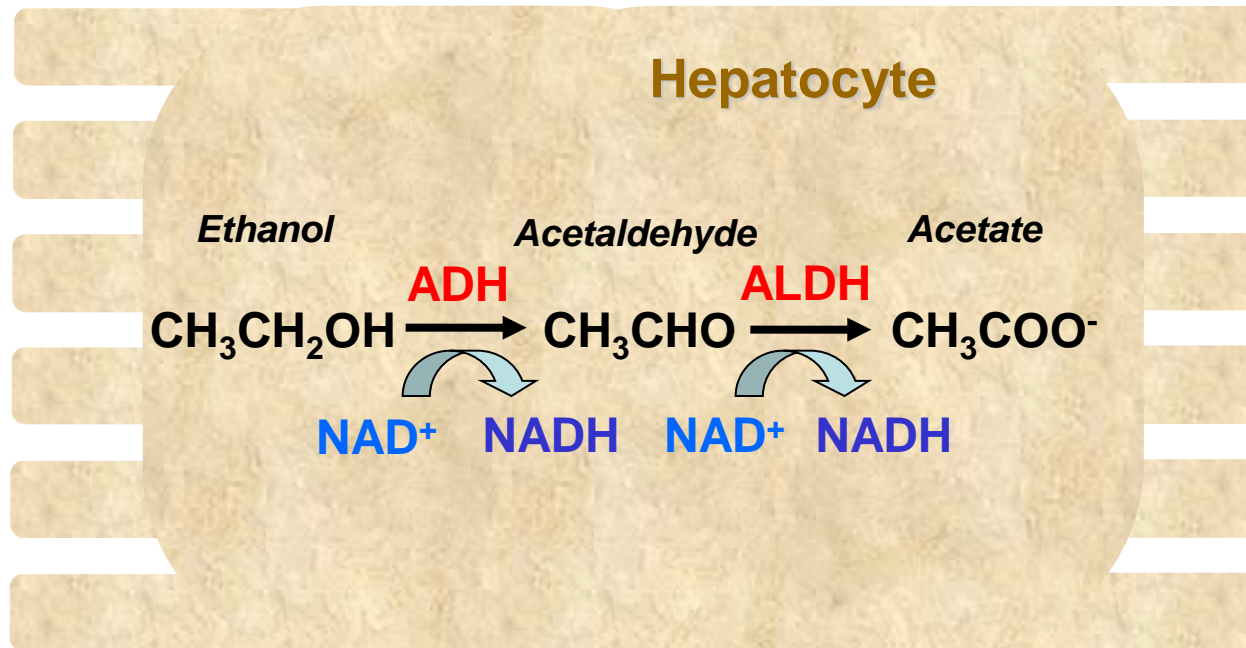
ADH variants found in most tissues (incl. lung, cornea, stomach, oesophagus) but highest in liver

Alcohol metabolism



- The first step in the metabolism of alcohol is the oxidation of ethanol to acetaldehyde catalyzed by ADH (in the cytosol) containing the coenzyme NAD^+ .
- Results in the generation of NADH (reduced nicotinamide adenine dinucleotide)

Alcohol metabolism

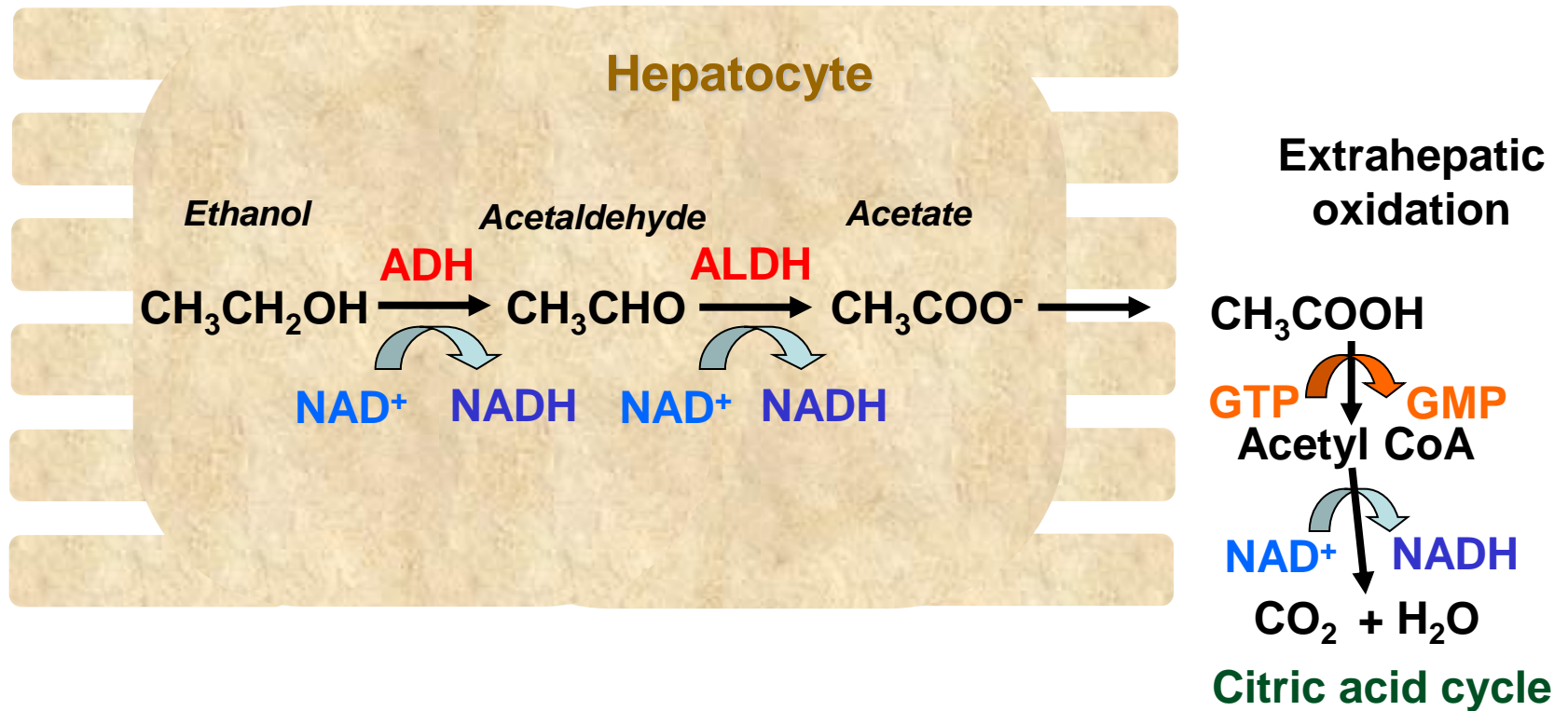


- Conversion to acetaldehyde into acetate by ALDH (in mitochondria) also results in the generation of NADH
- NADH is the hydrogen-transfer chemical (*i.e.*, *electron transporter*) that enables *oxidative phosphorylation* to take place (*i.e.*, production of ATP energy within the mitochondria through the utilization of oxygen).

Alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH)

- At least 7 ADH genes and 12 ALDH genes have been identified in humans
- Isoforms important for ethanol metabolism are the Class I, Class II, and Class IV ADH isozymes, and for acetaldehyde metabolism, mitochondrial ALDH2 and one of the cytosolic forms, ALDH1.
- Up to 40-50% of Japanese people lack ADH and ALDH2
- Inuit and American Indians have genetic weakness for ADH
- Inheritance of the high activity ADH $\beta 2$ enzyme (encoded by the *ADH2*2* gene) and the inactive *ALDH2*2* gene product have been conclusively associated with reduced risk of alcoholism.
- Strong correlation between *ALDH2*2* allele and pharyngeal & oesophageal cancers

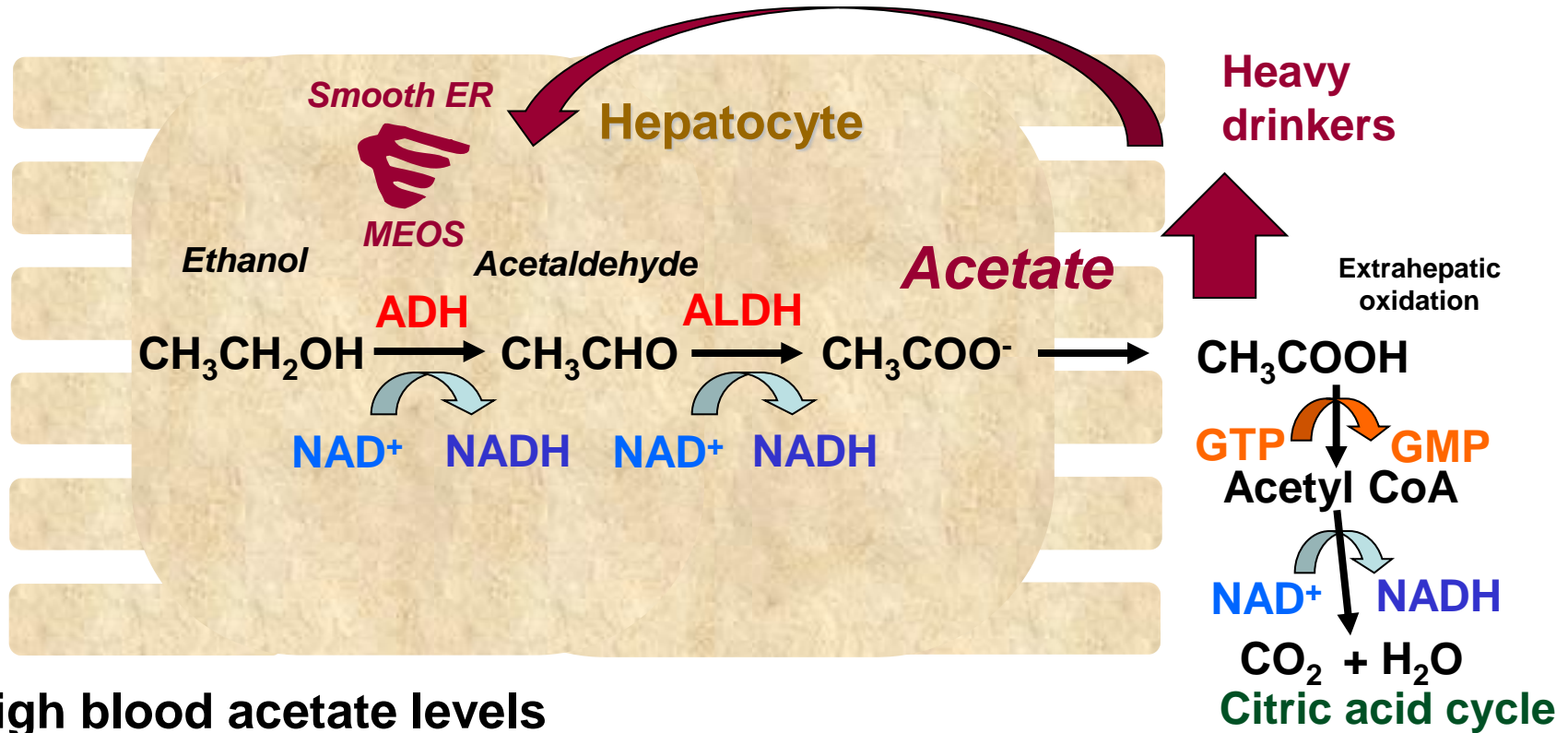
Alcohol metabolism



- The acetate is further oxidized (mitochondrial extrahepatic oxidation) to CO_2 and water through the citric acid cycle.
- The acetate entering the citric acid cycle generates even more **NADH**.

LO3 Metabolism of alcohol faster in heavy drinkers

– tolerance and enzyme induction

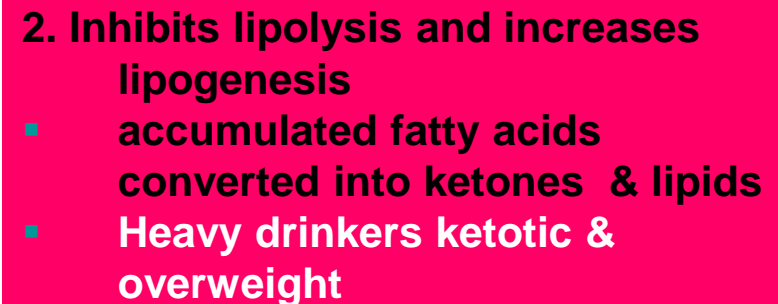


- high blood acetate levels
- brings the microsomal ethanol oxidising system into play
- dependent on liver enzyme cytochrome P450IIE1 (CYP2E1), which may be increased after chronic drinking.
- Enzyme induction is also produced by drugs metabolised by the liver (e.g. opiates) and other co-factors (such as smoking).

Alcohol metabolism has powerful effects on cellular energy production pathways

- **Drinking alcohol warms people up...for a short while!** Rapid NADH production from the alcohol dramatically increases energy availability and body temperature, especially in people who are chilled.
- Oxidation of alcohol can become a major energy source and particularly in the liver and intestine can inhibit metabolism of other nutrients

1. Converts pyruvic acid to lactic acid
 - hepatic gluconeogenesis inhibited by low [pyruvic acid]
 - glucose production is reduced
 - **risk of hypoglycaemia**
 - overproduction of lactic acid blocks uric acid excretion by the kidneys. **Acidosis**



3. Makes excess ATP

- inhibits fat oxidation and citric acid
- accumulated fatty acids or AcetylCoA converted into ketones (ketosis) and lipids
- Excess fat in liver
- Excess fat in blood (MI risk)

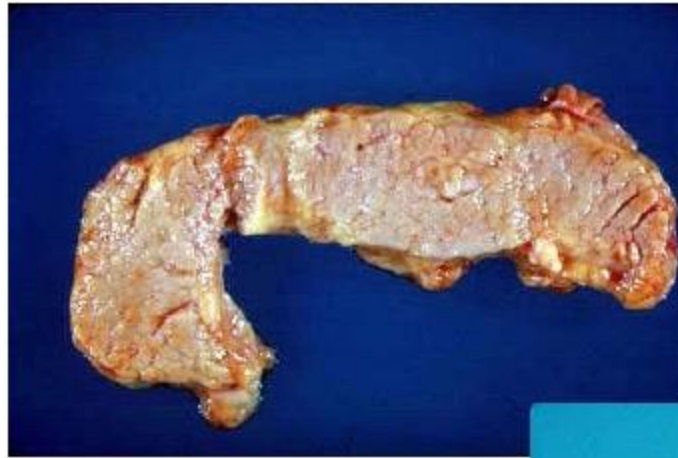
Alcohol damages the GI tract

- Causes inflammation of the tongue, stomach, pancreas, liver and intestines
- Breakdown products lead to fat deposition, fibrosis and scarring of the liver
- Impairs the digestion of food and absorption into blood. Alters food consumption behaviour/selection.
- Acetaldehyde (the oxidation product) can interfere with absorption & activation of vitamins.
- Motility problems ...diarrhoea
- Increased risk of cancer.....oesophageal, liver (hepatocellular carcinoma) and bowel (high calories)

Effects of alcohol on the pancreas

- **Stimulation of CCK and Secretin release from duodenum**
- **Changes in pancreatic blood flow and secretion**
- **Toxic metabolites** - Non-oxidative vs oxidative metabolism: generation of free radicals from ethanol metabolism leading to necrosis

Normal pancreas

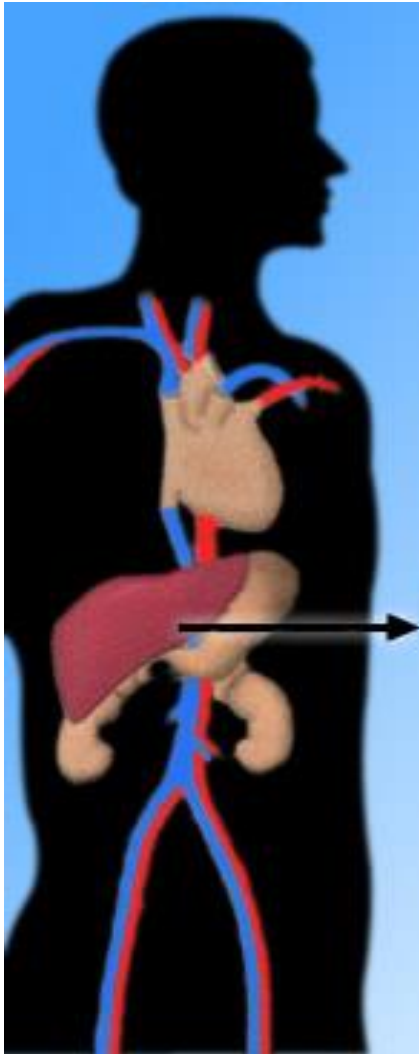


Acute pancreatitis



- **Sensitization to CCK** - Zymogen activation
- **Sphincter of Oddi spasm** - lead to an acute obstructive injury

Stages of alcohol-induced liver damage



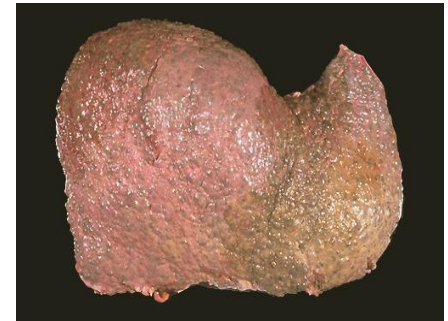
Fatty Liver



**Liver
fibrosis**



Cirrhosis



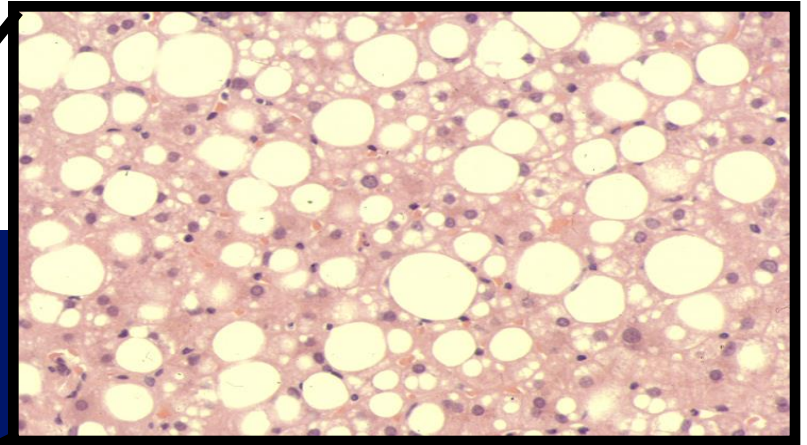
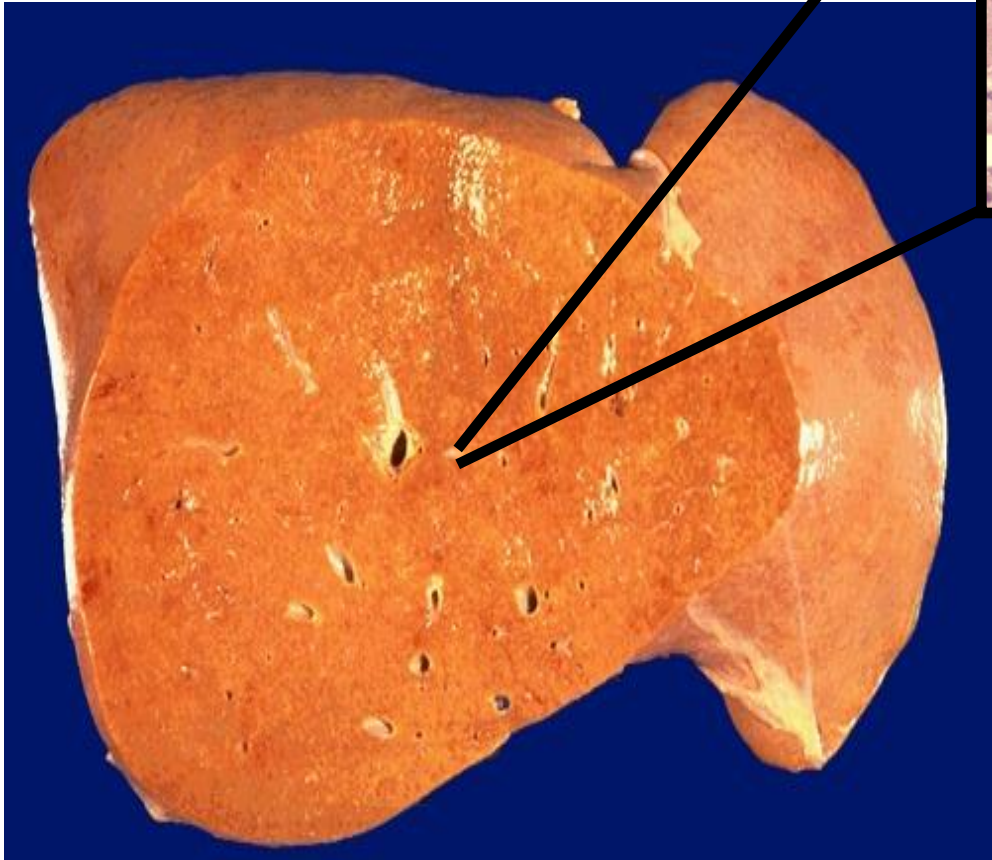
- Out of every 100 people who abuse alcohol:

***Almost all: fat in liver**

***Only 10-35: inflammation**

***10-20: scarring (cirrhosis)**

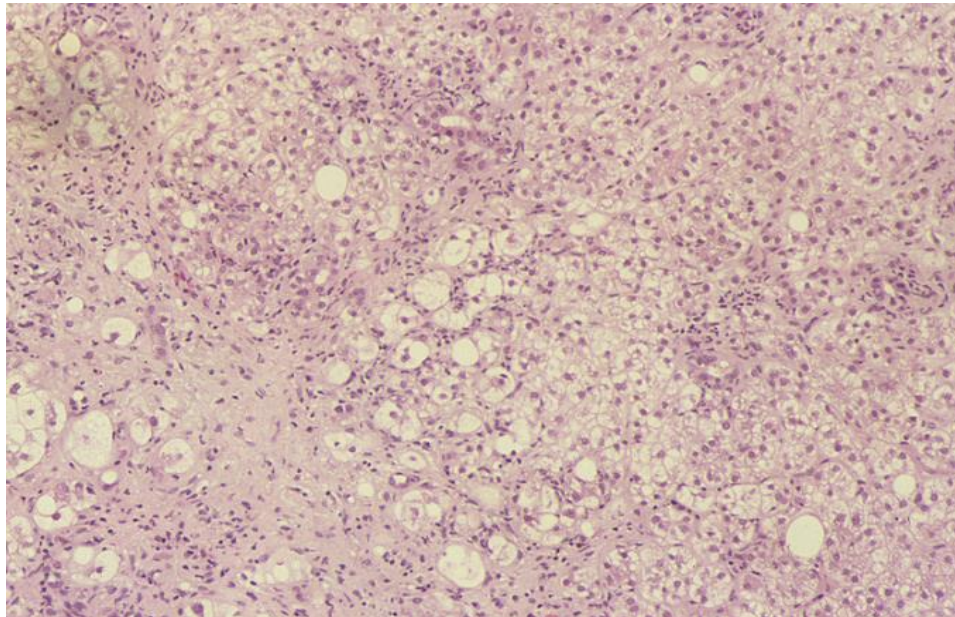
Fatty Liver



- Deposits of fat cause liver enlargement
- Steatosis can be reversed within a few weeks of sobriety

Alcoholic steatohepatitis

- inflammation induces production and accumulation of extracellular matrix (collagen) from hepatic stellate cells
→ liver fibrosis
- scar tissue forms; liver can recover but scarring remains



- severe ASH is associated with a high mortality; although glucocorticoid treatment has been reported to improve survival

Cirrhosis of the liver

- growth of connective tissue destroys liver cells
.....damage irreversible



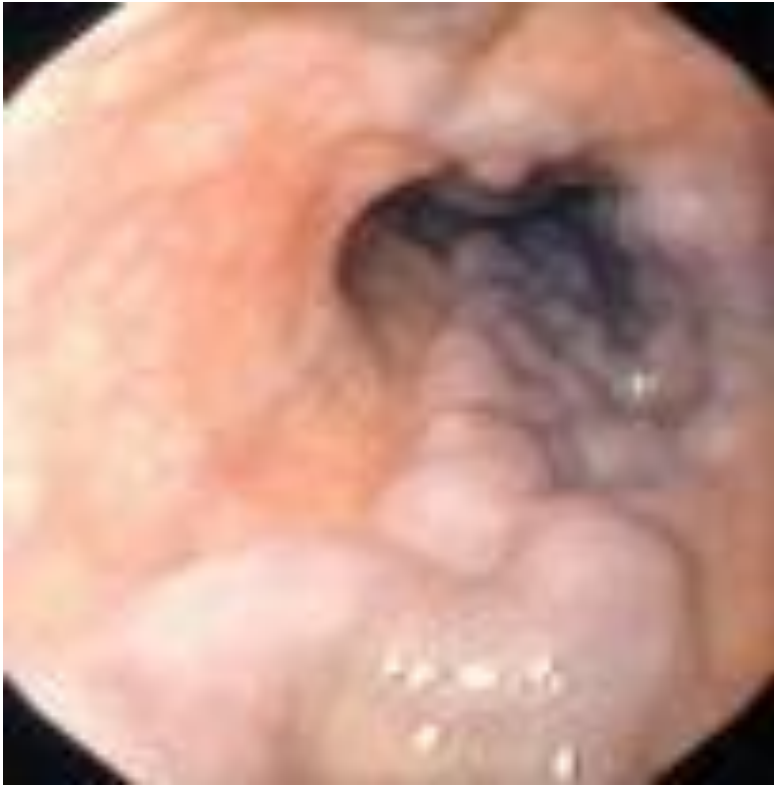
- Cirrhosis is often present in addition to alcoholic hepatitis and this combination has the worst prognosis.

Signs of cirrhosis

- Jaundice
- Fluid in the belly (ascites)
- Vomiting blood (haemetemesis)
- Confusion (hepatic encephalopathy)
- Spider naevi
- Gynaecomastia



Oesophageal varices



- **Abnormal dilatation of veins due to increase in portal vein pressure**
- **Can cause life-threatening bleeding**

Alcohol intoxication

**- Dependant on amount drunk
and previous experience**

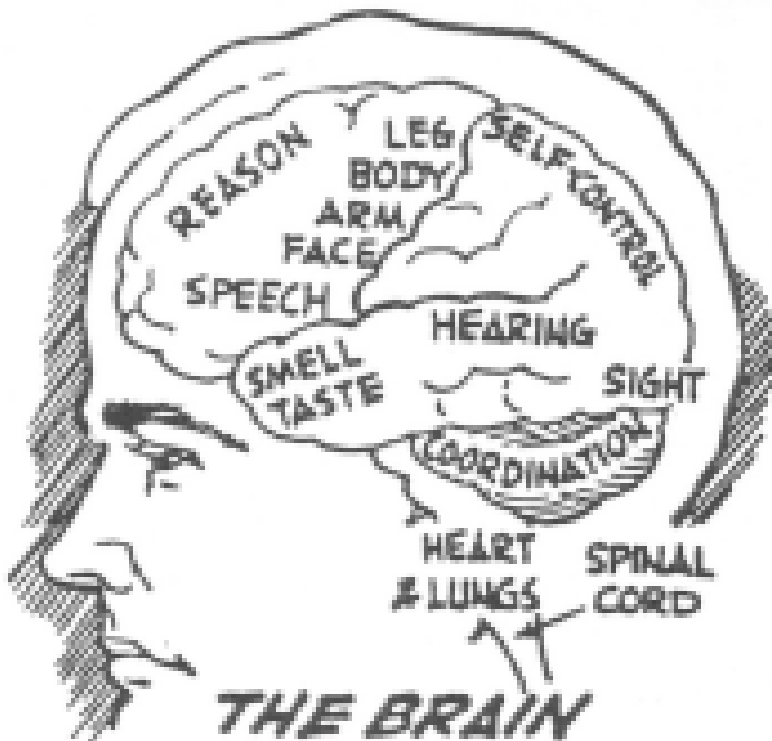
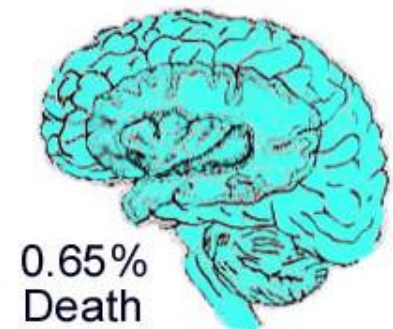
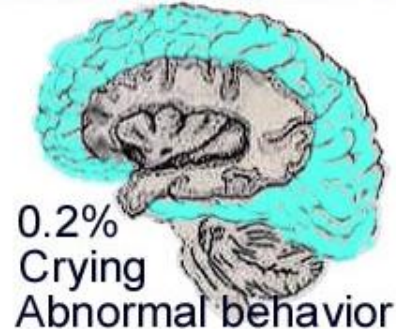
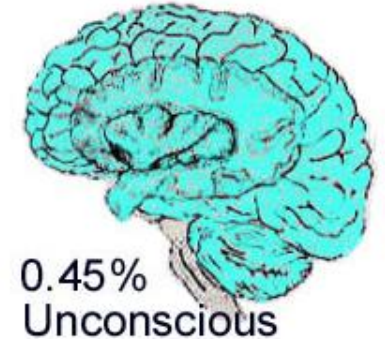
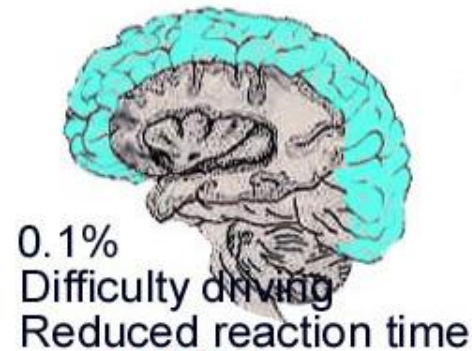
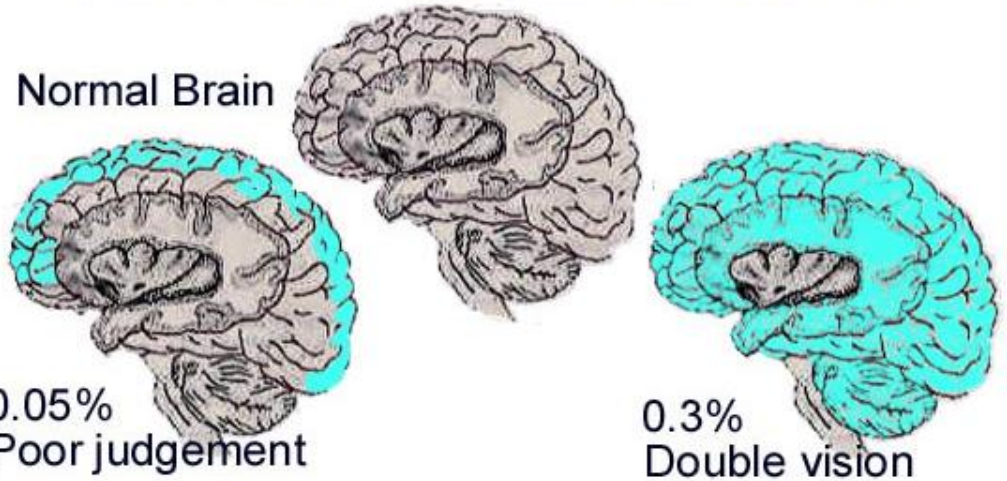
- Elation, euphoria, stimulation of pleasure & reward centres of brain
- Altered behaviour, personality, aggression etc
- Sedation (mild anaesthetic)

After effects

- ("hangover") includes dehydration, insomnia, nocturia, tiredness, nausea and headache

Blood alcohol & the brain

Blood alcohol concentration (BAC, %) is a measure of the amount of alcohol in 100 mL of blood.



Before any consumption of alcohol...

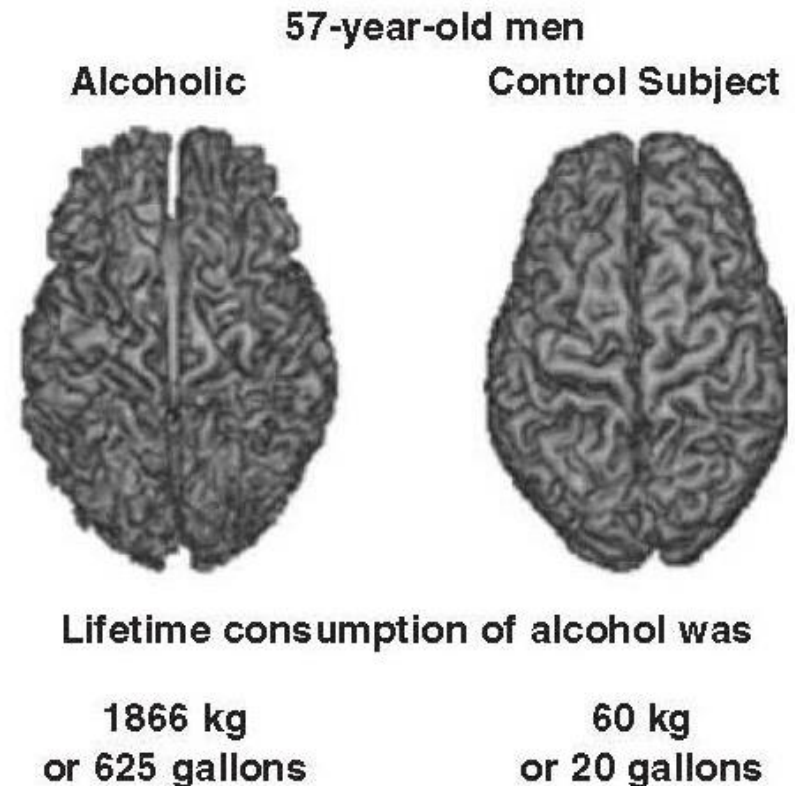
Drinking doesn't affect my driving.

Alcohol actions on the brain

- **Alcohol increases dopamine release to cause euphoria.** Absence causes depression and anxiety.
- **Alcohol inhibits glutamate receptor function.** Glutamate is an major excitatory neurotransmitter which when blocked results in cognitive impairment and amnesia...also inability to learn new information
- **Alcohol potentiates GABA-A receptor function.** GABA is major inhibitory neurotransmitter in the brain.
Receptor subtypes:
 - $\alpha 5$ - memory impairing effects*
 - $\alpha 2, \alpha 3$ - relaxation and pleasure mediating effects*
 - $\alpha 1$ – sedation, anaesthesia and unsteadiness*
- **Alcohol increases release of serotonin (5-HT) causing one to become sleepy (even pass out).** 5-HT plays a major role in the sleep-wakefulness cycle, mood and emotion.

Alcohol makes your brain shrink!

- **Loss of cortical grey matter**
- **Particularly in prefrontal cortex responsible for executive actions....**
- **judgement, planning & problem solving**
- **emotion, interpersonal activity & inhibiting unwanted behaviour**



Alcohol makes some brain cells grow!

April 2005 (Research by the Karolinska Institute, Stockholm, Sweden)

Brene *et al.* 2005.

Intl. J. Neuropsychopharmacol. 8: 557-67

- Boosts the growth of new nerve cells.
 - **Might help for pub quizzes!**
-
- Downside is that these new cells could contribute to development of alcohol dependence and addiction



LO7 Daily alcohol intake (1-3 U) protects from coronary heart disease!

...in middle aged men and post-menopausal women!

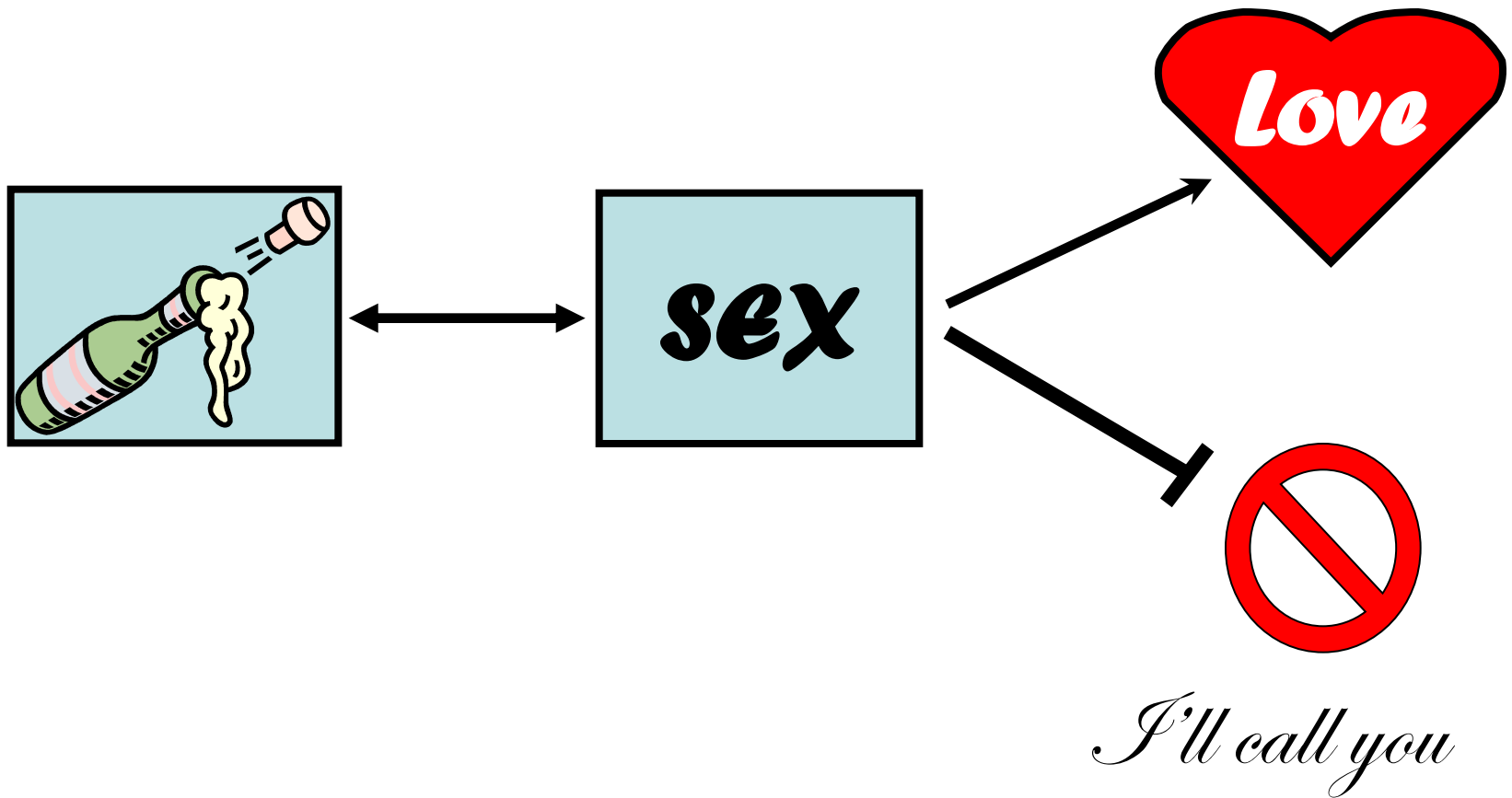
Benefits include inhibiting atheroma formation and decreasing rate of blood coagulation

- Increased high-density lipoprotein cholesterol/decreased low-density cholesterol
- reduced platelet aggregation
- prevention of clot formation
- lowering plasma apolipoproteins

Red wine – polyphenols (such as **procyanidins) reduce incidence of cardiovascular disease**

- anti-atherosclerotic through suppression of excess endothelin-1 (a vasoconstrictor), inducing dilation of blood vessels

Alcohol and sex



Alcohol and reproduction

- **Decreases sexual performance**
- **Loss of libido (sexual desire)**
- **Can lead to impotence/less sperm**
- **Atrophy (shrinkage) of the testicles - related to alcohol-induced testosterone deficiency.**
- **Decreased vaginal lubrication – discomfort**
- **Poor decisions increase risk of STI's and pregnancy**
- **Menstrual abnormalities.....cessation of the menstrual cycle and failure to ovulate. Ability to become pregnant is also impaired with alcohol abuse.**
- **Alcohol during pregnancy causes complications for the foetus including premature birth and foetal alcohol syndrome (FAS).**
- **Breast cancer is a risk for women who engage in even moderate drinking.**

*Thank you for
your attention.*

bjcampbl@liverpool.ac.uk

<http://pcwww.liv.ac.uk/~bjcampbl/Alcohol.htm>

