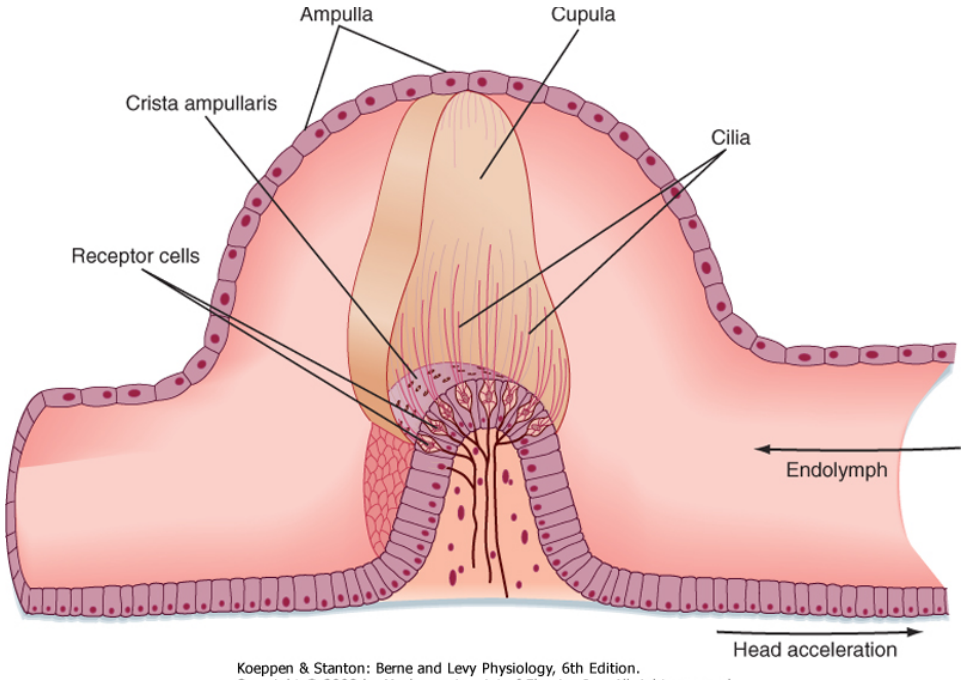
Objectives

- to understand
  - organ damage and mechanisms
  - fetal alcohol syndrome
  - Stages of alcohol withdrawal
  - pharmacological treatment of alcoholism

Bed spins

- Positional alcohol vertigo
- Data show that the buoyuancy of the cupula, an inner ear component, is altered with respect to surrounding endolymph fluid
- At BAC of around 0.04, ethanol diffuses into the cupula and makes it lighter than surrounding endolymph (30 min after drinking)
- As drinking increases, endolymph also is affected by ethanol and their density matches again (silent phase, 3 – 5 hrs after drinking)
- As drinking stops, ethanol diffuses out of cupula first, making it heavier than endolymph (hangover vertigo, 5 – 10 hrs after ingestion)
- When you lie down, difference in density tricks brain into thinking there is a gravitational effect usually due to physically spinning

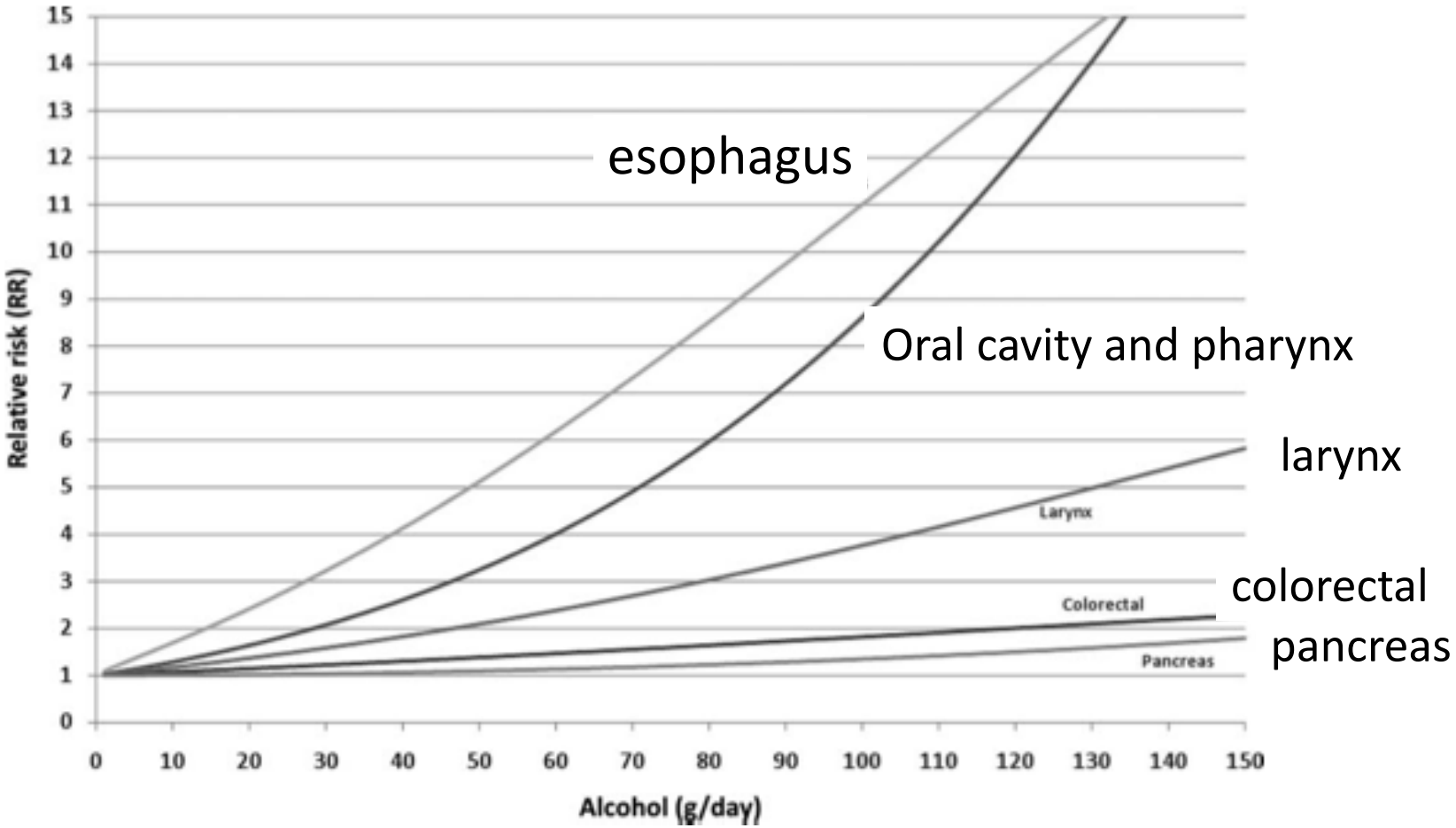


ethanol and cancer

- clear link between chronic consumption and cancer of upper gastrointestinal tract, liver, colorectum and female breast tissue
- In the upper GI, 50% of all cancers (both sexes) linked to alcohol consumption
- main culprits are acetaldehyde and reactive oxygen species
- While most of this data typically comes from heavy drinkers (>4 drinks/day) data shows there is no safe threshold for some cancers

Cancer risk vs. intake

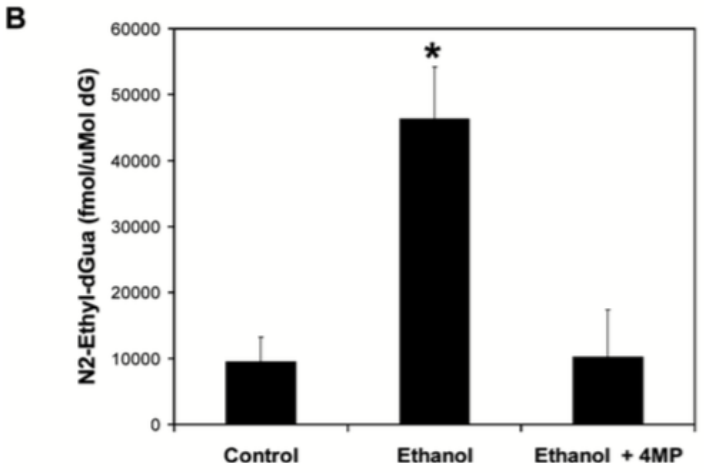
- There may be no safe level of ethanol consumption for some types of cancers



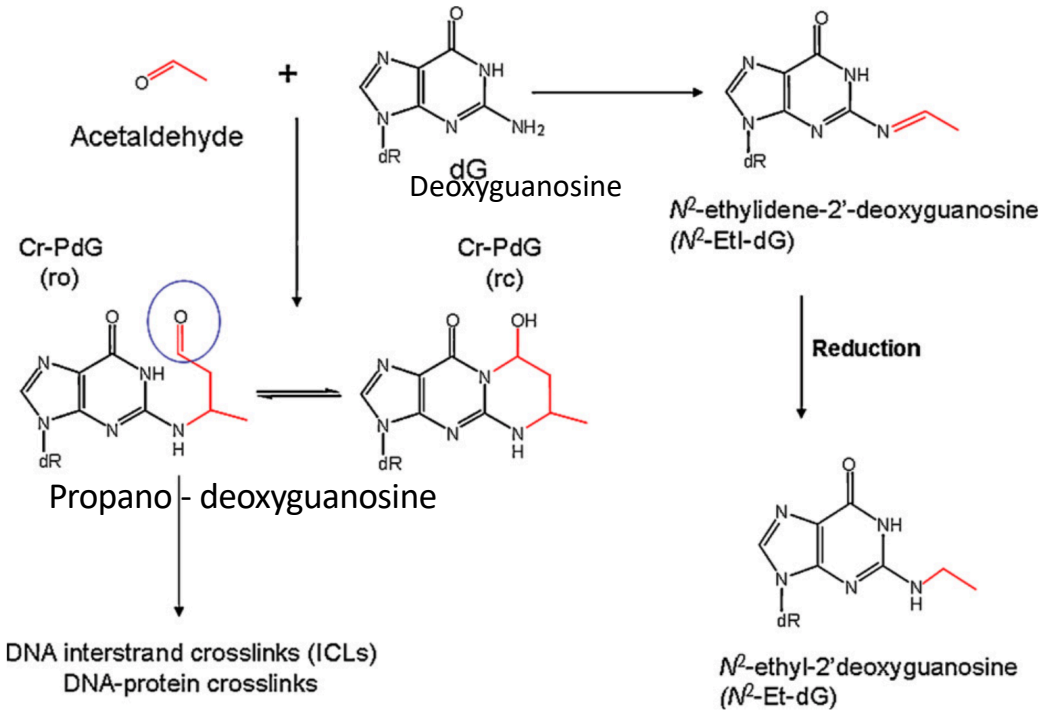
Pelucchi et al., 2011 Nutr. Cancer 63(7):983

acetaldehyde and cancer

- acetaldehyde interferes with DNA synthesis and repair
  - binds to and inactivates DNA repair enzymes
  - Also can covalently modify DNA bases
  - causes mutations and chromosomal abnormalities
  - Reaction with one acetaldehyde - N^2-ethylidene-dG
  - Reaction with two – propano-deoxyguanosine
  - if the ring doesn't close and the aldehyde group remains (circle) it can form covalently links with other DNA strands and/or proteins



4 MP – ADH inhibitor



why so much cancer in upper-digestive tract?

- ethanol is metabolized to acetaldehyde by microbes in the saliva
- can be 10 - 100 times higher concentration of acetaldehyde in saliva than in the blood
- poor dental hygiene increases the concentration as there are more microbes
- smoking shifts the microbes towards the types that produce higher (50%) acetaldehyde levels

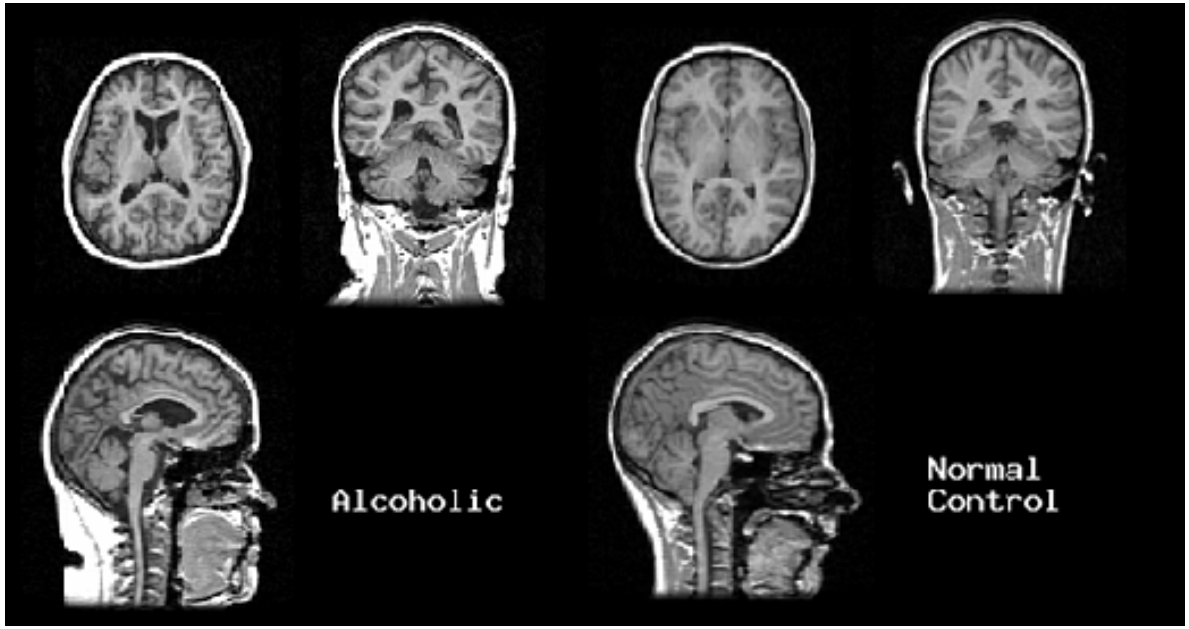
cancer of the liver

- ROS the main factor here from CYP2E1 and catalase, activated immune cells
- ROS can cause lipid damage and the production of reactive lipid species
  - Reactive lipids species will covalently modify DNA
  - This is highly mutagenic
- also CYP2E1 metabolizes retinoic acid (RA) - RA is thought to act as a negative regulator of malignant cells (in other words, it prevents their proliferation)
  - Low RA levels result in few RA receptors, changes in levels of proteins involved in gene regulation and proteins involved in liver cell proliferation

what causes brain damage?

- same culprits we see for liver damage
  - acetaldehyde, ROS
  - nutritional deficiency

From NIH image library



but also

- repeated head trauma
- hyperactivity of glutamatergic systems leading to excitotoxicity via excessive calcium influx which results in inappropriate activation of calcium-sensitive signaling pathways and cell death
- alcohol-induced neuroinflammation

other problems

Wernicke-Korsakoff syndrome

- Wernicke's disease- B1 (thiamine) deficiency - can be partially reversible
  - Deficiency because it is not absorbed well from GI due to inflammation
  - Thiamine is involved in myelin formation, glucose utilization and amino acid production
  - confusion, ataxia, abnormal eye movement – shaky eyes or paralysis of eye muscles that impair eye movement
- Korsakoff's psychosis - short and long-term memory loss, inability to learn new information, non-reversible - associated with neuronal loss

cardioprotective effects?

- at low ethanol doses
  - increased high density (good) lipoprotein
  - decreased platelet aggregation and coagulation
  - decreased inflammation in blood vessels
  - improved endothelial function - balance between blood vessel constriction and dilation
  - But does this really translate into a measureable clinical benefit?
    - There tends to be a risk for increased blood pressure in moderate - heavy users, so perhaps not

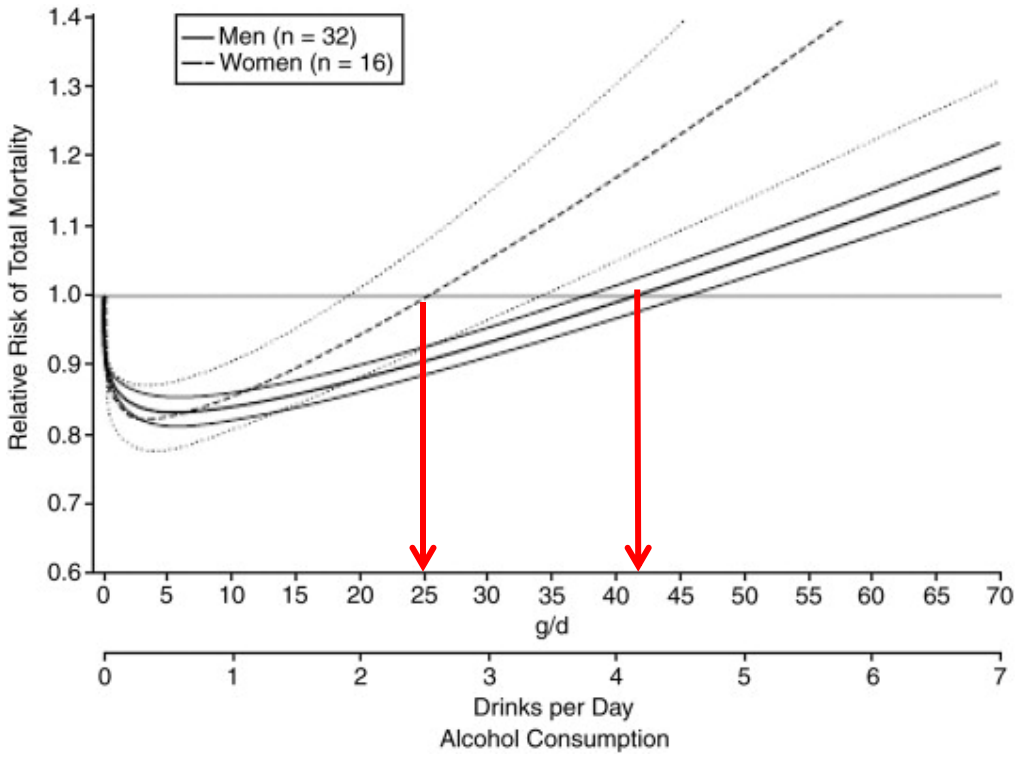
cardiotoxic effects

- at high doses of ethanol, get cardiomyopathy (disease of heart muscle)
  - alcohol is a direct myocardial depressant
  - acetaldehyde inhibits myocyte function by altering calcium homeostasis and myocardial protein synthesis
  - Calcium release from the sarcoplasmic reticulum is inhibited which has a negative effect on calcium-sensitive contractility proteins
  - ethanol metabolites result in mitochondrial dysfunction and poor energy usage

ethanol and mortality

- meta-analysis of 34 studies
- pooled from one million subjects
- J-shaped curve
- Suggests that drinking moderate amounts improves health and reduces mortality
- Studies such as this helped to establish “safe” levels of alcohol per week

Casteluovo et al, Arch Intern Med. 2006;166:2437-2445



Is this real?

- 2016 study from Centre for Addictions Research (B.C.)
- Reanalyzed some of the data (4 million people)
  - Found that the abstainer group included previous drinkers
  - They became so ill from drinking that they quit
  - This made the non-drinking group appear unhealthy
  - Therefore active drinkers looked healthier
  - Corrected for this, risk of even occasional drinking is higher than previously imagined
  - Makes more sense in light of cancer risk data
- This is important because previous studies were influencing medical advice and health policy

ethanol and mortality

- Latest study (August 2018) suggests that any amount of ethanol increases mortality risk
  - “our results show that the safest level of drinking is none.”
  - Consider Canada’s “safe” guidelines – 136g/w for women, 204 g/w for men
- Perspective – this is relative risk
  - For 100,000 people who drink one drink a day/year, 918 will experience one of 23-alcohol related problems
  - With no drinking, 914 will experience problems
  - At two drinks/day, problems increase to 977 vs 914 for non drinkers

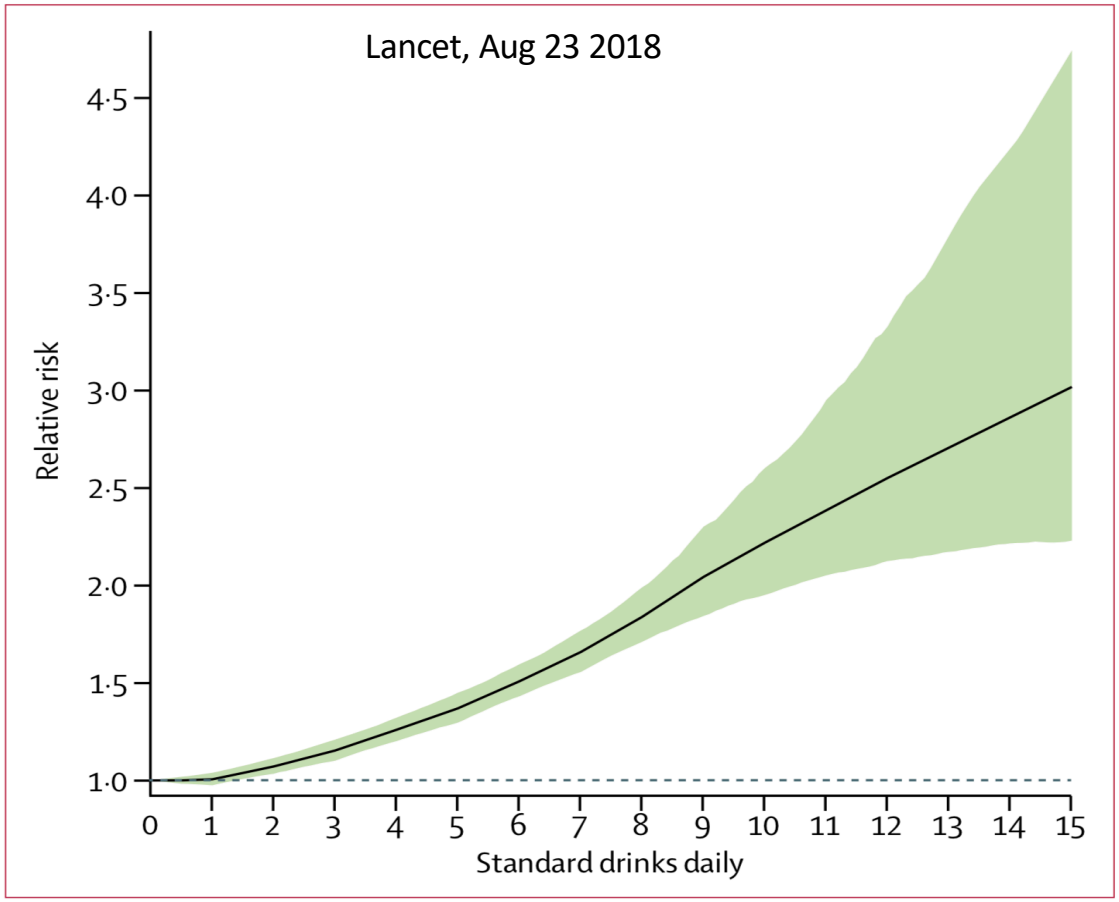
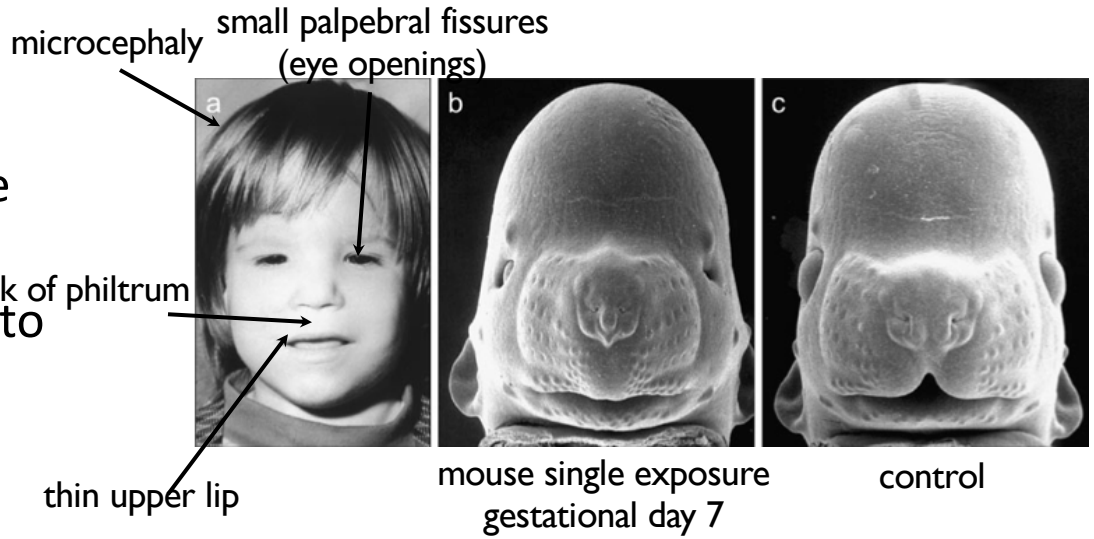


Figure 5: **Weighted relative risk of alcohol for all attributable causes, by standard drinks consumed per day**

fetal alcohol spectrum disorder

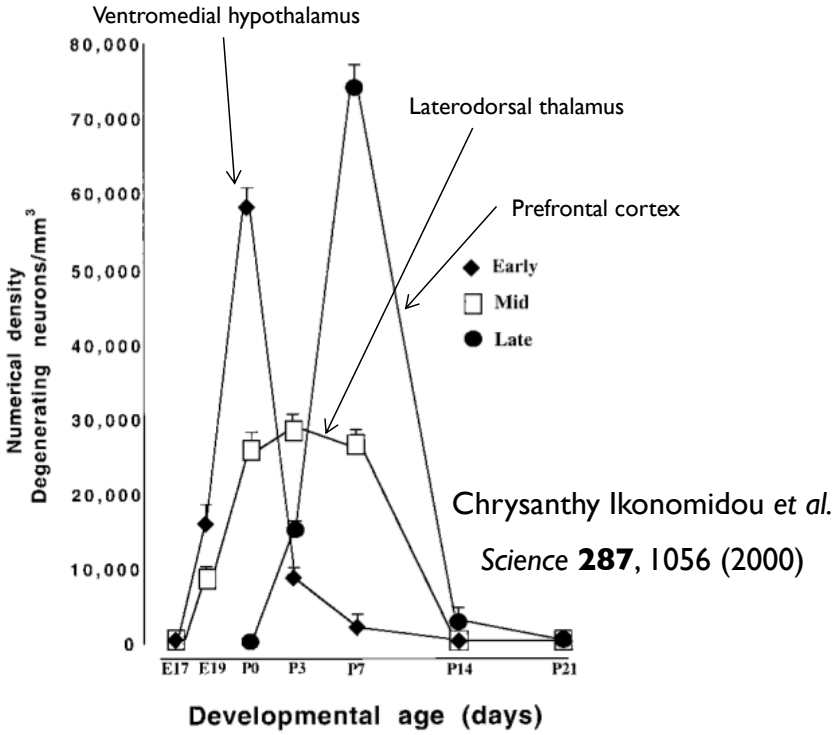
- leading cause of brain damage in the USA (est. 1 in 10 births)
- fetal alcohol syndrome is at the severe end of the spectrum
- mouse gestational day 7 is equivalent to third week of human gestation
- at this time ethanol exposure affects median aspects of face and forebrain
- poor impulse control, planning, impaired mental function, seizures
- Synaptogenesis occurs in third trimester which is why exposure here may be particularly harmful to the brain



O' Leary et al., 2011
Neuropsychol. Rev.
21:167

Fetal neuronal death and time of exposure

- Binge exposure can cause massive apoptotic (programmed) cell death
- Rat brains were exposed to ethanol from embyronic day17 (E17) to postnatal day 21 (P21) = third trimester in humans
- Researchers found that different brain regions were sensitive to ethanol during different stages within this time period
- Divided these regions into those that are affected either early, mid or late third trimester development
- specific brain regions are susceptible at different times with the third trimester
- Likely reflects the timing of the development of and connections made by these brain regions

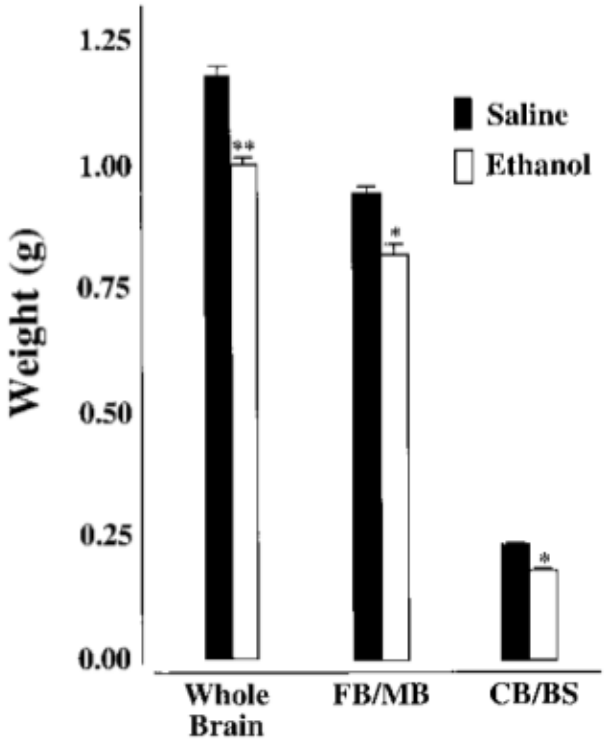


Chrysanthy Ikonomidou *et al.*

Science **287**, 1056 (2000)

Fetal neuronal death and time of exposure

- rat embryos equivalent to third trimester human development
  - Synaptogenesis is occurring during this period
  - BAC of 0.2 for 4 hours triggered apoptosis
  - Severity not linked to total dose of ethanol but peak concentration
  - Neuronal death reflected in loss of weight
  - Represents the loss of millions of neurons



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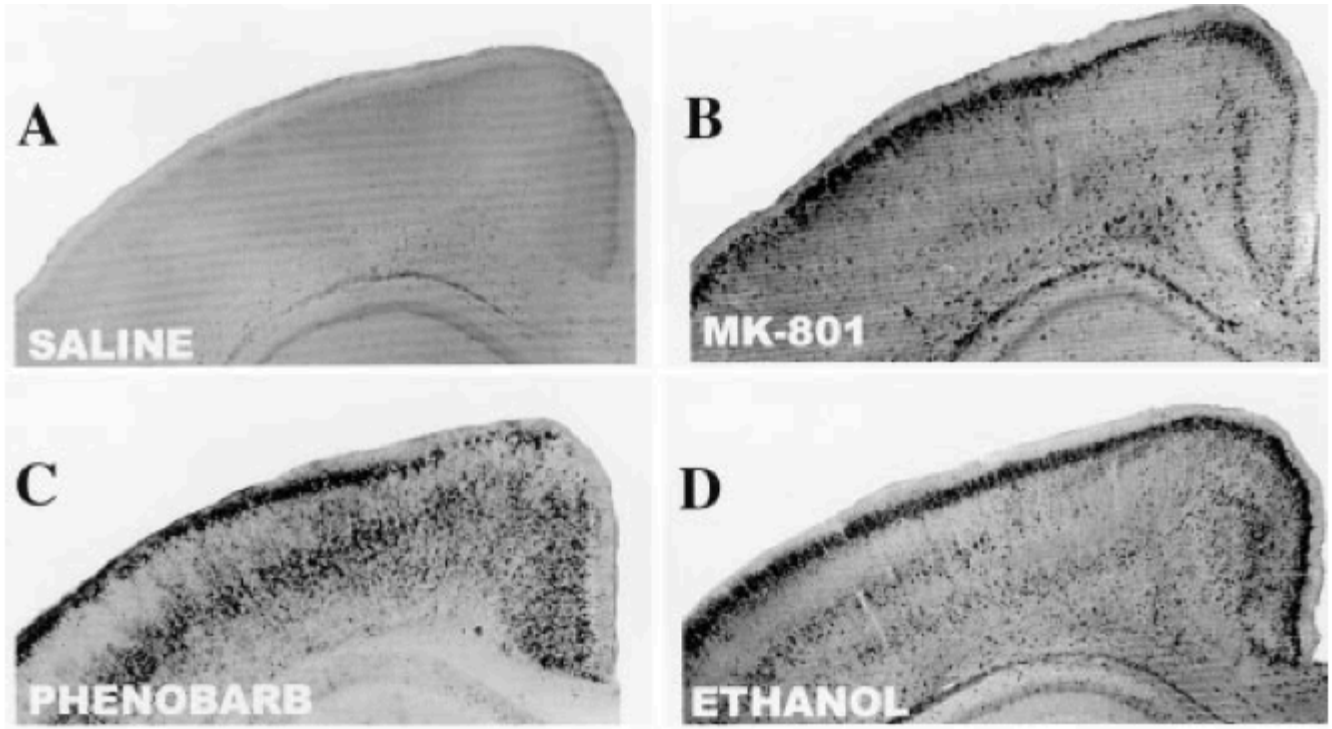
FB – forebrain
MB – midbrain
CB – cerebellum
BS – brain stem

How does ethanol cause apoptosis in developing fetuses?

- Apoptosis seems to occur due to a combination of GABA-A receptor activation and NMDA receptor block
- Most pronounced damage occurs in third trimester
- MK-801 – NMDA receptor antagonist; Phenobarbital – activates GABA-A receptors
- Ethanol dose produced peak of approx. 300mg/100ml; images were 24 hours post-treatment



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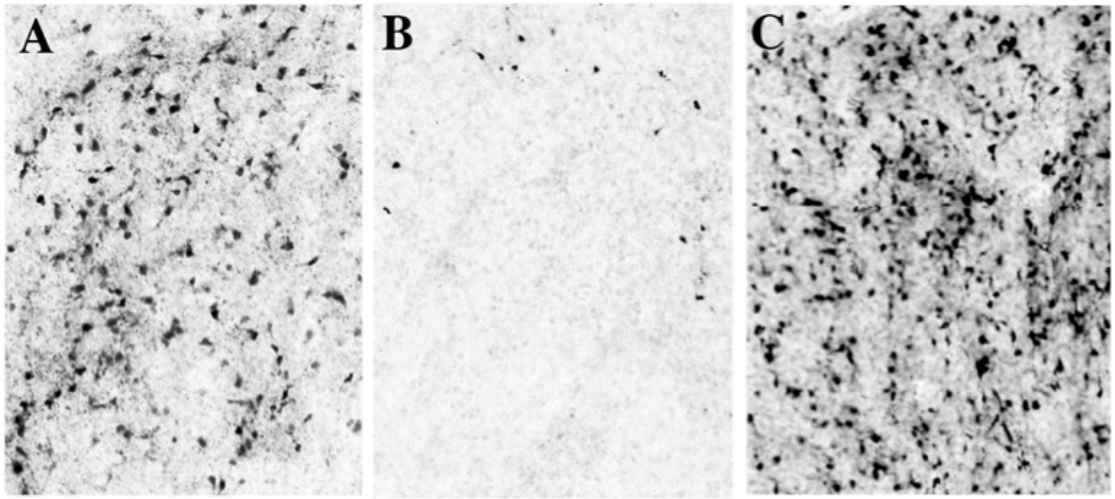
What do we know about alcohol-induced neuronal death in the fetus?

- Ethanol produces effects on GABA-A and NMDA receptor responses
- Ethanol exposure can result in lack of ERK (Extracellular signal-Related Kinase) phosphorylation (so it inhibits movement of ERK to the nucleus) and mitochondrial damage
- This ultimately seems to trigger the activation of enzymes called caspase 3 and caspase 9 that are important triggers for apoptosis
- These effects can occur with a single exposure

These are neurons stained positive for active caspase-3 in fetal monkey
This is from a single exposure
Dark stain indicates activated caspase 3

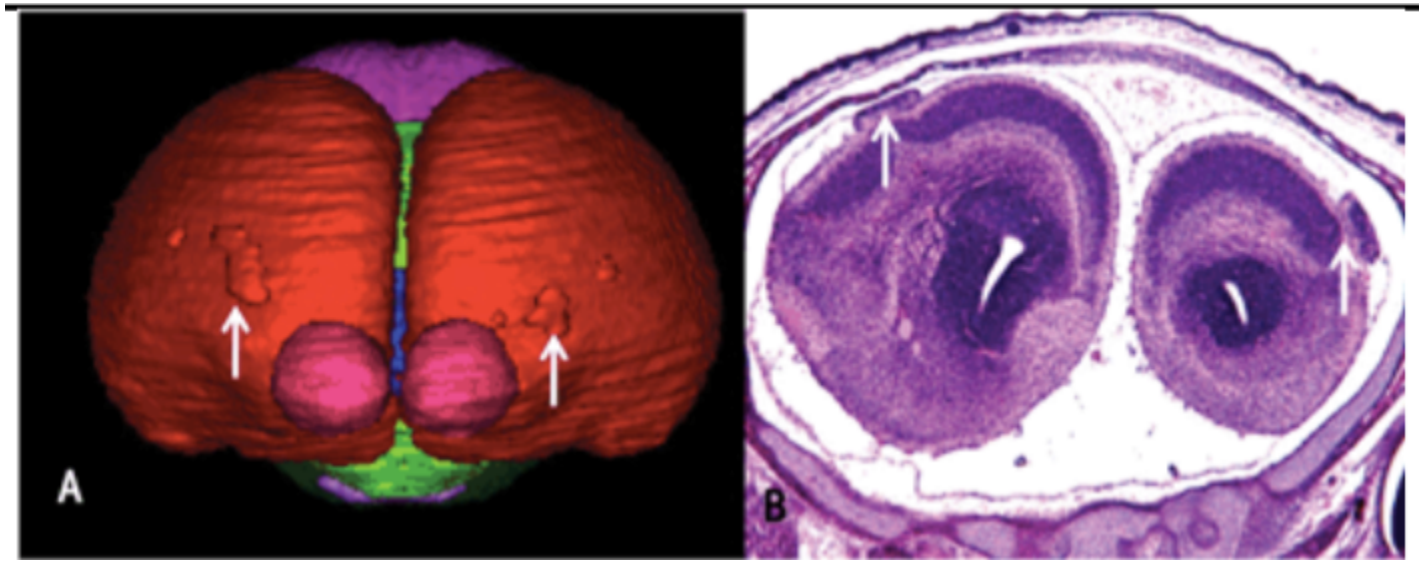


Creeley and Olney, Brain Sci. 2013, *3*, 1153-1181

Other effects of prenatal alcohol exposure

- Ethanol exposure alters the migration of surviving neurons
  - brain imaging has revealed heterotopias - clumps of neurons in the wrong part of the brain
- Genes associated with receptors for thyroid hormone and retinoic acid are affected
  - This leads to increased biological reactions to stress which is linked to increased risk of anxiety and depression coupled with poor coping skills

- Cortical heterotopias on mouse brain
- Fetus exposed to ethanol acutely during day 7 of gestation



Godin et al., (2010) Alc. Clin. Exp. Res. 34(1):98-111

withdrawal

- withdrawal is more severe and more likely to cause death than withdrawal from heroin and other “hard” drugs
- mortality can be one in seven if detoxification is not properly supervised and treated
  - stage 1 - tremors, rapid heart beat, hypertension, heavy sweating, no appetite, insomnia
  - stage II - hallucinations
  - stage III - delusions, delirium, disorientation, amnesia
  - stage IV - seizure activity

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- Delirium Tremens
- (DTs)
- peak 3 - 4 days after last drink

drugs to treat withdrawal

- sedatives such as benzodiazepines can be used - can prevent stages III and IV
- clonidine (an agonist at presynaptic adrenergic alpha 2 receptors) prevents excessive neurotransmitter release
- propranolol (a beta adrenergic receptor antagonist) blocks excessive sympathetic activity – slows heart rate and reduces tremour

drugs to prevent use

- disulfiram
  - prevents aldehyde dehydrogenase from working
  - results in high levels of acetaldehyde
  - headache, nausea, flushing etc
  - questionable efficacy over long term
  - does not stop craving
  - Will it cause cancer from increased acetaldehyde levels?

opioid antagonists

- alcohol increases the release of the endogenous opioid, endorphin, in VTA and NA
- naltrexone is an opioid antagonist at mu-opioid receptors
- Naltrexone prevents beta-endorphin from activating presynaptic receptors
  - principle action through presynaptic mu opioid receptors (prevents inhibition of GABA release in VTA)
  - some studies suggest it reduces craving
  - data are mixed - also problems with negative mood

Acamprosate

- antagonist at glutamate receptors
- thought to address hyperexcitability in chronic alcoholics due to up-regulation of glutamate receptors, esp in withdrawal
- thought to prevent craving
- european studies show success, north american studies are mixed at best