

# METABOLISM

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ



MID (last lecture) – Lecture 17

## Alcohol Metabolism

وَإِن تَتَوَلَّوْا يَسْتَبَدِلْ قَوْمًا غَيْرَكُمْ ثُمَّ لَا يَكُونُوا أَمْثَلَكُمْ

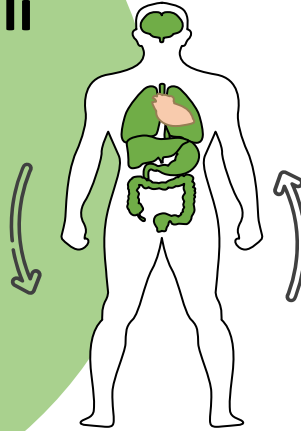
اللهم استعملنا ولا تستبدلنا

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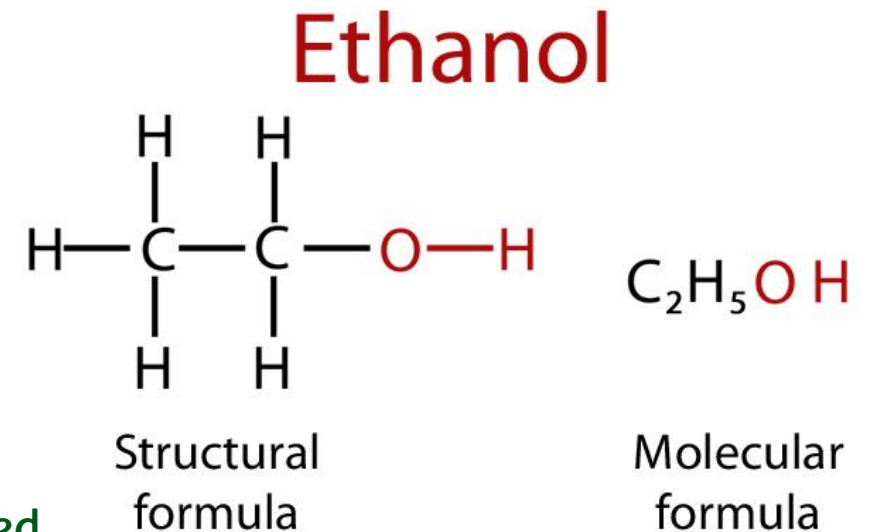
# Alcohol Metabolism

Dr. Diala Abu-Hassan

When we say alcohol, we mean ethanol, which is composed of two carbon atoms and one hydroxyl (OH) group. This compound is present in alcoholic beverages. We will discuss how your cells break down ethanol to eliminate it and reduce its effects on the CNS.

Ethanol has one polar side and one nonpolar side; making it amphipathic. This property facilitates its absorption through the stomach cells.

Once a person ingests an alcoholic beverage, the ethanol it contains moves easily through the stomach cells. A small portion is metabolized in the stomach, while the major metabolic pathway for alcohol degradation occur in the hepatocytes. This process is mediated by or catalyzed by the enzyme alcohol dehydrogenase.

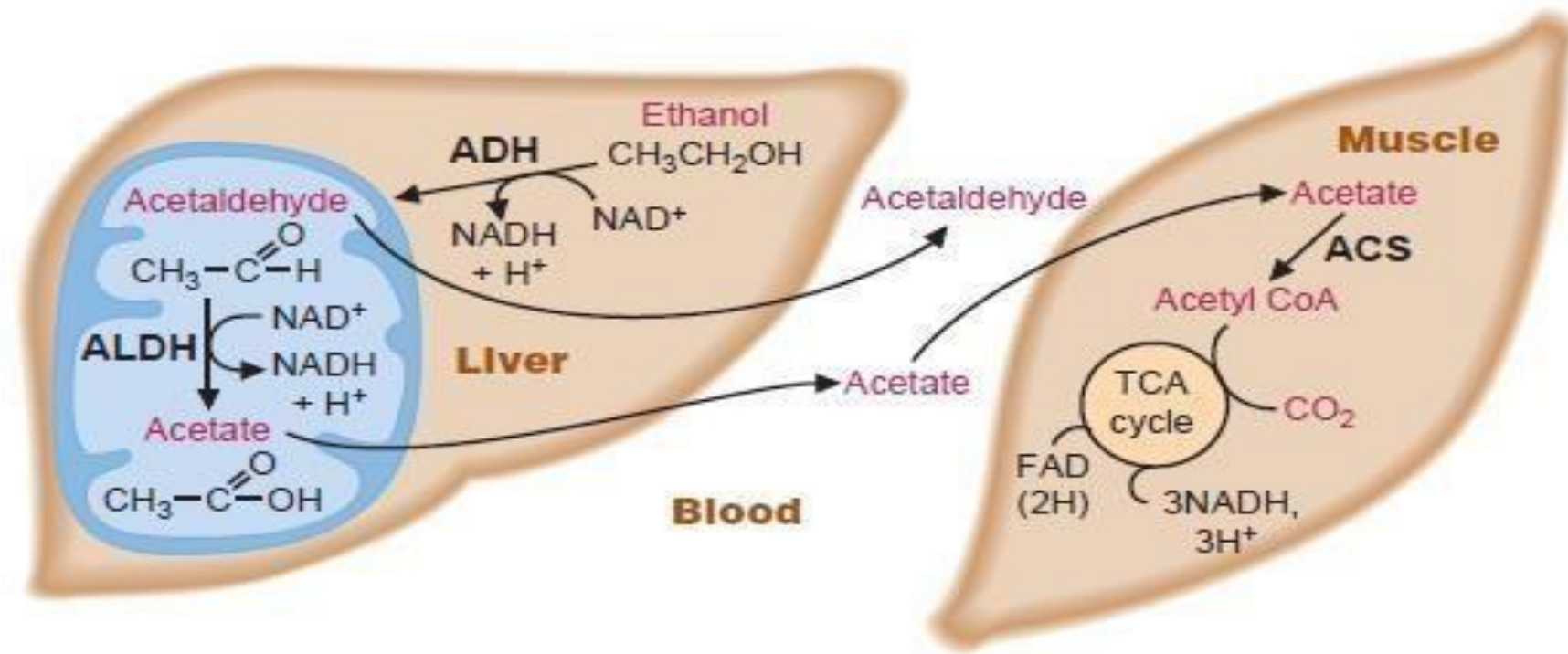


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# Metabolism of Alcohol

- ✓ When alcohol is ingested, a small amount is immediately metabolized in the stomach.
- ✓ Most of the remaining alcohol is subsequently absorbed from the gastrointestinal tract, primarily the stomach and upper small intestine

How do you prepare acetic acid from ethanol in organic chemistry?



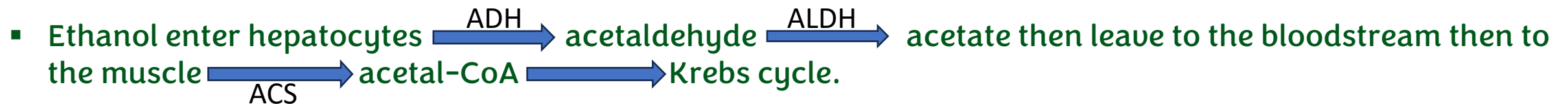
**ADH: Alcohol Dehydrogenase**

**ALDH: Acetaldehyde Dehydrogenase**

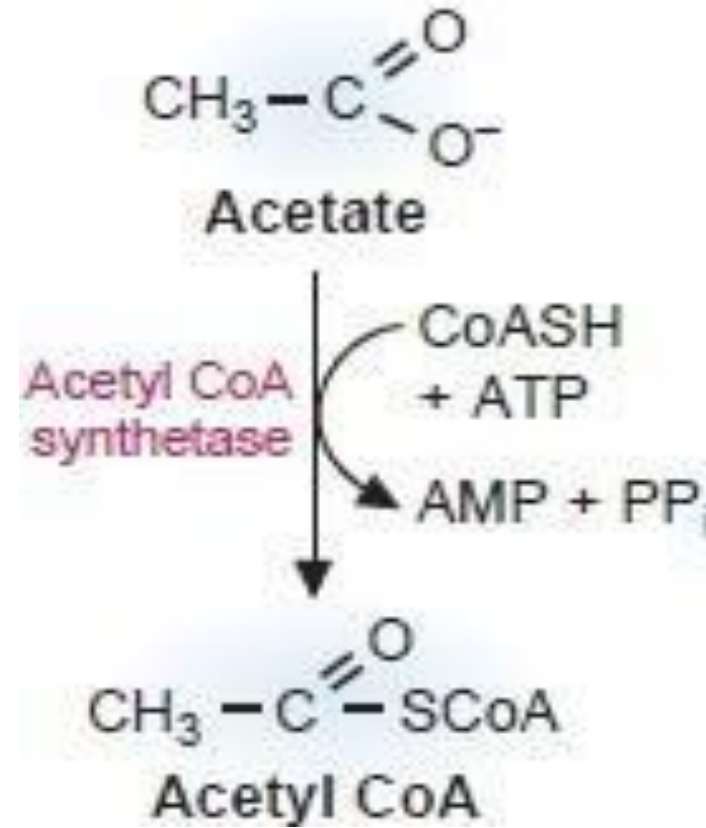
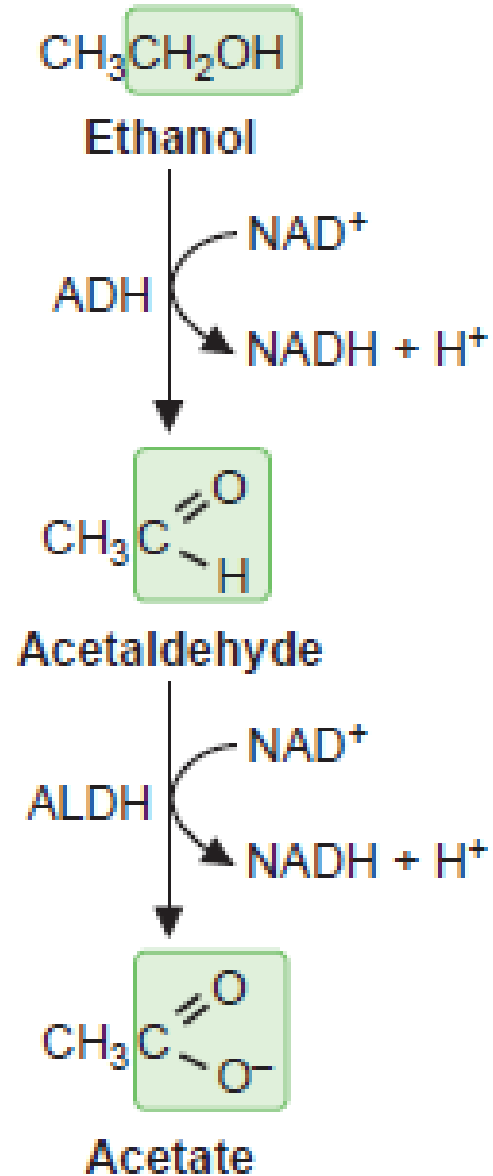
**ACS: Acetyl CoA Synthetase**

- When ethanol enters the hepatocytes, it is oxidized to acetaldehyde by ADH. This reaction reduces NAD<sup>+</sup> to NADH. This oxidative process occurs in the cytosol of the hepatocytes. The acetaldehyde enters the mitochondria inside hepatocytes.
- Acetaldehyde is highly toxic and must be further metabolized. In the mitochondria, acetaldehyde is oxidized to acetate (acetic acid) by ALDH. Acetate is less toxic and is released into the bloodstream to be utilized by other tissues. Muscle cells can take up acetate from the bloodstream.
- Muscle cells convert acetate into acetyl-CoA via acetyl-CoA synthetase, which then enter the Krebs cycle.
- The acetaldehyde can also still a small molecule, so it can exit the hepatocytes directly and appear in the bloodstream. It has an odor as an aldehyde so when you meet somebody who already under the effect of alcohol you might smell it.
- Acetaldehyde also is a carcinogen, and its accumulation in large amounts can lead to cellular mutations and an increased risk of cancer.

▪ So, this is the primary pathway:



# Metabolism of Alcohol-Steps



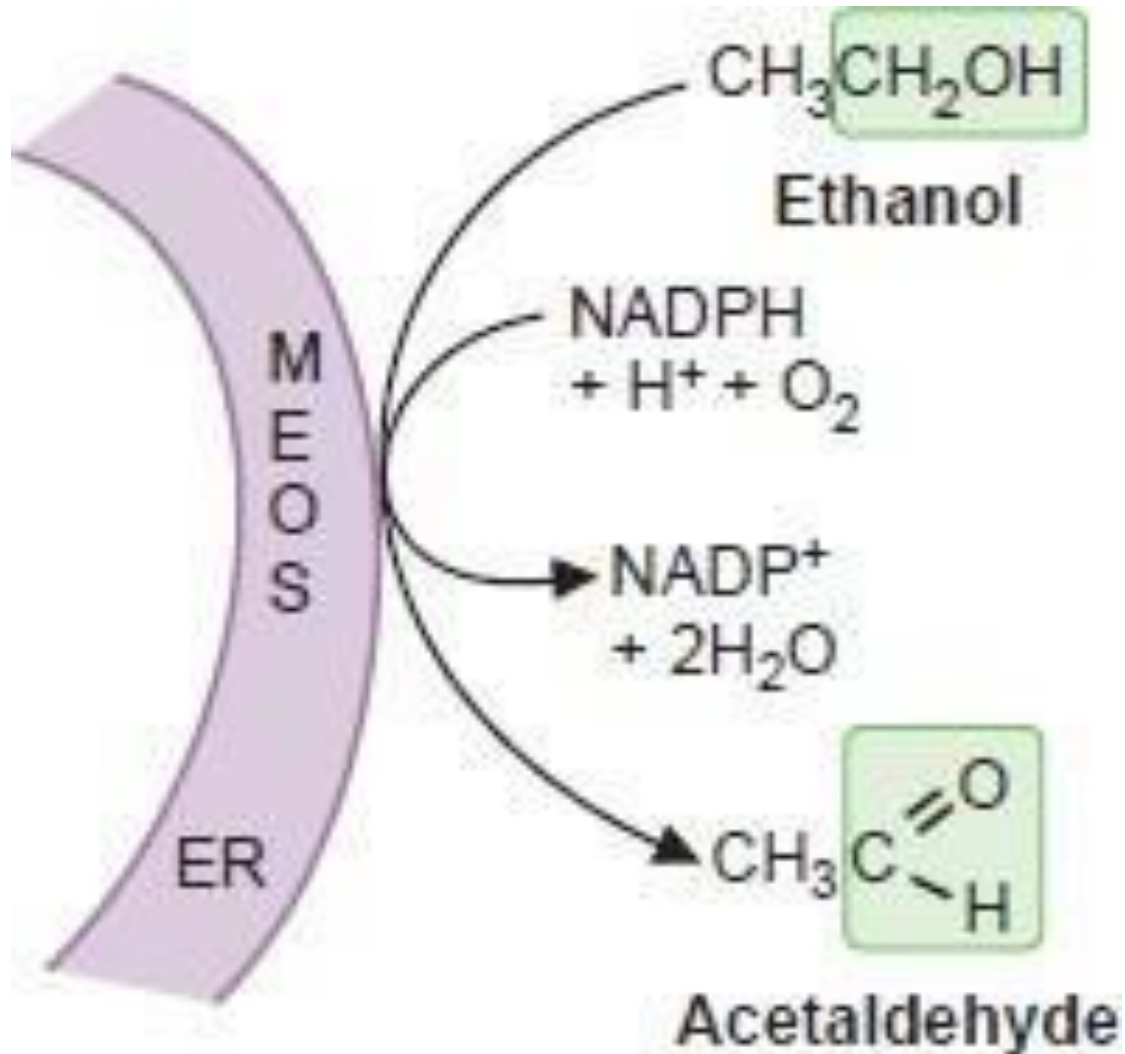
What happens when a high amount of Ethanol is metabolized? [See next slide](#)

- ✓ High NADH/NAD<sup>+</sup>
- ✓ Inhibition of FA oxidation
- ✓ Inhibition of gluconeogenesis
- ✓ Lactic acidosis

- Whenever there is a high consumption of ethanol or alcoholic beverages, then this pathway will be activated a lot, resulting in an increased ratio of NADH to NAD<sup>+</sup> due to more NADH in its reduced form. This would interfere with the activation of the Krebs cycle.
- Also, excessive alcohol metabolism inhibits fatty acid oxidation and gluconeogenesis, leading to lactate accumulation and lactic acidosis.
- To begin with, lactic acidosis occurs because insufficient NAD<sup>+</sup> prevents the Krebs cycle from functioning, leading to shift toward anaerobic metabolism and lactate accumulation.
- The effect of alcohol metabolism on gluconeogenesis due to the lower concentration of pyruvate produced by glycolysis. So, glycolysis will be inhibited because of the high NADH versus NAD<sup>+</sup>.
- High NADH levels inhibit fatty acid oxidation, as the produced acetyl-CoA cannot enter the Krebs cycle efficiently due to its suppression.

# Metabolism of Alcohol

## MEOS: Microsomal Ethanol Oxidizing System

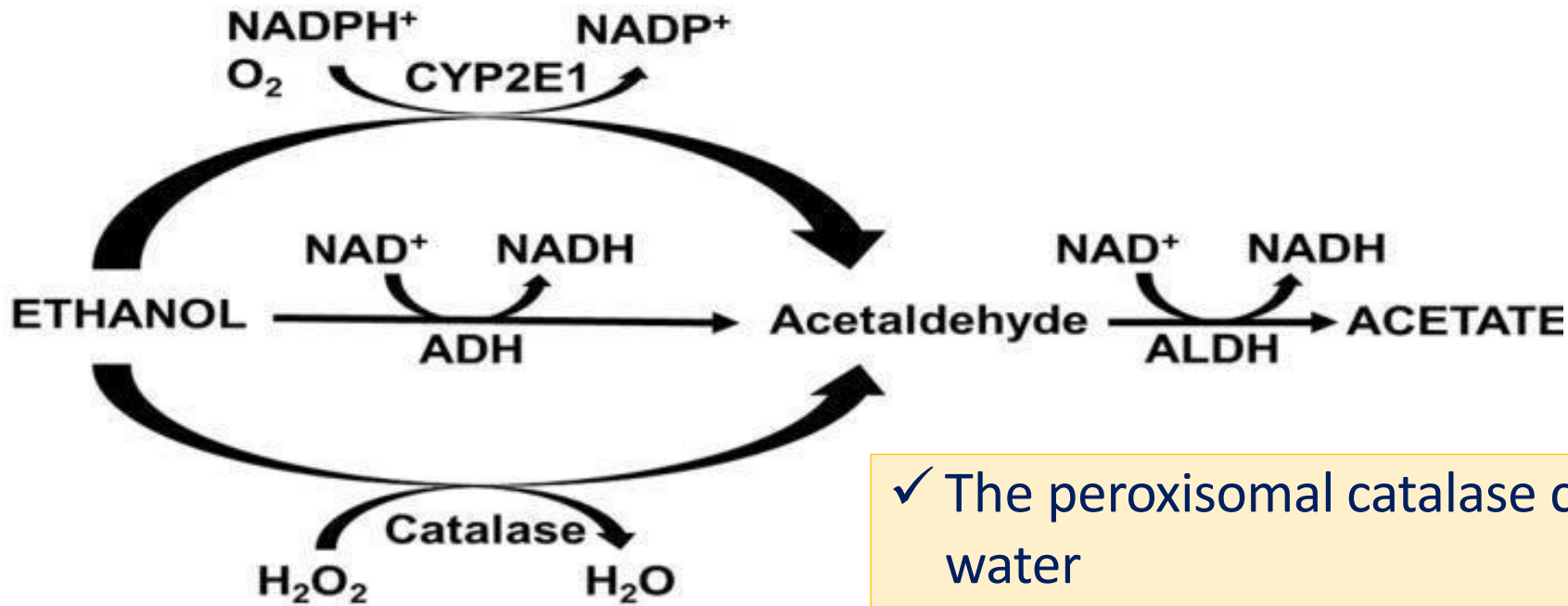


- ✓ An alternative pathway for ethanol metabolism
- ✓ 10-20% of the ingested ethanol
- ✓ Involves primarily the cytochrome P450 2E1 (CYP2E1)
- ✓ CYP2E1 is associated with NADPH-cytochrome P450 reductase in the
- ✓ High  $K_m$  for ethanol
- ✓ Inducible by ethanol
- ✓ CYP2E1 is a major contributor of oxidative stress in the hepatocytes by generating several reactive oxygen species (ROS) such as hydrogen peroxide ( $\text{H}_2\text{O}_2$ ), hydroxyethyl radical ( $\text{HER}\cdot$ ), hydroxyl radical ( $\text{OH}\cdot$ ) and superoxide ( $\text{O}_2^-$ )

- ❖ The second pathway responsible for alcohol degradation accounts for 10% to 20%. The primary pathway, involving alcohol dehydrogenase accounts for 80% to 90%.
- ❖ The microsomal ethanol oxidizing system (MEOS) is the alternative path and primarily depends on the cytochrome P4502E1 for oxidation. A similar mechanism occurs in this pathway.
- ❖ Ethanol is oxidized to acetaldehyde by a different enzyme system in the MEOS pathway. The MEOS has a high  $K_m$  for ethanol, meaning it is only active at high ethanol concentration. That's why it's just responsible for metabolism of a small amount of ethanol.
- ❖ This oxidation is associated with another oxidation of NADPH to NADP<sup>+</sup>, and oxygen will be reduced taking electron from both ethanol and NADPH to reduce the oxygen molecule into H<sub>2</sub>O molecules.
- ❖ This process generates reactive oxygen species (ROS), including hydrogen peroxide, hydroxyl radicals, and superoxide ions."



# Metabolism of Alcohol-Catalase



This enzyme is also expressed by the microflora in the colon. So, there might be some production of acetaldehyde in the GI tract. And this system is restricted or connected to H<sub>2</sub>O<sub>2</sub> availability. Then after acetaldehyde is formed, whether it's going to form by ADH, P4502E1 or catalase. It's going to continue by ALDH to be further oxidized to acetate.

Same idea different enzyme and system. In this enzyme system, catalase enzyme that's present in the peroxisome. So, the peroxisomal catalase gets rid of H<sub>2</sub>O<sub>2</sub> and convert it to H<sub>2</sub>O and oxidize ethanol to acetaldehyde.

- ✓ The peroxisomal catalase converts H<sub>2</sub>O<sub>2</sub> to oxygen and water
- ✓ It can also oxidize ethanol to acetaldehyde
- ✓ Is not a key pathway for ethanol elimination
- ✓ Catalase is ubiquitously expressed in almost all tissues
- ✓ Catalase is also expressed by colonic floras which may lead to acetaldehyde production in the lower gastrointestinal tract
- ✓ Catalase activity relies on the cellular level of H<sub>2</sub>O<sub>2</sub>

# Ethanol Metabolism Application

- ✓ ADH has 5 classes or isoenzymes
- ✓ Different isoforms are expressed in different tissues such as liver, lung, stomach and esophagus.
- ✓ People with different races inherit different sets of ADH isoenzymes, for example African Americans have an isoform with a high maximal velocity resulting in fast ethanol metabolism

Whereas the Southeast Asian have problems and mutations so, called polymorphism. Resulting in a less efficient and slower degradation of ethanol. That's why they can get drunk easily in comparison to other races.



ADH has 5 classes or isozyme, and they have different expression patterns. Also, have different kinetics. And in this case, some of them are faster in the metabolism of ethanol than the others. And the isoforms that are faster are going to remove the effect of ethanol on the CNS.

For any feedback, scan the code or click on it.



Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			

# Additional Resources:

# رسالة من الفريق العلمي:

## Reference Used:

(numbered in order as cited in the text)

1. Marks Book , Chapter 33

عن عبد الله بن عمر رضي الله عنهما  
أن رسول الله صلى الله عليه وسلم قال:

"لعن الله الخمر، وشاربها، وساقياها، وبائعها،  
ومبتاعها، وعاصرها، ومعتصرها، وحاملها،  
والمحمولة إليه، وآكل ثمنها."

رواه أبو داود والحاكم