

Effects of Alcohol

Metabolism, toxic injury, morphology, and multisystem consequences

A pathology lecture

Dr Abu Suraih Sakhri

MBBS, MD (Pathology)

www.abusuraihsakhri.com

Learning objectives

- Trace absorption and hepatic oxidation of ethanol through ADH, CYP2E1, catalase, and ALDH.
- Explain how acetaldehyde, excess NADH, reactive oxygen species, and inflammation cause tissue damage.
- Recognize acute toxicity and the organ-specific effects of chronic exposure.
- Connect characteristic liver morphology to clinical consequences and carcinogenesis.

Alcohol exposure is not risk-free

- Toxicity depends on the amount and frequency of ethanol consumption.
- Excess intake causes both physical and psychological injury.
- The textbook cautions that even low levels of consumption may carry serious health risks.

Risk assessment depends on the exposure pattern and the susceptible host.

Alcohol use disorder is a relapsing condition

- Alcohol use disorder (AUD) means impaired ability to stop or control drinking.
- Alcohol consumption continues despite adverse social, occupational, or health consequences.
- Repeated exposure creates cumulative organ injury in addition to episodic intoxication.

AUD describes impaired control and consequences—not simply an isolated high blood level.

Magnitude of alcohol exposure in the United States

Adults, 2021 survey

- 52% reported alcohol use in the preceding month.
- 28.6 million (11.3%) had AUD.

Adolescents, 2021 survey

- 7% reported alcohol use in the preceding month.
- Nearly 900,000 (3.4%) had AUD.

Historical U.S. Estimates reported in the source; Not current surveillance figures.

Alcohol contributes substantially to mortality

United States

- More than 140,000 alcohol-attributable deaths per year (source estimate).
- Over 13,000 deaths in alcohol-impaired driving in 2022.

Worldwide

- Approximately 3 million deaths annually in the source estimate.
- Estimated 5.3% of all deaths globally.

Numbers reflect the textbook's cited observation periods, not an updated 2026 estimate.

Two temporal patterns of toxicity

Acute exposure

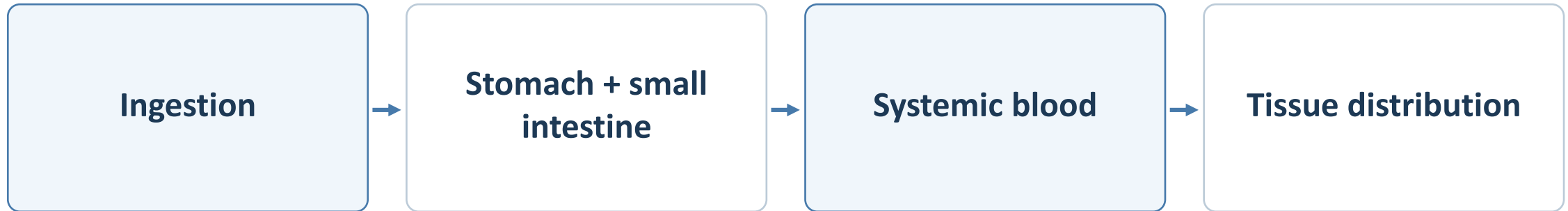
- Central nervous system depression
- Gastritis or mucosal injury
- Reversible hepatic steatosis

Chronic excessive exposure

- Progressive liver fibrosis and cirrhosis
- Neurologic and cardiovascular injury
- Pancreatitis, malignancy, malnutrition, fetal injury

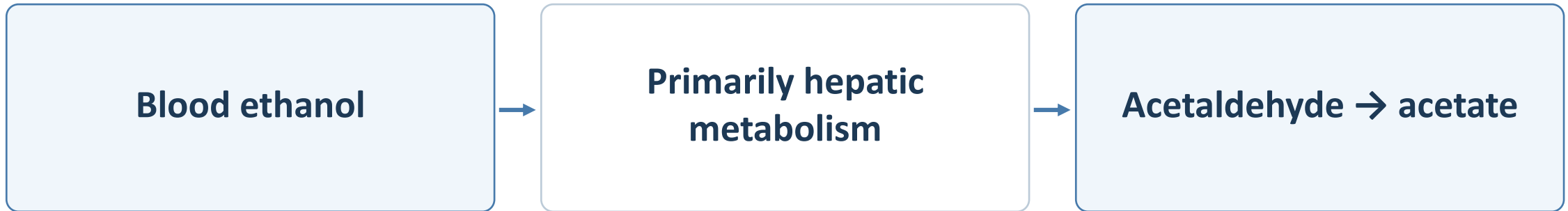
Timing helps predict dominant mechanisms, but acute and chronic processes can coexist.

Ethanol is absorbed without chemical alteration



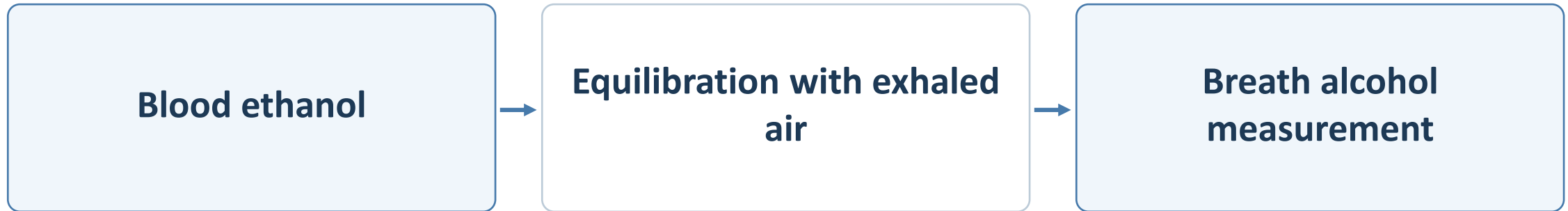
- Ethanol is absorbed unchanged from the upper gastrointestinal tract.
- Distributed body levels track blood ethanol concentration.

Only a small fraction is excreted unchanged



- Less than 10% is eliminated unchanged through urine, sweat, and exhaled air.
- Metabolic clearance therefore determines most of the duration of exposure.

The basis of breath alcohol testing



- Ethanol in exhaled air is proportional to the blood concentration.
- Breath testing estimates exposure; Legal thresholds depend on jurisdiction.

Blood alcohol and acute clinical effects

Blood ethanol	Textbook-described effect	Interpretation
80 mg/dL (0.08%)	Legal impairment threshold in many U.S. states	Not a universal safety threshold
~200 mg/dL	Drowsiness	Marked CNS depression
~300 mg/dL	Stupor	Severe intoxication
Higher concentrations	Coma; potential respiratory arrest	Life-threatening toxicity

These are source-described approximate effects; Individual responses vary.

Tolerance changes the concentration–effect relationship

Less tolerant individual

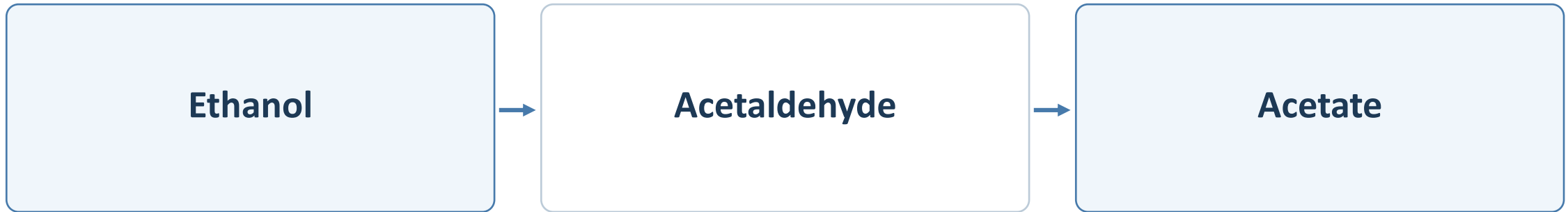
- A given intake tends to produce a higher peak blood level.
- Clinical depression becomes apparent at lower prior exposures.

Person with chronic AUD

- Metabolic adaptation can increase alcohol clearance.
- A similar intake may produce a lower peak blood concentration.

Tolerance does not protect against cumulative organ toxicity.

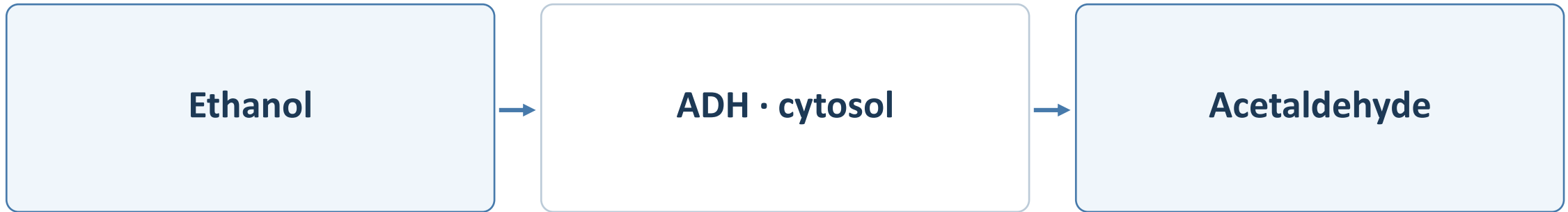
Three routes oxidize ethanol



ADH (major) · CYP2E1 (inducible) · catalase (minor)

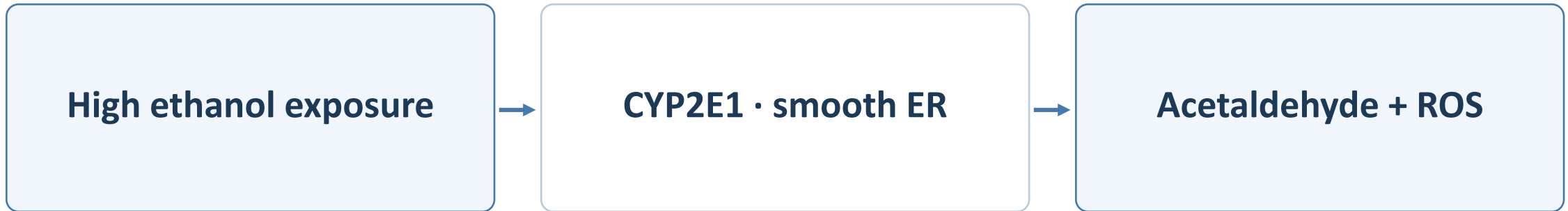
- Cytosolic alcohol dehydrogenase (ADH) is the dominant route.
- Microsomal CYP2E1 becomes important with heavy exposure; Catalase contributes minimally.

Alcohol dehydrogenase is the major pathway



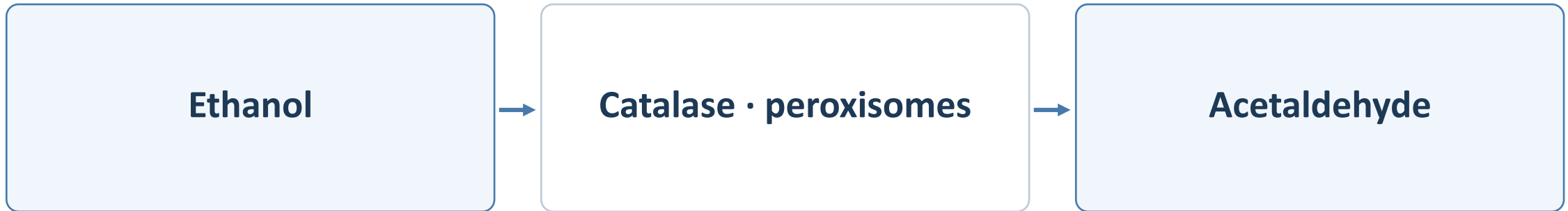
- Located predominantly in the cytosol of hepatocytes.
- Oxidation reduces NAD^+ to NADH, linking detoxification to redox injury.

CYP2E1 is a microsomal oxidation pathway



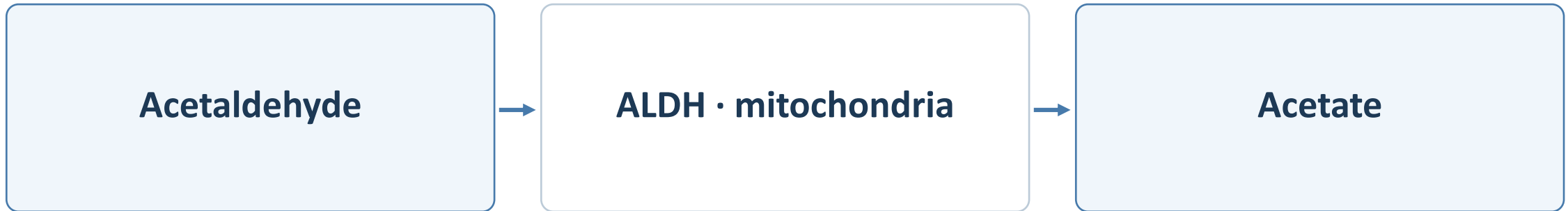
- CYP2E1 belongs to the hepatic cytochrome P-450 system.
- Its induction amplifies potential oxidative injury and drug interactions.

Catalase has a minor quantitative role



- Catalase uses hydrogen peroxide in ethanol oxidation.
- The source attributes approximately 5% of ethanol oxidation to this pathway.

Aldehyde dehydrogenase clears acetaldehyde



- Acetate can enter mitochondrial energy metabolism or lipid synthesis.
- Low ALDH activity permits acetaldehyde accumulation and toxicity.

Metabolic compartmentation explains toxicity

First oxidation

- ADH: Hepatocyte cytosol
- CYP2E1: Smooth endoplasmic reticulum
- Catalase: Peroxisome

Second oxidation

- ALDH: Mitochondria
- Acetaldehyde → acetate
- Enzyme genotype influences acetaldehyde clearance

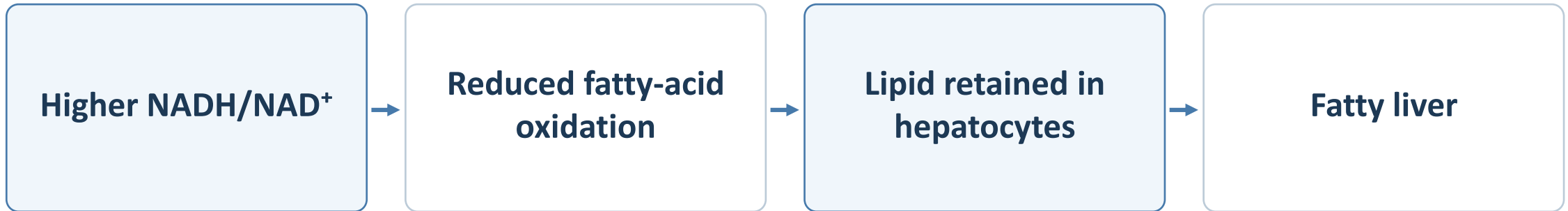
Compartment localization is critical to redox stress and ROS production.

Excess NADH shifts hepatic redox balance



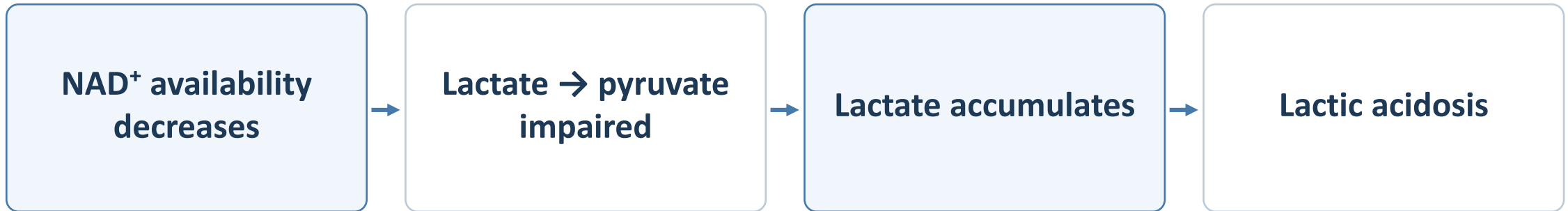
- The raised reduced/oxidized cofactor ratio changes many metabolic reactions.
- The liver becomes less capable of oxidizing fatty acids and handling lactate.

Redox imbalance drives hepatic steatosis



- Early hepatic fat accumulation can occur even with moderate intake.
- In source-described early disease, steatosis is usually reversible after abstinence.

The same redox shift increases lactate



- Lactate dehydrogenase reactions depend on available redox cofactors.
- Metabolic acidosis is a mechanistic consequence of ethanol oxidation.

Acetaldehyde is directly injurious

- Acetaldehyde is the immediate oxidative product of ethanol.
- It is responsible for some acute toxic effects and can form damaging protein adducts.
- Inefficient detoxification increases exposure to reactive acetaldehyde.

Toxicity can persist downstream of the parent ethanol molecule.

ALDH2 genotype influences alcohol responses



- The ALDH2*2 variant has very low activity.
- The source describes a dominant-negative effect even with one ALDH2*2 allele.

Homozygous ALDH2*2 causes marked intolerance

ALDH2*1 (usual allele)

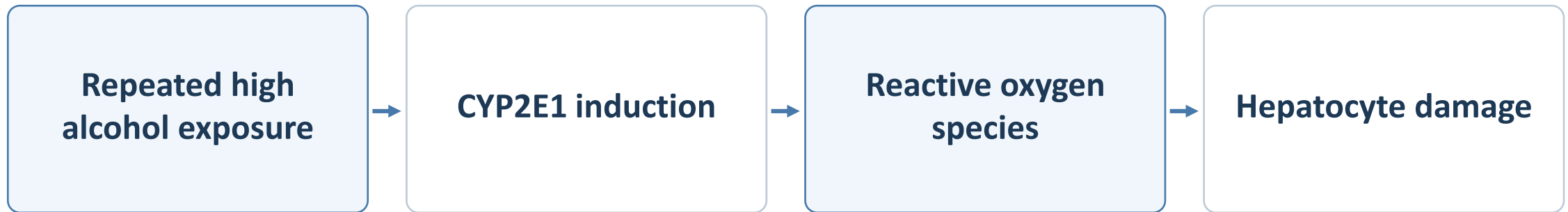
- More effective conversion of acetaldehyde to acetate.
- Lower acetaldehyde exposure at a matched intake.

ALDH2*2 homozygote

- Severely impaired acetaldehyde oxidation.
- Flushing, nausea, tachycardia, and hyperventilation after alcohol.

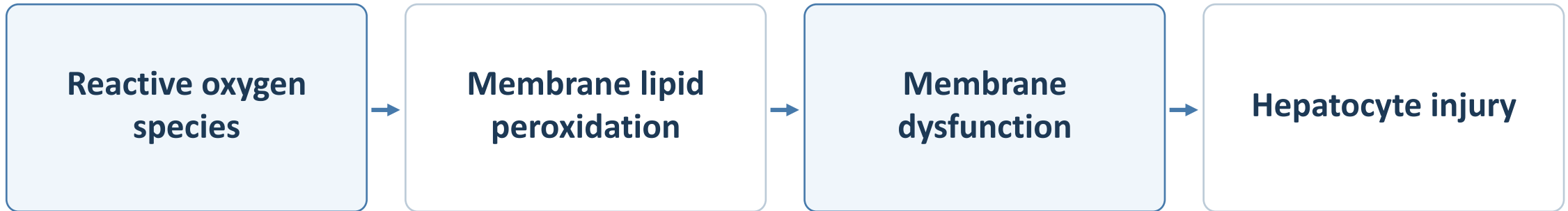
Genetic prevalence and effects vary among populations; Avoid stereotyping individuals.

CYP2E1 produces reactive oxygen species



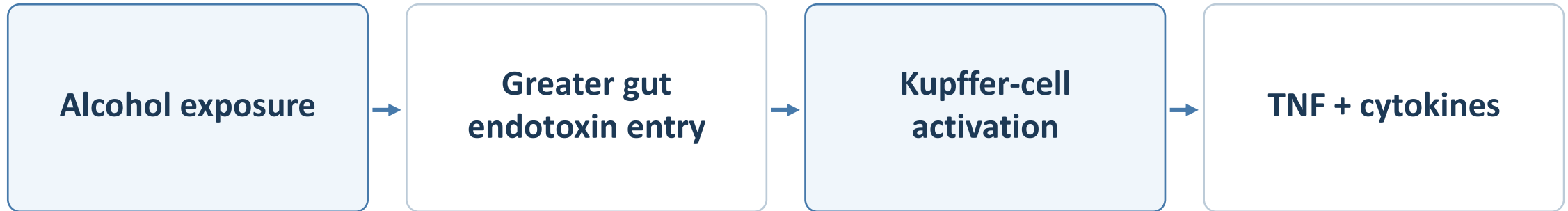
- ROS generation occurs during microsomal ethanol oxidation.
- Oxidative stress particularly affects membranes, proteins, and mitochondria.

ROS trigger lipid peroxidation



- This mechanism complements acetaldehyde toxicity and redox imbalance.
- Several pathways contribute simultaneously to alcohol-associated liver injury.

Gut-derived endotoxin drives hepatic inflammation



- Bacterial lipopolysaccharide from the intestinal microbiota reaches the liver.
- Inflammatory signaling recruits additional injury beyond direct ethanol metabolism.

Alcohol injury involves several convergent mechanisms

Metabolic

NADH excess

Chemical

Acetaldehyde adducts

Oxidative

CYP2E1-derived ROS

Hepatocyte injury

Inflammatory

LPS → Kupffer cells

Cellular

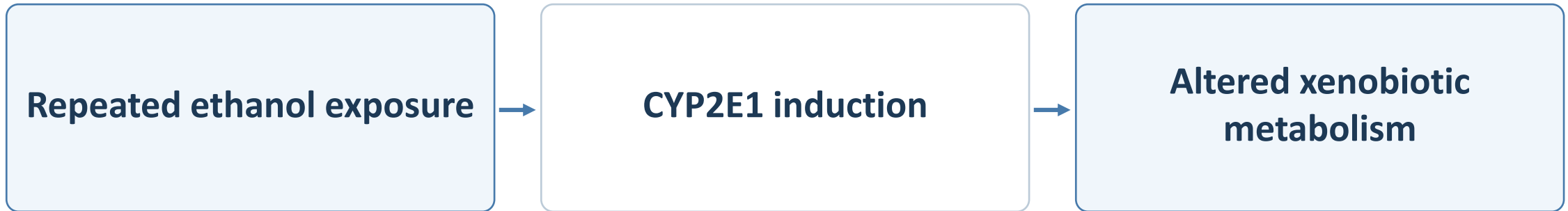
Mitochondrial injury

Tissue

Inflammation / fibrosis

Convergence explains why a single metabolic pathway cannot account for the full phenotype.

Chronic drinking changes drug metabolism



- Acetaminophen, cocaine, anesthetics, carcinogens, and solvents as relevant substrates.
- Induced oxidation may increase formation of toxic metabolites for some drugs.

Acute ethanol can compete for CYP2E1

During high ethanol concentrations

- Ethanol competes with other CYP2E1 substrates.
- Catabolism of other compounds may be delayed.

With chronic enzyme induction

- Enzyme capacity is increased.
- Metabolism of some xenobiotics can produce more reactive intermediates.

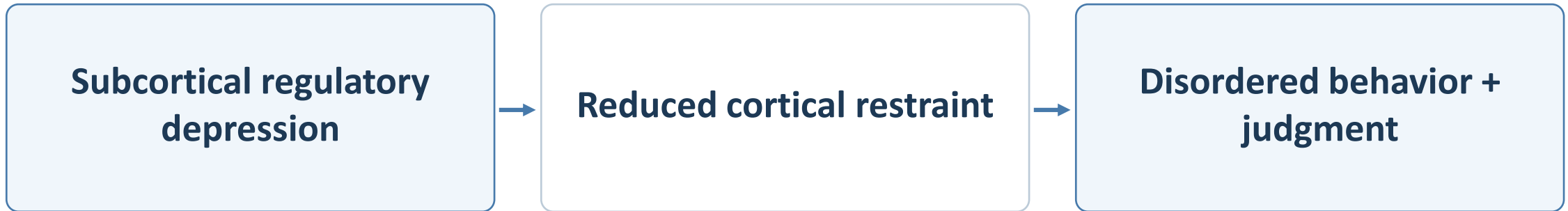
Acute competition and chronic induction are distinct phenomena.

The CNS is the main target of acute toxicity

- Ethanol is a central nervous system depressant.
- Early effects disturb regulatory circuits that normally constrain cortical behavior.
- Progression causes increasingly direct suppression of cortical and brainstem activity.

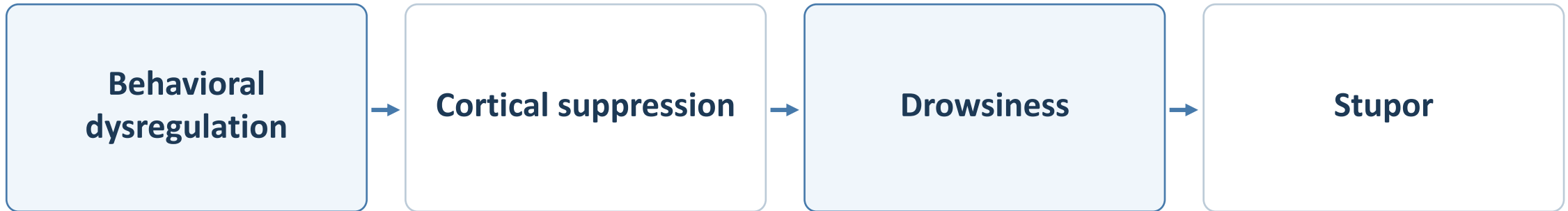
Apparent early excitation does not mean ethanol is a primary CNS stimulant.

Early intoxication causes disinhibition



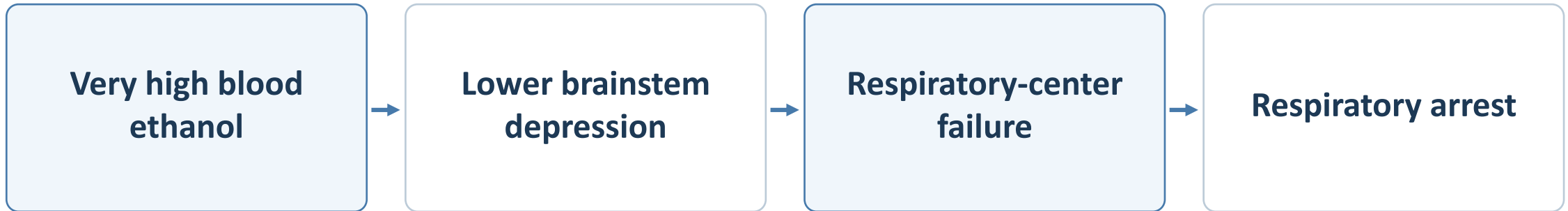
- Impaired regulatory activity can resemble stimulation.
- Motor coordination and intellectual performance become abnormal.

With rising exposure, cerebral function fails



- Severity generally increases with blood ethanol concentration.
- Clinical observation must consider individual tolerance and co-exposures.

Medullary suppression is the life-threatening endpoint



- Coma at high exposure may progress to fatal respiratory failure.
- The mechanism is central respiratory depression, not merely intoxicated behavior.

Acute alcohol can induce fatty change

- Lipid droplets may appear in hepatocyte cytoplasm even with moderate ethanol exposure.
- High NADH suppresses fatty-acid oxidation and promotes lipid accumulation.
- Abstinence can reverse this early metabolic injury.

Steatosis reflects disturbed intracellular lipid handling rather than inevitable cirrhosis.

Ethanol can acutely injure gastric mucosa

Gastric inflammation

- Acute gastritis accompanies excessive alcohol exposure.
- Mucosal damage can contribute to pain or bleeding.

Ulceration

- Ethanol-associated ulceration may develop.
- Bleeding can be serious, particularly with concurrent liver disease.

Acute gastric injury and portal-hypertensive variceal bleeding have different mechanisms.

Acute and chronic toxicities interact

Acute mechanisms

- CNS depression
- Gastric mucosal damage
- Metabolic redox shifts

Chronic consequences

- Cumulative inflammation / fibrosis
- Neurologic degeneration or deficiency
- Cardiac, pancreatic, and neoplastic disease

A patient with cirrhosis can also present with acute intoxication or acute gastritis.

Chronic exposure damages multiple organs

Liver

Steatohepatitis, cirrhosis

GI tract

Gastritis, hemorrhage

CNS

Atrophy, nutritional injury

Chronic alcohol toxicity

Heart

Dilated cardiomyopathy

Pancreas

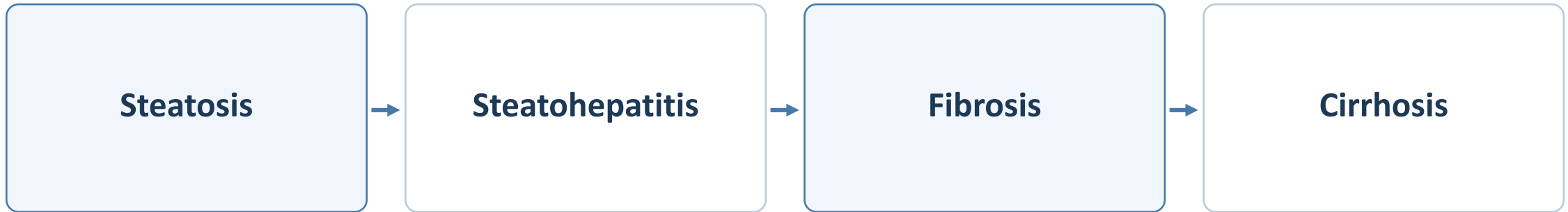
Acute or chronic pancreatitis

Fetus / cancer

Developmental and oncologic harm

Many of these effects reflect both direct toxicity and nutritional or secondary mechanisms.

Alcohol-associated liver disease is a spectrum



- The histologic categories overlap rather than representing an obligatory linear sequence.
- A subset of patients first presents with established cirrhosis.

Risk of advanced liver disease is heterogeneous

- Not all patients with alcohol use disorder develop cirrhosis.
- Biologic sex, inherited susceptibility, and other liver diseases influence progression.
- Daily ethanol dose and duration matter, but alone do not determine individual outcome.

Avoid predicting an individual's pathology solely from reported intake.

Other liver insults amplify alcohol-associated injury

Coexisting conditions

- Iron overload
- Hepatitis B or hepatitis C infection
- Metabolic dysfunction–associated steatohepatitis

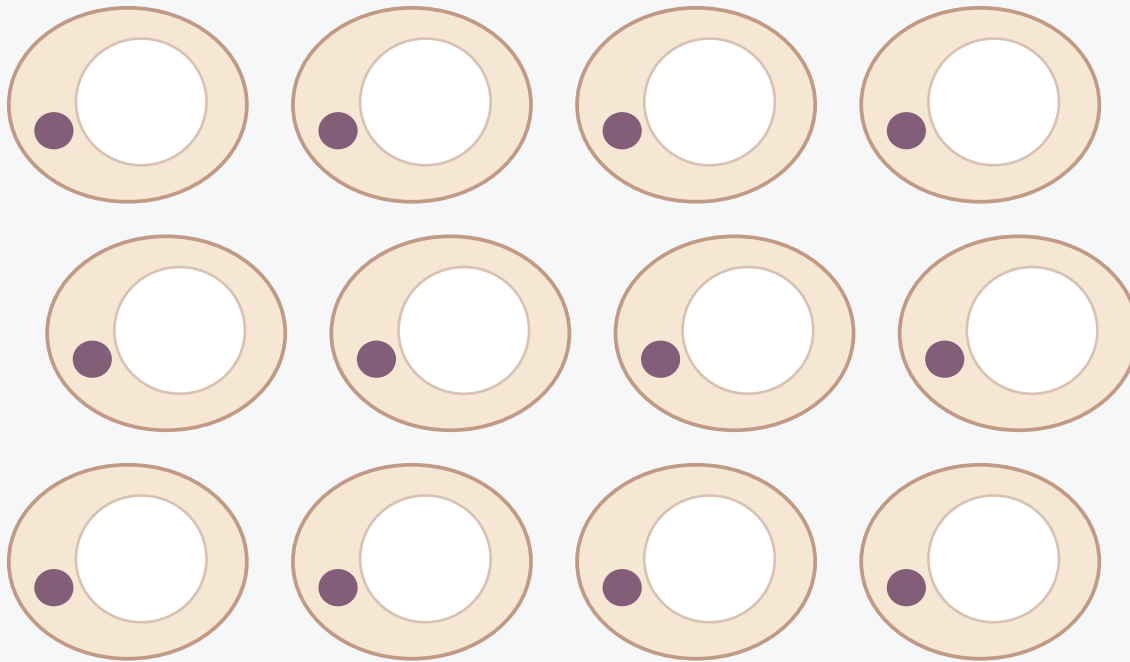
Why this matters

- Multiple insults can act synergistically.
- Steatosis alone is not diagnostic of alcohol as its cause.
- Clinical context is needed to assign etiology.

Coexisting etiologies need assessment before assigning the liver injury to ethanol.

Hepatic steatosis has recognizable morphology

Schematic — not a histologic specimen



Large clear lipid vacuoles displace nuclei

- Macrovesicular steatosis is the dominant pattern in alcohol-associated liver disease.
- Intracellular fat vacuoles enlarge and displace the nucleus.
- Grossly the liver may become enlarged, yellow, soft, and greasy.

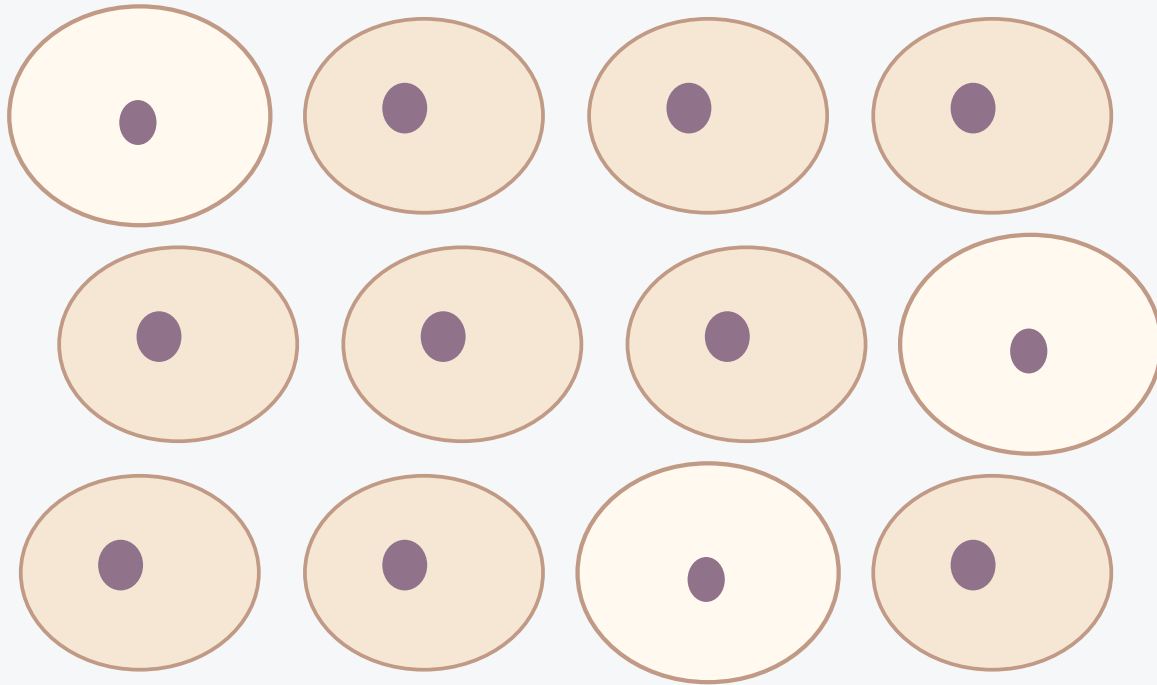
Alcoholic injury often begins near central veins



- Characteristic early injury begins near centrilobular zone 3.
- Greater injury extends away from central veins toward portal tracts.

Ballooning represents hepatocyte damage

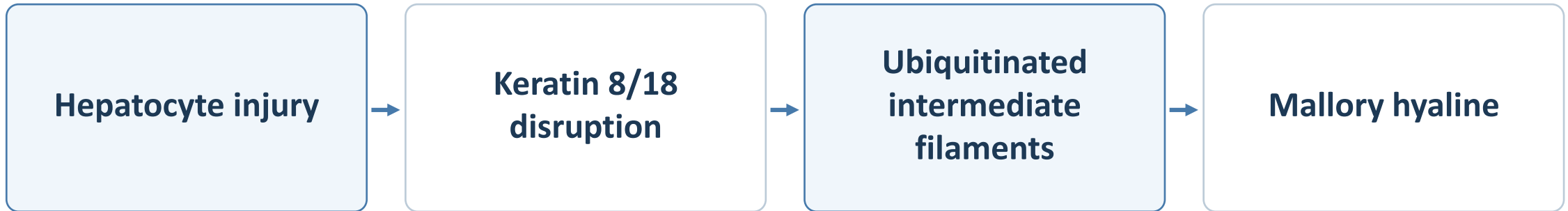
Schematic — not a histologic specimen



Selected hepatocytes are expanded and pale

- Ballooned hepatocytes are swollen with pale, cleared-out cytoplasm.
- Cytoskeletal dysfunction accompanies the cell injury.
- Ballooning is important in steatohepatitis but is not specific for alcohol.

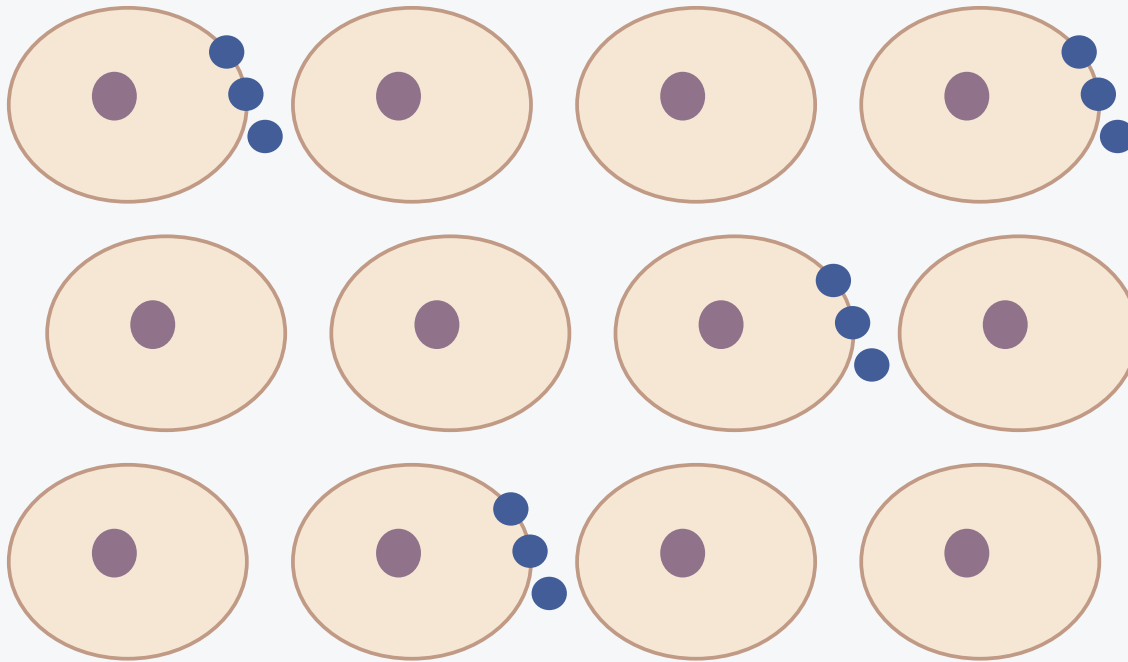
Mallory hyaline marks cytoskeletal injury



- Mallory hyaline consists of abnormal cytoplasmic intermediate filament aggregates.
- It can also be encountered in nonalcohol-associated liver disorders.

Neutrophils are conspicuous in alcohol-associated hepatitis

Schematic — not a histologic specimen

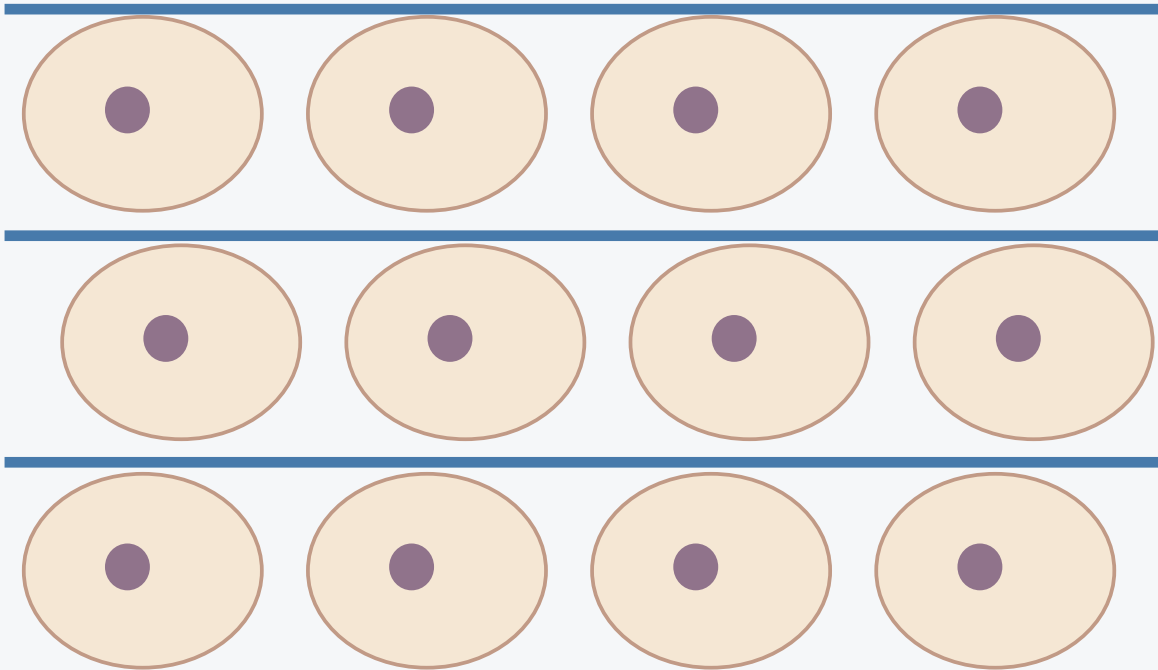


Inflammatory cells cluster near hepatocytes

- Neutrophils may cluster around injured, ballooned hepatocytes.
- Lobular lymphocytes and macrophages can also be present.
- Focal hepatocyte necrosis or apoptosis accompanies the inflammatory process.

Pericellular fibrosis has a chicken-wire pattern

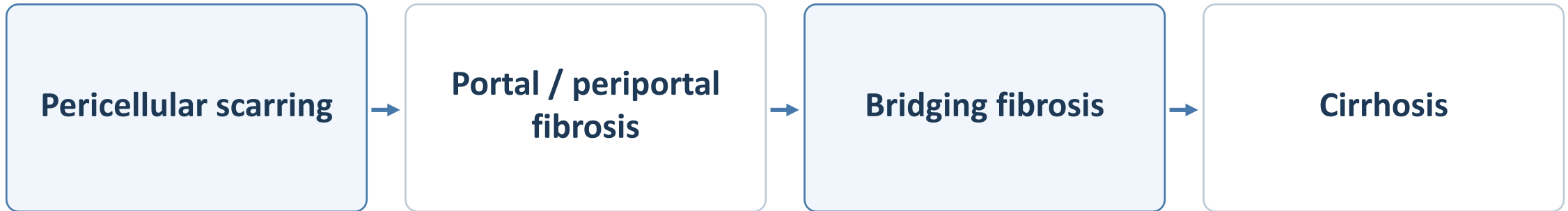
Schematic — not a histologic specimen



Pericellular network represents progressive collagen

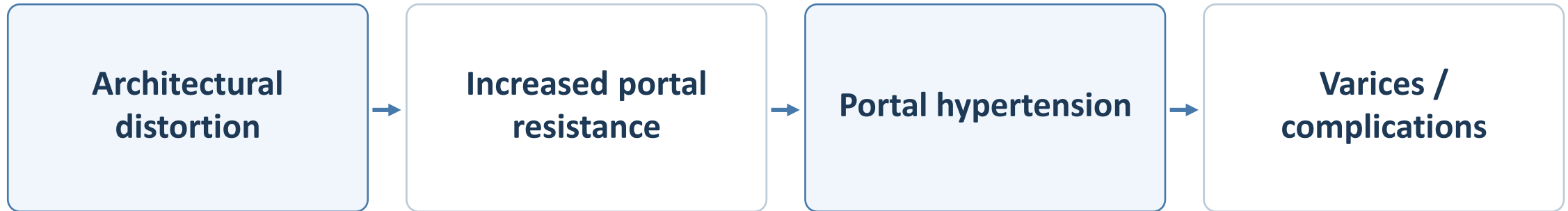
- Fibrosis commonly starts around sinusoids in acinar zone 3.
- Pericellular / perisinusoidal collagen surrounds hepatocytes in a network.
- The pattern can precede bridging fibrosis and cirrhosis.

Persistent injury reshapes liver architecture



- Fibrosis progressively remodels parenchyma and vascular channels.
- Micronodular cirrhosis is commonly described, although morphology can evolve.

Cirrhosis produces portal hypertension



- Cirrhotic vascular dysfunction can create life-threatening esophageal varices.
- Cirrhosis also increases hepatocellular carcinoma risk.

Alcohol-associated hepatitis has clinical correlates

Clinical features

- Malaise, anorexia, weight loss
- Upper abdominal discomfort
- Tender hepatomegaly

Laboratory changes

- Hyperbilirubinemia
- Aminotransferase elevation
- Neutrophilic leukocytosis may occur

These findings support context but are not individually specific for alcohol-related injury.

AST predominance is a useful clue—not proof

- AST commonly exceeds ALT in alcohol-associated liver disease.
- A ratio of AST:ALT of 2:1 or greater can raise suspicion.
- Clinical exposure history and exclusion of alternative causes remain necessary.

Do not use one aminotransferase ratio as a stand-alone etiologic diagnosis.

Early injury has greater reversibility

Steatosis

- Often completely reversible with abstinence.
- Cellular lipid accumulation can resolve without major architectural damage.

Established cirrhosis

- Dense scarring and vascular distortion limit full recovery.
- Complete regression is reported but uncommon.

Fibrosis at earlier stages can regress after removal of the injury.

Gastrointestinal bleeding has distinct sources

Primary mucosal injury

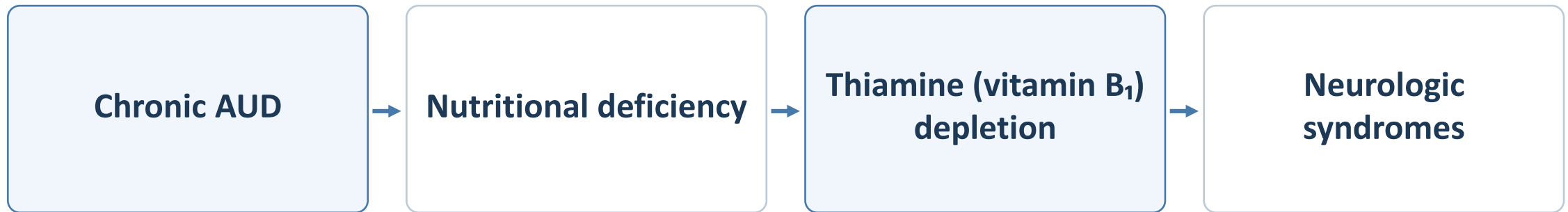
- Gastritis
- Gastric ulceration
- Mucosal bleeding

Secondary portal-hypertensive injury

- Cirrhosis increases portal venous pressure.
- Esophageal varices may rupture.
- Massive hemorrhage may be fatal.

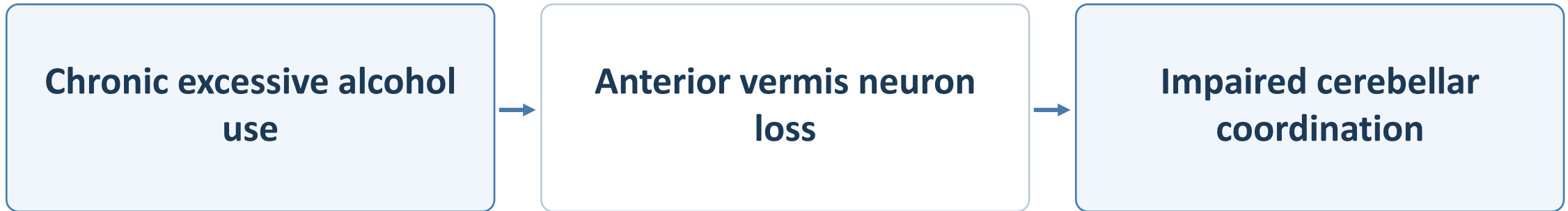
Not all bleeding in a patient with AUD comes directly from gastric mucosa.

Thiamine deficiency contributes to neurologic injury



- The source specifically links thiamine deficiency to neuropathy and Wernicke–Korsakoff syndrome.
- This mechanism differs from direct acute ethanol-induced CNS depression.

Cerebellar degeneration affects coordination



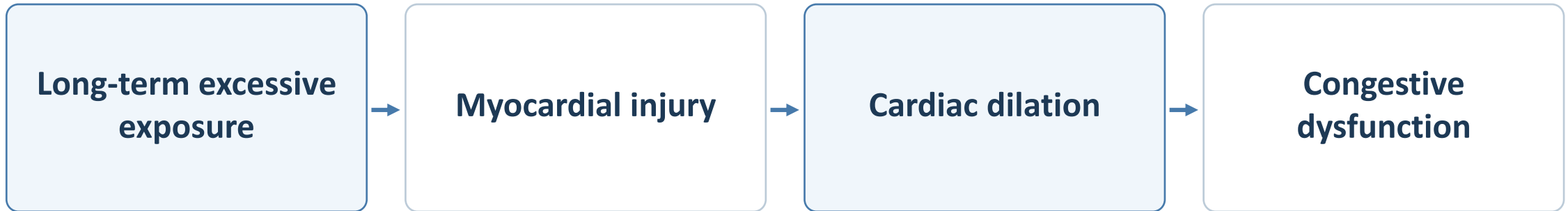
- Cerebellar degeneration is a described structural neurologic complication.
- Chronic cerebral atrophy and optic neuropathy can also occur.

Peripheral neuropathy is another chronic effect

- Peripheral nerve damage is recognized in chronic AUD.
- The textbook associates thiamine deficiency with peripheral neuropathies.
- Neurologic deficits may coexist with cerebellar disease or Wernicke–Korsakoff syndrome.

Separate a nutritional neuropathy mechanism from the direct sedative effect of ethanol.

Alcohol can cause dilated cardiomyopathy



- Alcoholic cardiomyopathy as a chronic cardiovascular effect.
- The damaged heart develops a dilated, poorly functioning phenotype.

Cardiovascular effects extend beyond cardiomyopathy

Recognized adverse effects

- Increased frequency of hypertension
- Myocardial injury and congestive cardiomyopathy

Interpreting lipid associations

- Severe liver injury may lower HDL cholesterol.
- Reported favorable associations with modest intake are not proof of benefit.

Cardiovascular risk cannot be inferred from HDL changes alone.

Excess alcohol increases pancreatitis risk

Acute pancreatitis

- Can occur with excessive intake.
- Represents pancreatic inflammatory injury.

Chronic pancreatitis

- Associated with repeated or prolonged heavy intake.
- Can contribute to lasting pancreatic dysfunction.

Both forms are recognized as important consequences of excessive intake.

Prenatal exposure may cause fetal alcohol syndrome

Growth

Growth retardation

Head

Microcephaly

Face

Facial abnormalities

Fetal alcohol syndrome

Development

Reduced later mental function

The source stresses first-trimester vulnerability and uncertainty regarding a safe exposure threshold.

Chronic alcohol intake is carcinogenic

Oral cavity

Increased risk

Esophagus

Increased risk

Liver

Increased risk

Alcohol-linked cancer risk

Larynx

Acetaldehyde implicated

Breast

Risk can rise even at low–
moderate intake

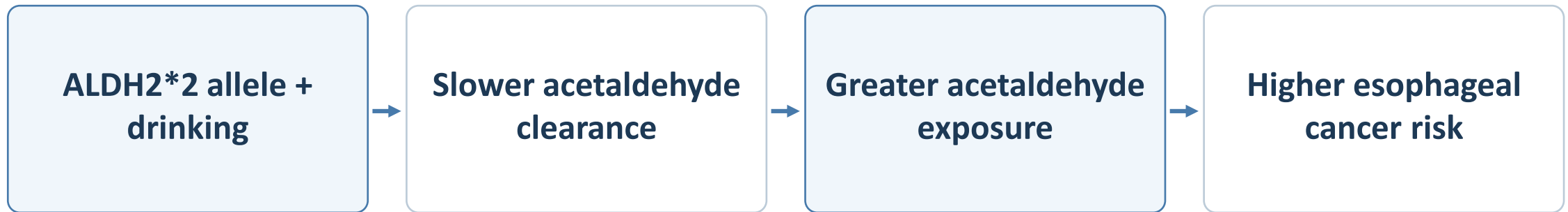
The source explicitly cautions that even light-to-moderate drinking can increase cancer risk.

Acetaldehyde can damage genomic DNA



- Acetaldehyde–DNA adducts have been detected in certain upper aerodigestive tract tumors.
- The source implicates acetaldehyde in laryngeal and esophageal carcinogenesis.

ALDH2 deficiency modifies esophageal cancer risk



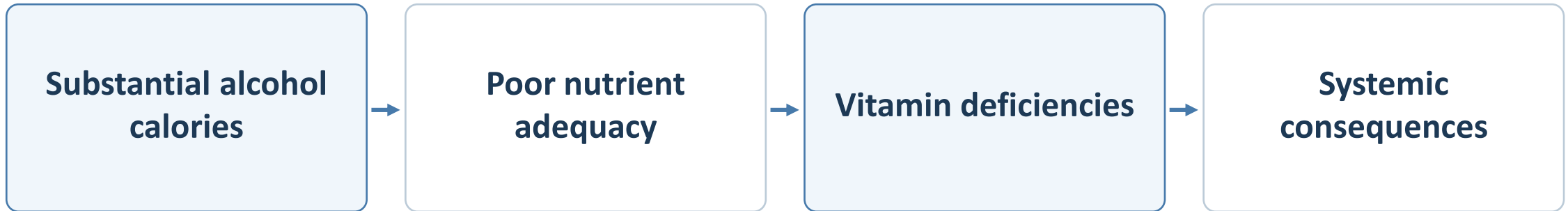
- The source highlights increased esophageal cancer risk in drinkers carrying one ALDH2*2 allele.
- Acute flushing therefore must not be interpreted as protection from cancer.

Alcohol and tobacco act synergistically



- Synergy for several cancers involving tobacco and alcohol.
- Joint exposure is more hazardous than considering each exposure in isolation.

Ethanol calories do not prevent malnutrition



- The source characterizes ethanol as a source of “empty calories.”
- Severe chronic AUD is associated with malnutrition, particularly B-vitamin deficiency.

Claims of moderate drinking benefit need caution

Reported observational associations

- Some studies found reduced cardiovascular mortality with moderate consumption.
- Proposed factors include HDL, platelet effects, and fibrinogen.

Why causality is uncertain

- Socioeconomic status, diet, and lifestyle can confound results.
- The textbook does not establish alcohol consumption as a safe intervention.

Association is not proof of cardioprotection or a recommendation to consume ethanol.

Alcohol and metabolic fatty liver may overlap

Alcohol-associated steatotic injury

- Exposure to ethanol and toxic metabolites
- Steatosis ± ballooning, inflammation, fibrosis

Metabolic dysfunction-associated disease

- Associated with cardiometabolic risk factors
- Many microscopic features overlap with alcohol-associated injury

Neither steatosis nor ballooning alone establishes the etiologic diagnosis.

Case 1: Progressive intoxication

Clinical stem

A person with marked ethanol exposure develops unsteady behavior, then drowsiness, and finally reduced responsiveness with poor respiratory effort.

Which sequence best explains the change in neurologic manifestations?

- Early depression of regulatory subcortical circuitry causes apparent disinhibition.
- Higher concentrations suppress cortical neurons and then medullary respiratory centers.
- Respiratory compromise is the critical life-threatening progression.

Case 2: Injured fatty liver

Clinical stem

A patient with sustained excessive ethanol consumption has hepatomegaly and abnormal aminotransferases. Biopsy shows steatosis, ballooned hepatocytes, neutrophils, and zone-3 pericellular fibrosis.

Which tissue mechanisms and stage of injury are suggested?

- NADH-driven steatosis plus oxidative and inflammatory hepatocyte injury.
- Ballooning and neutrophils support steatohepatitis; Zone-3 fibrosis signifies chronic injury.
- Steatosis may regress; Scarring may progress if exposure continues.

Case 3: Flushing and cancer susceptibility

Clinical stem

A person experiences facial flushing and tachycardia after ethanol intake but continues to drink. Genotyping identifies an ALDH2*2 allele.

How can acute intolerance coexist with longer-term cancer risk?

- Low ALDH2 activity prolongs acetaldehyde exposure.
- Acetaldehyde causes acute symptoms and can form DNA adducts.
- The source links ALDH2*2 in drinkers to increased esophageal cancer risk.

Mechanisms connect exposure to organ injury

Brain

Dose-related depression

Liver

Redox + ROS + LPS

Stomach

Gastritis / ulceration

Ethanol exposure

Heart

Myocardial damage

Pancreas

Inflammatory injury

Cancer / fetus

DNA damage / teratogenicity

Acute intoxication is only one component of total alcohol-associated pathology.

Core points for clinical pathology

- ADH, CYP2E1, and catalase form acetaldehyde; Mitochondrial ALDH converts it to acetate.
- NADH excess, acetaldehyde injury, ROS, and Kupffer-cell inflammation drive hepatotoxicity.
- The chronic liver spectrum includes steatosis, steatohepatitis, fibrosis, and cirrhosis.
- Alcohol affects brain, gut, cardiovascular system, pancreas, fetal development, and cancer risk.

Interpret findings by integrating exposure, metabolism, morphology, and organ effects.

Selected reference

- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th edition (2026).
- Primary textbook section: “Effects of Alcohol” (Environmental and Nutritional Diseases).
- Additional textbook section: “Alcohol-Associated Liver Disease” (Liver and Gallbladder).