

Chemical (Toxic) Injury

Mechanisms of cell injury and clinicopathologic examples

Pathology lecture

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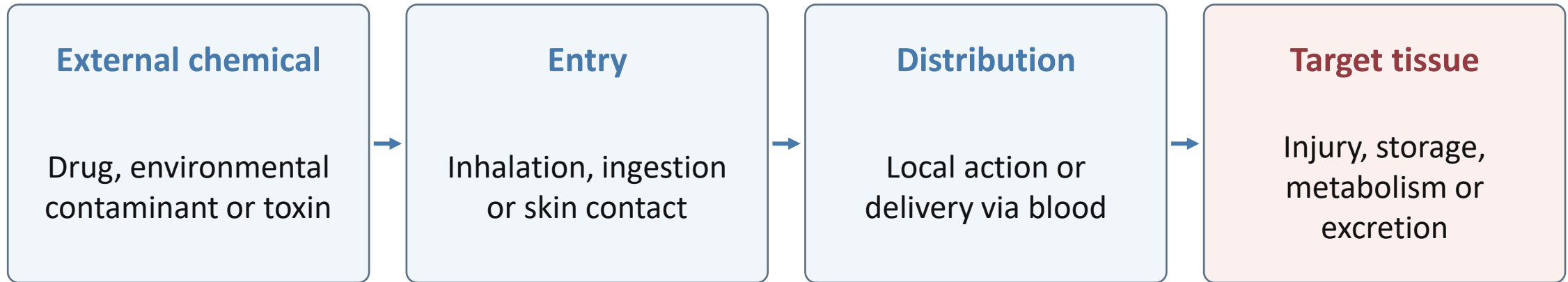
Learning objectives

- Distinguish direct toxicity from toxic-metabolite formation.
- Explain cytochrome P450, phase I/II reactions, and oxidative injury.
- Trace injury mechanisms for mercury, cyanide, CCl_4 , and acetaminophen.
- Connect molecular damage with organ selectivity and cell death.

Why chemical injury matters clinically

- Chemical injury is a frequent cause of cellular damage.
- Drug toxicity is an important limitation to treatment and development.
- The liver is particularly exposed because it metabolizes many drugs.
- Different chemicals converge on a small set of cellular targets.

Environmental exposure reaches target cells



The site of entry and the site of maximal injury need not be the same.

Local versus systemic toxic effects

At the site of entry

- Initial contact with skin, lung or gastrointestinal mucosa.
- Injury may precede extensive systemic distribution.
- Local concentration contributes to severity.

After distribution

- Blood delivers xenobiotics to distant organs.
- Liver may metabolize circulating compounds.
- Kidney may concentrate agents during excretion.

Organ tropism is determined partly by exposure, uptake, concentration, and metabolism.

Toxicity depends on exposure and the host

- Dose is fundamental: A therapeutic substance can become toxic.
- Absorption, distribution, metabolism and excretion alter effective exposure.
- Age, genetics and tissue susceptibility contribute to variable responses.
- Drug and environmental exposures may change metabolic enzyme activity.

Why one organ is injured more than another

**Concentration
≠
Uniform injury**

- Cells that absorb or concentrate a toxin receive greater exposure.
- A tissue may activate a relatively inert chemical.
- Cell-specific defenses modify susceptibility.

Examples: Gastrointestinal tract and kidney with mercuric chloride; Liver with many drugs.

Two major mechanisms of chemical injury

Direct toxicity

- Parent compound is itself injurious.
- Direct interaction with critical cell molecules.
- Examples: Mercury and cyanide.

Metabolic activation

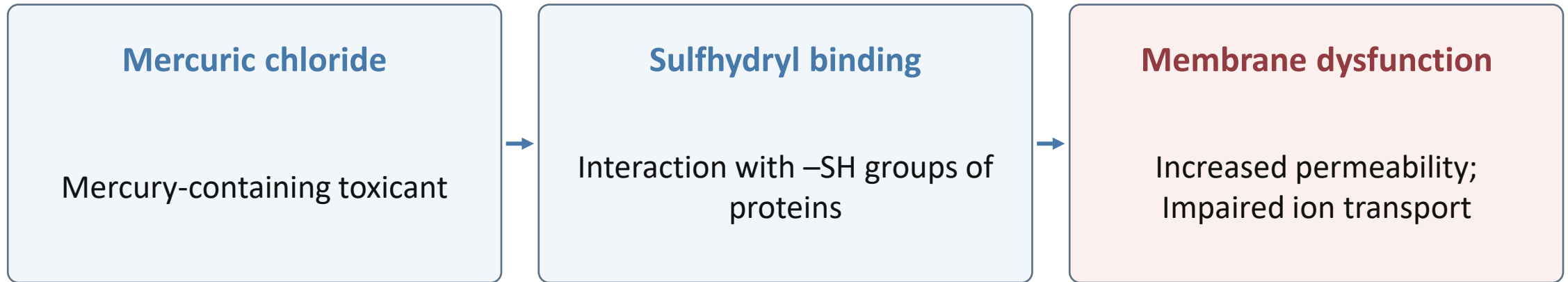
- Parent compound is converted to a reactive product.
- Reactive metabolites attack lipids and proteins.
- Examples: CCl₄ and acetaminophen.

This distinction is mechanistic: Both pathways can culminate in membrane or mitochondrial damage.

Direct toxicity starts at a molecular target

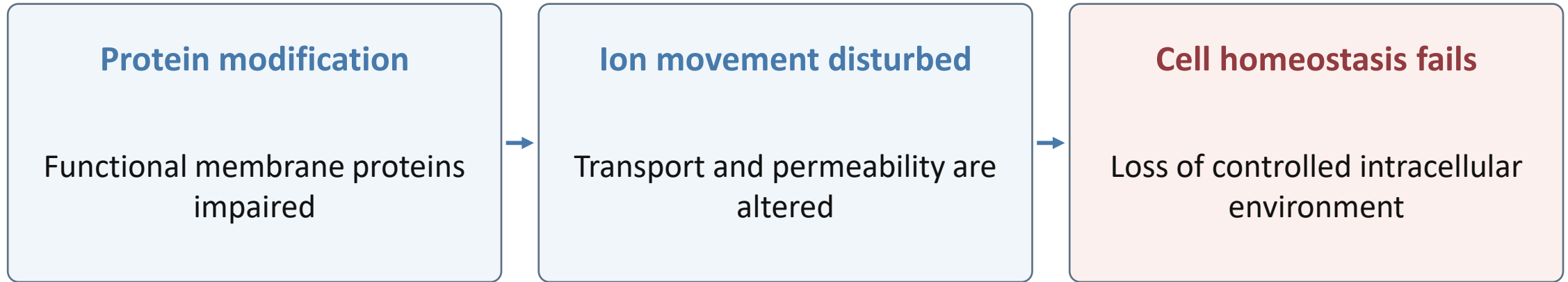
- A chemical binds to, inhibits, or otherwise disrupts a critical molecule.
- The immediate molecular lesion determines the first cellular dysfunction.
- Damage severity depends on exposure and cellular reliance on that target.

Mercury directly modifies membrane proteins



Direct binding to protein functional groups alters membrane physiology.

Membrane transport failure propagates injury



The membrane is a functional barrier, not merely an anatomical outline.

Mercury injury: Why gastrointestinal tract and kidney?

Gastrointestinal tract

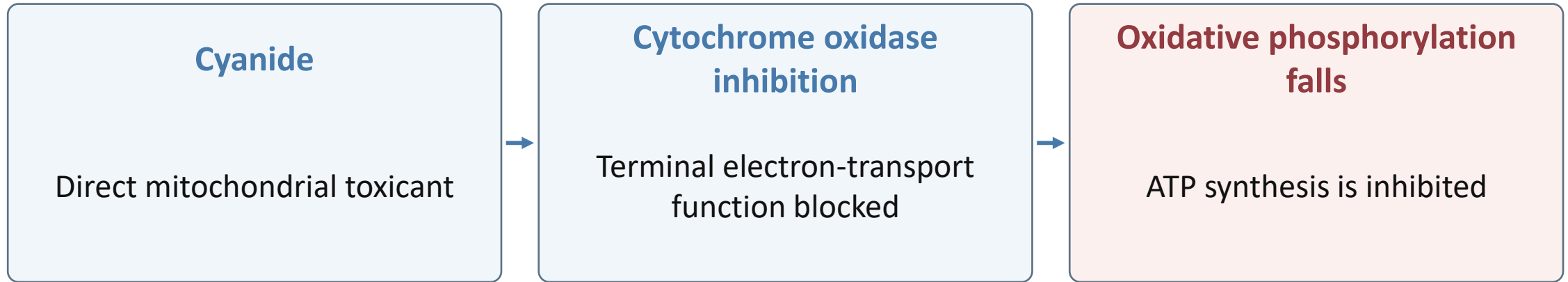
- A major site of contact after ingestion.
- Cells are exposed during passage or absorption.
- Direct protein interaction can injure the epithelium.

Kidney

- Renal cells handle circulating solutes.
- Excretion and concentration favor toxic exposure.
- The same molecular target can exist in different organs.

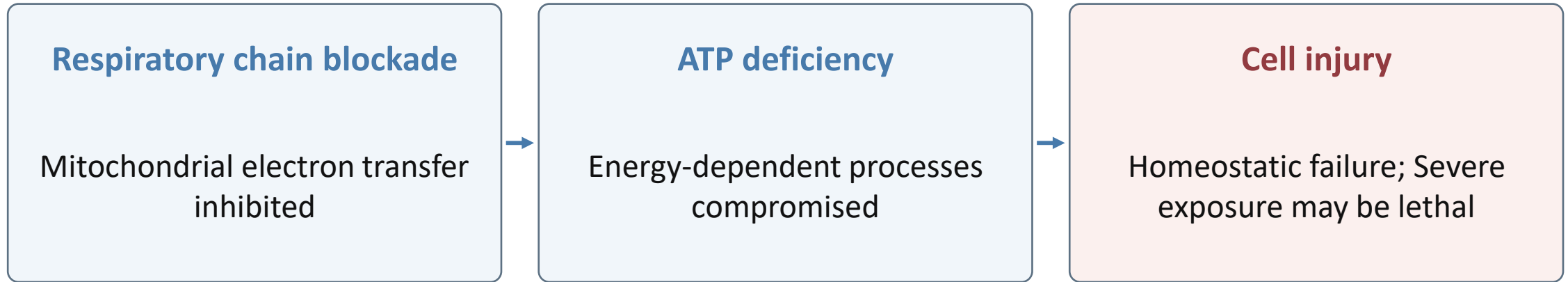
Target-organ distribution follows contact, use, absorption, excretion and concentration.

Cyanide inhibits the mitochondrial electron transport chain



Unlike mercury, the principal lesion here is inhibition of energy generation.

Cyanide injury is an energy-failure mechanism



The molecular lesion predicts broad vulnerability of metabolically active tissues.

Direct cytotoxicity is not confined to poisons

- Some antineoplastic agents damage cells through direct cytotoxic effects.
- Some antibiotics also have direct cell-damaging mechanisms.
- Therapeutic intent does not remove the potential for cellular toxicity.
- Specific organ toxicities require drug-specific evidence.

Direct chemical injuries: Different first targets

Agent / class	Initial molecular interaction	Immediate consequence
Mercuric chloride	Sulfhydryl groups of membrane proteins	Permeability and ion-transport disturbance
Cyanide	Mitochondrial cytochrome oxidase	Inhibited oxidative phosphorylation
Some cytotoxic drugs	Drug-dependent cellular targets	Direct damage to sensitive cells

Metabolic activation changes the toxic species

- The parent chemical may be relatively inactive as a toxin.
- Metabolism produces a reactive intermediate or metabolite.
- The newly formed species can attack critical cell molecules.
- Biotransformation can therefore produce harm rather than detoxification.

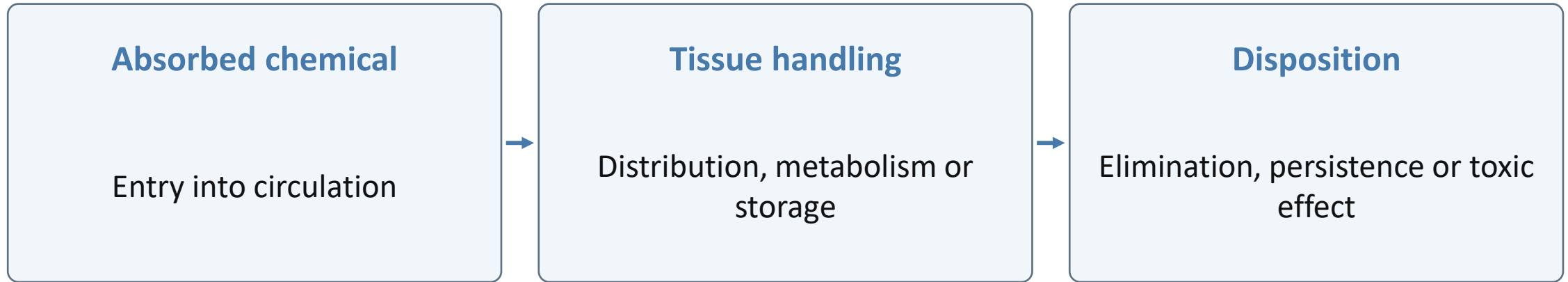
The liver is a central site of xenobiotic metabolism

High metabolic Activity

- Hepatocytes express substantial drug-metabolizing enzyme activity.
- Many cytochrome P450 enzymes localize in endoplasmic reticulum.
- The liver can both detoxify and activate xenobiotics.

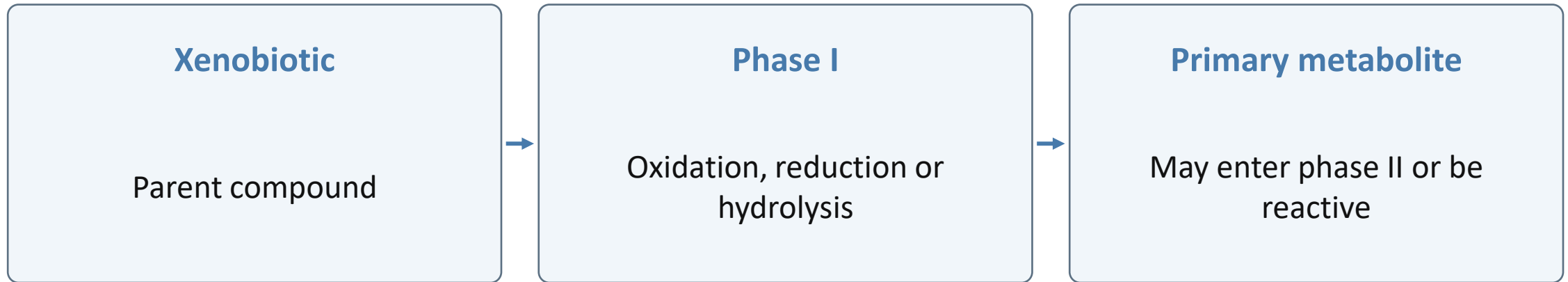
The liver's defensive function creates a mechanism for drug-induced liver injury.

The possible fates of an absorbed xenobiotic



Toxicity cannot be inferred from absorption alone.

Phase I reactions alter chemical structure

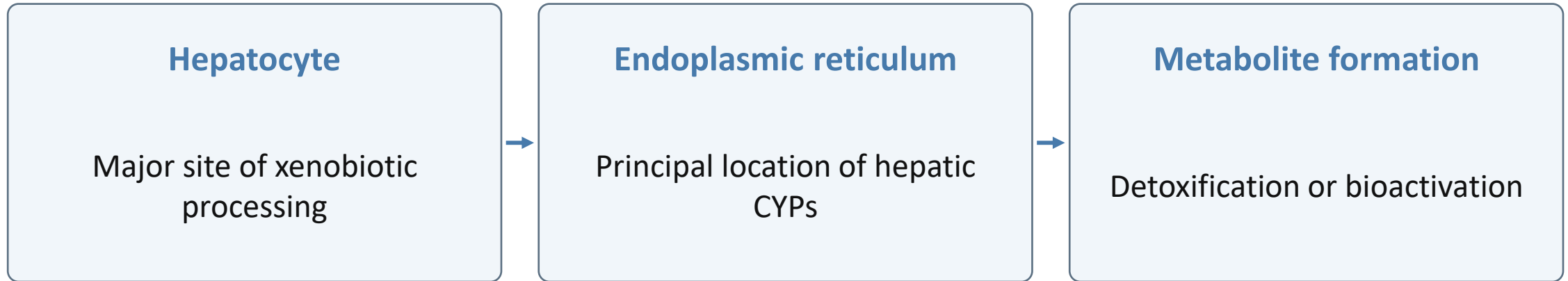


The metabolic product is not necessarily less toxic than the parent.

Cytochrome P450: The major phase I catalyst

- CYPs are a large family of heme-containing enzymes.
- Different CYP enzymes have distinct substrate preferences.
- The system catalyzes reactions involving many drugs and pollutants.
- Products may be inactivated or converted to reactive toxicants.

CYP enzymes occupy cellular metabolic compartments

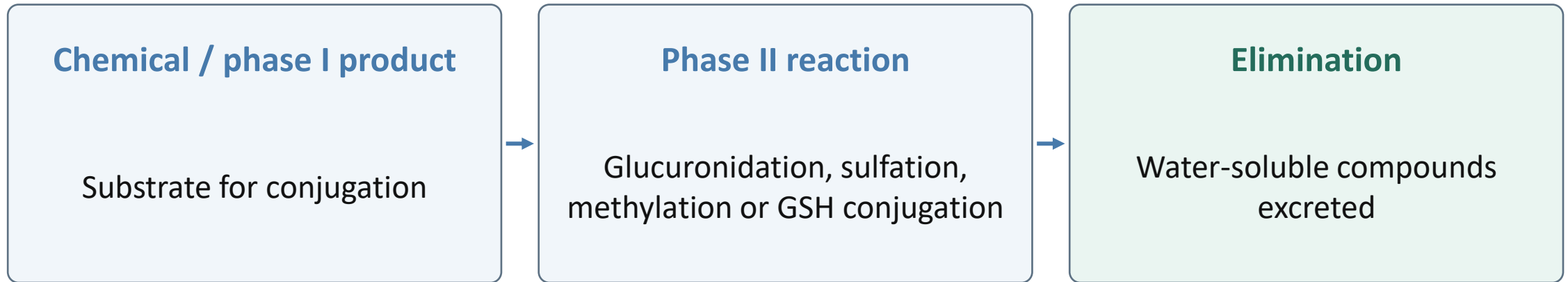


Subcellular localization is part of the causal mechanism, not simply a microscopy detail.

Cytochrome P450 is expressed beyond the liver

- CYP activity is prominent in hepatocytes.
- The textbook also identifies skin, lung and gastrointestinal mucosa.
- Extrahepatic metabolism can change local tissue exposure.
- Distribution of enzymes helps explain toxic effects in particular organs.

Phase II pathways increase water solubility

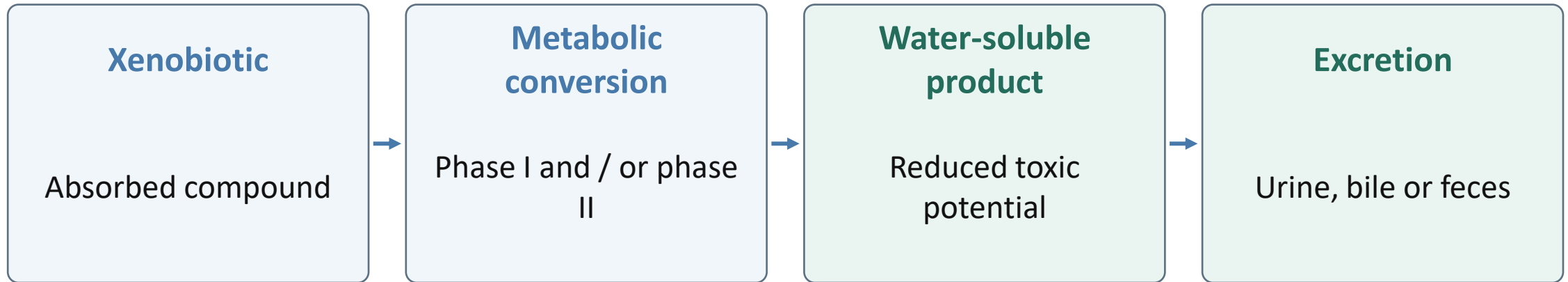


Conjugation commonly facilitates detoxification and excretion.

Phase I versus phase II metabolism

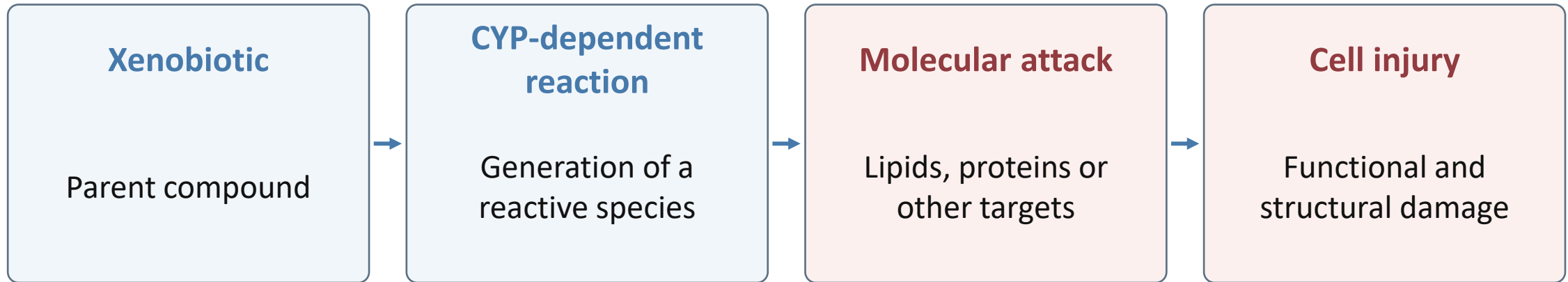
Feature	Phase I	Phase II
Representative reactions	Oxidation, reduction, hydrolysis	Glucuronidation, sulfation, methylation, GSH conjugation
Typical function	Functionalization / modification	Conjugation, often increasing water solubility
Toxicologic implication	May activate a chemical	Usually favors elimination; can remove reactive metabolites
Principal takeaway	Not always detoxifying	Important, but not an absolute safety guarantee

A detoxification route



The majority of xenobiotics are metabolized to facilitate elimination.

An activation route



The same metabolic machinery may create a more injurious compound.

Detoxification and activation can compete

Protection predominates

- Conjugation or inactivation is efficient.
- Reactive intermediates are neutralized.
- Products become suitable for elimination.

Injury predominates

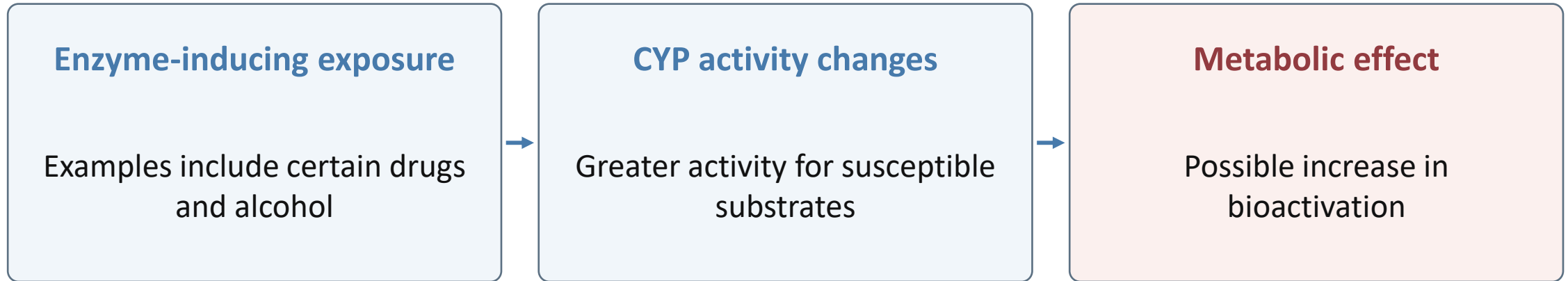
- Reactive intermediate production increases.
- Detoxification defenses are insufficient.
- Macromolecular damage accumulates.

Toxicity depends on production versus clearance of damaging species.

Why CYP activity varies among individuals

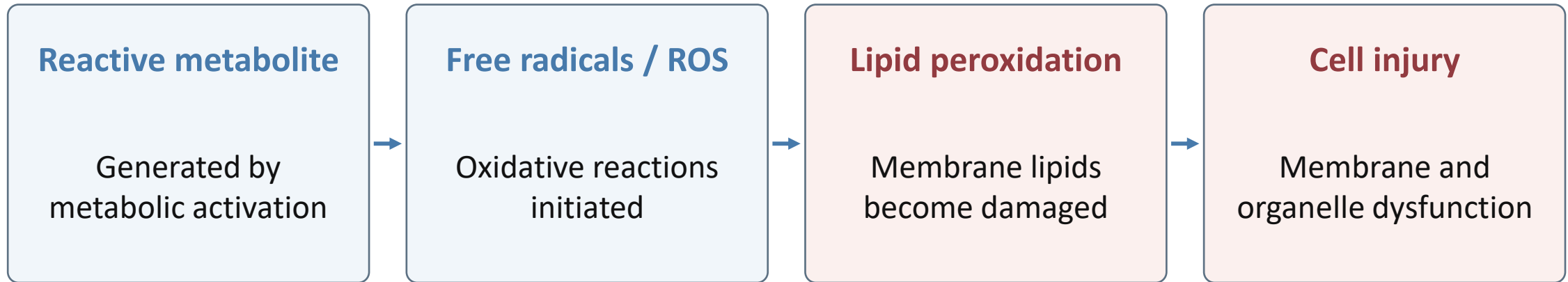
- Genetic polymorphisms can affect metabolic enzyme activity.
- Exposure to chemicals and drugs can induce or diminish CYP activity.
- Smoking, alcohol, hormones and other agents may alter activity.
- The same external exposure need not yield identical metabolic injury.

CYP induction changes the amount of reactive product



Induction is not intrinsically toxic; Its effect depends on the substrate and pathway.

Toxic metabolites commonly produce oxidative injury

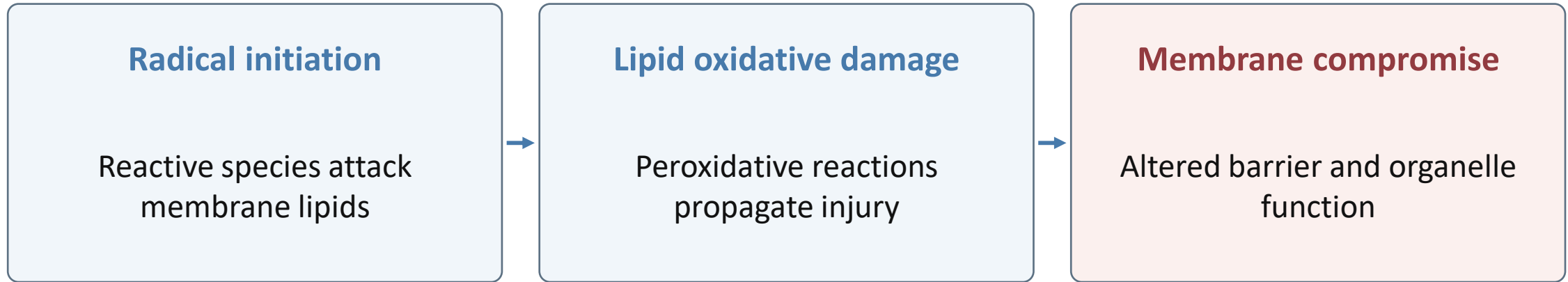


Oxidant-mediated membrane injury is a major pathway in this chapter.

Reactive species can affect several cell components

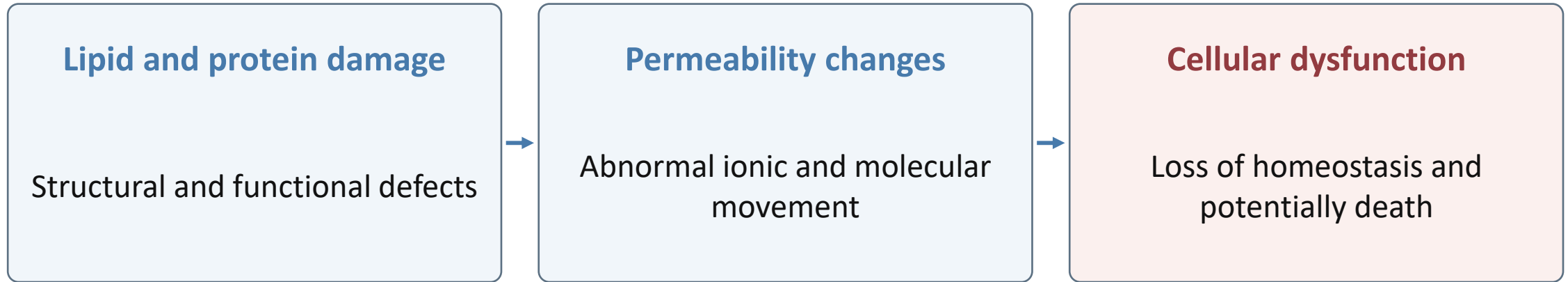
- Membrane lipids are vulnerable to peroxidation.
- Proteins can be altered by direct reactive-metabolite binding.
- Oxidative stress disrupts organelle and membrane function.
- Resulting injury is amplified when protective systems are overwhelmed.

Lipid peroxidation damages the membrane barrier



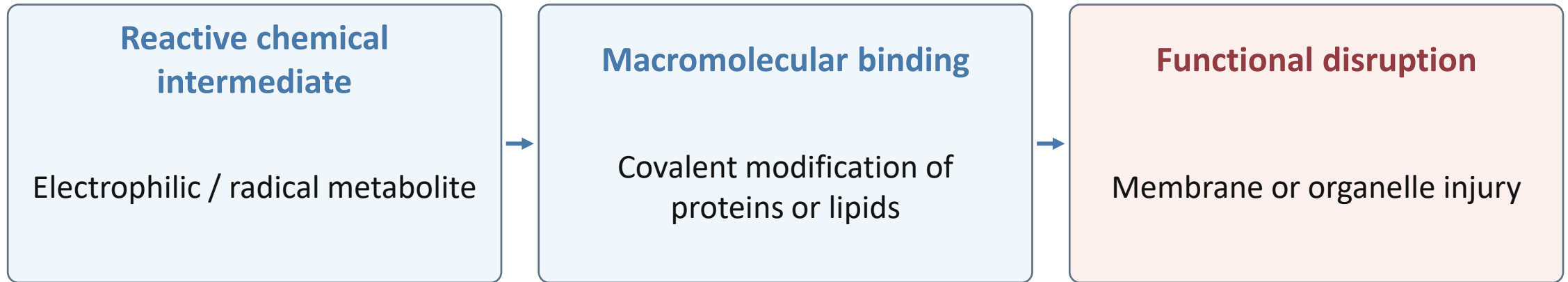
The biochemical lesion explains why cell membranes lose integrity.

Membrane injury has multiple consequences



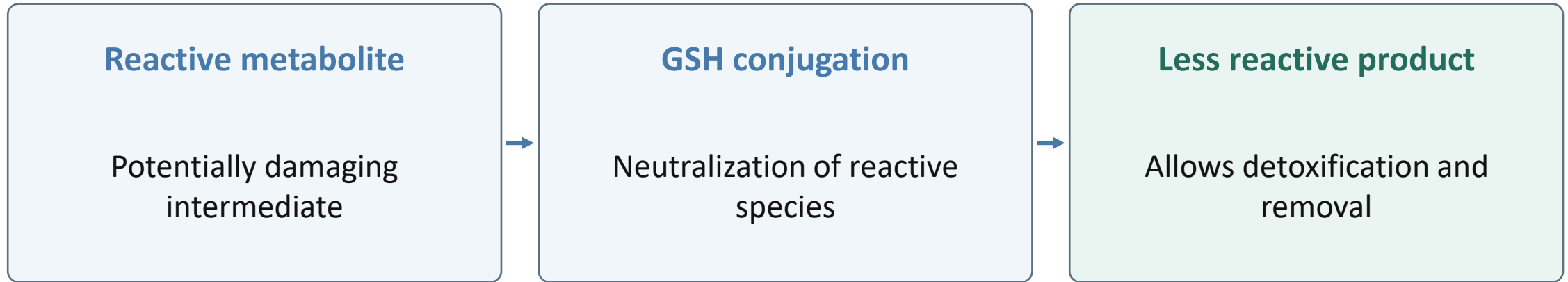
A damaged membrane impairs the entire cell, not just its boundary.

Reactive metabolites can bind covalently to cellular molecules



Covalent binding is distinct from injury driven only by oxygen radicals.

Glutathione is a chemical defense mechanism



Adequate glutathione availability is protective in acetaminophen metabolism.

Injury develops when defenses are outpaced

Sufficient defense

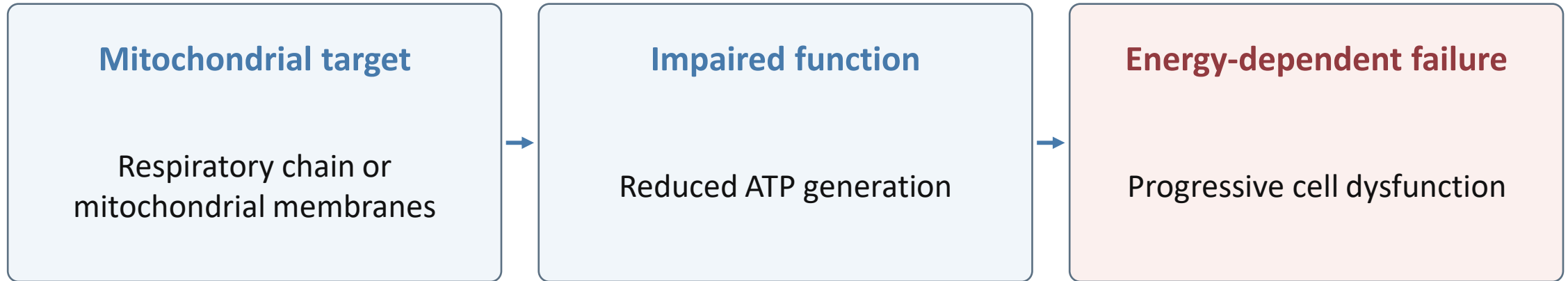
- Reactive species are neutralized.
- Covalent injury remains limited.
- Cell may maintain or restore homeostasis.

Insufficient defense

- Reactive species persist.
- Protein and membrane damage accumulates.
- Cell injury can become irreversible.

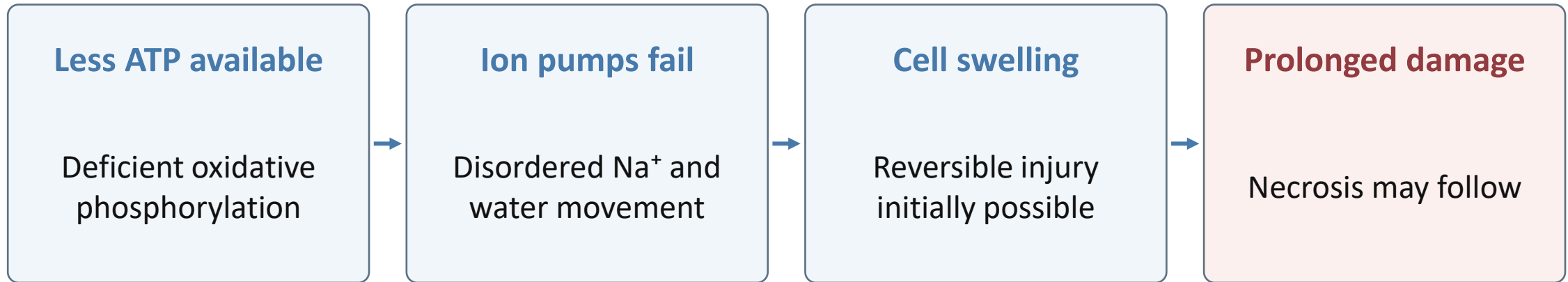
This schematic contrast explains the threshold behavior of many toxic exposures.

Mitochondria link chemical injury to energy failure



Cyanide acts directly; Reactive metabolites may damage mitochondria secondarily.

ATP depletion produces characteristic cell dysfunction



The severe end of ATP depletion converges with general mechanisms of cell injury.

Chemical injury may be reversible or lethal

Reversible injury

- Cell function is impaired.
- Homeostasis and membranes may recover.
- Swelling can precede irreversible changes.

Irreversible injury

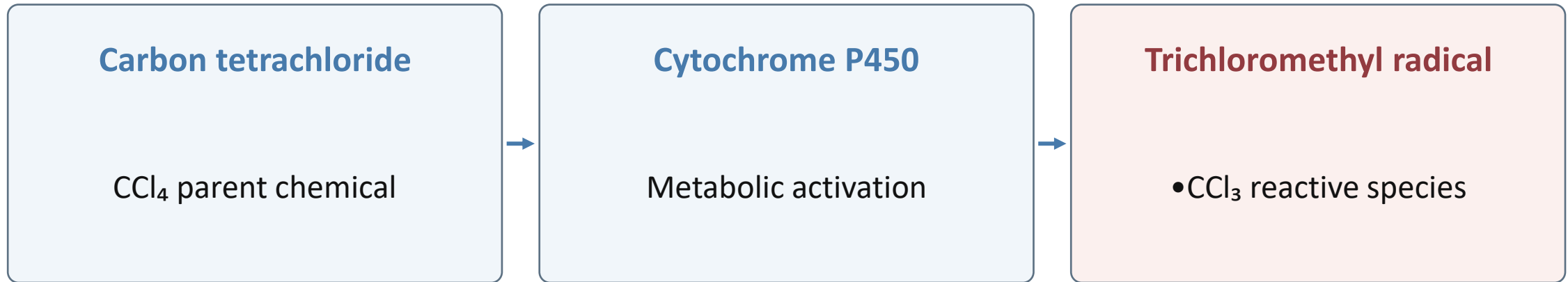
- Membrane and mitochondrial damage progresses.
- Necrosis may follow severe or sustained insult.
- Cell death is not a synonym for every toxic exposure.

Do not diagnose necrosis from exposure alone.

Carbon tetrachloride exemplifies metabolic activation

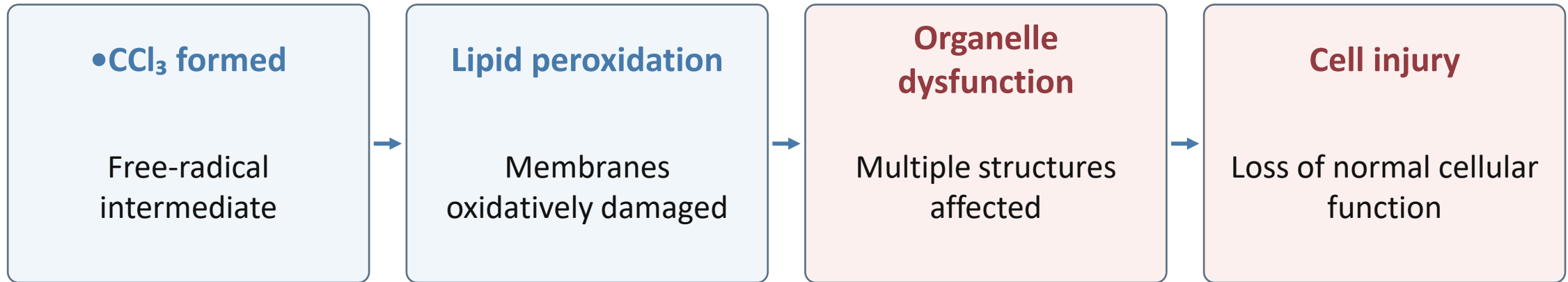
- CCl_4 was formerly used in the dry-cleaning industry.
- Its important toxic product is generated through CYP metabolism.
- The reactive product is the trichloromethyl radical ($\bullet\text{CCl}_3$).
- The radical causes lipid peroxidation and cell injury.

Carbon tetrachloride: The activating reaction



The product of biotransformation, rather than CCl₄ alone, drives the classic injury pathway.

Carbon tetrachloride: Injury cascade



This example links xenobiotic metabolism directly to radical-mediated membrane damage.

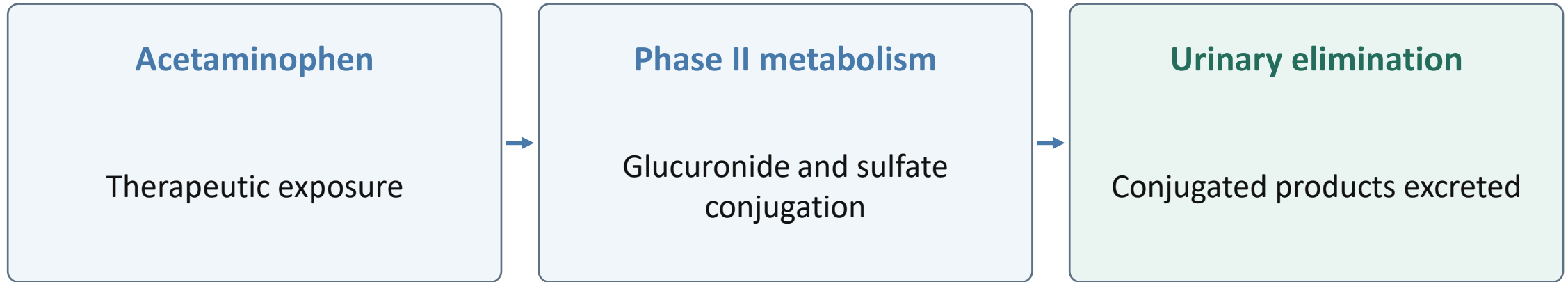
Carbon tetrachloride: Interpretive checkpoints

Observation	Mechanistic interpretation
Parent compound present	Exposure has occurred; exposure alone does not specify severity
CYP activity in target cells	Reactive metabolite can be generated
Trichloromethyl radical detected conceptually	Radical initiates oxidative injury
Membrane lipid peroxidation	Functional and structural membrane damage

Acetaminophen illustrates a dose-sensitive metabolic balance

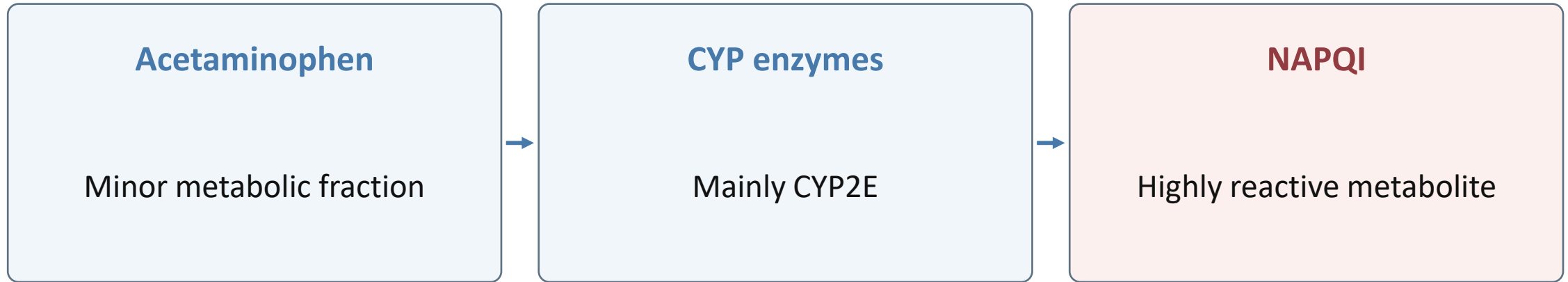
- At usual doses, most acetaminophen undergoes conjugation.
- A smaller fraction is bioactivated to a reactive product.
- Glutathione normally neutralizes that product.
- Excess exposure can overwhelm this protective pathway.

Most acetaminophen is safely conjugated



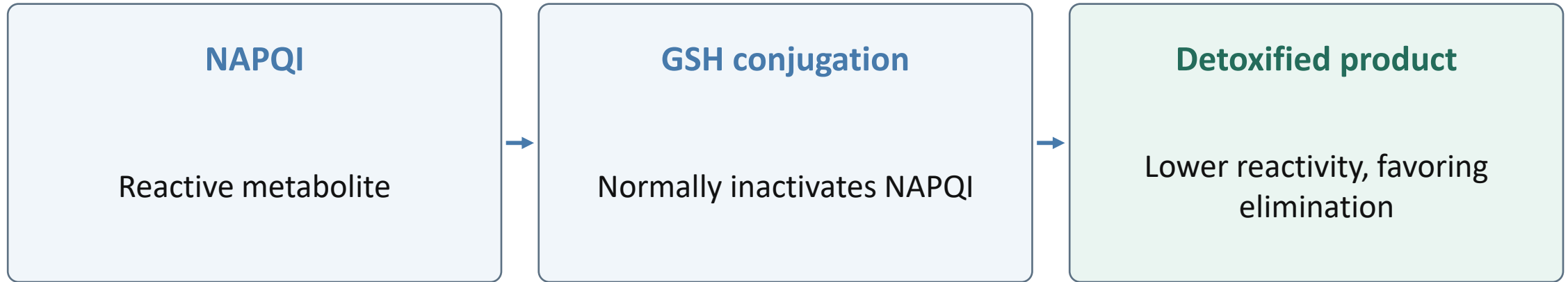
Conjugation is the main metabolic route under usual conditions.

A minority of acetaminophen forms NAPQI



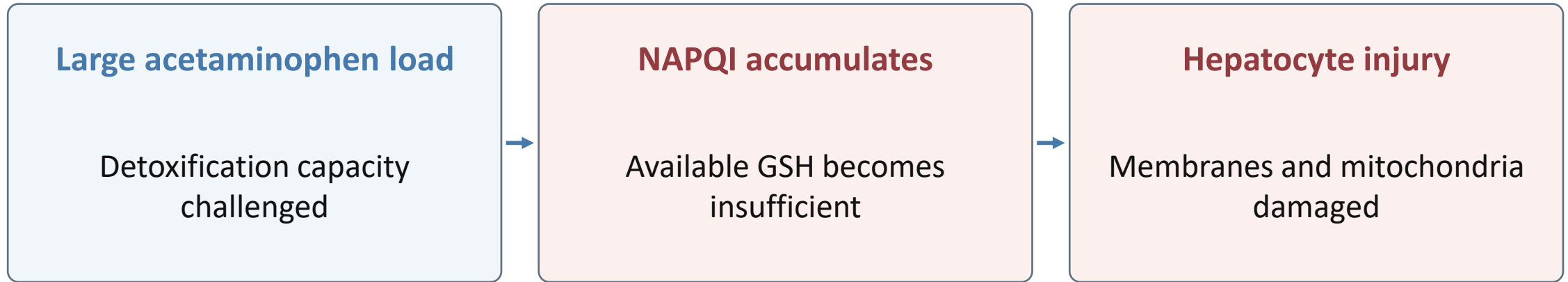
NAPQI = N-acetyl-p-benzoquinoneimine.

Glutathione normally neutralizes NAPQI



The protective pathway is dependent on available glutathione.

Excess acetaminophen shifts metabolism toward injury



Overdose toxicity reflects imbalance between reactive metabolite formation and detoxification.

NAPQI causes injury through two reinforcing pathways

Protein adduct formation

- Reactive NAPQI binds covalently to hepatic proteins.
- Membrane and mitochondrial functions are disrupted.
- This is a direct effect of the metabolite.

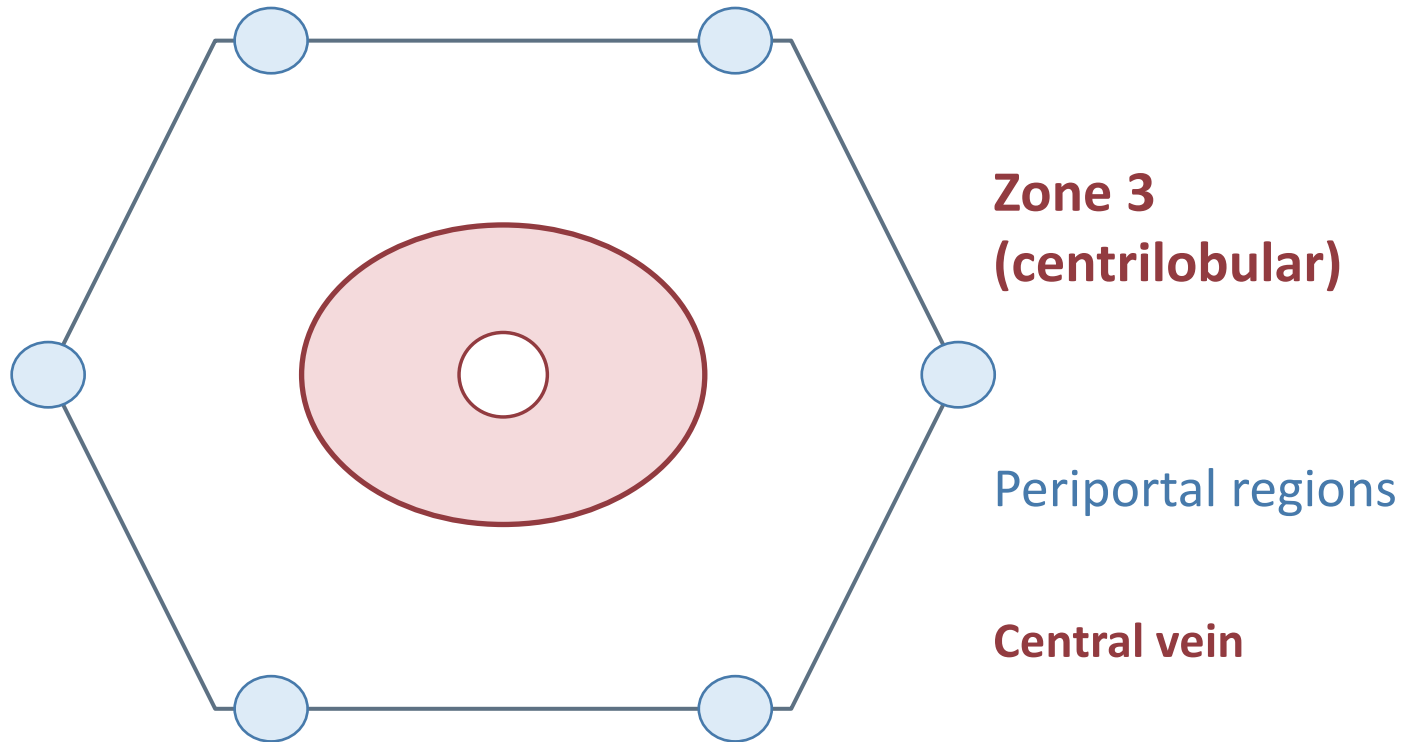
Glutathione depletion

- Consumption of GSH reduces antioxidant defense.
- Hepatocytes become susceptible to ROS.
- Oxidative damage magnifies the primary injury.

Both mechanisms contribute to hepatocellular damage.

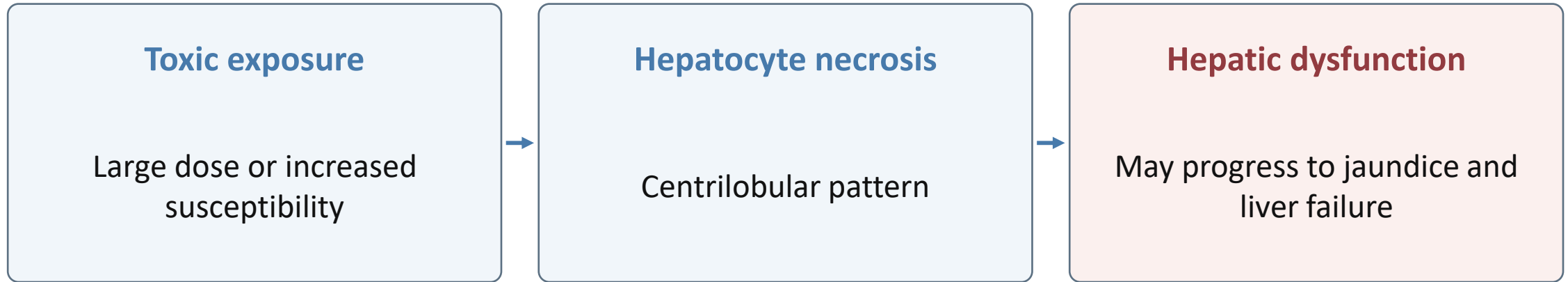
Acetaminophen toxicity: Centrilobular hepatic necrosis

Centrilobular necrosis means injury near the central vein.



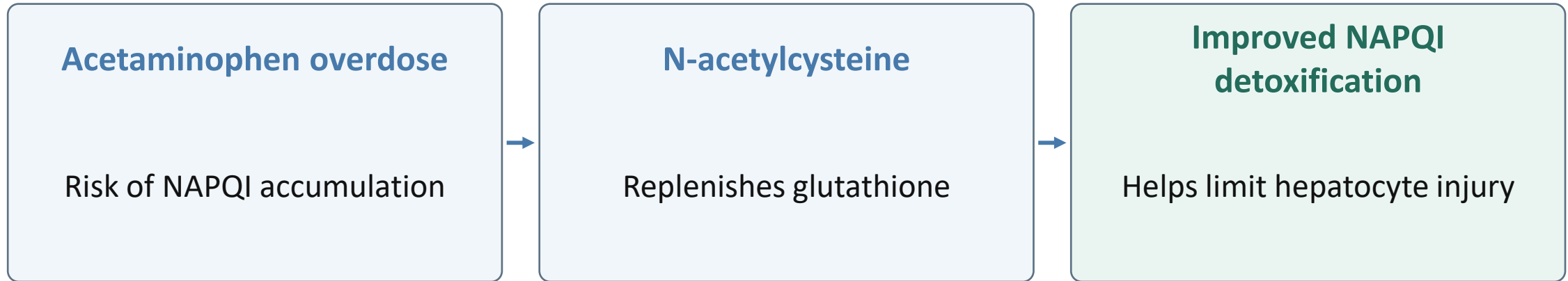
Schematic only: Not histology, not drawn to anatomical scale.

Acetaminophen poisoning: Clinicopathologic sequence



The morphologic pattern is a consequence of the biochemical toxicant pathway.

N-acetylcysteine acts on the toxic mechanism



Early treatment; This is mechanistic teaching, not a treatment protocol.

Acetaminophen toxicity may extend beyond hepatocytes

- Liver injury is the dominant clinicopathologic concern.
- Some poisoned patients also have concurrent kidney injury.
- The extent of tissue damage depends on exposure and defense mechanisms.
- Molecular pathway and injured organ must both be considered.

Carbon tetrachloride versus acetaminophen

Feature	Carbon tetrachloride	Acetaminophen
Parent compound	Industrial chemical	Analgesic drug
Toxic product	Trichloromethyl radical ($\bullet\text{CCl}_3$)	NAPQI
Key activation pathway	CYP-dependent radical formation	Minor CYP-dependent pathway
Primary emphasis	Lipid peroxidation	Protein adducts + GSH depletion
Organ relevance	Liver metabolic activation	Centrilobular hepatocellular necrosis

Toxic mechanism predicts the initial cellular defect

Initial insult	Immediate molecular defect	Downstream injury
Mercury	Protein sulfhydryl group binding	Membrane permeability / ion transport
Cyanide	Cytochrome oxidase blockade	ATP depletion
CCl ₄ metabolite	Free-radical formation	Lipid peroxidation
Acetaminophen metabolite	Protein adducts; depleted GSH	Mitochondrial and oxidant injury

Structural patterns are downstream of molecular injury

Potentially reversible changes

- ATP reduction may disturb ion transport.
- Intracellular sodium and water can accumulate.
- Swelling reflects impaired cell homeostasis.

Necrotic injury

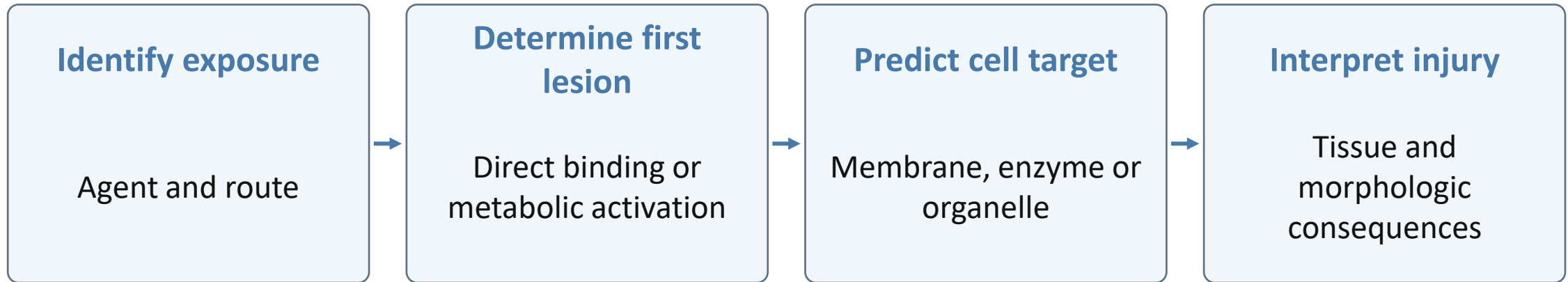
- Severe injury disrupts membranes and organelles.
- Loss of cell integrity reflects irreversibility.
- Acetaminophen can produce centrilobular necrosis.

The microscopic endpoint depends on insult severity and duration.

What a schematic cannot establish

- A mechanism diagram demonstrates an established causal sequence.
- It does not show actual histologic tissue damage in a patient.
- A specific morphologic diagnosis requires genuine microscopic evidence.
- The centrilobular drawing in this lecture is an anatomical teaching aid.

A practical toxic-injury reasoning framework



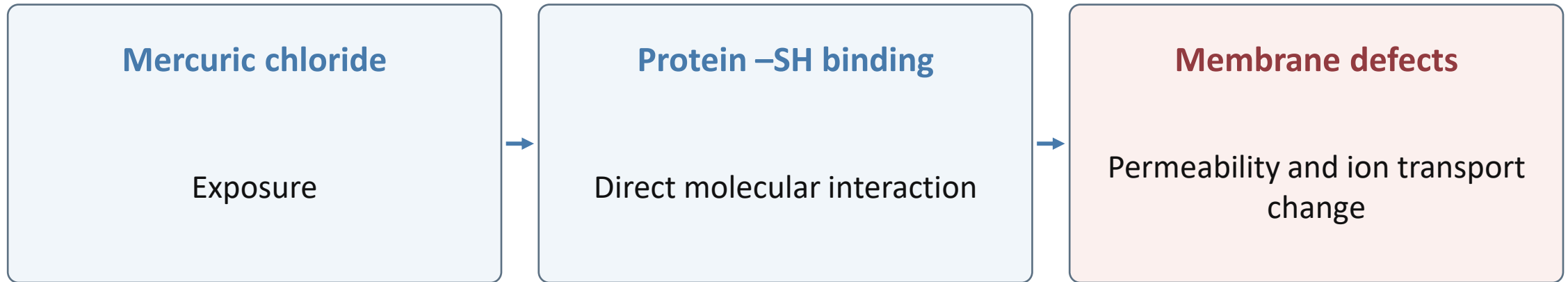
Follow the causal chain before memorizing the named toxin.

Case application: Mercury

A patient is exposed to mercuric chloride. Toxic injury develops in gastrointestinal and renal tissues. The mechanism includes impaired ion transport and increased membrane permeability.

Which cellular target explains these effects?

Mercury case: Causal explanation



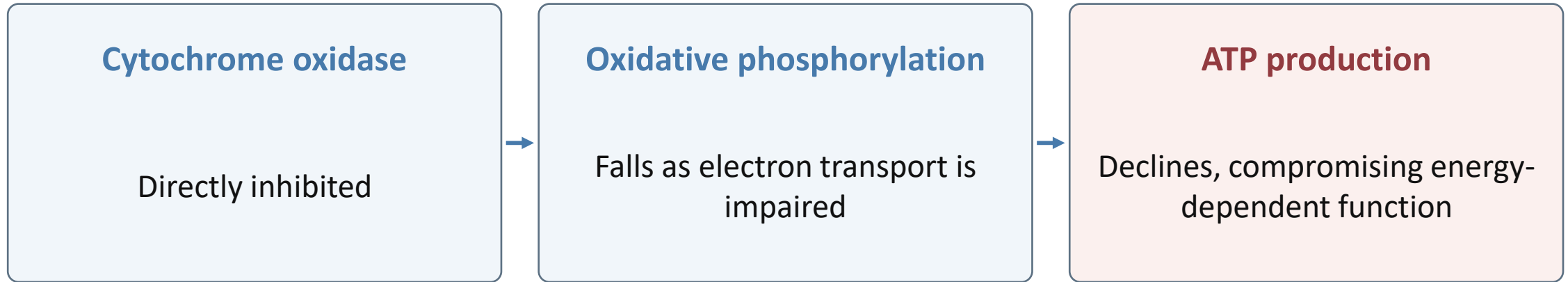
The primary mechanism is direct toxicity, not obligatory CYP bioactivation.

Case application: Cyanide

A toxic exposure rapidly interferes with mitochondrial oxidative phosphorylation. The affected process is downstream of direct inhibition of cytochrome oxidase.

Why does a respiratory enzyme lesion compromise the whole cell?

Cyanide case: Causal explanation



The central lesion is loss of bioenergetic capacity.

Case application: Acetaminophen

After an excessive acetaminophen exposure, a patient develops hepatic injury. The toxic product is generated by CYP-mediated metabolism, and glutathione buffering becomes insufficient.

Identify the reactive metabolite and its two key injury mechanisms.

Acetaminophen case: Causal explanation

Toxic metabolite

- The toxic intermediate is NAPQI.
- Formed through a minor CYP pathway.
- Accumulates when detoxification is exceeded.

Cellular mechanisms

- Covalent protein binding injures cell structures.
- GSH depletion increases vulnerability to ROS.
- Centrilobular necrosis can ensue.

This is metabolic activation with failure of a protective conjugation pathway.

Four toxins: A single mechanistic comparison

Toxicant	Direct target / active product	Dominant pathology mechanism
Mercuric chloride	Protein sulfhydryl groups	Membrane dysfunction
Cyanide	Cytochrome oxidase	Energy failure
Carbon tetrachloride	Trichloromethyl radical	Lipid peroxidation
Acetaminophen	NAPQI	Protein binding and GSH depletion

Five principles that organize toxic injury

- Identify whether the parent compound or a metabolite causes injury.
- Locate the affected molecular target before predicting morphology.
- Recognize that CYP enzymes can detoxify or bioactivate chemicals.
- Balance reactive-product formation against glutathione and clearance.
- Connect the cellular defect to tissue susceptibility and cell death.

Core reading and source limits

- Robbins, Cotran & Kumar: Pathologic Basis of Disease — Chemical (Toxic) Injury.
- The same textbook: Environmental and Nutritional Diseases — toxicant metabolism.
- The same textbook: acetaminophen metabolism and hepatotoxicity.
- Mechanistic drawings are original schematics; no textbook micrographs are reproduced.