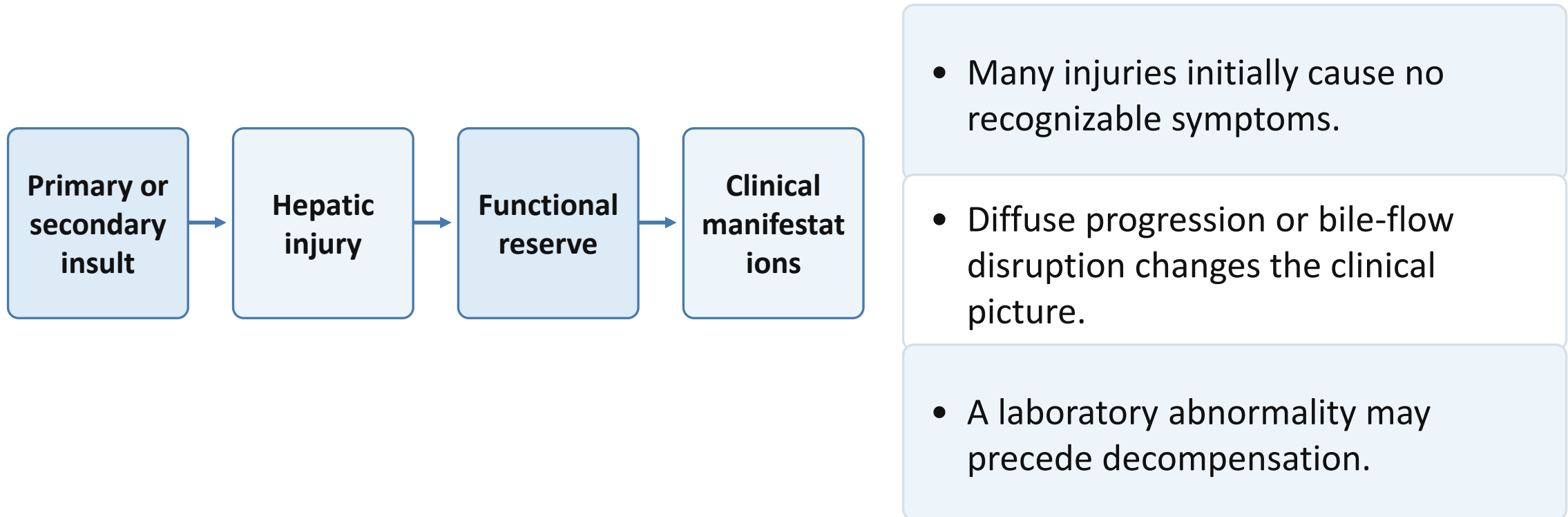


The liver: a large reserve organ

Hepatic disease may remain clinically occult until substantial functional disruption develops.



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Learning objectives

Organize liver disease from anatomy and exposure to functional expression.

Architecture

Portal tracts, central veins
and sinusoidal exchange

Etiology

Primary and secondary
categories of hepatic injury

- Locate the principal structures of a hepatic lobule.

- Distinguish the broad etiologic categories of liver injury.

Course

Functional reserve, silent
injury and decompensation

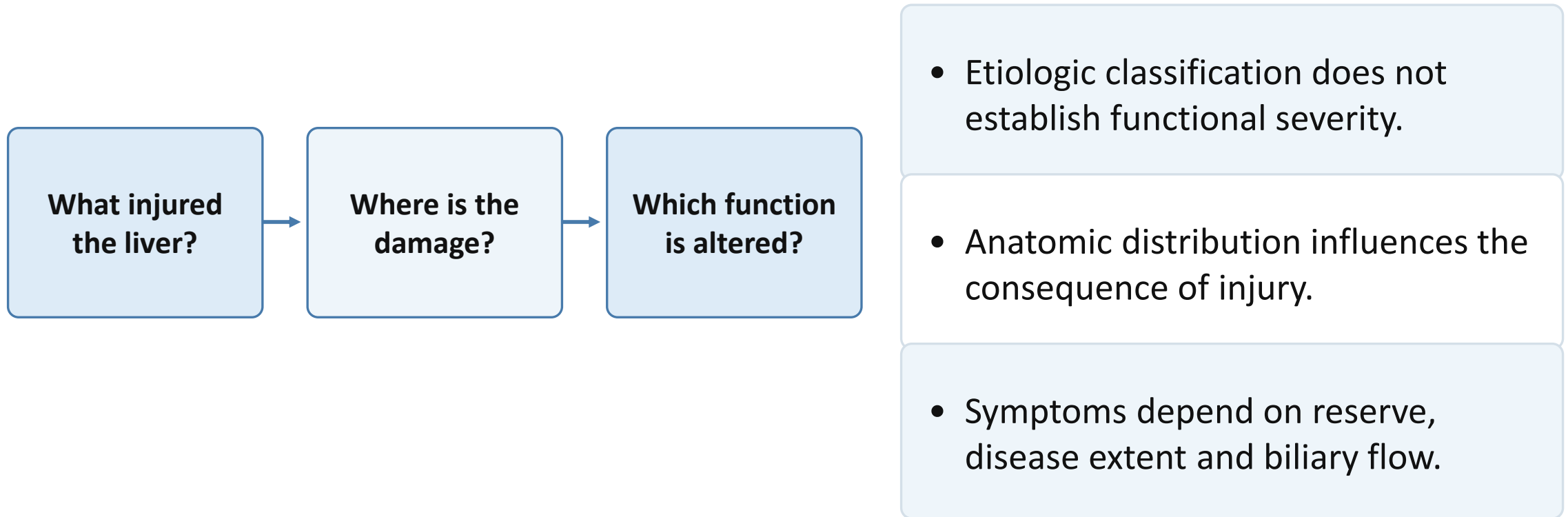
Evaluation

Integrity, excretory, synthetic
and metabolic tests

- Classify commonly measured liver laboratory tests.

Liver pathology: Three linked questions

A structural lesion, impaired physiology and the clinical syndrome need not appear simultaneously.



Normal adult liver: Anatomical baseline

The source describes a normal adult liver mass of approximately 1400–1600 g.

Mass

Normal adult liver: 1400–
1600 g

Organization

Portal inflow → sinusoids
→ hepatic venous
drainage

- An organ-level change must be interpreted against its normal architecture.
- Parenchymal cells and biliary channels form linked but distinct networks.
- Vascular supply and outflow help explain injury distribution.

Dual blood supply

The hepatic circulation combines portal venous and arterial inflow.

Portal vein

Accounts for 60%–70% of hepatic blood flow

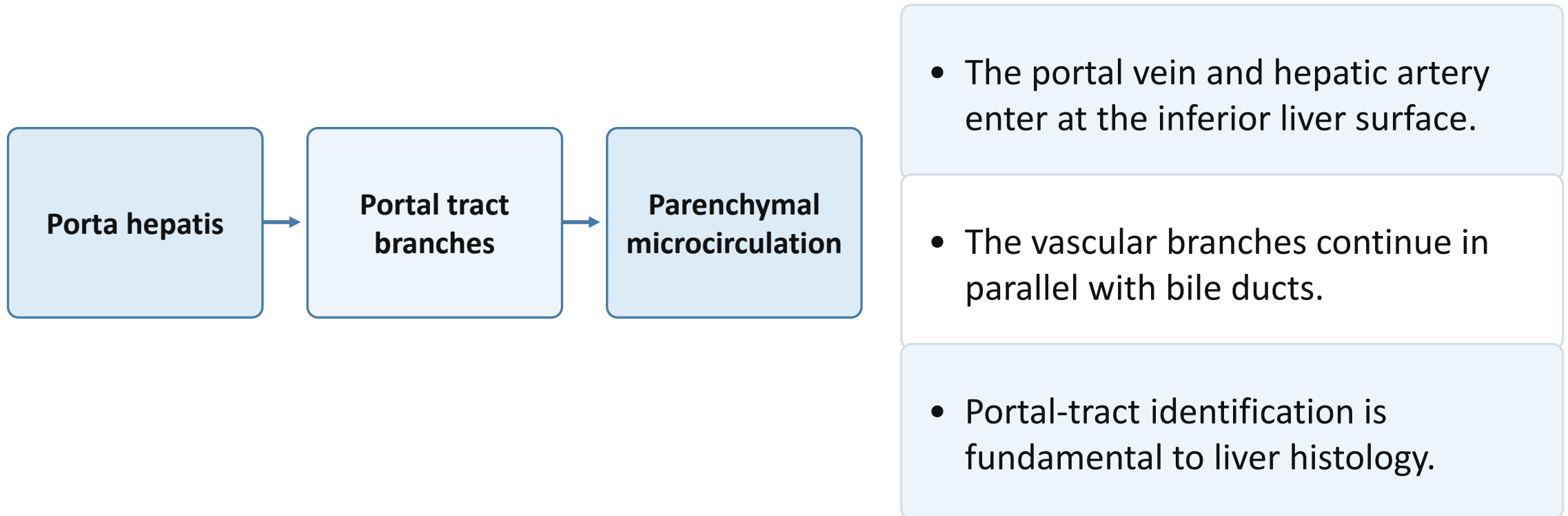
Hepatic artery

Accounts for the remaining 30%–40%

- The two inflows mix in the hepatic sinusoids.
- Both vessels reach the liver through the porta hepatis.
- A gradient of oxygen availability is established across the acinus.

The porta hepatis is a shared gateway

Portal veins, hepatic arteries and bile ducts travel together within portal tracts.



Identify the portal tract

Three structures define the major portal-tract components.

Portal vein branch

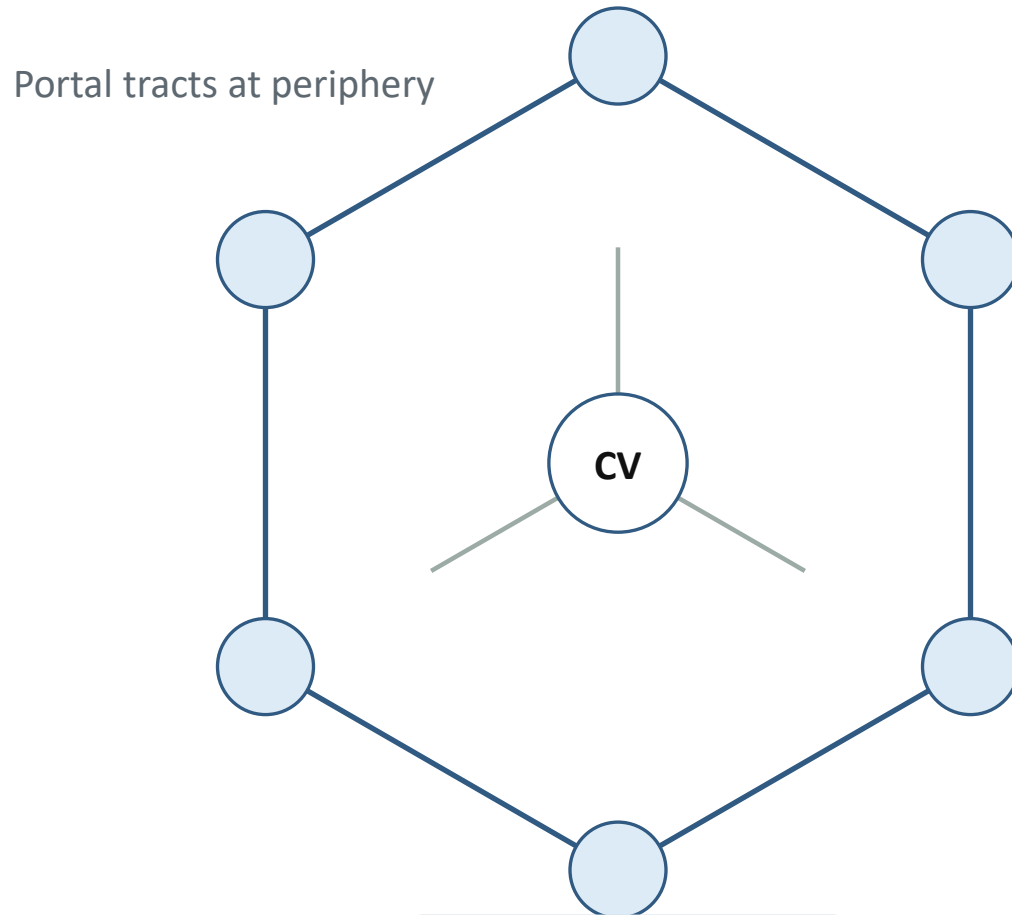
Hepatic artery branch

Interlobular bile duct

- Portal venous and hepatic arterial branches supply blood.
- The interlobular bile duct belongs to the biliary drainage system.
- These structures appear together at the lobular periphery.

The classical hepatic lobule

A hexagonal organizational model centers on a terminal hepatic vein.

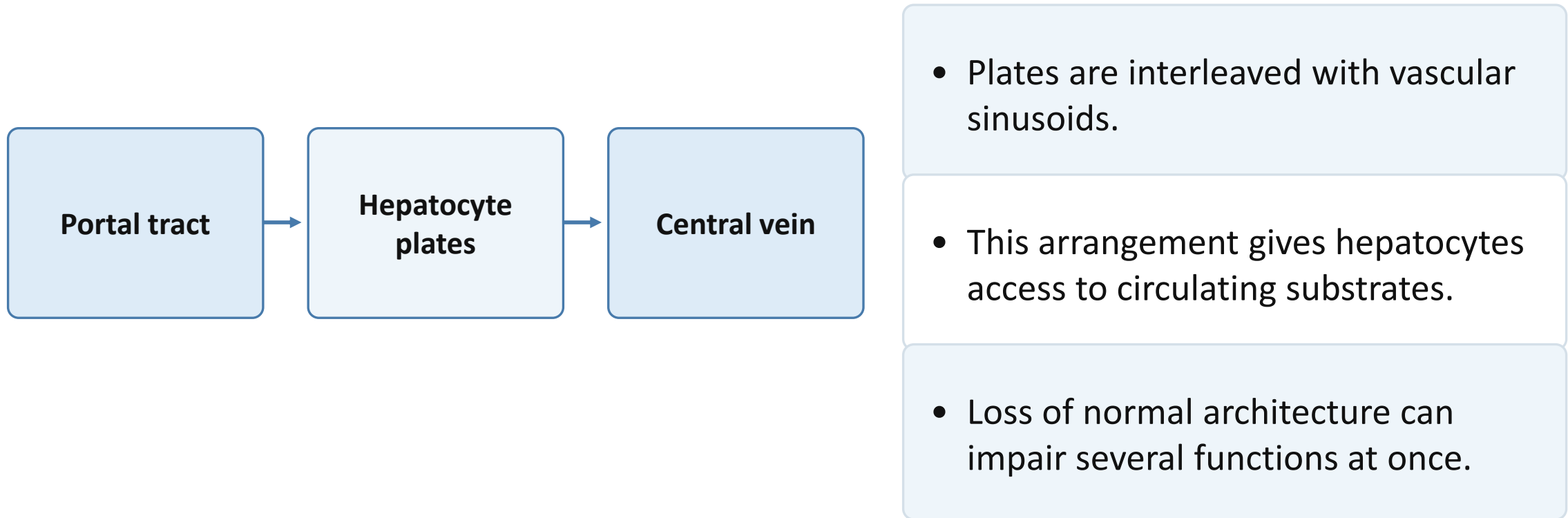


Schematic: Classic lobule

- The textbook lobular model spans approximately 1–2 mm.
- Central veins occupy the center of the lobular model.
- Portal tracts mark the peripheral vertices.

Hepatocyte plates form a connected mesh

Liver cells are organized in anastomosing sheets that span portal and central regions.



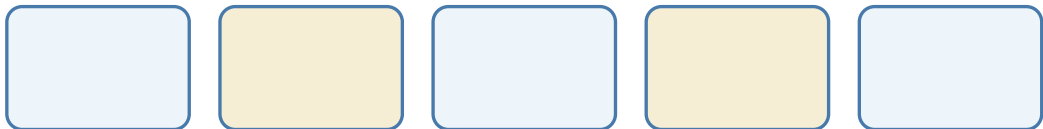
Sinusoids are vascular conduits

Blood passes between hepatocyte plates toward terminal hepatic veins.

Fenestrated endothelium

SINUSOID → blood toward central vein

Space of Disse



Hepatocyte plates

- Sinusoidal blood contains a mixture of portal and arterial inflow.
- Sinusoidal endothelial cells are fenestrated.
- The fenestrated lining facilitates communication with hepatocytes.

Two-sided exposure of hepatocytes

Anastomosing plates allow hepatocytes to interface with sinusoidal blood on two sides.

Sinusoidal face

Access to mixed portal and arterial blood

Canalicular face

Secretion into a separate bile pathway

- Vascular exchange and bile secretion are functionally distinct.
- The same cell participates in both systems.
- Hepatocellular damage may affect either or both functions.

Fenestrated sinusoidal endothelium

The sinusoidal lining separates blood from the space of Disse.

Blood in sinusoid

Fenestrated endothelium

Space of Disse

Hepatocyte microvilli

- The endothelium is not a conventional continuous barrier.
- The subendothelial compartment is the space of Disse.
- Hepatocyte microvilli extend into this exchange compartment.

Space of Disse: An exchange interface

The perisinusoidal compartment lies between hepatocytes and endothelial cells.

Blood in sinusoid

Fenestrated endothelium

Space of Disse

Hepatocyte microvilli

- Hepatocyte microvilli project into this space.
- Lipid-containing stellate cells are present here.
- Its location places stellate cells near injured hepatocytes.

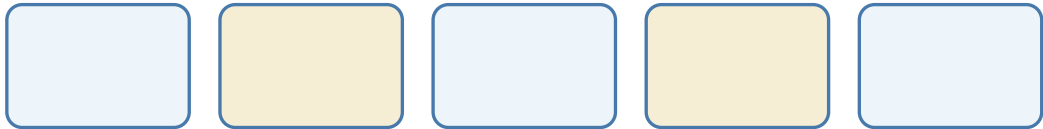
Kupffer cells: Sinusoidal macrophages

Resident macrophages occupy the luminal face of sinusoidal endothelial cells.

Fenestrated endothelium

SINUSOID → blood toward central vein

Space of Disse



Hepatocyte plates

- Kupffer cells are anatomically positioned to sample circulating material.
- Injury-associated debris is cleared by hepatic macrophages.
- Immune and parenchymal responses can occur in close proximity.

Stellate cells: Normal storage role

Quiescent hepatic stellate cells store lipids, including vitamin A.

Baseline

Lipid-containing stellate cells in the space of Disse

With injury

Can acquire fibrogenic myofibroblast features

- Stellate cells occupy the perisinusoidal space.
- Their altered state contributes to fibrosis during sustained injury.
- Persistent injury can redirect stellate cells toward collagen deposition.

Normal hepatic immune residents

Lymphocytes are present even in the uninjured liver.

$\gamma\delta$ T cells

Prominent
resident
lymphocyte
population

NK cells

Contribute to the
local lymphoid
compartment

Distribution

Near biliary tracts
and within
sinusoids

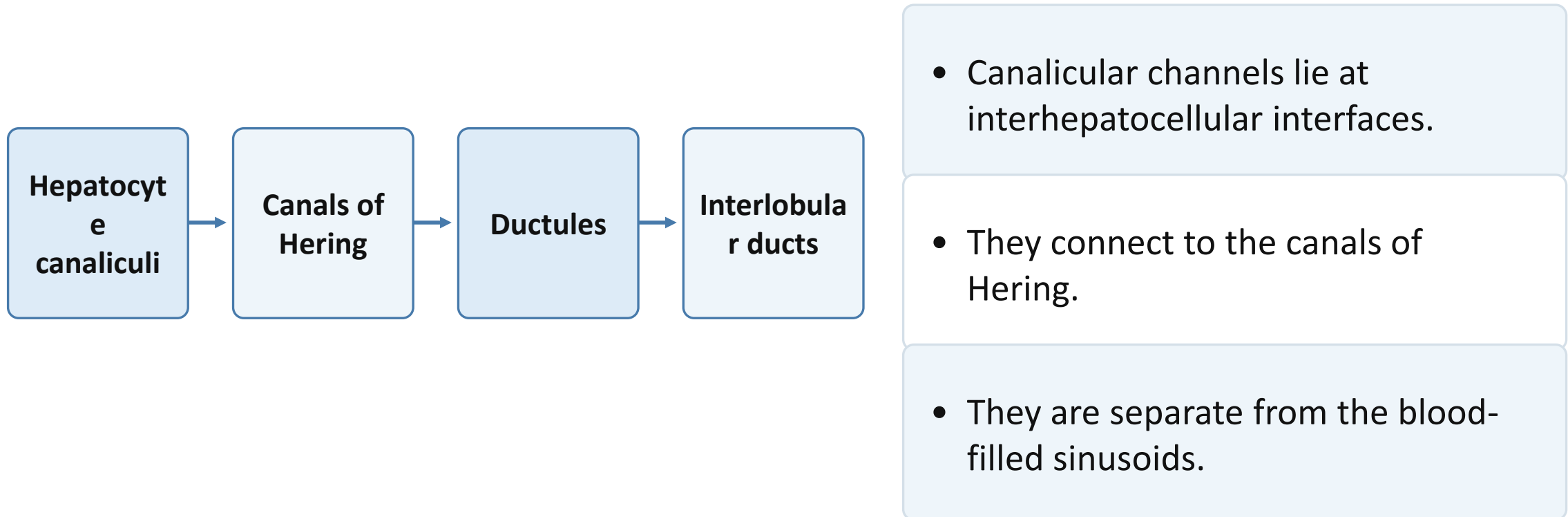
- $\gamma\delta$ T cells and natural killer cells occur in normal hepatic tissue.

- Their presence alone does not establish hepatitis.

- Interpret inflammatory changes in anatomical context.

Bile canaliculi: A distinct network

Canaliculi form between adjacent hepatocytes.



Tight junctions separate vascular and bile compartments

The canalicular lumen must remain segregated from the sinusoidal exchange space.

Sinusoidal compartment

Blood and exchanged
solutes near the
hepatocyte

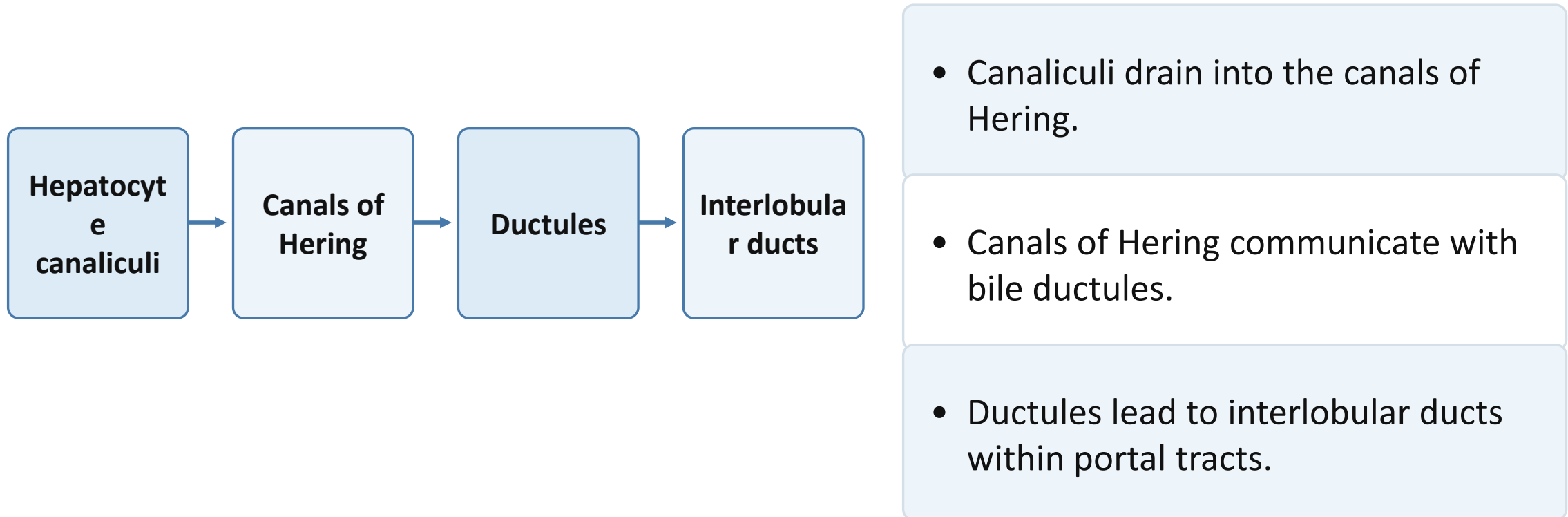
Canalicular compartment

Bile secretion between
neighboring hepatocytes

- Adjacent hepatocyte membranes form the canalicular lumen.
- Tight junctions maintain compartmental separation.
- Disruption of secretion or flow contributes to cholestatic dysfunction.

Bile follows a branching drainage route

Canaliculi feed progressively larger biliary channels.



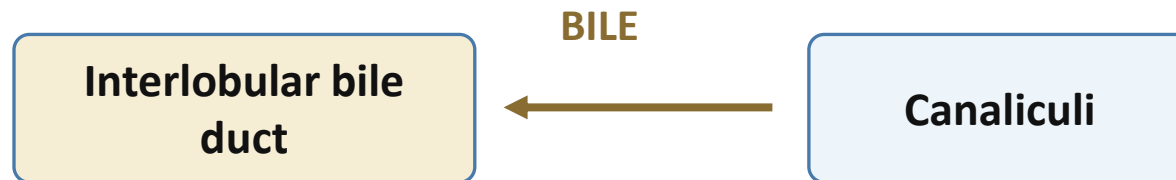
Blood flow versus bile flow

The vascular and bile circuits run in opposite functional directions.



- Blood travels from portal-tract inflow to central-vein outflow.

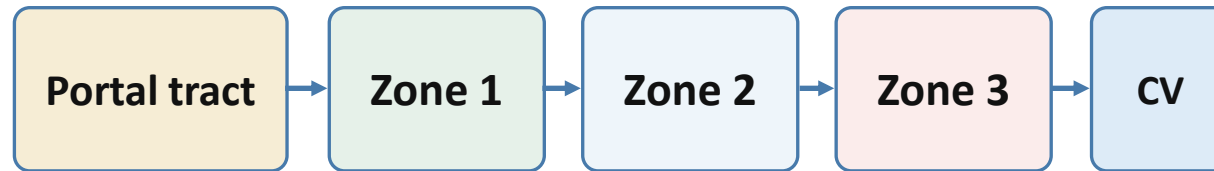
- Bile is collected toward ducts in portal tracts.



- This opposition is essential when localizing dysfunction.

The hepatic acinus models perfusion

Acinar zones are defined relative to the incoming blood supply.



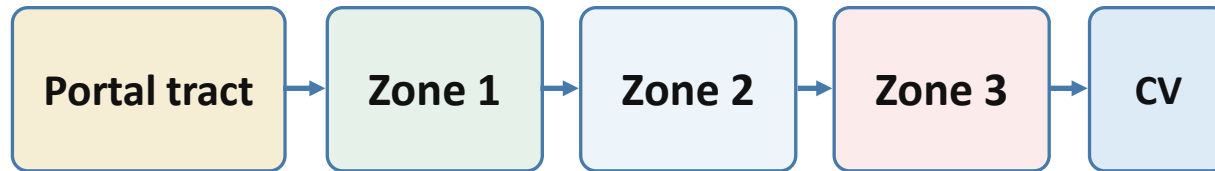
Blood flow →

- Zone 1 lies nearest the portal-tract inflow.
- Zone 3 lies closest to the central vein.
- Zone 2 represents an intervening region.

Schematic: Portal-to-central gradient

Acinar zone 1: Periportal

Zone 1 has the highest oxygenation in the hepatic acinus.



Blood flow →

- It receives blood before downstream pericentral regions.

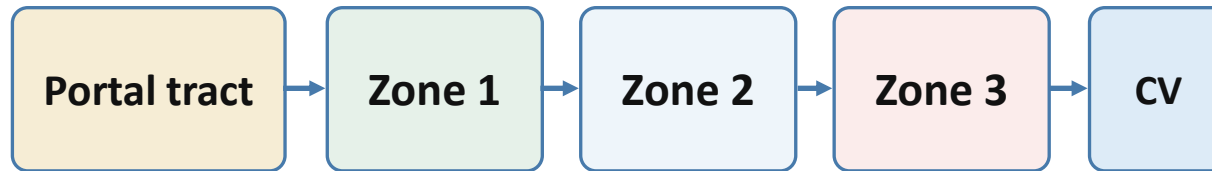
- Relative oxygen delivery contributes to zonal physiological differences.

- Zonal terminology should be linked to a visible landmark.

Schematic: Portal-to-central gradient

Acinar zone 3: Pericentral

Zone 3 is the region farthest from the portal inflow.



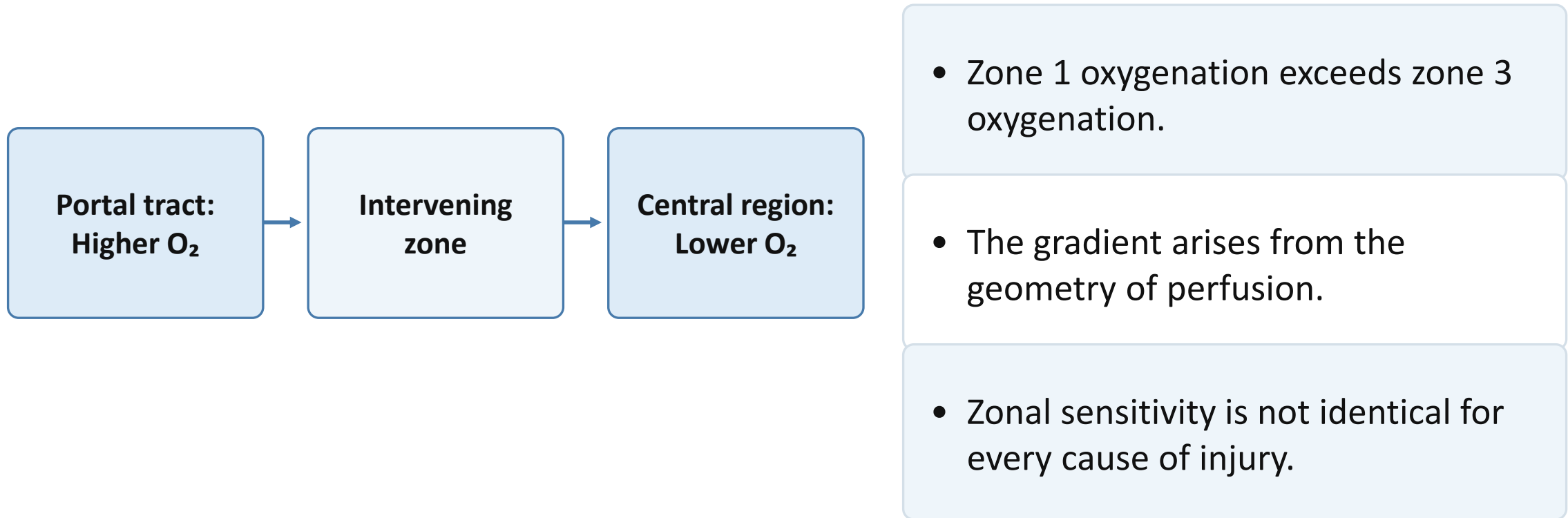
Blood flow →

- It has the lowest oxygenation of the three zones.
- Its location influences vulnerability in certain injuries.
- In the classical lobule, it lies around the central vein.

Schematic: Portal-to-central gradient

An oxygen gradient exists across the acinus

Blood traverses zones with progressively different oxygen availability.



Metabolic heterogeneity influences susceptibility

Hepatocytes are not metabolically identical from the periphery to the lobular center.

Oxygen availability

Varies from portal to central regions

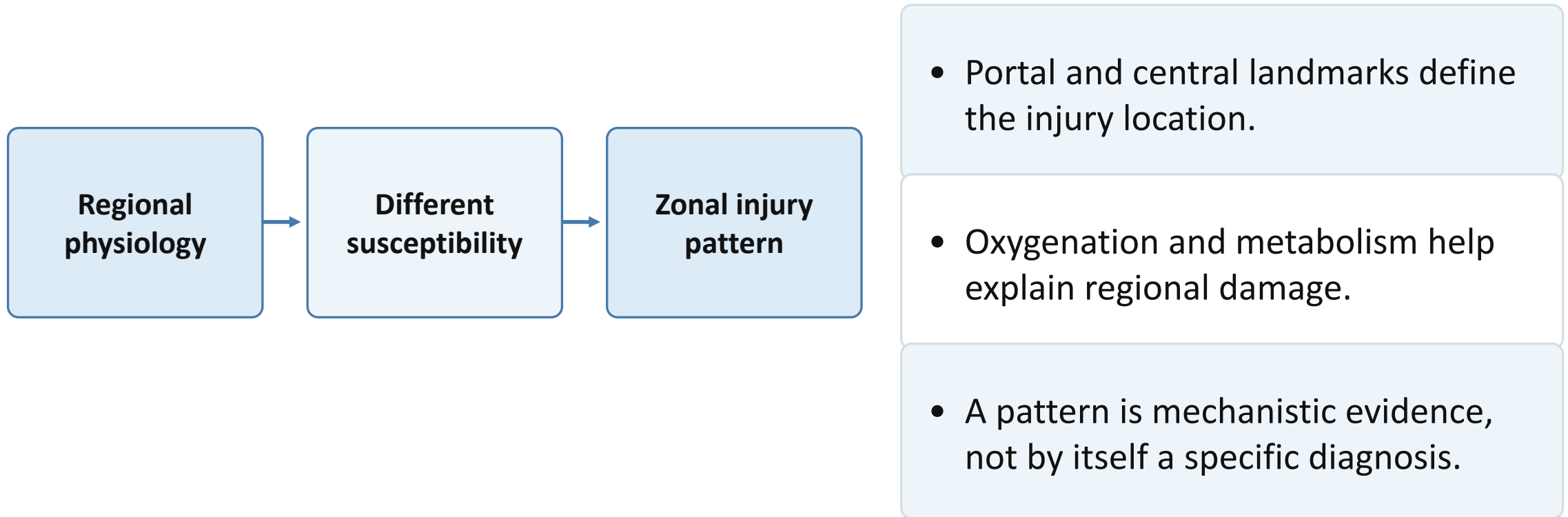
Metabolic activity

Also differs across the lobular axis

- Blood supply is one determinant of tissue vulnerability.
- Cellular metabolic specialization provides another determinant.
- Pattern recognition can point to a category of injury.

Why injury distribution matters

The same organ can show preferential damage in different anatomical zones.



Primary hepatic disease: Five broad classes

Robbins groups primary liver disorders by the nature of the initiating insult.

Metabolic

Altered cellular
metabolic
processes

Toxic

Chemical or drug-
associated
exposure

Microbial

Infectious insult

Circulatory

Perfusion or
vascular
disturbance

Neoplastic

Abnormal
proliferative
disease

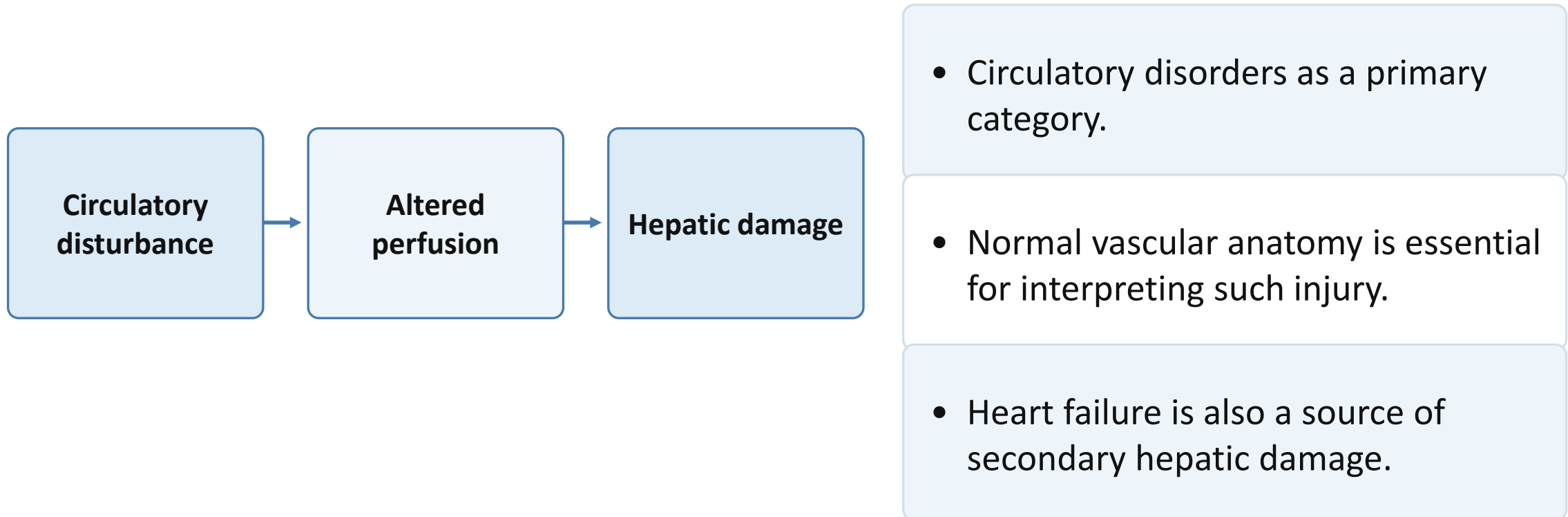
Interactions

More than one
pathway may be
present

- Etiologic classification is the starting point for diagnosis.
- Clinical severity is not predicted simply by the category name.
- Primary and secondary injuries belong to different causal categories.

Circulatory liver injury

Hepatic function depends on an intact inflow–sinusoid–outflow circuit.



Neoplastic involvement of the liver

Neoplasia may cause primary hepatic disease or represent spread from elsewhere.

Primary neoplastic disorder

Disease originates within the liver

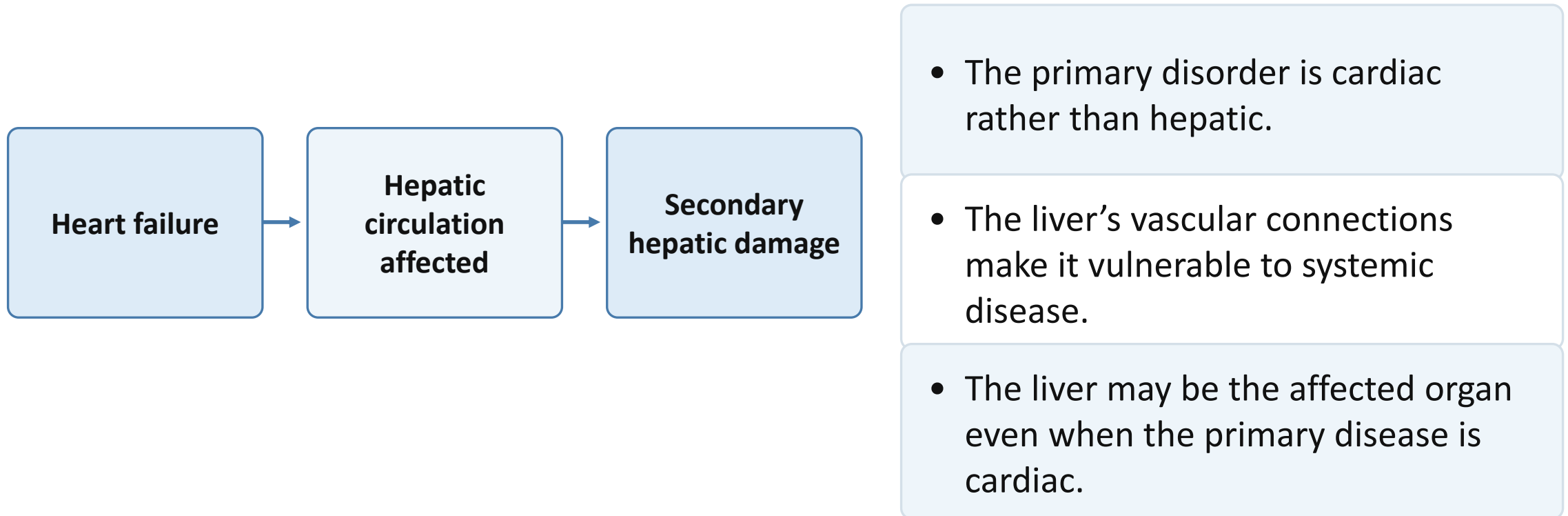
Disseminated cancer

Hepatic damage is secondary to extrahepatic malignancy

- A hepatic lesion need not be primary liver cancer.
- Both neoplasia and disseminated cancer.
- The cause must be distinguished from its site of manifestation.

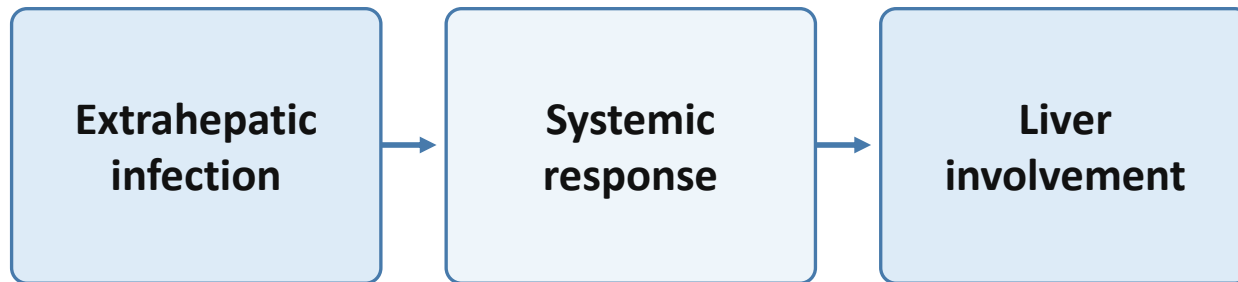
Heart failure: Systemic disease with hepatic consequences

Cardiac dysfunction is a named example of secondary liver injury.



Extrahepatic infection and hepatic dysfunction

An infection outside the liver may be accompanied by hepatic injury.



- The source lists extrahepatic infections as secondary causes.
- An abnormal liver panel does not automatically imply hepatotropic infection.
- Direct and indirect involvement must be considered separately.

Primary versus secondary: Diagnostic framing

The liver can be either the origin of disease or an affected downstream organ.

Primary

Metabolic, toxic,
microbial, circulatory or
neoplastic liver disorder

Secondary

Heart failure,
disseminated cancer or
extrahepatic infection

- Start with the systemic history, not only the liver panel.
- Separate the initiating disease from hepatic consequences.
- This distinction guides the differential diagnosis.

Common potentially reversible hepatocyte changes

The adjacent injury-response section provides the microscopic vocabulary.

Steatosis

Fat accumulation
within
hepatocytes

Cholestasis

Bile-related
pigment retention

Ballooning

Cell swelling,
clearing and
filament clumping

- These changes reflect perturbed cell function.
- None of the changes alone identifies every possible etiology.
- Here they illustrate the spectrum preceding irreversible injury.

Irreversible hepatocyte injury

Severe cellular damage can culminate in necrosis or apoptosis.

Necrosis

Swelling, membrane failure and cellular rupture

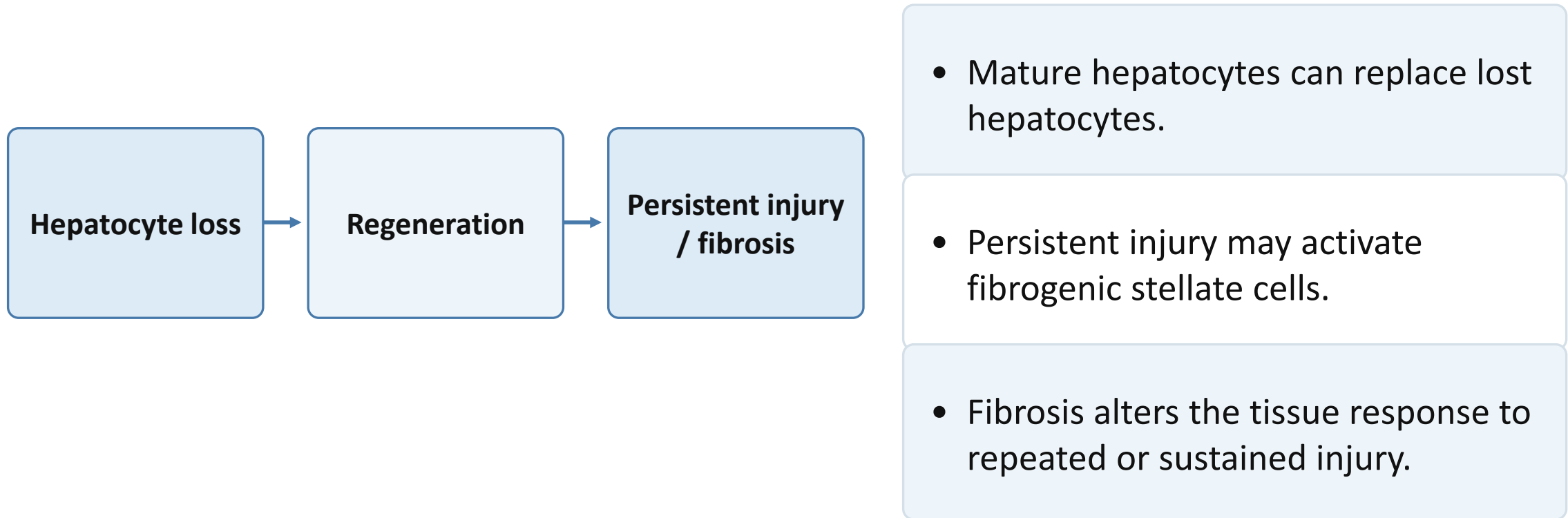
Apoptosis

Cell shrinkage and fragmentation into apoptotic bodies

- Both processes remove functioning hepatocytes.
- Membrane rupture differs from fragmentation into apoptotic bodies.
- Extent and distribution influence organ-level consequences.

Repair does not always restore architecture

Regeneration and scar formation are competing responses to sustained injury.



A normal reserve may conceal early injury

That mild hepatic damage can have little immediate clinical impact.

Mild damage: Capacity maintained



Progressive diffuse injury: Reserve consumed



Decompensation: Homeostasis impaired

- Clinical silence is compatible with ongoing tissue damage.
- Organ reserve can delay symptomatic expression.
- A lack of symptoms does not exclude liver disease.

Diffuse disease has greater functional implications

Loss of function becomes consequential when disease progresses throughout the organ.

Limited injury

Consider residual
functioning parenchyma

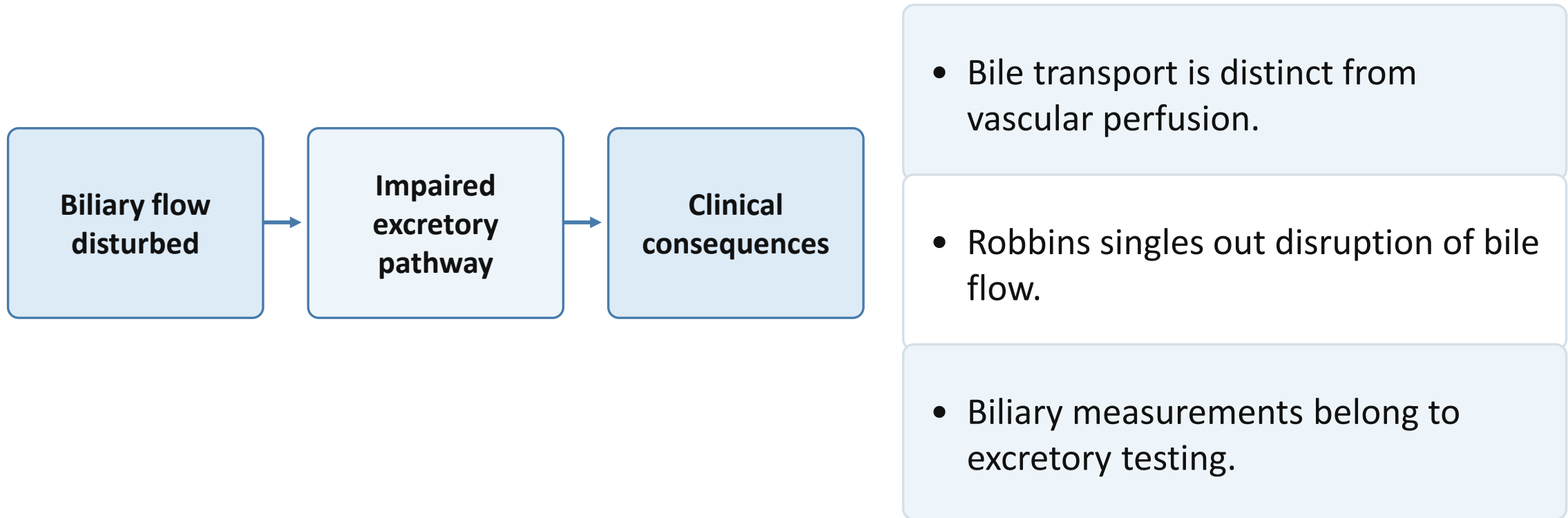
Diffuse progression

Broad loss or dysfunction
of parenchyma threatens
reserve

- The source highlights progression of diffuse disease.
- Anatomical extent and functional reserve interact.
- Apparent symptom severity may lag behind tissue injury.

Impaired bile flow is a distinct mechanism of illness

Dangerous dysfunction may occur with disruption of bile drainage, not only parenchymal loss.



Decompensation is a functional transition

The clinical threshold is failure to maintain necessary hepatic homeostasis.

Compensated: Reserve protects function



Subclinical abnormalities may accumulate

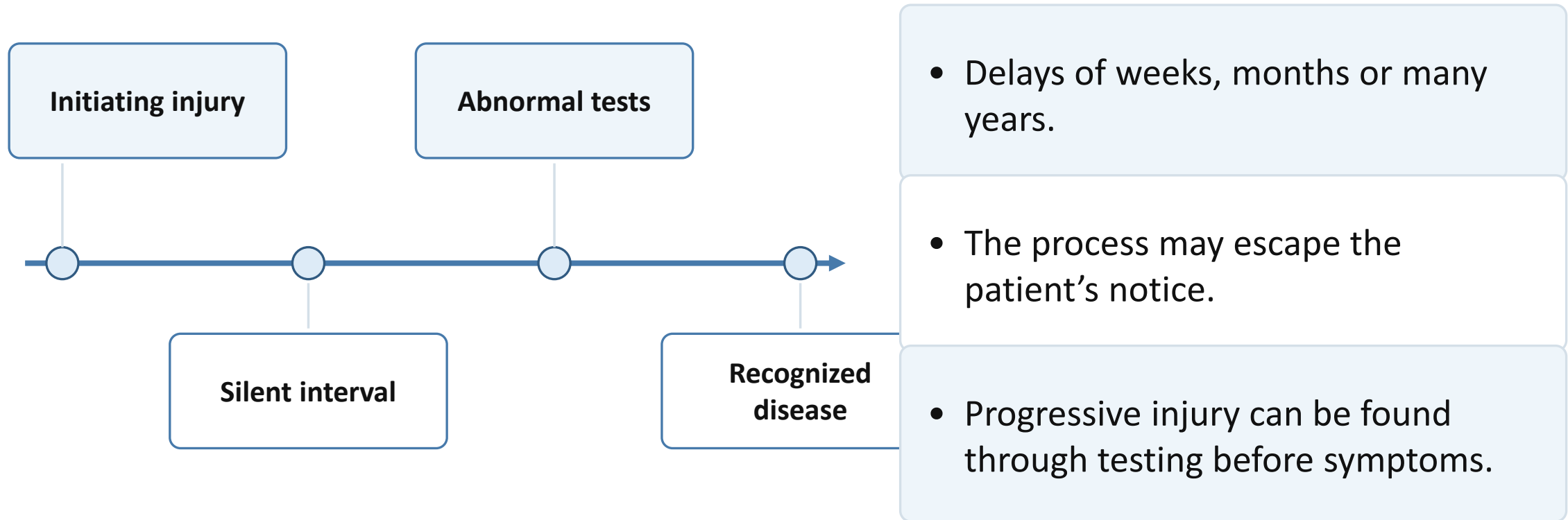


Decompensated: Dysfunction is apparent

- Decompensation is not synonymous with first liver-cell injury.
- It can emerge after a prolonged insidious process.
- The timing depends on the disease course and remaining capacity.

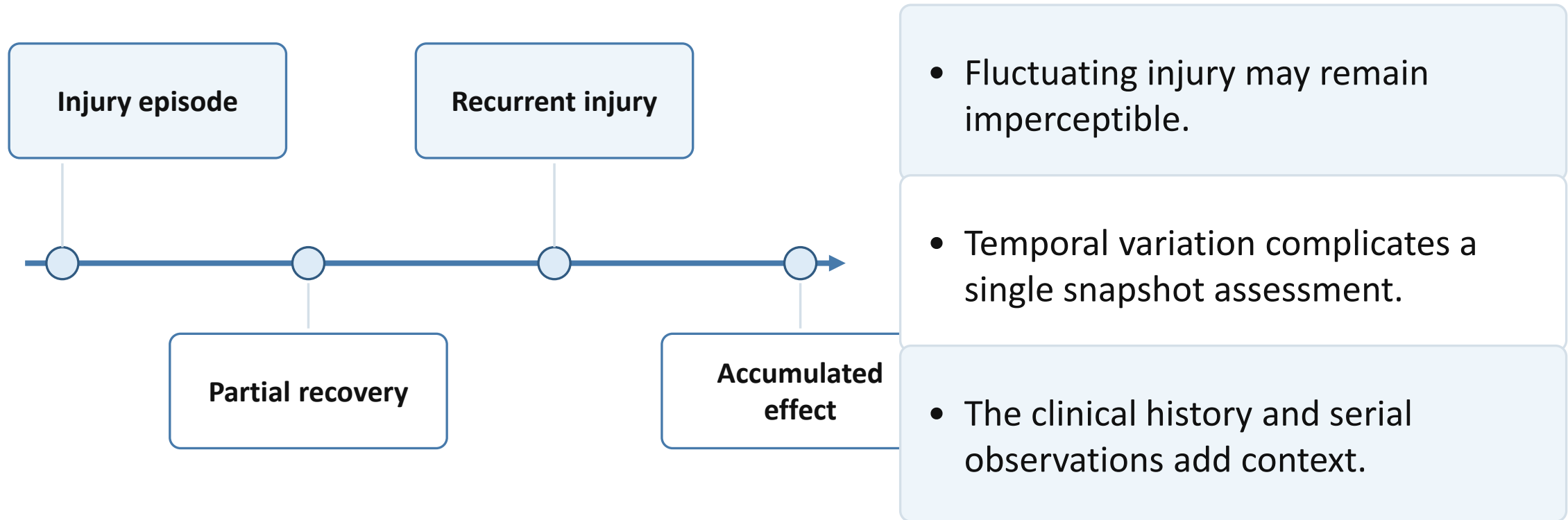
The insidious natural history of liver disease

Outside acute liver failure, symptoms can be delayed after injury begins.



Hepatic injury can ebb and flow

Clinical course need not be a monotonic decline.



Acute liver failure is the principal exception

Robbins separates acute liver failure from the usual slowly evolving presentation.

Usual disease course

Insidious progression;
Symptoms may be delayed

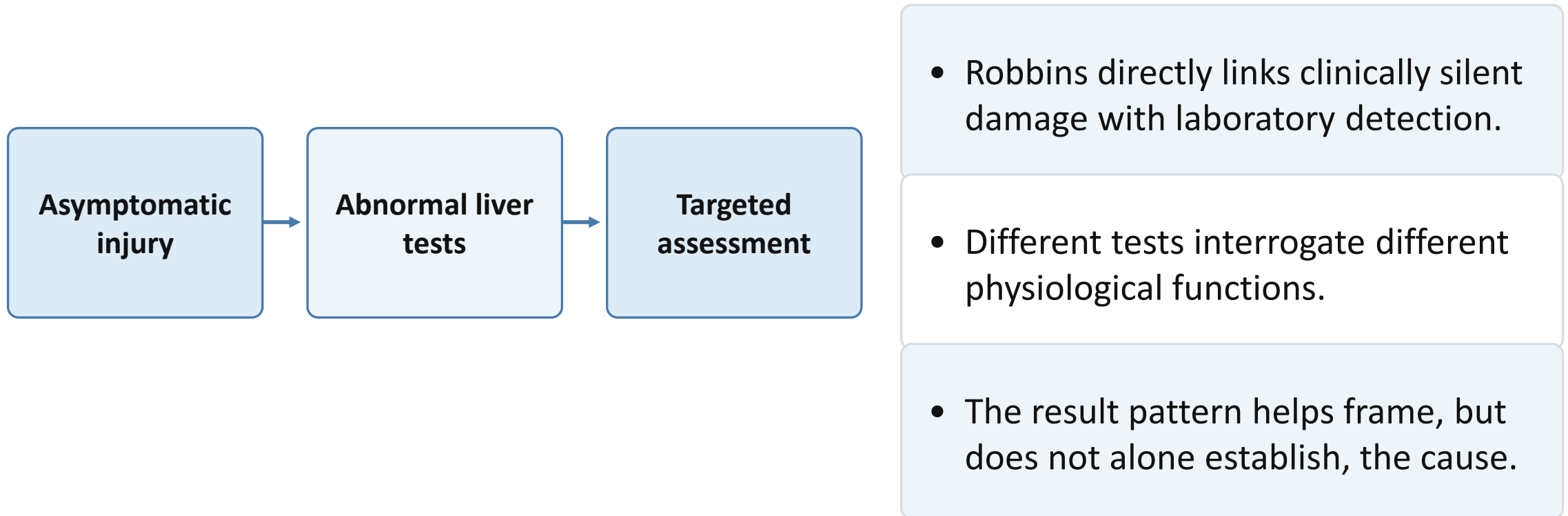
Acute liver failure

Rapid severe hepatic
dysfunction

- Acute failure involves rapid impairment of hepatic function.
- The general-features concept is delayed manifestation of many injuries.
- Rapid failure should not be assumed for all liver disorders.

Laboratory tests may identify occult disease

Abnormal biochemical tests can reveal injury before clinical decompensation.



Four laboratory evaluation domains

Table 18.1 groups tests by the function or injury they represent.

Integrity

Cytosolic enzyme leakage

Excretion

Bilirubin, bile acids and
biliary-associated enzymes

Synthesis

Albumin and coagulation-
factor measures

Metabolism

Ammonia and demethylation
function

- Test categories measure different aspects of liver disease.
- An abnormality in one domain need not imply equal impairment in another.
- A complete assessment integrates laboratory and clinical context.

Hepatocyte integrity: Cytosolic enzymes

Cell injury is reflected by increased circulating intracellular enzymes.

AST	Aspartate aminotransferase → increased
ALT	Alanine aminotransferase → increased
LDH	Lactate dehydrogenase → increased

- AST, ALT and LDH in the integrity category.
- These tests indicate hepatocellular damage.
- They do not directly quantify residual synthetic capacity.

Injury markers are not direct functional reserves

An elevated enzyme and reduced organ capacity answer different questions.

Integrity panel

Have hepatocytes released intracellular enzymes?

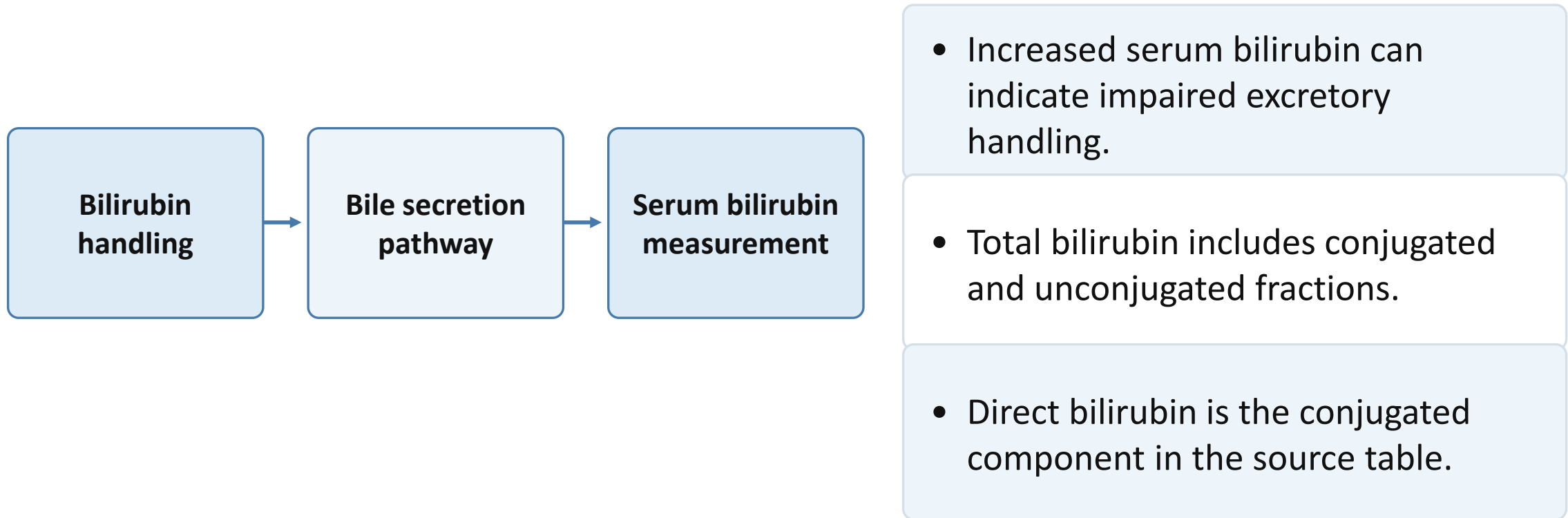
Function panel

Can the liver maintain excretion, synthesis and metabolism?

- Robbins separates injury markers from synthetic and metabolic tests.
- A cell-injury signal is not itself proof of failure.
- Interpret the categories together rather than interchangeably.

Bilirubin interrogates biliary excretion

Table 18.1 lists serum bilirubin among substances normally secreted in bile.



Total versus direct bilirubin

Total and direct bilirubin do not represent interchangeable analytes.

Total bilirubin

Conjugated +
unconjugated bilirubin

Direct bilirubin

Conjugated bilirubin as
stated in Table 18.1

- The fractions distinguish what is being measured.
- Bilirubin belongs to the biliary excretory function domain.
- Etiologic interpretation requires additional clinical information.

Canalicular-associated enzymes

ALP and GGT are grouped with biliary excretory markers.

ALP

Serum alkaline
phosphatase

GGT

Serum γ -glutamyl
transpeptidase

- Table 18.1 links both to canalicular plasma-membrane damage.
- Both are expected to increase in the table's disease context.
- Together they differ conceptually from cytosolic aminotransferases.

The excretory panel measures several compartments

Bilirubin, bile acids and canalicular enzymes are related but not identical.

Serum bilirubin

Excretory substrate

Urine bilirubin

Urinary analyte

Bile acids

Bile-secreted substances

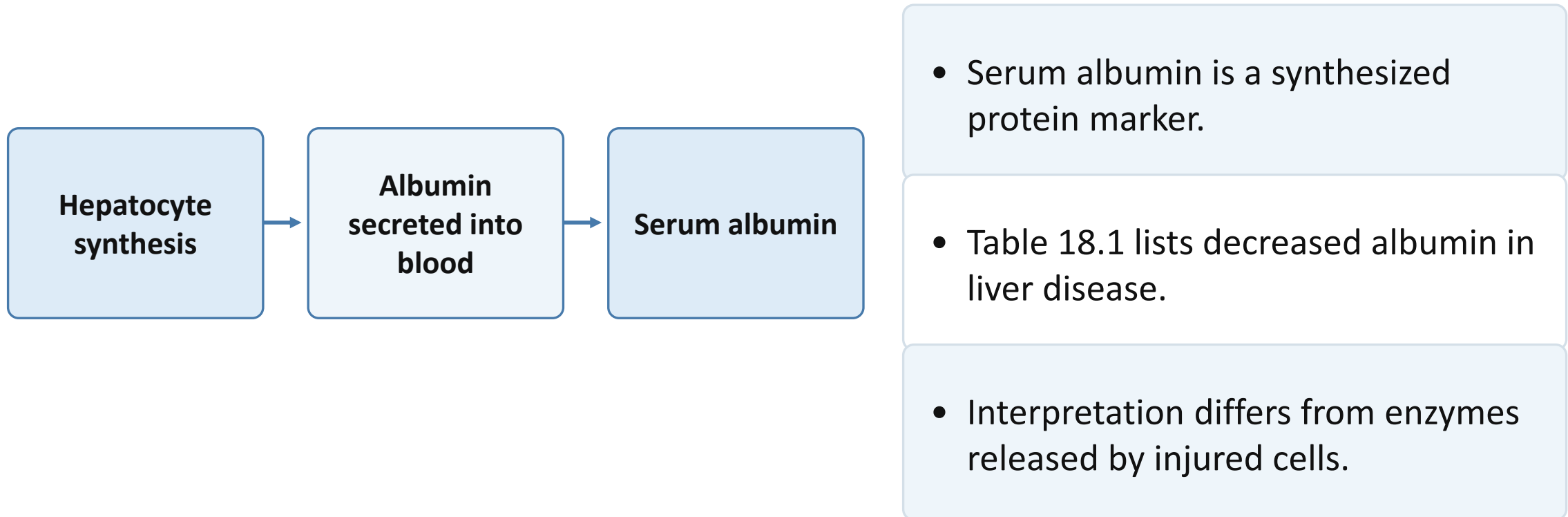
ALP / GGT

Canalicular-associated
enzymes

- The table combines substances secreted in bile with membrane enzymes.
- The measured entity determines the interpretation.
- No single marker exhausts all aspects of biliary dysfunction.

Albumin represents synthetic function

A decrease in circulating albumin appears under hepatocyte synthetic function.



Coagulation proteins represent synthesis

Hepatic synthetic function with coagulation-factor production.

Fibrinogen

Protein secreted into blood

Prothrombin

Coagulation-factor precursor

Factor V / VII

Examples in the table

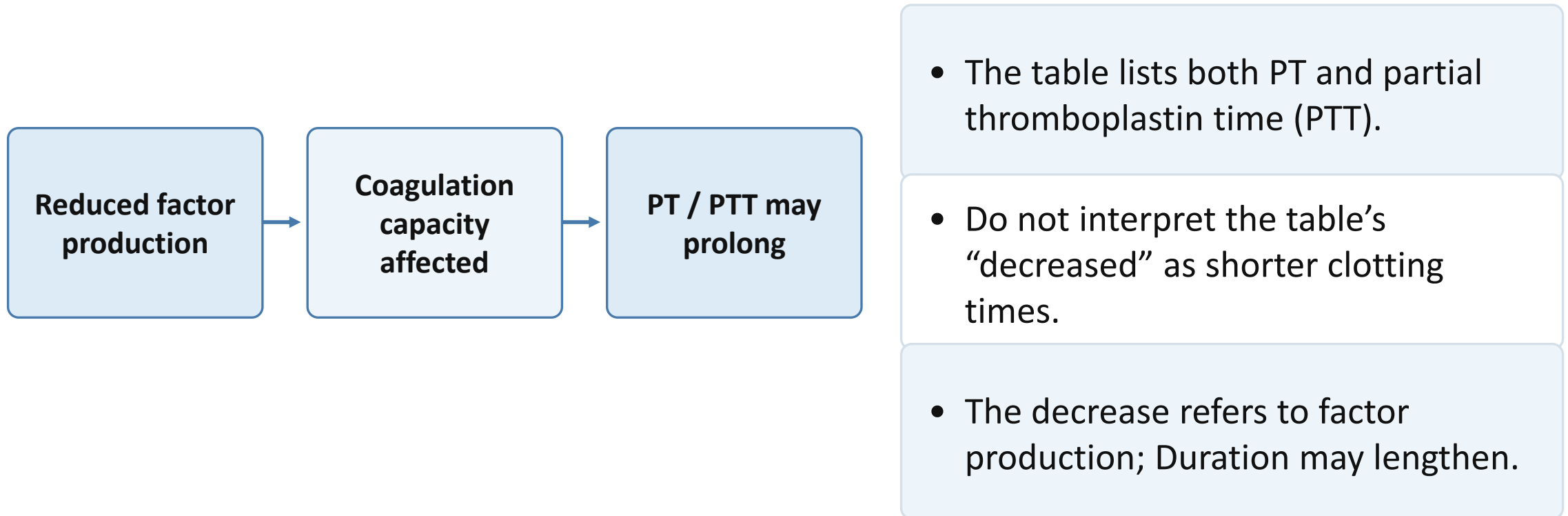
Factor IX / X

Additional table examples

- Several coagulation proteins depend on hepatic synthesis.
- The table places PT and PTT in the synthetic-function domain.
- Decreased coagulation-factor production can alter clotting times.

PT and PTT assess the coagulation pathway

Clotting times are functional readouts of multiple coagulation factors.



Synthetic function differs from integrity

Liver enzyme leakage and protein production describe separate physiological properties.

Hepatocyte integrity

AST, ALT and LDH increase
after cell damage

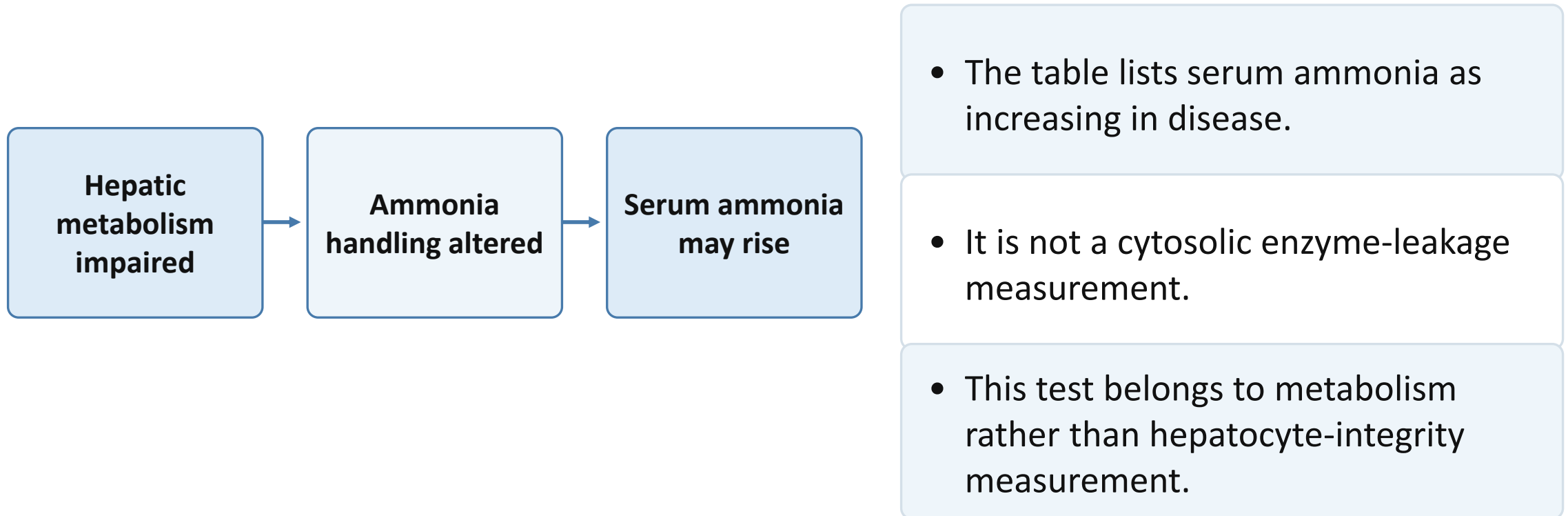
Hepatocyte synthesis

Albumin and coagulation-
factor production can
decrease

- An elevated transaminase alone does not prove synthetic failure.
- Synthesis may change as functional capacity is lost.
- Keep these measurement domains distinct.

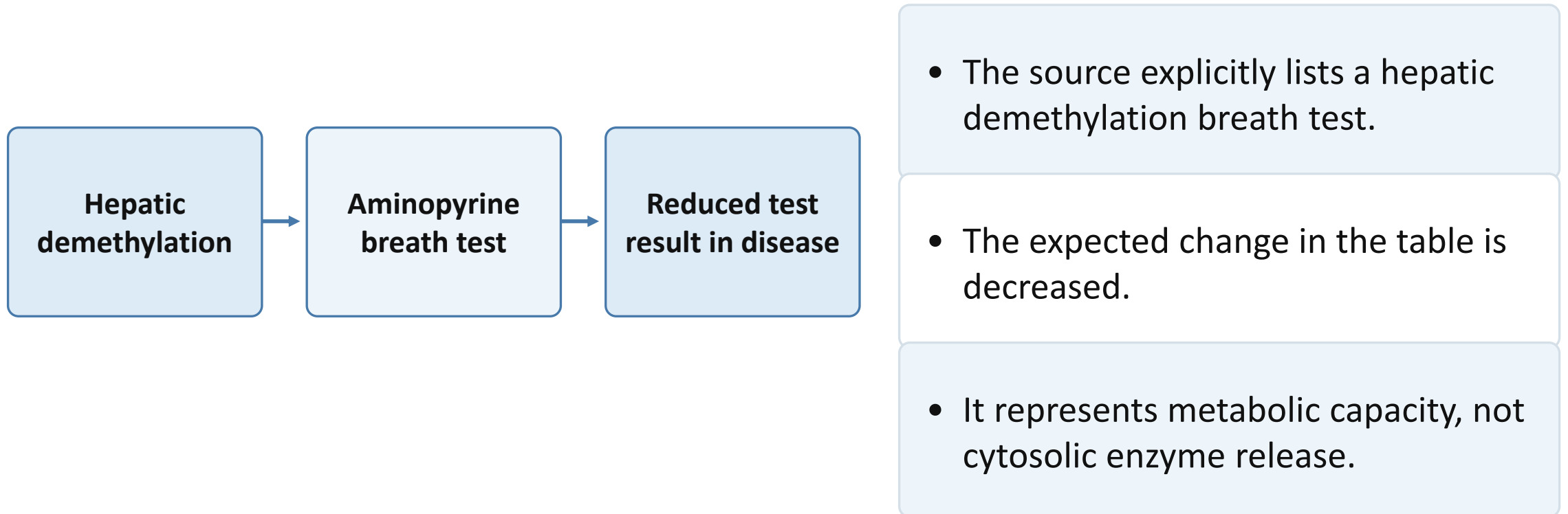
Ammonia is a metabolic-function measure

Serum ammonia appears under hepatic metabolism in Table 18.1.



Aminopyrine breath testing

Hepatic demethylation is presented as a distinct metabolic function.



The full liver-test framework

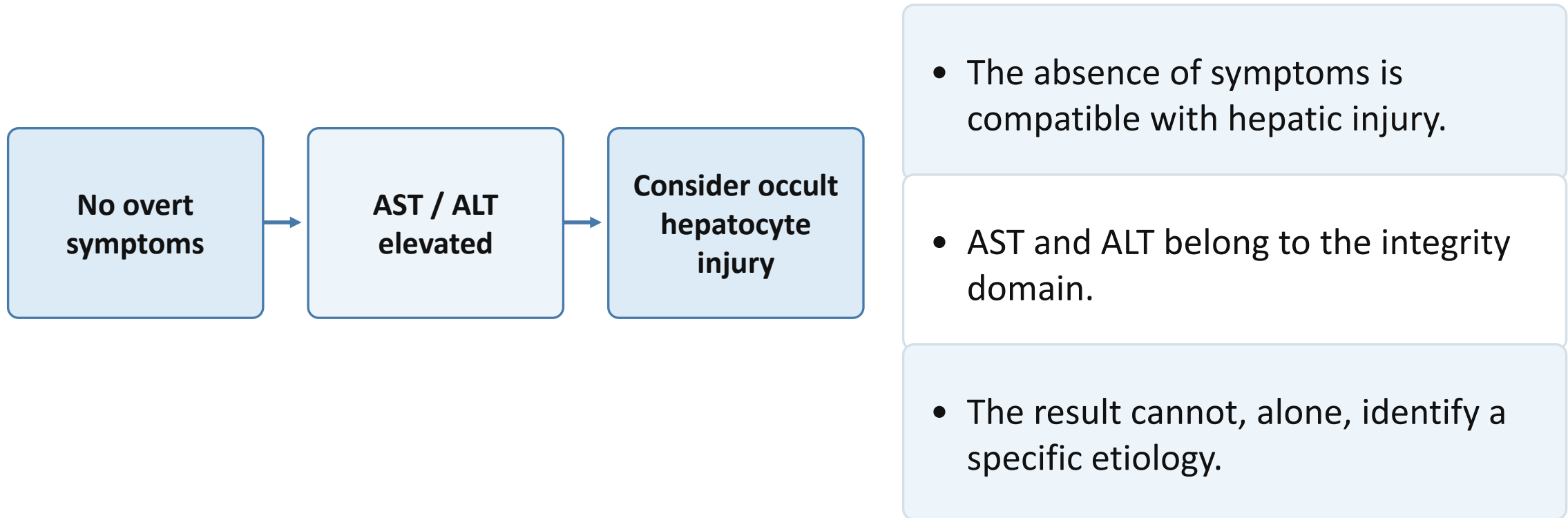
A coherent interpretation starts with the physiologic question asked by each result.

Integrity	AST, ALT, LDH ↑
Excretion	Bilirubin, bile acids, ALP, GGT ↑
Synthesis	Albumin and factor production ↓
Metabolism	Ammonia ↑; Aminopyrine test ↓

- Each domain captures a different aspect of liver disease.
- Directional changes should be interpreted with clinical context.
- Combine test patterns with clinical history and chronology.

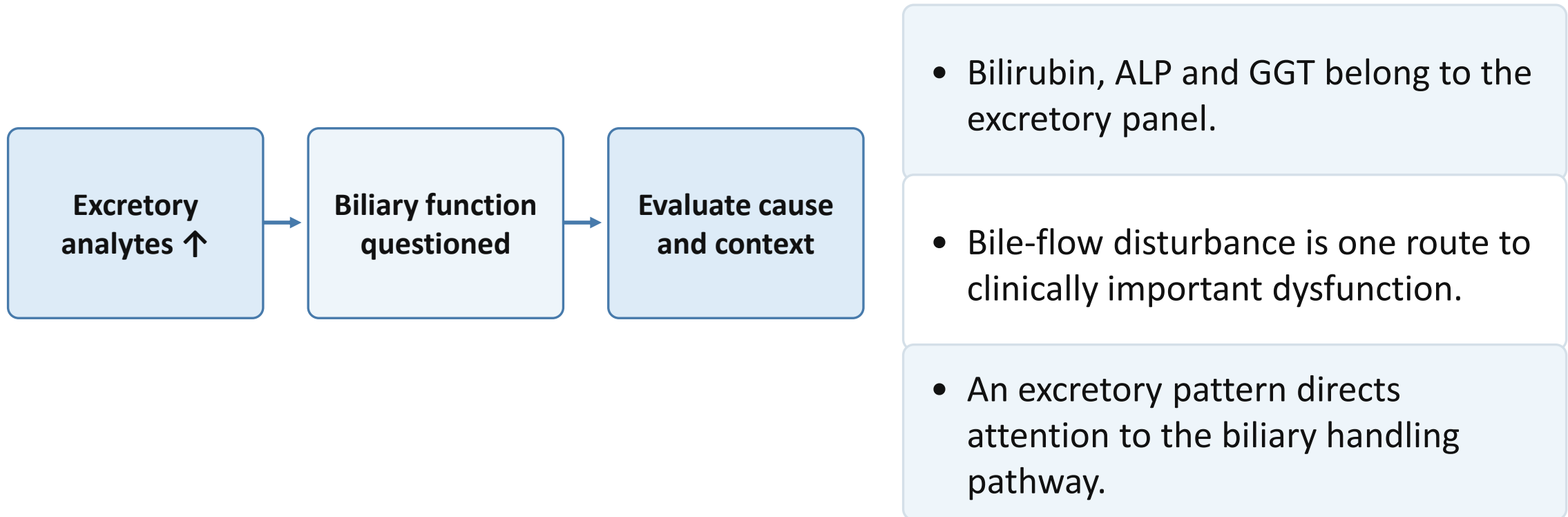
Case exercise: An asymptomatic abnormal enzyme result

Teaching vignette: A patient feels well but has newly abnormal AST and ALT.



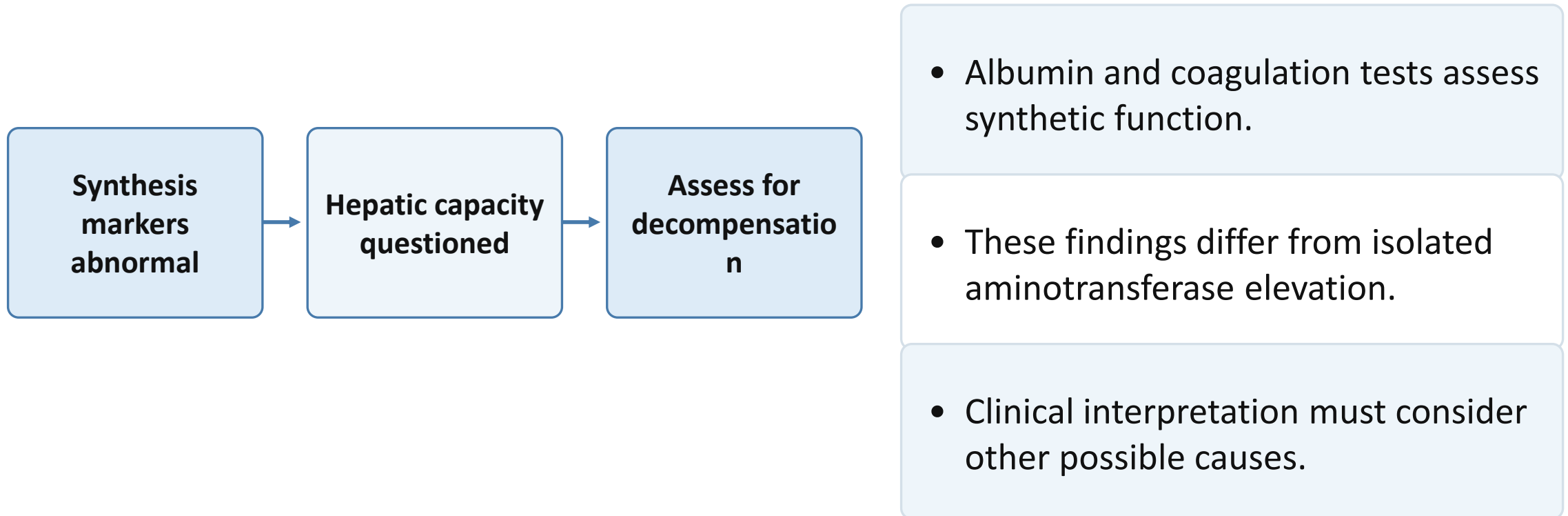
Case exercise: An excretory-pattern abnormality

Teaching vignette: Serum bilirubin, ALP and GGT are reported as increased.



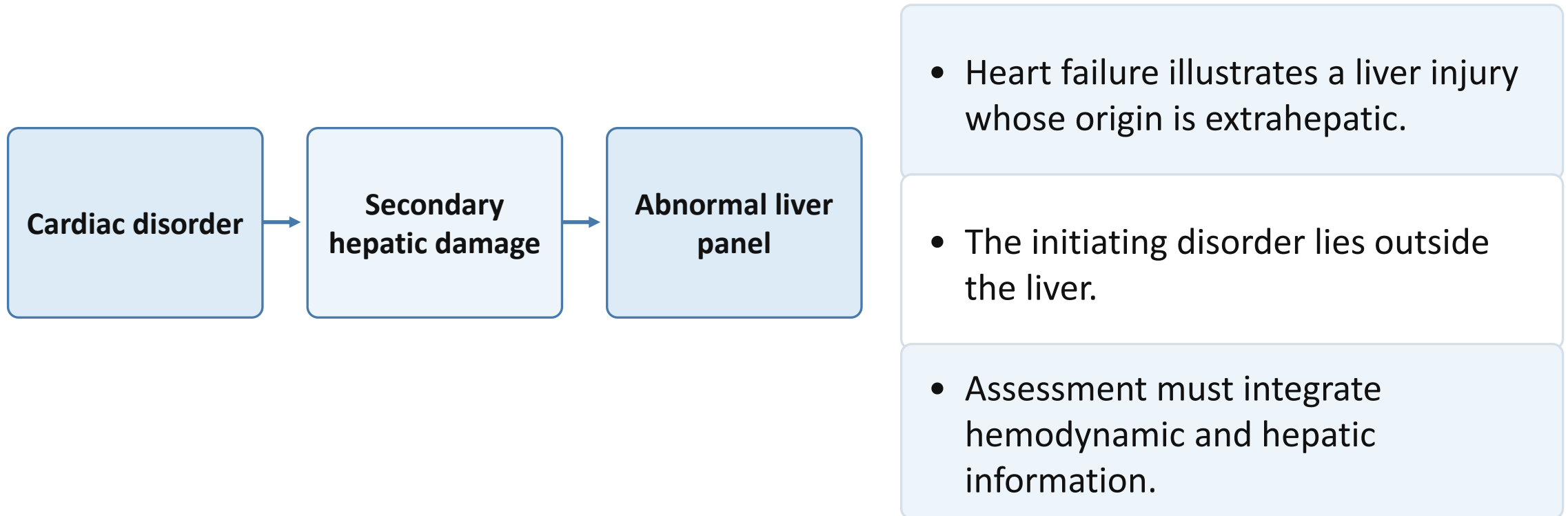
Case exercise: Loss of synthetic capacity

Teaching vignette: Serum albumin is low and clotting times are prolonged.



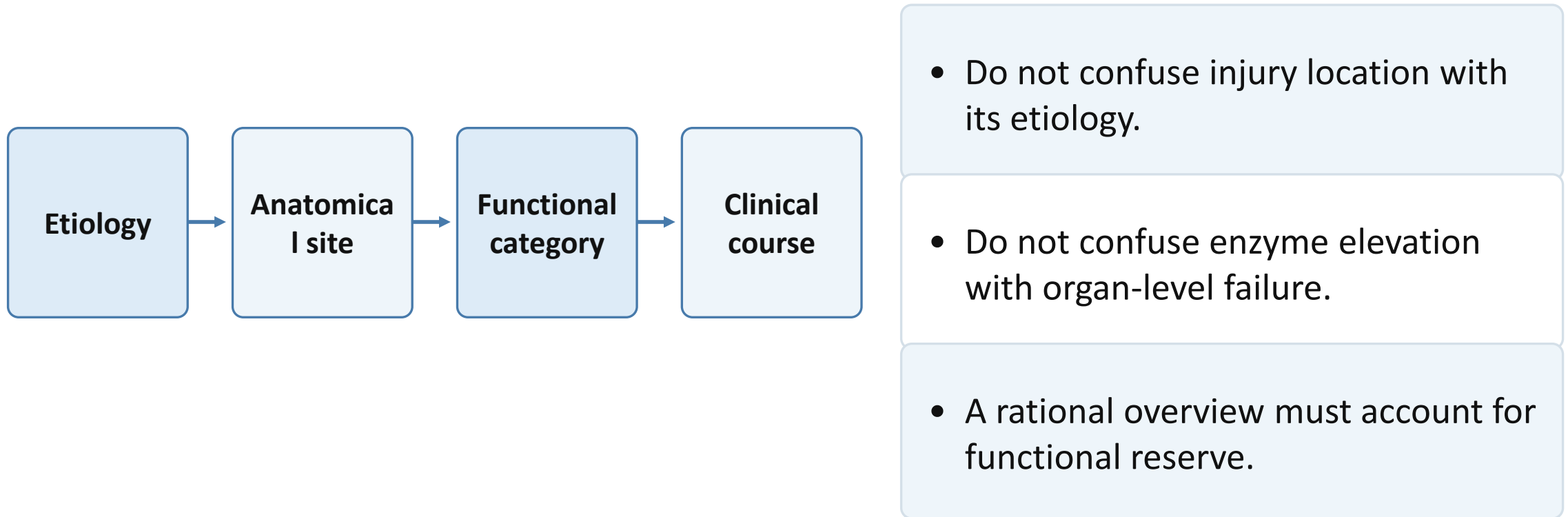
Case exercise: An extrahepatic cause

Teaching vignette: A patient with heart failure develops abnormal liver tests.



Integrated pathologic assessment

Anatomy, cause, injury, function and time should be considered together.



Five high-yield distinctions

These distinctions govern interpretation across the liver disease curriculum.

Portal vs central

Position defines the acinar axis

Blood vs bile

Separate and opposing flows

Primary vs secondary

Site of origin differs

Injury vs function

Enzymes $\neq$ synthesis

Silent vs overt

Reserve delays manifestations

Acute vs insidious

Time course matters

- A normal clinical appearance does not exclude liver damage.
- Laboratory tests should be grouped by physiological domain.
- Combine anatomic location, laboratory domain and time course.

References and source boundaries

Primary source and scope of the lecture.

Primary reference

Robbins, Cotran & Kumar:
Pathologic Basis of
Disease, 11th ed. (2026),
Chapter 18

Teaching scope

General Features of Liver
Disease; assigned parent
anatomy; Table 18.1; brief
context from adjacent
sections

- Original topic starts on page 749.
- Normal anatomy and Table 18.1 supplied supporting material.
- Detailed disease-specific mechanisms are reserved for their respective topics.