

Overview of Cellular Responses to Stress and Noxious Stimuli

Homeostasis · adaptation · injury · cell death

An integrated introduction to cellular pathology

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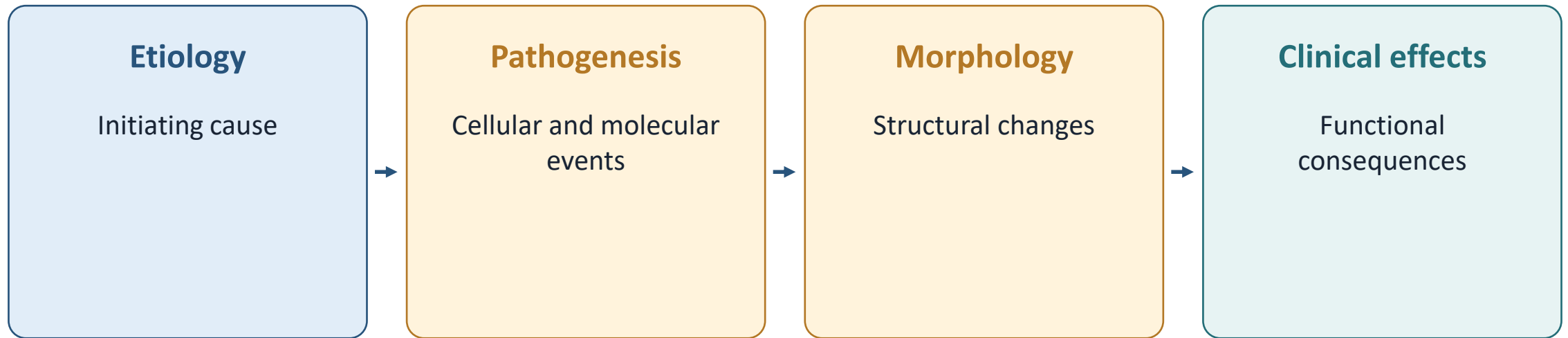
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Learning outcomes

- Define cellular homeostasis and adaptation.
- Distinguish adaptive change, reversible injury, and irreversible injury.
- Classify major causes of cellular injury.
- Use myocardial stress and ischemia to explain cell fate.
- Connect cellular events to tissue injury and clinical disease.

From etiology to clinical manifestations



Pathology begins at the cellular level

Cellular basis

Most diseases begin with molecular or structural alterations in cells.

Organ-level expression

Cell and extracellular matrix injury produce tissue dysfunction and manifestations.

Pathology connects mechanism to clinically detectable disease.

A normal cell operates within defined limits

Metabolic state

Energy production and substrate availability

Differentiation

Specialized structure and function

Local environment

Neighboring cells and tissue context

Functional demand

Physiologic work imposed on the cell

Homeostasis is a healthy steady state



Structure and function remain compatible with survival.

Steady state does not mean inactivity

Changing inputs

Metabolic demand and external conditions fluctuate.

Regulated outputs

The healthy cell maintains essential functions within tolerable limits.

Homeostasis is dynamic control, not a fixed metabolic rate.

Three principal responses to stress

Normal cell

Adaptation

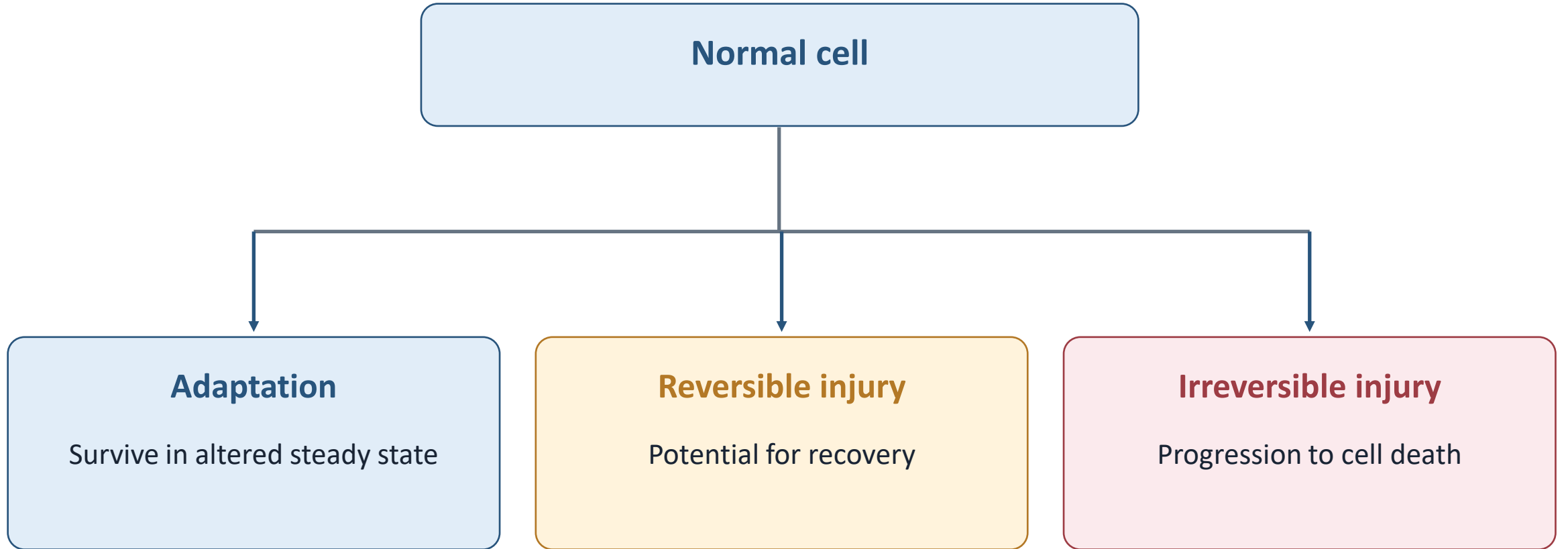
Survive in altered steady state

Reversible injury

Potential for recovery

Irreversible injury

Progression to cell death



Outcome depends on the nature of the insult

Type

Hypoxia, chemical, physical, immune, or other stimulus

Intensity

Demand and damage relative to cellular reserve

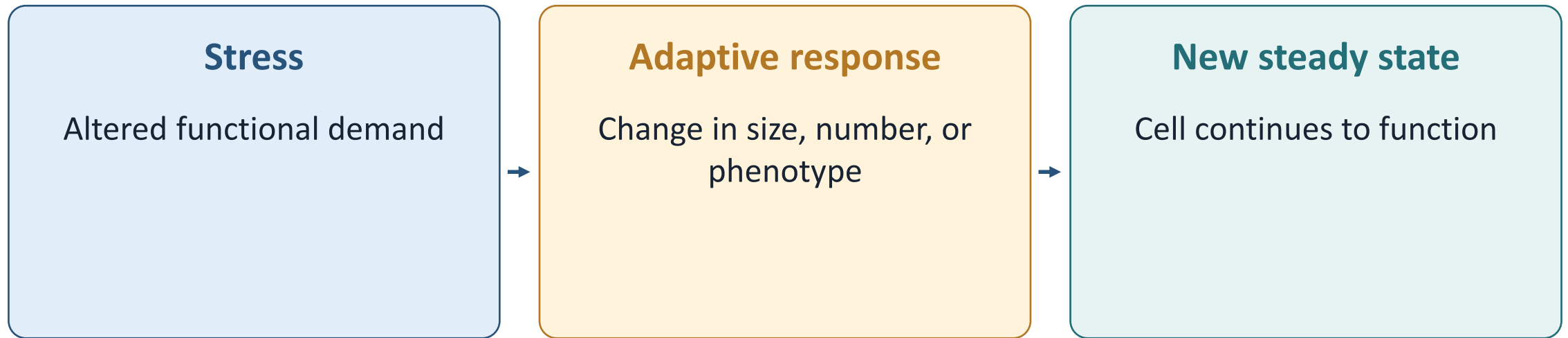
Persistence

Brief versus continuing exposure

Context

Cell type, baseline state, and available resources

Adaptation creates a different viable state



Original schematic

Adaptations can be physiologic or pathologic

Physiologic stimulus

Change in normal demand; E.g., pregnancy

Pathologic stimulus

Response to an abnormal burden; E.g.,
raised cardiac workload

Both are initially reversible strategies for cell survival.

Four fundamental adaptive patterns

Hypertrophy

↑ cell size

Hyperplasia

↑ cell number

Atrophy

↓ cell size / activity

Metaplasia

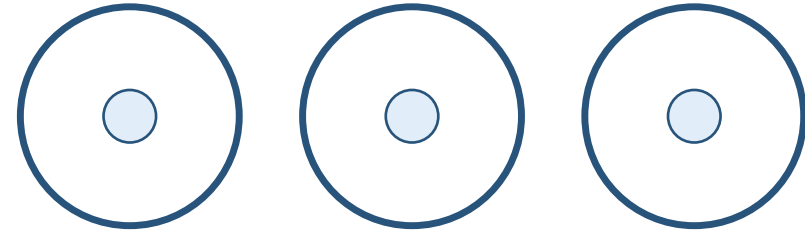
Changed differentiated phenotype

Hypertrophy means increased cell size

Usual-sized cells

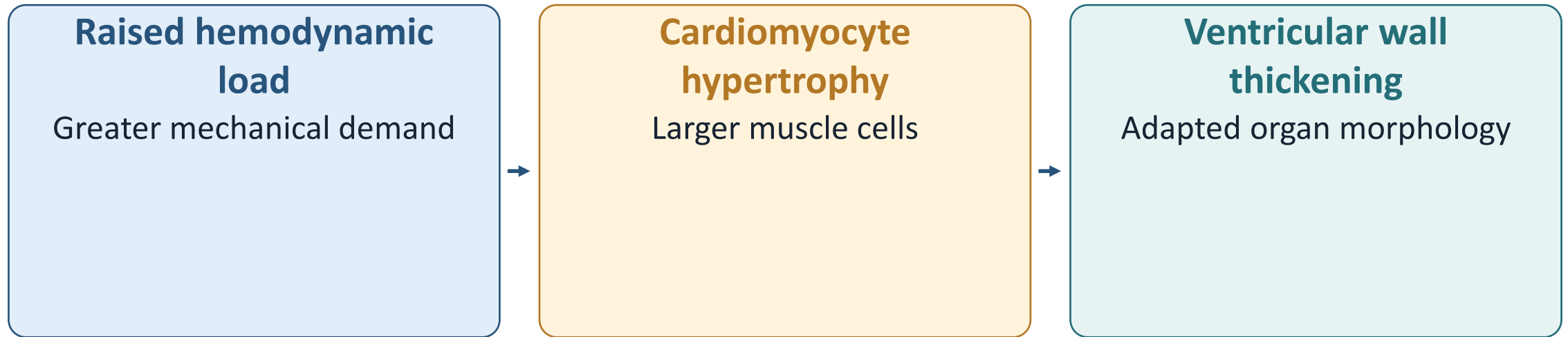


Enlarged cells



Increased workload may be met by greater cellular mass.

Cardiac workload illustrates hypertrophy



Original schematic

Adaptation can carry a metabolic cost

Immediate benefit

Increased cardiac muscle mass helps meet workload.

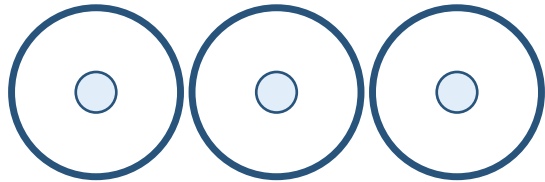
Potential vulnerability

Greater metabolic demand can make the heart more susceptible to injury.

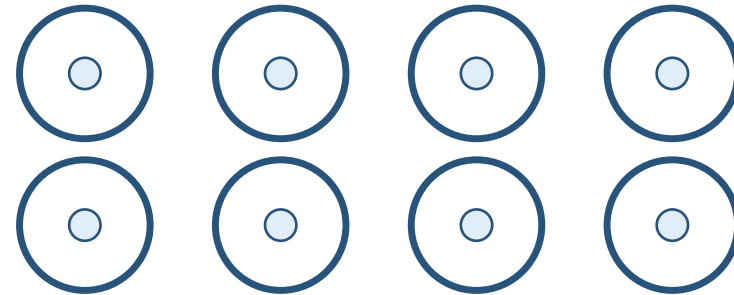
An adaptive response is not necessarily risk-free.

Hyperplasia means increased cell number

Baseline cell population



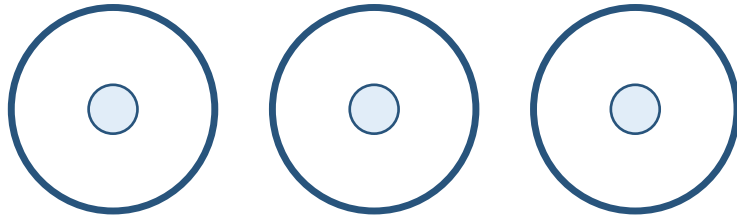
Expanded cell population



Adaptation occurs by an increase in the number of cells.

Atrophy reduces cell size and activity

Baseline size



Smaller cells



Reduced size is accompanied by decreased metabolic activity.

Gradual arterial narrowing may favor atrophy

Reduced arterial supply

Chronic diminution in
substrate delivery



Lower tissue demand

Adaptive reduction in size



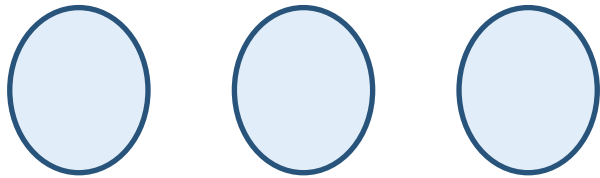
Atrophy

Tissue remains viable under
constraint

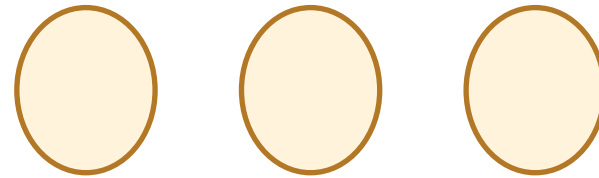
Original schematic

Metaplasia changes the cellular phenotype

Original differentiated cell type



Alternative differentiated phenotype

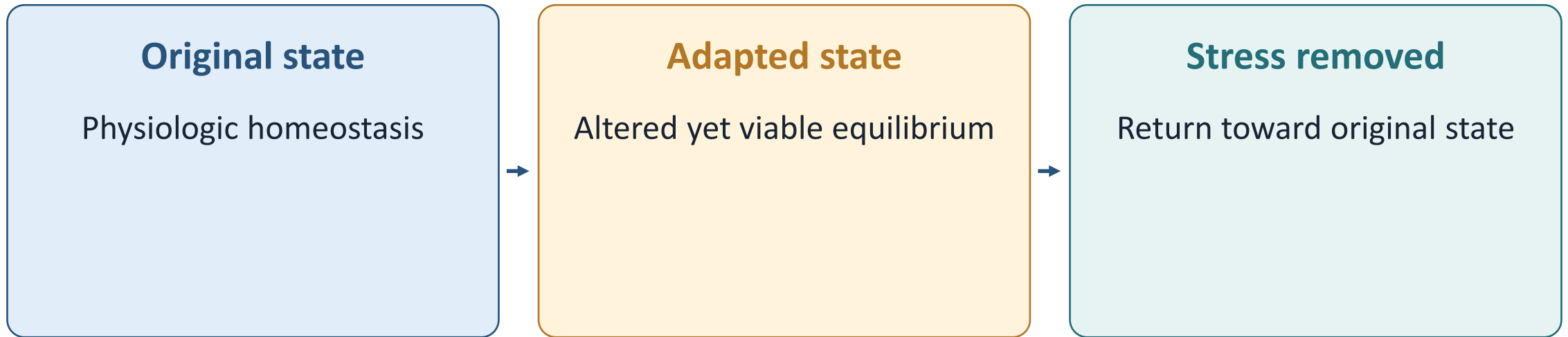


An altered phenotype may be more suited to persistent stress.

Adaptations differ in what changes

Response	Cell size	Cell number	Phenotype
Hypertrophy	Increases	Not defining	Retained
Hyperplasia	Not defining	Increases	Retained
Atrophy	Decreases	Not defining	Retained
Metaplasia	Not defining	Not defining	Changes

Remove the stress: Adaptation may regress



Original schematic

The limit of adaptation defines a key threshold

Stress persists or overwhelms capacity

Successful adaptation

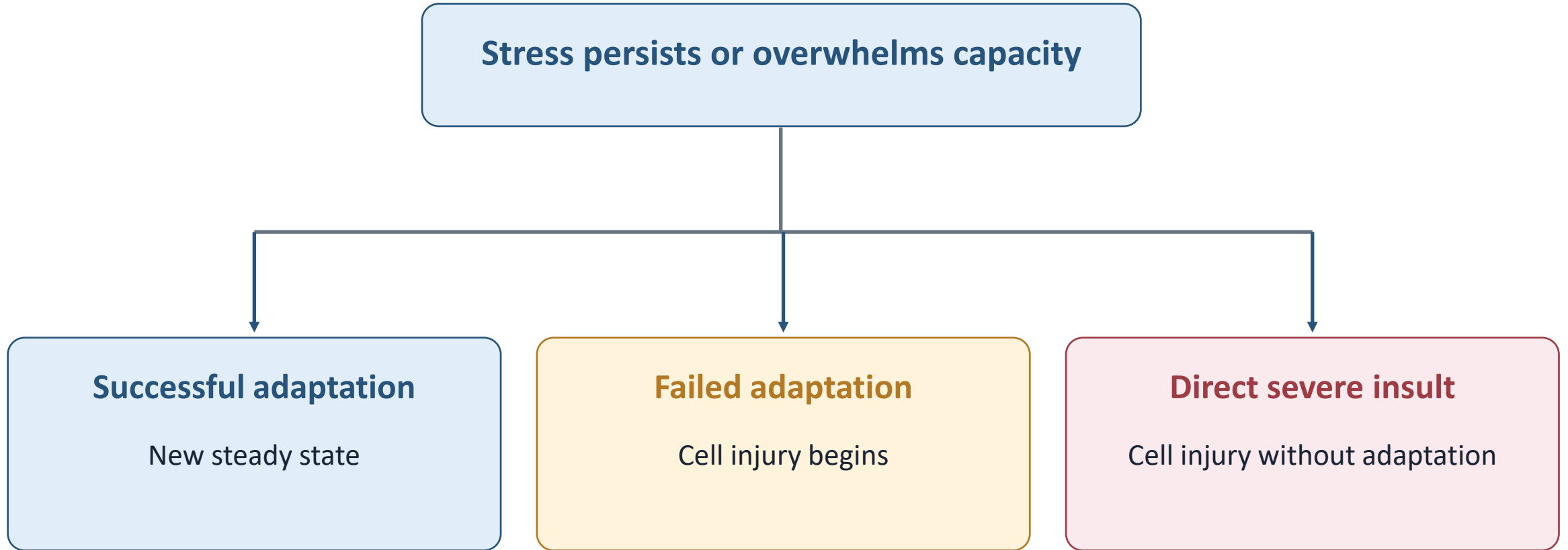
New steady state

Failed adaptation

Cell injury begins

Direct severe insult

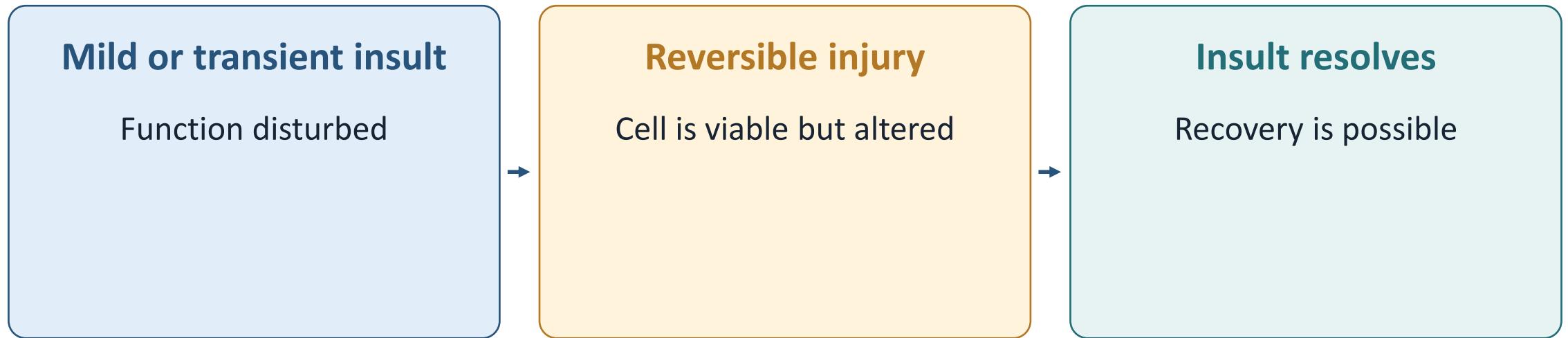
Cell injury without adaptation



Cell injury follows failure or direct damage

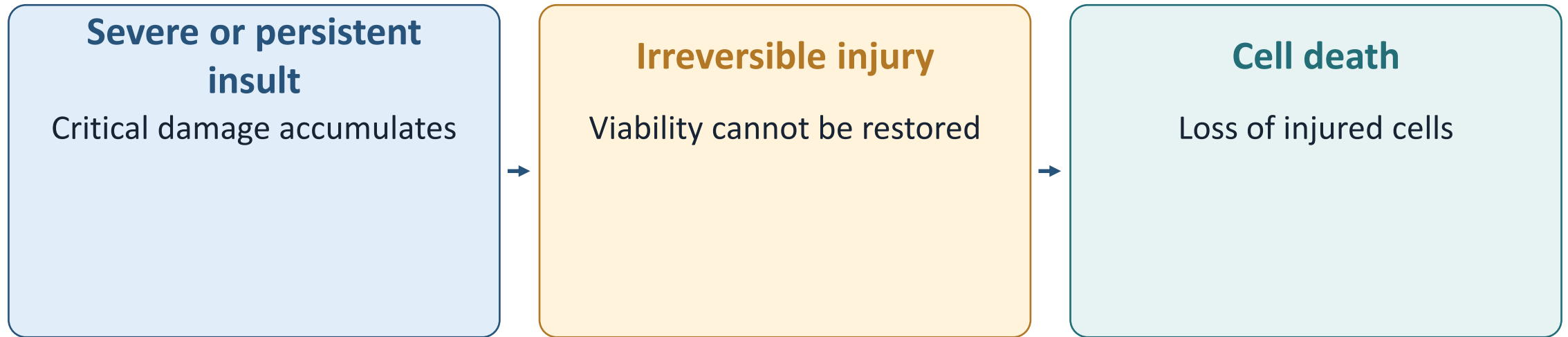
- The insult may exceed the limits of adaptive capacity.
- A cell may be deprived of critical nutrients or oxygen.
- Toxic exposures may damage essential cellular structures.
- Mutations can compromise functions required for survival.

Reversible injury preserves recovery potential



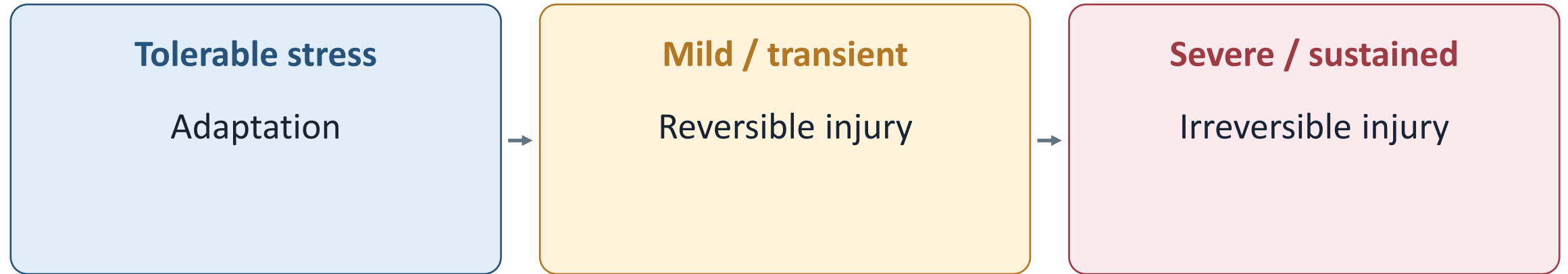
Original schematic

Irreversible injury leads to cell death



Original schematic

Severity and duration jointly influence cell fate



Qualitative continuum — not a numerical injury threshold

Progression is not an obligatory sequence

Gradually increasing workload

Adaptation may precede injury.

Abrupt major coronary occlusion

Severe ischemia can cause irreversible injury without prior adaptation.

Cell fate reflects the actual insult, not a required sequence of stages.

Restoration of blood flow can be decisive

Is perfusion restored before injury becomes irreversible?

YES

Recovery

Injured cells may recover

NO

Cell death

Continuing ischemia can produce
necrosis

Cell death has normal physiologic functions

Embryogenesis

Removes cells as structures develop

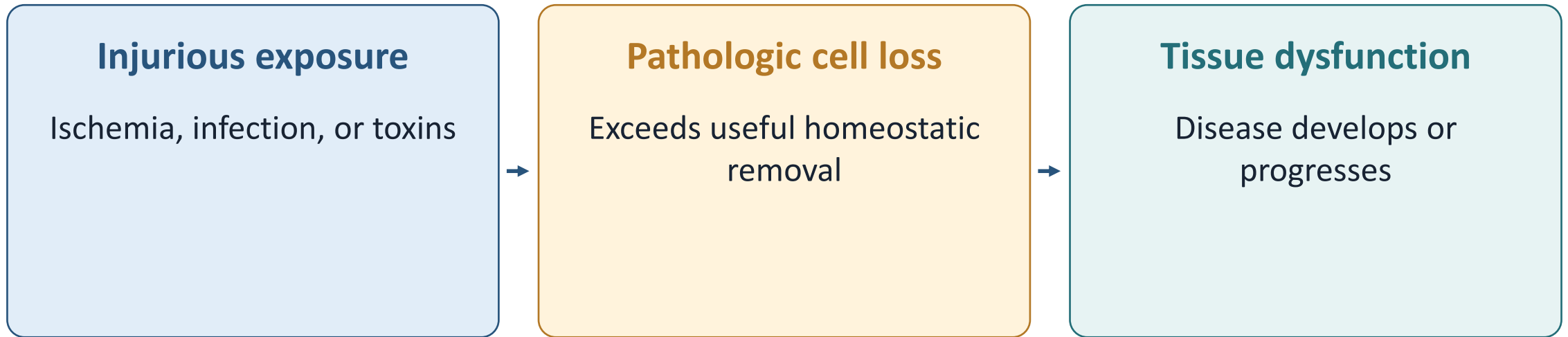
Organ development

Supports tissue remodeling

Adult homeostasis

Eliminates aged or unnecessary cells

Excess cell death causes disease



Original schematic

Main pathways of cell death: Orientation

Necrosis

Major pathway of death in many forms of pathologic injury.

Apoptosis

Major pathway; Also supports physiologic removal of cells.

The full molecular pathways belong to subsequent chapter topics.

Cell death mechanisms extend beyond two labels

Necroptosis

Additional regulated death
pathway

Pyroptosis

Additional regulated death
pathway

Ferroptosis

Additional regulated death
pathway

Not all stress responses are adaptation or death

Metabolic derangement or chronic injury

Intracellular accumulation

Proteins, lipids, carbohydrates

Pathologic calcification

Calcium at sites of dead tissue

Cellular aging

Characteristic structural and
functional change

Intracellular accumulations indicate disturbed handling

Proteins

Abnormal protein content
may accumulate

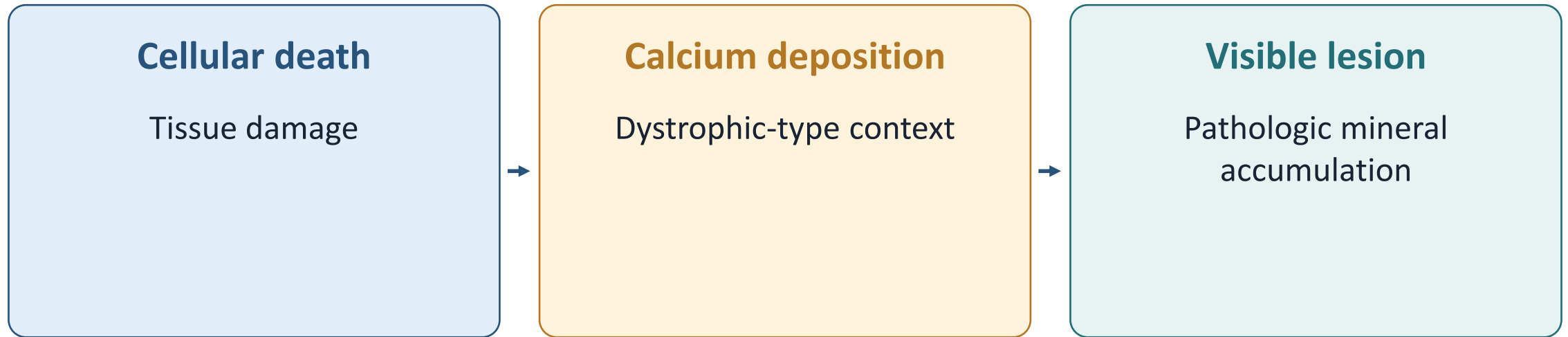
Lipids

Fat or other lipids can build
up

Carbohydrates

Stored carbohydrates may
become excessive

Calcification may follow tissue death



Original schematic

Cellular aging also changes structure and function

Structural dimension

Characteristic morphologic alterations occur as cells age.

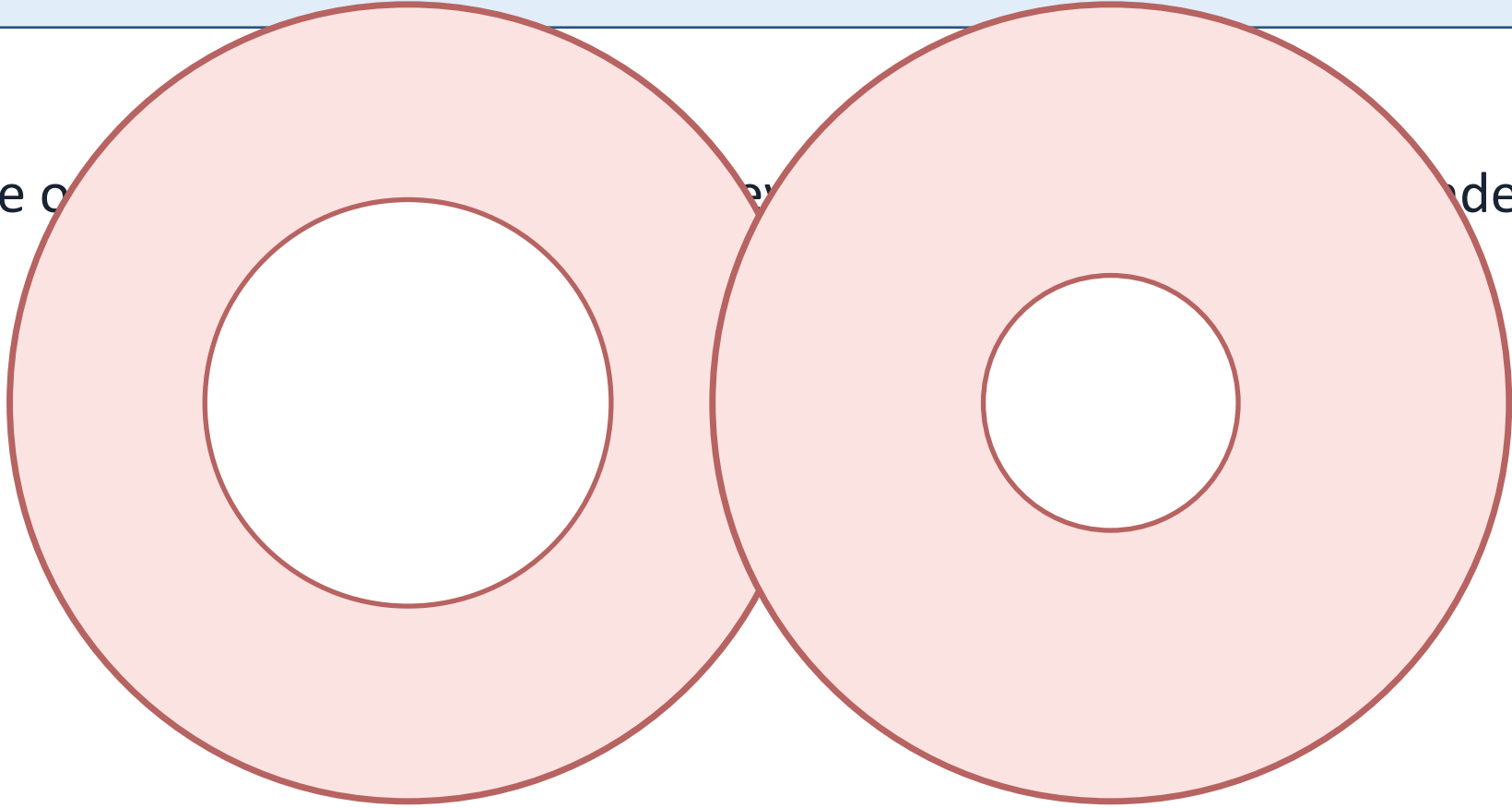
Functional dimension

Aging is accompanied by changed cell performance.

Aging belongs to the wider framework of altered cellular states.

Myocardium demonstrates the complete response model

A single cell can exist under different



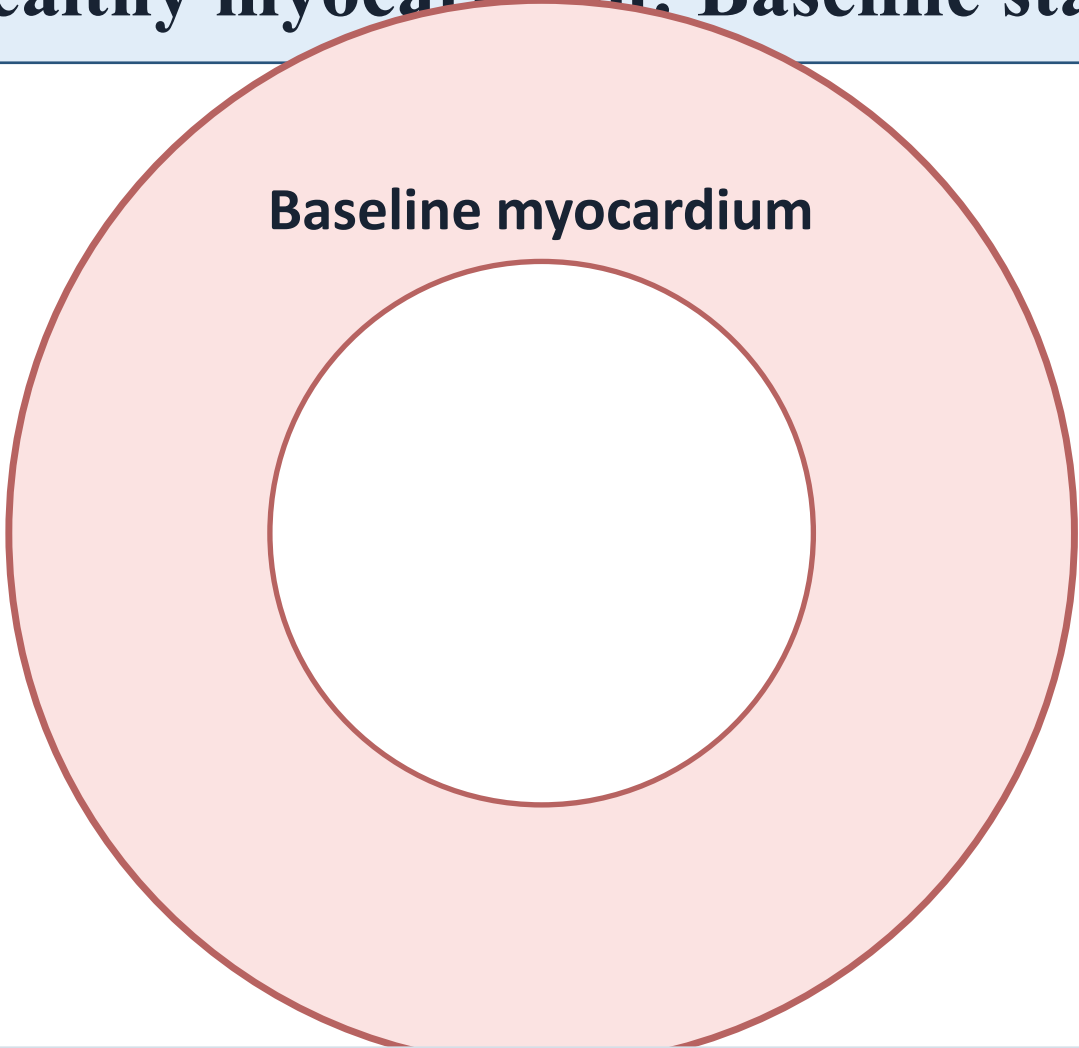
Schematic

Baseline

Adapted

Healthy myocardium: Baseline state

Baseline myocardium

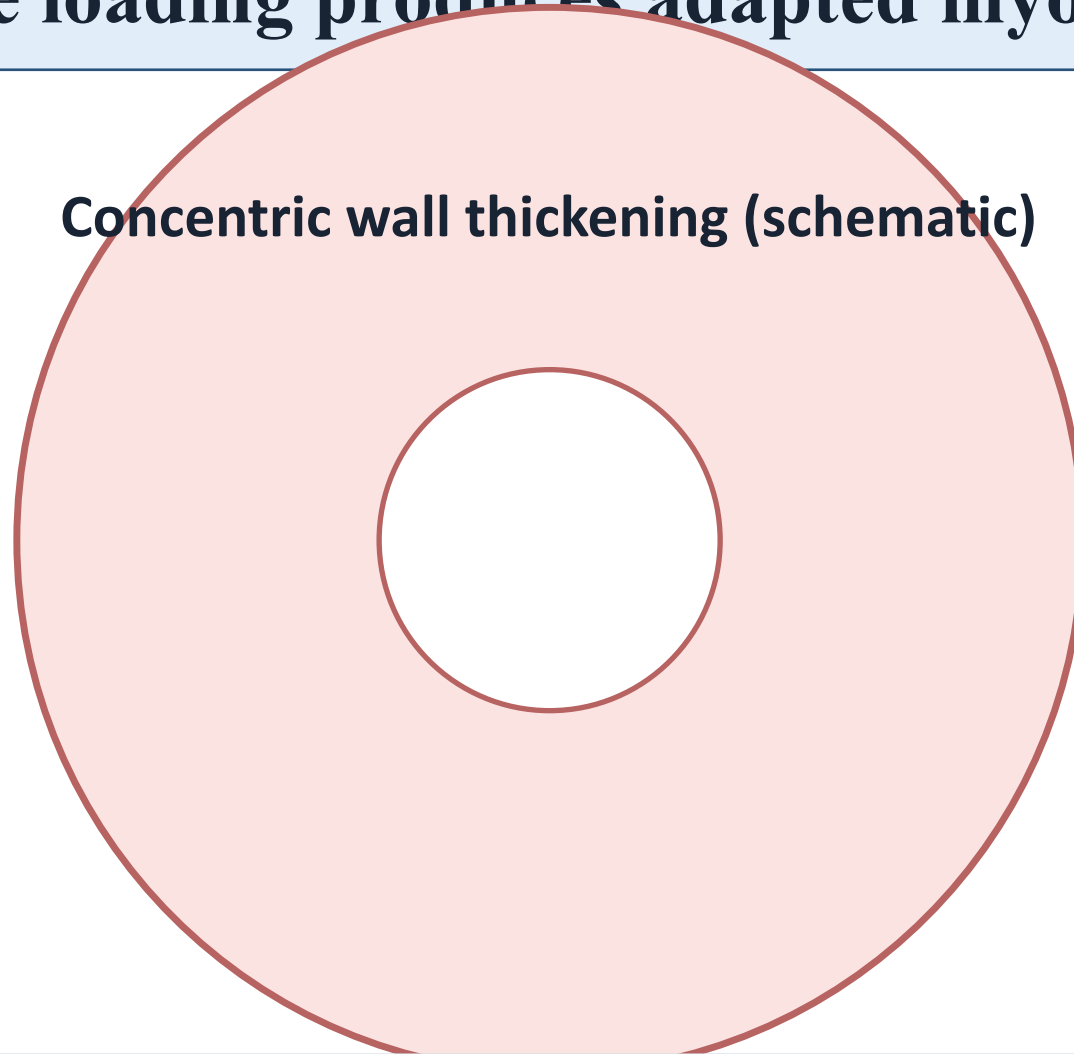


Original schematic

Wall structure and myocyte function meet prevailing workload.

Pressure loading produces adapted myocardium

Concentric wall thickening (schematic)

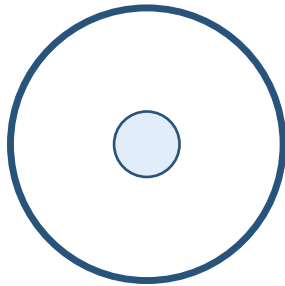


Original schematic

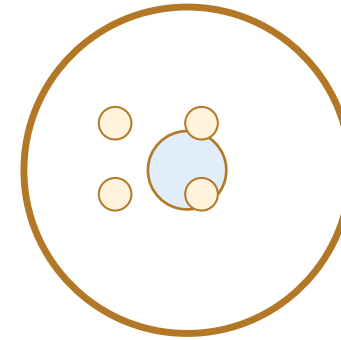
Larger myocytes are associated with a thicker left ventricular wall.

Compromised perfusion changes viable myocytes

Functional myocyte



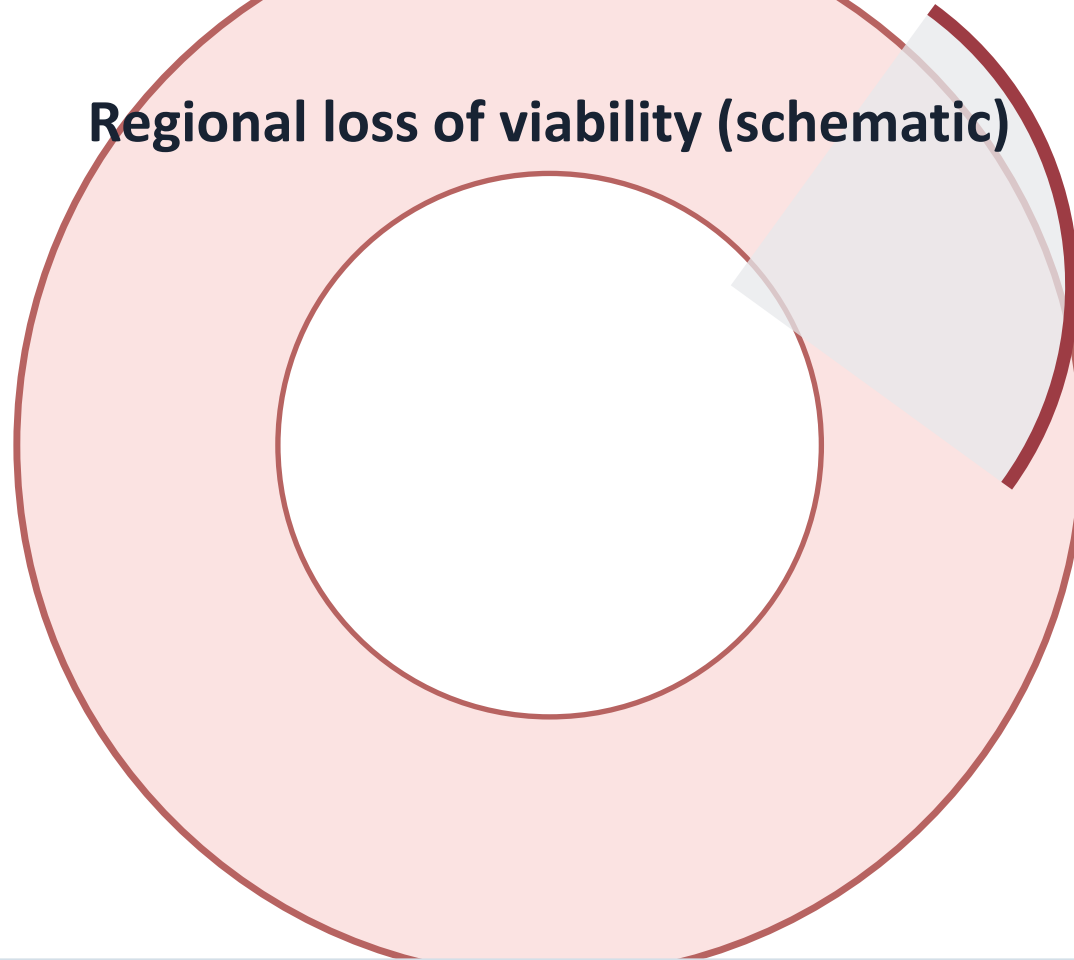
Reversibly injured myocyte



Early reversible injury may show swelling or lipid accumulation.

Irreversible ischemia culminates in infarction

Regional loss of viability (schematic)



Original schematic

A region of myocardium may become necrotic after loss of blood flow.

No gross change is required for reversible injury

Functional alteration

Cellular injury may disrupt function before overt gross changes appear.

Microscopic change

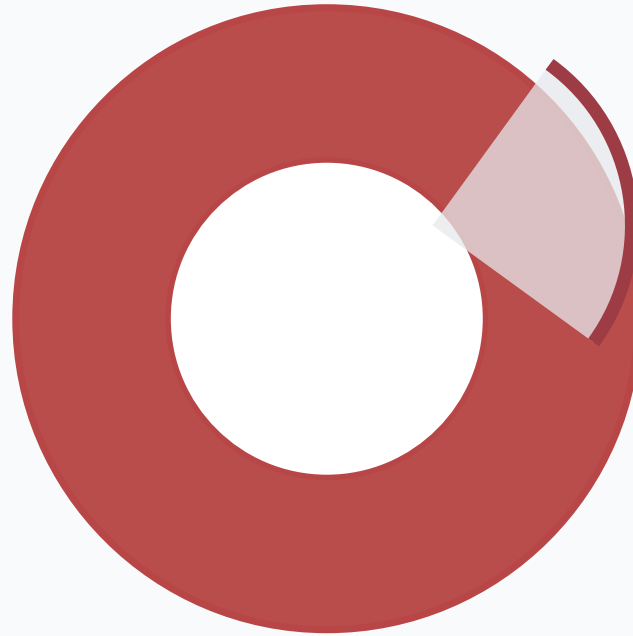
Swelling and fatty change may be detectable when present.

Absence of obvious gross abnormality does not prove normal cellular function.

Viability staining: Interpret the principle



Viable myocardium



Infarcted region unstained

Triphenyltetrazolium chloride stains viable myocardium brick-red; Nonviable infarcted areas remain unstained.

Cardiac enlargement is not the same as infarction

Hypertrophy

Adaptive increase in wall thickness after increased workload.

Infarction

Death of myocardium due to inadequate blood flow.

The two findings describe different processes and may coexist.

Two myocardial stresses, two distinct mechanisms

Increased pressure

Greater work



Myocyte enlargement

Hypertrophy

Reduced perfusion

Oxygen shortage



Myocyte injury

Possible necrosis

Sudden arterial occlusion tests the exception

Clinical situation

A major coronary artery becomes abruptly and completely occluded.

Question

Must the myocytes hypertrophy before they become irreversibly injured?

Interpretation

No. Severe acute ischemia can bypass an adaptive stage.

Etiologic categories organize the diagnostic search

Cause taxonomy

Oxygen deprivation

Physical agents

Chemicals / drugs

Cell injury

Response depends on insult
and cell state

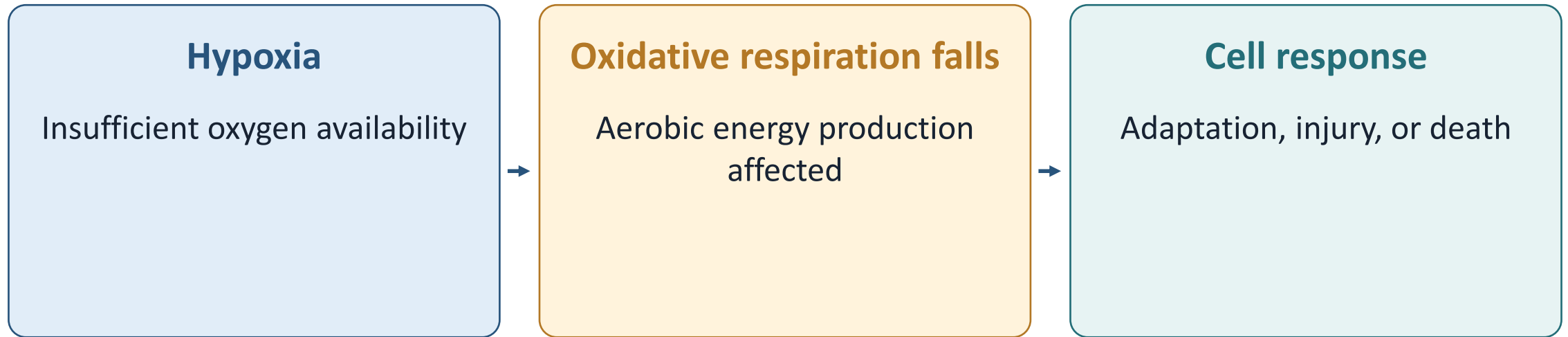
Infectious agents

Immunologic reactions

Genetic abnormalities

Nutritional imbalance

Oxygen deprivation impairs aerobic respiration



Original schematic

Three routes to tissue hypoxia

Ischemia

Reduced blood flow

Poor oxygenation

Cardiorespiratory failure

Low oxygen capacity

Anemia, CO poisoning,
severe blood loss

Ischemia is a flow problem, not a synonym for hypoxia

Hypoxia

Insufficient oxygen supply to the cell.

Ischemia

Reduced tissue blood flow; One important cause of hypoxia.

Causes of hypoxia also include impaired oxygenation or carrying capacity.

Physical agents can injure cells directly

Mechanical

Trauma and tissue disruption

Thermal

Burns and extreme cold

Pressure

Sudden atmospheric changes

Other

Radiation and electric shock

Chemical injury spans ordinary and unusual exposures

Common solutes

Hypertonic glucose or salt

Environmental

Pollutants and occupational toxins

Poisonings

Arsenic, cyanide, mercury

Drugs

Therapeutic adverse effects or substance use

Dose and context can turn normal substances toxic

Concentration matters

Hypertonic salt or glucose deranges cell fluid/electrolyte balance.

Essential is not always harmless

Oxygen can be toxic at high concentrations.

A substance's normal physiologic role does not ensure safety at every exposure.

Infectious agents cause diverse patterns of damage

Viruses

Submicroscopic infectious
agents

Bacteria and rickettsiae

Different pathogen groups

Fungi and parasites

Additional biologic causes

Immune defense can itself produce tissue injury

Protective role

Immune responses remove pathogens and other threats.

Injurious role

Responses to self-antigens or external agents can damage cells.

Autoimmune disease demonstrates injury driven by recognition of self.

Genetic changes can threaten essential functions

Protein function

Absent or defective enzyme function

Genome integrity

Unrepaired DNA damage

Protein quality

Accumulation of misfolded proteins

Susceptibility

Variants modify vulnerability to exposures

Nutritional deficiency is an injurious exposure

Global deficit

Protein–calorie malnutrition

Micronutrient deficit

Deficiency of specific
vitamins

Different origins

Food shortage, poor diet, or
restricted intake

Nutritional excess can also injure tissues

Overnutrition

Obesity-related disease risk

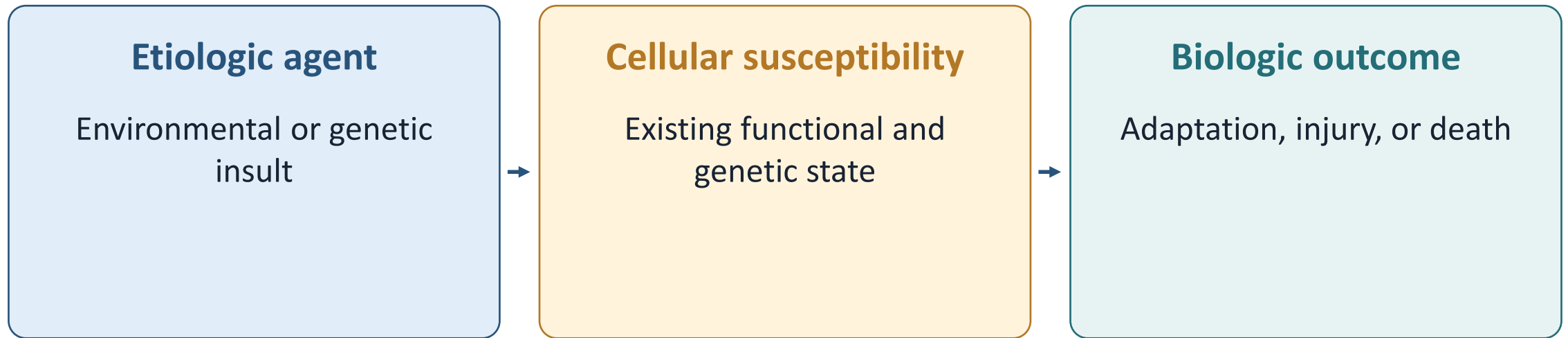
Lipid composition

Dietary patterns influence
circulating cholesterol

Tissue consequences

Metabolic disease and
atherosclerosis risks

Cause and cellular susceptibility interact



Original schematic

Stress pathways can initially protect cells

Integrated stress response

Modulates synthesis of stress-response proteins

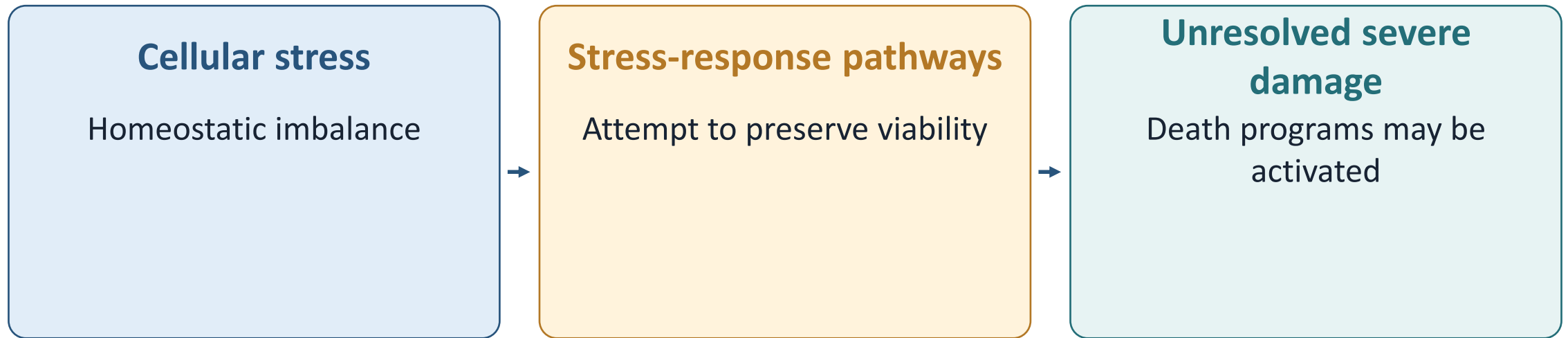
Unfolded protein response

Response to ER protein-folding stress

Autophagy

Cellular material recycling under stress

Protective responses may be insufficient



Original schematic

Clinicopathologic reasoning: A pressure-loaded heart

Clinical situation

A patient has longstanding increased hemodynamic load and a thickened left ventricular wall.

Question

What cellular adaptation best explains the wall thickening?

Interpretation

Hypertrophy: Increased cardiomyocyte size in response to workload.

Clinicopathologic reasoning: An acutely ischemic heart

Clinical situation

A patient develops abrupt prolonged obstruction of a major coronary artery.

Question

What determines whether affected myocytes recover or die?

Interpretation

Severity and persistence of ischemic injury; Irreversible injury causes cell death.

Decision map for any cellular stress

Cell experiences increased demand or damaging stimulus

Can adaptation sustain essential function?

Yes

Sustained viability

No

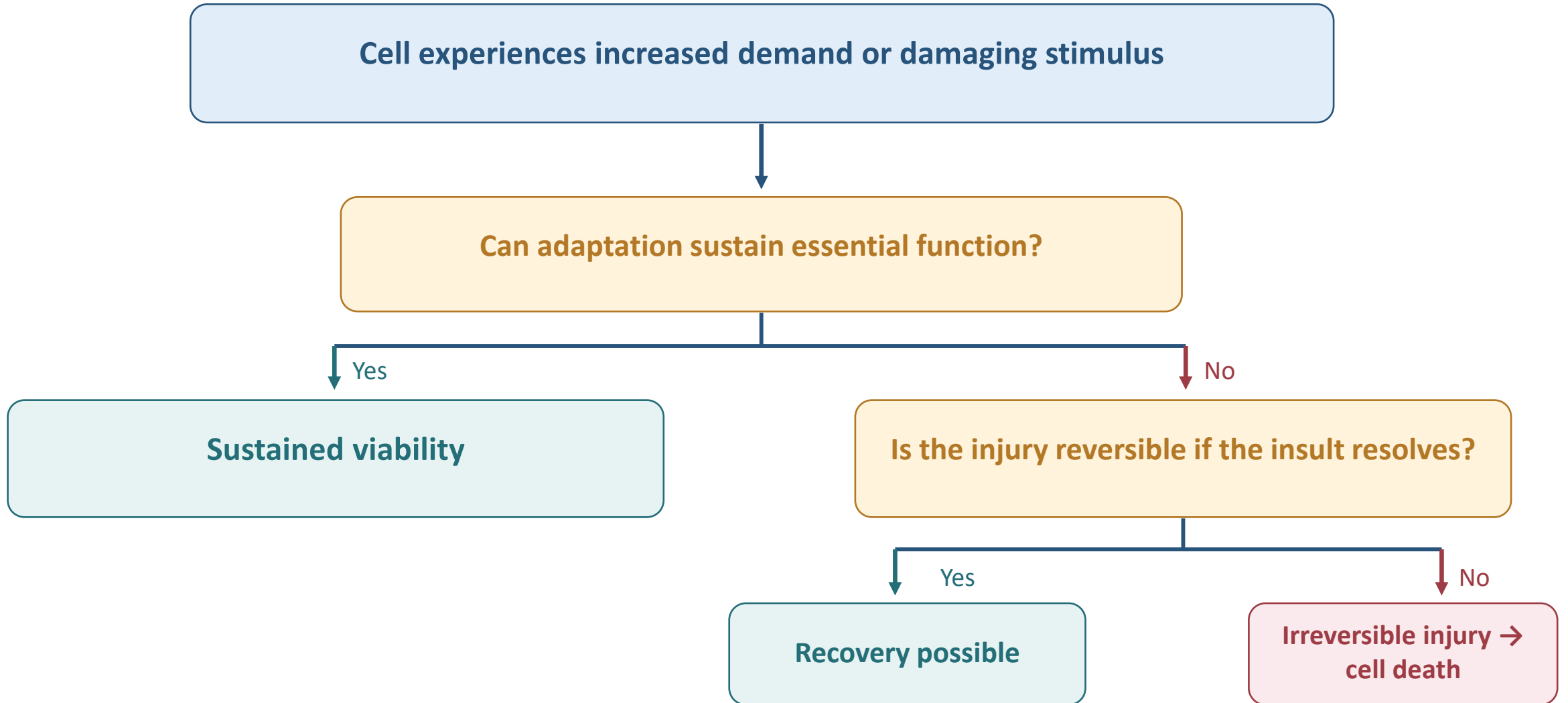
Is the injury reversible if the insult resolves?

Yes

Recovery possible

No

Irreversible injury →
cell death



Synthesis: The cellular response continuum

Homeostasis is the reference state.

Adaptation preserves survival under altered demand.

Mild/transient damage may be reversible.

Persistent/severe damage may produce cell death.

The exact cause and tissue context shape the result.

Primary source and scope

Robbins, Cotran & Kumar: Pathologic Basis of Disease. 11th ed. (2026). Chapter 2, pp. 29–34.

Primary teaching section: “Overview of Cellular Responses to Stress and Noxious Stimuli,” pp. 30–31.

Related contextual sections: “Causes of Cell Injury,” pp. 31–32, and introductory “Pathways of Cellular Response to Stress and Injury,” p. 32.

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