

Systemic Effects of Inflammation

Cytokine-driven physiology, hematologic responses, acute-phase proteins and severe systemic inflammation

Dr Abu Suraih Sakhri

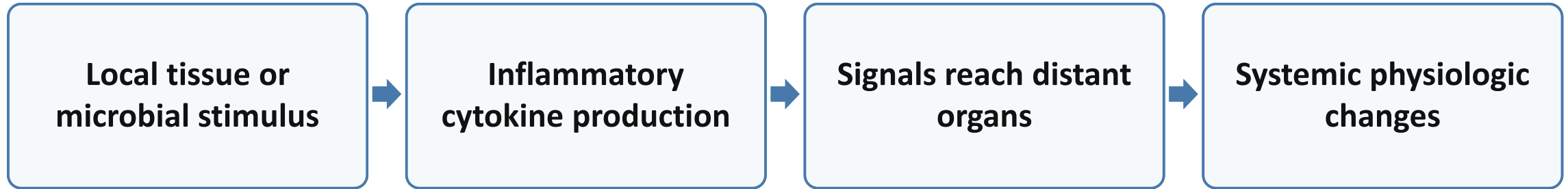
MBBS, MD (Pathology)

www.abusuraihsakhri.com

Learning outcomes

- Explain how local inflammatory stimuli induce systemic effects through cytokines.
- Trace fever and leukocytosis to their principal cellular mediators.
- Interpret acute-phase proteins and related blood-count changes.
- Connect excessive cytokine release with major manifestations of septic shock.

A local inflammatory focus can affect the whole body



- The initiating lesion need not be widespread.
- Circulating mediator effects produce clinically detectable manifestations.

Cytokines coordinate the systemic response

TNF

Principal mediator of systemic inflammation; Contributes to fever and severe sepsis.

IL-1

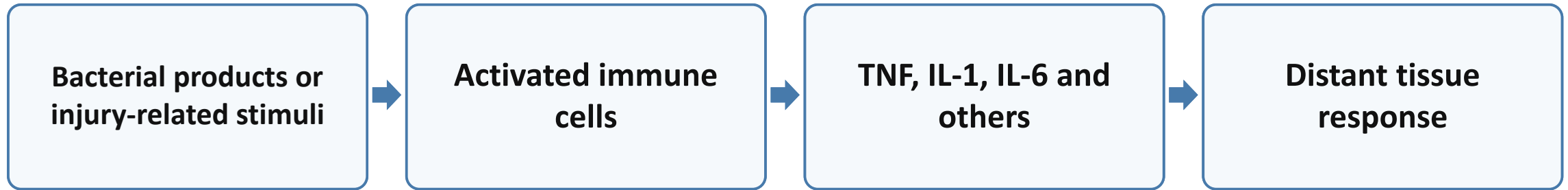
Principal mediator of fever and several acute-phase pathways.

IL-6

Major hepatic acute-phase response driver, especially CRP and fibrinogen.

Interferons and other cytokines also contribute; The response is not mediated by one molecule.

Inflammatory stimuli initiate a shared response



- Bacterial products are examples, not the only inflammatory triggers.
- The same cytokines may act on more than one target tissue.

Systemic responses involve several organ systems

Target / compartment	Major response	Clinical or laboratory clue
Hypothalamus	Temperature regulation	Fever, chills
Bone marrow / blood	Leukocyte mobilization	Leukocytosis or altered differential
Liver	Acute-phase synthesis	CRP, fibrinogen, SAA
Metabolic / vascular systems	Exaggerated cytokine response	Shock, DIC, hyperglycemia

Fever is a regulated increase in temperature

- Fever is prominent in systemic inflammation, particularly infection.
- A typical temperature elevation of approximately 1–4°C.
- The change reflects cytokine-associated resetting of thermoregulation, rather than simple failure to lose heat.

Pyrogens are fever-inducing substances

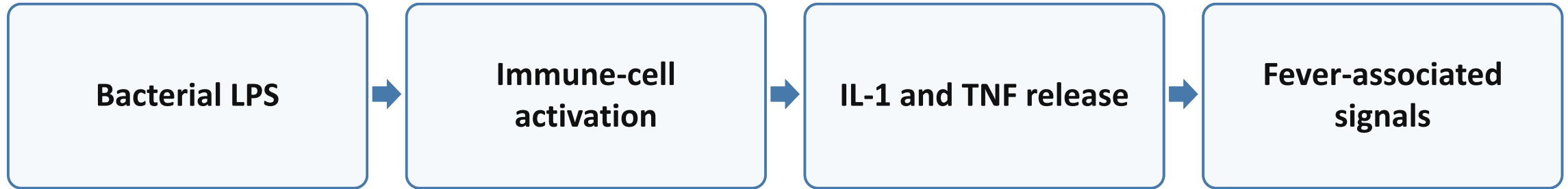
Exogenous pyrogens

- Derived from microbes or other external stimuli.
- Lipopolysaccharide (LPS) is the textbook example.
- Stimulate immune-cell release of endogenous mediators.

Endogenous pyrogens

- Produced by host immune responses.
- Principally IL-1 and TNF in the described pathway.
- Transmit the stimulus toward hypothalamic prostaglandin synthesis.

Bacterial LPS acts upstream of host mediators



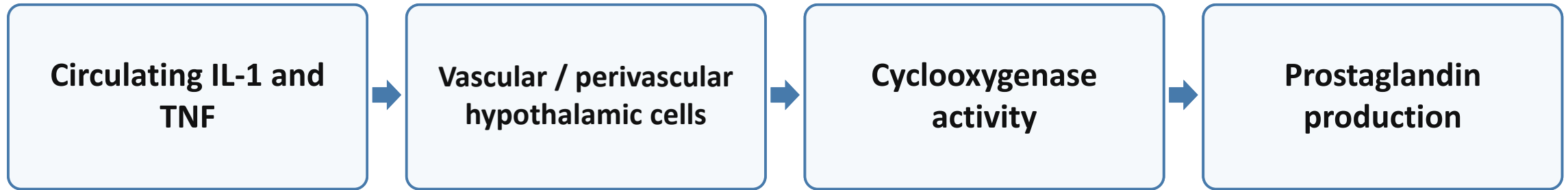
- LPS acts as an exogenous pyrogen.
- The fever pathway depends on the host cytokine response.

IL-1 and TNF are endogenous pyrogens

Origin	Action	Consequence
Inflammatory immune response to microbial or other stimuli.	Induce prostaglandin-producing machinery in responding cells.	Alter thermoregulatory signaling within the hypothalamic region.

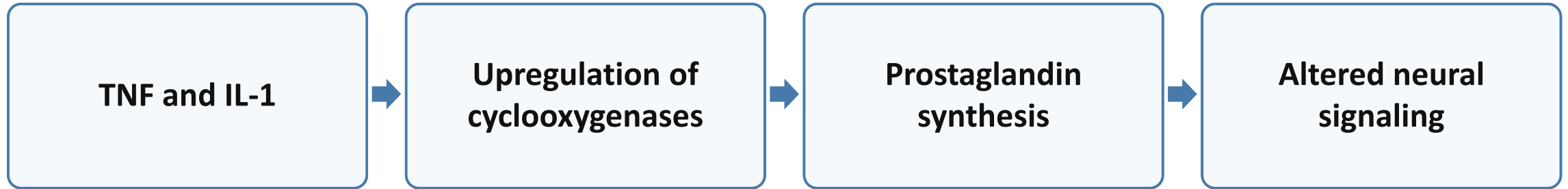
Other inflammatory mediators contribute, but IL-1 and TNF are emphasized in this pathway.

The hypothalamic vascular interface mediates fever



- The response can be initiated by signals arriving from peripheral inflammation.
- Hypothalamic vascular-associated cells respond to the cytokines.

Cyclooxygenases link cytokines to prostaglandins



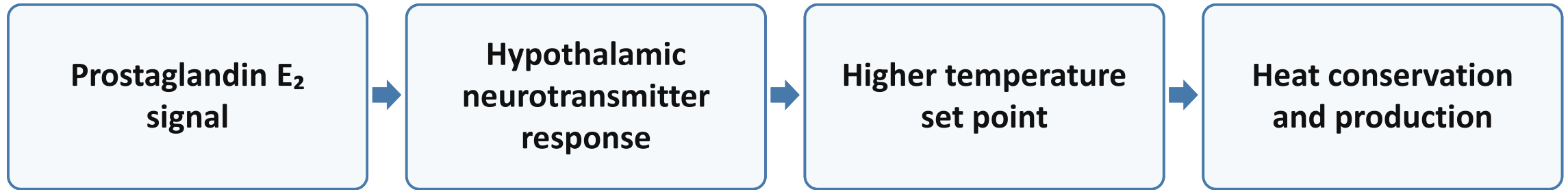
- Cyclooxygenases catalyze prostaglandin synthesis.
- Their induction provides a mechanistic bridge between cytokines and fever.

PGE₂ is a key prostaglandin in fever

Production	Target	Outcome
Induced after IL-1/TNF-dependent prostaglandin synthesis.	Hypothalamic networks governing temperature regulation.	A higher thermoregulatory set point.

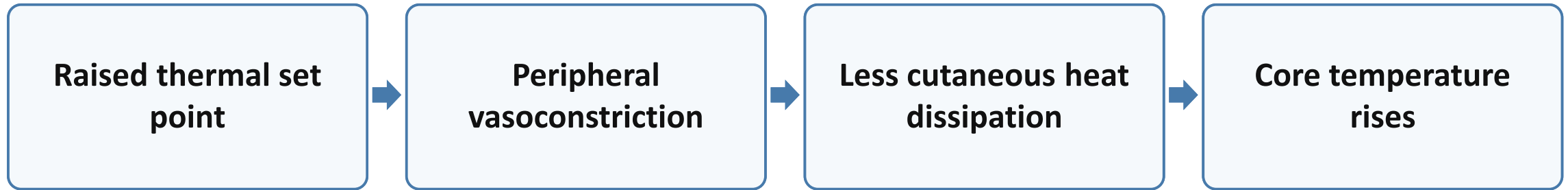
PGE₂ acts within a coordinated hypothalamic response, not as a direct source of heat.

The hypothalamus resets the temperature set point



- Temperature rises through regulated physiologic responses.
- This explains why chills may accompany the onset of fever.

Vasoconstriction reduces heat loss



- Reducing skin blood flow helps conserve body heat.
- This is one of the mechanisms supporting a higher temperature.

Brown fat and skeletal muscle contribute heat

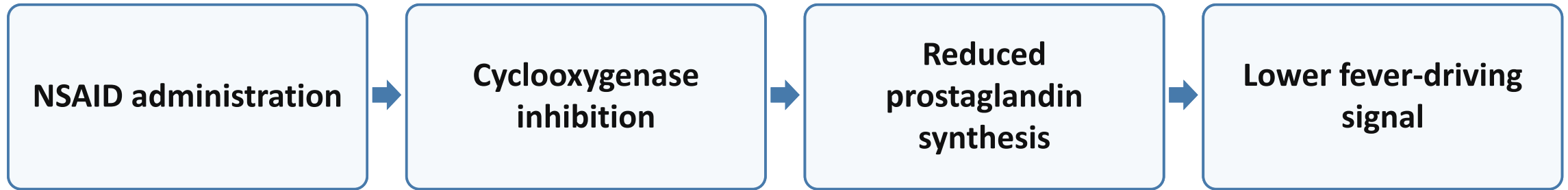
Brown adipose tissue

- Heat generation is influenced by hypothalamic signals.
- Contributes to thermogenic responses.

Skeletal muscle

- Muscle activity contributes to heat production.
- Shivering is a recognizable systemic manifestation.

NSAIDs reduce fever through prostaglandin inhibition

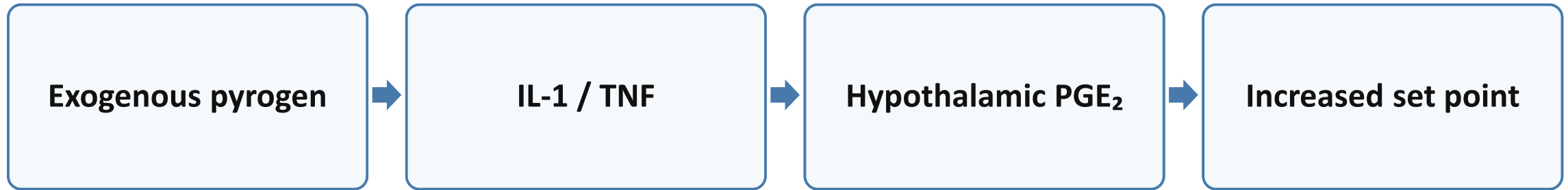


- Aspirin among NSAIDs affecting this pathway.
- The primary explanation is suppression of prostaglandin production.

The possible protective value of fever is uncertain

- Experimental evidence in amphibians supports a benefit of elevated temperature during microbial infection.
- A potential analogous benefit in mammals as a possibility.
- Avoid presenting fever as universally beneficial or universally harmful on this evidence alone.

Fever: The complete cytokine-to-temperature pathway

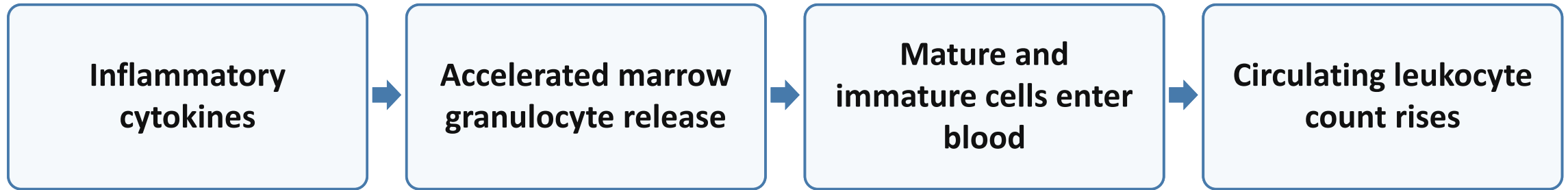


- Reduced heat loss and increased thermogenesis implement the new set point.
- NSAIDs interrupt the prostaglandin step.

Leukocytosis is a common systemic response

- An elevated circulating leukocyte count is common in inflammatory reactions.
- Bacterial infections frequently produce this response.
- The increase reflects both immediate marrow release and, during prolonged stimuli, expanded cellular production.

Early leukocytosis mobilizes marrow granulocytes

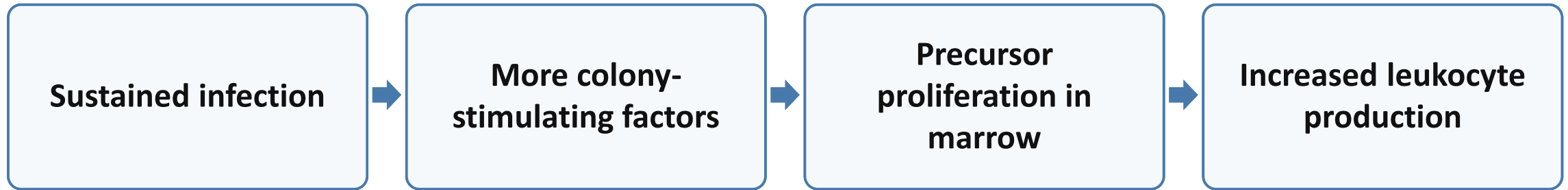


- TNF and IL-1 are among the cytokines linked to this early release.
- Rapid mobilization precedes later expansion of marrow precursors.

A left shift indicates immature neutrophils

Observation	Mechanism	Interpretation
Immature neutrophils appear in increased numbers in circulating blood.	Accelerated marrow release accompanies inflammatory demand.	A left shift supports a reactive marrow response but is not an etiologic diagnosis.

Prolonged inflammation changes marrow output



- Longer-lasting demand recruits hematopoietic production.
- This process differs temporally from rapid release of stored cells.

Colony-stimulating factors amplify myelopoiesis

Activated macrophages

Important source of colony-stimulating factors during persistent infection.

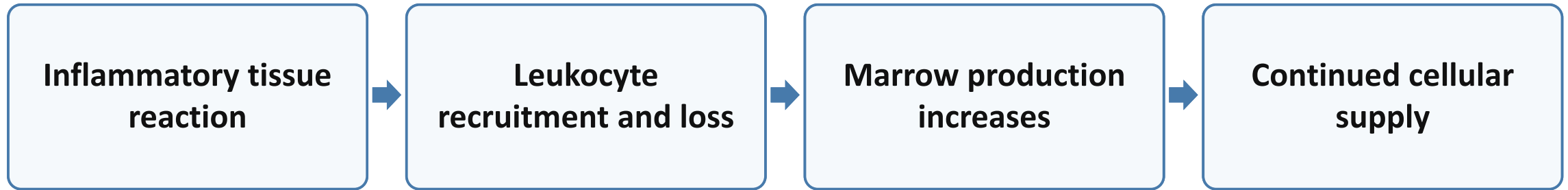
Marrow stromal cells

Additional source of the growth signals.

Marrow precursors

Expand to increase leukocyte production and replace cells lost at inflammatory sites.

Marrow recruitment offsets leukocyte consumption



- The circulating differential is linked to ongoing tissue demand.
- Systemic leukocytosis is one consequence of this compensatory program.

Bacterial infections often produce neutrophilia

- An increased absolute neutrophil count is typical of many bacterial infections.
- The pattern is consistent with accelerated granulocyte mobilization.
- An accompanying left shift indicates entry of immature neutrophils.

Selected viral infections cause lymphocytosis

- Some viral infections are associated with an increased absolute lymphocyte count.
- Robbins examples include infectious mononucleosis, mumps and rubella.
- This pattern contrasts with the neutrophilia often associated with bacterial infection.

Eosinophilia suggests particular inflammatory stimuli

Allergic inflammation

- Some allergic conditions increase circulating eosinophils.
- Interpret with the clinical phenotype.

Helminth infestation

- Certain parasitic infestations cause an eosinophilic response.
- The leukocyte pattern is not a stand-alone diagnosis.

Some infections produce leukopenia instead

- Leukopenia denotes reduced circulating white blood cells.
- Typhoid fever and some viral, rickettsial and protozoal infections as examples.
- Sequestration of activated leukocytes in vascular spaces and tissues can contribute.

A leukemoid reaction can resemble leukemia numerically

Leukemoid reaction

- Marked reactive elevation of circulating leukocytes.
- May occur with severe inflammatory stimuli.

Leukemia

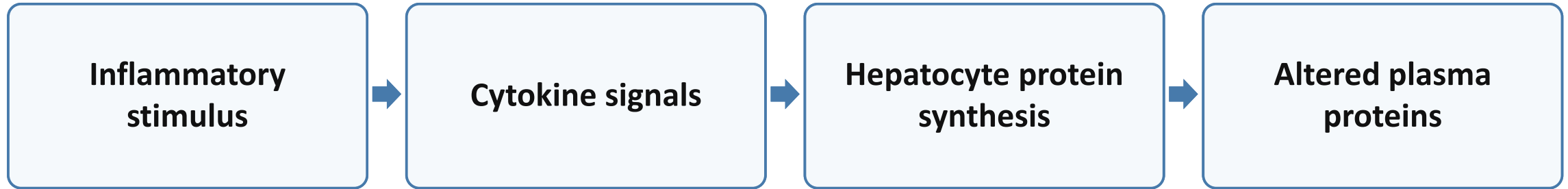
- Neoplastic cause of a high leukocyte count.
- Must be distinguished from reactive leukocytosis.

A striking count alone does not determine whether the process is reactive or neoplastic.

Differential patterns require etiologic context

Blood pattern	Inflammatory setting cited in Robbins	Interpretive caution
Neutrophilia	Many bacterial infections	Not specific for one organism
Lymphocytosis	Selected viral infections	Not universal to viruses
Eosinophilia	Some allergies and helminths	Requires clinical correlation
Leukopenia	Some infections incl. typhoid	Can result from sequestration

The acute-phase response is a hepatic program



- Acute-phase proteins are produced mainly by the liver.
- Their circulating levels can increase markedly during inflammation.

Acute-phase responses are not limited to acute disease

Acute inflammation

- Acute-phase proteins rise after inflammatory cytokine signaling.
- Useful evidence of an ongoing host response.

Chronic inflammation

- The same proteins may remain increased persistently.
- Prolonged synthesis can cause additional consequences.

Cytokines selectively influence hepatic products

Predominant signal in the source	Hepatic product	Relevant systemic manifestation
IL-6	C-reactive protein	Acute-phase marker
IL-6	Fibrinogen	Rouleaux and raised ESR
IL-1 or TNF	Serum amyloid A	Opsonin function; chronic amyloid risk

CRP is a cytokine-induced acute-phase protein

- C-reactive protein is one of the best-known acute-phase proteins.
- IL-6 is especially important for its hepatocyte synthesis.
- CRP may bind microbial structures and participate in host defense.

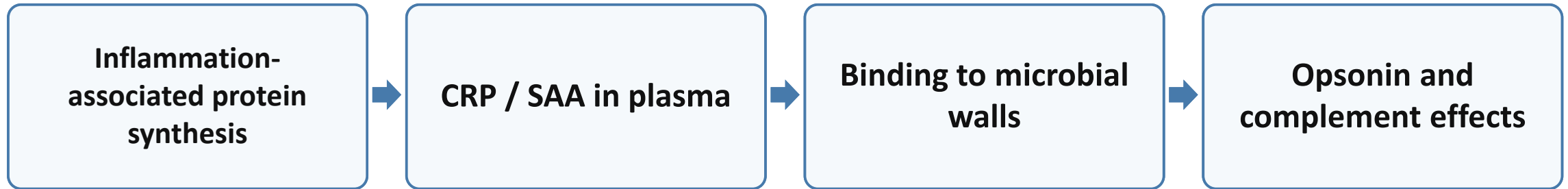
Fibrinogen is an inflammatory plasma protein

- Inflammatory cytokines, especially IL-6, stimulate hepatic fibrinogen synthesis.
- Fibrinogen affects red-cell aggregation in plasma.
- This physicochemical effect underlies the erythrocyte sedimentation rate.

Serum amyloid A responds to inflammatory signals

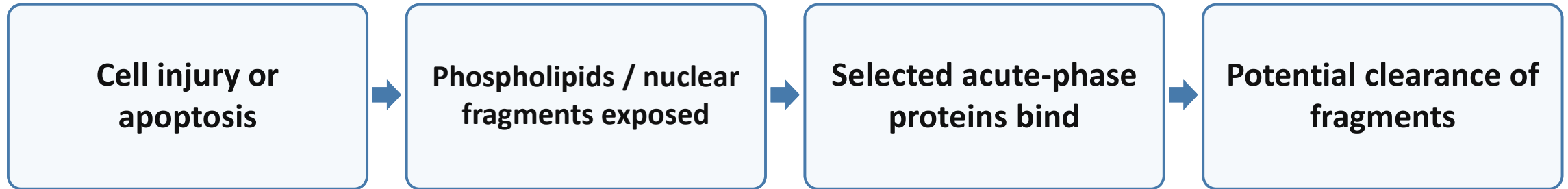
- Serum amyloid A is another prominent acute-phase protein.
- IL-1 and TNF among the signals stimulating its synthesis.
- Persistent SAA production in chronic inflammation has pathologic consequences.

CRP and SAA can support microbial recognition



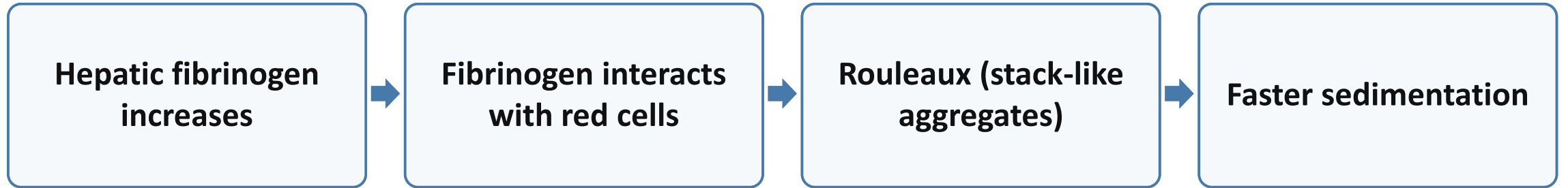
- These proteins may act as opsonins.
- Binding to microbial components can be accompanied by complement activation.

Acute-phase proteins may aid debris clearance



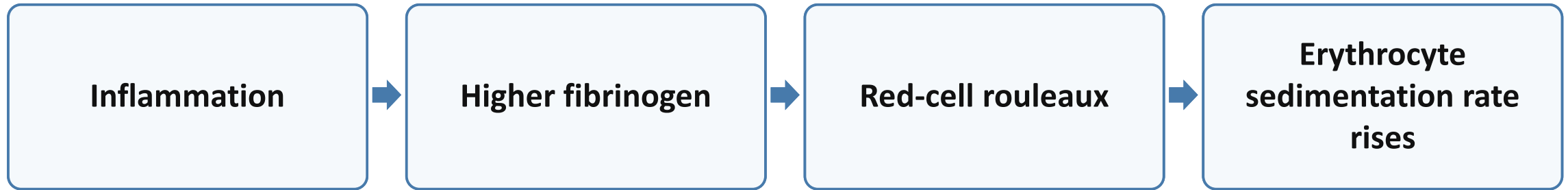
- Robbins frames this function as a possible contribution.
- Binding is not restricted to intact pathogens.

Fibrinogen promotes erythrocyte rouleaux



- Rouleaux refers to red cells forming linear stacks.
- Aggregated red cells sediment differently from isolated erythrocytes.

ESR reflects fibrinogen-associated red-cell stacking

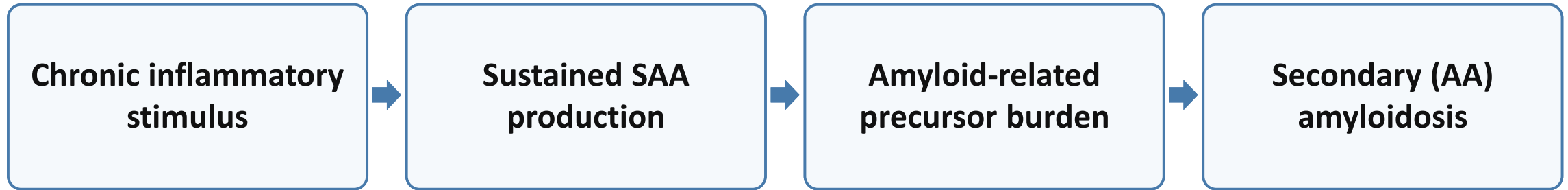


- ESR is an indirect consequence of inflammatory changes in plasma proteins.
- It is a general indicator of inflammation, not a test of the cause.

An elevated ESR is nonspecific

- Multiple inflammatory stimuli can produce an elevated ESR.
- The pathway depends on altered red-cell sedimentation behavior.
- An ESR result must be interpreted with clinical history and other findings.

Persistent SAA production can lead to amyloidosis

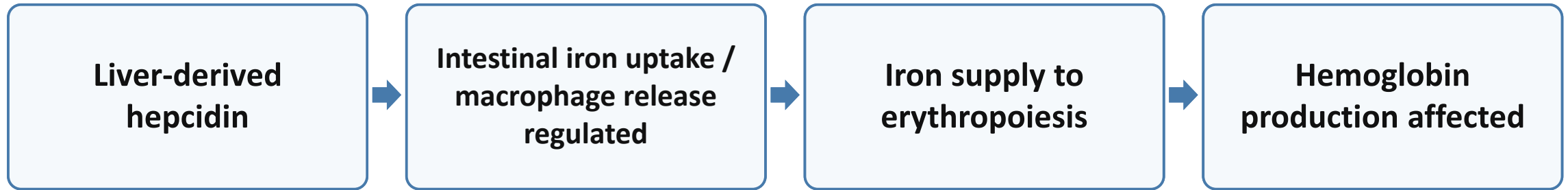


- This is a consequence of persistent, not merely transient, acute-phase activity.
- Secondary amyloidosis further in its amyloid chapter.

CRP and coronary risk: Interpret the source cautiously

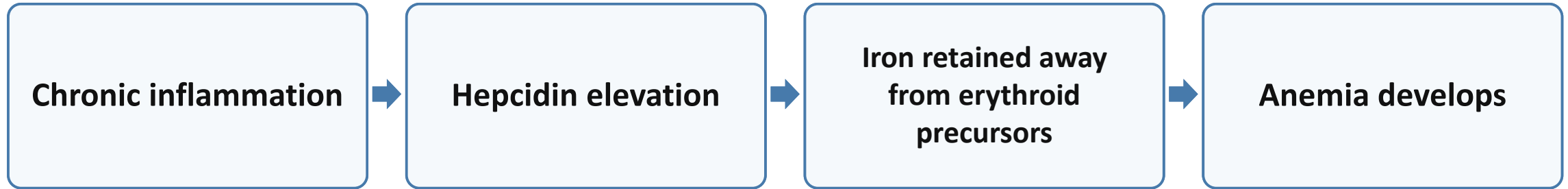
Reported association	Pathophysiologic rationale	Important limit
Elevated CRP was proposed as a marker of myocardial infarction risk in coronary disease.	Inflammation in coronary plaques may facilitate thrombosis.	The textbook passage presents a proposed marker and mechanism; It does not establish a diagnostic cut-off or causal proof.

Hepcidin regulates systemic iron availability



- Macrophages recycle iron from senescent erythrocytes.
- Hepcidin participates in controlling how that iron becomes available.

Inflammation-related hepcidin contributes to anemia



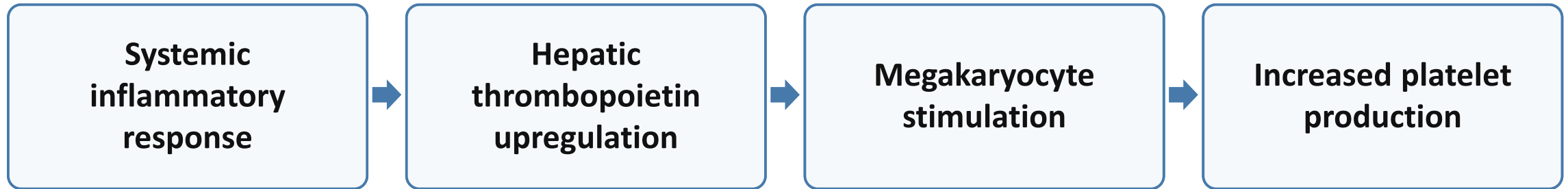
- The mechanism is altered iron availability rather than simply blood loss.
- This to anemia accompanying chronic inflammatory states.

Anemia can coexist with active inflammation

Trigger	Mediator	Effect
Persistent inflammatory cytokine response.	Increased hepatic hepcidin.	Iron sequestration limits access for developing erythroid cells.

The systemic inflammatory response affects blood counts beyond white cells.

Thrombopoietin supports platelet production



- Thrombopoietin is a major megakaryocyte growth factor.
- Megakaryocytes are platelet precursors in the bone marrow.

Inflammation may produce thrombocytosis

- An elevated platelet count can accompany systemic inflammation.
- Upregulated thrombopoietin provides a mechanistic link.
- The platelet response is a distinct finding from cytokine-driven leukocytosis.

Inflammation reshapes multiple blood compartments

Lineage / finding	Mediator or mechanism	Expected consequence
White cells	TNF, IL-1; colony-stimulating factors	Leukocytosis / altered differential
Erythrocytes	Hepcidin-mediated iron sequestration	Inflammation-related anemia
Platelets	Thrombopoietin upregulation	Thrombocytosis

Systemic symptoms extend beyond fever and blood counts

- Pulse and blood pressure may increase during the systemic response.
- Sweating may decrease as blood flow is redirected away from the skin.
- Chills, rigors, altered appetite, sleepiness and malaise are also described.

Chills and rigors are thermoregulatory manifestations

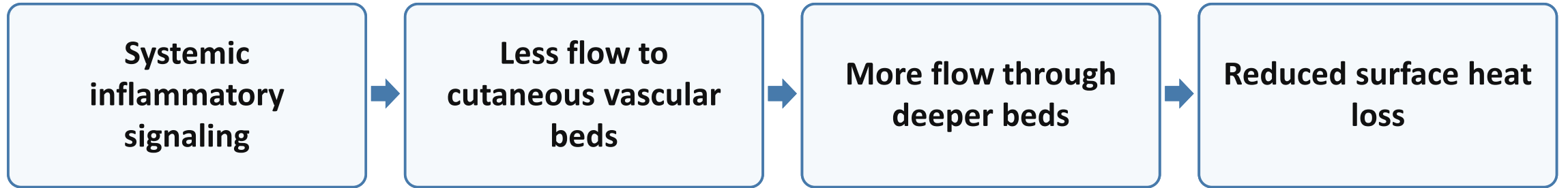
Chills

- Sensation of cold during the response.
- May prompt behaviors aimed at seeking warmth.

Rigors

- Shivering associated with systemic inflammation.
- Contributes to heat generation.

Redistribution of blood flow conserves heat



- Decreased sweating with this blood-flow pattern.
- The net effect supports elevated core temperature.

Cytokines also affect brain-associated behavior

Anorexia

Reduced appetite during systemic inflammation.

Somnolence

Increased sleepiness during illness.

Malaise

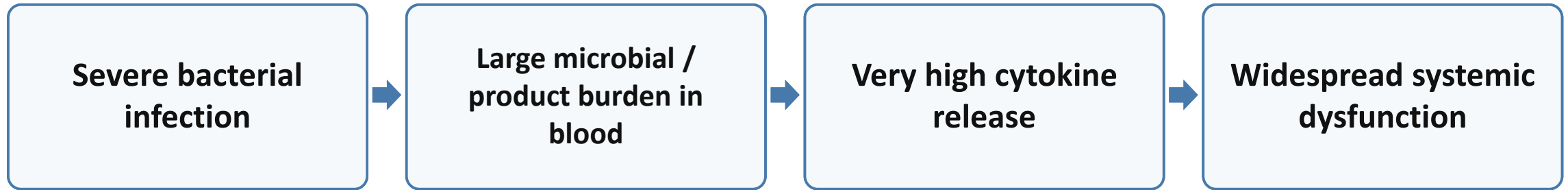
General feeling of illness and diminished well-being.

These manifestations probably to cytokine action on brain cells.

Cardiovascular and behavioral effects coexist

Systemic feature	Physiologic domain	Cytokine-linked context
Increased pulse / blood pressure	Circulatory	General inflammatory response
Chills / rigors	Thermoregulation	Conservation and production of heat
Anorexia / somnolence / malaise	Neurobehavioral	Probable brain-cell cytokine effects

Severe infection can overwhelm adaptive responses



- TNF and IL-1 in the excessive cytokine response.
- Severe systemic inflammation differs in scale and consequence from ordinary fever.

Excessive TNF and IL-1 contribute to septic shock

Initiating burden

Bacteria and bacterial products enter or persist in blood.

Mediator excess

Very large amounts of TNF, IL-1 and additional cytokines.

Systemic effects

Coagulation derangement, circulatory collapse and metabolic disturbance.

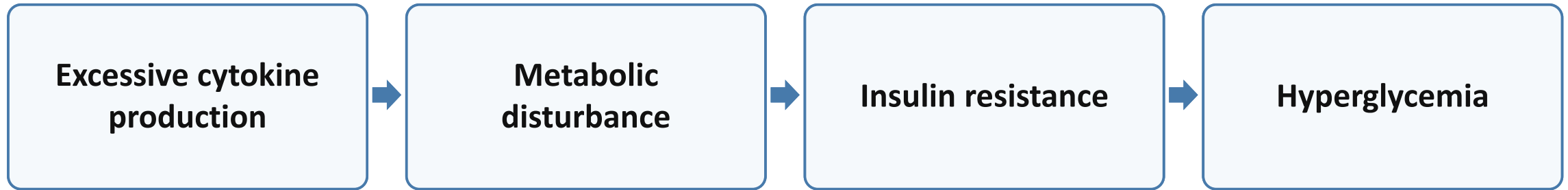
Disseminated intravascular coagulation is a severe effect

- Disseminated intravascular coagulation (DIC) among manifestations of severe systemic cytokine release.
- DIC reflects pathological activation of coagulation throughout the circulation.
- In this context, it marks a dangerous loss of localized inflammatory control.

Hypotensive shock signals circulatory failure

- Severe systemic inflammatory responses may produce hypotensive shock.
- This contrasts with the increased pulse and blood pressure that may occur during less severe systemic reactions.
- Shock is a major manifestation description of septic shock.

Severe inflammation disrupts glucose metabolism



- Insulin resistance and hyperglycemia are explicitly cited systemic abnormalities.
- They accompany other organ-system effects rather than defining the entire syndrome.

Three major shock features

Major manifestation	System-level consequence	Associated mechanism
Hypotensive shock	Marked circulatory dysfunction	Excess systemic inflammatory mediators
Disseminated intravascular coagulation	Disordered coagulation	Severe cytokine-driven systemic reaction
Insulin resistance / hyperglycemia	Metabolic dysregulation	Inflammatory cytokine excess

These are textbook-described manifestations, not a standalone contemporary diagnostic rule.

Magnitude determines whether the response becomes harmful

Ordinary systemic response

- Fever and constitutional symptoms.
- Leukocyte mobilization and hepatic protein synthesis.
- Often reflects a coordinated host response.

Excessive response in severe sepsis

- Very high circulating inflammatory mediators.
- Hypotensive shock, DIC and metabolic derangement.
- Can become a cause of tissue-threatening dysfunction.

Clinical application: Fever with left shift

Illustrative scenario: A patient develops fever during an acute bacterial infection and has increased neutrophils with immature forms.

Which two cytokine-linked pathways explain these findings?

- IL-1/TNF → hypothalamic prostaglandins → elevated thermal set point.
- Inflammatory cytokines → rapid granulocyte release from marrow → left shift.

Clinical application: Chronic inflammation and anemia

Illustrative scenario: An inflammatory condition persists; Anemia appears and the ESR is elevated.

What mechanisms can connect both findings to inflammation?

- Hepcidin elevation reduces iron availability to erythroid precursors.
- Fibrinogen promotes rouleaux formation, accelerating erythrocyte sedimentation.

Clinical application: Thrombocytosis and raised CRP

Illustrative scenario: A patient with persistent inflammatory disease has increased CRP and a reactive rise in platelet count.

Which hepatic products account for the laboratory pattern?

- IL-6 stimulates hepatocyte synthesis of CRP.
- Inflammation-associated thrombopoietin upregulation can increase platelet production.

Clinical application: Deterioration during sepsis

Illustrative scenario: Severe bacterial infection is accompanied by hypotension, coagulation abnormalities and hyperglycemia.

Identify the unifying source-described process.

- Extensive cytokine release, especially TNF and IL-1, links infection to widespread systemic disturbance.
- The major effects involve vascular, coagulation and metabolic systems.

Interpret systemic markers within their limitations

Finding	What it supports	What it does not establish
Fever	Systemic thermoregulatory response	Unique cause of inflammation
Neutrophilia / left shift	Reactive marrow mobilization	Specific infectious pathogen
CRP / ESR elevation	Inflammatory acute-phase activity	Specific etiology or lesion
SAA persistence	Potential amyloid precursor burden	Certain amyloid disease in every case

Integrating the principal systemic pathways

Cytokine-associated target	Molecular / cellular intermediary	Clinical effect
Hypothalamus	COX → PGE ₂	Fever
Bone marrow	Granulocyte release; CSFs	Leukocytosis
Liver	CRP, fibrinogen, SAA	Acute-phase response
Iron handling / platelets	Hepcidin; thrombopoietin	Anemia; thrombocytosis
Circulatory / coagulation / metabolism	Large-scale cytokine release	Shock, DIC, hyperglycemia

Reference and scope

Primary teaching source

Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th edition (2026).
Chapter 3: Inflammation and Repair — “Systemic Effects of Inflammation.”
Main section begins on printed page 91; continuation on page 92.

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