

Aplastic Anemia

Primary hematopoietic marrow failure

The defining syndrome combines reduced marrow production with pancytopenia.

Dr Abu Suraih Sakhri

MBBS, MD (Pathology)

www.abusuraihsakhri.com

Learning objectives

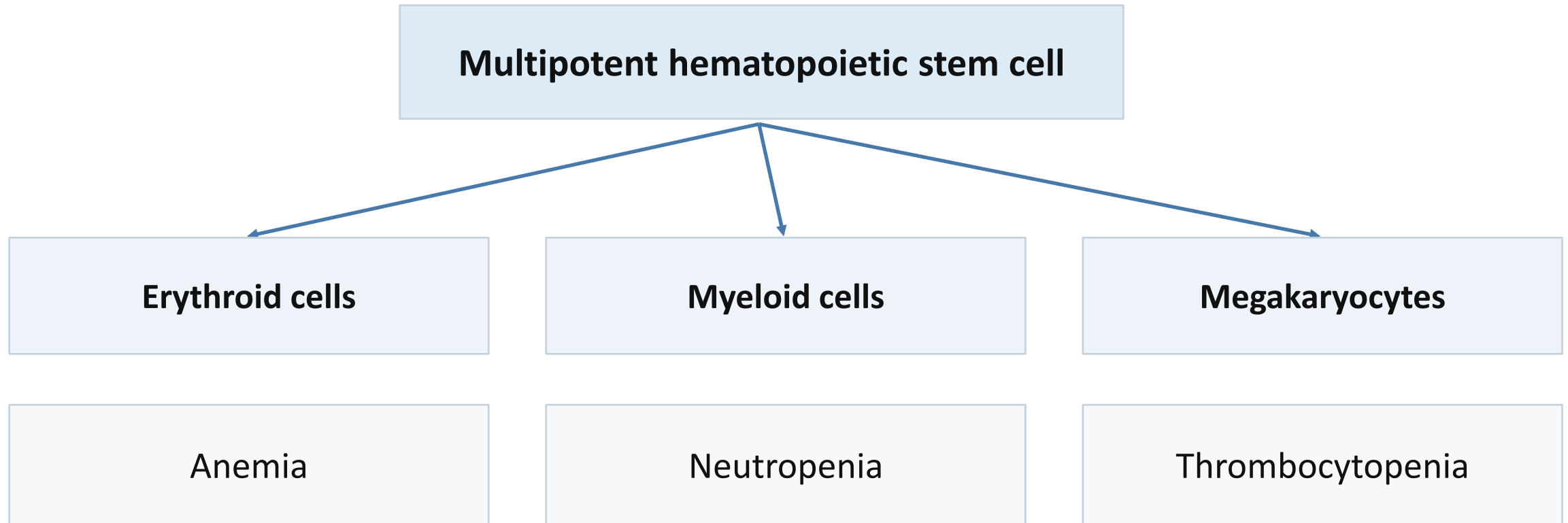
- Define aplastic anemia and explain its multi-lineage consequences.
- Distinguish acquired exposures, immune suppression, and inherited stem-cell defects.
- Recognize marrow morphology, clinical manifestations, and diagnostic contrasts.
- Relate immune and stem-cell mechanisms to the two major therapeutic approaches.

Aplastic anemia is a syndrome, not one etiology

Chronic primary hematopoietic failure + pancytopenia

Autoimmune suppression is suspected in most patients; Stem-cell defects also contribute.

Stem-cell failure produces three peripheral deficits



Schematic lineage overview; The shared stem-cell defect explains simultaneous cytopenias.

Pancytopenia: Three clinically different losses

Anemia

Loss of red-cell output
reduces oxygen-carrying
capacity.

Neutropenia

Loss of neutrophil production
impairs defence against
infections.

Thrombocytopenia

Loss of platelet production
increases mucocutaneous
bleeding.

A single marrow lesion can therefore produce weakness, infection, and bleeding.

Marrow failure versus isolated erythroid suppression

Aplastic anemia

- Hematopoietic failure involves multiple cell lineages.
- Pancytopenia develops as production falls.
- Biopsy shows marked overall hypocellularity.

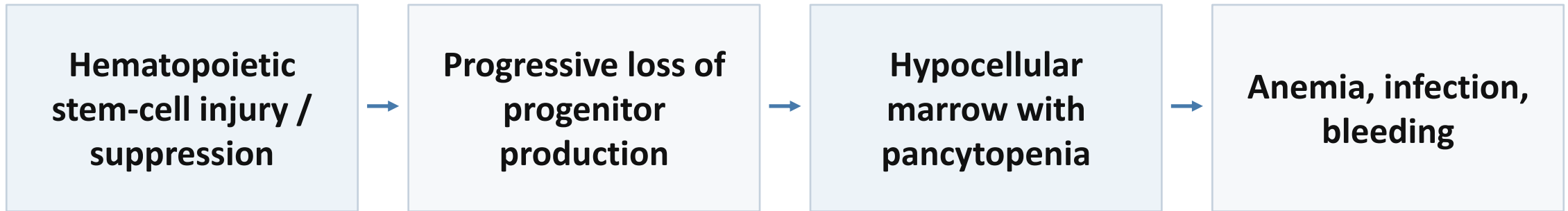
Pure red cell aplasia

- Erythroid progenitors are selectively suppressed.
- Other hematopoietic lineages are comparatively preserved.
- The pattern of cytopenia directs the diagnosis.

Occurrence and tempo

- Aplastic anemia can affect individuals of either sex and any age.
- The clinical onset is often insidious rather than abrupt.
- A predominant early cytopenia may shape presentation.
- Over time, all three cell lines typically become depressed.

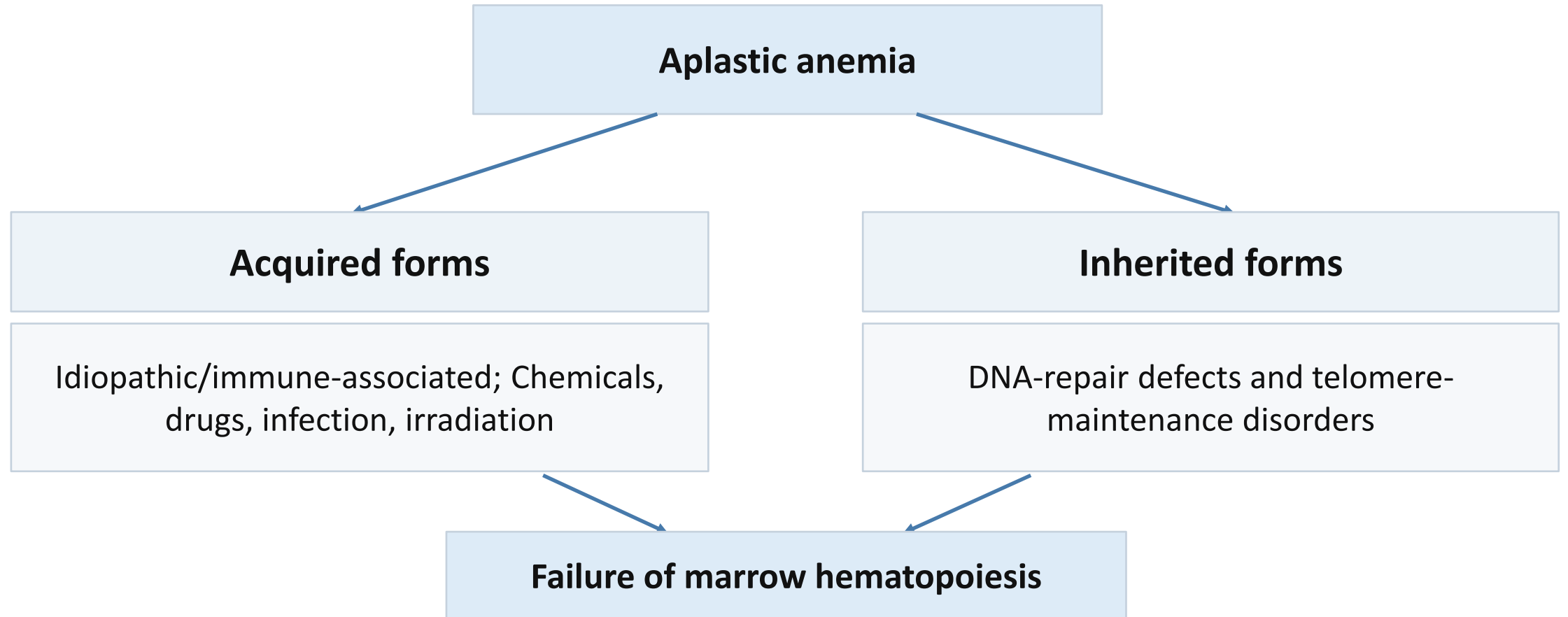
The core clinicopathologic sequence



The marrow biopsy connects the blood-count abnormalities to primary failure of production.

Etiologic framework

Two non-exclusive paths can converge on hematopoietic failure



Idiopathic cases predominate

~65%

That an initiating factor cannot be identified in about two-thirds of cases.

“Idiopathic” means unrecognized initiator; It does not establish absence of immune injury.

Exposure-related aplasia has different response patterns

Dose-related injury

Greater exposure to marrow-suppressing agents can produce predictable toxicity.

Idiosyncratic reaction

Severe aplasia may follow an exposure that usually causes little suppression.

An adverse exposure history cannot be interpreted from dose alone.

Dose-related chemical and drug injury

- Many anticancer chemotherapies can suppress the marrow in a dose-related manner.
- Alkylating agents and antimetabolites are listed associations.
- Benzene is a classic organic solvent linked to marrow suppression.
- Dose-related suppression by some agents as reversible.

Idiosyncratic drug-associated aplasia

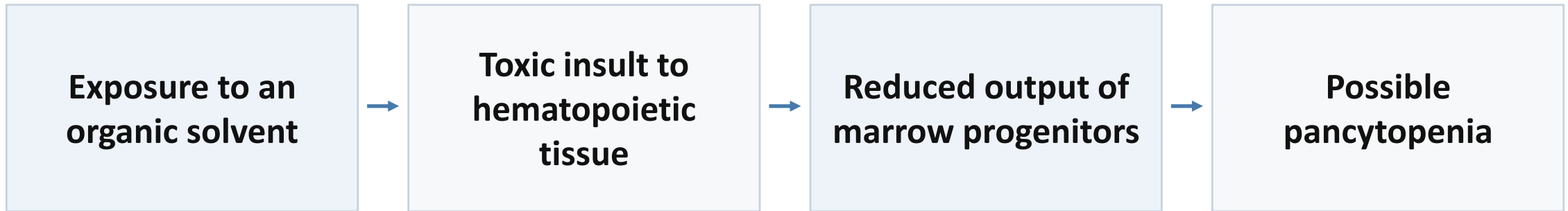
- Aplastic anemia can occur unexpectedly after drugs with little routine marrow toxicity.
- Chloramphenicol, gold salts, and carbamazepine among implicated agents.
- Phenylbutazone, penicillamine, and certain arsenicals also appear in the source table.
- The response is not predicted reliably by ordinary drug exposure.

Chloramphenicol illustrates two distinct associations

Listed under dose-related and idiosyncratic chemical agents

Distinguish general pharmacologic marrow suppression from an unusual persistent failure syndrome.

Benzene: Environmental marrow-toxic exposure



Benzene is classified with dose-related chemical exposures.

Post-hepatitis aplastic anemia

~5%

Viral hepatitis with approximately 5% of aplastic anemia cases.

Why only some infected individuals develop persistent aplasia remains unclear.

Other viral associations in the source

Cytomegalovirus

Listed among infections associated with persistent marrow aplasia.

Epstein-Barr virus

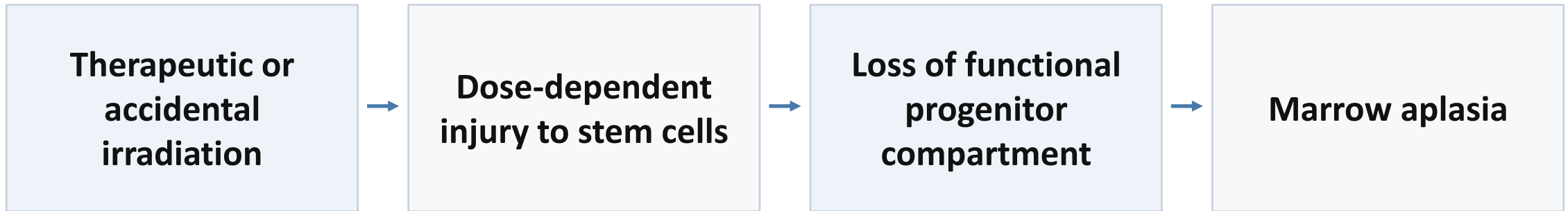
Listed among viral infections associated with the syndrome.

Varicella-zoster virus

Herpes zoster is also included among the source associations.

Association does not define a single known viral pathogenesis.

Whole-body irradiation can injure stem cells



Nuclear-accident and therapeutic exposures as examples.

Acquired and inherited disease differ in clinical clues

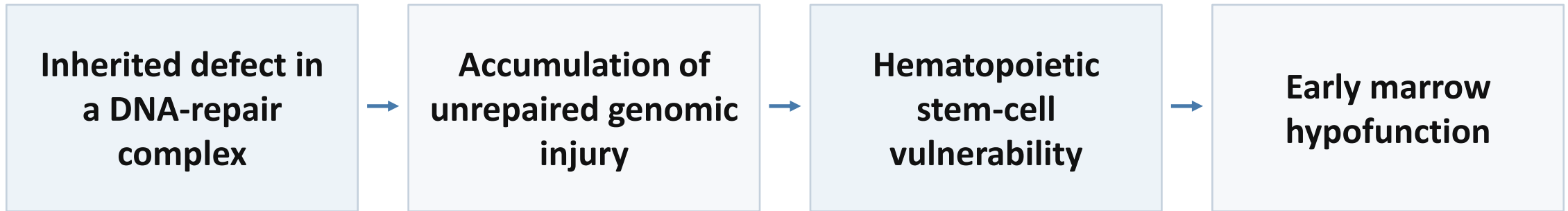
Acquired disease

- No family history or congenital abnormalities required.
- Potential relation to drugs, irradiation or viral illness.
- A substantial fraction has no identifiable inciting exposure.

Inherited disease

- Marrow failure may reflect failure of DNA repair.
- Some cases are associated with congenital anomalies.
- Telomerase defects can also present in adults.

Fanconi anemia: DNA repair failure



Fanconi anemia as a rare autosomal recessive disorder.

Fanconi anemia: Congenital associations

Bone abnormalities

Thumb or radial anomalies are highlighted.

Renal anomalies

Kidney hypoplasia may accompany marrow hypofunction.

Splenic anomalies

Spleen hypoplasia is another described feature.

These associations support a syndromic form of inherited marrow failure.

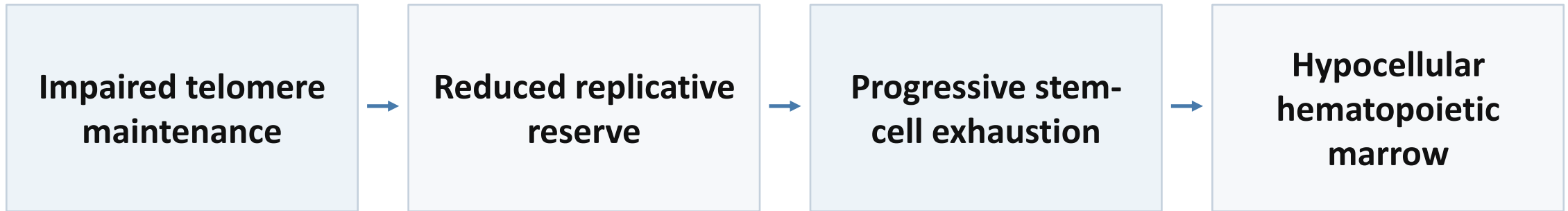
Adult-onset disease may involve telomerase

5–10%

Inherited telomerase defects in this proportion of adult-onset aplastic anemia.

This statistic is a textbook estimate, not a diagnostic screening threshold.

Telomerase deficiency: Stem-cell exhaustion



This causal model is proposed as a mechanistic explanation.

Short telomeres are not equivalent to telomerase mutations

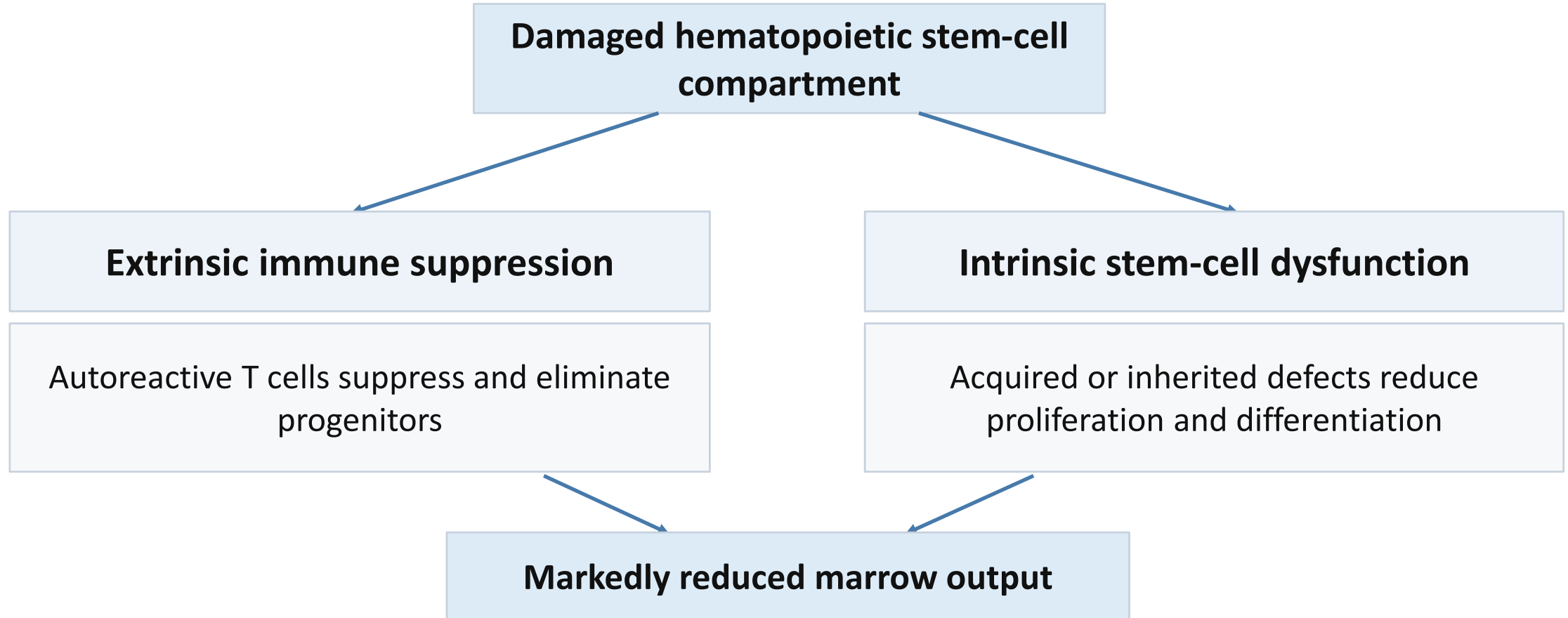
Up to $\frac{1}{2}$

Abnormally short telomeres are reported in marrow cells of as many as half of affected individuals.

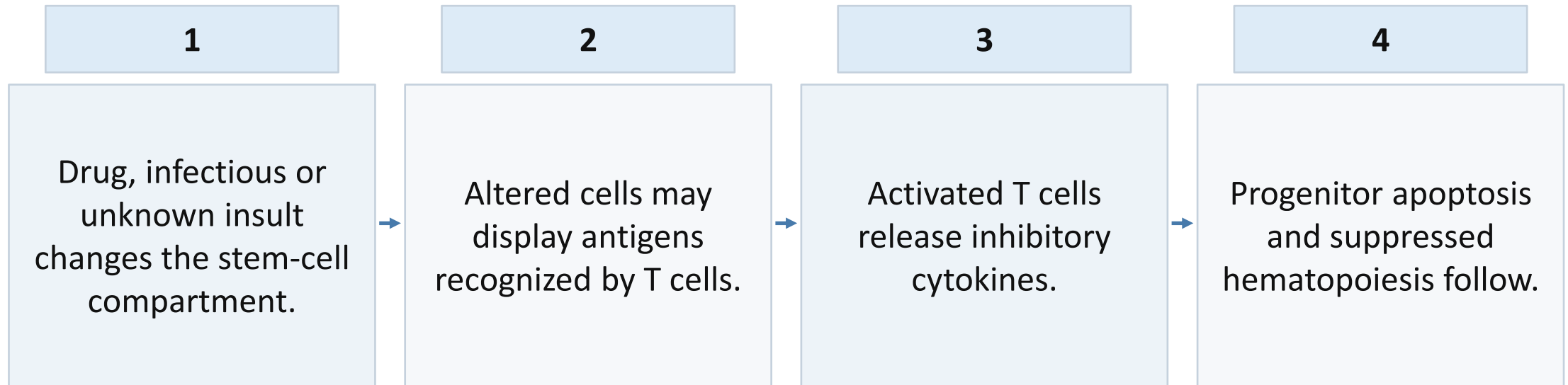
Shortening may reflect unrecognized defects or excessive stem-cell replication.

Two pathogenesis models are not mutually exclusive

Two non-exclusive paths can converge on hematopoietic failure



Proposed immune-mediated pathogenesis



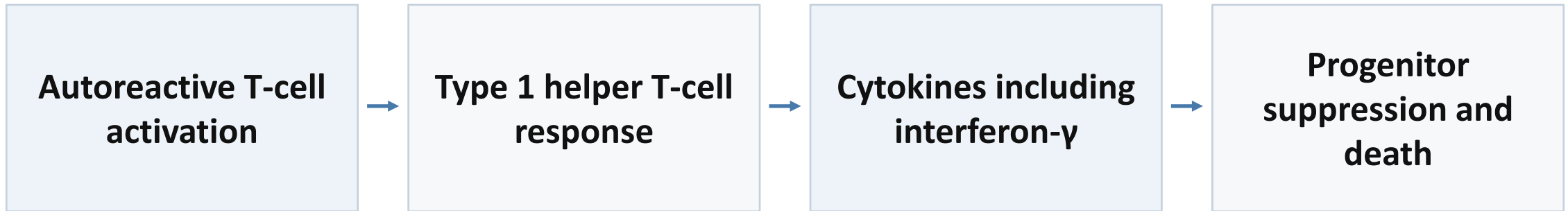
Antigens that trigger the autoreactive response remain incompletely identified.

Immune trigger: Antigenically altered stem cells

Injury may create immunologically recognizable neoantigens

This is a mechanistic proposal, not identification of a universal aplastic-anemia autoantigen.

Activated Th1 cells can inhibit marrow progenitors



IFN- γ -mediated effects in the proposed immune model.

Interferon- γ and apoptosis pathways

IFN- γ exposure is linked to expression of pro-death genes in stem cells

Residual stem cells from aplastic marrows show increased expression of apoptosis-related genes.

Gene-expression evidence supports immune injury

Observation in aplastic marrow

- Apoptosis and death-pathway genes are upregulated in residual stem cells.
- The remaining progenitor pool is profoundly depleted.

Experimental parallel

- Comparable gene activation occurs in normal stem cells exposed to IFN- γ .
- The similarity supports—but does not prove—causation.

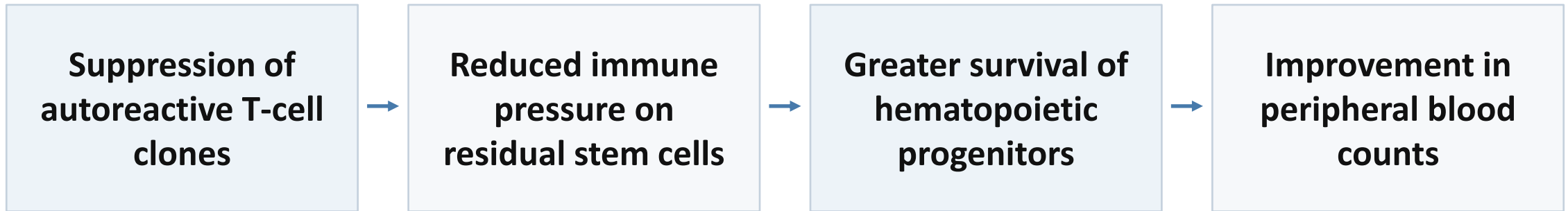
Response to immunosuppression supports an immune component

60–70%

Improvement in marrow function in this proportion of patients treated with antithymocyte globulin and related immunosuppressants.

An observed response rate is not proof that every case has the same autoimmune mechanism.

Why immunosuppressants can restore hematopoiesis



This is the mechanism proposed, not a guaranteed response in all patients.

Autoreactive antigens remain incompletely defined

- Robbins does not identify a single autoantigen shared by all cases.
- Immune attack may follow diverse stem-cell or environmental insults.
- GPI-linked proteins are proposed targets in a subset.
- Mechanistic heterogeneity is consistent with variable response to therapy.

Why aplastic anemia and PNH can coexist

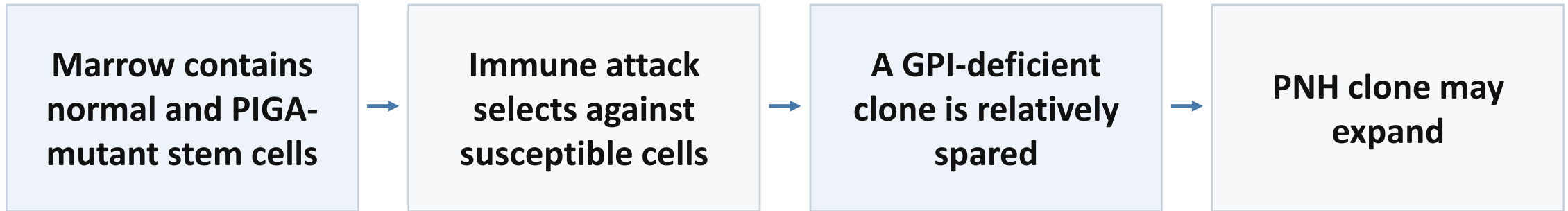
Aplastic anemia

- Autoimmune selection pressure is proposed in many patients.
- Residual stem cells may be subjected to antigen-directed attack.

Paroxysmal nocturnal hemoglobinuria

- A somatic PIGA mutation creates cells deficient in GPI-linked proteins.
- GPI-deficient clones may gain a selective advantage under immune pressure.

Proposed immune selection of a PNH clone



This is an explanatory hypothesis; Do not equate all aplastic anemia with PNH.

Intrinsic pathogenesis begins within the stem cell

The progenitor itself loses proliferative or differentiation capacity

Stem-cell injury may result from acquired genetic lesions or defects in genomic maintenance.

Evidence for intrinsic stem-cell defects

Chromosomal changes

Karyotypic abnormalities can be detected in some cases.

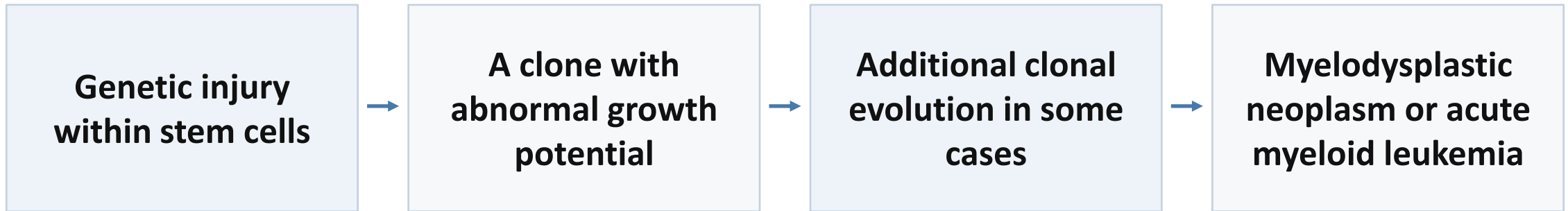
Somatic mutations

Acquired mutations in cancer-associated genes occur in many patients.

Telomere abnormalities

Short telomeres support impaired stem-cell replicative reserve.

Intrinsic damage can progress to clonal disease



Occasional evolution—not inevitable malignant transformation.

The immune and intrinsic models reinforce one another

From genetic injury to immunity

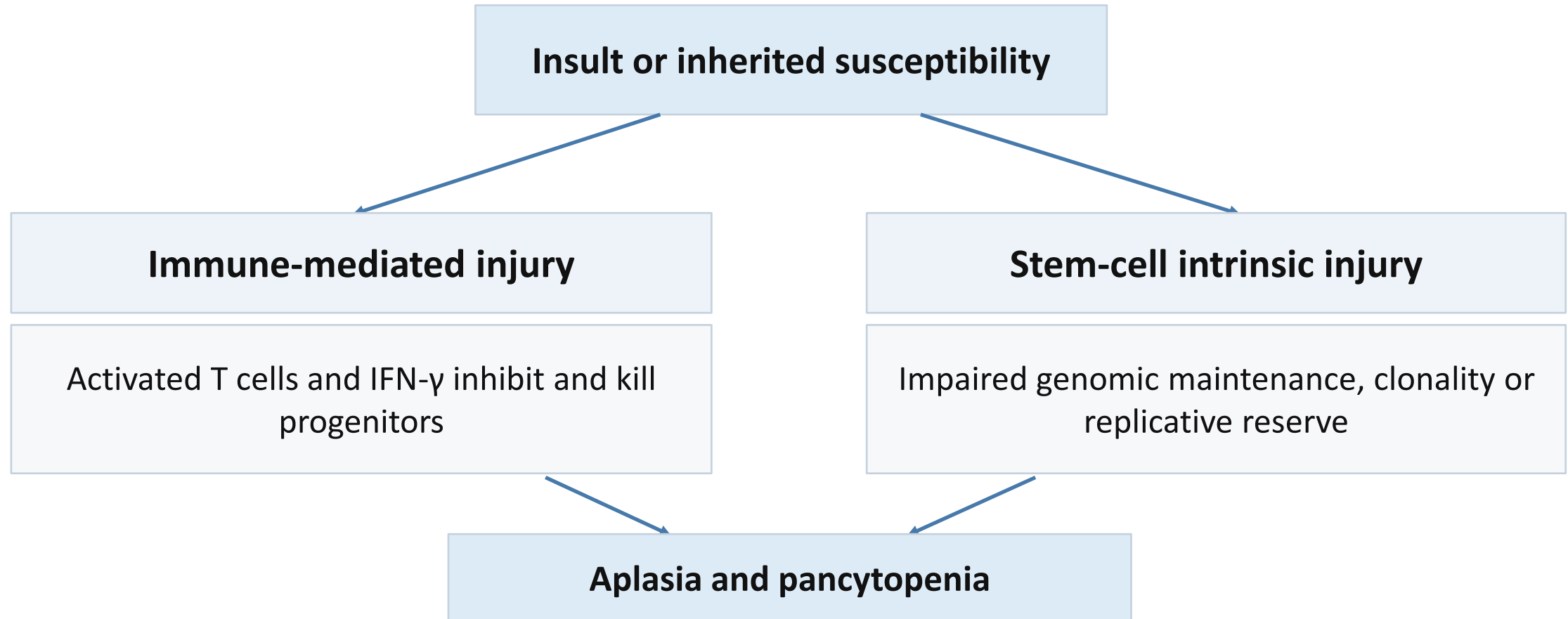
- Mutated stem cells may create new antigenic targets.
- T-cell surveillance may target these altered progenitors.

From immunity to clonal selection

- Immune pressure may preferentially eliminate susceptible clones.
- Residual populations can differ from the original stem-cell pool.

Convergent mechanism of marrow aplasia

Two non-exclusive paths can converge on hematopoietic failure



Mechanism predicts both reversibility and persistence

- Some dose-related chemical suppression may reverse after exposure ends.
- Persistent immune suppression can continue without a known initial trigger.
- Intrinsic defects may restrict the capacity of remaining stem cells to recover.
- Clinical outcome therefore depends on the underlying mechanism and residual marrow reserve.

Mechanistic evidence: Observation versus inference

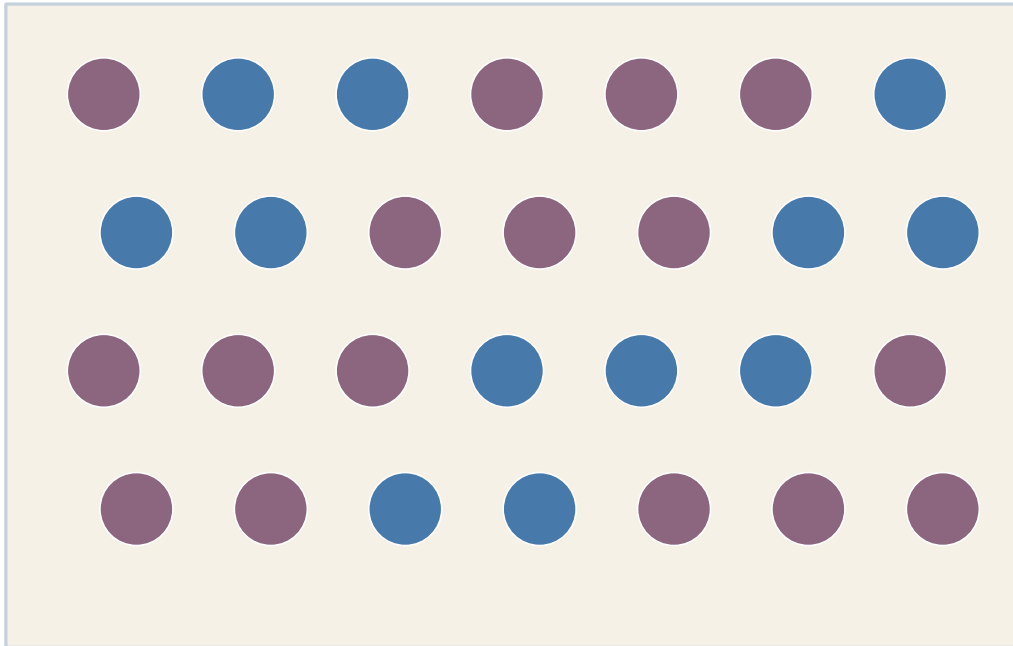
Observation	Intervention	Inference
Hypocellular marrow; Apoptosis-gene expression; Clonal abnormalities.	Improvement after T-cell– directed immunosuppression in a substantial subset.	Immune and stem-cell injury cooperate in at least some patients.

Mechanistic models integrate evidence; They do not replace patient-level diagnostic evaluation.

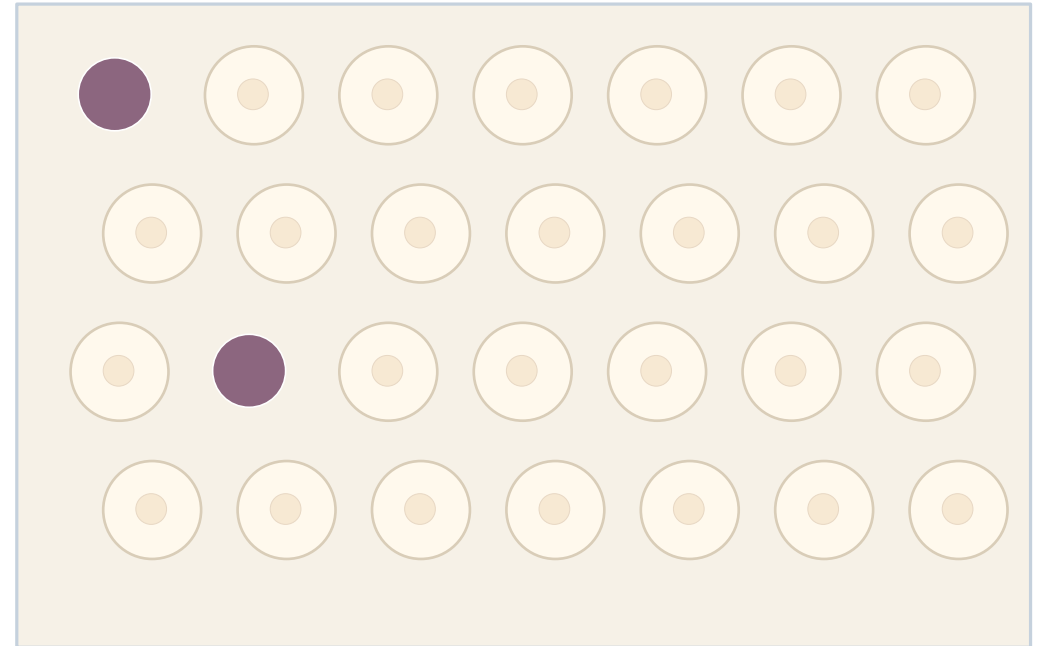
Marrow morphology: Cellularity collapses

Schematic architecture - not a histopathology image

Hematopoietically active marrow



Aplastic marrow (marked hypocellularity)



Native editable conceptual schematic; Not representative of a clinical specimen.

The marrow is dominated by nonhematopoietic elements

- Hematopoietic precursors are markedly depleted.
- Adipocytes occupy much of the biopsy space.
- Fibrous stromal elements remain.
- Scattered lymphocytes and plasma cells may still be present.

Aspirate and trephine biopsy answer different questions

Aspirate

- May recover very little marrow material.
- “Dry tap” is a recognized practical problem.
- A poor specimen cannot demonstrate architecture reliably.

Core biopsy

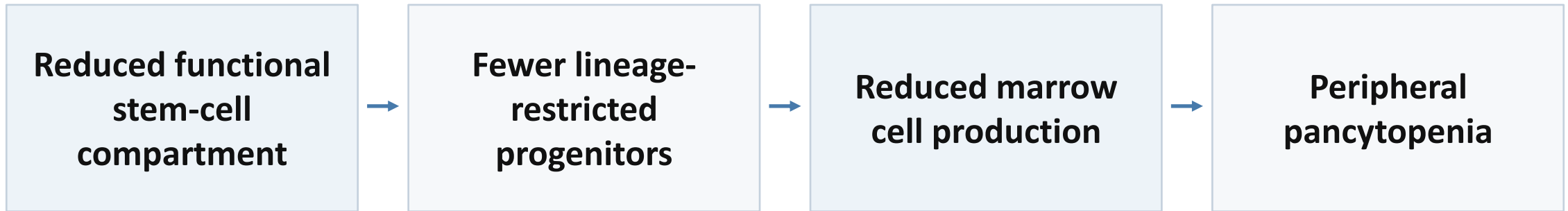
- Directly shows the relationship of fat and residual cells.
- Allows assessment of global hypocellularity.
- Biopsy as central to diagnosis.

The diagnostic morphology is hypoplasia

Marked depletion of marrow hematopoietic cells

The biopsy is usually the decisive evidence that pancytopenia reflects production failure.

Why peripheral counts are reduced



The defect is inadequate supply, not simultaneous independent destruction of all three lineages.

Peripheral tissues display secondary effects

Infection

Granulocytopenia predisposes to mucocutaneous bacterial infections.

Hemorrhage

Thrombocytopenia can produce abnormal bleeding and skin lesions.

Iron deposition

Multiple red-cell transfusions can be followed by systemic hemosiderosis.

Anemia: Oxygen delivery becomes inadequate

- Progressive weakness and fatigue reflect reduced red-cell mass.
- Pallor reflects diminished circulating hemoglobin.
- Dyspnea can develop as oxygen-delivery reserve falls.
- The anemia may dominate early symptoms in some patients.

Thrombocytopenia: Mucocutaneous bleeding pattern

- Petechiae may be an early visible manifestation.
- Ecchymoses are another characteristic cutaneous finding.
- Platelet depletion explains the increased bleeding tendency.
- Bleeding may bring patients to attention before anemia is pronounced.

Neutropenia: Infection may be the first warning

- Infections can become frequent or persistent.
- A sudden fever with chills and severe prostration can occur.
- The underlying deficit is ineffective granulocyte production.
- Severe infection can dominate the presentation despite a slow marrow process.

Blood morphology and reticulocyte response

Red-cell morphology

- Cells are usually normochromic.
- Slight macrocytosis may be present.
- Morphology alone is not diagnostic.

Reticulocytes

- Reticulocytopenia is expected.
- A low reticulocyte output demonstrates inadequate replacement.
- Interpret with the broader pancytopenia pattern.

Reticulocytopenia is a production clue

Few young red cells are released because erythropoiesis is impaired

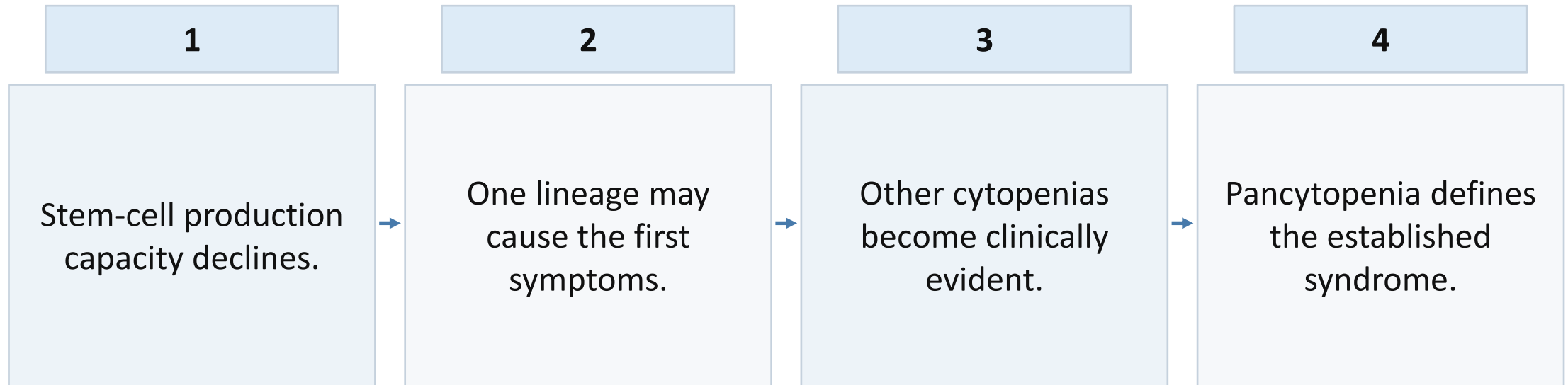
This finding helps localize the anemia to deficient marrow production rather than a compensatory marrow response.

An important negative sign: No splenomegaly

Typical finding	If enlarged
Splenic enlargement is characteristically absent.	Reconsider whether aplastic anemia explains the entire syndrome.

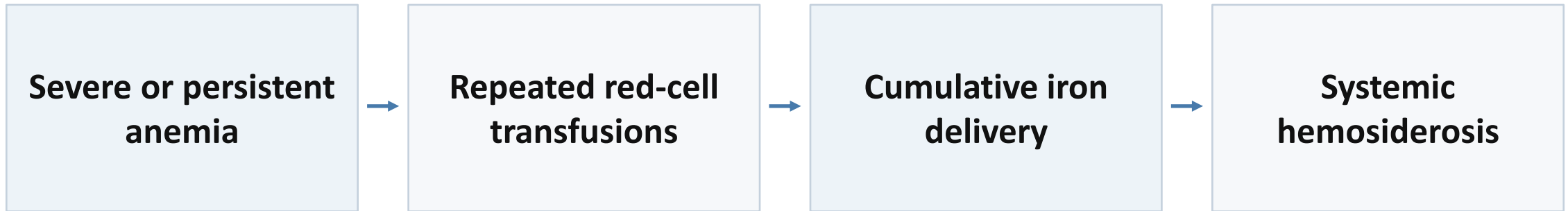
Robbins explicitly advises questioning the diagnosis when splenomegaly is present.

Clinical progression can be uneven



The order of symptoms depends on the cell lineage affected most strongly.

Repeated transfusions can produce hemosiderosis



The iron deposition is a secondary treatment-associated consequence, not the primary cause of aplasia.

Three clinicopathologic correlations

Weakness and pallor

Reduced erythroid progenitors → fewer red cells.

Petechiae and bruising

Reduced megakaryopoiesis → fewer platelets.

Persistent fever

Reduced granulopoiesis → impaired antimicrobial defence.

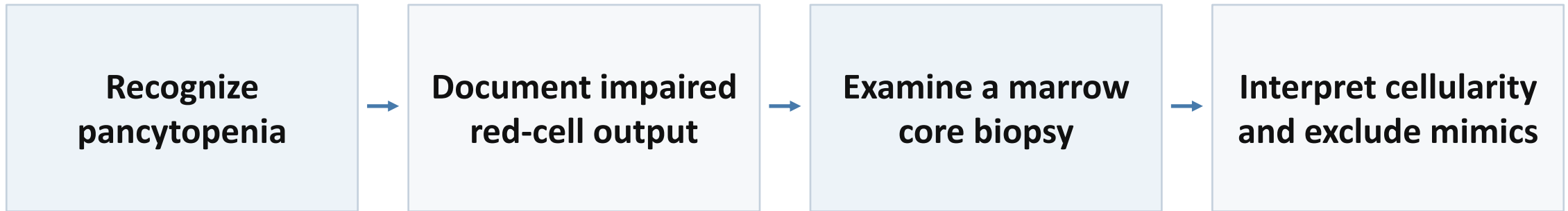
Clinical application: A new pancytopenia

Hypothetical case: An adult develops weeks of weakness, bruising, and recurrent febrile infections. A blood count shows anemia, neutropenia, and thrombocytopenia.

Which unifying tissue-level process should be investigated?

Primary failure of hematopoietic cell production; Bone marrow core biopsy is central to assessment.

Diagnostic logic in suspected aplastic anemia



This is a teaching framework, not a formal decision rule or diagnostic severity classification.

Marrow patterns help distinguish pancytopenias

Condition	Typical marrow pattern	Interpretive focus
Aplastic anemia	Marked hypocellularity	Depletion of all blood-forming elements
Myelodysplastic neoplasm	Usually hypercellular	Abnormal clonal hematopoietic precursors
Aleukemic leukemia	Neoplastic marrow involvement	Leukemia may be absent from peripheral blood

“Usually hypercellular” is the Robbins generalization; Exceptions require specialist assessment.

Why leukemia can mimic marrow failure

Shared clinical manifestations

- Anemia, thrombocytopenia and neutropenia.
- Bleeding and infection may dominate.
- Peripheral blood can be misleading.

Key discriminating observation

- Examine the marrow directly.
- Neoplastic progenitors support a myeloid neoplasm.
- Marked paucity of all progenitors supports aplasia.

Aplastic anemia versus myelodysplastic neoplasm

Aplastic anemia

- Hematopoietic elements markedly depleted.
- Marrow is typically very hypocellular.
- Intrinsic clonal injury can occur in a subset.

Myelodysplastic neoplasm

- An alternative myeloid neoplastic cause of cytopenia.
- The typical marrow as hypercellular.
- Occasional evolution from aplastic anemia is recognized.

Pure red cell aplasia versus aplastic anemia

Feature	Aplastic anemia	Pure red cell aplasia
Affected marrow lineages	Multiple hematopoietic lineages	Selective erythroid progenitors
Peripheral blood pattern	Pancytopenia	Predominantly anemia
Marrow lesion	Marked generalized hypocellularity	Marked erythroid depletion
Important clinical context	Drugs, irradiation, immune injury, inherited defects	Thymoma, LGL leukemia, autoimmunity, parvovirus B19

Pure red cell aplasia: Important associations

Thymoma

A well-established associated neoplasm.

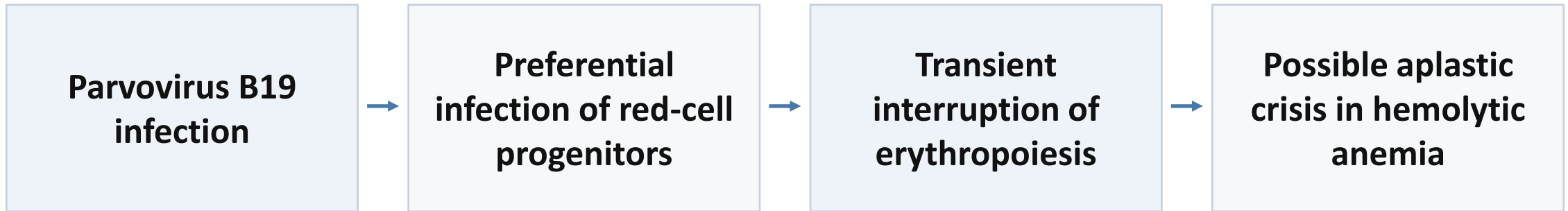
Large granular lymphocytic leukemia

Another relevant hematolymphoid association.

Immune and viral conditions

Autoimmune disorders and parvovirus B19 may suppress erythroid cells.

Parvovirus B19: Selective erythroid injury



This is erythroid-selective suppression; It should not automatically be equated with global aplastic anemia.

Why B19-related anemia depends on host context

Immunocompetent host

Most infections clear rapidly;
Transient aplasia is often
clinically minor.

Pre-existing hemolytic anemia

Brief loss of production can
precipitate an aplastic crisis.

Severe immunosuppression

Persistent infection may
cause chronic pure red cell
aplasia.

Clinical application: Selective red-cell failure

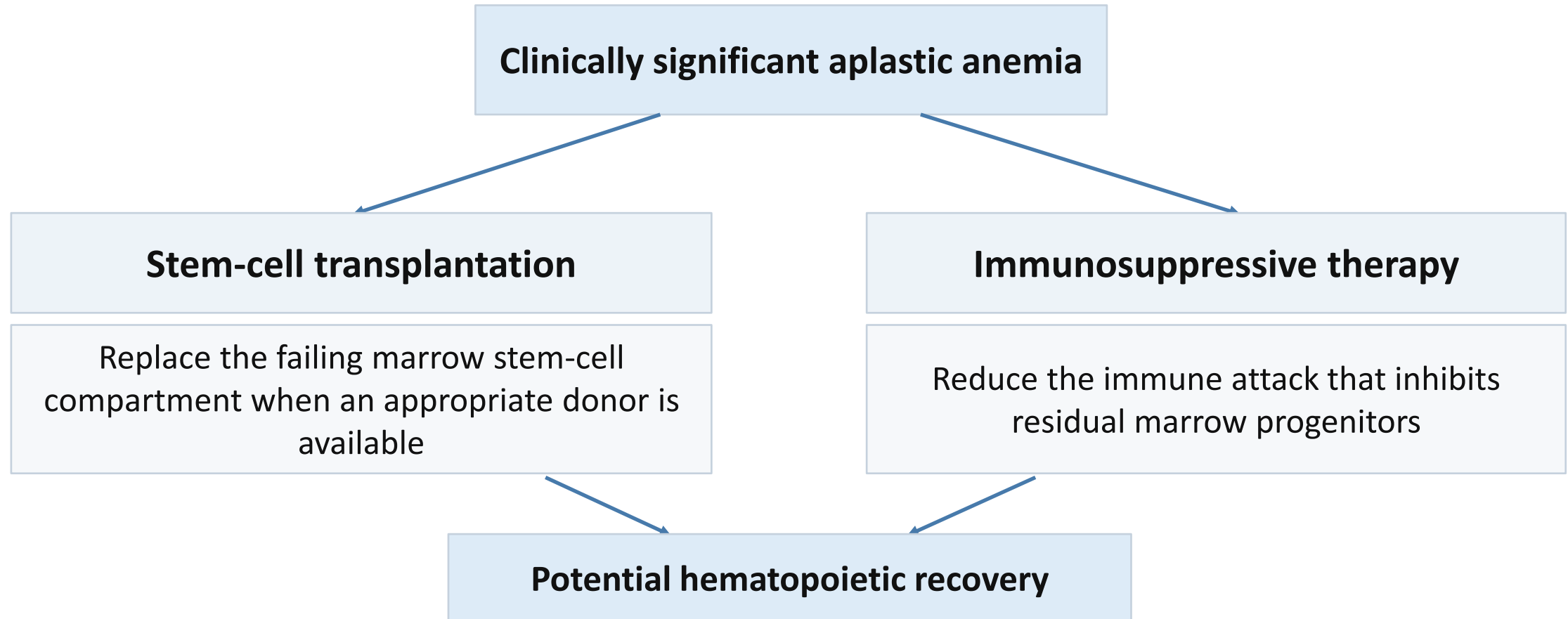
Hypothetical case: A patient with chronic hemolytic anemia develops sudden worsening of anemia during a parvovirus B19 infection, without a parallel decline in other blood-cell lineages.

Why is this not the classic presentation of global aplastic anemia?

B19 preferentially destroys erythroid progenitors; An aplastic crisis can reflect transient, lineage-selective failure.

Two principal treatment strategies

Two non-exclusive paths can converge on hematopoietic failure



Hematopoietic stem-cell transplantation

>75%

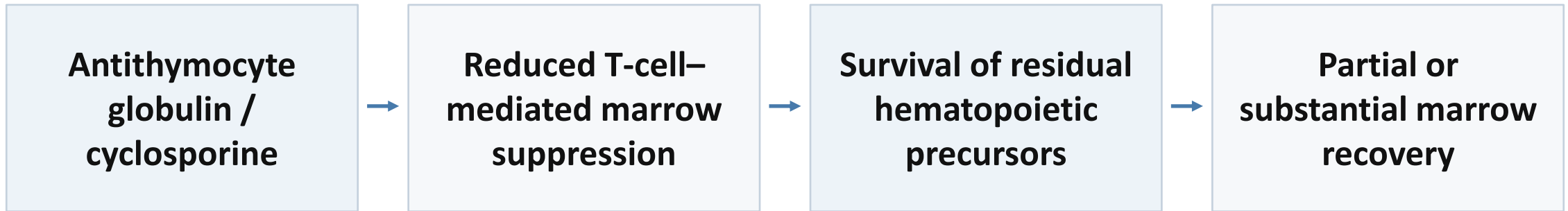
Five-year survival above 75% after transplantation in patients with a suitable donor.

The estimate is context-dependent and represents the textbook summary, not individualized prognosis.

Why donor suitability matters

- Transplantation aims to establish a functional hematopoietic stem-cell compartment.
- Transplantation as the preferred option when a suitable donor is available.
- Donor availability helps determine whether the transplant pathway is feasible.
- Clinical decisions cannot be made from marrow morphology alone.

Immunosuppression targets the extrinsic mechanism



This approach is valuable, particularly without a suitable donor.

Transplantation and immunosuppression act differently

Stem-cell transplantation

- Replaces the compromised hematopoietic system.
- Requires an appropriate donor and clinical eligibility.
- May provide durable restoration of marrow function.

Immunosuppressive therapy

- Attempts to release remaining progenitors from immune suppression.
- Does not directly replace the stem-cell pool.
- Can improve function in a substantial fraction of patients.

Prognosis must remain individualized

- Robbins characterizes the overall prognosis as variable.
- Mechanism, severity of marrow failure and treatment feasibility all matter.
- Clinical infection and bleeding complications arise from specific cytopenias.
- Clonal evolution to a myeloid neoplasm is possible in a subset.

Integrated clinicopathologic reasoning

Hypothetical case: A patient has pallor, petechiae, and recurrent bacterial infections. Blood testing confirms pancytopenia with a low reticulocyte count. Biopsy shows largely fatty marrow with few hematopoietic precursors.

Identify the syndrome, supporting morphologic feature, and key pathogenetic models.

Aplastic anemia; Markedly hypocellular marrow; Immune-mediated progenitor suppression and/or intrinsic stem-cell injury.

Pitfalls that undermine the diagnosis

Pancytopenia alone

A low blood count does not establish aplastic marrow architecture.

Splenomegaly

Splenic enlargement should trigger reconsideration of the diagnosis.

Anemia alone

Isolated erythroid failure may represent pure red cell aplasia.

Synthesis: Mechanism, morphology, clinical effects

Mechanism	Morphology	Clinical consequences
Autoimmune T-cell injury and intrinsic stem-cell defects may coexist.	Markedly hypocellular fatty marrow on core biopsy.	Reticulocytopenia, neutropenia and thrombocytopenia cause systemic symptoms.

Diagnostic anchor

Pancytopenia + reticulocytopenia + hypocellular marrow

Assess exposures and inherited clues, exclude neoplastic mimics, and correlate treatment with the mechanism.

Selected source and reading

- Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th edition (2026).
- Chapter 14, “Aplastic Anemia,” pages 599–601.
- Related chapter sections: “Pure Red Cell Aplasia” (page 601) and “Paroxysmal Nocturnal Hemoglobinuria” (pages 589–590).
- Textbook figures 14.23 and 14.24 are referenced conceptually; original figure plates were not supplied.