

Paget Disease of Bone

(Osteitis Deformans)

Remodeling • morphology • clinical consequences

Pathology teaching lecture

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Learning objectives

- Explain why enhanced bone turnover produces architecturally weak bone.
- Distinguish osteolytic, mixed, and osteosclerotic phases morphologically.
- Link SQSTM1–NF- κ B and RANK–OPG biology to osteoclast activity.
- Interpret characteristic distribution, complications, and laboratory findings.

Disease definition: Excessive, disordered remodeling

- Paget disease is characterized by increased but structurally abnormal bone formation.
- Excessive resorption and compensatory formation become poorly coordinated.
- Affected bone may enlarge and become sclerotic without gaining normal strength.

Density and strength are not equivalent.

The paradox of pagetic bone

Apparent gain

- Thickened trabeculae
- Expanded, frequently sclerotic bone
- High osteoblastic activity during active remodeling

Functional loss

- Disorganized lamellar units
- Relatively porous, mechanically weak cortices
- Microfractures, deformity, and fracture

Abnormal remodeling explains the coexistence of sclerosis and fragility.

Three cellular participants in bone remodeling

Osteoclast

Monocyte-derived, multinucleated cell;
Dissolves mineral and organic matrix.

Osteoblast

Synthesizes osteoid, builds matrix, and
regulates mineralization.

Osteocyte

Mechanosensory matrix cell that influences
local remodeling.

Osteoprogenitor

Provides osteoblast precursors; Expands near
active pagetic surfaces.

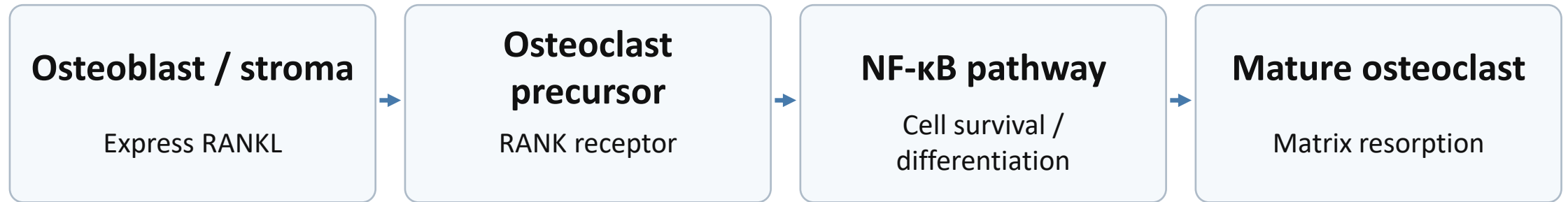
Normal bone-cell functions are summarized from the parent bone biology section.

Normal remodeling is a coupled sequence



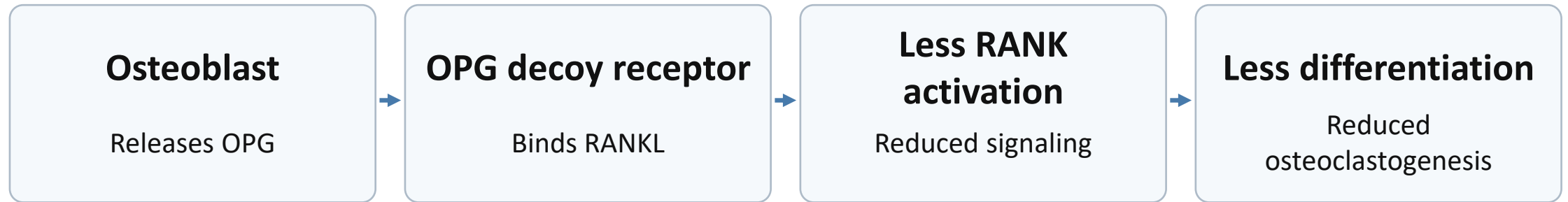
Paget disease exaggerates this remodeling program and leaves disorganized architecture.

RANKL promotes osteoclast differentiation



The axis supplies mechanistic context for Paget-associated increased osteoclast function.

Osteoprotegerin limits RANKL signaling



This negative control is relevant to the OPG gene defects linked to juvenile disease.

Woven and lamellar bone have different organization

Woven bone

- Rapidly formed bone matrix
- Randomly oriented collagen
- Reduced structural integrity

Lamellar bone

- Orderly layered collagen
- Greater structural organization
- Normal mature skeletal architecture

Paget disease can contain woven bone in its active phase and mosaic lamellar bone later.

Three sequential phases define disease evolution



Activity and microscopic appearances vary across time and between affected bones.

Osteolytic phase: Osteoclast-driven resorption

- The earliest stage contains numerous abnormally large osteoclasts.
- Active resorption pits indent the bone surface.
- Resorption creates the substrate for subsequent exaggerated formation.

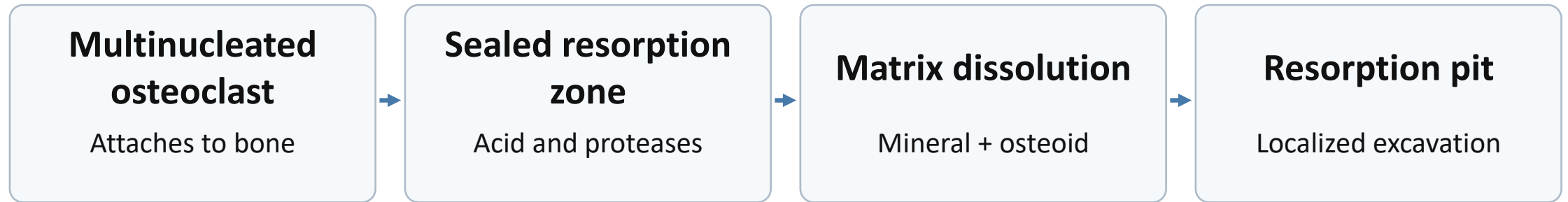
Hallmark: Excessive osteoclast activity.

Giant osteoclasts can be striking

- Pagetic osteoclasts may contain 100 or more nuclei.
- This as more than four times the normal nuclear count.
- Multinucleation must be interpreted with trabecular and phase-related changes.

Extreme osteoclast size is characteristic of an active lytic lesion.

Why resorption pits develop



This normal cellular mechanism becomes markedly exaggerated in the lytic phase.

Mixed phase: Both cell populations are active

- Osteoclasts remain conspicuous rather than disappearing.
- Osteoblastic activity increases alongside resorption.
- New bone is deposited rapidly but is architecturally disorganized.

Coexisting activity distinguishes the mixed stage.

Woven bone reflects rapid deposition

- Mixed-phase osteoblasts generate poorly mineralized woven bone.
- Collagen architecture lacks the orderly alignment of mature lamellar bone.
- Abundant new matrix does not guarantee mechanical competence.

Unorganized deposition is central to functional weakness.

Fibrovascular marrow accompanies active remodeling

- Marrow near bone-forming surfaces becomes loose connective tissue.
- Osteoprogenitor cells are present in this region.
- Numerous blood vessels accompany the active remodeling interface.

Active marrow change explains increased local vascularity.

Osteosclerotic phase: Cellular activity wanes

- The late “burned-out” stage becomes relatively quiescent.
- Prominent cement lines outline disorganized lamellar units.
- Thickened trabeculae coexist with mechanically weak cortical bone.

The signature microscopic pattern is mosaic lamellar bone.

The mosaic pattern: Irregular cement lines



Schematic (not a histologic image)

Prominent cement lines

Intersecting boundaries form an irregular “jigsaw” architecture.

The irregular orientation of lamellar units reflects disordered remodeling.

What creates the jigsaw-puzzle pattern?

- Multiple lamellar bone units have haphazard orientations.
- Unusually prominent cement lines demarcate the units.
- Irregularly intersecting cement lines generate the mosaic appearance.

The hallmark is architectural—not simply an excess of bone.

Marrow changes evolve with disease phase

Active mixed phase

- Loose fibrovascular connective tissue
- Osteoprogenitor cells near deposition surfaces
- Many vessels adjacent to bone

Quiescent late phase

- Periosseous fibrovascular tissue recedes
- More typical marrow returns
- Mosaic lamellar architecture persists

A specimen reflects disease timing and sampling site.

Bone enlargement does not imply strength

Orderly lamellar architecture



Aligned lamellar units

Pagetic remodeling



Thickened, disorganized units

Native vector schematic: Arrangement simplified; Not a specimen

Why the skeleton fractures despite sclerosis

- Newly formed bone is thick but irregular in architecture.
- Soft, porous cortices have diminished structural stability.
- Normal mechanical loading produces microfracture or gross failure.

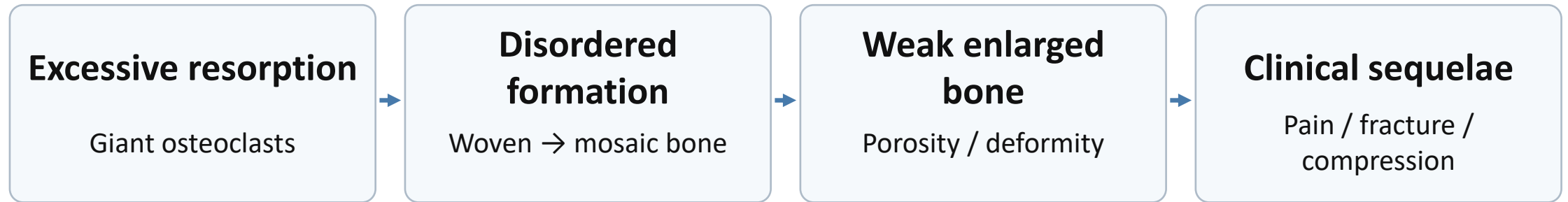
Bone mass, radiographic density, and quality must be distinguished.

Phase-dependent pathologic findings

Feature	Osteolytic	Mixed	Osteosclerotic
Dominant cell	Giant osteoclast	Osteoclast + osteoblast	Relatively fewer active cells
Matrix	Resorption pits	New woven bone	Mosaic lamellar bone
Marrow	Resorptive surfaces	Fibrovascular tissue	More normal marrow
Structure	Bone loss	High turnover	Thick but weak bone

Qualitative phase summary reconstructed; Not a diagnostic scoring system.

Pathogenesis connects histology to symptoms



Different phase appearances participate in the same mechanical disease process.

Etiology: Genetic and environmental contributions

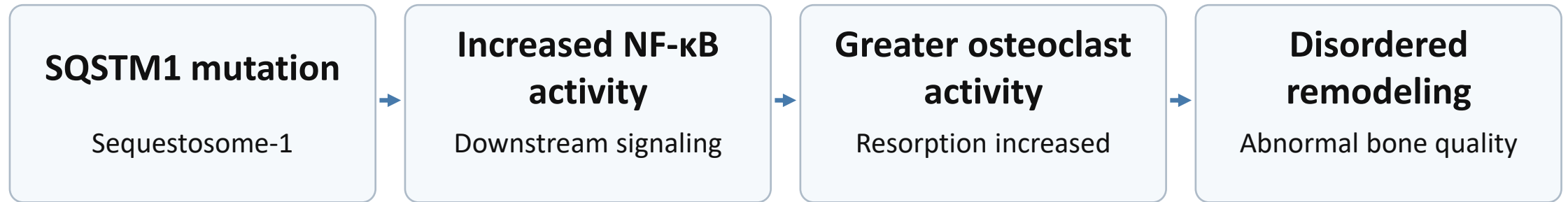
- The initiating cause is not fully established.
- Familial susceptibility supports genetic contributions.
- Geographic heterogeneity suggests environmental influences.
- No single environmental agent is confirmed by the textbook.

SQSTM1 mutations: Different familial burden

- About 60% of familial cases involve germline SQSTM1 mutations.
- About 10% of sporadic cases are associated with SQSTM1 germline mutations.
- SQSTM1 encodes the protein sequestosome-1.

Percentages are textbook-specific estimates; Not universal diagnostic probabilities.

SQSTM1 dysfunction amplifies osteoclast activity



The source describes this mechanism as an apparent disease pathway, not a complete causal model.

A negative SQSTM1 result does not exclude disease

Familial cases

- Higher reported SQSTM1 mutation fraction
- Family history can support inherited susceptibility
- Mutation is not present in every pedigree

Sporadic cases

- Smaller mutation-associated subset
- Absence of known mutation is common
- Clinical and morphologic findings remain important

Do not equate a molecular association with a universal diagnostic requirement.

Juvenile Paget disease: RANK and OPG genes



These are mechanisms for some juvenile cases, distinguished from typical late-adult onset.

Geography points to unidentified exposures

- The disease shows marked geographic heterogeneity.
- A decrease in new cases has been observed in some countries over recent decades.
- The responsible environmental factor remains unidentified.

Geographic association alone does not establish causation.

A viral hypothesis remains unproven

Experimental observation

- In vitro work proposed chronic viral infection of osteoclast precursors.
- Measles and other RNA viruses have been considered.

Evidence boundary

- Firm disease links have not been established.
- An etiologic model must not be taught as confirmed infection.

Distinguish experimental plausibility from established etiology.

Age distribution: Usually late adulthood

- Paget disease typically appears in later adult life.
- Frequency rises with increasing age.
- Many asymptomatic cases leave the exact incidence uncertain.

Age is contextual evidence, not a stand-alone diagnostic feature.

Population patterns are geographically uneven

- The textbook estimates approximately 1% of U.S. Adults over 40 years are affected.
- Relatively common: United Kingdom, central Europe, Greece, United States, Australia.
- Rare in native populations of Scandinavia, China, Japan, and Africa.

These are textbook estimates and geographic observations, not a current surveillance update.

Extent of involvement: One bone or many

Monostotic

- One affected skeletal site
- Approximately 15% of cases
- Limited anatomic distribution

Polyostotic

- Multiple affected bones
- Approximately 85% of cases
- Potential for greater skeletal and systemic burden

The supplied percentages describe the distribution reported by Robbins.

Which bones are most often involved?

- Axial skeleton and proximal femur are involved in up to 80% of cases.
- A wide spectrum of bones can be involved.
- Clinical consequences depend strongly on anatomic site.

Sites of load bearing and neural passage are especially consequential.

Incidental recognition is common

- Most patients are asymptomatic at presentation.
- An abnormal radiograph may be found during unrelated clinical workup.
- Incidental discovery can occur during staging of another malignancy.

Radiographic recognition must be interpreted within clinical context.

Radiology: Enlarged, sclerotic, deformed bone

- The source figure shows an enlarged bowed tibia.
- Cortical and cancellous regions show irregular thickening.
- Sclerosis coexists with altered shape and structural vulnerability.

Imaging illustrates morphology; It does not directly measure bone strength.

Weight bearing transforms weakness into deformity

Relatively straight axis



Long-axis load

Anterior bowing



Abnormally remodeled bone bends under load

How lower-limb bowing develops

- Pagetic bone lacks normal structural organization.
- Weight bearing can produce anterior bowing of femurs and tibiae.
- Deformity increases abnormal joint loading and mechanical symptoms.

Mechanical consequence follows architectural failure.

Craniofacial enlargement can be dramatic

- Overgrowth can enlarge the craniofacial skeleton.
- Severe enlargement may create leontiasis ossea (lion-like facial contour).
- Skull mass may increase substantially in advanced cases.

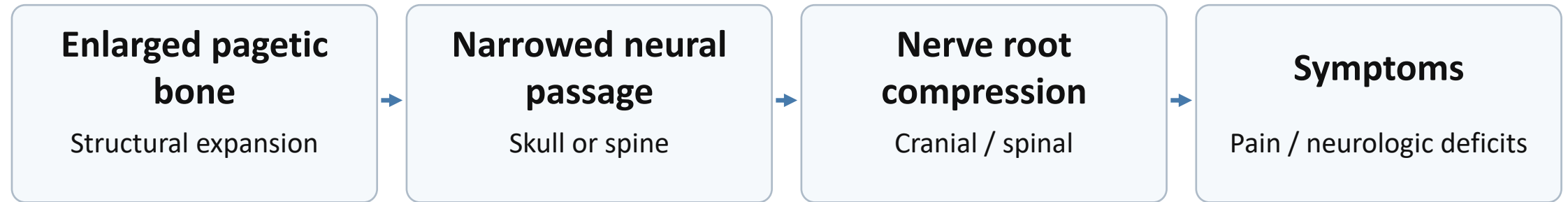
Overgrowth can produce both cosmetic and functional effects.

Skull-base deformity threatens the posterior fossa

- Pagetic weakness may permit invagination of the skull base.
- This distortion as platybasia.
- Compression of posterior fossa structures may result.

Anatomic location determines neurologic risk.

How bone overgrowth produces neurologic symptoms



Compression is a local mechanical effect—not a mandatory systemic manifestation.

Vertebral fracture can cause kyphosis and injury

- Compression fractures may occur in affected vertebrae.
- Multiple or severe collapse can accentuate kyphotic deformity.
- The source describes potential spinal cord injury.

Neurologic deficits warrant attention to structural compromise.

Hip deformity predisposes to osteoarthritis

- Pagetic deformation can distort the femoral head.
- Abnormal joint geometry increases mechanical stress.
- Severe secondary osteoarthritis may follow.

Joint pain need not originate solely from active bone remodeling.

Chalk-stick fractures reflect brittleness

- Long bones of the lower limbs are frequent sites.
- Chalk-stick–type fractures.
- A hard-appearing but poorly organized bone may fracture under load.

Clinical consequence: Fracture risk persists in radiographically sclerotic bone.

Sources of pain in Paget disease

Microfracture

Remodeled bone is vulnerable to local mechanical disruption.

Mechanical deformity

Bowing alters the loading of long bones.

Secondary osteoarthritis

Articular distortion produces degenerative joint symptoms.

Neural compression

Bony expansion may affect cranial or spinal nerve roots.

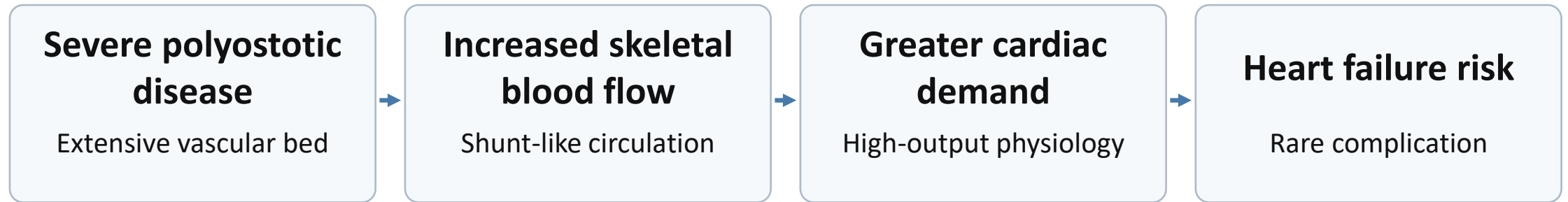
Multiple mechanisms can coexist; Do not ascribe all pain to one process.

Pagetic bone can become highly vascular

- The remodeling-associated connective tissue contains numerous vessels.
- In active disease, local hyperemia can warm the skin over the bone.
- The finding is uncommon rather than a universal diagnostic sign.

Increased local blood flow provides a pathologic clue in severe disease.

Rare systemic consequence: High-output failure



Possible new high-output failure or exacerbation of existing heart disease.

Serum biochemistry follows remodeling activity

Frequently observed

- Elevated serum alkaline phosphatase
- Osteoblastic response to high turnover
- Biochemical clue to active disease

Usually preserved

- Normal serum calcium
- Normal serum phosphate
- Does not resemble obligatory systemic mineral imbalance

Interpret ALP with imaging and the clinical picture.

Laboratory pattern: Contextual interpretation

Clinical vignette

An older adult has abnormal bone enlargement on radiography, increased alkaline phosphatase, and normal calcium and phosphate.

1. Which bone process best unifies these findings?
2. Why can ALP rise when serum calcium remains normal?

Interpretation

Disordered high bone turnover may elevate ALP without systemic calcium or phosphate abnormalities.

Secondary osteosarcoma is uncommon but serious

- Osteosarcoma in fewer than 1% of all individuals with Paget disease.
- In severe polyostotic disease, the reported proportion is 5%–10%.
- Paget-associated osteosarcoma is described as rapidly fatal.

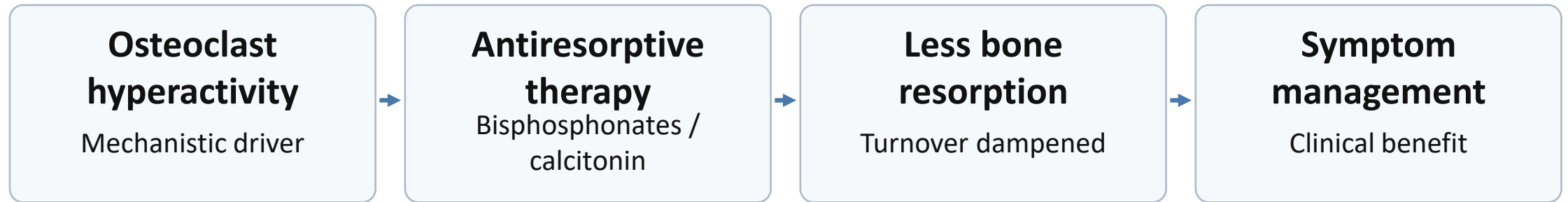
The subgroup estimate must not be applied to every affected individual.

Overall prognosis is usually favorable

- Without malignant transformation, most cases are not life threatening.
- Many patients have mild symptoms or no symptoms.
- Clinically important morbidity comes from fracture, deformity, joint disease, and compression.

Population prognosis differs substantially from rare severe complications.

Therapeutic rationale: Reduce osteoclast activity



The source states the therapeutic class rationale; Detailed drug regimens are outside this lecture scope.

Distinguish Paget disease from osteoporosis

Paget disease

- Increased, disordered turnover
- Often focally enlarged / sclerotic bone
- Abnormal mosaic architecture

Osteoporosis

- Reduced mass of normally mineralized bone
- Diffuse loss of bone quantity
- Fragility from reduced bone amount

Both predispose to fracture through different structural abnormalities.

Distinguish Paget disease from osteomalacia

Paget disease

- Disordered architecture during high turnover
- Mosaic lamellar bone in late phase
- ALP often increased; Ca/P often normal

Osteomalacia

- Inadequate mineralization of matrix
- Undermineralized remodeling bone
- A mineralization defect, not simply high bone mass

The distinction centers on disordered remodeling versus impaired mineralization.

Distinguish Paget disease from hyperparathyroidism

Paget disease

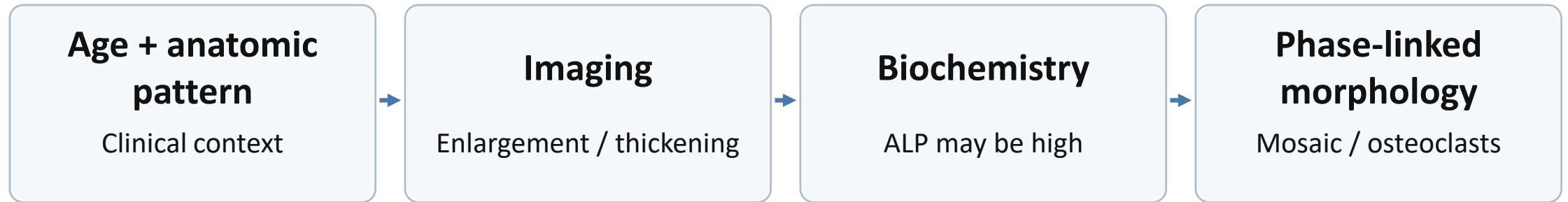
- Focal or multifocal mosaic remodeling
- Abnormally large osteoclasts in early lesions
- Local enlargement and deformity

Hyperparathyroidism

- PTH-driven skeletal resorption
- Brown tumors / osteitis fibrosa cystica in severe disease
- Often different laboratory context

Some osteoclastic features overlap; Mechanism and pattern separate the entities.

A coherent pathologic interpretation



No isolated feature substitutes for clinicopathologic synthesis.

Case: Incidental tibial sclerosis

Clinical vignette

A patient undergoing unrelated imaging has enlarged, irregularly sclerotic bone with cortical and trabecular thickening; There is no bone pain.

1. Is the absence of symptoms incompatible with Paget disease?
2. What is the mechanistic explanation for sclerosis?

Interpretation

No. Many cases are incidental; Intense disordered formation produces sclerosis.

Case: Enlarging skull and neural symptoms

Clinical vignette

An older individual has progressive craniofacial enlargement and symptoms referable to cranial nerve compression.

1. Which structural mechanism could account for neurologic symptoms?
2. Which additional skull-base consequence is?

Interpretation

Expansion may compress nerve roots; Skull-base invagination can compromise posterior fossa structures.

Case: Bowed limb and hip pain

Clinical vignette

A patient has a visibly bowed lower extremity and progressive hip symptoms alongside abnormal bone remodeling.

1. Why does the shaft bow?
2. Why can degenerative hip disease develop?

Interpretation

Architectural weakness permits bowing; Altered femoral head geometry promotes secondary osteoarthritis.

Case: Severe polyostotic disease

Clinical vignette

A patient with extensive pagetic skeletal involvement develops new, disproportionate focal symptoms.

1. Which serious bone neoplasm is a recognized rare complication?
2. Why must the risk estimate be stratified by disease severity?

Interpretation

Secondary osteosarcoma; Reported risk is far lower overall than in severe polyostotic disease.

Integrative morphology: The essential chain

- Lytic phase: Giant osteoclasts and resorption pits.
- Mixed phase: Osteoblasts, woven bone, and fibrovascular marrow.
- Late phase: Mosaic lamellar bone, thickened trabeculae, porous cortex.
- Clinical endpoint: Deformity, fracture, compression, and joint effects.

Five high-yield distinctions

- Paget disease increases bone turnover; It does not produce normal bone quality.
- Mosaic cement lines are a key late histologic feature.
- SQSTM1–NF- κ B is an important but not exhaustive pathogenesis model.
- Elevated ALP can coexist with normal calcium and phosphate.
- Secondary osteosarcoma is rare overall but clinically significant.

Source and verification boundaries

- Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th ed. (2026).
- Chapter 26: Bones, Joints, and Soft Tissue Tumors; Paget disease, pp. 1073–1075.
- Normal bone cells/remodeling and RANK–OPG context, pp. 1064–1066.
- Original, editable illustrations are conceptual schematics—not diagnostic images.