

Hirschsprung disease

Congenital aganglionosis and functional colonic obstruction

Development · enteric innervation · morphology · clinical consequences

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Learning objectives

- Define congenital aganglionosis and explain the functional obstruction.
- Connect neural crest development and genetic factors to the aganglionic segment.
- Interpret the gross, microscopic, and clinical findings.
- Explain diagnosis, operative principles, and serious complications.

A neural developmental disorder produces colonic obstruction

- Failure of enteric ganglion cells to populate a distal segment of bowel is the defining lesion.
- The affected segment is functionally obstructed despite the absence of a luminal mass.
- Proximal, normally innervated bowel dilates because fecal material cannot advance normally.

Functional obstruction versus an obstructing mass

Hirschsprung disease

- Enteric ganglion cells are absent in the affected distal bowel.
- Motility and relaxation fail; The contracted segment impedes transit.
- Proximal bowel may become massively distended.

Mechanical obstruction (conceptual contrast)

- A physical luminal narrowing or blockage impedes passage.
- Obstructing structures are not the defining lesion in Hirschsprung disease.
- The shared downstream effect is upstream retention and dilation.

A narrowed lumen does not itself reveal whether obstruction is neurogenic or mechanical.

The rectum is invariably involved

- Aganglionosis is distal and continuous with rectal involvement.
- Its proximal extent varies considerably between affected children.
- The length of the affected segment influences the gross distribution of obstruction and dilation.

Frequency and congenital associations

- An occurrence of approximately 1 in 5,000 live births.
- The disorder may be isolated or accompany other developmental abnormalities.
- Down syndrome and serious neurologic abnormalities are specifically associated conditions.

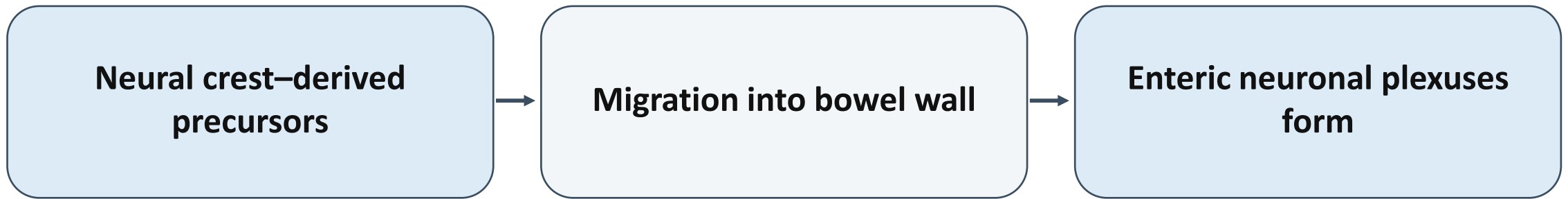
Association with Down syndrome

- Approximately 10% of Hirschsprung cases occur in children with Down syndrome (Robbins).
- The association supports an interaction between enteric development and genetic background.
- Not all children with Down syndrome have Hirschsprung disease; The figure describes the disease cohort.

The phenotype varies beyond the intestine

- Serious neurologic abnormalities in 5% of affected infants.
- Developmental associations require attention beyond a purely local colonic lesion.
- Associated abnormalities do not replace histologic confirmation of aganglionosis.

Normal enteric innervation begins with neural crest precursors



- Proliferation, migration, differentiation, and survival establish the enteric nervous system.
- Failure of this sequence can leave a distal aganglionic bowel segment.

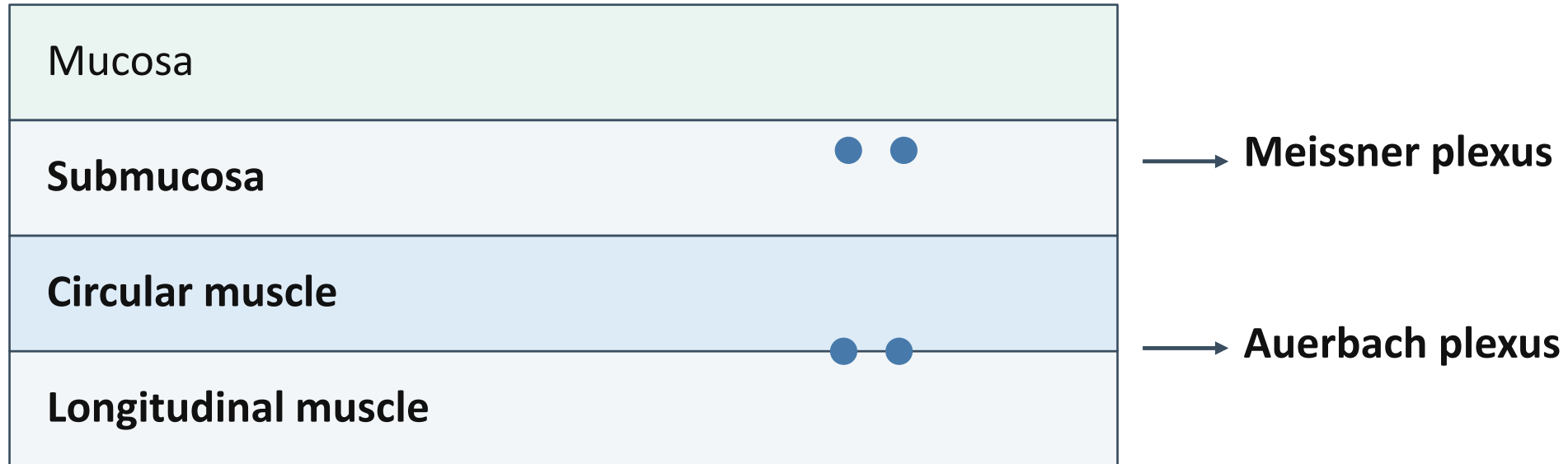
Enteric precursors migrate toward the distal bowel



- Normal migration is described from cecum toward rectum.
- Premature arrest of migration leaves bowel farther distally without ganglion cells.

Two plexuses supply the bowel wall

Schematic bowel wall — layers simplified



Schematic — not a histologic specimen

Meissner plexus lies in submucosa; Auerbach plexus lies between muscle layers.

Both plexuses lack ganglion cells within the aganglionic segment.

Meissner plexus: The submucosal neuronal network

- The submucosal plexus is one of the two enteric ganglion-cell networks.
- Loss of its ganglion cells contributes to the histologic definition of aganglionosis.
- Assessment cannot be limited to a grossly normal mucosal surface.

Auerbach plexus: Coordination of muscular activity

- The myenteric plexus lies between circular and longitudinal muscularis propria.
- Its ganglion cells normally contribute to coordinated intestinal motility and relaxation.
- Loss of these cells helps explain distal hypercontraction and failed peristalsis.

Enteric neurons coordinate propulsion and relaxation



- Functional propulsion requires coordination, not simply a contraction of smooth muscle.
- Distal aganglionosis breaks this coordinated sequence.

Normal bowel and aganglionic bowel differ functionally

Normally ganglionated colon

- Meissner and Auerbach ganglion cells are present.
- Propulsion and relaxation can be coordinated.
- Proximal bowel dilates secondarily when an obstruction lies downstream.

Distal aganglionic colon

- Both enteric ganglion-cell plexuses are absent.
- Normal relaxation and coordinated peristalsis are impaired.
- Functional hypercontraction narrows the passage.

Two developmental routes can lead to aganglionosis



- Alternatively, ganglion cells may undergo premature death after migration.
- Both routes converge on absence of ganglion cells in the distal bowel.

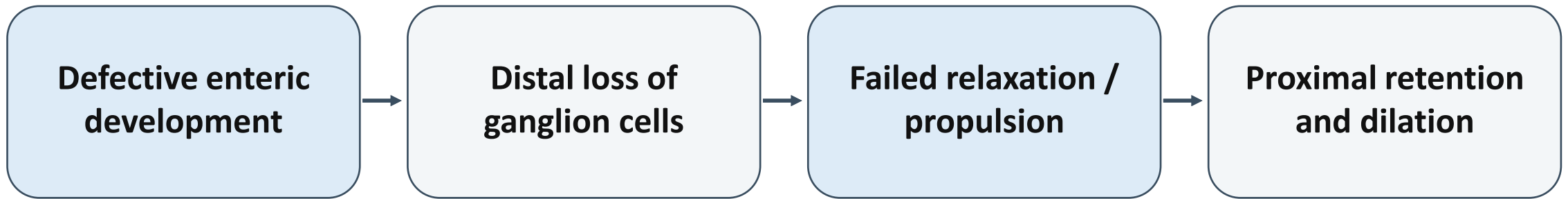
Premature migration arrest creates the distal deficit

- Neural crest–derived cells colonize bowel in a proximal-to-distal sequence.
- If migration ceases early, the rectum and additional distal bowel remain unpopulated.
- The level of arrest helps determine how far proximally aganglionosis extends.

Premature neuronal death is an alternative mechanism

- Ganglion-cell loss can follow premature death rather than primary failure to arrive.
- The endpoint remains absent enteric neurons within the affected segment.
- The microscopic and physiologic result is distal aganglionosis.

The full causal chain from embryogenesis to megacolon

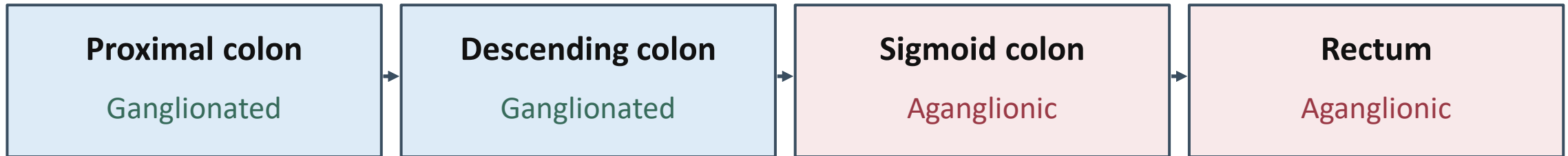


- Gross megacolon is secondary to a functional obstruction, not the primary developmental defect.

Short-segment disease predominantly involves rectosigmoid

Proximal

Distal



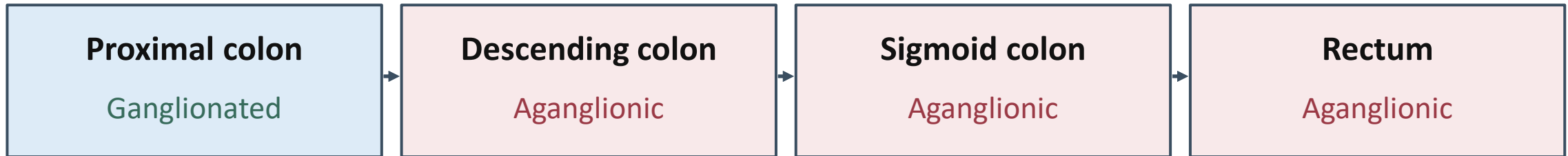
Schematic: Variable length of aganglionosis; Rectum always affected

- Rectosigmoid aganglionosis defines the short-segment pattern.
- This is the more common form.
- The bowel proximal to the aganglionic level remains ganglionated.

Long-segment disease extends farther proximally

Proximal

Distal



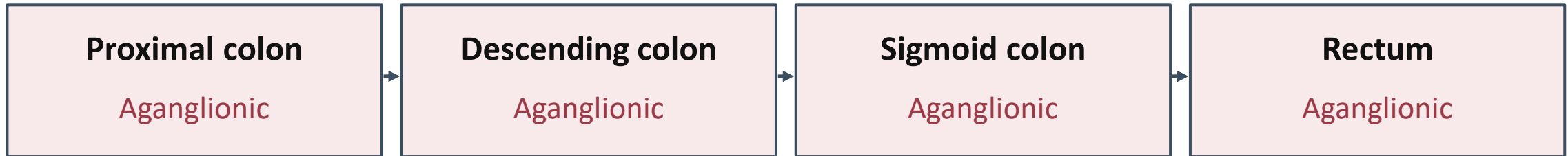
Schematic: Variable length of aganglionosis; Rectum always affected

- Long-segment disease extends proximal to the rectosigmoid region.
- The more proximal boundary differs between children.
- Histology, rather than gross appearance, defines the functional resection boundary.

The entire colon may be involved in severe cases

Proximal

Distal



Schematic: Variable length of aganglionosis; Rectum always affected

- Some severe cases involve the whole colon.
- Rectal involvement remains universal even with extensive aganglionosis.
- Gross dilation should not be used to estimate the true proximal extent.

Anatomic extent: Three useful teaching patterns

Pattern	Aganglionic territory	Interpretation
Short-segment	Rectosigmoid	Commonest pattern
Long-segment	Extends beyond rectosigmoid	Proximal boundary variable
Entire-colon involvement	Colon involved extensively	Described in severe disease

RET is a major Hirschsprung susceptibility gene

- RET encodes a receptor tyrosine kinase involved in neural crest development.
- Heterozygous loss-of-function variants account for the majority of familial cases.
- Disrupted RET signaling impairs appropriate enteric precursor development.

RET involvement differs between familial and sporadic disease

- Familial Hirschsprung disease frequently involves heterozygous RET loss-of-function variants.
- Approximately 15% of sporadic cases to RET variants.
- The absence of a documented RET mutation does not exclude Hirschsprung disease.

The endothelin ligand–receptor pair supports development



- Germline changes in EDN3 or EDNRB can contribute to Hirschsprung disease.
- Both genes are functionally linked to enteric precursor regulation.

RET and EDN3–EDNRB converge on enteric development

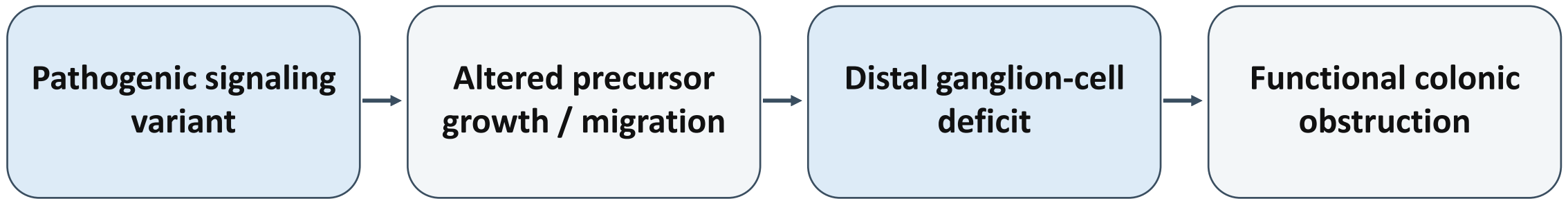
RET-related mechanism

- Receptor tyrosine kinase pathway.
- Supports neural crest precursor growth and maturation.
- Loss-of-function can yield incomplete distal innervation.

EDN3–EDNRB-related mechanism

- Receptor–ligand signaling pair.
- Controls neural crest cell development.
- Pathogenic variants can disrupt enteric colonization.

Altered signaling changes the developmental endpoint



- The molecular changes are causes of an embryologic innervation defect.
- Neither a mutation nor a signal diagram substitutes for tissue diagnosis.

Genetic causation extends beyond three named genes

- Contributions from other secreted proteins, transporters, and transcription factors.
- These additional genes account for smaller numbers of cases.
- The molecular etiology is genetically heterogeneous.

Incomplete penetrance modifies genotype–phenotype prediction

- Some people carrying pathogenic susceptibility variants do not manifest disease.
- Robbins therefore implicates modifying genes and/or environmental influences.
- A molecular result alone cannot establish the extent or presence of aganglionosis.

Sex and chromosomal context may modify susceptibility

- Male predominance is cited as evidence for possible sex-linked modifiers.
- An association with Down syndrome suggests possible chromosome 21–encoded modifiers.
- These modifiers are proposed rather than established as a single causal mechanism.

Genes and evidence: Distinguish roles

Gene / context	Role given by Robbins	Interpretive caution
RET	Receptor tyrosine kinase; strong familial contribution	Not present in every case
EDNRB	Endothelin receptor for neural crest development	One of multiple pathways
EDN3	Ligand of EDNRB	Variant does not confirm tissue status
Other genes / modifiers	Heterogeneous developmental influences	Incomplete penetrance

Absent ganglion cells explain distal hypercontraction



- The aganglionic portion as hypercontracted.
- This establishes a neurogenic functional blockage even when gross dimensions look normal.

Ineffective peristalsis is not absent muscular activity

- Visible bowel movements can occur yet fail to propagate contents effectively.
- Coordinated peristaltic contractions are impaired in the affected region.
- Clinical obstruction may coexist with apparent muscular activity.

Proximal megacolon is a secondary consequence



- Normally innervated bowel is the segment that becomes dilated.
- The dilated colon is not necessarily the segment lacking ganglion cells.

The gross paradox: Narrow diseased bowel, dilated normal bowel

Distal diseased segment

- Ganglion cells are absent.
- May appear contracted or grossly normal.
- Functional obstruction originates here.

Proximal normally innervated segment

- Enteric neurons remain present.
- Distends progressively due to downstream obstruction.
- Wall stretch may become extreme.

The most dilated region can be normally ganglionated.

A normal-looking rectum does not exclude disease

- The aganglionic bowel can appear normal externally.
- Gross inspection cannot establish normal enteric innervation.
- Histologic assessment is required when defining affected bowel and operative margins.

The cecum is vulnerable to pressure-related rupture

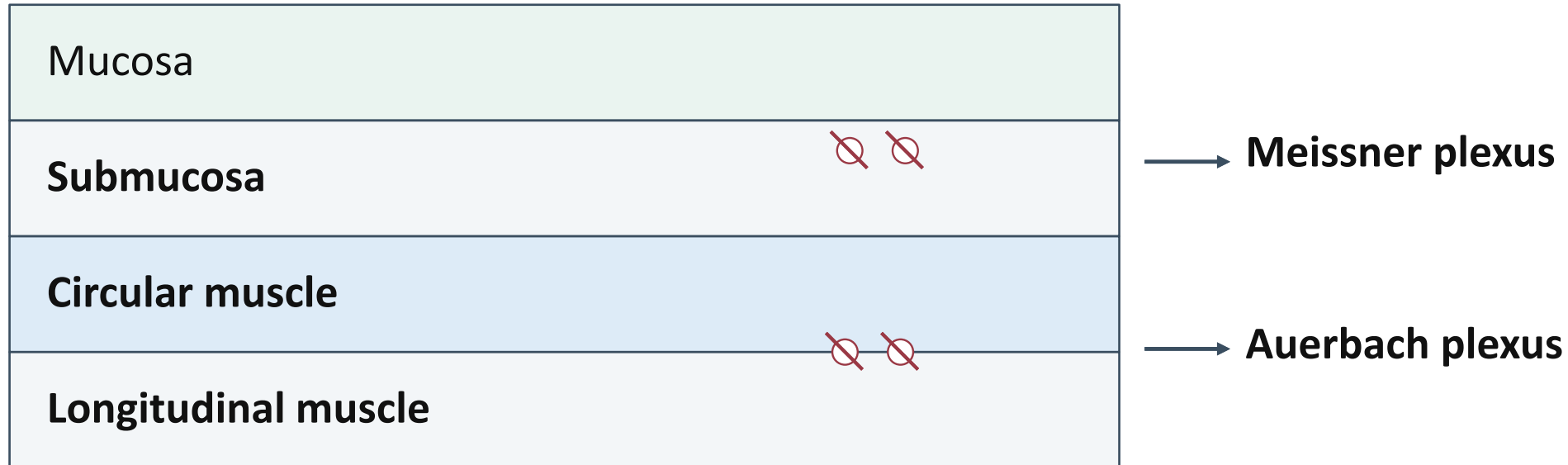
- Proximal dilation can become massive as distal obstruction persists.
- Rupture most often near the cecum in severe distension.
- Perforation converts an obstructive disorder into a potentially life-threatening abdominal emergency.

Proximal mucosal changes can confuse localization

- Mucosal inflammation or shallow ulcers may develop in normally innervated segments.
- These injuries do not necessarily indicate local aganglionosis.
- Neither mucosal appearance nor gross distension reliably maps enteric ganglion cells.

Microscopy: Ganglion cells are absent in the affected wall

Schematic bowel wall — layers simplified



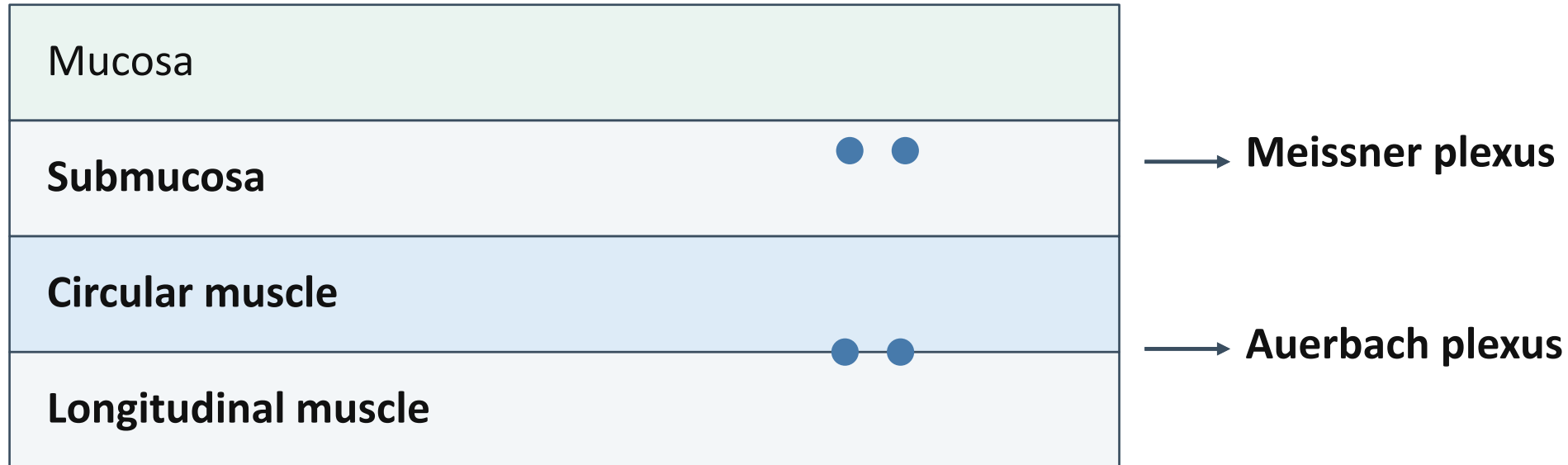
Schematic — not a histologic specimen

Histologic confirmation requires absence of ganglion cells in affected bowel.

Both Meissner and Auerbach plexuses are implicated in congenital aganglionosis.

Microscopy: An uninvolved margin must contain ganglion cells

Schematic bowel wall — layers simplified



Schematic — not a histologic specimen

A ganglionated bowel margin is the relevant operative endpoint.

Intraoperative histology can demonstrate ganglion cells before anastomosis.

Gross inspection and histology answer different questions

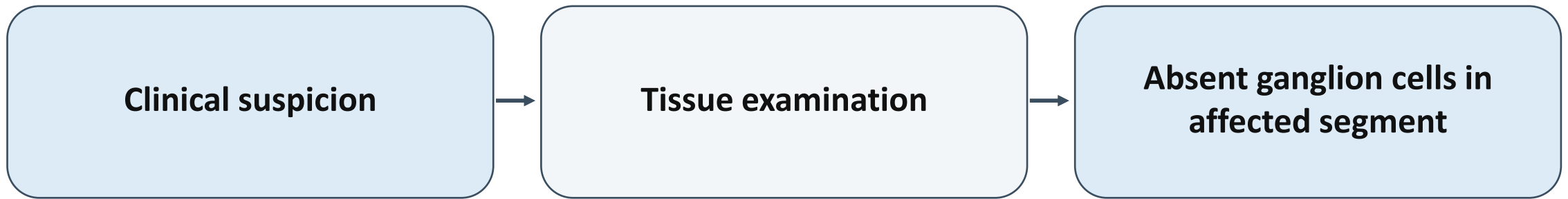
Gross examination

- Shows a contracted distal region and dilated proximal region.
- Severity of distension is readily appreciated.
- Cannot safely identify ganglionated resection margin.

Histologic examination

- Evaluates whether enteric ganglion cells are present.
- Confirms aganglionosis within affected territory.
- Guides the level of operative anastomosis.

Histology establishes the diagnosis



- Robbins specifies histologic confirmation as essential.
- Radiologic or gross patterns support suspicion but are not definitive.

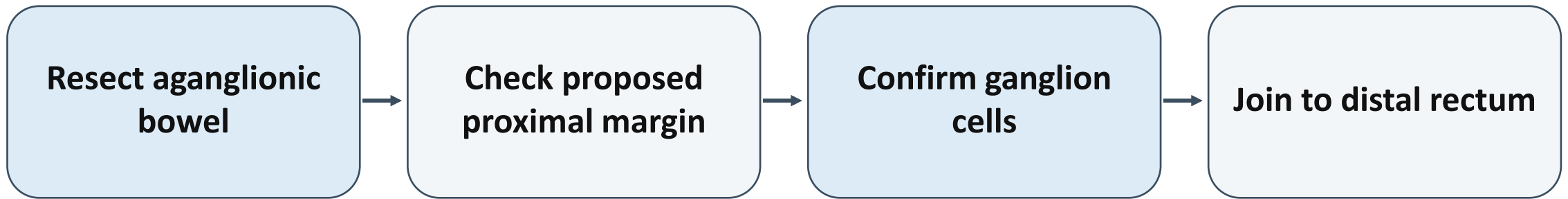
H&E shows ganglion-cell morphology

- Ganglion cells normally can be recognized morphologically on H&E-stained tissue.
- The affected segment lacks identifiable enteric ganglion cells.
- Adequate sampling and correct anatomic context are important for interpreting absence.

Interpreting the absence of ganglion cells

- An apparently normal mucosa does not establish that the underlying enteric plexuses are populated.
- Both the submucosal and myenteric ganglion-cell populations are absent in aganglionic bowel.
- Histologic assessment defines involvement more reliably than the gross transition.

Intraoperative histology protects the anastomotic level



- The text specifically identifies intraoperative frozen section as commonly used.
- A gross transition alone cannot confirm the tissue is fully ganglionated.

The earliest clinical clue is failure to pass meconium

- Hirschsprung disease typically presents in the immediate postnatal period.
- Failure to pass meconium is the classic early signal of impaired transit.
- Clinical findings arise from distal functional obstruction rather than an intrinsic fecal abnormality.

Constipation and obstruction follow the neonatal delay

- Persistence of distal transit failure leads to constipation or overt obstruction.
- Functional blockage can become evident as luminal material accumulates.
- Disease may be initially subtle if the aganglionic rectal length is very short.

Partial stool passage does not rule out aganglionosis

- A few centimeters of rectal involvement may permit some passage.
- This can obscure the diagnosis despite persistent abnormal innervation.
- A history of any stool passage must be interpreted alongside overall obstructive signs.

Abdominal distention reflects upstream accumulation

- Contents accumulate in bowel proximal to the contracted distal segment.
- Progressive dilation may become visibly dramatic.
- The physical finding maps the secondary proximal effect of obstruction.

Bilious vomiting signals severe intestinal obstruction

- Back-up of luminal material accompanies marked obstruction.
- Bilious vomiting as a feature of more obvious cases.
- In a neonate, obstructive vomiting and progressive distention warrant urgent clinical assessment.

Clinical finding and its mechanism

Finding	Mechanistic explanation
Delayed meconium	Distal transit is obstructed by aganglionic bowel
Constipation / obstipation	Ineffective propulsion across contracted distal segment
Distention / megacolon	Proximal retention and progressive dilation
Bilious vomiting	Severe obstruction with upstream back-up

Enterocolitis is a major threat to life

- Hirschsprung disease—associated enterocolitis can arise before or after repair.
- Presentations range from relatively mild symptoms to severe intestinal compromise.
- Early recognition matters because the complication may be life-threatening.

Enterocolitis may present before or after surgery

- Onset in untreated patients and after successful repair.
- Postoperative monitoring cannot end at confirmation of a ganglionated anastomosis.
- The mechanisms of Hirschsprung-associated enterocolitis remain incompletely understood.

Enterocolitis: Mild and severe manifestations

Relatively mild presentations

- Abdominal distention.
- Ileus and slowed passage.
- May evolve rather than remain mild.

Severe manifestations

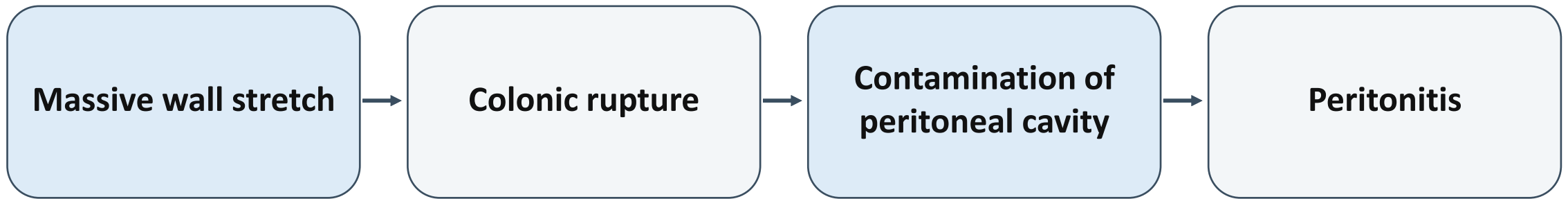
- Obstipation and marked intestinal distention.
- Pneumatosis intestinalis or pneumoperitoneum.
- Severe dehydration and electrolyte imbalance.

Enterocolitis is a clinicopathologic complication, not a synonym for aganglionosis.

Fluid and electrolyte disturbance follows severe illness

- Severe obstruction or enterocolitis can impair fluid balance.
- Dehydration and electrolyte disturbances among serious complications.
- These systemic consequences compound the hazards of intestinal distention and inflammation.

Perforation can progress to peritonitis



- Cecal-region perforation is a described vulnerability in severe megacolon.
- This sequence is a principal immediate threat to life.

Principal complications and clinical significance

Complication	Source-based consequence
Enterocolitis	Inflammatory illness that may arise around surgery
Dehydration / electrolyte loss	Potential systemic deterioration
Colonic perforation	Risk with extreme proximal distension
Peritonitis	Potentially life-threatening result of perforation

Operative treatment removes the aganglionic segment



- Surgical resection and anastomosis as treatment.
- The surgical goal is to restore a passage with normally innervated proximal bowel.

An intact operation does not ensure immediate normal function

- Bowel function and continence may take years to normalize after successful surgery.
- Enterocolitis risk can persist into the postoperative period.
- Functional follow-up remains necessary even when the aganglionic tissue has been removed.

Congenital and acquired megacolon are different entities

Congenital Hirschsprung megacolon

- Primary defect is embryologic enteric aganglionosis.
- Rectum always participates in the aganglionic zone.
- Proximal dilation is secondary to distal neurogenic obstruction.

Acquired megacolon

- Can develop at any age.
- Chagas disease, neoplasm, inflammatory stricture, and ulcerative colitis.
- The etiologic abnormality need not be developmental aganglionosis.

Chagas disease provides an important mechanistic contrast

- Among listed causes of acquired megacolon, ganglion-cell loss in Chagas disease.
- Both conditions can develop disordered propulsion from enteric neuronal loss.
- One is congenital; The other is acquired, so clinical context is essential.

Case: A neonate with delayed meconium

Clinical vignette (hypothetical)

A newborn has delayed meconium passage, progressive abdominal distention, and bilious vomiting.

Interpretation

- Which unifying lesion would account for obstruction without a luminal mass?
- Why can the bowel proximal to the lesion be severely dilated?

Expected reasoning: Distal aganglionosis → failed relaxation → proximal dilation.

Case: Partial passage despite true disease

Clinical vignette (hypothetical)

An infant passes some stool but subsequently develops persistent constipation and distention.

Interpretation

- Could a limited rectal aganglionic segment still explain the picture?
- What type of evidence is required to confirm the diagnosis?

Expected reasoning: Some passage does not exclude disease; Seek histologic confirmation.

Case: The gross transition does not settle resection level

Clinical vignette (hypothetical)

During surgery, a visibly narrow distal region is found below a dilated segment.

Interpretation

- Can the presence of ganglion cells be assumed from the dilated appearance?
- What does intraoperative frozen-section evaluation establish?

Expected reasoning: Gross extent is unreliable; Confirm ganglion cells at the margin.

Case: Deterioration after technically successful repair

Clinical vignette (hypothetical)

After aganglionic bowel resection, a child develops new distention, ileus, and dehydration.

Interpretation

- Which important postoperative complication needs consideration?
- Why does removal of the aganglionic segment not end clinical surveillance?

Expected reasoning: Enterocolitis can occur even after surgical repair.

Case: Megacolon developing later in life

Clinical vignette (hypothetical)

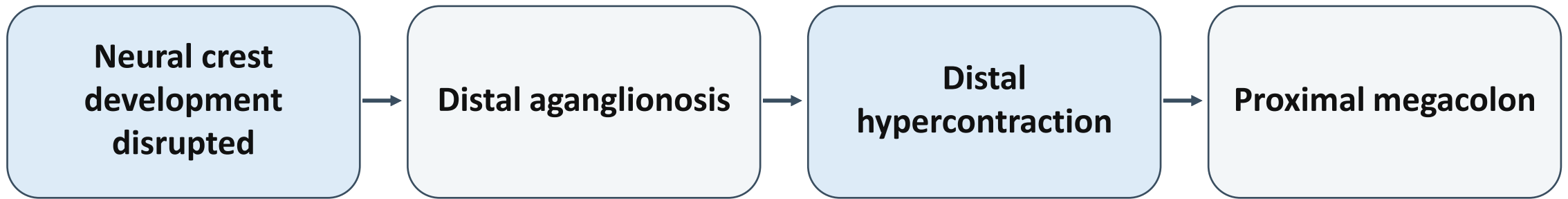
An adult develops a markedly dilated colon in the setting of an acquired disease.

Interpretation

- Why is “megacolon” insufficient to diagnose Hirschsprung disease?
- Which listed acquired condition may also involve enteric ganglion-cell loss?

Expected reasoning: Assess etiology; Chagas can cause acquired neuronal loss.

Integrating the disease as a single causal pathway



- The distal lesion is the cause; The proximal dilation is the result.
- Histology localizes the developmental defect more reliably than gross examination.

Five clinicopathologic anchors

- Rectum always affected; Proximal extent is variable.
- Both enteric plexuses lack ganglion cells in aganglionic bowel.
- Distal hypercontraction creates functional obstruction and proximal megacolon.
- Histology establishes the diagnosis and helps set a ganglionated operative margin.
- Enterocolitis, perforation, and prolonged functional recovery shape prognosis.

Primary reference and boundaries of this lecture

- Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th edition (2026).
- Chapter section: Hirschsprung disease, within congenital gastrointestinal abnormalities.
- Original textbook figures were not supplied as usable image assets; all displayed diagrams are editable schematics.
- Clinical criteria and laboratory protocols not established by the supplied excerpt were not added.