PATHOPHYSIOLOGY OF THE GASTROINTESTINAL TRACT

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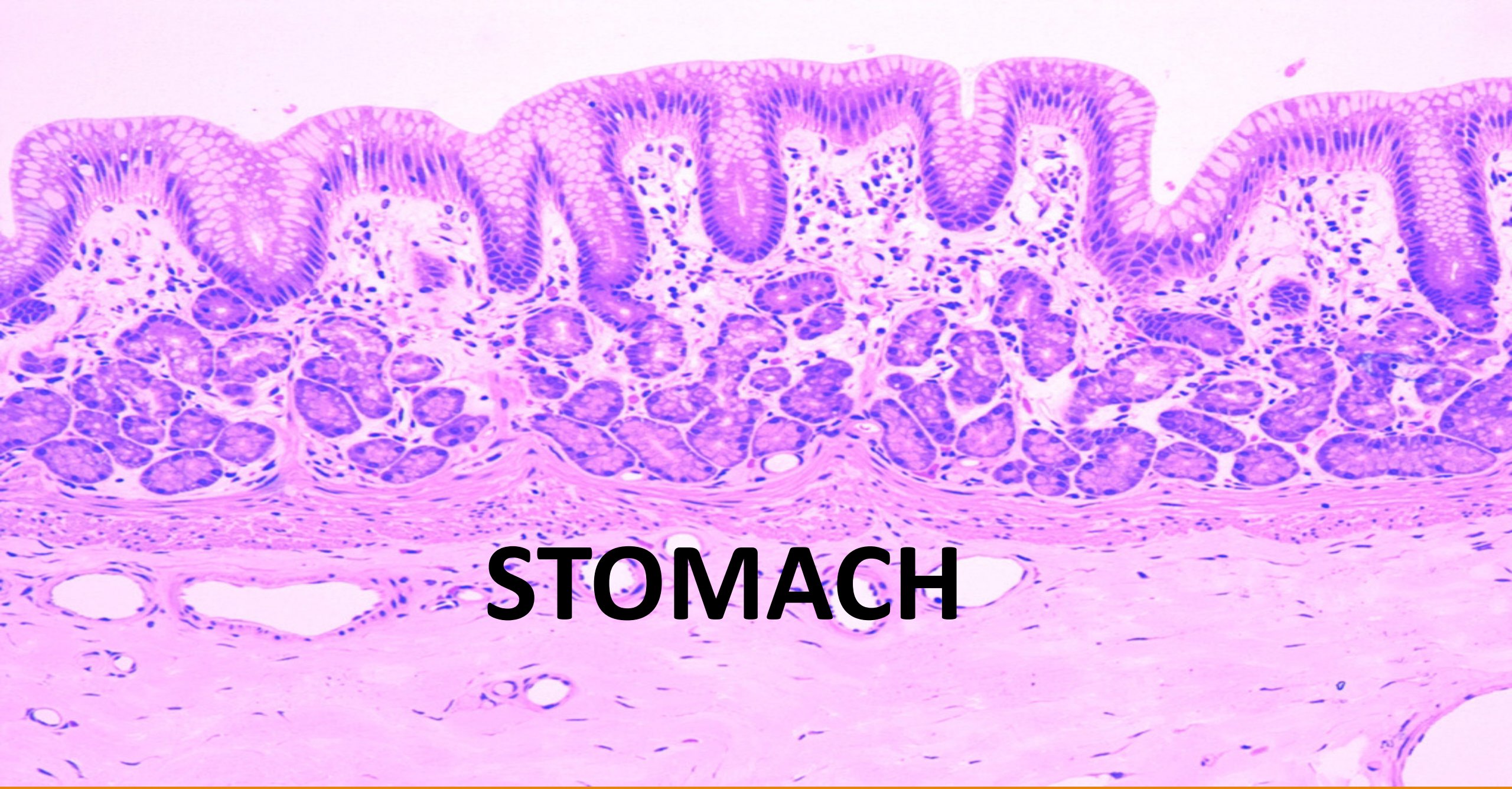


STOMACH

Histology of the stomach

Gastric mucosa contains numerous folds or rugae

Tall columnar mucous cells (1 cell thick) cover the luminal surface and communicate with the gastric pits (foveolae)

At the junction of the base of foveolae and upper portion of the neck of the fundic gland is isthmus, where pluripotential stem cells differentiate into foveolar mucous cells, migrating to the luminal surface, after which they are normally lost in 4-6 days

Multiple submucosal lymphoid patches are present

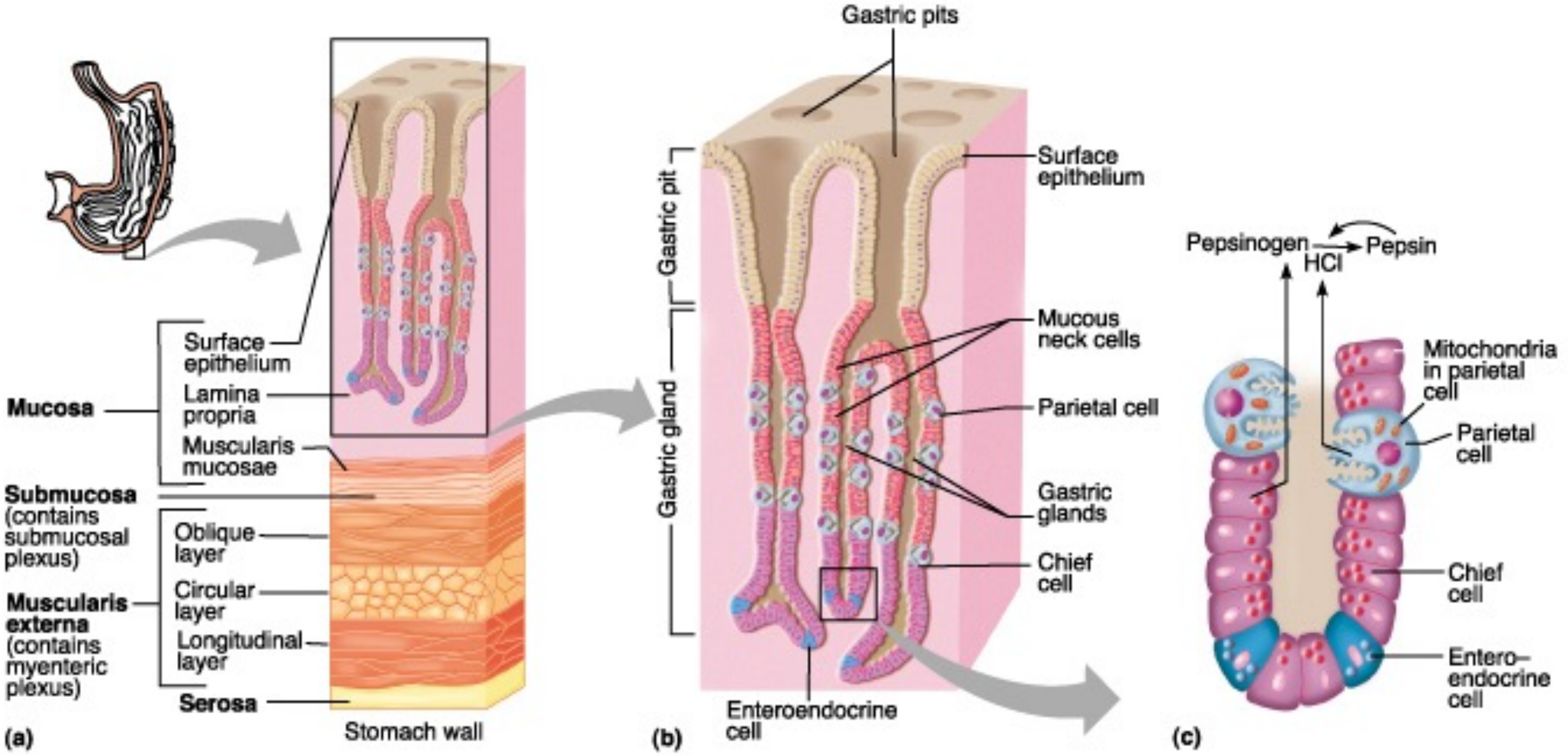
Histology of the stomach

Different cell types:

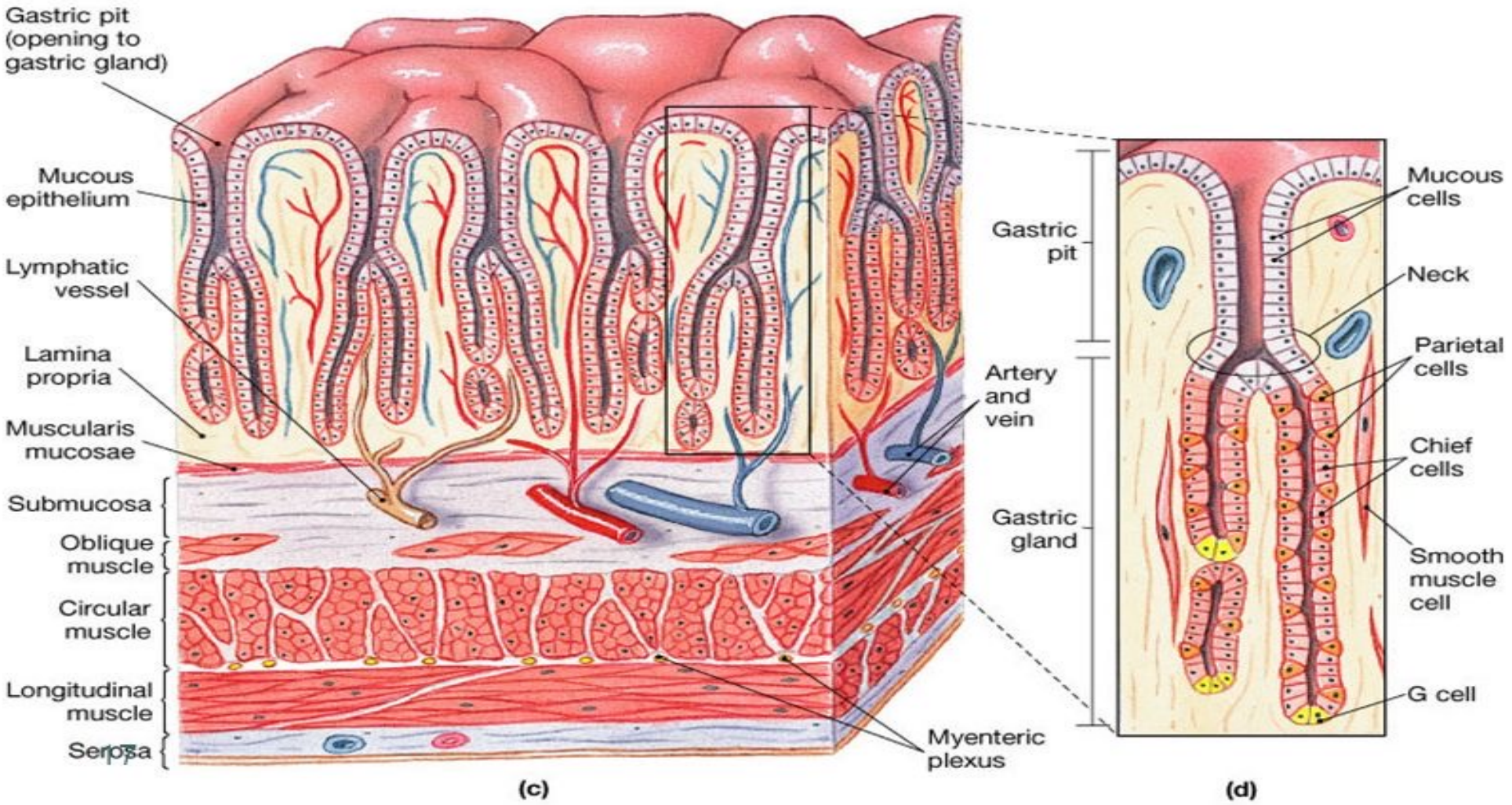
1. Columnar mucous and bicarbonate-secreting surface epithelial cells
2. Mucous neck cells, which are precursor stem cells for other cell types
3. Acid-secreting parietal cells
4. Pepsinogen-secreting chief (zymogen) cells
5. Neuroendocrine (enterochromaffin, argentaffin) cells that secrete gastrin, enteroglucagon and somatostatin

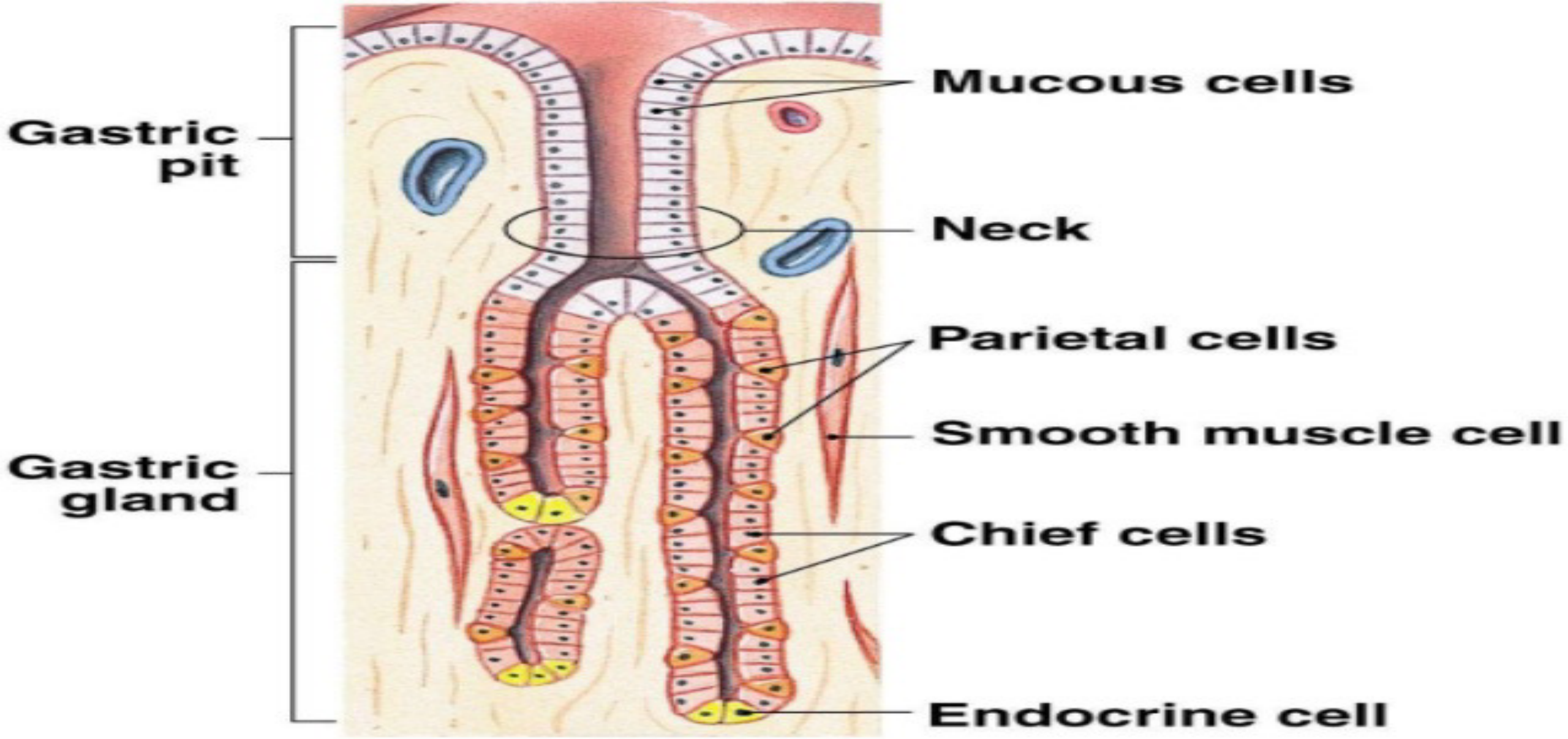
Species variability

In some species, such as rat and horse, the cranial part of the stomach is lined by stratified squamous epithelium (pars nonglandularis), while the distal portion (pars glandularis) is lined by glandular epithelium



Histology of the stomach





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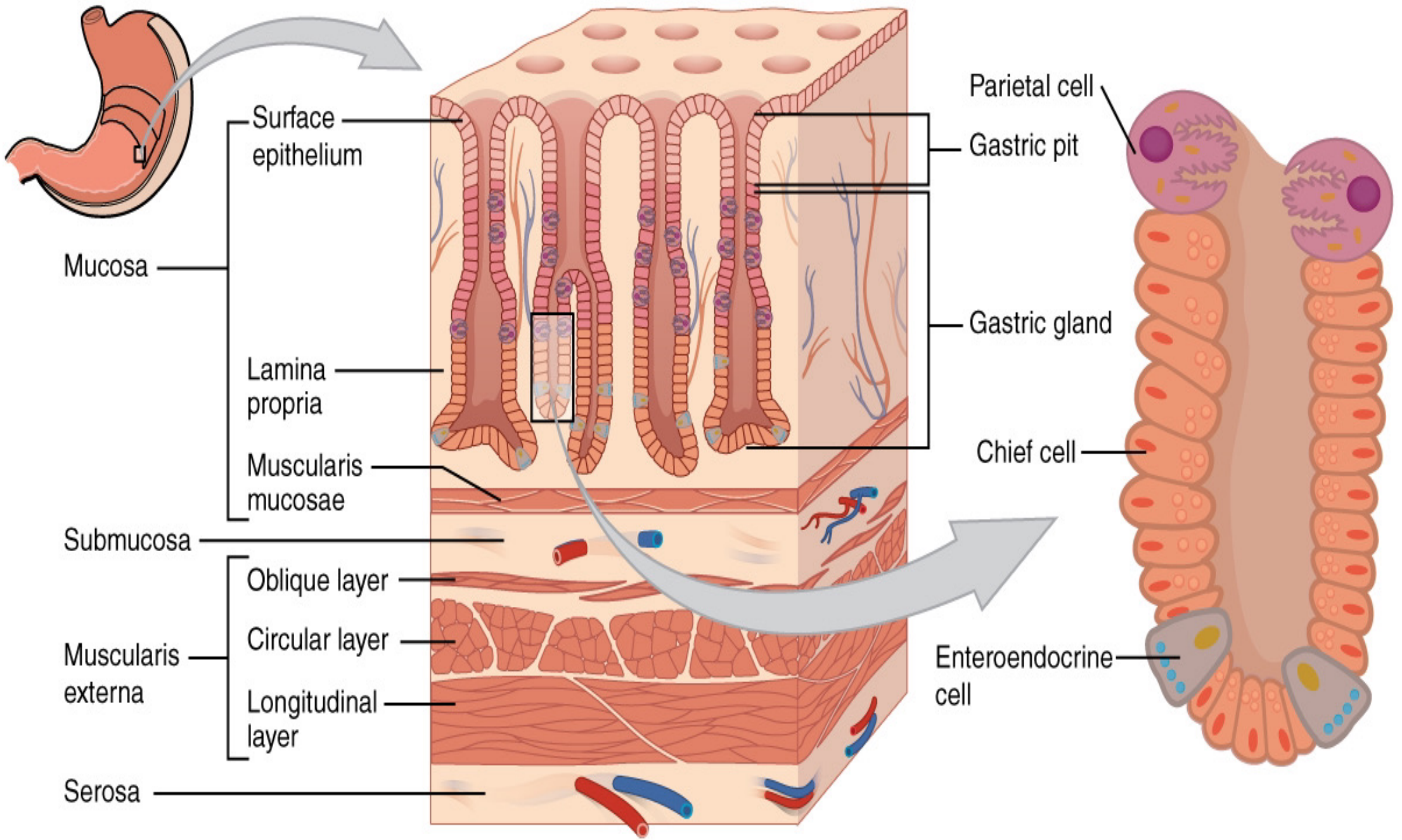

Surface epithelium
Mucosa
Lamina propria
Muscularis mucosae
Submucosa
Oblique layer
Muscularis externa
Circular layer
Longitudinal layer
Serosa
Parietal cell
Gastric pit
Gastric gland
Chief cell
Enteroendocrine cell

Gastric function

Hydrolysis of protein in preparation for subsequent intestinal digestion and absorption is effected by acid and pepsin in the stomach, activated by autocatalysis from pepsinogen

Oxyntic or parietal cells secrete acid and regulation of the volume and acidity of gastric secretion is complex and highly integrated, involving neurocrine, endocrine and paracrine (localised cell-to-cell communication) mechanisms

Parietal cells secrete hydrochloric acid in response to stimulation by histamine (a paracrine stimulant produced by mast and enterochromaffin-like cells), acetylcholine (from parasympathetic postganglionic neurons) and gastrin (released into the bloodstream by G cells)

Gastric motility

Controlled by an interaction between myogenic, hormonal and neuronal factors, the latter 2 acting on smooth muscle cells

Gastric mucosal barrier

Barrier to acid back-diffusion and autodigestion resides in the single layer of foveolar and surface mucous cells and their products

The capacity of these cells to maintain intercellular tight junctions, migrate rapidly to fill defects and maintain the continuity of the mucosal surface epithelium, and secrete mucous, bicarbonate, and a hydrophilic phospholipid surface layer is critical to protecting the gastric mucosa against injury by insults arising in the lumen

Gastric mucosal barrier

Mucus forms a layer immediately over gastric epithelial cells and is the first line of defence against injury

Gastric mucous is permeable to hydrogen ions and has little innate buffering capacity, but resists hydrolysis by intraluminal pepsin, thus protecting the mucosal surface

Acid is buffered by bicarbonate in the mucous layer, preventing back-diffusion into the mucosa

Response of the gastric mucosa to injury

Restitution of acute erosive physical or chemical trauma to the mucosal surface is by rapid (minutes to hours) migration of surviving attenuated surface and foveolar cells

Repair by stem cells in the isthmus follows, if the erosive lesion is superficial and spares the progenitor cells

A cap of mucous, exfoliated epithelium and fibrin over a mucosal defect may form a protective barrier conducive to effective restitution of the mucosal epithelium

Response of the gastric mucosa to injury

An acute inflammatory reaction demarcates severely eroded or superficially necrotic mucosa and haemorrhage may be present

Mitoses become common in the stem cell progenitor compartment

After a gastric insult, mucosal blood flow increases rapidly and is protective by aiding in dilution and removal of back-diffusing acid and injurious substance from the injured mucosa

In early repair, surface and foveolar lining cells are poorly differentiated and flattened, cuboidal or low columnar

Congestion, oedema and neutrophilic infiltration in lamina propria with fibroplasia

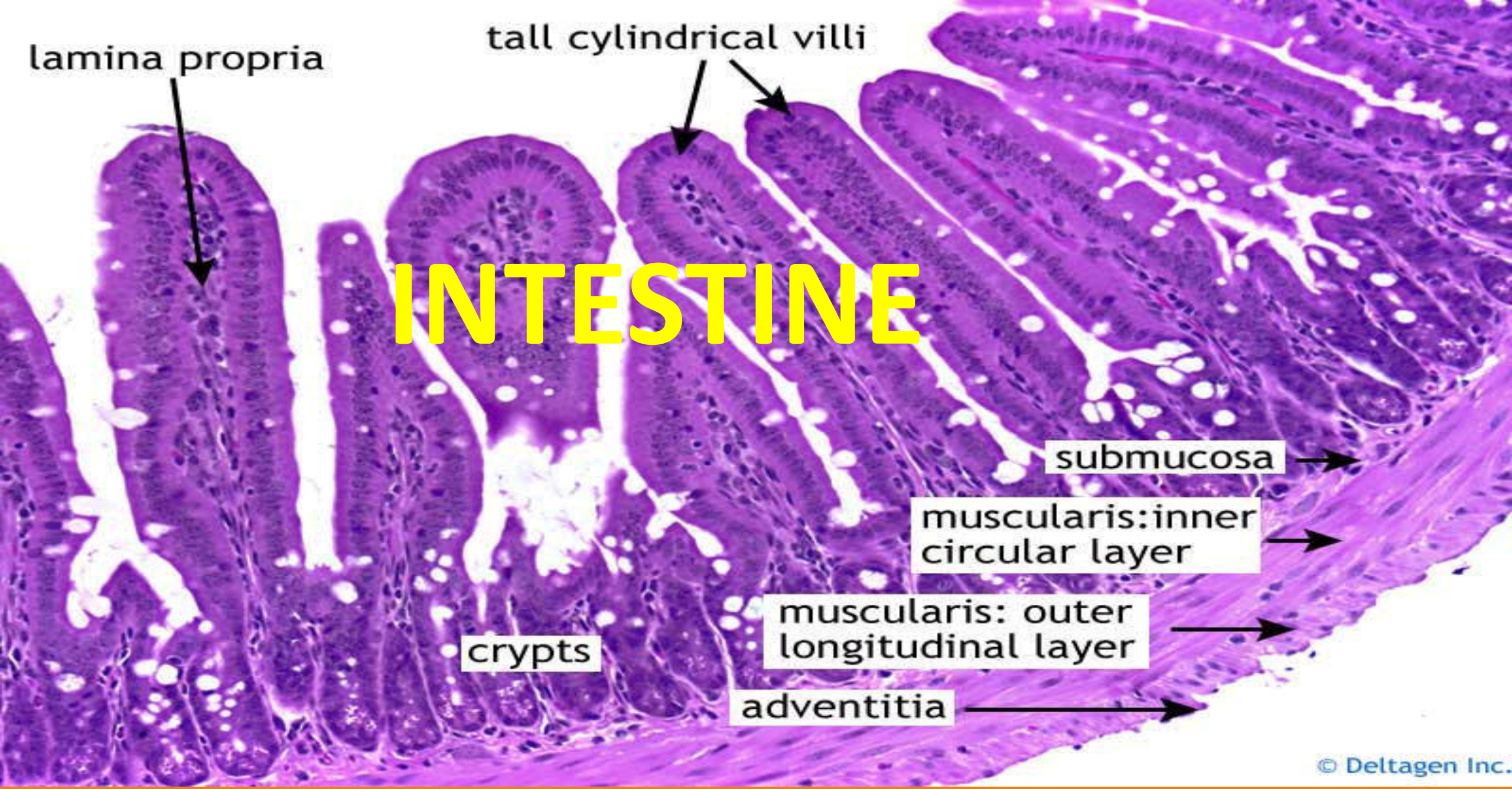
Response of the gastric mucosa to injury

Inappetence causes atrophy of parietal cells and, when extreme, achlorhydria occurs

Chronic inflammation produces mucous metaplasia and hyperplasia of glands, resulting in gross mucosal thickening

With chronic gastritis and mucous metaplasia, achorhydria ensues and the pH approaches neutrality as sodium ions replace hydrogen ions in the gastric content and bicarbonate is secreted

With decreased gastric acidity, progressive microbial colonisation of the stomach and upper intestine follows


lamina propria
tall cylindrical villi
INTESTINE
submucosa
muscularis:inner
circular layer
muscularis: outer
longitudinal layer
crypts
adventitia
© Deltagen Inc.

Normal histology and function of small intestine

Small intestinal mucosa is modified to increase the surface area by villi, which project into the lumen

Villi are projections of lamina propria covered by a layer of 1-cell thick epithelium, which expand the absorptive area 7-14 fold

Villi are usually tallest in the duodenum and decline in height towards the ileum

Length and shape of villi vary with species, age, intestinal microflora and immune status

Small intestine

Crypts of Lieberkuhn open to mucosal surface at the base of each villus and contain the **progenitor compartment** of the enteric epithelium

Epithelial cells **differentiate and move up the villous surface, mainly as absorptive enterocytes**, eventually being sloughed as effete cells from the villous tips

Stem cells are found at the base of the crypts and turnover rapidly

Small intestinal stem cells

4 main lineages:

Enterocytes

Paneth cells

Goblet cells

Neuroendocrine cells

Enterocytes

Cuboidal-to-low columnar when poorly differentiated with relatively few, short microvilli

Mature enterocytes are most prominent cell type in intestine

Function is the digestion and absorption of nutrients, electrolytes, and water

Tall columnar cells, joined at apical (lumenal) margin by tight junctions (but permit transport of small molecules and water)

Enterocytes

Large potential space between enterocytes below tight junctions and lateral cell membranes loosely interdigitate

Basolateral cell membrane is site of Na-K-dependent ATPase that drives the Na pump and carrier systems exporting macromolecules

Enterocytes lie on a basement membrane and interact by integrins

Myofibroblasts

Subjacent to basement membrane are myofibroblasts, which mediate signalling between epithelium and lamina propria

Involved in growth and tissue repair, inflammation, fibrosis and tumorigenesis

Largely responsible for the plasticity of villi as an adaptive change to changing milieu and damage

Paneth cells

Present in some species (especially horses), which have a slow turnover (~20 days), and present at the base of crypts

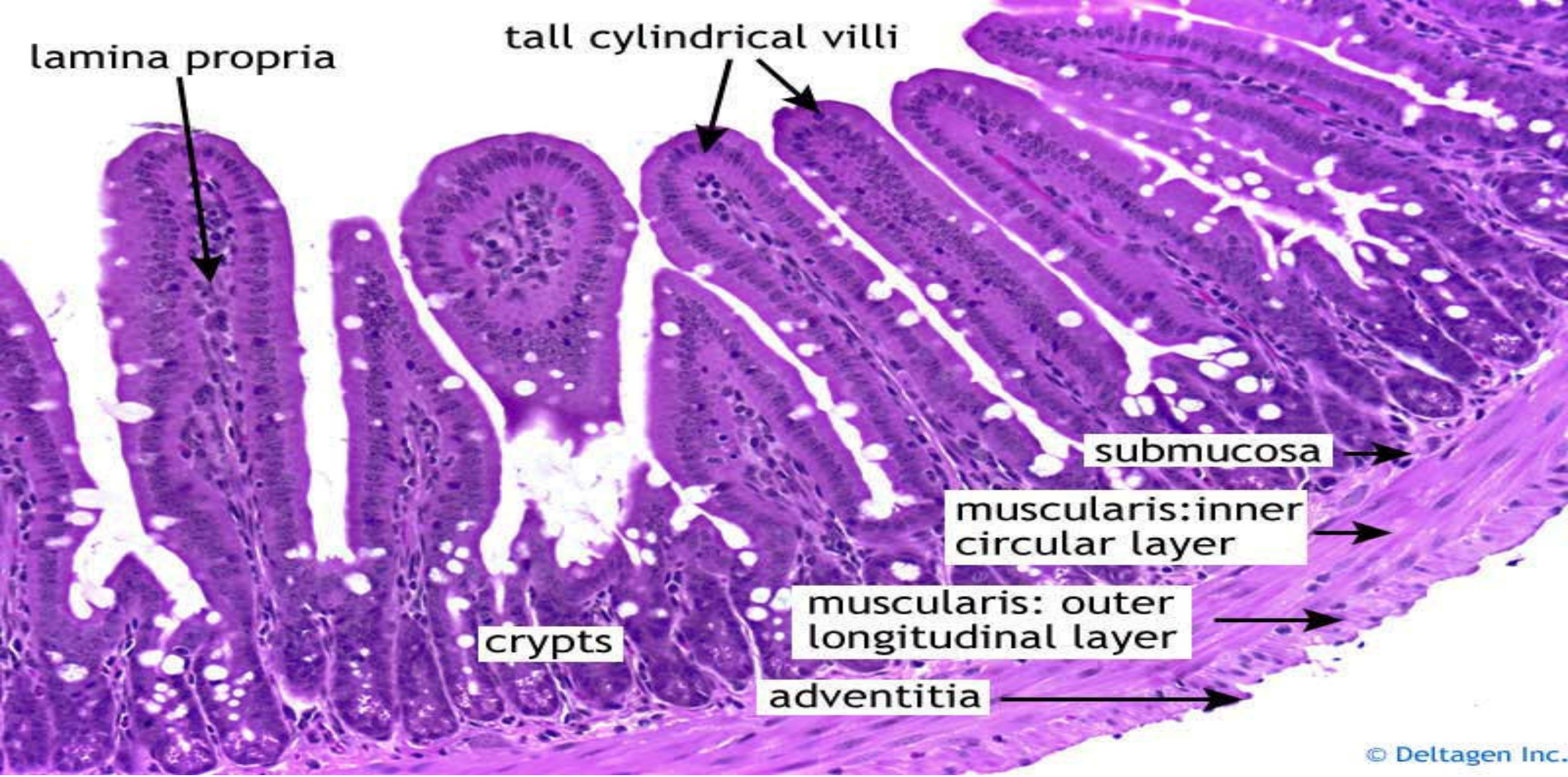
Secretory granules contain anti-microbial proteins and peptides, which are key mediators of homeostasis, host-microbe interactions, innate immune defence, and regulation of epithelial stem cells

Enterocytes

Apical surface contains microvilli "(brush border"), which increase the absorptive surface by 15-40 times

Microvilli contain massive numbers of enzymes, which digest peptides and carbohydrates

Absorbed lipid diffuses from micelles at the cell surface through the apical membrane, which is complexed with proteins and excreted as chylomicrons, which are then absorbed into lacteals (lymphatics)



HISTOLOGY OF THE SMALL INTESTINE

Goblet cells

Differentiate from oligomucous cells

Synthesise and secrete mucins, which are a component of mucous

Mucus provides lubrication and frontline host defence against irritants and microbes, while permitting nutrient transport

Also contains a factor (trefoil factor) that promotes epithelial restitution after injury

Goblet cells

Acutely, goblet cell hyperplasia and mucous secretion is promoted by noxious stimuli, inflammatory mediators, and cell-mediated immunity

But chronic infections can result in goblet cell depletion and reduced mucous protection

Enteroendocrine cells

Heterogeneous population of endocrine and paracrine (cell-to-cell) cells (~1% of epithelial cell population)

Secrete serotonin, somatostatin, cholecystokinin, peptides, and secretin

Regulate intestinal motility and peristalsis, secretions, visceral sensations, and appetite

Lamina propria

Supports the epithelium of the small intestinal mucosa

Composed of loose connective tissue interspersed with blood vessels, smooth muscle, inflammatory and immune cells

Lymphocytes, neutrophils, eosinophils and plasma cells scattered throughout lamina propria + intraepithelial lymphocytes

Macrophages, in addition to functioning as defence against microrganisms, phagocytose inert particulate matter reaching lamina propria from the lumen

Vascular supply to small intestinal mucosa

Arises in submucosal arteries, which become arterioles, then arborise near the villous tip into a dense fenestrated capillary plexus

Drained by venules into submucosal veins, which drain into mesenteric and hepatic portal veins

Lacteals (central lymphatic vessels of the villus) permit entry of macromolecules and chylomicrons and are the main route of lipid transport from the villous

Caecum and colon

Vary widely amongst domestic animals, depending largely on the significance of hindgut carbohydrate fermentation

Production of volatile fatty acids from carbohydrate is a significant energy source

Absorption of electrolytes ad water, an electrolyte-conserving mechanism, is a major function of the colon and, in some species, the daily fluid absorption > extracellular fluid volume

Mucosa lacks villi, but there are ridges and folds on the mucosal surface

Caecum and colon

Architecture of colonic glands resembles that of SI as epithelial cells differentiate from stem cells deep in glands, but microvilli are sparse and irregular

Goblet cells are present in the upper half of colonic glands and on the surface

Enteroendocrine glands of different types are also present

Lamina propria is minimal between closely packed glands

Enteric nervous system

Submucosal (Meissner's) and myenteric (Auerbach's) plexuses exist as ganglia and coordinate intestinal motility and function

Neurons of the enteric nervous system are equal in number to those in spinal cord

Influences especially absorption and secretion, local endocrine/paracrine secretion, blood flow, immune events, and gut motility

Branches extend to the crypts of Lieberkuhn, where they stimulate secretion of electrolytes, water and mucous

Enteric nervous system

Excitatory/inhibitory effects mediated by acetylcholine and amine/peptide neurotransmitters such as substance P

Myofibroblastic pacemaker cells of the intestine (interstitial cells of Cajal) are distributed throughout the intestinal musculature, integrated with extrinsic and enteric nervous systems and abnormalities can lead to disorders of gut motility

Intestinal immune functions

Intestine is continually presented with antigens in food, allergens, toxins, viruses, bacteria and parasites

The lining epithelium is only 1-cell thick and covers an enormous surface area

Hence epithelium and associated lymphoid and inflammatory cells form a complex system for handling these antigens and potential pathogens

Immune elements are sparse at birth and immune activity is stimulated by bacterial colonisation in the early postnatal period

Lymphoid tissue in mature animals comprises 25% of the intestinal mucosal mass (> spleen)

Intestinal mucosal defence mechanisms

Volume of water and peristalsis for diluting and flushing luminal contents, respectively

Gastric and bile acids and pancreatic secretions break down ingested antigens

Indigenous microflora competitively inhibits or actively excludes intruding bacteria

Mucosal mucous forms a secretory barrier

Enterocytes provide a physical barrier, produce pro-inflammatory cytokines, and provoke immunity by antigen uptake and presentation

Intestinal mucosal defence mechanisms

Mucosal lymphoid elements, including Peyer's patches and regional lymph nodes, generate antigen-activated T and B cells, augmented by macrophages and dendritic cells

Colostral transfer of immunoglobulin provides neonates with passive immunity for a restricted time period

Enterocytes express MHCII and can present antigen directly to T cells

Enterocytes detect pathogen-associated molecular patterns in viruses and bacteria

Intestinal mucosal defence mechanisms

Intestinal intraepithelial T lymphocytes comprise 10-20% of cells in epithelial layer and are located between basolateral surfaces of epithelial cells, constituting an important first line of defence

Peyer's patches are composed of follicular aggregates of B cells, surrounded by T cells

Overlying these lymphoid follicles is a mixed population of T and B lymphocytes - and dendritic cells that extend into the lamina propria as subepithelial domes between villi

Also membranous (M) cells actively sample and transport luminal antigens to the underlying mucosal immune system

Intestinal mucosal defence mechanisms

B and T lymphocytes gain entry to Peyer's patches via post-capillary venules and a major proportion of Peyer's patches are B cells committed mainly to IgA production

Lamina proprial T cells are mixed CD4+ and CD8+ and cytokine production by activated T lymphocytes plays a significant role in promotion of inflammation

Antigen is processed and presented to lymphocytes in Peyer's patches and mesenteric LN by dendritic cells, trafficking from the mucosa where they initially acquire antigens, and can directly sample luminal contents by extending their dendrites between enterocytes

Intestinal mucosal defence mechanisms

Macrophages, especially in the lamina propria, phagocytose and destroy invading pathogens

IgA-producing lymphocytes leave Peyer's patches, home to mucosal surfaces, and differentiate into IgA-secreting plasma cells

Functions of IgA include blocking attachment of viruses and bacteria to enterocytes, promoting pathogen clearance, neutralising intraluminal toxins, facilitating antigen sampling, limiting absorption of microbial antigens, and promotion of tolerance

Intestinal mucosal mast cells play a central role in immune and inflammatory responses in the gut

Intestinal microflora

After birth, no part of the intestine is sterile, but rather occupied by hundred of species of microorganisms, especially anaerobic bacteria

From an ecosystem of enormous complexity

Important in the metabolism of indigestible compounds, synthesis of essential vitamins, development of intestinal epithelial and immune systems, and protection from invasion by opportunistic pathogens

The complex gut flora imparts significant stability and is relatively resistant to intrusion by new microorganisms

Intestinal microflora

Thus bacterial diarrhoea occurs most commonly in neonates with poorly established microflora or after disturbances to bacterial populations by antibiotic therapy or husbandry changes

The normal microflora acts as a barrier to colonisation by pathogens

Normal microflora is important for the development of mucous layer properties and mucosal lymphoid structures, modulation of immune cell differentiation, and regulation of cytokine-chemokine production in the gut

Intestinal microflora

Host factors influencing the gut microflora include diet composition, peristalsis, lysozyme, and gastric acidity

Mucosal epithelial maturation is influenced by the microbiota

Germ-free animals have longer and thinner villi, less-developed proprial vascular networks, and fewer crypt stem cells

IgA plays an important role in the composition and function of the gut microflora

Intestinal electrolyte and water transport

Water movement in the intestine is passive, following osmotically the transport of electrolyte and nutrient solutes

Small intestinal mucosa is highly permeable to the passive movement of small ions and water, despite the presence of apical tight junctions

This ensures that the content of the small intestine is approximately isosmolal with the interstitial fluid space, in part because fluid and solute actively absorbed can leak back into the lumen

Water is secreted into the gut with digestive juices and is almost entirely resorbed into SI and LI, facilitated by aquaporin water channel proteins

Intestinal electrolyte and water transport

Sodium absorption depends on ATP-dependent Na pump on the basolateral cell membrane of enterocytes and solutes, especially Na, in the epithelial intercellular space cause water to follow from the intestinal lumen

Since enterocytes are highly permeable to water, movement is rapid in both directions and osmotic pressure differences are small between the lumen and intercellular space

The colon plays an important role in reducing the volume of water and electrolytes lost in faeces

Intestinal electrolyte and water transport

In contrast to SI, the colonic epithelium is relatively restrictive to the free movement of Na and Cl and, therefore, is capable of maintaining differences in osmotic pressure between lumen and lamina propria and is more efficient in absorbing some electrolytes and water than the SI

Solute movement across the intestinal epithelium is regulated by a number of hormones and neurotransmitters

Epithelial renewal in health and disease

Stem cells in the base of crypts differentiate into absorptive enterocytes or goblet cells and lose their mitotic capability

Enterocytes are generally shed from villous tips in 2-8 days, abetted by apoptotic cell death

The mass and topography of the mucosa are relatively stable, the result of a dynamic equilibrium between stem cell production and villous loss

The size of the proliferative compartment is reflected histologically in the length and diameter of the crypts and the location of the uppermost mitotic cell + measurement of the mitotic index

Epithelial renewal in health and disease

The degree of differentiation of enterocytes (and hence the functional status of villous enterocytes) can be inferred from their appearance

Cytoplasmic basophilia; loss of basal nuclear polarity; low columnar, cuboidal or squamous shape; and ill-defined brush border indicate poor differentiation and an increased rate of cell turnover

Restoration of epithelial integrity is dependent upon a finely regulated balance between proliferation, differentiation and migration of enterocytes

If enterocyte loss is minimal, restoration occurs by lateral migration of adjacent intact enterocytes within minutes

Epithelial renewal in health and disease

With enterocyte loss, villi contract due to myofibroblast activity and surviving epithelial cells become flattened and migrate across the denuded surface

Proliferation of epithelial cells then occurs and regeneration of the mucosa follows within hours to days after injury

Finally, maturation and differentiation of cells occurs with the original architecture restored within a few days

Villous atrophy

A common pathological change in the intestine of domestic animals

Causes malabsorption of nutrients and loss of plasma protein into the gut lumen

2 categories are recognised:

1. Villous atrophy with normal or hypertrophic crypts

2. Villous atrophy with evidence of damage to the proliferative stem cell compartment

Villous atrophy

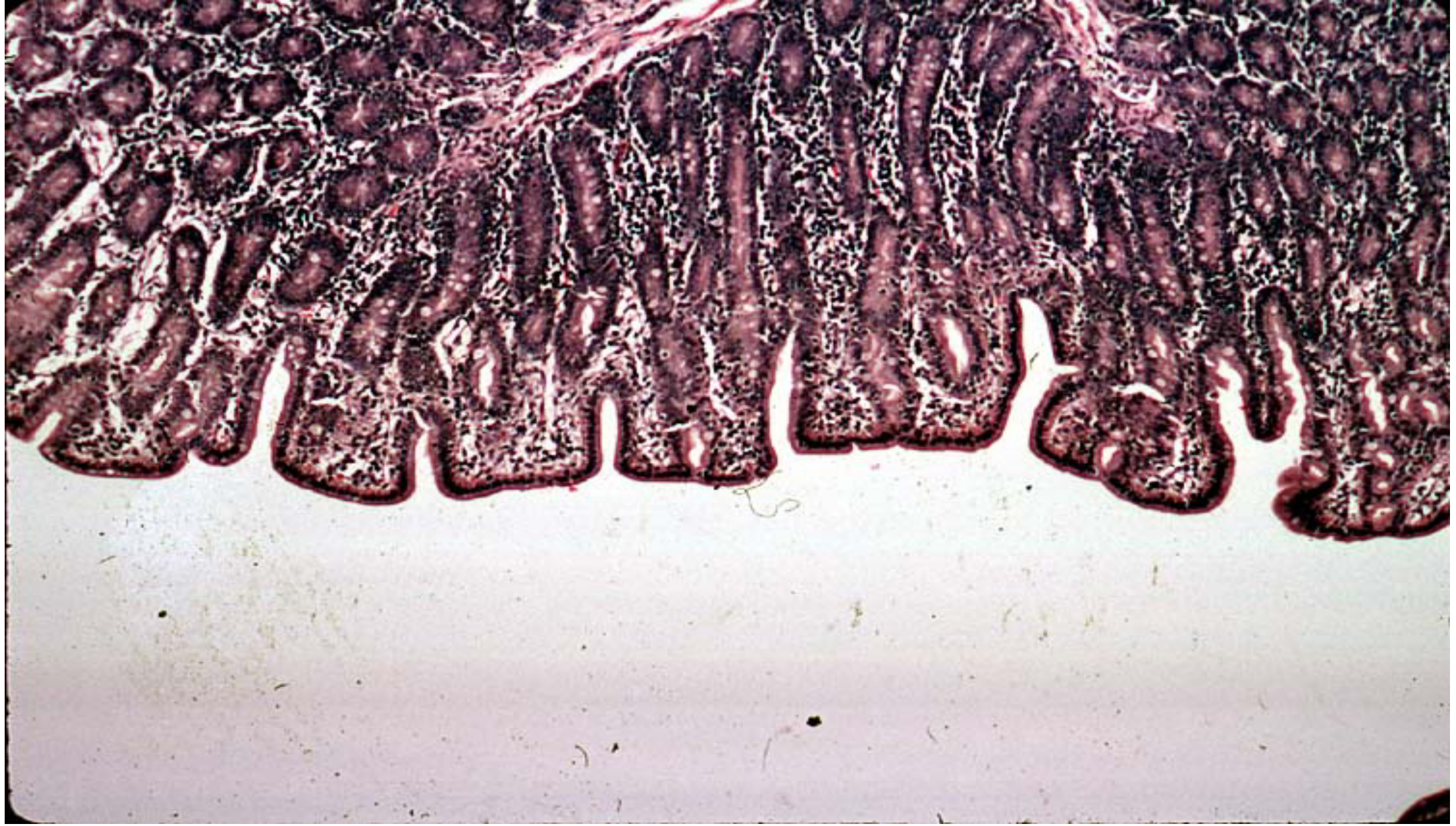
Villous atrophy with normal or hypertrophic crypts

Increased rate of enterocyte loss from villous tips

Villi are stunted (and may be fused) and covered by poorly differentiated low columnar, cuboidal or squamous epithelium. Crypts enlarge to accommodate more mitotic cells

Compensatory expansion of the stem cell proliferative compartment in crypts can permit complete recovery in a few days

Caused e.g. by rotavirus and coronavirus, enteroinvasive bacteria, and necrotising clostridial toxins



Villous atrophy with shortened, stunted villi and some villous fusion

Villous atrophy

Villous atrophy with evidence of stem cell damage

Sequel to insults that cause necrosis of crypt stem cells or impair their mitotic capacity

With severe damage to crypts, remaining epithelial cells become very flattened in an attempt to maintain the integrity of the crypt lining

Caused by agents that damage rapidly dividing cells (radiomimetic effect), including anti-cancer chemotherapeutic drugs, some viruses (e.g. parvovirus in dogs and cats), and ischaemia

Pathophysiology of enteric disease

Protein-energy malnutrition

Caused by inadequate food intake or deficiencies in quantity or quality of nutrients

Comorbidity in many diseases

When severe, causes depletion of fat and muscle mass, emaciation, and eventually death by starvation

Common cause of secondary immune deficiency and increased susceptibility to infection

Pathophysiology of enteric disease

Inappetence (anorexia) is a sharp decline in appetite and commonly associated with gastrointestinal disease

Pro-inflammatory cytokines associated with chronic inflammation and neoplasia are strategic mediators in the complex metabolic disorder constituting cachexia

Ghrelin, a stomach-derived hormone, is an important mediator of cachexia and may stimulate appetite centrally or attenuate inflammation and alter lipid/muscle metabolism to limit cachexia

Pathophysiology of enteric disease

In animals dying of inanition, muscle mass is reduced because of mobilisation of amino acids for gluconeogenesis

Fat in bone marrow, coronary groove, pericardial sac, and around kidneys is markedly depleted and has a gelatinous, clear pink appearance termed serous atrophy

Malassimilation

Digestion and assimilation of nutrients occurs in 3 phases:

1. **Intraluminal phase: major cause is exocrine pancreatic insufficiency due to pancreatic atrophy or necrosis/fibrosis**

2. **Epithelial phase: performed by enzymes in absorptive enterocytes and caused by loss of functional epithelial surface area, e.g. with villous atrophy and poorly differentiated epithelium**

3. **Delivery of nutrients by enterocytes to the interstitial fluid and eventually to blood and lymph**

Assimilation of fat

Can be impaired due to:

Pancreatic deficiency resulting in insufficient lipase

Failure of atrophic intestinal mucosa to release sufficient cholecystokinin to stimulate pancreatic secretions

Reduced surface area for lipid uptake

Decreased bile salts due to biliary obstruction

Also lymphatic obstruction, severe enteritis, and intestinal lymphoma

Malabsorption of lipids

May cause:

Steatorrhea (excess fat in the faeces)

Deficiency of fat-soluble vitamins

Colonic diarrhoea (see large bowel diarrhoea later)

Malabsorption of polysaccharides

Caused by:

Reduced levels of pancreatic amylase due to exocrine pancreatic damage

Villous atrophy leading to oligosaccharide deficiency due to insufficient oligosaccharidases and malabsorption of carbohydrate

Osmotic effect of malabsorbed disaccharide in small intestine can cause diarrhoea

Protein malabsorption

Due to:

Reduction of pancreatic protease to ~10% of normal due to exocrine pancreatic insufficiency

Villous atrophy leading to malabsorption of amino acids

Diarrhoea

Defined as the presence of water in faeces in relative excess in proportion to faecal dry matter

Leads to electrolyte depletion, acid-base imbalance, and dehydration

Large volumes of fluid enter the upper SI from ingesta and gastric, pancreatic, biliary and enteric secretions + passive movement of water from the circulation in response to osmotic effects

Diarrhoea

Most of this fluid is absorbed by enterocytes so only a small fraction enters the colon

But, because of the large size of this fluid flux, relatively small perturbations of electrolyte and water in the SI can have significant effects on the net movement of fluid

The colon has ultimate responsibility to minimise faecal water loss by conserving electrolytes and water by reabsorption

The colon has a finite capacity for absorption and, if this is exceeded, diarrhoea occurs

Small bowel diarrhoea

Causes infrequent passage of large amounts of fluid faeces

Can be secretory (due to excess secretion over absorption of fluid, e.g. diarrhoeagenic bacterial enterotoxins), malabsorptive (commonly due to villous atrophy) or effusive (increased permeability of the mucosa permits enhanced movement of solute and fluid from the lateral intercellular space of enterocytes into the lumen)

Large bowel diarrhoea

Characterised by frequent passage of small amounts of fluid faeces

Due a reduction in the innate capacity of the colon to absorb solute and fluid presented by the more proximal bowel

The colonic mucosa is not as leaky as SI mucosa and, therefore, is relatively resistant to alterations in permeability due to increased hydrostatic pressure or decreased plasma oncotic pressure in the lamina propria

Osmotic overload of large bowel results from delivery from SI of large volumes of substrate, especially carbohydrate, which initiates colonic overload and diarrhoea

Protein malabsorption in enteric disease

Due to:

Decreased protein intake

Villous atrophy

Protein-losing enteropathy – mainly due to effusion of plasma protein (especially albumin) into gut lumen and due to: (1) mucosal ulceration/erosion leading to protein exudation; (2) non-ulcerated mucosa with abnormal permeability; and (3) lymphatic disruption with leakage of protein-rich lymph

Permeability of tight junctions between enterocytes may be sufficiently altered to permit transit of plasma proteins

Protein-losing enteropathy

Involves 3 phases of albumin turnover:

As the size of the circulating pool of albumin decreases, so does the rate of protein loss

The size of the circulating pool then stabilises as the rate of liver albumin synthesis increases

Finally hypoalbuminaemia develops as protein loss exceeds the synthetic capacity of the liver

Glomerular and gastrointestinal disease are the 2 major routes of protein loss

Histology of inflammatory bowel disease

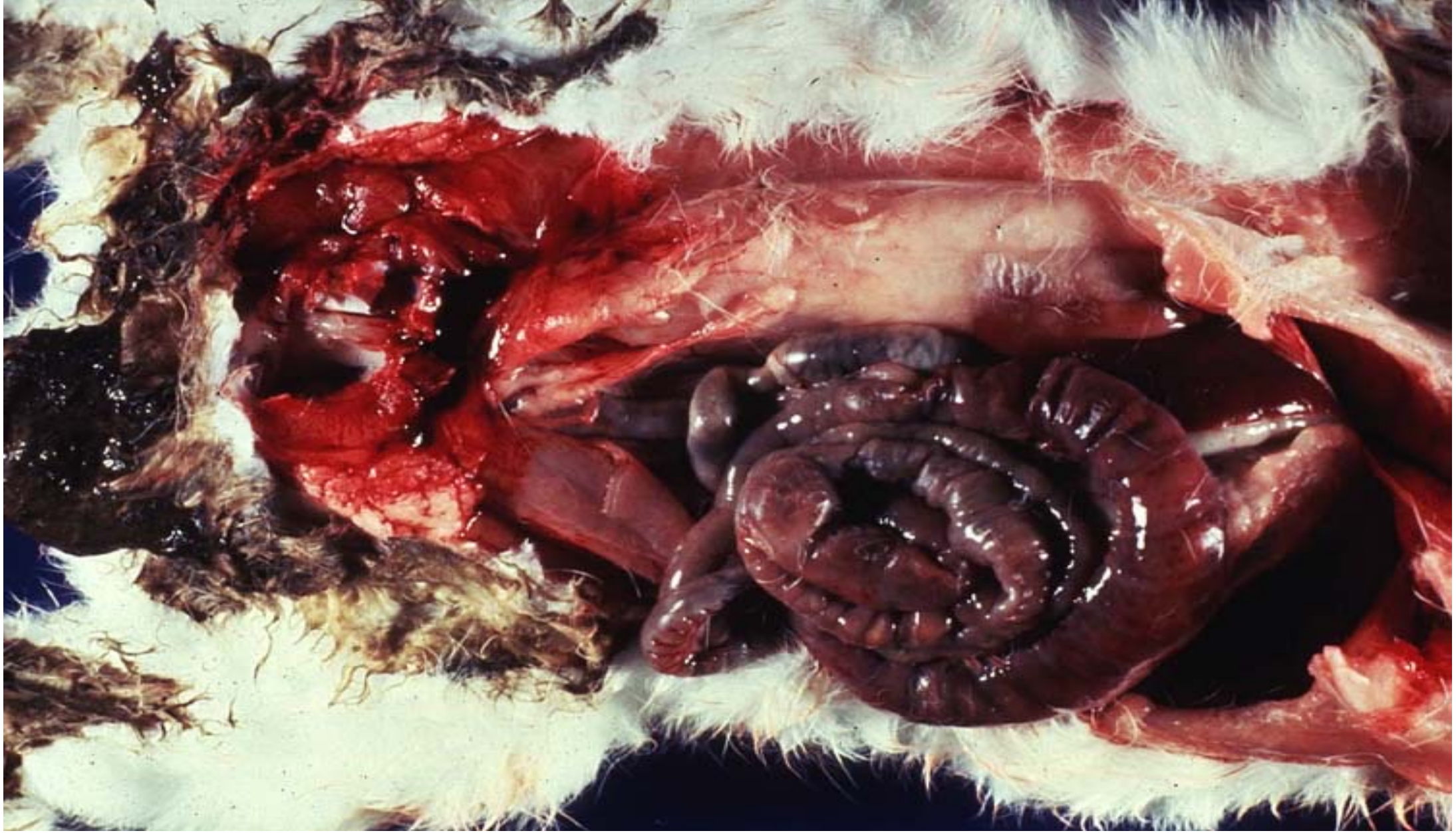
Histological changes:

1. Alterations in mucosal architecture reflecting active or recent epithelial abnormalities (enterocytes may be low columnar to cuboidal to squamous with indistinct brush border; can be mucous metaplasia; and villi may be atrophic and crypts hypertrophic)

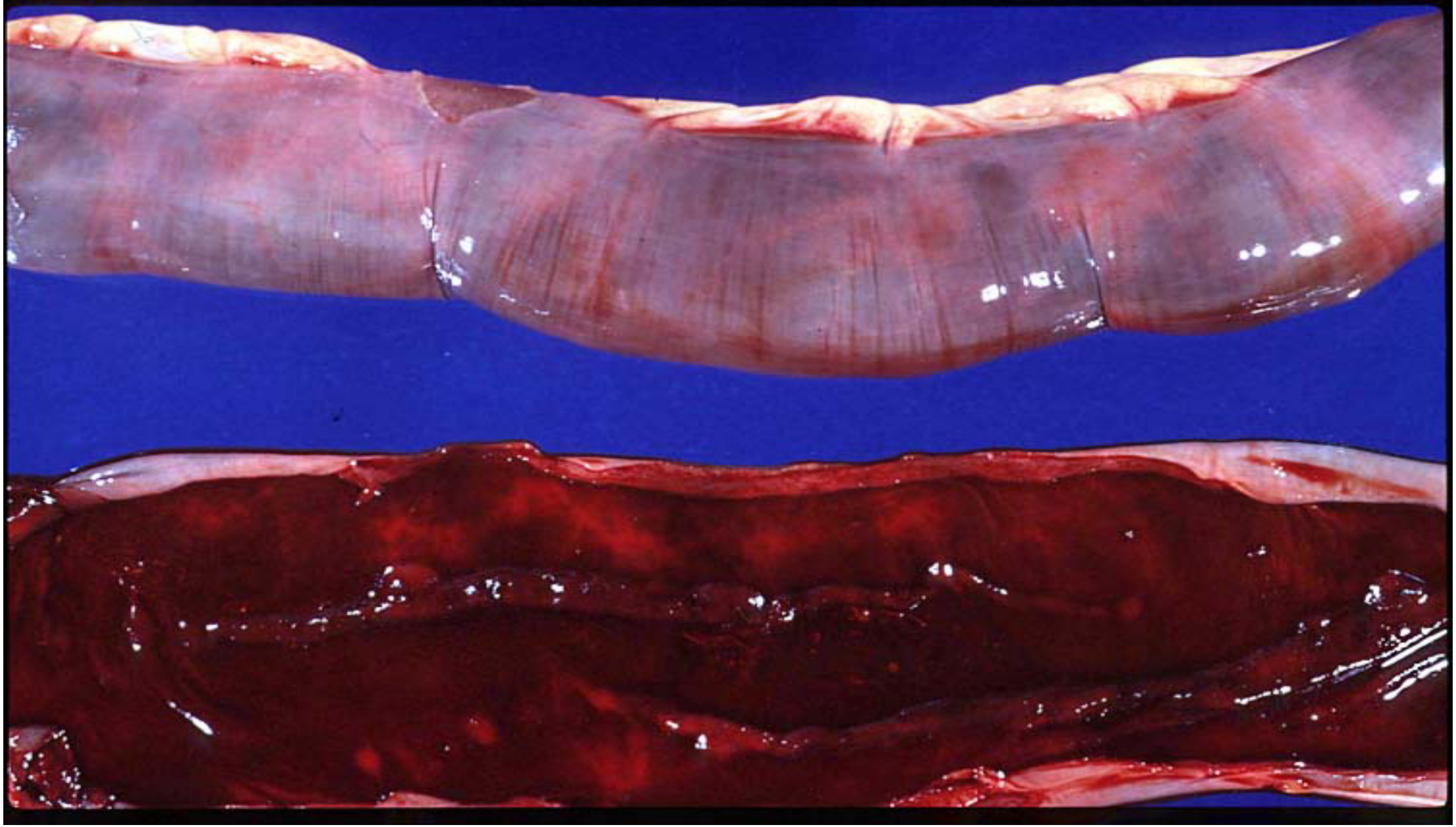
2. Increased numbers of proprial leucocytes (lymphocytes, plasma cells, neutrophils), above the normal mucosal population. Intraepithelial lymphocytes may be increased

3. Fibrosis of the lamina propria

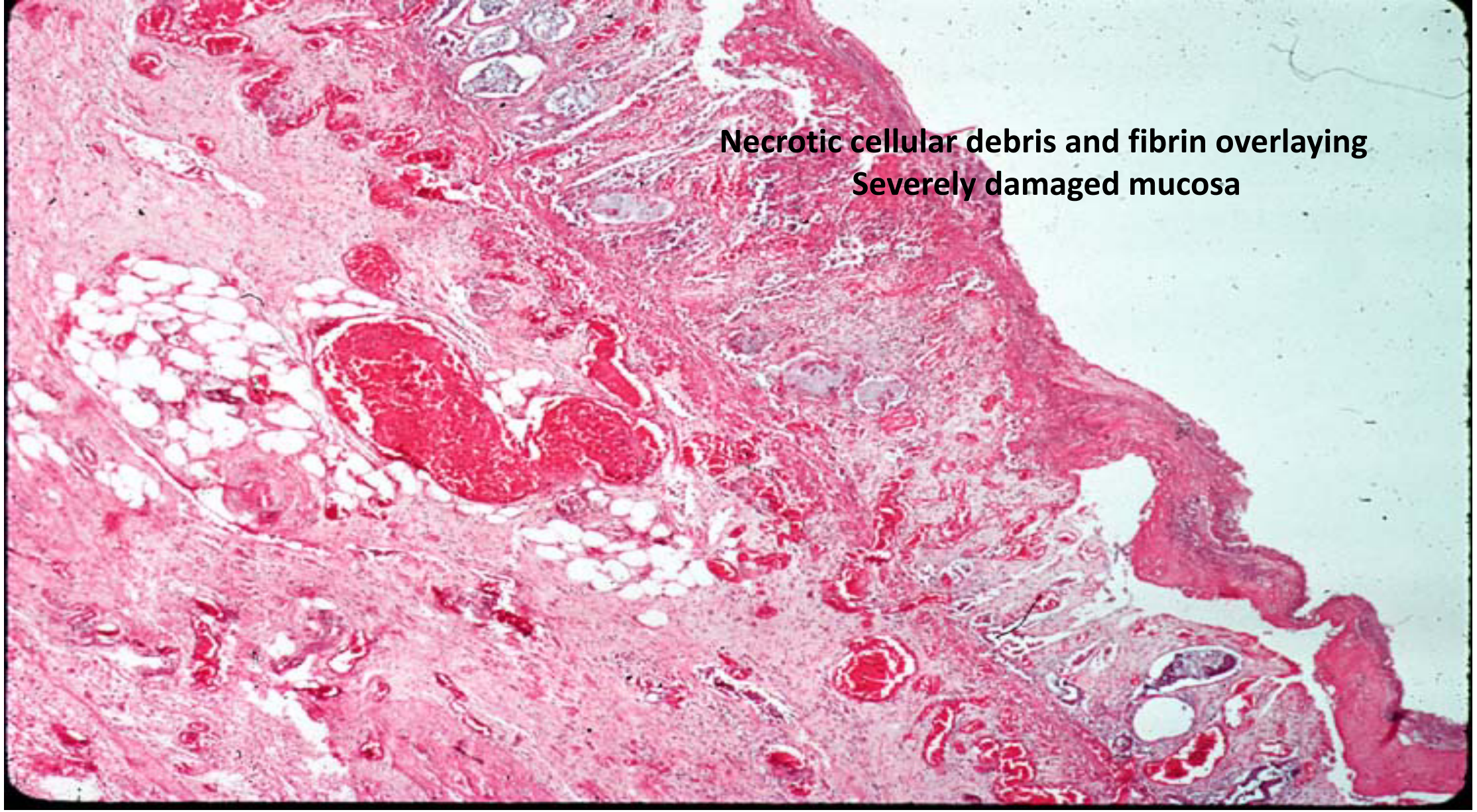
Images of different types of enteritis



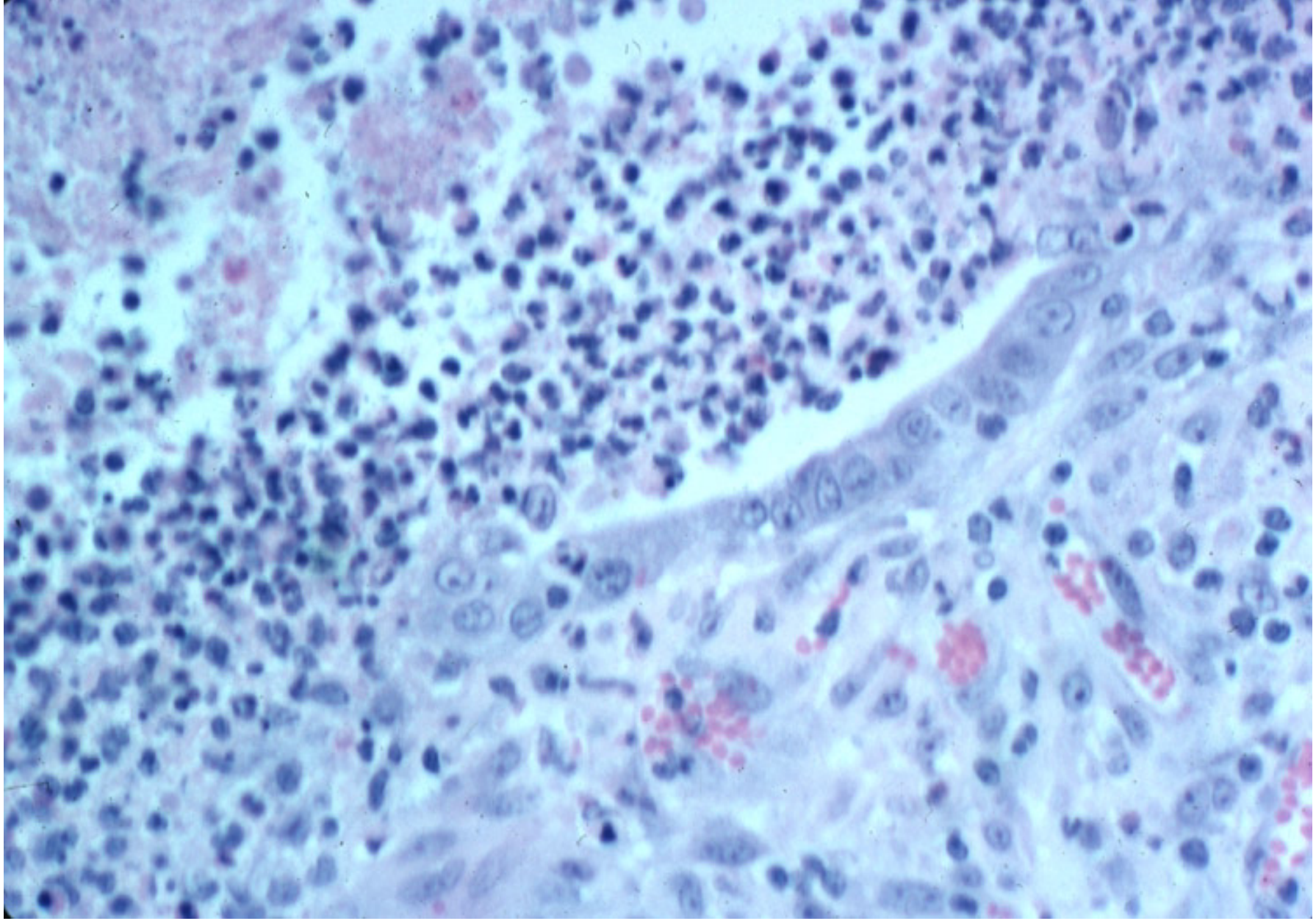
ACUTE HAEMORRHAGIC ENTERITIS



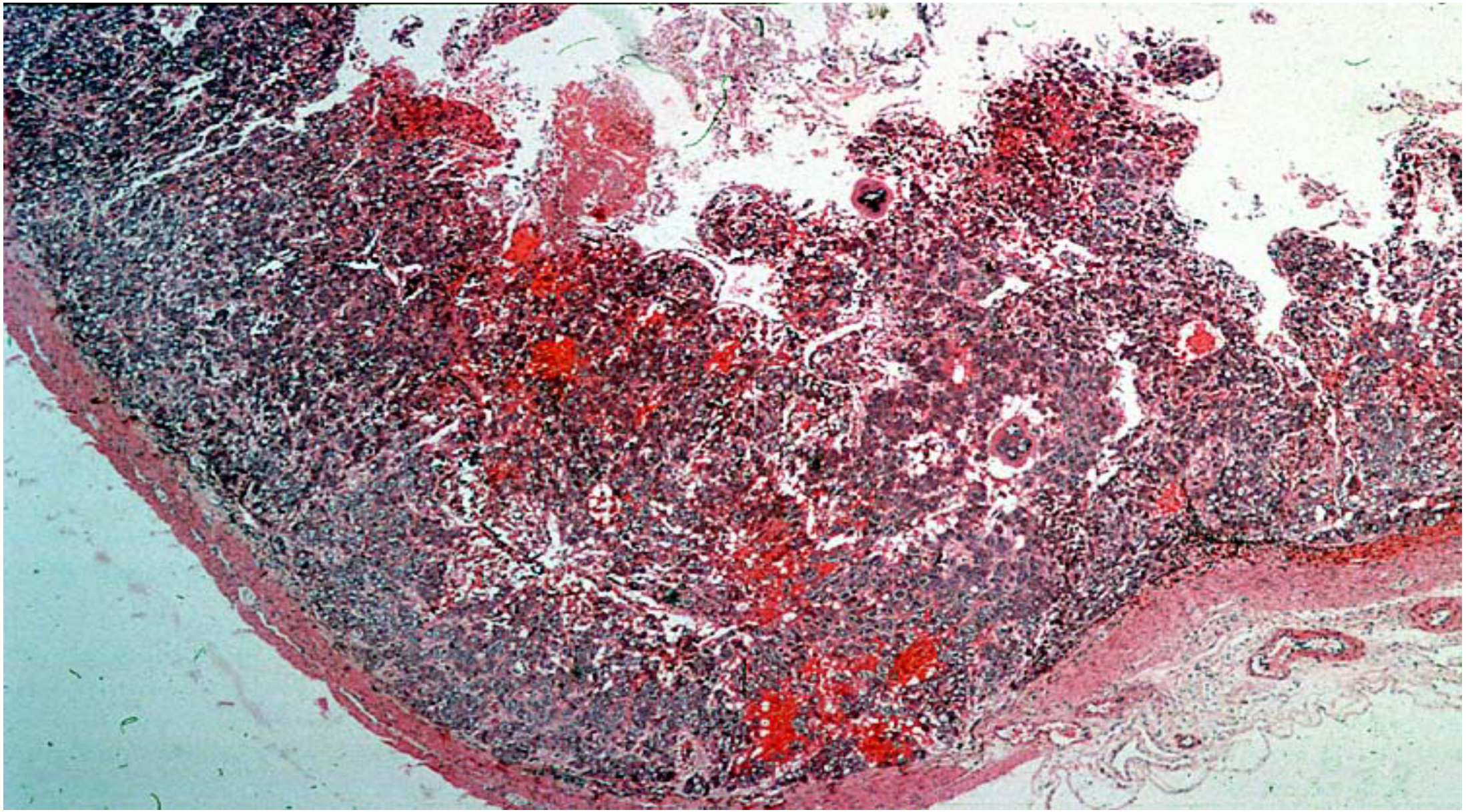
ACUTE HAEMORRHAGIC ENTERITIS



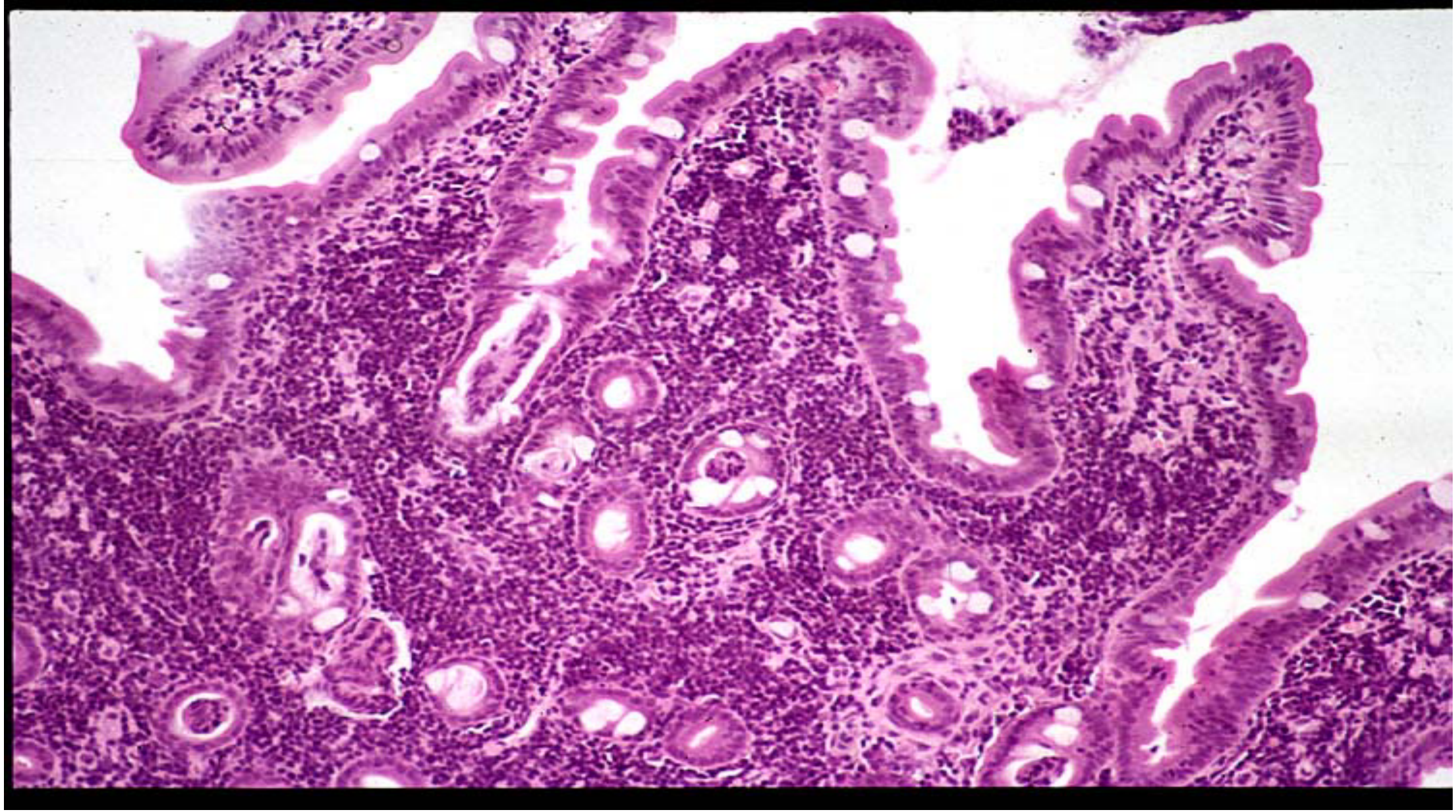
ACUTE NECROTISING BACTERIAL ENTERITIS



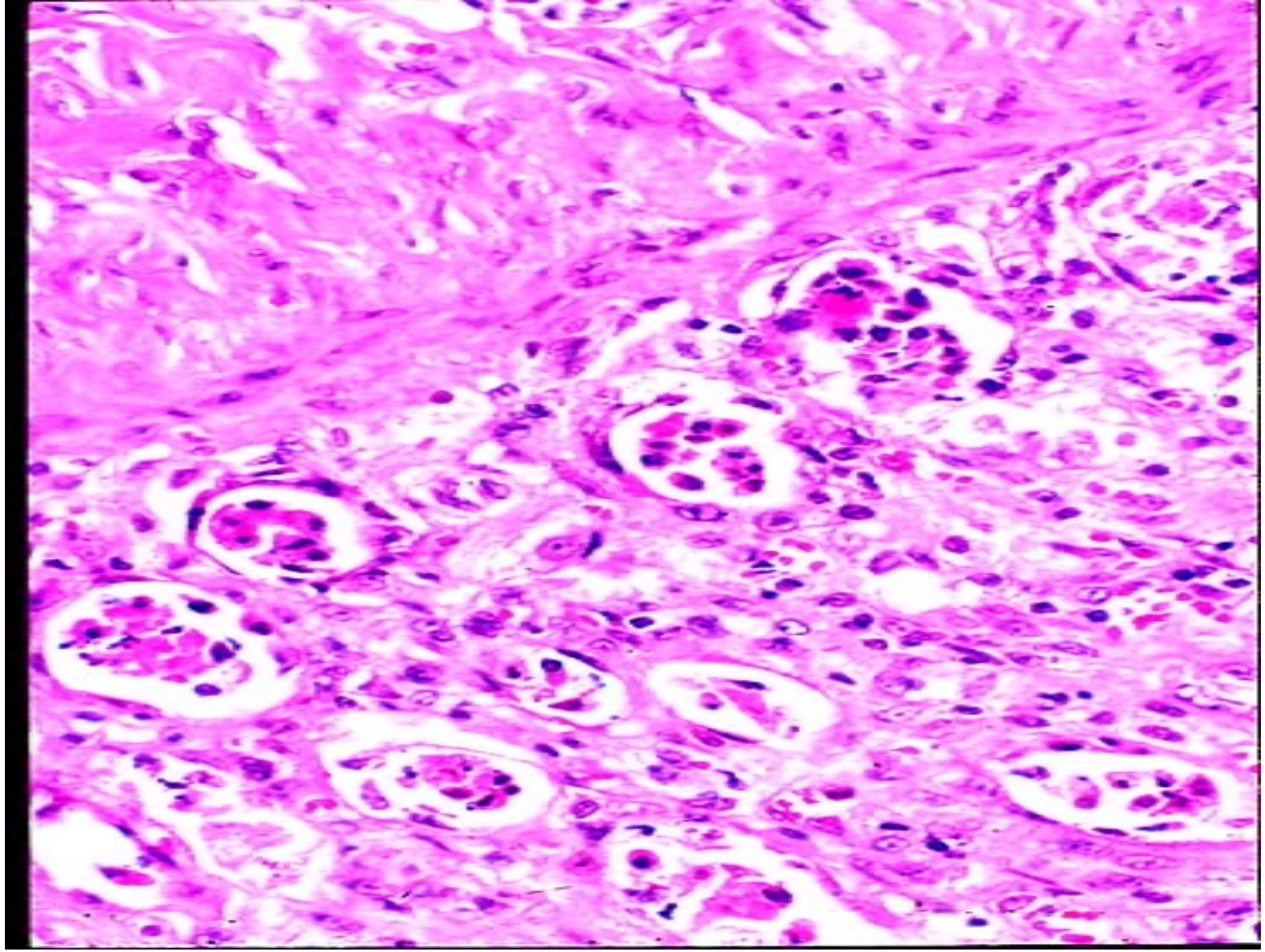
Severe crypt degeneration with loss of most epithelium and luminal accumulation of degenerate neutrophils and cellular debris



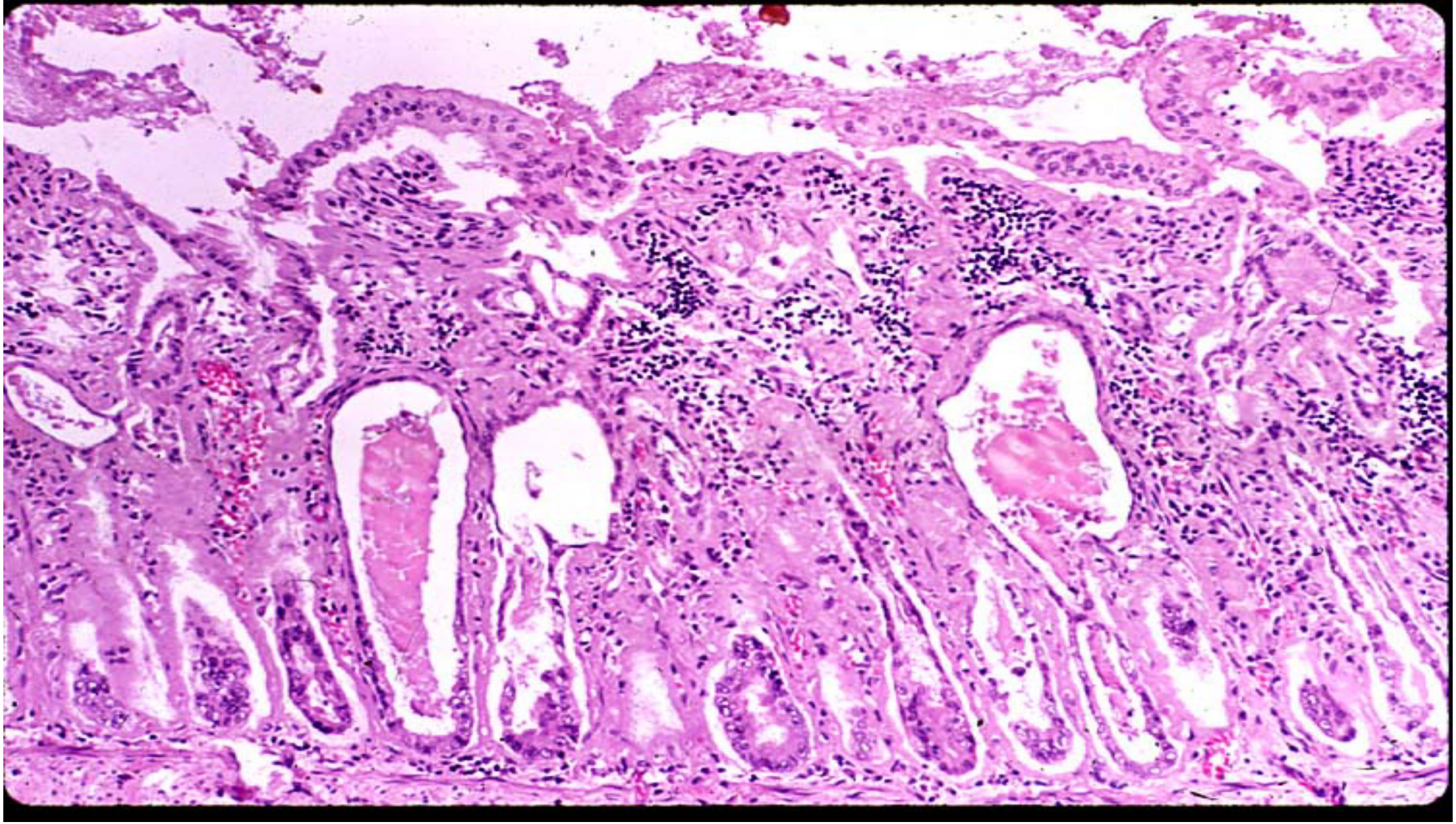
Severe acute necrotising enteritis with haemorrhage and loss of much of the mucosa



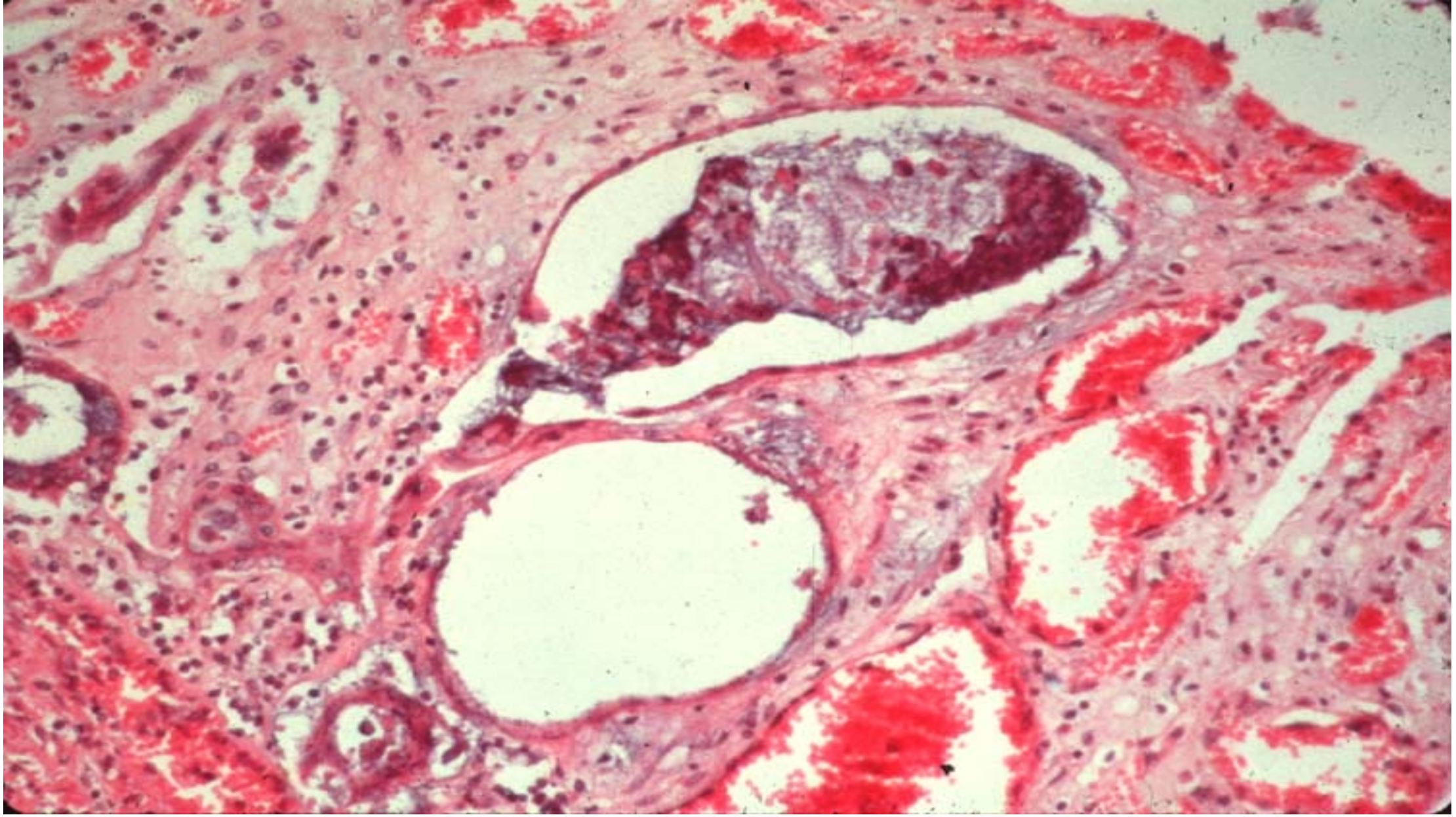
Chronic enteritis with villous enlargement by abundant infiltrating mononuclear cells, largely lymphocytes



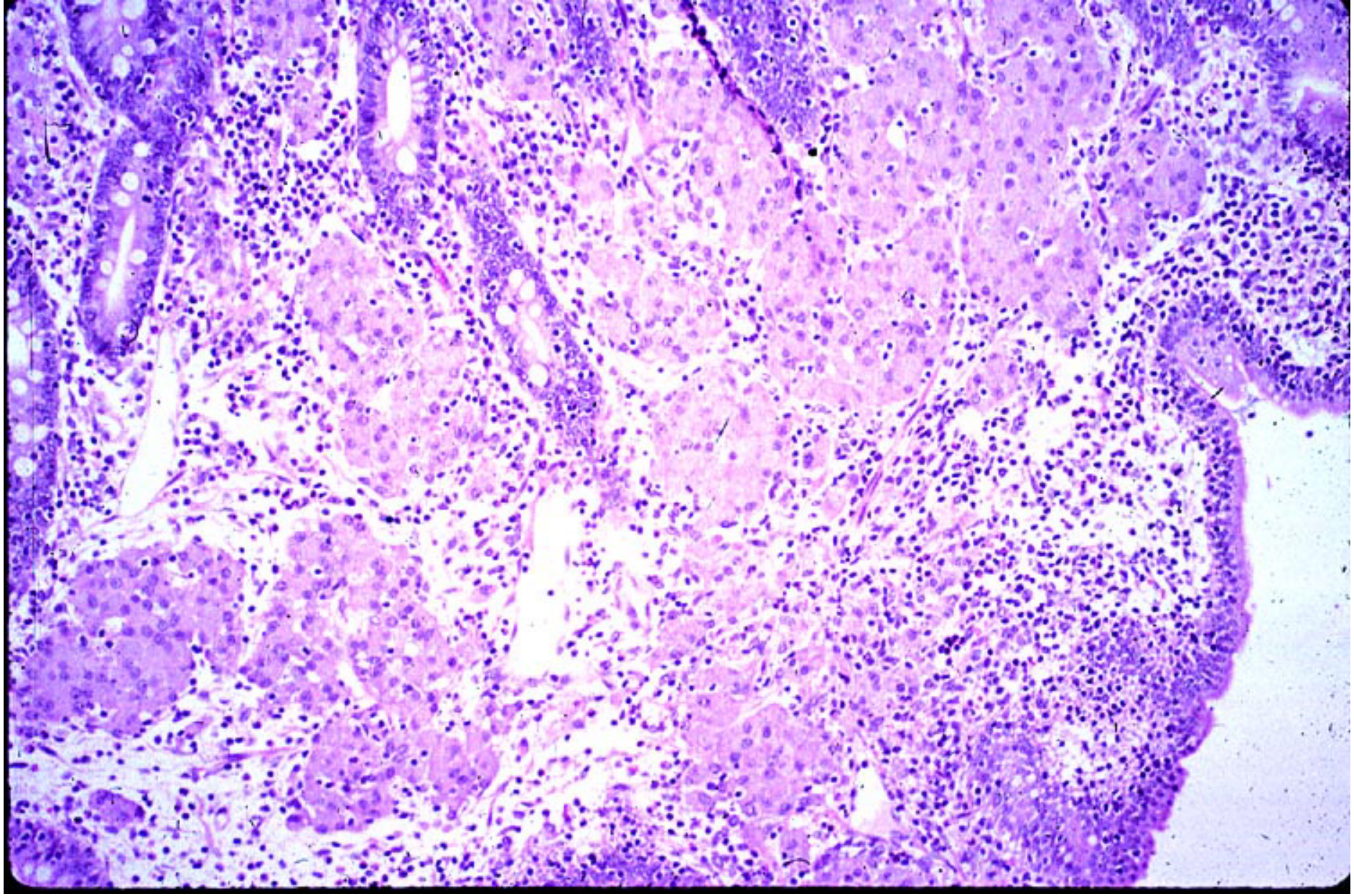
Viral (parvovirus) enteritis with marked cryptolysis and luminal accumulation of necrotic, desquamated cellular debris



Multifocal crypt damage with luminal dilatation and accumulation of necrotic cellular debris



Viral enteritis – marked crypt dilatation with loss of lining epithelium and luminal accumulation of necrotic cellular debris



Granulomatous enteritis with marked mucosal infiltration by epithelioid macrophages