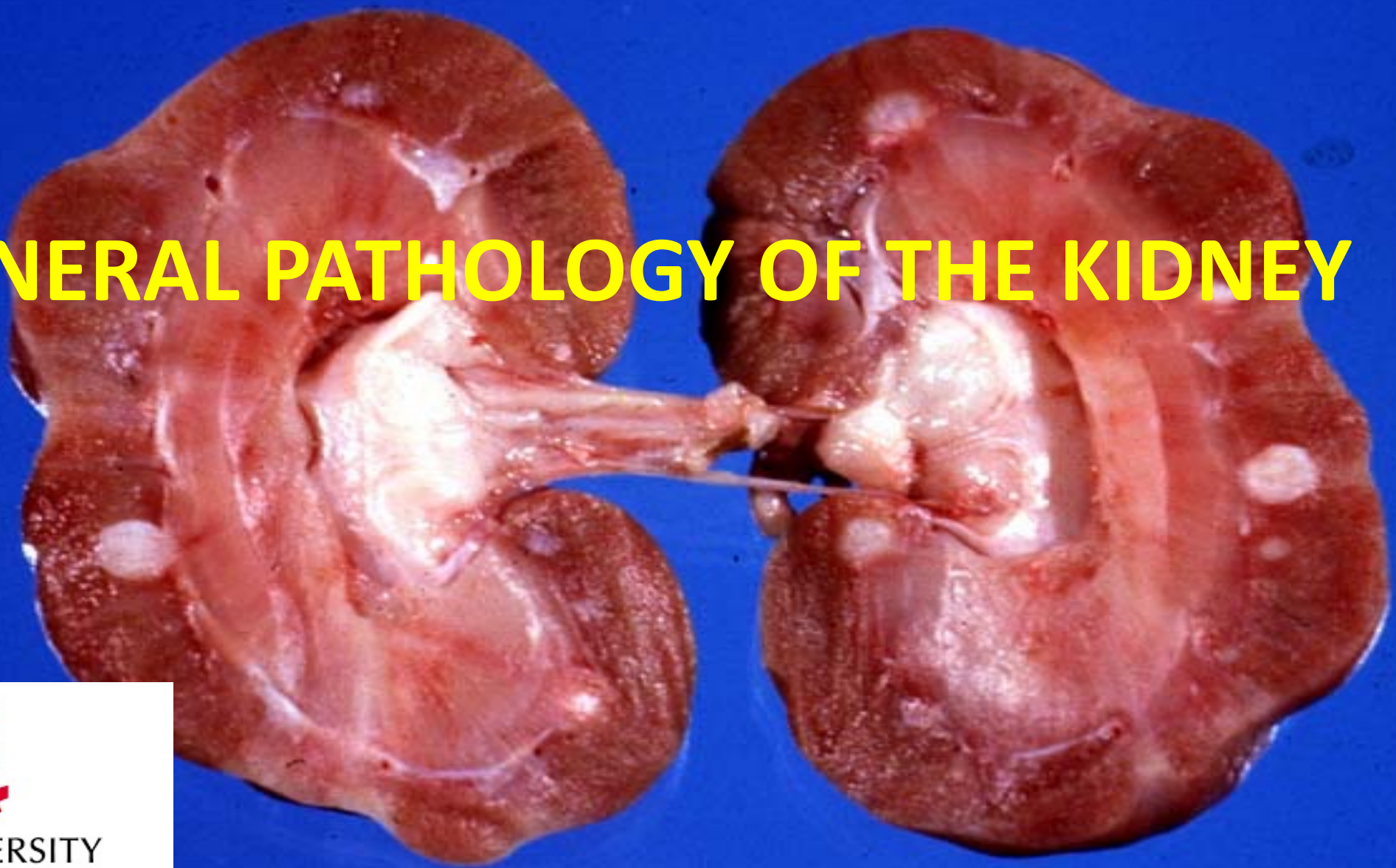
GENERAL PATHOLOGY OF THE KIDNEY



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The kidneys:

"A pair of handy tea strainers"

The following extract from the ABC's "Body Programme", written by Dr Earle Hackett, a former haematologist at the Institute of Medical and Veterinary Science in Adelaide, neatly outlines the principal functions of the kidney and why it is vulnerable to damage

Renal characteristics

It is at the butchers that most people get a butchers at a pair of kidneys. There is one very noticeable thing about them. The arteries and veins entering and leaving appear to be very large ….. almost a quarter of the circulating blood goes through the kidneys each time around

Everyone knows from experience that if you drink liquid, however turbid or flavoured or mixed, before long some clear straw-coloured pee will flush out at your other end. Some kind of filtering is going on. The connecting channel is the bloodstream. Water is absorbed into the blood from the gut and removed from the bloodstream by the kidney. So what the kidney is filtering is not tea, or beer, but blood. Urine is a concentrated filtrate of the blood

Renal characteristics

The main artery that enters each kidney promptly branches and re-branches until it has finally divided into about a million small blood vessels, tangled like a ball of thread, termed a glomerulus (from *glomus*, a Roman lady's ball of thread)

Each glomerulus hangs like a nipple into a small cellular receiving funnel that is closed around it like a baby's lips. Each of these funnels has a draining outlet that connects up with its million fellows through collecting tubules to form the ureter that carries pee to the bladder

Renal characteristics

The fine walls of the very small blood vessels that form the glomerulus are leaky. They leak like sieves. They have sieve holes that only hold back large molecules in the blood like plasma proteins, but let everything else through. There are also a few smaller protein molecules that the sieve would not retain were it not for electrostatic attractions

But everything else pours out from the blood through the little sieve holes into the collecting funnels – water (gallons of it), salt, sugar, amino acids, bicarbonate, potassium, calcium, phosphates, and urea – everything small and soluble. The only things that are held back are those that are differentially kept in the blood by being specifically carried on large, special blood plasma molecules into which they are temporally slotted. If this was all, the kidneys would be no more than blood strainers

Renal characteristics

But you need most of the water and the sugars and salt and so on that is being filtered out at an enormous rate. The blood vessel still continues in the kidney after it leaves the glomerulus

It continues beside the cell walls of the urinary tubule in which the watery filtrate is now flowing. The blood pressure in that blood vessel is now slacker. The effect is that much of the water and sugar and salt in the filtrate moves back by osmosis *across* the tube wall into the blood again

The rest of the urinary collecting tubes are quite lengthy, are lined by active cells that use energy to return to the blood the rest of the sugar, salts and amino acids and so on that the body does not want to lose

So by this combined mechanism of heavy filtration followed by first passive and then specific chemical reabsorption, the kidney eventually allows a concentrate of about 2 litres to run out as pee every 24 hours. Therefore, out of all that filtering of 200 litres from the blood, 198 litres has been absorbed back into the blood again

Renal characteristics

The kidney is cleansing the soluble components of the house of the body by constantly flinging everything out, then reorganising and bringing back in again only the familiar and the useful, and leaving the rest to leak away as unwanted sewerage

However, where the kidneys are vulnerable is where they are exceptional; which is where they handle so much blood and where they concentrate things. For example, some mildly harmful component that is in the circulation and damages small blood vessels could have heavy local effects in the kidney. So also might a small amount of a cell poison that could have become extra active when concentrated in the kidney tubules

Renal functions

Central organ involved in maintenance of a constant extracellular environment in the body

Vital homeostatic functions are:

Excretion of waste products

Maintenance of normal concentrations of salt and water in the body

Regulation of acid-base balance

Production of hormones (erythropoietin, renin, prostaglandins)

Metabolism of vitamin D to its active form

Essential requirements for normal renal function

Adequate perfusion with blood (pressure >60mmHg) – renal blood flow is high (up to 25% of cardiac output) and decreased blood flow causes injury, especially to the cortex. It is only reduced to preserve circulation to heart and brain

Adequate functional renal tissue

Normal elimination of urine

Renal functions

Water and salt are the most important constituents of body fluids and need to be conserved

Large quantities of metabolites also need to be excreted (nitrogenous wastes and a multitude of other organic and inorganic substances)

Excretion of wastes and conservation of water requires a concentrating mechanism capable of raising the osmotic pressure of urine above that of blood

Renal blood flow remains constant to ensure a stable glomerular filtration rate (GFR)

Renal functions

The glomerulus produces an ultrafiltrate due to high capillary hydrostatic pressure and low hydrostatic pressure in Bowman's space and difference in osmotic pressure. The glomerular basement membrane (GBM) is semi-permeable

Injury to the glomerulus can result from inadequate glomerular blood flow and/or structural changes that alter its permeability

After crossing the GBM, the ultrafiltrate enters the tubular lumen and many filtered substances are then retrieved by selective reabsoption

Main function of the kidney is regulation of salt and water balance, achieved by antidiuretic hormone (ADH) (also termed vasopressin) and the renin-angiotensin-aldosterone system

Renal pathology

In progressive renal disease, remaining nephrons hypertrophy as new nephrons cannot be formed in a mature kidney and glomerular filtration and tubular function increase to maintain homeostasis

All of the renal components are interdependent and, if one component is irreversibly damage, the function of other components will be impaired

There is a tendency for chronic renal disease to affect multiple kidney components, resulting in chronic renal failure and shrunken, scarred, end-stage kidneys (at which time, it can be impossible to determine the initiating cause)

Renal anatomy

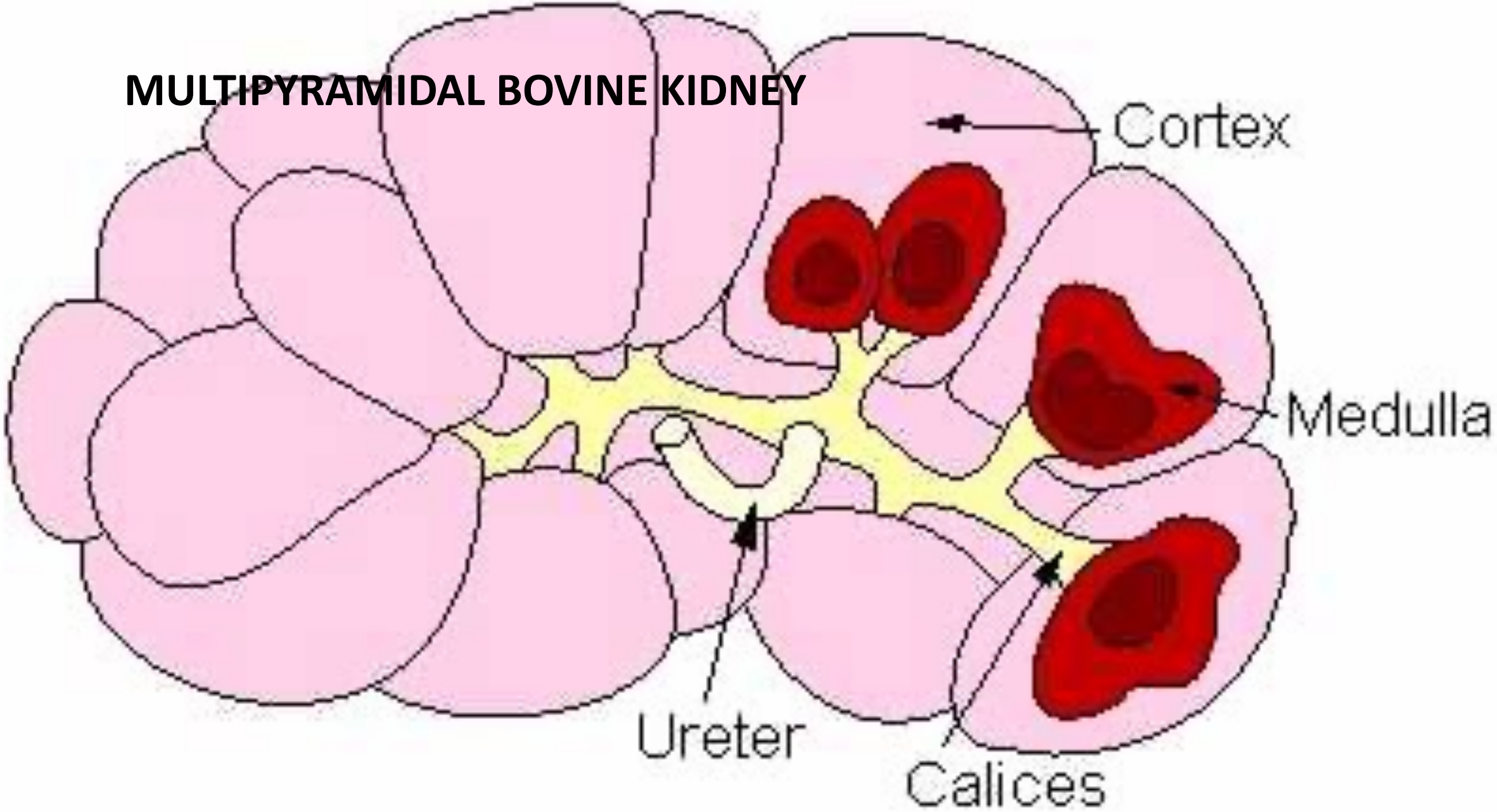
Kidneys in domestic animals are classified as unipyramidal or unilobar (cats, dogs, small ruminants and horses) or multipyramidal or multilobar (pigs, cattle)

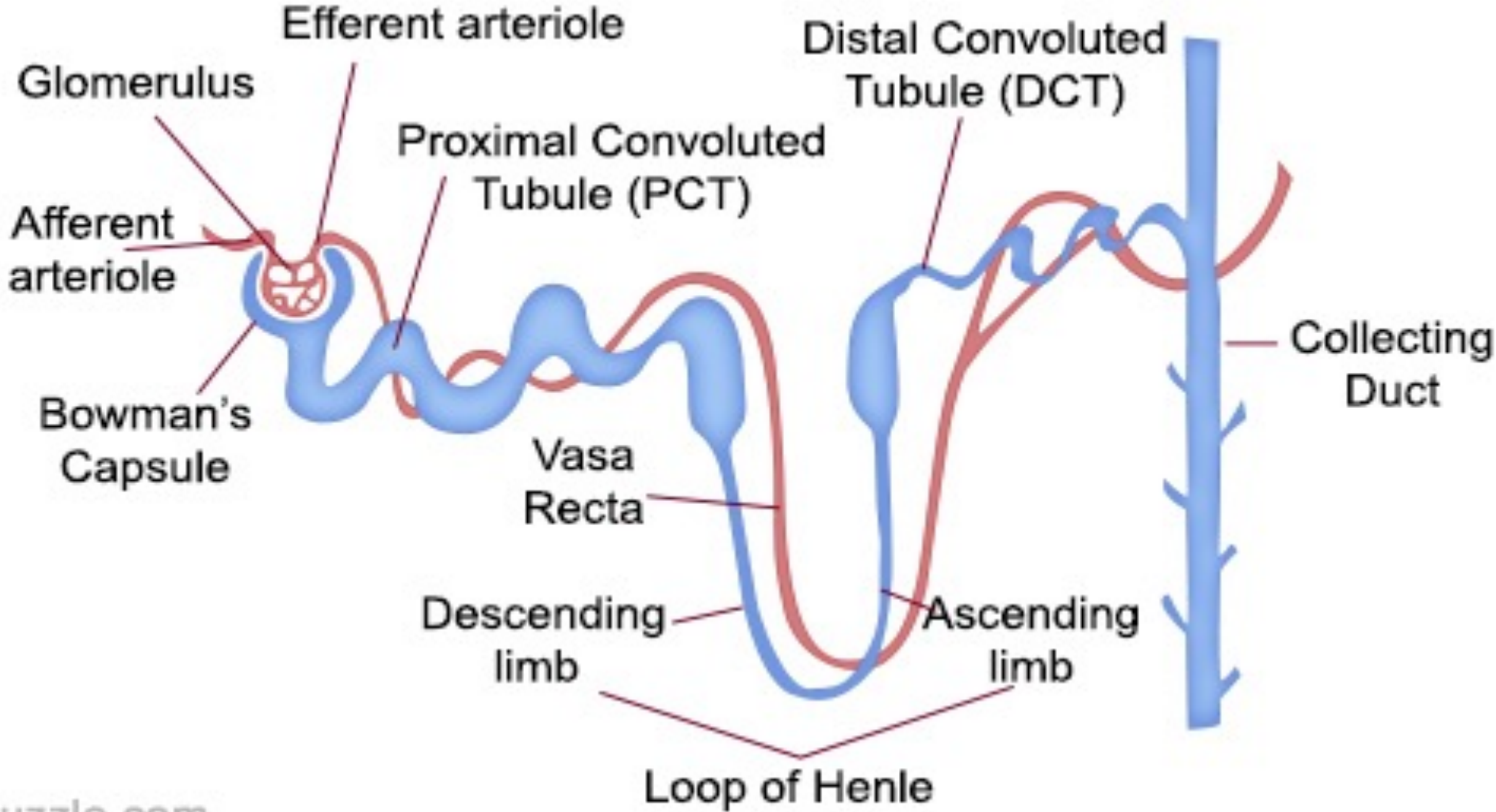
On section, subdivisions of cortex and medulla are discernible

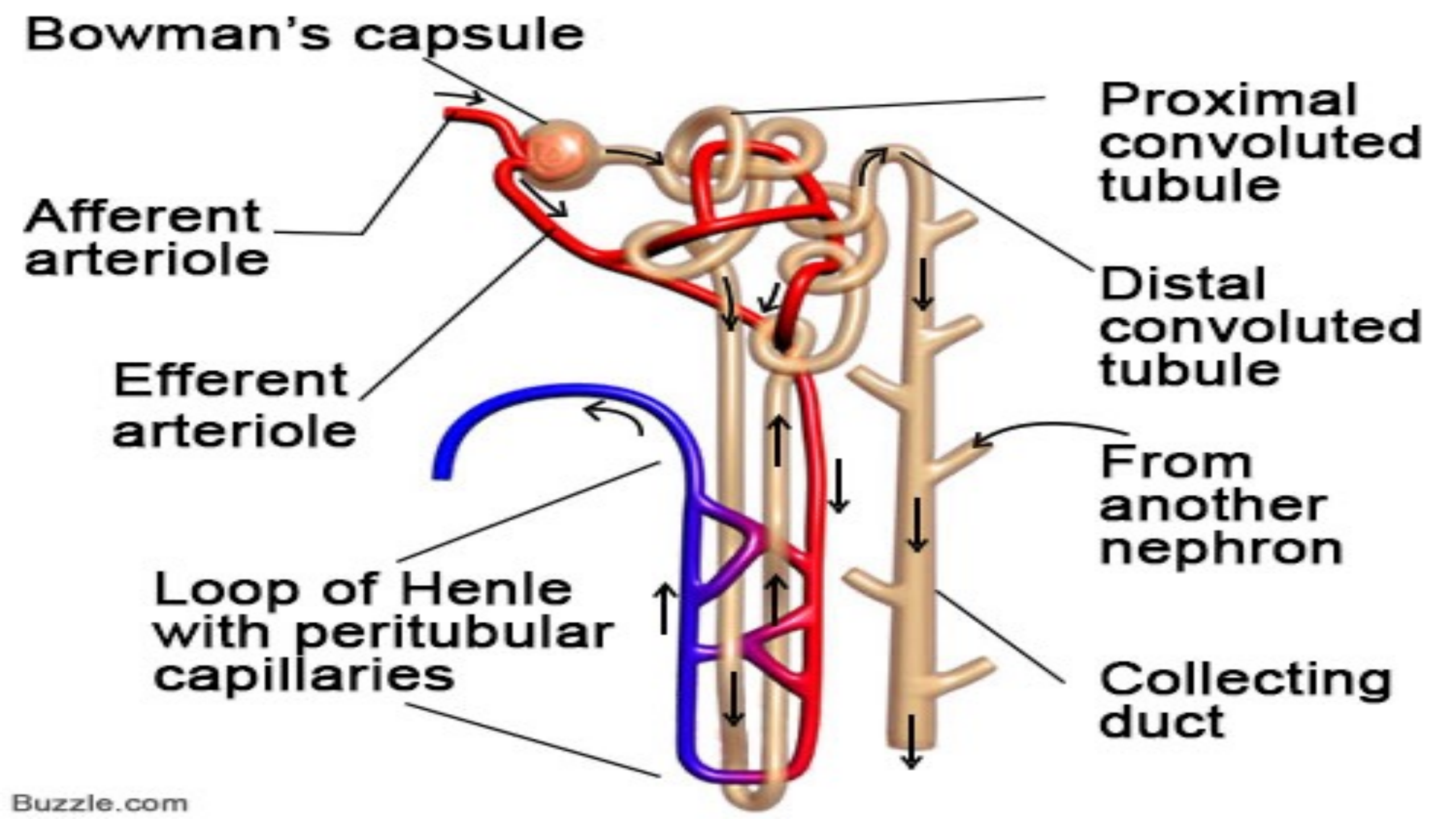
The functional unit of the kidney is the nephron, which consists of the renal corpuscle (glomerulus and Bowman's capsule), proximal and distal convolute tubules and the loop of Henle

4 main components of kidney: glomeruli, tubules, interstitium and blood vessels

MULTIPYRAMIDAL BOVINE KIDNEY




Efferent arteriole
Glomerulus
Distal Convoluted Tubule (DCT)
Proximal Convoluted Tubule (PCT)
Afferent arteriole
Collecting Duct
Bowman's Capsule
Vasa Recta
Descending limb
Ascending limb
Loop of Henle


Bowman's capsule
Afferent arteriole
Efferent arteriole
Loop of Henle with peritubular capillaries
Proximal convoluted tubule
Distal convoluted tubule
From another nephron
Collecting duct
Buzzle.com

Renal vascular supply

Renal artery divides to form **interlobular arteries**, which then branch as **arcuate arteries**, then becoming **interlobular arteries** which in turn form prearterioles

Prearterioles give rise to glomerular afferent arterioles, then glomerular capillary loops, which fuse to form efferent arterioles, then the peritubular capillary plexus

The **glomerular capillary tufts** are perfused at high pressure for filtration and the capillary bed arising from efferent arterioles is low pressure for reabsorption

Renal vascular supply

Renal arteries are end-arteries and occlusion leads to infarction

Medulla is very sensitive to ischaemia because of its relative avascularity

Glomerular filtration

Glomerular filtration rate (GFR) is controlled by tubuloglomerular feedback – low GFR causes decreased NaCl delivery to distal tubules, which is detected by the macular densa in these tubules, leading to contraction of efferent arteriole and dilation of afferent arteriole, increasing the GFR. A high GFR initiates the opposite response

Macula densa secretes prostaglandin E2, causing renin release from afferent arteriole juxtaglomerular cells, which acts on angiotensinogen (produced by liver) to generate angiotensin I which, in turn, is cleaved by angiotensin converting enzyme to angiotensin II, a potent vasoconstrictor

Angiotensin II also initiates (1) adrenocortical release of **aldosterone**, which increases resorption of Na from distal tubules and collecting ducts, resulting in water retention and (2) secretion of **ADH** by the posterior pituitary, which increases water resorption (via aquaporin channels) in collecting ducts

Glomerulus

Vascular and epithelial structure designed for the ultrafiltration of plasma

Visceral epithelium (podocytes) covers the abluminal surface of glomerular capillaries, while parietal epithelium lines basement membrane of Bowman's capsule

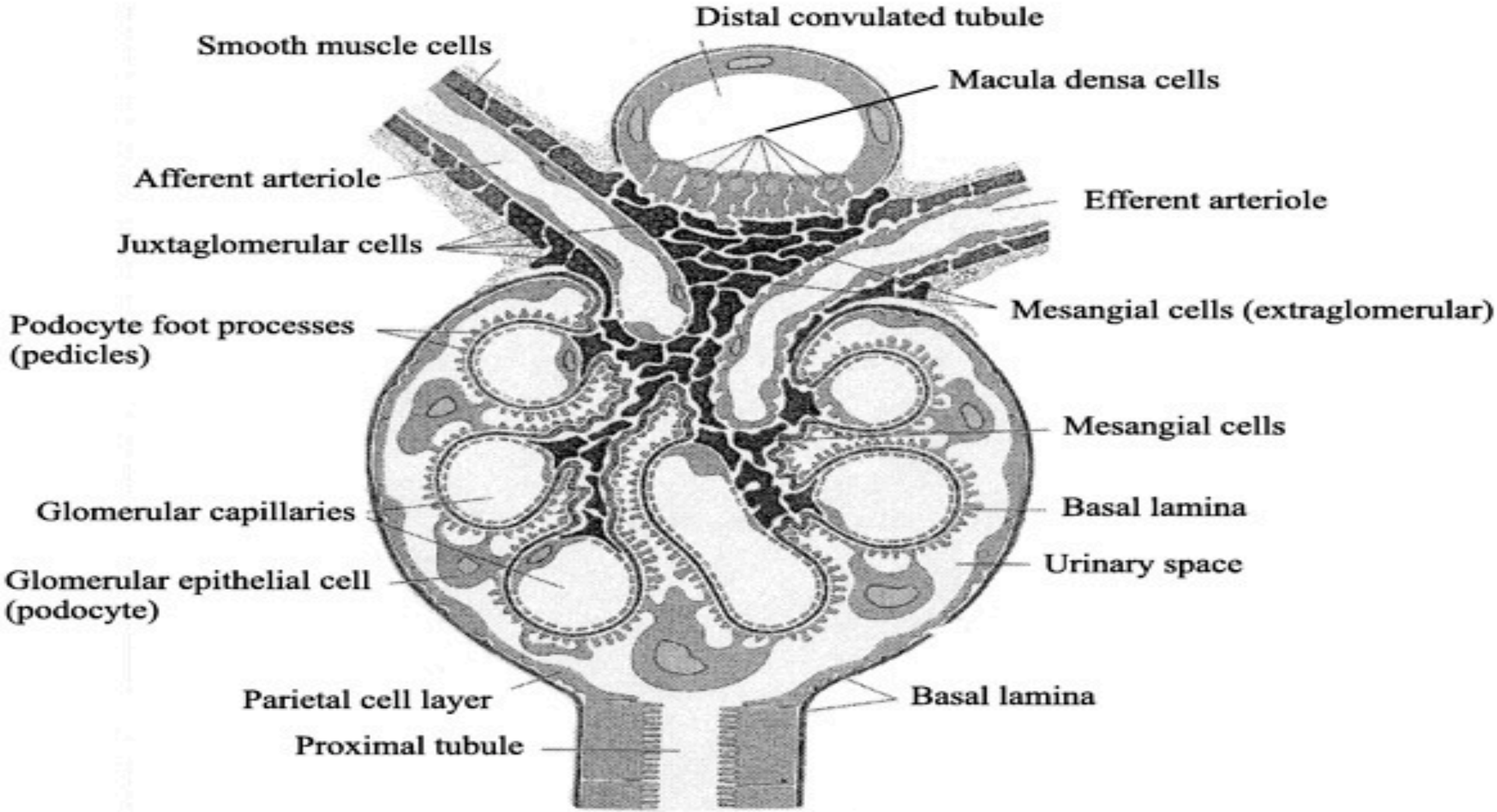
Arterioles enter and leave the glomerulus at vascular pole and urine enters proximal convoluted tubule at urinary pole

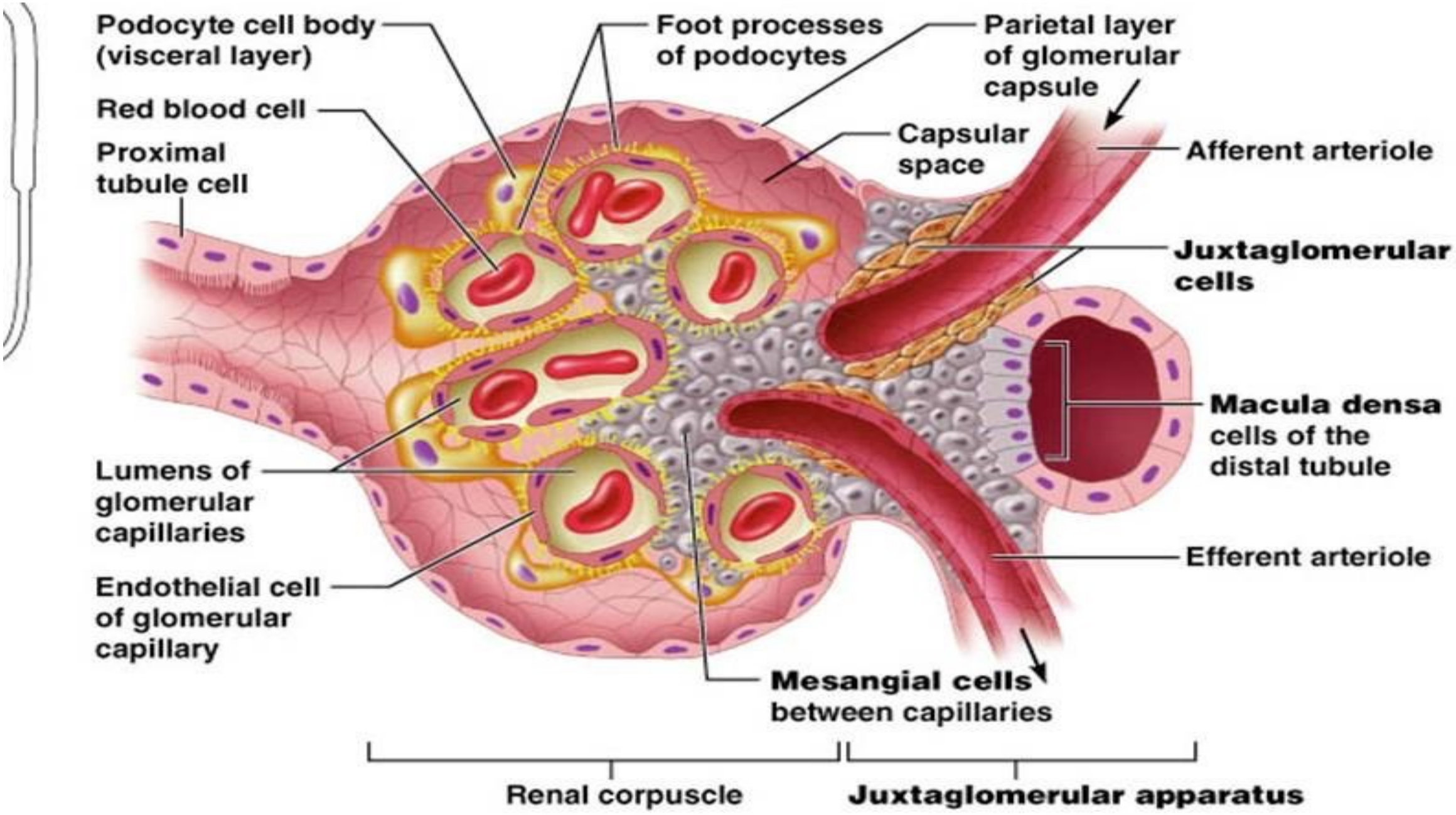
Glomerular filtration membrane consists of 3 layers

Fenestrated capillary endothelium

Glomerular basement membrane (GBM), a complex, porous meshwork and size- and charge-dependent barrier, produced by podocytes and endothelium

Podocytes, which have complex interdigitating trabeculae whose foot processes (pedicels) are embedded in GBM. Pedicels are separated by filtration slits, which are bridged by diaphragms with pores


Distal convulated tubule
Smooth muscle cells
Macula densa cells
Afferent arteriole
Efferent arteriole
Juxtaglomerular cells
Mesangial cells (extraglomerular)
Podocyte foot processes (pedicles)
Mesangial cells
Glomerular capillaries
Basal lamina
Urinary space
Glomerular epithelial cell (podocyte)
Parietal cell layer
Basal lamina
Proximal tubule


Podocyte cell body (visceral layer)
Red blood cell
Proximal tubule cell
Foot processes of podocytes
Parietal layer of glomerular capsule
Capsular space
Afferent arteriole
Juxtaglomerular cells
Macula densa cells of the distal tubule
Lumens of glomerular capillaries
Endothelial cell of glomerular capillary
Efferent arteriole
Mesangial cells between capillaries
Renal corpuscle
Juxtaglomerular apparatus

Glomerular basement membrane

GBM is highly permeable to water and small solutes, but excludes high MW plasma proteins

Changes in GBM porosity and charge alter glomerular permeability and can lead to proteinuria, a hallmark of glomerular damage

The Irish surgeon and poet, Oliver St John Gogarty knew the importance of proteinuria in renal disease, as can be seen in the last 3 verses of his poem entitled: "John Kidney who died of Acute Nephritis"

For the walls of the flesh which immure in

The spirit, as tubes do their lumen,

Came urine, and, mixed with the urine,

Were clouds of albumen.

And, though by the doctors unbidden, he
Passed out through these clouds to his goal:
Albumen and coma and kidney
Secreted his soul.

And there came on the *Dies Suprema*
That comes to all who draw breath
Death, ushered in by oedema,
Oedema and Death.

Mesangium

Occupies the central region of glomerulus and composed of basement membrane-like glycoprotein and phagocytic, contractile cells derived from vascular smooth muscle cells

Functions in phagocytic removal of macromolecules, removal of GBM, and may modulate intraglomerular blood flow

Also produces a variety of cytokines

Mesanglial cell hyperplasia and increased mesangial matrix are common lesions in glomerular disease

Renal tubules

These structures are correlated with function

Proximal convoluted tubule (PCT) has a well-developed brush border and numerous mitochondria and, since energy for resorption is produced by mitochondrial oxidative phosphorylation, it is especially vulnerable to hypoxia

Many toxins are resorbed/secreted by PCT, potentially causing chemical injury

60-80% of the glomerular ultrafiltrate is resorbed by PCT and the closely-associated peritubular capillaries permit rapid absorption of Na and Cl, which water follows (also resorbs glucose, amino acids, Ca, K, uric acid, proteins and phosphate – many of these are resorbed until a threshold is reached and, when this is exceeded, the substance appears in urine)

Renal tubules

Long loops of Henle penetrate deep into medulla and their urine concentrating ability is directly related to their length. NaCl is actively pumped from ascending limb (which is impermeable to water), draining water from descending limb and returning it to the cortex

If water preservation is required, ADH release increases the permeability of medullary collecting ducts (CD) to urea and water. Urea diffuses into the interstitium and water follows

Kidneys ultimately correct acid-base balance by excreting excess alkali or acid responsible for the disturbance

Renal interstitium

Contains peritubular capillaries, pericytes, and fibroblasts and any expansion (by oedema, cellular infiltration, and fibrosis) is abnormal

Histological examination of kidney

The kidney should be bisected longitudinally from pole to pole into equal halves in order that a section from capsule to papilla is for examination

Reactions of glomeruli to injury

Combinations of:

Cellular proliferation

Mesangial expansion

Leucocyte recruitment

Remodelling of glomerular basement membrane (GBM)

Sclerosis

Terminology

Uraemia (“urine in blood”) is a *clinical* syndrome of renal failure

Azotaemia is a *biochemical* abnormality characterised by increased blood urea and creatinine, which can be **prerenal** (decreased renal blood flow and lowered GFR) or **postrenal** (due to urinary tract obstruction and hence oliguria or anuria)

Renal tubular damage

Tubules, especially proximal convoluted tubule (PCT), are most susceptible to ischaemia and toxins

Delay in fixation causes epithelial sloughing into the lumen

Proximal convoluted tubule epithelium may be present in Bowman's space due to squeezing of kidney, termed infraglomerular herniation or reflux

Renal failure

Renal disease is usually subclinical, but

When severe, can lead **to renal failure** which can be:

Acute and potentially reversible (rapid onset of oliguria (reduced urine flow) or anuria (no urine flow) and azotaemia from glomerular, tubular or interstitial damage or

Chronic and usually irreversible with prolonged uraemia

Evolution from normal renal function to uraemia occurs in 4 stages

Diminished renal reserve – glomerular filtration rate (GFR) ~50% of normal and asymptomatic

Renal insufficiency – GFR 25-50% of normal and azotaemia occurs

Renal failure – GFR 20-25% of normal, kidney cannot maintain homeostasis, and uraemia ensues

End-stage renal disease – GFR <5% of normal and terminal stages of uraemia are present

Clinical pathology

Biochemical disturbances of uraemia reflect impairment of the kidney's regulation of fluid volume (resulting in dehydration), regulation of electrolytes (excess/deficit in plasma Na, K, and Ca) and acid-base balance, excretion of wastes, and metabolism of hormones

Elevated blood levels of urea and creatinine indicate decreased glomerular filtration and are a useful test of renal function, but

Azotaemia occurs only after loss of >75% of GFR and is thus an insensitive indicator of renal disease

Uraemia also causes a non-regenerative anaemia

Renal disease

With "end-stage" kidney disease and severe uraemia, kidney is fibrosed and mineralised (glomerulus and tubular basement membranes) with globally sclerotic glomeruli and a mixture of atrophic and hypertrophic tubules

Interstitial fibrosis and glomerulosclerosis are slowly progressive lesions that are common in end-stage renal disease, the former believed to be the final common pathway to chronic renal failure

Azotaemia

Azotaemia (increased blood urea nitrogen and creatinine) develops when GFR is reduced to 25% of normal

Before this stage, adaptive changes in intact nephrons maintain renal function at an adequate level as other nephrons are lost

The glomerulus is probably the limiting factor in this compensation as it has relatively limited ability to increase its function

Renal failure/infarction

Chronic renal failure tends to be progressive

GFR also decreases with normal ageing, leading to decreased renal reserve and lowered compensatory ability

Renal infarction is common due to necrosis produced by embolic and thrombotic occlusion of the renal artery or one of its branches and sequelae depend on whether the obstructing material is septic or sterile and size and number of vessels occluded

Glomerular disease

Important because interference with glomerular blood flow alters the formation of an ultrafiltrate and impairs peritubular perfusion, which can lead to loss of an entire nephron

Glomerulitis = inflammation restricted to glomerulus (e.g. in acute septicaemia)

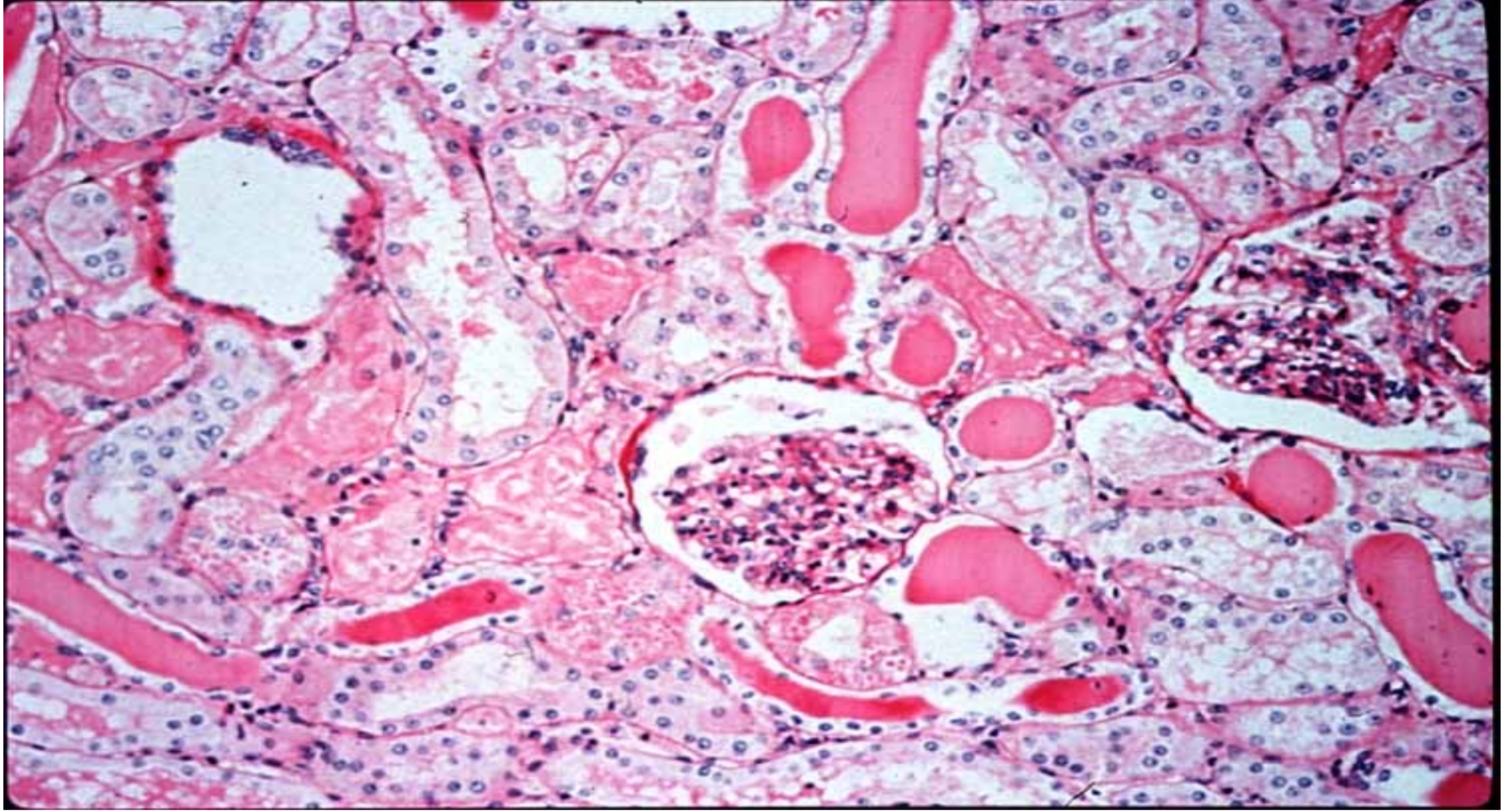
Glomerulonephritis implies primary glomerular disease is complicated by secondary tubulointerstitial and vascular changes

Glomerulopathy = glomerular disease without inflammatory cells or of uncertain aetiology/pathogenesis

Glomerular disease

Proteinuria as a result of increased glomerular permeability is suggestive of glomerular disease, in the absence of urinary tract inflammation.

When there is proteinuria, hypoalbuminaemia, generalised oedema and hyperlipidaemia, the term nephrotic syndrome is applied



Proteinuria leading to the formation of many protein casts in tubular lumina

Glomerular disease

Can be:

Diffuse (involves >50% of glomeruli)

Focal (involves <50% of glomeruli)

Global (involves the entire glomerular tuft)

Segmental (involves only part of a glomerulus)

Mesangial (affects primarily the mesangial region)

Classification of glomerular disease

Glomerular disease can be further classified as:

Membranous – GBM remodelling secondary to immune complex deposition with normal to mild hypercellularity

Proliferative – increased cellularity without significant alterations to GBM

Classification of glomerular disease (cont)

Mesangioproliferative – increased cellularity limited to mesangium with evidence of immune complex deposition in this region

Mesangiocapillary proliferation – capillary and mesangial proliferation with remodelling of capillary loop from immune complex deposition between endothelium and GBM

Segmental glomerulosclerosis – segmental effacement of capillary loops by ECM

Global glomerulosclerosis – tuft is shrunken, eosinophilic and hypocellular

Histological changes in glomerular disease

Cellularity of glomerular tuft may be increased by proliferation of endothelial, epithelial or mesangial cells + inflammatory cell infiltration

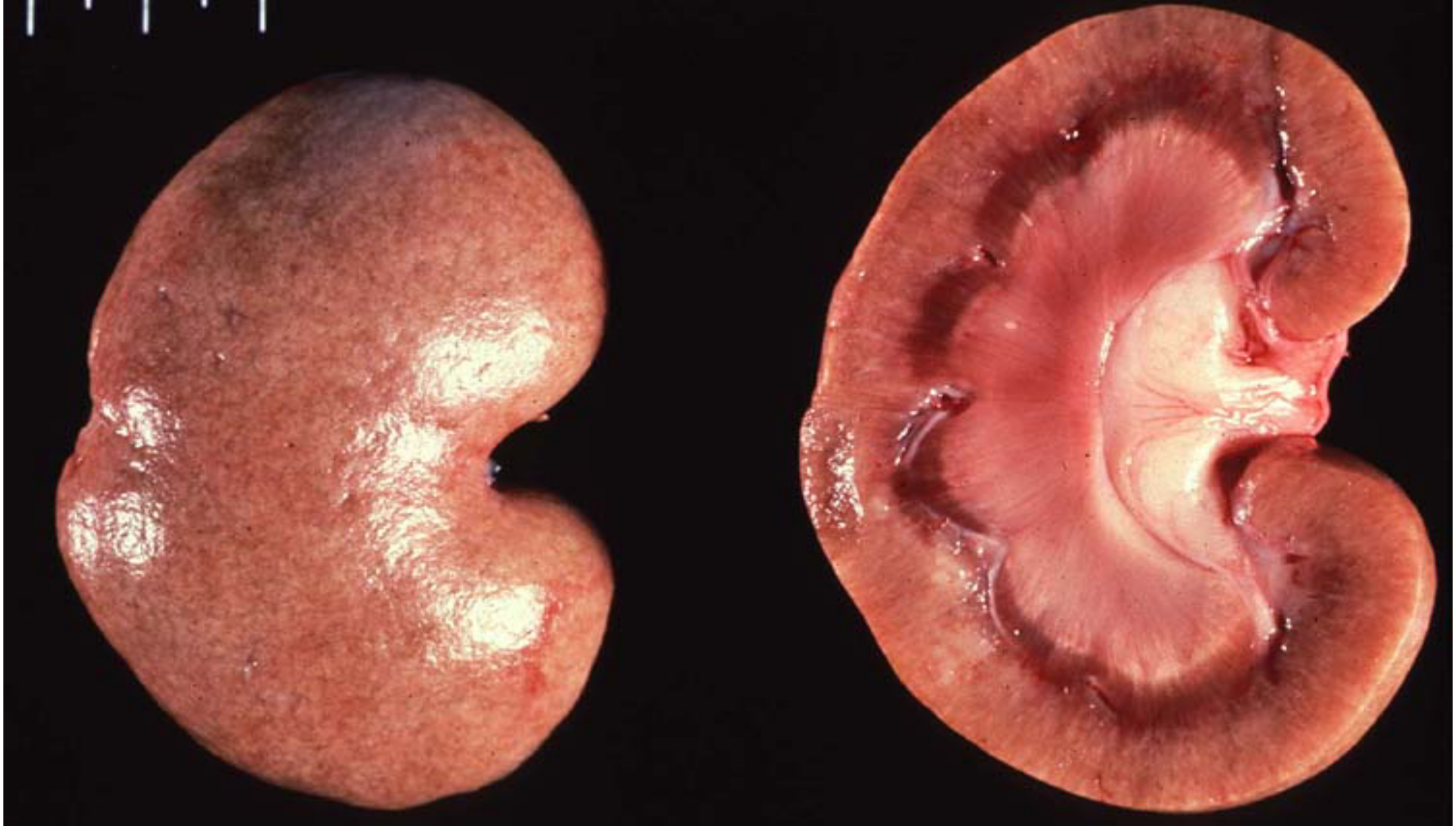
Mesangial cells may also migrate out into capillary loop (mesangial cell interpositioning)

Fibrin exudation and rupture of GBM results in proliferation of visceral and parietal epithelium + infiltration of macrophages, neutrophils and interstitial fibroblasts, forming glomerular crescents

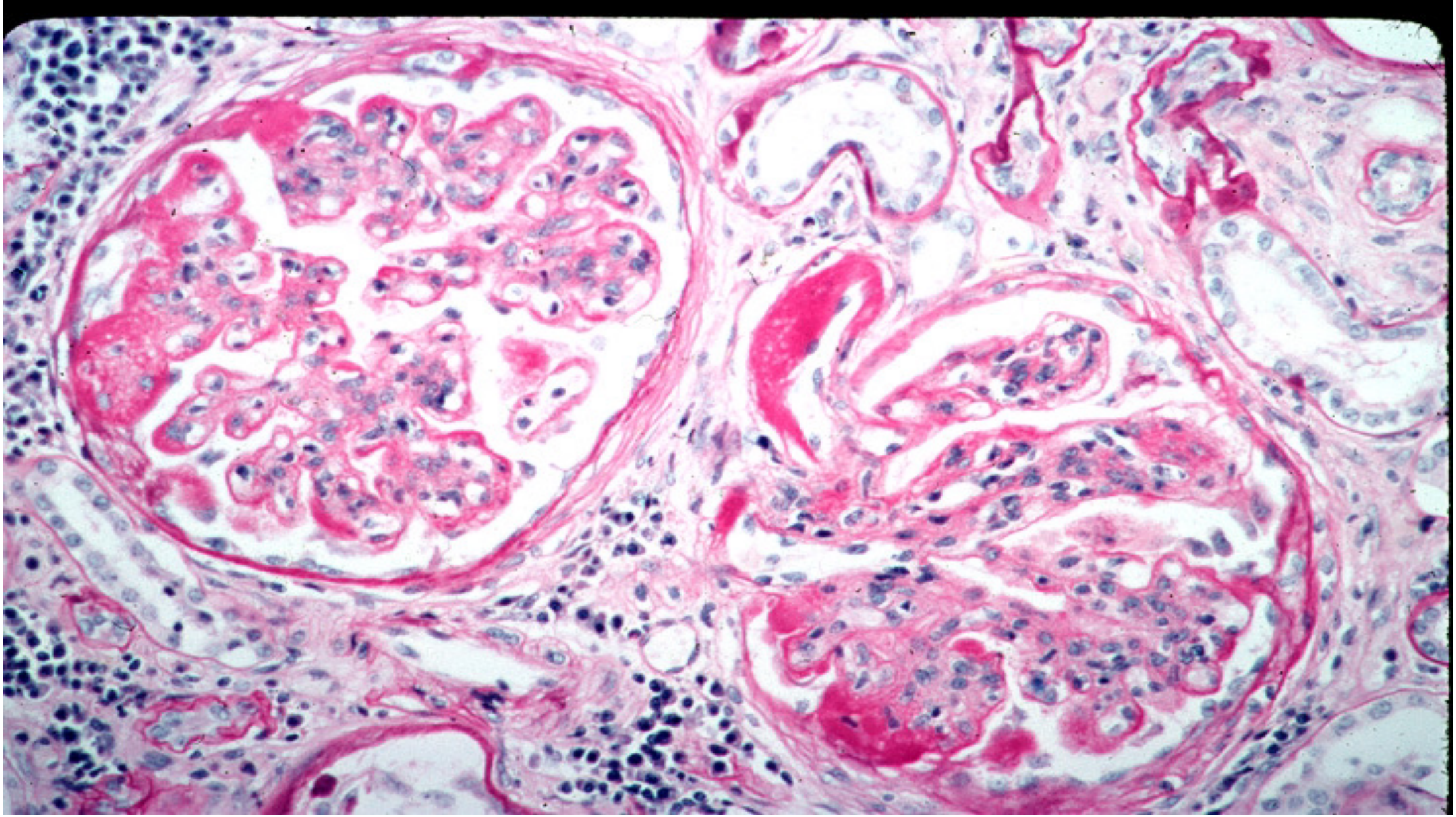
Histological changes in glomerular disease

Swelling of foot processes with subsequent retraction – reversible and associated with protein leakage

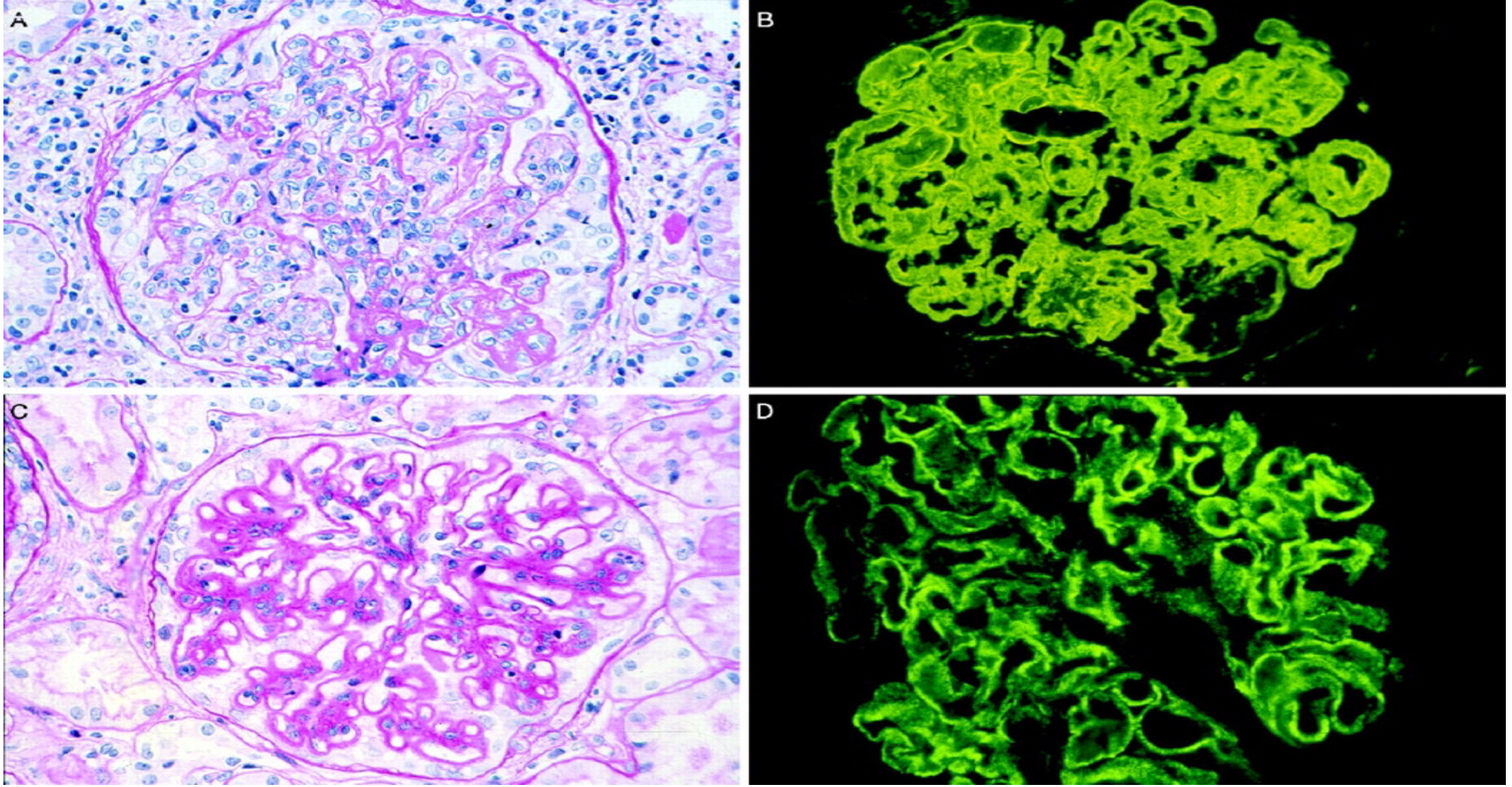
Thickening and remodelling of GBM due to immune complex deposition



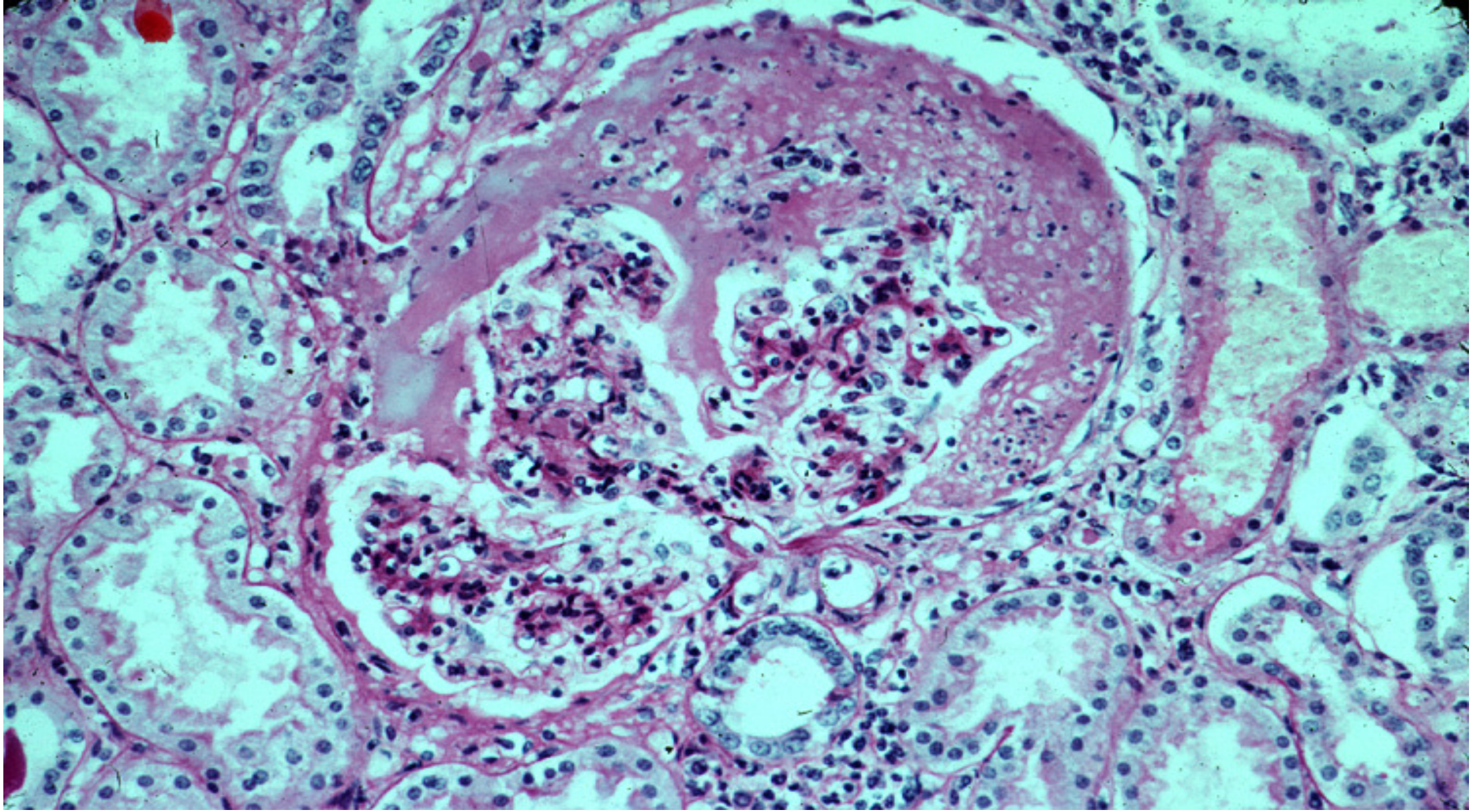
Chronic diffuse immune-mediated glomerulonephritis. Cortical surface is finely granular.



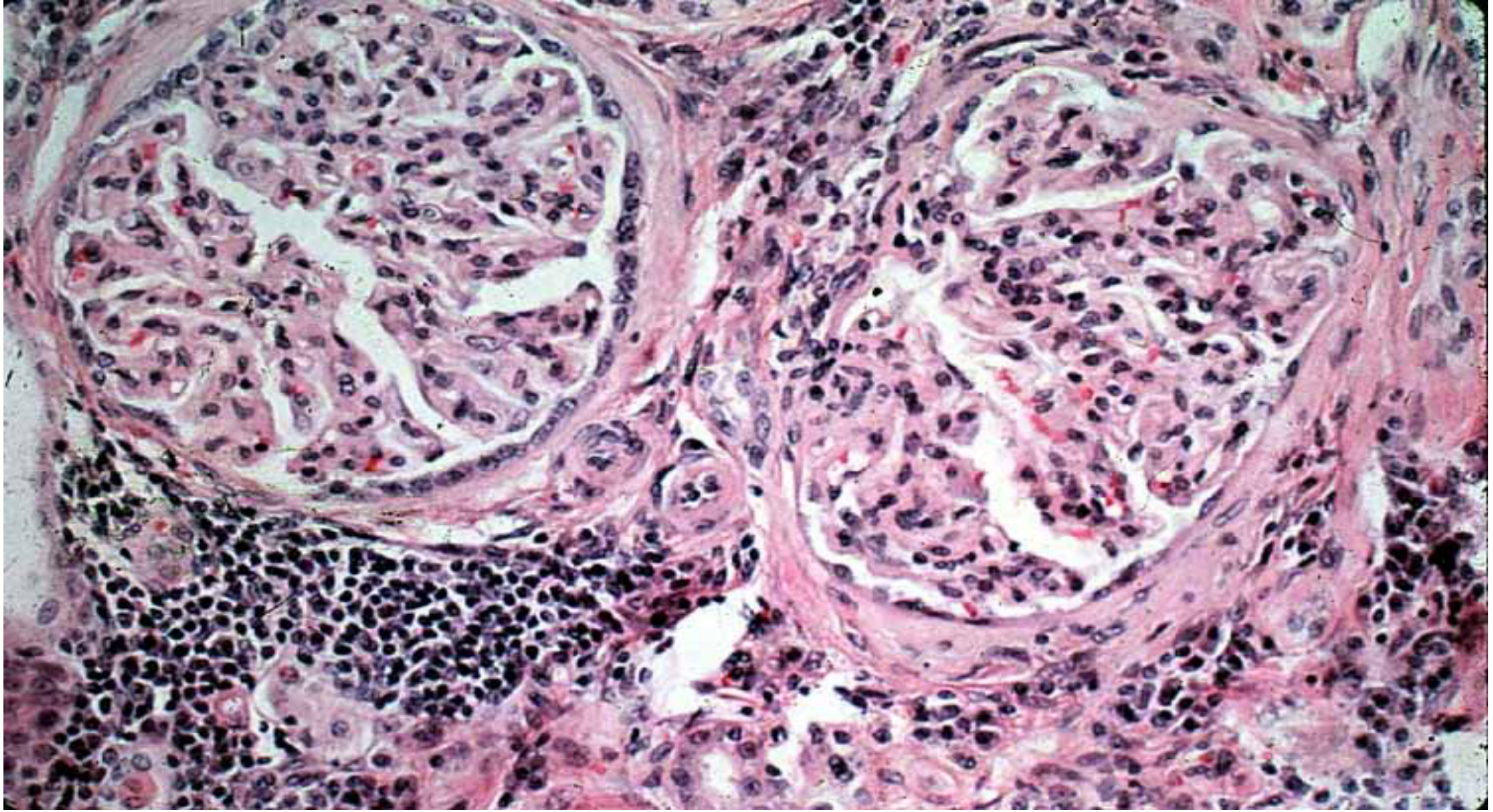
Chronic glomerulonephritis – thickening of glomerular and capsular basement membranes (PAS stain)



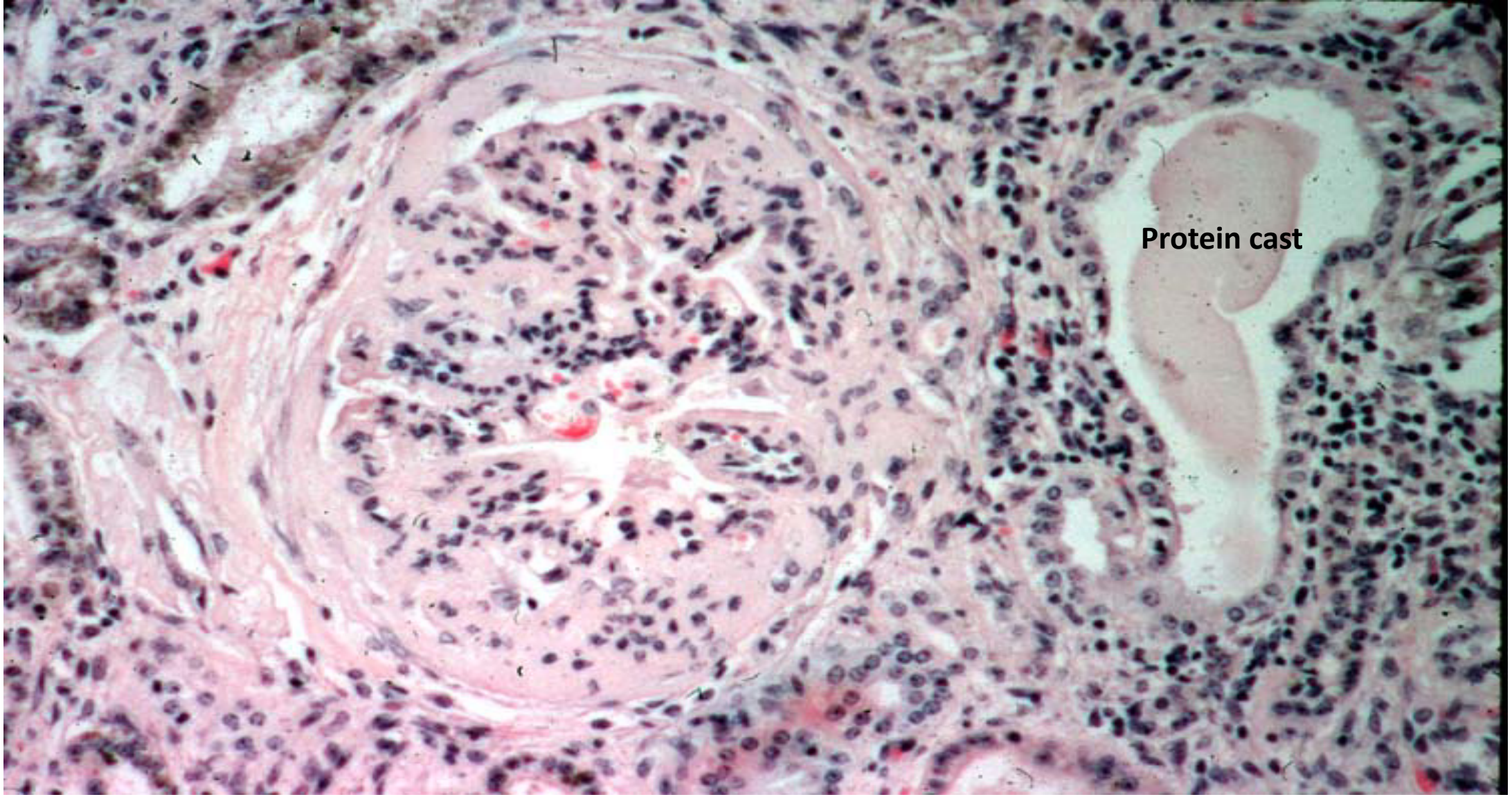
Glomerulonephritis – left panels show glomerular basement membrane thickening (PAS stain) and right panels show the pattern of immunofluorescence staining for IgG deposition



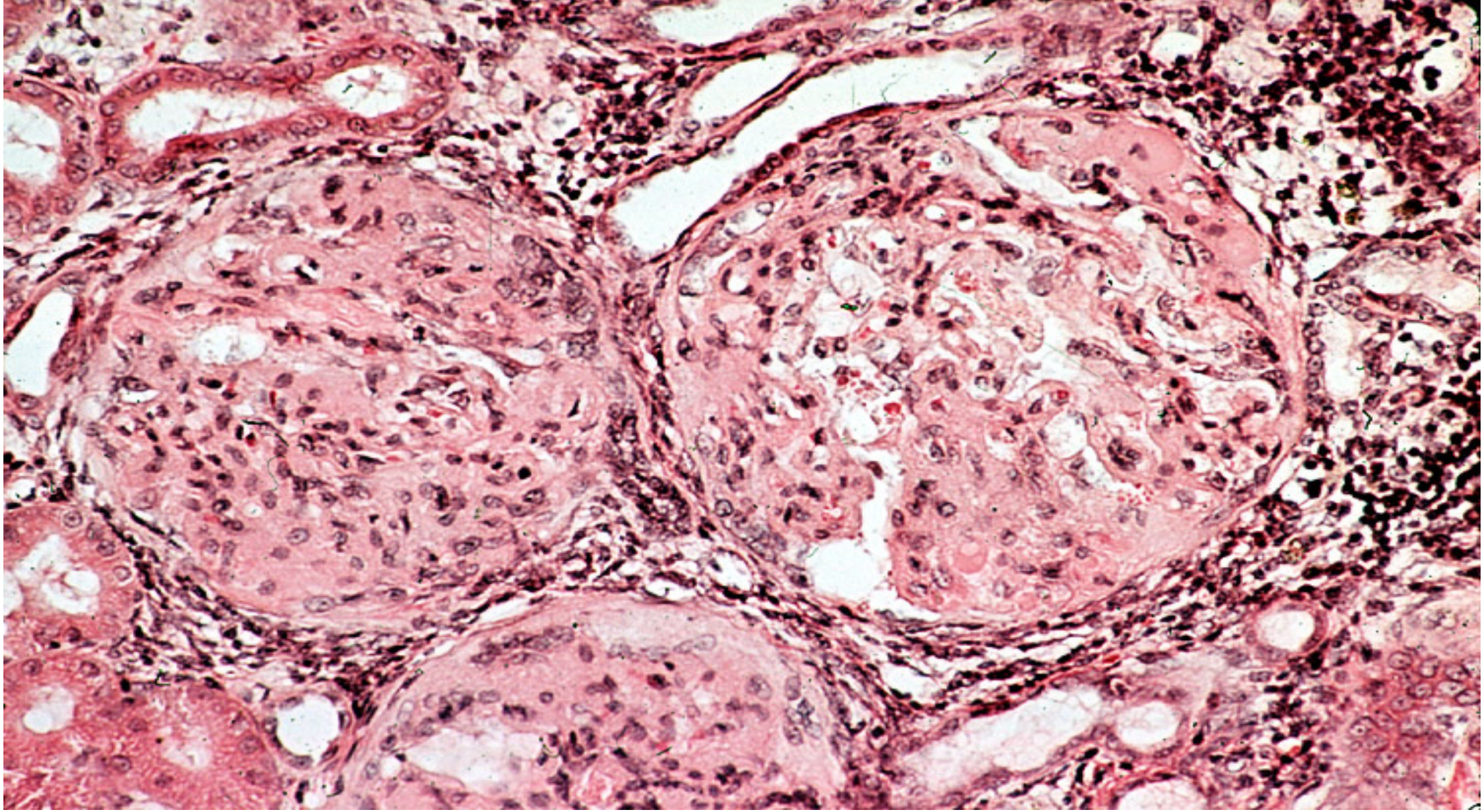
Fibrinous glomerulonephritis – fibrin deposition and leucocytic infiltration



Chronic glomerulonephritis – thickening of glomerular and capsular basement membranes and hyperplasia of parietal epithelium. Interstitial lymphocytic infiltration.



Chronic glomerulonephritis – abundant periglomerular fibrosis and hypercellularity of glomerular tuft



Chronic glomerulonephritis – “end-stage” glomerulus with marked basement membrane thickening and hyalinisation

Pathogenesis of glomerulonephritis

May result from:

Deposition of circulating, non-glomerular origin, antigen-antibody immune complexes in various glomerular sites (subendothelial, intramembranous, subepithelial, mesangial)

Formation *in situ* of antibodies against intrinsic GBM antigens

Activation of the alternative pathway of complement

Idiopathic

Pathogenesis of glomerulonephritis

Once immune complexes have formed, complement fixation occurs with resultant chemotaxis of neutrophils, which ingest complexes, but also release lysosomal enzymes, cytokines and free radicals that cause GBM damage

Complement fragments cause histamine release from mast cells, which increases capillary permeability and allows deposition of more immune complexes

Pathogenesis of glomerulonephritis

Many glomerular, tubular and interstitial elements also release chemokines (chemotactic cytokines) that attract leucocytes

Monocytes can remove immune complexes, but also cause enzymatic damage and mesangial cells can produce inflammatory mediators

Morphology of glomerulonephritis

In the acute phase, there is hypercellularity, mostly due to inflammatory cell infiltration, but also endothelial and mesangial proliferation

In subacute phase, often mesangial hypercellularity and/or remodelling of GBM

Morphology of glomerulonephritis

In chronic phase, scarring of glomeruli occurs, the interstitial reaction initiated in acute phase progresses with fibrosis and lymphocytic infiltration, tubules atrophy and are replaced by scar tissue, and fibrosis becomes self-perpetuating

Remaining tubules connected to functioning glomeruli show epithelial hypertrophy/hyperplasia

Once GFR has decreased to 30-50% of normal, progression to end-stage renal failure tends to become unavoidable

Diseases of renal tubules

Primarily reflected in morphological changes in epithelial cells, but tubules and interstitium are intimately associated and damage to one affects the other

Diseases involving both simultaneously = tubulointerstitial diseases

Regeneration of tubular epithelium can occur

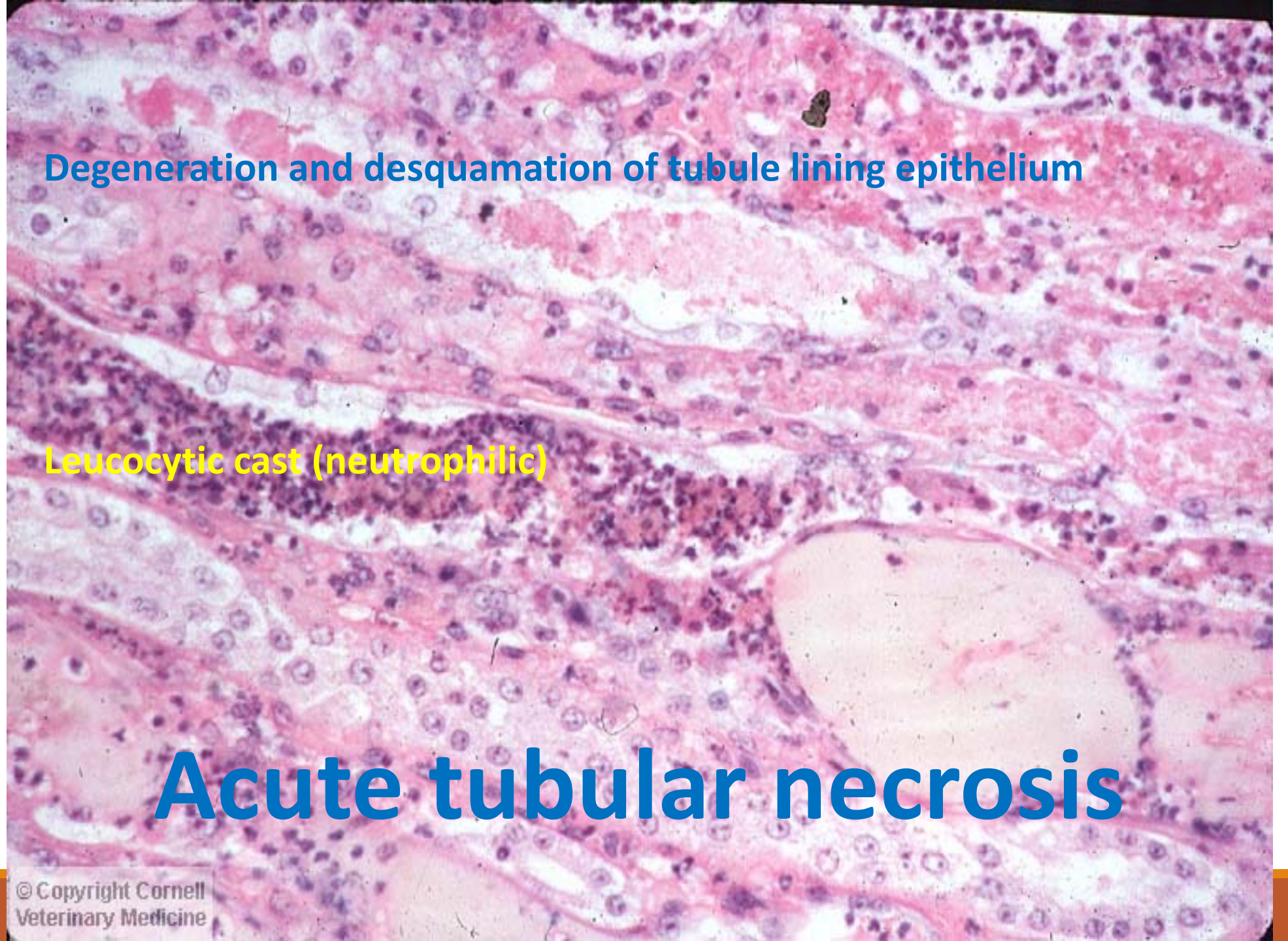
Histopathology of tubular damage

Acute cellular swelling results from damage to mitochondria with clear spaces/vacuoles in epithelial cytoplasm (potentially reversible)

Necrotic tubular epithelial cells are hypereosinophilic, have pyknotic nuclei and slough into the lumen, where they form cellular casts

Tubules filled with **proteinaceous fluid** usually indicates increased glomerular permeability and **hyaline droplets** form in PCT cytoplasm (lysosomes swollen by resorbed protein). **Tamm-Horsfall mucoprotein** is produced in ascending loop of Henle and distal tubules

Thickening of tubular basement membrane occurs in chronic disease and, in renal **amyloidosis**, amyloid deposition occurs in tubular basement membrane as well as glomeruli


Degeneration and desquamation of tubule lining epithelium
Leucocytic cast (neutrophilic)
Acute tubular necrosis
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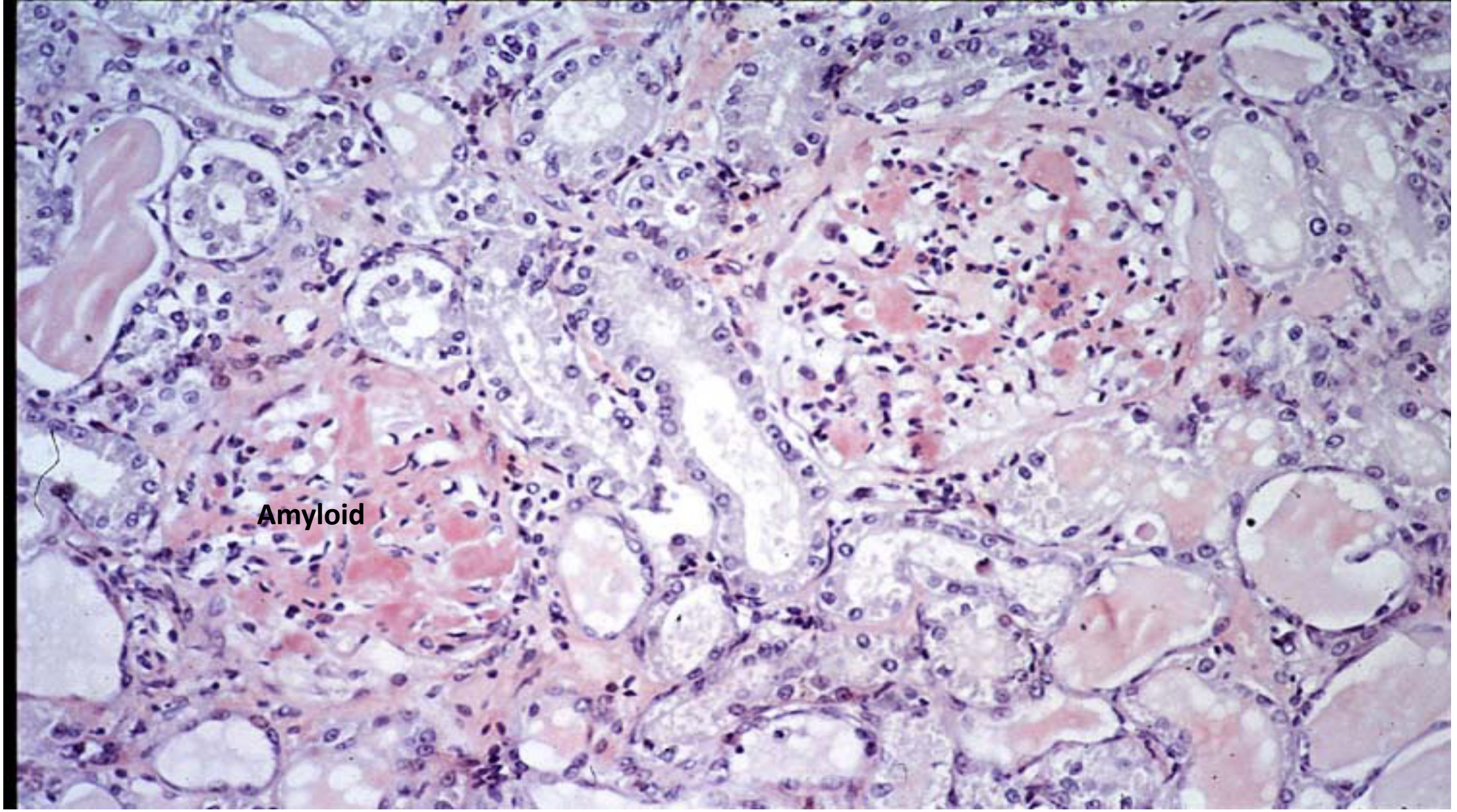
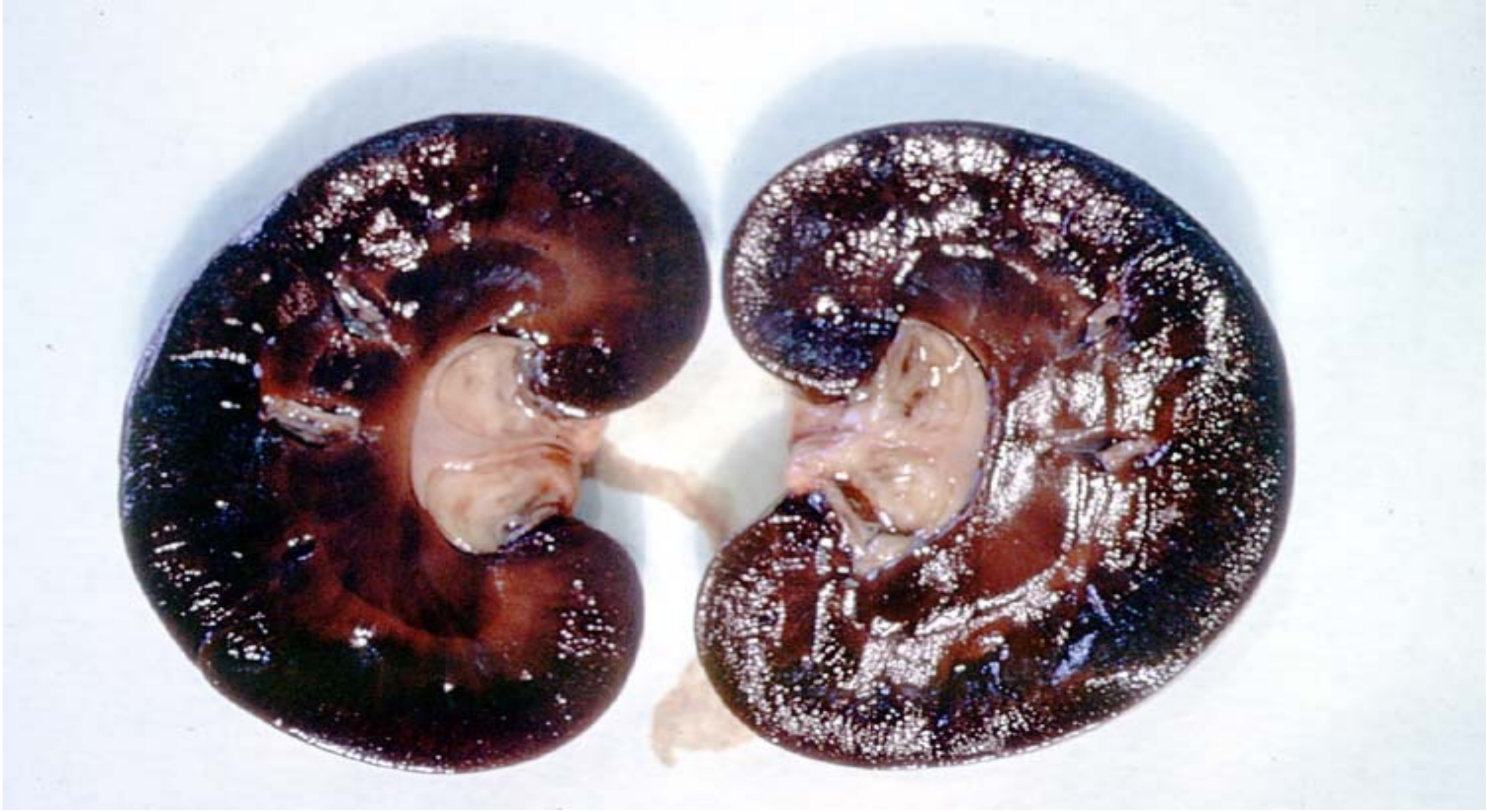


Renal amyloidosis – amyloid deposition in glomeruli (Congo red stain)

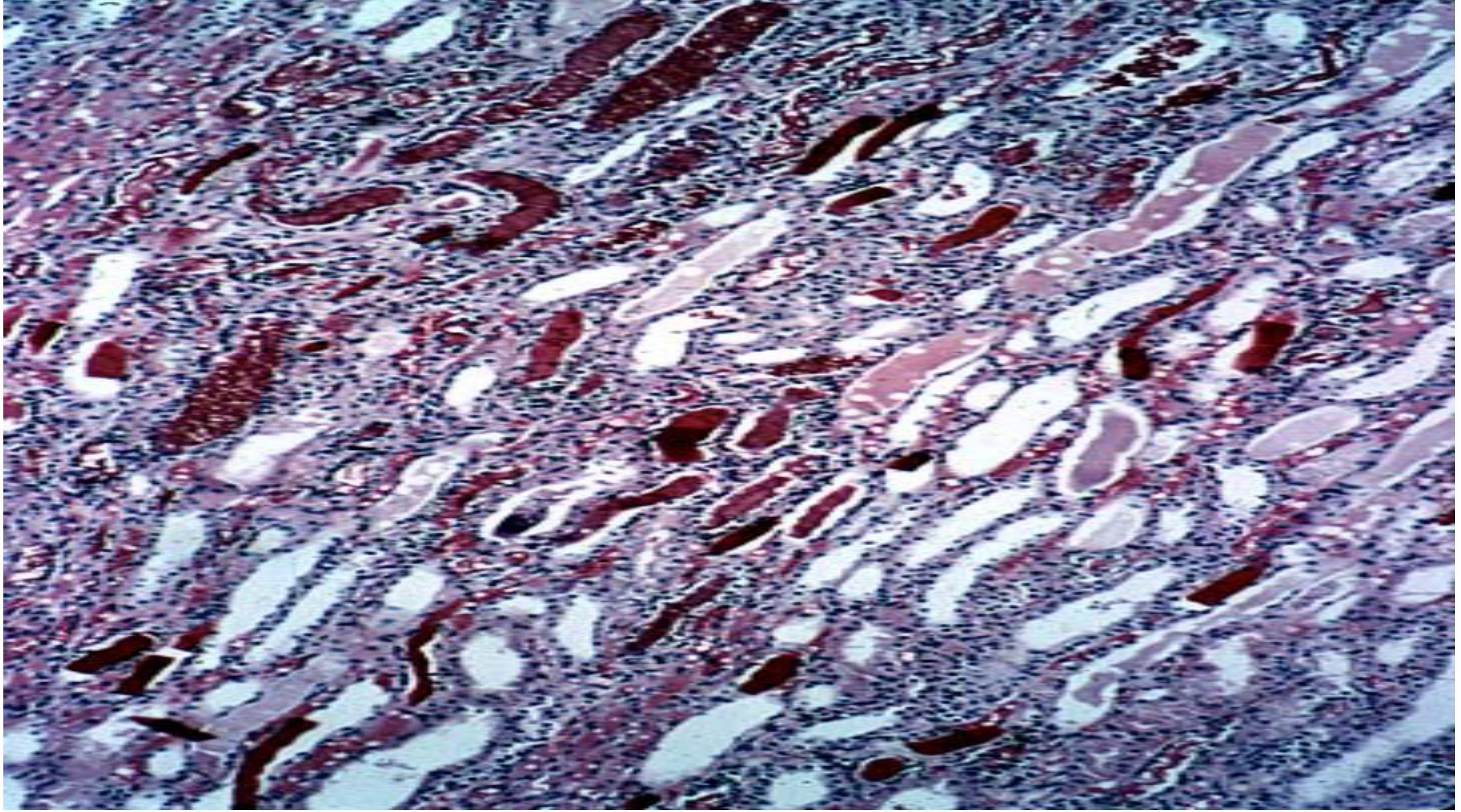
Acute tubular injury

Acute tubular injury is an important cause of acute renal failure, produces oliguria/anuria, and can cause death in days, chiefly caused by ischaemia and nephrotoxins

Haemoglobin from massive haemolysis and myoglobin from severe skeletal muscle breakdown are also primary nephrotoxins



Haemoglobinuric nephrosis



Haemoglobinuric nephrosis – numerous haemoglobin casts in tubular lumina

Tubulointerstitial disease

Involve both interstitium and tubules and acknowledges that these inflammatory and degenerative diseases almost always impair tubular function

Caused by a vast array of agents, including infections, toxins, immunological disorders, chemicals and therapeutic drugs

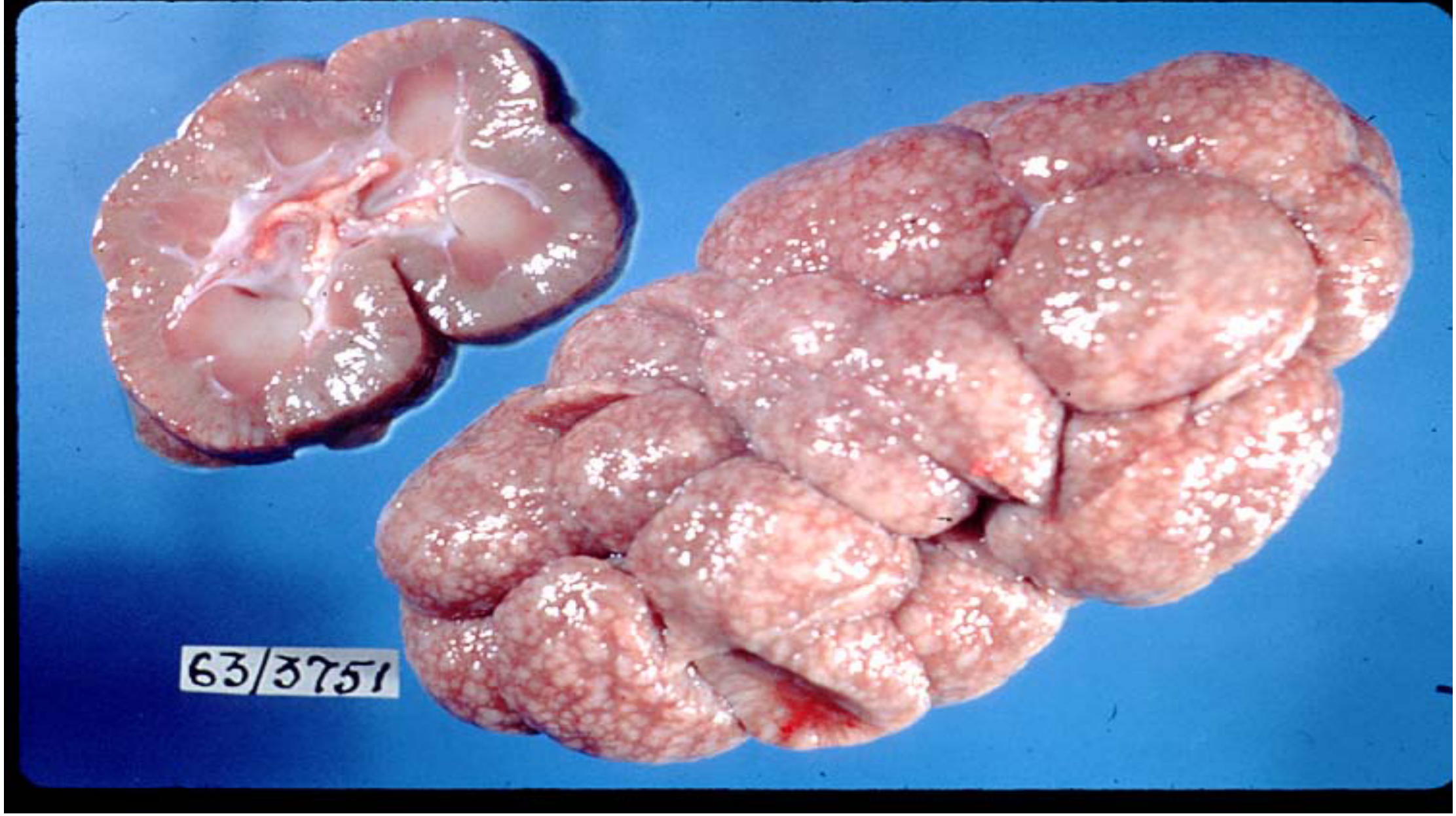
Tubulointerstitial disease

Clinically, usually results in impaired urine concentrating ability or specific tubular defects of resorption or secretion

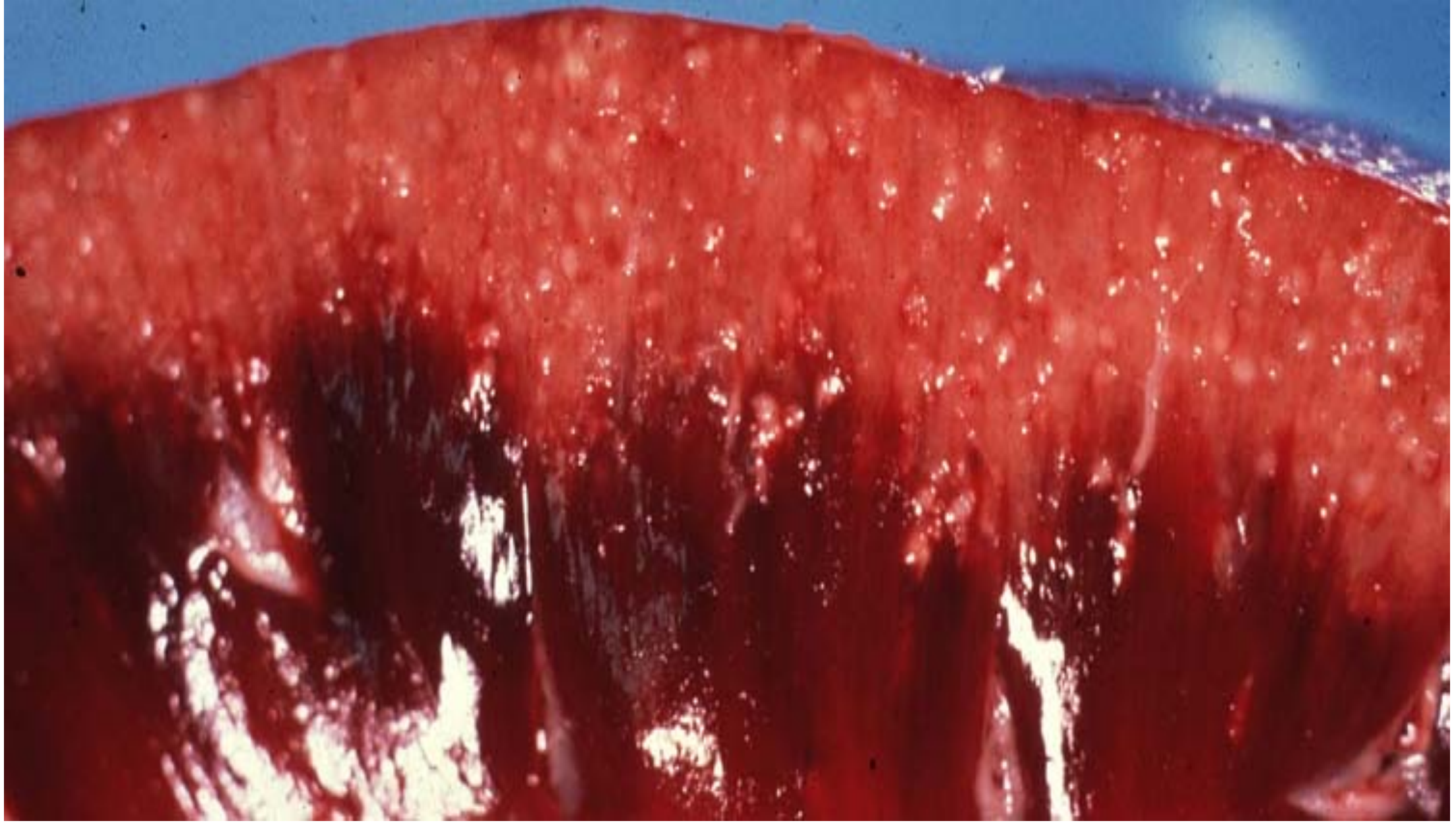
Histologically, interstitial inflammation and fibrosis and tubular dilatation and atrophy (versus persistent proteinuria with glomerular disease)

Non-suppurative interstitial nephritis – focal lymphohistiocytic inflammation with slight scarring is common in domestic animals (e.g. leptospirosis)

Suppurative interstitial nephritis – with bacterial infection, either haematogenous (embolic suppurative nephritis) or ascending from the lower urinary tract (**pyelonephritis** with inflammation of pelvis and renal parenchyma)



Suppurative nephritis – numerous pale nodules



Multifocal embolic bacterial nephritis – scattered pale cortical foci