

Learning Outcomes:

- **Explain the general principles and concepts of renal disease**
- **Be able to evaluate and assess the kidneys at post mortem examination**
- **Define azotaemia and uraemia and explain the different ways in which they can develop**
- **Explain the pathogenesis of the non-renal pathology that may occur in association with renal disease**
- **List and describe the main features of developmental disease of the kidney**
- **Explain the different types of renal haemorrhage which may arise**
- **Explain the pathogenesis of the development of renal infarcts**

Important general concepts in the pathophysiology of renal disease:

- All of the renal components are interdependent such that if one component is irreversibly damaged then the function of other components is impaired. Remember that **once renal maturity has been established, no new nephrons can be formed**. [although remaining tubules can undergo compensatory hypertrophy]
- This means that in chronic renal disease, the changes that are seen may not be specific to the original cause but are typical of an 'end stage' common pathway. End result of many chronic renal diseases. Chronic renal failure (CRF) is usually irreversible. May be referred to as '**end stage kidney**'
- The kidneys are particularly susceptible to toxic injury
 - they receive 20% of the cardiac output
 - the large glomerular capillary surface area provides a large area for toxicant-endothelial interaction
 - high metabolic rate of the PCT and thick ascending Loop of Henle render these areas particularly susceptible to toxic damage.
- In general the kidneys can be damaged as a consequence of ascending insults, haematogenous or as a consequence of metabolic processing.
- Vascular supply - the renal artery and its branches are end arteries hence occlusion of any branch will lead to **infarction**.

THE KIDNEYS HAVE A LARGE FUNCTIONAL RESERVE AND AS SUCH DETECTABLE RENAL DYSFUNCTION WILL ONLY MANIFEST WHEN THIS RESERVE CAPACITY IS EXCEEDED.

Pathological features of CRF:

- Kidneys appear shrunken and fibrosed. They are pale and firm - this can result in some difficulty in removal of the capsule from the kidney due to scarring and fibrosis. In addition to these specific renal changes, **non-renal changes** are also seen in association with CRF (see later)

THE KIDNEY AT POST MORTEM



Definitions:

- Azotaemia: An abnormal increase in non-protein nitrogenous substances (principally urea and creatinine) in the blood.
- Uraemia: The group of clinical signs resulting from azotaemia.

Azotaemia

Azotaemia develops mainly due to decreased renal excretion of urea and creatinine and may be pre-renal, renal or post-renal.

Pre-renal azotaemia occurs due to reduced renal perfusion e.g. dehydration, cardiac insufficiency, shock. Urea is increased but creatinine is not (or only slightly) because the decreased flow rate in the tubules allows increased resorption of urea (but not creatinine which is not reabsorbed by renal tubules). Urine SG will rise as urine output is reduced to increase blood volume. Pre-renal azotaemia may also be caused by increased protein catabolism e.g. in sepsis, starvation, fever and glucocorticoid administration.

Renal azotaemia develops when there is a decrease in GRF due to acute or chronic renal disease. There is decreased renal clearance of urea and creatinine so both will increase. In early renal disease, urea may be increased more than creatinine.

Post-renal azotaemia occurs where there is an obstruction of the urinary tract distal to the kidneys. GFR will decrease and serum urea and creatinine will increase.

Increased synthesis of urea is a rare cause of azotaemia e.g. intestinal haemorrhage, high-protein diet, protein catabolism. Creatinine is not expected to increase concurrently.

Expected values in different types of azotaemia

Azotaemia	Urine SG	Urine volume	Serum urea	Serum creatinine
Pre-renal (↓ GFR)	>1.030/1.035 (hypersthenuric)	↓	↑	normal to slightly ↑
Renal	1.007-1.013 (isosthenuric)	usually ↑, occasionally ↓	↑↑	↑↑
Post-renal	variable	↓	↑↑	↑↑
Increased urea synthesis	variable	variable	↑↑	normal

NON-RENAL PATHOLOGY ASSOCIATED WITH RENAL FAILURE

These are more common in chronic than acute renal failure cases.

1) Epithelial lesions

These lesions described can be attributed broadly to either:

- Degeneration and necrosis of endothelial cells resulting in vasculitis → thrombosis → infarction.
- Production of ammonia by action of bacteria on urea → caustic epithelial damage
Ulcerative necrotic **stomatitis**. Common in dogs resulting in brown mucoid material adherent to the oral mucosa. Ulcers are most common on the underside of the tongue. Additionally, haemorrhages and ulcers are common within the gastric mucosa leading to **gastritis** in dogs and cats and may also be associated with mucosal mineralisation. This can result in gastrointestinal signs of **vomiting** and **melaena** often combined with **anorexia**. In horses and cattle, there can be an ulcerative and haemorrhagic **colitis**.

2) Cardiovascular system

- Lesions of uraemic origin - necrosis of the wall of the left auricle and proximal aorta and pulmonary trunk. Erosion of the wall may be associated with thrombus formation.
- Lesions of hypertensive origin - cardiac hypertrophy (especially left side), medial hypertrophy of arterioles and fibrinoid degeneration of the muscle coats of small arteries. This is especially important in cats
- Fibrinous pericarditis –fibrin deposits on visceral pericardial surface
- Anaemia - a moderate normochromic, normocytic anaemia is often present in CRF in the dog - this anaemia has a multifactorial aetiology (increased RBC fragility, lack of EPO production).

3) Pulmonary lesions

Pulmonary oedema – resulting from increased vascular permeability due to vasculitis. May be an associated infiltrate of macrophages and neutrophils causing the lesion of **Uraemic pneumonitis**

4) Altered calcium-phosphorous metabolism

Serum phosphate: Decreased GFR results in decreased renal clearance of inorganic PO₄ so it is high in pre-renal, renal and post-renal disease.

Serum calcium: Serum calcium can be low, normal or high in chronic renal failure but most dogs and cats are hypocalcaemic or normocalcaemic. This is caused by decreased synthesis of 1,25-dihydroxycholecalciferol (calcitriol) by the kidney resulting in decreased calcium absorption from the intestine and resorption from bone. This is offset by stimulation of parathyroid hormone release which increases calcium absorption/resorption and may lead to secondary renal hyperparathyroidism. Thus, depending on the stage of the process, low, normal or high calcium concentrations may be seen.

These alterations can have the following consequences:

- **Parathyroid hyperplasia:** renal secondary hyperparathyroidism.
- **Soft tissue mineralisation:** a characteristic lesion seen particularly in dogs is calcium deposition in the subpleural connective tissue of the intercostal spaces (often described as 'ladder-like'). Calcification also occurs in other sites, e.g. stomach wall, lungs, kidneys.
- **Osteodystrophy:** can develop fibrous osteodystrophy with demineralisation of bone. Young/growing dogs: thickened maxillae, fibrous tissue around tooth roots. Adult dogs: softening of bone detectable clinically as 'rubber jaw'.

Other abnormal biochemistry results in renal disease

Serum potassium: Serum potassium is often high in renal failure where there is oliguria (i.e. acute renal failure or end-stage chronic renal failure) due to decreased renal excretion of potassium. *Remember one of the key roles of the kidney is to maintain normal extracellular potassium ion concentration mediated by aldosterone.*

Metabolic acidosis: This may also occur in acute renal failure or end-stage chronic renal failure due to decreased renal excretion of hydrogen. Furthermore, high serum potassium will result in uptake of excess potassium from the extracellular fluid into the intracellular fluid and consequent movement of hydrogen from the ICF to the ECF to maintain electrical neutrality.

DEVELOPMENTAL ANOMALIES

- 1) **Renal aplasia (agenesis).** Rare. Familial tendency in Doberman and Beagle. **Renal hypoplasia: also rare** – incomplete renal development. Clinical manifestations will depend on the extent of the deficit.

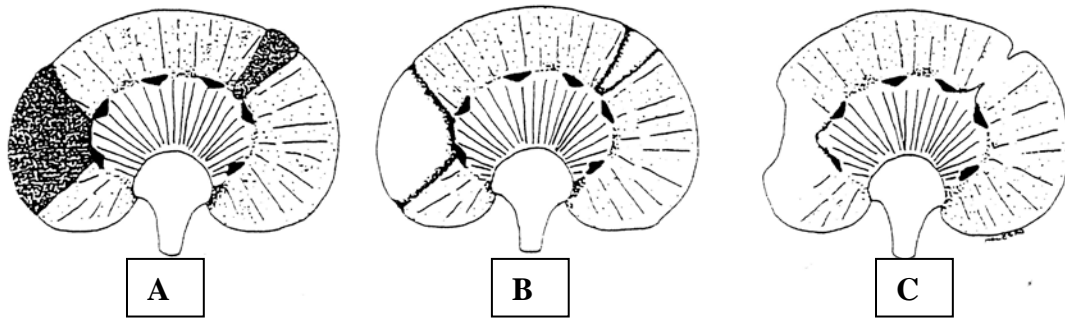
- 2) **Ectopic kidneys.** Most common in pigs and dogs. Kidney usually in a pelvic or inguinal location. Consequences include incontinence, hydronephrosis, pyelonephritis. **Fused (horseshoe) kidneys** due to abnormal nephrogenesis leading to one large kidney with 2 ureters.
 - 3) **Dysplasia:** Disorganised development of the renal parenchyma. Most affected kidneys are small - hence this may resemble hypoplasia. Usually congenital but can be acquired neonatally. May be secondary e.g. to infection, ureteral obstruction.
 - 4) **Cysts :**
 - **Congenital:** Common incidental finding in pigs and calves. Usually solitary. Must be differentiated from the much more significant polycystic kidney disease (PKD) where both kidneys contain many cysts and as such there is progressive compromise renal function (Persian cats, Cairn Terriers).
- Acquired:** Small (1-2mm) cysts can occur as a sequel to interstitial fibrosis. These occur because tubules become obstructed by scar tissue.
- Perinephric pseudocysts:** Develop between the renal capsule and the renal reflection of the peritoneum. As with the acquired cysts, these are usually found in conjunction with concomitant chronic renal disease.
- 5) **Familial renal disease/ juvenile nephropathy:** This is an important cause of renal failure in young animals, e.g. familial nephropathy of the soft-coated wheaten terrier. The renal failure is not associated with primary renal inflammation. [*Familial renal disease will be revisited in the glomerular diseases lecture*]

CIRCULATORY DISTURBANCES

- 1) **Hyperaemia/congestion:** active/passive/hypostatic.
- 2) **Haemorrhage:** Gross haemorrhage (subcapsular or intrarenal) due to trauma (e.g. RTA). This can lead to complete renal failure. Petechial haemorrhages are common in septicaemic disease, e.g. streptococcal infections, erysipelas. Renal cortical ecchymotic haemorrhages are a significant lesion in neonatal herpes virus infection of pups.
- 3) ***Infarction:** Vascular occlusion (usually following thrombosis or embolism) results in stasis and congestion followed by swelling of the parenchyma, necrosis and eventual repair by fibrosis. Consequences depend on the vessel which is occluded.
 - Renal artery - total/sub-total renal necrosis
 - Arcuate artery - necrosis of a wedge of the cortex and medulla
 - Interlobular vessel - cortical necrosis only.
 Endotoxin mediated arteriolar capillary thrombosis is common as a cause of infarction in gram negative sepsis/ endotoxic shock.

Figure 1 - Renal infarcts

- A -** Acute infarct - swelling and haemorrhage.
- B -** Becomes pale with surrounding zone of hyperaemia (2-3 days).
- C -** Chronic infarct - shrunken and fibrotic. Distortion of contour.



- 4) **Renal cortical necrosis:** Results from widespread thrombosis which can occur particularly following gram negative septicaemia, endotoxaemia, DIC. Results in destruction of both tubules and glomeruli.
- 5) **Renal papillary necrosis:** can occur as a result of reduced medullary blood flow or as a primary disease following NSAID therapy. Damage to renal tissue in this area reduces prostaglandin synthesis → reduced renal blood flow → ischaemia.
- 6) **Hydronephrosis:** Urinary obstruction at any level between the renal pelvis and the urethra can result in hydronephrosis. Ischaemic lesions develop in addition to the persistence of glomerular filtration resulting in increased pressure throughout the nephrons and ducts and pressure atrophy.

PIGMENTATION

Haemoglobin: can follow any acute haemolytic crisis → black discoloration as a consequence of concentrated haemoglobin e.g. chronic copper poisoning in sheep

Haemosiderosis : Occurs in association with chronic haemolytic anaemia or as residue from acute haemoglobinuria. Occurs in epithelial cells of proximal tubules and may → brown discolouration of the cortex (Remember haemoglobin can be demonstrated in tissue sections using Perls Prussian Blue Reaction to stain Ferric iron blue)

Learning Outcomes:

- **Define the nephrotic syndrome and understand the underlying pathophysiological mechanisms involved**
- **Be able to interpret the significance of the Urine protein:creatinine ratio**
- **Explain the pathophysiology of familial renal disease affecting the glomeruli, glomerulonephritis, amyloidosis and glomerulitis.**
- **Explain the pathophysiology of the common tubule and tubulointerstitial diseases of the kidney**

The main function of the glomerulus is to act as a filter for the ultrafiltration of plasma. Damage to this filter often results in the leakage of protein into the urine, i.e. **proteinuria**. Diseases which result in this proteinuria are called the **protein losing nephropathies**. Specifically, this can contribute to the development of the **nephrotic syndrome** – characterised by **PROTEINURIA, HYPOALBUMINAEMIA, HYPERCHOLESTEROLAEMIA AND OEDEMA**. Hypercholesterolaemia is caused by increased hepatic production and defective metabolism of the VLDL fraction of lipoproteins.

Urine protein:creatinine ratio

The urine protein:creatinine ratio is used to quantify urinary protein loss in dogs and cats. It does not indicate the cause of the proteinuria – it may be pre-glomerular (e.g. excretion of Bence-Jones proteins in multiple myeloma), glomerular (e.g. glomerular disease) or post-glomerular (e.g. pyelonephritis, lower urinary tract infection), although generally the higher the value, the more likely it is that glomerulonephropathy is present. Values >5 are very suggestive of glomerular proteinuria.

GLOMERULAR DISEASES

Familial renal disease (FRD) affecting the glomeruli

Several FRDs have been described which are characterised by specific glomerular changes. One of the best characterised of these is Samoyed hereditary glomerulopathy: this disease is characterised by splitting of components of the GBM.

Glomerulonephritis

May precede 'end-stage' kidneys and renal failure. Results from immune mediated mechanisms :

- a) **Immune complex glomerulonephritis:** characterised by the deposition of circulating antigen-antibody complexes in the glomeruli followed by complement fixation and neutrophil chemotaxis. Any disease process which is associated with a persistent presence of antigen and thus immune complexes theoretically could result in this form of immune complex disease. Glomerulonephritis has been associated with bacterial infection (notably pyometra in the dog), viral infection (e.g. FeLV, FIP), autoimmune disease and neoplasia. Note however that a specific underlying cause of the disease may not be identifiable - indeed most cases in animals are idiopathic.
- b) **Antibodies produced against the glomerular basement membrane.** Theoretically can occur but much less important mechanism.

Pathology

Gross pathology:

- **Acute GN:** the kidney is swollen and tense. Individual glomeruli may be prominent as pinpoint red dots on the surface of the cortex.
- **Chronic GN:** the gross changes resemble those of chronic interstitial nephritis, i.e. shrinking and pitting of the capsule, cortical thinning, fibrosis.

Histopathology: changes can include increased cellularity in the glomerular tufts, thickening of the capillary basement membrane, adhesions between the glomerular tuft and Bowman's capsule and thrombi in the glomerular capillaries.

Glomerulosclerosis refers to hypocellular and non-functional glomeruli which result from severe prolonged glomerular damage. This lesion is characterised by fibrosis within the glomeruli which may progress such that the glomeruli shrink and become hyalinised. The fibrosis can result in rupture of Bowman's capsule leading to glomerular fibrosis and interstitial fibrosis becoming continuous.

Amyloidosis

Amyloid is an insoluble fibrillar protein which can accumulate in the kidneys resulting in amyloidosis. The kidneys are enlarged and pale with a smooth to finely granular capsular surface. Results in substantial protein loss in the urine with resultant hypoproteinaemia and nephrotic syndrome. Hereditary predisposition to reactive amyloidosis in Shar Pei's and in Abyssinian cats.

Macroscopically: kidneys are swollen and pale. Glomeruli may be visible as fine dots on capsular or cut surface. The amyloid can be visualised by treating the kidneys with iodine.

Microscopically: amyloid appears on H&E stain as a homogeneous eosinophilic staining substance distending the glomerulus and often obliterating the urinary space. The stain Congo Red is often used to confirm the presence of amyloid.

Glomerulitis

Suppurative: often called embolic nephritis – caused by bacteraemia → localisation of bacteria within glomeruli and interstitial capillaries.

Viral: some viruses can attack capillary endothelium in glomeruli → swelling (e.g. infectious canine hepatitis, Newcastle disease)

TUBULAR DISEASE

Acute tubular necrosis/ ATN (nephrosis) - *The most important cause of acute renal failure*

Results from ischaemic or toxic insult to renal tubular epithelial cells. The PCT has a high metabolic rate and is therefore most susceptible to injury, especially from toxins – [rich P-450 enzyme system - detoxification enzymes]. The sequence of events is as follows :

Degeneration → necrosis → desquamation.

ATN often results in oliguria/anuria due to one or all of the following: intratubular obstruction, leakage of urine to the interstitium, activation of the renin-angiotensin system. Protein casts may be evident in the urine.

If the tubular basement membrane remains intact and the insult is removed then renal function can be restored.

Subtypes of ATN

1) **Ischaemic/ Tubulorrhectic ATN**

e.g. severe hypotension. Haemoglobinuria can complicate this. This form is more likely to cause basement membrane damage/ disruption (*Tubulorrhexis*)

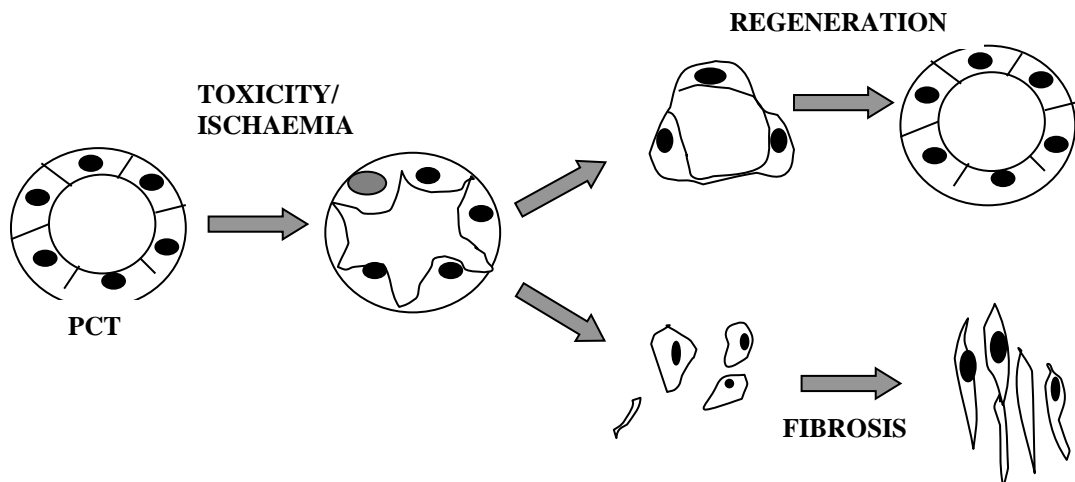
2) **Nephrotoxic ATN**

- **Heavy metals**, e.g. mercury, lead, arsenic.

- **Oxalates** - present in rape, kale, rhubarb and **ethylene glycol**. Excreted through kidneys and precipitate as crystals in the kidneys causing damage, obstruction and ultimately uraemia.
- **Antibacterials**, e.g. aminoglycosides, tetracyclines
- **Oak/acorns**: contain oak tannins which are GI irritants and also toxic to liver and kidneys. Spring (sap/ buds); Autumn (acorns) Most common in cattle

Figure 2 - Acute tubular necrosis

Consequences depend on the severity of the insult and integrity of the basement membrane.



TUBULOINTERSTITIAL/INTERSTITIAL DISEASE

Diseases affecting tubules and interstitium. This can arise as a consequence of systemic viral/bacterial disease. Grossly – lesions can be - diffuse or multifocal and acute, subacute or chronic

Some examples:

Dog	<i>Leptospira canicola</i> ¹ Infectious canine hepatitis virus
Cattle	<i>E. coli</i> septicaemia – ‘white spotted kidney’ Malignant catarrhal fever
Horse	Equine viral arteritis <i>Actinobacillus equuli</i> in foals

¹Exposure to organism followed by bacteraemia → localisation in the renal capillaries → migration through the vascular endothelium into the renal interstitium → migration through intercellular junctions of renal tubular epithelial cells → tubular lumen and become associated with the epithelial microvilli → persistence (within phagosomes of PCT and DCT) → degeneration of epithelial cells.

There is an accompanying marked interstitial inflammatory reaction. Chronic cases are characterised by generalised fibrosis separating scattered islands of renal parenchyma.

GRANULOMATOUS NEPHRITIS

Granulomatous nephritis usually accompanies chronic systemic diseases characterised by the formation of multiple granulomas. A good example of this is in cats with feline infectious peritonitis (FIP). Multiple granulomas are particularly a feature in ‘dry’/ non-effusive FIP. The lesions are present as multiple irregular cortical foci which bulge from the capsular surface.

RENAL PARASITES

Toxocara: Migrating *Toxocara canis* larvae can induce small 2-3 mm granulomas throughout the subcapsular renal cortex.

Dioctophyma renale: 'Giant kidney worm'. Fish eating mammals in North America. Resides in renal pelvis causing haemorrhage, inflammation and obstruction → hydronephrosis.

Stephanurus dentatus: kidney worm – adult pigs – southern USA. Encyst in perirenal fat or in kidney itself.

PYELONEPHRITIS

Pyelonephritis is inflammation of both the renal pelvis and renal parenchyma and is associated with suppurative tubulointerstitial inflammation. (Pyelitis = inflammation of the renal pelvis alone). Pyelonephritis usually arises as an ascending infection from the lower urinary tract establishing infection in the renal pelvis and inner medulla. **Rarely**, pyelonephritis can result from descending bacterial infection, i.e. haematogenously.

If bacteria reach the renal pelvis (e.g. due to lower UT infection compromising valve function), the inner medulla is then highly susceptible to infection due to: relatively poor blood supply, high osmolarity inhibiting neutrophil function and high ammonia concentration inhibiting complement activation.

A classic example of pyelonephritis is that caused by *Corynebacterium renale* in cattle. This organism adheres to the urinary epithelium via pili. *Eubacterium suis* in pigs causes a similar disease.

Grossly, the pelvis contains variable amounts of mucopus and the medulla exhibits streaks of inflammatory debris which extend into the kidney substance. It is often bilateral and in chronic cases the kidneys are markedly deformed due to the ongoing inflammation and scarring.

Histologically, organisms are present in the tubules which become involved in a vigorous inflammatory reaction arising in the interstitial tissue. In ascending infection, glomerular involvement tends to be confined to degeneration and fibrosis of Bowman's capsule. In long-standing cases, fibrosis dominates the picture.

Pyonephrosis

This is an extreme situation in which infection concomitant with obstruction of the ureters converts the kidney into a pus filled sac.

Learning Outcomes:

- **Name and describe the different types of primary and secondary renal tumours which can arise in domestic species.**
- **Describe the common developmental anomalies of the lower urinary tract and explain their possible pathophysiological consequences**
- **Define cystitis and explain the pathogenesis and possible consequences**
- **Define urolithiasis and explain the potential consequences in different species**
- **List and describe the different types of bladder tumours that occur in domestic species**
- **Describe the gross and histological appearance of common prostatic diseases of the dog and link this to the main cytological features**

RENAL NEOPLASIA

Although metastatic tumours, e.g. lymphosarcoma are common in the kidney, primary renal tumours are rare (<1% of total neoplasms).

Primary renal tumours:

- Renal adenocarcinoma: the most common **primary** renal neoplasm in dogs, cattle and sheep. Usually unilateral but occasionally bilateral. Commonly metastasise to the lung. [A variant is recognised in GSDs – multifocal bilateral adenomas/ carcinomas associated with nodular dermatofibrosis].
- Renal adenoma: usually incidental, small <3cm diameter. Rare.
- Nephroblastoma (Wilms' tumour): most common primary renal tumour of pigs and chickens. It is an embryonal tumour of mesenchymal origin (pluri-potent hence contains non-renal tissue).
- Occasionally primary haemangiosarcomas, fibromas/ fibrosarcomas can arise

Metastatic renal tumours

- Lymphosarcoma – common in cats and cattle- often in multicentric LSA.
- Dogs, e.g. haemangiosarcoma, malignant melanoma, mammary adenocarcinoma.

LOWER URINARY TRACT

ANOMALIES

Ureters:

Ectopic ureter - the most important ureteral anomaly. Most common in females with opening into the bladder neck, urethra or vagina. The resulting incontinence can be cured surgically. Ectopic ureters are more prone to obstruction/ infection.

Agenesis/aplasia - rare. Usually associated with failure of kidney development.

Bladder:

Patent urachus: failure of seal between bladder and umbilicus at birth resulting in a direct channel between the bladder apex and the umbilicus. Increased susceptibility to infection. Commonest in foals.

Diverticuli: congenitally weak areas of the bladder wall usually at the vertex. Can progress to cystitis.

BLADDER

Displacements

- Retroflexion: sequel of, e.g. vaginal prolapse, perineal hernia. Can be a serious complication of perineal hernia resulting in hydronephrosis or bladder rupture.
- Neuromuscular dysfunction. - Reflex dyssynergia – failure of sphincter relaxation during micturition.

INFLAMMATION

Urinary tract inflammation is a common problem in veterinary practice. The major predisposing factor is urine stasis and subsequent infection. Other risk factors include trauma, incontinence and some drug therapies.

CYSTITIS

Remember the normal antibacterial properties of urine.

The usual cause of cystitis is bacterial infection from the urethra. Predisposing factors include urine stagnation and epithelial trauma. A variety of bacterial pathogens can be involved, e.g. *E. coli*, staphs., streps. Important in large animals are *C. renale* (cattle) and *E. suis* (pigs). Note also that pathological urine can be a better growth medium for bacteria, e.g. glucosuria associated with diabetes mellitus.

Other more specific causes of cystitis include viruses, e.g. malignant catharral fever (haemorrhagic cystitis) and drugs, e.g. cyclophosphamide (sterile haemorrhage cystitis).

Pathology

Acute Cystitis

Described by the dominant morphologic features i.e. haemorrhagic, fibrinopurulent, necrotising, ulcerative – there may be a progression through these types in severe cases.

The histopathology is characterised by acute inflammation, oedema of the lamina propria and superficial hyperaemia/ haemorrhage. Urine is often thick, foul smelling and haemorrhagic.

Chronic cystitis

Several forms described based on the dominant type and pattern of the inflammatory reaction.

Diffuse: Thickened mucosa, thickened submucosa and in some cases hypertrophy of the muscularis. Inflammatory reaction is dominated by mononuclear cells.

Follicular: multifocal nodular proliferation of mononuclear cells (mostly lymphocytes). The nodules may be surrounded by a thin zone of hyperaemia. This type is often seen in association with chronic urolithiasis.

Polypoid: most common in the bitch. Single or multiple discrete polypoid masses resulting from chronic infection or chronic urolithiasis. Often associated with haematuria.

Emphysematous Cystitis

Develops in some dogs and cats with diabetes mellitus - relates to fermentation of sugar by glucose-fermenting bacteria.

Mycotic Cystitis

Colonisation of bladder by opportunistic fungi. e.g. following prolonged antibacterial therapy, immunosuppression (*Candida albicans*, *Aspergillus* sp.) . Can cause extensive inflammation and ulceration.

UROLITHIASIS

Urinary calculi - concretions formed in the urinary tract - most commonly in the bladder lumen. Urolithiasis occurs in both males and females however urinary obstruction caused by calculi is much more common in males due to the anatomy of the lower urinary tract.

Common sites of obstruction :

Dogs:	base of os penis
Bulls:	ischial arch
	proximal end of sigmoid flexure
Rams:	vermiform appendage
Cats:	urethra generally

BLADDER NEOPLASIA

Most common in cattle, dogs and cats.

- 1) **Enzootic haematuria:** This is a syndrome characterised by persistent haematuria and anaemia as a result of haemorrhages or neoplasms within the lower urinary tract. This is caused by chronic ingestion of bracken fern (*Pteridium aquilinum*) which contains several toxic substances.

Pathology

Microscopic haematuria can occur before gross lesions are visible. Ectasia and engorgement of capillaries occurs and these vessels are prone to haemorrhage. The tumours occur chiefly in the bladder but can also occur in the renal pelvis, ureter and liver. Several different types of tumour can arise including TCC, SCC, haemangioma and haemangiosarcoma. In addition multiple tumours can develop.

- 2) **Transitional cell carcinoma (TCC):** This neoplasm spreads through and along the bladder wall destroying the epithelium and invading the muscle layers. Metastases to regional nodes and lungs occurs in approximately 50% of cases. Peritoneal implantation or retrograde spread to soft tissue/bone of hindlimbs can also occur.
- 3) **Simple papilloma and squamous cell carcinoma (SCC):** Bladder papillomas are usually multiple and will often recur following excision. Carcinomas can arise from pre-existing papillomas.
- 4) **Leiomyoma:** Common. Occurs in the smooth muscle of the bladder wall forming well defined white nodular projections. The consequences of this benign tumour depend on its location. Malignant counterpart = **leiomyosarcoma**
- 5) **Botryoid rhabdomyosarcoma:** Occurs in the bladder (rarely urethra) of young (<18 months) large breed dogs (notably St. Bernards). Origin may be embryonic myoblasts. Usually occurs at the trigone of the bladder as large fungating mass which is infiltrative and can metastasise.

PROSTATIC DISEASE

Prostatic Cytology: See *clinical/surgery notes for method*. Normal prostatic epithelial cells occur in small/ medium sized clusters - regular centrally placed nuclei. Cells of non-prostatic origin which may also be evident are sperm and squamous cells (distal urethra or external genitalia).

- 1) **Hyperplastic And Metaplastic Change**
Benign Prostatic Hyperplasia (BPH)

The prostate gland slowly increases in size under the influence of testosterone such that 80% of 6 year old dogs and 95% of 9 year olds will have histological evidence of BPH. The prostate is usually diffusely involved and may contain cysts. The enlargement of the prostate gland may be associated with constipation due to physical pressure on the rectum. Much less commonly, there may be interference with the urinary tract manifesting as dysuria.

CYTOLOGY: CELLS FOUND IN SHEETS OF VARYING SIZE. NUCLEI MAY BE ECCENTRIC. MILD ↑ Nuclear:Cytoplasmic RATIO. OCCASIONAL NEUTROPHILS, LYMPHOCYTES, MACROPHAGES.

- 2) **Squamous Metaplasia of the Prostate**

Squamous metaplasia of the prostatic epithelium occurs in the dog following oestrogen administration or concurrently with testicular neoplasia (notably **sertoli cell tumour**).

This change results in conversion of the prostatic epithelium to stratified squamous epithelium and there is a predisposition of the prostate to inflammation.

CYTOLOGY: MODERATE CELLULARITY. LARGE CELLS WITH FLATTENED 'FLOPPY' APPEARANCE. OCCASIONAL INFLAMMATORY CELLS

- 2) **Suppurative prostatitis/prostatic abscess**

Prostatitis can occur either in conjunction with BPH or as a primary disease entity. The prostate may be diffusely or focally involved with signs typical of acute or chronic inflammation. Prostatic abscessation can occur as a sequel to prostatitis.

CYTOLOGY: NEUTROPHILS ARE THE DOMINANT INFLAMMATORY CELL - ALSO MACROPHAGES. BACTERIA OFTEN PRESENT (NB. IF BACTERIA ARE WITHIN NEUTROPHILS, IMPLIES INVOLVEMENT IN THE PATHOGENESIS)

3) Prostatic/ paraprostatic cysts

Prostatic cysts may be congenital or arise secondary to hyperplasia, inflammation or neoplasia.

Paraprostatic cysts which are thought to be a developmental anomaly can reach a large size (15cm diameter) and are lined by a secretory epithelium. The contents of these cysts is usually sterile.

CYTOLOGY: VARIABLE FINDINGS - FROM FEW CELLS → MODERATE NORMAL/ SLIGHTLY HYPERPLASTIC EPITHELIAL CELLS.

4) Prostatic neoplasia

The commonest form is **prostatic adenocarcinoma** (old dogs); it can occur also in male cats but is extremely rare. These tumours are usually highly aggressive and often metastasise to regional nodes and parenchymatous organs. Additionally, these tumours are capable of metastasising to lower lumbar vertebrae, pelvis and hindlimbs. 80% have metastasised before diagnosis.

CYTOLOGY: MODERATE/ MARKED CELLULARITY. ANISOKARYOSIS, LARGE IRREGULAR NUCLEI, ↑ N:C RATIO. NUCLEOLI MAY BE PROMINENT.