o Found within the renal cortex.

o The proximal tubule is the major site of reabsorption.

o ~70% of the water filtered in the glomerulus is reabsorbed in the proximal tubule. This water then enters the peritubular capillary network.

o The epithelial cells columnar epithelial cells with a prominent apical brush border. These cells are acidophilic and so appear red on H&E staining.

- Loop of Henle

o ~85% of nephrons are cortical nephrons, their loop of Henle does not pass into the medulla. The rest are juxtamedullary nephrons, which do pass into the medulla. The juxtaglomerular nephrons are therefore able to more highly concentrate the filtrate due to the greater osmolality in the medulla.

o The Loop of Henle is comprised of a cuboidal epithelium within the cortex, and a squamous epithelium within the medulla.

o The thick ascending limb of the loop has cuboidal epithelium, which has many actively transporting ion channels, in order to create a high osmolality within the medulla, for water reabsorption from the descending limb.

o The squamous epithelium facilitates passive movement of ions into the descending limb.

- Distal tubule

o Found within the cortex

o The epithelium in the distal tubule has no brush border, it also has no basal membrane invaginations – unlike the epithelium of the proximal tubule.

o The distal tubule serves to concentration urine and moderate the acid/base balance.

o The initial straight part of the distal tubule comes into contact with the renal corpuscle, forming the juxtaglomerular apparatus. A thickened region constitutes the macula densa, which is sensitive to NaCl concentration and blood pressure. The blood vessels adjacent to the macula densa have a modified tunica media, in which the smooth muscle cells (juxtaglomerular/granular cells) secrete renin in response to the adenosine released by the macula densa.

o The juxtaglomerular apparatus allow for autoregulation of renal flow and the secretion of renin, stimulating the Renin-Angiotensin-Aldosterone System.

- Collecting duct
3.1 Demonstrate an understanding of the role of the kidneys in osmoregulation and volume regulation.

Osmoregulation

Osmoregulation relies upon the AV3V. The blood brain barrier is incomplete at the AV3V, making it possible for the osmoreceptors to monitor blood osmolality. The osmoreceptors project into the SON and PVN and as such are capable of regulating release of ADH. Increased osmolality will increase the release of ADH into the blood, this will in turn increase the expression of AQP-2 in the distal tubule and collecting ducts, and UT-A1 in the collecting duct only. The result of which will be an increased reabsorption of water, and thus a decrease in osmolality. ADH also acts upon the venous vessels via V2 receptors (Gq) to induce vasoconstriction through the PLC pathway.

ADH is tonically active, however if the plasma osmolality drops below 280 mOsm.kg\(^{-1}\) secretion will stop.

Response to ADH;
- The maximal response – urine osmolality of 1400 mOsm.kg\(^{-1}\) and urine production of 6.0mL.min\(^{-1}\) (300-400mL/day)
- The minimal response – urine osmolality of 60-90 mOsm.kg\(^{-1}\) and urine production of 17mL.min\(^{-1}\) (25L/day)

Thirst increases in response to an increased osmolality resulting from an inadequate intake of water. Osmolality is still detected via the AV3V, however the sensory neurones project into the median preoptic area, stimulating an increase in thirst.

Oxytocin, which is also released from the SON and PVN, is the key trigger of the ‘let-down’ reflex in breast feeding. It is also an agonist at both V1 and V2 receptors. Breast feeding also commonly triggers thirst, as such oxytocin may have play a role in osmoregulation.

Volume regulation

(The kidneys are receptive to numerous sources of input for volume regulation, the following has been discussed previously in terms of hormonal, neuronal and haemodynamic influences upon the kidney, and the myogenic and tubuloglomerular reflex. So this will be a brief summary.)

The kidneys are capable of regulating blood volume via changing factors which would in turn increase urine production. External influences upon the kidneys include; ADH, aldosterone, angiotensin-II, ANP, sympathetic innervation and circulating catecholamines. The intrinsic regulation of volume lies primarily with the release of renin. There are three ways stimuli for the release of renin; decreased stretch upon the granular cells, sympathetic (β1) stimulation of granular cells, decreased [Na] in the distal tubule causing release of vasodilators by the macula densa and direct stimulation of renin by the granular cells. Renin then goes on to activate the RAAS which regulates blood volume via ADH secretion, electrolyte reabsorption and K excretion.)
3.4 To understand the concept of renal clearance, and to be able to perform calculations involving clearance, including first order processes.

Clearance is a measure of how plasma concentration changes over time, it is the volume of body fluid cleared of a substance per unit time. It is used to judge the method of elimination/metabolism of a drug. Two important examples of clearance are;

- Creatinine (or inulin) clearance; GFR
  - Filtered, but not actively secreted
- P-aminohippuric acid (PAH); plasma flow rate
  - Both filtered and actively secreted

Renal clearance of a substance is equal to the excretion rate / concentration within the plasma \( \frac{\text{Cl}_x}{\text{C}_x} = \frac{(\text{C}_x \times \text{V})}{\text{C}_x} \)

Whole body clearance is the sum of the individual organ clearances. There are two methods of calculating clearance from body clearance;

- ‘area under the curve’
- First order kinetics

The ‘area under the curve’ method is used when the excretion rate cannot be measured. It involves integration of a graph of concentration against time. Clearance = dose / area under the curve

First order kinetics states that the rate of clearance is proportional to flow rate, providing the tubular maximum is not exceeded.

- \( C = C_{\text{max}} e^{kt} \)
- \( \text{Half-life} = t_{1/2} \)
  - \( \frac{1}{2} C_{\text{max}} = C_{\text{max}} e^{kt_{1/2}} \)
- \( t_{1/2} = \ln 2/k \)
  - \( = 0.693/k \)
  - \( \ln C = \ln C_{\text{max}} - kt \)
    - therefore \( k \) = gradient
    - where \( C = y \)
    - and \( t = x \)

Relating \( k \), \( V_d \) (volume of distribution) and Clearance.

- \( \text{Cl} = \text{Cl} = kV_d \)
- \( V_d \) can be calculated based on patient weight and reference values
- Clearance can be estimated
  - Therefore the change in drug level over time can be predicted
stimulation of M₃ muscarinic receptors leads to the contraction of the detrusor muscle. Whereas sympathetic stimulation of β₃ adrenergic receptors causes relaxation of the detrusor muscle.

Sensation is relayed by general visceral afferents, the afferents from the superior surface following the sympathetic nerves, and those on the inferior surface following the parasympathetic nerves.

In order for urine to exit the bladder, both the autonomically controlled internal sphincter and the voluntarily controlled external sphincter must be open, problems with this lead to incontinence.

4.2 Understand the ways in which the bladder signals filling.

Stretching of the detrusor muscle leads to contraction of the detrusor muscle via parasympathetic efferents. Nerve terminals within the lamina propria detect both chemical and mechanical stimuli attributable to bladder filling. Interstitial cells have an unknown function, however it has been hypothesised that they regulate signalling between the urothelium and detrusor smooth muscle. Also there may be signalling molecules released by the urothelium in response to contact with urine products/content.

4.3 Understand the common causes of urinary incontinence.

Continence;

- The somatic system is active, keeping the external urethral sphincter closed.
- The sympathetic system is active, constricting the internal urethral sphincter (α₁) and keeping the storage element relaxed (β₃).
- The parasympathetic system is inactive.

Voiding;

- The somatic and sympathetic systems are switched off, relaxing both sphincters
- The parasympathetic system is activated, contracting the detrusor muscle, leading to voiding of the urinary bladder

Common causes of incontinence;

- UTI, wherein chemical stimuli increase the bladder activity, and so increasing the urge to void
- Spinal cord injuries or degenerative disease can impact the innervation of the urinary bladder. Damage to the pudendal nerve will impact the external urethral sphincter, leaving the individual with no somatic control over continence.
- Detrusor over-activity leading to contraction of the detrusor muscle and therefore voiding
- Atonic bladder, secondary to autonomic neuropathy
Demonstrate an appreciation of the common pathological processes that can affect the renal and urological system, and their manifestations and management.

KEY WORDS: RENAL FAILURE, TRANSPLANTATION, NEPHROTIC SYNDROME, NEPHRITIS

6.1 Demonstrate an understanding of the inter-relationships of the cardiovascular and renal systems, and the nervous and hormonal adjustments that occur following decreases in effective circulating volume (e.g. haemorrhage). Appreciate the factors that lead to shock.

(See above in functional properties of the renal system)
The kidneys also play an endocrinological role in calcium homeostasis, via 1, 25-dihydroxycholecalciferol production, and in erythropoiesis, via the secretion of EPO in response to hypoxia, in addition to the volume regulation via release of renin.

**Chronic kidney disease**

In chronic renal failure some/all of these functions are either partially impaired or completely impaired, meaning the patient may be put onto dialysis alongside EPO with various dietary modifications to account for impaired renal clearance. These patients will be looking for a transplant in order to replace the lost kidney function.

Chronic kidney disease (CKD) is both irreversible and progressive. CKD can be split up into 5 stages based on the diminishing GFR.

<table>
<thead>
<tr>
<th>CKD stage</th>
<th>eGFR</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>≥ 90</td>
<td>Kidney damage with normal GFR</td>
</tr>
<tr>
<td>2</td>
<td>60 – 89</td>
<td>Kidney damage with reduced GFR</td>
</tr>
<tr>
<td>3</td>
<td>30 – 59</td>
<td>Moderate reduction in GFR</td>
</tr>
<tr>
<td>4</td>
<td>15 – 29</td>
<td>Severe reduction in GFR</td>
</tr>
<tr>
<td>5</td>
<td>&lt; 15</td>
<td>Kidney failure</td>
</tr>
</tbody>
</table>

CKD stage 5 is the point of end-stage renal failure where renal function is insufficient to sustain life/health unaided. And so patients with CKD stage 5 are placed on a regimen of dialysis (haemodialysis / peritoneal dialysis), and if appropriate, placed on the donor recipient register.

CKD has a number of causes; systemic disease, immune-mediated nephropathy, infection, obstruction.

**Systemic disease;**

- Diseases such as diabetes (leading to diabetic nephropathy), hypertension and atherosclerotic disease can lead to diminished renal function.

- Diabetic nephropathy occurs in 40% of diabetic patients and is associated with poor diabetic control and hypertension. Hypertension leads to thickening of the basement membrane and mesangial expansion. By reducing the glomerular capillary filtration surface, mesangial expansion stimulates compensatory mechanisms designed to maintain GFR, however this contributes to renal damage. Glomerulosclerosis results from intraglomerular hypertension/ischaemic damage.