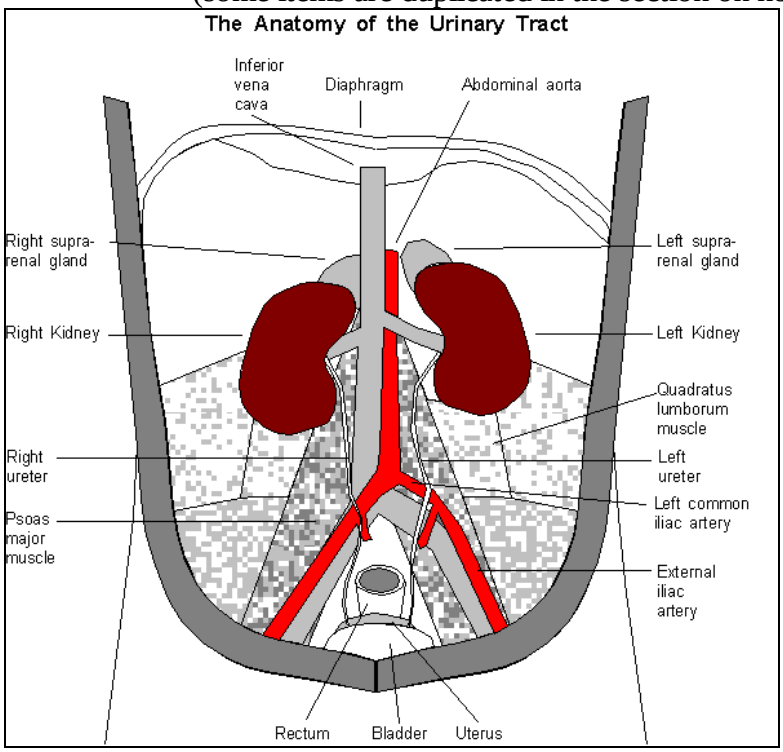
THE URINARY SYSTEM

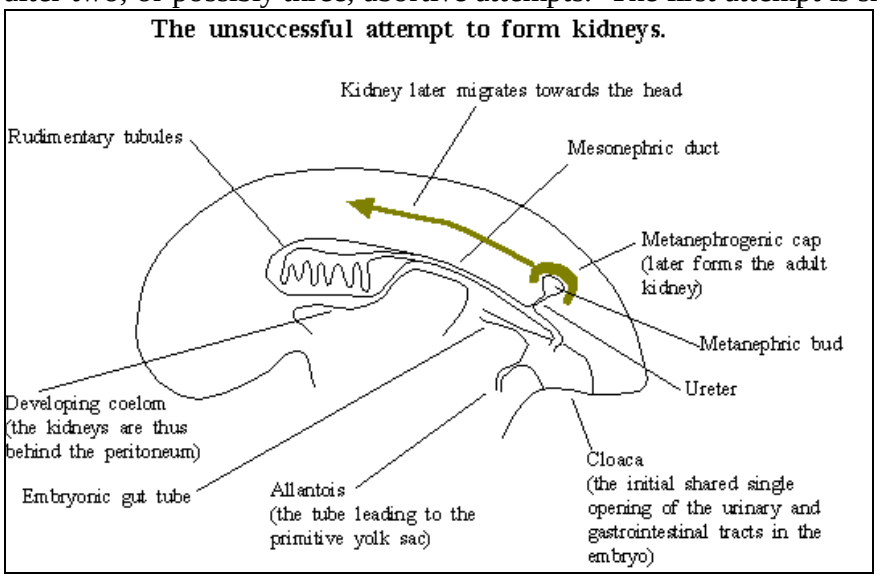
(some items are duplicated in the section on homeostasis)



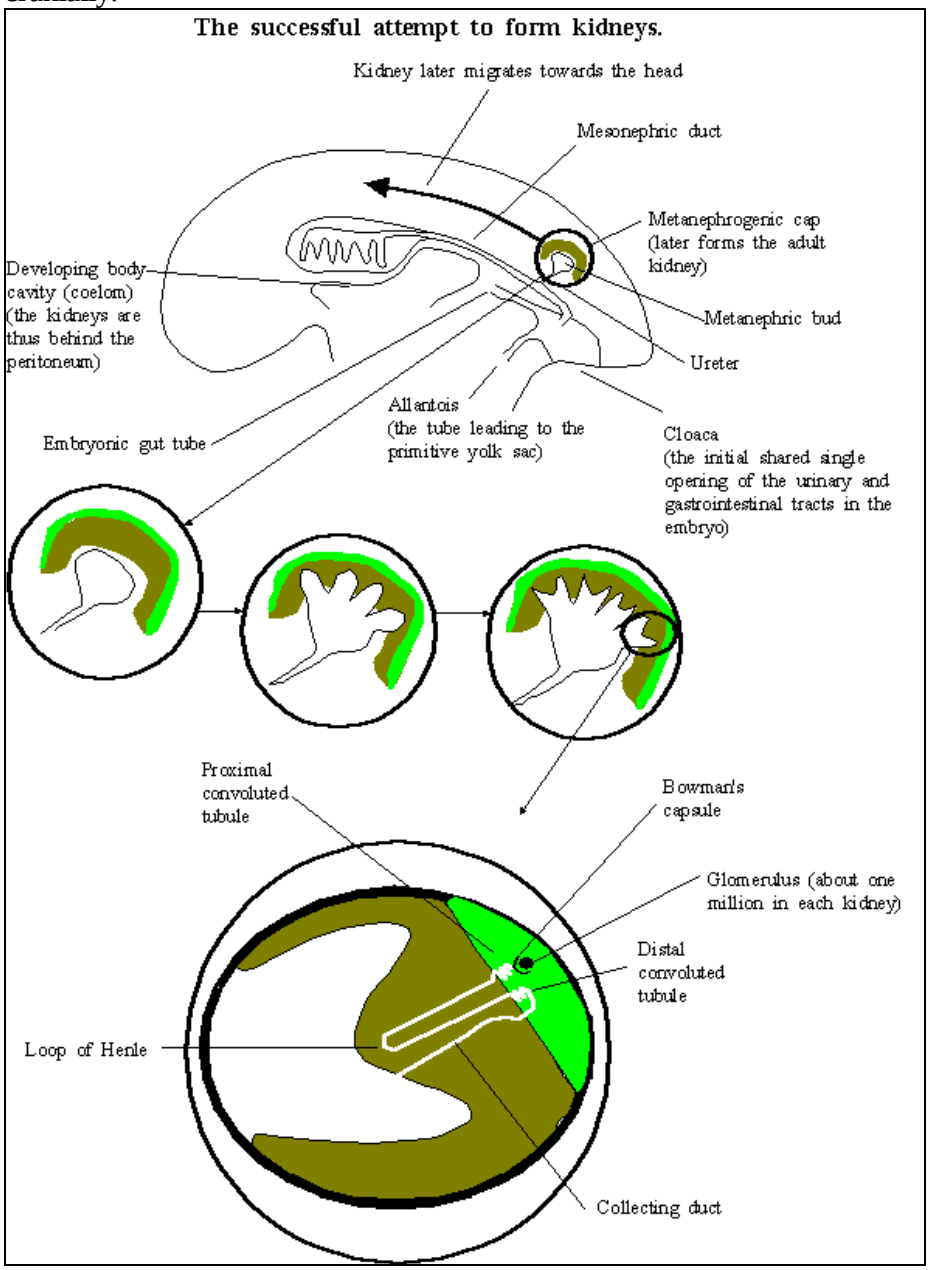
The anatomy of the urinary tract is shown above.

Embryological development: a simplified version

A small longitudinal area on each side of the ventral side of the spinal cord elongates and becomes hollow to form a tube (the mesonephric duct) which is associated with rudimentary tubules. This does not form the adult kidney but plays an important part in gonad formation (link). At the caudal-most part of each of these paired tubes a bud forms (each of which is later to become a kidney). The adult kidney is formed as if after two, or possibly three, abortive attempts. The first attempt is shown below.



This attempt is superseded by the growth of a (metanephric) bud the tip of which eventually forms the adult kidney, with the "stalk" forming the ureter. Initially the kidneys are small and lie in what is to become the bony pelvis, but they later migrate cranially.



If the two kidneys fuse together on their journey cranially (forming a horseshoe kidney) they are halted by the inferior mesenteric artery and the ureters (which drain urine from the kidneys into the bladder) arise, not from the usual medial surface, but from the ventral surface.

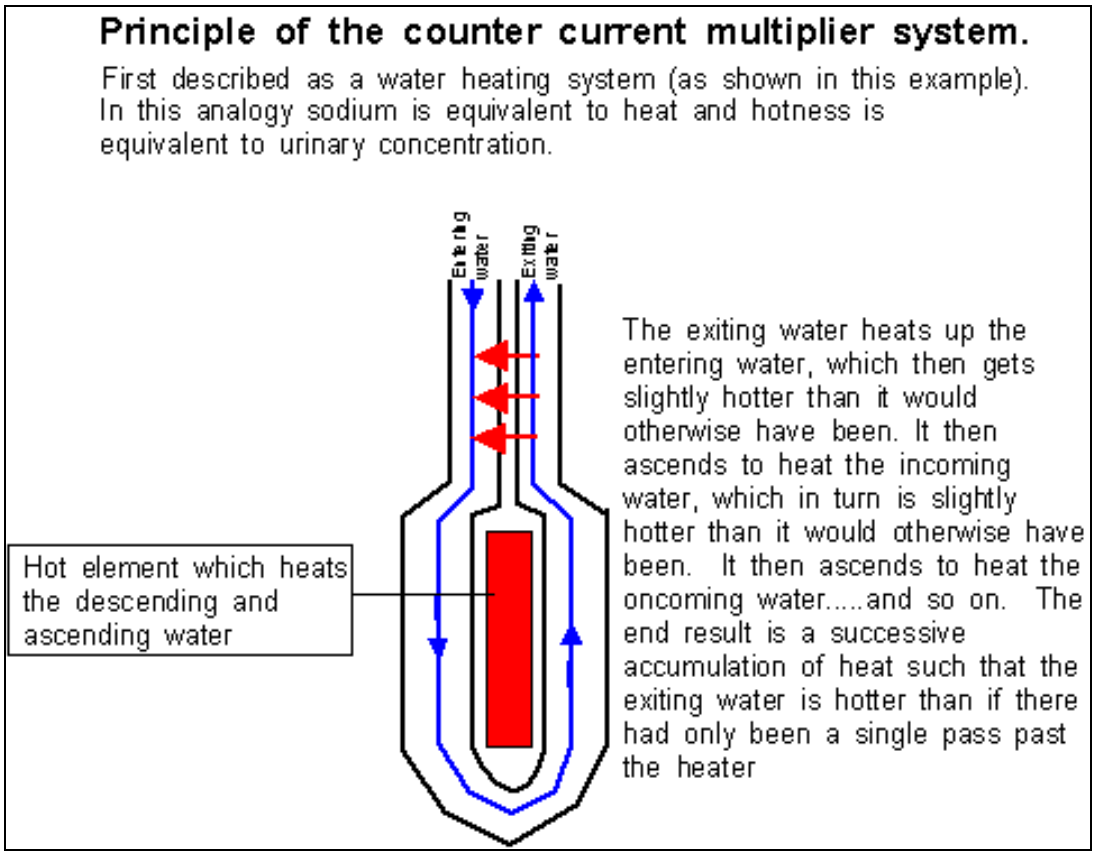
The kidneys are the main excretory organs for waste derived from protein metabolism, other soluble substances (including electrolytes) and water.

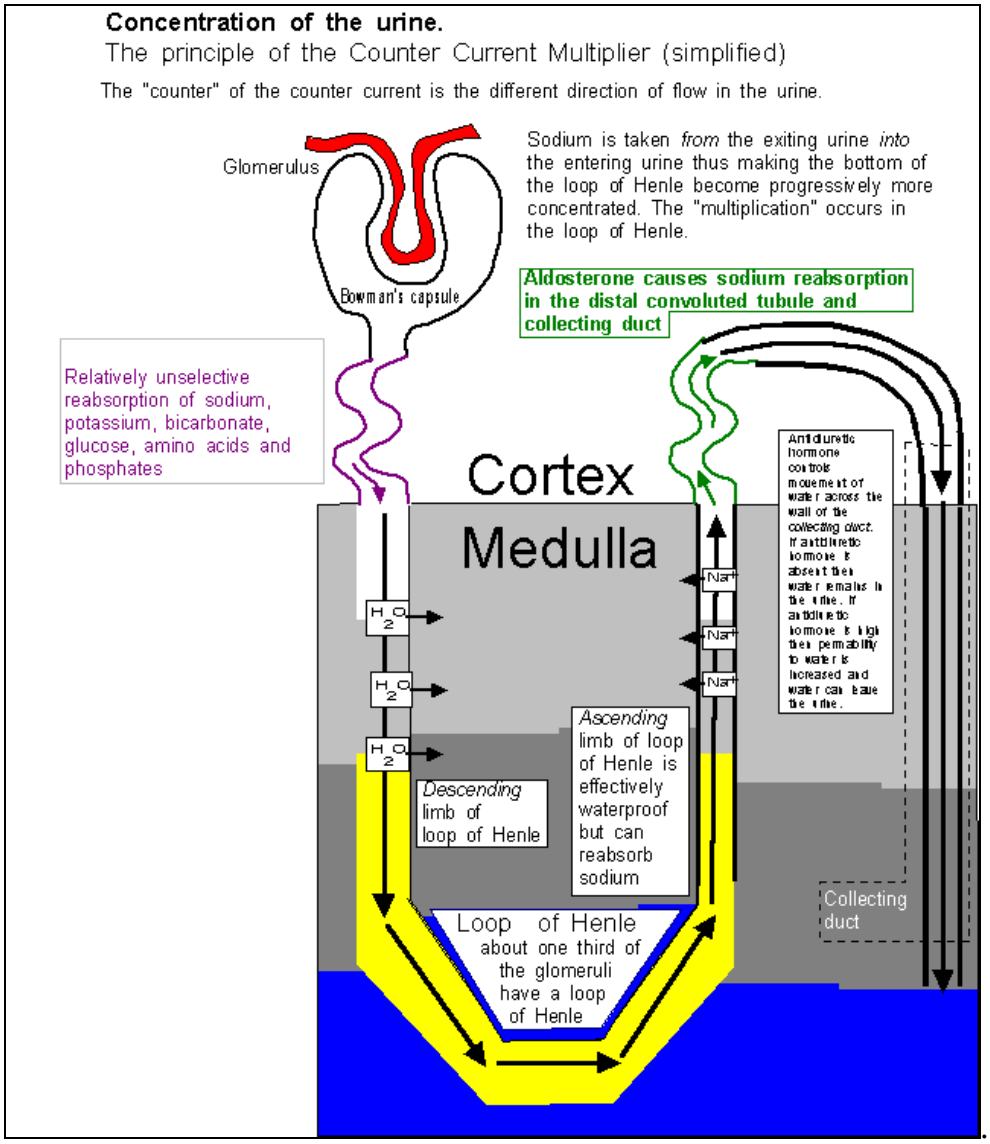
Urine is formed by filtration at the glomerulus (= small ball), of which there are about one million in each kidney, followed by selective reabsorption (and, to a lesser extent, excretion) of various substances by the convoluted tubules. Blood enters the

glomerulus and a proportion of the plasma water and solutes (but normally hardly any proteins) passes into Bowman's capsule. This filtrate then drains into the proximal convoluted tubule where most of the filtered sodium and water is reabsorbed without significant regulatory influences, down into the loop of Henle (if there is one) and finally ascends into the distal convoluted tubule before entering the collecting ducts.

Normally the glomeruli only allow substances of molecular weight less than about 40,000 (which includes urea, the principal breakdown product of protein) to be filtered into the urine. Each day about 180 litres (about 120ml/minute) of water is filtered by the glomeruli, containing about 1kg sodium chloride, about 400g sodium bicarbonate and about 140g glucose. Obviously a high proportion of the glomerular filtrate and its solute content must be reabsorbed because only 1.5 litres of water (the range can be from less than 0.5 ml/min up to about 20ml/min) and 5-10g of sodium chloride are finally excreted. The proximal convoluted tubules reabsorb about 7/8ths of the filtrate. The distal convoluted tubules and the collecting ducts, acts as the "fine tuner" of excretion.

The kidneys use a counter current multiplier system (that was first described in heat exchange systems) to concentrate the urine.





Sodium is actively excreted into the interstitial fluid by the cells of the *ascending* limb of the Loop of Henle which has a modest ability to secrete sodium but which is relatively impermeable to water. This unusual differential permeability is the essence of the counter current multiplier system as the sodium then osmotically sucks water from urine entering the *descending* limb. The deeper the descending loop then the more concentrated will be the fluid surrounding the bottom of the loop.

The system is then fine-tuned in that the remaining water in urine entering the distal convoluted tubule can be reabsorbed (or not) depending anti-diuretic hormone (ADH) levels from the posterior pituitary which alters distal convoluted tubule and collecting duct permeability, and thus water reabsorption. A fall in extracellular fluid osmolarity "sogginess"causes ADH levels to fall, leading to water excretion "a counterbalancing dehydration" whereas an increase in the extracellular osmolality or hyovolaemia "dehydration" causes antidiuretic hormone to rise leading to counterbalancing water retention (some neoplasms, especially of the lung, may secrete "ectopic" antidiuretic hormone-like substances causing extra water to be retained). Aldosterone, secreted by the adrenal cortex as a result of a series of reactions driven by the renin-angiotension system (link), increases sodium reabsorption by the distal convoluted tubules. If

sodium is not reabsorbed then both potassium and hydrogen ions have to be excreted instead of the sodium which leads to a hypokalaemic metabolic alkalosis.

If the kidney *cortex* is damaged the distal convoluted tubules may become unresponsive to ADH and diabetes insipidus (passage of large amounts of dilute urine) results. Similarly if there is loss of kidney medulla tissue with significant loss of loops of Henle then the counter current multiplier system will not work and the kidneys ability to concentrate the urine will be lost and large quantities of dilute urine (of low specific gravity) will be formed.

KIDNEY MANAGEMENT OF SPECIFIC SUBSTANCES

Urea is produced by the liver and is a breakdown product of many proteins whereas creatinine is a breakdown product of striated muscle. The plasma urea is usually used as a kidney function test but, the plasma creatinine is a better and more consistent test of kidney function because, unlike urea, the plasma level of creatinine is not affected by dietary intake of protein and the liver's synthetic capacity. The clearance of creatinine clearance from the plasma gives an even better measure of kidney function.

Relevant topics not included here include acid base metabolism (in homeostasis), *Parathormone* increases tubular reabsorption *of calcium, growth hormone, cortisol, sex hormones* (in hormones), *erythropoietin* (in blood) *and prostaglandins* (in inflammation.

The clearance of a substance is the amount of plasma that can be totally cleared of it in unit time.

Kidney clearance of a substance

The number of millilitres of plasma cleared per minute = $\frac{\text{Quantity in grams excreted in the urine per minute}}{\text{Quantity of substance in grams per ml of plasma}}$

= $\frac{\text{"The urinary concentration in g/ml x no of mls excreted each minute"}}{\text{"The plasma concentration"}}$

If the substance is all filtered at the glomerulus and not thereafter excreted or absorbed then the clearance of the substance will be the glomerular filtration rate

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Clearance of creatinine is useful because creatinine occurs naturally in the plasma (and thus does not need to be injected), is liberated at a constant rate from the muscles, (unlike urea) is not influenced overmuch by dietary intake of protein, and is fairly stable under most conditions. Furthermore glomerular filtration rates can be measured by assessing creatinine clearance because creatinine is excreted only by glomeruli and not secreted or reabsorbed by the convoluted tubules.

If the plasma urea rises then eventually "urea poisoning," uraemia, results. The symptoms of uraemia include:

- Weakness

- Weight loss
- Anorexia
- Vomiting
- Itching (urea toxicity to skin sensory nerve endings)
- Peripheral nerve dysfunction (uraemic neuritis)
- Pericarditis (urea deposits in the pericardium)
- Impaired conscious level or epileptic fits (brain urea poisoning)
- Phosphate retention with a secondary fall in calcium

The kidneys have substantial functional reserve and neither plasma urea nor creatinine increases until the glomerular filtration rate is reduced to 30mls/minute or less. The glomerular filtration rate falls from 120ml/min to about 50-60 ml/minute by age 70. The plasma creatinine in theory should rise but in practice tends to remain stable as muscle bulk also falls with age (the plasma urea tends to be slightly higher in the elderly).

Sodium regulation

Ingested sodium is absorbed by the gut and a small amount is excreted by perspiration or into the gastrointestinal tract (especially if there is vomiting and/or diarrhoea) but the kidneys are primarily responsible for sodium homeostasis.

The proximal convoluted tubules reabsorb about 80 percent of filtered sodium. A low sodium concentration in the an area near the glomerulus, the juxtraglomerular area, causes release of a hormone (renin) which causes release of another hormone (angiotensin I) from the liver, which is in turn converted to yet another hormone (angiotensin II) mostly in the lungs. Angiotensin II then encourages sodium retention by causing secretion of aldosterone from the adrenal cortex which then acts on the collecting ducts. Aldosterone also increases blood pressure by increasing arterial wall muscle tone.

Potassium regulation

Potassium tends to be intracellular, being pumped from extracellular fluid into the intracellular fluid.
Many cells have a physiologically important electrical gradient across their walls and this in part is caused by the tendency of potassium to leak out of cells.

The average daily diet intake of potassium is about 70 millimoles and in normal circumstances the kidney provides the major output. Diarrhoea and/or vomiting can cause considerable potassium loss.

A high level of blood potassium produces weakness and cardiac dysrhythmias and may be associated with:

- Increases in total body potassium (as may occur in kidney failure)
- Use of potassium retaining diuretics
- Leakage from cells into the extracellular fluid as may occur in severe acidosis in which hydrogen ions enter the cell (where it is buffered) in exchange for potassium)
- Insulin lack (insulin usually drive potassium into cells)

- Acute renal failure following gross tissue damage (which allows intracellular potassium to leak out into the blood) and often a failure of potassium excretion by the kidneys

A low plasma level of potassium produces generalized muscle weakness, gut hypomobility, tetany, cardiac dysrhythmias (especially if the patient is on digoxin). Causes of a low blood level of potassium include:

- Vomiting
- Diarrhoea
- Certain diuretics
- Kidney disease
- Aldosterone over secretion
- Administration of insulin
- Alkalosis (in which hydrogen ions leave cells in exchange for potassium)

Water balance

Water loss may occur if there is damage to the kidney medulla, if the distal convoluted tubules and collecting ducts are unresponsive to ADH, or if the glomeruli leak too many osmotically active particles such that the convoluted tubular reabsorption mechanisms cannot cope.

The tubules may have specific single defects which include failure of:

- Water retention caused by distal tubule insensitivity to antidiuretic hormone (renal diabetes insipidus)
- Glucose reabsorption (renal glycosuria)
- Leakage of amino acids with aminoaciduria (e.g. cystinuria)
- Calcium reabsorption (idiopathic hypercalcuria)
- Acid under-excretion into the urine and/or bicarbonate over-excretion (renal tubular acidosis)

Multiple defects may occur.

Diabetes: a persistent increase in urine formation
Diabetes mellitus: sweet urine usually caused by glucose in the urine
Diabetes insipidus: tasteless (non-sweet) urine
Polyuria: excessive amounts of urine.

If there is heart "pump" failure the kidneys retain sodium and water in an attempt to increase the blood volume (preload) presented to the heart, which would normally increases the force of cardiac contraction.

Acute kidney failure

If undamaged kidneys are dysfunctioning because of dehydration they will still be able to excrete urea (about 17 times or more of the simultaneous plasma level) but if there is intrinsic kidney damage the kidneys will not be able to excrete this proportion of urea.

The differentiation between dehydration and acute kidney failure "acute tubular necrosis."

	Urine volume	Urinary Sodium	Urinary urea	Osmolality Urine/plasma	Specific gravity
Dehydration	LOW	LOW <20 mmol/l "kidneys are successfully conserving sodium"	HIGH >40mmol/l "kidneys leaking sodium"	HIGH >1.3 "Kidneys can still concentrate the urine"	HIGH
Acute tubular necrosis	LOW	HIGH "Kidneys cannot retain sodium"	LOW Water depleted but otherwise normal kidneys will be able to excrete urea such that the urinary urea : plasma urea ratio will exceed 17:1.	LOW <1.1 "Kidneys can't concentrate the urine"	LOW
Comment		Damaged tubules cannot reabsorb sodium from the glomerular filtrate	In acute tubular necrosis the glomerular filtration rate falls causing a low urinary urea	Undamaged tubules, as in dehydration, can retain water leading to a concentrated urine	

Therefore simultaneous measurement of urine and plasma urea can give a guide as to whether there is intrinsic renal damage. If kidney damage particularly affects the convoluted tubules then sodium reabsorption fails and the amount of sodium in the urine rises.

Acute kidney failure is a rapid decline in kidney function with a fall in glomurular filtration rate and, initially, failure of water excretion. Thus water retention may precipitate heart failure or hypertension. Causes are usually classified anatomically:

- Pre-renal. The kidneys are failing but this is *secondary* to hypoperfusion resulting from dehydration, shock, or sepsis
- Renal. Intrinsic kidney diseases
- Post-renal. Mostly urinary tract obstruction usually caused by stone or tumour

Management of acute kidney failure thus includes:

- Exclusion or treatment of reversible causes
- Fluid challenge monitored by central venous pressure measurement (link) to ensure that fluid overload does not occur
- Fluid restriction if fluid challenge fails
- Restriction of sodium and potassium intake and/or take measures to reduce excessively high potassium levels

Acute bodily insults such as sepsis or a low blood pressure often produce changes suggesting predominant damage focussed on the convoluted tubules “acute tubular necrosis” The urea (which is not affected by convoluted tubule or loop function) rises because there is often a diversion of blood flow to the damaged convoluted tubules from the glomeruli which causes the glomerular filtration rate to fall. In the recovery phrase of acute tubular necrosis the urea may continue to rise with an electrolyte rich polyuria because the glomeruli recover function first with the convoluted tubules recovering later and thus reabsorbtion of electrolytes may be impaired.

If there is inflammation of the glomeruli (glomerulonephritis) then glomerular filtration is reduced and fluid, urea and creatinine cannot be excreted and their plasma levels rise. Usually the inflamed glomeruli leak protein into the urine.

Chronic kidney failure

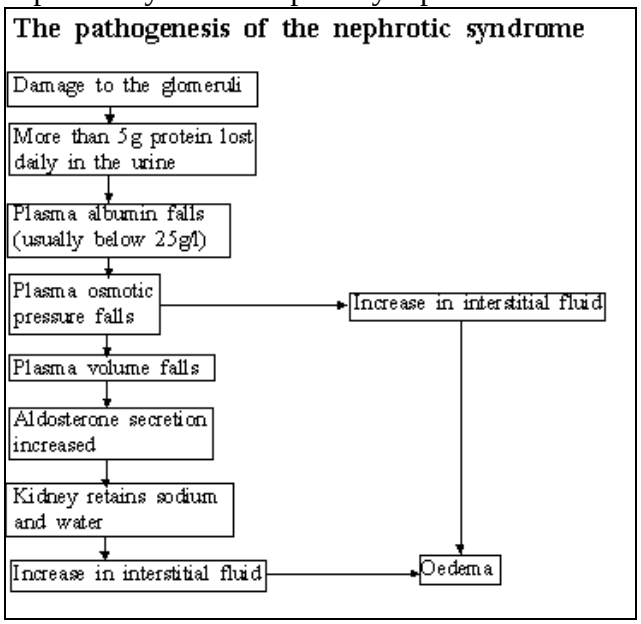
In chronic renal failure there is polyuria and a raised plasma urea and creatinine. Preterminally urine output may fall and fluid retention may occur.

The principles of management of chronic kidney failure include:

- Controlling high blood pressure
- Protein restriction. Before dialysis was available this was useful to reduce urea poisoning
- Reduction of anaemia if necessary. Erythropoeitin (link) can be used to stimulate the "poisoned" bone marrow
- Dialysis, either peritoneal or haemodialysis
- Kidney transplantation

Proteinuria

The normal 24 hour excretion of proteins in the urine is less than 150mg. Most of these proteins are small, including microglobulins, which are filtered at the glomerulus and absorbed by the proximal convoluted tubules. If glomerular damage is subtle then only smaller proteins spill over into the urine but if there is severe glomerular damage both albumin and smaller proteins spill over into the urine. Microalbuminuria thus may be an early sign of kidney damage, particularly in diabetes mellitus. If proteinuria is severe (usually caused by glomerulonephritis) then oedema may form as part of a nephrotic syndrome especially if proteinuria exceeds 5g/day.



Proteinuria in normals can sometimes occur after severe excercise or being in the upright position (orthostatic proteinuria).

Diuretics

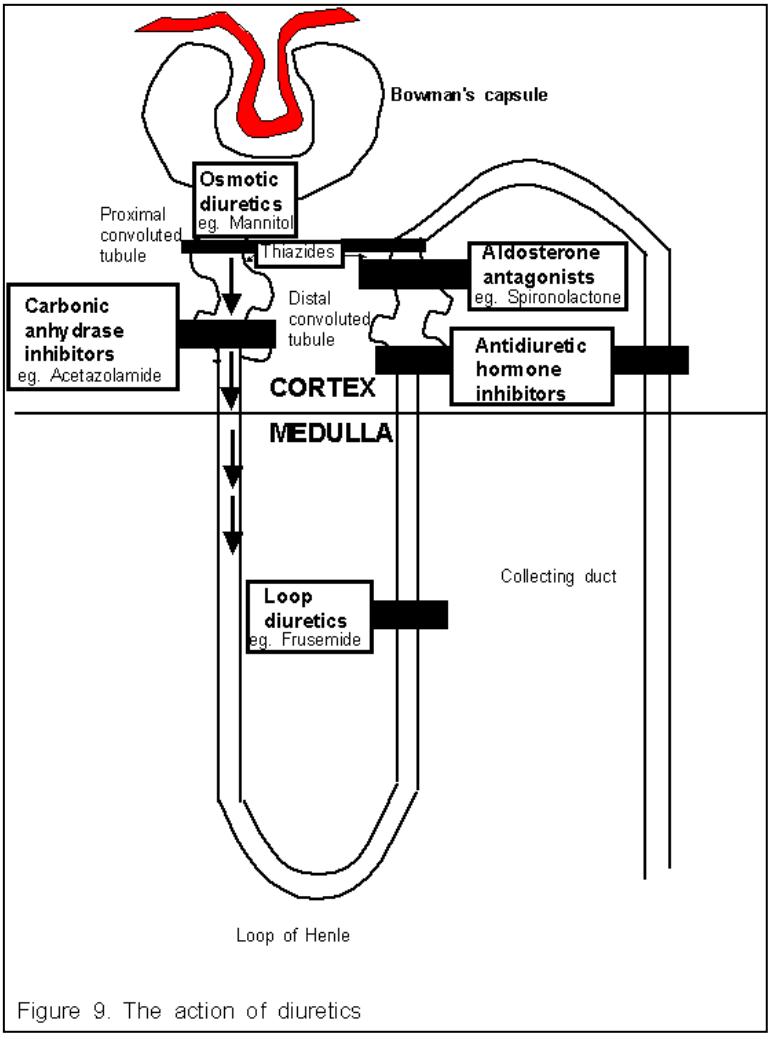


Figure 9. The action of diuretics

Diuretics increase production of urine. There are three main types of diuretics.

Osmotic diuretics are highly osmotically active substances, usually given intravenously, which are filtered by the glomeruli, are not reabsorbed, and which take away with them the necessary accompanying water. High plasma glucose levels in have a similar effect, explaining the polyuria of uncontrolled diabetes mellitus.

Sodium reabsorption inhibitors. Diuresis follows because the increased sodium excretion into the urine takes additional water with it. Loop diuretics (such as frusemide) which affect the loop of Henle or those that block aldosterone action at the distal convoluted tubule interfere with sodium reabsorption and thus sodium and the necessary accompanying water remain in the urine. An increased quantity of sodium reaches the distal convoluted tubules where some of the sodium is reabsorbed in exchange for potassium - thus explaining the low plasma potassium often seen with loop diuretics. Carbonic anhydrase inhibitors reduce formation of hydrogen ions and bicarbonate, mostly in the proximal convoluted tubule, which limits reabsorption of sodium in exchange for hydrogen ions (link).

Antidiuretic hormone antagonists which are usually drugs, such as lithium, that are often administered for non-diuretic reasons.