METABOLISM AND HOMEOSTASIS

The major homeostatic mechanisms

Heat regulating centre in the hypothalamus induces

Heat gain by	Heat Loss by
vasoconstriction	radiation
muscle activity	sweat
decreased sweating	breathing
	vasodilation

Respiratory centre in medulla and pons (sensitive to CO_2 and to a lesser extent O_2)

Thyroid
General
metabolic

Pituitary "orchestrating the endocrine system"

Parathyroid hormone increases

↓

Calcium

Vitamin D increases

Heart — Blood flow — Rate
- Sympathetic increases
- Parasympathetic decreases
Force — Sympathetic increases
Blood vessels — Sympathetic constricts

Adrenals

Blood glucose
- Dietary intake increases
- Liver increases (sympathetically mediated)
- Insulin from pancreas decreases

Blood pressure
- Force of heart contraction increases
- Vasoconstriction increases
- Vasodilation decreases
- Additional blood volume initially increases

Body weight
- Dietary intake increases
- Metabolic work decreases
- Urinary or faecal loss of organic compounds decreases

Sodium
- Dietary intake increases
- Sweat decreases
- Urine - variable excretion

Potassium
- Dietary intake increases
- Urine - variable excretion
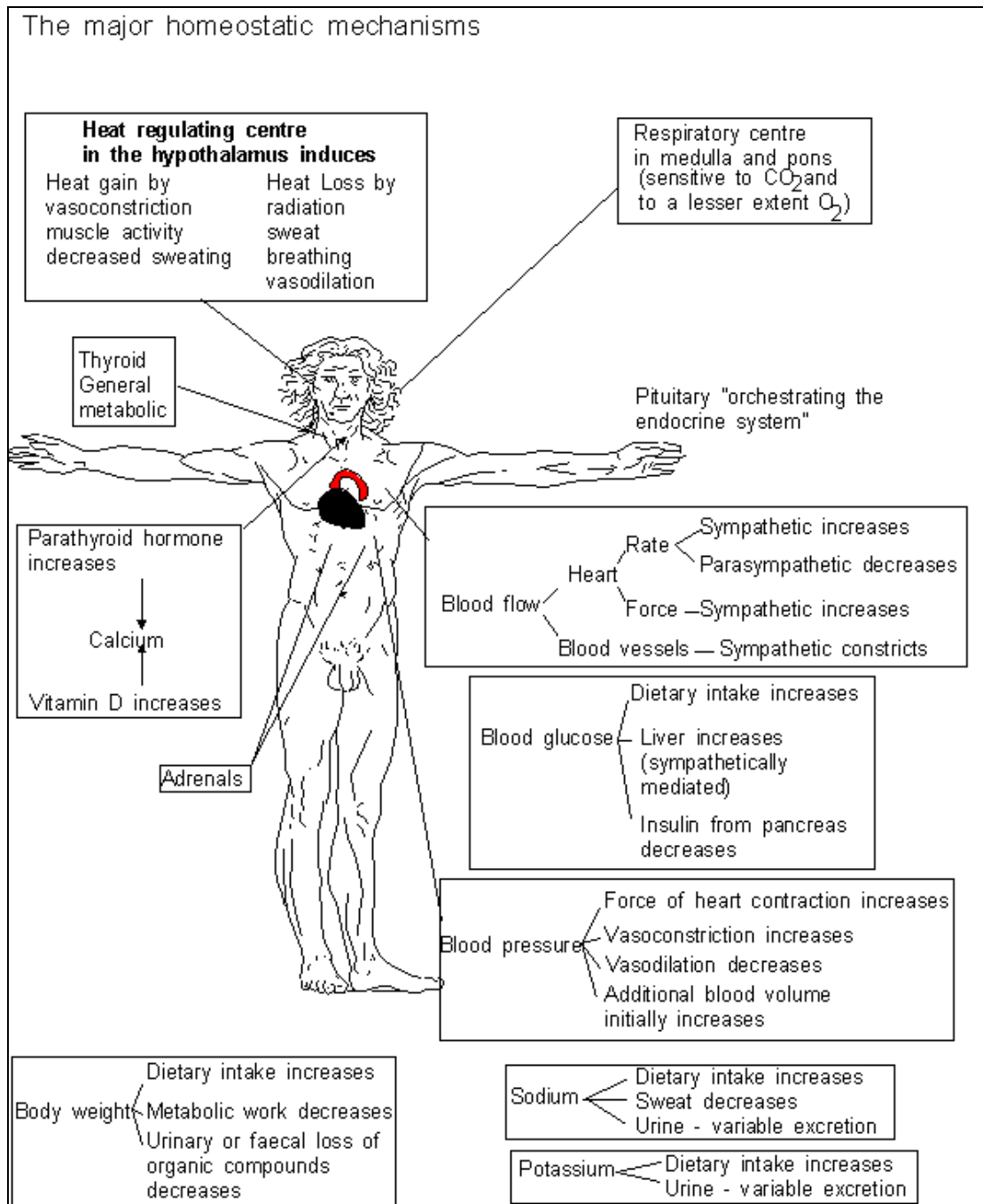
Homeostasis is the tendency to stability in the normal internal state of an organism. In the adult human this state represents a dynamic balance such that all of the 10 trillion cells cooperate to maintain their and each others metabolic state within narrow limits. That the human body can maintain homeostasis for about 70 years is achieved by cybernetic (self-regulating) systems that operate by positive and negative feedback mechanisms. To achieve homeostasis the organism must detect and react to changes in the internal and external environment to enable corrective responses. More complex environments or lifestyles require more complex homeostatic mechanisms. The

nervous system can react very quickly whilst the endocrine system reacts more slowly to environmental change.
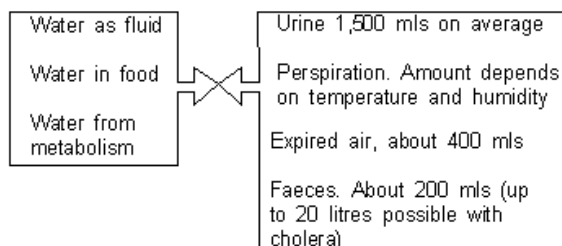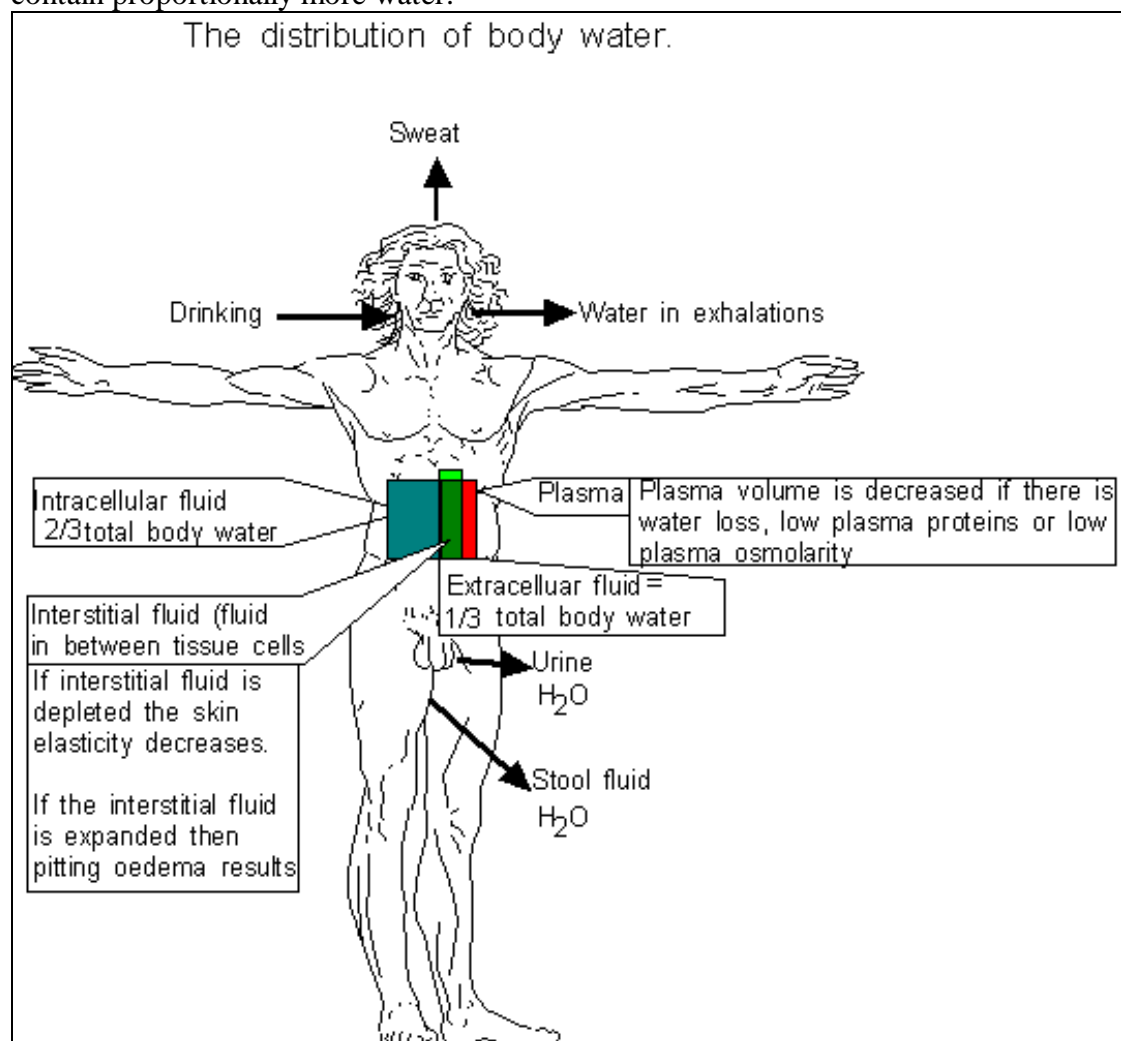
Water balance

Daily water balance.
Input has to equal output in the medium term
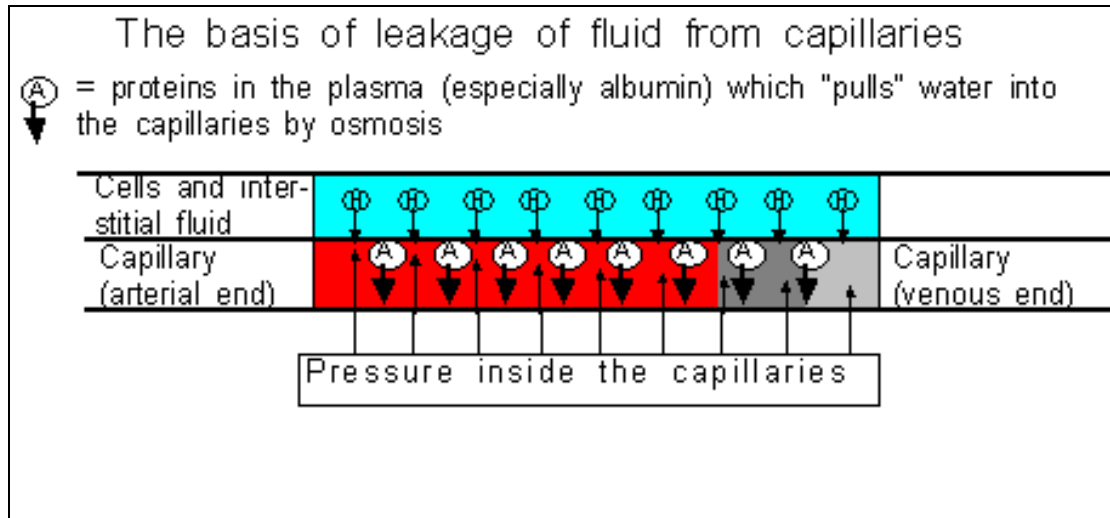
3 litres intake on average   3 litres output on average

| |
| Water as fluid |
| Water in food |
| Water from metabolism |

| |
| Urine 1,500 mls on average |
| Perspiration. Amount depends on temperature and humidity |
| Expired air, about 400 mls |
| Faeces. About 200 mls (up to 20 litres possible with cholera) |

Drinking or eating food containing water is the only natural way of obtaining water (unnatural ways include percutaneous medical infusions of various sorts). People vary in their water content. In general women contain proportionally less water than men, fat people contain less (because fat contains less water than other tissues), and infants contain proportionally more water.
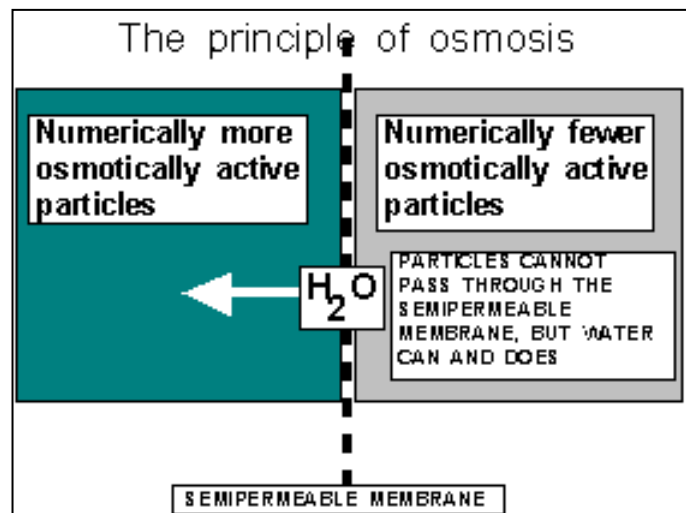
The distribution of body water.

Sweat

Drinking → ← → Water in exhalations

Intracellular fluid 2/3 total body water

Plasma — Plasma volume is decreased if there is water loss, low plasma proteins or low plasma osmolarity

Interstitial fluid (fluid in between tissue cells

If interstitial fluid is depleted the skin elasticity decreases.

If the interstitial fluid is expanded then pitting oedema results

Extracelluar fluid = 1/3 total body water

Urine H_2O

Stool fluid H_2O

The tendency of capillaries to leak is the basis of the filtering function of the kidneys and liver.

The basis of leakage of fluid from capillaries

Ⓐ = proteins in the plasma (especially albumin) which "pulls" water into the capillaries by osmosis

Osmosis is the movement of water *from* a solution of lower concentration *to* a solution of higher concentration across a membrane such as a cell wall which is permeable to water (but not to the solute) The number of particles in the solution determines osmotic activity.

Most bodily fluids have an osmolality of about 285 milliosmols. Isotonic (iso=same, tonic=concentration) fluids given to patients have the same value, hypertonic solutions have a greater osmolality, and hypotonic solutions lesser osmolality.

The principle of osmosis

Numerically more osmotically active particles

Numerically fewer osmotically active particles

PARTICLES CANNOT PASS THROUGH THE SEMIPERMEABLE MEMBRANE, BUT WATER CAN AND DOES

H_2O

SEMIPERMEABLE MEMBRANE

If plasma osmolarity falls then water leaves the plasma and mostly enters the interstitial fluid. This produces oedema (tissue swelling caused by increased interstitial fluid) which is pitting in type in that it can be indented by pressure with a finger. If the plasma protein concentration is very low (causes include severe leakage of protein into the urine, or failure of protein synthesis by the liver) then diffuse oedema will result.

About two thirds of total body water in humans is intracellular and about one third is extracellular. The extracellular fluid is either between cells (as interstitial fluid) or within the circulatory systems (mostly in plasma).

There are four ways of loosing fluid:
- Via the kidney (physiologically the most important)
- Through the skin as perspiration
- From the lung

- From the gut (the loss is small unless diarrhoea and/or vomiting are present).

All fluid losses initially deplete the extracellular fluid. In general intracellular fluid has to be kept stable, almost at all costs.

Electrolytes

An electrolyte is a compound which, when dissolved in water, separates into charged particles capable of conducting an electric current. In the long term negative charges have to equal positive charges but metabolism and life depend on temporary imbalances of electrically charged particles.

The negatively charged ions in intracellular fluid are mostly proteins (which are in general too large to diffuse out through the cell walls) and phosphates. The negatively charged ions in the extracellular fluid are chloride and bicarbonate.
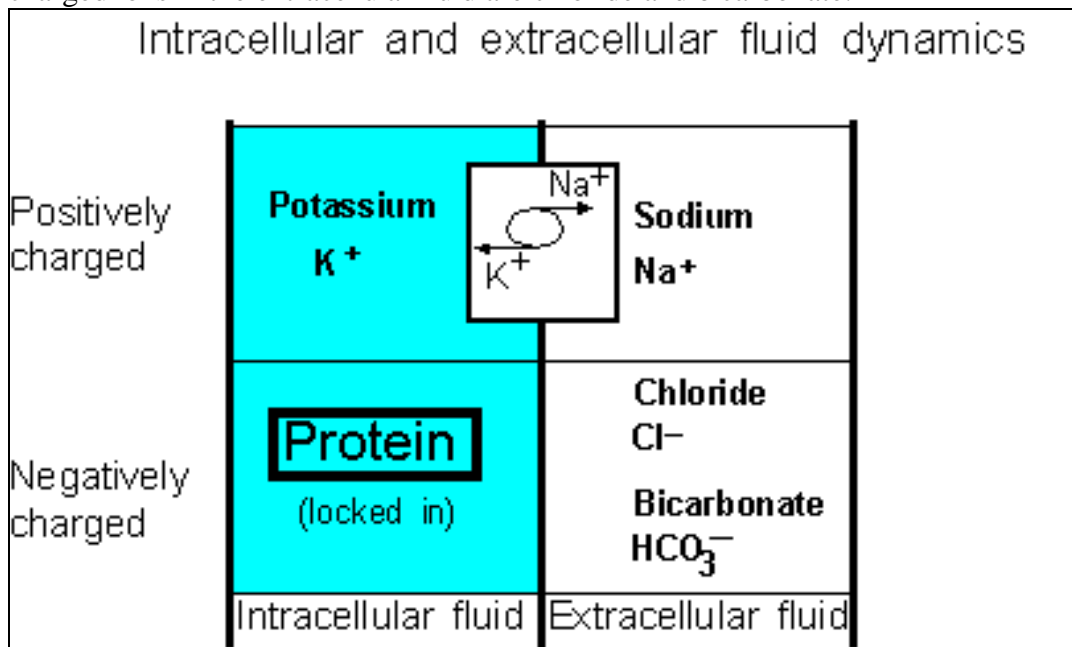
Sodium regulation and water balance
Changes in the more variable *extracellular* fluid, particularly the plasma, can usually be detected clinically whereas the *intracellular* fluid tends to be more stable and less amenable to clinical assessment.

Hydrogen ion balance

Some definitions:
- **Acid:** a substance which forms hydrogen ions in solution (the more hydrogen ions formed the more acidic the solution)
- **Alkali:** a substance which combines with and, wholly or partially, neutralises hydrogen ions
- **Enzyme**: a substance that participates in and accelerates a chemical reaction without being used up itself

- **pH:** pH is a logarithmic measure of hydrogen ion activity in a solution. It is a more convenient way of expressing wide ranges of acidity/alkalinity. The range of pH is from 1 (very acidic) to 14 (very alkaline). pH7 is neutral
- **Buffer**: a buffer is a substance that damps down variation in the concentrations of acid or alkalai, usually by accepting hydrogen ions or hydroxyl ions

The acid base state of the body must be maintained with narrow limits because almost all chemical reactions are influenced by the acidity or alkalinity of surrounding tissues or fluids.

In the body most hydrogen ions are bound to buffers and relatively few are "free-floating" and available for interactions. The extracellular fluid pH is 7.4 and pHs of less that 7 or greater than 7.7 are often found only in extreme circumstances.

Homeostasis requires a highly stable pH close to 7.4. Immediate changes in hydrogen ion concentration are dealt with by the rapid buffering systems, short term adjustments by the lungs, and medium to long term adjustments by the kidneys.

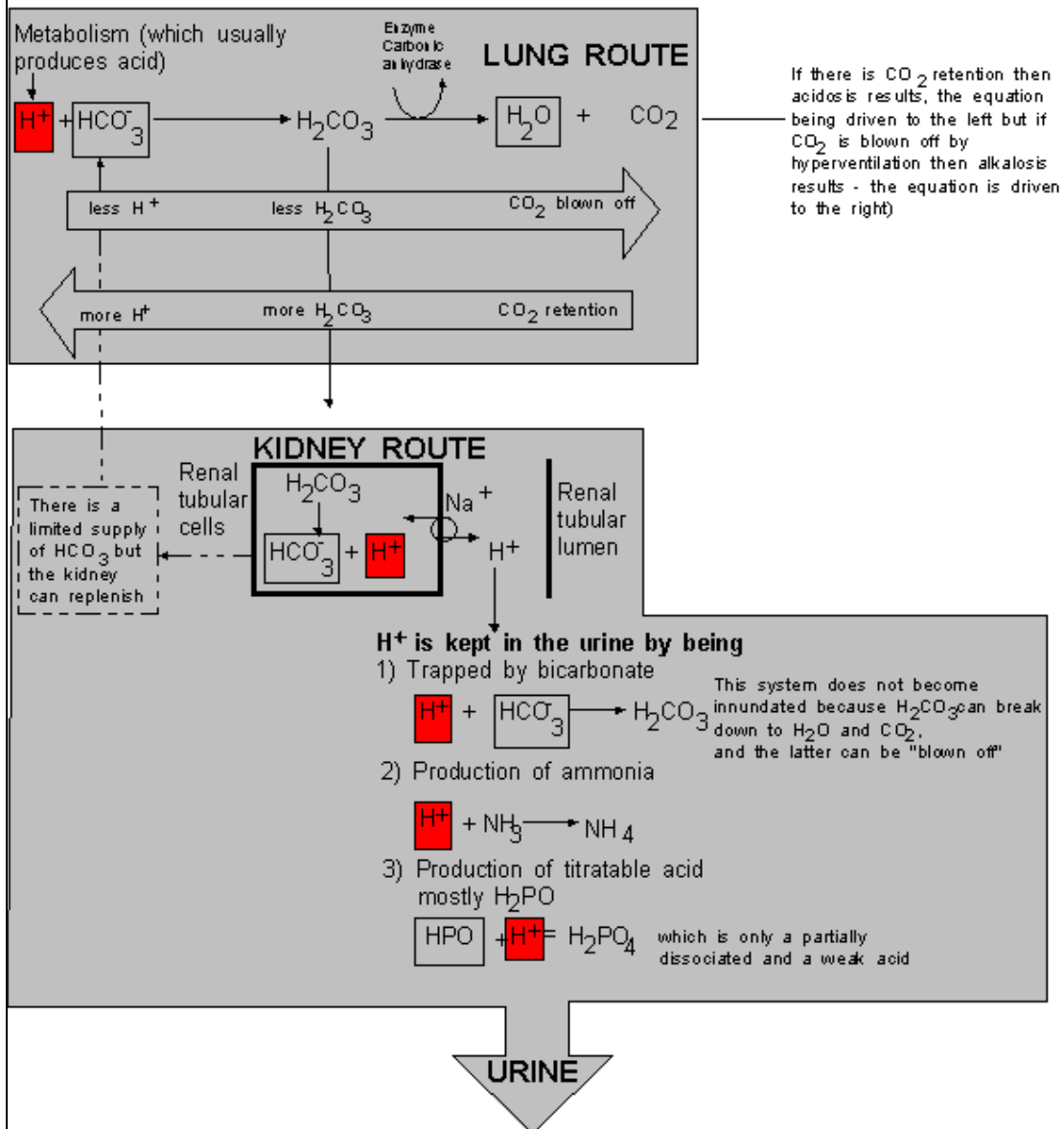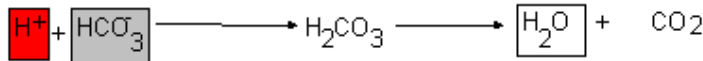## Immediate hydrogen ion homeostasis (buffering)
Hydrogen ions are linked with negatively charged ions. If binding is weak, hydrogen ions are relatively free to interact elsewhere and the solution is therefore acidic with a high hydrogen ion concentration (low pH). With extracellular buffering if such hydrogen ions can be combined with a negative ion (such as phosphate) then the free hydrogen ion concentration will fall and the pH will increase towards the normal level. Negative ions like phosphate thus function as buffers which can be saturated if there are too many hydrogen ions available. However over half of hydrogen ion buffering occurs intracellularly mostly utilising negatively charged proteins (including haemoglobin).

Short term hydrogen ion homeostasis
The bicarbonate buffer (which combines hydrogen ions and bicarbonate to form carbonic acid) does not become saturated because the carbonic acid can be broken down using an enzyme (carbonic anhydrase) into carbon dioxide and water. The carbon dioxide can then be excreted via the lungs. The only limiting factor to this buffering is the supply of bicarbonate.

Excretion of acid is either by the lungs (quicker)
or the kidneys (slower)

The basic equation for respiratory
and kidney mediated homeostasis

$$H^+ + HCO_3^- \longrightarrow H_2CO_3 \longrightarrow H_2O + CO_2$$

Metabolism (which usually
produces acid)

Enzyme
Carbonic
anhydrase

LUNG ROUTE

$$H^+ + HCO_3^- \longrightarrow H_2CO_3 \longrightarrow H_2O + CO_2$$

less H^+ less H_2CO_3 CO_2 blown off

more H^+ more H_2CO_3 CO_2 retention

If there is CO_2 retention then
acidosis results, the equation
being driven to the left but if
CO_2 is blown off by
hyperventilation then alkalosis
results - the equation is driven
to the right)

KIDNEY ROUTE

Renal
tubular
cells

$$H_2CO_3$$

$$HCO_3^- + H^+$$

Na^+

H^+

Renal
tubular
lumen

There is a
limited supply
of HCO_3 but
the kidney
can replenish

H^+ is kept in the urine by being
1) Trapped by bicarbonate

$$H^+ + HCO_3^- \longrightarrow H_2CO_3$$

This system does not become
inundated because H_2CO_3 can break
down to H_2O and CO_2,
and the latter can be "blown off"

2) Production of ammonia

$$H^+ + NH_3 \longrightarrow NH_4$$

3) Production of titratable acid
mostly H_2PO

$$HPO + H^+ = H_2PO_4$$ which is only a partially
dissociated and a weak acid

URINE

Medium to long term hydrogen ion homeostasis

Happily the kidneys can supply extra bicarbonate when required, and as it happens, to
do this they excrete the embarrassing hydrogen ions by breaking down carbonic acid
into bicarbonate and hydrogen ions. The hydrogen ions are excreted into the urine and
the bicarbonate buffers the remainder of the hydrogen ions. The bicarbonate
replenishes the short term buffer system and hydrogen ions are excreted into the urine.
The hydrogen ion is kept in the urine by several mechanisms, including ammonia
production.

Thus the respiratory:kidney axis will, given time, tend to keep the pH, concentration of carbon dioxide, and concentration of bicarbonate all within reasonable limits. Malfunction of either lungs or kidneys may threaten homeostasis by producing acidosis or alkalosis.

ACIDOSIS AND ALKALOSIS
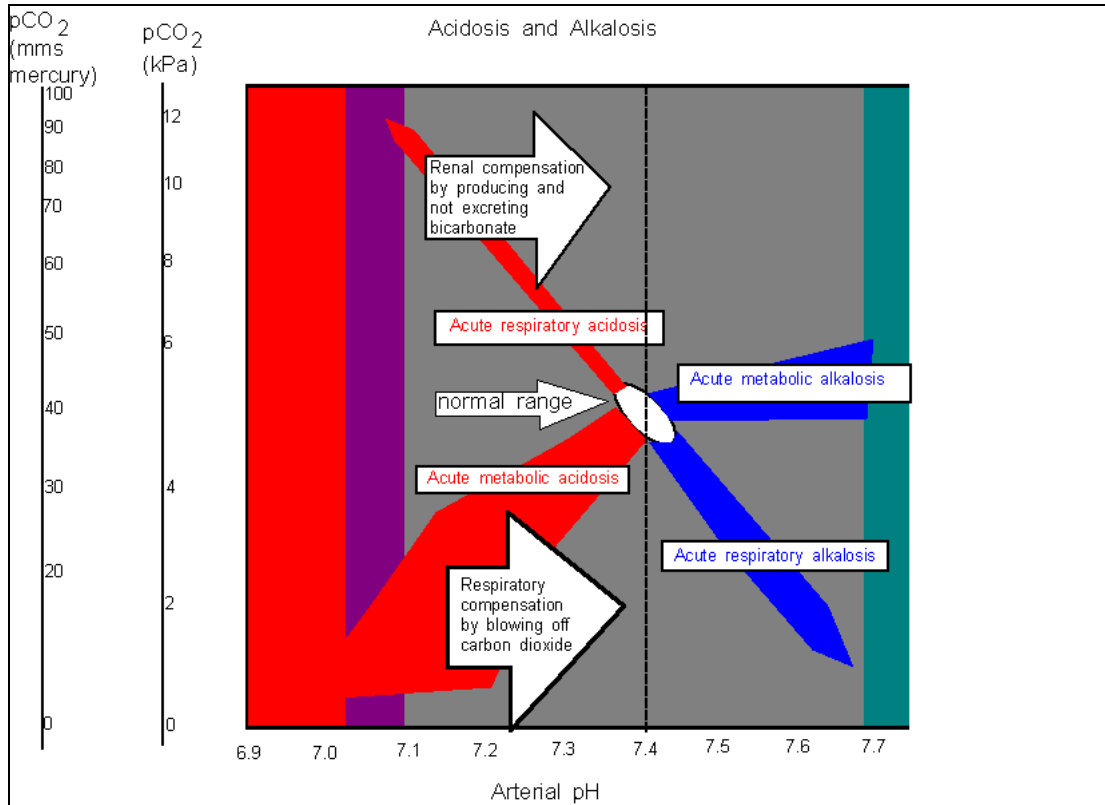
Respiratory acidosis
When there is an oxygen shortage metabolism produces excessive hydrogen ions. To compensate for this the kidney reacts by excreting excessive hydrogen ion and producing more bicarbonate. Thus in respiratory acidosis plasma hydrogen ion concentration increases, pH falls, and plasma bicarbonate increases – *but this bicarbonate increase only occurs once the kidneys respond.*

Respiratory alkalosis
Respiratory alkalosis occurs with hyperventilation in which the CO_2 concentration falls, plasma hydrogen ion concentration falls, pH rises and plasma bicarbonate levels fall. The kidneys have no need to excrete excessive hydrogen ions and thus do not make bicarbonate.

Metabolic (i.e. non-respiratory) acidosis
Metabolic acidosis may occur after excessive acid ingestion/retention or net loss of bicarbonate. Metabolic loss of bicarbonate may occur with diarrhoea (most diarrhoea is alkaline) or the kidneys may not be able to retain bicarbonate (in renal tubular acidosis for example). The pH falls and the concentration of carbon dioxide and plasma bicarbonate fall because the lungs react quickly to mount a compensatory

respiratory alkalosis. Accumulation of negatively recharged particles (including phosphate in renal failure and metabolites in diabetic hyperglycaemic coma) may have to be balanced by positively charged particles (including hydrogen ions) and thus acidosis results.

Metabolic alkalosis
Metabolic alkalosis may occur with excessive alkali ingestion or production, or loss of hydrogen ions. The pH tends to rise and the concentration of both carbon dioxide and plasma bicarbonate also rises. The lungs mount a compensatory respiratory acidosis but this is not particularly effective as the required hypoventilation would produce an unacceptably low pO_2 .

The figure below shows the findings on arterial blood gas analysis, which in the acute situation reflect the initial problem and the compensatory responses occur later.
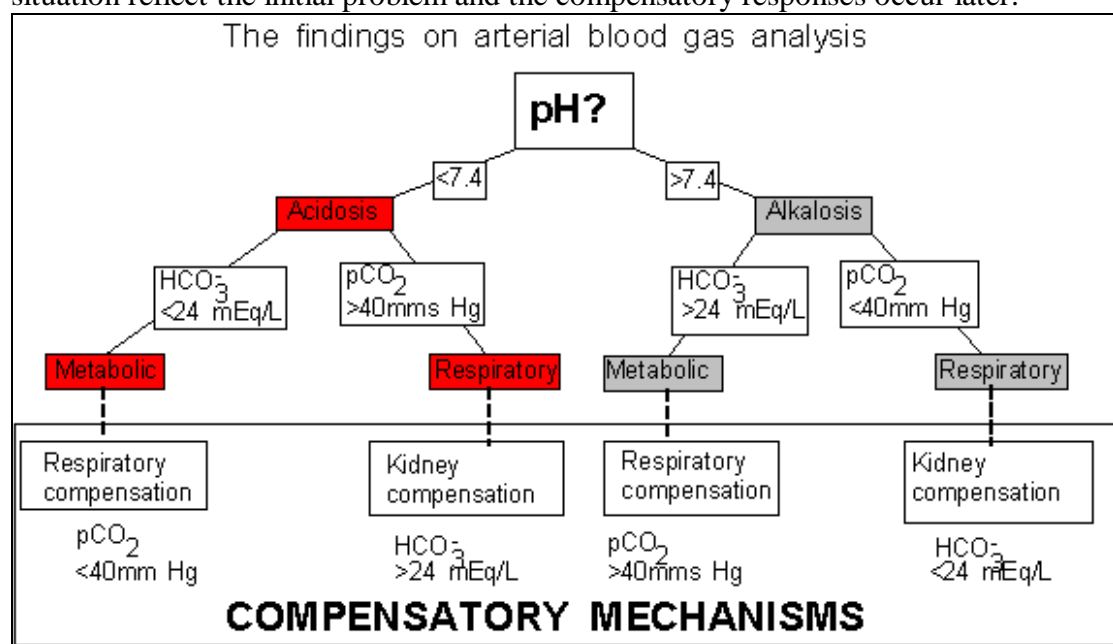
Calcium and phosphorus homeostasis
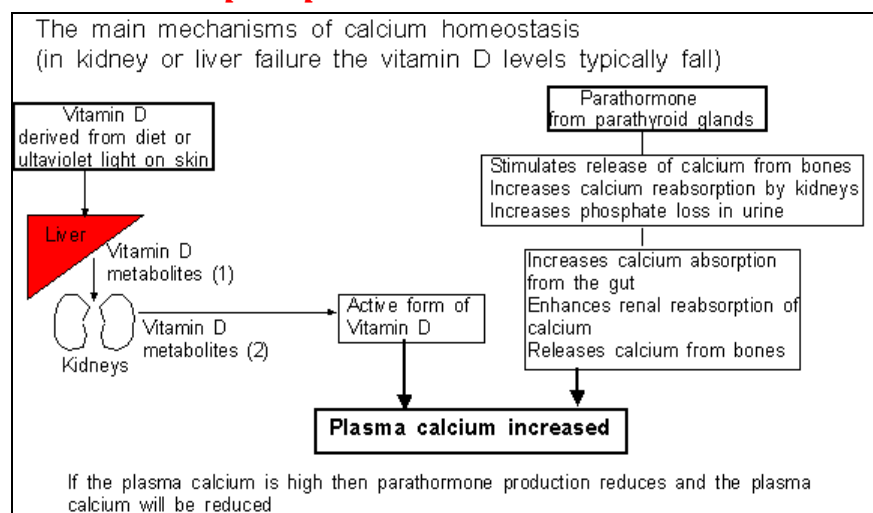
Both calcium and phosphorous are major constituents of bone. There is a working relationship such that increases in one usually mean a reduction in the other. If no such reduction occurs then calcium phosphate may precipitate together. The extracellular concentration of calcium has to be kept within strict limits to maintain health because extracellular calcium affects membrane excitability. This particularly affects nerve conduction, and skeletal muscle and cardiac muscle contraction. Extracellular fluid concentrations of calcium can be increased by increased absorption of calcium from the gut and/or release of calcium from bone stores. Extracellular concentrations can be decreased by calcium entering bone or by excretion (into the urine).

As an oversimplification the major effect of parathormone is to increase free ionised calcium by releasing calcium from bone and the major effect of vitamin D is to increase calcium absorption from the gut.

Usually the *total* calcium is measured in the blood but it is only ionised "free" calcium that is physiologically important (about half the remainder is bound to albumin or other negatively charged substances). In sudden onset alkalosis (intravenous alkali administration or acute hyperventilation) there will be less hydrogen ions to enjoy liaisons with negatively charged substances and the vacant sites can be occupied by the previously free ionised calcium, and thus free ionised calcium will fall whilst the total calcium levels (as are normally measured) will remain the same.

Vitamin D also plays a major role in calcium homeostasis. Vitamin D is either derived from the diet or by action of ultra violet light on the skin. The initial product is metabolised by the liver, then by the kidney, before its final product is released.

A high plasma calcium may be caused by excess vitamin D, increased sensitivity to vitamin D, or increased release of calcium from bone (as may occur in tumours invading bones) and high levels may cause kidney damage or tissue calcification.

Vitamin D deficiency produces bone deformities (rickets) in growing children whereas in adults osteomalacia (=bad bones) results with a tendency to fracture weight bearing bones. Kidney disease and to a much lesser extent liver disease may cause a similar picture because there is impairment in the sequential metabolism of Vitamin D to its most active form .


Glucose homeostasis

Glucose is the major "energy compound." It is ultimately derived from photosynthesis by plants and eventually absorbed by the human gut. Glucose is stored as glycogen in the liver.
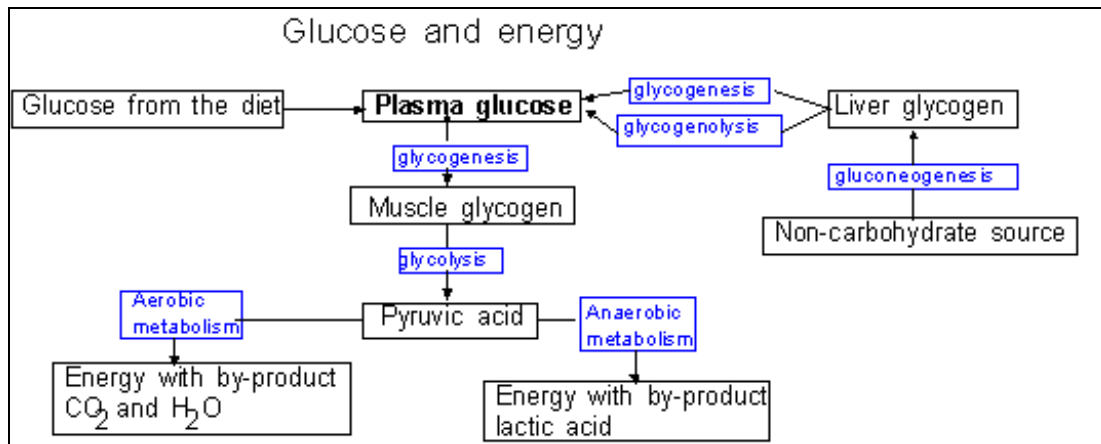
Metabolism of glycogen maintains the plasma glucose level. If the plasma glucose falls then the tissues, notably the brain, dysfunction because of lack of energy. Insulin is required for cells to metabolise glucose and if this occurs various metabolic consequences follow

Muscle glycogen is used directly for energy during exercise and replenished by metabolism of blood glucose thereafter. During exercise pyruvic acid is formed with release of some energy. If oxygen is available (aerobic conditions) pyruvic acid is converted to carbon dioxide and water with substantial energy release via Kreb's cycle.
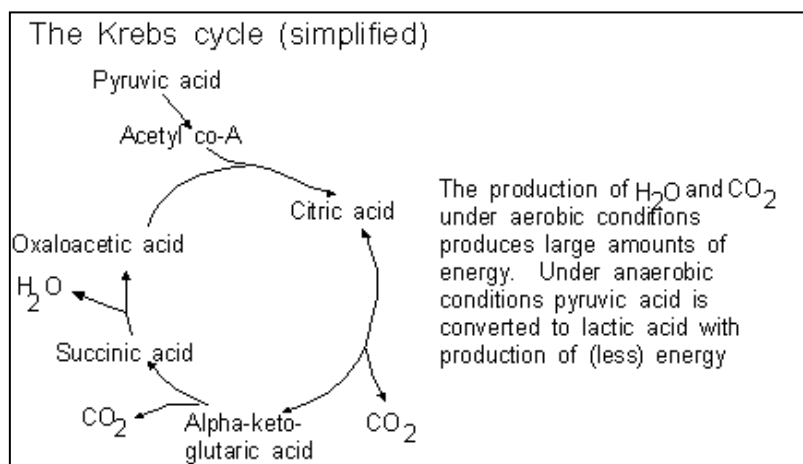

If there is insufficient oxygen (anaerobic conditions) pyruvic acid is converted to lactic acid (with less energy output than from the pyruvic acid route). However this method of anaerobic energy production leads to an oxygen debt which has to be repaid before normality returns.

Fat homeostasis

Dietary fat passes from the gut to the liver where it is metabolised to glycerol and fatty acids. The fatty acids can then enter into the Kreb's cycle and/or to form ketone bodies which can be used as an energy source by peripheral tissues. In insulin deficiency fat is used for metabolism because glucose cannot be metabolised effectively. The use of fatty acids for energy production produces ketone bodies which can often be smelt on the breath of patients with hyperglycaemic coma (starvation produces similar effects). Some ketone bodies are acids and thus patients are acidotic and may hyperventilate in an attempt to relieve the acidosis (Figs 7 and 8).

Protein homeostasis

Formation of peptides and proteins
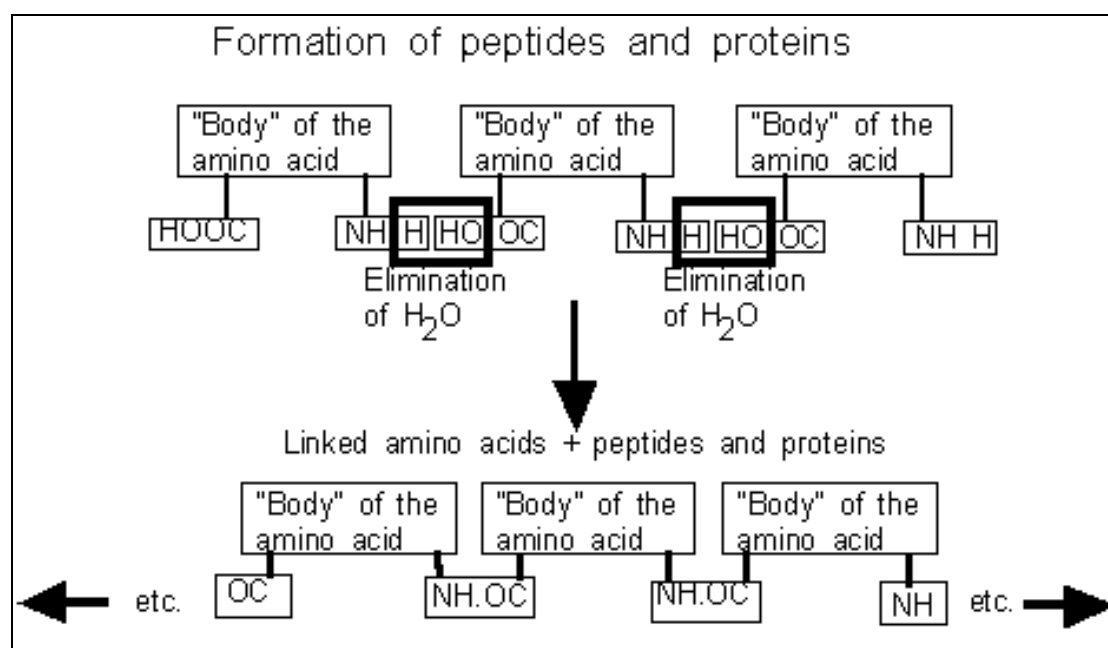
Amino acids are the building blocks of proteins. There are 22 amino acids, 8 of which have to be present in the diet as they cannot by synthesised in sufficient amounts by humans. Amino acids combine by means of peptide links to form complex physicochemical structures (peptides and proteins) required for building cells, tissues and organs. Some proteins are enzymes and thus can assist construction of carbohydrates, fats and other proteins.

Enzymes

Most chemical reactions proceed faster if the temperature is raised. Warm-blooded animals have evolved to keep their body temperature within well-defined limits so that the body as a whole is not at risk from the environmental temperature (cold blooded animals slow down when they get cold because their chemical reactions slow down) whereas warm blooded animals keep their temperature stable to allow their enzymes to continue functioning. Enzymes are usually folded proteins which may contain metal compounds. The activity of some enzymes is moderated by other metabolic compounds which are know as co-enzymes.

Living organisms have developed a large number of enzymes, each one of which has a specific function to speed up a chemical reaction. They can do this by physically trapping and forcing together reluctant chemicals so that they "have to" combine, or by acting an intermediates so that reactions can proceed faster than they would do otherwise to form compounds (synthesis) or break down compounds (degradation or, more loosely, metabolised).
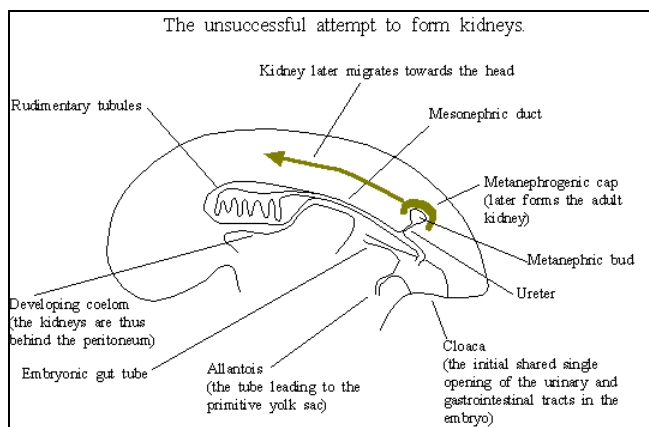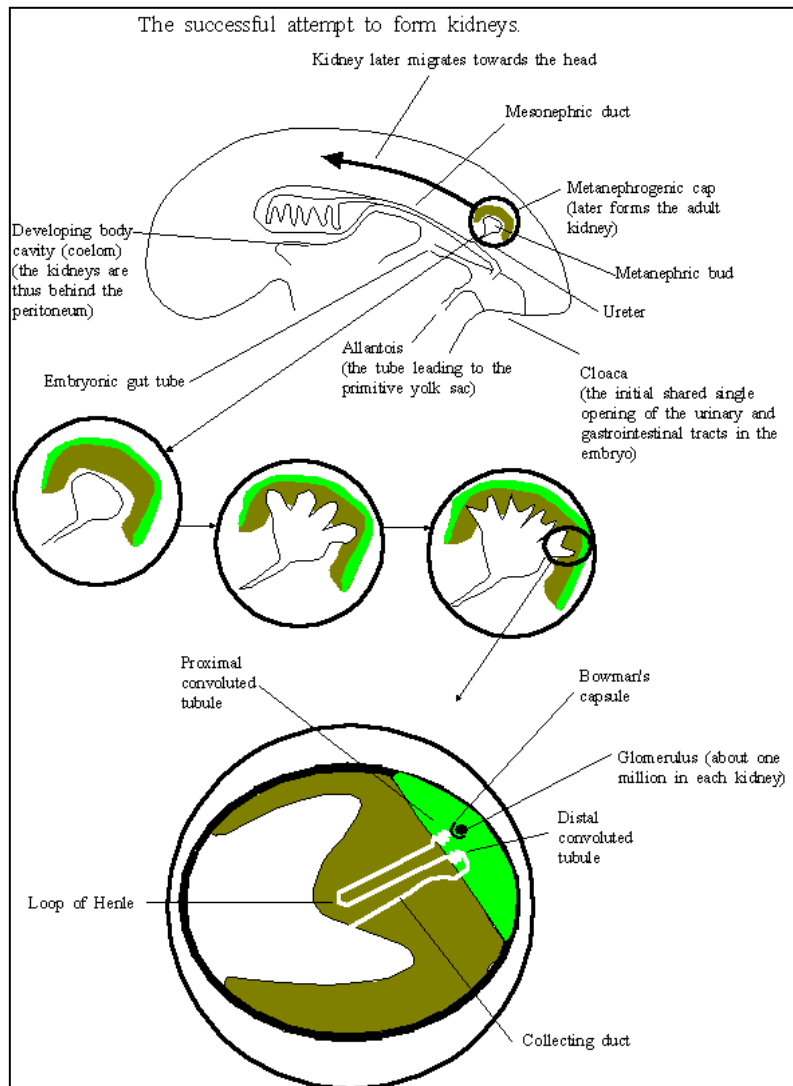
HOMEOSTASIS AND THE URINARY SYSTEM

The anatomy of the urinary tract is shown below.

The Anatomy of the Urinary Tract
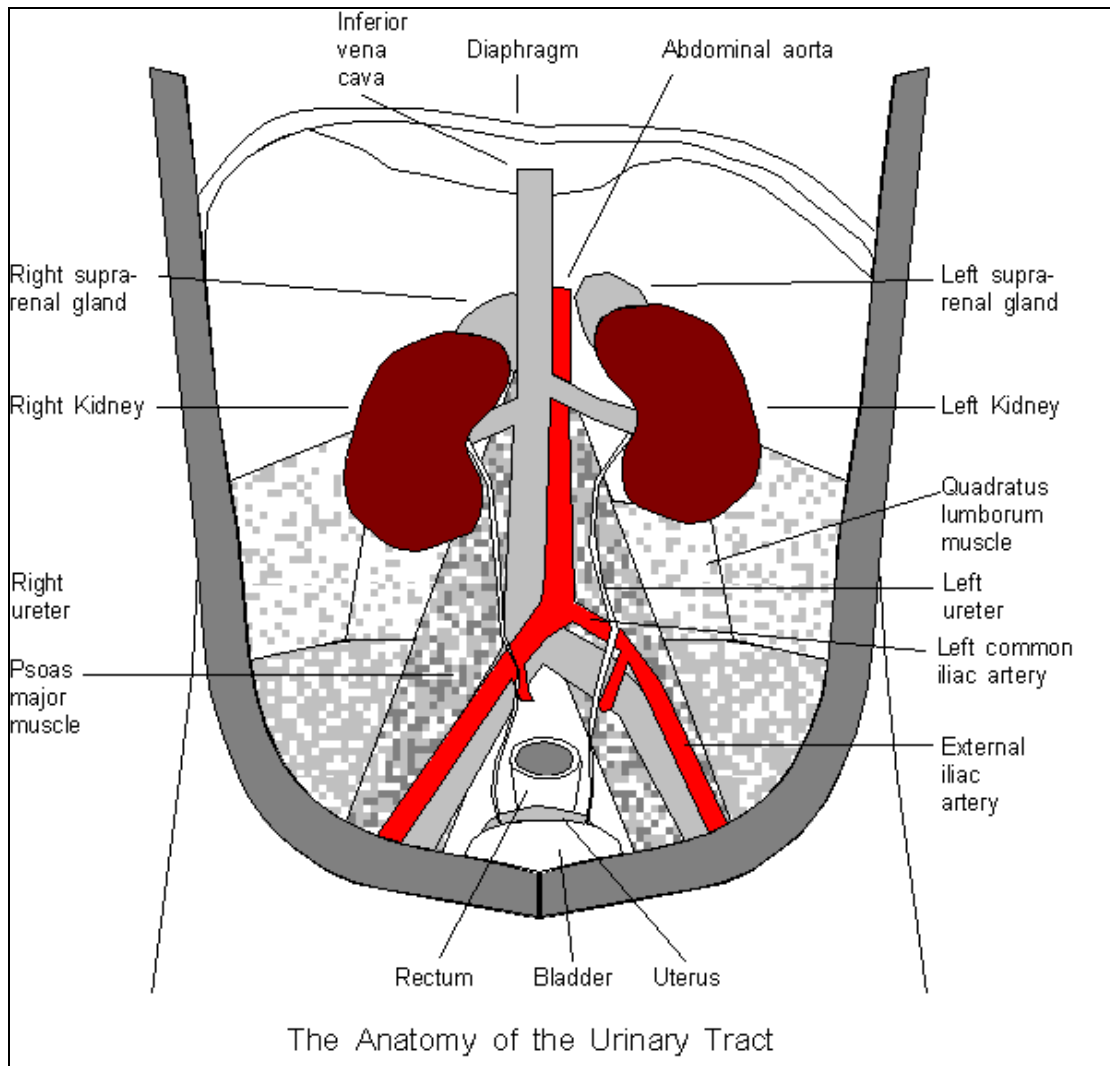
Embryological development: a simplified version

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. 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.

The unsuccessful attempt to form kidneys.

The successful attempt to form kidneys.

Kidney later migrates towards the head

Mesonephric duct

Metanephrogenic cap (later forms the adult kidney)

Developing body-cavity (coelom) (the kidneys are thus behind the peritoneum)

Metanephric bud

Ureter

Embryonic gut tube

Allantois (the tube leading to the primitive yolk sac)

Cloaca (the initial shared single opening of the urinary and gastrointestinal tracts in the embryo)

Proximal convoluted tubule

Bowman's capsule

Glomerulus (about one million in each kidney)

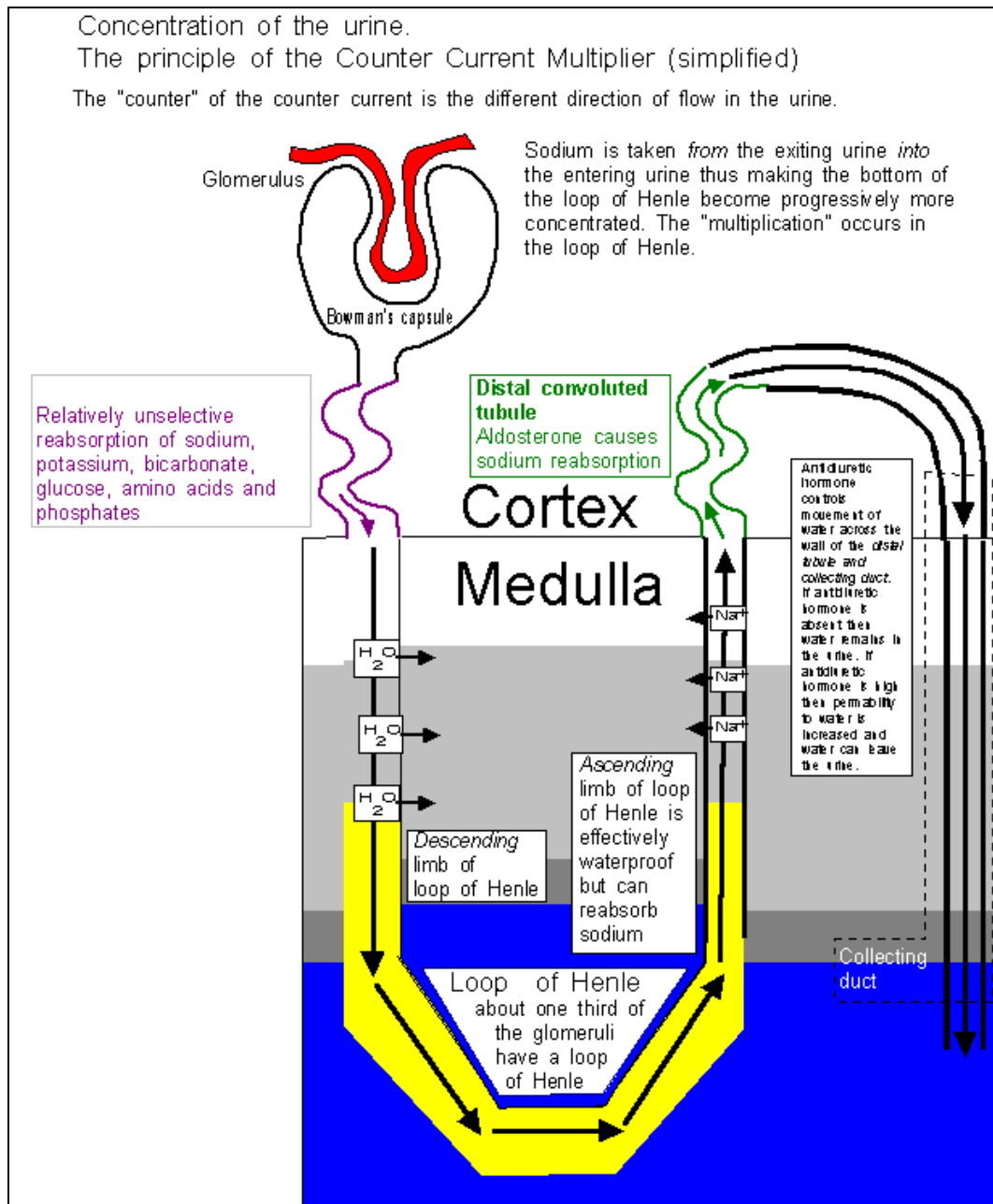Distal convoluted tubule

Loop of Henle

Collecting duct

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.

Concentration of the urine.
The principle of the Counter Current Multiplier (simplified)

The "counter" of the counter current is the different direction of flow in the urine.

Glomerulus

Sodium is taken *from* the exiting urine *into* the entering urine thus making the bottom of the loop of Henle become progressively more concentrated. The "multiplication" occurs in the loop of Henle.

Bowman's capsule

Relatively unselective reabsorption of sodium, potassium, bicarbonate, glucose, amino acids and phosphates

Distal convoluted tubule
Aldosterone causes sodium reabsorption

Cortex

Medulla

Antidiuretic hormone controls movement of water across the wall of the distal tubule and collecting duct. If antidiuretic hormone is absent then water remains in the urine. If antidiuretic hormone is high then permability to water is increased and water can leave the urine.

H_2O
H_2O
H_2O

Na+
Na+
Na+

Ascending limb of loop of Henle is effectively waterproof but can reabsorb sodium

Descending limb of loop of Henle

Collecting duct

Loop of Henle
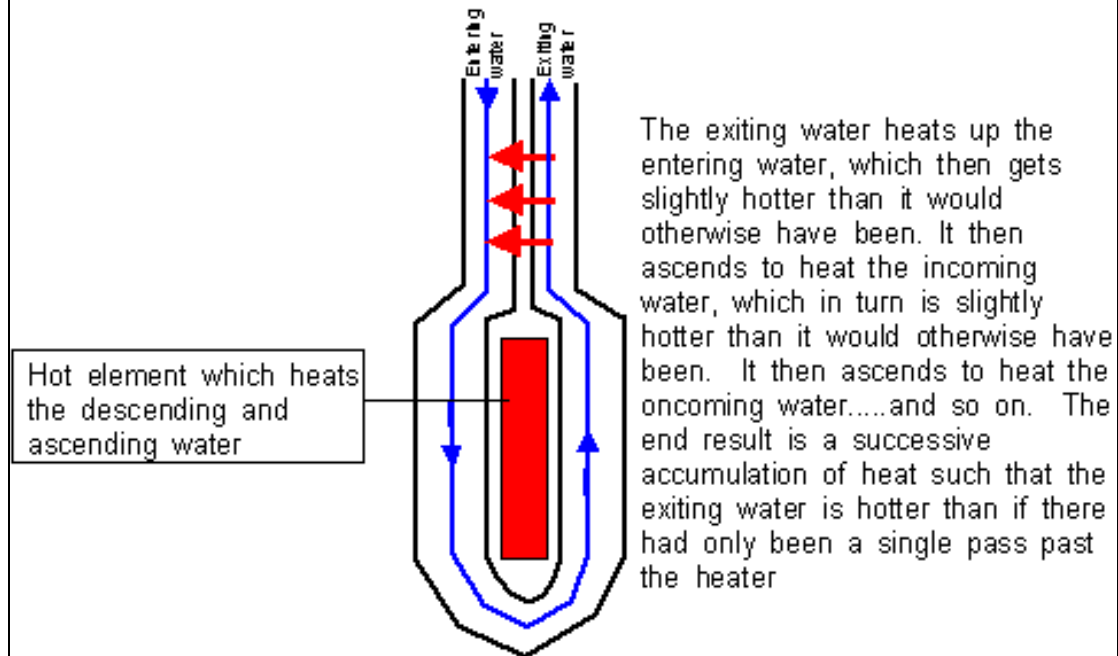about one third of the glomeruli have a loop of Henle

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 systemwhich was first described in heat exchange systems to concentrate the urine.

Principle of the counter current multiplier system.

First described as a water heating system (as shown in this example). In this analogy sodium is equivalent to heat and hotness is equivalent to urinary concentration.

Hot element which heats the descending and ascending water

The exiting water heats up the entering water, which then gets slightly hotter than it would otherwise have been. It then ascends to heat the incoming water, which in turn is slightly hotter than it would otherwise have been. It then ascends to heat the oncoming water.....and so on. The end result is a successive accumulation of heat such that the exiting water is hotter than if there had only been a single pass past the heater

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, increases sodium reabsorption by the distal convoluted tubules. If sodium is not reabsorbed then both potassium and hydrogen ions have to be excreted instead 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 from the plasma gives an even better measure of kidney function (Fig. 19).

The clearance of a substance is the amount of plasma that can be totally cleared of it in unit time. 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 total "uraemic syndrome" is multifactorial and produced by retention of substances other than urea. 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 with age 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 distal tubules and 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 generalised 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 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. Although more sophisticated tests are now usually performed the 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 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 concentration in the blood (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 maybe reduced and fluid, urea and creatinine cannot be excreted and their plasma levels rise. Usually the inflamed glomeruli leak protein and blood into the urine.
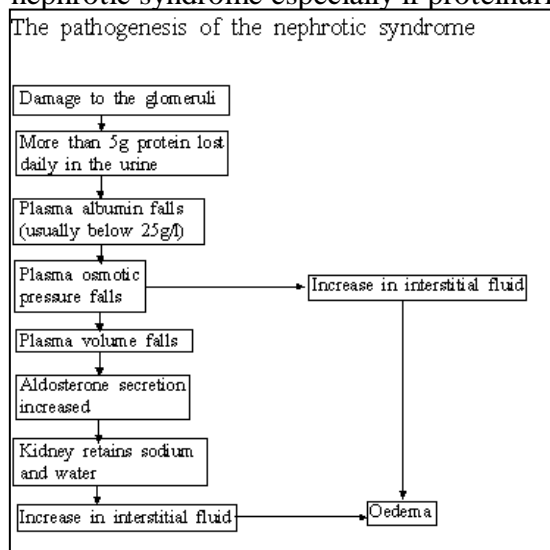
Chronic kidney failure

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 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.

The pathogenesis of the nephrotic syndrome

Damage to the glomeruli

More than 5g protein lost daily in the urine

Plasma albumin falls (usually below 25g/l)

Plasma osmotic pressure falls → Increase in interstitial fluid

Plasma volume falls

Aldosterone secretion increased

Kidney retains sodium and water

Increase in interstitial fluid → Oedema

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

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.

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