Definitions

1. **Mole**
   - that number of molecules contained in 0.012 kg of C^{12}, or,
     the molecular weight of a substance in grams = ***Avogadro's number***
     = 6.023×10^{23}
2. **Solution**
   - a homogeneous mixture of 2 or more substances of dissimilar molecular structure
   - usually applied to ***solids*** in ***liquids*** but applies equally to ***gasses*** in ***liquids***
3. **Crystalloid**
   - a non-colloid substance, which in solution,

   i. passes readily through biological membranes

   ii. displays ***colligative properties*** - see below

   iii. is capable of being crystallised
4. **Colloid**
   - a solution where the particles of the ***disperse phase***,

   i. are larger than ordinary crystalloid molecules,
   but are not large enough to settle out under the influence of ***gravity***

   ii. resist diffusion

   iii. range in size from ~ 1 to 100 nm (or up to 1000 nm), the range being arbitrary
   - ***emulsion colloids***, where the particles of the disperse phase are made of highly complex organic molecules, which absorb much of the dispersion medium, usually water, swell, and become uniformly distributed throughout and the dispersion medium
   - ***suspension colloids***, where the particles of the disperse phase are made of any ***insoluble*** substance, such as a metal, and the dispersion medium may be gaseous, liquid or solid
5. **Molality**
   - is the number of moles of solute per ***kilogram*** of ***solvent***
6. **Molarity**
   - is the number of moles of solute per ***litre*** of ***solution***
7. **Diffusion**
   - the constant random thermal motion of molecules, which leads to the net transfer of molecules, from a region of higher to a region of lower ***thermodynamic activity***
8. **Osmosis**
   - the movement of a ***solvent*** across a semipermeable membrane, down a thermodynamic activity gradient for that solvent
9. **Osmotic Pressure**
   - the ***hydrostatic*** pressure which would be required to prevent the movement of a solvent across a semipermeable membrane, down a thermodynamic activity gradient for that solvent

10. **Tonicity**
    - the effective osmotic pressure of a solution, relative to ***plasma***
    - usually referenced to red blood cells

11. **Colligative Properties**
    - are those properties of a solution which depend only upon the ***number*** of freely moving particles, and not on the nature of the particles themselves,

    i. osmotic pressure

    ii. depression of freezing point
        - commonly used to calculate ***osmolality***
        - 1 mosmol/kg $\rightarrow$ 1.86 °C depression of the freezing point of pure water

    iii. elevation of boiling point

    iv. depression of saturated vapour pressure

12. **Osmole**
    - the weight in grams of a substance producing an osmotic pressure of 22.4 atm. when dissolved in 1.0 litre of solution, or,
    - = (gram molecular weight) / (no. of freely moving particles per molecule)

13. **Osmotic Coefficient**
    - the degree of dissociation of a particular compound
    - eg., NaCl $\rightarrow$ 1.86 particles when dissolved in pure water
      $OC_{NaCl/H2O} = 0.93$

14. **Osmolality**
    - the number of osmoles of solute per ***kilogram*** of ***solvent***

15. **Osmolarity**
    - the number of osmoles of solute per ***litre*** of ***solution***

BODY FLUIDS

Body Compartment Volumes					
Normal Values	Premature	Term	25 yrs	45 yrs	65 yrs
TBW Male: Female:	80%	75%	60% 50%	55% 47%	50% 45%
ECF ICF	45% 35%	40% 35%	20% 40%		
Blood Volume	90-100 ml/kg	85 ml/kg	~ 70 ml/kg		

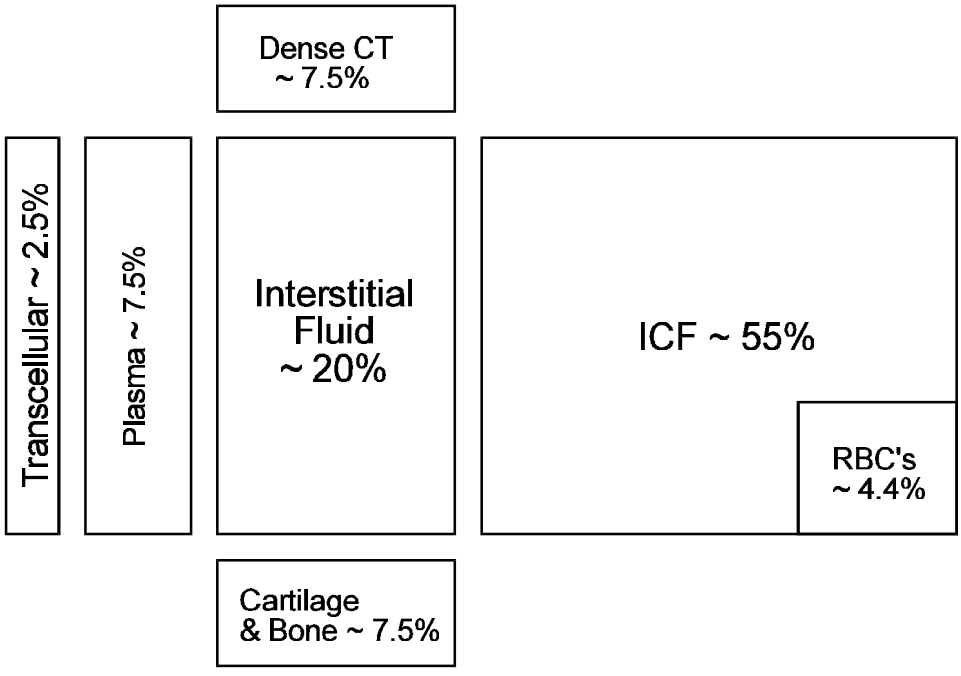
- neonates reach adult values by 2 yrs and are about half-way by 3 months
- average values ~ 70 ml/100g of lean body mass
- percentage of water varies with tissue type,

a. lean tissues ~ 60-80%

b. bone ~ 20-25%

c. fat ~ 10-15%

Distribution of TBW

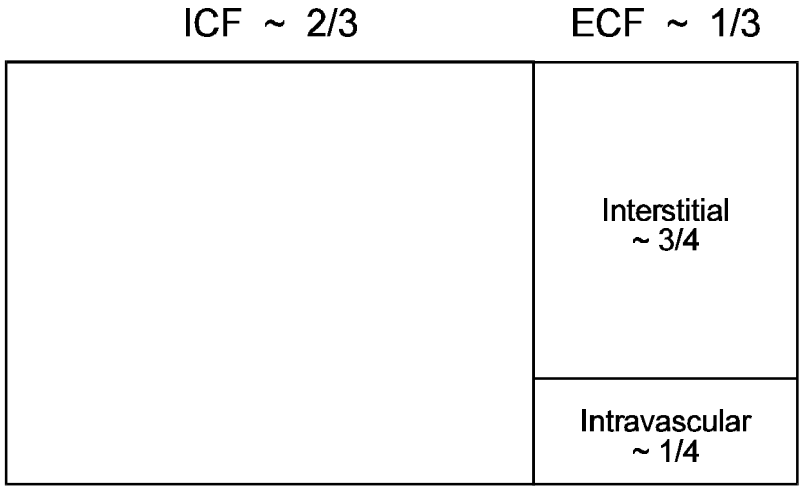


- distribution between various body compartments, percentage of TBW

a.	Intracellular Fluid		**~ 55%**
	i.	RBC's	~ 4.4%
	ii.	Others	~ 50.6%
b.	Extracellular Fluid		**~ 45%**
	i.	Interstitial	~ 20%
	ii.	Plasma	~ 7.5%
	iii.	Bone & Cartilage	~ 7.5%
	iv.	Dense CT.	~ 7.5%
	v.	Transcellular	~ 2.5%

■ ***Simplified Distribution for Fluid Therapy***

- bone, cartilage and dense connective tissue exchange slowly with the intravascular compartment
- thus, for the purpose of fluid therapy the follow distribution may be assumed



Measurement of Compartments

• most techniques involve ***indicator dilution***, whereby a given ***volume of distribution*** is calculated
• this method is based upon the ***conservation of mass*** principal, where the V_{dI} for an indicator is given by,

$$V_{dI} = \frac{Mass\ Injected - Mass\ Lost}{[I]_{Plasma}}$$

NB: the derived volumes are estimations only, and when stated should actually be stated as such, eg. the "12 hour tritium oxide volume", not TBW

■ ***Total Body Water***

• accurate estimation can only be derived from ***desiccation*** of cadaver specimens
• one of three indicators is usually used and results acceptably concur with to desiccation experiments,

a. ***deuterium oxide*** - measured by mass spectroscopy
   - cumbersome and more difficult

b. ***tritium oxide*** - weak β emitter and easily measured
   - radiation half-life ~ 12.4 years
   - biological half-life ~ 10 days
   - therefore small total radiation dose

c. ***antipyrene*** ~ 4 hrs equilibration, 6-8 hrs in the obese
   - measured by spectroscopy

■ ***Extracellular Fluid***

• quite difficult to measure as ***no*** indicator is truly confined to the ECF
• use either crystalloids or ionic substances,

a. radioactively labelled inulin
b. radioactively labelled mannitol
c. $^{82}Br^-$
d. $^{36}Cl^-$
e. $^{38}Cl^-$

• Br^- and Cl^- are distributed similarly, however not all Cl^- is extracellular and some cells contain quite high concentrations, eg. RBCs
• some workers in fact argue that RBC's should be included with the ECF due to this property
• the biological half-life of $^{82}\mathbf{Br}^-$ is more favourable than either of the isotopes of Cl^-

Plasma Volume

- use ***plasma protein*** bound markers, though, ~ 7-10% leaves the vascular compartment per hour
- this value is increased in a number of disease states
- therefore, equilibration time is kept to a minimum → ~ 15 mins
- alternatively, serial measures are taken and the plasma concentration extrapolated to time = 0
- markers include,

a. radiolabelled serum albumin

b. Evans blue labelled serum albumin

c. radiolabelled globulins

Red Blood Cell Volume

- RBCs labelled with either $^{51}Cr^{-}$, $^{59}Fe^{++}$, or ^{32}P
- alternatively may be labelled ***antigenically***

NB: the remaining volumes cannot be calculated directly and are therefore ***derived*** from the above volumes

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1. Intracellular Volume = TBW - ECF
2. Interstitial Volume = ECF - Plasma Volume
3. Blood Volume = Plasma Volume + RBC Volume
   = 1/(1 - Hct.)

REGULATION OF BODY WATER

• factors include,

1. Diffusion
2. Gibbs-Donnan Equilibrium
3. Osmosis
4. Ion pumps
5. Starling's forces

▪ *Diffusion*

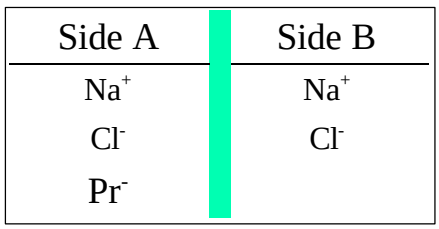
• water crosses all cell membranes freely, except the conducting tubules of the nephron and bladder
• membranes are variably permeable to solutes, depending upon their charge, size and the presence of specific membrane channels
• the effective size of an ion is determined by its ***hydrated radius***, rather than its actual size
• the degree of hydration is determined by the ***charge density*** of the given ion, eg,

a. $^{23}Na^{+} \rightarrow$ HR ~ 0.28 nm

b. $^{39}K^{+} \rightarrow$ HR ~ 0.35 nm

▪ *Gibbs-Donnan Equilibrium*

Def'n: "in the presence of a non-diffusible ion, the diffusible ion species distribute themselves such that at equilibrium their ***concentration ratios*** are equal", viz.



NB: Donnan effect dictates that, $[Na^+]_A.[Cl^-]_A = [Na^+]_B.[Cl^-]_B$

thus, $$\frac{[Na^+]_A}{[Na^+]_B} = \frac{[Cl^-]_B}{[Cl^-]_A}$$

but to maintain ***electroneutrality***, $[Na^+]_B = [Cl^-]_B$

therefore,

$$[Na^+]_A > [Cl^-]_A$$

- the net effects of this distribution are that, on the side of the ***non-diffusible species***, there is,
    a. an increase in the number of osmotically active particles
    b. an increase in the [cations]
    c. a decrease in the [anions]
    d. a ***charge difference*** across the membrane

    NB: → albumin acts as if its MW ~ 37,000, c.f. its actual MW ~ 69,000

- the predicted difference in concentrations between plasma and the interstitial fluid are **~ 5%**
- in reality the measured [Na^+] in the plasma and the ISF are approximately ***equal***
- this occurs as the G-D equilibrium refers to thermodynamic activity, which approximates water concentrations for dilute solutions, and **~ 7%** of the plasma volume is protein
- thus, the actual plasma water [Na^+] is ***higher*** than that measured

■ ***Osmosis***

- at equilibrium, all fluid compartments which allow free water movement across their membranes will be virtually ***isotonic***
- Na^+ and its anions are the major determinants of ECF osmolality
- K^+ and its anions are the major determinants of ICF osmolality
- plasma ***oncotic pressure*** is the effective osmolality which exists across most capillary membranes due to the relative impermeability to proteins

    → average value **~ 25 mmHg**

- maintained by, but effectively opposes, the capillary hydrostatic pressure
- contributed to principally by,
    a. albumin ~ 65%
    b. globulins ~ 15%

■ ***Ion Pumps***

- these maintain the transcellular ion balances
- the presence of non-diffusible species within cells would lead to a net inward flux of water, with subsequent swelling and rupture
- a number of ion pumps, mainly the Na^+-K^+-ATPase, allow cells to maintain isotonicity
- the net effect of this is that cells exist at steady state, away from the lowest energy equilibrium state for the system, further a potential difference exists across the cell membrane
- the loss of function of these pumps, eg. hypoxia, leads to cellular oedema

■ ***Starling's Forces***

• this equation predicts the net flux of water across a membrane,

$$J_v = K_f.[(P_c-P_i) - \sigma(\pi_c-\pi_i)]$$

where, J_v = net water flux
K_f = the filtration coefficient
$P_{c,i}$ = hydrostatic pressures
$\pi_{c,i}$ = oncotic pressures
σ = Staverman reflection coefficient

• the ***Staverman reflection coefficient*** is a measure of capillary permeability to protein,

$\sigma = 1 \rightarrow$ completely impermeable

• most studies assume a value of 1, ignore K_f, and simply refer to the net balance of forces which determine flow across the capillary
• this is invariably an over-simplification, quoted figures for lung varying from,

i. lung capillary → 2 to 12 mmHg
ii. lung interstitial → -7 to 1 mmHg
iii. plasma oncotic → 20 to 35 mmHg
iv. interstitial → 5 to 18 mmHg

NB: → this gives a total range of net driving pressure from **-29 to 17** mmHg

• the lung interstitial pressures are probably slightly negative
• interstitial protein concentrations vary considerably between tissues
• those in the lung are probably ~ 70-80% of plasma (Nunn ~ 50%)
• 99% of the interstitial fluid ***does not*** exist as free fluid but as a ***gel***, mainly composed of hyaluronic acid cross-linked with collagen
• thus, the ISF space can only accommodate small increases in volume before ISF pressure rises

NB: Starling's equation predicts the net movement of fluid across the capillary, it ***does not*** predict what happens to ISF volume

• this will only increase if lymphatic drainage is unable to accommodate the increase in flow
• the ability of the lymphatic system to increase flow also varies with tissue, the lung having the greatest reserve → ~ 20 fold increase
• this increase occurs within the ISF pressure range of ~ 0-4 mmHg
• lymphatics possess the ability to pump fluid from the ISF, partly explaining the negative pressure of some tissue beds

• the high pulmonary ISF protein concentration serves as a safety mechanism
• increases in flow washing out protein, reducing ISF oncotic pressure and the net driving pressure
• this has been supported by experimental work which shows that the capillary/ISF protein ratio returns to "normal" within ~ 3 hours of artificial lowering of COP

• the BBB is unique in that there is normally a total impermeability to protein, as well as a number of ions, and there is no lymphatic system
• the result of this is that variations in COP have little effect in ***cerebral oedema***, however, changes in plasma osmolality may have a large effect
• the BBB ion pumps and the generation of ***idiogenic osmoles*** account for the chronic adaptation of the brain to changes in plasma osmolality

Common Intravenous Solutions[1]

Solution	**Na^+**	**Cl^-**	**K^+**	**Ca^{++}**	**Glu**	**Osm.**	**pH**	**Lact.**	**kJ/l**
D_5W	0	0	0	0	278	253	5	0	840
NaCl 0.9%	150	150	0	0	0	300	5.7	0	0
NaCl 3.0%	513	513	0	0	0	855	5.7	0	0
D_4W / NaCl 0.18%	30	30	0	0	222	282	3.5-5.5	0	672
Hartmans	129	109	5	0	0	274	6.7	28	37.8
Plasmalyte	140	98	5			294	5.5	(27)	84
Haemaccel	145	145	5.1	6.25	0	293	7.3	0	0
NSA-5%	140	125	0	0	0		7	0	?
NSA-20%									?
Mannitol 20%	0	0	0	0	0	1,098	6.2	0	0
Dextran 70	154	154	0	0	0	300	4-7	0	0

[1] values in mmol/l, irrespective of common presentation volume

Plasmalyte:

Na^+	~ 140	Gluconate	~ 23
Cl^-	~ 98	Acetate	~ 27
K^+	~ 5	Osmo	~ 294
Mg^{++}	~ 1.5	pH	~ 5.5
kJ	~ 84		

Water Metabolism

NB: Daily Balance: $\rightarrow$ turnover ~ 2500 ml

a. Intake

i.	drink	~ 1500	ml
ii.	food	~ 700	ml
iii.	metabolism	~ 300	ml

b. Losses

i.	urine	~ 1500	ml
ii.	skin	~ 500	ml
	• insensible losses	~ 400	ml
	• sweat	~ 100	ml
iii.	lungs	~ 400	ml
iv.	faeces	~ 100	ml

- minimum daily intake ~ 500 ml with a "normal" diet
- minimum losses ~ 1500 ml/d
- losses are increased with,

a. increased ambient T

b. hyperthermia ~ 13% per °C

c. decreased relative humidity

d. increased minute ventilation

e. increased MRO_2

Plasma Osmolality

- plasma osmolality is $\equiv^T$ to total body osmolality, as virtually all of TBW is in equilibrium,

$$T_{osm} = \frac{\text{ECF solute + ICF solute}}{\text{TBW}}$$

- exchangeable Na^+ and K^+ and their anions account for most of these solutes
- water balance is the prime determinant of osmolality and the plasma $[Na^+]$

NB: thus, Na^+ balance determines ECFV

Controls of Water Balance

- ***Intake***

- altered by the thirst mechanism
- the hypothalamic centres are closely related to those controlling ADH release

a. Osmotic - δ osmolality ~ 1%

b. Non-osmotic

i. effective ECFV
- arterial baroreceptors
- venous baroreceptors
- angiotensin II
- ADH

ii. electrolytes
- thirst ~ $[Ca^{++}]$
- thirst ~ $1/[K^{+}]$

iii. hyperthermia

iv. hypoxia

v. drugs
- ETOH decreases
- chlorpropamide increases

- ***Losses***

a. ADH - major controlling factor, see below

b. glucocorticoids
- their exact role in water maintenance is uncertain
- in deficiency states, replacement of mineralocorticoid alone is insufficient to restore normal water balance

ADH Secretion Regulation of Osmolality & ECF Volume

• although protection of the ECF is linked to the **Na^+** ***mass***, the ability of water to follow Na^+ reabsorption is dependent on secretion of ADH
• therefore, decreases in plasma volume reflexly increase both ***aldosterone*** and ***ADH***
• ADH, or ***arginine vasopressin***, is an nonapeptide synthesised by discrete neurones in the ***supraoptic*** > ***paraventricular nuclei*** of the hypothalamus
• axons terminate in the ***posterior pituitary*** from where ADH reaches the blood-stream
• synthesised as a large and inactive ***prohormone*** + neurophysin + glycopeptide
• these are stored in granules and split to ADH-neurophysin during passage from the perikaryon to the terminal bulbs, neurophysin also binds oxytocin
• newly synthesised hormone appears in the posterior lobe within ~ 30 mins of a stimulus such as haemorrhage
• mechanism of vesicle release = depolarisation → Ca^{++} influx → ***exocytosis***
• some neurones also terminate in the external zone of the ***median eminence***, from where ADH enters the adenohypophyseal portal circulation and acts as an ***ACTH releasing factor*** (CRF)
• ADH undergoes rapid enzymatic cleavage *in vivo*, mainly in the liver and kidney

→ ***vasopressinase***

• deamination at the 1AA reduces its susceptibility to peptidases and substitution of *d*-Arg for *l*-Arg at the 8AA reduces pressor activity,

→ ***desmopressin*** **DDAVP**

NB: there are two principal physiological mechanisms for release,

1. hyperosmolality
2. hypovolaemia

■ ***Hyperosmolality***

• Verney (1947) showed that a **≤ 2%** increase in osmolality in the hypothalamus produced a sharp antidiuresis on dogs
• current candidates for the ***osmoreceptors*** of the hypothalamus are,

a. the organum vasculosum of the lamina terminalis (OVLT)
b. the subfornical organ (SFO)

• both of which are ***outside*** the blood brain barrier
• the threshold for secretion is **~ 280 mosmol/l**
• individuals vary but below this level ADH is virtually undetectable
• above this level [ADH] rises sharply and ***linearly*** with plasma osmolality
• there is also evidence for a direct functional interaction between neural centers for ***thirst*** and ADH secretion
• drinking decreases ADH release before any change of plasma osmolality

■ ***Volume Depletion***

• haemorrhage, Na^+ depletion, or other acute causes of decreased ECF volume, ***irrespective*** of plasma osmolality, increase release of ADH
• secretion appears to come from a readily releasable "pool" of hormone, which approximates 10-20% of ADH in the pituitary, subsequent release is at a slower rate
• other chronic conditions in which effective circulating volume is reduced are also associated with elevated levels of ADH,

i. CCF
ii. cirrhosis with ascites
iii. hypothyroidism
iv. excessive diuresis
v. adrenal insufficiency

• receptors include the ***baroreceptors*** of left atrium, pulmonary veins, also the carotid sinus and aortic arch
• the afferent pathways are in the vagus and glossopharyngeal nn.
• secretion of ADH is under tonic ***inhibitory*** control of the baroreceptors
• secretion in response to hypoxia, nausea and pain may also be mediated by receptors in the carotid sinus and aortic arch
• ***iso-osmotic*** contraction of the ECF produces little secretion **< 10%** change, after which [ADH] increases rapidly and ***exceeds*** the response due to osmolar stimulation
• levels produced under these circumstances are high enough for ADH to have a direct ***pressor*** effect on vascular smooth muscle

■ ***Other Mediators of ADH Release***

• mechanisms for which there is good evidence for stimulation of release include,

a. angiotensin II - synthesised by brain as well as peripherally
b. dopamine
c. endogenous opioids, pain/"stress"
d. hyperthermia
e. hypoxia
f. nausea
g. drugs - either stimulate or inhibit secretion

Stimulat^n:	Inhibit^n:
tricyclics	ethanol
vincristine, vinblastine	phenytoin
loop diuretics	glucocorticoids
cyclophosphamide	mineralocorticoids
colchicine	
chlorpropamide	

• release is inhibited by ***GABA*** → inhibitory interneurone is GABA'ergic
• ***prostaglandins*** may play a role in both osmotic and volumetric release of ADH

■ ***Renal Effects of ADH***

• after release into the circulation → $t_{\beta½}$ ~ 17 to 35 mins
• removed by enzymatic cleavage and receptor binding in smooth muscle
• smooth m. and hepatic receptors = V_1 receptors and act via phosphoinositol phosphate and Ca^{++}
• V_2 receptors in the kidney act via adenylate cyclase & cAMP
• water reabsorption in the cortical CT and beyond is governed by permeability of the luminal membrane under the influence of ADH:

1. high [ADH] - mass diffusion of water, urine iso-osmotic to medulla
2. low [ADH] - limited diffusion of water, large volume of dilute urine
   - virtually no H_2O reabsorbed after loop of Henle

• achievable osmolality,

a. minimal ~ 50 mosmol/kg
   • as much as 15% of filtered water may appear in the urine (15% of 180 l/d = 27l)
b. maximal ~ 1200-1400 mosmol/kg
   • corresponding to the medullary interstitium

• proposed sequence of events,

a. **V_2 *receptors*** on basolateral membrane activate adenylate cyclase
b. increase in $[cAMP]_i$
c. activated cAMP-dependent protein kinase ± phosphoprotein phosphatase
d. microtubules and microfilaments important in ADH response
e. aggregation of proteins at luminal membrane
f. ? insertion or phosphorylation of membrane protein channels
g. increased permeability of luminal membrane

• ADH in physiological concentration has virtually ***no effect*** on Na^+ transport
• ADH may promote Na^+ and water retention by a reduction in GFR secondary to contraction of afferent arterioles and mesangial cells
• ADH exerts local (-)'ve feedback due to induction of medullary synthesis of ***prostaglandins***, the later opposing ADH induced generation of cAMP
• altered PG synthesis may therefore account for the altered tubular responsiveness seen in various disease states
• eg. hypovolaemic shock associated high output renal failure

- ***Non-Renal ADH Effects***

• volume depletion may produce a high [ADH] with ***direct pressor*** effects on vascular smooth m.
• its effects on the heart are ***indirect*** → reduced coronary flow and reflex alterations in SNS/PNS
• also contracts smooth m. of the GIT and uterus
• increases ***Factor VIII*** concentrations in haemophilia and von Willebrand's disease, therefore may be used as a prophylactic during surgery
• increases ***platelet activity*** in renal failure, post-transfusion etc
• may play a role in regulation of ***ICP*** by altering the permeability of the arachnoid villi to water
• possible role as a ***neurotransmitter***, eg. CRF in the pituitary

DDAVP Desmopressin

• chemically modified ADH = **1-deamino-8-*d*-arginine vasopressin**,

a. deamination results in resistance to plasma and hepatic proteases
   • resultant long plasma half life $t_{½\beta}$ ~ 76 minutes

b. *d*-arginine greatly reduces vasoactive properties

• the duration of drug effect ~ 8 to 20 hrs
• intranasal bioavailability ~ 10%
• the dose for ***central DI*** is 10-40 µg/d nasally, or $1/10^{th}$ this amount IM
• for children the dose is ~ ¼ to ½ this amount

• for the ***procoagulant*** effects, an infusion of 0.4 µg/kg in 100 ml of NaCl, over 20 mins is usually sufficient to raise VIII:C, VIIIR:Ag and decrease the SBT
• further doses may be given 12 hrly as required
• indicated for haemophilia A and von Willebrand's d. but ***not*** for type II von Willebrand's disease, as platelet aggregation may be induced

Summary of ADH Effects		
Receptor Subtype	Second Messenger	Physiological Effects
V_1	IP_3 / Ca^{++}	• vasoconstriction especially coronary, mesenteric & skin • glycogenolysis
V_2	cAMP protein kinase ± phosphoprotein phosphatase	• increased DT/CD H_2O permeability • increased renal PGE_2 (opposes above) • increased PRA • tachycardia • facial flushing • lowered BP • increased PGI_2 • increased fibrinolytic activity (tPA) • increased Factor VIII related antigen • increased Factor VIII coagulant activity • increased von Willebrand factor multimers
V_3	??	• baroreceptor modulation • ? behavioural effects

- ***Osmolar Clearance***

Def'n: is the ***volume*** of urine necessary to excrete the osmotic load in a urine which is ***iso-osmolar*** with plasma, viz.

$$C_{osm} = \frac{U_{osm} \times V_U}{P_{osm}}$$

- ***Free Water Clearance***

Def'n: C_{FW} is equal to the urine volume minus the osmolar clearance, viz.

$$C_{FW} = V_U - \frac{U_{osm} \times V_U}{P_{osm}}$$

~ -1.9 to 21 l/d

- this may be inaccurate with a highly concentrated urine, as the majority of solute may be ***urea***
- urea is freely permeable and does not affect ***tonicity***, nor the distribution of body water
- therefore, we are really interested in the electrolyte free clearance of water

- ***Electrolyte Free Water Clearance***

$$C_{EFW} = V_U - \frac{U_{Na+K} \times V_U}{P_{Na+K}}$$

- urea is ignored in this equation, although it may increase urine volume as an obligatory solute
- this better predicts water balance and its effects on plasma [Na^+]

SODIUM

i. alkaline elemental metal
ii. atomic number = 11
iii. molecular weight ~ 23
iv. monovalent cation = the principal ***extracellular cation***

- total body content **~ 58 mmol/kg**,
  a. exchangeable ~ 70%
  b. ECF ~ 50%
  c. ICF ~ 5-10%
  d. bone ~ 40-45%

- concentration ranges vary between tissues,
  a. plasma ~ 132-146 mmol/l
  b. ICF ~ 3-20 mmol/l
     - muscle ~ 3-4 mmol/l
     - rbc ~ 20 mmol/l

- daily requirements ~ 2 mmol/kg/d (150 mmol/d)
- minimum requirement ~ 5-10 mmol/d

Control of Sodium Balance

1. **intake** - essentially unregulated in humans
2. **losses**
   i. ***renal***
      - GFR → glomerulo-tubular balance
      - aldosterone - angiotensin II
        - hyperkalaemia
        - ACTH
        ? hyponatraemia
      - ANF ∝ atrial stretch, CVP
   ii. ***GIT***
      - normal losses ~ 5-10 mmol/d
      - can markedly increase in disease states, eg. the secretory diarrhoeas (cholera)
   iii. ***sweat*** - insensible fluid losses are pure H_2O ~ 400 ml/d
      - $[Na^+]_{sw}$ is directly proportional to rate

NB: control of Na^+ excretion is via two variables, ***GFR*** and ***sodium reabsorption***, the later being quantitatively more important

Regulation of ECF Volume

NB: as Na^+ is actively pumped from cells and the intracellular $[Na^+]$ is low, so the total extracellular fluid volume depends primarily upon the ***mass*** of extracellular Na^+, which in turn correlates directly with the total body Na^+

- there are Na^+-sensitive receptors in the body, (adrenal cortex, macula densa and the brain), but these are less important in Na^+ regulation as these respond to the $[Na^+]$, not the total mass of Na^+ in the body
- total ECF volume is not monitored directly, its components, the ***intravascular*** and ***interstitial*** volumes are
- as Na^+ is not secreted by the tubules,

$$Na^+ \text{ excretion} = (GFR \times [Na^+]_{pl}) - Na^+ \text{ reabsorbed}$$

- although $[Na^+]_{pl}$ may alter significantly in disease states, in most physiological states it is relatively constant
- therefore, control of excretion is via two variables, ***GFR*** and ***Sodium Reabsorption***, the later being quantitatively more important

Control of GFR (see renal physiology notes)

Direct Determinants of GFR

$$GFR = K_F \times (P_{GC} - P_{BC} - \pi_{GC})$$

K_F [1]	• contraction/relaxation of mesangial cells alters SA & K_F → proportional changes in GFR	
P_{GC}	• ↑ renal a. pressure • ↓ afferent aa. resistance • ↑ efferent aa. resistance	↑ GFR
P_{BC}	• ↑ intratubular pressure	↓ GFR
π_{GC}	• ↑ plasma oncotic pressure → sets initial π • ↓ total renal plasma flow → determines rate of rise of π	↓ GFR

[1] effects of changes in K_F may be greatly reduced where NFP reaches ***filtration pressure equilibrium***, as GFR results from only a part of available SA anyway

Control of Tubular Sodium Reabsorption

▪ *Glomerulotubular Balance GTB*

• this is one reason for the lesser importance of alterations of the filtered load of Na^+
• the absolute reabsorption of solute and water in the PTs, and probably the loops of Henle and DTs, varies ***directly*** with the GFR
• that is, the percentage of filtrate reabsorbed proximally remains at **~ 65%**
• this requires no external neural or hormonal input, occurring in the isolated kidney

NB: the effect is to blunt large changes in Na^+ excretion secondary to changes in GFR, though, GFR is still does affect Na^+ excretion, as,

i. the absolute quantity of Na^+ leaving the PT does alter
ii. GTB is not perfect, reabsorption ***does*** change with GFR

• therefore,

1. ***autoregulation*** prevents large changes of GFR with δBP
2. ***GTB*** prevents large changes in Na^+ excretion with δGFR

NB: 2 lines of defence against profound haemodynamic alterations of Na^+ excretion

▪ *Aldosterone*

• this is the single most important controller of Na^+ balance
• produced in the adrenal cortex, in the ***zona glomerulosa*** and stimulates Na^+ reabsorption in the late DTs and the CTs (probably not in the medulla)
• proximal to this site of action, **≥ 90%** of the filtered Na^+ has already been reabsorbed
• therefore, the total quantity of Na^+ reabsorption dependent on aldosterone is ~ 2% of the filtered load, viz.

$$\begin{aligned} 2\% \text{ of } (GFR \times [Na^+]_{pl}) &= (0.02)(180 \text{ l/d})(145 \text{ mmol/l}) \\ &= 522 \text{ mmol/d} \\ &\sim \mathbf{30 \text{ g NaCl/d}} \end{aligned}$$

• aldosterone also stimulates Na^+ transport in other epithelia,

i. sweat glands
ii. salivary glands
iii. the intestine

• similarly, the effect is to reduce the luminal $[Na^+]$
• like other steroids, aldosterone combines with a ***cytosolic receptor***, migrates to nucleus, increases synthesis of specific ***mRNA*** with subsequent ***protein synthesis***
• the mode of action of this protein may involve,

i. ? activation of luminal Na^+-channels
ii. increased $[Na^+]_{ICF}$
iii. a 2° increased activity of basolateral Na^+/K^+-ATPase

• there is also a direct effect on activity of Na^+/K^+-pump which occurs over a longer time span
• this effect takes ~ 45 mins, due to the requirement for protein synthesis
• therefore, decreases in Na^+ excretion occurring in minutes, eg. orthostatic, are ***not*** due to aldosterone
• four direct inputs to the adrenal regulate ***aldosterone*** secretion,

1. angiotensin II → most important factor
2. ↑ plasma $[K^+]$ → stimulation
3. ACTH → permissive
4. ↑ plasma $[Na^+]$ → inhibition

• the effects of $[Na^+]$ are minor in humans, $[K^+]$ being far more important
• ACTH stimulates release only when present in high concentrations
• more importantly it is ***permissive*** for other factors within the physiological range

NB: however, ACTH secretion is not keyed to Na^+ balance

• other possible factors in release include β-endorphin, β-lipotropin and dopamine
• the former two are secreted with ACTH as products of POMC

• ***angiotensin II*** is by far the most important controller of aldosterone secretion in Na^+ balance
• accordingly, aldosterone secretion is largely determined by the release of ***renin***, which is determined by,

1. intrarenal baroreceptors ↑
2. the macula densa ↑
3. the renal sympathetic NS ↑
4. angiotensin II ↓

Other Factors Influencing Tubular Na^+ Handling

▪ ***Atrial Natriuretic Factor***

- 26 AA peptide hormone (sources range 24-28)
- synthesised from a 126 AA prohormone in atrial secretory granules
- released in response to atrial stretch / ***wall tension***
- plasma half life, $t_{½\beta}$ ~ 3 mins
- clearance ~ 34 ml/kg/min
- maximal natriuresis is ***less*** than that seen with frusemide, however ANF is ~ 100 times as potent
- receptors are concentrated in ***cortical*** glomeruli
- the postulated second messenger is **cGMP**
- ? there is no direct effect upon Na^+ transport, or the Na^+/K^+-ATPase
- neither amiloride nor prostaglandin inhibitors have an effect upon its actions
- ANF effects include,

a.	systemic vasodilatation	- transient hypotension IVI - predominantly venodilatation - decreases cardiac preload
b.	increases ***GFR/RBF ratio***	- efferent vasoconstriction - afferent vasodilatation - increases filtration fraction - increases salt delivery to DT
c.	increases K_F	
d.	increases MBF/CBF	
e.	decreases plasma renin	- direct & indirect
f.	decreases plasma aldosterone	- direct & indirect
g.	increases urinary excretion of	- Na^+, Cl^-, K^+ - Ca^{++}, $HPO_4^{=}$, Mg^{++}
h.	increases urine volume	

▪ ***Effects of Angiotensin II***

a.	vascular smooth muscle	- increased tone
b.	CNS/PNS	- facilitation of ***sympathetic activity***
c.	adrenal cortex	- increased secretion of ***aldosterone***
d.	kidneys	
	i. aa. constriction decreasing GFR but increasing GRF/RPF ratio	
	ii. direct tubular effect increasing Na^+ reabsorption	
e.	brain	- stimulates secretion of ADH - stimulates thirst

NB: all of which favour ***retention*** of salt and water and elevation of BP

Additional Factors

1. ***intrarenal physical factors***
   - the interstitial hydraulic pressure, while favouring the final ***bulk flow*** of reabsorbed solute & water into the capillaries, also produces ***back-diffusion*** and when elevated is associated with a reduced overall level of fluid reabsorption
   - the two main factors governing this pressure are the peritubular hydraulic and oncotic pressures
   - the peritubular oncotic pressure varies directly with the filtration fraction, the GFR/RPF ratio
   - this ratio increases as most mediators of renal vessel constriction affect both afferent and efferent aa.
   - these physical factors affect reabsorption only in the PT where large diffusional fluxes occur, and are probably only important in large alterations of ECF volume
2. ***distribution of RBF***
   - nephrons are not a homogeneous population, redistribution of flow to postulated "high-reabsorption" nephrons would affect Na^+ balance
3. direct tubular effects of ***catecholamines***
   - renal SNS tone and circulating adrenaline have direct action on tubular cells enhancing Na^+ reabsorption, definitely in the PT, ? others
4. direct tubular effects of ***angiotensin II***
   - same c.f. CA's, in addition to stimulation of aldosterone and its intrarenal vascular effects, has direct effect on tubular cells enhancing reabsorption
   - also like the CA's, the effect is seen in the PT but ? other segments

e. other ***humoral agents***
   - cortisol, oestrogen, growth hormone, and insulin ***enhance*** reabsorption
   - parathyroid hormone, progesterone, and glucagon ***decrease*** reabsorption

Summary of Sodium Regulation

- control of Na^+ excretion is via GFR and Na^+ reabsorption
- the later is controlled principally by the renin-angiotensin-aldosterone system but also by the SNS
- SNS activity is important in,
   i. control of [aldosterone] via renin-angiotensin
   ii. determination of intrarenal vascular factors & GFR
   iii. direct action on tubular function

- despite these functions, the denervated kidney maintains Na^+ balance
- reflexes that control these inputs are BP-regulating and initiated most often by changes in arterial ± venous pressure
- CVS function depends on plasma volume, which is a component of ECF volume, the later reflecting the mass of Na^+ in the body
- these reflex systems maintain Na^+ balance within 2% in normal individuals despite marked variations in intake and loss

Hyponatraemias

Def'n: plasma Na^+ **< 136 mmol/l**

- determined by TBW, $TBNa^+$, and TBK^+
- ie. this is a ***whole body*** water derangement
- more commonly ***water excess***, less often Na^+ deficit

1. ***iso-osmotic*** (factitious)
   - i. hyperlipidaemia - usually only when plasma TG's > 50 mmol/l
   - ii. hyperproteinaemia - multiple myeloma
   - iii. IVT arm sample

   - plasma water **~ 93%** of plasma volume
   - therefore increases in ***plasma solids*** will lower $[Na^+]_{pl}$ factitiously
   - ***osmolality*** is unaffected → ***no*** R_X required
   - actual $[Na^+]$ = $[Na^+]_{pl}$ x (measured osmolality)/(calculated osmolality)
2. ***hyper-osmotic*** → ↑ ***osmolar gap***
   - i. hyperglycaemia ↓ $[Na^+]$ ~ 1 mmol / 3 mmol ↑ BSL
   - ii. mannitol, glycine, glycerol, urea
   - iii. other solutes not entering cells
     - water is drawn into the ECF from the ICF
     - total body Na^+ may be normal or depleted
3. ***hypo-osmotic***
   - i. ***hypovolaemic*** → persistent ADH effect
     - extrarenal losses - GIT, vomiting / diarrhoea
       - 3^{rd} space
     - renal losses - Addison's disease
       - diuretics, osmotic diuresis
       - salt losing nephritis
       - hypo-aldosteronism
       - heparin (aldosterone suppression)
     - fluid replacement deficient in Na^+
   - ii. ***slightly hypervolaemic*** → fluid excess ~ 3-4 l, ***no oedema***
     - SIADH, reset osmostat
     - severe hypothyroidism
     - psychogenic polydipsia
     - inappropriate IV fluids, eg. CRF
   - iii. ***hypervolaemic*** → fluid excess > ~ 10 l, with oedema
     - CCF[§]
     - nephrotic syndrome[§]
     - cirrhosis[§]
     - renal failure

     [§]2° hyperaldosterone states

- ***Diagnosis***

a. physical examination
   - oedema
   - volume status

b. plasma biochemistry
   - U&E's
   - glucose
   - osmolality (measured & calc)

c. urinary $[Na^+]$

i. $[Na^+]_U < 20$ mmol/l
   - extrarenal losses with normal renal function
   - $[Cl^-]_U$ usually parallels $[Na^+]_U$ except in ***RTA*** and ***hypovolaemia***, where HCO_3^- losses are high and $[Cl^-]_U$ low
   - 2° hyperaldosteronism, with a low effective circulating blood volume

ii. $[Na^+]_U > 20$ mmol/l
   - states where there is renal wasting of sodium
   - Addison's, diuretics, ARF, CRF, SIADH

d. water challenge
   - giving a patient a water load will differentiate between,

i. SIADH $\rightarrow$ reducing $[Na^+]$ further

ii. reset osmostat $\rightarrow$ being able to excrete the load

   - obviously if hyponatraemia is severe this is contraindicated

e. saline infusion
   - will normalise those patients shedding Na^+ rich fluids and being replaced with low Na^+ fluids

Clinical Manifestations

• these depend upon both the ***extent*** of the derangement and the ***aetiology*** to a greater extent than the absolute $[Na^+]$

• isotonic/factitious hyponatraemias cause little problem, eg. ***glycine 1.5%*** absorption during TURPS, etc.

• the use of agents such as glycine, which do not alter ***tonicity***, avoids the problems associated with water shifts across membranes

• however, they ***do not*** prevent problems associated with a low $[Na^+]_{ECF}$

a. ***CNS*** - symptoms and signs are more severe with rapid falls in $[Na^+]_{pl}$ > 10% change

i. confusion

ii. decreased conscious level

iii. coma/convulsions ≤ 120 mmol/l $[Na^+]_{pl}$
≤ 50% mortality

- NB: mortality ~ 50% where $[Na^+]_{pl}$ falls below 120 mmol/l within 24 hours

b. ***CVS***

i. increased QRS duration @ $[Na^+]_{pl}$ < 115 mmol/l

ii. ST segment elevation @ $[Na^+]_{pl}$ < 115 mmol/l

iii. VT/VF @ $[Na^+]_{pl}$ < 110 mmol/l

iv. increase BP/HR with volume overload (unreliable)

c. ***neuromuscular***

i. muscle cramps

ii. muscle fasciculations

iii. neuromuscular irritability

- ***Treatment - Mild***

a. discontinuation of aetiological agent

b. fluid restriction - hypervolaemic (SIADH, reset osmostat)
→ ≤ 15 ml/kg/d

c. high protein, low CHO/fat diet reduces H_2O intake

d. normal saline - hypovolaemic
- replacement at 0.3x*

e. demethychlortetracycline - produces "nephrogenic DI"
→ - blocks renal ADH effects

f. underlying pathology

- ***Treatment - Severe***

a. ABC

b. IVT - initial ECF resuscitation should be with 0.9% NaCl
- Na^+ deficit calculated against TBW, viz.

$$\delta[Na^+]_{TBW} = \left(\frac{140 - [Na^+]_{PL}}{140}\right) \times Weight \times 0.6$$

- although sodium is only in the ECF, ***total body osmolality*** must be corrected (except - * below)

c. ***hypertonic NaCl*** - 3.0-5.0%
- the aim is to raise the $[Na^+]_{PL}$ ~ 2 mmol/l/hr
- rates greater than this are associated with ***central pontine myelinolysis***
- demyelination is mostly seen in ***alcoholics***
→ quadriplegia, bulbar & pseudobulbar signs
- may use 8.4% $NaHCO_3$ in an emergency
- **strong NaCl** 29.2% (5 mmol/ml) may be used to bring plasma Na^+ up to 120-130 mmol/l range if,

i. rapid development of severe hyponatraemia & CNS signs

ii. failure of above therapy

iii. complicated by fluid overload (CRF)

d. loop diuretics
- help prevent fluid overload & pulmonary oedema
- may exacerbate hyponatraemia
- some suggest mannitol is better

e. dialysis

Hypernatraemias

NB: these are always associated with ***increased osmolality***

- ***Classification***

a. ***hypovolaemic*** → H_2O loss > Na^+

- most fluid losses have a [Na^+] lower than plasma
- therefore there is a net loss of water greater than Na^+

i.	renal	- diuretics - glycosuria - ARF/CRF - partial obstruction
ii.	GIT losses	- diarrhoea, vomiting, fistulae - 3rd space losses
iii.	respiratory losses	- IPPV with dry gases
iv.	skin losses	- fever - ambient temperature - thyrotoxicosis

- (i) $[Na^+]_U$ increases / U_{Osm} decreases

  (ii-iv) $[Na^+]_U$ decreases / U_{Osm} increases

  ie., with extrarenal losses there is renal compensation, the net effect is a decrease in **ICF > ECF**

b. ***iso → hypovolaemic***

- these result from pure water loss
- 67% of TBW resides in the ICF
- dehydration increases plasma osmotic pressure, tending to maintain intravascular volume
- thus these patients do not become ***hypotensive*** until $[Na^+]_{PL} \geq 160\text{-}170$ mmol/l
- therefore, this group are sometimes called "isovolaemic"

i. inadequate water replacement
- iatrogenic
- inadequate IVT
- unconsciousness

ii. reset osmostat

iii. central diabetes insipidus
- head injuries
- post-surgical

iv. nephrogenic DI
- 1° = congenital renal resistance to ADH
- 2° = hypokalaemia
  hypercalcaemia
  lithium
  methoxyflurane

- produces a mild-moderate decrease in ***both*** ECF & ICF

c. ***iso → hypervolaemic*** → Na^+ gain > H_2O gain

- usually not sufficient H_2O gain to produce oedema

i. iatrogenic = the major cause
- $NaHCO_3$
- feeding formulae, TPN
- drinking sea water
- exogenous steroids

ii. mineralocorticoid excess
- Conn's syndrome
- Cushing's disease / syndrome

- the later group usually have 1-3 l of excess TBW
- plasma Na^+ is usually normal to high, with associated ***hypokalaemic alkalosis***
- the increased plasma osmolality increases ADH secretion, which in turn increases ECFV, with subsequent ***renal escape*** (see over)
- oedema in this group is therefore ***rare***
- ECFV is generally increased while ICFV decreases

- ***Secondary Hyperaldosteronism***

• characterised by persistent Na^+ retaining reflexes, (decreased GFR, increased aldosterone, etc.), despite progressive overexpansion of the ECF and the development of ***oedema***
• increased aldosterone is secondary to elevated ***renin*** via reflex control
• eg. cirrhosis of the liver, congestive cardiac failure, nephrotic syndrome

- ***Primary Hyperaldosteronism***

• Na^+ retention does occur initially but after several days ***renal escape*** occurs and Na^+ balance returns to normal
• elevated ECF volume initiates Na^+ losing responses $\rightarrow$ increased ANF, increased GFR etc.
• the net effect of which is to deliver an increased load of Na^+ to the collecting ducts, beyond their reabsorptive capability, thereby increasing excretion

NB: that is, persistent Na^+ retention ***cannot*** be initiated by an abnormality of only one of the pathways controlling balance

- ***Diagnosis***

a. history & examination
b. plasma biochemistry
c. urinary [Na^+] & urinary osmolality
d. water deprivation challenge
e. administration of ***desmopressin***

- ***Clinical Manifestations***

NB: as for hyponatraemia, these depend more upon the ***rate of change***, rather than the absolute change

a. **CNS**

i.	confusion	- membrane irritability - brain shrinkage
ii.	decreased LOC	- haemorrhage, venous thrombosis - spasticity, convulsions
iii.	***coma***	- generally only seen **$[Na^+]_{PL} \geq$ 160 mmol/l**
	• acute mortality	- children ~ 40% - adults ~ 70%
	• chronic mortality	- children ~ 10% - adults ~ 60%

b. **CVS**

i. decreased contractility $\propto [Ca^{++}]/[Na^{+}]^2$

ii. CCF $\propto$ volume overload

c. other
- loss of weight
- increased plasma Na^+
- increased serum osmolality
- thirst

- ***Treatment - Severe***

a. ABC

b. Hartman's solution
- slightly hypo-osmolar ~ 260 mosmol/l
- resuscitation if hypotensive

c. 0.45% saline
- use for replacement of H_20/Na^+ deficit
- aim to replace deficit in 24-48 hrs
~ 2.0 mmol/l/hr rate of reduction

$$H_2O_{(deficit)} \approx \left(\frac{[Na^+]_{PL} - 140}{140} \right) \times Weight \times 0.6$$

d. diuretics - for Na^+ excess

e. dialysis - for Na^+ excess

f. 5% dextrose - for H_2O losses in Na^+ excess

g. cease aetiological drugs

h. decrease Na^+ intake

- ***Treatment - Mild***

a. cease/decrease Na^+ intake

b. cease aetiological drugs

c. IVT - 5% dextrose, dextrose/saline, 0.45% saline

d. DDAVP - for central DI

Osmolar Gap

Def'n: = the difference between the measured and calculated osmolality
≤ 10 mmol/l normally, but may be up to 24 mmol/l

Calculated Osmolality ~ 1.86 x ($[Na^+]$ + $[K^+]$) + [urea] + [glu] mmol/l
~ **272-283 mmol/l** normal range

Measured Osmolality = osmometer freezing point depression
~ 0.001865°C / mmol
~ 285-295 mmol/l normal range

NB: some suggest using a value of 2 x $[Na^+]$, as the ***osmotic coefficient*** of 0.93 and the percentage of plasma water ~ 93% cancel out

- thus, hyperosmolar states may exist despite a normal or low $[Na^+]$
- OG increases due to an increase in ***unmeasured*** osmotically active particles,

a. alcohols - ethanol, methanol
- mannitol
- sorbitol, propylene glycol

b. hyperlipidaemia

c. hyperproteinaemia - multiple myeloma

d. glycine

- these particles fall into one of two groups,

a. ***impermeate*** solutes → hypertonic state - eg., mannitol

b. ***permeate*** solutes → isotonic states - eg., urea

- acute changes are more important than chronic

NB: ***hyperosmolality*** *per se* may decrease ***insulin*** release, therefore raising the BSL and establishing a vicious cycle

- thus, some patients with ***non-ketotic hyperosmolar coma*** may not require insulin once the plasma glucose is normalised
- with substances which affect ***tonicity***, eg. mannitol,

a. the reduction in ICFV may result in cellular shrinkage, with confusion and coma

b. reciprocal expansion of the ECFV may result in CCF

- providing renal function is normal, the ECFV may also decreased due to the subsequent ***osmotic diuresis***

POTASSIUM

i. alkaline elemental metal
ii. atomic number = 19
iii. molecular weight ~ 39
iv. monovalent cation = the principal ***intracellular cation***

- total body content **~ 55 mmol/kg**, (3,850 mmol/70kg), distributed as follows,

a. exchangeable ~ 90%
b. ICF ~ 98%
c. ECF ~ 2%
d. bone & brain ~ 10%

- daily requirement ~ 0.5-1.5 mmol/kg/d (35-105 mmol/d/70kg)
- concentration ranges vary between tissues,

a. plasma ~ 3.2-4.8 mmol/l (highly variable)
~ linear, semi-log relationship to TBK^+
b. ICF ~ 150 mmol/l
c. gastric secretion ~ 10 mmol/l
d. sweat ~ 10 mmol/l
e. SI, bile & pancreatic ~ 5 mmol/l
f. diarrhoea ~ 40 mmol/l

- ***Daily Balance***

a. ***intake*** ~ 70-100 mmol/d
   - GIT absorption passive down to luminal $[K^+]$ ~ 5-6 mmol/l
   - the majority of ingested K^+ is therefore absorbed

b. ***losses***~ 0.7 mmol/kg/day obligatory
   i. renal ~ 60-90 mmol/d
      - GFR → ~ 720 mmol/day
      - virtually all K^+ is reabsorbed by distal tubule
      - ***secretion*** along late DT & CT → 5-15% of filtered load
   ii. faeces ~ 10-20 mmol/d
      - this can increase greatly with diarrhoea or other SI losses
      - usual $[K^+]$ ~ 30 mmol/l
      - secretory lesions may also increase losses

Assessment of Potassium Status

a. **plasma [K^+]**
- difficult to assess, as ECF is only ~ 2% of body mass
- however, if $[K^+]_{PL}$ is low and the pH is normal, there is a substantial total body deficit of K^+
- a $[K^+]_{PL}$ < 3.0 mmol/l usually represents a total deficit > 200-300 mmol/70kg
- hyperkalaemia may, or may not represent an excess body K^+
- $[K^+]_{PL}$ is most important in the short term due to the effects of K^+ on transmembrane potentials

b. **radioactive isotope dilution** $^{42}K^+$
- requires 24 hours distribution and several inaccuracies

c. **urinary [K^+]**
- not very useful due to the limited ability of the kidney to conserve potassium
- a $[K^+]_U$ > 40 mmol/l is suggestive of ***hyperaldosteronism***

d. **ICF [K^+]**
- RBC, WBC and muscle
- subject to artefacts from preparation
- only really useful for research purposes

e. **ECG** - useful for monitoring acute changes only

Regulation of ECF Potassium Concentration

- ~ 98% of total body K^+ is ***intracellular*** due to the action of the membrane bound Na^+/K^+-ATPase
- thus, the ECF $[K^+]$ is a function of 2 variables,

a. total body K^+

b. ECF/ICF distribution

- due to relatively small extracellular component, even small shifts in internal balance can markedly alter the extracellular $[K^+]$
- such shifts are under physiological control, particularly in ***muscle & liver***, and these offset alterations of extracellular $[K^+]$

- major factors in this control are,

1. ***adrenaline***
   - results in a net movement of K^+ into cells
   - mediated by β_2-adrenergic receptors
   - predominantly ***muscle & liver***
   - important during exercise and major trauma
2. ***insulin***
   - at physiological concentration, insulin exerts a tonic permissive effect
   - promotes entry into muscle, liver and other tissues
   - more importantly, elevated plasma [K^+] stimulates insulin release, promoting its own entry into cells
3. ***glucagon***
   - counteracts the effects of insulin tending to raise the plasma K^+
   - however, also increases K^+ secretion in the late DT & CT
4. ***aldosterone***
   - the main site of action is the DT of the nephron
   - increases secretion, ? independent of Na^+
   - facilitates net movement of K^+ into cells, esp. with chronic elevated total body K^+
   - this is independent of renal handling of K^+

NB: other factors that affect the balance of internal K^+ are not linked to homeostasis of the internal environment but do affect K^+ significantly, of these ***plasma*** **[H^+]** is the most important

Potential Control Mechanisms

1. acid-base status
2. Na^+/K^+-ATP'ase
3. Gibbs-Donnan effect
4. non-absorbable anions in the urine
5. diuretics
6. ECF volume & its effects on urine output
7. intestinal secretion

- ***Functions***

a. ***total body osmolality***
- total body osmolality is related to the total exchangeable Na^+ & K^+ and TBW
- changes in either total body Na^+_E or K^+_E may result in changes in plasma osmolality, viz.

$$[Na^+]_{pl} \sim \frac{Na^+_E + K^+_E}{TBW}$$

b. ***resting membrane potentials***
- the $[K^+]_{ECF}$ is closely regulated due to the primary importance of K^+ in neuromuscular excitability
- the resting membrane potential being predominantly determined as follows

$$E_M = -61.5 \log \frac{[K^+]_o}{[K^+]_i}$$

thus,

i. increasing $[K^+]_o \rightarrow$ decreases E_m

ii. decreasing $[K^+]_o \rightarrow$ increases E_m
- changes in ICF $[K^+]$ having only a small effect
- acute changes having a greater effect than chronic, as with the latter both ECF & ICF levels are likely to move in the same direction

c. influences action potentials in ***excitable tissues***

i. neural

ii. cardiac

iii. smooth & skeletal muscle

d. intracellular osmotic pressure and electroneutrality

e. protein synthesis ~ 1 mmol/g of protein intake

Basic Renal Mechanisms

• K^+ is freely filterable at the glomerulus, though, the urine [K^+] may be slightly ***less*** than plasma due to a ***Donnan effect***
• final urinary [K^+] represents only **~ 10-15%** of the filtered fraction
• therefore, tubular reabsorption predominates, but it can be demonstrated under certain conditions that the tubules actively ***secrete*** K^+
• K^+ handling shows heterogeneity between short & long looped nephrons
• ~ 50% the filtered mass is reabsorbed in the convoluted PT
• this is primarily a passive process, driven by the electrochemical gradient created by water reabsorption but also by ***solvent drag***
• in the pars recta of the PT and DLH, K^+ ***secretion*** occurs primarily by diffusion due to the high interstitial $[K^+]_i$ in the medulla
• in the ALH, passive reabsorption is again the dominant process
• this is so effective in short-looped nephrons that the amount of K^+ entering the DT is only **~ 10%** of filtered mass
• therefore, in short-looped nephrons, the PT reabsorbs 50% and the ALH another 40% ***plus*** the mass secreted into the pars recta and DLH
• long-looped nephrons also show reabsorption in the ALH but the quantity is unknown, certainly < 40%
• the early DT plays little if any role in K^+ handling

> ***NB:*** the ***late DT*** and ***cortical CT*** are able to both ***reabsorb*** and ***secrete*** K^+, both processes being ***active*** (see below)

• the medullary CT usually manifests net reabsorption, this K^+ providing the high $[K^+]_i$ driving diffusion into the straight PT and DLH
• therefore, there is a recycling of K^+ from distal to proximal tubular segments analagous to that described for ***urea***

Important Generalisations

• the transport processes in the PT and loop are relatively unchanged by increases or decreases in total body K^+
• thus, the total mass of K^+ delivered to the DT is always a small fraction of the filtered mass
• physiological regulation of K^+ excretion is achieved mainly by altering K^+ transport in the DT and cortical CT and the major process regulated in these tubules is the rate of K^+ ***secretion***
• the effects on K^+ excretion mediated by the DT and cortical CT are so great that the effects of changes in the filtered load (GFR x $[K^+]_{pl}$) may be ignored

Exceptions

• under certain conditions, reabsorption in the PT and ALH may be decreased and the delivery of a large quantity of K^+ to the distal site may overwhelm reabsorptive processes, these include,

1. osmotic diuretics
2. loop diuretics
3. uncontrolled diabetes etc.

■ ***Mechanism of Distal Potassium Secretion***

• the critical event is the ***active*** entry of K^+ from the interstitium, via the basolateral membrane Na^+/K^+-ATPase, providing a high intracellular $[K^+]$
• backward diffusion is far less than diffusion into the lumen due to the low gK^+ of the basolateral membrane (see Renal Notes)
• the concentration gradient is opposed by the luminal membrane potential, E_L ~ 30 mV, cell (-)'ve, however, the overall δ[EC] favours secretion
• in addition to basolateral gK^+ being lower, the E_{BL} ~ 80 mV cell (-)'ve, therefore, K^+ pumped into cell favours net secretion
• the high luminal gK^+ is due to the presence of specific **K^+-*channels***
• the presence of these channels accounts for DT secretion, c.f. PT which also has a high $[K^+]$ but low luminal gK^+ and an unfavourable electrical gradient
• the ability of these segments to manifest reabsorption relies on the presence of an ***active luminal pump***, (probably cotransport with Cl^-)
• this pump is always operating, but at a low rate, and therefore opposes secretion, thus, when the activity of the basolateral pump is reduced, the tubule may show net reabsorption due to the unopposed action of the luminal pump
• this luminal pump may also be physiologically regulated, but this is far less significant than regulation of the basolateral Na^+/K^+-ATPase

NB: the fundamental step in secretion is the high intracellular $[K^+]$ created by the basolateral pump;
passive luminal diffusion depends on,

i. the opposing luminal E_M
ii. luminal membrane gK^+
iii. luminal $[K^+]$ gradient

■ ***Homeostatic Control Of Distal Secretion***

• cells of the ***adrenal cortex*** are sensitive to ?extracellular $[K^+]$, more likely their internal $[K^+]$
• increases in $[K^+]$ increase the secretion of ***aldosterone*** which acts on the distal segments by,

a. increasing the activity of the basolateral Na^+/K^+-pump
b. increasing the luminal permeability to K^+

• the former of these effects is coincident with aldosterone's action enhancing Na^+ reabsorption in the same segments
• the increased K^+ secretion induced by these changes occurs quite rapidly
• if plasma $[K^+]$ remains high for several days, potassium ***adaptation*** occurs and the ability of the distal segments to secrete K^+ is markedly increased
• mainly as a result of an increased number of basal pumps (? & luminal channels)
• low plasma $[K^+]$ has the directly opposite effects

NB: K^+ secretion is not the only factor governed by aldosterone secretion,
Na^+ and H^+ also being influenced by aldosterone

■ ***Other Factors Influencing Potassium Homeostasis***

- K^+ balance is affected by a large number of factors not designed to maintain homeostasis
- most important are the plasma $[H^+]$ and altered renal Na^+ handling, especially due to diuretics

1. ***acid-base balance***
   - the existence of an ***alkalosis***, either metabolic or respiratory in origin enhances K^+ ***excretion***
   - these stimulatory effects appear to be mediated, at least in part through an increased $[K^+]$ in distal tubular cells, alkalosis stimulating the basolateral entry of K^+
   - further, distal K^+ ***reabsorption*** may be inhibited by alkalosis, the distal luminal pump requiring co-transport with Cl^- which is reduced in alkalosis

   - ***respiratory acidosis*** and certain types of metabolic acidosis do tend to cause the opposite effects but only in the acute stages (< 24 hrs)
   - in other forms of metabolic acidosis other factors ***enhance*** K^+ excretion
   - even those forms that have an acute phase of K^+ retention, ultimately come to manifest ***increased*** K^+ excretion
2. ***renal sodium handling***
   - K^+ excretion is virtually always found to be ***enhanced*** when urinary Na^+ excretion is increased in the following situations,

   i. high NaCl dietary intake
   ii. saline infusion
   iii. osmotic diuresis
   iv. loop diuresis

   - increased excretion is due to enhanced distal tubular secretion, although there is some contribution of reduced PT reabsorption
   - all of these situations lead to an increased ***volume*** of fluid flowing through the distal segments, thereby reducing the rise in the luminal $[K^+]$ and enhancing diffusion from the tubule
   - these effects are ***not*** seen with a water diuresis with a ***low ADH***, as the site of action of ADH is largely ***distal*** to the sites of K^+ secretion

   - similarly a reduced flow of fluid in the distal segments tends to inhibit K^+ secretion
   - further, in low flow states, luminal $[Na^+]$ becomes very low and causes the membrane to become hyperpolarised (cell more negative c.f. lumen)
   - despite this tendency, in salt depletion and the diseases of ***secondary aldosteronism*** with oedema, K^+ secretion may be relatively unchanged due to the stimulatory effect of aldosterone

NB: these later conditions generally manifest normal rates of K^+ excretion, in contrast to ***primary aldosteronism*** where the elevated aldosterone and normal delivery of fluid to distal segments leads to severe K^+ depletion

Hypokalaemia

Def'n: serum $[K^+]$ < 3.5 mmol/l
plasma $[K^+]$ < 3.0 mmol/l

- ***Causes***

a. decreased intake - NBM

b. increased losses - ***renal***

i. ***tubular disorders*** - RTA
- leukaemia
- Liddle's syndrome
- increased DT flow

ii. ***mineralocorticoid excess***
- primary aldosteronism
- secondary aldosteronism - cirrhosis, nephrotic syndrome, CCF
- Barter's, JGA cell tumour, malignant ↑ BP
- glucocorticoid excess - Cushing's, ectopic ACTH, iatrogenic

iii. ***diuretics***
- PT agents - acetazolamide, mannitol
- loop diuretics - frusemide, bumetanide
- early DT - thiazides

iv. other drugs - amphotericin B
- anionic drugs, eg. penicillins, other antibiotics

v. hypomagnesaemia

vi. metabolic alkalosis

c. increased losses - ***GIT*** → - diarrhoea, fistulae
- malabsorption syndromes
- vomiting

d. increased losses - ***skin*** → - extreme sweating (rarely)

e. compartmental shifts

i. ***alkalaemia*** ↑ pH ~ 0.1
→ ↓ $[K^+]_{pl}$ ~ 0.5 mmol/l

ii. insulin

iii. Na^+/K^+-ATP'ase stimulation
- β_2-sympathomimetics - salbutamol, adrenaline
- methylxanthines

iv. familial periodic paralysis - hypokalaemic variant

v. ***hypomagnesaemia*** → - ICF depletion of K^+

vi. barium poisoning

- ***Manifestations***

a. **CVS**

i. electrophysiology
- E_m more negative at $[K^+] \leq 3.0$ mmol/l
- APD is ***increased*** significantly
- the following are slightly increased
  - $\delta V/\delta t_{max}$ phase 0
  - ERF
  - threshold potential
  - phase 4 depolarisation
  - conduction velocity v_c

ii. ECG
- depression of ST segments
- depression/inversion of T waves
+ U waves $\rightarrow$ ***"apparent" long QT***

iii. dysrhythmias
- VEB's, VT / VF
* $\uparrow\uparrow$ sensitivity to ***digoxin*** & ***hypercalcaemia***
* severe depletion $\rightarrow$ arrest in VF or systole

iv. chronic depletion $\rightarrow$ ***subendocardial necrosis***

b. **neuromuscular**

i. increased sensitivity to NDMR's $\propto$ increase of resting E_m

ii. muscle weakness / paralysis $\propto$ severe depletion

iii. chronic depletion $\rightarrow$ ***rhabdomyolysis***

c. **renal**

i. nephrogenic DI $\propto$ resistance to ADH

ii. increased ammonia production

d. **endocrinological**
- decreased insulin release
- $\downarrow [K^+] \leq 2.5$ mmol/l $\rightarrow$ $\uparrow$ BSL ≤ 20 mmol/l

e. **acid-base balance**
- allegedly hypokalaemia leads to a ***metabolic alkalosis***, due to an $\uparrow$ ICF $[H^+]$
- however, most hypokalaemia states coexist with NaCl deficits, and it is the $\mathbf{Cl^-}$ ***deficit*** which produces the metabolic alkalosis
- severe hypokalaemia leads to ***ADH resistance*** and a form of nephrogenic DI
- the subsequent ***volume depletion*** $\rightarrow$ a metabolic alkalosis
- hypokalaemia and a ***metabolic acidosis*** may occur in,

i. patients on carbonic anhydrase inhibitors

ii. RTA

iii. extra-renal HCO_3^- & K^+ losses - diarrhoeas, fistulae

iv. partially treated DKA

f. **GIT**
- severe hypokalaemia may lead to intestinal ***ileus***

- ***Treatment - Severe***

  a. ABC

  b. KCl ≤ 0.5 mmol/kg/d ***with*** ECG monitoring
     ≤ 0.25 mmol/kg/d ***without*** ECG monitoring

  c. replace Mg^{++} deficit

- ***Treatment - Mild***

  a. cease aetiological agent

  b. KCl - orally ~ 1 mmol/kg/d

  c. replace Mg^{++} deficit

  d. K^+ sparing diuretics

- ***Hypokalaemia & Alkalosis***

• if the hypokalaemia is associated with hypovolaemic/hypochloraemic alkalosis, then this will not be corrected until the **Cl^-** ***deficit*** is replaced
• this results from a deficiency of absorbable anion in the renal tubules
• in response the kidney synthesises more HCO_3^- to match Na^+ in the ECF, secreting more H^+ and K^+ into the tubules

NB: some argue hypokalaemia *per se* will ***not*** generate an alkalosis, but that it will ***maintain*** an alkalosis, once generated

Hyperkalaemia

Def'n: serum $[K^+]$ > 5.5 mmol/l
plasma $[K^+]$ > 5.0 mmol/l

- ***Aetiology - 1***

Def'n: divide according to the ***intake*** / ***output*** / ***distribution***

a. **increased intake** - rarely a problem, except with ↓'d renal function
- massive blood transfusion, IVT

b. **decreased losses** - renal

i. renal failure - acute, or severe chronic
- tubular disorders

ii. mineralocorticoid deficiency - hypoaldosteronism, heparin
- Addison's (see below)

iii. decreased distal tubular flow / decreased distal NaCl delivery

iv. potassium sparing diuretics - spironolactone, amiloride, triamterene

v. other drugs - indomethacin, ACE inhibitors

c. **compartmental shifts**

i. ***acidaemia*** **↓ pH ~ 0.1 / ↑ $[K^+]$ ~ 0.6 mmol/l**
- this effect is greater with non-organic acids (HCl), cf. organic acids (lactate)
- this may be due to the fact that Cl^- is an obligatory ECF anion, the unaccompanied movement of H^+ into the ECF forcing K^+ from the cell
- further, the half life for removal of lactate by the liver is shorter than excretion of H^+ by the kidney

ii. ***mineralocorticoid deficiency*** - Addison's disease, steroid withdrawal
- hypoaldosteronism

- plasma K^+ is multifactorial - $K^+_{ICF} \rightarrow K^+_{ECF}$
- decreased DT flow
- decreased DT aldosterone effects

iii. cellular damage - haemolysis, rhabdomyolysis, tumour lysis
- severe burns, massive ischaemia, exercise

iv. drugs - suxamethonium, arginine, β-blockers
- fluoride toxicity, digitalis toxicity

v. insulin deficiency

vi. familial periodic paralysis - hyperkalaemic variant

vii. hyperosmolality
- the movement of water from cells increases the $[K^+]_{ICF}$ and the gradient for passive diffusion
- seen with large doses of mannitol given rapidly (1.5-2.0 g/kg)
- the hyperkalaemia of DKA is due to this effect in addition to the acidaemia

d. **factitious**
   i. haemolysis, delayed analysis of sample
   ii. EDTA contamination
   iii. thrombocytosis > 750,000 / µl
   iv. leukocytosis > 50,000 / µl
   v. KCl administration / IVT arm sample

- ***Aetiology - 2***

Def'n: divide according to the ***origin*** & ***time course***

a. **factitious**
   i. haemolysis
   ii. delayed analysis of sample
   iii. EDTA contamination
   iv. thrombocytosis, leukocytosis
   v. KCl administration / IVT arm sample

b. **acute**

i.	excessive intake	- IVT, massive transfusion
ii.	shift out of cells	- metabolic acidosis - drugs, drug O/D - low insulin states - familial periodic paralysis
iii.	tissue damage	- rhabdomyolysis, burns, MH, etc.

c. **chronic**

i.	chronic renal failure	- esp. with acidosis, anuria
ii.	adrenal insufficiency	- Addison's - heparin (aldosterone suppression)
iii.	K^+ sparing drugs	- diuretics - ACE inhibitors - indomethacin

- ***Aetiology - 3***

Def'n: divide according to **HCO_3^- & anion gap**

a. **high HCO_3^-** - respiratory acidosis (do ABG's)

b. **normal HCO_3^-**

i. factitious
- thrombocytosis, leukocytosis
- haemolysis, delayed analysis of sample
- IVT arm sample, KCl administration
- EDTA contamination

ii. drugs
- digoxin overdose
- succinylcholine
- cessation of β-agonists
- fluoride

iii. Addison's
* $Na^+/K^+ < 25:1$
- steroid withdrawal

iv. hyperkalaemic periodic paralysis

c. **low HCO_3^- & normal anion gap**

i. early CRF, ARF - check urea & creatinine

ii. drugs / infusions
- K^+ sparing agents
- spironolactone, amiloride, triamterene
- captopril, enalapril
- indomethacin
- HCl infusion
- arginine HCl

iii. Addison's - or steroid withdrawal

iv. massive transfusion
- high K^+
- hypovolaemia, haemolysis

d. **low HCO_3^- & high anion gap acidosis**

i. CRF - U&E's

ii. metabolic acidosis
- lactate, ketones
- exogenous acids (ethanol, methanol, aspirin)

→ **$\uparrow[K^+]$ ~ 0.5 mmol / $\downarrow$pH ~ 0.1**

iii. tissue damage
- rhabdomyolysis
- burns, MH

iv. drug overdose
- methanol, ethylene glycol
- paraldehyde, salicylates

- ***Clinical Effects***

a. **CVS**

i. electrophysiology
- decreased resting V_m, phase 0 $\delta V/\delta t_{max}$, v_c
- decreased phase 4 depolarisation & automaticity
- little alteration in threshold V_t
- decreased APD & ERP
- decreased contractility

ii. ECG
- peaked T-waves
- widening of QRS "sine-wave"
- loss of P-waves
- increased PR interval

iii. rhythm
- effects are increased by decreased $[Na^+]_{pl}$ /$[Ca^{++}]_{pl}$
- atrial arrest
- AV block
- VT/VF occasionally precede arrest
- severe elevation $\rightarrow$ arrest in ***diastole***

b. **CNS/NMJ**
- ascending weakness
- cranial nerves affected last
- decreased sensitivity to NDMR's (2° V_m)

c. **anaesthesia**
- impaired spontaneous ventilation
- risk of suxamethonium hyperkalaemia
- cardiac arrhythmias
- increased toxicity of local anaesthetics

d. **renal**
- alleged that the increase $[K^+]_{pl}$ decreases renal H^+ excretion
- there is ***no*** convincing evidence for this

- ***Treatment - Hyperkalaemia > 6-7 mmol/l***

a. ABC

b. look for ECG / muscle changes ± recheck level

c. hyperventilate (if intubated)

d. **$CaCl_2$ 10%** ~ 5-10 ml (≡ Ca^{++} ~ 3.4-6.8 mmol)
? Ca-gluconate better as not an acidifying salt

e. **dextrose** ~ 25g (50 ml/50%) +
insulin ~ 10^U IV
- providing the BSL is near normal
- onset is quick, maximum effect seen ~ 1 hr

f. **$NaHCO_3$** ~ 50-100 mmol
- onset of action is immediate, however duration is only 1 hr
- *NB:* 100 mmol HCO_3^- → 2.24 l CO_2

g. if renal function normal
- IV fluids
- Frusemide 20 mg IV

h. if renal failure present
- Resonium A 30g PR & NG
- dialysis CVVHD

- ***Treatment - Mild***

a. cease aetiological agent

b. Resonium A
- exchanges Na^+ or Ca^{++} for K^+
- theoretically Ca^{++} exchange is better as there is less Na^+ load and Ca^{++} counteracts the cardiac effects of hyperkalaemia
- may be given orally or rectally
- onset of effect not seen until ~ 1 hr

c. decrease intake

d. correct underlying problem
- volume replacement
- steroid replacement

ACID-BASE BALANCE

Definitions

Acid: a proton, or hydrogen ion donor

Base: a proton, or hydrogen ion receiver

Plasma pH: the negative $\log_{10}$ of the hydrogen ion ***activity*** $\equiv^{\tau}$ $[H^+]$

Normal pH = 7.4 ± 0.4 $\equiv^{\tau}$ $[H^+]$ ~ 39 nmol/l

Acidosis: an abnormal process or condition which would lead to an acidaemia, if uncompensated

Alkalosis: an abnormal process or condition which would lead to an alkalaemia, if uncompensated

Acidaemia: a plasma pH $\leq$ **7.36**

Alkalaemia: a plasma pH $\geq$ **7.44**

Respiratory: a disorder those where the primary disorder is a change in the P_{CO2}

Metabolic: a disorder where the primary disturbance is in the plasma $[HCO_3^-]$

Base Excess: the amount of strong acid (1 molar) required to be added to 1.0 l of, fully saturated blood, at 37°C, at P_{CO2} = 40 mmHg, to return the pH to 7.4

Normal BE = 0 ± 2.0 mmol/l

Standard Bicarbonate: the HCO_3^- concentration in fully saturated blood, when the P_{CO2} = 40 mmHg at 37°C (** a ***derived variable***)

Normal = **24.0 ± 2.0 mmol/l**

Plasma Bicarbonate: the actual HCO_3^- concentration in plasma at that particular point in time; cannot be measured but is ***calculated*** from the Henderson-Hasselbalch equation, when the P_{CO2} and pH are known

NB: some laboratories report the plasma bicarbonate as the ***total CO_2***, where this is given by,

Total CO_2 = $[HCO_3^-] + [H_2CO_3]$
~ 24.0 ± 2.0 mmol/l

where, $[H_2CO_3]$ ~ 1.2 mmol/l

Anion Gap: = $[Na^+] - ([Cl^-] + [HCO_3^-])$ ~ 12.0 ± 2.0

or, = $([Na^+] + [K^+]) - ([Cl^-] + [HCO_3^-])$ ~ **16.0 ± 2.0**

NB: when assessing blood gas analyses,

i. the BE and standard bicarbonate give the ***same*** information, ie. the non-respiratory component to the acid-base disturbance

ii. the actual bicarbonate does not give any additional information as it has been ***derived*** from the pH and P_{aCO2}

Sources of Acid

1.	CO_2	~ 12,500	mmol/d	(R:12-20,000)
2.	lactate	~ 1,500	mmol/d	
3.	HSO_4	~ 45	mmol/d	
4.	H_2PO_4	~ 13	mmol/d	
5.	other acids	~ 12	mmol/d	
6.	organic acids in disease	- eg. ketoacids		
7.	alkalising salts	- K^+, lactate, acetate, citrate (little importance)		

■ ***CO_2***

• the principal acid product of metabolism is CO_2, equivalent to potential ***carbonic acid***
• excreted by the lungs & doesn't contribute to the net gain of plasma H^+

■ ***Non-Volatile, Fixed Acids***

• includes sulphuric and phosphoric acids (generated from the catabolism of proteins and other organic molecules), lactic acid and keto-acids
• in normal "Western" diets the net daily production **~ 40-80 mmol**
• in vegetarians there may be net production of alkali

■ ***Gastrointestinal Secretions***

• vomitus may contain a large $[H^+]$
• other GI secretions have a high $[HCO_3^-]$, therefore net loss $\equiv$ H^+ gain

■ ***Urine***

• the kidneys normally excrete the 40-80 mmol of fixed acids generated per day
• their H^+ excretion is also regulated to account for

a. any net excretion or retention of CO_2 by the lungs

b. any alteration in metabolic generation of fixed acid

- ***Body Response to Acid***

1. ***dilution*** - weak
2. ***buffering***
   - i. extracellular
     - HCO_3^-
     - protein (Hb, alb)
     - $HPO_4^=$
   - ii. intracellular
     - ~ 30 mmol/l protein
     - ~ 140 mmol/l $HPO_4^=$
     - ~ 10 mmol/l HCO_3^-

     → buffers
     - ~ 90% of respiratory disorders
     - ~ 60% of metabolic acidosis
     - ~ 30% of metabolic alkalosis
   - iii. renal
     - NH_3
       - ~ 60% glutamate conversion
       - ~ 35% free NH_3
       - ~ 5% leucine *et al.*
     - creatinine, $HPO_4^=$, HSO_4^-, HCO_3^-
3. ***exchange***
   - bone (Ca^{++})
   - ICF ions (K^+)
   - ? PTH may play a role (phosphaturia & H^+ loss)
4. ***renal acid excretion***
   - i. PT
     - high capacity, low gradient system
     - ~ 200 mmol/hr
     - influenced by
       - ICF acidosis
       - hypokalaemia
       - P_{aCO2}, luminal pH
       - functional ECF
       - reabsorbable anion (HCO_3^-)
       - carbonic anhydrase activity
       - PTH
   - ii. DCT
     - low capacity, high gradient system
     - ~ 30 mmol/hr → minimum achievable **pH ~ 4.5**
     - influenced by
       - ICF acidosis
       - hypokalaemia
       - luminal pH
       - mineralocorticoid activity
5. ***pulmonary CO_2 excretion***

Buffering

Def'n: serum survival limits → pH ~ 6.7-8.5
extracellular fluids → pH ~ 7.35-7.45
→ $[H^+]_{pl}$ ~ 45 to 35 nmol/l

- the intracellular pH is difficult to determine and varies from one organelle to another, a mean value pH_{ICF} ~ 6.9
- the normal $[CO_2]$ in body fluids is fixed at **1.2 mmol/l**, which corresponds to a P_{aCO2} ~ 40 mmHg
- the total buffer capacity of body fluids is **~ 15 mmol/kg** body weight
- this is essential for preventing any large change from the normal $[H^+]_{pl}$ ~ 39 nmol/l
- the normal daily acid load of 40-80 mmol would cause a profound change in plasma pH
- because intracellular and extracellular buffers are functionally linked, the ***isohydric principal***, measurement of the plasma bicarbonate system provides information about total body buffers
- the major intracellular buffers are proteins and phosphates
- these systems are in equilibrium and although 50-90% of buffering is intracellular, the assessment of HCO_3^- provides a reliable index
- from the dissociation of ***carbonic acid***,

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

$$K_A = \frac{[HCO_3^-] \,.\, [H^+]}{[H_2CO_3]}$$ by the ***law of mass action***

- but as K_A only applies to infinitely dilute solutions with negligible interionic forces, the ***apparent dissociation constant***, $\mathbf{K_A'}$, is used
- this may be rewritten for hydrogen ion, viz.

$$[H^+] = \frac{K_A' \times \alpha . P_{CO_2}}{[HCO_3^-]}$$

- K_A' cannot be derived and is determined ***experimentally*** by measuring all three variables under a wide range of physiological conditions
- under normal conditions, using mmHg → $\mathbf{\alpha K_A' \sim 24}$
- therefore, the equation may be written,

$$[H^+] = \frac{24 \,.\, P_{CO2}}{[HCO_3^-]}$$

so, $P_{CO2} \propto [HCO_3^-].[H^+]$

- as $[H_2CO_3]$ is always proportional to $[CO_2]$, which is proportional to P_{aCO2} the equation may be written,

$$pH = 6.1 + \log \frac{[HCO_3^-]}{0.0301 \times P_{aCO_2}}$$

Henderson-Hasselbalch Equation

• as is evident from the ***Henderson-Hasselbalch*** form of the equation, regulation of pH may be achieved by regulation of both CO_2 and HCO_3^-
• the kidneys function by two processes,

1. variable reabsorption of filtered HCO_3^-
2. addition of new HCO_3^- to renal plasma

• there are various methods of assessment of deviation from "normal" blood gas parameters,

1. graphical plot of plasma $[HCO_3^-]$ vs. pH → Davenport diagram (West 6.8)
2. graphical plot of log PCO_2 vs. pH → Siggaard-Andersen
3. normogram of $[HCO_3^-]_{pl}$ vs. P_{aCO2} → see Harrison's (preferred method)

■ ***Bicarbonate Reabsorption***

NB: Filtered HCO_3^-/d = GFR x $[HCO_3^-]_{pl}$ (ie. freely filterable)
~ 180 l/d x 24 mmol/l
~ 4320 mmol/d

• reabsorption of HCO_3^- is a conservation process and essentially none appears in the urine
• excretion of this load of bicarbonate would be equivalent to adding over 4000 ml of 1M acid to the body!
• minimal ***passive*** reabsorption occurs for HCO_3^- because,

a. luminal and basolateral ***permeability*** is low, c.f. Cl^-
b. ***active transport*** processes are dominant and eliminate δ[electrochemical]

• the mechanism for reabsorption of HCO_3^- involves secretion of H^+ into the lumen
• this is generated within the cell from CO_2 and water by ***carbonic anhydrase*** (CA), the generated H^+ destined for the lumen and the HCO_3^- entering the peritubular plasma by facilitated diffusion
• the luminal membrane also contains CA and filtered HCO_3^- combines with the secreted H^+ and is converted to CO_2 and water which are free to diffuse into the tubular cell
• therefore, the filtered HCO_3^- does not itself enter peritubular plasma
• **H^+ *secretion*** varies in different portions of the nephron,

a. in the PT → counter-transport with Na^+
b. in the distal segments → primary luminal H^+-ATPase pump

• these secreted H^+ ions are ***not*** excreted in the urine, but are reabsorbed as H_2O and CO_2
• therefore they ***do not*** constitute acid excretion, as is the case for any H^+ combining with HCO_3^-
• the process of H^+ secretion and HCO_3^- reabsorption occurs throughout the nephron with the exception of the ***DLH***
• in the **PT ~ 80-90%** of filtered bicarbonate is reabsorbed, the remainder normally being reabsorbed in the ALH, DT and CT
• the presence of ***luminal CA*** in the PT accounts for very large quantities of carbonic acid formed
• the later segments lack luminal CA, therefore distal conversion of $H_2CO_3 \rightarrow CO_2 + H_2O$ occurs slowly and often after urine has left the nephron
• therefore urine PCO_2 may be ***greater*** than plasma under certain conditions

Renal Excretion of Acid

• this is synonymous with "addition of new bicarbonate to plasma"
• secreted H^+ combining with luminal HCO_3^-, effects HCO_3^- reabsorption, not acid excretion
• secreted H^+ combining with urinary buffer is excreted in the urine and the generated HCO_3^- represents "new" bicarbonate entering the plasma
• only a very small quantity of H^+ is in free solution in equilibrium with buffer
• the source of essentially all excreted H^+ is ***tubular secretion***, glomerular filtration makes no significant contribution (~ 0.1 mmol/d)
• the two most important urinary buffers are ***phosphate*** and ***ammonia***
• the quantity of urinary buffer limits the rate at which the kidneys can excrete acid
• in the DT the ***minimum* pH ~ 4.4**, limited by inhibition of the luminal H^+-pump at low pH
• therefore, the quantity of buffer determines the ***mass*** of H^+ which may be secreted before the limiting pH is reached

■ *Urinary Phosphate and Organic Buffers*

• the relationship between monobasic and dibasic phosphate is as follows,

$$HPO_4^{=} + H^+ \longleftrightarrow H_2PO_4^-$$

$$pH = 6.8 + \log \frac{[HPO_4^{=}]}{[H_2PO_4^-]}$$

• therefore, at pH = 7.4 the ratio of ***dibasic:monobasic*** ~ **4:1**
• by the time the limiting pH of 4.4 is reached, the ratio ~ 1:250
• effectiveness as a buffer is limited by,

a. protein binding slightly reduces the amount filtered
b. only 80% of the filtered mass is in the dibasic form
c. tubular reabsorption of → ~ 75% of the filtered mass

→ end result is only **~ 35-40 *mmol/d*** is available for buffering secreted H^+

• normally, phosphate and ammonia are the only important buffers
• however, under abnormal conditions the urine may contain large quantities of anions of ***keto-acids***, acetoacetate and β-hydroxybutyrate
• these appear as their tubular T_{Max}'s are exceeded
• however, they have only limited usefulness as buffers due to their low pK_A's ~ 4.5
• therefore, only 1/2 of the excreted keto-acid anions are available to accept H^+

■ ***Urinary Ammonia Buffer***

• the ammonia/ammonium reaction is as follows,

$$NH_3 + H^+ \longleftrightarrow NH_4^+$$

$$pH = 9.2 + \log \frac{[NH_3]}{[NH_4^+]}$$

• at pH = 7.4, the ratio will be **~ 1:63**
• therefore, virtually all synthesised NH_3 entering the lumen will immediately pick-up a H^+ ion

NB: accordingly, as long as NH_3 is available from the tubular cells, urinary acid excretion and addition of bicarbonate to the plasma can continue

■ ***Ammonia Synthesis & Diffusion Trapping***

• glomerular filtration is ***not*** a significant source of NH_3, as its combined $[NH_3/NH_4^+]$ is very low, and only ~ 1.5% of this is in the NH_3 form
• the source of ammonia is synthesis in renal tubules from glutamine,

glutamine $\rightarrow$ glutamate + NH_4^+ *glutaminase*

glutamate $\rightarrow$ α-ketoglutarate + NH_4^+ *glutamic acid dehydrogenase*

glycine } + α-ketoglutarate $\rightarrow$ ***glutamate*** + α-keto-acids
alanine }

• the generation of **α-*ketoglutarate*** also generates **$2H^+$**, which has 3 possible fates,

1. complete oxidation to CO_2 and water
2. gluconeogenesis
3. recycling to glutamate (above)

• therefore, the generation of ammonia itself does ***not*** add H^+ to the body
• prolonged ***acidosis*** $\rightarrow$ adaptation of ammonia synthesis, involving enhanced transport of glutamine into the mitochondrion ± increased glutaminase levels
• once synthesised, ammonia diffuses rapidly across the luminal membrane by non-ionic diffusion, or diffusion trapping
• in both cell and lumen the base/conjugate-acid pair are in equilibrium, the relative quantities of each being pH dependent
• due to the low pH of luminal fluid, almost all NH_3 entering the tubule accepts a H^+ ion, thereby maintaining a concentration gradient for the diffusion of NH_3 from the cell
• ratio of NH_3:NH_4^+ at pH = 4.4 **~ 1:63,000**
• as the luminal membrane is virtually ***impermeable*** to ammonium, at low pH ammonia passively diffuses into the lumen and is trapped there by conversion to ammonium
• as long as ammonia synthesis can keep pace with acid secretion, tubular pH will not fall
• ammonium excretion can increase from the normal 20-30 mmol/d $\rightarrow$ **> 500 mmol/d**
• in contrast, phosphate may only increase by ~ 20-40 mmol/d

• conversely, if the urine pH is not low the luminal [NH_3] will rise opposing any further diffusion and ammonium excretion will be low
• ammonia is synthesised in both the PT and distal segments, however urine pH only falls significantly in the distal segments, therefore most ammonia synthesis and trapping occurs distally
• some of the ammonia in the DT actually short-circuits the loop by diffusing from the PT and enters the CT from the medullary interstitium

■ ***Integration of Bicarbonate Reabsorption and Acid Excretion***

• the fate of secreted H^+ depends on whether it combines with HCO_3^- effecting its reabsorption, or with urinary buffer effecting acid secretion
• which of these two processes occurs is determined by,

a. the ***mass*** of each buffer present
b. the independent **pK_A's** of the conjugate pairs
c. the ***luminal pH***

• compared to HCO_3^-, relatively little other buffer is present, therefore little non-bicarbonate buffer is titrated until almost all of the HCO_3^- is reabsorbed
• once the bicarbonate has been largely reabsorbed, most secreted H^+ combines with urinary buffer
• ergo, the PT secretes a far greater ***mass*** of H^+ than the distal segments, however this effects bicarbonate reabsorption and the luminal pH falls < 1 unit, only a small amount of H^+ being picked-up by phosphate etc.
• in contrast, the DT the [HCO_3^-] is low and secreted H^+ is sufficient to effect its reabsorption plus lower the pH allowing titration of other buffers and trapping of ammonia
• however, should a large quantity of bicarbonate reach the distal segments, most secreted H^+ would be expended in bicarbonate reabsorption rather than in titration of urinary buffer

■ ***Homeostatic Control of Tubular Acid Excretion***

1. ***glomerulotubular balance***
   - for bicarbonate = the same phenomenon as seen with Na^+ reabsorption,
     → H^+ secretion & HCO_3^- reabsorption varies ***directly*** with GFR
   - ie., if GFR increases 25%, bicarbonate reabsorption increases by a similar amount
   - prevents large alterations of acid/base balance with changes in GFR
2. **P_{aCO2}** and renal ***intracellular pH***
   - the single most important determinant renal H^+ secretion is the P_{aCO2}
   - in the physiological range, P_{aCO2} lies on "shoulder" of curve (??linear)
   - renal tubular cells respond directly to the P_{CO2} of perfusing blood
   - CO_2 raises the intracellular [H^+] by mass action and this increases the rate of H^+ secretion and increases the number of luminal H-pumps
   - intracellular pH is more dependent on P_{aCO2} than arterial pH due to the low membrane permeability to H^+ and HCO_3^-

Respiratory Acidosis and Alkalosis

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

$$K_A = \frac{[HCO_3^-] \cdot [H^+]}{[H_2CO_3]}$$ by the law of ***mass action***

- but as K_A only applies to infinitely dilute solutions with negligible interionic forces, the ***apparent dissociation constant***, $\mathbf{K_A'}$, is used
- CO_2 can be used instead of H_2CO_3 because their concentrations are always in direct proportion
- this may be rewritten for hydrogen ion, viz.

$$[H^+] = \frac{K_A' \times \alpha . P_{CO_2}}{[HCO_3^-]}$$

- in respiratory insufficiency the reaction is shifted to the right, with resulting acidosis
- bicarbonate increases but not to the same degree as CO_2, as $[H^+].[HCO_3^-] = K_A'.[CO_2]$

NB: increases in P_{aCO2} increase the ***product*** of $[H^+]$ x $[HCO_3^-]$

- pH is restored by elevating $[HCO_3^-]$ to the same degree as $[CO_2]$
- increased P_{aCO2} stimulates tubular H^+ secretion, which reabsorbs all the filtered bicarbonate and additional "new" bicarbonate is added to the blood by the formation of titratable acid and ammonium
- this continues to a new steady-state point where the elevated H^+ secretion can only serve to reabsorb the increased filtered load of HCO_3^-
- the sequence of events for alkalosis is the direct opposite

NB: renal compensation is not perfect, $[HCO_3^-]$ is not elevated to the same degree as $[CO_2]$

Metabolic Acidosis and Alkalosis

Metabolic Acidosis

• caused by the primary addition, or loss of either acid or alkali to the body
• eg. either loss of HCO_3^- or addition of H^+ ions will lower both the plasma [HCO_3^-] and pH
• the kidneys compensate by increasing H^+ ion secretion, thereby raising the plasma [HCO_3^-] and restoring the pH
• this occurs in the ***absence*** of any apparent stimulus to the kidney, in fact frequently occurs with a ***decreased stimulus***, due to reflexly increased ventilation and a lowered P_{aCO2}
• therefore, renal tubular cell pH is likely to be increased early in a metabolic acidosis
• in time the pH returns to normal, or actually decreases due to altered basolateral transport of H^+
• compensation is achieved as the ***mass*** of filtered bicarbonate is dramatically reduced and less H^+ ion secretion is required for HCO_3^- reabsorption and the formation of titratable acid and ammonium, eg.

	Normal		***Acidosis***	
Plasma HCO_3^-	24	mmol/l	12	mmol/l
Filtered HCO_3^-	4320	mmol/d	2160	mmol/d
Reasorbed HCO_3^-	4315	mmol/d	2160	mmol/d
Total H^+ secreted	4375	mmol/d	2360	mmol/d
Titratable Acid & NH_4^+	60	mmol/d	**200**	**mmol/d**

• thus, even in the presence of greatly reduced total ***acid secretion***, the kidneys are able to compensate for metabolic acidosis
• the limiting factor for this compensation is the availability of ***buffer***
• there is recent evidence that the rate of H^+ secretion in the collecting ducts may in fact be increased, despite the lowered CO_2, the mechanism is unknown but may involve ***aldosterone***

Metabolic Alkalosis

• situation for alkalosis is exactly the opposite
• despite the reflexly elevated P_{aCO2} and increased H^+ secretion, the load of filtered HCO_3^- becomes so great that much escapes reabsorption and little or no titratable acid or ammonium is formed
• there is some evidence that there may be active secretion of bicarbonate into the collecting ducts
• this description may not apply to chronic alkalosis

Other Factors Influencing Hydrogen Ion Secretion

■ *Extracellular Volume Depletion*

• presence of salt depletion and ECV contraction interferes with the ability of the kidney to compensate for a ***metabolic alkalosis***, as may occur in high GIT obstruction
• salt depletion not only stimulates Na^+ reabsorption but also H^+ secretion
• this occurs mainly in the proximal segments, the mechanism is unclear but probably involves Na^+/H^+ counter-transport across the luminal membrane
• therefore, all filtered HCO_3^- is reabsorbed and the metabolic alkalosis is uncompensated

NB: salt depletion itself ***will not*** generate an alkalosis,
merely impair the kidneys ability to compensate for such

• the major reason for this is that salt depletion *per se* has little effect on the distal nephrons secretion of H^+
• isolated losses of Cl^-, in addition to the above, maintain an alkalosis by stimulating hydrogen-ion secretion

■ *Aldosterone Excess and Potassium Depletion*

• ***aldosterone*** and other mineralocorticoids stimulate H^+ secretion and ammonia production by a direct action on the DT and collecting ducts
• this is distinct from their effects on Na^+ & K^+
• this effect alone is relatively small but is physiologically significant as aldosterone,

a. tonically facilitates H^+ secretion (permissive effect)
b. increases during metabolic acidosis and facilitates H^+ secretion in the collecting ducts
c. may contribute to the increased H^+ secretion seen in salt depletion
   • although more proximal factors are more important

• ***potassium depletion*** also stimulates H^+ secretion and ammonia production, presumably by decreasing tubular cell pH
• only when K^+ depletion is extremely severe will *de novo* alter the renal acid-base balance
• hypokalaemia decreases ***aldosterone*** secretion, tending to negate any increase in H^+ secretion

• the combination of ***hypokalaemia*** and ***hyperaldosteronism*** acts synergistically to markedly stimulate H^+ secretion and thereby ***generate*** a metabolic alkalosis
• this combination occurs in a number of clinical conditions,

a. primary hyperaldosteronism - may itself cause hypokalaemia
b. extensive use of diuretics - especially in CCF and cirrhosis

• the later may be worsened by concurrent ***salt depletion*** stimulating the reabsorption of bicarbonate
• the reverse can occur in patients unable to secrete aldosterone, ie. ensuing hyperkalaemia and modest metabolic acidosis

- ***Cortisol and PTH***

• when present in high concentration, cortisol will exert ***mineralocorticoid*** effects, ie.

i. sodium retention
ii. potassium depletion
iii. metabolic alkalosis

• PTH exerts a direct effect on the PT ***inhibiting*** H^+ ion secretion with ensuing loss of bicarbonate and metabolic acidosis

Influence of H^+ Secretion on NaCl Reabsorption

• H^+ ion secretion in the PT is directly coupled to ***countertransport*** of Na^+
• ergo, were H^+ ion secretion inhibited, Na^+ reabsorption would decrease
• moreover, even in the distal segments, Na^+ reabsorption is ***indirectly coupled*** to H^+ ion secretion by the δ[EC]
• this stems from the fact that bicarbonate ions are ~ 25% of the anions in glomerular filtrate, unless reabsorbed at the same rate as Na^+ a large charge separation occurs
• since bicarbonate is reabsorbed as a result of H^+ ion secretion, there is, effectively an "exchange" of Na^+ for H^+ even in the absence of direct coupling
• this also occurs with the formation of titratable acid and ammonium, both of which increase the (+)'ve charge of the lumen and facilitate the reabsorption of Na^+
• in effect, Na^+ is either reabsorbed with Cl^- or in exchange for H^+, thus,

a. there is usually an inverse correlation between the excretion rates of ***bicarbonate*** and ***chloride***

b. whenever acid secretion is inadequate to effect bicarbonate reabsorption, there is usually an obligatory excretion of Na^+

• increased renal excretion of Cl^- (a) is, therefore, one of the reasons plasma [Cl^-] decreases during renal compensation for metabolic acidosis
• in (b), Na^+ excretion is usually not as great as the losses of bicarbonate due to the increased K^+ secretion induced by an alkalosis

• inhibition of ***carbonic anhydrase*** therefore reduces renal acid excretion, thereby causing an increased excretion of sodium, bicarbonate and water
• further, this alkalinizes the tubular cells, increasing K^+ secretion so a large fraction of the excreted bicarbonate is accompanied by K^+

ACID-BASE BALANCE

• the major problem in clinical assessment stems from ***compensatory processes***
• multiple experimental observations of all primary acid-base disturbances is used to produce confidence bands (± 2SD) for assessment of blood gas measurements → ***normogram***

NB: given P_{aCO2} is proportional to the ***product*** of $[HCO_3^-].[H^+]$, as P_{aCO2} increases or decreases, so the $[HCO_3^-]$ increases or decreases by dissociation, however, ***not*** to the same degree as it is the product $[HCO_3^-].[H^+]$ which is proportional, therefore, the ratio $[HCO_3^-]/P_{aCO2}$ alters with a resultant change in the pH

- ***Correction Factors***

a. ***metabolic acidosis***
   i. P_{aCO2} ~ last two digits of pH ≥ 7.**10**
   ii. ↓ HCO_3^- ~ 10 mmol/l → ↓ P_{aCO2} ~ **12 mmHg**

b. ***metabolic alkalosis***
   i. P_{aCO2} ~ last two digits of pH ≤ 7.**60**
   ii. ↑ HCO_3^- ~ 10 mmol/l → ↑ P_{aCO2} ~ **7 mmHg**
   iii. less well compensated due to hypoxia 2° to hypoventilation

c. ***acute respiratory acidosis***

   ↑ P_{aCO2} ~ 10 mmHg → ↑ HCO_3^- **~ 1-2 mmol/l**

d. ***chronic respiratory acidosis***

   ↑ P_{aCO2} ~ 10 mmHg → ↑ HCO_3^- **~ 4 mmol/l**

e. ***acute or chronic respiratory alkalosis***

   ↓ P_{aCO2} ~ 10 mmHg → ↓ HCO_3^- **~ 2.5 mmol/l**
   ?? 10:4 for chronic fall

NB: low P_{aCO2} + normal δP_{A-aO2} = central hyperventilation

low P_{aCO2} + high δP_{A-aO2} = probable pulmonary disease

Respiratory Acidosis

- ***Aetiology***

a.	alveolar hypoventilation		
	i.	decreased V_M	- CNS, spinal cord, motor neurones - NMJ, myopathies - chest wall, pleural cavity, lung parenchyma, airways - drugs, poisons
	ii.	increased V_D	- alveolar / anatomical - equipment
b.	increased $FiCO_2$		- low FGF - exhausted soda lime - unidirectional valve malfunction
c.	increased CO_2 production		- fever - thyrotoxicosis - MH - TPN

- ***Blood Gasses***

↑ $\mathbf{P_{aCO2}}$ → ↑ $[HCO_3^-]$ by dissociation, but

ratio of $[HCO_3^-]$ / P_{aCO2} falls → ↓ **pH**

• increased P_{aCO2}, and to a lesser extent increased $[H^+]$ → ↑ renal tubular H^+ secretion
• thus, HCO_3^- reabsorption is increased and more H^+ ion is excreted with phosphate and NH_3
• Cl^- is the anion which accompanies these and subsequent ***hypochloraemia*** may ensue

• the ↑ $[HCO_3^-]$ compensates for the respiratory acidosis but is ***rarely complete***
• the extent of renal compensation is determined by the ***base excess***

• as the bicarbonate system is "unavailable" to moderate changes in pH, most of the buffering is intracellular → protein & phosphate
• in RBC's the protons formed from the dissociation of carbonic acid are buffered by Hb and the HCO_3^- formed diffuses into plasma
• Cl^- enters the cells to maintain ***electroneutrality*** → ***chloride shift***
→ ↑ RBC size & venous Hct. ~ 3%

	Acute	Chronic
pH	decreased	≤ 7.4
P_{aO2}	± low	± low
P_{aCO2}	increased	increased
HCO_3^-	increased 1 mmol/10 mmHg P_{aCO2}	increased 3-4 mmol/10 mmHg P_{aCO2}
BE.	increased	increased

Respiratory Alkalosis

- ***Aetiology***

a. normal δP_{A-aO2} gradient = ***non-pulmonary***
   i. physiological - pregnancy
      - high altitude
   ii. CNS disease - CVA, trauma
   iii. drugs - salicylates
      - catecholamines
      - progesterone
      - analeptics
   iv. thyrotoxicosis
   v. endotoxaemia
   vi. psychogenic hyperventilation
   vii. severe anaemia
   viii. IPPV

b. high δP_{A-aO2} gradient = ***pulmonary***
   i. ARDS, septicaemia
   ii. hepatic failure
   iii. pulmonary emboli
   iv. pulmonary oedema
   v. lung disease + increased work of breathing - asthma, emphysema

NB: any given cause may have both pulmonary and non-pulmonary components, eg. pregnancy

- ***Blood Gases***

↓ $\mathbf{P_{aCO2}}$ → ↓ $[HCO_3^-]$ by dissociation, but

ratio of $[HCO_3^-]$ / P_{aCO2} rises → ↑ **pH**

	Acute	Chronic
pH	increased	≥ 7.4
P_{aO2}	normal	normal
P_{aCO2}	decreased	decreased
HCO_3^-	decreased 2 mmol/10 mmHg P_{aCO2}	decreased 5 mmol/10 mmHg P_{aCO2}
BE.	normal	decreased

- decreased P_{aCO2} inhibits renal tubular H^+ secretion
- thus some bicarbonate escapes reabsorption and less H^+ is available for the formation of titratable acid and ammonium → the urine becomes alkaline
- decreased plasma $[HCO_3^-]$ compensates for respiratory alkalosis and may be nearly complete
- extent of renal compensation determined by ***base deficit***, or negative base excess

Metabolic Acidosis - Aetiology

- ***Increased Non-Respiratory Acids***

1. ***increased intake***

i. anion gap > 18

Acid	Anions[1]
Salicylates	• salicylate, lactate, ketoacids
Ethanol	• acetoacetate, lactate
Methanol	• ***formate***[2], lactate
Paraldehyde	• ***formate***, acetate, lactate, pyruvate
Xylitol, Fructose Sorbitol	• lactate
Ethylene glycol	• oxalate

[1] these are usually associated with the production of acid at some stage

[2] rationale for administration of ***ethanol*** for methanol toxicity is competition for alcohol dehydrogenase & ↓ production of ***formate***

ii. anion gap < 18

- always due to accumulation of ***HCl***
- ie. Cl^- accumulates as HCO_3^- falls → ***hyperchloraemic***
- usually ***hyperkalaemic***
- cationic amino acids → Arginine & Lysine HCl
- ammonium chloride → urea & HCl in the liver
- in liver failure → hyperammonaemia
- IV HCl used to sterilise central lines
- mineralocorticoid deficiency
- "potassium sparing" diuretics

2. ***increased production*** → anion gap > 18

Acidosis	Causes
Ketoacidosis	• diabetic ketoacidosis • alcoholic ketoacidosis • starvation
Lactic acidosis	• types A&B ± normal anion gap • cardiorespiratory failure • sepsis, major trauma • toxins, drugs - eg. phenformin • enzyme defects

3. ***decreased excretion*** → anion gap > 18
   - renal failure with retention of SO_4/$HPO_4^=$ acids

■ ***Decreased Bases***

1. ***increased renal losses*** *normal anion gap / ↑ Cl^-
   i. carbonic anhydrase inhibitors
   ii. renal tubular acidosis
      - proximal → equilibrium, ***no*** R_X with HCO_3^-
      - distal → requires R_X with HCO_3^-
   iii. early uraemia
2. ***increased GIT losses***
   i. diarrhoea
   ii. SI fistulae
   iii. ureterosigmoidoscopy

■ ***Dilutional Acidosis***

• if large volumes of low HCO_3^- fluids are given a metabolic acidosis will appear
• this is due to the fact that CO_2 readily diffuses into the solution which then attains a pH ~ 4.9
• it then takes the addition of ~ 24 mmol/l of HCO_3^- to raise the pH to 7.4
• Hartman's solution was designed with this in mind, containing 28 mmol/l of lactate, which is metabolised in the liver to HCO_3^-
• lactate is present as the ***sodium salt*** of the acid anion, therefore cannot generate an acidosis in its own right

NB: when hepatic blood flow is low and metabolism slow, the plasma lactate level may rise, however lactate itself is not toxic

- ***Blood Gases***

$[H^+]$ increases, or $[HCO_3^-]$ decreases → plasma $[HCO_3^-]$ decreases

ratio of $[HCO_3^-] / P_{aCO2}$ falls → decreasing pH

	Acute	Chronic
pH	decreased	≤ 7.4
P_{aO2}	normal	normal
P_{aCO2}	normal	decreases*
HCO_3^-	decreased	± decreased
BE.	negative	negative

*12 mmHg/10 mmol $[HCO_3^-]_{pl}$

NB: P_{aCO2} ~ last two digits of pH ≥ 7.***10***

↓ HCO_3^- ~ 10 mmol/l → ↓ P_{aCO2} ~ 12 mmHg

- decreased pH stimulates ventilation, predominantly via ***peripheral chemoreceptors***, decreasing P_{aCO2} and compensating the acidosis
- the kidney increases excretion of titratable acid ***despite*** the decrease in P_{aCO2}
- this occurs as the filtered load of HCO_3^- decreases to a greater extent than the reduction in distal tubular H^+ secretion

→ more H^+ is available for titration against NH_3 and $HPO_4^=$

- the decreased plasma $[HCO_3^-]$ shows as a ***base deficit***

- ***Treatment***

a. ABC

b. treatment of the causative factor

c. NaCl 0.9%
   - if the acidaemia is not affecting cardiac function, giving NaCl will allow the kidney to excrete HCl

d. Na-Bicarbonate 8.4% - see below

e. dialysis

■ ***Bicarbonate Administration***

NB: "unanimous feeling that the routine administration of bicarbonate was counterproductive" AHA (JAMA 1986)

• ***no*** studies demonstrate a benefit in ***outcome***, most show deleterious effects
• 100 mmol of HCO_3^- produces 2.24l of CO_2, therefore the P_{aCO2} will rise if ventilation is fixed
• is only the R_X of choice where the origin of the acidaemia is loss of bicarbonate
• the dose of HCO_3^- is usually calculated on the empirical assumption that the ion has a $V_D \sim 50\%$ of body weight
• this takes into account diverse buffer reactions in both ECF & ICF
• initial correction should be aimed at ≤ ½ this amount as the initial action is in the ECF
• the AHA recommendations for administration include,

1. CPR > 10 minutes
2. only when an increase in V_M is possible (ie. ventilated)
3. AGA's → pH < 7.0
4. $R_X \leq 1$ mmol/kg slowly IV
5. VF associated with,
   i. TCA overdosage
   ii. hyperkalaemia

• potential problems associated with administration include,

1. produces a paradoxical ***ICF acidosis***
2. may produce an ***ECF alkalosis***,
   i. shifts the HbO_2 curve to the left, decreasing O_2 availability at a cellular level
   ii. shifts K^+ into cells and may result in,
      • hypokalaemic cardiotoxicity in K^+-depleted patients
      • tetany in renal failure or Ca^{++} depletion
3. the solution is ***hyperosmolar***, 1M → 50 ml = 50 mmol
   • the excessive **Na^+** ***load*** may result in cardiovascular decompensation ± CCF
4. CSF equilibrates slowly with $[HCO_3^-]_{pl}$, therefore ventilation may be maintained despite the increase in $[HCO_3^-]_{pl}$, resulting in a ***respiratory alkalosis***
5. where the acidaemia is due to organic acids, the subsequent metabolism of such acids and regeneration of HCO_3^- will produce a ***metabolic alkalosis***

- ***Bicarbonate - Clinical Uses***

1. treatment of ***hyperkalaemia*** - $K^+ \geq 6.0$ mmol/l
   - respiratory insufficiency
   - widened QRS / P wave loss
2. treatment of arrhythmias in ***tricyclic overdose***
3. alkalinising the urine
   i. drug overdosage - phenobarb, salicylates
   ii. rhabdomyolysis
4. treatment of
   i. acidosis 2° HCO_3^- loss - type 1 RTA
      - diarrhoeal or fistula losses from SI
   ii. neonatal/paediatric cardiac arrest
   iii. severe persistent acidosis - pH < 7.0[§]
      - lactic acidosis
      - prolonged severe ketoacidosis
      - neonatal cardiorespiratory failure + severe acidosis
      - [§]no proven benefit, probably harmful

NB: non-CO_2 producing agents may be of benefit, eg. carbicarb, THAM, dichloroacetate → however, studies show ***no*** significant benefit in outcome

Metabolic Alkalosis

- ***Aetiology***

NB: commonly associated with ***hypovolaemia*** and/or ***hypokalaemia***

a. any ***fluid loss*** replaced with insufficient $Na^+ \rightarrow H^+$ excretion

b. ***acid loss*** is either renal or GIT

c. common causes
- diuretics
- vomiting
- following correction of hypercarbia

d. increased proton losses

i. renal
- $\uparrow Na^+$ reabsorption (hypovolaemia, dehydration, etc.)
- hyperaldosteronism
- steroid / ACTH secreting tumours
- Cushing's syndrome
- Barter's syndrome (JGA hyperplasia)
- hypercalcaemia / hypomagnesaemia $\rightarrow$ NDI
- drugs: steroids
  diuretics
  carbenoxolone

ii. GIT
- N/G suctioning
- protracted vomiting
- occasionally diarrhoea

e. increased bases

i. administration of $NaHCO_3$

ii. metabolic conversion of exogenous acid anions
- citrate
- lactate
- acetate

iii. milk/alkali syndrome

iv. renal conservation of HCO_3^-
- acidosis
- hypercarbia

f. factors tending to ***maintain*** an alkalosis

i. hypovolaemia

ii. hypochloraemia

iii. hypokalaemia

iv. hypomagnesaemia

v. chronic hypercapnia

vi. mild chronic renal failure

- ***Chloride Responsiveness***

1. chloride ***responsive*** alkalosis → ECF Na^+ or Cl^- deficit
2. chloride ***resistant*** alkalosis →
   i. ICF hypokalaemia and acidosis
   ii. ECF alkalosis with normo-volaemia & Cl^-
   iii. renal failure

- ***Blood Gasses***

↓ $[H^+]$, or ↑ $[HCO_3^-]$ → ↑ $[HCO_3^-]$ plasma

ratio of $[HCO_3^-]$ / P_{aCO2} rises → ↑ pH

	Acute	Chronic
pH	increased	> 7.4
P_{aO2}	normal	normal ± low
P_{aCO2}	normal	increases[1]
HCO_3^-	increased	increased
BE.	positive	positive

[1] minimally due hypoxic drive

NB: P_{aCO2} ~ last two digits of pH ≤ 7.***60***

↑ HCO_3^- ~ 10 mmol/l → ↑ P_{aCO2} ~ 7 mmHg

** this is the least well compensated form of acid-base disturbance

- ***Treatment***

a. treat the causative factor

b. prevent tubular (PT) loss of H^+ → increase ***functional ECF***
   i. NaCl 0.9% ± KCl
   ii. NSA-5%, albumin or blood transfusion
   iii. inotropic support of cardiac output and GFR
   iv. acetazolamide

c. prevent DCT loss of H^+
   i. replace K^+ and Cl^- deficits
   ii. suppress aldosterone with spironolactone
   iii. triamterene, amiloride

d. addition of HCl to ECF

i.	IV HCl infusion	~ 200 mmol/l D_5W ~ 10-15 mmol/hr ***centrally***
ii.	NH_4Cl	- weak acid, pK_A ~ 9.3 - doesn't alter pH rapidly or require CVC line - NH_4^+ dissociates and is metabolised to ***urea*** - H^+ thus formed correcting the alkalosis
iii.	arginine-HCl, lysine-HCl	- also metabolised to urea and HCl by liver

- ***Other Alkaloses***

1. ***diuretic*** induced alkalosis
   - is the result of ***chloride deficiency*** and is corrected by replacement
   - the body defends ECF volume by Na^+ retention but if Cl^- is deficient then only HCO_3^- is available to maintain electroneutrality
2. ***steroid*** induced alkalosis
   - is the result of increased DT exchange of Na^+ for K^+ & H^+
   - this leads to ECFV overload, hypokalaemia and alkalosis
   - chloride replacement does ***not*** correct this condition as the normal mechanisms for the excretion of HCO_3^- are interfered with
3. ***hypokalaemia*** and alkalosis
   - the evidence relating these is weak
   - mostly the two are associated rather than cause/effect, eg. thiazides
   - severe hypokalaemia may result in a form of nephrogenic DI which may lead to hypovolaemia, with subsequent increased aldosterone secretion
4. ***hypercalcaemia*** probably acts via the same mechanism
5. ***hypomagnesaemia*** may only be associated, eg. thiazides

CALCIUM

i. elemental alkaline earth metal
ii. atomic number = 20
iii. molecular weight ~ 40
iv. divalent cation - fifth most plentiful cation in the body

- total body content **~ 380 mmol/kg**, distributed as follows,
  a. ICF ~ 0.004%
  b. ECF ~ 0.01%
  c. bone ~ 99%
  d. exchangeable ~ 1%

- this equates to ~ 1100 g/average adult, ~ 27.5 mol of Ca^{++}
- the daily requirement in the adult ~ 0.11 mmol/kg
- concentration ranges vary between tissues,
  a. ECF **~ 2.2-2.8 mmol/l**
     i. 45% - ionised Ca^{++}
     ii. 15% - complexed to low MW anions (citrate, HPO_4^-)
     iii. 40% - reversibly bound to plasma proteins (alb, glob.)
     - non-filterable fraction
  b. ICF ~ 1 mmol/l total
     ~ 10^{-4} mmol/l as free ionised Ca^{++}
     ~ 99% bound to enzymes in SR, cisternae, & tubules

- only plasma ionised Ca^{++} is biologically active
- the most important influence on protein binding is ***plasma pH***
- an increase of pH increasing the binding of Ca^{++} due to the exposure of more anionic sites
  → decreased ionised Ca^{++}

Important Functions of Calcium

a. ***cytoplasm***
   i. excitation contraction coupling in all muscle
   ii. enzyme cofactor
   iii. regulation of mitotic activity

b. ***cell membrane***
   i. excitability of nerve / muscle membrane
      • setting the threshold V_m for excitation
   ii. automaticity - smooth muscle
      - SA & AV nodes
   iii. neurotransmitter release at nerve terminals (NMJ)
   iv. neuro-hormonal release & activity
      • 1. α-adrenergic - smooth muscle
         - hepatic glycogenolysis
         - salivary secretion
      • 2. ACh - smooth muscle
         - GIT, GB, bladder contraction
      • 3. ADH - smooth muscle (V_1)
      • 4. oxytocin - uterine & myoepithelial
      • 5. angiotensin II - aldosterone secretion from Z.G.
      • 6. CCK - pancreatic secretion
         - GB contraction
      • 7. histamine (H_1) - bronchial contraction
         - GIT smooth muscle contraction

c. ***extracellular***
   i. coagulation cascade - I, II, VII, IX, X
   ii. complement cascade
   iii. bone & teeth formation - Ca^{++} hydroxyapetite

- ***Effector Sites for Calcium Homeostasis***

a. **GIT**
   - ***absorption*** major variable under control ~ 1000 mg typical daily intake
     ~ 10% absorption
   - GIT secretes up to 600 mg/d
   - this is reabsorbed along with the above 10%

b. **kidney**
   - ~ 60% of plasma Ca^{++} is ultrafilterable
   - reabsorption throughout the nephron, except in the ***DLH***, similar to Na^{+}
   - ~ 60% in the PT, remainder in the ALH and DT
   - ~ 98-99% of filtered mass is reabsorbed
   - ~ 5% of an increment in dietary Ca^{++} appears in the urine
   - reabsorption is under control of ***PTH***
   - affected by large number of other inputs, especially Na^{+} and acid-base changes
   - there is some coupling of Na^{+}/Ca^{++} in the PT and ALH
   - this coupling is lost in more distal segments,
   i. ***aldosterone*** & ***PTH*** do not affect distal handling of both ions
   ii. ***thiazides*** inhibit distal Na^{+} reabsorption, however enhance Ca^{++} reabsorption
   iii. proximal or loop diuretics increase excretion of both ions
   - chronic ***metabolic acidosis*** markedly ***increases*** Ca^{++} excretion with subsequent loss from bone
   - alkalosis produces the opposite

c. **bone**
   - ~ 99% of total body Ca^{++} held as ***hydroxyapetite***
   - interchanges of Ca^{++} between ECF and bone affect the internal distribution not body mass of Ca^{++}
   - acts as an enormous sink for exchange with the ECF

- ***Control Mechanisms***

a. $[Ca^{++}].[HPO_4^{=}]$ solubility product
   - product > 6 increases the likelihood of ectopic calcification

b. parathyroid hormone

c. vitamin D - 1,25 dihydroxycholecalciferol

d. calcitonin

- ***Secondary Influences***

a. steroids - decrease Ca^{++}

b. growth hormone - increase Ca^{++}

c. albumin levels ~ 0.02 mmol Ca^{++} / gram albumin (**0.2 mmol/10g**)

d. acid-base status

i. acidosis - increases Ca^{++}

ii. alkalosis - decreases Ca^{++}

e. renal function - GFR
- tubular excretion
- 1-hydroxylation of 25-(OH)-D_3

f. thyroid hormones - increase Ca^{++}

g. glucagon - decrease Ca^{++}

- ***Hormonal Control of Effector Sites***

a. **parathyroid hormone**

i. increases movement of Ca^{++} and $HPO_4^{=}$ out of bone

ii. increases renal tubular reabsorption of Ca^{++}

iii. reduces renal tubular reabsorption of $HPO_4^{=}$

iv. stimulates production of Vit. D $\rightarrow$ ***indirect effects***

- inhibits proximal tubular H^+ secretion & HCO_3^- reabsorption

$\rightarrow$ $\downarrow$ plasma pH $\rightarrow$ displaces Ca^{++} from plasma protein
increases bone reabsorption

- increased $HPO_4^{=}$ excretion aids further reabsorption from bone due effect on $[HPO_4^{=}].[Ca^{++}]$ solubility product

- ***NB:*** ***hyperparathyroidism*** causes,

i. an elevated plasma calcium with a low to normal phosphate

ii. enhanced bone reabsorption with cysts

iii. ectopic calcification

iv. renal stones

- renal Ca^{++} excretion ***increases***, despite the elevated PTH, as the filtered mass increases >> the reabsorptive increase

b. **vitamin D**

- actually a group of closely related ***sterols***,

7-dehydrocholesterol	+ UV light		→	D_3
D_3	+ liver	25-hydroxylation	→	25-(OH)-D_3
25-(OH)-D_3	+ kidney	**1-hydroxylation**	→	1,25-$(OH)_2D_3$

- by definition this is a ***hormone*** not a vitamin
- also absorbed from the GIT, the plant form differing only slightly
- **1-*hydroxylation*** is increased by PTH and a low plasma $HPO_4^{=}$
- also increased by oestrogen and prolactin (pregnancy)
- the major actions of vitamin D are,

i. enhance GIT absorption of Ca^{++} and $HPO_4^{=}$

ii. enhance the reabsorption of Ca^{++} and $HPO_4^{=}$ from bone

iii. stimulates the renal tubular reabsorption of Ca^{++}
(the significance of this is unsettled)

- ***NB:*** ***hypervitiminosis D***, results in an elevated Ca^{++} ***and*** $HPO_4^{=}$

c. **calcitonin**

- secreted by the ***parafollicular cells*** of the thyroid gland in response to a raised plasma Ca^{++}
- lowers the plasma calcium principally by inhibiting bone reabsorption
- overall contribution to homeostasis is ***minor***

Hypocalcaemia

Def'n: total corrected Ca^{++} ≤ 2.1 mmol/l (R: 2.10-2.55 mmol/l)
corrected calcium ~ total $[Ca^{++}]$ + 0.02[44 - albumin (g/l)] mmol/l
ionised calcium ≤ 1.20-1.30 mmol/l

- ***Aetiology***

a. factitious
- hypoalbuminaemia (N: 37-55 g/l)
  ↓ **Ca^{++} ~ 0.01-0.02 mmol / ↓ 1g** per litre
- K^+-EDTA tube sample

b. acute
- respiratory alkalosis
- primary hypoparathyroidism (post-surgical)
- hypomagnesaemia (↓ PTH release)
- acute pancreatitis, rhabdomyolysis, tumour lysis, MH
- citrate toxicity

c. chronic
- renal failure
- vit. D deficiency
  - reduced intake
  - liver / renal disease
- vit. D resistance
  - renal disease
  - familial
- high dietary $HPO_4^=$ intake

- ***Aetiology HPIM***

1. PTH absent
   i. hereditary hypoparathyroidism
   ii. acquired hypoparathyroidism
   iii. hypomagnesaemia
2. PTH ineffective
   i. chronic renal failure
   ii. active vit.D lacking
   - ↓ dietary intake or sunlight
   - defective metabolism
     - anticonvulsant therapy
     - vit.D-dependent rickets type I

   iii. active vit.D ineffective
   - intestinal malabsorption
   - vit.D-dependent rickets type II - end-organ resistance

   iv. pseudohypoparathyroidism
3. PTH overwhelmed
   i. severe acute hyperphosphataemia - ARF, tumour lysis, rhabdomyolysis
   ii. osteitis fibrosa following parathyroidectomy

- ***Clinical Features***

a. CNS
- increased irritability, personality changes
- oculogyric crises, extrapyramidal signs
- tetany & ***convulsions***

b. NMJ
- reduced threshold V_m
- neuromuscular excitability
- reduced ACh release NMJ
- Chvostek's sign, Trousseau's sign
- cramps ± tetany
- stridor ± ***laryngospasm***

c. CVS
- reduced SVR*
- negative inotropy* *→ ***hypotension***
- negative chronotropy
- ***prolonged*** $\mathbf{QT_C}$ = QT / √RR < 0.45 s female
  < 0.40 s male
- atrial & ventricular ectopics

d. other
- cataracts
- rickets, osteomalacia
- coagulopathy (very rare)

- ***Treatment***

a. **Ca Gluconate 10%** ≡[t] 0.22 mmol/ml
~ 2-4 mmol every 6-8 hrs
~ 0.5 ml/kg to a maximum of 20 ml

b. **$CaCl_2$ 10%** ≡[t] 0.68 mmol/ml x 10 ml

- the injection rate should be slow ≤ 1 ml/min
- faster rates may → high concentration and cardiac arrest
- this is an ***acidifying salt***, therefore undesirable in the setting of renal insufficiency
- the solution is very irritating and should never be injected into the tissues
- injections are accompanied by peripheral vasodilatation and vessel irritation

c. Vit. D - calciferol ~ 1.25 mg twice weekly

d. R_X of concomitant electrolyte abnormalities
i. hypomagnesaemia
ii. hypokalaemia

Hypercalcaemia

Def'n: total corrected Ca^{++} > 2.6 mmol/l (R: 2.10-2.55 mmol/l)
corrected calcium ~ total $[Ca^{++}]$ + [0.02 x (44 - albumin (g/l))] mmol/l
ionised calcium > 1.20-1.30 mmol/l

- ***Aetiology***

1. ***factitious*** - stasis
   - post-prandial
   - polycythaemia, dehydration, high plasma albumin
2. ***common*** ~ 90% of all cases
   i. hyperparathyroidism - 1° & 3°
   ii. neoplastic diseases
   - solid tumour with bony 2°'s - breast, prostate
   - ectopic parathormone - kidney, lung (~ 10-15%)
   - osteocyte activation factor - haematological malignancies[§]
   - ?? PGE_2, PTH-rP, OAF, IL-1, TNF, 1,25-$(OH)_2$-D_3
3. ***parathyroid related***
   i. 1° hyperparathyroidism - solitary adenomas
   - MEN I & II
   ii. lithium therapy ↑ parathyroid function (~ 10%)
   iii. familial hypocaliuric hypercalcaemia - auto.D, ***benign***
4. ***malignancy related***
   i. solid tumour with metastases
   ii. solid tumour with hormonally mediated hypercalcaemia
   iii. haematological malignancies - ***m. myeloma***[§], leukaemia, lymphoma
5. ***vitamin D related***
   i. vitamin D intoxication
   ii. ↑ 1,25-$(OH)_2$-D_3 - ***sarcoid*** & other granulomatous diseases
   - TB, berylosis
   iii. idiopathic hypercalcaemia of infancy
6. ***increased bone turnover*** - hyperthyroidism
   - ***thiazide diuretics***
   - immobilisation
   - vitamin A intoxication
7. ***associated with renal failure*** - severe 2° hyperparathyroidism
   - milk/alkali syndrome
   - aluminium intoxication
8. other causes - Addisonian crisis
   - phaeochromocytoma
   - excess IVT/ TPN

- ***Clinical Features***

NB: initial polyuria, thirst, fatigue, nausea, vomiting & abdominal pain

a.	CNS	- mental disturbance - personality change - paraesthesia - headache, fever, increased thirst
b.	CVS	- bradycardia - asystolic arrest - increased digoxin toxicity
	ECG	- shortened QT_C - bradyarrhythmias - AV blockade
c.	NMJ	- increased ACh release - increased excitation / contraction - increased threshold V_m * but ***decreased sensitivity*** of motor EP $\rightarrow$ weakness, fatigue, paralysis
d.	renal	- polyuria ~ nephrogenic DI, 2° to impaired tubular reabsorption - nephrocalcinosis
e.	musculoskeletal	- weakness, fatigue, paralysis - bone pain, arthralgia
f.	GIT	- nausea, vomiting, abdominal pain - constipation, anorexia, weight loss - gastric hyperacidity, peptic ulcer - pancreatitis

- ***Treatment***

a.	ABC	- ventilatory/CVS support
b.	correct dehydration	- replace deficit with normal saline
c.	initiate diuresis	- N.Saline at 4-6 l/d - frusemide 20-40 mg IV q4-8h * hypokalaemia, hypomagnesaemia
d.	corticosteroids	- $\downarrow$ GIT absorption / increase excretion - ***not*** effective in 1° hyperparathyroidism
e.	diphosphonate	- etidronate
f.	correct $\downarrow HPO_4^{=}$	- $\uparrow$ GIT absorption - $\downarrow$ bone uptake & $\uparrow$ reabsorption
g.	decrease bone release	- calcitonin - mithramycin

PHOSPHATE

- involved in most metabolic processes and is a major constituent of ***bone***
- normal adult content ~ 1000 g, of which 85% is in bone
- present in plasma as ***inorganic phosphate*** ~ 0.9-1.5 mmol/l
- there is diurnal variation in the level, even during fasting
- ***ethanol*** can induce phosphate depletion despite adequate intake
- $HPO_4^{=}$ is well absorbed from the GIT
- ***urinary excretion*** is the major homeostatic regulator for total body phosphate balance
- ~ 5-12% is protein bound, therefore ~ 90% is filterable at the glomerulus
- ~ 75% is actively reabsorbed, mostly in the PT in co-transport with Na^+
- there is no conclusive evidence for tubular secretion of phosphate
- the reabsorptive T_{max} for phosphate is very close to normal filtered load
- therefore even small increases in the plasma concentration result in relatively large increases in renal excretion
- there is increased loss with mechanisms which increase Na^+ loss and also with 1° hyperparathyroidism
- the reabsorptive rate and T_{max} alter over time, in response to alterations in plasma phosphate levels, not as a result of PTH or Vit.D
- the mechanism for this change is still unclear

- factors affecting ***tubular reabsorption*** of phosphate are,

a.	PTH	↓
b.	Glucagon	↓
c.	Dietary Phosphate	↓
d.	$1,25\text{-}(OH)_2D_3$	↑
e.	Insulin	↑

Hyperphosphataemia

Def'n: $H_2PO_4^-$ > 1.35 mmol/l

- ***Aetiology***

a. acute = release from cells
   i. metabolic acidosis
   ii. diabetic ketoacidosis
   iii. rhabdomyolysis
   iv. ischaemic gut
   v. severe catabolic states
   vi. tumour lysis syndrome

b. chronic
   i. renal failure
   ii. hypoparathyroidism / pseudohypoparathyroidism
   iii. vitamin D toxicity
   iv. excessive intake - TPN
   - diphosphonate therapy

- occurs more commonly in infants, children and post-menopausal women
- clinical effects include,

a. hypocalcaemia - $[Ca^{++}][HPO_4^{=}] < 5$
b. ectopic calcification - arteries, skin
   - kidneys, nephrocalcinosis
c. keratopathy
d. 2° hyperparathyroidism - renal osteodystrophy

- treatment depends upon renal function,

a. normal - diuresis
b. renal failure - oral $Al(OH)_3$ & dialysis

Hypophosphataemia

Def'n: $H_2PO_4^- \leq$ 0.8 mmol/l

- ***Aetiology***

a. acute ∝ ***entry into cells***
   - i. respiratory alkalosis - any cause
   - ii. insulin - post-prandial, R_X of hyperkalaemia, DKA
     - glucagon, adrenaline, androgens, cortisol, anovulatory hormones
   - iii. R_X of acidosis - diabetic ketoacidosis
     - rhabdomyolysis
     - hypercapnia
   - iv. nutritional - TPN in malnourished or anorexic patient
     - glucose, fructose, lactate, AA's, glycerol

b. acute ∝ ***increased loss / utilisation***
   - i. phosphaturia from diuresis - osmotic / diuretic
   - ii. severe illness - sepsis, hypercatabolic states
     - recovery from hypothermia

c. chronic
   - i. decreased intake - rickets, osteomalacia
     - prolonged TPN
     - alcoholics
     - anorexia
   - ii. decreased absorption - vitamin D deficiency
     - intestinal dysfunction
     - steatorrhoea/malabsorption
   - iii. increased loss - diuresis
     - 1° hyperparathyroidism
     - renal tubular acidosis
   - iv. increased utilisation - hypercatabolic states, multitrauma
     - cancer, lymphoma & leukaemia especially

- ***Symptoms***

a. asymptomatic

b. anorexia, dizziness

c. weakness, paraesthesia, bone pain (osteomalacia)

d. dyspnoea - respiratory muscle weakness

- ***Clinical Signs***

1. proximal myopathy
2. waddling gait
3. paraesthesia
4. anaemia
5. respiratory insufficiency, failure
6. cardiac failure

- ***"Clinical Syndromes" of Hypophosphataemia***

a. "GBS-like syndrome"
- acute muscular weakness
- respiratory insufficiency / failure to wean
- nervous system dysfunction

b. haematological
- low 2,3-DPG & intracellular ATP
- haemolysis
- left shift HbO_2 curve
- WBC dysfunction

c. neurological
- peripheral neuropathy
- CNS dysfunction
- paraesthesia, waddling gait
- epilepsy

d. metabolic acidosis & osteomalacia

e. myocardial dysfunction & cardiac failure

- ***Treatment***

a. $H_2PO_4(K^+)$ ~ 50-100 mmol/day

b. $H_2PO_4(K^+)$ ~ 30 mmol/2-3 hrs in DKA

c. also available is NaH_2PO_4

MAGNESIUM

i. elemental alkaline earth metal
ii. atomic number = 12
iii. molecular weight ~ 24.3
iv. divalent cation - second most plentiful intracellular cation

- total body content **~ 15 mmol/kg**, (~ 1000 mmol/70 kg) distributed as follows,
  - i. ICF ~ 45%
    ~ 2.5-15 mmol/l - highly variable
  - ii. ECF ~ 5%
    - plasma ~ 0.75-1.1 mmol/l ~ 35% protein bound
  - iii. bone ~ 50%
  - iv. exchangeable ~ 65-70%

NB: ICF and ECF concentrations may vary ***independently*** of each other,
∴a significant deficit in one may be accompanied by minimal change in the other

- about 1/3 of the bone pool is exchangeable, far more readily in children than adults

■ ***Absorption & Excretion***

- average daily requirement ~ 0.04 mmol/day
- the average adult ingests ~ 10-20 mmol Mg^{++}/d
  ~ 3-6 mmol/d of this is absorbed across the GIT
- this occurs predominantly in the upper SI via an active process, possibly linked to Ca^{++}
- Mg^{++} is excreted principally by the ***kidney*** → freely filtered
- the majority is reabsorbed in the PT → ~ 3-5% appears in the final urine
- control mechanisms for homeostasis are poorly understood,
  a. PTH & vit.D increase GIT absorption
  b. follows Ca^{++} flux in bone
  c. follows K^{+} flux across cells
  d. excreted by GFR, ∴increased by diuretics
  e. lost in diarrhoea, intestinal fistulae

■ ***Important Functions of Magnesium***

a. neuromuscular function and excitability
b. Na^{+}/K^{+}-ATPase pump cofactor
c. enzyme cofactor - anabolic functions in brain & liver
d. involved in all phosphate transfer reactions
e. release of hormones - PTH

Hypomagnesaemia

Def'n: plasma Mg^{++} < 0.7 mmol/l

- ***Aetiology***

a. factitious
- haemodilution
- severe hypoalbuminaemia

b. common
- GIT losses
- diuretics, renal failure

c. acute
   i. β-adrenergic agonists - catecholamines
   ii. diarrhoea, vomiting, SI fistulae
   iii. acute pancreatitis

d. chronic
   i. nutritional
   - NBM
   - prolonged Mg^{++} deficient TPN
   - protein/calorie malnutrition
   - infants given cows milk ($HPO_4^{=}$:Mg^{++})
      - enteral treatment of hypocalcaemia, with concomitant Mg^{++} deficiency and reduced absorption of the later

   ii. cirrhosis & chronic alcoholism

   iii. GIT
   - diarrhoea, malabsorption
   - SI fistulae
   - NG aspiration

   iv. drugs
   - diuretics
   - gentamicin, other aminoglycosides
   - cis-platinum

   v. endocrine
   - hyperthyroidism
   - hyperaldosteronism
   - hyperparathyroidism + osteitis fibrosa cystica
   - diabetes mellitus

   vi. renal
   - chronic diseases
   - haemodialysis / haemoperfusion

   vii. SIADH

   viii. familial hypomagnesaemia

- Mg^{++} deficiency is therefore frequently accompanied by ***hypokalaemia*** and ***hypocalcaemia***
- Mg^{++} frequently follows K^{+} in the ICF environment
- when deficits of Mg^{++} and K^{+} coexist, Mg^{++} repletion is often required to correct the later

NB: the interaction of the two ions is thought to be mediated by the effects of adrenal ***steroids*** on renal excretion

- ***Clinical Manifestations***

a. enzyme systems - Mg^{++} is a vital cofactor for,
   i. all nucleotide-$PO_4^{=}$ transfer reactions
   ii. reversible association of intracellular particles
   iii. association macromolecules with subcellular organelles
   eg., mRNA to ribosomes
   → there is a decrease in energy substrate utilisation

b. CNS
   i. increased irritability
   ii. disorientation, psychotic behaviour
   iii. athetosis, nystagmus, tremor
   iv. twitching, tetany ± convulsions

c. renal
   i. microlith formation in the thick ALH
   ii. damage to tubular cells
   iii. ± hypokalaemia / hypocalcaemia

d. neuromuscular function
   i. increased release of ACh from motor neurones
   ii. increased sensitivity of the motor EP to applied ACh
   iii. neuromuscular excitability ± tetany

e. CVS
   i. ± decreased levels of K^+ in cardiac cells
   ii. ± susceptibility to toxicity with ***cardiac glycosides***
   iii. changes to cardiac muscle → decreased contractility
   iv. ***tachyarrhythmias*** → AF, SVT, torsade de pointes

f. ***hypocalcaemia*** 2° to decreased PTH release

- ***Treatment***

a. remove causative factor

b. enteral supplementation - Mg^{++} citrate, sulphate & hydroxide

c. parenteral supplementation → $MgSO_4$
   - the dose is expressed in terms of the hydrated salt,
     1.0g $MgSO_4$-$(H_2O)_7$ → 4.06 mmol Mg^{++}
   - * acute administration ~ 0.5-1.0 mmol/kg over 4 hrs
     ≤ 0.5 mmol/min
     ≤ 15-20 mmol/d, in two divided doses
   - available as ampoules **10 mmol/5 ml** ~ 2.5g

Hypermagnesaemia

- ***Causes***

a. increased intake - most common causes
   i. Mg^{++} containing cathartics & antacids
      - especially seen with renal impairment
      - these undergo rapid absorption in patients with large gastro-jejunal stomas
   ii. $MgSO_4$ administration for pre-eclampsia/eclampsia
   iii. inappropriate IVT / TPN replacement

b. decreased excretion
   i. renal impairment - any cause
   ii. hypoadrenalism

c. compartmental shifts - rarely a cause
   i. metabolic acidosis & diabetic ketoacidosis
   ii. hypothermia

- ***Clinical Manifestations***

a. CNS
   - a number of effects are $\equiv^{t}$ to those of Ca^{++} $\rightarrow$ sedation & confusion
   - the flaccid, anaesthesia-like state following large doses is probably due to peripheral NMJ blockade

b. NMJ
   - direct depressant effect on skeletal muscle
   - decreased release of ACh from motor neurones
   - reduces the sensitivity of the motor EP $\rightarrow$ muscular weakness
   - depressed deep tendon reflexes ± respiratory paralysis (> 7 mmol/l)
      - of these the second is the most important
      - these effects are antagonised by Ca^{++}

c. CVS
   - increased ***conduction time*** $\rightarrow$ PR, QRS and QT prolongation (> 5 mmol/l)
   - decreased discharge rate of SA node
   - may abolish digitalis induced VPC's
   - peripheral vasodilatation ~ direct vascular effect & ganglionic blockade

$\rightarrow$ hypotension, conduction disturbances ± complete heart block

d. neonate - depressed conscious state
- hypotonia
- respiratory difficulties

→ ***low Apgar scores***

NB: in infants experiencing ***hypoxia*** during delivery the unionised fraction increases and toxicity is enhanced

Clinical Manifestations of Hypermagnesaemia	
Plasma Level	Clinical Features
2.0-4.0 mmol/l	• anticonvulsant ?? vasodilatation • sedation • mild vasodilatation • increased AV & intraventricular conduction
~ 5.0 mmol/l	• loss of ***monosynaptic reflexes*** • increase in PR & QRS duration • hypotension • respiratory centre depression
~ 6.0 mmol/l	• NMJ blockade, severe weakness
6.0-8.0 mmol/l	• respiratory paralysis
8.0-12.0 mmol/l	• cardiac arrest ***asystolic***

- ***Treatment***

a. ABC

b. remove causative factor

c. IV NaCl 0.9% - providing renal function is normal
~ 4-6 l/d
± add Ca^{++} 2.5-4.5 mmol/l

d. $CaCl_2$ / Ca Gluconate ~ 2.5-5 mmol IV
*cases of severe CVS, CNS or respiratory compromise

e. frusemide ~ 20-40 mg IV

f. haemodialysis

- ***Therapeutic Uses Of Magnesium***

a.	hypomagnesaemia		
	i.	weakness & CNS signs	
	ii.	cardiac disturbance	- torsade de pointes - digitalis induced VT - uncontrolled SVT
	iii.	suspected severe depletion	- alcoholics, malnourished
	iv.	routine in TPN replacement	
b.	seizure states		- pre-eclampsia/eclampsia - acute nephritis
c.	uncontrolled hypertension		
d.	severe acute asthma		
e.	enteral preparations		- cathartics - antacids