Neuroendocrine Regulation

- the anterior, intermediate, and posterior lobes of the pituitary are effectively 3 separate endocrine organs, secreting 14 or more hormonally active substances
- the 6 established hormones secreted by the ***anterior pituitary*** are,

a.	thyroid stimulating hormone	TSH[§]
b.	adrenocorticotrophic hormone	ACTH
c.	growth hormone	GH
d.	follicle stimulating hormone	FSH[§]
e.	leutinizing hormone	LH[§]
f.	prolactin	PRL

NB: [§] these are ***glycoproteins***, c.f. the others which are simple polypeptides

- the hormones of the ***posterior pituitary*** are,

a.	vasopressin	ADH
b.	oxytocin	

- the pituitary is under control from,

1. ***hypothalamic*** hormones
   - i. thyrotropin releasing hormone — TRH
   - ii. corticotropin releasing hormone — CRH
     - ***serotonin***
   - iii. luteinizing hormone releasing hormone — LHRH
   - iv. growth hormone releasing hormone — GHRH
   - v. growth hormone releasing inhibiting hormone — GHRIH
     - ***somatostatin***
   - vi. prolactin releasing factor — PRF
   - vii. prolactin release inhibiting factor — PRIF
     - ***dopamine***
2. ***negative feedback*** from target endocrine glands/hormones
   - i. thyroid
   - ii. adrenal
   - iii. gonads

- ***Changes in Acute Stress***

1.	sympathetic NS and adrenal medulla	→	↑ catecholamines
2.	renin-angiotensin-aldosterone axis	→	↑ angiotensin II + aldosterone
3.	hypothalamopituitary axis	→	↑ corticotrophin ↑ corticotrophin related peptides ↑ vasopressin ↑ prolactin

- ACTH is synthesised from ***POMC***, which itself is synthesised in the,
  1. corticotropes of the anterior lobe
  2. intermediate lobe
  3. hypothalamus
  4. other parts of the CNS, the lungs, the GIT and in the placenta

- in the ***corticotropes*** this is hydrolyzed to,
  a. ACTH
  b. β-LPH - β-lipotropin, a linear 91 AA polypeptide
     - contains the sequences for the ***endorphins*** (α, β & γ) and ***enkephalins***
  c. β-END - small amount only
  d. γ-MSH

- during "stress" the gonadal steroids and thyroid hormones ***decrease***
- pituitary production of LH, FSH & TSH may increase, decrease or remain unchanged

Endocrine "Stress Response"	
Sympathetic nervous system	• noradrenaline
Adrenal medulla	• adrenaline & noradrenaline
Renin-angiotensin axis	• angiotensin II & aldosterone
Neurohypophysis	• antidiuretic hormone
Adenohypophysis	• ACTH • β-LPH • prolactin

Effect	Starvation	Sepsis	Trauma
BMR	-	+	+
Malnutrition	slow	rapid	rapid
Primary Hormones			
• glucagon	+	+	+
• catecholamines	-	+	+
• glucocorticoids	-	+	+
Energy substrates			
• glucose	-	+	+
• triglycerides	-	+	+
• FFA	+	+	+
• ketones	+	-	-
• lactate	-	+	+
• alanine/glutamine	+	+	+
Energy supply sites			
• adipocytes	+	±	+
• muscle	+	+	-
• protein reserves	-	-	+
Metabolic processes			
• glycogenolysis	+ (early)	-	-
• gluconeogenesis	+ (early)	+	+
• proteolysis	+ (early)	+	+
• lipolysis	+	+	+
• ketogenesis	+	+	-
• ureagenesis	±	+	+

- ***Role of TPN***

a. starvation
- beneficial
- reverses process

b. sepsis
- little effect unless sepsis controlled

c. trauma
- preserves protein substrate supply
- does not prevent negative nitrogen balance

ADRENAL CORTEX

- the only steroids secreted in physiologically significant amounts are,
    a. mineralocorticoid - aldosterone
    b. glucocorticoids - cortisol, corticosterone
    c. androgens - dehydroepiandrosterone, androstenedione

- hypothalamus secretes CRH, which in turn increases pituitary secretion of ACTH
- ACTH release is also increased by,
    1. ADH & oxytocin
    2. angiotensin II
    3. β-adrenergic agonists

- ***cortisol*** has direct negative feedback on both CRH release & the pituitary response to CRH
- ACTH release is also decreased by somatostatin, β-END and enkephalins

- ACTH is the ***only*** known stimulus to adrenal cortisol synthesis (? SNS input)
- plasma half-life ~ 10-15 min
- ACTH binds to specific receptors on the plasma membrane
    → adenylate cyclase / cAMP / activated protein kinases
- normal daily output of ***cortisol*** ~ 40-80 µmol/d
    1. maximum level ~ 220-770 nmol/l 08:00-09:00
    2. minimum level < 220 nmol/l 22:00-24:00

- normal daily output of ***aldosterone*** ~ 0.1-0.7 µmol/d
- response to ***stress*** →
    1. cortisol levels > 500 nmol/l
    2. loss of diurnal rhythm
    3. maximal output of adrenal cortex ~ 550 µmol/d
        → plasma levels ~ 1600 nmol/l

- cortisol concentrations appropriate for acute illness are ***unknown***
- there is ***no correlation*** between plasma cortisol levels and the severity of disease
- in critically ill patients, cortisiol replacement should be considered if,
    1. baseline cortisol < 350 nmol/l
    2. short synacthen rise < 250 nmol/l

Addison's Disease

- ***Aetiology***

a. ***primary*** adrenal insufficiency **> 90%** destruction of functioning tissue
   i. autoimmune ~ 70% of cases
      ~ 50% of whom have positive plasma Ab's
   ii. infection
      - TB
      - overwhelming septicaemia
      - histoplasmosis, coccidioidomycosis, cryptococcosis
      - viral (CMV) - especially in AIDS
   iii. haemorrhagic/coagulopathic adrenal necrosis
      - overwhelming sepsis → Waterhouse-Friderichsen syndrome
      - meningococcaemia (usually children), Pseudomonas, *H. influenzae*
      - adults during pregnancy, or with anticoagulant therapy
      - retroperitoneal haemorrhage following trauma or ruptured AAA
   iv. surgical removal - breast carcinoma
   v. rare causes - bilateral metastatic carcinoma
      - amyloidosis
      - sarcoid

b. ***secondary*** adrenal insufficiency
   i. hypopituitary syndromes
      - post-partum necrosis - Sheehan's syndrome
      - pituitary apoplexy - acute haemorrhagic infarction of adenoma
   ii. pituitary supression by ***exogenous steroids***
      - increases with ↑ doses > physiological range
        ↑ duration of therapy (may be seen after 5 days)
      - daily dose > 37.5 mg hydrocortisone
        > 7.5 mg prednisolone
        > 2 mg dexamethazone
   iii. pituitary supression by steroid secreting tumours

c. interference with ***hormone synthesis***
   i. congenital hypoplasia - C_{21}, C_{11}, C_{17}
      - C_{21}-hydroxylase - adrenal virulisation ± hypoaldosteronism
      - C_{11}-hydroxylase - hypertension & virulisation
   ii. enzyme inhibitors - metyrapone, mitotane, aminoglutethamide
      - ***ketoconazole***, etomidate
   iii. cytotoxics

d. enhanced metabolism
   - ***rifampicin*** induces cytochrome P_{450} & may unmask latent hypoadrenalism

- ***Precipitating Factors***

a. surgery, trauma, sepsis
b. severe acute illness
c. cessation of steroid therapy
d. commencement of thyroid hormone replacement
e. coagulopathy

- ***Clinical Features***

a. weakness, fatigue ~ 100%
b. excess pigmentation ~ 90%
c. hypotension ± hypovolaemia ~ 90%
d. vomiting, diarrhoea, abdominal pain ~ 60%
e. biochemistry
   i. mild ***hyponatraemia***, hypoosmolality ~ 90%
   ii. ***hyperkalaemia*** (Na^+:K^+ ratio < 25:1) ~ 70%
   iii. ***hypoglycaemia***
   iv. mildly elevated urea
   v. mild anion gap ***acidosis*** - renal impairment, hypovolaemia, lactate, etc. + mild type IV RTA
   vi. hypercalcaemia
f. FBE
   i. normocytic anaemia - may be masked by hypovolaemia
   ii. ***eosinophilia*** & lymphocytosis
g. short Synacthen test * Synacthen 250 µg IMI
   i. no response - primary adrenal failure
   ii. normal response - hypopituitarism
h. thyroid function tests
   - R_X for ***myxoedema*** must include hydrocortisone to guard against adrenal crisis
   - may have ↑ TSH with low-normal T_4 levels, reversible with cortisol
i. CT scan - may show haemorrhage or carcinomatous infiltration

- crisis patients may appear clinically "septic", however ***eosinophilia*** and ***hypoglycaemia*** are unusual findings in sepsis *per se*
- patients with primary ***ACTH deficiency***,

1. are not hyperpigmented - absence of excess ACTH & MSH
2. not hyperkalaemic - adrenal responds to angiotensin II

Short Synacthen Test[1]			
Sample 1	09:00[2]	• 220-770 nmol/l	
Sample 2	09:30	• > 270 nmol/l	***increase***
Sample 3	10:00	• > 500 nmol/l	***minimum***

[1] Synacthen 0.25 mg IM

[2] in Addison's baseline levels are frequently < 100 nmol/l

NB: if secondary adrenal insufficiency is suspected (ACTH < 10 ng/l), then

Synacthen 1 mg IM daily / 3 days
SST performed 48 hours post last dose

- ***Treatment***

a. O_2 and ventilatory support

b. IV fluids
   i. colloids to restore blood volume
   ii. saline to replace Na^+ deficit
   iii. hypoglycaemia → $D_{50}W$ ~ 50 ml / 5 mins
   iv. ***hyperkalaemia*** rarely requires specific therapy *per se*

c. hydrocortisone → 200 mg stat, then 100 mg q6h
   - theoretically, a loading dose of 10 mg, followed by 8-10 mg/hr is sufficient
   - this gives a total dose of 200 mg / 24 hrs, which is normal maximal production

d. inotropes / vasopressors prn - may have decreased sensitivity

e. treatment of primary cause, or initiating factor

- ***Major Surgery***

- excess replacement is associated with,

1. ↑ susceptibility to infection
2. poor wound healing
3. ↓ glucose tolerance

NB: the normal adrenal response to major surgery ~ 75-150 mg / 24 hrs

R_X hydrocortisone 25 mg stat, followed by 25 mg qid

Cushing's Syndrome

- ***Aetiology***

  a. ***iatrogenic steroid administration*** = most common
  b. ***pituitary adenoma*** **~ 70%** (of remainder)
  c. ectopic ACTH ~ 15%
     → biochemical effects, ***not*** clinically Cushingoid
  d. adrenal adenoma / carcinoma ~ 15%

- ***Clinical Features***

  a. truncal obesity ~ 90%
  b. hypertension ~ 80%
     - ↑ renin substrate, ↑ vascular reactivity, ↑ blood volume 2° fluid retention
  c. plethoric face ~ 75%
  d. hirsutism ~ 70%
  e. proximal myopathy ~ 60%
  f. osteoporosis ~ 60%
  g. bruising, striae ~ 50%
  h. poor wound healing ~ 40%

  NB: patients with excess "ACTH" from ***rapidly*** growing tumours (eg. oat cell) usually present with hypokalaemia, muscle weakness & wasting, and hyperpigmentation; cf. ACTH from ***slowly*** growing tumours (ovary, thyroid medullary, thymic, pancreatic, bronchial adenoma), which present with classical Cushingoid features

- ***Electrolyte Abnormalities***

  a. high Na^+, HCO_3^- & glucose
  b. low K^+ & Ca^{++}
  c. metabolic ***alkalosis***

- ***Secondary Endocrine Effects***

  a. insulin resistance / glucose intolerance
  b. **2° *hyperparathyroidism*** ∝ ↑ urinary Ca^{++} excretion / ↓ GIT absorption
  c. antagonism of GH effects
  d. ↑ ACTH → ↑ pigmentation
  e. androgen excess

- ***Laboratory Investigations & Diagnosis***

1. increased urinary **17-(OH)-*steroids***
   - urinary 24 hr cortisol reflects freely filtered, ie. unbound cortisol and reflects hypercortisolaemia
   - may be falsely positive with stress or depression, & negative with renal failure
2. high plasma cortisol and loss of ***diurnal variation***
   - normal range ~ 140-690 nmol/l
   - trough level ~ 2400 hrs
   - peak level ~ 0600 hrs
3. dexamethasone suppression test
   - normal pituitary secretion is suppressible. cf. autonomous adenoma
   - suppressible function ***excludes*** Cushing's with 98% specificity

   i. ***low dose***
      - day 1 - baseline 09:00 plasma cortisol, ***optional***
        - dexamethasone 2mg orally at 23:00
      - day 2 - 09:00 plasma cortisol < 140 nmol/l
        < 50% of baseline on day 1
      - false positives - depression, alcohol abuse, "stress", OCP, 20-35% of obese

   ii. ***high dose***
      - plasma cortisol & ACTH - daily 09:00 for **7 *days***
      - day 1,2 - baseline, no dexamethasone
      - day 3,4 - dexamethasone 2 mg/d
      - day 5,6,7 - dexamethasone 8 mg/d
      - failure to suppress usually indicates ***ectopic ACTH*** or neoplasm
      - LIGW states suppression not achievable in ***critically ill*** ??
4. ACTH level

   i. low (< 20 pg/ml) → adrenal autonomy
      suppression by exogenous steroids

   ii. normal / high → pituitary

   iii. very high → ectopic ACTH
5. localisation procedures

   i. pituitary ~ 50% demonstrable by MRI
      - selective inferior petrosal vein sampling for ACTH

   ii. adrenal - majority demonstrable by CT

- ***Management***

1. resection of ***pituitary microadenoma***
   - usually trans-sphenoidal approach
   - Roizen, "anecdotally higher CVP and greater blood-loss, cf. other microadenoma"
2. unilateral / bilateral ***adrenalectomy***
   - preoperative suppression of hypothalamic/hypophyseal axis
     → ***glucocorticoid*** supplementation postoperatively
     → ***mineralocorticoid*** supplememtation after several days
   - ~ 10% will have an undiagnosed ***pituitary adenoma***, (Nelson's syndrome)
     i. rapid enlargement following adrenalectomy
     ii. ↑ pigmentation due to ACTH/MSH secretion
     iii. field defects / hypopituitarism from mass effect
3. ***radiotherapy***
4. ***medical therapy***
   - tumour (pituitary, adrenal, ectopic) not amenable to surgical resection
   - following unilateral adrenalectomy for adenoma/carcinoma, the other gland frequently enlarges & hypersecretes

i.	***ketoconazole***	~ 200-300 mg q6h - inhibits cytochrome P_{450} dependent steroid synthesis * also affects hepatic function, ∴ monitor LFT's
ii.	metyrapone , mitotane	- inhibition of steroid synthesis
iii.	spironolactone	- aldosterone antagonist
iv.	cyproheptadine	- hypothalamic ***serotonin*** (CRH) antagonist

NB: the aim of therapy is ***complete*** adrenal suppression,
\ may require perioperative ***steroid replacement***

Phaeochromocytoma

- rare ***neuroectodermal*** tumour → "autonomic hyperreflexia"
- produces different features in children and adults,

a. episodic or sustained hypertension
b. malignant hypertension
c. palpitations, tachyarrhythmias
d. angina, CCF
e. headaches
f. nausea, vomiting, weight loss
g. abdominal or thoracic pain
h. profuse diaphoresis

- ***"Rule of Tens"***

NB: ***all*** of the following occur with **~ 10% *incidence***,

1. ***not*** associated with hypertension
2. occur in children
3. occur as a familial tendency * ***MEN II***, MEN IIb
   - medullary carcinoma of the thyroid (***p***arafollicular)
   - ***phaeochromocytoma*** & ***p***arathyroid adenoma
4. multiple tumours
5. extra-adrenal location
6. extra-abdominal location if extra-adrenal

- ***Diagnosis***

a. elevated urinary metabolites * 24 hr urine
   i. spot metanephrine > 0.8 µg per mg of creatinine
   ii. *metanephrine > 2.2 µg / mg creatinine
   iii. *VMA > 5.5 µg / mg creatinine
b. raised urinary free catecholamines
c. elevated plasma catecholamines
d. CT with ^{131}I-labelled MIBG (^{131}I-meta-iodobenzylguanidine)

- ***Complications***

  a. malignant hypertension
  b. intracranial haemorrhage
  c. arrhythmias
  d. cardiomyopathy, IHD/AMI, LVF
  e. decreased intravascular volume

- ***Emergency Management***

  a. phentolamine 2-5 mg IV prn
  b. IV fluid expansion
  c. nifedipine 10 mg SL
  d. ± low dose β-blockers

- ***Preoperative Preparation***

  NB: **a-blockers + b-blockers + a-methyltyrosine**

  1. control hypertension BP < 160/90 mmHg for 48 hrs
  2. orthostatic hypotension BP ~ 80/45 mmHg
  3. no ST/T wave changes on ECG for > 2 weeks
     - ?? this may take weeks to months to achieve
  4. VPB's < 1 per 5 mins

- ***Anaesthetic Management***

NB: * avoid drugs which release endogenous catecholamines, histamine, etc.

- intraoperative problems, ***prior*** to tumour removal,

a. hypertensive episodes - intubation, laryngoscopy
- surgical stimuli
- tumour manipulation

b. haemorrhage from surgical site

c. arrhythmias

d. LVF

- intraoperative problems, ***following*** to tumour removal,

a. ***hypotension*** - relative lack of catecholamines
- unopposed α/β-blockade
- blunted reflexes
- relative hypovolaemia

b. hypovolaemia - blood loss
- vasodilatation

c. ***hypoglycaemia*** - relative lack of catecholamines
- insulin resistance
- β-blockade

d. persistent hypertension/tachycardia up to 2 weeks postoperatively

e. incomplete removal - return of signs/symptoms

NB: ***all patients*** should have repeat urinary screen 2/52 following removal

Conn's Syndrome

Def'n: benign ***adenoma*** of the zona glomerulosa of the adrenal cortex
rarely due to bilateral hyperplasia or carcinoma

a. hypertension — - mild diastolic hypertension
± headaches

b. ***hypokalaemia*** — - may be severe
- weakness ± paralysis
- polyuria 2° nephrogenic DI
- U waves, PVC's, arrhythmias

c. metabolic alkalosis

d. polyuria — ∝ hypokalaemic nephrogenic DI
± polydipsia

e. biochemistry
   i. hypokalaemic metabolic alkalosis
   ii. hypernatraemia — - Na^+ retention + water loss (DI)
   iii. low plasma renin activity — - ie. not 2° hyperaldosteronism

f. oedema — * classically ***absent***
- exhibit intrinsic renal "escape" from mineralocorticoid
- may occur in longstanding cases 2° to CCF & azotaemia

- ***Diagnosis***

1. diastolic hypertension ***without*** oedema
2. hypersecretion of ***aldosterone***- no decrease with volume expansion
3. hyposecretion of ***renin*** — - low PRA
   * no rise with volume depletion

- ***Hypokalaemic Alkalosis***

1. diuretics — - low Na^+ & Cl^-
   - high urea
2. vomiting — - very low Cl^-, low/normal Na^+
   - high urea
3. diarrhoea | laxatives — - low Cl^-, normal Na^+
   - high urea
4. mineralocorticoid excess — - normal/***high*** Na^+ & Cl^-
   - normal urea
5. citrate metabolism & correction of acidosis following massive blood transfusion

Secondary Hyperaldosteronism

1. nephrotic syndrome[§]
2. cirrhosis[§] *see below
3. CCF[§]
4. pre-renal failure[§]
5. renal artery stenosis
6. bronchogenic carcinoma

NB: [§]decreased ***effective*** circulating blood volume

- HPIM classifies these as follows,

1. ***normotensive*** states
   - i. pregnancy
   - ii. diuretic therapy
2. ***hypertensive*** states
   - i. 1° reninism - renin secreting tumours
   - ii. 2° reninism - renal artery stenosis (FMD, atheroma)
     - arteriolar nephrosclerosis
     - accelerated hypertension
   - iii. diuretic therapy
3. ***oedematous*** states
   - i. cirrhosis
   - ii. nephrotic syndrome
   - iii. CCF
4. Bartter's syndrome

▪ ***Cirrhosis***

- the diminution of effective plasma volume activates the renin-angiotensin system with elevation of plasma ***aldosterone***, further enhanced by the decreased metabolism in the liver
- however, early theories that hyperaldosteronism *per se* is responsible for the sodium retention in cirrhosis have been questioned
- there appears to be ***dissociation*** of aldosterone & distal tubular sodium reabsorption
- the dominant factor appears to be decreased distal delivery of filtrate
- this may relate to,

1. impaired intrarenal ***PGE_2 synthesis***
2. direct renal effects of angiotensin II
3. direct effects of the SNS
4. decreased kinin synthesis

- ***Bartter's Syndrome***

1. autosomal recessive - frequently symptomatic in childhood
2. renal juxtaglomerular apparatus ***hyperplasia***
3. high plasma ***renin*** activity, angiotensin I/II & aldosterone secretion
4. ***normal BP***
   - decreased vascular response to noradrenaline & angiotensin II[§]
5. ***hypokalaemia*** ± alkalosis
   ± hypomagnesaemia
   - weakness & periodic paralysis
   - polyuria → nephrogenic DI
   - overproduction of ***prostaglandins*** → altered Na^+/K^+ handling

NB: the principal defect is reduced NaCl absorption in the ***thick ascending LOH***
→ volume depletion → ↑ renin-angiotensin-aldosterone

- ↑ NaCl delivery to the late DT + ↑ aldosterone → severe K^+ wasting
- defective function of TA-LOH results in ***hypomagnesaemia*** & exacerbation of K^+ wasting
- ***hypokalaemia*** → ↑ PGE_2, PGI_2
  → further ↑ renin secretion
- angiotensin-II & aldosterone → ↑ renal kallikrien
  → ↑ plasma ***bradykinin***
- ***normal BP*** reflects,
  a. ↓ vasopressor activity of angiotensin-II - ? diminished by downregulation
  b. vasodepressor actions of PGE_2 & bradykinin

- ***Treatment***

a. oral K^+ supplementation
b. propranolol /atenolol - ↓ renin release
c. captopril - ↓ angiotensin II
d. spironolactone - antagonise angiotensin
e. PG synthesis inhibition - indomethacin, ibuprofen
   - aspirin

NB: → $\equiv^T$ ***opposite to RTA***

HYPOPITUITARISM SIMMOND'S DISEASE

- ***Aetiology***

a. hypophysectomy
b. irradiation
c. chromophobe adenoma
d. post-partum pituitary necrosis- Sheehan's syndrome
e. sarcoidosis
f. TB meningitis
g. head injury

- presentation is ***age dependent***,

a. child → dwarfism, failure to thrive
b. adult → ***hypothyroidism*** + loss of 2° sex characteristics
   - characteristic order of function loss,
   i. hypothyroidism
   ii. loss of 2° sex characteristics
   iii. bitemporal hemianopia
   iv. coma - hypothyroid
   - hypoglycaemia
   - Addison's

NB: ***aldosterone*** production usually masks ACTH & cortisone deficiency
central DI occurs late in the disease course

CARCINOID SYNDROME

Def'n: clinical syndrome due to ***malignant*** and ***metastatic*** carcinoid tumour which releases vasoactive substances in sufficient quantities to cause ***systemic effects***,

1. serotonin, histamine
2. bradykinin, kallikriens
3. PGE & PGF

• only ~ 5% of patients with a tumour develop the ***carcinoid syndrome***
• the ***primary*** site is usually either,

1. jejunum or ileum
2. bronchus
3. ovary

▪ ***Clinical Presentation***

1. episodic flushing
2. cyanosis
3. ***asthma***
4. vomiting, abdominal pain, ***diarrhoea***
5. fever
6. tachyarrhythmias
7. telangectasia*
8. tricuspid regurgitation*
9. pulmonary stenosis* *occur later

▪ ***Investigations***

a. ***hypoglycaemic*** episodes
b. hypoalbuminaemia
c. increased urinary excretion of ***5HIAA*** (≥ 10 mg/day)

- ***Indications for Surgery***

  a. primary resection

  b. debulking of metastases

  c. vascular surgery

• medical therapy is aimed at blockade of active hormonal agents,

1.	***somatostatin***	~ 50 µg IV or SC
2.	$5HT_1$ receptors	- ***ketanserin*** ~ 5-10 mg/hr
3.	5HT & H_1 receptors	- ***methotrimeprazine*** 2.5-5.0 mg IV - cyproheptadine 4-8 mg ó tds
4.	H_2 receptors	- ***ranitidine*** / cimetidine
5.	bradykinin	- steroids reduce release
6.	kallikrein	- ***aprotinin*** 200,000U over 60 min preop

THYROID DYSFUNCTION

- functions of thyroid hormones,
    1. regulation of basal VO_2 → ↑ NaK-ATPase, mitochondrial function
    2. regulation of lipid and CHO metabolism
    3. normal growth & maturation * especially CNS

- ***thyrotrophin releasing hormone*** acts predominantly in the adenohypophysis to release **TSH**
- however, also found in,
    1. neurohypophysis, brain, brainstem, medulla, spinal cord
    2. pancreas, GI tract
    3. adrenal
    4. placenta

- other actions include partial opioid antagonism and inhibition of pancreatic secretion
- ***thyroid stimulating hormone*** is released in response to TRH and is inhibited by,
    1. T_3 / T_4
    2. somatostatin
    3. glucocorticoids
    4. ***dopamine*** TRHIH

- T_3 has ~ 3x the potency of T_4 & 85-90% of the circulating T_3 is formed peripherally from T_4
- hence, virtually all of the activity of peripheral T_4 is due to T_3 → ie. $T_4 \equiv$ ***prohormone***
- normally ~ 45% of T_4 → **rT_3** which is effectively inactive
- ratio of rT_3:T_3 increased by,
    1. severe systemic illness
    2. malnutrition
    3. drugs - propylthiouracil, propranolol, glucocorticoids
       - amiodarone

Thyroid Hormone Binding				
Protein	Concentration (mg/dl)	Half-life (days)	**T_4** binding %	**T_3** binding %
Albumin	3,500	13	13	53
TBG	2	5	**67**	46
TBPA	15	2	10	1
Total percentage protein bound:			99.98%	99.8%
Normal Plasma level:			13-23 pmol/l	4-8 pmol/l

- ***Thyroid Function Tests***

		Hypo-thyroid	Lower limit	Normal	Upper limit	**Hyper-thyroid**
TSH	mU/l	> 4.5	0.2-0.4	0.5-3.5	3.6-4.5	< 0.2
Free T_4	pmol/l	< 8	8-12	13-23	24-26	> 26
Free T_3	pmol/l			4-8	8.1-10	>10

- in pituitary (secondary) hypothyroidism, the TSH is low relative to FT_4
- TSH levels are suppressed by adequate replacement in 1° hypothyroidism, but allow 8 weeks
- in early 1° hypothyroidism, plasma TSH is a more sensitive marker than FT_4
- patients on adequate replacement have plasma FT_4 levels at the upper range of normal
- FT_3 is insensitive in 1° hypothyroidism as levels only fall late in the disease

- artefactual increases in ***total*** $\mathbf{T_4}$ occur with increases in TBG,
    1. OCP, pregnancy
    2. hepatitis
    3. biliary cirrhosis

- decreases in TBG occur in,
    1. androgen therapy, corticosteroids
    2. chronic liver disease
    3. severe systemic illness * malnutrition, CRF, autoimmune

    NB: ***free hormone*** levels should always be used, as they correlate better with metabolic state and are uninfluenced by alterations of protein binding

- may also perform ***TRH stimulation*** test to assess 2° hypothyroidism & TSH response

- ***Other Tests***

1. ultrasound - thyroid masses, cystic, nodular, multinodular
   - needle biopsy
2. radionuclide scan
3. autoantibodies - anti-thyroglobulin, anti-thyroid microsomal
   - thyroid stimulating
   - especially for multinodular lesions
4. CT neck/thoracic inlet

Sick Euthyroid Syndrome

• severe illness, caloric deprivation, physical trauma, physiological stress may result in,

1. altered regulation of TSH sercetion
   - ↓ serum TSH → diagnosis of primary hypothyroidism difficult
   - TSH decreases markedly at 24-48 hrs, then tends to return to normal
2. ↓ peripheral conversion to T_3 → ↑ rT_3
   - inhibitor of peripheral ***5-monodeiodination*** ? cortisol, starvation
3. ↓ protein binding of thyroid hormones
   - circulating inhibitor of thyroid hormone binding to TBP's
   - artefactual decrease in resin uptake of T_3 & ∴ the FTI is also low
4. FT_4 levels are low/normal & plasma $t_{½\beta}$ ~ 1-5 days
   cf. normal ~ 7 days
5. ***euthyroid state*** is maintained by increased tissue T_3 receptors

NB: ↓ serum T_3
T_4 may be low, normal, or rarely ↑'d

• the presence of a very low T_4 in severe non-thyroidal illness → ***poor prognosis***
• measurements of T_3, T_4 and levels of hormone binding are usually adequate

NB: when direct assays of FT_4 are low, studies giving replacement show ***no improvement*** in survival, therefore these patients are considered ***euthyroid***

• differentiation from hypothalamic hypothyroidism can be helped by 3rd generation sensitive TSH assays,

a. non-thyroidal ilness > 0.05 µU/ml
b. hypopituitary insufficiency < 0.05 µU/ml

NB: prolonged ***dopamine*** infusion may produce true ***secondary hypothyroidism*** due to direct dopamine suppression of TSH secretion, some would provide thyroxine replacement in this group

• when the calculated FTI is low, presumably due to inhibition of TBP's, a euthyroid state is established by a ***normal TSH***

NB: abnormal thyroid function studies in acutely ill patients, ***without*** clinical signs of thyroid disease, should ***not*** be treated but reviewed after the acute illness has resolved (LIGW)

Hyperthyroidism

Causes

1. disorders associated with ***thyroid hyperfunction***
   - i. ***intrinsic*** → thyroid autonomy
     - hyperfunctioning thyroid adenoma
     - toxic multinodular goitre
   - ii. ***extrinsic*** → abnormal thyroid stimulator
     - excess TSH - ***rarely*** with pituitary adenoma
     - ***Graves' disease*** - most common, diffuse multinodular goitre
       - LATS, LATS-p, TSI, and TBII
     - trophoblastic tumour - choriocarcinoma (TSH-like)
2. disorders ***not*** associated with thyroid hyperfunction
   - i. disorders of hormone storage
     - subacute thyroiditis - with or without neck pain
     - chronic throiditis with transient thyrotoxicosis (CT/TT)
   - ii. extrathroidal source of hormone
     - thyrotoxicosis factitia - exogenous ingestion
     - ectopic thyroid tissue - struma ovarii
       - functioning follicular carcinoma
3. ***pregnancy*** ~ 5%, up to 3-6 months post-partum

Grave's Disease

- 3 clinical manifestations, which may appear separately or in combination,
  1. hyperthyroidism with diffuse multinodular goitre
  2. dermopathy
  3. opthalmopathy

  NB: ***most common cause***, diffuse multinodular goitre

- circulating IgG class Ab's attach to TSH receptor - LATS, LATS-p, TSI, and TBII
- high association with other ***autoimmune*** diseases,
  1. pernicious anaemia
  2. IDDM
  3. Addison's disease
  4. myasthenia gravis

- phases of exacerbation/remission, frequently progressing to thyroid failure & ***hypothyroidism***

Toxic Multinodular Goitre

- results from an ***autonomous nodule*** & often seen in elderly patients with a long history of goitre
- onset is often slow & may present with,

1. myopathy
2. resistant atrial fibrillation

Major Clinical Manifestations

a. nervousness, agitation, insomnia

b. weight loss, increased apetite

c. diarrhoea ± fluid & electrolyte disturbances if severe

d. warm moist skin, heat intolerance

e. muscular weakness
- especially proximal mm.
- common in ***apathetic*** form & in elderly

f. cardiac dysrhythmias - AF, VEB's, sinus tachycardia

g. cardiac / papillary muscle dysfunction ± mitral valve prolapse

h. congestive heart failure

i. menstrual abnormalities

j. Grave's disease → ***ocular signs***

i.	sympathetic overstimulation	- widened palpebral fissure - stare, lid-lag
	***opposite** of Horner's	- failure to wrinkle brow on upward gaze - tremor of eyelids on closing
ii.	ophthalmoplegia	- inability of upward / outward gaze - failure to converge, proptosis
iii.	congestive oculopathy	- chemosis, conjunctivitis - periorbital swelling, corneal ulceration
iv.	other manifestations	- optic neuritis | atrophy - hypertrophy of lacrimal glands

k. ***apathetic*** form
- most commonly seen in the elderly - resistant AF, CCF
  ± proximal myopathy

- ***Investigations***

1. biochemistry
   - hypercalcaemia, hyperglycaemia
   - hypokalaemia, hypomagnesaemia
   - ***type I RTA*** → metabolic acidaemia
   - ↑ ALP and hyperbilirubinaemia often occur
2. blood picture ± mild leukocytosis
3. TFT's
   - plasma TSH is unrecordable and non-responsive to TRH
   - FT_4 / FT_3 levels are elevated
   - rarely FT_3 levels are increased in isolation in **T_3** ***thyrotoxicosis variant***

- ***Management General***

• when the thyroid is functioning abnormally the ***cardiovascular system*** is the one most stressed
• although b-***blockade*** will control the rapid HR, this carries the risk of precipitating CCF
• however, decreasing the ***ventricular rate*** will usually improve LV filling and function
• occasionally patients require emergency surgery with uncontrolled hyperthyroidism, and control of the rate with propranolol (or esmolol) is unavoidable
• its use in this situation should be cautious, with the aid of PAOP measurement
• the aim, however, is not to anaesthetise anyone prior to control of their hyperthyroidism, ie. "life-threatening" cases only
• control may be achieved by the use of "anti-thyroid" medications, such as ***propylthiouracil*** or methimazole, both of which decrease the synthesis of thyroxine
• PTU also decreases the peripheral conversion of $T_4 \rightarrow T_3$
• there is now a trend toward preparation with β-blocker and iodides alone
• the later approach is quicker, 7-14 days, c.f. 2-6 weeks for the former
• both methods treat the symptoms and achieve ***devascularisation*** of the gland
• however, the later does not treat the abnormalities of LV function
• regardless of the approach, anti-thyroid medication should be administered chronically and through the morning of surgery
• prior to the euthyroid state being achieved, control during surgery may be achieved with ***propranolol*** ~ 0.2 to 10.0 mg IV, providing CCF does not supervene
• fluid and electrolyte balance should also be restored
• treatment with β-blockers ***does not*** invariably prevent the onset of ***thyroid storm***
• some recommend ***anticholinergics*** be avoided, due to the inhibition of sweating and tachycardia

• patients possessing large goitres and obstructed airways can be handled in the same way as for any patient with ***upper airway obstruction***,

a. premedication should avoid excessive sedation
b. an airway should be established, often with the patient awake
c. a firm armoured tube should be used
d. ? the patient should not be paralyzed prior to intubation

• preoperative CT scanning may be desirable to determine the extent of ***compression*** and ***retrosternal extension***

• the most important perioperative ***complications*** of thyroid surgery include,

1. thyorid storm
2. recurrent laryngeal nerve injury
3. hypocalcaemic tetany

• bilateral recurrent laryngeal nerve injury results in ***stridor*** and airway obstruction due to unopposed adduction of the vocal cords and closure of the glottic aperture
• immediate intubation is required, usually followed by ***tracheostomy***
• unilateral recurrent laryngeal nerve injury often goes unnoticed due to compensation by the patent side

Thyroid Storm

1. without treatment → ***mortality*** **~ 10-20%**
2. F > M - usually unrecognised or poorly controlled Grave's disease
3. ↑ T_3 & FT_4 - but levels ***do not*** correlate with the severity of the state
   - results more from loss of ***end-organ*** ability to modulate response
4. ***precipitating factors*** **~ 50%**
   i. intercurrent illness - especially infection
   ii. trauma
   iii. operative procedures
   iv. uncontrolled ***diabetes mellitus***
   v. ***labour*** and pre-eclampsia/eclampsia
5. associated with surgery
   - excessive palpation of the gland
   - incomplete preparation
   - inadequate doses of β-blockers perioperatively
6. uncommon factors
   - radio-iodine in unprepared patients
   - iodide drugs - amiodarone, haloperidol
   - large doses of thyroid hormones ~ 3-7 days onset

NB: now ***uncommon*** in association with thyroid surgery

- ***Clinical Presentation***

1.	***fever***	≥ 41°C * usually absent in uncomplicated thyrotoxicosis - usually moist warm skin
2.	CVS	- dyspnoea and fatigue - sinus ***tachycardia*** (may be > 160 bpm) - resistant AF, ***ventricular arrhythmias*** - ***congestive failure***, cardiomegaly ± ECG changes of LVH - mitral valve prolapse (both treated and active disease)
3.	CNS / MSS	- tremor, increasing restlessness, nervousness and insomnia - progressing to ***delerium***, then ***coma*** and death - hyperactive tendon reflexes, hyperkinesis - muscle weakness, especially in ***apathetic*** form - syndrome $\equiv^{t}$ UMN lesion with asymmetrical reflexes - ***rhabdomyolysis***
4.	GIT	- nausea, vomiting and diarrhoea - poor ***oral bioavailability*** of drugs, rapid intestinal transit - severe abdominal pain, suggesting intra-abdominal pathology - ***jaundice*** is a poor prognostic sign
5.	neck	- goitre & thyroid bruit if Grave's disease, ***difficult intubation*** - dysphagia, ***aspiration risk***
6.	biochemistry	~ 15% have ***hypercalcaemia***, but rarely an emergent problem * ***hypokalaemia & hypomagnesaemia*** may be severe, especially in apathetic form * don't use digoxin for control of AF → amiodarone
7.	FBE	- leukocytosis common

- ***Differential Diagnosis***

1.	drug induced	- amphetamine overdose, cocaine - MAO inhibitors & hypertensive crisis
2.	drug withdrawal	- delerium tremens - opioid withdrawal
3.	hyperthermic synd.	- MH, MNS, heat stroke
4.	phaeochromocytoma	
5.	panic attack, mania/hypomania	

- ***Management***

1. ***ABC***
   - supportive measures
   - IV fluids, dextrose, ***thiamine*** & B group vitamins
2. b-***adrenergic blockade***
   - antagonises the effects of thyroid hormones and decreases the sensitivity to circulating catecholamines
   - inhibits the peripheral conversion of $T_4 \rightarrow T_3$
   - tachycardia, fever, hyperkinesis & tremor respond promptly
   - improves proximal myopathy, periodic thyrotoxic paralysis, bulbar palsy and thyrotoxic hypercalcaemia
   - ***propranolol* ~ 0.5 mg** increments IV with CVS monitoring (up to 10 mg)
   - oral doses 20-120 mg q6h but may need to ↑ dose due to ↑↑ clearance
   - β_1-selective antagonists ***do not*** inhibit the conversion of $T_4 \rightarrow T_3$ as effectively, but may be preferred in the presence of CCF or airways disease
   - ***reserpine*** has been largely superseded, but may be of benefit in propranolol resistant hyperthyroidism
3. ***steroids***
   - usually administered as a ***relative deficiency*** may be present
   - also, potential for associated autoimmune disease, ie. Addison's
   - inhibit the peripheral conversion of $T_4 \rightarrow T_3$
   - hydrocortisone ~ 100 mg IV q6h
4. ***thioamides***
   - ***no*** parenteral preparation is available
   - theoretical advantages of PTU have ***not*** been supported in clinical trials

   i. ***prophylthiouracil***
      - rapid onset, though, GIT absorption is impaired and unreliable during a crisis
      - blocks the iodination of tyrosine and the peripheral conversion of $T_4 \rightarrow T_3$
      - administered orally or via NG tube ~ 1g loading dose
        ~ 200-300 mg q4-6h

   ii. ***methimazole***
      - ***does not*** inhibit the peripheral conversion of $T_4 \rightarrow T_3$
      - use only if PTU contraindicated
      - less rapidly absorbed but longer acting
      - doses are ~ $1/10^{th}$ those for propylthiouracil ~ 100 mg loading dose

   iii. ***carbimazole***
      - metabolised to methimazole, relative potency ~ 0.6:1
      - transient ***leukopenia*** is common but agranulocytosis rare

5. ***iodine***
   - large doses inhibit the synthesis and release of thyroid hormones
     → ***Wolff-Chaikoff effect***
   - administration delayed ³ **1 *hr*** after thioamides ? why
   - Lugol's iodine, saturated solution potassium iodide (SSKI), potassium iodide, or sodium iodide
   - NaI ~ 1g IV q12h or continuous infusion, or equivalent doses of other agents
6. ***lithium***
   - same effects as iodine and may be used in allergic patients
   - doses 500-1500 mg daily but takes 5-7 days for steady state
   - requires monitoring plasma levels ~ 0.7-1.4 mmol/l
7. ***digoxin***
   - following the correction of ***hypokalaemia*** if AF is present
   - requires larger doses due to ↑ clearance & ↓ efficacy
   - usually ineffective alone ± β-blockers, verapamil, amiodarone, reserpine
   - ***amiodarone*** also inhibits peripheral de-iodination of T_4
8. other measures
   i. IVT, electrolytes, glucose
   ii. treat fever, but ***not aspirin***, as this displaces $T_{3\text{-}4}$
   iii. vitamins, especially ***thiamine***
   iv. ***cholestyramine*** binds thyroxine in the GIT
   v. ***activated charcoal*** in thyroxine overdosage
   vi. ***plasma exchange*** in refractory cases, following 24-48 hrs aggressive R_X
   vii. ***dantrolene*** has been used with symptomatic improvement

Hypothyroidism

NB: common, ranging from **3-6%** of the population,
usually ***subclinical*** → normal T_4/T_3 but ↑ TSH

- ***Aetiology***

1. thyroidal ³ **95%**
   - i. ***thyroprivic***
     - ***primary idiopathic*** - circulating antithyroid Ab's
       ± multiple endocrine neoplasia syndrome (MEN I, pituitary adenoma)
       ± IDDM, SLE, RA, Sjögren's synd., pernicious anaemia, chronic hepatitis
     - postablative - surgery & radio-iodine for Graves' disease
       * ***most common cause***
     - post-radiation - lymphoma, SCC
     - congenital developmental defects
   - ii. ***goitrous***
     - congenital biosynthetic defects
     - maternally transmitted - iodides, antithyroid drugs
     - chronic thyroiditis - Hashimoto's
     - iodine deficiency
     - drug induced - aminosalicylate, phenylbutazone
       - amiodarone, lithium, iodides
2. suprathyroidal **< 5%**
   - i. pituitary - Sheehan's syndrome
     - panhypopituitarism
   - ii. hypothalamic
3. self-limiting
   - i. following suppressive therapy with ***antithyroid drugs***
   - ii. following surgical excision of ***functioning adenoma***
   - iii. thyrotoxicosis of ***pregnancy***
   - iv. subacute thyroiditis
   - v. chronic thyroiditis & transient hypothyroidism

- ***Common Causes of Goitre***

   - i. nontoxic endemic goitre - iodine deficiency, most common worldwide
   - ii. Graves' disease
   - iii. toxic multinodular goitre
   - iv. adenoma, carcinoma
   - v. Hashomoto's thyroiditis
   - vi. chronic thyroiditis

- ***Clinical Features***

a. ↓ BMR ~ 40-50%

b. CNS
- slow mentation, lethargy
- sensitivity to ***sedatives / opioids***
- tendency to hypothermia, cold intolerance
* $CMRO_2$ not decreased, except with ***hypothermia***

c. CVS

i. ↓ LV function
~ 50-60% decrease in contractility
~ 40% decrease in CO
~ 60% pericardial effusion
- cardiomegaly and increased CAD

ii. ↓ blood volume ~ 10-25%

iii. baroreceptor dysfunction ↓ responses ∝ IPPV, hypovolaemia, valsalva etc.

iv. bradyarrhythmias, AF

v. accelerated ***athersclerosis***

d. respiratory - ↓ MBC, ↓ DL_{CO}

- ↓ ***central respiratory drives*** ~ 10-15% of normal O_2 drive
~ 30-40% of normal CO_2 drive → ↑ P_{aCO2}
- obstructive sleep apnoea syndrome

e. gastrointestinal

i. decreased apetite, increased weight

ii. gastric stasis & ↓ airway reflexes → ↑ ***aspiration risk***

iii. constipation

f. decreased motor activity, stiffness & muscle cramps, prolonged relaxation of DTR's

g. connective tissue → ***myxoedema*** (**pretibial = hyperthyroidism*)

i. dry & thickened skin & hair, loss of outer 1/3 of eyebrows

ii. deepening of voice

iii. thickened tongue

iv. amyloidosis

v. carpal tunnel syndrome

h. drugs
- impaired liver / renal function → ↑ $t_{½\beta}$'s
- ↓ MAC for volatile agents
- ↑ sensitivity to sedatives / opioids

- ***Investigations***

a. electrolytes
   - ↓ blood volume / ↑ ECF fraction
   - ***hyponatraemia*** - ↑ ADH secretion
     - ↓ tubular Na^+ reabsorption / ↓ free water clearance

b. FBE
   - normochromic normocytic anaemia
   - ***pernicious anaemia*** **~ 12%**

c. AGA's ↑ P_{aCO2} / ↓ pH
   ↓ P_{aO2}

d. ECG
   - low amplitudes, flattened / inverted T waves
   - ↓ phase 4 depolarization, ↑ APD & QT_C
   - bradyarrhythmias, AF ± J-waves if hypothermic

e. TFT's
   - ↑ TSH - except pituitary hypothyroidism
   - ↓ FT_4 / FT_3

f. CXR
   - cardiomegaly, effusion, CCF

- ***Clinical Assessment***

a. severity
   - bradycardia
   - hyporeflexia & slow recovery, "hung-up" reflex
   - temperature
   - skin, hair, facies, voice

b. CNS
   - conscious state
   - airway protection reflexes

c. CVS
   - bradycardia
   - IHD, CCF, pericardial effusion
   - if heart normal size, then ?? hypothalamic origin
   - may be ***hypertensive*** 2° hypercarbia

d. respiratory
   - hypoventilation ± hypercarbia
   - pulmonary oedema
   - recurrent infection
   - OSAS ± 2° pulmonary hypertension

Myxoedema Coma

- likely scenarios,
    1. hypothyroidism unmasked by ***concurrent illness***
    2. known hypothyroid and ***emergency surgery***

- precipitating factors,
    1. surgery, trauma
    2. anaesthesia, sedatives, narcotics
    3. sepsis, hyperthermia
    4. any severe illness

    NB: ***mortality*** $\leq$ **50%**

- ***Treatment***

    a. assisted ventilation with ***slow*** correction of ***hypercarbia***

    b. IV dextrose for ***hypoglycaemia*** - 50% not D_5W

    c. water restriction ± hypertonic saline for ***hyponatraemia***

    d. passive rewarming for ***hypothermia*** $\leq$ 0.5°C/hr

    e. T_3 ~ 5-20 µg IV in 100 ml N.saline slowly over 30-60 min, or
    T_4 ~ 200-500 µg IV ($\rightarrow$ more constant T_3 levels)

    ** ***no*** studies as to best dose or form of replacement

    f. ***hydrocortisone*** ~ 400 mg on first day, then reducing
    - assess adrenal function with ***short Synacthen*** test once euthyroid
    - correction of hypothyroidism may unmask underlying associated adrenal deficiency

    g. screen for ***sepsis***

    h. treat underlying illness

    i. avoid sedatives, narcotics, etc.

- ***Management for Emergency Surgery***

a. ABC
   - avoid sedatives, narcotics | use conservative doses
   - intubate if airway reflexes absent ? antacids, ranitidine

b. ***hydrocortisone*** ~ 100 mg IV q6h for first 24 hrs
   - acute adrenal crisis may be precipitated in severe hypothyroidism with thyroxine

c. commence **T_3** replacement if,
   i. no active IHD ? how to be sure
   ii. no depression of conscious state - pre-coma or coma
   iii. surgery can be delayed several hours to assess the effect of T_3
   iv. continuous ECG monitoring available

   → ~ 5-20 µg in 100 ml N.saline IV slowly over 30-60 min

NB: otherwise ***withhold*** until after surgery and give low dose slowly

- excessive thyroxine doses may precipitate myocardial ischaemia / infarction even in the presence of normal coronary vessels
- therefore, use T_3 with 5%NSA as the carrier & monitor FT_3 & TSH levels

- LIGW suggests T_3 →

1. ***loading dose*** ~ **10 µg**
2. infusion ~ 20 µg/d

Simple (nontoxic) Goitre

- causes,

1. idiopathic
2. excess TSH - iodine deficiency
   - ingested goitrogen
   - biosynthetic defect
3. early toxic MNG - should be detected by newer sensitive assays

NB: R_X $\downarrow$ TSH stimulation - remove offending agent
- I^- supplementation
- L-thyroxine ~ 100-200 µg/day

Thyroid Nodules

- ***Adenomas***

1. papillary
2. follicular - most common & most likely to be functional
3. Hurthle cell

NB: ***functional nodules*** of any type are ***less*** likely to be malignant

- ***Carcinoma***

- males > females
- previous irradiation to the neck

1. follicular epithelium
   i. anaplastic - rare, highly malignant & rapidly fatal
   ii. follicular
   iii. papillary ~ 60%, bimodal frequency of presentation
   - simple excisions $\equiv^t$ radical neck resections
2. parafollicular C cells - more aggressive
   - familial incidence
   - ***MEN II*** $\rightarrow$ medullary carcinoma
     + ***phaeochromocytoma***
     + parathyroid adenomas

DIABETES MELLITUS

Aetiology

a. ***primary, idiopathic, diabetes mellitus***

i. *type I*

- "juvenile onset" ≤ 40 years onset
  peak ~ 12-14 years
- absolute insulin deficiency ≥ **90%** loss of islet mass
- plasma insulin/C-peptide levels are unmeasurable & elevated glucagon
- HLA & autoimmune associations ≤ 85% antipancreatic B cells
  ~ 50% antipancreatic T cells
- family history ***rare***, MZ concordance ~ 50%

ii. *type II*

- "maturity onset" ≥ 40 years onset
  peak ~ 60 years
- have both ***insulin resistance*** and relative ***insulin deficiency***
- hyperglycaemia does not occur until insulin secretion decreases
- exaggerated glucagon response to ingested nutrients
- obesity & gestational DM are associated & are risk factors
- ***strong*** family history, MZ concordance ~ 100%

b. ***secondary diabetes mellitus***

i.	drugs	- corticosteroids, thiazide diuretics, oestrogen therapy - β_2-adrenergic agonists (inotropes)
ii.	adrenal	- Cushing's syndrome, Conn's syndrome - phaeochromocytoma
iii.	pancreatic disease	- chronic pancreatitis, haemochromatosis - pancreatic calcification (hyper-Ca^{++}) - cystic fibrosis - glucagonoma, somatostatinoma, carcinoma - hypocalcaemia - amyloidosis - congenital β-cell absence
iv.	viral pancreatitis	- rubella, coxsackie B_4, mumps
v.	pituitary tumours	- acromegaly, Cushing's disease
vi.	hyperlipidaemias	- III, IV, V
vii.	others	- Down's syndrome - G6PD deficiency - acute intermittent porphyria - muscular dystrophy - many congenital syndromes

■ ***Insulin***

• synthesised from ***proinsulin*** in β-cells of pancreas,

a. storage ~ 200^{U}

b. plasma activity ~ 10-15% cf insulin
   - but ***more*** effective in suppressing hepatic glucose production

c. forms equal amounts of ***insulin*** & ***C-peptide***

• basal insulin release,

a. during fasting limits ketosis & catabolism ~ 1 U/hr

b. total daily secretion of insulin ~ **40 U** (50% removed by liver)

• only **~ 7%** of plasma insulin activity is supressed by anti-insulin Ab's
• the remaining 93% constitutes ***nonsuppressible insulinlike activity, NSILA***

a. somatomedins ~ 5%
   - insulinlike growth factors - IGF I & II

b. nonsuppressible insulinlike protein - NSILP

Factors Influencing Insulin Release

Stimulation[1]	**Inhibition**
glucose & fructose	somatostatin
amino-acids • leucine, arginine	insulin
drugs • sulphonylureas • theophylline (PDE inhibitors) • acetylcholine	drugs • diazoxide, thiazide diuretics • phenytoin • 2-deoxyglucose
b-***agonists*** ↑ glucose & K^+ uptake	α_1-agonists
GIT hormones • gastrin, secretin • cholecystokinin-pancreozymin • enteroglucagon (GIP)	
glucagon	

[1] insulin production in a normal adult ~ **40 U/d**, though only ~ 50% reaches the systemic circulation

■ ***Insulin Resistance***

• state in which normal amounts of insulin (0.5U/kg/day) produce a subnormal biological response
• clinically this is not usually considered until patients are on > **2 U/kg/day**

▪ ***Diagnosis***

- sample should be ***venous plasma*** not whole blood, as later levels may be ~ 13% lower
- fasting level < 6 mmol/l, or random level < 8 mmol/l → diagnosis excluded
- WHO criteria,

1. fasting venous ***plasma glucose*** ³ **7.8 mmol/l** (NB: plasma 15% > whole blood)
   ≥ 2 occasions
2. glucose tolerance test
   - loaded with CHO ~ 150 g/day for 3 days
   - fasted > 8/24 overnight - apart from H_2O
     * no smoking, no alcohol, no exercise
   - blood samples taken at time 0, 1 and 2 hrs post **75g** of dextrose (300 ml 25%)
   - if the **2 hr** venous plasma glucose is,

   i. **< 7.8 mmol/l** → normal

   ii. ³ **11.1 mmol/l** → diabetic
   - at least one other test value ≥ 11.1 mmol/l
   - ie. a minimum of 2 values are required during the test interval

   iii. **7.8 - 11.0 mmol/l** → diagnosis of ***impaired glucose tolerance***
   - if one other value during the 2 hr test is ≥ 11.1 mmol/l
   - ***do not*** get ***microangiopathy***, but are at risk of large vessel disease
   - rate of progression to diabetes is ~ 3% pa untreated
     ~ 1.3% with dietary control
     ~ 0.1% with oral hypoglycaemics

- believed the degree of hyperglycaemia is relevant to the risk of microangiopathy
- selection of 11.0 mmol/l is taken as some individuals below this show ***spontaneous remission***
- causes of an abnormal GTT,

1. prolonged inactivity
2. major stress with previous 3/12 - AMI, stroke, trauma, surgery
3. minor stress within previous 2/52 - "flu-like" illnesses
4. dietary irregularity - starvation
   - recent weight change > 2 kg
5. hepatocellular disease
6. endocrinopathies
7. hypokalaemia - inhibits insulin release
8. pyridoxine deficiency
9. drugs - thiazides, adrenergic agonists

- ***Other Investigations***

  a. plasma lipid studies

  b. glycosylated Hb Hb_{A1c}
     - normal individuals have levels **< 6%**
     - control to this level in diabetics is associated with excessive ***hypoglycaemia***
     - debate as to the optimal level for control

  c. ECG

  d. E,C&U

  e. opthalmology review

- ***Type I Diabetes***

  a. ***juvenile onset*** - usually but not essential

  b. an ***autoimmune*** disease with a MZ ***concordance* ~ 40-50%**
     - auto-Ab's to ***glucose transporter*** of β-cells

  c. a relative or absolute deficiency of insulin

  d. a tendency to both,
     i. ketotic hyperglycaemic coma
     ii. hyperglycaemic, hyperosmolar, non-ketotic coma

- insulin levels are low or immeasurable, as are those of C-peptide
- increase insulin requirement in postmidnight hours → "dawn phenomenon"
- results in early morning hypoglycaemia due to nocturnal surges in GH secretion

- ***Type II Diabetes***

  a. usually an adult onset & frequently associated with ***obesity***
     - also pregnancy, drugs and other endocrine abnormalities

  b. MZ ***concordance* ~ 100%**

  c. peripheral ***insulin resistance***

  d. no tendency toward ketoacidosis or hyperosmolar, non-ketotic coma

- management varies from diet, to oral hypoglycaemics ± insulin

■ ***Oral Hypoglycaemics***

• ***sulphonylureas*** act by,

1. increasing release of insulin from the pancreas
   - primarily by ↑ β-cell ***sensitivity*** to glucose ∝ ↑ membrane gK^+
   - they ***no not*** ↑ insulin production & are not useful in IDDM
2. improving peripheral utilisation of glucose
   - ? increased receptor numbers, or increased binding

• alcohol may potententiate their action, cf. thiazides which are antagonistic
• newer agents, ***glyburide & glipizide*** have a longer duration of hypoglycaemic effect (~ 24 hrs) and fewer drug interactions
• ***chlorpropamide*** has the longest half-life & these agents may produce hypoglycaemia for up to **50 *hrs*** post-administration
• therefore hypoglycaemic episodes due to these agents require ***observation***
• side-effects,

a. rashes, pruritis
b. hyponatraemia ("SIADH"), hypoglycaemia
c. "disulphiram-like" reaction to alcohol
d. nausea, vomiting, cholestasis
e. haemolytic anaemia, bone marrow aplasia

• the ***biguanides*** act by,

1. ↓ ***hepatic gluconeogenesis***
2. ↑ glucose utilisation through ***anaerobic metabolism***
3. ↓ intestinal absorption of glucose

• unlike the sulphonylureas, these agents are unlikely to result in weight gain
• ***contraindicated*** with,

a. renal insufficiency - entirely renally excreted
b. pregnancy
c. liver disease
d. alcoholism
e. cardiopulmonary insufficiency- anaerobic metabolism

• side-effects,

a. diarrhoea
b. ***lactic acidosis***
c. rarely hypoglycaemia

- ***Complications: Acute***

1. hypoglycaemia ± coma
2. ketoacidosis ± coma
3. hyperglycaemic, hyperosmolar, non-ketotic coma

- ***Complications: Chronic***

1. ***cardiovascular***
   - i. ↑ atherosclerosis - IHD, AMI, HT, CVA, PVD, foot ulcers
   - ii. microangiopathy
     - retinopathy - capillary microaneurysms, haemorrhages
       - venous dilatation, waxy exudates
       - new vessel formation
       - fibrotic bands, retinal destruction, blindness
     - peripheral & autonomic neuropathy
   - iii. hypertension
   - iv. cardiomyopathy - infiltrative/ischaemic with diastolic dysfunction
2. ***other ocular***
   - cataracts, Horner's syndrome, Argyll-Robinson pupil
   - cranial nerve palsies - III, IV & VI are common
3. ***renal***
   - range from mild renal impairment to ESRF 2 ° progressive GN
   - recurrent UTI, papillary necrosis, CRF
   - higher rate of renal transplant rejection
4. ***joint-collagen tissue*** abnormalities
   - stiff joint syndrome - TMJ and atlanto-axial immobility
   - poor wound healing - decreased tensile strength / rate of tissue healing
   - necrobiosis lipoidica - breakdown of collagen
   - lipodystrophy, xanthelasma
5. ***immune deficiency***
   - nosocomial infections - wound, respiratory tract, UTI
6. ***neuropathic***
   - i. peripheral neuropathy - trophic changes, ulcers, infections
     - neuropathic joints
   - ii. autonomic neuropathy - postural hypotension, CVS instability
     - silent MI, asymptomatic hypoglycaemia
     - bladder retention, impotence
     - gastric stasis, diarrhoea, diminished sweating
7. ***psychological***
   - chronic disease state & recurrent hospitalisation

- ***Degree of Control***

NB: the evidence that ***tight control*** of the BSL reduces the rate of progression, or that poor control accelerates the progression, is ***suggestive*** but ***not definitive***

• high concentrations of glucose promote non-enzymatic ***glycosylation*** reactions, which may be in part responsible for,

1. ↓'d tissue elastance
   - stiff joint syndrome
   - poor wound healing
   - ↓ myocardial compliance
2. ↑ macroglobulin synthesis
   - ↑ blood viscosity
3. ↑ ICF volume
   - production of nondiffusable species (sorbitol etc) with intracellular swelling
   - newer therapies (aldose-reductase inhibitors) aim to reduce formation

• however, ***insulin*** may be directly toxic to small blood vessels and retinopathy initially ***worsens*** with tight control
• chronic therapy does reduce the leakiness of the glomerular capillaries to albumin, and the retinal capillaries to fluorescein dyes
• problems secondary to high levels of peripheral insulin are absent with administration into the ***portal system***

• tight control does improve wound tensile strength & decrease infections in animal models
• hyperglycaemia, neuropathy, athersclerosis & microangiopathy may contribute to wound failure
• insulin is necessary in the early stages of the inflammatory response, but appears to have no effect on collagen formation after the first 10 days
• epithelial wounds do not require leukocyte infiltration and collagen formation for healing and are thus not impaired in the diabetic patient

• ***infections*** account for
   ~ 2/3 of postoperative complications
   ~ 20% of perioperative deaths,

a. altered leukocyte function
   - ↓ chemotaxis & ↓ phagocytic activity of granulocytes
   - ↓ intracellular killing of pneumococci & staphlococci

b. function is returned to near-normal levels with tight control BSL < 12.5 mmol/l

• Cruse *et al.* (Arch.Surg 1973) in a review of 23,649 surgical patients,

a. diabetic wound infection ~ **10.7%** cf. 1.8% in non-diabetics

b. when ***age*** is accounted for, the difference in incidence ***is not*** statistically significant

NB: ie. diabetes increases in frequency with ***age***
wound infection increases with ***age***

- 430 consecutive patients from ***out-of-hospital arrest***, mean BSL levels at presentation,
  a. patients who never wakened ~ 341 ± 13 mg/dl (~ 19 mmol/l)
  b. patients who wakened ~ 262 ± 7 mg/dl (~ 14.5 mmol/l)
     i. with CNS deficit ~ 286 ± 15 mg/dl (~ 16 mmol/l)
     ii. with CNS intact ~ 251 ± 7 mg/dl (~ 14 mmol/l)
  c. consistent with ***hyperglycaemia*** → worse neurological outcome
  d. supported by studies of ***global ischaemia,*** not those of focal ischaemia

  NB: 1. ? does hyperglycaemia worsen neurological outcome, or is it simply a marker of more profound physiological derangement & prolonged resuscitation

  2. current recommendation for diabetics undergoing procedures with potentially decreased CBF is to maintain ***BSL < 14 mmol/l*** (250 mg/dl)

- in a 1980 study of 340 diabetics vs. 2522 nondiabetics undergoing ***CABG***,
  1. moderate increase in ***operative mortality*** ~ 1.8% vs. 0.6%
  2. requirement for ***inotropic support & IABP*** ~ 5x ↑

- reasons for these differences include,
  1. more extensive and ***diffuse*** CAD
  2. higher incidence of,
     i. preoperative hypertension
     ii. cardiomegaly
     iii. diffuse hypokinesis
     iv. previous MI
  3. IDDM patients with CAD have stiffer LV's → ↑ LVEDP
  4. autonomic dysfunction → ↓ preload regulation
  5. CPB, hypothermia and stress reactions decrease the responsiveness to insulin
     - results in marked ***hyperglycaemia***, even without glucose in the IVT
     - washed cells have been advocated as ***ACD*** significantly increases BSL
     - insulin administration has little effect until rewarming
     - ***lactate*** containing solutions are gluconeogenic & poorly absorbed
  6. IDDM with poor LV function may have operative ***mortality ~ 10-15%***

▪ ***Emergency Surgery & Ketoacidosis***

• the likelihood of intraoperative cardiac arrhythmias, CCF or hypotension are markedly reduced if the metabolic decompensation can be at least partially reversed
• however, delaying surgery where the underlying condition will continue to exacerbate ketoacidosis is futile, \

a. resuscitate - ABC

b. ***fluid / volume*** resuscitation

i. colloid ~ 10-20 ml/kg prn

ii. crystalloid ~ 15 ml/kg/hr → 5 ml/kg/hr over 4-5 hours
- **0.9% saline** + KCl 20 mmol/l[§]
- **0.45% saline** - if Na^+ > 150 mmol/l

iii. dextrose - when BSL < 20 mmol/l
* total body ***deficit***

c. ***insulin*** ~ 10-20[U] IV ~ 0.25[U]/kg
+ infusion **U/hr ~ BSL (mmol/l)/8**

d. ***potassium***[§] ~ 20 mmol/hr ~ 0.3 mmol/kg/hr
- 30-50 mmol/hr if HCO_3^- used
± HCO_3^-, $H_2PO_4^-$ and Mg^{++}

i. $NaHCO_3$ - consider if persistent pH < 7.0
- give 1 mmol/kg in 500 ml (~ 1.4%) over 1 hr
* ***no*** evidence for benefit

ii. KH_2PO_4 - consider if [plasma] < 0.7 mmol/l
- give as K^+ salt 7-10 mmol/hr

iii. $MgSO_4$ - no need unless tachyarrhythmia

e. ***treat underlying cause***

• the actual amount of insulin given is less important than regular ***monitoring*** of the BSL, H^+ & K^+
• the number of insulin binding sites is limited, thus the rate of decline of plasma glucose is limited to a fairly constant → ↓ max ~ ***4-5.5 mmol/l/hr***
• the ***anion gap*** component of the acidaemia may be due to any, or a combination of,

1. ketoacids
2. lactic acid
3. organic acids due to renal insufficiency

• hyperchloraemic, normal anion gap acidosis may result from DKA treated with N.saline only
• ***bicarbonate*** therapy is controversial,

1. respiration and myocardial function are depressed at pH < 7.0
2. rapid correction with HCO_3^- may result in,
   i. paradoxical CSF & ICF acidosis due to diffusion of CO_2
   ii. altered CNS oxygenation & decreased CBF
   iii. production of unfavourable osmotic gradients

Regimens for Control

- ***General***

1. two distinct disease entities → different perioperative management
2. different regimens permit almost any degree of blood glucose control,
   i. ***frequent measurement*** of BSL is recommended
   ii. the tighter the desired control, the more frequently BSL must be monitored
3. there is debate as to how "tight" perioperative control should be,
   i. chronic tight control of type I → ↓ complications
   ii. some benefit has been shown for - ***pregnancy***
   - ***CABG***
   - focal/global ***CNS ischaemia***
   iii. the extent of benefit in relation to risks for other cases is ***uncertain***
4. excepting these cases, diabetes *per se* may not be as important to outcome as the end-organ ***complications*** thereof,
   i. cardiovascular dysfunction - atherosclerosis (CAD / PVD)
   - hypertension
   - cardiomyopathy
   ii. renal dysfunction - nephrosclerosis
   iii. joint-collagen tissue abnormalities - joint immobility, "stiff-joint syndrome"
   - impaired tissue healing
   iv. immune dysfunction - nosocomial infections
   v. neuropathies - peripheral / autonomic

NB: the combined presence of ***diabetes, hypertension & renal dysfunction*** caries a significantly worse prognosis

- ***Classical Non-Tight Control***

NB: ***aim:*** to prevent hypoglycaemia, ketosis & hyperosmolar states

1. fast from 2400 hrs the night before surgery,
   a glass of orange juice being beside the bed for emergency use
2. commence IVT at 0600 with D_5W at a rate of **125 ml/70kg/hr**
3. administer ½ the usual morning insulin dose s.c.
4. continue this IVT throughout the operative period
5. monitor BSL in the recovery and treat with a ***sliding scale q4h***

- ***Tight Control***

NB: ***aim:*** to achieve a BSL ~ 4.5-11.0 mmol/l, possibly improving wound healing

1. determine preprandial BSL the preceeding evening
2. commence IVT with D_5W at a rate of **50 ml/70kg/hr**
3. commence an insulin infusion = 50^U / 50 ml N.Saline,
   use a metered pump set the infusion to run at,

$$Insulin(U/Hr) = \frac{BSL\ (mmol/l)}{8.0}$$

4. repeat BSL every 4 hours & adjust infusion to a BSL ~ 5.5-11 mmol/l
   - denominator should be 5.0 in patients taking ***corticosteroids***
   - 100 mg/dl ~ 5.55 mmol/l $\rightarrow$ denominator ~ 150 mg/dl
5. determine the BSL preinduction and repeat 2/24'ly for the next 24 hours

NB: alternatively feedback could be performed by a ***mechanical pancreas***

Hyperglycaemic Ketoacidosis

Def'n: pre-coma / coma resulting from an imbalance in the ***insulin:glucagon ratio***, resulting in,

1. extracellular hyperglycaemia
2. intracellular glucose deficit
3. ketoacidosis
4. marked fluid & electrolyte shifts

- the fall in insulin:glucagon ratio, due to absolute or relative insulin deficiency, results in,
  a. hyperglycaemia
  b. ↑ lipolysis
  c. ↑ hepatic ketogenesis
  d. ↑ catecholamines, cortisol, GH, and glucagon

NB: small amounts of insulin will prevent ketosis (cf. basal pancreatic secretion)

- normal hepatic glucose production ~ 50 mmol/hr/70kg fasting
  ~ 100 mmol/hr/70kg without insulin
- production actually returns to normal as ketoacidosis develops
- normal peripheral metabolism ≤ 150-300 mmol/hr/70kg

NB: ∴ hyperglycaemia is predominantly due to decreased ***peripheral ultilisation***

- ***Clinical Features***

a.	thirst, polyuria, blurred vision, leg cramps	∝	osmotic diuresis
b.	nausea, vomiting, abdominal pain	∝	ileus, gastric stasis
c.	hypotension, tachycardia, dehydration	∝	fluid losses
d.	Kussmaul's breathing	∝	acidaemia
e.	ketotic breath	∝	acetone, β-OH-butyrate
f.	drowsiness, coma	∝	hyperosmolality
g.	warm, dry skin	∝	vasodilatation
h.	hypothermia	∝	↓ VO_2 & ↓ CNS

NB: 1. abdominal pain is due to reversible ***autonomic neuropathy***,
other causes → pancreatitis, appendicitis, perforated viscus
2. if ketoacidotic patient is ***hyperthermic***, then suspect ***sepsis***

- ***Precipitants***

a. unknown ~ 30%
b. acute infection ~ 30%
c. undiagnosed diabetic ~ 15%
d. no insulin in known diabetic, especially with poor diet control
e. trauma | surgery

Typical Early Biochemical Abnormalities		
Acidaemia • pH • P_{aCO2} • HCO_3^- • ketoacidosis • lactic acidosis	 ~ 6.9 - 7.15 ~ 8-15 mmHg ~ 5 mmol/l ~ 5 mmol/l ~ 10-15 mmol/l ~ 4-6 mmol/l	 • acetoacetate (N < 0.3) • β-OH-butyrate (N < 1.2)
hyperglycaemia	~ 20-40 mmol/l	
hyperkalaemia	~ 5-8 mmol/l	• total ***deficit*** ~ 200-700 mmol
hyperosmolar ***hyponatraemia***	~ 130 mmol/l	• 2° to high glucose & lipids
hyperosmolality	~ 310-350 mosm/l	
hyperuricaemia		• protein breakdown
↑ FFA	~ 2-4 mmol/l • if higher may → low Na^+ ~ 110 mmol/l	
uraemia	~ 25 mmol/l	
high creatinine	~ 0.3-0.5 mmol/l	

- ***Late Biochemical Abnormalities***

• following treatment these may progress to,

1. hypernatraemia
2. ***severe hypokalaemia***
3. hypophosphataemia
4. hypochloraemia, or hyperchloraemic metabolic acidosis
5. hypomagnesaemia

- ***Other Features***

a. fluid loss ~ 3-8 litres

b. full blood count

i. high Hct

ii. leukocytosis ~ 15-90,000/μl with left shift
* with or ***without*** infection
→ B_{12} or folate deficiency

c. NaCl usually normal - vomiting → low Cl^-, and lower Na^+

d. K^+ normal or low * severe deficiency ≥ 400 mmol

e. uraemia - ↑↑ creatinine
- low ***urea:creatinine ratio*** ∝ ketones

f. anion gap > 17 - predominantly ketones
+ some lactate
± $SO_4^=$ & $PO_4^=$

g. increases in - amylase (salivary glands)
- triglycerides, VLDL and CM
- uric acid
- LFT's (ketones interfere with assays, acute fatty liver)

h. phosphate - initially high but with R_X may fall precipitately like K^+
- no proven benefit on mortality
- replacement may reduce the time to recovery and insulin needs

i. ketones drag H^+ with them in urine, up to 10 mmol H^+/hr

j. ***lactic acidosis*** may mask a small ketoacidosis → a ***low redox state***

- ↑ βOHB - which is ***not*** measured by ketone tests
- ↓ AcAc - which is measured by ketone tests
- normal ratio βOHB:AcAc ~ 3:1
  ≥ 9:1 in reduced redox states
- levels during starvation ~ 2-4 mmol/l
  ketoacidosis > 5 mmol/l
- may be as high as 15 mmol/l in severe DKA and totally account for anion gap

Treatment

a. resuscitate - ABC

b. fluid/volume resuscitation

i. colloid ~ 10-20 ml/kg prn

ii. crystalloid*

- **0.9% saline** - total body Na^+ deficit (200-700 mmol)
- **0.45% saline** - if corrected Na^+ > 150 mmol/l

iii. dextrose - when BSL < 20 mmol/l
- total body ***deficit*** in energy substrate

Fluid Requirements	
Hour	Crystalloid*
1st	• 15-20 ml/kg
2nd	• 10-15 ml/kg
3rd	• 5-10 ml/kg
4th	• 5-10 ml/kg
5th & over	• 2-5 ml/kg

c. ***insulin*** ~ $10\text{-}20^U$ IV ~ 0.25U/kg
+ infusion (U/hr) ~ BSL (mmol/l)/8

- results in receptor ***saturation*** & ↓ BSL at ~ **3-5 mmol/l/hr**
- efficacy of insulin reduced in shock states, ∴ must resuscitate first
- 20-30% bound to plastic/glass surfaces, ∴ some use protein carrier

d. ***potassium*** ~ 20 mmol/hr ~ 0.3 mmol/kg/hr
- total body deficit ~ 100-200 mmol/l (rarely < 700)

- NB: 30-50 mmol/hr if HCO_3^- used ± $H_2PO_4^-$ and Mg^{++}

e. HCO_3^-

- consider if,

i. persistent pH < 7.0, or

ii. ***normal AG*** hyperchloraemic acidosis develops

- give 1 mmol/kg in 500 ml (~1.4%) over 1 hr
- ***no*** evidence for benefit

f. $Na/K\text{-}H_2PO_4$ - consider if [plasma] < 0.7 mmol/l
- give as K^+ salt 7-10 mmol/hr

g. $MgSO_4$ - no need unless tachyarrhythmia

h. ***treat underlying cause***

- ***Other Management***

a. repeated monitoring
   - plasma glucose & K^+ monitored hourly if $[K^+] < 3.0$ or > 6.0 mmol/l
   - otherwise monitor 2 hrly for first 6 hrs, then prn
   - vital signs, UO, CVP, Na^+, K^+, glucose, pH, P_{aO2}

b. low dose ***heparin***

c. other Ix
   i. CXR
   ii. ECG & CKI
   iii. blood cultures and sepsis workup
   iv. coagulation studies

d. ***antibiotics*** for evidence of infection only

- ***Causes of Hypokalaemia***

a. osmotic diuresis → major cause

b. vomiting

c. neutralisation of ketones

d. extracellular shift with acidosis

e. renal Na^+/K^+ exchange ~ 2° hyperaldosteronism

f. total body K^+ deficit **~ 200-700 mmol**
   ~ 15-55 grams !

- ***Complications of Rapid Correction***

1. ***hypokalaemia***
2. hypernatraemia
3. hypophosphataemia
4. ***hypomagnesaemia*** & dysrhythmias
5. ***cerebral oedema*** * especially children

- ***Causes of Death***

a. mortality **~ 5-10%**

b. adults
   i. precipitating cause - ***sepsis***, AMI, CVA
   ii. respiratory failure, aspiration pneumonitis, ARDS
   iii. hypokalaemia
   iv. vascular thrombosis

c. children
   i. cerebral oedema * too rapid treatment
      - especially if BSL lowered to < 14 mmol/l
   ii. hypokalaemia

Euglycaemic Ketoacidosis

Def'n: ketoacidosis in a diabetic patient with euglycaemia or mild hyperglycaemia

- ~ 18% of diabetic emergencies
- occurs in young, known ***type I diabetics***
- rapid onset, within hours
- clinical features include,

1. present with ***hyperventilation*** but usually "look well"
2. coma and dehydration are rare
3. investigations
   i. severe ketoacidosis
   ii. relatively "normal" glucose ≤ 20 mmol/l
   iii. osmolality only mildly elevated

- ***Treatment***

a. IVT with normal saline, then 5% dextrose

b. insulin in ***normal doses***

NB: ?? absence of marked hyperglycaemia due only to rapid onset, normal kidneys and ECF volume, with subsequent glycosuria

Hyperosmolar, Hyperglycaemic, Non-ketotic Coma

Def'n: hyperglycaemia & dehydration, ***without*** ketosis
hyperosmolarity ≥ 320 mosm/l → ***mortality* ~ 50%** (40-70%)

NB: Osmolarity ~ (2 x Na^+) + glucose + urea
True Na^+ ~ measured Na^+ + [(glucose - 6)/3]

- ***Pathogenesis***

1. insulin deficiency → hyperglycaemia, but enough to ***prevent ketosis***
2. impaired renal function → exaggerating high glucose and hyperosmolality
3. fluid restriction ∝ impaired thirst mechanism
   CNS disease or sedatives
4. osmolality ≥ 350 mosm/kg → ***coma***
   - correlation of osmolality & coma difficult due to variable contribution of urea
   - if ***urea*** is excluded, then ***coma*** generally occurs > 320 mosmol/kg

- ***Presentation***

a. precipitating event
- infection
- AMI, stroke
- haemorrhage, trauma

b. drugs
- diphenylhydantoin, propanolol, immunosuppressants, thiazides, cimetidine
- all impair insulin ***secretion*** or insulin ***action***

c. fever - with or without infection

d. neurological
- disorientation, tremors
- seizures ~ 30%
- coma ~ 50%

- ***seizure activity*** - usually due to ***cortical vein thrombosis***
  - rarely 2° hyperosmolality

e. dehydration
~ 99%
+ tachycardia, hypotension
+ hyperventilation

NB: classically an elderly NIDDM patient with an intercurrent illness, clinical features relate to,

i. hyperglycaemia - polyuria, polydipsia, hypotension
ii. hypertonicity - confusion, disorientation, coma

Investigations[1]			
glucose	~ **50-60**	mmol/l	• ~ **2x** DKA
acetone (ketones)	~ 4-6	mmol/l	• normal or slightly elevated • equal to ***fasting*** levels
osmolality	~ **380**	mosm/l	• often > 50%
pH	~ 7.3-7.4		• normal or mild acidosis
HCO_3^-	~ 17-22	mmol/l	
Na^+	~ 144	mmol/l	~ 160 mmol/l "corrected"
K^+	~ 5	mmol/l	
urea	~ 10-15	mmol/l	→ ***low*** U:C ratio
creatinine	~ 0.4	mmol/l	
average fluid deficit	~ 10	litres	
DIC			• occasionally

[1] average values, Arieff 1972, HPIM 12th Edition

- ***Treatment***

a. ABC

b. expand ECF initially with N. saline, then 0.45% saline, according to CVP and U/O
   - Na^+ deficit ~ 400 mmol / H_2O deficit ~ 4-18 l → ~ 60 mmol/l ideal

c. infuse insulin at ***slow rate*** ~ **3-4 U/hr**
   - elderly are sensitive to insulin
   - a rapid fall in plasma glucose may result in ***cerebral oedema***
   - ∴ aim to reduce

   i. glucose: ***rate*** ≤ 3 mmol/l/hr
   minimum ≥ 10-15 mmol/l

   ii. osmolality: rate ≤ 2 mosmol/kg/hr

d. replace K^+ / Mg^{++} / $HPO_4^=$
   - if plasma $[K^+]$ ~ 4-5 mmol/l → ~ 20 mmol/hr
   < 4 mmol/l → ~ 40 mmol/hr

e. low dose Heparin ??? anticoagulate

f. investigate & treat cause

- ***Causes of Death***

a. primary inderlying disease

b. cerebral infarction - thrombosis
- haemorrhage

c. cerebral oedema

HYPOGLYCAEMIA

- ***Clinical Features***

1. ***adrenergic*** stimulation
   - ↑ HR, palpitations, diaphoresis
   - anxiety, tremor, irritability
   - hunger, nausea
   - symptoms may be absent in diabetics with severe ***autonomic neuropathy***
   - also in patients on b_2-***blockers*** → ↓ glycogenolysis
2. ***neuroglycopaenia***
   - headache, blurred vision, paraesthesiae, weakness, confusion, dizziness, etc.
   - hemiplegia, seizures, coma
   - cerebral oedema & death

- ***Investigation***

1. fasting plasma glucose **< 2.8 mmol/l** generally significant
2. insulin:glucose ratio < 50 normally
3. plasma C-peptide & pro-insulin
4. prolonged 72 hr fast
   - plasma obtained 6 hrly for first 24 hrs, then 4 hrly
     → plasma glucose, insulin & C-peptide levels
5. 6 hr glucose tolerance test

- ***Management***

1. dextrose 50% ~ 0.5 ml/kg
2. dextrose 20% ~ 50-100 ml/hr 10-20g/hr
3. ***glucagon*** ~ 0.5 mg IM/IV
   - standard dose of 1 mg → excessive rise in BSL and N&V

Causes of Fasting Hypoglycaemia

- ***Underproduction of Glucose***

1.	substrate deficiency	- severe malnutrition, wasting - post-gastrectomy, gastroenterostomy - late pregnancy - ketotic hypoglycaemia of infancy - prematurity
2.	enzyme deficiencies	- G-6-phosphatase, F-1,6-diphosphatase - liver phosphorylase, glycogen synthase - pyruvate carboxylase - idiopathic leucine sensitivity
3.	acquired liver dysfunction	- severe hepatitis, FHF any cause - hepatic congestion, cirrhosis - uraemia (multiple mechanisms) - hypothermia
4.	endocrine	- hypopituitarism (ACTH, GH) - Addison's - glucagon deficiency - autonomic nervous dysfunction - hypothyroidism
5.	drugs	- alcohol - propranolol, salicylates

- ***Overutilisation of Glucose***

1. ***hyperinsulinism***
   - i. islet cell tumours — ~ 85% benign / ~ **15% *malignant***
   - ii. exogenous insulin
   - iii. sulphonylureas
   - iv. infant of diabetic mother
   - v. immune disease with insulin and/or receptor Ab's
   - vi. drugs — - quinine, disopyramide, pentamidine
   - vii. endotoxic shock
2. ***normal insulinism***
   - i. factitious — - leukocytosis
   - ii. tumours — - adrenal cell carcinoma, ? carcinoid
- Ca of stomach, hepatoma, fibrosarcoma
   - iii. systemic carnitine deficiency
   - iv. enzyme deficiencies — - oxidation of fatty acids, 3-OH-3-MG-CoA lyase
   - v. cachexia with fat depletion

Alcoholic Hypoglycaemic Ketoacidosis

- a disorder of CHO metabolism after heavy alcohol intake
- ethanol is metabolized by ***alcohol dehydrogenase*** to acetaldehyde and then to Acetyl-CoA
- results in reduction of NAD^+ to NADH and increased H^+

$$\mathbf{C_2H_5\text{-}OH} \xrightarrow[\text{(alcohol dehydrogenase)}]{\mathbf{NAD^+ \rightarrow NADH + H^+}} \mathbf{Acetaldehyde} \longrightarrow \mathbf{Acetyl\text{-}CoA}$$

- glycolysis and gluconeogenesis are impaired because of the deficiency of **NAD^+**
- regeneration of NAD^+, through complete metabolism of ETOH through the CAC would limit hepatic metabolism of alcohol
- ***ketogenesis*** allows continued ETOH metabolism close to the v_{max} of alcohol dehydrogenase
- ***starvation*** and lack of glucose intake are usually present
- hypoglycaemia stimulates ***lipolysis***, which then results in both a ***lactic acidosis & ketoacidosis***
- this may produce coma before, or after the blood alcohol returns to a low level
- the presentation therefore comprises,

1. coma
2. ***hypoglycaemia***
3. ketoacidosis
4. lactic acidosis

- predisposition is predominantly from heavy alcohol intake, other factors frequently include,

1. younger individuals
2. exercise
3. diabetes
4. Addison's disease
5. hypopituitarism
6. hyperthyroidism

- ***Treatment***

a. IV fluids (rehydrate)

b. glucose

c. ***thiamine*** - required as cofactor for ***pyruvate dehydrogenase***
- when ketoacids fall, will require gluconeogenesis for brain

NB: insulin is ***not*** required & in fact ***contraindicated***

DIABETES INSIPIDUS

- suspected clinically with the presence of ***polyuria & hypernatraemia***

Diagnostic Features			
Severe Forms			Mild Forms
• polyuria	≥ 200	ml/hr	• polyuria
• hypotonic urine	~ 1001-1005	SG	• SG < 1020
• urine osmolality	~ 50-200	mosm/kg	• urine ≤ 700 mosm/l
• urine [Na^+]	< 20	mmol/l	
• high serum osmolality & raised [Na^+]			• raised serum osmolality
• unresponsive to ***water deprivation***			
• absence of hypervolaemia			

Central DI

a. ***idiopathic*** ~ 30%

b. ***traumatic*** ~ 30%
- CHI, neurosurgery

c. ischaemia
   i. hypoxic brain damage
   ii. vascular lesions
   - post-partum necrosis
   - aneurysm
   - hyperviscosity syndrome

d. infection - TB

e. inflammatory
- sarcoidosis
- other granulomatous diseases

f. neoplastic
- 1° or 2°
- commonly breast or lung

Nephrogenic DI

a. congenital / familial
   - ***x-linked*** recessive
   - variable expression in female carriers

b. acute renal failure
   i. post-obstructive renal disease
   ii. recovery phase of ATN
   iii. pyelonephritis
   iv. post-transplantation
   v. polycystic kidney disease

c. drugs
   - methoxyflurane, enflurane, F^- ion
   - diuretics, lithium
   - demeclocycline

d. biochemical
   i. hypercalcaemia
      - hyperparathyroidism, malignancy
   ii. hypokalaemia
      - Conn's syndrome
      - Bartter's syndrome
      - chronic depletion

e. systemic disease
   - amyloidosis
   - multiple myeloma
   - sickle cell disease

f. ADH resistant DI of pregnancy
   - high ***vasopressinase***

Treatment

a. fluid and electrolyte replacement

b. ADH analogues
   - vasopressin (IV, SC, nasal)
   - DDAVP

c. other drugs
   - thiazides
   - chlorpropamide, chlofibrate

HYDROGEN ION

Def'n: elemental gas, atomic number and molecular weight = 1.0

Average Concentrations			
arterial blood	~ 39	nmol/l	7.4
venous blood	~ 45	nmol/l	7.35
interstitial fluid	~ 45	nmol/l	7.35
CSF	~ 47	nmol/l	7.33
ICF	~ 100	nmol/l	7.0 range ~ 4.5-7.4
urine (maximal)	~ 30,000	nmol/l	4.5

NB: serum pH survival limits ~ 6.8-8.0

- ***Functions / Effects***

1. sets intracellular H^+/OH^- ratio for optimal ***enzyme function***
   - protein & amino-acid ionisation status
2. product/substrate in many reactions
   - usually involve $NAD^+/NADP^+$
   - important by-product of anaerobic metabolism
3. influences O_2 supply to tissues
   - increases respiration
   - shifts HbO_2 dissociation curve to the right *acutely
   - regional control of blood flow
4. ***digestion*** of foodstuffs in the stomach
5. alters binding sites on proteins, especially albumin
6. affects myocardial contractility
7. influences K^+ & Ca^{++} homeostasis & plasma levels

- ***Sources of Acid***

1.	CO_2	~ 12,500	mmol/d
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. alkalinising salts - K^+, lactate, acetate, citrate (little importance)

- ***Body Response to Acid***

a. ***dilution*** - weak

b. ***buffering***

i. extracellular - HCO_3^-, protein (Hb, alb), $HPO_4^=$

ii. intracellular

~ 140	mmol/l	$HPO_4^=$
~ 30	mmol/l	protein
~ 10	mmol/l	HCO_3^-

buffers
~ 90% of respiratory disorders
~ 60% of metabolic acidosis
~ 30% of metabolic alkalosis

iii. renal
- NH_3 - conversion of glutamate ~ 60%, free NH_3 35%, leucine et al 5%
- other - creatinine, $HPO_4^=$, HSO_4^-, HCO_3^-

c. ***exchange*** - bone (Ca^{++}) / ICF ions (K^+)
- PTH may play a role → phosphaturia & H^+ loss

d. ***renal acid excretion*** ~ 70 mmol/day

i.	free H^+	~ 40	**µ**mol/l	(pH ~ 7.4)
ii.	HCO_3^- reabsorption	~ 4,300	mmol/day	
iii.	NH_4^+	~ 30	mmol/day	(max ~ 500 mmol/d)
iv.	$H_2PO_4^-$, $H_2SO_4^-$	~ 20-40	mmol/d	(max ~ 40 mmol/d)
v.	PT	~ 200	mmol/hr	

- influenced by ICF acidosis, P_{aCO2}, hypokalaemia, luminal pH, functional ECF, reabsorbable anion (HCO_3^-), carbonic anhydrase activity, PTH

vi. DT ~ 30 mmol/hr → pH ~ 4.5
- influenced by ***mineralocorticoid*** activity
- also ICF acidosis (**P_{aCO2}**), hypokalaemia & luminal pH

e. ***pulmonary CO_2 excretion*** ~ 288 l/day
~ 12,800 mmol H^+/day

Anion Gap

Def'n: = **$[Na^+ + K^+] - [Cl^- + HCO_3^-]$**

~ 12-17 mmol/l

Unmeasured cations			Unmeasured anions		
Mg^{++}	~ 1.2	mmol/l	albumin	~ 15	mEq/l
Ca^{++}	~ 2.2	mmol/l	$H_2PO_4^-$	~ 2	mEq/l
IgG	small		HSO_4^-	~ 1	mEq/l
			organic	~ 5	mEq/l
	~ 7.0	mEq/l		~ 23	mEq/l

- ***organic anions*** include lactate, pyruvate, β-OH-B, acetoacetate, formate, oxalate, salicylate
- aetiology of ***large anion gap*** includes,

a. renal failure - $H_2PO_4^-$, HSO_4^-
   * rarely > 23

b. lactic acidosis - types A&B

c. ketoacids - diabetes mellitus, starvation, alcohol
   - β-OH-butyrate, acetoacetate

d. rhabdomyolysis - organic acids

e. drugs
   - aspirin - salicylate, lactate, ketones
   - ethanol - acetoacetate, lactate
   - methanol - formate (***formaldehyde***), lactate
   - paraldehyde - formate, acetate, lactate, pyruvate
   - ethylene glycol - oxalate
   - xylitol, sorbitol - lactate
   - fructose - lactate

NB: a normal anion gap ***does not*** exclude a lactic acidosis

- a low or normal anion gap is typically seen with,

a. hyperchloraemic metabolic acidosis

b. metabolic alkalosis due to HCO_3^- gain

c. hypoalbuminaemia

d. ***myeloma*** - IgG has positive charge, ∴ ↓'s AG

e. rarely with increased Mg^{++} or Ca^{++}

f. artefactually elevated Cl^- ? hyperlipidaemia

Acid-Base Correction Factors

a. ***metabolic acidosis***

i. P_{aCO2} ~ last two digits of pH ~ 7.**10**

ii. $\downarrow HCO_3^-$ ~ 10 mmol/l $\rightarrow$ $\downarrow P_{aCO2}$ ~ **12 mmHg**

iii. P_{aCO2} ~ 1.5 x $[HCO_3^-]$ + 8 ± 2 mmHg M&K

b. ***metabolic alkalosis***

i. P_{aCO2} ~ last two digits of pH ~ 7.**60**

ii. $\uparrow HCO_3^-$ ~ 10 mmol/l $\rightarrow$ $\uparrow P_{aCO2}$ ~ **7 mmHg**

iii. less well compensated due to hypoxia 2° hypoventilation

c. ***respiratory acidosis***

i. ***acute*** $\uparrow P_{aCO2}$ ~ 10 mmHg $\rightarrow$ $\uparrow HCO_3^-$ **~ 1-2 mmol/l**

ii. ***chronic*** $\uparrow P_{aCO2}$ ~ 10 mmHg $\rightarrow$ $\uparrow HCO_3^-$ **~ 4 mmol/l**

d. ***respiratory alkalosis***

i. ***acute, or***

ii. ***chronic*** $\downarrow P_{aCO2}$ ~ 10 mmHg $\rightarrow$ $\downarrow HCO_3^-$ **~ 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

Metabolic Acidosis - Aetiology

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

1. ***increased intake***
   - i. anion gap **> 18**
     - salicylates → salicylate, lactate, ketoacids
     - ethanol → acetoacetate, lactate
     - methanol → ***formate***, lactate
     - paraldehyde → ***formate***, acetate, lactate
     - xylitol, fructose, sorbitol → lactate
     - ethylene glycol → oxalate
     - NB: 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

2. ***increased production*** → anion gap **> 18**
   - i. ketoacidosis
     - diabetic ketoacidosis
     - alcoholic ketoacidosis
     - starvation
   - ii. lactic acidosis *types A&B ± normal anion gap
     - cardiorespiratory failure
     - sepsis, major trauma
     - toxins, drugs - eg. phenformin, cyanide, salicylate
     - enzyme defects
     - vitamin deficiency

3. ***decreased excretion*** → anion gap **<> 18**
   - i. renal failure with retention of $SO_4/HPO_4^=$ acids
   - ii. mineralocorticoid deficiency
   - iii. "potassium sparing" diuretics

NB: effectively, any decreased renal H^+ excretion → ↑ HCO_3^- loss

- ***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 ***sodium lactate***, which is metabolised in the liver to HCO_3^-
• when hepatic blood flow is low and metabolism slow, the plasma lactate level may rise, however lactate itself is ***not toxic***

- ***Blood Gases***

$\uparrow [H^+]$, or $\downarrow [HCO_3^-]$ $\rightarrow$ $\downarrow$ plasma $[HCO_3^-]$ $\rightarrow$ $\downarrow P_{aCO2}$ by dissociation

$\downarrow$ ***ratio*** of $[HCO_3^-] / P_{aCO2}$ $\rightarrow$ $\downarrow$ 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***

~ 1.5 x $[HCO_3^-]$ + 8

$\downarrow HCO_3^-$ ~ 10 mmol/l $\rightarrow$ $\downarrow P_{aCO2}$ ~ 12 mmHg

• decreased pH stimulates ventilation, predominantly via ***peripheral chemoreceptors***, decreasing P_{aCO2} and compensating the acidosis
• remember P_{aCO2} & intracellular pH are the principal stimuli to distal renal excretion of acid
• 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

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

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

- ***Treatment***

a. treatment of the ***causative factor***

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

c. Na-Bicarbonate 8.4%
   - ***no*** studies demonstrate a benefit in outcome, most show deleterious effects
   - 100 mmol produces 2.24l of CO_2 $\rightarrow$ P_{aCO2} will rise if ventilation is fixed
   - is only the R_X of choice where the origin of the acidaemia is ***bicarbonate loss***
   - the dose of HCO_3^- is usually calculated on the empirical assumption that the ion has a V_{dSS} ~ 50% of body weight
   - this takes into account diverse buffer reactions in both ECF & ICF
   - initial correction should be < ½ this amount as the initial action is in the ECF
   - M&K state that this assumption is ***inaccurate*** at low plasma [HCO_3^-] levels
   - the AHA recommendations for administration include

   i. CPR > 10 minutes

   ii. an increase in V_M possible (ie. ventilated)

   iii. AGA's $\rightarrow$ pH < 7.2

   iv. R_X ~ 1 mmol/kg slowly IV

d. 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
- ***respiratory acidosis*** has a greater negative inotropic effect cf. metabolic acidosis
- HCO_3^- does not,
  1. improve the ability to ***defibrillate*** the heart, or
  2. increase response to ***circulating catecholamines***

- is only the R_X of choice where the origin of the acidaemia is loss of bicarbonate
- the dose is calculated on the empirical assumption that the ion has a $\mathbf{V_D \sim 50\%}$ 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. 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
  6. cardiac arrest in children

- problems associated with administration include,
  1. paradoxical ***ICF acidosis*** *significance argued by M&K
  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,
     - ***hypokalaemia*** & cardiotoxicity in K^+-depleted patients
     - ***tetany*** in renal failure or Ca^{++} depletion
  3. ***hyperosmolality***
     - the solution is 1M, ie. 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***

a. treatment of ***hyperkalaemia***
   i. $K^+ \geq 6.0$ mmol/l
   ii. widened QRS / P wave loss
   iii. respiratory insufficiency

b. treatment of arrhythmias in ***tricyclic overdose***

c. alkalinising the urine
   i. drug overdosage - phenobarb, salicylates
   ii. rhabdomyolysis

d. treatment of HCO_3^- losing acidosis

e. ? treatment of 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 - carbicarb, THAM, dichloroacetate
studies show ***no*** significant benefit in ***outcome***

Body Fluids							
	Vol/day	Na^+	K^+	Cl^-	HCO_3^-	IVT	+ KCl
Plasma		136-144	3.5-5.0	95-110	25		
Gastric	1-5 l	30-120	10-15	140	(pH=1.5)	N.Sal	~ 20-50
Bile	< 1000 ml	145	5	100	35-70	Hart	20
Pancreas	< 1000 ml	140	5	60	90	Hart	20
SI	1-3 l	120	5-10	105	25	Hart	20
LI	100-500 ml	< 80	20-40	< 50	< 45	Hart	20-50
Sweat	~ 400 ml	50	5-10	45		D_4W-N/5	20

Lactic Acidosis

$$\text{pyruvate} + \text{NADH} + H^+ \longleftrightarrow \text{lactic acid} + NAD^+$$

- NAD^+ is necessary for the conversion of phosphoglyceraldehyde to 3-phosphoglycerate
- traditional teaching is that under ***anaerobic*** conditions, this NAD^+ is supplied by the above reaction, allowing glycolysis to continue
- actually, the 'reverse' events predominate,

1. the production of ***lactate*** $\propto$ K_A'.[Pyruvate].[H^+].[NADH] / [NAD^+]
2. continued anaerobic glycolysis increases both ***pyruvate*** & NADH:NAD^+
   - the former is the principal driving force for lactate production
   - a low pH and redox state alone will only marginally increase production
   - however, when present with a raised [pyruvate] produce marked increases
   - production of pyruvate also produces H^+ by, PGA $\rightarrow$ 3PG
   - NB: alcohol metabolism reduces NAD^+:NADH ratio $\rightarrow$ $\uparrow$ lactate

- normal plasma lactate level at rest,

a. venous ~ 0.3-1.3 mmol/l
b. ***arterial*** ~ 0.3-0.8 mmol/l

- normal ***lactate:pyruvate ratio*** ~ 10:1 (pyruvate ~ 0.03-0.1 mmol/l)
  $\rightarrow$ estimate of cytoplasmic redox state

- however, this may not be the same as the mitochondrial redox state
- therefore, lactate production will ***increase*** with,

a.	high pyruvate production	- high BMR - exercise, catecholamines - stress, trauma - asthma
b.	intracellular acidosis	- eg. ischaemia, hypoxaemia
c.	high NADH:NAD^+ ratio	- intracellular hypoxia - mitochondrial dysfunction - alcohol excess
d.	low uptake & metabolism	- liver disease - circulatory failure - thiamine deficiency (PDH cofactor)

NB: the significance of this is that the ***plasma lactate*** level correlates with disease severity and ***mortality***

- daily production ~ 1400 mmol
- the major sites are the GIT and skeletal muscle

- ***lactate*** is metabolised in the,
  a. liver ~ 50-80% (Cori cycle)
  b. kidneys ? %
  c. heart
  d. muscle

- lactic acidosis may mask a small ***ketoacidosis*** in the presence of a low redox state
  → more β-(OH)-butyrate & less acetoacetate
- the β-OB:AA ratio is normally ~ 2-3:1, but may be as high as 7-8:1 in lactic acidosis
- β-OB is not measured by ketone tests, ∴ plasma ketone estimations will be artefactually low

■ ***Laboratory Findings***

Def'n: plasma lactate ³ **5 mmol/l**

1.	pH ≤ 7.25	
2.	± high ***anion gap*** (> 16)	~ 100% if lactate > 10 mmol/l ~ 50% if lactate 5-10 mmol/l
3.	hyperphosphataemia	- unreplenished ATP → ADP
4.	hyperuricaemia	- competition at PT of nephron
5.	***normokalaemia***	- lactate enters cells
6.	leukocytosis	- WBC demargination ∝ catecholamines

NB: the AG may be normal with a mild lactic acidosis

- ***Type A Imbalance of Oxygen Supply/Demand***

1. hypermetabolic states
   - extreme exercise, seizures
   - sepsis, trauma
   - MH, MNS
   - catecholamines, theophylline, amphetamines
2. impaired tissue DO_2
   - i. respiratory
     - low F_IO_2, hypoventilation
     - lung disease, V/Q abnormality/shunt
   - ii. CVS
     - hypovolaemia, cardiogenic shock
     - thromboembolism, other embolism
   - iii. vascular
     - vasodilators
     - sepsis
     - spinal shock
     - anaphylaxis
   - iv. haemopoietic
     - severe anaemia
     - methaemoglobinaemia
     - haemoglobinopathies

- ***Type B Cellular Metabolic Block***

1. common disorders
   - i. diabetes
     - insulin regulates *pyruvate dehydrogenase*
     - catabolism increases [alanine] $\rightarrow \uparrow$ pyruvate
   - ii. liver failure
   - iii. renal failure
   - iv. neoplasia
     - leukaemia, lymphoma, Hodgkin's, oat cell Ca
     - overproduction, liver infiltration
     - inhibition of metabolism by metabolites of tryptophan
2. drug induced
   - phenformin, metformin
   - fructose
   - ethanol, methanol, sorbitol, xylol
   - salicylates
   - cyanide
3. enzyme deficiency
   - G6PD
   - F-1,6-diphosphatase deficiency
   - pyruvate decarboxylase
   - pyruvate dehydrogenase
   - thiamine deficiency
4. other
   - septicaemia
   - pancreatitis
   - *d*-lactic acidosis (infusions, short gut syndrome)

Ketoacidosis

Ketone Bodies

• in many tissues ***acetyl-CoA*** molecules condense to form ***acetoacetyl-CoA***
• the liver possesses ***deacylase*** and free ***acetoacetate*** is formed
• this β-keto acid is then converted to b***-hydroxybutyrate*** and ***acetone***
• these two are metabolised poorly and diffuse into the circulation
• together with acetoacetate → ***ketone bodies***

• ***acetoacetate*** is also formed from β-hydroxy-β-methylglutaryl-CoA (**HMG-CoA**) and this is quantitatively more significant
• tissues ***other*** than the liver transfer CoA from succinyl-CoA to acetoacetate and metabolise the "active" acetoacetate to CO_2 & H_2O via the citric acid cycle
• ketones are normally metabolised as rapidly as they are formed
• therefore, normal serum concentrations are low £ **1 mg/dl**
• ***acetyl-CoA*** accumulates and conversion to ketone bodies in the liver increases if,

1. the entry of acetyl-CoA into the CAC is depressed due to a decreased supply of the products of glucose metabolism, or
2. the entry does not increase when acetyl-CoA concentrations rise

• the capacity of tissues to oxidise ketones is soon exceeded → ketosis
• acetoacetate & β-hydroxybutyrate are anions of moderately strong acids and their buffering in plasma is exceeded in a number of conditions resulting in a metabolic acidosis
• 3 conditions lead to deficient ***intracellular glucose*** supplies,

1. starvation
2. diabetes mellitus
3. a high fat :: low CHO diet

• other causes of ***ketoacidosis***,

1. ethanol, isopropyl alcohol - usually associated with glucose deficiency
2. paraldehyde
3. von Gierke's disease → G-6-phosphatase deficiency
   → hypoglycaemia, hepatomegaly
   - this usually produces a ***lactic*** acidosis
   - this is due to the absence of a significant path for the conversion of fat to glucose
   - small amounts of glucose will abolish this ketosis and glucose is antiketogenic

Metabolic Alkalosis

- ***Aetiology***

NB: commonly associated with ***hypovolaemia*** and/or ***hypokalaemia***
*these are associations, ***not*** 'causations'

a. common causes
   i. diuretics
   ii. vomiting
   iii. following correction of hypercarbia

b. any ***fluid loss*** replaced with ***insufficient*** $\mathbf{Na^+} \rightarrow H^+$ excretion

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

d. ***increased proton losses***
   i. renal
      - $\uparrow Na^+$ reabsorption (hypovolaemia, dehydration, etc.)
      - Cushing's syndrome, exogenous steroids
      - steroid / ACTH secreting tumours
      - hyperaldosteronism 1° / 2°
      - Bartter's syndrome (JGA hyperplasia)
      - Liddle's syndrome
      - hypercalcaemia / hypomagnesaemia $\rightarrow$ NDI
      - drugs: steroids
        diuretics
        carbenoxolone
   ii. GIT
      - N/G suctioning
      - protracted vomiting
      - rarely 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. hypokalaemia
   iii. hypochloraemia
   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 normovolaemia & Cl^-
   iii. renal failure

- ***Blood Gasses***

↓ $[H^+]$, or ↑ $[HCO_3^-]$ → ↑ plasma $[HCO_3^-]$ → ↑ P_{aCO2}

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

- ***Hypokalaemia & Alkalosis***

• Maxwell & Kleeman, mechanisms resulting in ***hyperbicarbonataemia***,

1. enhanced proximal tubular HCO_3^- reabsorption
2. increased renal tubular ammonia synthesis & ammonium formation
3. chloride depletion - DT inhibition, nephrogenic DI
   → ↑ aldosteronism
4. ICF flux of H^+ in exchange for ECF K^+

• other workers feel the evidence relating these is weak, and effects are species dependent
• in the presence of ***normovolaemia*** these effects are mild, however with volume contraction marked alkalosis can result

- ***Other Alkaloses***

1. ***diuretic*** induced alkalosis
   - 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
   - the result of increased DT exchange of Na^+ for K^+ & H^+
   - this leads to ECF overload, hypokalaemia and alkalosis
   - chloride replacement does ***not*** correct this condition as the normal mechanisms for the excretion of HCO_3^- are inhibited
3. ***hypercalcaemia*** probably acts via the same mechanism
   - nephrogenic DI & chloride depletion
4. ***hypomagnesaemia*** may only be associated, eg. thiazides

- ***Treatment***

a. treat the causative factor

b. prevent tubular (PCT) loss of H^+ $\rightarrow$ 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. inhibit aldosterone effects with ***spironolactone***
   iii. triamterene, amiloride

d. addition of HCl to ECF

i.	IV HCl infusion	~ 200 mmol/l D_5W ~ 10-15 mmol/hr
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

Hydrochloric Acid Infusion

- CVC infusion of HCl,
    a. concentration ~ 120-240 mmol/l
    b. ***rate*** £ **0.2 mmol/kg/hr**

- complications of infusion include,
    a. haemolysis
    b. thrombophlebitis
    c. reduction in some amino acids
    d. precipitation of intralipid
    e. tissue necrosis
    f. hyperventilation and hypocapnia at > 400 mmol/day
    g. metabolic, non-anion gap acidosis

- indications include,
    a. persistent metabolic alkalosis
    b. ? CVC infection
    c. ? CVC thrombosis

- requisites for infusion include prior correction of,
    a. hypovolaemia
    b. hypokalaemia
    c. steroid excess
    d. renal failure

CO_2 Transport

a.	arterial content	~ 48	ml/100ml
b.	venous content	~ 53	ml/100ml
c.	CO_2 added by tissues	~ 3.75	ml/100ml

i. by location
- plasma ~ 2.35 ml (65%)
- rbc's ~ 1.4 ml (35%)

ii. by type
- HCO_3^- ~ 2.43 ml (65% - 90% in rbc's)
- Hb carbamino ~ 1.0 ml (26%)
- dissolved CO_2 ~ 0.3 ml (8%)
- pl. protein carbamino < 1.0%

Def'n: the ***Haldane effect*** → ***left shift*** of the **$HbCO_2$** dissociation curve
∝ ***decrease*** in HbO_2 saturation

• this limits the rise in P_{vCO2} which would otherwise occur at the tissue level
• this is partially responsible for the acute rise in P_{aCO2} with administration of O_2 to chronic respiratory failure patients in extremis

	Arterial	Mixed Venous
P_{aCO2}	40 mmHg	46 mmHg
C_{aCO2}	49 ml/100ml 22 mmol/l	53 ml/100ml 24 mmol/l
pH	7.4	7.37
P_{aO2}	100 mmHg	40 mmHg
S_{aO2}	97.5 %	75 %

- ***Effects of Hypocapnia***

1. cerebral vasoconstriction
2. placental vasoconstriction
3. ↑ TPR
4. ↓ cardiac output
5. ↓ ICP
6. ↑ pain threshold
7. hypoventilation
8. respiratory alkalosis
9. ***left shift*** of the HbO_2 dissociation curve
10. hypokalaemia → ICF shift
11. ↓ HCO_3^- reabsorption by the kidney
12. ↓ plasma ionized Ca^{++} → tetany

- ***Effects of Hypercapnia***

1. cerebral vasodilatation
2. ↑ ICP
3. ↑ CNS sympathetic outflow
4. ↑ cardiac output & BP - indirect effect
5. direct depressant effect upon the CVS
6. cardiac arrhythmias
7. hyperventilation
8. respiratory acidosis
9. ***right shift*** of the HbO_2 dissociation curve
10. hyperkalaemia
11. ↑ HCO_3^- reabsorption by the kidney

Respiratory Alkalosis

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

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

SODIUM METABOLISM

a. alkaline elemental metal
b. atomic number = 11
c. molecular weight ~ 23
d. 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***
      - δGFR - MAP, sympathetic NS
        - GTB, TGF, intrarenal PG synthesis, angiotensin II, kinins
      - 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

Control of Tubular Sodium Reabsorption

a. ***glomerulotubular balance***
- the absolute quantity of Na^+ leaving the PT ***does*** alter
- GTB is not perfect, % reabsorption does change with GFR

b. ***tubuloglomerular feedback***
- alteration of GFR with NaCl delivery to macula densa

c. ***aldosterone***
- the single most important controller of Na^+ balance
- produced in the zona glomerulosa of the adrenal cortex
- Na^+ reabsorption dependent on aldosterone is **~ 2%** of the filtered load

~ 522 mmol/d
~ 30 g NaCl per day

- four factors directly stimulate aldosterone secretion

i. ***angiotensin II*** - most important*
ii. ↑ plasma $[K^+]$
iii. ACTH - permissive
iv. ↓ plasma $[Na^+]$ - minor in humans

- * keyed to release of ***renin*** which is determined by

i. intrarenal baroreceptors stimulation
ii. macula densa
iii. renal sympathetic NS
iv. angiotensin II - negative feedback

d. ***atrial natriuretic factor***

i. ↑ GFR::RBF - efferent vasoconstriction; - afferent vasodilatation
ii. ↑ K_f
iii. ↑ MBF::CBF ratio
iv. ↓ plasma ***renin*** - direct & indirect
v. ↓ plasma ***aldosterone*** - direct & indirect
vi. ↑ urinary excretion of - Na^+, Cl^-, K^+; - Ca^{++}, $HPO_4^{=}$, Mg^{++}
vii. ↑ urine volume
viii. systemic vasodilation

e. other factors
   i. intrarenal physical factors
      - the interstitial ***hydraulic pressure***
      - the peritubular hydraulic and ***oncotic pressures***
   ii. distribution of RBF
   iii. direct tubular effects of ***catecholamines***
   iv. direct tubular effects of ***angiotensin II***
   v. other humoral agents
      - cortisol, oestrogen, growth hormone & insulin → ↑ reabsorption
      - parathyroid hormone, progesterone & glucagon → ↓ reabsorption

f. ***effects of angiotensin II***
   i. vascular smooth muscle - ↑ tone
   ii. CNS/PNS - facilitation of sympathetic activity
      - stimulates secretion of ***ADH***
      - stimulates ***thirst***
   iii. adrenal cortex - ↑ secretion of ***aldosterone***
   iv. kidneys
      - aa. constriction decreasing GFR but ↑ ***GRF:RPF ratio***
      - direct tubular effect increasing Na^+ reabsorption

Hyponatraemia

Def'n: plasma Na^+ **< 135 mmol/l**

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

a. ***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, ∴ increases in ***plasma solids*** will lower $[Na^+]_{pl}$ factitiously when ***flame emission*** & ***indirect ISE*** methods are used
- ***osmolality*** is unaffected, thus ***no*** R_X required
- actual $[Na^+]$ = $[Na^+]_{pl}$ x (measured osmolality)/(calculated osmolality)

b. ***hyper-osmotic*** → ***- osmolar gap***

i. hyperglycaemia ↓ $[Na^+]$ ~ 1 mmol / 3 mmol ↑ BSL

ii. mannitol, glycine, glycerol ? ± urea
- depending upon the concentration used, these may be iso-osmotic

iii. other solutes not entering cells
- water is drawn into the ECF from the ICF
- total body Na^+ may be normal or depleted

c. ***hypo-osmotic***

i. ***hypovolaemic*** → persistent ADH effect
& fluid replacement deficient in Na^+
- extrarenal losses - GIT, vomiting/diarrhoea
  - 3rd space
- renal losses - diuretics, osmotic diuresis
  - salt losing nephritis
  - Addison's disease
  - heparin (aldosterone supression)

ii. ***slightly hypervolaemic*** → fluid excess ~ 3-4 l, ***no oedema***
- SIADH, reset osmostat
- severe hypothyroidism, pituitary glucocorticoid deficiency
- psychogenic polydipsia, inappropriate IV fluids
- managed by H_2O restriction alone

iii. ***hypervolaemic*** → fluid excess > ~ 10 l, ***with oedema***
- CCF§
- nephrotic syndrome§ §2° hyperaldosterone states
- cirrhosis§
- renal failure

- ***Diagnosis***

a. physical examination - oedema
- volume status

b. plasma biochemistry - U&E's
- glucose
- measured & calculated ***osmolality***

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
- ARF/CRF
- SIADH, cerebral salt wasting syndrome
- Addison's
- diuretics
- hypothyroidism

d. water challenge
- giving a patient a water load will differentiate between SIADH and ***reset osmostat***
- the later being able to excrete the load, the former reducing $[Na^+]$ further
- 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

f. response to fluid restriction
- will tend to correct the ADH excess group

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***, avoid the problems associated with water shifts across membranes
• however, they ***do not*** prevent problems associated with a low $[Na^+]_{ECF}$
• also, agents which are metabolised, leaving free water behind may produce delayed true hyponatraemia

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. ↑ 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. volume overload
- ↑ BP/HR - unreliable
- CCF, pulmonary oedema

c. ***neuromuscular***

i. muscle cramps
ii. muscle fasciculations
iii. neuromuscular irritability

- ***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 may be associated with ***central pontine myelinolysis***, or ***osmotic demyelination syndrome***
- 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, ie. fitting
ii. failure of above therapy
iii. complicated by fluid overload (CRF)

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

- ***Treatment - Mild***

a. discontinuation of aetiological agent

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

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

d. demethychlortetracycline - blocks renal ADH effects (→ "nephrogenic DI")

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

f. underlying pathology

Hypernatraemia

Def'n: plasma Na^+ **> 145 mmol/l**

- 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 - rarely with diabetes insipidus - partial obstruction
ii.	GIT losses	- diarrhoea, vomiting - fistulae, SBO
iii.	respiratory losses	- IPPV with dry gases
iv.	skin losses	- fever - high ambient temperature - thyrotoxicosis - vasodilatory states - exfoliative skin disorders

- (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
- ∴these patients do not become ***hypotensive*** until $[Na^+]_{PL}$ ~ 160-170 mmol/l
- ∴this group are sometimes called "isovolaemic"
- produces a mild-moderate decrease in both ECF & ICF

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

ii. reset osmostat

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

iv. nephrogenic diabetes insipidus
- 1° = congenital renal resistance to ADH
- 2° = hypokalaemia, hypercalcaemia
  lithium, methoxyflurane
  multiple myeloma, sickle cell anaemia, nephrocalcinosis, amyloid

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

ii. mineralocorticoid excess
- Conn's, Cushing's syndrome
- steroid excess

- the later group usually have 1-3 l of excess TBW
- the increased plasma osmolality increases ADH secretion, which in turn increases ECFV, with subsequent renal escape
- oedema in this group is therefore ***rare***
- ECFV is generally increased while ICFV decreases

- ***Diagnosis***

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

- ***Clinical Manifestations***

NB: as for hyponatraemia, these depend more upon the ***rate of change*** 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. ↓ contractility $\propto [Ca^{++}]/[Na^+]^2$
   ii. CCF $\propto$ volume overload

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

- ***Treatment - Severe***

a. ABC

b. IVT

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

ii. 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

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

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

c. diuretics - for Na^+ excess

d. dialysis - for Na^+ excess

e. cease aetiological drugs

f. decrease Na^+ intake

- ***Treatment - Mild***

a. cease/decrease Na^+ intake

b. cease aetiological drugs

c. D_5W

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*** ~ (2 x [Na^+]) + [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: 1. 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
2. the RCPA uses 1.85x ([Na^+] + [K^+]) + [urea] + [glu]

- 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
b. ***permeate*** solutes → isotonic states

- acute changes are more important than chronic
- ***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,

1. the reduction in ICFV may result in cellular shrinkage, with confusion and coma
2. reciprocal expansion of the ECFV may result in CCF

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

SIADH

Def'n: clinical syndrome produced by continued secretion of ADH in the absence of appropriate ***osmotic*** or ***haemodynamic*** stimuli

*original report by Schwartz & Bartter (AJM 1957)
of 2 patients with ***bronchogenic carcinoma***

▪ ***Diagnosis***

1. hypoosmolar hyponatraemia
2. urinary Na^+ > 20 mmol/l
3. urine relatively hypertonic cf. serum
4. normal renal, adrenal, cardiac and hepatic function
5. absence of ***drug therapy*** resulting in "SIADH"
6. corrected by water restriction alone

NB: the definition of ***true SIADH*** requires the absence of drugs, normal cardiac, renal, adrenal and liver function, and correction by ***water restriction*** alone

▪ ***Aetiology***

1. malignancies → autonomous ADH release
   - lung, pancreas, sarcomas, Hodgkin's, thymoma
2. non-malignant pulmonary disease
   - TB, lung abscess, empyema, pneumonia, viral pneumonitis, CAL
3. CNS disease
   - trauma - CHI, fractures
   - vascular accidents - SAH, SDH, thrombosis
   - infections - encephalitis, meningitis (TB, bacterial)
   - GBS, SLE, AIP
4. miscellaneous - IPPV
   - hypothyroidism, (? hypoadrenalism)

NB: patient age and anaesthetic technique have ***no effect*** on occurrence of SIADH

- clinical features relate to ***hyponatraemia*** and ***cerebral oedema***

a. weight gain, weakness, lethargy, confusion

b. obtundation, disordered reflexes, convulsions

- ***Biochemistry***

a. urinary sodium **> 20** mmol/l - ie. not Na^+ retaining
b. serum sodium < 130 mmol/l
c. serum osmolality < 270 mosm/l
d. low serum urea, creatinine, urate & albumin
e. urine ***hypertonic*** relative to plasma
f. inability to excrete a water load
g. ↑ plasma ADH level

- ***Management***

NB: → aim ≤ 2 mmol/l/hr change unless seizures

1. fluid restriction
2. N.saline & diuretics
3. hypertonic saline - rarely
4. ***demethylchlortetracycline*** → ↓ tubular ADH response
   → "nephrogenic DI"

- ***Drug Induced ADH Excess***

1. chlopropamide, carbamazepine, clofibrate
2. cyclophosphamide, vincristine, vinblastine
3. GA's, opioids
4. TCA's
5. oxytocics

POTASSIUM

a. alkaline elemental metal
b. atomic number = 19
c. molecular weight ~ 39
d. monovalent cation = the principal ***intracellular cation***

- total body content ~ **55 mmol/kg** (3,850 mmol/70kg)
  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 **~ 3.1-4.2 mmol/l** (highly variable, QEH ~ 3.5-4.8)
     serum ~ 3.8-4.9 mmol/l
     ~ 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 → filtered ~ 720 mmol/day
        - 50-60% reabsorbed in PCT, secretion into late PT and LOH
        - virtually all remainder 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 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 artifacts from preparation
- only really useful for research purposes

e. **ECG** - useful for monitoring acute changes only
- individual variation & dependent upon rate of change

▪ *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,

1. total body K^+
2. 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***
- these tend to offset alterations of extracellular $[K^+]$

- the 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 or major trauma
   - also seen with β_2-adrenergic ***tocolysis***
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
   - conversely, ↓ $[K^+]$ inhibits insulin release & worsens hyperglycaemia
3. ***glucagon***
   - counteracts effects of insulin
   - also directly increases K^+ secretion in the late DT & CT
4. ***aldosterone***
   - DT of the nephron is the main site of action
   - 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

Other Influencial Factors

1. acid-base status
2. Na^+/K^+-ATP'ase ? endogenous digoxin-like substances
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***

1. ***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.

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

2. ***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

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

   thus,

   i. $\uparrow [K^+]_o \rightarrow E_m$ approaches 0 mV

   ii. $\downarrow [K^+]_o \rightarrow E_m$ more negative
      - 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 ***excitable tissues*** - cardiac
   - neural
   - smooth & skeletal muscle

d. intracellular osmotic pressure and electroneutrality

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

Hypokalaemia

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

- ***Causes***

a. decreased intake - NBM

b. ↑ ***renal*** losses

i. ***diuretics***

- PT agents - acetazolamide
  - mannitol
- loop diuretics - frusemide
  - bumetanide
- early DT - thiazides

ii. other drugs - amphotericin B
- anionic drugs, eg. penicillins

iii. ↑ DT flow

iv. hypomagnesaemia

c. ↑ ***GIT*** losses

i. diarrhoea, fistulae

ii. malabsorption syndromes

d. ***skin*** losses - extreme sweating

e. compartmental shifts

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

ii. insulin

iii. adrenaline

iv. familial periodic paralysis

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

vi. refeeding effect

- ***Manifestations***

a. ***CVS***

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

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

iii. dysrhythmias - VEB's, VT / VF, AF, SVT
* ↑↑ sensitivity to ***digoxin*** & ***hypercalcaemia***
* severe depletion → arrest in VF or systole

iv. chronic depletion → ***subendocardial necrosis***

b. ***neuromuscular***

i. ↑ sensitivity to NDMR's ∝ ↑ resting E_m

ii. muscle weakness / paralysis ∝ severe depletion

iii. chronic depletion → ***rhabdomyolysis***

c. ***renal***

i. nephrogenic DI ∝ ***ADH resistance***

ii. ↑ NH_3 production → ?? generation of alkalosis

d. ***endocrine***
- ↓ insulin release
- ↓ $[K^+] \leq 2.5$ mmol/l → ↑ BSL up to 20 mmol/l

e. ***acid-base balance***
- allegedly hypokalaemia leads to a ***metabolic alkalosis***, due to an,

i. ↑ NH_3 production in DT

ii. ↑ $[H^+]_{ICF}$ as K^+ moves into ECF

iii. ↑ PT HCO_3^- reabsorption
- however, most hypokalaemia states coexist with NaCl deficits, and it is the **Cl^-** ***deficit*** which produces the metabolic alkalosis
- severe hypokalaemia leads to ***ADH resistance*** and a form of nephrogenic DI, the subsequent ***volume depletion*** leading a metabolic alkalosis
- hypokalaemia and a metabolic acidosis may occur in patients on carbonic anhydrase inhibitors, or RTA

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

- ***Treatment - Severe***

a. ABC
b. IV KCl
   i. ≤ 0.5 mmol/kg/d ***with*** ECG monitoring
   ii. ≤ 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 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
• some argue hypokalaemia *per se* will ***not*** generate an alkalosis, but that it will maintain an alkalosis, once generated
• Maxwell & Kleeman, however would support that even in normovolaemia there is a tendency for hypokalaemia to produce an alkalaemia, though, this effect in mild

Hyperkalaemia

Def'n: serum $[K^+]$ > 4.8 mmol/l
plasma $[K^+]$ > 4.2 mmol/l QEH > 4.8 mmol/l

- ***Aetiology - 1***

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_2-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. HCl gain
- HCl infusion
- arginine HCl

iii. drugs
- K^+ sparing agents - spironolactone, amiloride, triamterene
- ACE inhibitors - captopril, enalapril
- PG inhibitors - indomethacin

iv. Addison's - or steroid withdrawal

v. 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)

→ **-$[K^+]$ ~ 0.5 mmol / $^-$pH ~ 0.1**

iii. tissue damage
- rhabdomyolysis
- burns, MH

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

- ***Aetiology - 2***

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

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

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 the intake / output / distribution

a. ***increased intake*** - rarely a problem
- except with marginal renal function

b. ***decreased losses*** - renal

i. renal failure

ii. hypoaldosteronism - mineralocorticoid deficiency
- type IV RTA

iii. ↓ distal tubular flow

iv. ↓ distal NaCl delivery

v. potassium sparing diuretics
- aldosterone antagonists - spironolactone
- inhibitors of distal Na^+ channels - amiloride, triamterene

c. ***compartmental shifts***

i. acidaemia **¯ pH ~ 0.1 / - [K^+] ~ 0.5 mmol/l**
- 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. hypoaldosteronism - plasma K^+ is multifactorial,
- $K^+_{ICF} \rightarrow K^+_{ECF}$
- ↓ DT flow
- ↓ DT aldosterone effects

iii. insulin deficiency - DKA

iv. familial periodic paralysis

v. suxamethonium

vi. cellular damage - haemolysis, rhabdomyolysis
- severe burns, massive ischaemia
- exercise
- thrombocytosis > 750,000
- leukocytosis > 50,000

vii. increased ECF tonicity
- 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 & insulin deficiency

- ***Clinical Effects***

a. **CVS**

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

ii. ECG
- peaked T-waves
- widening of QRS
- ↑ PR interval → loss of P-waves

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

c. **$CaCl_2$ 10%** ~ 5-10 ml $\equiv^{T}$ Ca^{++} ~ 3.4-6.8 mmol

d. **$NaHCO_3$** ~ 50-100 mmol
- onset of action is immediate, however duration is only 1 hr
- * 100 mmol HCO_3^- $\rightarrow$ 2.24 l CO_2

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. look for ECG / muscle changes ± recheck level

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. decrease intake

c. 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

d. correct underlying problem - volume replacement
- steroid replacement

Familial Periodic Paralysis

NB: three types, dependent upon the K^+ level

1.	***hypokalaemic***		< 3.0 mmol/l
	i.	inherited	- ***familial*** hypokalaemic periodic paralysis
	ii.	acquired	- precipitated by large meals - post-exercise - glucose/insulin infusion - catecholamines * common
2.	***normokalaemic***		~ 3.0-5.5 mmol/l - precipitated by alcohol, exercise and stress
3.	***hyperkalaemic***		> 5.5 mmol/l - precipitated by exercise (? release of K^+ from muscle) - K^+ infusions - hypothermia (decreased activity of Na^+/K^+ pump) - usually localised to tongue and eyelids

- ***Causes of Episodic Paralysis***

1. myasthenia gravis
2. myasthenic syndrome
3. thyrotoxicosis
4. hyperaldosteronism
5. antibiotics
6. botulinism
7. multiple sclerosis
8. familial periodic paralysis
9. TIA, RIND
10. hysterical

CHLORIDE ION

• normal plasma range ~ **98-108 mmol/l**
• normal ratio of Na^+:Cl^- ~ 1.4:1
• the kidneys reabsorb Na^+:Cl^- ~ 1:1, therefore syndromes associated with avid Na^+ retention often have associated ***hyperchloraemia***

- ***Hyperchloraemia***

  a. any hypernatraemic state
  b. respiratory alkalosis - decreased availability of HCO_3^-
  c. ***metabolic acidosis*** with normal anion gap
     i. renal - RTA
        - CA inhibitors
        - hypoadrenalism
        - early uraemia
     ii. non-renal - diarrhoea
        - ureterosigmoidoscopy
        - treated DKA
        - exogenous HCl

- ***Hypochloraemia***

  a. hyponatraemic states
  b. metabolic alkalosis - increased HCO_3^-
  c. respiratory acidosis
  d. chloride loss - gastric suction, vomiting
     - upper GIT obstruction, eg. pyloric stenosis
     - chloride (secretory) diarrhoea

CALCIUM

a. elemental alkaline earth metal
b. atomic number = 20
c. molecular weight ~ 40
d. divalent cation - fifth most plentiful cation in the body

- total body content ~ 380 mmol/kg
  → ~ 1100 g/average adult
  ~ 27.5 mol of Ca^{++}

a. bone ~ 99%
b. ICF ~ 0.004%
c. ECF ~ 0.01%
d. exchangeable **~ 1%**

- 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%** - ionized 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 ionized Ca^{++}
   ~ 99% bound to enzymes in SR, cisternae, & tubules

- only plasma ionized Ca^{++} is biologically active
  → normal range ~ 1.2-1.3 mmol/l

- the most important influence on protein binding is ***plasma pH***

↑ pH → ↑ binding of Ca^{++} ∝ exposure of anionic sites on albumin
→ ↓ 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)
      • $\propto$ calmodulin & vesicle coupling
   iv. ***neuro-hormonal*** release & activity
      • 1. α_1-adrenergic (NA) - smooth muscle
         - hepatic glycogenolysis
         - salivary secretion
      • 2. ACh - smooth muscle
         - GIT, GB, bladder contraction
      • 3. ADH - vascular smooth muscle (V_1)
      • 4. angiotensin II - aldosterone secretion from Z.G.
      • 5. oxytocin - uterine & myoepithelial
      • 6. CCK - pancreatic secretion
         - GB contraction
      • 7. histamine (H_1) - bronchial contraction
         - GIT smooth muscle contraction

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

- ***Effector Sites for Calcuim 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
- reabsorbed 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 is lost in more distal segments
- ***aldosterone*** & ***PTH*** do not affect distal handling of both ions
- ***thiazides*** inhibit distal tubular Na^{+} reabsorption, however ↑ Ca^{++} reabsorption
- 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***

1. $[Ca^{++}].[HPO_4^{=}]$ solubility product **> 6** → ↑ ***ectopic calcification***
2. parathyroid hormone
3. vitamin D - 1,25-dihydroxycholecalciferol
4. calcitonin

- ***Secondary Influences***

a.	acid-base status		
	i.	acidosis	- ↑ Ca^{++}
	ii.	alkalosis	- ↓ Ca^{++}
b.	steroids		- ↓ Ca^{++}
c.	glucagon		- ↓ Ca^{++}
d.	growth hormone		- ↑ Ca^{++}
e.	albumin levels		~ 0.02 mmol Ca^{++} / gram albumin (**0.2 mmol/10g**)
f.	renal function		- GFR - tubular excretion - 1-hydroxylation of 25-(OH)-D_3
g.	thyroid hormones		~ 15% of ***hyperthyroid*** patients are hypercalcaemic - rarely clinically significant

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

1. ***parathyroid hormone***
   - i. ↑ movement of Ca^{++} and $HPO_4^{=}$ out of bone
   - ii. ↑ renal tubular reabsorption of Ca^{++}
   - iii. ¯ renal tubular reabsorption of $HPO_4^{=}$
   - iv. ↑ production of Vit. D → ***indirect effects***

   - inhibits proximal tubular H^+ secretion & HCO_3^- reabsorption → ↓ pH → displaces Ca^{++} from plasma protein and bone
   - ↑ $HPO_4^{=}$ 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
     - rarely may result in ***nephrocalcinosis***

2. ***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 (ie. pregnancy)
   - the major actions of vitamin D are,

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

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

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

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

3. ***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 very ***minor***

Hypocalcaemia

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

- ***Aetiology***

a. ***factitious*** - hypoalbuminaemia (N: 37-55 g/l)
¯ Ca^{++} ~ 0.2 mmol / ¯ 10g per litre
- K-EDTA tube sample

b. ***acute***
i. acute post-surgical hypoparathyroidism - ***most common***
ii. respiratory alkalosis
iii. acute pancreatitis
iv. rhabdomyolysis, MH
v. hypomagnesaemia * ↓ PTH release
vi. citrate toxicity

c. ***chronic***
i. primary hypoparathyroidism
- iatrogenic - post-thyroid or parathyroid surgery, $^{131}I^-$ therapy
- infiltrations - neoplasia
- granulomatous diseases
- haemosiderosis, Wilson's disease
- idiopathic hypothyroidism
- persistent neonatal form
- branchial dysembryogenesis (DiGeorge's syndrome)
* multiple endocrine deficiency autoimmune candidiasis (MEDAC)

ii. chronic renal failure
iii. disordered vitamin D metabolism
- deficiency - reduced intake, liver / renal disease
- resistance - renal disease, familial

iv. high dietary PO_4 intake

- ***Polyglandular Autoimmune Syndrome Type 1***

• at least 2 of the following, not necessarily simultaneously

1. mucocutaneous candidiasis ~ 3-6 yrs of age
2. hypoparathyroidism ~ 5-8 yrs
3. Addison's disease ~ 8-11 yrs

NB: previously called multiple endocrine deficiency autoimmune candidiasis (***MEDAC***)

▪ ***Clinical Features***

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

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

c. CVS
- ↓ SVR*
- negative inotropy* *→ ***hypotension***
- negative chronotropy*
- ***prolonged*** QT_C = $QT / \sqrt{RR}$ > 0.45 s female; > 0.40 s male
- atrial & ventricular ***ectopics***

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

▪ ***Anaesthetic Considerations***

• management of hypoparathyroidism is not surgical, \ usually presenting for unrelated reasons
• prolongation of the QT interval may progress to 2:1 ***AV block***
• QT_C is a reliable marker of hypocalcaemia in a given ***individual***, but not within a population
• CCF rarely results from hypocalcaemia, but in the presence of preexisting heart disease, correction of plasma Ca^{++} and Mg^{++} will improve LV performance
• similarly hypotension from any cause will be worse in the presence of hypocalcaemia
• patients may suffer petit mal, focal, Jacksonian or grand mal ***seizures***
• these are resistant to normal therapy, and may actually be made worse due to an anti-vit.D effect
• post-surgery for hyperparathyroidism, marked falls in Ca^{++} & Mg^{++} may be seen in patients with advanced osteitis & "hungry" bones
• potentially fatal complications include ***laryngeal spasm & seizures***

• ***hypomagnesaemia*** results principally in,

1. ventricular tachyarrhythmias
2. hypocalcaemic tetany and neuromuscular irritability

NB: which are ***independent*** of calcium

• management,

1. ionised Ca^{++}, Mg^{++} and $HPO_4^{=}$ should be measured before & after surgery
2. QT_C should be checked on a 12 lead ECG
3. significant or ***symptomatic*** levels should be corrected

- ***Treatment***

a. **Ca Gluconate 10%** $\equiv^{t}$ Ca^{++} 0.22 mmol/ml

- administer at ~ 2-4 mmol every 6-8 hrs (1-2 10ml ampoules)
  ~ 0.5 ml/kg to a maximum of 20 ml

b. **$CaCl_2$ 10%** $\equiv^{t}$ Ca^{++} 0.68 mmol/ml x 10 ml

- the injection rate should be slow $\leq$ 1 ml/min
- faster rates may $\rightarrow$ 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 vasodilation and vessel irritation

c. Vit. D $\rightarrow$ calciferol ~ 1.25 mg twice weekly

d. R_X associated conditions
   i. hypomagnesaemia
   ii. hypokalaemia
   iii. fitting

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
ionized calcium ~ 1.20-1.30 mmol/l

- ***Aetiology***

NB: incidence ↑'s in the 3-5th decades, F:M ~ 3:1

1. ***factitious*** - venous stasis sample, post-prandial
   - polycythaemia, dehydration, high plasma albumin
2. **1°** ***hyperparathyroidism***
   i. ***solitary adenoma*** ~ 80%
   ii. MEN I - pituitary adenoma and pancreatic islets
   - hypergastrinaemia with Zollinger-Ellison syndrome
   iii. ***MEN II*** - medullary carcinoma of the thyroid (***p***arafollicular)
   - ***phaeochromocytoma*** & ***p***arathyroid adenoma
   iv. lithium therapy ~ 10% show ↑ parathyroid function
   v. rarely carcinoma
3. ***malignancy***
   i. solid tumour with bony 2°'s - breast, prostate
   ii. ectopic parathormone - lung (~ 10-15%), kidney, ?? PGE_2
   iii. haematological malignancies - ***m. myeloma***, leukaemia, lymphoma
   * osteocyte activation factor
4. ***increased bone turnover*** - ***thiazide diuretics***
   - hyperthyroidism
   - immobilization
   - vitamin A intoxication
5. ***vitamin D***
   i. vitamin D intoxication * high Ca^{++} & $HPO_4^{=}$
   ii. ↑ 1,25-$(OH)_2$-D_3 - ***sarcoid*** & other granulomatous diseases
   - TB, berylosis
   iii. idiopathic hypercalcaemia of infancy
6. familial hypocaliuric hypercalcaemia - FHH
   - autosomal dominant trait → > 99% renal calcium reabsorption
   - PTH levels are usually normal, no medical or surgical intervention is required
7. renal failure - severe 2° hyperparathyroidism
   - milk/alkali syndrome, Al^- intoxication
8. other causes - Addisonian crisis
   - phaeochromocytoma
   - excess IVT/ TPN

- ***Clinical Features***

NB: initially → polyuria, thirst, fatigue, nausea, vomiting & abdominal pain

a. CNS
- mental disturbance, personality change
- paraesthesia, headache, fever, increased thirst
- cerebral calcifications (basal ganglia) ± epileptic fits

b. CVS
- bradycardia, asystolic arrest
- ↑ digoxin toxicity

ECG
- ↓ QT_C, bradyarrhythmias, AV blockade

c. renal
- polyuria ∝ nephrogenic DI
- type II RTA ∝ impaired tubular reabsorption
- ***nephrocalcinosis*** ~ 60-70%

d. NMJ
- ↑ ACh release
- ↑ excitation / contraction
- ↑ threshold V_m

* but ***decreased sensitivity*** of motor EP
→ weakness, fatigue, paralysis

e. musculoskeletal
- weakness, fatigue, paralysis, arthralgia
- osteitis fibrosa cystica, bone pain, fractures

~ 5x ↑ bone turnover → ↑ ALP

f. GIT
- nausea, vomiting, anorexia, weight loss
- constipation, abdominal pain
- gastric hyperacidity (↑ ***gastrin*** secretion), peptic ulcer
- ***pancreatitis***

- ***Anaesthetic Considerations***

NB: moderate hypercalcaemia, in the absence of cardiovascular or renal compromise presents no specific intraoperative problems

1. CNS - lethargy, ***confusion*** may compromise recovery
2. ECG - shortened QT_C & risk of ***AV blockade*** etc.
3. biochemistry - associated electrolyte disorders
4. volume status - ***polyuria*** may result in hypovolaemia
5. NMJ blockade - ↑ sensitivity to nondepolarising agents, difficulty in ***reversal***

- ***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 * beware ***hypokalaemia & hypomagnesaemia***
d.	corticosteroids	- ↓ GIT absorption / increase excretion - especially sarcoid, Vit.D, granulomatous diseases * ***not*** effective in 1° hyperparathyroidism
e.	diphosphonate	- etidronate, ***pamidronate***
f.	correct hypophospataemia	- ↑ GIT absorption - ↓ bone uptake & ↑ reabsorption
g.	decrease bone release	- calcitonin - mithramycin

- ***Pamidronate Disodium***

- potent inhibitor of bone reabsorption
- effective in hypercalcaemia of malignancy and hyperparathyroidism
- administered as 30 mg/500 ml saline over 4 hours
- studies against 60 mg doses show no advantage
- results in a gradual decline in plasma Ca^{++} over several days
- effects may last from weeks to months
- side effects,
    1. mild transient leukopaenia
    2. ***fever*** ≤ 2°C ↑ T

MAGNESIUM

a. elemental alkaline earth metal
b. atomic number = 12
c. molecular weight ~ 24.3
d. divalent cation - second most plentiful intracellular cation

• total body content **~ 15 mmol/kg**, (~ 1000 mmol/70 kg)

a. ICF ~ 45% - highly variable
b. ECF ~ 5%
c. plasma ~ **0.75-1.1 mmol/l** ~ 35% protein bound
d. bone ~ 50%
e. 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

▪ *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*

1. neuromuscular function and excitability
2. Na^{+}/K^{+}-ATPase pump cofactor
3. enzyme cofactor - anabolic functions in brain & liver
4. involved in all phosphate transfer reactions
5. 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
- cisplatinum

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 -PO_4 nucleotide 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 utilization***

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. ↑ release of ACh from motor neurones
   ii. ↑ 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 → ↓ 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 ~ 0.05-0.15 mmol/kg
     ≤ 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 - pre-eclampsia/eclampsia
      - SVT, torsade
   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
   - $\downarrow$ release of ACh from motor neurones
   - $\downarrow$ 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
   - $\uparrow$ ***conduction time*** $\rightarrow$ PR, QRS and QT prolongation (> 5 mmol/l)
   - $\downarrow$ 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 unionized 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 • ↑ AV & intraventricular conduction
~ 5.0 mmol/l	• loss of ***monosynaptic reflexes*** • ↑ 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	- weakness & CNS signs - torsade de pointes - digitalis induced VT - suspected severe depletion (alcoholics, malnourished)
b.	enteral preparations	- cathartics - antacids
c.	seizure states	- pre-eclampsia/eclampsia - acute nephritis
d.	SVT	
e.	severe acute asthma	? marginal indication

PHOSPHATE

- involved in most metabolic processes and is a major constituent of bone
- normal adult content ~ 1000g, 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
    a. ~ 5-12% is protein bound, $\therefore$ ~ 90% is filterable at the glomerulus
    b. ~ 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	$\downarrow$
b.	Glucagon	$\downarrow$
c.	Dietary Phosphate	$\downarrow$
d.	$1,25\text{-}(OH)_2D_3$	$\uparrow$
e.	Insulin	$\uparrow$

Hyperphosphataemia

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

- ***Aetiology***

a. acute ∝ ***release from cells***
   i. metabolic acidosis
   ii. diabetic ketoacidosis
   iii. rhabdomyolysis, haemolysis
   iv. ischaemic gut
   v. severe catabolic states
   vi. malignancies treated with cytotoxic agents

b. chronic
   i. renal failure
   ii. vitamin D toxicity
   iii. excessive intake (TPN)
   iv. 1° hyperparathyroidism - rare, usually normal

- 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.	↑ insulin	- post-prandial - treatment of hyperkalaemia
ii.	R_X of acidosis	- diabetic ketoacidosis - rhabdomyolysis - hypercapnia
iii.	TPN in malnourished or anorexic patient	

b. acute ∝ ***increased loss / utilization***

i.	phosphaturia from diuresis	- osmotic / diuretic
ii.	severe illness	- sepsis, hypercatabolic states

c. chronic

i.	decreased ***intake***	- prolonged TPN - alcoholics, aged & debilitated patients - anorexia
ii.	decreased ***absorption***	- vitamin D deficiency - rickets, osteomalacia - intestinal dysfunction - steatorrhoea / malabsorption syndromes
iii.	increased ***loss***	- diuresis - 1° hyperparathyroidism - renal tubular acidosis
iv.	increased ***utilisation***	- hypercatabolic states - multitrauma - cancer

- ***Symptoms***

a. asymptomatic

b. anorexia

c. weakness, dizziness

d. dyspnoea - respiratory muscle weakness

e. paraesthesia

f. bone pain (osteomalacia)

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

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

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 (Na)H_2PO_4

Effects of Electrolyte Imbalance						
		CNS	**CVS**	**Muscle**	**GIT**	**Renal**
Na^+	• high	excite	-	-	-	-
	• low	excite	-	-	-	-
K^+	• high	-	depress	weakness	-	-
	• low	-	excite	weakness	ileus	DI-renal
Ca^{++}	• high	depress	slow	weakness	N & V	DI renal
	• low	excite	depress	excite	-	-
$HPO_4^=$	• high	-	depress	-	-	-
	• low	depress	depress	weakness	-	-
Mg^{++}	• high	depress	depress	weakness	-	-
	• low	-	excite	-	-	DI renal

HEAT STROKE

Def'n: excessive heat storage due to combination of overheating and failure of the thermoregulatory system → ***"cardinal features"***

1. hyperthermia ≥ 40°C
2. hot, dry skin
3. ± hypotension
4. severe CNS disturbance

• predisposing features,

a. high environmental temperature

b. impaired heat response

i.	age	- elderly, neonates
ii.	obesity	
iii.	underlying disease	- CCF, debilitating illness

c. dehydration

d. drugs
- phenothiazines
- atropine, anticholinergics
- diuretics
- alcohol

e. excessive physical activity (relative)

■ ***Clinical Features***

a.	CNS	- confusion, convulsions, coma
b.	CVS	- initially high CO / low SVR / hyperdynamic circulation - relative & absolute hypovolaemia - later CO & SVR fall, and PVR rises - δST-T waves ∝ myocardial injury
c.	respiratory	- hyperventilation - initially respiratory alkalosis - later respiratory / metabolic acidosis - aspiration, ARDS, LVF
d.	muscle	- rhabdomyolysis
e.	renal	- ATN, myoglobinuric renal failure
f.	metabolic	- hyperthermia - high K^+, Na^+, $HPO_4^=$, LDH, CK - low Ca^{++}, Mg^{++} & glucose
g.	haematological	- DIC, coagulopathy, liver failure

- ***Treatment***

a. O_2 and respiratory support
b. rehydration and CVS support
c. rapid cooling
d. prevention of renal failure - hydration and mannitol
e. prevent ***hypoglycaemia***
f. manage ***hyperkalaemia*** - hyperventilation
- Ca^{++}, HCO_3^-
- insulin/glucose
- resonium, dialysis

g. anticonvulsants prn

Fever / Hyperthermia

a. ***infectious causes***
   i. common sites
      - surgical wounds
      - UTI, indwelling catheters
      - respiratory tract - upper & lower
      - line infection - IA, IV, CVC, PA
      - GIT - antibiotic induced colitis, ischaemic colitis
        - hepatitis
        - calculous/acalculous cholecystitis

   ii. uncommon / occult sites
      - SBE
      - subphrenic, other intra-abdominal collection
      - cholangitis, ascending cholangitis
      - sinusitis, periodontal abscess
      - decubitus ulcers
      - prostatitis, endometritis
      - meningo-encephalitis
      - parasitic, eg. malaria
      - TB

b. ***non-infectious causes***

i.	inflammatory	- pancreatitis - vasculitis - acute arthritis, gout - AMI - familial mediterranean fever - sarcoidosis
ii.	autoimmune	- SLE, RA, PAN, temporal arteritis - Wegener's granulomatosis ($cANCA^+$) - Kawasaki's disease
iii.	allergic	- blood transfusion, blood products - drug induced fever (see below)
iv.	blood-borne	- haemolysis, transfusion reaction - DVT, pulmonary embolus - internal haemorrhage (CNS, joints, AAA, retroperitoneal) - cyclic neutropaenia
v.	metabolic	- hypercalcaemia - adrenal insufficiency
vi.	hyperthermic syndromes	- MH, malignant neuroleptic syndrome - heat stroke - hyperthyroidism - central anticholinergic syndrome
vii.	neoplasm	- lymphomas, carcinoma (renal, colon) - hepatoma, liver secondaries - atrial myxoma - carcinoid
viii.	drugs	- ↑ production | ↓ heat loss - disordered central regulation - mixed
	• withdrawal syndromes	- delerium tremens, opioids, other
	• sympathomimetics	- vasoconstriction & muscle activity
	• epileptogenics	
	• salicylates	- ↑ VO_2, reset hypothalamic set-point
	• phenothiazines	- CNS regulation
	• anticholinergics	- in overdosage
	• MH & MNS triggers	
ix.	others	- Fabry's disease - hyperlipidaemias - granulomatous hepatitis

- ***Mechanisms of Drug-Induced Fever***

1. overdose
2. withdrawal syndrome
3. allergic reaction
4. interference with temperature regulation
   - i. central - hypothalamic set-point
     - sympathetic outflow
   - ii. peripheral - skin vasomotor tone, sweating
5. alteration of BMR
   - i. alteration of cellular activity - basal VO_2
   - ii. uncoupling of oxidative phosphorylation
6. hyperthermic syndrome triggers
   - i. malignant hyperpyrexia
   - ii. neuropleptic malignant syndrome
7. antibiotic induced superinfection

Hypothermia

Def'n: ***core temperature*** **< 35°C**
homeotherms regulate core temperature ~ 36-37.5°C (T.Oh)
~ 37 ± 0.4°C (RDM)

1. mild > 33°C
2. moderate ~ 30-33°C
3. severe < 30°C

NB: demarcation is arbitrary, but effects more pronounced & ***loss of compensation***
lowest recorded core T in a survivor ~ 18°C

- ***Aetiology***

a. extremes of ***age***

b. debilitating ***illness***
   i. CNS - CVA, head injury, neoplasm
      - progressive mental deterioration
   ii. CVS - CCF, MI, PVD, PTE
   iii. infections - septicaemia from any cause, pneumonia
   iv. renal - uraemia

c. ***exposure*** - environment
   - IV fluids, irrigating fluids

d. ***drugs*** - alcohol
   - GA, barbiturates, benzodiazepines, etc.
   - antipyretics, chlorpromazine
   - vasodilators

e. ***endocrine*** - hypothyroidism, panhypopituitarism
   - Addisonian crisis, hypoglycaemia
   - diabetes, hyperosmolar coma, ketoacidosis (~ 20%)
   - protein / calorie malnutrition

f. ***spinal cord trauma***

g. ***skin diseases*** - burns
   - psoriasis, icthyosis, erythroderma

h. ***iatrogenic*** - induced hypothermia & inadequate rewarming

- ***Cardiovascular***

1. increased sympathetic tone - ↑ plasma NA/AD and FFA's
2. initially → vasoconstriction, tachycardia & ↑ CO
   later → bradycardia, hypotension & ↓ CO
3. cardiac output - ↓ CO ~ 30-40% at 30°C ∝ decrease in VO_2
   - mainly 2° to ***bradycardia***, SV well preserved
   - coronary perfusion well maintained
4. ECG changes - exacerbated by ***acidosis & hyperkalaemia***
   i. bradycardia / shivering artefact
   ii. ↑ PR, QRS, QT_C duration
   iii. J point elevation ≤ 33°C
   - delayed repolarisation of inferior heart surface
   iv. AF ~ 25-34°C (commonest arrhythmia)
   v. AV block 1° ~ 30°C
   3° ~ 20°
   vi. VF ≤ **28°C**
   vii. asystole ≤ 20°C
5. CPK & LDH levels are elevated
   - ? leakage from cells or microinfarction

- ***Central Nervous System***

- reasonably well preserved to 33°C, below this function deteriorates progressively,

1. initial confusion → coma at ~ 30°C with ***pupillary dilatation***
2. ↓ CBF ∝ ↓ C-VO_2 ~ **6-7% / °C**
   ~ similar change cf. whole body VO_2
3. progressive brainstem depression → ↓ HR & ↓ RR
4. ↓ ***temperature regulation*** → ↓ shivering ≤ 33°C
   → loss of temperature control ≤ 28°C
5. cerebral protection
   i. greater than achieved by metabolic depression
   ii. deep circulatory arrest
   iii. recovery from near drowning

- ***Pulmonary Changes***

1. central depression→ ↓ RR ≤ 33°C ~ 4 bpm ± respiratory arrest at 25°C
   ↓ CO_2 drive
   * no change in ***hypoxic drive***
2. impaired cough & gag reflexes → ***aspiration risk***
3. ↑ V/Q mismatch
   i. impaired hypoxic pulmonary vasoconstriction
   ii. ↓ FRC → atelectasis
   iii. ↓ gaseous diffusion capacity
4. ↑ VO_2 with ***shivering*** → ↓ VO_2 ≤ 33°C
5. ↑ HbO_2 affinity / ***left shift*** → ↓ O_2 availability
6. ↑ ***gas solubility***
   i. ↑ αCO_2 / ↓ P_{aCO2} → ↑ pH (but, also ↑ neutral point of H_2O)
   ii. anaesthetic gases → ↓ rate of rise of F_A/F_I & elimination
   - halothane $MAC_{27°C}$ ~ 50% $MAC_{37°C}$

- ***Metabolic***

1. ↓ VO_2 ~ 6-7% / °C
2. severe ***acidosis*** → HbO_2 curve shifts to the ***right***
   i. respiratory ↓ CO_2 elimination due to hypoventilation
   ii. metabolic ↓ tissue perfusion
   ↓ hepatic lactate clearance
   ↓ renal tubular H^+ excretion
   iii. temperature correction of blood gas values offers ***no advantage*** in management
   → δ pH ~ -0.0147 / °C
3. ***hyperkalaemia / hypokalaemia***
   • causes for expected rise in K^+
   i. decreased activity Na^+/K^+-ATPase → ↓Na^+ / ↑K^+
   ii. cellular hypoxia, membrane damage & acidosis
   • however, ***hypokalaemia*** is more commonly observed
   i. ? 2° diuresis
   ii. ICF shift
4. ***hyperglycaemia*** - ↓ insulin secretion & ↓ peripheral glucose utilisation
   - ? mild pancreatitis
   - hypoglycaemia may ensue in longstanding hypothermia
5. ↑ drug $t_{½\beta}$ ∝ ↓ hepatic blood flow & enzyme reaction rates
   → ***heparin, citrate & lactate***

- ***Renal***

1. ↓ GFR ∝ ↓ renal blood flow ~ 50% at 30°C
   → ↓ drug clearance
2. decreased tubular function
   i. cold diuresis - volume of urine initially increased or the same
   ii. hypoosmolar urine
   iii. glycosuria, kaluria → additional diuresis

- ***Neuromuscular Junction***

1. shivering occurs ~ 33-36°C
2. ↑ muscle tone → ***myoclonus*** ~ 26°C
3. ↑ sensitivity to ***both*** depolarising & nondepolarising NMBs with mild hypothermia

- ***Haematological***

1. ***coagulopathy***
   i. ↓ coagulation ↓ enzyme activity
   ii. thrombocytopaenia ↑ portal/splenic platelet sequestration
   ↑ bleeding time
2. increased blood ***viscosity*** - dehydration, haemoconcentration & ↑ Hct.
   - ↓ rbc deformability
   - ↓ microcirculatory blood flow
3. ***immunoparesis*** - ↓ WCC (sequestration) & function
4. marrow hypoplasia

- ***Immunological***

1. decreased neutrophils, phagocytes, migration, bactericidal activity
2. organ hypoperfusion & increased infection risk
3. diminished gag / cough reflexes
4. atelectasis

- ***Monitoring***

a. central - lower oesophageal & PA → heart
- tympanic membrane → brain

b. rectal - intermediate
- changes lag behind core/shell during cooling & warming

c. shell - skin/peripheral
- may estimate vasoconstrictor/vasodilator responses

NB: useful to measure both core & shell,
core-shell gradient → better assessment of overall body temperature
→ adequacy of rewarming & predicts "afterdrop"

- ***Management***

1. resuscitation
   - major hazard is peripheral vasodilatation & ***hypovolaemia***
2. monitoring
   i. routine BP, HR, RR, GCS
   ii. T°, ECG, U/Output
   iii. EC&U, AGA's, FBE
   iv. ***blood cultures*** & septic work-up
3. rewarming
   i. ***passive*** ~ 0.5-1.0°C / hr in the absence of shivering
   ~ 0.5-2.0°C / hr with shivering
   - adequate for the vast majority of cases
   - only require active rewarming if haemodynamically unstable

   ii. ***active***
   - surface - 'Bear hugger' type
   - temperatures no greater than 40 °C, cease at ~ 35°C
   - core - CVVHD, CPB, PD
   - should be ceased at ~ 33°C
4. antibiotics - broad spectrum cover pending cultures

- ***Hypothermic Cardiac Arrest***

a. defibrillation virtually useless < 30°C
b. extracorporeal rewarming if possible
c. don't pronounce dead until T > 35°C
d. normally ***hypokalaemic***, if markedly hyperkalaemic then unlikely to succeed

MORBID OBESITY

Def'n: ***body mass index*** **> 35** BMI = $kg/ht(m)^2$
~ 22-28 normal
> 42 MO in pregnancy
> **2x** ideal body weight, or
> **45 kg** over ideal body weight

- ***Pathophysiology***

1. BMR increased ***proportionally*** to body weight
2. ***cardiovascular***
   i. ↑ blood volume, plasma volume & cardiac output ∝ ↑ weight
   ii. adipose BF ~ 20-30 ml/kg at rest → ↑ CO ~ 1.5 l/min / 50 kg
   iii. HR usually unchanged, \ ↑ CO ∝ - **SV**
   iv. ↑ CO ∝ ↑ VO_2 → δCa-vO_2 normal
   v. later develop progressive ***hypertensive*** and ***ischaemic heart disease***
      • progressive dilatation of LV, ↓ exercise response & ↑ LVEDP
   vi. reduced ***exercise tolerance***
3. ***respiratory***
   i. ↑ VO_2 → ↑ CO_2 production
   ii. altered lung mechanics ∝ loading of thoracic wall with fat
      • ↓ FRC & ERV predominantly
      • encroachment of closing capacity on FRC
      • ↓ chest wall compliance
      • ↑ work of breathing
   iii. ↑ V/Q mismatch - increased δP_{A-aO2} ± ***hypoxia***
      • the young obese usually have normal blood gases
      • daytime hypoxaemia associated with OSAS
   iv. tendency to ***hypercapnia*** with increased loads
      • increase in V_M & max $P_{Insp.}$ with ↑ P_{aCO2} diminished
   v. central CO_2 / O_2 drive abnormalities →
      • ***obesity hypoventilation syndrome*** - central
      • ***obstructive sleep apnoea syndrome*** - central & peripheral
4. ***endocrine***
   i. higher than normal calorie intake
   ii. ↑ ***glucose intolerance***, NIDDM
   iii. ↑ pancreatic dysfunction

5. ***gastrointestinal***
   - i. gastric stasis / reflux due to hiatal hernia → ↑ ***aspiration risk***
   - ii. > 90% have fasting gastric volume > 0.4 ml/kg & pH < 2.5
     - risk data from Roberts & Shirley in Rhesus monkeys
     - not supported by subsequent studies (Raidoo *et al.*)
   - iii. fatty liver infiltration
   - iv. hepatic dysfunction 2° intestinal bypass

6. ***general***
   - i. intubation - decreased atlanto-axial movement
     - chin & upper thoracic fat pads
     - large tongue, palatal & pharyngeal fat pads
   - ii. technical problems - CVC insertion
     - IV access
     - epidural catheters, etc.
     - * patient transfers
   - iii. reduced ***immune response***
   - iv. skin infections - bacterial & fungal
   - v. psychology
   - vi. increased risk of,
     - IHD, CVD
     - DVT/PTE
     - perioperative morbidity & mortality
     - infections

7. ***pharmacokinetics/dynamics***
   - i. ↓ percentage body water & muscle mass / ↑ percentage fat
   - ii. ***hepatic dysfunction*** ∝ fatty infiltration
   - iii. high incidence of ***cholelithiasis*** & ***pancreatitis***
   - iv. ***hydrophilic drugs*** - NMJ blockers
     - similar absolute volumes of distribution, clearance & elimination half-lives
     - vecuronium administered mg/kg has prolonged activity, suggesting relative overdose → dose based on ***lean body mass***
     - atracurium recovery similar to non-obese
   - v. ***lipophilic drugs*** - STP, BZD's
     - ↑ V_{dSS} & normal clearance → ↑ elimination half-lives
   - vi. fentanyl kinetics similar to non-obese
     - alfentanyl/sufentanyl → ↑ $t_{½\beta}$
   - vii. ↑ plasma ***pseudocholinesterase*** activity → SCh ~ 1.5 mg/kg

- ***Anaesthetic Management***

1. ***premedication*** - H_2 blockers, metoclopramide, clear antacid
   - anticholinergics if fibreoptic intubation anticipated
   - sedatives only when the patient can be monitored
2. ***monitoring*** - ECG → II + V_5
   - IABP, NIBP difficult and increased inaccuracy
   - F_IO_2, S_pO_2, spirometry, $ETCO_2$, Temp., PNS
3. ***airway maintenance*** * always use an ETT, CP & RSI
   - mask SV → ↑ $ETCO_2$ & ↓ S_pO_2

   ≤ 13% incidence of ***difficult intubation***, \ prepare !

   ? awake fibreoptic if 75% > IBW
   - skilled assistance where possible
4. ***general anaesthesia***
   - STP ≤ 7 mg/kg, but allowances for CVS dysfunction
   - ↑ %volatile agents presented to the liver for metabolism → ***isoflurane***
   - supposition of prolonged recovery from volatile agents has been ***disproven***
   - SV relatively contraindicated → hypercarbia, hypoxia
   - N_2O would appear logical due to low solubility, but ↓'s F_IO_2
   - ↓ FRC & ↑ VO_2 → rapid desaturation, \ initial F_IO_2 = 1.0
   - extubation when fully reversed & awake
5. ***regional anaesthesia***
   - SA & epidural dose requirements for MO patients are ~ 70-80% of normal
   - SA block to T_5 results in little change in ventilatory function
   - SA block > $\mathbf{T_5}$ may produce significant desaturation/hypercarbia, accompanying autonomic blockade may result in CVS compromise
   - MO patient should receive supplemental O_2 and minimal sedation
   - monitoring should be the same cf. GA
6. ***postoperative considerations***
   - ↑ incidence of complications with - PH_X of CVS or RS disease
     - thoracic or abdominal operations
   - hypoxaemia may persist ≤ 7 days following intra-abdominal surgery & is a universal finding → ***all*** should have ***supplemental oxygen***
   - ↑ incidence of DVT & ***all*** should have ***heparin*** prophylaxis ± leg stockings
   - IM drug administration may be unreliable & unpredictable, \ intravascular route should be used
   - PCA is preferrable to IV infusions as lesser total dose
   - ***epidural*** administration is associated with a lower incidence of respiratory complications & ? faster recovery
   - postoperative analgesic doses (opioid + LA) are the same cf. normal patients
   - patients with a strong history of OSAS / OHS should be observed for the first 24-48 hours in a ***high dependency area***

PORPHYRIA

Def'n: group of metabolic disorders of porphyrin production,
2 functional groups,

1. ***hepatic porphyrias***
   i. porphyria cutanea tarda (PCT) * ***commonest form***
      → uroporphyrinogen decarboxylase deficiency

   ii. acute intermittent porphyria (AIP)
      → uroporphyrinogen synthetase I deficiency

   iii. variegate porphyria (VP)
      → ? protoporphyrin oxidase deficiency

   iv. hereditary coproporphyria (HC)
      → coproporphyrin synthetase deficiency

2. ***erythropoietic porphyrias***
   i. congenital erythropoietic uroporphyria (CEU)*
      → uroporphyrinogen synthetase II deficiency

   ii. erythropoietic protoporphyria (EP)
      → ferrochetelase deficiency

NB: all are ***autosomal dominant***, except the rare CEU*

Clinical Features						
Type	**AIP**	**PCT**	**VP**	**HC**	**CEU**	**EP**
photosensitivity	-	+	+	±	+	+
liver affected	+	+	+	+	-	+
CNS involvement	+	-	+	+	-	+
barbiturate sens^{y}	**+++**	-	++	++	-	-
Abnormal Metabolites						
red cells	-	-	-	-	+	+
urine	+	+	+	+	+	-
faeces	-	-	+	+	+	+
urine colour	black	pink brown			red	

- ***Clinical Features***

- usually relate to either ***skin*** or ***neurological*** abnormalities
- the ***hepatic porphyrias*** are characterised by the 4 "P's",
    1. abdominal ***pain***
    2. ***peripheral neuritis***
    3. ***psychosis***
    4. ***port-wine*** / purple urine

Acute Intermittent Porphyria

- ***autosomal dominant*** disorder of porphyrin metabolism
- most serious of the hepatic porphyrias
- ***uroporphyrinogen synthetase*** deficiency → accumulation of ***porphobilinogen***
- diagnostic features include,
    1. ↑ urinary δALA and porphobilinogen during an attack
    2. urine turns ***black*** on standing
    3. ↓ RBC uroporphyrinogen synthetase level

- ***Clinical Features***

    a. usually young to middle aged female

    b. episodes of acute ***abdominal pain***

    c. variable neurological defects due to ***demyelination***,
        i. motor weakness
        ii. arreflexia
        iii. autonomic dysfunction
        iv. occasional bulbar and cerebellar signs *Δ GBS

    d. trigger factors
        - starvation, dehydration
        - sepsis
        - pregnancy
        - drugs

    e. alleged trigger drugs
        * ***barbiturates & benzodiazepines***
        - ketamine, althesin, etomidate
        - ethanol, phenytoin
        - glutethimide, pentazocine
        - steroids and sulpha's

    f. alleged "safe" drugs
        - volatiles, N_2O
        - fentanyl, morphine, pethidine
        - ***propofol***, droperidol, propanidid
        - relaxants, anticholinergics & anticholinesterases
        - promethazine, chlorpromazine

- ***Management***

    a. rehydrate

    b. IV ***dextrose*** - decreases porphobilinogen production

    c. ***haematin*** 3-4 mg/kg/day - blocks δALA synthetase

    d. pain control - chlorpromazine ± opioids

    e. IPPV may be required for respiratory failure

Reperfusion Injury

Def'n: pathophysiological changes occurring in ischaemic organs upon reperfusion

- determinants of severity,
  1. organ type
  2. organ blood flow
  3. ischaemic time
  4. cellular Ca^{++} content
  5. ?? plasma glucose at onset of ischaemia
  6. circulatory status upon reperfusion
  7. oxygen content of reperfusing blood

- "critical" ischaemic times for vital organs,
  1. brain ~ 10 min
  2. heart ~ 60 min
  3. limbs ~ 120-180 min
  4. gut ??

- cellular events leading to tissue damage,
  a. ↑ ATP metabolites
     - ADP, cAMP
     - adenosine, inosine
     - hypoxanthine / xanthine
     * ***xanthine dehydrogenase*** / NAD^+
  b. increased substrate
  c. production of O_2^- instead of NADH (low NAD^+)
  d. neutrophil chemotaxis

     → production of O_2 radicals occurs in initial ***reperfusion***

- production of O_2 radicals is ***increased*** by,
  1. O_2, H_2O_2
  2. neutrophils, leukotrienes
  3. Fe^{+++}
  4. hyperthermia
  5. increased Ca^{++}
  6. nitric oxide
  7. f-met-leu-phen

- production of O_2 radicals is ***decreased*** by,
    1. vitamins E & C
    2. folate
    3. selenium
    4. PGE_1
    5. lipoxygenase inhibitors
    6. Ca^{++} entry blockers
    7. glutathione
    8. SH-group containing compounds
    9. xanthine oxidase inhibitors - allopurinol
    10. hypothermia
    11. low O_2

- potentially harmful ***mediators*** released during reperfusion,
    1. CO_2, H^+, lactate
    2. K^+, $HPO_4^=$
    3. activated coagulation factors, FDP's, thromboplastins
    4. Hb, myoglobin
    5. prostaglandins, leukotrienes, cellular enzymes
    6. membrane lipids & metabolites

- these produce a number of deleterious effects,
    a. cellular destruction
        - protein, DNA
        - membrane, lysosomes
        - mitochondria
    b. local effects
        - vasodilatation
        - increased vascular permeability
        - interstitial oedema
        - extravascular matrix disruption
    c. specific tissue effects
        - reperfusion arrhythmias
        - disruption of BBB
        - rhabdomyolysis
    d. systemic
        - decreased SVR
        - venodilatation
        - high or low CO
    e. myoglobin induced renal failure
    f. metabolic lactic acidosis

- ***Clinical Examples***

  a. myocardium after CPB
  b. lower limbs after AOX-clamp - AAA
  c. rhabdomyolysis, crush injuries
  d. prolonged hypovolaemic shock
  e. cardiogenic shock
  f. ARDS
  g. brain after hypoxic event, trauma

RHABDOMYOLYSIS

Def'n: the disintegration or dissolution of muscle,
associated with the excretion of ***myoglobin*** in the urine

- ***Aetiology***

1. skeletal muscle ***trauma*** | ***ischaemia*** | ***exhaustion***
   - i. crush | compartment syndromes
   - ii. burns, electric shock
   - iii. hyperthermic syndromes
     - heat stroke
     - malignant hyperthermia, malignant neurolept syndrome
   - iv. arterial embolism | thrombosis
   - v. torniquets | antishock trousers
   - vi. drug induced
     - suxamethonium in myopathic disorders
     - myopathic - alcohol, salicylates, amphetamines
       - aminophylline, phencyclidine, LSD, heroin
     - overdose of any sedative agent & pressure necrosis
   - vii. envenomation
   - viii. overuse - prolonged exercise, pretibial syndrome
     - status epilepticus, tetanus
     - delerium tremens
2. infection / inflammation
   - i. viral myositis
   - ii. gas gangrene | synergistic necrotizing "Cellulitis"
   - iii. Legionaires' disease
   - iv. acute polymyositis
3. metabolic defects
   - i. severe - hypokalaemia $\leq$ 2.5 mmol/l
     - hypophosphataemia
     - hyperosmolality
   - ii. myxoedema | thyrotoxicosis
   - iii. McArdle's syndrome
4. familial myoglobinuria
5. muscular dystrophy

NB: systemic release of ***myoglobin*** by itself is ***not nephrotoxic***, however when combined with hypotension and renal hypoperfusion may result in ATN

- ***Investigations***

1. muscle compartment pressures
   - normal < 10 mmHg
   - if > 30-40 mmHg, or
     > BP_{Dias} - 30 mmHg → ***fasciotomy***
2. biochemistry
   - high CPK ~ 30-50,000 (CK-MM)
     > 5x or greater
   - high K^+ & $HPO_4^=$
   - low HCO_3^- & Ca^{++}
   - hyperuricaemia
   - ↑ LDH, AST
   - metabolic acidosis - high anion gap
   - thrombocytopaenia & haemoconcentration
3. myoglobinuria
   - false negative tests may occur in up to **36%** of cases
   - both haemoglobin & myoglobin test positive to urine "dipstick"

- ***Crush Injuries & Renal Failure***

1. activation of renin-angiotensin system, ↑ catechoamines & ADH
2. nephrotoxicity of ***myoglobinuria*** & ***uricosuria***
   - potentiated by acidification & concentration in tubules
3. acute increase in plasma Ca^{++}-$PO_4^=$ product
   - may result in suppression of renal function
4. ***microthrombi*** in renal vasculature

- ***Complications***

1.	hyperkalaemia	- weakness - bradycardia, cardiac arrest
2.	hyperphosphataemia	- hypocalcaemia, hypomagnesaemia
3.	myoglobinuric renal failure	- ATN
4.	muscle infection	- gangrene - tetanus - gram (+)'ves
5.	systemic inflammatory response	- reperfusion injury - ARDS - sepsis syndrome - MODS, DIC

- ***Management***

1. early, aggressive IVT to support intravascular volume & urine output
   - saline loading → prevent hypovolaemia / dehydration
2. mannitol
   - theoretically increases proximal tubular flow & reduces effects of pigmenturia
   - supported by the "Israeli" school but no controlled trials to support use
3. bicarbonate
   - alkalinisation of urine improves solubility of myglobin, ∴ reducing cast formation
   - animal studies showing reduction in ATN
   - cf mannitol, no controlled trials to support use
4. acetazolamide
   - increases proximal tubular output & alkalinises tubular lumen
5. treat hyperkalaemia
   - Ca^{++}/HCO_3^-
   - insulin/dextrose
   - ± dialysis

- ***Management Israel (Nephron 1990)***

1. early aggressive volume replacement, preferrably at the sceen of injury
   - immediate resuscitation
   - N.saline or Ringer's lactate @ 1500 ml/hr adult
     @ 20 ml/kg/hr child
2. forced mannitol-alkaline diuresis
   - 5% Dextrose + NaCl 70 mmol
     + mannitol 20% 50 ml = 10g
     + bicarbonate 8.4% 50 ml = 50 mmol
     @ **500 ml/hr**
   - 12 l/day → 600g dextrose = **2400 kcal**
     840 mmol NaCl + **600 mmol $NaHCO_3$**
     120 g mannitol
3. acetazolamide - if plasma pH > 7.45
   - due to enhancement of metastatic calcification

Intravenous Fluids

- ***Normal Saline 0.9%***
  - Na^+ ~ 154 mmol
  - Cl^- ~ 154 mmol
  - pH ~ 5-7
  - osmolality ~ 308 mmol/l, ie. ***hypertonic*** (measured)
- ***4% Dextrose & 0.18% Saline***
  - Na^+ ~ 30 mmol/l
  - Cl^- ~ 30 mmol/l
  - dextrose ~ 222 mmol/l
  - pH ~ 3.3-5.5
  - calories ~ 160 kcal
  - osmolality ~ 282 mosm/l
- ***5% Dextrose***
  - dextrose ~ 277 mmol/l (slightly hypoosmolar)
  - pH ~ 3-5
  - calories ~ 200 kcal
- ***Hartmann's Compound Sodium Lactate***
  - Na^+ ~ 131 mmol/l
  - Cl^- ~ 111 mmol/l
  - K^+ ~ 5.0 mmol/l
  - Ca^{++} ~ 2.0 mmol/l
  - lactate ~ 29 mmol/l
  - pH ~ 5-7 (6.5)
  - osmolality ~ 278 mosm/l - slightly hypotonic

  - advantages,
    i. more physiological than D_5W or N.Saline
    ii. less postoperative Na^+ retention
    iii. less acidosis than D_5W
    iv. enhances H^+/HCO_3^- excretion

  - disadvantages,
    i. lactate converted to glucose
    ii. lactate not metalolised in hepatic failure, hypotensive arrest etc.
    iii. 25-30% retained in the intravascular compartment
    iv. Ca^{++} - coagulation

- ***Plasmalyte***

• Na^+	~ 140	mmol/l
• Cl^-	~ 98	mmol/l
• K^+	~ 5	mmol/l
• Mg^{++}	~ 1.5	mmol/l
• Gluconate	~ 23	mmol/l
• Acetate	~ 27	mmol/l
• Osmo	~ 294	mosm/l
• pH	~ 5.5	

- ***Haemaccel***

• synthetic polypeptide plasma volume expander, **3.5% *gelatin*** solution, MW ~ 35,000-45,000
• gelatin prepared from hydrolysis of animal collagen, cross linked by urea bridges
• plasma expansion by **~ 70%** of infused volume
• renal excretion by GFR complete by 48 hours
• useful as a synthetic plasma substitute & as an insulin carrier

• gelatin	~ 35g	
• Na^+	~ 145	mmol/l
• Cl^-	~ 145	mmol/l
• K^+	~ **5.1**	mmol/l
• Ca^{++}	~ **6.25**	mmol/l
• HSO_4/HPO_4	~ small amounts	
• pH	~ 7.3	
• osmolality	~ 300-306	mosm/l

• advantages,

a. cheap, safe, reliable synthetic colloid
b. low incidence of adverse reactions
c. renal excretion
d. long shelf half-life ~ 8 years at 15°C
~ 3 years at 30°C

• disadvantages,

a. allergic reactions ~ 0.146%
   • skin rashes, pyrexia, anaphylactoid reaction
   • ? due to ***hexamethylene diisocyanate***
   • renal failure rare
b. short $t_{½\beta}$ ~ 1.5-6 hrs
c. renal excretion
d. Ca^{++} & K^+ problems in ARF patients

Dextrans

- polysaccharides produced by fermentation of sucrose by ***Leuconostoc mesenteroides*** bacteria
- these are then hydrolysed and fractionated into different molecular weights
- advantages,
    a. stable, cheap, non-toxic
    b. non-pyrogenic plasma substitutes & expanders

Dextran 40 - Rheomacrodex

- 10% (100g/l) solution in normal saline or 5% dextrose
- average MW ~ 40,000, osmolality ~ 350-370 mosm/kg, ie. ***hypertonic***
- plasma $t_{½\beta}$ ~ 2-3 hrs with ~ 5% being metabolised (70 mg/kg/day)
    i. plasma volume expansion **~ 1.5-2x** infused volume
    ii. thromboembolic prophylaxis
    iii. rheological microcirculatory benefit
    iv. CPB pump priming

- contraindications,
    i. thrombocytopaenia
    ii. coagulopathy
    iii. hypersensitivity

- problems,
    i. hypervolaemia, circulatory overload, CCF
    ii. anaphylactoid/anaphylactic reactions ~ 0.07%
        - reduced by Promit (0.001%)
    iii. renal failure

- does ***not*** interfere with blood cross-matching or Coomb's testing
- maximum dose ~ 30 ml/kg/day

Dextran 70 - Macrodex

- 6% (60g/l) solution in normal saline or 5% dextrose
- average MW ~ 70,000, osmolality ~ 335 mosm/kg, ie. mildly ***hypertonic***
- plasma $t_{½\beta}$ ~ 6 hrs with ~ 5% being metabolised (70 mg/kg/day)
- problems are the same as for dextran 40, plus, interference with ***haemostasis*** with large volumes
    a. fibrinogen coating
    b. interferes with factor VIII
    c. decreased platelet adhesion and aggregation

- ***NSA-5% Albuminex-5%***

- heat treated plasma protein solution
- prepared from fractionated plasma from pooled human donors
- ***pasteurised*** to kill HBV etc.
- shelf-life ~ 5 years at 2-8°C and 1 year at 25°C
- ***Na^+-octanoate*** is added to stabilise the short chain FFA and heat stabilise albumin
- NaOH is added to bring the pH to 7.0
    - protein 50g ~ 100% albumin
    - Na^+ ~ 140 mmol/l
    - Cl^- ~ 125 mmol/l
    - octanoate ~ 8 mmol/l
    - pH ~ 7.0
    - osmolality ~ 300 mosm/kg

- main problem with SPPS was ***anaphylactoid reactions*** (~ 0.02%)
  ? due to a heat labile ***pre-kallikrein factor***
- other plasma substitutes include,
    a. hydroxy ethyl starch - $t_{½\beta}$ ~ 24 hrs
       - reactions ~ 0.08%
    b. fluosol DA
    c. FFP
    d. NSA | Albuminex-20%

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

Mixed Venous Oxygen Saturation

- rearranging the Fick equation for O_2 uptake,

$$C_{vO2} = C_{aO2} - VO_2/CO$$

- S_{vO2} and mixed venous P_{vO2} are used for the calculation of,
    1. cardiac output
    2. oxygen flux
    3. pulmonary shunt fraction

- S_{vO2} may be used as a rough guide of cardiac output,
    - ~ 75% normal
    - > 60% acceptable
    - **< 60%** ***cardiac failure***
    - < 40% cardiogenic shock

Low S_{vO2}	High S_{vO2}
• low cardiac output • increased VO_2 • low P_{aO2} • anaemia	• high CO and low VO_2 • sepsis & peripheral shunting • hypothermia • CN^- toxicity

- ***Monitoring Pitfalls***

    a. technical - wedged PA sample & factitious high S_{vO2}

    b. influenced by many factors

    c. represents ***global*** oxygenation & poor indicator of regional ischaemia/organ hypoperfusion

    d. trends more useful than single figures

Wilson's Disease

Def'n: ***autosomal recessive*** disorder due to the inability to excrete copper cleaved from ceruloplasmin into the bile, resulting in,

1. accumulation of copper in brain, liver & other organs
2. inhibition of the formation of ceruloplasmin from apoceruloplasmin

- ***Clinical Features***

1. hepatic
   - i. acute hepatitis
   - ii. chronic active hepatitis
   - iii. cirrhosis
   - iv. asymptomatic hepatomegaly
2. CNS
   - i. resting, or intention tremors
   - ii. schizophrenia, manic-depressive psychoses, neuroses
3. Kayser-Fleischer rings

- ***Diagnosis***

1. serum ceruloplasmin < 200 mg/l
   - plus Kayser-Fleischer rings
2. serum ceruloplasmin < 200 mg/l
   - plus liver biopsy elevated copper deposition
3. treatment
   - lifelong penicillamine

Hyperlipiaemia

- ***Hypercholesterolaemia***

    1. familial lipid disorders
    2. biliary obstruction
    3. nephrotic syndrome
    4. hypothyroidism
    5. pancreatitis