| ASA Risk Classification[1] | |
|---|---|
| Class I | • healthy patient |
| Class II | • mild systemic disease<br>• no functional limitation |
| Class III | • severe systemic disease[2]<br>• definite functional limitation |
| Class IV | • severe systemic disease[2]<br>• disease is a constant threat to life |
| Class V | • moribund patient<br>• not expected to survive 24 hours, with or without surgery |

[1] modified by Dripps *et al.* 1961

[2] whether or not the disease is that for which the patient is presenting

# DIABETES MELLITUS

1. diabetes actually represents two distinct disease entities,
   i. type I IDDM juvenile onset
   ii. type II NIDDM mature onset
   → 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 end-organ ***complications***
   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

- ***Diagnosis WHO***

1. fasting venous ***plasma glucose*** ³ **7.8 mmol/l** (NB: plasma 15% > whole blood)
   - on at least 2 occasions
2. glucose tolerance test
   - following ingestion of **75g** of glucose
   - 2 hr venous plasma glucose ³ **11.1** **mmol/l**
   - at least one other test value ≥ 11.1 mmol/l
   - ie. a minimum of 2 values are required during the test interval
   - if the 2 hr value is between 7.8 & 11.0 mmol/l, and one other value during the 2 hr test is ≥ 11.1 mmol/l, then the diagnosis of ***impaired glucose tolerance*** is made

## Pathophysiology

- ***Insulin***

- synthesised from ***proinsulin*** in β-cells of pancreas ~ $200^{U}$ stored
- steady-state basal release during fasting limits ketosis & catabolism
- 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** | **Inhibition** |
| ***glucose & fructose*** | somatostatin |
| amino-acids<br>• leucine, arginine | insulin |
| drugs<br>• theophylline (PDE inhibitors)<br>• sulphonylureas<br>• acetylcholine | drugs<br>• diazoxide<br>• thiazide diuretics<br>• phenytoin<br>• 2-deoxyglucose |
| b-***agonists*** ↑ glucose & $K^+$ uptake | $\alpha_1$-agonists |
| GIT hormones<br>• gastrin, secretin<br>• cholecystokinin-pancreozymin<br>• enteroglucagon (GIP) | |
| ***glucagon*** | |

- ***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 - ketotic hyperglycaemic coma &
     - hyperglycaemic, hyperosmolar, non-ketotic coma

- insulin levels are low or immeasurable
- 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. a peripheral resistance to insulin

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

- management varies from diet, to oral hypoglycaemics ± insulin
- ***sulphonylureas*** act by,

  1. increasing release of insulin from the pancreas
  2. improving peripheral utilisation of glucose
     - ? increased receptor numbers, or increased binding

- 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
- the ***biguanides*** act by,

  1. increasing glucose utilisation through anaerobic metabolism
  2. decreasing gluconeogenesis
  3. decreasing intestinal absorption of glucose

- ***Complications***

1. acute
   - i. hypoglycaemia ± coma
   - ii. ketoacidosis ± coma
   - iii. hyperglycaemic, hyperosmolar, non-ketotic coma

b. chronic

- i. ***cardiovascular***
  - accelerated atherosclerosis (CAD / PVD)
  - microangiopathy - retinopathy, neuropathy, etc.
  - hypertension
  - cardiomyopathy - diastolic pump dysfunction
    - infiltrative decrease in compliance
- ii. ***renal***
  - mild renal impairment to ESRF 2° progressive GN
  - higher rate of renal transplant rejection
- iii. ***joint-collagen tissue*** abnormalities
  - stiff joint syndrome - TMJ and atlanto-axial immobility
  - poor wound healing - decreased tensile strength
    - rate of tissue healing
- iv. ***immune deficiency***
  - nosocomial infections - wound
    - respiratory tract
- v. ***neuropathic***
  - peripheral neuropathy - trophic changes, ulcers, infections
  - autonomic neuropathy - CVS instability
    - silent myocardial ischaemia
    - asymptomatic hypoglycaemia
- vi. ***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
   - decreased 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

• ***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

- 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. without 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 derrangement & 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 with elevated 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*** ~ $10\text{-}20^U$ 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 ***~ 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

- ***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***

| **BSL:** mmol/l | **Insulin:** Units s.c. |
|---|---|
| < 10.0 | $0^U$ |
| 10.1 - 15.0 | $4^U$ |
| 15.1 - 20.0 | $8^U$ |
| > 20.0 | $12^U$ |

- ***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,

$$Insulin(U/Hr) = \frac{plasma\,glucose\ (mmol/l)}{8.0}$$

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

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

# ADRENAL DISORDERS

- ***Adrenal Cortex***

1. ***glucocorticoids***
   - ***cortisol*** integral in regulation of CHO, protein, lipid & nucleic acid metabolism
   - stereospecific intracellular cytoplasmic receptor, stimulating nuclear transcription of specific mRNA and subsequent protein synthesis
   - plasma $t_{½\beta}$ << clinical effect, \ dose according to later
   - majority bound to ***cortisol binding globulin***, transcortin, which is altered in disease states (↑ pregnancy, OCP / ↓ liver disease, nephrotic syndrome)
   - metabolism primarily in the liver to 17-OH-steroid, also filtered unchanged
   - ***urinary cortisol*** is most accurate reflection of plasma activity, as represents the filtered free fraction
   - secretion under control of pituitary ACTH/CRF, with ***diurnal rhythm***
2. ***mineralocorticoids*** - aldosterone, secreted by zona glomerulosa
3. ***androgens*** - androstenedione, dehydroepiandrosterone

- ***Adrenal Medulla***

***NB: sympathomimetic amines***

## Glucocorticoid Excess

- ***Aetiology***

1. ***iatrogenic steroid administration*** - most common
2. pituitary adenoma ~ 80% (of remainder)
   - Cushing's disease
   - bilateral adrenal hyperplasia
3. ectopic ACTH ~ 15%
   - biochemical effects, ***not*** clinically Cushingoid
4. adrenal adenoma ~ 4%
5. adrenal carcinoma ~ 1%

- ***Clinical Features***

1. symptoms & signs
   i. ***hypertension*** - ↑ renin substrate & ↑ vascular reactivity
      - ↑ blood volume 2° fluid retention
   ii. truncal obesity, bruising, striae
   iii. poor wound healing
   iv. plethoric "moon" face, hirsutism
   v. weakness
   vi. osteoporosis
2. electrolyte abnormalities
   i. high $Na^+$, $HCO_3^-$ & glucose
   ii. low $K^+$ & $Ca^{++}$
   iii. ***metabolic alkalosis*** - normal anion gap
3. secondary endocrine effects
   i. insulin resistance
   ii. antagonism of GH effects
   iii. **2° *hyperparathyroidism*** ∝ ↓ $Ca^{++}$
   iv. ACTH excess & increased pigmentation
   v. androgen excess

- ***Laboratory Investigations & Diagnosis***

a. high plasma cortisol and loss of ***diurnal variation***
   - normal range ~ 140-690 nmol/l
   - trough level ~ 2400 hrs
   - peak level ~ 0600 hrs

b. increased urinary 17-(OH)-steroids

c. ***loss of suppression*** with dexamethasone 2mg

d. ACTH level
   i. normal / high → pituitary
   ii. low → adrenal, ectopic cortisol administration
   iii. very high → ectopic ACTH

- ***Management***

1. resection of ***pituitary microadenoma***
   - usually trans-sphenoidal approach
   - Roizen states anecdotally higher CVP and greater blood-loss, cf. other pituitary 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***,
   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. metyrapone , mitotane - inhibition of steroid synthesis
   ii. cyproheptadine - hypothalamic ***serotonin*** (CRH) antagonist
   iii. spironolactone - aldosterone antagonist
   - the aim of therapy is ***complete*** adrenal suppression,
     \ may require perioperative steroid replacement

## Mineralocorticoid Excess

- ***Aetiology***

1. concomitant with glucocorticoid excess
2. primary hyperaldosteronism - ***low renin*** substrate
   i. Conn's syndrome - benign ***adenoma*** of the zona glomerulosa
   ii. bilateral adrenal hyperplasia ~ 25-40%
3. secondary hyperaldosteronism - ***high renin*** substrate
   i. CCF
   ii. cirrhosis
   iii. nephrotic syndrome
   iv. pre-renal failure
   v. renal artery stenosis
   vi. bronchial carcinoma
   vii. Bartter's syndrome - hyper-reninaemic hyperaldosteronism

- ***Clinical Features Conn's Syndrome***

a. hypertension ~ 0.5-1.0% of hypertensive patients
b. high incidence of ischaemic heart disease
c. hypernatraemia / hypokalaemia
d. metabolic alkalosis
e. polyuria ~ hypokalaemic nephrogenic DI
f. low plasma renin activity - ie., not 2° hyperaldosteronism

- ***Management***

1. spironolactone - aldosterone antagonist
   - slow onset of effects, usually takes 1-2 weeks
   - aim to normalise ***volume status*** & ***hypokalaemic metabolic alkalosis***
2. surgical resection

## Glucocorticoid Deficiency

- ***Aetiology***

a. ***primary*** adrenal insufficiency
   i. autoimmune - Addison's disease
   ii. surgical removal - breast carcinoma
   iii. infection - TB, septicaemia, viral (especially in AIDS)
   iv. metastatic carcinoma
   v. haemorrhagic/coagulopathic adrenal necrosis
      - Waterhouse-Friderichsen syndrome
      - predominantly children - *Pseudomonas,* meningococcaemia
      - adults during pregnancy, or with anticoagulant therapy during stress
b. ***secondary*** adrenal insufficiency
   i. hypopituitary syndromes
   ii. pituitary supression * ***exogenous steroids*** (most common cause)
   - 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 - hypertensive variant of adrenal virulisation
   ii. enzyme inhibitors - metyrapone, mitotane, aminoglutethamide
   - ***ketoconazole***
   iii. ***cytotoxics***

- ***Precipitating Factors***

  a. surgery, trauma
  b. cessation of steroid therapy
  c. sepsis, coagulopathy
  d. acute illness

- ***Clinical Features***

  a. ***weakness***, fatigue ~ 100%
  b. excess ***pigmentation*** ~ 90%
  c. ***hypotension*** ± hypovolaemia ~ 90%
  d. mild ***hyponatraemia***, hypoosmolality ~ 90%
  e. ***hyperkalaemia*** ($Na^+$:$K^+$ ratio < 25:1) ~ 70%
  f. vomiting, diarrhoea, abdominal pain~ 60%
  g. ***hypoglycaemia***
  h. mildly elevated urea
  i. mild anion gap ***acidosis*** - renal impairment, hypovolaemia, lactate, etc.
  j. short ***Synacthen test***
     i. no response - primary adrenal failure
     ii. normal response - hypopituitarism

- ***Treatment***

  a. $O_2$ and ventilatory support
  b. IV fluids
     i. colloids to restore blood volume
     ii. saline to replace $Na^+$ deficit
     iii. glucose
  c. hydrocortisone - 200 mg stat
     - 100 mg q6h
  d. inotropes / vasopressors prn - resistant in absence of cortisal replacement
  e. treatment of primary cause, or initiating factor

## Hypoaldosteronism

***NB:*** associated with ***low renin*** activity and ***normal cortisol*** secretion, failure of aldosterone response to fluid/sodium restriction

i. hereditary defect - rare
ii. post-surgical for unilateral adenoma
iii. prolonged ***heparin*** / heparinoid administration
iv. pretectal nervous system disease
v. severe postural hypotension
vi. long-standing diabetes
vii. chronic renal failure
viii. renal insufficiency & therapy with PG inhibitors (NSAID's)

- ***Clinical Features***

1. hyperkalaemic acidosis
2. myocardial conduction defects
3. hyponatraemia / hypovolaemia
4. ***hypertension*** - present in many, despite volume contraction
   - requires monitoring during mineralocorticoid replacement

## Patients on Steroid Therapy

1. perioperative stress relates to the degree of trauma and the depth & type of anaesthesia
2. deep GA, or high RA delays the normal cortisol surge to the postoperative period
3. patients with suppressed HPA axes rarely suffer CVS complications if they ***do not*** receive steroid replacement perioperatively
4. acute adrenal insufficiency occurs very ***rarely***, but may be ***life-threatening***
   - CVS collapse 2° catecholamine "insufficiency", due to permissive cortisol effects
5. there appears to be a ***minor risk*** in perioperative steroid administration
   i. aggravation of hypertension, sodium & $H_2O$ retention
   ii. delayed wound healing and increased infection rate
   iii. stress ulceration of the gastric mucosa
   iv. psychiatric disturbances

***NB:*** give supplementation to ***all*** patients receiving steroids in the preceeding ***12 months***

# THYROID DYSFUNCTION

## Hyperthyroidism

- ***Causes***

1. disorders associated with ***thyroid hyperfunction***
   - i. excess production of TSH - ***rarely*** with pituitary adenoma
   - ii. extrinsic → abnormal thyroid stimulator
     - ***Graves' disease*** - most common, diffuse multinodular goitre
       - LATS, LATS-p, TSI, and TBII
     - trophoblastic tumour - choriocarcinoma
   - iii. intrinsic → thyroid autonomy
     - hyperfunctioning thyroid adenoma
     - toxic multinodular goitre
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

- ***Major Clinical Manifestations***

a. weight loss
b. diarrhoea ± fluid & electrolyte disturbances if severe
c. nervousness, agitation
d. warm moist skin, heat intolerance
e. muscular weakness - especially proximal, apathetic form, elderly
f. menstrual abnormalities
g. cardiac dysrhythmias
h. cardiac / papillary muscle dysfunction ± mitral valve prolapse
i. congestive heart failure

• when the thyroid is functioning abnormally the ***cardiovascular system*** is the one most stressed
• hyperthyroidism may also take an ***apathetic*** form, most commonly seen in the elderly, where CVS effects predominate
• 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 PCWP 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 $T_4$ to $T_3$
• 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
• although both methods treat the symptoms and achieve devascularisation of the gland, 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***
• with regard to anaesthetic agents, no study has been performed which can attribute any increased incidence of adverse effects due to an anaestheic agent, or technique
• some recommend ***anticholinergic*** medications be avoided, due to the inhibition of sweating and tachycardia
• ***atropine*** has been used as a test for the adequacy of antithyroid treatment

• 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. abrupt onset → ***mortality* ~ 10-20%** - without treatment
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 preoperatively
6. uncommon factors
   - radio-iodine in unprepared patients
   - iodide drugs, amiodarone, haloperidol
   - large doses of thyroid hormones

***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)
   - 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 ≡ 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
   - dysphagia, ***aspiration risk***, difficult intubation
6. biochemistry ~ 15% have ***hypercalcaemia***, but rarely an emergent problem
   * ***hypokalaemia & hypomagnesaemia*** may be severe, especially in apathetic form
7. FBE - leukocytosis common

- ***Management***

1. ***ABC*** - supportive measures
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
   - $\beta_1$-selective antagonists ***do not*** inhibit the conversion of $T_4$ to $T_3$ as effectively, but may be preferred in the presence of CCF or airways disease
   - ***reserpine*** has been largely superseeded, but may be of benefit in propranolol resistant hyperthyroidism
3. ***steroids***
   - usually administered as a ***relative deficiency*** may be present
   - inhibit the peripheral conversion of $T_4 \rightarrow T_3$
   - hydrocortisone ~ 100 mg IV q6h
4. ***thioamides***
   - ***no*** parenteral preparation is available

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

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

   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 ≥ 1 hour 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
   - 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. ***plasma exchange*** in refractory cases, following 24-48 hrs aggressive $R_X$
   vi. ***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 ≥ 95% of cases
   - i. ***thyroprivic***
     - congenital developmental defects
     - postablative - surgery & radio-iodine for Graves' disease
       * ***most common cause***
     - post-radiation - lymphoma, SCC
     - ***primary idiopathic*** - circulating antithyroid Ab's
       ± multiple endocrine neoplasia syndrome (MEN I, pituitary adenoma)
       ± IDDM, SLE, RA, Sjögren's synd., pernicious anaemia, chronic hepatitis
   - ii. ***goitrous***
     - congenital biosynthetic defects
     - maternally transmitted - iodides, antithyroid drugs
     - chronic thyroiditis - Hashimoto's
     - iodine deficiency
     - drug induced - aminosalicylate, lithium, phenylbutazone
       - amiodarone, iodides
2. suprathyroidal < 5% of total cases
   - 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. endemic, nontoxic 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 to ∝ IPPV, hypovolaemia
- valsalva etc.

iv. ECG
- low amplitudes, flattened / inverted T waves
- ↓ phase 4 depolarization, ↑ APD
- bradyarrhythmias

d. respiratory
- ↓ MBC, ↓ $D_{CO}$
- impaired ***central respiratory drives***
~ 10-15% of normal $O_2$ drive
~ 30-40% of normal $CO_2$ drive
- 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. electrolytes
- ↓ blood volume
- increased ECF fraction
- ↑ ADH secretion / low plasma $[Na^+]$
- impaired renal function / ↓ free water clearance

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

- ***Clinical Assessment***

| | | |
|---|---|---|
| a. | severity | - bradycardia<br>- hyporeflexia & slow recovery, "hung-up" reflex<br>- temperature<br>- skin, hair, facies, voice |
| b. | CVS | - bradycardia<br>- IHD, CCF, pericardial effusion<br>- if heart normal size, then ?? hypothalamic origin<br>- may be ***hypertensive*** 2° hypercarbia |
| c. | respiratory | - hypoventilation ± hypercarbia<br>- pulmonary oedema<br>- recurrent infection<br>- OSAS ± development of pulmonary hypertension |
| d. | CNS | - conscious state<br>- airway protection reflexes |
| e. | investigations | - ECG 12 lead<br>- FBE, WCC<br>- U&E's, BSL, LFT's<br>- TFT's<br>- CXR |

## 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 ~ 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*** ≤ 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 (→ more constant $T_3$ levels)
** ***no*** studies as to best dose or form of replacement

f. ***hydrocortisone*** ~ 400 mg on first day, then reducing
- test adrenal function with ***short Synacthen*** test

g. treat underlying illness

h. avoid sedatives, narcotics, etc.

- ***Management for Emergency Surgery***

a. avoid sedatives, narcotics

b. intubate if airway reflexes absent ? antacids, ranitidine

c. hydrocortisone ~ 100 mg IV q6h for first 24 hrs

d. commence $\mathbf{T_3}$ 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

## Sick Euthyroid Syndrome

- severe illness, physical trauma, physiological stress may result in,
  1. ↓ protein binding of thyroid hormones
  2. ↓ peripheral conversion to $T_3$ → ↑ $rT_3$
  3. altered regulation of TSH sercetion

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

- measurements of $T_3$, $T_4$ and levels of hormone binding are usually adequate
- in hypo/hyperthyroidism, changes in free hormone levels parallel changes in total thyroxine
- when the FTI is low, in extremely ill patients, a euthyroid state is established by a normal TSH

## 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 ≡[t] radical neck resections
  2. parafollicular C cells - more aggressive
     - familial incidence
     - ***MEN II*** → medullary carcinoma
       + ***phaeochromocytoma***
       + parathyroid adenomas

# PARATHYROID DISORDERS

## Hypercalcaemia

***NB:*** incidence ↑'s in the 3-5$^{th}$ decades, F:M ~ 3:1

- ***Aetiology***

1. ***factitious*** - stasis, 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
     - ***phaeochromocytoma*** & parathyroid adenoma
   - iv. lithium therapy - ↑ parathyroid function in ~ 10%
   - v. rarely carcinoma
3. ***malignancy***
   - i. solid tumour with bony 2°'s - breast, prostate
   - ii. ectopic parathormone - kidney, lung (~ 10-15%), ?? $PGE_2$
   - 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 ± epileptic fits

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

ECG
- ↓ $QT_{C,}$ bradyarrhythmias, AV blockade

c. NMJ
- ↑ ACh release
- ↑ excitation / contraction
- ↑ threshold $V_m$

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

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

e. musculoskeletal
- weakness, fatigue, paralysis, arthralgia
- osteitis fibrosa cystica
~ 5x ↑ bone turnover (↑ ALP), bone pain, fractures

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<br>- frusemide 20-40 mg IV q4-8h<br>* beware ***hypokalaemia & hypomagnesaemia*** |
| d. | corticosteroids | - ↓ GIT absorption / increase excretion<br>* ***not*** effective in 1° hyperparathyroidism |
| e. | diphosphonate | - etidronate |
| f. | correct hypophospataemia | - ↑ GIT absorption<br>- ↓ bone uptake & ↑ reabsorption |
| g. | decrease bone release | - calcitonin<br>- mithramycin |

# Hypocalcaemia

- ***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
- thyroid or parathyroid surgery, $^{131}I^{-}$ therapy
- 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

- ***Clinical Features***

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

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

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

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

■ ***Anaesthetic Considerations***

• management of hypothyroidism 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 for 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 is ***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

# PITUITARY DYSFUNCTION

## Anterior Pituitary Hypersecretion

- ***Secretory Cell Types***

| | | |
|---|---|---|
| 1. | somatotrophs | - GH |
| 2. | corticotrophs | - ACTH |
| 3. | lactotrophs | - prolactin |
| 4. | gonadotrophs | - FSH, LH |
| 5. | thyrotrophs | - TSH |

- ***Hypothalamic Hormones***

| | | |
|---|---|---|
| 1. | ***dopamine*** | - prolactin release ***inhibiting*** hormone (PRIH) |
| | • PRL | - ↑ by metoclopramide<br>- ↓ by bromocriptine |
| 2. | somatostatin | - growth hormone release inhibiting hormone (GHRIH) |
| 3. | GHRH | - growth hormone releasing hormone |
| 4. | CRH | - corticotrophin releasing hormone ? ***serotinin*** |
| | • ACTH | - ↓ by cyproheptadine |
| 5. | GnRH / LHRH | - gonadotrophin releasing hormone |
| 6. | TRH | - thyrotropin releasing hormone |

- ***Clinical Features***

1. pituitary adenomas - classified according to hormone secretion
   ~ 60% are hypersecretory
2. most common modes of presentation
   - i. prolactin - amenorrhoea, galactorrhoea, infertility
   - ii. ACTH - Cushing's syndrome
   - iii. GH - acromegaly
   - iv. nonfunctioning - hypopituitarism

## ■ ***Hyperprolactinaemia***

• often but not invariably associated with ***galactorrhoea***,

i. females → amenorrhoea

ii. males → impotence

• optimal therapy still controversial
• the dopamine agonist, ***bromocriptine***, is effective in restoring pituitary function
• also useful for reducing pituitary size prior to surgery
• there is a risk of rapid growth during ***pregnancy***, \ surgery is recommended

1. initial surgery cure rate ~ 80%
2. 5 year relapse rate ≤ 50%

• DXRT has not been uniformly effective
• artefactual hyperprolactinaemia may be seen with DA antagonists

→ ***metoclopramide*** may be used to augment breast milk production

## ■ ***Acromegaly***

• characteristic facies, thickened tongue, difficult intubation
• enlarged nose & mandible, with spreading of the teeth
• enlarged hands & feet, thickened skin & "myxoedematous" appearance
• elevated basal GH secretion with absence of ***glucose suppression***
• ***glucose intolerance*** (GH insulin antagonism)
• $Na^+$, $K^+$ and $H_2O$ retention, progressing to ***hypertension***
• cardiomegaly and accelerated ***atherosclerosis***
• osteoporosis ± kyphoscoliosis, may progress to lung pump failure
• > 99% due to solitary ***pituitary adenoma*** →

1. transphenoidal hypophysectomy if localised
2. transfrontal hypophysectomy if suprastella extension
3. local DXRT if incomplete excision

## ■ ***Cushing's***

***NB:*** 60-70% of all cases are associated with a ***pituitary microadenoma***

| | | | |
|---|---|---|---|
| 1. | ***iatrogenic steroid administration*** | - most common | |
| 2. | pituitary adenoma | ~ 80% | (of remainder) |
| 3. | ectopic ACTH | ~ 15% | |
| 4. | adrenal adenoma | ~ 4% | |
| 5. | adrenal carcinoma | ~ 1% | |

## Anterior Pituitary Hypofunction

1. deficiencies in GH, TSH, ACTH, prolactin or gonadotropin
2. may result in ***panhypopituitarism***
3. specific preoperative preparation is required for,
   i. ↓ TSH - ***hypothyroidism***
   ii. ↓ ACTH - ***Addisonian***
   iii. ↓ GH - deficiency may result in ***myocardial atrophy***
4. no preparation required for prolactin or gonadotropin
5. acute deficiencies are often the result of ***haemorrhage*** into a tumour
   - ~ 25% of histological specimens show haemorrhage
   - may result in
     - headache
     - N&V, vertigo
     - visual loss, ocular palsies
     - ↓ LOC, hemiparesis
     - fever
   - this requires rapid transphenoidal decompression with steroid cover

## Posterior Pituitary Dysfunction

- ***SIADH***

1. ***aetiology***
   - i. malignancies → autonomous ADH release
     - lung, pancreas, sarcomas, Hodgkin's, thymoma
   - ii. non-malignant pulmonary disease
     - TB, lung abscess, empyema, pneumonia, viral pneumonitis, CAL
   - iii. CNS disease
     - trauma - CHI, fractures
     - vascular accidents - SAH, SDH, thrombosis
     - infections - encephalitis, meningitis (TB, bacterial)
     - GBS, SLE, AIP
   - iv. drugs
     - chlopropamide, cyclophosphamide, carbamazepine, clofibrate
     - GA's, opioids, TCA's, oxytocics
     - vincristine, vinblastine
   - v. miscellaneous - IPPV, hypothyroidism, (? hypoadrenalism)
2. patient age and anaesthetic technique have ***no effect*** on occurrence of SIADH
3. clinical features relate to ***hyponatraemia*** and ***cerebral oedema***
   - weight gain, weakness, lethargy, confusion
   - obtundation, disordered reflexes, convulsions
4. biochemistry
   - i. urinary sodium **> 20** mmol/l - ie. not $Na^+$ retaining
   - ii. serum sodium < 130mmol/l
   - iii. serum osmolality < 270mosm/l
   - iv. low serum urea, creatinine, urate & albumin
   - v. urine hypertonic relative to plasma
   - vi. inability to excrete a water load
   - vii. elevated plasma ADH level
5. management → aim < 2 mmol/l/hr change unless seizures
   - fluid restriction
   - N.saline & diuretics
   - hypertonic saline - rarely
   - ***demethylchlortetracycline*** → ↓ tubular ADH response
     → "nephrogenic DI"

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

- ***Diabetes Insipidus***

1. ***central DI***
   - i. idiopathic ~ 30%
   - ii. traumatic ~ 30%
     - CHI, neurosurgery
   - iii. neoplastic
     - 1° or 2°
     - commonly breast or lung
   - iv. vascular lesions
     - post-partum necrosis
     - aneurysm
     - hyperviscosity syndrome
   - v. infection - TB
   - vi. inflammatory - sarcoidosis
   - vii. hypoxic brain damage
2. ***nephrogenic DI***
   - i. congenital and familial
   - ii. hypercalcaemia - eg. hyperparathyroidism
   - iii. hypokalaemia - Conn's syndrome
   - iv. acute renal failure
     - post-obstructive renal disease
     - recovery phase of ATN
     - pyelonephritis
     - transplantation
     - polycystic kidney disease
   - v. drugs
     - methoxyflurane, enflurane, $F^-$
     - diuretics, lithium
     - demeclocycline
   - vi. systemic disease
     - amyloidosis
     - myeloma
     - sickle cell disease
   - vii. ADH resistant DI of pregnancy - high vasopressinase

- ***Anaesthesia***

a. fluid and electrolyte replacement
   - avoid hypertonic solutions & check biochemistry regularly

b. ADH analogues
   - vasopressin IV
     - use minimum required amount
     - especially in pregnancy, or patients with IHD
     - interaction with catecholamines etc.
   - DDAVP ~ 1-4 µg q12h (adult)

c. other drugs
   - thiazides
   - chlorpropamide, chlofibrate

# RENAL DISEASE

- ***Assessment***

***NB:*** minimal physical findings unless - disease is advanced, or
- hypertension is present

1. **urinalysis**
   - i. gross appearance - macroscopic haematuria, infection
   - ii. microscopy - cellular casts, bacteria, abnormal cell forms
   - iii. ***pH*** - normal acid load ~ 60-70 mmol/day
     - minimum normal pH ~ 4.4
     - failure of acidification & acidaemia in insufficiency
     - normally three mechanisms for renal excretion of acid,
       - reabsorption of filtered $HCO_3^-$
       - acidification of tubular buffers (titratable acid)
       - formation of ammonia & excretion of ammonium
   - iv. ***specific gravity*** - measure of concentrating ability
     ~ 1.030-1.050 → good concentrating ability
     ~ 1.0101 → ~ plasma 290 mosm/kg
     * ***fixed*** in renal disease
   - v. ***protein*** ≤ 150 mg/day normally excreted
     > 750 mg/day → ***massive proteinuria***
     - usually indicative of severe ***glomerular disease***
     - may also be seen in - failure of normal protein reabsorption
       - increased plasma protein concentrations
       - presence of an abnormal plasma protein
   - vi. ***glucose*** - normally small amount escapes reabsorption
     - abnormally increased filtered load (IDDM, pregnancy)

2. **complete blood picture**
   - i. ***anaemia***
     - decreased ***erythropoietin*** (erythropoiesis stimulating factor, ESF)
     - absence of ESF in anephric patients → Hb ~ 6-8 g/dl
   - ii. ***WCC***
     - decreased with marrow suppression 2° immunosuppressive therapy
     - delayed rise in systemic infection but an ominous sign
   - iii. ***platelets***
     - usually normal number, or mild thrombocytopaenia
     - abnormal function in absence of dialysis

3. **creatinine & urea**

i. ***creatinine***

| | | |
|---|---|---|
| newborn | ~ maternal | |
| infant | ~ 18-35 | µmol/l |
| child | ~ 30-60 | µmol/l |
| youth | ~ 45-90 | µmol/l |
| male | ~ 55-120 | µmol/l |
| female | ~ 45-95 | µmol/l |
| pregnancy | ~ 30-80 | µmol/l |

- virtually constant production from muscle turnover
- freely filtered at the glomerulus & ***negligible secretion*** in distal nephron
  → ∝ 1/GFR
- ***creatinine clearance*** almost a direct measure of GFR
- however, the wide range of "normal" values allows ~ 50% ↓ GFR with a creatinine in the "normal" range
- not a reliable indicator when GFR is rapidly changing, ie. lags behind

ii. ***urea***

- wide range of "normal" values ∝ dietary protein intake
  anabolism / catabolism
  hydration
  rate of urine flow

4. **serum electrolytes**

- $Na^+$, $K^+$, $Cl^-$ and $HCO_3^-$
- these are usually normal until there is marked deficiency of renal function
- ***hyperkalaemia*** does not develop until there is ***uraemia***

5. **blood gases**

i. pH - metabolic acidaemia

ii. $P_{aCO2}$ - incomplete respiratory compensation

iii. $P_{aO2}$ - usually normal until GFR < 50%
- may be decreased in fluid overload / pulmonary oedema

6. **CXR**

- presence & extent of hypertensive CVS disease, ie. decompensated LVH & CCF
- fluid overload in severe CRF
- pericardial effusion in uraemic patients

7. **ECG**

i. hypertension / LVH

ii. IHD

iii. hyperkalaemia

iv. digitalis toxicity - ↓ QT interval & ST segments, VPC's

v. hypocalcaemia - ↑ QT interval

- ***Common Causes of CRF***

1. diabetic nephropathy ~ 28%
2. hypertension ~ 24%
3. glomerulonephritis ~ 21%
4. polycystic kidney disease

- ***Effects of Renal Failure***

1. metabolic
   - $Na^+$ retention or depletion
   - hyperkalaemia
   - metabolic acidosis
   - hyperphosphataemia, hypocalcaemia
   - hypermagnesaemia
   - hyperuricaemia
2. endocrine
   - 2° hyperparathyroidism
   - vitamin D deficiency
   - renal osteodystrophy
   - glucose intolerance
   - amenorrhoea
   - impaired testicular function, impotence
3. haematologic
   - anaemia
   - thrombocytopenia / thrombocytopathy, poor haemostasis
   - abnormal WBC function
4. cardiorespiratory
   - hypertension
   - accelerated atherosclerosis
   - CCF
   - pericarditis ± effusion
   - pleuritis ± effusion
   - pneumonitis
5. neuromuscular
   - encephalopathy
   - peripheral neuropathy
   - dialysis dementia
   - dialysis disequilibrium
6. gastrointestinal
   - anorexia, nausea, vomiting
   - peptic ulcer disease
   - gastroenteritis
   - ascites
   - diverticulosis
   - viral hepatitis
7. skin
   - pruritis
   - ecchymoses
   - increased pigmentation

- ***Consequences of CRF***

• the specific causes of the ***uraemic syndrome*** are unknown
• probably the beakdown products of protein and amino acids,

1. urea - most abundant
   - may account for nausea, anorexia & malaise
2. ***guanidosuccinic acid*** - contributes to ***platelet dysfunction***
3. "middle molecules" are indicted in uraemic neuropathy
4. high levels of circulating polypeptide hormones - PTH, CRF

• with progressive nephron loss there is decreased concentrating ability

→ ***isosthenuria***, polyuria & nocturia

• early in CRF $Na^+$ balance is maintained by increased ***fractional excretion***
• later the remaining nephrons are unable to compensate and retention of dietary sodium results in ***hypertension & volume overload***
• however, $Na^+$ restriction may equally result in depletion and superimposed prerenal azotaemia
• little or no change occurs in pH, $P_{aCO2}$ or $HCO_3^-$ until the GFR < 50%
• early retention of $H^+$ causes only mild non-progressive acidosis, probably due to buffering in bone
• later retention of phosphate, sulphate & other unmeasured anions reults in a high ***anion gap acidosis***

• with advanced disease, ***phosphate*** balance is achieved by a decrease in tubular reabsorption, mediated by an increased secretion of ***PTH***
• this is mediated by,

1. a decrease in plasma $Ca^{++}$ 2° to phosphate retention
2. the elevated plasma phosphate itself

• results in many of the bone changes of ***renal osteodystrophy***
• this is complicated by,

1. ***skeletal resistance*** to PTH, and
2. reduced 1,25-$(OH)_2$-$D_3$

• signs & symptoms generally occur late, when GFR < 25%

## Applied Pharmacology

1. ***barbiturates***
   - except for ***phenobarbital*** all of the barbiturates are hepatically excreted
   - termination of action is by redistribution & extensively metabolised
   - STP is ~ 75-85% protein bound & the ***free fraction*** ↑'s from ~ 15% → 30%

   i. acidaemia → ↑ nonionised fraction & ↓ protein binding

   ii. ↓ albumin → ↓ protein binding

   - therefore, require ***decreased*** induction dose
   - however, clearance and $V_{dSS}$ are increased and elimination half-life normal
   - redistribution is more rapid & supplemental doses may be required
2. ***propofol***
   - renal disease has little effect on the pharmacokinetics of propofol, confirming the high capacity of the liver to metabolise the drug
3. ***opioids***

   i. fentanyl
      - metabolised in the liver, only ~ 7% eliminated by the kidney
      - protein binding ~ 80% & $V_{dSS}$ is large and little altered

   ii. morphine
      - protein binding is low ~ 20-45%, therefore little altered
      - $V_{dSS}$ is large and metabolism mainly in the liver, ?? *inactive* glucuronides
      - "thus, administration...in premedicant doses should not cause prolonged depression" (RDM)
4. ***benzodiazepines***
   - extensively hepatically metabolised prior to exceretion
   - increased effect from these drugs is generally ascribed to the uraemic process
5. ***muscle relaxants***

   i. ***suxamethonium***
      - used without problems in anephric patients
      - haemodialysis & uraemia reduce pseudocholinesterase levels but not to a significant degree
      - acetylcholinesterase levels are <u>unaltered</u> by haemodialysis
      - may result in transient ***hyperkalaemia***, therefore dialyse first

   ii. ***dTC & pancuronium***
      - ~ 50% cleared through the kidney, for pancuronium as 3,17-OH metabolites
      - there is ***no change*** in NMJ receptor sensitivity in uraemia
      - elimination half-life prolonged ~ 2x, therefore avoid in renal insufficiency

   iii. ***vecuronium***
      - originally thought unaltered, but ~ 20-30% cleared through the kidney
      - elimination half-life prolonged ~ 1.5x

   iv. ***atracurium*** → no significant change
      - nonenzymatic alkaline hydrolysis & ester hydrolysis (non-BuChE)

6. ***anticholinesterases***
   - there are no major differences between the changes for neostigmine, pyridostigmine or edrophonium
   - renal excretion is important for ***all*** 3, with 50-70% being renally excreted
   - elimination is delayed, slightly greater than for NMJ blockers
   - \ recurarisation following reversal in renal failure is usually due to some cause other than diminished action of anti-ACh therapy
   - for both anti-AChE and NMJ blockers, excretion appears normal in well functioning transplants

7. ***anticholinergics***
   - 25-50% of atropine & glycopyrrolate are excreted unchanged in the urine
   - potential for accumulation, however, no problems with single dose administration
   - ***scopolamine*** should probably not be substituted due to its potent CNS depressant side-effects, though, single doses are probably OK

8. ***digoxin***
   - ~ 70% excreted unchanged in the urine
   - monitoring of blood levels is the most reliable guide > 0.8 ng/ml therapeutic
     > 1.8 ng/ml toxic

9. vasoactive agents
   - propranolol & CEB's have virtually complete hepatic metabolism
   - thiazides / frusemide 70-90% renal excretion, \ prolonged duration of action
   - trimethaphan is hydrolysed by BuChE and suitable for acute reduction of BP
   - use of SNP carries the risk of ***cyanide & thiocyanate*** toxicity, the later having a half-life of 4 days, which is prolonged further in renal failure
   - hydrallazine is ~ 15% renally excreted & may show some accumulation

| Drugs with Significant Renal Excretion | | |
|---|---|---|
| dTC<br>pancuronium<br>gallamine<br>metocurine | neostigmine<br>pyridostigmine<br>edrophonium<br>atropine<br>glycopyrrolate | penicillin G<br>carbenicillin<br>ampicillin<br>cephaloridine<br>cephlexin |
| ***digoxin***<br>hydrallazine<br><br><br><br>cycloserine<br>methotrexate | diazoxide<br>acetazolamide<br>chlorthiazide<br>amiloride<br>chlorpropamide<br>frusemide | colistin<br>polymixin B<br>kanamycin<br>gentamicin<br>neomycin<br>vancomycin<br>lincomycin<br>streptomycin<br>sulphonamides |

## Acute Renal Failure

- ***Definition ARF***

| | | | | |
|---|---|---|---|---|
| a. | biochemistry | - urea | > 20 | mmol/l |
| | | - creatinine | > 200 | µmol/l |
| | | - U/P creatinine | < 20 | "filtration failure" |
| b. | persistent ↓ GFR | < 15-20 | ml/min | |
| | | < 10-15 | ml/min/$m^2$ | |
| c. | urinary indices | - $Na^+$ & osmolality → tubular dysfunction | | |
| d. | urine output | < 0.5 ml/kg/hr | | |
| | | * but "oliguria" ≠ ARF | | |

- ***Aetiology***

a. prolonged impairment of renal blood flow
   i. hypovolaemia, dehydration
   ii. hypotension
   iii. cardiac failure
   iv. renovascular disease
   v. intra-abdominal hypertension
   vi. hepatorenal disease

b. intrinsic renal disease
   i. nephrotoxic tubular disease - ATN
   ii. ischaemic tubular disease ? ATN
   iii. glomerulonephritis
   iv. interstitial nephritis
   v. infection - bacteria, TB
   vi. trauma

c. obstructive renal disease
   i. calculi, prostatic, stricture, tumour
   ii. trauma, surgical, retroperitoneal fibrosis

***NB:*** alternative classification

1. filtration failure
2. tubular dysfunction
3. oliguric or non-oliguric

- ***Risk Factors***

a. acute disease states
- sepsis, SIRS
- jaundice, liver dysfunction
- raised intra-abdominal pressure
- renal trauma, soft tissue trauma
- transfusion reaction, DIC
- anaphylaxis, anaphylactoid reactions
- muscle injury, thermal burn, electrocution

b. chronic disease states
- advancing age
- CCF, poor LV function
- hypertension
- diabetes mellitus
- renal disease
- hyperuricaemia
- peripheral vascular disease

c. metabolic changes
- advancing age
- tachycardia, hypotension
- elevated CVP, reduced RVPP
- high or low CO, SVR
- abnormal $O_2$ extraction ratio, cellular block
- oliguria, polyuria, osmolar diuresis
- abnormal urine indices ± fluid balance, oedema
- high or low protein intake

d. acute drug therapy

i. ATN
- aminoglycosides, amphotericin, cephalosporins
- diuretics, radiocontrast agents, rifampicin
- lithium, cisplatin, mithramycin

ii. interstitial nephritis
- penicillins, sulphonamides, rifampicin, cephalosporins
- frusemide, thiazides, triamterene
- aspirin, NSAID's
- cimetidine, captropril

e. chronic drug therapy
- NSAID's, diuretics, cyclosporin

f. procedures
- aortic / renal cross-clamping
- major transfusion
- surgery (CNS, toracic, major orthopaedic & abdominal)

g. impaired RBF
- hypotension, malignant hypertension
- renal artery occlusion
- hepatorenal failure
- endotoxaemia
- renal vein thrombosis
- renal venous hypertension (CVP, IABP, abdo surgery)
- HUS, DIC

h. <u>toxic causes</u>
- allopurinol, aminoglycosides, cephalosporins, amphotericin, chemotherapeutic agents, hydrallazine, EDTA, lithium, mannitol, methoxyflurane, paracetamol, penicillamine, probenecid, procainamide, propylthiouracil, radiocontrast media, rifampicin, sulphonamides, thiazides, vit. D
- $CCl_4$, ethylene glycol, heroin, $HgCl_2$, heavy metals, methanol, organophosphates, toluene, uranyl nitrate

i. <u>metabolic causes</u>
- hypercalcaemia, hypokalaemia
- hyperuricaemia
- pigments (bilirubin, myoglobin, Hb)
- hyperphosphataemia
- high plasma oncotic pressure

j. <u>post-renal</u>
- urethral/bladder neck obstruction
- bilateral ureteral obstruction
- stones, clot, tumour
- papillary necrosis
- retroperitoneal fibrosis
- surgical ligation
- bladder rupture, urethral trauma
- renal pelvic trauma

Urinary Indices of Renal Failure

| Parameter | **Pre-Renal ARF** | **ATN** |
|---|---|---|
| urine osmolality | > 500 mosm/l | < 350 mosm/l |
| U/P osmolality | > 1.8 | ~ 0.8-1.2 |
| urine SG | > 1.020 | ~ 1.010-1.015 |
| urine $[Na^+]$ | < 20 mosm/l | > 40 mosm/l |
| urine $[Cl^-]$ | < 20 mosm/l | > 20 mosm/l |
| U/P urea | > 8 | ≤ 3 rarely ≤ 8 |
| U/P creatinine | > 40 | < 20 |
| RFI | < 1 | > 1 |
| $FE_{Na}$ | < 1 | > 1 |

## ARF Prophylaxis & Protection

- ***Methods***

1. ***physiological***
   - i. blood volume
   - ii. cardiac output, RBF/GFR
   - iii. $O_2$ delivery
   - iv. sodium excretion
   - v. nutrition
2. ***pharmacological***
   - i. avoidance of nephrotoxins - contrast dyes, antibiotics, pigments, etc.
   - ii. avoidance of inhibition of autoregulation - NSAID's
   - iii. diuretics
   - iv. renodilators
3. ***physical***
   - i. limitation of aortic clamp times
   - ii. avoidance of embolisation
   - iii. minimise direct trauma & handling
   - iv. limitation of increases in intra-abdominal pressure
   - v. avoidance of post-renal obstruction

- ***Physiological Defence***

1. defence of blood volume - IV fluids ($Na^+$ containing[§])
   - euvolaemia or mild hypervolaemia
2. maintenance of CO ± MAP - IV fluids
   - antiarrhythmics
   - inotropes
3. high sodium excretion[§] - ↓ tubular reabsorption → ↓ renal $VO_2$
4. maintain $DO_2$ - normal [Hb], $S_pO_2$ and avoidance of hypercarbia/acidosis
5. nutrition - proven benefit in ***outcome*** from established oliguric renal failure

## ***Diuretics***

1. ***mannitol***
   - found to be protective in many animal studies
   - mainly ischaemic (NA & renal artery clamping) and nehprotoxic models
   - few human studies, most uncontrolled
     → reversal of oliguria but ***not*** renal function
   - probably beneficial in ***nephrotoxic injury***
     → pigments, amphotericin, cisplatin, IV contrast etc.
   - ?? mechanisms,

   i. increase renal vasodilatory PG synthesis
   ii. free-radical scavenger
   iii. osmotic diuresis
   iv. "anti-sludging" tubular cytoprotection

2. ***frusemide***
   - animal studies variable → benefit in ***ischaemic*** but not nephrotoxic injury
   - conflicting results for prophylactic use in surgical patients
   - effects negligible once ***volume*** is aggressively controlled
   - no overall benefit in established oliguric renal failure
   - theoretical benefit in ***critical ischaemic lesion*** (↓ $O_2$-demand)

   ***NB:*** Brown, Ogg & Cameron (1980)

   i. non-oliguric converted to polyuric renal failure ~ 80%
      polyuric renal failure maintained ~ 100%
   ii. no difference in the number of ***dialysis runs*** required (7 vs 6)
   iii. no difference in ***mortality***
   iv. no difference in biochemical ***renal recovery***

3. ***low dose dopamine***
   - ↑ $DO_2$ via modest ↑ CO (~ 20% on low dose), and usually an ↑ RBF
   - potential ↓ renal $VO_2$ due to inhibition of $Na^+$ reabsorption
   - potential renal vasodilator in normal man, but ?? not in ***septic*** patients
   - conflicting animal evidence regarding protective effect
   - known ***diuretic effect*** → demonstrated in uncontrolled human studies
   - no controlled human studies looking at long term renal function or mortality
   - adverse effects include,

   i. extrarenal side-effects
      - tachyarrhythmias
      - ↑ PCWP, RV & LV afterload
      - ↑ shunt fraction & ↓ $P_{aO2}$
      - ↓ central respiratory drive
   ii. impairs TGF mechanism, thereby may worsen $O_2$ supply/demand
   iii. the induced diuresis is not always associated with an increase RBF
   iv. diuresis may mask, or augment hypovolaemia & renal hypoperfusion
   - similar ↑ RBF achievable with inotropes ***not*** affecting tubular function

- tubular & $DA_1$-receptor effects blocked by commonly used drugs

***NB:*** "if dopamine, or other ***diuretics*** are used in the setting of ARF, then greater attention must be paid to the basic elements of critical care - blood volume, renal perfusion pressure (MAP) and cardiac output - as ***urine output*** can no longer be used as a guide to the adequacy of RBF" Duke, Bersten AIC 1992

## ***Other Agents***

- $Ca^{++}$ entry blockers, proven ***lack*** of benefit
- agents with promise but inadequate studies,

1. ATP-$MgCl_2$
2. inosine
3. clonidine
4. chlorpromazine

## Renal Transplantation Surgery

- ***Preoperative Preparation***

1. management of CRF ***"psyche"***
2. routine ***dialysis*** *many factors ***are not*** corrected by dialysis
   i. control of hypertension
   ii. correction of metabolic abnormalities - fluid & $Na^+$ overload
   - $K^+$, $PO_4$, $Ca^{++}$, acidosis
   - glucose intolerance
   iii. correction of platelet dysfunction / coagulopathy
3. control / elimination of intercurrent ***infection*** or tumour
4. provision of an adequate ***haematocrit***
   i. transfusion - previous studies showed improved graft survival
   - effect negligible since introduction of ***cyclosporin***
   ii. rDNA erythropoeitin
   iii. [Hb] > 10 g/dl - difficult to achieve and carries risk of circulatory overload
5. correction of residual ***coagulopathy*** of present
6. assessment & optimisation of concurrent problems
   i. atherosclerosis, IHD, CCF
   ii. diabetes
   iii. peptic ulcer
7. premedication

- ***Anaesthetic Management***

1. obtain IV access - CVC line if to be used by home team
   * avoid use of fistula arm
2. ensure adequate ***volume status*** prior to induction (NB: body weight)
3. ***immunosuppressive & antibiotic*** therapy is begun prior to induction - check!
4. preoxygenation
5. IV induction / intubated relaxant GA / IPPV to normocarbia
   i. slightly smaller induction dose of STP
   ii. suxamethonium if required, atracurium for maintenance
   iii. isoflurane probably agent of choice
   iv. moderate doses of opioid - fentanyl/morphine
6. ***regional anaesthesia*** has advantages, but length of procedure effectively necessitates combined GA/epidural
   i. reduced anaesthetic requirements - analgesia & muscle relaxation
   ii. good postoperative analgesia
   iii. decreased stress response
7. support of ***transplanted kidney function***
   i. maintain MAP, CO, filling pressures (CVP)
   ii. mannitol ± frusemide
   iii. avoid nephrotoxic agents
8. control of perioperative haemodynamics - hypertension, tachycardia
9. postoperative ***pain relief***

***NB:*** no outcome studies showing any difference between any of the used techniques

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***NB:*** with current transplant preservation techniques there is little or no justification in anaesthetising a patient who is inadequately prepared from a haemodynamic or biochemical viewpoint;
***dialysis*** should be performed preoperatively in all patients if not recently done; patients with severe concomitant system disease are infrequently offered transplantation, however the odd exception occurs

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## TRANSURETHRAL RESECTION TURP

• ***glycine 1.5%*** is the most commonly used irrigating fluid,

a. permeate solute

b. tonicity ***~ 188 mosm/kg***

c. intracellular oedema may occur following absorption

d. toxic effects may occur 2° to,

i. ***ammonia*** - metabolic by-product of glycine

ii. ***glycine*** itself

***NB:*** acute severe ***hyponatraemia*** leading to ***cerebral oedema*** is the most serious result,

***hyperglycinaemia*** → may cause ***visual disturbances***
***hyperammonaemia*** → may result in ***delayed coma***

elevated levels of nonessential amino-acids may result in N & V

■ ***Presentation***

1. neurological
   i. nausea, vomiting
   ii. apprehension, disorientation
   iii. visual disturbances
      • only with glycine and in the presence of hyponatraemia
      • usually "dimming" or "no light perception"
      • usually alert but also complain of N&V
      • onset within 30 minutes & duration up to 12 hours
      • fundoscopy normal, light responses ***normal*** with mild cases
   iv. stupor, coma
      • onset of coma is variable, from 15 minutes to 10 hours
      • examination consistent with metabolic encephalopathy
      • duration from 8-120 hours, with no long-term functional decrement
   v. seizures
2. cardiovascular
   i. ↑ CVP, ↑ BP, ↓ HR
   ii. angina ± ECG changes of IHD
   iii. CCF & cardiovascular collapse

## ▪ ***Aetiology***

• ideal properties for an irrigating fluid would be,

i. allow clear visibility
ii. non-electrolytic - allow diathermy
iii. isotonic, nonhaemolytic
iv. non-toxic when absorbed
v. not metabolised
vi. rapidly excreted
vii. mild osmotic diuretic

• other solutes used include sorbitol, mannitol and urea
• factors affecting the rate of absorption,

1. hydrostatic pressure → limit ***height*** ≤ 70 $cmH_2O$
2. duration of surgery → limit ***duration*** ≤ 1 hour
3. number & size of venous openings
4. surgical skill / experience
5. peripheral venous pressure

• absorption may be intravascular or extravascular, the later producing effects over a longer time frame cf. intravascular absorption

## ▪ ***Glycine Absorption***

1. ***dilutional hyponatraemia***
   - a ↓ $[Na^+]$ of 20-30 mmol/l implies absorption of 3-4 litres of solution
   - $[Na^+]$ < 120 mmol/l indicates a severe situation
   - the $[Na^+]$ post-surgery only roughly correlates with the volume absorbed
   - diffusion of $H_2O$ into the ICF and renal elimination reduce the degree of change

     \ the ***rate*** of absorption is also important

   - also the symptoms of hyponatraemia are related to the speed of onset of change,

   i. $[Na^+]$ < 120 mmol/l → widened QRS
      restlessness, confusion
   ii. $[Na^+]$ < 115 mmol/l → widened QRS, elevated ST segments
      N&V, confusion, stupor (rarely coma)
   iii. $[Na^+]$ < 110 mmol/l → VT or VF
      seizures, coma

2. ***osmolality*** ~ 2.$[Na^+ + K^+]$ + [glucose] + [urea] mmol/l
   - glycine 1.5% ~ 188 mosm/l, cf/ plasma ~ 285 mosm/l
   - therefore, hyponatraemia may occur but the plasma osmolality remains ~ normal
   - patients with the "TURP syndrome" → ***osmolar gap > 10 mosm/l***

3. ***tonicity***
   - describes the osmotic effect of a solute relatively restricted to one body compartment
   - cannot be measured but estimated by $2.[Na^+]$ + [glucose]
   - mannitol & sorbitol are osmotically active solutes, being confined to ECF
   - urea passes freely into cells and has no significant effect on tonicity
   - ***glycine*** is a small amino-acid and also moves into the ICF upon absorption

     → ie. urea & glycine expand ***both ECF & ICF*** upon absorption
   - alterations of tonicity are responsible for changes of cell volume, and acute hypotonicity is associated with cerebral oedema
4. ***colloid osmotic pressure***
   - acute decreases in COP ***do not*** result in oedema in the noninjured brain
5. ***potassium***
   - usually no change during TURP using glycine
   - may be small rise ~ 0.5 mmol/l, possibly due to alteration of transmembrane electrolyte exchange
   - there may be a small amount of ***haemolysis***, but clinically insignificant
6. ***plasma glycine***
   - glycine is an ***inhibitory neurotransmitter*** in the mammalian CNS
   - may act upon receptors in the ***retina*** with transient blindness
   - reports of visual loss may be 2° to cerebral oedema or direct toxicity
   - ***ammonia*** and other nonessential amino acids are metabolic byproducts
   - N&V has been associated with increases of serine, alanine & glutamate
   - hyperammonaemia results in ↑ inhibitory neurotransmitters
     ↓ excitatory neurotransmitters
     → stupor & coma
   - plasma ammonia levels may correlate poorly with glycine levels
   - $NH_3$ usually converted to ***urea*** in the liver
   - patients deficient in arginine or with liver disease → high $NH_3$ levels
   - urinary excretion is ***not*** a significant pathway of glycine

## Management

- ***Mildly Symptomatic Patient***

  i. continue monitoring
  ii. supplemental $O_2$
  iii. send blood for electrolytes & measured osmolality
  iv. small dose of loop diuretic if overloaded
     - most will spontaneously diurese without treatment
  v. conclude surgery if appropriate

## ***The Unconscious Patient***

1. causes of ***unresponsiveness***
   i. supratentorial mass lesions
   ii. infratentorial mass lesions or destruction
   iii. metabolic coma
   iv. anaesthesia / paralysis
   v. psychiatric unresponsiveness
2. evaluation of ***metabolic coma***
   i. HR, BP, ECG, $S_pO_2$
   ii. venous blood
   - BSL
   - $Na^+$, $K^+$, $Cl^-$, $Ca^{++}$, $PO_4^{=}$, $HCO_3^-$
   - Cr/Ur
   - osmolality
   - glycine & ammonia
   - LFT's

   iii. arterial blood - $P_{aO2}$, $P_{aCO2}$, pH, $HCO_3^-$
   iv. drugs - therapeutic & recreational
3. acute ***hyponatraemia*** $[Na^+] < 120$ mmol/l
   i. N.Saline or 2N.Saline ± loop diuretic
   - only until the plasma $Na^+$ is > 120 mmol/l
   - complete correction is then achieved by fluid restriction over days
   - little evidence that mild hypo-osmolality is harmful
   - too rapid correction may → central pontine myelinolysis or ICH
   - CPM not yet reported following correction of acute hyponatraemia & TURP
   - supported by animal studies showing CPM with chronic states

   ii. dialysis if in CRF ? SCUF
   iii. others
   - $NaHCO_3$ 8.4% if hypertonic saline is not available
   - $Ca^{++}$ if there is an associated deficiency

## ***Prevention***

1. limited ***rescetion time*** < 1 hour
2. ***hydrostatic pressure*** < 70 $cmH_2O$
3. early detection of symptoms more feasible under ***spinal anaesthesia***
4. management of spinal induced hypotension better with ***vasopressors***, cf. large volumes of crystalloid
5. facility for rapid measurement of plasma $[Na^+]$ in the institution
6. open prostatectomy should be considered a viable alternative
   - reduced reoperation rates & higher 5 year survival

## Bladder Perforation

- a not uncommon complication of TURP ~ 1%
- majority are made with the cutting loop or knife blade, rarely with the resectoscope or from overdistension of the bladder
- most are extraperitoneal & result in periumbilical, inguinal or suprapubic pain
- there may be irregular return of irrigating fluid

## Extracorporeal Shock-Wave Lithotripsy

- moderate to severe levels of pain from dissipated energy through the tissues
- epidural frequently used, though GA also used in some centres
- problems encountered include,

1. monitoring while immersed in a water bath
   i. remote position of the patient
   ii. difficulty obtaining an adequate QRS signal, necessary for timing of the SW
   iii. electrical hazards associated with water immersion
   iv. demand pacemakers may be damaged by ESWL
2. physiological changes with immersion
   i. increased venous return
   ii. decreased FRC & TV
3. effects of ESWL
   i. arrhythmias - seen with early use due to timing of SW
      - now timed 20 msec after the R-wave, during ERP
   ii. pain
   iii. damage to other tissues - pregnancy
      - orthopaedic hip prostheses

- later generation lithotripters do not require water immersion & use lower energy pulses
- these require considerably less sedation/analgesia

- Melbourne course lecturer → preferred technique is SV/GA using a laryngeal mask
- due to positional discomfort and moderate pressure effects of transducer

# LIVER DISEASE

## Parenchymal Disease

- ***Causes of Acute Hepatitis***

| | | |
|---|---|---|
| 1. | ***infective*** | - Hepatitis A, B, C, Delta<br>- EBV, CMV, HSV, Coxsackie, HIV |
| 2. | ***drugs*** | |
| | i. cholestasis | - alcohol, chloramphenicol, androgens, tetracyclines, oestrogens, OCP, erythromycin, chlorpromazine, chlorpropamide |
| | ii. hepatitis | - a ***-methyl-dopa*** → 5% abnormal LFT's<br>1% hepatitis<br>0.15% CAH<br>- ***paracetamol***, phenytoin, isoniazid<br>- ***halothane***, enflurane |
| 3. | ***toxins*** | - $CCl_4$, vinyl chloride, methanol (formaldehyde)<br>- *Amanita phalloides* (mushroom) |
| 4. | ***cardiovascular*** | - hypovolaemic shock, ***ischaemia***<br>- cor pulmonale, RV failure, CCF, acute TI<br>- Budd-Chiari syndrome |
| 5. | ***metabolic*** | - Wilson's disease<br>- Haemochromatosis<br>- alcohol<br>- parenteral nutrition<br>- $\alpha_1$-antitrypsin deficiency |
| 6. | ***autoimmune*** | - chronic active hepatitis<br>- drugs<br>- vasculitis, SLE, UC, PN<br>- 1° biliary cirrhosis |

| Hepatitis | | | | |
|---|---|---|---|---|
| **Parameter** | **A** | **B** | **C** | **Delta** |
| **Virus** | 27 nm | 42 nm, DNA | ***togavirus*** | defective RNA |
| **Incubation** | 2-6 wks (~4) | 6-24 wks (~10) | 2-24 wks (~7) | |
| **Onset** | acute | insidious | insidious | |
| **Seasonal** | winter | no | no | |
| **Age** | children, young adults | any | adults | IV drug users |
| **Transmission** | faecal/oral | haematogenous, percutaneous, placental, STD | haematogenous percutaneous | coinfection, or superinfection with HBV |
| **Severity** | mild | often severe | mod-severe | |
| **Prognosis** | good | HB&CV worse with ***age & debility*** | | poor |
| **Chronicity** | rare | occasional ~ 5-10% | ***common*** ~ 10-50% | common |
| **IgG-Ab** | good | needle stick HBV-IgG | none ? pooled IgG | none |
| **Carrier** | rare | 0.1-1.0% (< 30% O/S) | ~ 1.0% | common |
| **Mortality** | rare | ~ 1% | ?? | ~ 2% |
| **Diagnosis** | anti-HAV IgM | HBsAg anti-HBs,c,e | anti-HCV | anti-HDV |

- ***Complications of Hepatitis B***

| | | |
|---|---|---|
| a. | cirrhosis with portal hypertension | ~ 15-30% |
| b. | carrier state (HBsAg / HBcAb) | ~ 5% |
| c. | chronic active hepatitis | ~ 3-5% |
| d. | massive hepatic necrosis | ± encephalopathy |
| e. | primary hepatic carcinoma | |
| f. | immune complex syndromes | - serum sickness<br>- polyarteritis<br>- glomerulonephritis<br>- urticaria |

## Perioperative Considerations

| Liver Function Tests | | |
|---|---|---|
| Test | Hepatocellular injury | Obstruction |
| Aspartate transaminase[1] **AST** / SGOT<br>Alanine transaminase **ALT** / SGPT | ↑ to ↑↑↑ | ↑ |
| Alkaline Phosphatase[2] **ALP** | ↑ | ↑↑↑ |
| Gamma-glutamyl transpeptidase **GGT** | N to ↑↑↑ | ↑↑↑ |
| 5-Nucleotidase | N to ↑ | ↑ to ↑↑↑ |
| Albumin | ↓ to ↓↓↓ | N |
| Prothrombin time[3] | ↑ to ↑↑↑ | N to ↑[4] |
| Bilirubin | N to ↑↑↑ | N to ↑↑↑ |

[1] **AST** also in heart, rbc's, muscle **ALT** is more specific for liver,
enzyme rise reflects extent & acuteness of cellular injury, but ***does not*** correlate with ***prognosis***

[2] origins of **ALP** include: liver, bone, intestine, placenta & lung

[3] increase does have worse ***prognosis***
shorter half-life & more rapid change cf. albumin

[4] correctable with vitamin K

- ***Liver Dysfunction***

| | | |
|---|---|---|
| a. | hypoalbuminaemia | - low COP, increased tendency to ***oedema*** formation |
| b. | coagulopathy | - ↓ vit K dependent factors |
| c. | septicaemia | - immune dysfunction |
| d. | toxaemia | - metabolites, bacteria, toxins |
| e. | amino-acid imbalance | - low branched-chain / high aromatic |
| f. | drugs | - prolonged effect |
| g. | hyperammonia | - not cleared |
| h. | severe ***hypoglycaemia*** | - impaired glucose metabolism |
| i. | citrate toxicity | - impaired metabolism with large volume transfusions<br>- especially the anhepatic phase of transplantation<br>- $R_X$ $CaCl_2$ |

- ***Bilirubin***

1. the water soluble ***conjugated*** fraction gives a ***direct reaction*** to diazo reagent
2. the lipid soluble, ***indirect reacting*** (total - direct), primarily ***unconjugated*** fraction
   - complicated as there is also an albumin-bound conjugated fraction
3. plasma levels
   i. total < 20 mmol/l
   ii. direct < 7 mmol/l
4. direct / ***conjugated hyperbilirubinaemia*** *actually ***mixed*** direct + indirect
   - disorders which impair excretion after conjugation
   i. hepatocelular disease
   ii. intra & extra-hepatic cholestasis
5. indirect / ***unconjugated hyperbilirubinaemia***
   - rate of bilirubin production exceeds either the rate of uptake, or conjugation
   i. overproduction - haemolysis, ineffective erythropoeisis
   ii. liver disease - Gilbert's, Crigler-Najjar
6. ***bilirubinuria***
   - only occurs following ***conjugation***
   - usually detectable by dip-stick prior to clinical onset of jaundice
   - otherwise not very useful
7. ***urobilinogen***
   - appears only after metabolism in the gut
   - therefore ***absent*** in total bile duct obstruction

- ***Central Nervous System***

a. early ***frontal area*** impairment (behaviour/motor/sensory) with ***brainstem sparing***
b. followed by varying degrees of coma, with brainstem dysfunction resulting in
   i. respiratory failure
   ii. vasomotor imbalance - vasodilatation, arrhythmias
c. Wernicke-Korsakoff syndrome
d. very high sensitivity to - sedatives, narcotics, general anaesthetics
e. EEG - slowing of rhythm
   - low frequency theta rhythm
   - high amplitude delta waves (deep coma)
f. ***cerebral oedema*** * often ***without*** clinical or CT signs
g. ***delerium tremens*** in acute withdrawal state → ↑ sympathetic outflow
h. associated ***thiamine deficiency*** - neuropathy
   - cardiomyopathy, vasodilatation

- ***Renal / Electrolytes***

a. renal failure - hypotension, haemorrhage
- sepsis
- hepatorenal syndrome

b. 2° hyperaldosteronism - hypokalaemia
* ***hypo***natraemia cf. expected hypernatraemia

c. hypomagnesaemia & hypophosphataemia

d. respiratory ***alkalosis*** - central hyperventilation

e. later metabolic alkalosis - renal, vomiting

f. metabolic acidosis occurs late with hypoxia & hypoglycaemia

- ***Respiratory System***

a. early → central ***hyperventilation***

b. late → central respiratory failure

c. aspiration, infection

d. intra-abdominal hypertension due to ascites
   i. ↓ chest wall compliance
   ii. ↓ FRC / TV

e. vasodilatation / ↓ HPV → ↑ ***shunt fraction***

- ***Cardiovascular System***

a. initially high cardiac output with ***peripheral vasodilatation***

b. central ***vasomotor depression*** * low HR, CO and SVR

c. arrhythmias - hypo-$K^+$, hypoxia
- cerebral oedema

d. acute ethanol ingestion → myocardial depression

e. chronic ethanol ingestion → cardiomyopathy

- ***Coagulation Disorders***

a. fall in production of coagulation factors
   i. ***VII*** - shortest $t_{½}$ ~
   ii. vit K dependent factors - II, VII, IX, X
   iii. low ***factor V*** implies liver impairment other than vit K lack
   iv. fibrinogen falls last * ↓ I → probably DIC

b. ***DIC*** is usually secondary to sepsis, severe hypovolaemia and rarely to the liver failure

- ***Gastrointestinal Tract***

a. gastric ***erosions*** / ulceration ~ 50%

b. bacterial breakdown of protein may produce ***encephalopathy***

c. enteric bacteria are a source of ***septicaemia*** ↑ translocation
↓ hepatic RES function

d. spontaneous bacterial peritonitis

- ***Prognosis***

Child's Classification[1]
Severity of Chronic Liver Disease

| Class | A | B | C |
|---|---|---|---|
| total bilirubin | < 34 µmol/l | < 60 µmol/l | > 60 µmol/l |
| albumin | > 35 g/l | > 30 g/l | < 30 g/l |
| ascites | none | controlled | uncontrolled |
| nutrition | good | fair | poor |
| encephalopathy | absent | absent | present |
| **surgical risk** | **5%** | **10%** | **50%** |
| prothrombin time[2] | + 1 1-4 s | + 2 4-6 s | + 3 > 6 s |

[1] Child *et al.* 1964 surgical cohort undergoing portasystemic shunting

[2] Pugh *et al.* 1973 increased risk for each group, according to prolongation of PT

• other factors which are important in ***prognosis*** include,

1. mechanical ventilation - respiratory failure
   - tissue hypoxia (Bihari)
2. high creatinine - renal failure, HUS
3. coagulopathy
4. biochemical derrangement - hypo/hyper-$Na^+$
5. sepsis - uncontrolled

- ***Management Principles***

1. remove cause where possible
2. prevent infection - superinfection of the patient
   - transmission to staff
3. prevent vasomotor instability
4. prevent respiratory failure
5. maintain ***renal function*** * central hypovolaemia / arterial underfilling
6. minimise and treat ***cerebral oedema***
7. prevent ***hypoglycaemia***

- ***Treatment Hepatic Encephalopathy***

a. minimise protein load
   i. dietary protein restriction
   ii. avoid GIT bleeding
   iii. clear the gut
      - Neomycin / Lactulose
        → given orally lowers gut pH to inhibit gram (-)'ve bacteria, favours the growth of ***lactobacilli***, traps $NH_3$ in the gut, and cathartic
      - $MgSO_4$ enema

b. treat and prevent electrolyte disturbances
   i. $Na^+$, $K^+$, osmolality
   ii. pH, especially ***alkalosis***

c. experimental
   i. alter amino-acid balance in favour of ***branched-chain*** amino-acids
   ii. infusion of neurotransmitter precursors (L-dopa)
   iii. charcoal haemoperfusion / haemofiltration

d. avoid narcotics, sedatives, etc.

- ***Treatment Cerebral Oedema***

a. regular neurological assessment
b. early institution of controlled ventilation to maximise $P_{aO2}$ & lower $P_{aCO2}$
c. ICP monitoring
d. maintain MAP / CPP
e. fluid restriction and diuretics (mannitol)
f. high dose steroids of ***no*** benefit

- ***Treatment Nutrition***

a. low total protein with high ratio of branched-chain amino-acids

b. high glucose intake, no fats / intralipid

c. vitamin supplements
- Vit K ~ 15-20 mg/day
- thiamine ~ 200 mg/day
- folate ~ 1-2 mg/day
- Vit C ~ 500 mg/day

- ***Treatment Liver***

a. maintain adequate oxygen and blood supply

b. minimise complications

c. ? insulin/glucagon infusion to stimulate hepatic regeneration

d. charcoal haemoperfusion

e. ? liver transplant

- ***Anaesthetic Agents***

1. thiopentone
   - ↓ ***protein binding*** directly related to ↓ albumin (~ 50%)
   - ↑ free fraction, but ↓ intrinsic hepatic clearance → ***normal*** plasma clearance
   - ↑ $V_{dSS}$ / ↑ terminal elimination half-life
   - induction doses generally may be reduced by 50-75%
   - increased doses may be required in acute intoxication due to cross-tolerance
2. volatile agents
   - most result in 20-30% ↓ liver blood flow
   - cirrhotic rats exposed to 3 hours of 1.8% halothane showed ***no*** ↓ function
   - may actually be preferred agents, due to respiratory elimination
   - probably should avoid halothane, but no absolute evidence
3. muscle relaxants
   - vecuronium (< 0.15 mg/kg) and atracurium (< 0.6 mg/kg) will ***not*** have a significantly prolonged duration of action
   - with larger doses atracurium offers some advantage, hydrolysis being independent of plasma pseudocholinesterase
   - plasma pseudocholinesterase levels are rarely reduced sufficiently to prolong the duration of action of suxamethonium
4. opioids & sedatives
   - ↑ sensitivity to all CNS depressants is seen in hepatic encephalopathy

## Cholestatic Liver Disease

***Def'n:*** reduction or cessation of flow of bile, either ***intrahepatic*** or ***extrahepatic***

- ***Intrahepatic Cholestasis***

1. hepatitis with cholestatic picture - see previous list
2. hypoxia / hypotension
3. sepsis
4. drugs - steroids, synthetic oestrogens, etc.
5. increased bilirubin load

- ***Extrahepatic Cholestasis***

1. gallstones, acalculous cholecystitis
2. ascending cholangitis
3. stricture, post-ERCP
4. tumour - bile duct, gallbladder, Ampula of Vater
   - intrahepatic, primary or secondary
   - head of pancreas

- ***Complications***

***NB:*** proportional to the severity and duration of the ***hyperbilirubinaemia***

1. pruritis, nausea & vomiting
2. ascending infection
3. hepatocellular death with fibrosis, portal hypertension & cirrhosis
4. fat malabsorption & diarrhoea * hypovitaminoses A, D, E, K
5. coagulopathy - responsive to parenteral vitamin K
6. cutaneous xanthomatosis
7. acute oliguric renal failure

- ***Perioperative Considerations***

***NB:*** 25% of jaundiced patients $I_X$ for obstruction have ***hepatocellular*** disease, every attempt should be made to delineate the aetiology prior to anaesthesia.

1. defend $S_pO_2$ , MAP & blood volume
   i. maintain liver perfusion & oxygenation
   ii. maintain GFR - especially elderly & deeply jaundiced
2. pharmacology
   i. parenteral vitamin K 10 mg & FFP should be available
   ii. avoid agents reliant on biliary excretion
   iii. opioids may ↑ tone in the sphincter of Oddi, \ avoid pre-induction
   iv. avoid potential hepatotoxins

## Postoperative Jaundice Aetiology

a. increased bilirubin load
   i. haemolysis
   ii. haematoma - reabsorption
   iii. transfusion - old cells, incompatibility, sepsis

b. hepatocellular dysfunction
   i. congenital
      - Gilbert's - ***ligandin*** deficiency → ¯ ***uptake***
        ~ 7-10% of otherwise "normal" patients
      - Crigler-Najjar Type II - low ***glucuronyl transferase*** ¯ ***conjugation***
      - Rotor & Dubin-Johnson - low biliary excretion → ¯ ***excretion***
   ii. acquired
      - postoperative intrahepatic cholestasis
      - circulatory failure - hypovolaemia, hypotension, hypoxia
        → hepatic ischaemia
      - drug-induced hepatitis - halothane, methoxyflurane
        - steroids, anti-TB agents, phenothiazines, etc.
      - infective hepatitis
      - septicaemia
      - trauma

c. obstructive
   i. bile duct trauma, oedema, ligation
   ii. cholelithiasis, cholecystitis
   iii. cholangitis
   iv. pancreatitis

- ***Intrahepatic Cholestasis***

***Def'n:*** mild form ~ "benign postoperative intrahepatic cholestasis"
severe form ~ "ICU liver"

***NB:*** common after major, abdominal, or emergency surgery,
especially if associated with ***hypotension & hypoxia***

• pathogenesis,

1. sepsis
2. liver ischaemia
3. increased bilirubin load - haematoma, transfusion
   ~ 10% of $T_X$ RBC's in 24 hours
4. post-CPB - usually day 2-3, benign
5. reduced renal excretion

• if sensitive markers are used, mild postoperative dysfunction occurs in ~ 50%
• postoperative jaundice occurs in £ **20%** of patients undergoing major surgery

1. ***hyperbilirubinaemia*** ≥ 100 µmol/l
   - disproportionate to enzyme levels
   - common at 2-14$^{th}$ day
2. moderate ↑ ALP ~ 3-10x - "obstructive jaundice" pattern (ie. biliary stasis)
3. only mild ↑ AST

• prolonged form also has severe ***hypoalbuminaemia*** → INR ≥ 1.4
• associated reduction in protein synthesis, reduced AA clearance, & low redox potential

# LIVER TRANSPLANTATION

- first performed 1963 but limited survival
- current 5 year survival in USA ~ 60%
- ***fulminant hepatic failure***, onset of encephalopathy within 8 weeks in the absence of chronic liver disease, is increasingly an indication for transplantation
- survival with medical $R_X$ ~ 20-30%, cf. following transplantation **~ 65%**

## ▪ *Considerations Preoperative*

1. malnutrition
2. coagulopathy
   - factor deficiency < 20% **V** → ↑ intraoperative haemorrhage
   - thrombocytopaenia ∝ splenomegaly
   - splenectomy → ↑ portal vein thrombosis, \ not an option
   - ± ? relationship to transfusion requirements
3. immunosuppression - spontaneous bacterial peritonitis
4. respiratory insufficiency - ↑ shunt / ↓ compiance / central failure
   - infection, aspiration
5. cardiovascular insufficiency - ↓ effective blood volume despite ascites
6. renal failure * hepatorenal syndrome

## ▪ *Intraoperative*

1. RSI
2. cerebral oedema - ↑ ICP ∝ ↑ permeability of BBB & toxins
   - steroids ***not effective***
   - limit use of volatile agents, vasodilators
3. high risk of VAE ? avoid using $N_2O$
   - monitoring
4. prolonged procedure ~ 8 hrs
5. massive transfusion ~ 25 units average
   - IV access & fluid warmers
   - monitoring: CVP/PAP, IABP, CUD
   - citrate toxicity & ↓ $Ca^{++}$ when ***anhepatic***
6. electrolyte disturbances - ↓ $Na^+$, ↓ $K^+$, ↓ $Mg^{++}$
   * BSL usually OK
   - progressive ***metabolic acidosis***
   ± $NaHCO_3$ ~ 50 mmol prior to unclamping
7. coagulopathy - INR, APTT, fibrinogen & platelets hourly
8. maintenance of renal perfusion

| | | |
|---|---|---|
| 9. | venovenous bypass | - used by some institutions<br>- ↓ CVS compromise, inotropes & blood loss<br>- ***no*** difference in morbidity / mortality |
| 10. | unclamping | - $H^+$ & $K^+$ load, plus cold fluid<br>- highest risk of VAE<br>- arrhythmias (↓ HR), ↑ PCWP, ↓ CO<br>- risk of PTE |
| 11. | fibrinolysis ∝ | ↑↑ tissue plasminogen activator<br>- treat with Amicar (EACA)<br>- monitor with ***thromboelastography*** |

- ***Postoperative Considerations***

| | | |
|---|---|---|
| 1. | 1° graft non-function | - small percentage, ? reperfusion injury |
| 2. | fluid requirements | |
| 3. | transfusion | - blood, FFP, platelets |
| 4. | hypothermia | |
| 5. | renal failure | - ***cyclosporin*** nephrotoxicity<br>- ATN* |
| 6. | electrolyte changes | |
| | i. hyper- | - $Na^+$, osmolarity, glycaemia |
| | ii. hypo- | - $Mg^{++}$, $K^+$ |
| | iii. uraemia | |
| | iv. ***metabolic alkalosis*** | |
| 7. | pulmonary | - ARDS, pneumonia |
| 8. | CNS | - seizures<br>- IC haemorrhage<br>- ***cyclosporin*** neurotoxicity |
| 9. | graft rejection / liver failure | ~ 5-20% |

- ***Aetiology of Renal Dysfunction****

a. hypovolaemia, hypoperfusion
b. inefficiency of venovenous bypass
c. poor graft
d. nephrotoxins - cyclosporin, aminoglycosides
e. IVC obstruction
f. intra-abdominal hypertension
g. septicaemia

***NB:*** $R_X$ $\rightarrow$ IV fluids, ? dopamine, reduce Cyclosporin dose

- ***Transplant Rejection***

| | | |
|---|---|---|
| a. | 1° graft rejection | ~ 2%<br>- rise in GGT, later ALP<br>- fever, tachycardia |
| b. | 'preservation injury' | - reversible centrilobular lesion |
| c. | vascular $\propto$ thrombosis | - rise in AST & ALT first |
| d. | intrahepatic cholestasis | - common, spontaneous remission |
| e. | biliary tract complications | |
| f. | chronic rejection | |
| ***NB:*** | Acute rejection $R_X$ | - pulse steroids<br>- monoclonal Ig $OKT_3$ |
| | Maintenance $R_X$ | - azathioprine<br>- cyclosporin A, steroids |

## 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 ~ 2-3 ml/100g 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
      • reduced chest wall compliance
      • increased work of breathing
   iii. increased V/Q mismatch - increased $\delta P_{A-aO2}$ ± ***hypoxia***
      • the young obese usually have normal blood gases
   iv. tendency to ***hypercapnia*** with increased loads
   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. ↑ incidence of ***glucose intolerance***, NIDDM
   iii. ↑ incidence of pancreatic dysfunction
5. ***gastrointestinal***
   i. gastric stasis, reflux due to hiatal hernia → increased ***aspiration risk***
   ii. fasting > 90% have gastric volume > 0.4 ml/kg & pH < 2.5
   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
- 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*** & pancreatic disease

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 ? why

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 → ~ 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 agentshas 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 > $T_5$ 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
   - ↑ incidence of DVT & ***all*** should have ***heparin*** prophylaxis ± leg stockings
   - hypoxaemia may persist ≤ 7 days following intra-abdominal surgery & is a universal finding → ***all*** should have ***supplemental oxygen***
   - 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

# THE ELDERLY

***Def'n:*** ***life expectancy***, actuarial term describing the average number of years a member of a ***specific population*** may be expected to live, given environmental constraints,

***life span***, is the maximal attainable biological age ~ 110-115, being species specific and virtually unaltered throughout history,

specialised texts discriminate between elderly, aged and very old, however, for practical purposes ***elderly*** or ***geriatric*** $^3$ ***65 years***,

***aging***, is a progressive, universally prevelant physiological process, producing measurable changes in structure and function of organ systems

## Physiological Changes with Aging

- ***Body Composition***

1. ***body weight*** ↑'s to 60 years (M ~ 25% / F ~ 18%), then decreases
2. loss of ***skeletal muscle*** (lean body mass) → ↓ exercise $VO_2$ ~ 30-50%
   → ↓ basal $VO_2$
   - parallel reduction in resting CO
   - ↓ heat production and ability to compensate for heat loss
3. ↑ percentage ***body fat*** *↑F > ↑M
   - ↑ body stores for lipid soluble agents
   - more gradual elimination & prolonged anaesthetic effect
4. ***plasma volume*** → ↓ 20-30% by 75 yrs (ASA: McLeskey)
   → ***unchanged*** in healthy (RDM: Muravchick)
   - most studies showing ↓ $V_{dInit.}$ were in small numbers of hospitalised, ill patients
   - no change is seen in healthy, active elderly patients, however, those patients presenting for surgery may well have factors → $^{-}\mathbf{V_{dInit}}$
5. 4 factors result in $^{-}$ ***protein binding***
   i. quantitative ↓ protein - mainly ↓ albumin
   ii. qualitative changes in circulating protein
   iii. effects of co-administered drugs
   iv. effects of concurrent disease states
   - however, ↓ protein binding has minimal clinical effect on the anaesthetic or adjuvant agents, except for ***pethedine***
6. red cell mass, WCC, platelets & coagulation
   - change little in the absence of age-related disease
   - there may be some age-related increase in ***capillary fragility***
7. osteoporosis and loss of skeletal mass

- ***Hepatic Function & Metabolism***

1. little qualitative change in hepatocellular enzyme function
2. significant ↓ plasma cholinesterase activity in elderly men (not women)
3. ↓ hepatic mass ~ 40% by age 80 years
   - parallel ↓ hepatic blood flow
4. ↓ hepatic metabolism of drugs, especially ***high clearance / flow limited*** agents
   - morphine, pethedine, fentanyl, naloxone
   - methohexital, ketamine, propofol, ? midazolam
   - lignocaine, β-receptor agonists / antagonists, TCA's
5. progressive ***glucose intolerance*** ↓ hepatic function
   ↓ lean tissue mass

- ***Renal Function***

1. ARF → ~ 20% of postoperative deaths in the elderly
2. ~ 30% of elderly surgical patients have pre-existing renal insufficiency
3. ↓ renal mass ~ 30% by age 80 years
   - selective loss of parenchyma, with fibrosis & infiltration
4. ***glomerulosclerosis*** results in effective shunting of RBF
   → both RPF & GFR decrease > expected by % loss of renal mass
5. total ↓ RBF ~ 10% / decade
   > ↓ GFR ∝ ↑ filtration fraction
6. serum ***creatinine*** usually "normal" ∝ ↓ muscle mass
7. ↓ response to ADH
8. ↓ $T_{max}$ for glucose - plus drugs secreted by the proximal tubule ($AB_X$)
9. ↓ concentrating ability & $Na^+$ conservation
10. ↑ susceptibility to ***medullary ischaemia***

- ***Central Nervous System***

1. ↓ brain mass — ~ 20% by age 80 years
   - loss accelerates > 60 years
   ~ 50,000 neurons/day (10 x $10^9$ total)
2. loss is selective — ~ 30-50% loss in cortex, thalamus & basal ganglia
3. parallel ↓ CBF — ~ 20%, with regional flows maintained
4. autoregulation and vasomotor responses to $CO_2$ remain normal
5. generalised depletion of neurotransmitters, NA, DA, 5HT & tyrosine, plus ↑ activity of COMT & MAO & ↓ receptor "upregulation" in response
6. ? reduced receptor affinity for DA & NA

- ***Peripheral & Autonomic Nervous Systems***

1. progressive ***deafferentation*** with ↑ stimulation threshold for all modalities
2. concomitant deterioration of conduction pathways → ↓ $v_c$
3. motor end-plate proliferation & ↑ cholinergic receptors
   - however, actual number of end-plate units decreases
   - sensitivity to non-depolarising blockers ***does not*** alter significantly
4. adrenal mass → ↓ 15% by 80 years
5. plasma levels of ***catecholamines*** are 2-4x ***higher***
   - both at rest and during exercise
   - marked reduction in end-organ responsiveness
6. ***receptor downregulation*** may be due to,
   i. ↓ numbers of end-organ receptors
   ii. ↓ affinity for catecholamines - both agonists & antagonists
   iii. ↓ G-protein coupling & adenylate cyclase activation
   iv. ? ↓ membrane fluidity
7. dysfunction of reflex ***autonomic homeostasis***
   i. baroreceptor reflex → ↓ postural reflexes
   ii. vasoconstrictor response to cold
   iii. beat-to-beat HR variability

- ***Analgesic & Anaesthetic Agents***

1. peripheral deafferentation, decreased receptor numbers, decreased central conduction and decreased CNS mass ***do not*** result in a clinically demonstrable increase in the ***pain threshold***
2. may have a small increased threshold for superficial discrete stimuli but reduced threshold for visceral pain, or that associated with injury / illness
3. ↓ anaesthetic **MAC** £ **30%**, regardless of molecular species

- ***Cardiovascular Function***

1. ~ 50-65% of elderly patients have coexisting ***CVS disease***
   - this figure may be higher in surgical populations
2. ↑ resting HR in fit elderly patients ∝ ↓ parasympathetic tone
   - this also results in - loss of HR variability with respiration
     - ↓ HR response to atropine, pancuronium & isoflurane
     - ↓ HR response to intubation (BP response normal)
   - ↓ HR in most debilitated & medicated patients
3. LV becomes both preload & afterload dependent,
   i. ↑ ventricular wall thickness - fibrosis & amyloid infiltration
      - ↓ LV ***compliance***
   ii. valvular fibrocalcification & ***sclerosis***
   iii. ↓ elasticity of large arteries & ↑ ***impedance*** to LV ejection
4. ↓ resting CI ∝ ↓ muscle mass & $VO_2$
5. ↓ maximal CI ∝ ↑ activation/contraction & relaxation times
   ↓ HR ***response*** → ↑ LVEDV & SV to compensate
   ↓ response to β-stimulation
6. ↑ fibrosis of conducting tissue
   - increased incidence of conduction abnormalities

- ***Respiratory Function***

1. progressive ↓ alveolar ***surface area***
2. ↑ ***dead space*** - both anatomical & alveolar
3. ↓ elastic recoil ∝ ↓ elastin content / ↑ fibrous connective tissue
   - - ***lung compliance*** but ↓ support for small airways with closure
   - non-uniform ↓ elastic tissue → ↑ spread of time constants
     ↑ V/Q mismatch
4. ¯ ***chest wall compliance*** due to thoracic cage calcification
   - although $C_L$ increases, total respiratory compliance changes little
   - the ↑ FRC is only modest
   - however, ↑ RV → ↓ ERV & VC
     ↓ $FEV_1$/FVC & ↓ MBC, $FEF_{25-75}$
     ↑ work of breathing
5. - ***closing capacity*** → CC ≥ FRC
6. ↑ $\delta P_{A-aO2} \leq 40$ mmHg → $P_{aO2} \sim 105 - Age/3$ mmHg
7. ↓ CNS response to hypoxia / hypercapnia
8. ↑ frequency & duration of ***apnoeic periods*** during sleep
   - ↑ apnoeic periods seen with opioids ∝ higher peak plasma levels

## Perioperative Outcome & Risk

- ***Risk Factors***

• for elderly patients ≥ 65 years, 30 day perioperative ***mortality* ~ 5-10%**
• consistent evidence eldery have higher morbidity / mortality cf. younger patients
• major risk factors for eldery patients,

1. emergency surgery
2. the operative site
   - major vascular, abdominal or thoracic ~ 10-20x ↑ mortality
   - cf. TURP, inguinal herniorrhaphy or cataract surgery
3. physical status of the patient ≥ ASAIII
4. ***infection & sepsis*** continue to be major causes of death

• ***inadequate preparation*** and cursory evaluation are commonplace in eldery patients, and are likely worse in emergency procedures

***NB:*** a review of emergency procedures in the elderly found a 65% incidence of ***correctable*** deficiencies in blood volume, electrolyte imbalance or $O_2$ transport

• in general, the greater the average age of the surgical population, the greater will be the incidence of ***age-related disease***,

| | | |
|---|---|---|
| i. | hypertension | ~ 46% |
| ii. | renal disease | ~ 31% |
| iii. | atherosclerosis | ~ 27% |
| iv. | previous MI | ~ 18% |
| v. | CAL | ~ 14% |
| vi. | cardiomegaly | ~ 14% |
| vii. | diabetes | ~ 9% |
| viii. | liver disease | ~ 9% |
| ix. | CCF | ~ 8% |
| x. | angina | ~ 6% |
| xi. | CVA | ~ 6% |

***NB:*** seen in 1000 elderly patients presenting for surgery

• therefore, the widespread perception of increased mortality with advancing age actually reflects the relationship between preoperative status & operative outcome

***NB:*** recent studies actually show that the morbidity/mortality rates for fit, healthy octagenarians are ***not significantly*** higher than those for fit younger patients

## Anaesthetic Management

- RDM states, that whatever the patients age, an uncomplicated anaesthetic depends upon,
    1. a technique compatible with the patients physical status and the type of surgery
    2. consistent monitoring
    3. attention to detail

    ***NB:*** multiple retrospective & prospective studies have arrived at the same conclusion; ***no significant difference*** in outcome can be attributed solely or predominantly to the use of any specific agent, and no clear and objective benefit can be demonstrated for using ***regional*** rather than ***general anaesthesia***

    ?? incidence of PTE with orthopaedic procedures, RA versus GA

- ***Important Issues***

    1. psychological preparation & premedication
    2. transportation
    3. ***positioning*** - fragile skin, bruising
       - bony protuberances
       - joint contractures/stiffening
    4. IV access
    5. pharmacokinetic/dynamic differences
    6. intubation - cervical & TMJ stiffness, nuisance teeth, dentures
       * exaggerated pressor response & IHD/CVD
    7. maintenance - absolute drug doses
       - CVS depression
       - tendency to mild hypovolaemia
       - hypoxaemia & $\uparrow F_IO_2$ requirement
       - temperature regulation

# CONNECTIVE TISSUE DISORDERS

## Rheumatoid Arthritis

- prevalence ~ 1% with a F:M ratio ~ 3:1
- most common in the $4^{th}$ & $5^{th}$ decades
- moderate genetic predisposition ~ 30% monozygous twins
  ~ 5% dizygous twins
- multisystem disease of ***unknown aetiology***
- characterised by a perisistent ***inflammatory synovitis***, usually symmetrical, with associated destruction of cartilage and bone, resulting in charcteristic joint deformities

### ▪ *Clinical Features*

1. ***articular features***
   - insidious onset with joint stiffness, pain and swelling - usually peripheral
   - swelling of proximal >> distal interphalangeal joints
     → 'swan neck' & 'button hole' deformities
   - may involve wrists, elbows, shoulders, knees, ankles and subtalar joints
   - ***cervical spine*** involvement is common

   i. atlanto-axial subluxation
      - anterior AAS ~ 80% and most common
        - transverse ligament destruction, worse in ***flexion***
      - posterior AAS ~ 3-7%, due to odontoid peg destruction
        * ***extension*** may → anterior cord compression by atlas
      - vertical AAS ~ 10-20%, loss of lateral masses of $C_1$
        - odontoid may sublux through foamen magnum
        - potentially life-threatening cervicomedullary pressure
      - lateral/rotatory AAS

   ii. subaxial subluxation
      - less common ~ 10-20% of RA population
      - direct laryngoscopy generally well tolerated

2. ***systemic features***
   - ~ 10% have onset with acute polyarthritis, malaise, fever & weight loss
   - Raynaud's phenomenon
   - lymphadenopathy - especially draining active joints
   - osteoporosis
   - muscle weakness and wasting
   - tenosynovitis, bursitis, popliteal cysts
   - subcutaneous nodules ~ 20% over the disease course

3. ***cardiovascular***
   - asymptomatic pericarditis or constrictive pericarditis
   - pericardial effusion, tamponade
   - nodular & granulomatous complications
     - heart block
     - AMI, coronary insufficiency
     - cardiomyopathy
     - AI
   - diffuse necrotising vasculitis - nodular seropositive disease
   - mononeuritis multiplex due to involvement of vasa nervorum (cf. PN)

4. ***pulmonary***
   - pleurisy ± pleural effusion ~ 25%
   - chronic interstitial fibrosis
   - obliterative bronchiolitis
   - Caplan's syndrome, RA + 0.5 - 5.0 cm pulmonary nodules
     + pneumoconiosis (coal or other)

5. ***neurological***
   - entrapment neuropathies - carpal tunnel
   - peripheral neuropathy - usually symmetrical & lower limbs
   - cervical ***cord compression*** - atlanto-axial or subaxial
     * common in long-standing RA
     > 4 mm odontoid-arch distance in flexion
   - nerve root compression, vertebrobasilar insufficiency, spinal artery occlusion

6. ***haematological***
   - normochromic normocytic anaemia
   - low serum $Fe^{++}$, low iron binding capacity, not responsive to oral iron
   - true iron deficiency 2° GIT haemorrhage from NSAID's
   - thrombocytosis with active disease
   - ***Felty's syndrome*** - splenomegaly, neutropenia & RA
     - seropositive, longstanding, but ***inactive*** disease
     - anaemia, thrombocytopaenia, lymphadenopathy
     - weight loss, skin pigmentation & vasculitic changes

7. ***ocular features***
   - episcleritis - benign but common in seropositive, usually painless
   - scleritis - inflammation of sclera & uveal tract, synechiae ± 2° glaucoma
   - scleromalacia & scleromalacia perforans
   - keratoconjunctivitis sicca ~ 10%
   - ***Sjögren's syndrome*** - keratoconjunctivitis sicca + xerostomia + CT disease
     - RA, SLE, PSS, polymyositis, myasthenia, etc.
     - multiple organ system Ab's

8. ***amyloidosis***
   - ~ 25-50% of autopsies, making RA the leading cause
   - usually limited to ***mild proteinuria***
   - rarely associated with nephrotic syndrome or renal failure

## Ankylosing Spondylitis

- chronic inflammatory arthritis, affecting predominantly the SI joints and spine
- characterised by progressive stiffening and fusion of the axial skeleton

1. typically young ***males***, 2nd & 3rd decades
2. M:F ratio ~ 9:1
3. strong genetic disposition
   i. > 90% HLA-B27 positive
   ii. 1st degree relatives show an increased incidence of,
      - psoriatic arthritis
      - inflammatory bowel disease
      - Reiter's syndrome
4. ***articular features***
   - usually insidious onset, with recurring lower back pain & stiffness
   - worse in mornings and following inactivity
   - usually ***without*** associated nerve root signs
   - chest pain due to involvement of the costovertebral joints
   - plantar fasciitis, Archilles tendonitis
   - severe spinal fusion & rigidity ocurs only in a ***minority***, and in most is not associated with marked deformity
   - rarely develop kyphosis of the thoracic and cervical spine
5. ***extra-articular features***
   - non-granulomatous anterior uveitis
   - aortic regurgitation
   - cardiac conduction defects
   - apical pulmonary fibrosis
   - amyloidosis
   - osteoporosis & myelopathy, associated with ***atlanto-axial subluxation***

## Systemic Onset Juvenile Chronic Arthritis Still's Disease

- occurs in 20% of children with juvenile chronic arthritis
- lymphadenopathy, hepatosplenomegaly, pleurisy, pericarditis, macular rash & high fever
- myalgias, arthralgias and eventually polyarthritis, weight loss and growth retardation
- high ESR, anaemia of chronic disease, PMN leukocytosis, RF and ANF (-)'ve
- remission usually occurs within 6 months, 25% develop severe chronic polyarthritis

## Systemic Lupus Erythematosus

***Def'n:*** multisystem CT disorder of unknown aetiology, characterised by,

i. multiple ***autoantibodies***
ii. circulating ***immune complexes***, and
iii. widespread immunologically mediated tissue destruction

- incidence ~ 10-15:100,000, with 90% being ***female***, usually of childbearing years
- overall survival over 10 years ~ 70%

### ***Antibodies***

| | | | |
|---|---|---|---|
| 1. | antinuclear | ~ 95% | - multiple nuclear & cytoplasmic Ag's |
| 2. | anti-DNA | ~ 70% | |
| 3. | antihistone | ~ 70% | - ↑ % in drug induced SLE |
| 4. | ***anticardiolipin*** | ~ 50% | - phospholipid Ag |
| | • ↑ risk of | | - arterial & venous thrombosis<br>- spontaneous abortion<br>- thrombocytopaenia & lupus anticoagulant (↑ APTT)<br>- false (+)'ve VDRL |
| 5. | antierythrocyte | ~ 60% | - small % develop haemolysis |
| 6. | antiplatelet | | |
| 7. | antilymphocyte | ~ 70% | - leukopenia & ↓ T-cell function |
| 8. | antineuronal | ~ 60% | - CNS lupus |

### ***Aetiology***

***NB:*** multifactorial → genetic, envorinmental, and sex hormonal

1. ***polyclonal B-cell*** hyperactivity
2. disordered immunoregulation
   - ↓ T-cell supressor function
   - ↑ idiotype / anti-idiotype Ab production
3. delayed clearance of circulating immune complexes
4. ↑ HLA-DR2 & DR3
5. suspected, but not proven ***viral activation***
6. phospholipid from enteric bacterial cell walls acts as polyclonal B-cell activator

- ***Clinical Features***

1. ***systemic***
   - fatigue, malaise, fever
   - anorexia, nausea, weight loss
2. ***cutaneous***
   - malar "butterfly" rash - exacerbated by UV light
   - discoid rash
   - photosensitivity
   - other rashes - diffuse maculopapular rash
     - urticarial, bullous
   - alopecia - regrows except in discoid lupus
   - vasculitic skin lesions - subcutaneous nodules
     - ulceration (usually on the legs)
     - pupura
   - mucous membrane lesions - small painless ulcers
3. ***musculoskeletal***
   - arthralgias & myalgias
   - seronegative polyarthritis
   - hand deformity & errosions - rare ± subcutaneous nodules
   - myopathy / myositis - inflammatory or 2° to therapy
   - ischaemic necrosis of bone - hip, knee & shoulder pain
4. ***renal***
   - ***all*** have Ig-$C_3$ deposits in glomeruli
   - nephritis - persistent proteinuria > 500 mg/d
   - nephrotic syndrome
   - cylinduria, proteinuria and haematirua
   - most with mesangial or mild focal GN ***do not*** progress to CRF
   - in those with more active disease, CRF is a major cause of death
   - these tend ***not*** to respond to immunosupression & require dialysis & transplantation
5. ***nervous system***
   - any section may be involved - spinal cord, peripheral nerves
     - cortex, meninges
   - headache, depression & anxiety
   - organic brain syndrome - phychosis
     - seizures (grand mal, petit mal, or focal)
   - hypothalamic dysfunction, SIADH, pseudotumour cerebri
   - focal infarction, extrapyramidal or cerebellar dysfunction
   - optic neuritis, cranial nerve palsies
   - transverse myelitis - paraplegia, quadriplegia
   - mononeuritis multiplex

6. ***haematological***
   - anaemia of chronic disease ± haemolytic anaemia
   - leukopaenia, lymphopaenia
   - splenomegaly, lymphadenopathy
   - thrombocytopaenia
   - ***circulating anticoagulant*** - phospholipid of prothrombin activator complex
     → ↑ APTT & 3 clinical sequelae,

   i. venous or arterial ***thromboses***

   ii. ***haemorrhagic*** sequelae - especially if ↓ platelets or ↓ prothrombin
   - Ab's to factors VIII, IX

   iii. benign laboratory minifestation

7. ***cardiopulmonary***
   - pericarditis ± effusion
   - myocarditis
   - endocarditis - Libman-Sachs
   - pleurisy ± effusions
   - lupus pneumonitis
   - interstitial fibrosis
   - pulmonary hypertension
   - ARDS, pulmonary haemorrhage

8. ***gastrointestinal***
   - nonspecific - anorexia, N&V, mild pain, diarrhoea
   - vasculitis - bleeding, vascular thrombosis, or perforation
   - ascites
   - abnormal liver function

9. ***ocular***
   - retinal vasculitis
   - conjunctivitis, episcleritis
   - sicca syndrome

10. ***obstetric***
    - normal fertility
    - ***recurrent abortion*** ~ 30-50%
    - ↑↑ disease activity - 1st trimester & postpartum

- ***Drug-Induced Lupus***

1. ***procainamide*** ~ 50-75% → ANA-Ab, 20% LE
2. ***hydrallazine*** ~ 25-30% → ANA-Ab, 10% LE
3. others → methyldopa, chlorpromazine, d-penicillamine, OCP, isoniazid, ethosuximide, practolol

## Marfan's Syndrome

***Def'n:*** defined upon the basis of characteristic changes in three connective tissue systems,

i. skeleton
ii. eyes
iii. cardiovascular system

1. autosomal dominant - variable expression
   ~ 15-30% may be due to new mutations
   - the system abnormalities can be inherited independently in some families
2. ***skeletal changes***
   i. tall with long limbs
   ii. long slender fingers & toes - ***arachnodactyly***
   iii. overgrowth of the ribs - pes excavatum, pes carinatum, asymmetry
   iv. scoliosis / kyphosis
   v. hypermobility of joints - most are mild
      - rarely similar to Ehler's Danlos
      - very rarely stiff joint syndrome
3. ***cardiovascular changes***
   i. mitral valve prolapse
   ii. aortic dilatation - from aortic root & progressive
      - dissection & rupture are common
   iii. high risk during ***pregnancy*** - up to 50% mortality in some series
4. ***ocular***
   i. subluxation of the lens - ***ectopia lentis***, usually upward
   ii. glaucoma - usually 2° lens dislocation or surgery
   iii. increased axial globe length - ***myopia***
      - retinal detachment