# Section 1: Physiology

## A. Cellular

## B. Respiratory
1. Anatomy
2. Control
3. Mechanics
4. Ventilation
5. Diffusion
6. V/Q matching
7. Gas transport
8. Circulation
9. Tests
10. Applied physiology

## C. Cardiovascular
1. Structure and function
2. Electrical properties
3. Cardiac output
4. Peripheral vasculature
5. Control
6. Regional circulations
7. Applied physiology
8. Measurement

## D. Renal

## E. Fluids and Electrolytes

## F. Acid-Base

## G. Nervous system

## H. Muscle

## I. Liver

## J. Haematology

## K. Nutrition & Metabolism

## L. Thermoregulation

## M. Immunology

## N. Endocrine

## O. Maternal

## P. Fetal & Neonatal

## Q. Gastrointestinal

## R. Physics and Measurement

# Section 2: Pharmacology

## A. General
1. Pharmacodynamics
2. Pharmacokinetics
3. Pharmacokinetics of inhalational agents
4. Variability in response
5. Pharmaceutics

## B. Specific
1. Sedatives
2. Opioids
3. Pain
4. NSAIDs
5. Intravenous anaesthetics
6. Inhalational anaesthetics
7. Relaxants
8. Anticholinesterases
9. Anticholinergics
10. Local anaesthetics
11. Autonomic nervous system
12. Adrenoceptor blockers
13. Antihypertensives
14. Antidysrhythmics
15. Antiemetics
16. Histamine & serotonin
17. Diuretics
18. Coagulation
19. Obstetrics
20. Endocrine
21. Gastrointestinal
22. Intravenous fluids
23. Poisoning & Antimicrobials
24. New developments
25. Psychotropics

## C. Statistics
Section 3: Practice of Anaesthesia

A. Anaesthesia
   1. Assessment
   2. Drug reactions
   3. Fluids
   4. Complications
   5. Inherited Conditions
   6. Pain
   7. Miscellaneous

B. Equipment
   1. Measurement
   2. Monitoring
   3. Physics
   4. Vaporizers & gas delivery
   5. Miscellaneous

C. Medicine
   1. Cardiology
   2. Endocrinology
   3. Gastroenterology
   4. Haematology
   5. Metabolic
   6. Neurology
   7. Respiratory
   8. Oncology
   9. Renal
   10. Miscellaneous

D. Surgery
   1. Cardiac
   2. Vascular
   3. Neurosurgery
   4. Orthopaedics
   5. Urology
   6. ENT
   7. Thoracic
   8. Upper GI
   9. General
   10. Miscellaneous

E. Obstetrics & Gynaecology
   1. Labour and delivery
   2. Gynaecology

F. Paediatrics

G. Anatomy
   1. Thorax
   2. Abdomen and pelvis
   3. Lower Limb
   4. Back
   5. Upper Limb
   6. Head
   7. Neck
   8. Miscellaneous

H. Regional

I. Intensive Care

J. Trauma and Resuscitation
   1. General principles
   2. Burns
   3. Other injuries
   4. Remote anaesthesia

K. Principles
   1. Statistics
   2. Ethics
   3. Economics
   4. Policies
About these notes

These notes are my study notes from preparing to sit the ANZCA Primary exam in 1997 and the ANZCA Fellowship exam in 2000. A few people wanted a copy of my notes in early 1998, so I made some photocopies. I have been asked if I mind them being copied or distributed; I don't mind as long as they aren't modified and are correctly attributed as my work. Of course they're not exclusively my own work, they have been prepared from the standard texts and from notes from people I have studied with. All the graphs and diagrams I have redrawn myself.

The quality is pretty variable and some topics are not covered in the detail required for the exams. This is because I find the process of making notes far more useful than having them. Early on I started writing prose paragraphs, but most of the material is in outline format.

There's probably not much point in trying to give advice about studying for these exams; depending on how your assessments at school were performed, the Primary exam is between the 15th and 30th set of exams you will sit so you probably have a fair idea of how to study. The significant difference is that for many registrars it is the first time they will fail an exam.

So how did I study? I started reading the parts of the texts I found interesting about 18 months before I sat the Primary. I was working as a psychiatric resident so I had plenty of time. I prepared notes on a few of the less important topics to get warmed up before tackling the major physiology topics (respiratory and cardiovascular) in detail. I was part of a study group of five from about eight months before the exam. We met once a week for four or five hours. We started by choosing major topics from the red book, splitting up the objectives on that topic between us and each preparing notes to present and share at the weekly session. Later we started going through an old written paper, sharing out the questions between us and each preparing a marking scheme or “model answer” to our questions so that if we did the other questions as timed exam practice we got a marking scheme to assess our answers with. The last couple of sessions we did previous exams strictly to time.

Study for the Fellowship was similar except that we had to go through the MCQ bank as well. We went through it twice, the second time focusing on the new questions from the previous exam and also the marker questions. The syllabus wasn't as clearly defined as for the Primary, so the notes are correspondingly somewhat haphazard in their coverage.

Can you have the notes in electronic format? The answer is yes and no. They are all ClarisWorks/AppleWorks files on my Mac but they don't export well as Word or HTML (or anything else except EPS) without a lot of tweaking. If I get around to making them into PDFs then I'll let you have a copy.

James.
jam@netspace.net.au

April 2000.
Texts used

Primary

Pharmacology
- Wood & Wood
- Stoelting: Pharmacology and Physiology in Anaesthetic Practice
- Katzung: Pharmacology
- Rang, Dale & Ritter: Pharmacology
- Cass: Pharmacology for Anaesthetists

Statistics
- Miller: Anaesthesia

Physiology
- Guyton: Textbook of Medical Physiology
- Ganong: Physiology
- Despopoulos: Color Atlas of Physiology
- Berne & Levy: Cardiovascular Physiology
- Vander: Renal Physiology
- West: Respiratory Physiology
- Nunn: Applied Respiratory Physiology
- Brandis: The Physiology Viva

Physics & Measurement
- Davis, Parbrook & Kenny: Basic Physics and Measurement in Anaesthesia
- Miller: Anaesthesia

Fellowship

Practice of anaesthesia
- Miller: Anaesthesia
- Clinical Anaesthesia Procedures of the Mass. General
- Brown: Regional Anaesthesia
- Cousins & Bridenbaugh: Neural Blockade
- Shnider & Levinson: Anaesthesia for Obstetrics
- Lippincott-Raven Interactive Anaesthesia Library on CD-ROM
- ATLS Handbook
- ANZCA Policy Documents
- Australian Anaesthesia Biennial

Anatomy
- Black & Chambers: Essential Anatomy for Anaesthesia

Equipment
- Rosewarne: Anaesthetic Equipment
- Russell: Equipment for Anaesthesia and Intensive Care

Supplemental (used for occasional reference)
- Oh: Intensive Care Manual
- Stryer: Biochemistry
- Harrison’s Principles of Internal Medicine
- Souhami & Moxham: Medicine
- Gray’s Anatomy
- RCPA Manual of Pathology Tests
- MIMS Annual
- NHMRC and AHA websites
- The main anaesthetic journals
- Lots of other books left over from undergraduate medicine
A. Cellular Physiology

a. Describe the cell membrane and its properties.

b. Describe the functions of mitochondria, endoplasmic reticulum and other organelles.

Plasma membrane semipermeable lipid bilayer 7.5 nm thick
phospholipids, cholesterol
proteins
structural
pumps active ion/molecule transport
channels
receptors
clathrins cluster to endocytose bound ligands
insulin & other peptides, lipoproteins, viruses
enzymes
intercellular connections
tight junctions
desmosomes
belt with bands of filaments containing actin
spot central stratum of filaments
hemi- epithelial cell to connective tissue
gap junctions
connexons allow molecules up to 800 d to pass
rise in Ca$^{2+}$ closes

Cytoplasm

Golgi complex
vesicles $\rightarrow$ secretory granules
Endoplasmic reticulum (rough and smooth)
RNA $\rightarrow$ protein transcription in ribosomes
glycosylation of proteins
formation of vesicles and lysosomes
Lipid droplets
Lysosomes
merge with (auto-)phagocytic vacuoles and release
ribonuclease, deoxy--, phosphatase, glycosidases, arylsulfatases, collagenase, cathespins
release of enzymes into the cell causes damage in vit A toxicity, ?gout
enzyme defects cause lysosomal storage disorders

Mitochondria
separate DNA (female lineage)
outer and inner membrane with cristae
operate the citric acid cycle “cellular respiration” $\rightarrow$ ATP

Secretory granules
Centrioles
2 cylinders and right angles near nucleus
made of 9x3 microtubules
form the mitotic spindle in cell division

Microfilaments
long fibres of actin 4-6 nm diameter operate microvilli and attach to belt desmosomes

Microtubules
25 nm diameter tubules made of $\alpha$ and $\beta$ tubulin (5 nm thick)
maintain cell shape, constantly form and disassemble

Cilia
contain 9x2 +2 microtubules and basal granule of 9x3 microtubules

Nucleus
Chromosomes
2x22 + sex chromosomes
composed of DNA (2.5x10^9 base pairs), histones
contain genes, promoters, enhancers, junk
Nucleolus
site of RNA synthesis by transcription
Envelope with perinuclear cisterns
very permeable to allow RNA out

c. Explain mechanisms of transport of substances across cell membranes.
Diffusion
rate determined by (Fick’s Law)
chemical gradient
electrical gradient
cross-sectional area of boundary
thickness of boundary
Donnan Effect
non-diffusible ions affect diffusion of other ions.
ratio of diffusable cations between compartments equals inverse ratio of
diffusible anions.
Solvent drag
unimportant effect. Solvent bulk flow carries solute.
Filtration
rate determined by
pressure gradient
surface area of boundary
permeability of boundary
Osmosis
solvent molecules cross a membrane to a region of higher activity of a non-diffusible
solute.
P=nRT/V
Carrier-mediated transport
facilitated diffusion
transport usually of large, non-ionized molecules down a
concentration/electrical gradient across the cell membrane via membrane
proteins. e.g. glucose uptake
active transport
transport of molecules or ions against of concentration or
electrical gradient, usually mediated by ATPase proteins in
the cell membrane e.g. Na^+-K^+ ATPase, Ca^{2+} ATPase, H^+-K^+ ATPase
3Na^+
transports 3 Na^+ out of and 2 K^+ into cells
inhibited by cardiac glycosides
composed of 2 α (95 kd binds ATP and digoxin) and 2 β
(40 kd glycoprotein) subunits.
Na^+ binding is associated with phosphorylation
generates a membrane potential
rate-limited by intracellular Na^+
responsible for most of BMR
symport
transport coupled to an electrical or chemical gradient
e.g. Na^+-glucose exchange in mucosal cells, Ca^{2+}-Na^+ exchange in cardiac muscle
Transport of large molecules

Cellular metabolism
1.A.2
James Mitchell (November 5, 2001)
proteins and hormones are commonly transported by exo- or endo-cytosis

d. Explain the Gibbs-Donnan Effect.

e. Outline the role of cellular receptors and the function of secondary messengers within the cell.

f. Outline the sources of energy available to cells through metabolic processes.

Sources of energy

High energy phosphate compounds: ATP, phosphorylcreatine, GTP, CTP, UTP, ITP
Thioesters of Coenzyme-A: acetyl-CoA (≡ 1 ATP)
Reduced coenzymes: NADH, NADPH (≡ 3 ATP) via flavoprotein-cytochrome system
H₂ donor, NAD⁺, FAD, Co Q, Cyt B, Cyt c₁, Cyt c, Cyt a, Cyt a₃, O₂.

Carbohydrates

Dietary sugars → di- and mono-saccharides in gut → circulating glucose, fructose and galactose (→ glucose) → intracellular glucose ↔ glucose 6-PO₄ (- ATP)
Embden-Meyerhof pathway
glycogen ↔ n glucose 1-PO₄ ↔ glucose 6-PO₄ ↔ fructose 6-PO₄ ↔ fructose 1,6 diPO₄ (-ATP) ↔ dihydroxyacetone PO₄ (↔ glycerol) + phosphoglyceraldehyde → → pyruvate (+ 2 ATP, 1 NADH)
Hexose-monophosphate shunt
glucose 6-PO₄ ↔ 6-phosphogluconic acid → pentoses → fructose 6-PO₄ or phosphoglyceraldehyde
Tricarboxylic acid cycle
pyruvate + CoA → acetyl-CoA (+ 2H + CO₂) ... + oxaloacetic acid → citric acid → → oxaloacetic acid + 8H + 2CO₂
net yield = 10H → 5NADH → 15ATP
Aerobic glycolysis proceeds via the Embden-Meyerhof pathway and TCAC for 38 ATP per glucose molecule.
Anaerobic metabolism relies on the Embden-Meyerhof pathway only, yielding 4 ATP per glucose molecule less one for the phosphorylation of fructose 6-PO₄ and one more if glucose 6-PO₄ is generated from circulating glucose. The generation of NAD⁺ required is via the conversion of pyruvic acid to lactic acid, generating an “oxygen debt”.
Control of glucose metabolism is regulated by
β adrenergic receptors which promote glycolysis via cAMP, protein kinase, phosphorylase kinase and phosphorylase a as well as inhibition of glycogen synthase when it is phosphorylated. This causes a rise in blood glucose and lactate largely arising from glycolysis in liver and muscle respectively.
α adrenergic receptors which activate phosphorylase kinase via intracellular Ca²⁺.
Glucagon which stimulates phosphorylase in liver only, causing a rise in blood glucose without lactate.
Insulin

g. Explain the ways in which cells use energy for the various cellular processes.

h. Describe the composition of intracellular fluid and its regulation including the role of the sodium-potassium pump.

ECF (20%) ≈ estuarine water
Interstitial fluid (15%)

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<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Na⁺</td>
<td>143 mEq/l</td>
</tr>
<tr>
<td>K⁺</td>
<td>4 mEq/l</td>
</tr>
<tr>
<td>Ca²⁺</td>
<td>5 mEq/l</td>
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<tr>
<td>Cl⁻</td>
<td>117 mEq/l</td>
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<tr>
<td>HCO₃⁻</td>
<td>27 mEq/l</td>
</tr>
<tr>
<td>HPO₄²⁻</td>
<td>2 mEq/l</td>
</tr>
</tbody>
</table>

Cellular metabolism 1.A.3 James Mitchell (November 5, 2001)
Mg$^{2+}$ 3  SO$_4^{2-}$ 1  
  org acid  6  
  protein  2  

plus H$_2$CO$_3$ and non-electolytes

Plasma (5%)  
Na$^+$  152 mEq/l  Cl$^-$  113 mEq/l  
K$^+$  5  HCO$_3^-$  27  
Ca$^{2+}$  5  HPO$_4^{2-}$  2  
Mg$^{2+}$  3  SO$_4^{2-}$  1  
  org acid  6  
  protein  16  

plus H$_2$CO$_3$ and non-electolytes

Transcellular fluid (small)  
CSF, aqueous humor, GIT contents etc.

ICF (40%)  
Very rough concentrations:  
Na$^+$  14 mEq/l  PO$_4^{2-}$  113 mEq/l  
K$^+$  157  HCO$_3^-$  10  
Mg$^{2+}$  26  protein  74  
plus H$_2$CO$_3$ and non-electolytes

i. Describe the role of G-proteins.

j. Describe the general response to injury.
B. 1 Anatomy of the respiratory system.

**a. Relate function of the upper airway and larynx to their structure.**

The larynx connects the pharynx above with the trachea below and lies opposite C3-6. It is composed of cartilages connected by ligaments and membranes and is lined with mucosa. The walls of the larynx are formed from the thyroid and cricoid cartilages.

The thyroid cartilage is composed of two laminae, joined anteriorly at an angle and ending posteriorly in the superior and inferior cornua.Externally, the laminae are attached to sternothyroid, thyrohyoid and the inferior constrictor of the pharynx. Superiorly they attach to the thyrohyoid membrane and inferiorly to the cricothyroid membrane. The superior cornu attaches to the lateral thyrohyoid ligament and the inferior cornu articulates with the cricoid cartilage. Internally, the laminae attach to the thyroepiglottic ligament medially and more laterally to the vestibular and vocal ligaments and the thyroarytenoid, thyroepiglottic and vocal muscles.

The cricoid cartilage is a continuous ring, much wider posteriorly, which forms the inferior part of the larynx. The posterior lamina attaches to the tendon of the oesophagus in the midline and more laterally the cricoarytenoid. Superolaterally, the lamina articulates with the arytenoid cartilages and inferiorly the cricoid attaches to the trachea.

The arytenoid cartilages are approximately tetrahedral and articulate with the superolateral corner of the cricoid lamina. Posteriorly they attach to the transverse arytenoid which connects them, anteriorly they have a vocal process which attaches to the vocal ligament, posterolaterally the muscular process attaches to posterior and lateral cricoarytenoids. The medial surface forms part of the rima glottidis and the anterolateral part attaches to the vestibular ligament.

The corniculate cartilages sit at the superior tips of the arytenoids, in the aryepiglottic folds. The cuneiform cartilages are in the aryepiglottic folds anterosuperior to the arytenoids. The epiglottis is a fibrocartilage leaf attached inferiorly to the thyroid cartilage, laterally to the aryepiglottic folds and anteriorly to the glossoepiglottic folds which form the vallecula.

The arytenoids can rotate medially and laterally and at the same time slide a small distance medially or laterally to separate or appose the posterior parts of the vocal ligament. The cricoid cartilage can rotate in the sagittal plane to increase or decrease the anteroposterior diameter of the rima glottidis.

The posterior cricoarytenoids rotate and slide the arytenoids laterally, opening the glottis. The lateral cricoarytenoids rotate the arytenoids medially and close the glottis. The transverse arytenoid approximates the arytenoids, bringing the posterior ends of the vocal folds together. The cricothyroids tilt the cricoid, lifting the anterior part and increasing tension on the vocal folds. The thyroarytenoids draw the arytenoids anteriorly, slackening the vocal folds. The oblique arytenoids and aryepiglottici act to close the inlet of the larynx by bringing the aryepiglottic folds together. All of the intrinsic muscles of the larynx are supplied by the recurrent laryngeal nerves except for cricothyroid which is supplied by the external branch of the superior laryngeal nerve.

Below the cricoid cartilage, the trachea extends to the level of T5 where it bifurcates into the right and left main bronchi. These divide further into segmental bronchi:

<table>
<thead>
<tr>
<th>Left</th>
<th>Right</th>
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<tbody>
<tr>
<td>upper</td>
<td>upper</td>
</tr>
<tr>
<td>apical</td>
<td>apical</td>
</tr>
<tr>
<td>posterior</td>
<td>anterior</td>
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<tr>
<td>anterior</td>
<td>posterior</td>
</tr>
<tr>
<td>inferior</td>
<td>(medial)</td>
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<tr>
<td>superior</td>
<td>lateral</td>
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<tr>
<td>lower</td>
<td>lower</td>
</tr>
<tr>
<td>medial</td>
<td>medial</td>
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<td>anterior</td>
<td>anterior</td>
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<td>posterior</td>
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<tr>
<td>medial</td>
<td>medial</td>
</tr>
<tr>
<td>lateral</td>
<td>lateral</td>
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</tbody>
</table>

Also in head anatomy (3.G.6)

**b. Explain the structure of the chest wall and diaphragm and relate these to**

Respiratory anatomy 1.B.1.1 James Mitchell (November 5, 2001)
respiratory mechanics.

In Respiratory Mechanics (1.B.3)
B. 2 Control of Respiration

a. Describe the medullary and pontine respiratory control centres and explain how the ventilatory pattern is generated and controlled.

There are three main groups of neurones involved in control of respiration, each present bilaterally. In the medulla there is a dorsal respiratory group, mostly in the nucleus of the tractus solitarius, which receives sensory input from the vagus and glossopharyngeal nerves. In the ventrolateral part of the medulla is the ventral respiratory group in the nucleus ambiguus and nucleus retroambiguus. In the superior pons lies the pneumotaxic centre in the nucleus parabrachialis and in the lower pons, the apneustic centre.

Inspiration is initiated rhythmically by the dorsal respiratory group, generating periodic bursts of action potentials. This results in an “inspiratory ramp” signal of two seconds of increasing signals to the primary inspiratory muscles. This then ceases for three seconds before the cycle repeats. There are two parameters which vary in the inspiratory ramp signal: its rate of increase, controlling the depth of inspiration and its duration, controlling frequency. Output from the pneumotaxic centre limits the duration of the inspiratory ramp.

When rapid and deep respiration is required, output from the dorsal respiratory group recruits neurones in the ventral respiratory group which generate activity in secondary muscle of respiration, allowing for forceful inspiration and expiration.

The apneustic centre in the lower pons acts to prolong the duration of the inspiratory ramp signal. In the absence of the pneumotaxic centre, it results in sustained inspiration.

Regulation of respiration from breath to breath is maintained by projections of the vagus nerve from stretch receptors in the bronchi and bronchioles which result in ending of the inspiratory ramp signal at tidal volumes over 1.5 l, ending inspiration. This results in the Hering-Breuer inflation reflex.

b. Describe the chemical control of breathing via central and peripheral chemoreceptors, and indicate how this is altered in abnormal clinical states.

Respiration is responsive to blood PO₂ and PCO₂. In normal states, PCO₂ plays the major role as it is far more dependent on ventilation. CO₂ diffuses readily across the blood-brain barrier, altering brain and CSF pH in accordance with the Henderson-Hasselbalch equation:

\[
\text{pH} = 6.1 + \log \frac{[\text{HCO}_3^-]}{0.03 \text{ PCO}_2}
\]

In the ventral medulla there is a chemosensitive area of neurones which are highly sensitive to H⁺ ion concentration in both the interstitial fluid of the brain and particularly the CSF (which is not well-buffered). Stimulation of the chemosensitive area results in stimulation of the inspiratory (dorsal) group, resulting in increased rate of increase of the inspiratory ramp signal and decreased duration, greatly increasing alveolar ventilation (by a factor of 10 over the range of PCO₂ from 40 to 80 mmHg).

The effect on alveolar ventilation of a change in PCO₂, is of limited duration. Renal compensation for a respiratory acidosis increases [HCO₃⁻] and normalizes pH over a few days, eliminating most of the effect of a rise in PCO₂.

PO₂ plays a role in the control of respiration only in unusual circumstances. Chemoreceptors in the carotid and aortic bodies are directly sensitive to PO₂, producing a strong response as PO₂ falls below 60 mmHg. They are also sensitive to PCO₂ and pH, but this effect is less than that of the central chemoreceptors. The output of the chemoreceptors in the aortic arch is conducted to the medulla via the vagus nerves and that from the carotid bodies via the glossopharyngeal nerves.

Stimulus from the chemoreceptors results in increased alveolar ventilation via action on the dorsal respiratory group. If gas exchange is normal, the increase in ventilation is considerably damped by the effect of a fall in PCO₂, however if PCO₂ does not fall or pH is...
normalized by renal compensation over a few days, the increase in ventilation is sustained.

c. Describe the reflex control of respiration.

The Hering-Breuer reflex is initiated by pulmonary stretch receptors in the airway smooth muscle. The afferent limb is the vagus nerve. The response is via the medulla, inhibiting inspiratory muscle activity. This reflex is not active in adult humans at rest, but may play a role when tidal volume exceeds 1 litre.

Irritant receptors, or rapidly adapting receptors, are present in the airway epithelium and respond to noxious stimuli such as smoke or dust or cold air. They are innervated by the vagus nerve and result in bronchoconstriction and hyperpnoea.

Juxtacapillary ("J") receptors lie in the alveolar walls close to pulmonary capillaries. They respond to chemicals injected into the pulmonary circulation and conduct impulses via non-myelinated fibres in the vagus to the medulla. Stimulation results in rapid shallow breaths or apnoea. They may play a role in the perception of dyspnoea.

The cough reflex is initiated in response to physical or chemical irritation of receptors in the upper airway, particularly the larynx or carina. The afferent limb is the vagus nerve which projects to the medulla. The reflex is a series of responses of the respiratory centres: inspiration to about half VC, closure of the epiglottis and vocal cords, contraction of the muscles assisting expiration (including rectus abdominis and internal intercostals) to raise intrathoracic pressure to about 100 mmHg and sudden opening of the cords and epiglottis to expel air rapidly through airways partly collapsed by the high intrathoracic pressure. This helps to remove any foreign matter in the airways.

The sneeze reflex is similar except that the afferent limb is the trigeminal nerve from the nasal mucosa and during forceful expiration, the uvula is depressed allowing air to leave through the nose, and the eyes are closed.

In regulation of breathing, the same proprioceptive reflexes operate as in other parts of the body: muscle spindles, Golgi tendon organs and joint receptors.

Breathing control is also affected by responses to stimuli outside the respiratory tract. Pain or sudden cold may result in apnoea followed by hyperventilation. Stimulation of the aortic and carotid body baroreceptors by an increase in blood pressure results in hypoventilation.

d. Describe the ventilatory response to exercise.

With exercise, alveolar ventilation can rise from 5 l/min to over 120 l/min and O₂ use from 0.2 l/min to 4 l/min. These changes parallel the rise in metabolism, maintaining pH, PO₂ and PCO₂ at normal values. The increase in alveolar ventilation starts immediately on starting exercise, resulting from central and possible proprioceptive stimuli rather than following a rise in PCO₂. Thus the initial change in PCO₂ is a fall, followed by a rise back to normal as increased CO₂ production matches the increased alveolar ventilation. The normal ventilatory response to a change in PCO₂ is superimposed on the response to exercise.

The rise in ventilation on starting exercise is partly a learned response.

e. Explain the consequences of altitude on respiratory function.

Barometric pressure falls with altitude from 760 mmHg at sea level to 349 mmHg at 20000 feet. Inspired PO₂ falls proportionally from 159 to 73 mmHg. Alveolar water vapour pressure remains the same at 47 mmHg and P₅CO₂ remains in the same relationship to P₅CO₂, further reducing P₅O₂. At 20000 feet, a person not acclimatized to the altitude will hyperventilate on hypoxic drive to a P₅CO₂ of about 24 mmHg, yielding a P₅O₂ of 40 mmHg, not compatible with normal function.

The respiratory rate at altitude rises because of hypoxic drive. The acute rise is limited by inhibition from a fall in P₅CO₂ and rise in CSF pH. As the pH is normalized over a few days, respiratory rate rises further and P₅CO₂ falls, allowing for a higher P₅O₂ and optimal gas exchange. Levels of 2,3-DPG rise with hypoxia, moving the oxygen-haemoglobin
dissociation curve to the right. This opposes the left shift due to alkalaemia and reduced \( P_{CO_2} \). Over a longer period, haematocrit rises (up to 200 g/l), blood volume increases, tissue vascularity increases and cellular oxygen usage improves, providing further compensation for hypoxia.

Acute complications of high altitude are: hypoxia with accompanying cerebral dysfunction, acute cerebral oedema due to vasodilatation resulting from hypoxia and acute pulmonary oedema of uncertain mechanism.

Long term complications are termed Chronic Mountain Sickness: a rise in haematocrit and pulmonary vasoconstriction leads to pulmonary hypertension and falling blood flow and oxygen transport as well as shunting through non-alveolar pulmonary vessels. High pulmonary pressure and poor oxygenation results in right heart failure with secondary biventricular failure. Treatment is by oxygen supplementation, generally by moving to a lower altitude.

In an acclimatized person at 20000 feet, \( PACO_2 \) falls to 10 mmHg and \( PAO_2 \) rises to 53 mmHg, allowing for an oxygen saturation of 85%.

f. Explain the consequences of pregnancy on respiratory control.

in Maternal Physiology (1.O)

g. Describe and explain the effects of anaesthesia on respiratory control.

Anaesthesia affects the \( CO_2 \) response curve by flattening the curve and raising the \( PCO_2 \) which will be tolerated in apnoea. In an individual patient, ventilation falls as the level of inhalational agent rises, coming to equilibrium at a higher \( PCO_2 \) and lower minute volume. Apnoea cannot be sustained on spontaneous ventilation of inhalational agent alone.

Induction and preinduction agents, especially narcotics, flatten the \( CO_2 \) response further, surgical stimulus antagonizes it. The inhalational agents all display similar degrees of respiratory depression for a given depth of anaesthesia, but diethyl ether produces less depression up to 2.5 MAC.

The hypoxic ventilatory response is extremely sensitive to inhalational agents, being markedly blunted at 0.1 MAC, and abolished at 1.1 MAC. This is thought to be through action at the carotid body chemoreceptors. This effect necessitates continuous \( SaO_2 \) monitoring in anaesthesia and is particularly dangerous for patients reliant on hypoxic drive: those with severe COAD.

The ventilatory response to metabolic acidosis is reduced as much as that to hypoxia.

Breathing reflexes remain intact in spontaneously ventilated anaesthesia. Increased force of inspiration in the face of resistance is a muscle spindle reflex which is unchanged. Increasing resting volume in response to expiratory obstruction is also preserved. The Hering-Breuer response remains unimportant under anaesthesia.

The mechanics of breathing are affected by anaesthesia. Movement from the intercostals is reduced far more than diaphragmatic movement, producing “abdominal breathing”. The resting position of the diaphragm is higher in the thorax than when awake, reducing FRC. These are partially compensated for by a movement of blood from thorax to abdomen in the supine position in anaesthesia, but FRC remains reduced by about 450 ml. Paralysis does not alter FRC further.

Whether the reduction in FRC is accompanied by a fall in closing volume is uncertain. Airway calibre is reduced at lower FRC, but the increase in resistance which is expected from this is offset by the bronchodilator effect of inhalational agents. The anaesthetic circuit introduces additional resistance to breathing, particularly with small ET tubes, resistance varying inversely with greater than the fourth power of radius for turbulent flow. Without assistance, upper airway resistance is frequently very high due to obstruction by the tongue.

Compliance is reduced almost immediately upon induction of anaesthesia. The cause of this is uncertain, but the change is in pulmonary compliance, not in the chest wall. It may be due to interference with the activity of surfactant or pulmonary collapse due to the
reduction in FRC.

Metabolic rate is reduced a little by anaesthesia, particularly cerebral and cardiac oxygen consumption.

Gas exchange is impaired in anaesthesia because of the fall in minute volume in spontaneous ventilation, and because of the increase in V/Q scatter which is an unavoidable consequence of anaesthesia. The increased V/Q scatter is manifest in calculations of physiological dead space and shunt.

There is little rise in physiological dead space in spontaneous ventilation, but with paralysis, physiological dead space increases measurably. The increase occurs in alveolar dead space, anatomical dead space remaining unchanged. Alveolar ventilation is normally well-maintained as minute ventilation is increased to keep PCO₂ stable. The mechanism for the increase in dead space is thought to be maldistribution of ventilation.

Physiological shunt increases with anaesthesia from about 1-2% in healthy individuals to about 10%. This results in a substantial increase in A-a gradient. This effect is most marked in older patients and less in young adults. The cause of the increase in shunt may be impairment of the hypoxic vasoconstrictor response as well as maldistribution of ventilation or localized pulmonary collapse. The last possibility seems unlikely given the lack of benefit from PEEP in anaesthesia. PEEP may have some effect in improving ventilation, but it also reduces cardiac output, negating any improvement in oxygen flux.
B. 3 Mechanics of breathing

a. Describe the inspiratory and expiratory process involving the chest wall, diaphragm, pleura and lung parenchyma.

Inspiration

In quiet respiration, inspiration is caused by contraction of the diaphragm, innervated by the phrenic nerve from cervical segments 3-5. The dome of the diaphragm moves about 1cm caudally, increasing the volume of the chest cavity and moving the abdominal contents down. This lowers intrathoracic pressure which is transmitted through the pleural space to the lungs, expanding the lungs and causing a pressure gradient between the mouth and small airways, resulting in gas flow into the lungs.

In rapid respiration other muscles have a role in increasing the rate of gas flow into the lung. The diaphragm contracts forcefully, moving as much as 10 cm, the external intercostals lift the ribs, increasing the lateral and anteroposterior dimensions of the chest and the scalenes and sternocleidomastoid lift the first two ribs and sternum.

Expiration

Expiration is normally a passive process, relying on the elasticity of the lung parenchyma and chest wall to return the lung to its resting volume (functional residual capacity). In active expiration, the rectus abdominis, internal and external obliques and transversus contract to increase intraabdominal pressure and force the diaphragm up. The internal intercostals bring the ribs together and stiffen the intercostal spaces. These effects markedly increase intrathoracic pressure resulting in more rapid exhalation (up to a limit imposed by airway collapse).

b. Define compliance (static and dynamic) and relate this to the elastic properties of the lung.

Compliance is defined as volume change per unit pressure change. This is the reciprocal of elastance. The isolated human lungs have a compliance of about 200 ml/cmH₂O in the normal pressure range of –2 to –10 cmH₂O. The lungs and chest wall as a unit have a compliance of 100 ml/cmH₂O. At higher pressures (and volumes), compliance is reduced. Compliance is less on the inspiratory than the expiratory phase of respiration. This phenomenon is called hysteresis.

Static compliance is determined at zero flow and is usually quoted as the expiratory compliance over the litre above FRC. Dynamic compliance is determined over a range of respiratory frequencies as uneven time constants of adjacent alveoli in diseased lungs reduce compliance at high frequencies. Specific compliance equals compliance divided by FRC.

Compliance is a result of the elastic properties of the lung. This is partly a result of the arrangement of fibres of collagen and elastin in the alveoli and airways and substantially a result of the surface tension in the alveoli.

Surface tension in the alveoli is modified by surfactant secreted by type II pneumocytes. It displays non-linear properties, being much greater at high volumes than low volumes and thus produces hysteresis.

Specific compliance = static compliance / FRC (normal 0.05 /cmH₂O)

c. Explain the concept of time constants and relate these to “fast” and “slow”
Compliance equals change in volume per unit pressure. Resistance equals airway pressure per unit flow. The product of compliance and resistance is the “time constant” of a component of the lung; a measure of the rate of filling of that lung unit. A large time constant can result from airway obstruction or extreme distensibility of the unit. Areas of lung with a long time constant fill more slowly than the rest of the lung during inspiration and may still be filling (from the rest of the lung) when expiration has already begun. This is called “Pendelluft”.

Lungs with a wide range of time constants among their alveoli require slow respiration to be ventilated properly. As frequency of respiration increases, “slow” alveoli fill only partially before alveolar pressure rises high enough in expiration for them to start to empty again. This reduces the tidal volume and thus the apparent compliance of the lung as the frequency of respiration increases.

d. Describe the elastic properties of the chest wall and plot the pressure-volume relationships of the lung, chest wall and total respiratory system.

The chest wall is elastic. At resting volume, it pulls against the pleural space with a pressure of about -5 cmH₂O. This balances the elastic recoil of the lung, yielding a negative pleural pressure and zero pressure within the airways and outside the chest wall. Under normal circumstances the pleural space has a total volume of only a few ml. If it is opened, air is rapidly drawn in, the chest wall springs out and the lung collapses.

e. Describe the properties of surfactant and relate these to its role in determining respiratory mechanics.

Surfactant is secreted by type II pneumocytes. It lines the air-tissue interface of the alveoli and modifies the surface tension at the interface, preventing collapse and greatly increasing compliance. A major constituent of surfactant is dipalmitoyl phosphatidyl choline, synthesized from fatty acids. This is a long molecule with hydrophilic and hydrophobic ends.

When densely packed, DPPC molecules provide a strong repulsive force which opposes surface tension. As the surface area of an alveolus increases, the repulsion between DPPC molecules is reduced as they spread apart. At the same time, surface tension is less as it varies with the reciprocal of the radius of an alveolus.

The behaviour of surfactant is complex as it displays a greater effect as surface area is falling (during expiration) than rising. Normal detergents reduce surface tension but usually do so by a fixed amount regardless of area and do not display hysteresis.

The effect of surface tension is responsible for more than 80% of the work or inflating the lung, having a much greater effect at normal volumes than the tissue elasticity of the lung.
f. Explain the vertical gradient of pleural pressure and its significance.

In the erect position at resting volume, pleural pressure varies from –2.5 to –10 cmH₂O from base to top of the lung because of its weight. The resting volume of alveoli at the apex of the lung is much greater than at the base because of the more negative pleural pressure. However, the ventilation of the apex of the lung is proportionally less than the base during the respiratory cycle because the lung is more compliant at the lower volume and expanding pressure.

At low volumes, the pleural pressure at the base of the lung may become greater than atmospheric, resulting in airway closure and poor ventilation, while the apex benefits from a greater compliance and better ventilation. Transpulmonary pressure is defined as alveolar minus pleural pressure.

g. Explain the physics of gas flow and the significance of the relationship between resistance and pressure in the respiratory tract.

At low speeds and in smooth, small tubes, laminar flow is present, with a steady increase in flow speed from the edge to the centre of the tube. Under these circumstances, flow is described by the Poiseuille equation:

\[ \dot{V} = \frac{\pi Pr^4}{8\eta l} \]

As speed and tube size increase, flow may become turbulent after a transitional phase. Turbulent flow exists when Reynolds number exceeds 2000 and laminar flow below 200. The transition from laminar to turbulent flow is not predictable. Reynolds number is given by the equation:

\[ RN = \frac{\nu \rho d}{\eta} \]

where \( \rho \) is density, \( d \) diameter, \( \nu \) velocity and \( \eta \) viscosity. Where flow is turbulent, its relationship to the radius of the tube is not simple, being proportional to greater than the fourth power. The relationship to pressure, density and length of tube is:

\[ \dot{V} \propto \frac{P}{\sqrt{\rho}} \]

flow being unrelated to viscosity.

Resistance is equal to pressure gradient per unit flow, so each of these flow equations can be transformed into an expression of resistance.

In the respiratory tract, air flow is turbulent in the trachea, transitional in all the large airways down to the level of terminal bronchioles and probably laminar in the very small airways. The relationship between driving pressure and air flow is complex and of the form:

\[ P = K_1 \dot{V} + K_2 \dot{V}^2 \]

The first term reflecting laminar flow and the second turbulent flow.

h. Describe the factors affecting resistance and how to measure airway resistance.

Most of the resistance to air flow in healthy lungs is in the medium sized bronchi, Though diameter falls with each generation of airways, the total number of airways rises exponentially, reducing resistance to very low levels by the tenth generation.

Density and viscosity of inspired gas are related to resistance as described in the above equations.

Lung volume has a major effect on airway resistance.
At low lung volumes there is little support of small airways by the surrounding parenchyma and consequently high resistance, varying with the reciprocal of lung volume.

Smooth muscle tone in bronchioles can markedly increase airway resistance. The bronchioles are innervated by the vagus. Contraction can be from parasympathetic outflow, local irritant factors or systemic factors such as histamine release. Bronchiolar smooth muscle also relaxes in response to a rise in PCO₂.

In the special case of maximal expiratory flow, resistance rises as the gradient from intrapleural pressure to airway pressure exceeds the force supporting the airways and collapse occurs. This limits flow regardless of the resistance downstream. The force supporting the airways depends on lung volume. This produces an effort-independent maximal flow envelope related only to lung volume in any individual.

Airway resistance is measured using a plethysmograph. By measuring airflow at the mouth and pressure change in the plethysmograph, having first measured lung volume, it is possible to calculate the pressure gradient between alveoli and mouth which when divided by flow equals total airway resistance.

Less satisfactorily, intrapleural pressure can be measured with an oesophageal manometer in the lower \( \frac{1}{3} \) of the oesophagus when erect. If the recoil due to chest wall elasticity is reliably calculated, the pressure gradient due to both airway and tissue resistance can be determined.

Information about resistance can also be obtained using a single forced expiration. The conventional measures are FEV₁/FVC (normal >80%) and FEF₂₅₋₇₅ which is an average flow over the middle 50% of expiration (by volume). A simpler measure is PEFR, commonly used to assess the severity of obstruction in asthma.

More detailed information can be obtained from a flow-volume curve, in which the expiratory flow rates are much lower in airway obstruction and the mean volume may be increased in chronic disease.

i. Define closing capacity and its relationship to airway closure and explain its clinical significance and measurement.

In a single breath N₂ washout test, (used to measure anatomical deadspace), the exhaled nitrogen concentration rises above its alveolar plateau at a low lung volume (in healthy individuals). This represents the exhalation of alveolar gas from less well-ventilated alveoli, usually in the upper part of the lung, following closure of airways in the bottom of the lung.

The volume at which this rise starts is that at which airway closure first occurs in the more dependent part of the lung. This is about 10% of VC in healthy young adults and rises with age (45 ml/year) and airway disease to equal FRC at 45 years in the supine position and 65 years when erect. Closing capacity is also higher in infants, falling to FRC at 8 years.

j. Describe the work of breathing and its components.

Work is equal to pressure times volume. The work of breathing may be described using a pressure-volume graph. The area of the graph represents the work of breathing; the pale part being work against elastic forces (on inspiration) and the dark area work against viscous forces such as airway resistance. On expiration, the viscous work required is less than the energy stored in elastic forces during quiet breathing.

In exercise or during rapid breathing, the work against viscous forces increases.
dramatically and on expiration will exceed the work done against elastic forces on inspiration. Expiration then becomes an active process and the expiratory limb of the curve falls outside the pale area.

Work of breathing at rest is about 2% of BMR (2 W or 7.2 kJ/hr) with 10% efficiency. There is a characteristic frequency of minimal work of breathing for a given minute volume and elastic properties and airway resistance, with high elastic work at low frequencies and high airway resistance work at high frequencies. Conversely the frequency of minimum work is reduced by an increase in airway resistance and increased by a rise in elastic resistance.

**k. Describe altered lung mechanics in disease states.**
B. 4 Pulmonary gas volumes and ventilation

a. Explain the measurement of lung volumes and capacities and indicate the normal values.

The total volume of gas the lung can contain is total lung capacity (TLC). This is divided into the volume which can not be exhaled which is residual volume (RV) and the proportion which can be exhaled: vital capacity (VC).

The volume moved in resting ventilation is known as tidal volume (TV) and the volume remaining in the lung at the end of a normal breath is functional residual capacity (FRC). The volumes which can be inspired or exhaled in addition to TV are called inspiratory and expiratory reserve volumes (IRV and ERV).

VC, TV, IRV and ERV can easily be measured by a spirometer. FRC can be measured by helium dilution and RV and TLC derived from these measurements. Alternatively FRC can be measured by nitrogen washout with 100% oxygen over several minutes.

FRC can also be measured in a plethysmograph using a manometer to measure pressure change in the chamber and also in the airway during inspiration against a closed tube. The volume change of the chest can be derived from the pressure change in the chamber and the volume of gas in the chest determined from its volume change and pressure change. This measures the total gas volume in the chest, including areas which are not being ventilated, unlike the helium dilution method which measures the ventilated volume.

The functions of FRC are as an oxygen reserve, to prevent airway closure, to smooth alveolar gas composition and to minimize PVR, work of breathing and V/Q mismatch.

Typical values (l)
- TLC 6
- VC 4.8
- RV 1.2
- TV 0.5
- FRC 2.4

These are highly variable according to body size. The values given are for a 1.8 m male, normal VCs range from 2.5 to 7 l.

Normal ventilation at rest consists of about 15 breaths/min of a TV of 0.5 l, giving a ventilation of 7.5 l/min. Each breath ventilates an anatomic dead space (upper airways not participating in gas exchange) of about 150 ml or 2.25 l/min. This leaves 5.25 l/min of alveolar ventilation. This is roughly equal to pulmonary blood flow at rest of about 5 l/min.

These values can be measured with the spirometer except for dead space and alveolar ventilation. Dead space can be measured using a N₂ washout curve, giving anatomic dead space. Physiological dead space can be determined from the CO₂ output of the lung if tidal volume and expired and alveolar (or arterial) CO₂ are measured:

\[ V_T P_{A}CO_2 = V_A P_ACO_2 \]
\[ V_D = V_T - V_A \]
\[ V_D = V_T (1 - P_ACO_2 / P_ACO_2) \]

Once dead space has been measured, alveolar ventilation can be calculated.
b. Describe the factors influencing lung volumes and capacities.

Body size and sex are major determinants of lung volumes. VC varies approximately linearly with height and decreases gradually with age. These relationships are described empirically:

\[
\text{male } \text{VC} = 5.2 \times h - 0.022 \times a - 3.6 \pm 0.58 \\
\text{female } \text{VC} = 5.2 \times h - 0.018 \times a - 4.6 \pm 0.42
\]

where VC is in litres, h is height in metres, and a age in years. Thus VC falls about 20 ml/year.

Any disease process which occupies space in the thorax will reduce TLC and consequently VC. Pleural effusion is an example of a pathology which results in compression of the lung. Disease such as bronchial cancer within the lung may cause obstruction of ventilation to part of the lung, reducing VC. Reversible or lung volume-dependent obstruction from asthma or emphysema will increase RV dramatically without reducing TLC. This usually results from early airway closure on exhalation in obstructive disease.

Restrictive lung disease such as asbestosis can reduce TLC and VC by limiting inspiration without much change in RV.

c. Define dead space and apply the Bohr Equation and the Alveolar Gas Equation.

Dead space is the ventilated volume which does not participate in gas exchange. Anatomical dead space is the volume of the large upper airways and is measured using a N₂ washout test. Physiological or functional dead space is a similar volume in healthy individuals and can be measured using the Bohr Equation as described above.

The alveolar gas equation relates alveolar oxygen partial pressure to inspired oxygen partial pressure and CO₂ partial pressure:

\[
\frac{P_{A}O_2}{R} = \frac{FIO_2}{R} + \frac{P_{A}CO_2}{R} - \frac{1 - R}{R} 
\]

d. Explain normal ventilation-perfusion matching including the mechanisms for these as well as the normal values.

Ventilation of the lung in the erect position is greater at the base than at the apex because of the difference in intrapleural pressure between the top and bottom of the lung. Similarly perfusion of the lung is less at the apex than at the base, largely due to the hydrostatic pressure difference between arterial pressure at the top and bottom of the lung. The difference in perfusion is greater than the difference in ventilation. Thus the ratio of ventilation to perfusion is greatest at the apex and least at the base of the lung.

The differences in ventilation and perfusion result in differences in gas concentrations:

<table>
<thead>
<tr>
<th></th>
<th>Apex</th>
<th>Base</th>
</tr>
</thead>
<tbody>
<tr>
<td>ventilation</td>
<td>0.24</td>
<td>0.82</td>
</tr>
<tr>
<td>perfusion</td>
<td>0.07</td>
<td>1.29</td>
</tr>
<tr>
<td>V/Q</td>
<td>3.3</td>
<td>0.63</td>
</tr>
<tr>
<td>PO₂</td>
<td>132</td>
<td>89</td>
</tr>
<tr>
<td>PCO₂</td>
<td>28</td>
<td>42</td>
</tr>
<tr>
<td>pH</td>
<td>7.51</td>
<td>7.39</td>
</tr>
</tbody>
</table>

Matching of ventilation and perfusion is also partly due to local vascular tone. Pulmonary vessels constrict in response to high PCO₂ or low PO₂, helping to match...
perfusion to ventilation. V/Q matched alveoli are far more efficient at gas exchange; over ventilated alveoli can not compensate for under ventilated ones because of the non-linear nature of the O₂ and CO₂ dissociation curves.

e. Describe the composition of ideal alveolar and mixed expired gases.

Ideal alveolar gas is described by the alveolar gas equation. It is the gas composition expected in alveoli if there were no ventilation-perfusion mismatch in the lung:

\[ P_A CO_2 = P_a CO_2 = 40 \text{mmHg} \]

\[ P_A O_2 = P_i O_2 \cdot \frac{P_A CO_2}{R} + P_A CO_2 \cdot F_i O_2 \cdot \frac{1 - R}{R} \]

\[ = 100 \text{ mmHg} \]

Mixed expired gas is the gas sampled at the mouth during exhalation. It is a mixture of gas from the dead space and from the alveolar space from alveoli with a range of V/Q ratios. Typically:

\[ P_E CO_2 = 33 \text{ mmHg} \]

\[ P_E O_2 = 115 \text{ mmHg} \]
B. 5 Diffusive transfer of respiratory gases

a. Describe and explain the oxygen cascade.

The partial pressure of oxygen falls at each stage of its transport from air to peripheral tissues.

<table>
<thead>
<tr>
<th>Stage</th>
<th>PO2 (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry air</td>
<td>159</td>
</tr>
<tr>
<td>Air at BTPS</td>
<td>149</td>
</tr>
<tr>
<td>Alveolar gas</td>
<td>100</td>
</tr>
<tr>
<td>Pulmonary capillary blood</td>
<td>40 →&lt;100</td>
</tr>
<tr>
<td>Mean capillary blood</td>
<td>40</td>
</tr>
<tr>
<td>Interstitial fluid</td>
<td>15-40</td>
</tr>
<tr>
<td>Intracellular fluid</td>
<td>≥1</td>
</tr>
</tbody>
</table>

The fall from dry to saturated air results from the increase in the partial pressure of water from 0 to 47 mmHg. The pressure in inspired gas also depends upon barometric pressure.

The difference between inspired gas and ideal alveolar gas depends on ventilation and oxygen usage. With high alveolar ventilation, alveolar PO2 approaches inspired PO2 asymptotically. Alveolar PO2 is also reduced by oxygen uptake and CO2 release in the alveoli.

The gradient between alveolar gas and pulmonary capillary blood depends on the factors affecting diffusion described below. In addition it is increased by shunt and V/Q scatter. A high inspired PO2 increases the pressure gradient because the content gradient remains constant while the content/pressure graph becomes very flat at high PO2. A fall in cardiac output causes a rise in the proportion of shunted blood as well as a fall in mixed venous PO2 due to constant tissue oxygen uptake. A very marked rise in cardiac output can also increase the A-a gradient by reducing transit time in the pulmonary capillaries to the extent that oxygen uptake becomes diffusion-limited. Factors which influence the shape of the oxygen dissociation curve also affect A-a gradient: pH, temperature, and 2,3-DPG. An increase in haemoglobin concentration also reduces A-a gradient.

An increase in ventilation can cause a rise in A-a gradient both due to the rise in alveolar PO2 and the fall in cardiac output which accompanies the fall in PCO2. If there is more than 3% shunt, increasing ventilation starts to cause a fall in arterial PO2 because of the fall in cardiac output.

The gradient from blood to interstitial fluid to intracellular fluid differs markedly from tissue to tissue and regionally within any tissue. It is dependent on perfusion, haemoglobin concentration and oxygenation of blood. In most tissues passive diffusion carries oxygen down the concentration gradient from capillary blood to the mitochondria. Some tissues such as muscle have specialized oxygen carrying proteins (myoglobin) to improve oxygen transport and storage.

b. Explain the capillary exchange of oxygen and carbon dioxide, and the relationship of erythrocyte transit to oxygen and carbon dioxide transfer.

O2 and CO2 cross the blood-gas barrier by passive diffusion. The distance from alveolar lumen to erythrocyte cytoplasm is about 0.3 μm. O2 diffuses rapidly across this barrier, equilibrating with blood in about 0.25 s. At rest, erythrocyte transit time in alveolar capillaries is about 0.75 s, however in exercise it falls to as little as 0.25 s. The time taken for diffusion can be greatly increased by lung disease which results in
thickening of the blood-gas barrier and consequent diffusion-limitation of oxygen transport. A reduction in the pressure gradient driving diffusion will also slow diffusion. This is seen at high altitude, where P\textsubscript{a}O\textsubscript{2} is reduced by a greater amount than the fall in venous PO\textsubscript{2}.

CO\textsubscript{2} is much more soluble than O\textsubscript{2}, however the pressure gradient driving its diffusion is only 5 mmHg. In healthy lungs the time taken for alveolar gas to equilibrate with pulmonary capillary blood is about the same as with O\textsubscript{2}: 0.25 s.

c. Explain perfusion-limited and diffusion-limited transfer of gases.

In gas exchange at the blood-gas barrier, the rate-limiting step differs according to the gas being examined. In the case of oxygen, as described above, the partial pressure equilibrates in much less time than the blood spends in alveolar capillaries. Thus transport of oxygen is limited by the total alveolar blood flow at rest; it is perfusion-limited. N\textsubscript{2}O is an extreme case of perfusion-limitation as it reaches equilibrium with blood in around 0.1 s. Perfusion-limitation is a characteristic of gases and anaesthetic vapours which are roughly equally soluble in the blood-gas barrier and in blood.

In exercise, when the transit time for blood is reduced substantially and if the diffusion capacity for oxygen is reduced by lung disease, the partial pressure of oxygen in pulmonary venous blood may still be much lower than in alveolar gas. CO diffuses much less readily than O\textsubscript{2}, with a very gradual rise in blood partial pressure. Its transport is thus almost entirely dependent on the rate of diffusion through the blood-gas barrier, hence its use in measuring diffusion capacity. This is a case of diffusion-limited gas transport and is characteristic of gases which have widely differing solubilities in the blood-gas barrier and in blood.

d. Define diffusion capacity and its measurement.

Diffusion capacity is a measure of the rate at which a gas can diffuse across the blood-gas barrier. It is described by Fick’s law of diffusion. The rate of diffusion is proportional to the area (A) and pressure gradient and inversely proportional to the thickness (T) of the sheet. It is proportional to the diffusion constant which is equal to the solubility of the gas (Sol) divided by the square root of its molecular weight (MW):

\[ V_{\text{gas}} \propto \frac{A \cdot \text{Sol}(P_1 - P_2)}{T \sqrt{\text{MW}}} \]

Because area and thickness of the blood-gas barrier are not readily measurable, an empirical “diffusing capacity” for each gas is defined such that:

\[ V_{\text{gas}} = D_L \cdot (P_1 - P_2) \]

where D\textsubscript{L} is the diffusion capacity for the gas being tested. In the case of O\textsubscript{2} and CO, uptake is also limited by reaction with haemoglobin. This is also included in D\textsubscript{L}. D\textsubscript{L} can then be split into two components, with D\textsubscript{M} representing the conductance of the blood-gas membrane, V\textsubscript{c} the capillary blood volume, and \( \theta \) representing the rate of reaction with Hb (in ml/min/ml blood/mmHg):

\[ \frac{1}{D_L} = \frac{1}{D_M} + \frac{1}{\theta \cdot V_c} \]

Diffusion capacity is conventionally measured using CO as its transport across the blood-gas barrier is diffusion-limited and its normal blood concentration is nearly zero. This can be done with a 10s single breath-hold of a 0.3% CO and 10% He containing mixture to measure both lung volume and D\textsubscript{L}CO or using a steady-state technique with measurement of CO uptake over several breaths.

At rest D\textsubscript{L}CO is typically 25 ml/min/mmHg. With exercise it increases by a factor of three or more due to pulmonary vasodilatation and alveolar recruitment.

e. Describe the physiological factors that alter diffusion capacity.

Increase

\emph{Respiratory diffusion} 1.B.5.2 James Mitchell (November 5, 2001)
blood-gas barrier area
  lung size
  alveolar recruitment
alveolar gas concentration
pulmonary vasodilatation
uptake of CO or O₂ by Hb or buffering of CO₂
Decrease
  blood-gas barrier thickness
  systemic venous blood gas concentration
  temperature (reduces solubility)
  functional dead space
B. 6 Ventilation-perfusion inequalities

a. Describe West's zones of the lung and explain the mechanisms responsible for them.

Perfusion of the lung is not uniform in the erect position, but increases from the top to the bottom of the lung. This is a result of hydrostatic forces combined with the effect of airway pressure. Conceptually, the lung may be divided into three zones.

Zone 1 is a region at the top of the lung in which arterial pressure falls below alveolar pressure. This does not happen under normal circumstances, but can result from marked hypotension or from raised alveolar pressure in IPPV. The capillaries in this zone remain collapsed and no perfusion occurs.

Zone 2 is the region of lung where pulmonary arterial pressure is greater than alveolar pressure but venous pressure remains below alveolar pressure. Here perfusion is dependent on the gradient from arterial pressure to alveolar pressure as vessels collapse at the point where intravascular pressure has fallen below alveolar pressure, limiting flow. Pulmonary venous pressure has no influence on flow, but perfusion increases from top to bottom of zone 2 as arterial pressure rises further above alveolar pressure.

Zone 3 is where both arterial and venous pressure exceeds alveolar pressure. Now airway pressure does not influence perfusion as flow is dependent on the arterial-venous gradient. Flow increases in moving down zone 3 because the mean volume of the vessels does, as both arterial and venous pressure rise, distending the capillary bed. The pressure gradient remains the same.

A so-called zone 4 arises in areas of lung where low lung volume reduces the size of extra-alveolar vessels, increasing their resistance and reducing blood flow. This can be seen at the lung bases at low lung volumes.

b. Explain the shunt equation.

Part of the difference between mixed PaO2 and PAO2 is conceptualized as being due to “shunted” blood which circulates through the lung without being exposed to the blood-gas barrier. Part of the “shunt” blood is certainly that in the bronchial circulation and blood perfusing alveoli which are not ventilated, but the calculated value for shunted blood flow includes both anatomically shunted blood and a proportion of blood from inadequately ventilated alveoli where PaO2 is lower than the ideal value.

Because the total volume of oxygen carried in the pulmonary venous blood is conserved in the mixing of shunted and ventilated blood, and the alveolar and systemic venous oxygen concentrations can be measured, it is possible to calculate the proportion of pulmonary perfusion which is represented by shunted blood:

\[ \dot{Q}_T \cdot C_sO_2 = \dot{Q}_S \cdot C_VO_2 + (\dot{Q}_T - \dot{Q}_S) \cdot C_CO_2 \]

which can be rearranged to give:

\[ \frac{\dot{Q}_S}{\dot{Q}_T} = \frac{C_CO_2 - C_sO_2}{C_CO_2 - C_VO_2} \]

If the end-capillary blood is assumed to have equilibrated with alveolar oxygen, its oxygen concentration can be determined from the oxygen dissociation curve. The arterial and mixed venous oxygen concentrations can be measured directly, allowing for calculation of the shunt flow.
c. Describe the oxygen-carbon dioxide diagram and apply it to clinical use.

The oxygen-carbon dioxide diagram relates PCO\(_2\) and PO\(_2\) in the alveolus to V/Q ratio. With a V/Q ratio close to 1, PCO\(_2\) has its normal value of around 40 mmHg and PO\(_2\) 100 mmHg. As V/Q ratio increases, the gas partial pressures approach those of inspired gas. This is the situation in functional dead space.

As V/Q ratio falls, the gas partial pressures approach those of mixed systemic venous blood; the situation of shunt. Thus the curve always runs from the values of venous blood to those of inspired gas, whatever their compositions. The composition of alveolar gas must always lie on the curve: there is a 1-1 correspondence of values for PCO\(_2\) and PO\(_2\).

In a normal lung there is a spread of V/Q ratios among the alveoli, causing some alveoli (with high V/Q) to return blood with a gas composition closer to inspired gas and some (with low V/Q) to return blood which is more similar to mixed venous blood. With disease this spread gets much wider, causing a rise in PCO\(_2\) and a fall in PO\(_2\).

The normal physiological response to a fall in PCO\(_2\), is a rise in respiratory rate and volume. This increases the ventilation of all alveoli and shifts the distribution of V/Q ratios towards the higher end of the curve. As is clear from the curve, with increasing ventilation the PCO\(_2\) of some units approaches 0, while the PO\(_2\) (on air) approaches only 1.5 times normal. As a result, an increase in ventilation is much better at normalizing PCO\(_2\) than PO\(_2\). This problem can also be seen in the oxygen and carbon dioxide dissociation curves; the oxygen curve is quite flat with above normal ventilation while the carbon dioxide curve remains almost linear.

d. Describe and explain regional ventilation-perfusion inequalities, their clinical importance and changes with posture.

In the upright position, V/Q ratio decreases from top to bottom of the lung. This is caused by the variation in both ventilation and perfusion resulting from pressure differences from top to bottom of the lung. Ventilation is greater at the base due to the lower mean volume at rest and thus greater compliance at the base of the lung. Perfusion is also greater at the base of the lung due to hydrostatic pressure increasing both arterial and venous pressure. The increase in perfusion at the base is greater than that in ventilation, hence the fall in V/Q.

<table>
<thead>
<tr>
<th></th>
<th>Apex</th>
<th>Base</th>
</tr>
</thead>
<tbody>
<tr>
<td>ventilation</td>
<td>0.24</td>
<td>0.82</td>
</tr>
<tr>
<td>perfusion</td>
<td>0.07</td>
<td>1.29</td>
</tr>
<tr>
<td>V/Q</td>
<td>3.3</td>
<td>0.63</td>
</tr>
<tr>
<td>PO(_2)</td>
<td>132</td>
<td>89</td>
</tr>
<tr>
<td>PCO(_2)</td>
<td>28</td>
<td>42</td>
</tr>
<tr>
<td>pH</td>
<td>7.51</td>
<td>7.39</td>
</tr>
</tbody>
</table>

The normal V/Q scatter is responsible for a proportion of the A-a gradient. There is a greater blood flow from the base of the lung where the PO\(_2\) is low and relatively less from the apex. The small rise in oxygen content of blood flow from the apex cannot
compensate for the larger flow from the base and so the mean PO₂ is depressed. This effect is exacerbated by the shape of the oxygen dissociation curve which is steeper below ideal PO₂ than above.

With a change to the supine position, the range of V/Q scatter is reduced because the vertical dimension of the lungs is reduced. There is a reduction in physiological dead space.

In the lateral position, the same gradient of ventilation and perfusion occurs as in the upright position, except that it extends from the superior to inferior lung. With the introduction of IPPV in the lateral position, the dependent lung is no longer much better ventilated than the upper lung, presumably due to the reduced compliance of the compressed side of the chest. Detail in *Thoracic surgery*.

e. Outline the methods used to measure ventilation-perfusion inequalities.

To detect regional defects in ventilation or perfusion, radiolabelled tracer is used in conjunction with a gamma camera. A perfusion scan is performed using radiolabelled (Tc99m) dye. The corresponding ventilation scan uses a low concentration of radioactive gas (Xe). The images obtained show gross areas of defective perfusion or ventilation and allow differentiation between large isolated perfusion defects such as pulmonary emboli and matched defects such as pneumonia.

Physiological uniformity of ventilation can be assessed using a single- or multiple-breath N₂ washout test. The single-breath method shows a rise in N₂ concentration at the end of the alveolar plateau as inadequately ventilated alveoli are emptied. The change in N₂ concentration between 750 ml and 1250 ml expired volume is used as an indicator of uneven ventilation.

The multiple-breath method relies on the exponential washout of N₂ over multiple breaths containing no N₂. In a perfectly ventilated lung this would result in a straight line on a semi-log plot of N₂ concentration versus breath number. Where alveoli with large time-constants delay the washout of N₂, the curve becomes curved (concave-up). This can be quantified by modelling the shape of the curve using more than one “compartment”.

An assessment of the V/Q distribution can also be made from the PO₂ difference between ideal alveolar gas and arterial blood. Real alveolar gas PO₂ is difficult to measure unless there is completely even ventilation.

As V/Q scatter widens, the difference between the composition of alveolar gas and arterial blood widens, diverging from the point of ideal matching (i). The alveolar gas composition (A) falls on the line of gradient R, connecting i with the composition of inspired gas. The arterial gas pressures (a) follow a line to the mixed venous composition, with PCO₂ initially held constant by the ventilatory response to any rise in PCO₂. The point a can be measured directly with blood gases and the point A calculated from the alveolar gas equation.

Other measures of V/Q inequality include physiological shunt and alveolar dead space. These are measures of the amount of venous blood or inspired gas added to produce the measured alveolar or arterial composition from the ideal composition:

\[
\frac{Q_{\text{PS}}}{Q_T} = \frac{C_{i}O_2 - C_{a}O_2}{C_{i}O_2 - C_{v}O_2}
\]
\[
\frac{V_{\text{Dalv}}}{V_T} = \frac{P_{\text{CO}_2} - P_A \text{CO}_2}{P_{\text{CO}_2}}
\]

Alveolar dead space is difficult to calculate because of the difficulty of measuring alveolar PCO₂, so mixed expired PCO₂ and arterial PCO₂ (to approximate ideal PCO₂) are used instead, giving physiological dead space.

\[
\frac{V_{\text{phys}}}{V_T} = \frac{P_a \text{CO}_2 - P_E \text{CO}_2}{P_a \text{CO}_2}
\]

f. Explain venous admixture and explain its relationship to shunt.

Venous admixture is a conceptual quantity, being the amount of mixed venous blood which would have to be added to ideal pulmonary capillary blood to produce the measured gas composition of arterial blood. In a lung where V/Q matching was perfect, it would equal the amount of shunted blood. It is also called physiological shunt and is a measure of the degree of V/Q mismatch. The equation for its calculation is given above.

g. Explain the clinical significance of changes in anatomical and physiological dead space.

Anatomical dead space is the volume of the conducting airways. It may be measured most commonly using an N₂ washout test or by making a cast of the airways in a cadaver or using the Bohr equation using end expiratory CO₂ and mixed expired CO₂ in the same manner as the N₂ washout test:

\[
\frac{V_{\text{Danat}}}{V_T} = \frac{P_{\text{ET CO}_2} - P_E \text{CO}_2}{P_{\text{ET CO}_2}}
\]

Physiological dead space is the volume of airways which do not participate in CO₂ exchange and is determined from the Bohr Equation as given above. The two values are very similar in a healthy individual.

Anatomical dead space represents the difference between total ventilation and gas available for alveolar ventilation. It is typically about 150 ml and is decreased with intubation by the volume of the larynx and pharynx bypassed by the ETT or LMA. The addition of a circuit introduces apparatus dead space which is the volume of the circuit beyond the Y-piece in a circle system.

An increase in anatomical dead space increases the mean inspired CO₂ and reduces the mean inspired O₂, as the first gas inspired will be of end-tidal composition. This results in an increase in minute ventilation in response to the rise in PCO₂ in a spontaneously ventilating patient. The rise in anatomical dead space required to produce significant compromise is large.

Small increases in anatomical dead space are seen with changes in posture: the erect position increasing dead space by about 50 ml over the supine position and neck extension increasing volume of the pharynx another 25 ml. Small increases are also seen with bronchodilation and with deep inspiration.

Physiological dead space increases both with an increase in volume of the conducting airways and with any increase in alveolar dead space. Alveolar dead space may increase as a result of V/Q mismatch: non-perfused alveoli, poorly perfused alveoli and non-vascular air space (in emphysema).

h. Explain the effect of ventilation-perfusion inequality on carbon dioxide elimination and oxygen transfer.

Increased V/Q mismatch impairs both CO₂ and O₂ transfer, but to different degrees. Oxygen uptake is more markedly affected because of the shape of the oxygen uptake curve. Alveoli with a low V/Q and consequently lower PO₂ cause a substantial fall in the oxygen concentration of blood leaving poorly ventilated alveoli, but alveoli with a high...
V/Q and high PO₂, produce only a small rise in oxygen concentration. If mixed venous blood contains 14.6 ml/100 ml O₂, a normal alveolus (V/Q = 1) will raise this to 19.5. A V/Q ratio of 0.1 will result in a rise to only 16 and a ratio of 10 will produce an oxygen concentration of only 20 ml/100 ml.

CO₂ elimination is less affected by V/Q mismatch. This is partly due to the more linear relationship between PCO₂ and CO₂ concentration and mostly due to the importance of PaCO₂ in determining ventilatory drive. Any rise in PaCO₂ resulting from V/Q mismatch will result in an increase in ventilation to normalize PaCO₂. A rise in total ventilation is effective in increasing the elimination of CO₂ from both well- and poorly-ventilated alveoli, so PaCO₂ is easily normalized.
B. 7 Gas transport in the blood

a. Describe the carriage of oxygen in blood.

Oxygen is carried either bound to haemoglobin or dissolved in solution. The solubility of oxygen in blood is 0.003 ml/100 ml/mmHg so normal arterial blood contains about 0.3 ml/100 ml. The large proportion of oxygen in the blood is bound to haemoglobin, a protein tetramer with an iron-porphyrin ring attached to each chain. Oxygen coordinates with each Fe atom, inducing a conformational change which promotes the binding of oxygen to the other Fe atoms. The total oxygen binding capacity of haemoglobin in blood (at normal pH, temperature and PCO₂) is 1.39ml/g, giving a total oxygen carrying capacity of blood with an Hb of 150 g/l of 20.8 ml/100 ml. Normal arterial blood has a PO₂ of 100 mmHg and is 97.5% saturated; venous blood has a PO₂ of 40 mmHg and is 75% saturated.

b. Explain the oxyhaemoglobin dissociation curve and factors that may alter it, such as carbon monoxide, temperature, carbon dioxide, hydrogen ion concentration and 2,3 diphosphoglycerate.

Normal adult haemoglobin (Hb A) consists of two α and two β chains composing a tetramer. Each chain surrounds a porphyrin ring and Fe²⁺ ion. An oxygen molecule can coordinate with each Fe²⁺ ion, inducing a conformational change in the tetramer from its tense (T, deoxy) to relaxed (R, oxy) state. This change requires the breakage of salt links within each chain and extrusion of 2,3 DPG (2,3 bisphosphoglycerate) from a site where it binds both β chains. The conformational changes with oxygen binding are cooperative, resulting in the sinusoidal shape of the dissociation curve.

2,3 DPG has a major effect on the affinity of Hb for oxygen. It is present within erythrocytes at approximately the same molar concentration as Hb. It is a highly negatively charged molecule:

\[ \text{PO}_4^{2–} – \text{CH}_2– \text{CHPO}_4^{2–} – \text{COO}^- \]

which in the tense state of Hb occupies a site in the centre of the tetramer where it binds three positively charged sites on each β chain. This binding must be broken when Hb binds oxygen. This greatly reduces the affinity of Hb for oxygen. In the complete absence of 2,3
DPG, Hb is 50% saturated at 1 mmHg PO$_2$ instead of at 26 mmHg. The concentration of 2,3 DPG varies slightly in the erythrocyte, rising with glycolysis in anaerobic conditions and thus promoting the release of oxygen in the presence of hypoxia.

\[
\begin{align*}
&\text{G-6-P} \\
&\downarrow \\
&3\text{-phosphoglyceraldehyde} \\
&\downarrow \\
&1,3\text{-bisphosphoglycerate} \\
&\downarrow \\
&3\text{-phosphoglycerate} \\
&\downarrow \\
&\text{pyruvate} \\
&\text{2,3-diphosphoglycerate (2,3-DPG)} \\
&\text{2,3-DPG mutase} \\
&\text{2,3-DPG phosphatase}
\end{align*}
\]

A rise in PCO$_2$ or in H$^+$ ion concentration also promotes the release of oxygen (moving the dissociation curve to the right). This occurs as both CO$_2$ and H$^+$ compete to bind to Hb, which plays a major role in pH buffering. CO$_2$ reacts with the $\alpha$ NH$_3$ groups of Hb, reversibly forming a carbamate which forms salt bridges and helps stabilize the T form. H$^+$ similarly binds more readily to aspartate and histidine residues which display a rise in pKa with the conformational change from R to T state. This linkage of the affinity for oxygen and H$^+$ and CO$_2$ binding sites on Hb through conformational change is known as the Bohr Effect.

Temperature rise reduces the affinity of Hb for oxygen, producing a right shift in tissues which are substantially above normal temperature, such as exercising muscles.

Carbon monoxide binds to Hb about 240 times as avidly as oxygen, having a P$_{50}$ of about 0.1 mmHg. It coordinates similarly with the Fe$^{3+}$ ion and moves the oxygen dissociation curve to the left.

Other factors which move the curve to the left include high altitude (due to alkalosis), neonatal haemoglobin and thalassaemia. Factors which move the curve to the right include: Hb S, anaemia, hyperthyroidism and normal physiology in the infant (not neonate). More detail in Monitoring (3.B.2)

c. Describe the carbon dioxide carriage in blood including the Haldane effect and chloride shift.

CO$_2$ is carried in three ways in blood, as dissolved CO$_2$, as HCO$_3^-$, and combined with proteins as carbamino compounds. It is far more soluble in blood than O$_2$, with about 0.06ml/100ml/mmHg dissolving. In solution it is in equilibrium with carbonic acid and bicarbonate ion:

\[
\text{CO}_2 + \text{H}_2\text{O} \rightleftharpoons \text{H}_2\text{CO}_3 \rightleftharpoons \text{HCO}_3^- + \text{H}^+
\]

which reacts only slowly in plasma but rapidly within red cells where carbonic anhydrase catalyzes the first reaction.

HCO$_3^-$ formed within red cells diffuses easily back into plasma in exchange for Cl$^-$ ion, according to the Gibbs-Donnan equilibrium in which diffusible ions distribute themselves such that their concentration ratios are equal between compartments. This movement of Cl$^-$ is known as the chloride shift.

The H$^+$ ion formed inside red cells does not diffuse readily into plasma as the cell membrane is relatively impermeable to cations. It partly buffered by binding to deoxygenated Hb, helping to stabilize the T form. This buffering allows a greater amount of CO$_2$ to be carried as HCO$_3^-$ than would otherwise be possible. The net increase in CO$_2$ carrying capacity of blood when it is deoxygenated is known as the Haldane effect.

Some CO$_2$ is also carried in combination with globin by reacting with terminal NH$_2$ groups to form carbamates: Hb-NH-COO$^-$. This reaction is also facilitated by the deoxygenation of haemoglobin.

Of the total CO$_2$ content of arterial blood, 90% is as HCO$_3^-$, and 5% each dissolved CO$_2$ and carbamino compounds. However, of the amount of CO$_2$ exchanged between tissues and lungs, only 60% is carried as HCO$_3^-$, 30% as carbamino compounds and 10% dissolved.
d. Explain the carbon dioxide dissociation curve and its clinical implications.

The carbon dioxide dissociation curve of blood is more evenly sloped and steeper than that of oxygen. The major component of the total CO₂ concentration is HCO₃⁻ ion which over the physiological range varies almost linearly with PCO₂. The contribution of carbamino compounds varies very little with PCO₂, but strongly with the proportion of oxyhaemoglobin, favouring the uptake of CO₂ in the tissues where PO₂ is low.

A rise in temperature reduces the solubility of CO₂ in blood.

The shape of the dissociation curve makes CO₂ transport less dependent on V/Q matching, as the contribution of high V/Q alveoli can compensate for that of low V/Q ones, as neither lies on a “plateau” on the curve.

The substantial contribution from CO₂ not bound to Hb makes CO₂ transport much less dependent upon Hb concentration than O₂ transport is.

e. Describe the oxygen and carbon dioxide stores in the body.

The total body stores of oxygen are small compared with the basal requirements for metabolism:

<table>
<thead>
<tr>
<th></th>
<th>on air</th>
<th>on 100% O₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>lungs (at FRC)</td>
<td>270 ml</td>
<td>1800 ml</td>
</tr>
<tr>
<td>blood</td>
<td>820 ml</td>
<td>910 ml</td>
</tr>
<tr>
<td>interstitial fluid</td>
<td>50 ml</td>
<td>55 ml</td>
</tr>
<tr>
<td>myoglobin-bound</td>
<td>200 ml</td>
<td>200 ml</td>
</tr>
</tbody>
</table>

thus any change in gas exchange results in a rapid change in arterial and tissue PO₂ (t½ about 30 s). Breathing 100% O₂ results in an increase in the lung store, but increases the blood content by only 50 ml bound to Hb and 50 ml dissolved. O₂ consumption can be approximated using the Brody formula where BW is weight in kg and VO₂ is in ml/min:

\[
\dot{V}O_2 = 10.15 \cdot BW^{0.73}
\]

The total body stores of carbon dioxide are very large and conform best to a multi-compartment model. The blood and interstitial fluid of well-perfused organs represents a rapid compartment which equilibrates with alveolar CO₂ in minutes. Less well perfused organs such as skeletal muscle produce a medium compartment and poorly perfused tissue (fat) and carbonates bound in bone compose the largest and very slow compartment.

The blood content of CO₂ is about 2.5 l and total body stores about 120 l. Because of the multiple compartments, arterial PCO₂ does not equilibrate as quickly following a fall in ventilation as following a rise. Hyperventilation can deplete blood CO₂ rapidly (t½ about 3 min). Apnoea causes a slower rise in PCO₂, because the normal rate of production at rest is small compared with the capacity for excretion and equilibrates into the medium compartment as well as blood and alveolar gas. PCO₂ rises 3-6 mmHg/min with a t½ to equilibrium of about 15 min. In practice this allows for Ben-Jet ventilation with oxygen to provide adequate oxygenation and build up a CO₂ surplus over 15 or 20 minutes without harmful effects.
B. 8 Pulmonary circulation

a. Outline the vascular anatomy and structure of the pulmonary and bronchial circulations.

The pulmonary trunk arises from the right ventricle and branches into left and right pulmonary arteries. These pass posterolaterally to the main bronchi and follow them into the lungs. The pulmonary arteries give off multiple branches, generally following the bronchi so that bronchopulmonary segments have their own artery and bronchus without anastomosis.

Pulmonary capillaries line the walls of alveoli. They form a mesh in which the holes are smaller than the vessels themselves. The capillaries have very thin walls which are fused to the basement membrane of the alveolar epithelium.

Pulmonary veins drain oxygenated blood from the pulmonary capillaries. They are generally at the periphery of bronchopulmonary segments and drain adjacent segments. The large veins do accompany the bronchi and arteries and drain as two veins from each lung into the left atrium. The upper vein drains the upper lobe on each side and the lower vein the lower lobe. On the right, the middle lobe is drained by the upper vein.

The histology of the pulmonary arteries is different from systemic arteries of similar size. There is little smooth muscle tissue and a large amount of elastin in the artery walls. The walls overall are thin compared to the diameter of the vessels. This is consistent with the low pressures of the pulmonary circulation. The pulmonary veins are very thin-walled.

The pulmonary capillaries are lined with endothelial cells which share their basement membrane with that of the type I pneumocytes lining the alveolar air space.

The bronchial arteries arise from the thoracic aorta or from the upper intercostal arteries. There may be one or more on each side. Occasionally additional bronchial vessels arise from the descending aorta and travel in the pleural ligament. They follow the bronchi, forming a capillary plexus around the large bronchi, supplying the bronchial muscle coat and forming a second plexus in the mucosa. These plexi extend as far as the respiratory bronchioles where they anastomose with the pulmonary vessels.

The deep bronchial veins drain the bronchi within the lung and join the pulmonary veins. The superficial bronchial veins drain the bronchi near the hilum outside the pleura and join the azygous on the right and accessory hemiazygous or intercostal vein on the left.

The histology of the bronchial arteries is the same as that of other systemic arteries.

b. Describe the physiological features of the pulmonary circulation and compare them with those of the systemic circulation.

The pulmonary circulation differs from the systemic circulation in several major respects. The high-pressure side of the pulmonary circulation carries deoxygenated blood and the low-pressure side oxygenated blood. Typical pulmonary arterial pressures are much lower than in the systemic circulation:

<table>
<thead>
<tr>
<th></th>
<th>Right (mmHg)</th>
<th>Left (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventricular</td>
<td>25/0</td>
<td>120/0</td>
</tr>
<tr>
<td>Arterial</td>
<td>25/8</td>
<td>120/80</td>
</tr>
<tr>
<td>Capillary</td>
<td>12→8</td>
<td>30→10</td>
</tr>
<tr>
<td>Atrial</td>
<td>5</td>
<td>8</td>
</tr>
</tbody>
</table>

There is no need for higher pressures in the pulmonary circulation as there is little variation in the hydrostatic pressure to be overcome and less need for preferential perfusion of one area over another. The difference in pressure is reflected in the histology of the arterial vessels.

Flow in the pulmonary vessels is dependent not only on the arterial and venous
pressures but also on the airway pressure and lung volume as West’s zones show. With high airway pressures or low venous pressure, flow is limited by the collapse of vessels where airway pressure exceeds blood pressure. At high lung volumes, the vessels are supported not only by blood pressure but by elastic forces within the lung parenchyma, allowing the effective pressure outside larger vessels to be less than intrathoracic pressure.

The volume within the pulmonary circulation is around 0.5 to 1.0 l, depending on posture, the cardiac cycle and airway pressure.

The pulmonary circulation has a number of metabolic functions which distinguish it from the systemic circulation. It is the site of synthesis of a number of hormones, including prostaglandins, histamine and kallikrein. It is the main site of conversion of angiotensin I to angiotensin II. It is a major site for removal from circulation of bradykinin, prostaglandins $E_2$ and $F_{2\alpha}$, leukotrienes, adenine nucleotides, serotonin, noradrenaline and acetylcholine. It is also the major site for removal of emboli from circulation and their fibrinolysis.

c. Explain the factors that affect pulmonary vascular impedance.

Impedance is the term for resistance under particular flow conditions. Resistance in a vessel equals pressure gradient per unit flow. Under normal resting circumstances, total pulmonary blood flow is about 6 l/min and the pressure drop from mean arterial to venous pressure is about 10 mmHg, giving a resistance of 1.7 mmHg/l/min (or about 100 dyne/cm$^5$/s), which is about a tenth of systemic vascular resistance.

Pulmonary vascular resistance falls with an increase in arterial or venous pressure as any rise in capillary pressure causes increased distension and recruitment of capillaries and less resistance to flow. Similarly an increase in lung volume lowers large and medium vessel resistance as it increases the distending tension on the larger vessels. Capillary resistance is increased at high lung volumes as stretching of the alveolar walls compresses the capillaries. Thus total pulmonary vascular resistance is high at both very low and very high lung volumes and low between.

Smooth muscle contraction in the walls of pulmonary vessels plays some role in determining pulmonary vascular pressures, but is not as significant as in the systemic circulation. Vasoconstrictors such as noradrenaline, serotonin and histamine increase pulmonary artery pressure.

d. Describe the control of pulmonary vascular tone.

Pulmonary arterioles respond autonomously to the PO$_2$ in adjacent alveoli. A PO$_2$ below 70 mmHg results in marked vasoconstriction, largely independent of arterial oxygenation. There is little constriction above 100 mmHg. The mediator of this response has not been identified, but endothelial cells normally produce NO which acts as a vasodilator and which can relieve vasoconstriction when inhaled in low concentrations.

This response serves to direct blood flow into the best oxygenated parts of the lung when there are areas which are poorly ventilated. At high altitude, where there is a prolonged and generalized reduction in alveolar PO$_2$, widespread vasospasm causes a rise in pulmonary artery pressure and may result in right heart failure and acute mountain sickness.

In the transition from foetus to newborn, this response plays a major role in allowing the changeover from 15% of cardiac output going through the hypoxic foetal lung to 90% of cardiac output passing through a much more vasodilated pulmonary circulation in the newborn after the first few breaths (with 10% shunt).

Acidosis also results in some pulmonary vasoconstriction. There is sympathetic innervation of the pulmonary arterioles with increased sympathetic outflow causing vasoconstriction.

e. Outline the mechanisms which raise pulmonary vascular resistance and describe the circulatory effects of such a rise.
Pulmonary arterial tone is raised in response to the stimuli given above. Capillary resistance rises with lung volume.

Even if total pulmonary resistance rises (for example in living at high altitude), pulmonary blood flow must still remain equal to slightly less than total systemic blood flow. In the short term this requires increased work of the right ventricle and in the long term cardiac output tends to fall. There is commonly arterio-venous shunting of blood seen within the pulmonary circulation. In persistent pulmonary vascular obstruction (as in embolism), anastomosis with the bronchial circulation increases to provide perfusion to the embolized segment.

f. Describe the pulmonary circulation in the foetus and the newborn.

The foetal circulation is substantially different from the adult, primarily because of the difference in the source of oxygenation: the foetus obtains oxygenated blood from the placenta and the newborn from the lungs. Oxygenated blood returns from the placenta in the umbilical vein which joins the portal vein and then passes through the liver into the hepatic vein or bypasses the liver in the ductus venosus and passes directly into the IVC.

Much of the blood from the IVC passes through the foramen ovale into the left atrium and then into the systemic circulation. The remainder, together with blood from the SVC, passes into the RV and then into the pulmonary trunk. In the foetus, the pulmonary circulation is of a high resistance because of the lack of oxygen in the lungs and only about a third of the RV output passes through the lungs (12% of cardiac output), the remainder being diverted through the ductus arteriosus into the arch of the aorta and the systemic circulation.

Because of the high pulmonary resistance, the pressure in the pulmonary trunk is about 5 mmHg higher than that in the aorta. The parallel operation of the right and left ventricles allows them to have substantially different outputs with the left ventricle pumping 20% more blood.

About 75% of total cardiac output ends up in the descending aorta and the majority of this flows into the umbilical arteries (over 50% of cardiac output).

The oxygen saturation of haemoglobin in the foetus is much lower than in the newborn. In the umbilical vein, the blood is about 80% saturated, falling to 62% in the LV after mixing with other venous blood. This is the saturation of the blood perfusing the head and upper body. After mixing with blood from the ductus arteriosus, saturation falls to 58% for perfusion of the remainder of the body. Foetal haemoglobin ($\alpha_2\gamma_2$) has a higher affinity for oxygen than adult haemoglobin as it binds 2,3 DPG less strongly, so in the placenta oxygen is transferred from maternal to foetal haemoglobin at the same $P_{O_2}$.

After birth, pulmonary vascular resistance falls by 90% as air enters the airways. This results in a rapid fall in right heart pressures and reversal of flow passing through the ductus arteriosus which constricts and closes over several days. The foramen ovale closes functionally as the pressure gradient between LA and RA pushes the valve shut.

In response to the trauma at delivery, the umbilical arteries constrict distal to the superior vesical arteries, and the cord is usually clamped. The cessation of flow through the umbilical vein coincides with closure of the ductus venosus which has a sphincter mechanism. The closing of the placental circulation causes a sharp rise in systemic resistance and blood pressure.

In the weeks following these changes, the muscle lining of the pulmonary vessels thins and the left ventricular wall starts to thicken to a greater extent than the right. The foramen ovale, ductus arteriosus and ductus venosus are sealed with fibrous tissue and the circulation shows the characteristics of the adult circulation.
B. 10 Clinical pulmonary function tests

a. Distinguish between obstructive and restrictive lung disorders using the family of curves measuring forced expiratory volume, peak expiratory flow rate and vital capacity.

The forced expiratory volume-time and flow-volume curves are useful in distinguishing between lung disorders. The volume-time curve which is obtained from a spirometer shows forced vital capacity (FVC) and allows reading of forced expiratory volume in 1 second (FEV₁).

FVC is a good measure of the severity of restrictive lung disease. The expected normal value can be calculated from height, sex and age and a result less than 70% of predicted is indicative of restrictive lung disease. In isolated restrictive lung disease, the FEV₁/FVC is normal or increased.

The ratio of FEV₁ to FVC is a good measure of obstructive airway disease. A value of less than 0.7 (70%) is indicative of airway obstruction limiting expiratory flow abnormally. This is independent of FVC. FVC is commonly reduced in patients with obstructive disease as many have a concomitant restrictive deficit as well.

Peak expiratory flow rate (PEFR) can be read from the flow/volume curve or measured separately with a Wright peak flow meter. In a patient with known obstructive disease it is a useful measure of the degree of obstruction and so is routinely used in asthma to assess severity and response to therapy. Normal values are calculated on height, sex and age and have a large variability.

In restrictive lung disease, PEFR is similarly reduced as lung volume is the major determinant of the flow rate in the effort-independent part of the flow-volume curve. Thus PEFR alone cannot distinguish obstructive from restrictive disease.

Lung volume on the flow-volume curve is also a distinguishing feature of lung disease. In restrictive disease, FVC is lost “from the top” with inspiration limited by disease but expiratory flow rates slightly increased at low volumes because of increased elastic recoil in the lungs. In obstructive disease, FVC is lost “at the bottom” as airway closure occurs prematurely in expiration and the patient is forced to operate at higher lung volumes.

b. Outline methods used for measuring mechanics of breathing including flow-volume loops and interpret such results.

Volume-time curves are easily measured using mechanical devices such as the Benedict-Roth spirometer (traditionally) or bellows Vitalograph. The tracings produced by these devices are cumbersome to turn into flow-volume curves as the tracing needs to be differentiated with respect to time to yield flow.

Practically, a pneumotachograph can be used to produce flow-volume curves. This is a tube with a section of fine parallel tubes in it which induce laminar flow. Pressure transducers either side of the laminar flow section measure the pressure drop across the
section of laminar flow and thus the flow rate can be calculated if the length of the section of laminar flow and the characteristics of the gas are known. This is recorded electronically and can be integrated with respect to time to yield volume expired and thus flow-volume curves.

PEFR is measured in isolation using a Wright peak flow meter. This is a chamber in which a leaf is pushed against a spring by the expiratory flow. Its excursion is calibrated to expiratory flow and it moves a pointer which remains at the point of furthest excursion of the leaf (highest flow). These devices are cheap and the results readily reproducible with practice and maximal effort.

c. Describe the carbon dioxide and oxygen response curves and how these may be used to assess the control of breathing.

- $\text{PCO}_2$ vs. $\text{PO}_2$
- Ventilation (l/min) vs. $\text{PO}_2$ (mmHg)
- Ventilation (l/min) vs. $\text{PCO}_2$ (mmHg)

***

d. Interpret and explain normal and abnormal blood gases

In Acid-Base (1.F)

e. Describe the measurement of lung volumes including functional residual capacity and residual volume.

In Respiratory Mechanics (1.B.3)
B. 10 Applied Respiratory Physiology

a. Describe the physiological consequences of intermittent positive pressure ventilation and positive end-expiratory pressure.

Intermittent positive pressure ventilation (IPPV) is artificial ventilation produced by imposing a positive pressure from a sealed circuit into the airway, followed by passive expiration, usually at atmospheric pressure. The major physiological difference from spontaneous ventilation is in the range of airway and intrathoracic pressures involved. Spontaneous ventilation involves small pressure excursions above and below atmospheric pressure in airway pressure. IPPV involves much higher airway pressures in inspiration, typically 15-25 mmHg in a healthy adult. Much of this pressure is transmitted to increase intrathoracic pressure.

Positive end-expiratory pressure (PEEP) is a modification of IPPV such that the expiratory airway pressure does not fall as low as atmospheric pressure. A typical level of PEEP is 5-15 mmHg.

Consequences of IPPV and PEEP:

respiratory
- end-expiratory alveolar pressure = PEEP,
- producing an increase in FRC according to PEEP level and compliance
- may lift FRC above closing capacity in patients with a high closing volume
- reduces airway resistance
- alters relative compliance of upper and lower parts of the lung
- reduces pulmonary shunt
- intrapleural pressure rises according to the transmural pressure gradient (increased in most pathology)
- increases dead space with prolonged application due to bronchiolar dilation

cardiac
- increased intrathoracic pressure
- reduced systemic venous return, reduced cardiac output, increased ADH, reduced ANF
- increased pulmonary capillary resistance
- increased “Zone 1” may make PCWP measurement unreliable

renal
- decreased perfusion pressure
- fluid retention

overall effect of PEEP
- increased P\textsubscript{a}O\textsubscript{2} in diseased lung
- decreased cardiac output
- increased oxygen flux up to “best PEEP”
- not useful in healthy lungs
- mostly used in ICU setting

b. Explain the physiological consequences of hypoxaemia, hyper and hypocapnia and carbon monoxide poisoning.

Hypoxaemia
- low P\textsubscript{a}O\textsubscript{2}
- classified as hypoxic hypoxia (low P\textsubscript{a}O\textsubscript{2}), anaemia hypoxia (low O\textsubscript{2} carrying capacity),
stagnant hypoxia (poor tissue perfusion) and histotoxic hypoxia (failure of cellular respiration)

cellular
- anaerobic metabolism ($P_{O_2}<20\text{ mmHg}$ or histotoxicity)
  - accumulation of lactate, acidosis
  - depletion of high energy phosphates: ATP and phosphocreatine
time to cellular “arrest” depends on energy requirements vs stores

respiratory control
- hypoxia detected by peripheral chemoreceptors (carotid & aortic bodies)
- hyperventilation at $P_{O_2}<55\text{ mmHg}$, maximal at $P_{O_2}<30\text{ mmHg}$
- secondary hypocapnia
- central respiratory depression with severe hypoxia
- pulmonary vasoconstriction (primarily related to $P_AO_2$)

cardiovascular
- systemic vasodilation (especially cerebral): ↑ CO, ↓ MAP
- acidosis and increased 2,3-DPG shifts Hb-O$_2$ dissociation curve to the right
- increased erythropoietin and haematocrit in chronic hypoxia

Hypercapnia
- high $P_{CO_2}$ causes acidosis (in blood, ECF and CSF) via carbonic anhydrase

neurological
- cerebral vasodilation, ↑ ICP
- convulsant at high $P_{CO_2}$
- central depressant effect at high $P_{CO_2}$ (>95 mmHg, MAC=32%)

autonomic
- increased sympathetic outflow
- increased sensitivity to parasympathetic tone via ↓ AChE activity in acidosis

respiratory control
- hypercapnia detected at central chemoreceptor (80% of sustained response) in the ventral medulla and in peripheral chemoreceptors (rapid response)
- hyperventilation up to $P_{CO_2}$ of 100-150 mmHg
- pulmonary vasoconstriction (weaker effect than hypoxia)

cardiovascular
- systemic vasodilation
  - ↑ contractility and heart rate via sympathetic action (direct depressant action)
  - arrhythmogenic
- acidosis shifts Hb-O$_2$ dissociation curve to the right

renal
- chronic hypercapnia results in renal compensation by retention of HCO$_3^-$

endocrine
- sympathetic response raises blood glucose and K$^+$

Hypocapnia
low $P_{CO_2}$
mainly opposite effects to those of hypercapnia
alkalosis ($\downarrow$ free $Ca^{2+}$)

neurological
  cerebral vasoconstriction: $\downarrow$ ICP
  $\uparrow$ neural excitability at low $P_{CO_2}$

respiratory
  detected at central and peripheral chemoreceptors
  reduced respiratory drive (dangerous in labour)
  can produce apnoea in anaesthetized patients, but not usually when conscious
  pulmonary vasodilation

cardiovascular
  $\uparrow$ peripheral resistance
  $\downarrow$ cardiac output
  Hb-O$_2$ dissociation curve shifted to the left

Carbon-monoxide (CO) poisoning
  CO binds to haemoglobin (Hb) with approximately 270 times the affinity of oxygen under physiological conditions ($P_{50}=0.1$ mmHg). It binds at the same site and in the same manner as $O_2$, so binding is cooperative with either CO or $O_2$; CO poisoning moves the Hb-O$_2$ dissociation curve to the left. The toxicity of CO is mediated by its reduction of the oxygen carrying capacity of blood by binding with Hb and by impairing tissue oxygenation through its effect on the Hb-O$_2$ dissociation curve.

  The reduction in oxygen concentration at a given oxygen tension results in reduced oxygen delivery and tissue hypoxia if there is sufficient reduction in oxygen concentration. The $P_{O_2}$ is not reduced, but normal oxygen extraction results in a lower mixed venous $P_{O_2}$ and a lower tissue $P_{O_2}$.

  This reduction in oxygen carrying capacity causes hypoxaemia, and the physiological responses are given above.

  CO poisoning can be reversed with removal of the source of CO, and hyperventilation with high $FiO_2$ to accelerate dissociation of COHb. In the conscious patient, use of a raised $FiCO_2$ is described as a method of increasing spontaneous ventilation.

c. Explain the effects of the supine and erect postures on ventilatory function.

Changing from erect to supine:

  increased
    diffusing capacity (due to reduced V/Q scatter)
  decreased
    FRC by 500-1000 ml, approaching closing capacity
    anatomical dead space by 100-150 ml
    physiological dead space by 5% (from 35% of $V_T$ to 30%)
    alveolar dead space (due to reduced V/Q scatter)

d. Define humidity and give an outline of the importance of humidification.

  Absolute humidity
    the mass of water vapour per unit volume of a gas.
  Humidity at saturation
    the maximum mass of water which can be present in a gas per unit volume at a
Relative humidity
the ratio of absolute to saturation humidity at a specified temperature expressed as a percentage.

Air at 37° with a 100% relative humidity contains 44gm⁻³ of water (SVP=47 mmHg)

Inspired gas is normally humidified in the nose and mouth before entering the lower respiratory tract. Inadequate humidification of inspired gas due to use of dry gas by mask or bypassing of the upper airway by intubation results in:

acute
impaired ciliary and mucous belt function
tenacious mucus, crusting of secretions
increased airway resistance and reduced compliance
heat loss by evaporation

chronic
squamous metaplasia
↓ FRC
↑ shunt
impaired surfactant function
atelectasis

e. Explain the importance of the cough reflex and describe the relationship between lung volume and ability to cough.

The cough reflex is the major mechanism for clearing the upper and lower airways of foreign material larger than can be carried by the mucociliary elevator. It is initiated by mechanical or chemical irritation of the airway. It consists of a deep inspiration to about \( \frac{2}{3} \) of VT followed by tight closure of the glottis and contraction of expiratory muscles causing a rise in airway pressure often in excess of 100 mmHg, then a forceful expiration through upper airways narrowed by high transmural pressure, producing a high air velocity to dislodge foreign material.

The maximum expiratory flow rate and velocity which can be generated depends on both expiratory muscle strength and lung volume. With normal strength, it is limited by lung volume due to airway closure which makes expiratory flow effort independent as lung volume decreases.

f. Explain the effects of general anaesthesia on respiratory function.

Intraoperative
Control
Altered patterns with depth of anaesthesia and agent used
Hyperventilation in excitatory stage
Depressed ventilation when deep
↓ response to PCO₂ with ↑ MAC value
abolished hypoxic response with minimal anaesthetic agent in Respiratory Control (1.B.2)

Mechanics
Supine position ↓ FRC
Altered \( V/Q \) matching with anaesthesia
↑ shunt, ↑ A-a gradient
V̅d altered by position and instrumentation
Gas exchange
  Altered inspired gases or volatile agents
  Second gas effect
Defence mechanisms
  Drying of mucosa, volatiles, tube cuff: ↓ ciliary function
Postoperative
  Immediate
    Drug effects (above)
    Diffusional hypoxia
    ↑ O₂ requirement with shivering
Pain-related
  ↓ FRC, ↓ VC most with upper abdominal surgery
  Narcotic respiratory depression
  Posture effects
a. Describe the structure and functional significance of the contractile elements of cardiac muscle and how they differ from skeletal muscle.

Cardiac muscle cells are of three types: atrial, ventricular and specialized excitatory and conductive cells.

Atrial and ventricular muscle

- Cellular anatomy is similar to skeletal muscle
  - interdigitated actin and myosin filaments
  - T-tubules are opposite the Z-line rather than A-I junction
  - many mitochondria
  - cells are small and connected via intercalated disks which have many gap junctions and a very low electrical resistance. This renders cardiac muscle a functional syncytium.

Gross anatomy

- Two syncitia: the atria and the ventricles, separated by a fibrous ring around the mitral and tricuspid valves, connected only by the AV node

Electrical activity

- Resting membrane potential is -90 mV, maintained by the Na⁺-K⁺ ATPase pump
- Action potential is prolonged and divided into several phases
  - fast Na⁺ channels open causing depolarization
  - slow Ca²⁺-Na⁺ channels open for 200-300 ms
  - K⁺ conductance is inhibited while the Ca²⁺-Na⁺ channels are open, but rises rapidly to produce repolarization
- Excitation-contraction coupling is similar to skeletal muscle, except that metabolism is exclusively oxidative and Ca²⁺ diffuses in from the T-tubules as well as the sarcoplasmic reticulum
- There is no summation of action potentials to produce contraction, unlike skeletal muscle
- The refractory period is about 0.15 s in the atria and 0.3 s in the ventricles, this limits the maximum rate of contraction
- Action potentials propagate at about 0.5 m/s in muscle and between 0.02 m/s and 4 m/s in the conducting cells
C 2. Electrical properties of the heart

a. Explain the ionic basis of the spontaneous electrical activity of cardiac muscle cells (automaticity).

resting membrane potential \( (V_m) \) maintained by Na\(^+\)-K\(^+\) ATPase pump and ion channels in Physiol G normally -90 mV
depolarization phase 0
m-gates open over 0.2 ms around \( V_m \) -65 mV, raising \( g_{Na} \) markedly
rapid influx of Na\(^+\) (and Ca\(^{2+}\)), \( V_m \) rises to +30 mV
h-gates close over 1 ms and \( g_{Na} \) falls again
h-gates remain closed until repolarization (refractory period)
phase 1
when \( V_m \) is positive in phase 0, K\(^+\) efflux through \( i_{to} \) channels is increased due to electrochemical gradient
this is the \( i_{to} \) “transient outward current” of phase 1
\( i_{to} \) is pronounced in atrial cells which merge phases 1 and 3
phase 2
plateau is maintained by Ca\(^{2+}\) influx through
L channels (predominant) open at \( V_m \) +30 mV
stay open to maintain plateau
T channels open briefly at \( V_m \) -20 mV
minor effect
Ca\(^{2+}\) influx is balanced by K\(^+\) efflux
K\(^+\) current through \( i_{K1} \) channels is \textit{inwardly rectified}
\( g_{K} \) is high for inward currents and low for outward currents
\( g_{K} \) is low during phase 2 and the small K\(^+\) current balances the Ca\(^{2+}\) current
Ca\(^{2+}\) channels slowly inactivate and \( i_{K} \) channels slowly open
phase 3
delayed rectifier \( i_{K} \) channels finally open
\( i_{K} \) current rises as \( V_m \) falls
outward K\(^+\) current through \( i_{to} \), \( i_{K1} \) and \( i_{K} \) repolarize cell
phase 4
Ca\(^{2+}\) concentration is restored by Ca\(^{2+}\)-Mg\(^{2+}\) ATPase pump and Ca\(^{2+}\)/Na\(^+\) secondary active transport
Na\(^+\) and K\(^+\) gradients are maintained by Na\(^+\)-K\(^+\) ATPase pump
in automatic cells, specific Na\(^+\) channels open with hyperpolarization to produce \( i_{n} \), an inward current depolarizing the cell
when \( V_m \) becomes partly depolarized, Ca\(^{2+}\) channels open, initiating a rapid rise in \( V_m \) until an action potential is initiated

Many cardiac muscle cells display automaticity (spontaneous regular action potentials). The cells of the conducting system display the greatest automaticity; usually the SA node cells start the regular action potentials which spread to the rest of the myocardium.

The cells of the SA node have membranes which are relatively permeable to Na\(^+\) and so have a resting membrane potential of only -55 mV to -60 mV. At this potential the fast Na\(^+\) channels remain permanently closed and refractory. The gradual leak of Na\(^+\) into the cell causes a progressive rise in the membrane potential until the slow Ca\(^{2+}\) channels are activated. The influx of Ca\(^{2+}\) and Na\(^+\) generates an action potential for 100 to 150 ms before the channels close and the K\(^+\) channels open, repolarizing the cell.
b. Describe the normal and abnormal processes of cardiac excitation.

The sinus nodal fibres fuse with the atrial cardiac muscle fibres, carrying the action potential throughout the atria. There are several condensation of muscle fibres which carry the action potential more rapidly: the anterior interatrial band and the internodal pathways which run to the AV node. The action potential reaches the AV node after 30 ms. Propagation of the action potential throughout the atria takes under 100 ms.

The AV node consists of transitional fibres from the internodal pathways, a node within the atrium and penetrating fibres connecting to the distal portion of the AV bundle in the ventricle. The fibres of the AV node conduct the action potential very slowly due to their low degree of polarization, small size and few gap junctions. This results in a delay in transmission of the action potential of about 130 ms. The AV node can conduct only one way in normal contraction.

Within the interventricular septum, the AV bundle joins the Purkinje fibres. These conducting cells are of a large diameter and have many gap junctions, transmitting the action potential rapidly throughout the ventricles. The transmission time for the entire Purkinje system is 30 ms. Propagation to the entire ventricular muscle takes another 30 ms, yielding a coordinated contraction.

Abnormalities of cardiac conduction

- accessory atrioventricular muscle bundle (WPW) may lead to recurrent arrhythmias or rapid conduction of AF or flutter.
- EAD early after depolarization occurs in phase 3 at a slow heart rate
  Ca\(^{2+}\) channels recover and can be reactivated before phase 4
- DAD delayed after depolarization occurs in phase 4 at high heart rate
  raised ICF [Ca\(^{2+}\)] results from high rate and produces spontaneous Ca\(^{2+}\) release from sarcoplasmic reticulum
- ectopic pacemaker
  AV node or Purkinje fibres or even muscle may generate action potentials at a higher frequency than the SA node and thus become the pacemaker
  If transmission of action potentials is blocked, automaticity of more distal cells will produce a continued but slow rate of contraction
- fibrillation
  if electrical activity in the atria or ventricles becomes uncoordinated because of high rate or abnormal conduction, a stable state of fibrillation may result
- abnormal cardiac may be terminated by external initiation of action potentials
  overdrive pacing
  DC reversion

c. Explain the physiological basis of the ECG.

The ECG is a representation of the net electrical potential detected at the skin from the electrical events taking place in the cardiac cycle. Depolarization moving towards the observed lead gives a positive deflection as the extracellular fluid becomes more negatively charged around depolarized tissue than around polarized cells. The P wave represents atrial depolarization, the QRS complex, ventricular depolarization and the T wave ventricular
During the plateau phase of depolarization, there is little effect on the ECG as there is little flow of current. The initial depolarization of the ventricles produces the Q or R wave, the gradual reduction in membrane potential is represented in the ST segment and the repolarization produces the T wave.

Thus the PR interval represents the time between atrial and ventricular depolarization, usually 160 ms, and the QT interval is close to the period of ventricular contraction, about 350 ms.

The standard leads of the ECG are I, II, III, aVR, aVL, aVF and V₁ to V₆.

Depolarization of the atria proceeds from the SA node around the walls, giving a net vector at about 60°. Repolarization of the atria takes place in the same direction, but occurs at the same time as ventricular depolarization which obscures it on the ECG.

Because depolarization of the ventricles proceeds from the septum down to the apex and around the left and right ventricles, finishing with the superior part of the left ventricle, the net electrical vector during the QRS complex is initially towards the apex (60°), then swinging to the left (-60°). Repolarization proceeds from the apex and outer surface back towards the base of the heart, generating a net vector about 40° in the frontal plane.

The QRS axis may be altered by the position of the heart. LAD is seen in expiration and in short fat people and RAD in inspiration and in tall thin people. The normal range is 20° to 100°. Ventricular hypertrophy causes axis deviation towards the hypertrophied ventricle, because of the increased muscle mass and delay in depolarization. Bundle branch block causes a delay in depolarization of one ventricle and thus results in axis deviation towards the blocked side as well as widening of the QRS complex. Bundle branch block also causes repolarization of the blocked ventricle much later than the ventricle with normal conduction, causing the axis of the T wave to deviate away from the blocked side.

The size of the QRS complex is determined by the muscle mass of the ventricles and the effective conduction of electrical potentials to the skin. Thus it is increased in ventricular hypertrophy and reduced in pericardial effusion or COAD.

When part of the ventricle is acutely injured (usually infarcted) it remains constantly depolarized. This produces an electrical vector directed away from the infarct. As the point in the ECG during which no current flows is the start of the ST segment when the entire ventricle is depolarized (J point), the ST segment is elevated relative to the TP segment in the leads over the site of injury. This is because the ST segment remains the true baseline, while the TP segment is depressed by the vector produced by the infarcted muscle while the rest of the ventricle is polarized. With reperfusion or fibrosis, this effect on the TP segment diminishes over time.

Digoxin prolongs the period of depolarization of cardiac muscle, causing changes in the T wave and ST segment in overdose as well as impairing conduction at the AV node.

d. Describe the factors that may influence cardiac electrical activity.

**Na⁺**
- gradient has little effect on resting membrane potential
- high ECF [Na⁺] is required for phase 0 $V_{\text{max}}$
- gradient required for secondary transport of Ca²⁺ out of the cell

**K⁺**
- gradient is the major determinant of resting membrane potential
- low ECF [K⁺] is required for maintaining the electrical gradient which drives phase 0
- high ECF [K⁺] causes low $V_{\text{max}}$ and slow conduction

*Cardiac electrical function 1.C.2.3 James Mitchell (November 5, 2001)*
Ca$^{2+}$

low ECF [Ca$^{2+}$] or blockade of Ca$^{2+}$ channels increases the slope of phase 2 and reduces its duration, it also markedly reduces force of contraction
cycle length
i$_{K}$ inactivates very slowly
rapid heart rate results in i$_{K}$ being active in phase 2
increased slope and reduced duration of phase 2 (adaptive)

Activity of the SA and AV nodes is controlled by parasympathetic and sympathetic nerves. Vagal stimulation releases acetylcholine which increases membrane permeability to K$^+$ and thus hyperpolarizes the cells. This reduces the rate of discharge at the SA node and delays or blocks conduction in the small fibres of the AV node.

Sympathetic nerve stimulation releases noradrenaline which increases intracellular cAMP via G-protein-linked β-receptors. A rise in protein kinase activity increases membrane permeability to Na$^+$ and Ca$^{2+}$ as well as upregulating the Ca$^{2+}$ uptake by sarcoplasmic reticulum. Increased Na$^+$ and Ca$^{2+}$ permeability leads to more rapid depolarization of cells and more rapid uptake leads to quicker relaxation. These changes thus yield both chronotropic and inotropic effects.

e. Describe and explain the mechanical events of the cardiac cycle and correlate this with the electrical and ionic events.

The cardiac cycle consists of diastole and systole. During diastole, the heart initially fills with blood passively from venous return. The SA node initiates the electrical activity which drives the cardiac cycle. This leads first to atrial depolarization, which produces the P wave of the ECG and contraction which increases the end diastolic volume of the ventricles about 25% and produces the venous a wave.

After a delay of about 160 ms, the conducting system of the ventricles and the ventricles themselves depolarize, generating the QRS complex, and contract, closing the AV valves (S$_1$) and producing the venous c wave. Intraventricular pressure rises rapidly (isovolumetric contraction), opening the aortic and pulmonary valves at around 80 mmHg and 8 mmHg respectively.
There is a period of rapid ejection in systole, followed by slower ejection and then closure of the aortic and pulmonary valves ($S_2$). During systole the atria have filled with venous blood, producing the $v$ wave. Relaxation of the ventricles also coincides with the $T$ wave of the ECG. The cycle then begins again with passive filling of the ventricles.
**C 3. Determinants and control of cardiac output**

a. **Explain Starling's law of the heart and its relation to excitation-contraction coupling.**

The Frank-Starling mechanism is the rise in developed force of contraction with increasing stretch of the myocardium with the result that within physiological limits, stroke volume rises with end diastolic volume: the heart pumps out as much blood as comes in. This mechanism is produced by the increased force of contraction developed by cardiac muscle with increasing distension of the heart producing both an increased passive tension and active contraction as the interdigitation of actin and myosin fibres is optimized up to a point by increased stretch. Stretch on the right atrial wall also produces a small direct chronotropic effect.

The pressure-volume relation was originally described in vitro as a length-energy relationship for isolated myofibrils. The energy term is interpreted as force, tension, work, pressure or cardiac output with decreasing reliability. The length term is measured as LVEDV, LVEDP, LAP, PCWP, RAP or CVP with decreasing reliability.

b. **Define preload, afterload and myocardial contractility.**

**preload**
- the wall-stress of the ventricle in diastole
  - a description of the filling pressure of the heart
  - increased by
    - systemic filling pressure
    - intravascular volume, vascular compliance
    - posture, activity, atrial contraction
  - decreased by
    - gravity, PEEP, IPPV, tamponade, mitral stenosis
    - resistance to venous return (SVR)

**afterload**
- the wall stress of the ventricle in systole
- a description of the resistance against which the heart ejects blood
- increased by
  - diastolic pressure, SVR (major determinant normally)
  - aortic valve impedance
  - circulatory impedance: elastic vessels, blood flow characteristics
  - ventricular inertia
- decreased by
  - wall thickness (T = Pr/2h)

**contractility**
- the force of contraction of the ventricle independent of preload and afterload
- measured as dP/dt or systolic pressure curve over a range of preloads
- increased by
  - intracellular Ca²⁺ (digoxin, Treppe & Bainbridge effects)
c. Describe the factors that control preload, afterload and myocardial contractility.

The stroke volume of the ventricles depends on end diastolic and end systolic volumes. EDV ranges typically from 120 ml to 180 ml and ESV from 10 ml to 50 ml. Thus cardiac output can be at least doubled by increases in stroke volume. Increases in rate can increase cardiac output by a factor of about 3 to 4 depending on fitness.

Cardiac output is determined largely by systemic factors as the Frank-Starling mechanism ensures that in most circumstances cardiac output equals venous return. Preload is determined by total venous return (in turn determined by the autoregulation of components of the systemic circulation and dependent on metabolic activity). It is also dependent upon effective function of the atria and upon the duration of diastole to allow adequate ventricular filling.

Afterload is a function of total peripheral resistance, provided there is no local problem such as aortic valve disease. Peripheral resistance is determined by arteriolar tone, much of which is autoregulated in the splanchnic circulation under resting conditions. In exercise, a substantial fall in resistance of the circulation to skeletal muscle and in hyperthermia dilatation of skin circulation can result in a big fall in TPR and consequent rise in cardiac output in order to maintain blood pressure.

Myocardial contractility is increased by preload, heart rate (force-frequency relation), circulating catecholamines acting at cardiac β₁-receptors and inotropic agents such as digoxin and phosphodiesterase inhibitors. It is reduced by parasympathetic tone, hypoxia, hypercapnia, acidosis, myocardial depressants and loss of myocardium.

d. Describe myocardial oxygen demand and supply.

Myocardial contraction is around 20% efficient in producing physical work in pumping blood, the remainder of energy used being liberated as heat. Metabolism in cardiac muscle is almost exclusively aerobic, oxygen demand being directly related to work. The oxygen requirement is proportional to the tension-time product. Wall tension is equal to Pr/2h (proportional to pressure and radius and inversely to wall thickness). Thus afterload is a major determinant of oxygen requirement as it increases the pressure derived in systole and heart rate and stroke volume are not major elements in oxygen demand.

Oxygen supply to cardiac muscle is via the coronary arteries. There is significant anatomical variation in their distribution. The usual pattern is of a right coronary supplying the right ventricle and extending around to the posterior aspect of the left ventricle and a left coronary dividing into LAD supplying the anterior of the left ventricle and a circumflex artery extending to the apex and posterior of the heart, anastomosing with the RCA territory. There is significant anastomosis of the arterial supply, allowing for retrograde perfusion in some cases of coronary stenosis or occlusion.

Resting flow is about 225 ml/min with a 70% efficiency at extracting O₂, increasing up to about 800 ml/min in exercise. Perfusion is best in diastole, especially in the subendocardial region of the LV, where there is very little perfusion during systole.
e. Describe Guyton’s cardiac output curves and explain the factors that affect them.

![Cardiac output curves](image)

These are the curves for cardiac output and venous return as related to right atrial pressure. Two curves for a particular situation intersect at the cardiac output, assuming that the Frank-Starling mechanism is operating. This enables easy analysis of the effects of physiological changes which affect either curve.

The cardiac output curve shows a progressive rise in output as filling pressure rises up to a maximum level. Changes in intrathoracic pressure shift the whole curve left or right as the right atrial pressure is shifted relative to systemic venous pressure. Changes in contractility shift the maximum level of the output curve. Cardiac tamponade flattens the curve as the non-compressible fluid in the pericardial cavity makes diastolic filling unresponsive to rises in filling pressure.

The venous return curve runs from zero where right atrial pressure is equal to systemic filling pressure back to a maximum level. Further reduction in right atrial pressure well below atmospheric pressure causes collapse of extrathoracic veins rather than any further increase in venous return. Reduced resistance to venous return, from shunting or dilatation of arteriolar or venous circulation, increases the slope of the curve. A rise in systemic filling pressure, from infusion of fluid or effective autotransfusion from vasoconstriction in response to sympathetic activity, shifts the curve up and to the right. Vasoconstriction will also increase resistance and reduce the slope of the curve.

As the cardiac output curve has quite a steep section, manipulating venous return to shift the intersection of the curves to the right can produce a very marked increase in cardiac output in the short term. Examples include transfusion, sympathomimetics and A-V shunting.

g. Describe the pressure-volume relationship of the ventricle and its clinical applications.

Acute cardiac damage from infarction or other injury results in a marked reduction in the effectiveness of contraction, with a resultant rise in right atrial pressure and fall in CO (1→2). Reflex sympathetic discharge followed by recovery (if any) and fluid retention produces a rise in contractility and in systemic filling pressure, leading to a recovery of CO at a higher right atrial (and systemic filling) pressure (2→3).

Thus a certain amount of fluid retention is adaptive in cardiac failure and is a normal response to
a fall in cardiac output. However excess fluid retention becomes maladaptive as the volume-
pressure curve of the ventricle shows a fall in effectiveness of contraction at very high filling pressures, presumably as a result of distraction of actin and myosin filaments beyond their optimal interdigitation. Increased ventricular radius and wall tension also directly increases myocardial oxygen demand, further compromising the heart. Rising filling pressures lead to systemic and pulmonary oedema.

This example illustrated both the clinical usefulness of increasing circulating volume in circumstances of reduced effectiveness of contraction (AMI or spinal anaesthesia) and also of limiting circulating volume with diuretics in chronic cardiac failure.
a. Describe the distribution of blood volume in the various regional circulations and explain the factors that result in redistribution of blood in health and disease.

Distribution of blood volume:
- Pulmonary circulation: 9%
- Heart: 7%
- Arteries: 13%
- Arterioles: 2%
- Capillaries: 5%
- Veins: 64%

The distribution of cardiac output to various tissues is determined largely by local factors affecting arteriolar tone and to a lesser extent by sympathetic and parasympathetic nervous activity. For laminar flow, \( Q = \frac{\Delta P}{R} \) where \( R \) is resistance in the vessel, equal to \( 8\eta l/\pi r^4 \).

Thus:
\[
Q = \frac{\pi Pr^4}{8\eta l}
\]
(Poiseuille’s Law)

Laminar flow occurs in situations where Reynold’s number is less than 200 and turbulent flow at over 2000, with turbulent flow at branching points and other irregularities at values between 200 and 2000. Reynold’s number = \( \frac{vd}{\rho} \) where \( \rho \) is density and \( \eta \) viscosity.

Blood flow distribution at rest:

<table>
<thead>
<tr>
<th>Tissue</th>
<th>% CO</th>
<th>ml/min</th>
<th>ml/min/100g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>14</td>
<td>700</td>
<td>50</td>
</tr>
<tr>
<td>Heart</td>
<td>4</td>
<td>200</td>
<td>70</td>
</tr>
<tr>
<td>Bronchi</td>
<td>2</td>
<td>100</td>
<td>25</td>
</tr>
<tr>
<td>Kidneys</td>
<td>22</td>
<td>1100</td>
<td>360</td>
</tr>
<tr>
<td>Adrenal</td>
<td>0.5</td>
<td>25</td>
<td>300</td>
</tr>
<tr>
<td>Liver</td>
<td>27</td>
<td>1350</td>
<td>95 (75% portal)</td>
</tr>
<tr>
<td>Muscle</td>
<td>15</td>
<td>750</td>
<td>4</td>
</tr>
<tr>
<td>Bone</td>
<td>5</td>
<td>250</td>
<td>3</td>
</tr>
<tr>
<td>Skin</td>
<td>6</td>
<td>300</td>
<td>3</td>
</tr>
</tbody>
</table>

Local control of blood flow in the short term is determined by tissue metabolism. Flow rises slower than a rise in metabolism as extraction of oxygen and nutrients is not maximal at rest. The exact mechanism of local vasodilatation is not known. Candidates as local vasodilators include adenosine (and its phosphates), \( \text{CO}_2 \), lactate, histamine, \( K^+ \) and \( H^+ \). It is also theorized that oxygen lack causes vasodilatation by relaxing precapillary sphincters.

These mechanisms operate from minute to minute to regulate local flow in most tissues. They also operate over a longer period after an episode of nutrient or oxygen lack, causing reactive hyperaemia after release of a tourniquet or active hyperaemia in a muscle after exercise. The net effect is a constant perfusion of most tissues at rest over a wide range of arterial pressure.

Specialized mechanism operate to regulate local flow in the renal, cerebral and coronary circulations. In the kidney, the juxtaglomerular apparatus adjusts constriction of afferent and efferent arterioles to maintain GFR. In the brain, \( \text{CO}_2 \) and \( H^+ \) ions act as potent vasodilators.

Arteriolar flow responds to local demands as a result of the release of nitric oxide (NO). Increased flow through an arteriole causes increased shearing of endothelial cells and results in the release of NO, dilating the arteriole. Many other noxious stimuli also cause the release of NO.
In the longer term, hypoxia is a stimulus for the development of new vessels in most tissues over the course of weeks and months.

b. Explain the factors which determine systemic blood pressure and its regulation.

The physiological determinant of systemic blood pressure are cardiac output and total peripheral resistance. The physical determinants are arterial blood volume and arterial compliance. Systemic blood pressure varies between systolic and diastolic pressures, the mean arterial pressure is the average pressure over time.

In physical terms the mean arterial pressure equals arterial volume divided by arterial compliance. Arterial volume (\( V_a \)) is determined by the cardiac output entering the arterial system (\( Q_h \)) and the peripheral flow leaving it (\( Q_r \)).

\[
\frac{dV_a}{dt} = Q_h - Q_r
\]

Peripheral resistance is defined as pressure drop divided by flow:

\[
R = \frac{(P_a - P_{ra})}{Q_r}
\]

Compliance of the large vessels is determined by their physical composition. In the smaller arteries and arterioles, smooth muscle in the vessel walls plays a large role in determining compliance and resistance. It is defined as change in volume per unit change in pressure:

\[
C_a = \frac{dV_a}{dP_a}
\]

It is more useful in physiological terms to describe mean arterial pressure in terms of cardiac output and peripheral resistance. \( P_a \) will approach equilibrium for a given \( R \) and \( Q_h \). The rate of approach will depend on arterial compliance:

\[
\frac{dP_{sa}}{dt} = \frac{(Q_h - R \cdot (P_a - P_{ra}))}{C_a}
\]

In normal circumstances, \( P_{ra} \) is small compared with \( P_a \). Integrating with respect to time gives an exponential equation for \( P_a \) approaching \( Q_h \cdot R \) with a time constant proportional to \( C_a \). So a non-compliant system will show rapid pressure changes in response to changes in cardiac output or peripheral resistance.

The difference between diastolic and systolic pressures is pulse pressure. It is determined by stroke volume and arterial compliance. As cardiac output is the product of stroke volume and heart rate, an increase in stroke volume at a fixed heart rate will increase both mean and pulse pressures. With age and atherosclerosis, arterial compliance falls, resulting in greater pulse pressure without necessarily changing mean pressure. This places greater strain on the heart as it is more efficient at volume work than pressure work.

Control in Cardiac control (1.C.5)

c. Describe total peripheral vascular resistance and the factors that affect it.

Resistance in fluid flow is defined as pressure drop per unit flow. Total peripheral resistance (\( R \)) can therefore be determined as \( (P_a - P_{ra})/Q_r \). In the systemic circulation the majority of resistance is in the arterioles. This is because of the relationship of radius to resistance in vessels:

\[
R = \frac{k}{r^4}
\]

Although the arterioles have a greater total cross sectional area than the large vessels, their smaller average radius more than outweighs this. In capillaries, the situation is reversed, mean radius being far smaller again, but the total number of vessels in parallel making it a low resistance section of the circulation.

Peripheral resistance is maintained largely by sympathetic tone maintaining a basal level of vasoconstriction in vascular beds in skeletal muscle and skin. Skeletal muscle constitutes the largest single vascular bed and the major determinant of total peripheral resistance. Resistance in other circulations is also partly controlled by neural factors but also by local control (especially in the brain and myocardium).

The main effect of increased sympathetic tone is vasoconstriction of the arterioles via \( \alpha \)-receptors. Circulating adrenaline may oppose this effect by causing skeletal muscle vasodilation via \( \beta_2 \)-receptors at low concentrations.

Many local metabolites and transmitters affect vascular tone at a local level,
vasodilators including adenosine, H⁺, CO₂, lactate, K⁺ and phosphate, and some acting via EDRF (NO): bradykinin, histamine and leukotrienes. In anaphylaxis, sepsis or severe metabolic acidosis, circulating levels of these mediators can result in generalized vasodilation and hypotension (shock).

d. Describe the general mechanisms involved in local vascular control.

Local vasodilation results from increased metabolism via a number of mediators. The products of metabolism H⁺, CO₂, lactate, adenosine, K⁺ and phosphate all act as vasodilators, adenosine playing a key role. Oxygen may play a role as a vasoconstrictor. These factors combine to provide a negative-feedback mechanism to match blood flow and oxygen supply to tissue requirements. In the pulmonary circulation, the situation is reversed, oxygen acting as a vasodilator and CO₂ as a vasoconstrictor.

Mechanical factors play a role in local perfusion in muscle tissue. Blood flow is severely limited during contraction in both myocardial and skeletal muscle due to extrinsic compression of vessels. This effect is opposed by the myogenic mechanism in which vascular smooth muscle contracts in response to an increase in transluminal pressure.

Endothelium-mediated tone results in vasodilation in response to an increase in longitudinal pressure gradient through release of NO, allowing flow to increase with driving pressure.

e. Describe the essential features of microcirculation in relation to its structure, fluid exchange and control mechanisms present in the pre- and post-capillary sphincters.

The systemic microcirculation consists of arterioles, metarterioles, capillaries and venules. Arterioles range from 5 µm to 100 µm in diameter and have a media containing smooth muscle. They give rise to capillaries and metarterioles (10-20 µm). Capillaries are around 5 µm in diameter and 0.5-1 mm long forming an interconnecting network. They rejoin to form venules.

Blood flow in the capillary network is regulated at the arteriolar-capillary junction (precapillary sphincter) and is intermittent in any one capillary, varying from zero to several mm/s. The amount of capillary flow is regulated upstream by arteriolar tone and downstream by venous pressure. Arteriolar tone responds to local factors (myogenic mechanism, EDRF, metabolites and vasodilators) and also to systemic control via sympathetic tone and circulating vasoactive mediators.

The major locally acting vasodilators are EDRF (NO) which acts via cGMP and is released in response to many agents as well as longitudinal pressure gradient and possibly PGI₂, released in response to shear stress and acting via cAMP. Metabolites which act as direct vasodilators in adenosine, CO₂, H⁺ and K⁺.

Capillary blood has a lower haematocrit (around 15%) than arteriolar blood (more than 30%) because the obligatory cell-free boundary layer of plasma at the endothelial surface represents a significant proportion of the volume of a capillary (Fabraeus Effect). There is also less red cell flow into side-opening capillaries than end-opening ones with regard to arteriolar flow.

The wall of capillaries consists of a single layer of endothelial cells bounded by a basement membrane. The junctions of the endothelial cells include some pores of about 4 nm which are more permeable than the rest of the lining. Some capillaries in the liver, kidney and gut have fenestrations which are large discontinuities in the endothelium covered by membrane. Pinocytotic vesicles are prominent in the endothelial cells.

The capillary wall is permeable as the function of capillaries is the transport of mediators, substrates and metabolic products to and from the periphery. Diffusion is the major transport mechanism across the capillary wall. The rate of diffusion of a substance (J) is described:

\[ J = -PS \cdot (C_o - C_i) \]

Where P is the capillary permeability, S the surface area and C_o - C_i the
concentration gradient. For small molecules and ions and highly lipid-soluble molecules, the capillary permeability is very high and their transport across the membrane is flow-limited. For lipid insoluble molecules, permeability falls rapidly with molecular size to almost zero at 60 kd. Thus albumin, being polar and over 60kd, shows negligible diffusion.

The equilibration of ions and molecules across the membrane is complicated somewhat by the presence of non-diffusible charged molecules such as albumin because of the Gibbs-Donnan effect.

Though most of the water movement across the capillary membrane is a result of diffusion, the net water flow is determined by capillary filtration. Water filtration or absorption across the membrane depends on the net pressure across the membrane. The components of the net pressure are hydrostatic pressure and oncotic pressure. Hydrostatic pressure within the capillary ranges from around 32 mmHg at the arterial end to 15 mmHg at the venous end. Tissue hydrostatic pressure is between –1 and –7 mmHg.

The oncotic pressure ($\pi$) depends on the concentration of non-diffusible solute (mainly albumin) and its reflection coefficient ($\sigma$, close to 1 for albumin) and absolute temperature:

$$\pi = \sigma RT \cdot (C_i - C_o) (R = \text{gas constant})$$

The net water flow by filtration depends on the total pressure gradient and the filtration constant for water across the membrane ($k$):

$$\text{flow} = k \cdot [(P_c + \pi_i) - (P_i + \pi_p)]$$

Total flow is also proportional to the area of membrane and inversely proportional to the viscosity of water and thickness of the membrane.

In most tissues, the net flow of water out of capillaries is small, as the hydrostatic gradient from the arterial to venous end of the capillaries ensures that the rate of water loss at the arterial end is almost balanced by the water absorption at the venous end. In the glomerulus, a high hydrostatic pressure ensures filtration over the whole capillary length whereas in the intestinal mucosa, a high plasma oncotic pressure results in absorption over the entire length.

This mechanism also acts to compensate for blood loss. A fall in both arterial and venous pressure results in a lower hydrostatic pressure over the whole capillary length and consequent absorption of water from the interstitial compartment into the circulation. Similarly, a rise in venous and arterial pressures, though initially partly compensated for by increased arteriolar tone, results in extravasation of fluid: oedema. Net loss of fluid and albumin is dealt with by the lymphatics which ultimately return them to the circulation.

The last mechanism by which molecules are transferred across the capillary membrane is by pinocytosis. Small amounts of large molecules which are otherwise non-diffusible can be transferred in these vesicles.
C 5. Control of circulation

a. Describe the role of the vasomotor centre and the autonomic nervous system in the regulation of cardiac output and venous return.

The peripheral vasculature is innervated by the sympathetic nervous system, from fibres of the coeliac plexus in the abdominal viscera and from fibres from the sympathetic chain in the somatic circulation. Sympathetic activity also causes the release of systemic adrenaline and noradrenaline which act on the circulation as circulating factors. Parasympathetic innervation is significant only in the vagal innervation of the heart, where stimulation produces a reduction in rate, transmission and contractility.

Integration of the autonomic control of circulation takes place in the vasomotor centre in the medulla and lower third of the pons. Within the vasomotor centre lies the vasoconstrictor centre, anterolateral in the upper medulla, which stimulates sympathetic vasoconstrictor fibres via noradrenergic transmission. The vasodilator area lies anterolaterally in the lower medulla and acts to inhibit the vasoconstrictor area. A sensory area lies posterolaterally in the medulla and receives projections from the vagus and glossopharyngeal nerves. It projects to the vasoconstrictor and vasodilator areas and produces the baroreceptor reflex.

In the resting state there is a baseline discharge throughout the sympathetic vasoconstrictor fibres, producing vasomotor tone which is partially responsible for maintaining arterial pressure. There is also baseline tone in the sympathetic and parasympathetic innervation of the heart. Many higher centres affect activity of the vasomotor centre, especially the hypothalamus.

The vasomotor centre acts to compensate rapidly for changes in blood pressure. A fall in blood pressure, increased motor activity or a fright generates a rapid response inhibiting parasympathetic outflow, increasing sympathetic vasoconstrictor tone and releasing adrenal hormones. This produces a rise in heart rate and contractility, arteriolar constriction which increases blood pressure, and increased venous tone which increases venous return and EDV. These effects can double arterial pressure within 5 to 10 seconds. The reverse effects are produced by reducing sympathetic tone (as in spinal anaesthesia).

b. Describe the functions of baroreceptors and relate this knowledge to clinical situations.

Baroreceptors are pressure-sensitive nerve endings in the major arteries of the neck and thorax. They are particularly prominent in the carotid sinus and the aortic arch. Signals from the carotid sinuses are transmitted via Hering’s nerve and IX to the tractus solitarius in the medulla. Signals from the arch of the aorta go via X to the same projection.

The firing rate from baroreceptors is extremely responsive to arterial pressure in the normal range, varying markedly from diastole to systole. They respond to both arterial pressure and the rate of rise in arterial pressure. They accommodate rapidly to changes in the baseline blood pressure. Baroreceptor firing has a strong inhibitory effect on the vasoconstrictor centre, so any sudden fall in arterial pressure (for example, from standing up), results immediately in an autonomic response to increase CO and TPR. The carotid sinus receptors have a stronger influence on the vasoconstrictor centre than those of the aortic arch.

Baroreceptors are required for the reflex responses to short-term changes in blood pressure. This is required for normal response to changes in posture and in theatre for normal response to hypotension resulting from hypovolaemia. They adapt rapidly to sustained changes in blood pressure and become less sensitive due to reduced vessel wall compliance in long-standing hypertension.

External pressure on the carotid sinus particularly can cause a marked fall in blood pressure and heart rate. This is used clinically in cases of SVT or rapid AF and is also described as causing syncope in some individuals with tight collars.
The cardiopulmonary baroreceptors are found in the atria, ventricles and pulmonary vessels. The atrial receptors are divided into A-receptors which respond to atrial tension during systole and B-receptors which respond to wall tension during atrial filling. Stimulation of these receptors results in secretion of ANF and decreased sympathetic outflow to the kidneys, increasing RBF and urine output as well as decreased sympathetic tone to the heart. ANF inhibits the release of ADH, renin and aldosterone. These effects are important in the regulation of plasma volume and blood pressure over hours to days.

c. Explain the role of the autonomic nervous system in controlling systemic vascular resistance and redistribution of blood volume.

Sympathetic innervation of the blood vessels and the adrenals plays a major role in the regulation of TPR and volume distribution. Baseline tone in sympathetic outflow from the vasoconstrictor centre maintains arteriolar and venous tone which maintain systemic blood pressure.

An increase in sympathetic tone, as a result of stimulation of the vasoconstrictor centre, results in increase arteriolar tone, increasing TPR and blood pressure and also in increased venous tone, reducing venous capacitance, rapidly increasing venous return and EDV in the short term, thus boosting CO.

Circulating noradrenaline from the adrenals acts on $\alpha$ receptors in vessels to produce vasoconstriction. Adrenaline at low concentrations acts on $\beta$ receptors in skeletal muscle, producing vasodilatation, but at higher concentrations, its $\alpha$ effects predominate.

The vascular beds which are most responsive to changes in sympathetic tone are skeletal muscle and skin. Skeletal muscle overall constitutes the largest vascular bed and plays a major role in determining TPR. The splanchnic and renal circulations are less responsive to sympathetic tone and the cardiac and cerebral hardly at all.

d. Explain the neural and humoral regulation of blood volume.

Effective blood volume is affected by the compliance of the venous side of the circulation. This is reduced with an increase in sympathetic tone or by circulating $\alpha$ agonists resulting in increased filling pressure and increased cardiac output.

True blood volume is determined by net loss or gain from the intravascular compartment. Volume gain can result from oral fluid intake, intravenous infusion and to a minor extent from products of metabolism. Volume loss can result from bleeding, evaporative loss in expired air, secretion as sweat and enteric losses from malabsorption. Redistribution between intravascular and interstitial spaces can result from changes in hydrostatic or osmotic pressures detailed above.

Circulating volume is maintained within narrow bounds by renal loss or retention of fluid and to some extent by the hypothalamic stimulus of thirst.

Renal blood flow and consequently GFR is determined by the afferrent and efferent arteriolar tone at the glomerulus, given an adequate systemic blood pressure. The main external control of renal arteriolar tone is via sympathetic innervation. An increase in stimulation of atrial baroreceptors results in a reduction in renal sympathetic tone, causing increased RBF and GFR.

***

e. Explain the integrated cardiovascular responses to exercise.

The response to exercise consists of central, local and baroreceptor responses. The central response starts in anticipation of exercise with inhibition of vagal output and increased sympathetic tone resulting in an increase in heart rate and contractility before exercise begins. Increased sympathetic tone also causes vasoconstriction of skin, splanchnic and renal vascular beds.

Local responses in muscle are due to local contraction and metabolites stimulating mechanoreceptors and chemoreceptors which are carried to the medulla in...
type III and IV nerve fibres and result in increased sympathetic tone. The local effects of metabolites and the myogenic response are also important in increasing blood flow to working muscle. Myocardial blood flow also increases with cardiac output in response to local control of coronary vessel tone.

The baroreceptor response helps maintain sympathetic-mediated vasoconstriction of inactive beds and cardiac sympathetic outflow to maintain blood pressure. The arterial chemoreceptors play no role in exercise as arterial gases and pH are usually unchanged.

With prolonged exercise, body temperature rises and so skin vessels dilate to maintain temperature homeostasis. Local metabolites become the major determinant of active muscle vasodilation and muscle blood flow rises to a maximum of 15 to 20 times resting flow. There is still some vasoconstrictor effect from sympathetic innervation even in active muscle. Vasodilation increases capillary hydrostatic pressure and causes increased fluid movement into active tissues and increased lymphatic return. Acidosis, increased temperature and increased O₂ demand and CO₂ production in muscle move the Hb-O₂ dissociation curve to the right, enhancing O₂ extraction and lowering mixed venous PO₂. Oxygen consumption rises to 60 times resting values.

The cardiac response to exercise is an almost linear rise in CO with workload. This is achieved mainly through a rise in heart rate to a maximum of about 180/min, accompanied by a smaller increase in stroke volume of 10%-35% depending on the level of training. The rise in CO is to a maximum of between four and six times resting output and is the limiting factor in heavy exercise.

Venous return is enhanced by the skeletal muscle pump, by reduced venous compliance with higher sympathetic tone and by the increase in respiratory effort. Blood volume is usually slightly reduced because of fluid losses into tissue, as sweat and in exhaled air. This is opposed to some extent by the increased osmotic effect of metabolites and the rise in tissue hydrostatic pressure. Renal blood flow and urine output is reduced.

There is usually a small rise in blood pressure and pulse pressure as the rise in CO is usually greater than the fall in TPR.

At the extreme of exercise, stroke volume and blood pressure fall, sympathetic tone causes cutaneous vasoconstriction resulting in a rise in temperature and blood pH begins to fall and PCO₂ to rise. These changes usually cause sufficient distress to limit exercise, but if it continues, the rise in body temperature can cause rhabdomyolysis and renal failure.

After exercise, sympathetic outflow falls abruptly, resulting in a fall in CO and BP as TPR remains low due to accumulated metabolites. This is corrected by the baroreceptor reflex.

f. Explain the integrated cardiovascular responses to pregnancy.

g. Explain the integrated cardiovascular responses to anaesthesia and regional anaesthesia/analgesia.
C. 6. Regional Circulation

a. Describe the relationship between organ blood flow and demand and the role of autoregulation.

metabolic autoregulation
products of metabolism act as vasodilators
adenosine, PGs, H+, CO2, K+, lactate, osmolarity...
duration of vasodilation after ischaemia depends on the duration of ischaemia

myogenic autoregulation
vascular smooth muscle contracts in response to stretch
prominent in cerebral circulation
acts over seconds

endothelium-mediated autoregulation
longitudinal shear (or flow) causes NO release from endothelium
results in ↑cGMP and dephosphorylation of MLCK
vascular relaxation

neural control
α receptor stimulation
↑intracellular Ca2+, vasoconstriction
predominantly in skin and gut
increases O2 extraction
O2 extraction remains constant until critical flow is reached

β2 receptor stimulation
↑intracellular cAMP, vasodilation
predominantly in muscle
5HT, other innervation
specialized role, active in cerebral and coronary circulations

b. Describe the features of the coronary circulation and explain the clinical significance of these.

The coronary circulation consists of the coronary arteries and veins, the arteriosinusoidal, arterioluminal and thebesian vessels. The right and left coronary arteries arise from the root of the aorta behind the right and left cusps of the aortic valve. The right coronary runs along the right A-V margin and supplies the right atrium and ventricle. The left coronary divides near its origin into the circumflex and left anterior descending arteries. They supply the left side of the heart and commonly a little of the right ventricle. Dominance of the coronary vessels is variable.

The arteriosinusoidal vessels originate from the cardiac chambers and penetrate a short distance into the myocardium where they form endothelium-lined sinuses. The arterioluminal vessels similarly arise from the chambers and the thebesian vessels are veins which drain the myocardium into the chambers. These vessels all play a minor role in supplying myocardial oxygen demands.

The major venous drainage of the heart is via the coronary veins which follow a similar distribution to the arteries except that their common drainage is to the coronary sinus on the posterior aspect of the heart, draining into the right atrium.

There is no significant anastomosis between coronary vessels in normal human hearts. Anastomoses will develop in response to gradual stenosis and occlusion of the coronary vessels but acute obstruction will result in infarction.

Cardiac muscle consumes 8-10 ml/min/100 g of oxygen at rest. O2 extraction is quite efficient with cardiac venous blood having about 5 ml/100 ml O2. Thus any rise in myocardial activity must be accompanied by an increase in blood flow. As a pump it is about 18% efficient (net), but is more efficient at volume work than pressure work. This is
important in aortic stenosis and other high afterload conditions. Myocardium uses both carbohydrate and fatty acids as substrates for energy production and will use ketone bodies or lactate if they are present in high concentrations. Metabolism is aerobic in all but extreme conditions.

The coronary arteries display the same autoregulatory responses as other systemic vascular beds. Local factors are most important in regulating coronary flow. The coronary vessels are best perfused in diastole, as they are not externally compressed by ventricular contraction at this time. The left coronary displays no or retrograde flow at the start of systole as the ventricular pressure compressing the vessels is greater than aortic pressure perfusing them. Later in systole there is anterograde flow which increases dramatically after aortic valve closure and ventricular relaxation when the perfusion pressure is high and external pressure low. The coronary vessels display a very active myogenic mechanism. Right coronary artery flow is more consistent as the right ventricular pressure is lower than aortic pressure throughout the cardiac cycle.

The advantageous perfusion gradient in diastole can be enhanced further by use of an intraaortic balloon pumps. In severe hypotension, perfusion of the endocardial muscle layers is poorest, and this is the site of worst ischaemic damage following hypotension. In tachycardia, the time for perfusion in diastole is reduced, but coronary dilatation from local metabolites is sufficient to maintain perfusion.

Sympathetic innervation of the coronary vessels has a vasoconstrictor effect in isolation, but the increased CO and metabolic demand resulting from the inotropic and chronotropic effects of increased sympathetic tone result in net vasodilation in normal hearts.

c. Describe autoregulation in the cerebral circulation and the factors that may affect it.

in Nervous system (1.G)

d. Describe the renal circulation and explain its significance in maintaining renal function.

anatomy
renal arteries from aorta
→ interlobar, arcuate, cortical radial arteries
→ afferent arterioles, glomerular capillaries, efferent arterioles
→ peritubular capillaries (including vasa recta)
→ progressive rejoicing to form renal veins → IVC

renal blood flow
20% of cardiac output
dependent on CO, MAP and
low net O₂ extraction
most O₂ demand is in tubular reabsorption
countercurrent mechanism of vasa recta reduces medullary PO₂ to ≈20 mmHg
↑ filtrate flow → ↑ metabolic demand → medullary hypoxia
opposed by tubuloglomerular feedback
↑ macula densa flow → adenosine release → ↓ GFR
limits O₂ demand of tubules
analogous to metabolic autoregulation in other tissues
anuria is adaptive in acute stress

e. Describe the hepatic and splanchnic circulation.

anatomy
aorta → coeliac axis, superior and inferior mesenteric arteries → gut
villous countercurrent flow results in better absorption but reduced PO₂ at villus tips

Regional circulations 1.C.6.2 James Mitchell (November 5, 2001)
→ portal venous drainage → liver → hepatic vein → IVC

blood flow
hepatic artery supplies 1/3 of liver flow but 50% of oxygen delivery
portal flow supplies the remainder, total 30% of CO
oxygen extraction is constant down to a level of critical ischaemia
gut ischaemia results in bacterial translocation
hepatic failure (ischaemia) allows endotoxin to circulate
lack of monitoring options has hampered investigation of gut perfusion

f. Describe the skin circulation.

g. Describe skeletal muscle circulation.

h. Describe uteroplacental circulation.

in Maternal physiology (1.O).
C 7. Applied aspects of CVS physiology

a. Describe the responses to changes in posture.

standing
venous pooling in legs and abdomen (less effect if active)
  ↓ right heart venous return
  ↓ right and left heart output
  ↓ BP (also hydrostatic effect due to carotid sinus being above heart)
  ↓ baroreceptor firing
  ↑ sympathetic tone
    peripheral arteriolar and venous constriction
    ↑ HR, contractility
  maintains cerebral perfusion
    (or else fainting → horizontal posture)

b. Account for the cardiovascular changes seen in haemorrhage and hypovolaemia.

haemodynamic
  ↓ filling pressure
  ↓ stroke volume
  ↓ CO
  ↓ MAP
baroreceptor (response maximal at MAP 60 mmHg)
  ↓ stimulation at carotid sinus and aortic receptors
  ↓ vagal tone, ↑ sympathetic tone
    ↑ HR, contractility
    peripheral vasoconstriction
    ↑ SVR, filling pressure
    centralized blood volume
chemoreceptor
  some augmentation of sympathetic response below MAP 60 mmHg
  hypoxia, hypercapnia, acidosis stimulate carotid and aortic bodies
  ↑ sympathetic tone
  ↑ respiratory drive
  minor increase in venous return

cerebral ischaemic response
  further augmentation of sympathetic tone below MAP 40 mmHg
  also ↑ vagal tone (maladaptive)
autoregulatory vascular response
  arteriolar constriction due to myogenic mechanism
reabsorption of tissue fluids
  ↓ capillary hydrostatic pressure
  reversed Starling forces
  transfer of fluid from interstitium into circulation
  up to 1 l/h
  transfer from ICF to interstitial fluid also occurs in response to cortisol
endogenous vasoconstrictors
  adrenaline and noradrenaline
  from adrenal medulla and sympathetic nerves
  responsible for acute sympathetic response
ADH
  rapid secretion from posterior pituitary in response to hypotension
  vasoconstrictor, ↑ water reabsorption from collecting ducts
  ↑ expression of vWF, VIIIc
renin
catalyzes conversion of angiotensinogen to angiotensin I
angiotensin II
vasoconstrictor
↑ ADH, aldosterone
renal conservation of fluid
low MAP reduces RBF, GFR and UO
↑ sympathetic tone causes
afferent and efferent constriction
↓ RBF, GFR
↑ renin secretion (direct and via JGA)
↑ angiotensin II causes
↑ Na⁺ reabsorption
arteriolar vasoconstriction
↑ aldosterone causes
↑ Na⁺ reabsorption from DCT and collecting ducts
ADH above
↓ ANF (minor effect)
timecourse
seconds
baroreceptor, chemoreceptor, cerebral ischaemic responses
minutes
autoregulatory, angiotensin, ADH, capillary fluid shift
hours
full effect of renal fluid retention
C 8. Measurement of CVS function

a. Outline the physics of blood flow.

b. Give a detailed account of the various methods of measuring blood pressure.

in Physics and Measurement (1.R).

c. Explain the various methods of measuring cardiac output as well as their limitations.

Fick principle (Adolph Fick)

pulmonary venous oxygen flux \( (q_3) \) equals pulmonary arterial oxygen flux \( (q_1) \) plus alveolar oxygen uptake \( (q_2) \)

\[
q_1 + q_2 = q_3
\]

\[
q_1 = Q \cdot [O_2]_{pa}
\]

\[
q_3 = Q \cdot [O_2]_{pv}
\]

\[\Rightarrow Q = \frac{q_2}{([O_2]_{pv} - [O_2]_{pa})}\]

so cardiac output \( (Q) \) can be calculated from pulmonary O₂ uptake, and mixed venous and pulmonary venous oxygen concentrations.

Mixed venous oxygen concentration can be measured using a Swan-Ganz catheter and pulmonary venous oxygen concentration approximated with a systemic arterial sample.

This method requires determination of oxygen uptake over several minutes and so requires either a completely closed breathing circuit in anaesthesia or an approximation using mixed expired and inspired oxygen concentrations or a laboratory setting.

Indicator dilution

A known amount of an indicator is introduced into the circulation at a point where the entire cardiac output is passing.

The concentration of the marker is measured downstream before any of the flow is diverted to other vessels and its value is plotted over time. For example, the indicator might be injected in the right atrium and the sampling done from the pulmonary outflow tract.

The amount of indicator \( (n) \) is related to its mean concentration \( (\bar{c}) \), cardiac output \( (Q) \) and the time for which it is detected \( (t_2 - t_1) \):

\[
n = \bar{c}Q(t_2 - t_1)
\]

\[
\bar{c} = \frac{\int c \, dt}{t_2 - t_1}
\]

\[\Rightarrow \dot{Q} = \frac{n}{\int c \, dt}\]

The conventional expression is in the Stewart-Hamilton equation:

\[
\dot{Q} = \frac{n}{\int c \, dt} = \frac{k(T_{core} - T_{indicator})V_{indicator}}{\int_{t_1}^{t_2} -\Delta T \, dt}
\]

This can be done using a dye indicator (which requires a semi-log plot to determine \( t_2 \) when recirculation occurs) or more commonly using cold saline with temperature being the “indicator”. There is an inherent inaccuracy in thermodilution when thermal exchange occurs between the blood and the vessel and structures surrounding it and when cool fluids may be being infused peripherally in a variable fashion.
Echocardiography

Cardiac output (Q) can be calculated using the TOE probe to measure cross-sectional area (A) and flow velocity (V) over the duration of one cardiac cycle (t) at a point where the entire cardiac output is passing (e.g. pulmonary outflow tract).

\[
\bar{V} = \frac{\int V \, dt}{t} \\
Q = A \times \bar{V}
\]

This method assumes equal flow over the whole area and it is technically difficult to perform.

d. Outline methods and principles used to measure regional blood flow.

hepatic
  Fick principle with indocyanine green

cerebral
  Kety-Schmidt technique

renal
  PAH clearance
D. Renal physiology

a. Describe the functional anatomy of the kidneys and explain the physiology of renal blood flow.

The kidneys are paired organs located in the retroperitoneum. Each consists of a cortex, medulla and pelvis which is connected to the ureter which carries urine from the kidney to the bladder. Each kidneys is supplied by a renal artery from the aorta and drained by one or more renal veins to the IVC. The medulla consists of papillae which correspond with the calyces of the collecting system. The medulla and cortex above each papilla composes a lobe.

Innervation of the kidney is by sympathetic noradrenergic nerves.

The renal artery divides into interlobar and then arcuate arteries. These divide into cortical radial arteries which run radially towards the cortical surface. Perpendicular to the cortical radial arteries arise the afferent arterioles, each of which supplies a glomerulus. The afferent arteriole is muscular and regulates flow into the glomerulus.

The glomerulus consists of a group of specialized capillaries, having fenestrated endothelium, a narrow basement membrane and a surrounding of podocytes, all of which allow filtration of fluid into the space surrounding the capillary tuft: Bowman’s space.

The glomerulus is drained by the efferent arteriole which plays a regulatory role like the afferent arteriole. It supplies the peritubular capillaries which surround the cortical tubules and also vascular bundles which extend into the medulla and surround the loops of Henle (the descending and ascending *vasa recta*).

Total renal blood flow (RBF) is 1.1 l/min (20% of CO)

\[ \text{RBF} \text{ determined by MAP and renal vascular resistance} \]
\[ \text{autoregulating over a wide MAP (90 to 200 mmHg)} \]
\[ \text{myogenic mechanism} \]
\[ \text{tubuloglomerular feedback} \]
\[ \text{high Na}^+ \text{ and Cl}^{-} \text{ at macula densa stimulates adenosine production} \]
\[ \downarrow \text{ by constriction of either afferent or efferent arteriole} \]
\[ \text{sympathetic tone (noradrenaline)} \]
\[ \text{angiotensin II} \]
\[ \text{response to macula densa or direct effect of flow on granular cells or sympathetic stimulation of granular cells to increase renin secretion from granular cells} \]
\[ \text{adenosine} \]
\[ \text{local mediator from JGA} \]
\[ \text{afferent constrictor, efferent dilator} \]
\[ \text{ADH in high concentrations} \]
\[ \text{possibly thromboxanes, leukotrienes, endothelin} \]
\[ \text{opposed by} \]
\[ \text{renal PGE}_2 \text{ and PGI}_2 \text{ release} \]
\[ \text{ANF from heart (afferent dilator, efferent constrictor)} \]
\[ \text{possibly dopamine, bradykinin} \]
90% to cortex, 10% to medulla

b. Describe glomerular filtration and tubular function.

Glomerular filtration

bulk flow of fluid from glomerular capillary to Bowman’s space

volume = 20% of RPF (filtration fraction), \approx 125 \text{ ml/min} 

barriers to filtration

endothelial fenestrae

basement membrane

podocytes
all negatively charged

composition
  water
  freely filtered solutes
    small, unbound ions and molecules
  partly filtered solutes
    macromolecules MW 7000 to 70000
    less filtration if negatively charged
dextran 70 5-10%, albumin 0.02%

GFR = K_f · NFP (filtration coefficient x net filtration pressure)
NFP = (P_{bc} + \Pi_{bc}) - (P_{bc} + \Pi_{gc})
in capillary transit
  \Pi_{bc} = 0, P_{bc} and P_{bc} change little, \Pi_{gc} rises from 21 to 33 mmHg
  NFP falls from 24 to 10 mmHg
determinants
  K_f decreased in disease (↓ glomerular surface area)
  P_{gc} ↑ MAP, efferent constriction
    ↓ afferent constriction
  P_{bc} ↑ obstruction
  \Pi_{gc} ↑ plasma oncotic pressure, low RBF

Tubular functions
mechanisms
diffusion
  simple transfer of a substance across the tubular epithelium down its electrochemical gradient
  small lipid-soluble molecules diffuse through membranes
  ions diffuse through channels
facilitated diffusion
  transfer of molecules across the tubular epithelium down a electrochemical gradient via specific transmembrane proteins which bind and release the substrate
  displays saturability, specificity and competition
primary active transport
  transfer of ions or molecules against their electrochemical gradient via a specific transmembrane protein which consumes ATP
  four identified transporters: Na^+/-K^+, H^+, H^+-K^+ and Ca^{2+}-ATPase
secondary active transport
  transfer of multiple ions or molecules across a membrane by a specific transmembrane protein in which one substrate is transported down its electrochemical gradient, providing energy for the transport of the other substrates against their electrochemical gradients
  classified as cotransport or countertransport according to whether substrates travel in the same or opposite directions
endocytosis
  uptake of large molecules by invagination of the cell membrane, forming vesicles
solvent drag
  transfer of small ions or molecules by mass movement of water (solvent) through pores

sites of transport
basolateral membrane
  the only site of primary active transport
luminal membrane
site of diffusion, facilitated diffusion and secondary active transport
paracellular
diffusion across tight junctions between cells
site of Na\(^+\) and Cl\(^-\) diffusion in parts of the tubule

c. Explain the countercurrent mechanisms in the kidney.

The loop of Henle maintains a high tissue osmolarity in the renal medulla, allowing for reabsorption of water and the production of a concentrated urine. It uses a countercurrent multiplier.

**loop of Henle**
- **descending limb**
  - high permeability to water
  - low permeability to Na\(^+\) and Cl\(^-\)
  - water reabsorption due to high tissue osmolarity secondary to NaCl reabsorption in ascending limb
- **ascending limb**
  - low permeability to water
  - high permeability to Na\(^+\) and Cl\(^-\)
  - active reabsorption of NaCl in thick limb and passive in thin limb
  - a small gradient across the tubule is multiplied by the flow through the loop to produce a high tissue osmolarity in the medulla and a hyposoosmotic tubular fluid at the distal end of the loop

**vasa recta**
- medullary blood vessels travel parallel to the loop of Henle
  - start in cortex, run straight to medulla and return to cortex
  - this allows for countercurrent exchange to produce a high plasma osmolarity in the medullary part of the vasa recta and a return to close to normal on returning to the cortex
  - there is an overall increase in osmolarity of plasma in the vasa recta due to reabsorption of NaCl (and urea)

**collecting ducts**
- run from cortex to medulla
- variable permeability to water increased by ADH
- receive hypotonic or isotonic fluid
- actively reabsorb NaCl in the cortex according to ADH and aldosterone levels
- passively reabsorb water (and urea) from the medullary collecting duct due to the high tissue osmolarity (maintained by the ascending loop)

d. Explain the mechanisms involved in the regulation of renal function.
local autoregulation
constriction of afferent arterioles maintains constant RBF for MAP 80-200 mmHg
  myogenic mechanism
tubuloglomerular feedback
  ↑ GFR
  ↑ NaCl concentration at end of loop
  ↑ NaCl uptake by macula densa
release of adenosine
afferent constriction, efferent dilation
  ↓ GFR and RBF
glomerulotubular balance
  reabsorption of Na⁺ is a roughly constant proportion of GFR
  ↑ GFR → ↑ reabsorption of Na⁺ and water in PCT
  tends to stabilize tubular flow over changes in GFR

neurological sympathetic
response to hypotension (baroreceptor), hypoxia, acidosis or stress
noradrenergic sympathetic innervation (and circulating adrenaline)
  β₁ adrenergic response of granular cells
  ↑ renin release
  α₁ adrenergic response in PCT
  ↑ Na⁺ reabsorption
  α adrenergic vasoconstrictor response in afferent and efferent arterioles
  ↓ RBF, GFR
endocrine renin
enzyme cleaved from prorenin in granular cells
released controlled by
  afferent arteriolar baroreceptors (hypotension)
  macula densa (↓ NaCl uptake)
sympathetic response
  angiotensin II, ANF (inhibition)
cleaves circulating angiotensinogen to angiotensin I
angiotensin II
  octapeptide cleaved by ACE from angiotensin I
  acts at AT₁ and AT₂ receptors
  vasoconstrictor of renal and other arterioles
  efferent > afferent constriction (↑ Kf)
  increases release of aldosterone and ADH
  directly increases Na⁺ reabsorption
  increases sympathetic activity
  increases thirst
prostaglandins PGE₂ and PGI₂
  synthesized and released in response to
  sympathetic activity
  angiotensin II
  vasodilators limiting the local action of vasoconstrictors
ANF
peptide hormone
released from atrial cardiac muscle in response to dilation
actions (via cGMP)
  ↓ Na⁺ reabsorption in collecting ducts
  afferent vasodilator, efferent vasoconstrictor in kidney (↑ GFR)
  increases plasma filtration as lymph in spleen
aldosterone, renin, ADH release

**Aldosterone**

Steroid hormone produced by zona glomerulosa of the adrenal cortex
released in response to
- ACTH
- ↑ plasma K⁺
- angiotensin II
- inhibited by ANF

acts on collecting ducts
- ↑ Na⁺ reabsorption
- ↓ K⁺ reabsorption
- ↑ H⁺ secretion

also acts on all other sites of Na⁺ transport (sweat, gut etc.)

**ADH**

Peptide hormone synthesized in suprachiasmatic and paraventricular nuclei
released from posterior pituitary neurones in response to
- hypotension (7-10% volume change → low pressure baroreceptors)
- ↑ osmolarity (change of 1-2%)
  - overcome by volume effect
- angiotensin II
- sympathetic activity, stress
- drugs (chlorpropamide, barbiturates)

actions
- $V_1$ vasoconstrictor acting on smooth muscle
- $V_2$ ↓ collecting duct permeability to water (via ↑ cAMP)
  - results in insertion of aquaporin 2 in membrane
  - ↑ release of VIIIc and vWF

other vasoactive agents at the kidney (role uncertain)
- TXA₂, leukotrienes, endothelin, dopamine, bradykinin, many others

**e. Outline the endocrine functions of the kidney.**

**Functions of the kidney**
- regulation of water and ion balance
- removal and excretion of metabolic waste products from the blood
- removal and excretion of foreign chemicals from the blood
- gluconeogenesis
- endocrine functions
  - renin secretion
    - from granular cells of the JGA
    - converts circulating angiotensinogen to angiotensin I
      - rate limiting step in production of angiotensin II
  - erythropoietin secretion
    - glycoprotein hormone (168 amino-acids, 4 sugar residues)
    - produced in interstitial renal cells
    - $t_/_{1/2}$ 5 h
    - release stimulated by renal hypoxaemia or hypoperfusion
    - stimulates maturation of erythroid precursors in bone marrow
  - 1,25-dihydroxyvitamin D production
    - produced by 1-hydroxylation of 25-hydroxyvitamin D
    - produced in proximal tubule cells
    - synthesis stimulated by PTH
    - rate-limiting step in production of active 1,25-(OH)₂D₃
    - acts to increase plasma Ca²⁺
bone resorption
↑
tubular Ca\(^{2+}\) resorption
↑
intestinal Ca\(^{2+}\) absorption
also ↑ tubular phosphate resorption (antagonized by PTH)

**f. Describe the role of the kidneys in the maintenance of acid-base balance.**

H\(^+\) ion regulation
increased by
- gain in CO\(_2\) from metabolism
- non-volatile acids from metabolism of protein and other molecules
- loss of HCO\(_3\)\(^-\) in GIT fluid or urine
decreased by
- loss of CO\(_2\) in lungs
- metabolism of organic anions (e.g. lactate)
- loss of H\(^+\) in GIT fluid or urine

normal concentration of H\(^+\) flux is diet: high protein → acid load

H\(^+\) concentration (pH) is controlled by buffering
- intracellular phosphate and proteins (greatest capacity)
- extracellular HCO\(_3\)\(^-\)/CO\(_2\) (precise control)
  - PCO\(_2\) controlled by respiratory system
  - HCO\(_3\)\(^-\) regulated by kidneys

\[
\text{pH} = 6.1 + \log \left( \frac{[\text{HCO}_3^-]}{0.03 \text{ PCO}_2} \right)
\]

mechanism
HCO\(_3\)\(^-\) filtered at glomerulus
actively reabsorbed in PCT (80%), ascending loop (15%) and collecting ducts
type A intercalated cells
- secrete H\(^+\) into lumen
  - active H\(^+\) ATPase pump in luminal membrane
  - Na\(^+\)/H\(^+\) countertransport in PCT and loop
  - H\(^+\),K\(^+\) ATPase in collecting ducts
produce HCO\(_3\)\(^-\) from CO\(_2\) and OH\(^-\) via carbonic anhydrase
HCO\(_3\)\(^-\) moves into blood via Na\(^+\) cotransport or Cl\(^-\) countertransport
luminal H\(^+\) combines with HCO\(_3\)\(^-\) to form CO\(_2\) which diffuses into cells
H\(^+\) secretion is increased by high PCO\(_2\) and low pH independently

minimal active HCO\(_3\)\(^-\) secretion by type B intercalated cells in collecting ducts
increased in alkalosis (?mechanism ?importance)

some secreted H\(^+\) in collecting ducts is lost in urine, causing net addition of HCO\(_3\)\(^-\) to blood
H\(^+\) combines with HPO\(_4\)\(^{2-}\) and may be excreted in urine
75% of HPO\(_4\)\(^{2-}\) is reabsorbed
other anions and buffers also contribute to H\(^+\) loss
e.g. β-hydroxybutyrate or acetoacetate in DKA
bound H\(^+\) excreted in this way is “titratable acid”

glutamine is catabolized in PCT
glutamine \(\rightarrow 2 \text{ NH}_4^+ + 2 \text{ HCO}_3^-\)
with secretion of NH\(_4^+\) into lumen and HCO\(_3^-\) into blood
NH\(_4^+\) mostly ends up being excreted in urine
catabolism increased in acidosis
reabsorption reduced in acidosis
compensation for acid-base disorders

respiratory acidosis
- high CO₂ and low pH
  - ↑ NH₄⁺ secretion
  - full HCO₃⁻ reabsorption (increased H⁺ secretion)
  - ↑ titratable acid

alkalosis
- low CO₂ and high pH
  - ↓ NH₄⁺ secretion
  - ↓ H⁺ secretion causes HCO₃⁻ loss
  - no titratable acid
  - (↑ HCO₃⁻ secretion)

metabolic acidosis
- low pH and low CO₂ (low HCO₃⁻)
  - ↓ filtered load of HCO₃⁻
  - full HCO₃⁻ reabsorption despite ↓ H⁺ secretion
  - ↑ NH₄⁺ secretion
  - ↑ titratable acid

alkalosis
- high pH and high CO₂ (high HCO₃⁻)
  - ↑ filtered load of HCO₃⁻
  - HCO₃⁻ loss despite ↑ H⁺ secretion
  - ↓ NH₄⁺ secretion
  - (↑ HCO₃⁻ secretion)

generation of acid-base disorders
hypovolaemia
- ↑ aldosterone
  - Na⁺ retention, K⁺ and H⁺ loss

metabolic alkalosis
Cl⁻ depletion
- ↓ HCO₃⁻ secretion, ↑ H⁺ secretion
metabolic alkalosis
K⁺ depletion
- ↑ NH₄⁺ secretion, H⁺ secretion
metabolic alkalosis

these factors combine in
diuretic use: volume depletion and K⁺ depletion
prolonged vomiting: alkalosis, volume depletion, Cl⁻ and K⁺ depletion

g. Describe the role of the kidneys in the maintenance of fluid and electrolyte balance.

normal flux
water intake
- drink 1.2 l, food 1.0 l, metabolism 350 ml
output
- insensible 0.9 l, sweat ≥50 ml, faeces 100 ml, urine 1.5 l

NaCl
- small obligatory loss in sweat and faeces
- urine balances the remainder of dietary intake
both freely filtered, reabsorbed
- water by osmotic pressure from solute reabsorption
- Na⁺ by active transport
Cl mainly passive

PCT
reabsorbs 65% of NaCl and water independent of GFR (isoosmotic)
Na⁺ reabsorbed in cotransport with glucose etc., countertransport with H⁺
NaCl reabsorbed in coupled organic base transporter
isotonic filtrate

loop
passive water reabsorption
active NaCl reabsorption (Na⁺, K⁺, 2Cl⁻ cotransport, Na⁺/H⁺ countertransport)
produces hypotonic filtrate (80-100 mOsm/l)
25% of Na⁺ reabsorbed

DCT
impermeable to water
active NaCl reabsorption (cotransporter) 5% reabsorbed
reduces osmolarity
collecting ducts
variable water permeability (according to ADH)
controls free water loss
active Na⁺ reabsorption by principal cells (according to aldosterone)
active Cl⁻ reabsorption by B intercalated cells (with HCO₃⁻ secretion)

control
Na⁺ content determines ECF volume and systemic filling pressure
ANF release
blood pressure
baroreceptor response
sympathetic tone, renin, AT II, aldosterone, ADH
pressure natriuresis

pathology
cardiac failure
low BP, GFR
↑ renin, AT II, aldosterone, ADH
inappropriate Na⁺, water retention
opposed by ANF
nephrotic syndrome
↑ protein filtration, loss in urine
↓ oncotic pressure, loss of plasma volume to interstitium
intravascular depletion
Na⁺, water retention despite expanded ECF volume

primary hyperaldosteronism
initial Na⁺ retention
↑ BP, GFR, ANF
return to Na⁺ balance at higher ECF volume

potassium balance
98% intracellular, buffers changes in ECF concentration
movement into ICF
↑ by insulin, adrenaline, alkalosis

PCT
freely filtered, 55% reabsorbed in PCT (diffusion)
loop
active reabsorption in Na⁺, K⁺, 2Cl⁻ cotransporter
diffusion due to transtubular potential
30% reabsorbed
DCT, cortical collecting duct
reabsorption by $\text{H}^+ / \text{K}^+$ countertransport in type A intercalated cells
secretion by principal cells with $\text{Na}^+$ reabsorption
$\uparrow$ by aldosterone, plasma $[\text{K}^+]$, fluid delivery to duct
some $\uparrow$ with ADH (opposed by $\downarrow$ flow)

pathology
alkalosis
$\uparrow$ intracellular $\text{K}^+$
$\uparrow$ $\text{K}^+$ loss from collecting ducts
$\text{K}^+$ depletion

calcium balance
turnover 0.1-0.2 mmol/kg/day
free fraction filtered (45%)
40% protein bound
15% complexed with organic anions
PCT and loop
passive reabsorption $>60\%$ of filtered load
dependent on $\text{Na}^+$ reabsorption
$\uparrow$ $\text{Na}^+$ loss causes $\uparrow$ $\text{Ca}^{2+}$ loss
DCT
active reabsorption
basal $\text{Ca}^{2+}$ ATPase and $\text{Na}^+ / \text{Ca}^{2+}$ countertransporter
secondary luminal reabsorption
inhibited in acidosis

control
PTH
dopeptide hormone secreted by parathyroids
$\uparrow$ by low $[\text{Ca}^{2+}]$
actions
$\uparrow$ $\text{Ca}^{2+}$ mobilization from bone
$\uparrow$ DCT $\text{Ca}^{2+}$ reabsorption
$\downarrow$ phosphate reabsorption
$\uparrow$ vitamin D hydroxylation
1,25-(OH)$_2$D$_3$
above
calcitonin
peptide hormone secreted by parafollicular thyroid cells
$\uparrow$ by high $[\text{Ca}^{2+}]$
actions
minor role
$\downarrow$ bone resorption
GH
$\uparrow$ $\text{Ca}^{2+}$ excretion and intestinal absorption
cortisol
$\uparrow$ $\text{Ca}^{2+}$ excretion and $\downarrow$ intestinal absorption

phosphate balance
5-10% protein bound
rest freely filtered
75% of load reabsorbed in PCT ($\text{Na}^+$ cotransport)
$\uparrow$ reabsorption due to
1,25-(OH)$_2$D$_3$, insulin
$\downarrow$ reabsorption due to
PTH, glucagon

h. Describe the role of the kidneys in the maintenance of osmolarity.
receptors
  osmoreceptors in hypothalamus (paraventricular)
  control ADH secretion from posterior pituitary
  controls free water loss and thirst

i. Describe the role of the kidney in the handling of glucose, nitrogenous products and drugs.

proteins and peptides
  little protein is present in filtrate (10 mg/l)
  endocytosis of large proteins
    e.g. albumin, GH
    merge with lysosomes $\rightarrow$ amino acids
    low $T_m$ so easily saturates if filtration of proteins increases
  small polypeptides
    catabolized in lumen by peptidases
    active uptake of amino acids, di- and tri-peptides
    site of metabolism of small peptide hormones (e.g. AT II)
  damaged tubular cells release some proteins into urine

urea
  freely filtered
  50% reabsorbed in PCT (with water)
  concentrated in filtrate in loop and DCT (impermeable)
  facilitated diffusion absorption in collecting tubule (under ADH control)

organic anions and cations (including many drugs)
  non-specific active secretion in PCT
  several carrier proteins
  displays competition and $T_m$

organic acids and bases
  secretion or reabsorption depends on concentration gradient of diffusible species
  acids $AH \leftrightarrow A^- + H^+$
    acid species is diffusible
    reabsorbed at low urine pH
    secreted at high urine pH
    e.g. bile salts, fatty acids, uric acid
      acetazolamide, frusemide, penicillin, probenecid, salicylates, sulfas
  bases $B + H^+ \leftrightarrow BH^+$
    basic species is diffusible
    secreted at low urine pH
    reabsorbed at high urine pH
    e.g. ACh, choline, catecholamines, 5HT, histamine
      atropine, cimetidine, pethidine, morphine, local anaesthetics

glucose
  freely filtered
  secondary active cotransport with $Na^+$ in PCT
  $T_m$ exceeded with plasma concentration $>10$mmol/l
  $T_m$ varies from nephron to nephron

j. Describe the principles of measurement of glomerular filtration rate and renal blood flow.

Clearance
  the volume of plasma which is completely cleared of a substance per unit time
  $C_x = \text{rate of excretion} / \text{plasma concentration}$
  so if a urine specimen of volume $V$ is taken over time $t$ and the concentration of $X$ is
measured in plasma ($P_x$) and urine ($U_x$):

$$C_x = U_x \cdot V \div P_x \cdot t$$

**GFR**

if a substance is
- freely filtered
- not actively secreted or reabsorbed by tubules
- not synthesized or metabolized in tubules

its clearance must equal GFR

e.g. inulin (an exogenous polysaccharide)

in practice inulin is inconvenient as it equilibrates throughout ECF so a long infusion time is required to yield stable plasma levels

in practice creatinine is used
- continuous production from muscle (altered by exercise)
- freely filtered
- secreted by tubules (about 10% of excreted quantity)

slight overestimate of GFR, but plasma creatinine is also an overestimate

a halving of GFR should result in a doubling of plasma creatinine, so a single measurement of plasma creatinine can be used to estimate GFR based on age, weight and sex using the Cockcroft-Gault equation (males):

$$\text{creatinine clearance (ml/min)} = \frac{(140-\text{age}) \times \text{weight (kg)}}{72 \times \text{creatinine (in mg/dl)}}$$

(creatinine in mg/dl is 11 times the level in mmol/l)

urea can also be used
- 40-60% is reabsorbed
- $2 \times C_{urea} = GFR$

**RPF**

if a substance is
- filtered and actively secreted so that its concentration in venous blood from the kidney is zero

its clearance must equal RPF

as 10-15% of RBF is supplied to non-secreting tissue, no substance can meet these criteria

a substance which is completely cleared from blood supplied to secretory tissue of the kidney is used to measure effective RPF (ERPF)

e.g. para-aminohippurate

- freely filtered and actively secreted
- not reabsorbed
- completely cleared at low plasma concentrations

**RBF**

$$\text{ERBF} = \text{ERPF} \div (1 - \text{Hct})$$

**k. Describe the physiological effects and clinical assessment of renal dysfunction.**

**l. Explain the effects of hypovolaemia on renal function.**

**m. Explain the effect of general anaesthesia on renal function.**
E. Body fluids and electrolytes

a. Explain the distribution of body fluids and their measurement.

total body water 60% of bodyweight (75% newborn → <50% old age)
  intracellular fluid 55% of TBW
    approx 2 l is in circulating cells as part of blood volume
  extracellular fluid 45% of TBW
    exchangeable interstitial fluid 66% of ECF (30% of TBW)
      slightly lower cation concentration than plasma due to less protein
    water in dense CT and bone 33% of ECF (slow exchanging)
    plasma 15% of ECF
      approx 3 l
    lymphatic fluid
    transcellular fluid 5% of ECF
      small volume
      CSF, gut, synovial, peritoneal, pleural, pericardial, intraocular etc.

measurement
  by indicator dilution
    non-toxic, rapid distribution, confined to compartment, no effect on fluid distribution
    not metabolized or excreted or has predictable kinetics

TBW
  tritiated or deuterium water
  antipyrene

ECF
  radiolabelled Na⁺, Cl⁻, Br⁻, SO₄²⁻ (overestimate)
  inulin, mannitol (underestimate)

ICF
  calculated as TBW - ECF

plasma
  radiolabelled albumin, Evans blue dye, horseradish peroxidase

interstitial volume
  calculated as ECF - plasma

blood volume
  calculated as plasma ÷ (1 - Hct)
  measured with ⁵¹Cr labelled red cells

b. Describe the function, distribution and physiological importance of sodium, potassium, magnesium, calcium and phosphate.

Sodium
  total body content 60 mmol/kg = 1.4 g/kg
  distribution
    ECF 50%, bone 45%, ICF 5%
    70% exchangeable, 30% fixed (in bone)
  concentrations
    plasma, ISF 135-145 mmol/l
      reflects total body tonicity due to rapid equilibration of osmolality with ICF
    ICF 15 mmol/l
  with accompanying anions accounts for 86% of ECF osmolality, 92% of tonicity
  NaCl is only 75% dissociated in solution
  absorption
    freely absorbed, typical 3 g/day (range 0-20 g/day)
  control
delivery to macula densa → aldosterone
↑ Na+ retention in DCT (and other sites of exchange)

excretion
freely filtered at glomerulus
reabsorbed in PCT, loop and DCT
also lost in all secretions

Potassium
total body content 45 mmol/kg = 1.8 g/kg
distribution
ICF 90%, bone 8%, ECF 2%
92% exchangeable
concentrations
plasma 3.5-5 mmol/l
ICF 150 mmol/l
effects
high ECF
↑ membrane potential, ↓ Vmax
↑ T waves, ↓ Q-T, ↑ P-R, wide QRS, arrest in diastole
drowsiness
low ECF
↓ membrane potential, ↑ Vmax
ectopics, arrhythmia, ↓ T, ↑ P-R, U waves
irritability, weakness, tetany

absorption
freely absorbed, typical 1.0 g/day
control
primarily controlled by aldosterone → increased renal loss
moves across cell membranes opposite to H+
↑ movement into ICF with ↑ insulin

excretion
freely filtered at glomerulus
reabsorbed in PCT, loop (part active, part due to transtubular potential)
DCT, collecting duct secretion by type A cells, absorption by principle cells.
Loss ↑ by aldosterone, ADH, plasma [K+], high flow

Calcium
total body content 400 mmol/kg = 15 g/kg (1.5% bodyweight)
distribution
bone 99%, ECF <1%, ICF 1%
2% exchangeable
concentrations
plasma 2.2-2.4 mmol/l
free 40%, albumen 45%, other anions 15%
ICF 10^-7 mmol/l free
effects
high ECF
drowsiness, weakness, confusion, dehydration, systolic arrest
low ECF
irritability of excitable tissues

absorption
oral intake 25 mmol/day, ≈2.5 mmol absorbed
control
PTH, vit D₃, calcitonin in Physiol D

excretion
unbound fraction (55%) filtered at glomerulus
85% reabsorbed in PCT and loop
DCT reabsorption controls loss (↑ loss with PTH)
Magnesium

- total body content 12 mmol/kg = 0.3 g/kg
- distribution
  - ECF 1%, ICF 99%: bone 50%, muscle 20%
- concentrations
  - ECF 0.7-1.0 mmol/l (1.4-2.0 mEq/l)
  - ICF 20 mmol/l
- effects
  - intracellular cation, exchanged for Ca\(^{2+}\) at sarcoplasmic reticulum
  - Ca\(^{2+}\)-antagonist-like effects
  - cofactor in many enzymes including all ATPases
  - increases threshold potential
  - inhibits ACh release and excitation-contraction coupling
  - vasodilation, bronchodilation, muscle weakness, anticonvulsant activity
- absorption
  - intake 0.4 g/day
- control
- excretion
  - unbound fraction (75%) filtered at glomerulus
  - 25% reabsorption in PCT
  - 60-65% controlled reabsorption in loop

### c. Outline the composition and functions of lymph.

Starling forces across the capillary wall cause net transudation of fluid from plasma into the interstitial space. This fluid is collected and pumped by the lymphatic system via lymph nodes or the spleen to return to the circulation via the thoracic duct.

**Starling forces**

- hydrostatic pressure in capillaries and interstitium
  - mean capillary pressure 17.3 mmHg
  - interstitial pressure -3 mmHg
- oncotic pressure in capillaries and interstitium
  - plasma oncotic pressure 28 mmHg
  - interstitial oncotic pressure 8 mmHg
- mean net force is 0.3 mmHg out of capillaries
- filtration coefficient 7 ml/mmHg/min for whole body
- net lymph flow 2 ml/min at rest
- varies widely from tissue to tissue with capillary pressure, permeability, protein concentration changes

\[ J_v = K_v (\Delta P - \sigma \Delta \pi) \]

<table>
<thead>
<tr>
<th></th>
<th>systemic</th>
<th>pulmonary</th>
<th>glomerular</th>
</tr>
</thead>
<tbody>
<tr>
<td>P(_c)</td>
<td>30 → 10</td>
<td>12 → 6</td>
<td>60 → 58</td>
</tr>
<tr>
<td>(\pi)</td>
<td>28</td>
<td>28</td>
<td>21 → 33</td>
</tr>
<tr>
<td>P(_i)</td>
<td>-3</td>
<td>-5</td>
<td>15</td>
</tr>
<tr>
<td>(\pi)</td>
<td>8</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>net</td>
<td>+13 → -7</td>
<td>+1 → -5</td>
<td>+24 → +10</td>
</tr>
<tr>
<td>K(_v)</td>
<td>0.01/100g</td>
<td>?</td>
<td>12.5</td>
</tr>
</tbody>
</table>

**Lymph**

- an ultrafiltrate of plasma
- includes interstitial contents
- composition highly variable depending on source
e.g. splanchnic lymph after a meal can be 2% lipid and 60 g/l protein
can include bacteria
actively pumped by lymph vessels and intrathoracic pressure
foreign particles and organisms removed in lymph nodes

d. Define osmotic pressure and explain the factors that determine it.

osmotic pressure
The pressure required to prevent net diffusion of water through a membrane with
differing osmolalities of the solutions on each side.
proportional to the number of osmotically active particles in solution
calculated using van’t Hoff’s Law
\[ \pi = CRT \]
where \( \pi \) is osmotic pressure, \( C \) is concentration of solutes in osmoles/l, \( R \) is the gas
constant and \( T \) the absolute temperature
1 mOsm/l exerts 19.3 mmHg pressure at 37°C
normal osmolarity of plasma is 282 mOsm/l (5443 mmHg)
whole-body equilibration of osmotic pressure takes less than 30 minutes

e. Outline the significance of oncotic pressure, colloid osmotic pressure and
reflection coefficients.

oncotic pressure (or colloid osmotic pressure)
The osmotic pressure exerted across the capillary wall by the non-diffusible elements
of plasma.
ions and small molecules diffuse readily across capillary walls (reflection coefficient
close to 0)
plasma proteins have high reflection coefficients, close to 1
total plasma protein osmotic pressure is about 19 mmHg in plasma and 8 mmHg in
interstitial fluid
most pressure (12 mmHg) is due to albumin as it is in high concentration and is a
smaller molecule than most other plasma proteins
The Gibbs-Donnan effect results in increased cation concentration in plasma to
balance anionic non-diffusible proteins. The “excluded volume” effect results from
proteins not being an “ideal solute” and increases oncotic pressure. These effects
increase plasma oncotic pressure by another 9 mmHg, total 28 mmHg
measured using an “oncometer”
calibrated isotonic saline solution separated from the test solution by a
membrane excluding particles larger than MW 30,000 with a sensitive
pressure transducer to measure the osmotic pressure generated

f. Describe the measurement of osmolality and the control mechanisms involving
the regulation of osmolality.

osmolarity
number of osmotically active particles per liter of solution (not used)

osmolality
number of osmotically active particles per kilogram of solvent
measured directly by freezing point depression
1 osm/kg of water depresses freezing point by 1.86°C
approximated from electrolyte results
2 ([Na⁺] + [K⁺]) + [glucose] + [urea]
normal 280-290 mOsm/l
less than the sum of concentrations of solutes because of particle interactions
approximation is an underestimate when other solutes are present in high
concentrations
mannitol, ketoacidosis, alcohol

Control in Renal physiology (1.D).
F. Acid-Base Physiology

a. Explain and describe acid-base chemistry using the Henderson-Hasselbalch equation.

pH is defined as \( \log_{10}[H^+] \). Normal ECF pH is from 7.35 to 7.45 ([H+] 35-45 nmol/l). Survivable ECF pH is from 6.8 to 7.6. Acids are compounds which donate H+ ions and bases are compounds which accept H+ ions. Organic acid and bases in solution are partially dissociated, according to the pH of their surroundings and their pKa. pKa is defined as the pH at which half of the quantity of an acid is dissociated in solution. The relationship between pH, pKa and the dissociation of an acid or base is described by the Henderson-Hasselbalch equation:

\[
\begin{align*}
H^+ + A^- & \leftrightarrow AH \\
pH &= pK_a + \log \frac{[A^-]}{[AH]}
\end{align*}
\]

Where AH is an acid and A- its corresponding base. In ECF, examples of organic acids include many proteins such as haemoglobin, lactic acid and ketone bodies. Examples of simple acids include phosphoric and carbonic acid.

b. Describe the chemistry of buffer mechanisms and explain their relevant roles in the body.

A buffer is an acid/base pair which reversibly dissociates. A buffer acts to stabilize the pH of a solution as the introduction or removal of H+ from a buffered solution is partially compensated for by a change in the relative concentrations of the forms of the buffer according to the Henderson-Hasselbalch equation which results in a return of the pH towards its initial value. This is most readily seen in the transformation of the equation:

\[
K_a = \frac{[A^-][H^+]}{[AH]}
\]

Any rise in [H+] will result in recombination of H+ and A- to form AH to maintain the constant K_a. (H+ + A- \rightarrow AH) A fall in H+ or a rise in OH- will have the opposite effect. Most organic acids are capable of acting as buffers. The maintenance of pH in a very tight range is vital for the normal function of most physiological processes. The activity of most enzymes is highly pH dependent. The principle buffers in the blood are:

- Haemoglobin which allows dissociation of some of its 38 histidine residues (HHb \leftrightarrow H+ + Hb). This is also responsible in part for the right shift of the Hb-O2 dissociation curve with a fall in pH.
- Plasma proteins (and haemoglobin) bearing carboxyl or amine groups (RCOOH \leftrightarrow RCOO^- + H+ or RNH3+ \leftrightarrow RNH2 + H+).
- Carbonic acid which is itself in equilibrium with Pco2 (CO2 + H2O \leftrightarrow H2CO3 \leftrightarrow HCO3- + H+). This provides for the compensation for pH changes by changes in respiration.

- Intracellular fluid contains little haemoglobin or protein and is buffered by carbonic acid.
- Intracellular fluid is buffered by proteins as described above and also by phosphate (H2PO4- \leftrightarrow HPO4^{2-} + H+).

c. Describe the regulation of acid-base balance.

The second line of regulation of pH (after buffers), is in the respiratory and renal regulation of acid-base balance. The major buffer in extracellular fluid is the carbon dioxide/carbonic acid/carbonate system, catalyzed by carbonic anhydrase:

\[
CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow HCO_3^- + H^+
\]
The extracellular CO₂ concentration is regulated by respiration. If an increase in metabolic activity or a fall in pH occur, PCO₂ rises. An increase in ventilation increases the rate of elimination of CO₂ from the lungs, bringing PCO₂ back to normal and raising pH. The reverse occurs when a rise in pH causes a fall in PCO₂.

A doubling in alveolar ventilation can compensate for a fall of 0.2 in pH and a halving for a rise of about 0.25. The capacity for changing alveolar ventilation ranges from almost 0 to 15 times normal. Reducing ventilation to compensate for a rise in pH is limited by the requirement to maintain PO₂.

The control of ventilation is directly affected by pH. The effectiveness of the whole mechanism is 50-75% and the time to equilibrium 3-12 minutes. The system is impaired by respiratory disease, with COAD patients developing a respiratory acidosis because of their limited ventilation and a greatly impaired ability to compensate for a metabolic acidosis.

The extracellular concentrations of HCO₃⁻ and H⁺ as well as non-volatile acids are regulated by the kidney. 80 mEq/day of H⁺ are lost in association with non-volatile acids. HCO₃⁻ is freely filtered at the glomerulus (4320 mEq/day). In the proximal convoluted tubule and loop of Henle H⁺ is secreted into the tubule by secondary transport in exchange for Na⁺. H⁺ combines with filtered HCO₃⁻ to form CO₂ which diffuses into tubule cells and generates H⁺ and HCO₃⁻ which diffuses back into the ECF. The net effect is resorption of HCO₃⁻. This mechanism resorbs 95% of filtered HCO₃⁻, but has little effect on urine pH. In the presence of a high pH or low Pco₂, less H⁺ is secreted, and HCO₃⁻ is lost in the urine, compensating for the alkalosis.

In the DCT, H⁺ is secreted into the urine by an ATPase H⁺ pump. This allows for resorption of the remaining HCO₃⁻, and allows the generation of a maximally acidic urine of about pH 4.5. In the presence of a low pH or high Pco₂, excess H⁺ is secreted and combines with other buffers in the urine: HPO₄²⁻ or NH₃. The HCO₃⁻ generated intracellularly by carbonic anhydrase in forming the H⁺ diffuses back into the ECF as “new” HCO₃⁻.

The ammonia buffer in the urine is generated by the metabolism of glutamine in PCT cells to produce 2HCO₃⁻ which diffuse into the ECF and 2NH₄⁺ which are transported into the urine by Na⁺ exchange secondary transport. A low pH stimulates the metabolism of glutamine in this way. In chronic acidosis this is the major system for renal compensation.

A minor determinant of renal H⁺ secretion is the effect of aldosterone in increasing active transport of H⁺ in the DCT and collecting ducts.

Infusion of acid buffering

immediate HCO₃⁻ buffering in plasma
ISF equilibrium in 15 minutes
ICF equilibrium in 2-4 hours
with Hb, HPO₄²⁻, other proteins
H⁺ displaces K⁺ (and Na⁺) from ICF → hyperkalaemia
Cl⁻ and HCO₃⁻ enter cells with H⁺
physiological effects
shifts O₂ dissociation curve to the right
sensed by carotid and aortic bodies
respiratory stimulation → partial compensation
limited by initial rise in CSF pH

**d. Explain the principles of blood gas and acid-base analysis.**

**measurement in** [Physics and Measurement (1.R)](#).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal Range</th>
<th>Equation</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.35-7.45</td>
<td>6.1 + log ([HCO₃⁻] ÷ 0.03 PₐCO₂)</td>
</tr>
<tr>
<td>pCO₂</td>
<td>36-46 mmHg</td>
<td>1.5 [HCO₃⁻] + 8</td>
</tr>
</tbody>
</table>

*Acid-base* 1.F.2  
*James Mitchell (November 5, 2001)*
Acid-base disorders can be categorized as acidaemia or alkalaemia, acidosis or alkalosis, respiratory or metabolic. This classification can be determined from the pH, PCO₂, and HCO₃⁻ in arterial blood. Their normal values are 7.4, 40 mmHg and 24 mEq/l respectively. A respiratory acidosis results from underventilation, resulting in increased PCO₂, low pH and compensatory rise in HCO₃⁻. A respiratory alkalosis results from overventilation, with a high pH, low PCO₂ and lowered HCO₃⁻. A metabolic acidosis displays a low pH, primary low HCO₃⁻ and compensatory low PCO₂. A metabolic alkalosis has a high pH, high HCO₃⁻ and raised PCO₂.

These problems do not always occur in isolation. Combined respiratory and metabolic acidosis is common in patients with multiple medical problems. The compensatory mechanisms require time to stabilize the pH: 6 to 12 hours for respiratory compensation and 3 to 5 days for renal compensation.

A graph of [HCO₃⁻] versus pH with PCO₂ isobars is used to readily classify acid-base disturbances. Alternatively rule-of-thumb equations can be used to relate “expected” [HCO₃⁻] and PCO₂.

Management of acid-base disturbances in the acute setting focuses primarily on the underlying cause. Respiratory acidosis can be corrected by increasing ventilation. Respiratory alkalosis can be corrected by reducing ventilation within the limits of maintaining adequate oxygenation. Sometimes, for example in neurosurgical procedures, a respiratory alkalosis is desirable and deliberately generated by hyperventilation.

Metabolic acidosis
- high anion gap
  - ketoacidosis, lactic acidosis, ethylene glycol poisoning, renal failure
- normal anion gap
  - loss of HCO₃⁻
    - GIT fluid loss (diarrhoea, drains, ureteroenterostomy)
    - renal tubular acidosis, interstitial disease
    - recovery from ketoacidosis
  - drugs: carbonic anhydrase inhibitors, absorbable acids

Metabolic alkalosis
- renal
  - K⁺ depletion, Cl⁻ depletion and volume depletion all ↑ H⁺ loss seen in diuretic use, prolonged vomiting
  - Conn’s syndrome: ↑ aldosterone, ↑ H⁺ loss
- drugs
  - oral (or IV) HCO₃⁻
G. Nervous system physiology

a. Explain the basic electrophysiology of neural tissue.

Cell Membrane Potential

Resting potential is maintained by active transport of ions by Na⁺,K⁺ ATPase against the passive diffusion of K⁺ out of the cell. Conventionally negative (inside cell) -70 to -90mV

Ion gradients in nerve cell

<table>
<thead>
<tr>
<th>Ion</th>
<th>ICF (mM)</th>
<th>ECF (mM)</th>
<th>Potential (mV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na⁺</td>
<td>15</td>
<td>150</td>
<td>+60mV</td>
</tr>
<tr>
<td>K⁺</td>
<td>150</td>
<td>5.5</td>
<td>-90mV</td>
</tr>
<tr>
<td>Cl⁻</td>
<td>9</td>
<td>125</td>
<td>-70mV</td>
</tr>
</tbody>
</table>

net resting potential -70mV

relationship between gradient and potential is described by the Nernst equation:

\[ E = \frac{RT}{FZ} \ln \frac{C_o}{C_i} = 61.5 \log \frac{C_o}{C_i} \]

the membrane potential as a whole is described by the Goldman field equation:

\[ V = \frac{RT}{F} \ln \left( \frac{P_R[K^+]_o + P_{Na}[Na^+]_o + P_{Cl}[Cl^-]_o}{P_K[K^+]_i + P_{Na}[Na^+]_i + P_{Cl}[Cl^-]_i} \right) \]

The membrane is much more permeable to K⁺ and Cl⁻ than to Na⁺ or Ca²⁺. K⁺ causes most of the potential, Cl⁻ is passively distributed according to the membrane potential.

Nerve cells

A myelinated nerve cell consists of a soma with dendrites, an axon hillock with axon attached, sheathed in Schwann cells punctuated by Nodes of Ranvier, and ending in terminal buttons.

When an electrical or other stimulus raises or lowers the resting potential of the nerve cell slightly, the normal potential is restored over 0.5 to 1 ms by K⁺ and Cl⁻ flux. When the resting potential is raised above -63 mV, Na⁺ permeability through ion channels increases, helping to sustain the electrotonic potential. Above -55 mV, Na⁺ permeability increases suddenly, flux becoming greater than the rate of transport out of the cell and an action potential results. The membrane potential spikes to +35 mV. There is a rapid reduction in Na⁺ permeability and a slower increase in K⁺ permeability and flux, repolarizing the cell. The Na⁺ channels enter an inactivated state, causing the absolute refractory period, before returning to the resting state.

Channels are concentrated at the Nodes of Ranvier. When an action potential occurs at one node, it induces a depolarization at the adjacent node, starting another action potential if the node is not refractory. This is saltatory conduction. Because of the refractory period, saltatory conduction is unidirectional.

Extracellular Na⁺ concentration does not affect excitability much as the membrane isn’t very permeable. A rise in extracellular K⁺ stabilizes cells by decreasing the membrane potential. A rise in extracellular Ca²⁺ stabilizes cells by increasing the depolarization required to initiate an action potential.

Ca²⁺ may play a role in the spike due to influx through Na⁺ channels and also enters the cell through separate channels during the late phase of hyperpolarization.

Nerve fibres

Classified by diameter (∝ conduction velocity)

- Aα (I) proprioceptive, somatic motor
- Aβ (II) light touch, pressure
- Aγ motor to muscle spindles
- Aδ (III) pain, heat, touch
B preganglionic autonomic
C (IV) pain, sympathetics
Larger fibres are more susceptible to pressure and hypoxia and less susceptible to local anaesthetics.
When bundled into nerves, the electrical behaviour seen is different from individual fibres due to a range of sensitivities and conduction velocities of the fibres in a nerve. Nerves display compound action potentials and show a ceiling response to maximal stimuli.

Synapses
Junctions between nerve cells.
May be electrical (gap junction) or chemical:
- consist of a synaptic knob containing vesicles of transmitter, a 20-30 nm synaptic cleft and postsynaptic membrane.
- Release of neurotransmitter is initiated by rising intracellular Ca\(^{2+}\) during action potentials causing exocytosis.
- Neurotransmitter binds to receptors on the postsynaptic membrane, opening specialized Na\(^+\) channels which raise the membrane potential (Excitatory Post-Synaptic Potential) or to Cl\(^-\) channels which lower the membrane potential (IPSP). Slow EPSPs and IPSPs are caused by transmitters which alter the permeability to K\(^+\).
- Each neurone releases only one neurotransmitter and so is either excitatory or inhibitory. Inhibitory interneurones allow one neurone to act to generate both EPSPs and IPSPs.
- If enough EPSPs sum in time and place, an action potential can be generated. There is also direct transmission of electrical potential within a single cell without action potentials.

b. Describe sensory and motor pathways.

sensation
receptors
mechano
- skin (multiple types), deep tissue, muscle (spindle), tendon
- others: hearing, balance, baroreceptors
temperature
- warm and cold, peripheral and hypothalamic
pain
mechano and polymodal
chemo
- general: taste, smell
- specific: carotid/aortic bodies (O\(_2\) and CO\(_2\)), hypothalamic (osmolarity, glucose, amino acids, fatty acids)
stimulation produces a change in discharge frequency which decays with adaption. Vibration and light touch require rapid adaption, pain and proprioception display minimal adaption.
afferent pathways
- fibre types are specific to receptor types
  - Ia 17 µm annulospiral muscle spindle fibres
  - Ib 16 µm Golgi tendon organs
  - II 8 µm most skin receptors
  - III 3 µm crude touch and sharp pain
  - IV unmyelinated 0.5 µm to 2 µm pain, itch, temperature, touch
transmission from the primary afferent is often transmitted by both a fast transmitter, causing a brief depolarization and one or more slow transmitters causing a prolonged EPSP which causes sensitization to further signals
signals can also be prolonged by reverbatory circuits, or reveratory curcuits can produce a continuous rate of depolarization which is modified by inhibitory or excitatory inputs

perception in the cord is sharpened by convergence and lateral inhibition excitation in the cord is limited by descending inhibitory pathways and synaptic fatigue

ascending pathways
dorsal column-medial lemniscal system
primary large myelinated afferents divide into two branches
medial runs directly to the brain in the dorsal columns
lateral synapses in the dorsal horn to provide
spinal reflexes
spinocerebellar tracts
spinothalamic tract
input to contralateral spinthalamic tract
dorsal column fibres synapse in the cuneate and gracile nuclei, cross and ascend to the thalamus and then the cortex

anterolateral pathway
transmits pain, heat, cold, itch, tickle and crude touch
primary afferents synapse in the ipsilateral dorsal horn
secondary fibres cross to the opposite anterolateral tract and ascend as the anterior and lateral spinothalamic tracts, the spinoreticular and spinotectal tracts
synapse in the reticular nuclei of the brainstem and the thalamus

descending pathways

c. Describe the physiology of pain.

In Pain Pharmacology (2.B.3).

d. Describe the physiology of cerebrospinal fluid.

function
protection “floating” of brain and spinal cord
constant chemical environment
some nutrient content
some excretory function
transport of neurohormones within CNS

production
0.35 ml/min (500 ml/day) not affected by ICP unless CPP <70 mmHg
total volume 150 ml
choroid plexus produces 40-70%
fenestrated endothelium in capillaries
controlled secretion by epithelial cells
Na⁺/K⁺ ATPase-driven transport of ions, glucose and nutrients
ependyma adds 30-60% by oxidation of carbohydrates and ultrafiltration

composition

<table>
<thead>
<tr>
<th></th>
<th>CSF</th>
<th>plasma</th>
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</thead>
<tbody>
<tr>
<td>pH</td>
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<td>7.41</td>
</tr>
<tr>
<td>Na⁺</td>
<td>141</td>
<td>140</td>
</tr>
<tr>
<td>K⁺</td>
<td>2.9</td>
<td>4.6</td>
</tr>
<tr>
<td>Ca²⁺</td>
<td>1.3</td>
<td>2.5</td>
</tr>
<tr>
<td>Mg²⁺</td>
<td>1.2</td>
<td>0.8</td>
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<tr>
<td>Cl⁻</td>
<td>124</td>
<td>101</td>
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<tr>
<td>glucose</td>
<td>3.5</td>
<td>4</td>
</tr>
<tr>
<td>protein</td>
<td>0.3</td>
<td>70</td>
</tr>
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</table>

Nervous 1.G.3 James Mitchell (November 5, 2001)
reabsorption
90% in arachnoid villi
10% in spinal subarachnoid
determined by ICP
zero at 68mmCSF
equilibrium at 112mmCSF
drugs
diuretics ↓ production
acetzolamide reduces H+ availability for Na+/H+ exchange
frusemide inhibits NaCl transport
ethacrynic acid inhibits Na+/H+ exchange
spironolactone inhibits Na+ transport
steroids ↓ production
digoxin weak ↓ production from Na+,K+ ATPase inhibition
volatile agents
most ↓ absorption
some ↓ production (halothane, sevoflurane)

e. Describe the autonomic nervous system and explain its role in controlling body function.

In Thoracic Anatomy (3.G.1).
f. Describe neurotransmitters and their physiological role.

released from presynaptic neuron
synthesis
only one type of fast transmitter in one neuron
ACh
choline + acetyl-CoA
amines
synthesized in cytoplasm
e.g. tyrosine → DOPA → dopamine → noradrenaline → adrenaline
glutamate → GABA
tryptophan → 5-OH trp → 5HT
histidine → histamine
amino acids are derived from uptake from blood and transamination
NO
synthesized from arginine by NO synthase
neuropeptides
synthesized in RER
very small quantities
transported to terminals by axonal transport
much more potent but act slowly and for a prolonged period
storage
vesicles near the synaptic junction for all transmitters except NO
release
in response to action potential
detail above and in Physiol H and Pharm B VII
metabolism
ACh
cholinesterase
amines
reuptake by pre- and post-synaptic membrane transport
MAO and COMT
GABA transaminated by GABA-T → succinic semialdehyde → succinate
rapid

Class I
  acetylcholine

Class II (amines)
  noradrenaline
  adrenaline
  dopamine
  serotonin
  histamine

Class III (amino acids)
  γ-aminobutyric acid
  glycine
  glutamate
  aspartate

Class IV
  NO
  lipids
    arachidonic acid derivatives
    neurosteroids

slow

hypothalamic
  TRH
  LHRH
  somatostatin

pituitary
  β-endorphin
  MSH
  prolactin
  LH
  TSH
  GH
  ADH
  oxytocin

gut and brain
  leu-enkephalin
  met-enkephalin
  substance P
  CGRP
  gastrin
  cholecystokinin
  VIP
  neurotensin
  insulin
  glucagon

others
  angiotensin II
  bradykinin
  carnosine
  sleep peptides
  calcitonin

receptor types (not dealt with elsewhere)

\( \text{GABA}_A \)
  pentameric transmembrane ligand-gated Cl\(^-\) channel
  multiple subunit types (α, β, γ, δ, ρ) → hundreds of receptor subtypes
  several binding sites

---

Nervous  

1.G.5  

James Mitchell (November 5, 2001)
GABA → opens Cl channel, IPSP
BDZ requires α, β, γ subunits, binds α → ↑ GABA binding
   several subtypes of BDZ binding site
β-carboline binds at BDZ site → ↓ GABA binding (inverse agonist)
alcohol, barbiturates, progesterone also facilitate GABA transmission

GABA<sub>β</sub>
   G-protein linked receptor
   ↑ K<sup>+</sup> conductance, ↓ Ca<sup>2+</sup> conductance
   presynaptic inhibitory role in pain transmission and elsewhere
   activated by baclofen, midazolam → analgesia
other GABA receptor roles
   monoocyte chemotaxis
β cells in the pancreas

glutamate receptors
   AMPA, kainate
      ligand-gated Na<sup>+</sup> channels
      4 or 5 subunits, multiple subunit types, hundreds of channel subtypes
     fast excitatory response
NMDA
   complex receptor, Ca<sup>2+</sup> channel when activated
   normally inactive with Mg<sup>2+</sup> in channel
   inhibited by ketamine, phencyclidine binding in channel
   binding of glycine facilitates activation
   prolonged depolarization causes escape of Mg<sup>2+</sup>
   activation causes ↑ Ca<sup>2+</sup> conductance
      prolonged activation causes NO production, c-fos expression
     may play a role in neuronal death (↑ glutamate released from ischaemic nerve cells)
glycine
   pentameric Cl<sup>-</sup> channel → IPSP
   α and β subunits
   antagonized by strychnine → convulsions

**g. Explain the physiology of the control of intracranial and intraocular pressure.**

**ICP**
   uniform pressure within cranial vault
   normal range 5-13 mmHg at rest
   rises with intrathoracic pressure due to transmission of BP changes
determined by
   brain volume
   blood volume
   CSF volume
   changing one must alter the others (Monroe-Kellie Doctrine) as volume is constant
measurement
   qualitative
      MRI, CT
   quantitative
      catheter in ventricle/cerebrum/subarachnoid/extradural space
      transducer outside or at tip of catheter

cerebral circulation
   Circle of Willis supplied by ICA and basilar arteries
   grey matter 80 ml/100 g/min, white 20 ml/100 g/min, total 50 ml/100 g/min
   slightly less in cord
measurement

Kety-Schmidt technique
uses Fick principle
uptake of tracer = perfusion x extraction
\[ Q_b = F \int (C_a - C_v) \, dt \]
\[ Q_b = C_b \cdot \text{Mass}_b \]
\[ C_b = C_v \cdot \lambda \text{ (at equilibrium)} \]
\[ F = \frac{C_v \cdot \lambda}{\text{Mass}_b} \int (C_a - C_v) \, dt \]

\( N_2O \) at low concentration is the tracer used
\( C_a \) and \( C_v \) are measured continuously
at radial artery and IJV
until equilibrium
\( \lambda \) is assumed to be 1 for \( N_2O \)
result is expressed in ml/100 g/min

radioactive tracers
\( ^{133}\text{Xe}, ^{85}\text{Kr} \) as gases
organic compounds including \( ^{11}\text{C}, ^{15}\text{O}, ^{13}\text{N} \) or \( ^{18}\text{F} \)
detected by scintigraphy, PET, autoradiography

flow probes
doppler, electromagnetic
MRA

O\(_2\) extraction monitoring
jugular bulb oximetry
near IR spectroscopy

flow is autoregulating
CPP 50-150 mmHg (CPP = MAP - ICP)
largely myogenic and gas pressure determined
\( \text{PCO}_2 \) causes linear response in CBF over 20-70 mmHg
1-2 ml/100 g/min/mmHg
due to pH change, so attenuated with buffering over time
\( \text{PO}_2 \) causes rise in CBF below 50 mmHg
no change at 60-300 mmHg
small fall >300 mmHg
vessels are innervated by sympathetic, parasympathetic, trigeminal and
intrinsic nerves which have little effect
if BBB is impaired: \( \alpha \) agonists ↓ CBF, \( \beta \) agonists ↑ CBF

requirements
22 ml/100 g/min EEG changes
15 ml/100 g/min isoelectric EEG
6 ml/100 g/min cell death
directly related to \( O_2 \) requirement (CMRO\(_2\))
normal 3-3.5 ml/100 g/min
5-10 s reserve before unconsciousness
reduced by
cerebral depressants (barbiturates etc) up to 60% reduction
hypothermia up to 90% reduction at 17°

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h. Describe the integration of central nervous system activity via the cerebellum, hypothalamus and limbic system.

i. Describe the physiology of sleep.

j. Outline the basis of the electroencephalogram.
In Monitoring (3.B.2).
H. Muscle Physiology

a. Describe the muscle spindle and explain its physiological role. Use this knowledge to describe the integration of voluntary movement.

A muscle spindle consists of 3 to 12 specialized fusiform myocytes attached at their ends to the normal muscle cells of a skeletal muscle. There are two types of spindle cell: nuclear bag and nuclear chain. The cells have contractile units at their ends innervated by γ motor neurones independently of the extrafusal muscle. The central portion of the myocytes has no contractile filaments but generates sensory signals depending on the stretching of the spindle (either by lengthening of the muscle or contraction of the spindle cells).

The sensory innervation of the spindle cells is dual: a Ia annulospiral fibre surrounding the central portion of all cells and II fibres away from the centre and surrounding only the nuclear chain cells.

The response characteristics of the muscle spindle are of two types. The static response is generated by the nuclear chain cells and is a signal with a frequency related to stretch of the spindle and persistent for several minutes after stretching. The dynamic response is a response to rapid change in the length of the spindle with a big rise in impulse frequency with lengthening and reduction with shortening. It is produced by the nuclear bag cells and is seen only in the Ia fibres.

The γ innervation is also divided into static and dynamic components, each producing an increase in sensitivity of the respective response. These compose 31% of all motor neurones, the rest being Aα fibres. The γ fibres are stimulated at the same time as Aα fibres in voluntary movement, maintaining coordination between then length of the muscle spindle and the muscle as a whole. Coordination of this effect is primarily in the bulboreticular facilitatory area of the brain stem with secondary input from the cerebellum, basal ganglia and cortex.

In the spinal cord, the Ia afferent neurones synapse directly with motor neurones supplying the same muscle, providing the monosynaptic spinal reflex (jerk reflexes and clonus). The IIa fibres produce a weaker but more sustained reflex in response to continued stretch rather than “jerks”. These reflexes have an important application in smoothing the motor neurone (and muscle) response to the very uneven signals from higher centres and compensating for the sudden forces involved in walking or running. Muscle spindles in antagonist muscles are stimulated to stabilize a joint for precise movement.

b. Describe the physiology of the neuromuscular junction and its receptors.

The neuromuscular junction is the interface between lower motor neurones and skeletal muscle cells. Motor neurones end in multiple terminals which interdigitate with the muscle cell membrane, forming a motor end-plate. The space between the cells is the synaptic cleft and is 20-30 nm across.

The nerve terminals contain mitochondria and vesicles of acetylcholine. When an action potential reaches the terminal, about 125 (of the 300,000) vesicles are released or their contents diffuse through the cell membrane. This process is mediated by influx of Ca²⁺ through voltage dependent channels. Acetylcholine binds to nicotinic receptors which are transmembrane proteins in the muscle cell’s subneural clefts.

Nicotinic post-junctional receptors are grouped at the “shoulders” of the subneural clefts. The receptor is a cone-shaped protein consisting of five subunits which binds with two molecules of acetylcholine. The ion channel when opened allows passage of Na⁺, K⁺ and Ca²⁺, but the main effect at the time of opening is influx of Na⁺.

The receptor is a pentamer composed of four different units (α₂βγδ) all of which span the cell membrane. The ACh receptor sites are on the α subunits. There is a central ion
channel which opens due to conformational changes when both receptor sites are occupied by agonists.

The nicotinic receptors on nerve tissue are composed of a different combination of units (\(\alpha, \beta\)).

Opening of ACh-gated ion channels generates an excitatory end plate potential which triggers an action potential by opening voltage-dependent Na\(^+\) channels if it lifts the membrane potential above the threshold potential, about -70mV.

The acetylcholine is broken down within a few milliseconds by acetylcholinesterase. The action potential lasts 1-5ms and propagates down the T-tubules at 3-5m/s. The generation of the action potential is the same as in nerve tissue with influx of Na\(^+\) followed by efflux of K\(^+\) repolarizing the cell.

The action potential triggers voltage-dependent Ca\(^{2+}\) channels in the sarcoplasmic reticulum which open, allowing an influx of Ca\(^{2+}\) into the intracellular space. Ca\(^{2+}\) binds to troponin C, causing a conformational change which allows the active site of actin to bind to adjacent myosin heads, initiating muscle contraction. The Ca\(^{2+}\) is rapidly transported back into the sarcoplasmic reticulum within 50ms in skeletal muscle (300ms in cardiac muscle) and contraction ends unless a further action potential is received.

c. Describe the comparative physiology of skeletal, smooth and cardiac muscle.

Muscle tissue

Skeletal

Cellular anatomy
striated, not functionally syncitial
Composed of sarcomeres (Z line to Z line) A band is thick myosin filaments, the I band is thin filaments of actin, troponin and tropomyosin.
Fibrils are surrounded by the sarcotubular system of transverse tubules, continuous with the cell membrane, and sarcoplasmic reticulum. Two T-tubules per sarcomere.

Electrical activity
Nerve endings at the motor end plate release acetylcholine which opens Na\(^+\) channels to initiate the action potential. Membrane potential is -90 mV, action potential is 2-4 ms and propagates at 5m/s. It is transmitted along the transverse tubules. This starts release of Ca\(^{2+}\) from sarcoplasmic reticulum which binds to troponin C, releasing the myosin-binding sites on actin. The myosin cross-bridges swing, lysing ATP and shortening the fibril. The contraction takes several ms, the refractory period of the muscle is less, so repeated action potentials result in tetanic muscle contraction. ATP for muscle contraction is derived from hydrolysis of phosphocreatine near the myosin heads and from anaerobic and aerobic glycolysis and from oxidation of free fatty acids, depending on the activity of the muscle and availability of oxygen. ATP will supply tetanic contraction for 1-2 s, phosphocreatine for 5-8 s, and glycolysis for 1-2 minutes in skeletal muscle. ATP is also required for relaxation of muscle as it drives the Ca\(^{2+}\),Mg\(^{2+}\) ATPase pump which returns Ca\(^{2+}\) to the sarcoplasmic reticulum.

Muscle structure
Muscles fibres are classified as types I, IIB and IIA (few in humans). I are slow contracting with high oxidative capacity and are most common in postural muscles. IIB and fast and support more glycolytic metabolism and are more common in “quick” muscles such as the extraocular muscles. All muscles have a varying proportion of fibre types. Fibre type is determined by the pattern of discharge from the
motor neuron innervating a particular motor unit.

Cardiac Muscle

Cellular anatomy
striated, functionally syncitial
Composed of sarcomeres, but fibrils branch and attach at the ends with intercalated disks and membrane fusion with gap junctions. The transverse tubules are aligned with the Z lines (one per sarcomere). Fibres are “slow” type with high oxidative capacity and many mitochondria. Myosin type and consequently ATPase activity are determined by thyroid hormone levels.

Electrical activity
Membrane potential is -80 mV
Depolarization is started by (fast) Na\(^+\) channels opening for a few ms, then maintained by (slow) Ca\(^{2+}\) channels which remain open for 150-250 ms, depending on rate. K\(^+\) channels open at the same time and remain open to repolarize the cell.

Muscle contraction is initiated by Ca\(^{2+}\) from both sarcoplasmic reticulum and ECF and lasts 1.5 times as long as the action potential. There is no tetanic contraction. Ca\(^{2+}\) release from sarcoplasmic reticulum is Ca\(^{2+}\)-mediated rather than voltage-gated as in skeletal muscle.

In specialized pacemaker cells, the membrane potential rises due to falling K\(^+\) permeability, initiating repeated action potentials. These cells compose the SA node and conducting bundles.

Muscle behaviour
Force of contraction is determined by
diastolic filling (graph)
\(\beta\) agonism increasing Ca\(^{2+}\) influx mediated by cAMP (also shortens systole)
digoxin inhibiting Na\(^-\)K\(^+\)ATPase leading to a higher intracellular [Ca\(^{2+}\)]

Smooth Muscle

Cellular anatomy
not striated, functionally syncitial
Cells contain actin, myosin and tropomyosin but no troponin. Fibres are not organized. There are few mitochondria; cells rely on glycolysis.
There is no sarcotubular system.
Visceral smooth muscle is found in the walls of viscera. Cells have low-resistance junctions.
Multi-unit smooth muscle is found in the iris. Cells are not linked.

Electrical activity
Membrane potential varies continually with spontaneous action potentials at irregular intervals. Action potentials propagate through the muscle and initiate contractions lasting seconds.
Myosin links to actin only after phosphorylation by myosin light-chain kinase which is activated by calmodulin-bound Ca\(^{2+}\).

Muscle behaviour
The spontaneous variation in membrane potential is affected by hormones. The response varies with the location of the smooth muscle. Acetylcholine, cold and stretch all increase frequency and strength of contraction.
Smooth muscle is plastic in response to prolonged stretch.
I. Liver Physiology

a. Describe the storage, synthetic, metabolic, and excretory functions of the liver and identify the physiological consequences of hepatic disease.

The liver is composed of lobules, 0.8 to 2 mm in diameter. They comprise a central vein (which drains to the hepatic vein) surrounded by plates of hepatocytes sandwiching bile canaliculi and surrounded by the space of Disse (which drains to lymphatics). Between the plates are sinusoids filled with blood derived from the hepatic artery (350 ml/min) and portal vein (1.1 l/min).

The liver receives a total of 29% of resting cardiac output. It is a low-resistance circulation, the portal vein being at 9 mmHg and hepatic vein at 0 mmHg. In cirrhosis the vascular resistance is increased. In right heart failure, venous pooling in the liver can amount to 2 l (normal 450 ml). With high intrahepatic capillary pressure, fluid is rapidly transudated into lymph and directly into the abdominal cavity as ascites. This involves loss of plasma protein.

Kupffer cells in the sinusoids are part of the mononuclear phagocytosing system, removing bacteria from portal blood very effectively.

Carbohydrate metabolism (glucose buffering)

glycogen synthesis
polymerized from UDP-glucose
hydrolyzed by phosphorylase to glucose 1-PO₄. Phosphorylase is activated by adrenaline or glucagon via cAMP and enzyme intermediates.
represents up to 8% of hepatocytes' weight
conversion of galactose and fructose to glucose
galactose (+ATP) \( \rightarrow \sim 1-PO_4 \leftrightarrow UDP \sim \leftrightarrow UDP \) glucose \( \rightarrow \) glycogen
fructose (+ATP) \( \rightarrow \sim 6-PO_4 \leftrightarrow glucose 6-PO_4 \leftrightarrow \sim 1-PO_4 \leftrightarrow UDP \sim \)
Only glucose is readily released back into blood by the action of glucose phosphatase on glucose 6-PO₄.

gluconeogenesis
from glycerol released from fats or by deamination and conversion of many amino-acids (e.g. alanine \( \rightarrow \) pyruvic acid + NH₃). This is promoted by glucocorticoids via liberation of amino-acids from protein catabolism in peripheral tissues.

Fat metabolism
oxidation of fatty acids
Triglycerides are split into glycerol (\( \rightarrow \) gluconeogenesis) and fatty acids. Fatty acids are split by β oxidation into a shorter fatty acid, acetyl-CoA, FADH₂, NADH and H⁺. The net gain from oxidation of a molecule of stearic acid (C₁₇H₃₅COOH) is 146 ATP. Acetyl-CoA can enter the TCAC or is converted to acetoacetic acid which circulates to peripheral tissues as acetoacetic acid, β-hydroxybutyrate and acetone (ketone bodies). These are converted back to acetyl-CoA in cells and enter the TCAC provided that there is adequate oxaloacetic acid (derived from carbohydrate metabolism), otherwise ketosis develops.

synthesis of lipoproteins
The liver synthesizes VLDL, a lipoprotein containing large amount sof triglyceride and some cholesterol and bearing the apoprotein B-100 marker. VLDL circulates to the periphery where lipoprotein lipase hydrolyzes the triglycerides, allowing free fatty acids and glycerol to be taken up by peripheral tissue. The VLDL thus becomes IDL and then LDL, containing mainly cholesterol esters. IDL and LDL are taken up by the liver and by peripheral tissue by pinocytosis following binding of apo B-100 to its receptor.
HDL is formed in the liver and bears apo A-I or A-II on its surface. It is thought to absorb cholesterol from vessels. The details of its circulation are not
fully known.
synthesis of cholesterol and phospholipids
90% of phospholipids are synthesized in the liver and transported via lipoproteins. They are a heterogeneous group of compounds, all containing fatty acids and at least one phosphoric acid radical; most also contain a quaternary nitrogen. They include lecithins, cephalins and sphingomyelin and are required for the formation of cell membranes, lipoproteins, and in specialized applications such as sphingomyelin in nerve sheaths, thromboplastin in clotting and as phosphate donors.

CH₃

CHCH₅-(CH₂)₃-CH(CH₃)₂

HO

Cholesterol is synthesized de novo in the liver from acetyl-CoA. The rate-limiting step in synthesis is at hydroxymethylglutaryl-CoA reductase which is directly inhibited by cholesterol and by statin drugs. The plasma level of cholesterol is determined partly by dietary intake and substantially by the availability of acetyl-CoA in the liver (which is determined by dietary saturated fat intake).

Most cholesterol in the body is in cell membranes where it affects fluidity of the membrane and also deposits in the stratum corneum to improve the waterproofing of the skin. The majority of non-membranous cholesterol is converted to cholic acid in the liver and conjugated with glycine or taurine to form bile salts which solublize fats in the gut and are reabsorbed (enterohepatic circulation). A small amount is used in the synthesis of steroid hormones.
synthesis of fatty acids from glucose or amino-acids
Excess acetyl-CoA can be converted to fatty acids.

acetyl-CoA + CO₂ + ATP ⇌ malonyl-CoA + ADP + PO₄³⁻
malonyl-CoA + acetyl-CoA + 2NADPH + 2H⁺ → butyryl-CoA + CoA + CO₂ + 2NADP⁺ + H₂O.

This process is repeated until the fatty acid is 14-18 carbons long, when the fatty acids are condensed with glycerol to form triglycerides. This process is about 85% efficient in storing energy from glucose. Triglycerides are stored in the liver or transported to peripheral fat cells via lipoproteins.

Protein metabolism
storage of amino acids
After absorption from the gut, amino acids are rapidly taken up by cells in the liver and throughout the body by active transport and facilitate diffusion. They are rapidly incorporated into proteins. Intracellular protein is in equilibrium with free amino acids and so is readily broken down for release of amino acids back into the circulation or for their metabolism.

Uptake of amino acids and synthesis of protein is promoted by GH and insulin and antagonized by glucocorticoids.

Albumin is also taken up directly by phagocytosing cells and broken down to amino acids which are then released into circulation.

transamination of amino acids
Nonessential amino acids are formed in the liver primarily by the synthesis of the appropriate α-keto acid followed by transfer of an amino radical from glutamine, glutamate, aspartate or asparagine.
glutamine + pyruvic a. → α-ketoglutamic a. + alanine
Several of the aminotransferase enzymes which catalyze these reactions are derivatives of pyridoxine (B6).
deamination of amino acids
Deamination predominantly occurs by the same pathway as transamination, with the amino radical transferred from an amino acid to α-ketoglutamic acid and subsequent deamination of glutamine:

\[ \text{glutamine} + \text{NAD}^+ + \text{H}_2\text{O} \rightarrow \alpha\text{-ketoglutamic a.} + \text{NADH} + \text{H}^+ + \text{NH}_3 \]

The α-ketoacid derived from the amino acid which was deaminated can be oxidized, usually through the TCAC.
formation of urea
The NH₃ generated by deamination is toxic and so is used to synthesize urea:

\[ \text{ornithine} + \text{CO}_2 + \text{NH}_3 \rightarrow \text{citrulline} + \text{H}_2\text{O} \]

\[ \text{citrulline} + \text{NH}_3 \rightarrow \text{arginine} + \text{H}_2\text{O} \rightarrow \text{urea} + \text{ornithine} \]

net: \(2\text{NH}_3 + \text{CO}_2 \rightarrow \text{H}_2\text{N-CO-NH}_2 + \text{H}_2\text{O}\)

Urea is cleared by the kidneys.
synthesis of plasma proteins
90% of plasma proteins are formed in the liver (the remainder are mainly immunoglobulins). Albumin, fibrinogen and globulins as well as clotting factors and some hormones are formed in the liver. The rate of synthesis is 15-50g/day.

Secretion of bile
The liver secretes 600-1200 ml of bile a day. It forms in the bile canaliculi between plates of hepatocytes and passes into collecting ducts, hepatic ducts and the bile duct. The lining of these ducts add volume, Na⁺ and HCO₃⁻ to the bile in response to secretin. Some empties directly into the duodenum and the remainder is temporarily stored in the gall bladder where it is concentrated.

Bile contains plasma electrolytes, bile salts, bilirubin, cholesterol, fatty acids and lecithin. It is relatively alkaline. The mixture may become supersaturated with cholesterol or bile salts, leading to the formation of stones. Emptying of the gallbladder is initiated by cholecystokinin after a meal.

Other functions
The liver stores vitamins A, D and B₁₂.

It stores excess iron by binding with apoferritin to form ferritin, as well as synthesizing transferrin for the transport and absorption of iron.

Detoxification of many drugs and metabolism of many hormones occurs in the liver. Many compounds are oxidized or demethylated by the cytochrome P450 system of enzymes, others are conjugated with UDP by glucuronyl transferase, competing with bilirubin for this pathway.

Excretion of bilirubin
Bilirubin is derived from the breakdown of haem in tissue macrophages. It circulates bound to albumin and is absorbed into hepatocytes. Here it is conjugated with glucuronic acid (80%), sulfate (10%) or other compounds and excreted by active transport into the bile.

In the gut, some conjugated bilirubin is converted to urobilinogen by bacteria which is reabsorbed and filtered by the kidneys, appearing in the urine where it is oxidized to urobilin. Urobilinogen which is not absorbed in the gut is converted to stercobilinogen and oxidized to stercobilin.

Physiological consequences of hepatic disease
Carbohydrate metabolism
- reduced ability to metabolize a glucose load
- reduced sensitivity to insulin both in the liver and peripherally
- reduced ability to metabolize lactate
- reduced glycogen stores

Protein metabolism
- disrupted metabolism of non-branched-chain amino acids, leading to elevation
in circulating levels of aromatic amino acids
impairment of the urea cycle and a rise in plasma ammonia
secondary rise in ammonia due to poor excretion of urea and \( \text{NH}_3 \) by the kidneys with enterohepatic circulation of urea (converted in the gut to \( \text{NH}_3 \)) and potentiation of the effect of \( \text{NH}_3 \) because of alkalosis.

Lipid metabolism
the pathogenesis of fatty liver is uncertain
possibly reduced synthesis of apoproteins, causes accumulation of triglycerides
possibly increased synthesis of lipids
longstanding cholestatic disease causes increased LDL and cholesterol and reduced HDL

Synthetic functions
reduced albumin synthesis, reducing plasma oncotic pressure and binding sites
reduced clotting factor synthesis (II, V, VII, IX, X) except for fibrinogen

Metabolism of drugs and hormones
portosystemic shunting
decreased phase I and II reactions
↑ insulin, glucagon, oestrogens

b. Describe the clinical laboratory assessment of liver function and hepatic failure.

Assessment of liver function with laboratory tests requires serial measurements of parameters related to different hepatic functions, interpreted in a clinical context.

Bilirubin metabolism is assessed by plasma conjugated and unconjugated bilirubin, assessing the conjugation and excretion functions. Elevated conjugated bilirubin can also be detected by dipstick testing of urine.

Hepatocellular enzyme levels in plasma are used to assess cellular injury. Aminotransferases (AST and ALT) reflect cellular injury. ALT is more specific to liver tissue but is elevated in alcoholic hepatitis. Alkaline phosphatase is not specific to liver tissue but is elevated in cholestasis of any cause. \( \gamma \)-Glutamyl transferase is a sensitive indicator of biliary disease and is elevated by all causes of induction of microsomal enzymes.

Serum proteins provide an indicator of the synthetic function of the liver. Albumin has a half-life of about 20 days and is reduced in severe cirrhosis, and also by malnutrition, nephrotic syndrome and other causes. Clotting factors II, VII, IX, X, V and fibrinogen are produced in the liver. A prolonged INR may indicate a failure of synthesis of these factors (especially VII) due to hepatic failure or vitamin K malabsorption.

Other tests include blood ammonia, which is elevated in hepatic failure due to impairment of the urea cycle and correlates with encephalopathy. Elevated triglycerides and abnormal lipoproteins may also reflect impaired lipid metabolism.

Specific tests for causes of liver disease include hepatitis serology, antimicrosomal antibody (PBC), antinuclear antibodies (SLE), \( \alpha \)-fetoprotein (hepatoma), Fe studies (haemochomatosis), ceruloplasmin (Wilson’s disease), and dozens of other specific tests.

c. Describe the handling of bilirubin in the body.

Bilirubin is derived from the breakdown of haem in tissue macrophages. It circulates bound to albumin and is absorbed into hepatocytes. Here it is conjugated with glucuronic acid (80%), sulfate (10%) or other compounds and excreted by active transport into the bile.

In the gut, some conjugated bilirubin is converted to urobilinogen by bacteria which is reabsorbed and filtered by the kidneys, appearing in the urine where it is oxidized to urobilin. Urobilinogen which is not absorbed in the gut is converted to stercobilinogen and oxidized to stercobilin.
d. Describe the anatomical and physiological considerations in hepatic blood flow, and the changes that occur with anaesthesia.

e. Outline the reticulo-endothelial functions of the liver.

The venous sinusoids in the liver are lined with Kupffer cells, the mononuclear phagocytosing cells of the liver. Portal blood usually contains significant numbers of enteric organisms, especially gram negative bacteria, and Kupffer cells phagocytose foreign organisms, preventing them from entering the systemic circulation.

f. Explain the protective function of the liver between the gut and body.

The liver provides a barrier between the portal and systemic circulations. In its reticulo-endothelial functions it acts as an effective barrier against infection. It also acts as a metabolic buffer between the highly variable contents of the gut and portal blood and the tightly controlled systemic circulation.

By absorbing, storing and releasing glucose, fat and amino acids, the liver plays a vital role in homeostasis. It also stores and releases vitamins A, D and B₁₂. It metabolizes or deactivates most of the biologically active compounds absorbed from the gut, such as drugs and bacterial toxins. It performs many of the same functions in systemic blood entering from the hepatic artery, processing a total of 29% of cardiac output.

g. Describe the portal circulation and its significance.

The gut receives its blood supply from the coeliac axis, superior and inferior mesenteric arteries. Venous drainage from the gut from the level of the lower oesophagus to the anal canal ultimately drains into the portal vein and into the liver. The total flow from the portal vein is about 1.1 l/min at about 9 mmHg. All substances absorbed from the gut, with the exception of lipids which pass into the lymph, must pass through the liver before entering the systemic circulation.

Cirrhosis or right heart failure cause an increased resistance to flow in the liver, leading to a rise in pressure in the portal venous system. This causes transudation of fluid into the gut and peritoneal cavity, and in the long term, dilatation of veins at the sites of portosystemic anastomosis: the lower oesophagus, bare area of the liver, umbilicus and anal canal.
a. Explain the origin and importance of blood groups.

ABO blood groups are determined by an autosomal gene. Each copy may express A, B or no antigen on the surface of erythrocytes. Blood is thus classified as O (45%), A (41%), B (10%) or AB (4%) according to whether none, one or both antigens are expressed. The A antigen can be further subtyped as A1 (plain A) or A2 (A and A1) and other rare groups.

People normally express IgG and IgM against the AB antigens not expressed on their own red cells. Thus if blood expressing an antigen against which a high IgM titre is present is transfused, rapid agglutination of the infused red cells occurs with activation of complement and rapid haemolysis: a major transfusion reaction. This leads to circulatory collapse and renal failure. In the presence of a lower titre of IgM or IgG, agglutination and haemolysis occurs more slowly. Prior to any matched transfusion, donor and recipient blood are mixed in vitro and checked for agglutination.

Rhesus antigens are expressed on all red cells. They are of three classes: C, D, and E and each antigen is expressed as one of two types (C or c, D or d etc.) The C and E antigens are not strongly antigenic. The D antigen is most antigenic so RhD is described as “Rhesus positive” and Rhd as “Rhesus negative”. RhD has an 85% prevalence in Caucasians and higher in negroes.

Anti-D IgG is usually only formed in Rh negative people in response to exposure to Rh positive blood. This can occur through unmatched transfusion or more commonly through carriage of an Rh positive foetus with foetal-maternal haemorrhage at delivery or earlier. Sensitization to D antigen results in expression of anti-D IgG in the mother. As IgG is transferred across the placenta, this results in haemolysis in any subsequent Rh positive foetus, called Erythroblastosis foetalis. This can be prevented by the administration of anti-D antibody at the time of likely foetal-maternal haemorrhage to remove any Rh positive blood from the mother's circulation before antibodies are expressed.

b. Outline the constituents and functions of plasma.

Plasma comprises about 18% of extracellular fluid, or 5% of bodyweight. It is the non-cellular part of the blood, being about 60% of blood volume. It is 0.7% solids, so measured concentrations of ions per litre plasma are lower than the actual concentrations per litre of water present.

The ionic composition of plasma is similar to that of interstitial fluid, except for a higher protein concentration and (because of the Gibbs-Donnan equilibrium) a slightly higher concentration of diffusible cations. Typical constituents (in mOsm/l) are:

<table>
<thead>
<tr>
<th>Ion</th>
<th>Concentration (mOsm/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na⁺</td>
<td>142</td>
</tr>
<tr>
<td>K⁺</td>
<td>4.2</td>
</tr>
<tr>
<td>Ca²⁺</td>
<td>1.3</td>
</tr>
<tr>
<td>Mg²⁺</td>
<td>0.8</td>
</tr>
<tr>
<td>Cl⁻</td>
<td>108</td>
</tr>
<tr>
<td>HCO₃⁻</td>
<td>24</td>
</tr>
<tr>
<td>phosphates</td>
<td>2</td>
</tr>
<tr>
<td>SO₄²⁻</td>
<td>0.5</td>
</tr>
<tr>
<td>amino acids</td>
<td>2</td>
</tr>
<tr>
<td>creatine</td>
<td>0.2</td>
</tr>
<tr>
<td>lactate</td>
<td>1.2</td>
</tr>
<tr>
<td>glucose</td>
<td>5.6</td>
</tr>
<tr>
<td>protein</td>
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</tr>
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<td>urea</td>
<td>4</td>
</tr>
<tr>
<td>other ions</td>
<td>4.8</td>
</tr>
</tbody>
</table>
The osmolality of protein in plasma is low but the high molecular weight of proteins means that they are a major constituent of plasma when measured by weight.

The protein constituent of plasma can be fractionated by electrophoresis into albumin and α, β, and γ globulins and other proteins such as fibrinogen. Albumin makes up over half the protein content by weight and 75% of the oncotic pressure. It and a number of globulin proteins bind circulating hormones and drugs. Albumin also provides a source of amino-acids to tissues.

The globulin proteins include many specialized binding proteins, the immunoglobulins and enzymes such as the clotting factors. Fibrinogen plays an important role in blood clotting.

c. Describe platelets and their role in coagulation.

Platelets are non-nucleated membrane-bound elements of blood 2-4 µm in diameter derived from megakaryocytes in the marrow. They are normally present in blood at 150-300x10⁹/l with a half life of 8-12 days. Though they have no nucleus, they do have contractile elements (actin, myosin and thrombosthenin), SER and Golgi apparatus and mitochondria and are capable of synthesizing prostaglandins and thromboxane, peptides and other messengers.

Function
  - adhesion
damaged endothelium via vWF to group Ib, IX receptors
collagen via group IV receptors
each other via IIb, IIIa receptors
  - activation and shape change
    release of ATP, ADP, serotonin (activate other platelets)
vWF, factor Va, VIIIa, phospholipid, βTG (activate coagulation)
synthesize TXA₂
express receptors for aggregation (IIb, IIIa)
aggregation
via receptors and fibrin
activation of factor XIII to crosslink fibrin
activation of contractile elements

d. Describe the coagulation cascade.

The coagulation cascade is described in two pathways: extrinsic and intrinsic, which converge on the activation of factor X and the common pathway.

The extrinsic pathway is the simpler and, in vivo, more rapid. Traumatized tissue releases a tissue-specific combination of compounds called tissue thromboplastin. This activates factor VII which, together with Ca²⁺, activates factor X.

Prothrombin activator is formed as a complex of Xa, V and phospholipids from tissue or platelets in the presence of Ca²⁺. The factor V is initially inactive, but once prothrombin activator converts prothrombin to thrombin, this activates factor V and greatly accelerates the action of prothrombin activator.

The intrinsic pathway is a slower clotting mechanism which does not require initiation from tissue damage. Exposure of the blood to a wettable surface such as glass or collagen will both activate platelets and factor XII. The cascade of
clotting factor activation proceeds through factors XI and IX.

Activation of factor X requires the presence of not only factor IX but also VIII, Ca$^{2+}$ and phospholipids from activated platelets or damaged tissue.

Factor Xa participates in the formation of prothrombin activator as in the extrinsic pathway. There are a number of inherited defects of clotting factors which impair clotting on the intrinsic pathway: haemophilia A (VIII), haemophilia B (IX), von Willebrand’s disease (VIII cofactor) and other rarer conditions.

The common pathway is the means by which prothrombin activator leads to clot formation. In the presence of activated platelets, prothrombin is bound to the platelet surface where it is more readily cleaved to form thrombin.

Thrombin cleaves fibrinogen, exposing its reactive sites for polymerization which occurs spontaneously, forming long fibres. These are weakly bound until activated factor XIII, derived from platelets catalyzes the covalent cross-linking of fibrin.

e. Describe the normal mechanisms of preventing thrombosis including endothelial factors and natural anticoagulants.

Endothelium absorbs mediators involved in inflammatory response and coagulation: PGF$_2$, serotonin, adenosine, histamine, complement and other mediators. It synthesizes or releases plasminogen activator, proteoglycan, PGI$_2$, heparin and protein C which play an inhibitory role in coagulation as well as factor VIII, von Willebrand factor and tissue factor. Antithrombin III is synthesized in the liver and circulates in the plasma.

Because normal blood coagulation is a positive-feedback process, there are mechanisms to prevent inappropriate spontaneous coagulation and limit the spread of clot. The endothelium is smooth and lined with glyocalyx which repels platelets and clotting factors. Thrombomodulin is bound to the endothelial membrane. It binds thrombin and, when thrombin is bound, activates protein C and protein S which inactivate factors V and VIII.

The release of PGI$_2$ from the endothelium inhibits thrombus formation. It acts via intracellular cAMP on endothelial smooth muscle to produce vasodilation and platelets to inhibit aggregation and the production of phospholipid.

In the process of clot formation, thrombin is strongly bound to fibrin fibres, limiting its range of action. The plasma protein antithrombin III binds circulating thrombin and
inactivates it. The action of antithrombin III is greatly enhanced by binding of antithrombin III to heparin. Heparin-antithrombin III complex also binds activated factors XII, XI, IX and X. Small amounts of heparin are released from mast cells and basophils and this presumably plays a role in the lysis of small pulmonary emboli, but systemic anticoagulation is rapidly induced using large IV doses of heparin derived from animal tissues.

Heparin is a collection of polysaccharides of different molecular weights, all of which are highly negatively charged. Fractions of the range of heparin molecules are used clinically. The effect of heparin can be titrated using protamine, a highly positively charged molecule which binds circulating heparin and prevents it from acting as an anticoagulant.

Alpha2-macroglobulin is a plasma protein which binds activated clotting factors but does not inactivate them.

f. Describe fibrinolysis and its regulation.

Plasminogen is a plasma protein which is trapped in the formation of a clot. Tissue plasminogen activator (tPA) is slowly released from injured endothelium and tissues and activates plasminogen to form plasmin. Kallikrein also activates plasmin. Plasmin is a protease which degrades fibrin, factors V, VIII and XII, thrombin and fibrinogen, causing lysis of the clot. This typically occurs hours to days following clot formation.

The action of plasmin is limited by PAI-1 and 2 and circulating alpha2-antiplasmin which prevents any low levels of circulating plasmin from lysing clots. tPA or the similar enzyme streptokinase can be used to initiate the lysis of clots in the coronary or cerebral circulation as a therapeutic intervention. It is also used for clearing clot from long-term indwelling central lines.

g. Outline methods for assessing coagulation, platelet function and fibrinolysis.

A functional test of clotting is a bleeding time. A standardized cut is made on the skin and the time of bleeding measured. Unfortunately this is a difficult test to calibrate. It is a good test of platelet function as the formation of a platelet plug is usually the reaction limiting the duration of bleeding, but if the time is prolonged, it does not indicate the nature of the clotting defect.

A platelet count has good predictive value of the risk of bleeding if the platelets are known to be of normal function. A count below 50x10⁹/l is associated with substantially prolonged bleeding time and below 20x10⁹/l is associated with dangerous spontaneous haemorrhages.

The function of the extrinsic and common pathways is assessed by prothrombin time (or INR). A specimen of plasma at 37˚ is citrated (to bind any ionized Ca²⁺) and an excess of tissue factor and Ca²⁺ are added as a timer is started. The time taken to coagulate is most commonly used to assess the effect of coumarin anticoagulants which impair synthesis of factors VII, IX, X and prothrombin.

The function of the intrinsic and common pathways is commonly measured using activated partial thromboplastin time (APTT). Citrated plasma at 37˚ is combined with kaolin and cephalin before an excess of Ca²⁺ is added and the time taken to coagulate is measured. This screens for the adequacy of factors XII, XI, IX, VII, PK and HMWK as well as the common pathway. It is used to adjust the dose of heparin used for anticoagulation.

The common pathway is assessed using a thrombin time (TT). Thrombin as added to plasma and the time taken to coagulate measured. Ca²⁺ is not required for coagulation in this test.

In cardiopulmonary bypass, large doses of heparin are used, and clotting is assessed using the activated clotting time (ACT), an automated device optimized for assessing supratherapeutic heparinization. ACT is in excess of 400 s for bypass.

None of these tests will detect factor XIII or alpha2-antiplasmin deficiency and they may miss vWF deficiency which can be cyclical, so they cannot exclude the possibility of excessive bleeding. There is also a substantial functional reserve in the concentration of
most clotting factors. In haemophilia A, symptoms are uncommon while the factor VIII level is above 5% of normal.

To determine a specific cause for defective clotting, it is necessary to do specific factor assays and test for the presence of anticoagulant factors such as anti-factor antibodies.

The function of the fibrinolytic system can be assessed by clot lysis time. This is shortened in alpha2-antiplasmin deficiency. Circulating fibrin degradation products can be assayed and give some information about the amount of clot lysis occurring. Fibrin cross-linking can be assessed by clot solubility in 5 M urea, which is increased in factor XIII deficiency.

h. Explain the physiological consequences of acute and chronic anaemia.

Anaemia is defined as a reduction in red cell mass below the normal range. The normal range differs with age, sex, environment and pregnancy. Acute blood loss, as in surgery, results in rapid fluid shift from the interstitial compartment to the intravascular compartment, usually supplemented by IV fluid. This results in a rapid fall in red cell count due to dilution.

The immediate effects of an acute fall in red cell mass are a reduction in the viscosity of blood and a reduction in the oxygen carrying capacity of blood. The majority of the oxygen carrying capacity is made up by haemoglobin, so a fall in Hb from 150 g/l to 100 g/l results in a fall in oxygen carrying capacity from 20 ml/100 ml to 14 ml/100 ml. If metabolic rate is unchanged, this requires a lower mixed venous Po2 or increased cardiac output to maintain oxygen flux. Both of these changes occur, the rise in CO being facilitated by the reduction in viscosity. Impaired tissue oxygenation also results in increased production of 2,3DPG which facilitates oxygen transfer by moving the dissociation curve to the right. Dyspnoea results in increased ventilation with some increase in Pao2.

Within hours of acute blood loss, red cell production rises, stimulated by the impairment of tissue oxygenation causing release of erythropoietin. A rise in reticulocyte count to 10-15% over a week and a rise in platelet and white cell counts occur as they are mobilized from marginal sites.

The physiological changes in chronic anaemia depend partly on the cause of the anaemia. Reduction in oxygen carrying capacity is always present and results in the same physiological responses as acute anaemia: increased ventilation, CO, 2,3DPG and reduced mixed venous Po2.

The haematological changes depend on the cause of the anaemia which can be classified as haemorrhagic, aplastic or haemolytic and subclassified in more detail.

i. Outline the production of blood constituents including red blood cells, haemoglobin and plasma proteins.

The cellular elements of blood are derived from the bone marrow and lymphoid tissue (and liver and spleen in the neonate). Putative pluripotent stem cells in the marrow give rise to lymphoid and myeloid stem cells. Lymphoid stem cells differentiate into pro-T and pro-B lymphoid cells which mature in the thymus or lymph nodes into T and B lymphocytes (and plasma cells). Lymphoid cell lines are distinguishable only by cell surface markers.

Myeloid stem cells differentiate into colony forming units (CFU) of the eosinophil (CFU-Eo), granulocyte/monocyte (CFU G/M) or erythroid/megakaryocyte (E/Mega) lines which further differentiate into five distinct lineages. The committed stem cells (pro-lymphoid and CFU cells) are capable of self-replication and this is the level at which the marrow population of stem cells in maintained. The replication and differentiation of the precursor cells is regulated by stimulating factors (erythropoietin, G-CSF, GM-CSF and others).

The myeloid and erythroid cell lines differentiate through several morphologically distinct stages. The erythroid line begins with the proerythroblast, a nucleated cell devoid of haemoglobin which gradually increases its haemoglobin content and reduces its size, finally losing all cytoplasmic organelles as a reticulocyte. The differentiation from stem cell
to erythrocyte takes about a week.

Haemoglobin is synthesized in erythroid cells from the proerythroblast stage. It consists of four globin chains (αβ2 in adult Hb) each covalently linked to a haem molecule. Haem is synthesized from glycine, succinyl-SCoA and Fe2+. Synthesis is commonly limited by Fe deficiency, resulting in hypochromic microcytic anaemia. The rate-limiting step in haem synthesis is the condensation of succinyl-SCoA and glycine to form δ-aminolaevulinic acid. This step also requires pyridoxine. 2 δ-aminolaevulinic acid molecules are condensed to form a pyrrole ring, 4 of which are required to form protoporphyrin IX. This coordinates with four of the six coordination points on Fe2+, to form haem.

The globin chains are synthesized in the RER of erythroid cells, each having a molecular weight of about 16,000. 97% of haemoglobin in normal adults is Hb A (αβ2), most of the remaining 3% is Hb A2 (αδ2), with very small amounts of Hb F (αγ2). These proportions are different in thalassaemia, where the production of one chain type is disordered.

Plasma proteins can be subdivided by electrophoresis into α1, α2, β1, β2 and γ fractions and fibrinogen. All the fractions are produced almost entirely in the liver, with the exception of γ-globulins which are produced in lymph nodes and small quantities of other proteins and peptide hormones which are produced in many different organs.

Albumin turnover is about 200-400 mg/kg/day from a total pool of 4-5 g/kg.

**j. Outline the constituents of blood products, their source, role and risks.**

**Whole blood**

Rarely used in Australia. A single donation of 450 ml of whole blood in 63 ml acid-citrate-dextrose anticoagulant including all cellular and plasma protein elements. Donors are screened by questionnaire and blood is screened for HIV, HTLV, Hep B, Hep C, CMV, syphilis and other antibodies. There is still a risk of infective blood being taken prior to seroconversion. This is a serious problem with hepatitis C and there remains a 0.01% risk of contracting hepatitis C from donor blood. There is also a smaller risk of contracting other hepatitides (hep B 1/250,000) or theoretically HIV. All blood transfusions must be ABO matched and other antigens are matched if possible to minimize the risk of transfusion reaction.

**Packed red cells**

A single donation of blood with most of the plasma removed and resuspended in isotonic solution, giving a volume of about 350 ml. The infection and reaction risks are the same as for whole blood. PRBC are typically deficient in white cells, clotting factors (especially V and VIII) and platelets, increasing the risk of bleeding following large transfusions. Transfusion also has a general immunosuppressive effect, possibly increasing the risk of infection or metastasis.

Used for replacement of blood loss if the loss of red cell mass is likely to cause problems with oxygen transport (not just for volume expansion).

There are special preparations of packed cells: neonatal and paediatric volumes, CMV negative, washed, irradiated and phenotyped units.

**Platelets**

The platelet fraction of a single donation of blood in plasma (30-60 ml). Usually 5x10^10 platelets. Rise in platelet count is highly variable. Platelets lose function rapidly and so are kept agitated at 20˚C and used within 5 days. Small numbers of white cells remain in the plasma fraction and carry the risk of febrile reactions, CMV infection and also GVH disease in marrow transplant patients.

Platelets express HLA antigens and so transfusions will provide a more sustained rise if major HLA antigen matching is performed. This is not common practice. Febrile reactions and rigors are common (20%) with platelet transfusion.

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Haematology 1.J.6

James Mitchell (November 5, 2001)
Platelet transfusion is used in well patients with a count below 10x10^9/l as they risk spontaneous haemorrhage and in patients undergoing unavoidable surgical procedures with a count less than 80x10^9/l or dysfunctional platelets.

one unit should raise platelet count by 10x10^9/l

most common source of bacterial contamination in transfusion

**FFP**

Fresh frozen plasma is the plasma fraction of a single blood donation (180-240 ml), frozen to maintain function of clotting factors and other plasma proteins. It is thawed immediately before use.

Infection risk as for whole blood

FFP is used in patients with multiple clotting factor deficiencies who are at risk of serious bleeding (e.g. DIC, warfarin overdose).

cryoprecipitate

a fraction of about 10 ml which precipitates when a unit of FFP is thawed contains high concentrations of factors VIII, XIII, vWF, fibronectin and fibrinogen, though less than a unit of FFP

previously used for factor VIII deficiency

used in fibrinogen deficiency induced by massive transfusion and some chemotherapy agents

probably does not require ABO matching, but may cause alloimmunization

factors

Heat-treated fractions of pooled human plasma containing high concentrations of factor VIII or IX are used for haemophilia. These solutions no longer carry HIV, but did prior to 1988.

**Intragam**

60 g/l solution of human IgG fraction. Used for ITP, myasthenia gravis, CFS (controversial) and immune deficiencies.

**Other immunoglobulins**

Human immunoglobulin fractions are available for specific purposes: hepatitis B, rabies, CMV, Rh D, tetanus and zoster IgG solutions are available for patients with high-risk exposures or immune deficiency. These are all heat-treated.

Some animal-derived immunoglobulin fractions are used as antisera for envenomations. They are sheep, horse or rabbit derived and often cause hypersensitivity reactions. There is unlikely to be any risk of infection transmission from other species.

**Albumex**

Heat-treated human albumin solution available as 40 g/l (500 ml) and 200 g/l (100 ml). Used as a plasma expander or for priming bypass equipment, an (expensive) alternative to Haemaccel. Derived from pooled plasma, but should carry no risk of infection as it is heat-treated.

A number of other hormone preparations are still blood- or tissue-derived.

**k. Describe the changes during blood storage and the problems of massive blood transfusion and their management.**

At the time of collection, a blood donation is a normal venous sample. In the production of packed cells, most of the plasma and plasma proteins are removed and the remaining cells and fluid are sealed in a sterile plastic bag in an isotonic solution and stored at 1-6˚C. This is an anaerobic environment in which red cell metabolism continues, though at a greatly reduced rate due to the low temperature. Hypoxia results in progressive depletion of ATP from red cells and consequent failure of the Na⁺/K⁺-ATPase pump, resulting in unopposed leakage of K⁺ from the cells. Red cells have a mean lifetime of 120 days, so a small proportion of the cells will lyse within the storage period. Almost all the white cells and platelets remaining within the unit will lyse within a few days.

**Haematology**

1.7

James Mitchell (November 5, 2001)
The gas and electrolyte changes in packed cells are usually rapidly compensated for on transfusion. Respiratory compensation occurs for the high PCO₂ and low PO₂. Citrate and lactate enter the TCAC, releasing Ca²⁺. The red cell Na⁺/K⁺-ATPase pump restarts and sequests much of the K⁺ load.

Erythrocytes can also be frozen. This requires preparation in glycerol and storage at −65°C for up to 3 years. There is little change in frozen preparations from the time of freezing and near-normal function on thawing and deglycerolization. The cost of this sort of storage restricts its use to rare blood types.

Problems associated with massive blood transfusion

defined as replacement of blood volume in under 24 hours
problems with any blood transfusion: acute and delayed reactions

volume
difficulty maintaining normal volume status (monitor CVP, PCWP, UO)
hypothermia from infusion below body temperature (blood warmer, monitor T)
dilution of any drugs in the circulating compartment
electrolytes
CO₂ and acid load causes transient acidosis
K⁺ load may cause hyperkalaemia, arrhythmia (monitor ECG, gases)
citrate load requires hepatic metabolism to avoid hypocalcaemia
citrate is metabolized to pyruvate and HCO₃⁻, raising pH a little
red cells
poor oxygen carrying capacity on infusion (high FiO₂, monitor SaO₂)
free haemoglobin from lysed cells may cause renal failure
iron load
clotting
dilution and consumption of platelets and clotting factors results in coagulopathy
treat with FFP for clotting factors and platelets
other
increased risk of blood-borne virus infection
alloimmunization (minor RBC antigen or HLA)
haemolytic or febrile reactions
adenine metabolites may cause renal impairment (>60 units required)

1. Describe the breakdown of haemoglobin.

When red cells break down in circulation, most commonly in the sinusoids of the spleen, their haemoglobin is phagocytosed by mononuclear cells. The globin chains are metabolized as are any proteins to amino acids which are returned to circulation. The Fe is split from haem and bound to ferritin where it is again available for metabolism or transport bound to transferrin. The porphyrin ring is oxidized to biliverdin and carbon monoxide and then to bilirubin which is transported bound to albumin.
Unconjugated bilirubin is conjugated in the liver with UDP glucuronate, this more soluble conjugate is excreted in bile. Some of the excreted bilirubin is converted by gut organisms to urobilinogen which is reabsorbed across the mucosa and renally excreted as urobilin. Urobilinogen which is not absorbed may be converted to stercobilinogen and stercobilin, colouring the faeces.

**m. Describe abnormal haemoglobins and their clinical significance.**

There are over 500 haemoglobin variants described, most of which are rare and of little clinical significance. The genes coding for globin chains are on chromosomes 16 (α and ζ) and chromosome 11 (β, γ, δ and ε). The ζ and ε chains are expressed only in the embryo.

Many Hb variants are single amino acid substitutions in the β chain. In Hb S, valine is substituted for glutamic acid in position 6. This results in Hb which when deoxygenated will polymerize via hydrophobic bonding between two loci on the β chain. The polymerized crystals of Hb S and Hb A result in cell rupture and infarction of tissue as well as haemolytic anaemia.

Homozygotes for Hb S have a reduced life expectancy and persistent anaemia due to a red cell survival time of only 10-15 days. They suffer multiple painful infarcts, particularly to the renal medulla and spleen, and may have aplastic crises precipitated by folate deficiency or by infection. Hb S has a reduced affinity for oxygen, so homozygotes have reduced saturation for their PO₂ and display increased physiological shunt. Crises are precipitated by hypoxia, hypovolaemia and cold.

Heterozygotes for Hb S will also express normal β chains and so have a mixture of Hb SS, AS and AA. They suffer the same complications of sickling, but a much lower PO₂ is required to induce sickling, so symptoms are less frequent and severe.

Hb C is the result of a substitution in the β chain of lysine for glutamic acid at position 6. It is largely asymptomatic in the Hb AC heterozygote. In SC heterozygotes, symptoms similar to mild Hb SS disease are seen, with ocular complications prominent. CC homozygotes have a mild haemolytic anaemia and splenomegaly with target cells on the blood film due to intracellular water and potassium depletion.

Hb E (β26 Glu→Lys) is more common in SE Asians. It results in decreased Hb synthesis but normal oxygen binding. It is asymptomatic and causes a microcytosis on blood film.

Many other Hb variants are poorly soluble but have normal oxygen affinity. These are asymptomatic, but cause Heinz bodies on the blood film.

Some Hb variants have increased oxygen affinity, resulting in reduced tissue oxygenation and secondary polycythaemia.

Rare Hb variants such as Hb M have decreased oxygen affinity which is manifest as familial cyanosis.

Thalassaemias are manifestations of defective α or β chain genes, resulting in an abnormal proportion of globin chains in erythrocytes. There are normally four α and two β genes.

α thalassaemia is clinically manifest when there is only one functional α gene. The excess of β chains results in precipitates of Hb H (β₄) seen as Heinz bodies. There is anaemia
with microcytosis and hypochromia and many target cells. α thalassaemia is most common in negro and Mediterranean groups. The complete absence of functional α genes results in hydrops foetalis, which is incompatible with life as Hb Barts (γ₄) is the only foetal Hb produced.

β thalassaemia is more common in SE Asians and Southern Italians. Those with one non-functioning β gene show a mild anaemia with an increased red cell count and marked microcytosis. There is mild splenomegaly and no clinical signs. Hb electrophoresis shows increased Hb A₂.

Homozygotes (thalassaemia major) develop severe anaemia from 4-6 months of age as production of Hb A should be increasing. They develop delayed growth and maturation with abnormal bone growth from marrow expansion. Splenectomy, transfusion and possibly bone marrow transplantation are required for survival if there is no production of Hb A. Some homozygotes have sufficiently increased Hb A₂ and Hb F to reduce their symptoms somewhat or have reduced rather than absent β chain synthesis.

All the possible heterozygote states have been described: Hb S/βthal etc. and show varying severity and range of symptoms.
K. Nutrition and Metabolism

**a. Define basal metabolic rate and describe its measurement.**

The rate of energy expended by the body at rest at room temperature 12 hours after a meal. Normal value is expressed divided by surface area: 40 kcal/m²/hr (50 W/m²).

Measured directly using an Atwater-Benedict chamber (calorimeter).

Measured indirectly using O₂ consumption at rest and assuming 4.82 kcal/O₂ (20 kJ/O₂). A more accurate measure can be obtained from measuring CO₂ production concurrently and calculating R or allowing for dietary constituents.

**b. Describe the factors that influence basal metabolic rate.**

**sex**
- males 10-15% more than females

**age**
- BMR double adult value per unit bodyweight at birth
- falls to a plateau through adulthood and falls further in old age

**increased**
- fever, hyperthyroidism, ↑ GH, sympathetic stimulation
- ingestion of food, especially protein
- activity

**decreased**
- sleep (by 10-15%)
- starvation

**c. Describe relevant cellular biochemical pathways and the control of fat, carbohydrate and protein metabolism including the role of vitamins and trace elements.**
yield
- acetyl-CoA: 12 ATP per turn of the TCAC
- glucose: 2 ATP anaerobic, 38 ATP aerobic
- G-6-P: 3 ATP anaerobic, 39 ATP aerobic
- fats: 17 ATP per 2 C unit less 7 ATP overhead

energy value
- carbohydrate: 4 kcal/g
- protein: 4 kcal/g
- ethanol: 7 kcal/g
- fat: 9 kcal/g

d. Explain the physiological principles of parenteral nutrition.

acute stress responses below
TPN will not help as excess energy substrate is already being mobilized
just increases CO₂ load, urinary N load and risk of fatty liver
after several days
benefits from providing energy substrates to reduce protein catabolism
fat up to 1 g/kg/day as Intralipid (omega-6-fa → immunosupression)
carbohydrate up to 4 g/kg/day
monitored with metabolic cart
measures RER
normal 0.85
>1 suggests fat synthesis (→ ↓ carbohydrate intake)
nitrogen around 0.2 g/kg/day (= a.a. 1.3 g/kg/day)
depends on nitrogen balance
= urea₂ urine ÷ 16.7 x 28/60 - Δurea₂ plasma x 0.6 x weight
increased N increases urinary solute load
some units tie caloric input to N input (possibly obsolete)
total energy intake typically 1700 kcal/day (usage ≈ 2500 kcal/day)
hypocaloric nutrition is practised in some units
electrolytes must be monitored separately
- tendency to loss of K⁺ and Cl⁻ resulting in alkalosis
- intracellular K⁺ deficit reflected in ↓ [Na⁺] plasma due to osmolarity effect

starved patients
small glucose load in first few days until ketosis resolves
then fat
trace element and vitamin deficiencies are unmasked by nutrition
e. Describe the consequences of anaerobic metabolism.

glucose → 2 pyruvate → 2 lactate yields net 2 ATP per glucose molecule
does not require O₂ or NAD⁺ or mitochondrial e⁻ transport function
does not produce CO₂
results in ↑ lactate ↓ pH
subsequent metabolism of lactate to glucose (Cori cycle) requires O₂ (oxygen debt)
f. Describe the physiological consequences of starvation.

reserves
- fat: 15 kg 141,000 kcal
- protein: 6 kg 24,000 kcal (available)
- glycogen: 75 g 300 kcal

Nutrition & Metabolism 1.K.2 James Mitchell (November 5, 2001)
muscle glycogen cannot be liberated as glucose

liver glycogen provides for a few hours of metabolism
some tissues are glucose-dependent
    RBC, marrow, renal medulla, peripheral nerves
the brain requires some glucose, but can also use ketones
during starvation, adaption gradually reduces the glucose requirement to a minimum
obligatory glucose use requires protein breakdown and nitrogen loss
    initial rapid protein breakdown until adaption occurs
nitrogen loss falls after two days
ketone bodies rise for two to three weeks
    renal ketone excretion is titrated with NH₄⁺
    ↑ glutamine use by the kidney
supplemental glucose or glycerol (in fat) reduces protein breakdown

gluconeogenesis
transamination of pyruvate yields alanine and α-ketoglutarate yields glutamate and glutamine (mainly from muscle)
brached-chain amino-acids are used to provide amine groups and their keto-acids enter the TCAC
alanine and glutamine enter the gluconeogenic pathway in liver and kidney, yielding glucose and urea
glycerol from triglyceride breakdown also provides a substrate for gluconeogenesis
    capacity: 85 g/day (20 g from protein, 15 g from glycerol, rest from recycling lactate etc.)
ketosis
    low intracellular glucose → low pyruvate, oxaloacetate (carrier for TCAC)
    acetyl-CoA cannot enter the TCAC (lack of oxaloacetate)
    → acetoacetyl-CoA → acetoacetate, β-hydroxybutyrate (in liver)
circulating ketone bodies can be taken up by other cells and enter the TCAC

g. Describe the metabolic consequences of sepsis, burns and trauma, as well as the effects of anaesthesia in this setting.

stress response
local mediators
tissue damage
    inflammatory mediators: PGs, bradykinin, substance P, serotonin, histamine, cytokines
    nociceptive afferents (Aδ and C fibres) → anterolateral and dorsal columns
central mediators
    ↑ ACTH, GH, prolactin, ADH
    ↑ sympathetic outflow
    produces endocrine and metabolic responses
endocrine
    steroid response
        ↑ cortisol, aldosterone
        ↑ renin-angiotensin
        ↑ insulin, ↑ glucagon
inflammatory mediators
        NO, 20-HETE, PGF₂α, TXA₂, PAF, LTs, ILs
        expression of cellular iNOS
metabolic
    ↑ MR, T, O₂ consumption, CO₂ output
    mediators alter distribution of blood flow: ↓ α response, vasodilation
catabolism of protein, fats and carbohydrate stores
↑ plasma glucose, rapid glucose turnover in anaerobic metabolism

catabolism of muscle protein for gluconeogenesis and synthesis of protein
inflammatory mediators

does not fall after a few days if stress continues (unlike starvation)

↓ synthesis of albumin, prealbumin, transferrin

rapid cycling of triglycerides to fatty acids and back again in the liver
inadequate VLDL production causes fatty liver
excess exogenous glucose worsens futile cycling and fatty liver

modification by anaesthesia
volatiles: little effect
intravenous: only etomidate has any effect (↓ cortisol)
opioids: ablate response in very high dose
regional

spinal, epidural LA
ablative the response from lower body surgery
attenuate response to upper abdominal & thoracic surgery

spinal opioids
no effect despite analgesia
L. Thermoregulation

a. Outline the mechanisms for heat transfer between the body and its environment.

radiation
by electromagnetic radiation
dependent on difference of fourth power of T of body and surroundings

evaporation
by vaporization of water
dependent on T of body, sweating, air flow, humidity

convection
by transfer to or from fluids (usually air)
dependent on air flow and T

conduction
by direct transfer to solids
from body contact with cold surfaces

mass transfer
loss of warm fluids (urine, blood)
inflow of cold or warm fluids (IV, irrigation, soup)

b. Describe the mechanisms by which heat is produced by the body.

heat production by metabolism of energy substrates

\[
\text{carbohydrate, protein, fat + } O_2 \rightarrow CO_2 + H_2O
\]

Basal Metabolic Rate (BMR) = 100 W or 2000 kcal/day
must be dissipated exactly to maintain a constant temperature

c. Describe the mechanisms by which heat is lost from the body.

above
in an anaesthetized patient losses are approximately
radiation 50%
evaporation 30%
convection 10%
conduction 10%

d. Explain the processes used for conserving as well as generating heat under situations of lowered environmental temperature and the effects of anaesthesia on these processes.

e. Explain the processes used for losing heat as well as increasing heat loss under situations of raised environmental temperature and the effects of anaesthesia on these processes.

afferent
peripheral
skin, viscera
central
spinal cord, preoptic nuclei of hypothalamus, midbrain, great vessels

pathways
peripheral cold (10°-40°C) and warm (30°-45°C) sensors
90% of skin thermoreceptors are cold receptors
nociceptors activated at <10°C or >45°C
Aδ fibres carry cold sensation only
C fibres carry warm and cold
spinal and ascending pathway similar to pain pathway

integration
preoptic hypothalamic nuclei
interthreshold range maintained in hypothalamus
narrow range (±0.2˚C) within which no response is triggered altered by
circadian rhythm, menstrual cycle, exercise, food, infection, thyroid function, sex (F > M), drugs, climatic adaption

efferent
cold
sympathetic
cutaneous vasoconstriction (400 → 50 ml/min)
centralizes circulation, maintains core temperature and allows periphery to cool
piloerection
nonshivering thermogenesis
brown fat ↑ heat production 10% in adult (100% in neonate)
central
shivering
↑ heat production 100% (adults only)
behavioural responses

heat
sympathetic cholinergic
sweating
up to 0.7-1.5 l/h, 0.58 kcal/g water evaporated
cutaneous vasodilation
400 → 2500 ml/min (increases heat loss by factor of 8)
central
behavioural responses

anaesthesia
afferents
regional anaesthesia blocks afferent “cold” transmission
increases central perception of warmth
integration
general anaesthesia broadens interthreshold range
vasoconstriction threshold falls 3˚C/MAC for all agents
sweating threshold rises 1˚C/MAC for volatiles, no rise for propofol
gain is preserved for all responses
efferents
regional anaesthesia directly blocks sympathetic outflow → vasodilation
direct vasodilation and ↓ sympathetic tone increase peripheral circulation
typical response is triphasic
initial rapid fall in core temperature due to vasodilation and redistribution of heat (not heat loss) typically 1˚C
continued slow fall in core temperature due to loss > production
plateau as thermoregulatory responses are elicited = 34˚C
plateau is higher if effective warming is used
due to heat loss = production + gain
not due to regulatory responses
monitoring
best with a central probe: PA, oesophagus, tympanic, nasopharynx
preservation of heat
prewarming of peripheral compartment reduces redistribution fall in T
high ambient temperature can prevent hypothermia, but impractical
radiant warmers effective for babies only
warming IV fluids prevents a fall of ≈0.25˚C/l in adults

Thermoregulation 1.L.2 James Mitchell (November 5, 2001)
HME or humidification prevents 10% of loss in adults, more in babies
blankets prevent ≤30% of loss (proportional to % coverage)
water heated mattress covers are ineffective
forced warm air blankets are the most effective method
transfer up to 50 W

f. Define thermoneutral zone.

The ambient temperature range within which a stable core temperature can be maintained with minimal rise in metabolic rate.

adult 22-24˚C
neonate 32-34˚C
premature 33-35˚C

g. Explain how the neonate differs in the regulation of body temperature compared with the adult and explain the physical and physiological reasons for these differences.

more rapid loss
  high SA to weight ratio
  high BMR (double adult rate per unit SA)
impaired responses
  poor vasoconstriction, little peripheral compartment
  no shivering
  no sweating
  limited behavioural responses
increased response
  non-shivering thermogenesis from brown fat is effective in doubling MR

mild intraoperative hypothermia

advantages
  cerebral and tissue ischaemic protection from ↓ metabolic rate
  ↓ MAC requirement
  ↓ triggering of MH?
disadvantages
  ↑ oxygen demand due to hypothermic responses during cooling
  ↑ risk of AMI, arrhythmia
  impaired clotting, immunity, wound healing
  slowed drug metabolism (e.g. atracurium)

Hypothermia in more detail in Metabolic (3.C.5).
M. Immunology

a. Use basic immunological principles to explain how the body defends against infection.

Immune organs

thymus
develops from third and fourth pharyngeal pouches
active from early fetal life, necessary until 20 weeks
site of development of self recognition of T lymphocytes
atrophies from 3-6 months (T cells are seeded peripherally)
marrow
site of development of most circulating cells from birth
site of development of lymphocyte precursors
spleen
major site of clearance of opsonized and antigen-coated particles
many B cells, site of Ig production, phagocytosing cells
lymph nodes
contain follicles of lymphocytes (B and T) and antigen-presenting cells
major site of Ig response
other lymphoid tissue
associated with gut, bronchi, skin

Immune cells

T lymphocytes
develop in thymus in early life
differentiate into CD4 and CD8
cytotoxic T cells (CD8)
lyse cells bearing viral antigen and MHC I
suppressor T cells (CD8)
modulate T and B cell response
regulator/helper T cells (CD4)
recognize antigen with MHC II
control B and T cell proliferation via cytokines

B lymphocytes
express surface Ig
activated by antigen and T helpers to transform into plasma cells
initially produce IgM when activated, then IgG (or A or E if stimulated by IL-4 or IL-5)
phagocytes (monocytes, macrophages etc.)
engulf opsonized particles without specific recognition
produce cytokines
present antigens

NK cells (lymphocytes without T or B cell markers)

Innate immune mechanisms

barriers

skin
dry, hydrophobic stratum corneum
fatty acids from glands
mucosae
mucus
cilia
IgA
flora
skin, gut, pharynx, vagina etc.
specialized defences
gastric acid
specialized cells
phagocytes: neutrophils and macrophages
NK cells
macrophages have multiple functions
activation of lymphocytes, complement and chemotactic secretion
direct toxicity to tumour and microbial cells
secretion of tissue reorganization factors
plasma proteins
complement
ABO antibodies (not provoked by antigen)
individual
susceptibility to particular diseases: TB, candida

Adaptive (acquired, anamnestic) immunity
antigen binds to surface Ig on B lymphocytes
induces proliferation and memory cells
phagocytosed and presented to T helper cells
antigen also can be presented by mononuclear phagocytes or dendritic cells
T helper cells modulate the response of
T cytotoxics, NKs, macrophages, granulocytes, B cells and ADC cells via cytokines
T suppressor cells influence T and B lymphocytes
macrophages also produce cytokines which affect NK, ADC and granulocyte cells
antigen presented to B lymphocyte
production of specific antibody (requires stimulation: IL, T_h, APC)
clonal expansion on reexposure

b. Identify effects of anaesthesia and critical illness on immune function.

Difficult situation to analyze due to
premorbid illnesses
drugs
age
surgical trauma
stress response
post-op nutrition
infection
pain
Cell-mediated immunity
↓ chemotactic migration
↓ oxygen radical production, impaired phagocytosis
↑ WCC
↓ NK cells (less antitumour effect)
↓ T cell proliferation
Humoral immunity
↓ B cell proliferation
no change to Ig levels
↓ complement
Effects worsened by
hypothermia
increased wound infection
decreased oxygen tension in wound
blood loss
↓ NK cell function
reduced effect if volume is replaced
transfusion
immunosuppressive (NK, T-helper)
stress response
  anxiety, starvation, tissue trauma, pain
result in catabolism, hyperglycaemia, hypercoagulability, immunosuppression
Specific agents
  halothane: effects above
  N₂O: impaired B₁₂ metabolism, haematopoietic dysfunction
  propofol: better maintenance of T cell numbers
  etomidate: inhibits 11-β hydroxylase, reduces stress response
  opioids
    ↓ NK cells, ↓ polymorph function, transient ablation of stress response
Regional
  attenuates stress response
  less impairment of phagocytes and NK cells

c. Explain the immunological basis and pathophysiological effects of hypersensitivity.

I  IgE cross-linking on mast cells (e.g. penicillin anaphylaxis on reexposure)
II Ig-mediated cell lysis (e.g. haemolytic transfusion reactions, HITS)
III antigen-antibody complex deposition (e.g. Farmer's lung)
IV cell-mediated hypersensitivity (e.g. contact allergies)
V stimulation by Ig directed against cell receptors (e.g. Graves' disease)
anaphylactoid
  reaction clinically similar to type I without being IgE-mediated
  e.g. direct activation of complement and mast cells by drugs

d. Outline the principles of management strategies for anaphylactic and anaphylactoid reactions.

e. Describe the role of complement.

Complement
  complex group of 20 or more plasma proteins
  alternative pathway
    C3 circulates in plasma at 1.2 mg/ml
    spontaneous cleavage to C3b, binding to factor B and Mg²⁺ (C3bB), activation
    by factor D to C3bBb which catalyzes C3 breakdown
    limited by factors H and I (inactivators)
    C3bBb may bind to microorganism surfaces via a thioester, protecting it from
    factor H and causing runaway C3b formation
    C3b complexes C5 which is cleaved to C5b
    C5b complexes C6, C7 and C8
    C9 is bound and undergoes conformation change, yielding the membrane
    attack complex
    MAC opens a channel permeable to Na⁺ in the cell membrane, usually causing
    lysis
  classical pathway
    bound antibody complexes with C1q which activates C1r and C1s to form
    C 1qrs
    this cleaves C4 to C4b which complexes C2 and Mg²⁺ (C4b2)
    C 1qrs activates C4b2 to C4b2a
    this activates C3 as in the alternative pathway
    C4b can also bind to a microorganism via a thioester bond
    promotion of phagocytosis
C3b and C3bi bind to receptors on phagocytes, producing phagocytosis of organisms to which they are bound. C3a and C5a stimulate granulocytes and degranulate mast cells.

f. Describe the role of cytokines.
O. Maternal Physiology

a. Explain the cardiovascular and respiratory changes during pregnancy and their consequences.

cardiovascular

blood
- volume ↑ 35% (1-2 l) from 12 weeks to term
- partly due to ↑ aldosterone, ADH
- red cell mass ↑ 20%
- anaemia common due to high iron requirement of mother and fetus
- Hb 140 → 120 g/l (lower without iron supplementation)
- ↑ platelets (usually)
- ↑ clotting factors (except XIII), ↑ fibrinogen (3 g/l → 5 g/l)
- ↓ albumin

peripheral
- 700 ml/min through uterus (80% to placenta)
- >1 l/min through the uterus in labour
- ↑ flow to skin, breasts and uterus
- ↓ SVR by 20%, BP ≈ 100/70 (fall of 15 mmHg)
- potential for aortocaval compression
- dilation of epidural veins, reduction of epidural space

cardiac
- ↑ venous compliance, CVP unchanged
- CO rises to 40% above normal by 32 weeks and plateaus
- SV ↑ 30%, HR ↑ 15%
- acute rise in labour up to a further 65%
- contractions produce autotransfusion of 500 ml
- ↑ CVP, BP, CSF and epidural pressure
- heart position altered by enlarged uterus, LAD on ECG

respiratory

mechanical

airway
- weight gain, fluid retention and vasodilation causes difficult airway
- resistance ↓ 36%, unchanged work of breathing

diaphragm
- rises 4cm
- ↓ RV (20%), FRC (20%), reduced oxygen reserve

chest wall
- increased AP and transverse diameters
- ↑ IRC (5%) so VC unchanged, ↓ TLC (5%)

metabolic
- BMR rises 20% over pregnancy
- VO₂ ↑ 20%
- increased respiratory drive due to progesterone increasing PCO₂ sensitivity
- ↑ TV (40%), RR (15%)
- PaCO₂ 32-34 mmHg by end of first trimester
- compensatory low HCO₃⁻ (20 mmol/l)
- reduced buffering ability
- during labour minute volume doubles, PaCO₂ swings as low as 20 mmHg
- ↓ CO₂, ↑ pH, ↓ respiratory drive
- typically followed by hypoventilation and fall in PaO₂

gastrointestinal

mechanical
- pressure on stomach and diaphragm from uterus
- ↑ gastric pressure, reflux
aspiration risk from 16 weeks

hormonal
progesterone slows gastric emptying
\(\uparrow\) gastrin reduces pH
\(\downarrow\) hepatic metabolism of drugs, PlChE \(\downarrow\) 30%

renal
\(\uparrow\) RBF and GFR parallel rise in CO
\(\downarrow\) urea, creatinine
\(\uparrow\) aldosterone
\(\downarrow\) renal threshold for glucose
uterus may obstruct ureters

other
relaxin softens connective tissue
progesterone \(\downarrow\) MAC (by 40% for halothane, 15% for isoflurane)
\(\downarrow\) volume of epidural space, \(\uparrow\) pressure

b. Explain the consequences of the supine posture during pregnancy.

gastrointestinal
increased gastric pressure, reflux

respiratory
diaphragmatic splinting

cardiovascular
aortocaval compression
may occur from second trimester, peaks at 36-38 weeks
greatly reduced IVC flow, venous return and CO
reduced aortic flow to pelvic organs (including uterus)
venous diversion through azygous and vertebral systems
prevented by 15˚ tilt when supine

c. Outline the functions of the placenta

structure
forms from the trophoblast tissue which invades the endometrial decidua
circulation begins at the 16th day from fertilization
consists of placental villi from the trophoblast and blood sinuses from the endometrium
surface area of 1.8 m\(^2\), thickness 3.5 \(\mu\)m

function
diffusion of nutrients from mother to fetus

oxygen
simple diffusion from 50 mmHg to 30 mmHg
30 mmHg is adequate for the fetus because of
higher haematocrit
higher affinity of HbF for oxygen (P50=19 mmHg)
double Bohr effect
\(\text{PCO}_2\) falls in fetal circulation and rises in maternal
circulation through the placenta
secondary pH change decreases affinity for oxygen in maternal blood and increases affinity in fetal blood
total capacity 1.2 ml/min/mmHg gradient

glucose
facilitated diffusion via carrier molecule
main energy source for fetus

fat
simple diffusion
amino acids, vitamins, Ca\(^{2+}\), Fe\(^{2+}\) 
active transport 
other substance also exchanged by simple diffusion include 
ketone bodies, Na\(^+\), K\(^+\), Cl\(^-\) 
diffusion of excretory products from fetus to mother 
carbon dioxide 
simple diffusion down a 2-3 mmHg gradient 
diffusion capacity 20 times that of oxygen 
Haldane effect 
deoxygenation of Hb in the maternal circulation increases its H\(^+\) binding affinity and consequently the HCO\(_3^-\) carrying capacity of red cells, facilitating CO\(_2\) removal 
the reverse occurs in the fetal circulation 
non-protein nitrogen 
urea, uric acid, creatinine transferred by simple diffusion 
endocrine function 
secretion of hCG by syncytiotrophoblast cells 
results in secretion of relaxin, oestrogens and progesterone by corpus luteum 
relaxin softens ligaments and the cervix at the time of delivery 
results in secretion of testosterone by testes in male fetuses 
stimulates maternal thyroid 
secretion of oestrogens by syncytiotrophoblast cells 
mostly oestriol (low potency) 
derived from maternal and fetal DHEA and 16-OH DHEA 
produces maternal physical changes in pregnancy 
enlargement of uterus, breasts 
relaxation of ligaments 
secretion of progesterone by syncytiotrophoblast cells 
maintains decidua 
\(\downarrow\) uterine contractility 
plays a role in lactation 
\(\downarrow\) gastric motility 
\(\downarrow\) SVR (smooth muscle tone) 
\(\downarrow\) MAC by 40% 
secretion of human chorionic somatomammotrophin (HPL) 
weak prolactin and GH-like activity 
decreases maternal insulin sensitivity 
promotes free fatty acid mobilization 
secretion of human chorionic thyrotropin 
stimulates maternal thyroid 
secretion of gastrin 
\(\downarrow\) gastric pH 

**d. Describe the transfer of gases between the mother and fetus including the double Bohr and Haldane effects.**

placenta 
area 1.8 m\(^2\) for exchange (11 m\(^2\) total villous area) 
thickness 3.5 \(\mu\)m 
diffusing capacity 
\(\text{O}_2\) 1.2 ml/min/mmHg 
\(\text{CO}_2\) 25 ml/min/mmHg 
maternal 
uterine perfusion 700 ml/min (80% placental) 
reduced by contractions, \(\alpha\) agonists, hypotension, abruption
PO₂ 100 → 40 mmHg content falls 4 ml/100 ml (16 → 12)
PCO₂ 32 → 45 mmHg
pH 7.42 → 7.3

fetal
placental perfusion 300 ml/min (50% of cardiac output)
reduced by cord compression, α agonists, hypoxia, hypoglycaemia
PO₂ 18 → 28 mmHg content rises 6 ml/100 ml (10 → 16)
PCO₂ 55 → 40 mmHg
pH 7.21 → 7.32
e. Describe the endocrine changes that occur during pregnancy and their consequences.

Placental hormones outlined above.
pituitary
50% enlargement of anterior pituitary
suppression of LH, FSH due to high oestrogen and progesterone levels
increased secretion of ACTH, TSH, MSH and prolactin
adrenal cortex
cortisol
moderately increased throughout pregnancy
increases amino acid mobilization and raises blood glucose
aldosterone
rises to double normal levels by the end of pregnancy
increases Na⁺ and water retention
thyroid
enlarges up to 50% in pregnancy and increases T₃ and T₄ release
parathyroid
enlarge and increase PTH secretion (continues during lactation)
increases Ca²⁺ mobilization and absorption for fetal use
ovaries
corpus luteum
relaxin, progesterone and oestrogens as above
weight gain
fetus 3 kg
other POC 2 kg
uterus 1 kg
breasts 1 kg
ECF 2.5 kg
fat 1.5 kg
total 11 kg range 0-35 kg
f. Describe the haematological changes with pregnancy.

proteins
↓ albumin and γ globulin due to dilution
↑ α and β globulin
↑ clotting factors, fibrinogen and plasminogen
↓ fibrinolytic activity
g. Describe the physiology of labour.

Maternal Physiology 1.O.4 James Mitchell (November 5, 2001)
P. Fetal and neonatal physiology

a. Describe the fetal circulation

The fetal circulation is substantially different from the adult, primarily because of the difference in the source of oxygenation: the fetus obtains oxygenated blood from the placenta and the newborn from the lungs. Oxygenated blood returns from the placenta in the umbilical vein which joins the portal vein and then passes through the liver into the hepatic vein or bypasses the liver in the ductus venosus and passes directly into the IVC.

Much of the blood from the IVC passes through the foramen ovale into the left atrium and then into the systemic circulation. The remainder, together with blood from the SVC, passes into the RV and then into the pulmonary trunk. In the fetus, the pulmonary circulation is of a high resistance because of the lack of oxygen in the lungs and only about a third of the RV output passes through the lungs (12% of cardiac output), the remainder being diverted through the ductus arteriosus into the arch of the aorta and the systemic circulation.

Because of the high pulmonary resistance, the pressure in the pulmonary trunk is about 5 mmHg higher than that in the aorta. The parallel operation of the right and left ventricles allows them to have substantially different outputs with the left ventricle pumping 20% more blood.

About 75% of total cardiac output ends up in the descending aorta and the majority of this flows into the umbilical arteries (over 50% of cardiac output).

The oxygen saturation of haemoglobin in the fetus is much lower than in the newborn. In the umbilical vein, the blood is about 80% saturated, falling to 62% in the LV after mixing with other venous blood. This is the saturation of the blood perfusing the head and upper body. After mixing with blood from the ductus arteriosus, saturation falls to 58% for perfusion of the remainder of the body. fetal haemoglobin (α2γ2) has a higher affinity for oxygen than adult haemoglobin (P50=19 mmHg) as it binds 2,3 DPG less strongly, so in the placenta oxygen is transferred from maternal to fetal haemoglobin at the same PO2. The Bohr and Haldane effects also operate at the placenta to facilitate transfer of oxygen from mother to fetus.

After birth, pulmonary vascular resistance falls by 90% as air enters the airways. This results in a rapid fall in right heart pressures and reversal of pressure gradient between LA and RA which pushes the foramen ovale shut. The rise in arterial oxygen tension and reversal of flow initiate constriction and closure of the ductus arteriosus (may be prostaglandin-mediated).

In response to the trauma at delivery, the umbilical arteries constrict distal to the superior vesical arteries, and the cord is usually clamped. The cessation of flow through the umbilical vein coincides with closure of the ductus venosus which has a sphincter mechanism. The closing of the placental circulation causes a sharp rises in systemic resistance and blood pressure.

In the weeks following these changes, the muscle lining of the pulmonary vessels thins and the left ventricular wall starts to thicken to a greater extent than the right. The foramen ovale, ductus arteriosus and ductus venosus are sealed with fibrous tissue and the circulation shows the characteristics of the adult circulation.

Hypoxia in the neonate can produce pulmonary vasoconstriction and raise right side pressures enough to cause the reopening of the ductus arteriosus and foramen ovale (“transitional circulation”). The shunting produced by this circulation tends to worsen and prolong desaturation despite administration of oxygen. It can be reversed with continued oxygen administration or by inhalation of NO.

Neonatal heart

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>120-160</td>
</tr>
<tr>
<td>Systolic</td>
<td>70-90 mmHg</td>
</tr>
<tr>
<td>MAP</td>
<td>45-65 mmHg</td>
</tr>
<tr>
<td>PAP</td>
<td>labile (with hypoxia or hypercapnea)</td>
</tr>
<tr>
<td>CO</td>
<td>180-240 ml/min/kg</td>
</tr>
</tbody>
</table>
low compliance
dependent on preload and rate to maintain output
poor tolerance of hypovolaemia or bradycardia
equal muscularity of left and right ventricles
little sympathetic activity
bradycardia easily provoked
little change in vascular tone with spinal or caudal

Lungs
not viable before 24 weeks
inadequate surface area, inadequate surfactant, immature control
airway
jew angle 140˚, high larynx (C3-4), long epiglottis, narrow cricoid
short trachea (4 cm), large nasal airway
first breath
results from stimulation at birth, ↑reset of chemoreceptors with ↑ SVR
from “zero” volume, requires >60 cmH₂O transpulmonary pressure
volume rises and transpulmonary pressure falls over first few breaths
control
high rate minimizes work of breathing
increased response to ↑ PCO₂
unreliable response to hypoxia
transient apnoea is normal
true apnoea: >15 s, ↓ PO₂, ↓ HR
values
same as adult
TV 7 ml/kg, V₅ 2.2 ml/kg, FRC 30 ml/kg, spf comp 0.05 /cmH₂O
different
VC 35 ml/kg (55), resistance 27 cmH₂O/l/s (1.6), RR 35 /min (14)
minute vol 125 ml/min/kg (60), O₂ uptake 6.8 ml/min/kg (3.3)
P₅O₂ 65-80 mmHg, P₅CO₂, 35 mmHg
low P₅O₂ due to CC>FRC (→airway closure) and shunt
very compliant chest wall limits transpulmonary pressure
chest compliance 260 ml/cmH₂O
lung compliance 5 ml/cmH₂O

c. Explain temperature regulation in the neonate and how this differs from the adult.

d. Compare the physiological differences in organ function between the neonate and the adult.

Renal
immature at birth
GFR/SA 15 ml/m² at birth, 35 at 2 months, 70 at 2 years (adult)
concentrating ability 600 mOsm/l (1200 in adult)
protein synthesis is a major contributor to nitrogen metabolism
hepatic metabolism
conjugation less developed than phase 1 reactions

e. Explain the control of body fluids in the neonate and how the control and composition differ from the adult.
R. Principles of Measurement

http://www.netspace.net.au/~jam/anaesth/measurement.html

a. Explain mathematical concepts such as exponential functions, integration and differentiation.

Any process in which the rate of change of a quantity is proportional to the quantity is an exponential function. An example is the emptying of a bath: the rate of change of the volume of the bath (the plug-hole flow) is proportional to the volume remaining in the bath (which determines the pressure at the plug-hole):

\[ \dot{V} = -kV \]

Integrating with respect to time gives the exponential function:

\[ V = V_t e^{-kt} \]

This situation is analogous to the elimination of a drug which demonstrates first-order kinetics, such as the washout curve of an inhaled anaesthetic. It is also analogous to the natural expiration from the lungs where \(-k\) equals the rate constant of expiration, the reciprocal of the time constant (compliance times resistance).

Integration is the derivation of a function which expresses the area under a function \( y = f(x) \) from \( x = 0 \) to any value of \( x \).

Differentiation is the reverse process: deriving a function which expresses the rate of change of \( f(x) \).

b. Explain electrical concepts such as current, potential difference, resistance, impedance and capacitance as they relate to biomedical apparatus.

Current is the flow of charged particles resulting from a potential difference or changing magnetic field. Most commonly this is a flow of electrons through a metal or other conductor (such as graphite) which has freely mobile electrons. A current can also flow through solutions containing charged particles. All body fluids contain ions and so are capable of conducting current. The unit of current is the Ampere (1 Coulomb/second). Many quantities in monitoring devices are measured indirectly as electrical current. Nerve stimulators are calibrated to deliver a determined current through the tissue between the electrodes.

Solids which do not contain many unbound electrons and solutions with few ions are poor conductors and are known as insulators.

Semiconductors contain electrons which are loosely bound and may conduct a current if electrons are given enough energy to become unbound. This effect is seen in thermistors and photodetectors used in monitoring equipment. It is also the basis for transistors and silicon-based integrated circuits which are universally present in electronic equipment.

Potential difference is the difference in electrical energy between two points. Its unit is the Volt (1 Joule/Coulomb) and it generates a electromotive force which drives a current of charged particles.

Resistance is a measure of the electromotive force required to drive a current through a material. Its unit is the Ohm (1 Volt/Ampere). Thermistors display a change in resistance over a range of temperature and so with calibration the current flow for a specified voltage can be measured and used to determine temperature. Similarly some materials display an increase in resistance as they are stretched, allowing for tension or pressure to be measured indirectly.
When a small change in resistance is to be measured, a Wheatstone Bridge circuit is commonly employed. Classically, \( R_4 \) is measured by adjusting \( R_3 \) until the galvanometer reads 0. In this situation, \( R_1/R_2 = R_3/R_4 \). In practice, a monitor is set up so that \( R_1 \) and \( R_2 \) vary together and inversely to \( R_3 \) and \( R_4 \). The deflection of the galvanometer is then read as output.

Impedance is the resistance of a component or circuit with a specified characteristic current flowing. Resistance of many components (capacitors and inductors) varies with frequency of alternating current. In a surgical diathermy device, a capacitor is part of the circuit, providing low impedance at the high frequency typically used (1 MHz), but high impedance to low frequency currents likely to cause arrhythmias (50 Hz).

Capacitance is a measure of the charge a device can hold. Its unit is the Farad (1 Coulomb/Volt). Defibrillators are based on a capacitor which is charged with a calibrated voltage to provide a determined energy output for DC reversion. The energy stored in a capacitor is \( 0.5 \times \text{charge} \times \text{potential} \). A typical output of 360 J is usually produced by about 5000 V across about 150 mC. An inductor is used to slow the discharge of the defibrillator.

c. Explain the SI system of units.

Seven basic SI units from which all other units are derived
- mass \( \text{kg} \)
- time \( \text{s} \)
- distance \( \text{m} \)
- current \( \text{A} \)
- temperature \( \text{K} \)
- luminous intensity \( \text{cd} \)
- amount of substance \( \text{mol} \)

Derived SI units (some of them)
- temperature \( ^\circ \text{C} \), \( \text{K} - 273.15 \)
- force \( \text{N} \), \( \text{kg m s}^{-2} \)
- pressure \( \text{Pa} \), \( \text{N m}^{-2} \)
- energy \( \text{J} \), \( \text{N m} \)
- power \( \text{W} \), \( \text{J s}^{-1} \)
- frequency \( \text{Hz} \), \( \text{s}^{-1} \)
- volume \( \text{l} \), \( 10^3 \text{m}^3 \)
- charge \( \text{C} \), \( \text{A s} \)
- potential \( \text{V} \), \( \text{W A}^{-1} \) or \( \text{J C}^{-1} \)
- capacitance \( \text{F} \), \( \text{C V}^{-1} \)
- resistance \( \text{\Omega} \), \( \text{V A}^{-1} \)
- magnetic flux \( \text{Wb} \), \( \text{V s} \)
- radiation dose \( \text{Gy} \), \( \text{J kg}^{-1} \text{ water} \)
- radiation exposure \( \text{Sievert Gy} \cdot \text{ tissue factor} \cdot \text{ radiation type factor} \)
Prefixes (multipliers)

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<thead>
<tr>
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<th>Symbol</th>
<th>Value</th>
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<tr>
<td>atta</td>
<td>a</td>
<td>$10^{-18}$</td>
</tr>
<tr>
<td>femto</td>
<td>f</td>
<td>$10^{-15}$</td>
</tr>
<tr>
<td>pico</td>
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<tr>
<td>exa</td>
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Some non-SI units with conversions

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<th>Conversion</th>
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<td>Pressure</td>
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<tr>
<td>mmHg</td>
<td>132 Pa</td>
</tr>
<tr>
<td>cmH₂O</td>
<td>98 Pa</td>
</tr>
<tr>
<td>atm</td>
<td>101.325 kPa</td>
</tr>
<tr>
<td>psi</td>
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<tr>
<td>Energy</td>
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</tr>
<tr>
<td>calorie</td>
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</tr>
<tr>
<td>Resistance</td>
<td></td>
</tr>
<tr>
<td>dyne s cm⁻⁵</td>
<td>80 mmHg l⁻¹min</td>
</tr>
<tr>
<td>Catheter size</td>
<td>French external circumference in mm</td>
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<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose</td>
<td>mmol/l x 18</td>
</tr>
</tbody>
</table>

**d. Outline the conversion between different units of pressure measurement.**

Given above.

**e. Describe the laws governing the behaviour of fluids.**

Fluids are gases or liquids. They exhibit flow, which is defined as quantity (Q) moved per unit time (t):

$$\dot{Q} = \frac{Q}{t}$$

Flow is characterized as laminar or turbulent. In laminar flow, fluid moves without eddies and flow is equal to pressure (P) over resistance (R):

$$\dot{Q} = \frac{P}{R}$$

In a cylindrical tube, resistance to flow is related to radius (r) and length (l) of the tube and viscosity ($\eta$) of the fluid, yielding the Hagen-Poiseuille equation:

$$\dot{Q} = \frac{\pi Pr^4}{8\eta l}$$

Above a critical speed, laminar flow changes to turbulent flow. For a smooth cylindrical tube, the transition occurs when Reynolds number is approximately 2000. For rough or bent tubes, the transition occurs at lower numbers. Reynolds number (RN) is defined in terms of speed ($v$), density ($\rho$) and viscosity ($\eta$) of the fluid and diameter (d) of the tube:

$$RN = \frac{v\rho d}{\eta}$$

For turbulent flow, the relationship determining flow is described empirically:

$$\dot{Q} \propto \sqrt{\frac{P}{lP}}$$

The relationship with tube diameter is complex and roughly related to slightly
The behaviour of gases is described by the gas laws. Because gases are composed of small molecules or atoms widely spaced, their physical properties are very similar regardless of the identity of the molecules or atoms.

Boyle’s Law states that for a constant quantity of gas at a constant temperature, the absolute pressure is inversely proportional to the volume. Charles’s Law states that for a constant quantity of gas at a constant pressure, the absolute temperature of the gas is proportional to its volume. Avogadro’s Hypothesis states that equal volumes of gas at the same temperature and pressure contain the same number of molecules. One mole of gas occupies 22.4 dm$^3$ at s.t.p. (273.15 K, 101.325 kPa). These laws combine to give the relation:

$$PV = nRT$$

Where $R$ is the universal gas constant.

Real gases all have a temperature at which they condense into liquids (boiling point at standard pressure). Over a range of pressures, the temperature at which a gas will condense varies below the critical temperature (the temperature at which the gas will condense at critical pressure and above which it will not condense). At a temperature well below critical temperature, a gas will start to condense with decreasing volume, maintaining a constant pressure over a range of volume until it is entirely condensed.

With gas mixtures, separation of the constituents by condensation of one into the liquid phase may occur below the “pseudo-critical” temperature over a range of pressures.

**f. Describe the principles of measurement employed by apparatus in clinical use, including transducers and describe their calibration.**

**Resonance**

All oscillating systems display resonance with a peak resonant frequency ($f_0$)

$$f_0 = \frac{1}{2\pi} \sqrt{\frac{\text{stiffness}}{\text{mass}}}$$

Frequencies close to the resonant frequency will be distorted in the absence of damping.

High resonant frequency allows accurate reproduction of waveforms.

**Damping**

The property of a system which diminishes resonance.

Damping ratio is the ratio of the amplitude of successive resonant peaks following a “square-wave” stimulus ($D_2 \div D_1$).

Damping coefficient is derived from damping ratio

$$\beta = \frac{(\ln \frac{D_2}{D_1})^2}{\pi^2 + (\ln \frac{D_2}{D_1})^2}$$

$\beta = 0.64$ is the coefficient for optimal damping.

Corresponds to a damping ratio of about 0.07.

Eliminates phase lag.

Allows accurate reproduction of frequencies up to $\frac{2}{3}$ of the resonant frequency.

Underdamped systems (small $\beta$, damping ratio close to 1) respond rapidly but overshoot, so they oscillate around their final value e.g. bathroom scales.

Overdamped systems ($\beta$ close to 1, damping ratio close to 0) move slowly to their final value and do not overshoot e.g. thermometer, arterial line with bubbles.

**g. Describe the measurement of flow, pressure and velocity in fluids.**

Flow is the change of volume over time. In gases it may be most simply be measured by a device which records volume against a time baseline, such as the Benedict Roth spirometer in which a sealed drum moves up as it is filled with gas, recording directly...
onto a chart moved with time, or with a bellows which moves a pen with its expansion as in the Vitalograph more commonly used for spirometry.

For the measurement of continuous flows, an alternating bellows device is used in gas and water supplies, with the direction of flow into the bellows alternating as it is filled. In anaesthesia, the Wright respirometer connects in series with the circuit and records tidal volume with each breath. A set of slits generates a circular flow inside the meter which spins a vane connected directly to a rotating dial via a gearing system. It is not accurate for continuous flow.

Most commonly in anaesthesia, tidal volume and flow is measured using an electronic flow meter. Sets of blades cause the flow of gas to spin a mounted vane which interrupts a light beam shone through the housing of the device. Electronic processing of the frequency and duration of the interruption of the light beam allows calculation of flow (Ohmeda). Alternatively the cooling of a fine heated wire across the gas flow can be used to calculate flow (Dräger). These devices all measure gas flows at ambient temperature and pressure.

Measurement of continuous flow also occurs in the flowmeters of the anaesthetic machine. These consist of a calibrated glass tube of variable internal diameter in which a grooved bobbin is suspended by the flow of gas. The flow through a flowmeter tube is complex and dependent on the characteristics of the particular gas being measured, so they are calibrated empirically for a specific gas or mixture at a specific temperature and pressure. The pressure drop across the bobbin is constant and determined by the weight of the bobbin. The size of the orifice around the bobbin increases as it moves up the glass tube, allowing more gas flow for the fixed pressure drop. This is a “fixed pressure, variable orifice” flowmeter.

Highly variable flows may be measured with specific devices such as the peak flow meter. In this a ratcheted marker is moved against a variable resistance as the patient breathes out forcefully. The maximum displacement of the marker is calibrated to show the peak flow rate. This measurement is highly effort-dependent.

For constant measurement of respiratory flows, a pneumotachograph may be used. In this device a heated gauze screen maintains a region of laminar flow which provides a fixed resistance which results in a pressure drop across the gauze proportional to flow. By electronically integrating this pressure drop against time, the device can calculate the flow continuously.

Measurement of flow in liquids is simpler than gases because the variations in volume with temperature and pressure are much less. In IV giving sets, flow may be measured using a calibrated drop chamber in which the drop rate is counted either manually or electronically. The accuracy of this method depends on the composition of the fluid.

More common in slow infusions is the use of volumetric pumps. These incorporate an electric pump in the infusion line which is calibrated to deliver a controlled volume and operated at a rate programmed into the pump.

For small volumes, a mechanical syringe-driver operated by a stepper motor is used. Combined with calibrated syringes, this can deliver very accurate flows of small volumes over extended periods, such as in subcutaneous infusion of narcotics by portable battery-driven devices.

Measurement of liquid flow in the body is generally by indirect methods with the exception of dialysis and bypass devices where mechanical or electromagnetic methods can be used. Dilution of a marker such as fluorescent dye, radioactive tracer or thermal dilution with cold crystalloid produces a washout curve when introduced into a fluid flow. The curve can be integrated to calculate flow rate. This technique is used to measure cardiac output.

Flow can also be deduced from concentration changes in a marker across an organ if the rate of excretion or absorption of the marker can be separately measured. This is the Fick principle and is used in the calculation of cardiac output from the rate of oxygen uptake from the lungs and the change from mixed venous to arterial oxygen concentration. It is also used in the calculation of GFR from creatinine output.

An approximation of flow can be determined from ultrasound Doppler studies of
fluid velocity and vessel area. This is used to estimate flows across heart valves.

h. Describe and compare the methods of measuring temperature.

Heat
The quantity of thermal energy contained in a substance.

Temperature
An expression of the specific heat of a substance and the amount of thermal energy in it.
Determines the direction of flow of thermal energy (from hotter to cooler).

Specific heat
The thermal energy required to produce a given temperature rise in a substance.

Mercury thermometer
A bulb contains mercury which expands to force its way up a narrow calibrated column containing a vacuum. To produce a maximum-reading thermometer, a constriction just above the bulb splits the column when it contracts. Alternatively, a metal index sits above the column.
It is slow to equilibrate (with the time constant of equilibration being printed on the side), fragile and cannot read temperatures below -39°C.

Bimetallic thermometer
A coiled strip of two metals turns a pointer as the two metals expand at different rates with heat. It is slow to equilibrate.

Bourdon thermometer
A pressure-measuring device in which expansion of a fluid turns a dial. It is slow and sensitive to pressure changes.

Resistance thermometer
A piece of wire displays increasing resistance linearly with a rise in temperature. A Wheatstone bridge provides accurate measurement of the resistance. The changes in resistance over a useful clinical range are very small.

Thermistor
Many metal oxides display large resistance changes over small temperature ranges. These provide for accurate measurement in the clinical range using a very small probe. It is sensitive to heat damage from sterilization.

Thermocouple
Different metals generate an electrical potential when in contact which is related to their temperature. This allows for thin needle probes to be made to measure temperature. Their disadvantage is that the reference electrode must be kept at a fixed temperature, or compensation made for its temperature.

In practice
In the anaesthetized patient, the most practical method of measuring temperature is a small probe (thermistor) inserted into the nasopharynx, oesophagus or rectum.

i. Describe and compare the methods of measuring humidity.

Humidity
The amount of water vapour present in air or another gas
Absolute (gm⁻³) or relative (% of saturation) terms
Saturation humidity of air is highly dependent on temperature
17 gm⁻³ at 20°, 44 gm⁻³ at 37°

Hair hygrometer
A hair stretches more readily as it becomes moist. If balanced against a spring, a simple hygrometer is formed. This is a primitive device, accurate over a limited range.

Wet and dry bulb hygrometer
Evaporation of water from around the bulb of a constantly moistened thermometer cools the thermometer an amount dependent upon the relative humidity and air flow over the bulb. If the air flow is constant, the relative humidity can be determined from the ambient temperature and this cooling effect.

Regnault’s hygrometer

Air is blown through ether in a tube until condensation occurs on the outside of the tube. The temperature at which this occurs is the “dew point”: the temperature at which the current absolute humidity represents 100% relative humidity. From this temperature, the absolute humidity can be determined and the relative humidity derived from knowledge of the saturated vapour pressure at ambient temperature. This is an impractical device as it involves ether and measurement of the dew-point with precision is difficult.

Other devices

Electrical measures of humidity depend on probes whose resistance or capacitance depends on their water-content. Ultraviolet absorbance spectrophotometry can measure absolute humidity as can mass spectrometry. These are more precise and rapid methods of measuring humidity.

j. Explain in detail the principles of pulse oximetry including calibration, sources of errors and limitations.

Pulse oximeter

Device which measures functional saturation of haemoglobin by spectrophotometry through intact tissue.

Haemoglobin species absorb light of different wavelengths with different intensities

Oxyhaemoglobin absorbs less red light and more infrared than deoxyHb

Beer-Lambert Law describes absorption of light in a fluid

$$I_{\text{transmitted}} = I_{\text{incident}} e^{-\varepsilon d C}$$

where \( I \) is light intensity, \( d \) is path length, \( C \) is concentration, \( \varepsilon \) is extinction coefficient

Practical application

Two wavelengths: 660 nm (red) and 940 nm (infrared)

Rapidly alternating LEDs, one on at a time

\( I_{\text{incident}} \) known

Single photodetector for both wavelengths measures \( I_{\text{transmitted}} \)

Constant absorbance due to tissue, venous and capillary blood

Variation in \( I_{\text{transmitted}} \) for each wavelength assumed to be due to arterial pulsation

Rate of pulsation read as heart rate

Ratio of pulsatile to constant proportions at different wavelengths is calculated

$$R = \frac{\text{pulse}_{660} \div \text{const}_{660}}{\text{pulse}_{940} \div \text{const}_{940}}$$

Functional saturation varies with \( R \) (non-linear)

100% corresponds to \( R=0.4 \), 85% to 1.0 and 0% to about 3.4

Functional saturation

Saturation assuming

HbO₂ and deoxyHb are the only species present

Dissociation curve is not markedly shifted (pH, temp normal)

$$\text{Functional } SaO_2 = \frac{[\text{HbO}_2]}{[\text{HbO}_2] + [\text{Hb}]}$$

Fractional saturation

Percentage of total Hb present which is HbO₂.

Measured in arterial sample with co-oximeter (typically 7 wavelengths used)

Sources of error

Sensor
Inadequate light transmitted (nail polish, onychomycosis)
Extraneous light
Movement or diathermy causing “noise” in received signal

Processing
Human calibration only for SpO₂ > 80%
Increasingly unreliable with low SpO₂

Haemoglobin
High concentration of MetHb (↓ to 85%), COHb (↑) or other species
Other light-absorbing species in blood (methylene blue, other dyes)

Blood flow
Poor perfusion (vasoconstriction, hypothermia, BP cuff)
Pulsatile venous flow (tricuspid regurgitation)

The clinical usefulness of pulse oximetry diminishes with high haematocrit, as an adequate PO₂ may yield a lower saturation than expected. The peripheral placement of the probe reduces its usefulness in cold or peripherally vasoconstricted patients as the oxygen saturation in the central circulation may be substantially higher than in the fingertips.

k. Explain the principles involved in the analysis of gases using ultraviolet or infrared absorption, paramagnetic analysis, gas chromatography, mass spectrometry and Raman scattering.

Absorption spectrophotometry
covered in j. and l.

Paramagnetic analysis
Most gases are diamagnetic, being repelled by a magnetic field, because of the characteristics of their outer shell electrons. Oxygen is paramagnetic because of its unpaired outer shell electrons and so is attracted by a magnetic field. This effect is used to produce a paramagnetic analyzer to determine oxygen concentration.

In a paramagnetic analyzer, a dried gas sample flows through a chamber in which a nitrogen-filled dumbbell is balanced in a magnetic field. The dumbbell is displaced by the paramagnetic force on the oxygen in the sample and either its displacement against a torsion spring or else the force required to keep it in position is measured.

By calibrating the device with 100% nitrogen and 100% oxygen, a very accurate measurement of the oxygen concentration in a gas sample may be made.

A more modern design of paramagnetic analyzer uses an alternating magnetic field at the junction of two gas streams (sample and reference). A pressure wave is induced by the change in magnetic field and a pressure transducer between the gas streams can detect differential pressure and allows calculation of the oxygen concentration of the sample rapidly and continuously.

Gas chromatography
Chromatography relies on the separation of compounds by their different affinities for a stationary and mobile phase in a chromatography column. In the case of gas chromatography, the mobile phase is usually an unreactive gas such as nitrogen or argon and the stationary phase is a fine crystalline material such as silica coated in polyethylene glycol or silicone oil. The column is kept at a constant temperature and the sample to be analyzed is injected into the gas flow before the column.

At the end of the column a detector records the appearance of the components of the sample against the time since injection. The detector may be a flame ionization detector, a thermal conductivity detector (suitable for inorganic gases) or an electron capture detector (best for halogenated compounds).

Control samples are used to determine the chromatographic characteristics of known gases. These are compared with the unknown sample’s trace to determine its constituents. The detector can also be calibrated for quantitative analysis of the sample.
Gas chromatography is suitable for analysis of all gases and many compounds which can be made to yield volatile products.

Mass spectrometry
Mass spectrometry separates molecules or atoms according to their mass and charge after stripping their outer electrons. A sample is allowed to leak very slowly into an ionization chamber in which an electron beam is used to ionize the sample. The ions are accelerated and focussed through an electric field and then deflected either using a strong magnetic field or an oscillating electric field between four rods (“quadrupole mass spectrometer”).
The ions are separated according to their mass and charge and so the components of the sample can be determined quantitatively by analyzing the composition of the ionized sample which will include breakdown products of the components of the sample. This analysis is simple for small molecules and difficult for mixtures of several larger molecules because of the wide variety of breakdown products.
Mass spectrometry can measure very small concentrations in very small samples and can be made to have a response time as little as 0.1 s, but it remains a complex and expensive analysis tool.

Raman scattering
The Raman effect occurs when gas molecules absorb energy from photons resulting in quantized changes in vibrational or rotational states. Light is re-emitted with further changes in state producing a spectrum of wavelengths characteristic of the molecules involved. Spectral analysis allows identification of known compounds by comparison with their Raman spectra. This is a technique of similar accuracy to mass spectrometry.

Oxygen electrodes
The Clarke oxygen electrode is a polarographic electrode. Oxygen from the sample fluid equilibrates across a membrane with a buffered KCl solution surrounding a glass electrode. The electrode has a platinum cathode and a Ag/AgCl anode. With between 0.5 V and 0.9 V applied across the electrode, the consumption of O₂ at the cathode and hence the current in the circuit is dependent on the O₂ concentration in the solution which rapidly equilibrates with the sample. In practice, 0.68 V is used. Performance is affected by N₂O and halothane.

\[
\text{anode: } 4\text{Ag} \rightarrow 4\text{Ag}^+ + 4e^- \\
\text{cathode: } \text{O}_2 + 2\text{H}_2\text{O} + 4e^- \rightarrow 4\text{OH}^- 
\]

The fuel cell detector operates on the same principle as the Clarke electrode, but using a lead anode which is oxidized in the operation of the cell. It is oxygen-powered with a voltage output proportional to the oxygen concentration in the electrolyte. In this case the electrolyte is KOH solution.

\[
\text{anode: } 2\text{Pb} + 4\text{OH}^- \rightarrow 2\text{PbO} + 2\text{H}_2\text{O} + 4e^- \\
\text{cathode: } \text{O}_2 + 4e^- + 2\text{H}_2\text{O} \rightarrow 4\text{OH}^- 
\]

Both these devices require temperature and pH compensation and have limited lifespans.

Blood gas electrodes
Arterial sample stored on ice in lithium heparin tube and analyzed quickly
PO₂, PCO₂ and pH are measured directly
PO₂ using a Clark electrode
pH using a pH electrode
Ag/AgCl or Hg/Hg₂Cl₂ reference electrode in contact with sample via KCl solution and membrane
solution and membrane
Buffer solution of 0.1 M $[H^+]$ in contact with sample via $H^+$-sensitive glass
Voltage generated by $H^+$ gradient converted to pH reading
PCO$_2$ using a Severinghaus electrode
Similar to pH electrode except $H^+$-sensitive glass is surrounded by NaHCO$_3$
solution in contact with sample via CO$_2$-permeable membrane
CO$_2$ equilibrates across membrane, changing pH of buffer solution
pH change read by glass electrode and converted to PCO$_2$ reading
HCO$_3^-$ (mmol/l) calculated from pH and PCO$_2$ (mmHg)

$$\text{pH} = 6.1 + \log_{10} \frac{[\text{HCO}_3^-]}{0.03 \text{ PCO}_2}$$

$$\Rightarrow [\text{HCO}_3^-] = 0.03 \text{ PCO}_2 \cdot 10^{\text{pH}-6.1}$$

Base excess is measured by determining the sample’s buffering capacity
Sample is equilibrated to two known PCO$_2$ values
pH is measured at each PCO$_2$
These two points fall on a “titration line” on the Siggaard-Andersen curve nomogram

Nomogram is a graph of log(PCO$_2$) versus pH
Intersection of the titration line with the PCO$_2$=40 mmHg line gives a value
for “standard bicarbonate” which represents what the [HCO$_3^-$] would be
without respiratory compensation
Titration line also intersects two curves on the nomogram, reading “buffer base” (concentration of proton acceptors in the blood, normal 48 mEq/l) and
“base excess” (mEq/l of $H^+$ required to correct blood to pH 7.4 at PCO$_2$
40 mmHg)

Other values commonly measured by blood gas machines
Na$^+$, K$^+$, Ca$^{2+}$ using sensitive glass electrodes
Hb, glucose, lactate
1. Explain in detail the principles of capnography including calibration, sources of errors and limitations.

Capnography is the continuous measurement of PCO₂ in a gas sample. It is used in anaesthesia to monitor respiration and, by measuring P₆₇CO₂, to give information about acid-base status and adequacy of gas exchange. Capnographs are usually set up either as “main stream” with a sensor on the circuit or “side stream” with gas sampled from the circuit at around 150 ml/min and analyzed separately. Side stream circuits are more common as they are cheaper and more robust.

Capnographs measure the CO₂ content of gas by infrared spectrophotometry. CO₂ molecules absorb infrared light at a 4.28 µm by altering their vibration and rotation. Infrared radiation is shone through the sample chamber containing a continuous flow of sampled gas at a controlled pressure. The absorbance at the specified wavelength may be compared with that in a calibration cell containing no CO₂ and must also be calibrated periodically to zero. The absolute amount of absorbance may be increased by using a reflected beam which passes through the sample chamber many times.

Some capnographs use multiple light wavelengths and so are able to measure the concentration of volatile anaesthetics and other gases such as NO₂.

There are several potential problems with capnography. Side stream capnography has an increased response time as gas from the circuit must be drawn through the sampling line. There is potential for leakage at each connection of the sample line, reducing the CO₂ concentration. The gas drawn from the circuit is not a true end-tidal sample even at the end of expiration because of the dead-space in the large airways and circuit, and so there is always an underestimate of P₆₇CO₂. Mixing within the sample chamber will “blunt” changes in the CO₂ trace. Pressure changes in the sample chamber either as a result of airway pressure changes or constriction of the sample line will alter the absolute CO₂ concentration in the chamber. Physiological derangements such as V/Q mismatch may result in a wide disparity between P₆₇CO₂ and P₆₇CO₂ (an increased A-a gradient), reducing the usefulness of capnography.

Main stream capnographs avoid the problems associated with the sample line but are more prone to pressure changes and as the sample chamber windows are made of sapphire, they are very expensive if damaged in handling or cleaning.

Measurement of cardiac output

Fick principle (Adolph Fick)

Pulmonary venous oxygen flux (q₃) equals pulmonary arterial oxygen flux (q₁) plus alveolar oxygen uptake (q₄)

\[
q₁ + q₄ = q₃
\]

\[
q₃ = Q \ [O₂]pv
\]

\[
q₄ = Q \ [O₂]pa
\]

\[
⇒ Q = q₄ ÷ ([O₂]pv - [O₂]pa)
\]

so cardiac output (Q) can be calculated from pulmonary O₂ uptake, and mixed venous and pulmonary venous oxygen concentrations.

Mixed venous oxygen concentration can be measured using a Swan-Ganz catheter and pulmonary venous oxygen concentration approximated with a systemic arterial sample.

This method requires determination of oxygen uptake over several minutes and so requires either a completely closed breathing circuit in anaesthesia or an approximation using mixed expired and inspired oxygen concentrations or a laboratory setting.

Indicator dilution

A known amount of an indicator is introduced into the circulation at a point where the entire cardiac output is passing. The concentration of the marker is measured downstream after mixing has occurred and its value is plotted over time. The entire cardiac output need not be passing the
sampling point so long as no other blood flow has been added. For example, the indicator might be injected in the right atrium and the sampling done from the pulmonary circulation.

The amount of indicator (n) is related to its mean concentration (\( \bar{c} \)), cardiac output (\( \dot{Q} \)) and the time for which it is detected (\( t_2 - t_1 \)):

\[
n = \bar{c} Q(t_2 - t_1)
\]

\[
\bar{c} = \frac{\int c \ dt}{t_2 - t_1}
\]

\[
\Rightarrow \dot{Q} = \frac{n}{\int c \ dt}
\]

The conventional expression is in the Stewart-Hamilton equation:

\[
\dot{Q} = \frac{n}{\int c \ dt} = \frac{k(T_{\text{core}} - T_{\text{indicator}}) V_{\text{indicator}}}{\int \Delta T \ dt}
\]

This can be done using a dye indicator (which requires a semi-log plot to determine \( t_2 \) when recirculation occurs) or more commonly using cold saline with temperature being the “indicator”. There is an inherent inaccuracy in thermodilution when thermal exchange occurs between the blood and the vessel and structures surrounding it and when cool fluids may be being infused peripherally in a variable fashion.

Echocardiography

Cardiac output (\( \dot{Q} \)) can be calculated using the TOE probe to measure cross-sectional area (A) and flow velocity (V) over the duration of one cardiac cycle (t) at a point where the entire cardiac output is passing (e.g. pulmonary outflow tract).

\[
\bar{V} = \frac{\int V \ dt}{t}
\]

\[
\dot{Q} = A \times \bar{V}
\]

This method assumes equal flow over the whole area and it is technically difficult to perform. With continuous wave Doppler and a multiplane probe this method should have a bias of zero and limit of agreement of 1 l/min compared to thermodilution.

**Outline methods and principles used to measure regional blood flow.**

Cerebral

Kety-Schmidt technique

Uses Fick principle

Total uptake of tracer = perfusion x extraction

\[
Q_b = F \int (C_a - C_v) \ dt
\]

\[
Q_b = C_b \ Mass_b
\]

\[
C_b = C_v \lambda \ (\text{at equilibrium})
\]

\[
F = \frac{C_v \lambda}{\int (C_a - C_v) \ dt}
\]

\[
\text{N}_2\text{O at low concentration is the tracer used}
\]

\[
C_a \ (\text{arterial concentration}) \text{ and } C_v \ (\text{venous concentration}) \text{ are measured continuously at radial artery and IJV until equilibrium}
\]

\[
\lambda \text{ is assumed to be 1 for N}_2\text{O}
\]

Total quantity of tracer in brain (\( Q_b \)), total brain blood flow (F) and brain mass (Mass_b) don’t need to be known to calculate brain blood flow per unit mass.

Result is expressed in ml/100 g/min.
Radioactive tracers

- $^{133}$Xe, $^{85}$Kr as gases
- Organic compounds including $^1$C, $^1$O, $^1$N or $^1$F
- Detected by scintigraphy, PET, autoradiography

Flow probes
- Doppler, electromagnetic
- MRA

$O_2$ extraction monitoring
- Jugular bulb oximetry
- Near IR spectroscopy

Hepatic
- Fick principle with indocyanine green

Renal
- PAH clearance

### Ultrasound

**Physical principles**

- Intermittent pulses of sound waves
  - 2.5 to 7.5 MHz generated by piezoelectric quartz crystals
  - ↑ frequency → ↑ resolution (to 1 mm), ↓ penetration (10-25 cm)

- Sound waves passing through tissue of differing densities causes reflection of part of the sound energy
  - Loudness of reflection is interpreted as intensity
  - Delay of reflection is interpreted as distance from the probe
  - Sound assumed to travel at 1540 m/s in tissue at 37°C

**A-mode (“Amplitude”)**

- Brief ultrasound pulses in a single direction
- Amplitude of reflected ultrasound is graphed against time (50-300 µs) for each pulse
- Peaks in amplitude correspond to reflective interfaces
- Time taken before reflection corresponds to distance from the probe
- Used to measure eye axial length (“A-scan”)

**B-mode (“Brightness”)**

- Same as A-mode, but one dimensional graphical display with brightness corresponding to amplitude of reflected sound

**M-mode (“Motion”)**

- B-mode scan with repeated pulses graphed against a time-base
- Up to 1000 pulses per second: excellent time resolution
- Provides a one-dimensional image of tissue against a time-base
- Useful for valve motion

**2-D**

- Multiple crystals (linear or phased-array) or moving crystal
- Sequential B-mode pulses sweeping up to 90° across a plane
- Displayed as a single image
- Up to 30 images per second (dozens of pulses per image)
- Moving in real-time

**Pulsed wave Doppler**

- Doppler shift is an alteration in the frequency of reflected sound depending on the velocity of the source of the reflection
- Velocity ($V$) of the source of reflection (e.g. blood cells) can be calculated
\[ V = \frac{F_d C}{2F_0 \cos \theta} \]

where \( F_d \) is the Doppler shift, \( C \) is the speed of sound, \( F_0 \) is the ultrasound frequency and \( \theta \) is the angle between the direction of flow and the sound wave.

An area of the 2-D scan is specified and the Doppler shift in reflections from that area is used to provide a graph of velocity versus time.

Limitations
- If \( \theta \) is small (<15°) it can be ignored, if large the results are imprecise.
- Flow faster than the Nyquist limit (0.4-0.6 m/s) cannot be unambiguously measured because of the intermittent sampling causing “aliasing.”

Continuous wave Doppler
- Separate crystals are used to emit and receive ultrasound continuously along a single axis.
- The frequency spectrum of reflected sound is related to the velocity of all interfaces along the axis.
- A graph of the range of velocities against time is produced.

Advantages
- Can measure very fast flows.
- Used to calculate valve gradients (=4V^2 where V is peak velocity).

Limitations
- \( \theta \) must be small.
- No pulses, so no information about location of measured velocities.

Colour Doppler
- Pulsed wave Doppler used on an area of a 2-D scan.
- Velocity is depicted as a colour in each pixel of the area.

Advantages
- Easy visualization of flows across valves or shunts.

Limitations
- Above the Nyquist limit, colour reversal is seen.
- Rapid turbulent flow produces “colour jets.”

TOE probe
- Phased-array 2-D probe with 64 crystals.
- May be monoplane, biplane (2 arrays) or multiplane (array can rotate).
- Mounted on 9 mm gastroscope.
A. 1 Pharmacodynamics

a. Explain the concept of drug action with respect to receptor theory, enzyme interactions and physico-chemical interactions.

Drug action may occur by one of several means. A drug-receptor interaction occurs where a drug binds to a specific ligand for an endogenous regulatory substance, inducing or blocking a conformational change in the receptor which initiates a series of cellular changes which characterize the effect of the drug. Many specific receptors have been characterized and specific agonist and antagonist drugs are available (e.g. β₂ adrenoceptors). The effect of a drug reflects its concentration, affinity for receptors, the concentration of receptors (affected by up- or down-regulation) and the inherent agonist or antagonist potency of the drug.

Some drugs act by interaction with the active or other site on enzymes, exerting an effect by blocking the action of the enzyme and the metabolic pathway of which it forms part (e.g. allopurinol).

At a molecular level, drug action occurs by physico-chemical interaction. This may be by covalent bonding (e.g. organophosphates), ionic bonds, hydrogen bonds or van der Waals forces. These interactions may be between drug and receptor or between a drug and other compounds, e.g. chelating agents, antacids. Drugs operating by physico-chemical interaction usually have non-specific effects, are less potent and are without specific antagonists (e.g. ethanol).

b. Explain receptor activity with regard to: ionic fluxes, second messengers and G proteins, nucleic acid synthesis, evidence for the presence of receptors, regulation of receptor number and activity.

serpentine receptors
  - cell-surface receptors
  - seven transmembrane domains
  - amine terminal extracellular, carboxyl terminal intracellular
  - loop between domains V and VI (intracellular) is the binding site for G-proteins
  - C-terminal chain is phosphorylated to alter sensitivity (e.g. β-ARK)
  - phosphorylated chain binds β-arrestin, inhibiting G-protein activation
  - agonist binding site is between the clustered transmembrane domains

G-proteins

evidence for receptors
  - drug action is tissue-specific
  - log(dose)-response curve is sigmoid
  - ceiling effect suggests saturation of receptors
  - response is molecule-specific e.g. stereo-specific
  - antagonism is drug-specific

c. Define and explain dose-effect relationships of drugs, especially: graded and quantal response, therapeutic index, potency and efficacy, competitive and non-competitive antagonists, partial agonists, mixed agonist-antagonists and inverse agonists.

d. Compare efficacy and potency on the basis of dose-effect curves.

e. Explain the Law of Mass Action and apply this to pharmacodynamics to understand affinity and dissociation constants, the Hill plot and the Lineweaver-Burke plot.

assuming no interaction between receptors and one drug molecule per receptor:

Pharmacodynamics 2.A.1.1 James Mitchell (November 5, 2001)
drug + receptor ↔ drug-receptor
\[ D + R \leftrightarrow DR \]

\[ [R] + [DR] = [R_{total}] \]

\[ K_D = \frac{[D][R]}{[DR]} \]

\[ K_D[DR] = [D] \cdot ([R_{total}] - [DR]) \]

\[ K_D + [D] = \frac{[D][R_{total}]}{[DR]} \]

\[ \frac{[D]}{K_D + [D]} = \frac{[DR]}{[R_{total}]} \]

= proportion of receptors occupied = “effect”

\[ \text{Effect} = \frac{E_{max}}{K_D + [D]} \]

plot of log (dose) vs effect is approximately linear for effect 20%–80% of E_{max}.

Lineweaver-Burke plot
plot of 1/dose vs 1/effect is linear

\[ \frac{1}{\text{Effect}} = \frac{1}{E_{max}} + \frac{K_D}{E_{max}[D]} \]

with y-intercept 1/E_{max}, x-intercept -1/K_{D} and gradient K_{D}/E_{max}.

Hill plot
plot of log (dose) vs log \( \frac{E}{E_{max} - E} \) is linear:

\[ \log \frac{E}{E_{max} - E} = n \cdot \log(\text{dose}) - \log K_D \]

where n is the number of molecules binding to each receptor

for competitive antagonists, pA2 expresses their affinity with a receptor
\[ pA_2 = -\log_{10} \text{[antagonist]} \text{ required to produce a doubling of } K_D \text{ for an agonist} \]

f. Explain theories of action of general anaesthetic agents.

g. Explain the concept of side effects.

h. Explain the concept of toxicity.
A. 2 Pharmacokinetics

a. Explain the concept of pharmacokinetic modelling of single and multiple compartment models and define: half-life, clearance, volume of distribution, bioavailability, area under the “plasma concentration-time curve”, extraction ratio.

**Half-life**

The time taken for the plasma concentration of a drug to fall by 50% when first-order kinetics are observed

Many drugs have an initial redistribution phase with a short half-life ($t_{1/2}^\alpha$) followed by an elimination phase with a longer half-life ($t_{1/2}^\beta$)

**Clearance**

The apparent volume of plasma from which a drug is entirely removed per unit time

Usually expressed in proportion to bodyweight or surface area

**Volume of distribution**

The volume into which a drug appears to be uniformly distributed at the concentration measured in plasma

Usually a steady state volume of distribution equal to the amount of drug in the body (n) divided by the plasma concentration (C)

$$V_d = \frac{n}{C}$$

Also equal clearance (Cl) times elimination half-life divided by ln2

$$V_d = \frac{1}{ln2} \cdot Cl \cdot t_{1/2}^\beta$$

**Bioavailability**

The proportion of a dose of a specified drug preparation entering the systemic circulation after administration by a specified route

Usually used to mean “oral bioavailability”: the ratio of the areas under the plasma concentration-time curves of intravenous and oral administration of the same dose of a drug

**Area under plasma concentration-time curve**

The integral of plasma concentration with respect to time from the time of administration to the time of no detectable drug is equal to the amount of drug appearing in the systemic circulation. This is used in calculating bioavailability.

A semi-logarithmic plot gives more information about the kinetics of a drug’s distribution and elimination as first-order (exponential) curves become straight lines.

This allows easier calculation of distribution and elimination half-lives (proportional to gradients of lines $\alpha$ and $\beta$ in the graph).

**Extraction ratio**

The proportion of a drug removed from blood by a single pass through the liver.
Equal to 1 - bioavailability.
A high extraction ratio indicates perfusion-dependent hepatic metabolism. A low ratio suggests enzyme activity dependent metabolism.

b. Apply Fick's Law to absorption of drugs by enteric, sublingual, rectal, nasal, intramuscular, subcutaneous, transmucosal and transdermal routes.

Fick's Law relates rate of diffusion ($J$) to permeability coefficient ($P$), thickness ($T$), area ($A$) and concentration gradient ($C_1 - C_2$) for a drug diffusing across a membrane.

$$J = \frac{PA(C_1 - C_2)}{T}$$

permeability coefficient is related to solubility of the drug in the tissue between the site of administration and the blood draining the tissue
concentration gradient is maintained by a high concentration of drug at the site of administration and rapid blood flow
diffusion is also accelerated by a rise in temperature

c. Explain factors influencing the distribution of drugs and apply these in disease states.

Distribution occurs by several processes, the effect of each is determined by aspects of the drug involved.

bulk flow
drugs of MW < 200 flow with water through intercellular pores
facilitated diffusion
some drugs bind specific membrane receptors which facilitate transport across the membrane. This mechanism displays saturability and competition.
active transport
secondary active transport of many organic molecules
e.g. glucose, amino acids active uptake from gut
diffusion
determined by solubility in water
hydrophilic groups
molecule size
membrane penetration is related to lipid solubility
reduced with ionization
depends on pH for basic or acidic drugs
other polar groups
reduced with increasing size
protein binding
most drugs which are protein bound, bind either albumin or $\alpha_1$-acid glycoprotein according to their $pK_a$
some bind specialized proteins e.g. steroid binding globulin, transcortin etc
increases $V_d$ and reduces free fraction of drug
reduces renal clearance by filtration but not active secretion
is a source of interactions
albumin
the largest component of plasma proteins
has three major binding sites
warfarin, bilirubin, salicylates, phenytoin, sulfonamides
benzodiazepine, NSAIDs, penicillin
digoxin, verapamil, quinidine
level is reduced by
catabolic states: burns, malignancy, renal/hepatic disease
pregnancy, old age, neonates

α1-acid glycoprotein
level increased in
catabolic states: burns, renal transplant, malignancy, trauma
inflammatory diseases: RA, UC, Crohn’s
myocardial infarct
level decreased in
pregnancy, neonates

d. Identify the mechanisms of hepatic and non-hepatic metabolism of drugs.

hepatic
phase I
microsomal
mixed function oxidases (including cytochrome P450)
reaction with active oxygen species derived from O₂ and NADPH
oxidation, dealkylation, hydroxylation, deamination, desulfuration,
some reductions, dehydrogenation
activity is unregulated by many drugs
barbiturates, rifampicin
inhibited by a few drugs

cimetidine
increase polarity of drugs

phase II
conjugation with polar groups which increase renal and biliary secretion
glucuronide, sulfate, acetate, amino acids

First order kinetics
elimination is proportional to concentration, clearance is constant
Cl = V_d · k_{el}
where k_{el} is the elimination constant
so for a single compartment, concentration falls exponentially
C_t = C_0 · e^{-kt}
where k is the rate constant, equal to ln2 ÷ t'/ß
in a two compartment model, with both distribution and elimination
C_t = Ae^{-αt} + Be^{-βt}
where A and B are the intercepts on the log plasma concentration-time graph and α and β are the gradients of the lines drawn to approximate the two compartments at a steady state with repeat dosing
dose rate = elimination rate
dose x bioavailability ÷ time interval = mean concentration x clearance
\[
\frac{nF}{t} = C_{ss} V_d k_{el}
\]
\[
C_{ss} = \frac{nF}{V_d k_{el} t}
\]

e. Explain the mechanics and significance of drug absorption and elimination such as first-order and zero-order kinetic processes and factors affecting renal excretion of drugs.

f. Explain and apply concepts related to infusion kinetics as well as absorption and distribution of drugs following epidural and spinal administration.

g. Calculate loading and maintenance dosage regimens.

Pharmacokinetics 2.A.2.3 James Mitchell (November 5, 2001)
h. Explain clinical drug monitoring with regard to peak and trough concentrations, minimum therapeutic concentration and toxicity.
A. 3 Pharmacokinetics of inhalational agents

a. Define and explain the concept of partition coefficients, boiling point and saturated vapour pressure.

**partition coefficient**
the ratio of the amount of substance present in one phase compared with another, the two phases being of equal volume and in equilibrium at a specified temperature.

The partition coefficient is a measure of the relative solubility of a compound in two specified phases (gas, liquid or solid). For example, the blood-gas partition coefficient of N₂O at 37°C is 0.47. That is, at equilibrium, the concentration of N₂O in blood is 0.47 times that of N₂O in a gas in contact with the blood.

This is a useful measure of how quickly one phase can become saturated and of the quantity of compound which will be taken up by one phase over time. It is applied to volatile anaesthetic agents and gases in partition with blood, tissues and the materials in the anaesthetic circuit. It is also applied in other solution equilibria such as in chromatography.

**boiling point**
the temperature at which a compound changes entirely from liquid to gas at standard pressure (101.325 kPa).

At boiling point the mean kinetic energy of individual molecules in a liquid is sufficient to overcome the attractive forces between them, allowing them to separate into a gas.

**saturated vapour pressure**
the pressure at which (at a specified temperature) a compound begins to condense from gas into liquid.

At any temperature below the critical temperature, a gas can be liquefied by compression. As the saturated vapour pressure is reached, the volume of the gas and liquid can be reduced without further increase in pressure until all the gas is condensed to liquid.

Any sealed container of liquid contains in the space above the liquid, gas at saturated vapour pressure, this pressure being dependent on temperature. In the case of N₂O at 20°C, the SVP is 5.25 MPa, in the case of water at 37°C, it is 47 mmHg.

b. Define MAC, MAC\(_{\text{awake}}\), MAC-hr and MAC-BAR and outline their value and limitations of each as well as describe the factors affecting them and how they are measured.

**MAC**
Minimum Alveolar Concentration of an agent at equilibrium at 1 atmosphere pressure in oxygen needed to suppress purposeful movement in response to a standard surgical stimulus in 50% of subjects.

MAC is a useful measure of the relative potency of inhaled anaesthetic agents and a guide to the concentration required to eliminate awareness. It is also used to standardize comparable doses of inhaled agents for research purposes.

Its limitations are that it is a population mean which is not representative of the response of an individual to an inhaled agent and it requires measurement of alveolar gas which can only be approximated by clinical monitors. The sedative response to 1 MAC is standardized, but EEG findings at higher MAC levels differ between agents; it is an oversimplification of the response to inhaled agents.
Increased
infants, hyperthermia, thyrotoxicosis, alcoholism, central stimulants

Decreased
old age, pregnancy, hypothermia, MAP < 40 mmHg, PaCO₂ > 95 mmHg, PO₂ < 38 mmHg, sedative or anaesthetic drugs

MAC is measured in humans with a skin incision in the forearm and in animals using other standards. It is approximated in individual patients by analysis of end-expiratory gas for concentrations of N₂O and volatile agents.

\[ \text{MAC}_{\text{awake}} \]

The MAC needed to abolish eye opening on command in 50% of subjects.
\[ \approx 0.5 \text{ MAC} \]

Subject to the same limitations and influencing variables as MAC. It is used as a means of comparing the sedative effect of inhaled agents.

MAC-hr

The integral of MAC by time for exposure of an individual patient to an inhaled agent.

Exposure to 1.5 MAC of an agent for 30 minutes represents 0.75 MAC-hr exposure. This is used as a comparative measure of exposure to an inhaled agent in calculation of adverse effects of inhaled agents and for setting dose-limits.

It is easily calculated but if used in setting safe doses, does not take into account differences in metabolism and effects which may occur at different concentrations, nor the effects of other factors in an agent’s safety such as the level of fresh gas flow and flushing of metabolites from the circuit.

MAC-BAR

The MAC needed to abolish the sympathetic response to a surgical stimulus in 50% of patients.
\[ \approx 1.5 \text{ MAC} \]

Sympathetic response is measured as changes in heart rate or blood pressure or plasma noradrenaline levels.

c. Explain and apply the concepts of the concentration effect and the second gas effect.

d. Explain how uptake is affected by factors such as alveolar ventilation, cardiac output, shock states and ventilation-perfusion inequalities.

e. Explain the significance of the distribution of cardiac output and tissue partition coefficient on uptake and distribution of volatile agents.

f. Explain how patients recover from volatile agents by describing recovery curves and the factors affecting the rate of recovery.

g. Describe diffusion hypoxia and explain its significance.
A. 4 Variability in drug response

a. Define tachyphylaxis, idiosyncrasy, tolerance, addiction and habituation.

Tachyphylaxis is a rapid diminution in responsiveness following administration of a drug. e.g. GTN

An idiosyncratic reaction is an unusual adverse reaction, sensitivity or resistance to a drug, usually genetically determined. An example is suxamethonium apnoea in pseudocholinesterase deficiency.

Tolerance is a reduced effect or increased dose requirement after repeated administration of a drug. It may be due to receptor down-regulation or increased metabolism. e.g. opiates, barbiturates.

Addiction is a state of physical or psychological dependence on a drug. Physical dependence is manifest as pathological signs or symptoms on withdrawal of a drug. Psychological dependence is manifest as compulsive drug-seeking behaviour which compromises physical wellbeing or social function.

Habituation is the neural mechanism by which a response is gradually reduced or eliminated following repeated stimuli.

b. Explain alteration in drug response due to the physiological consequences of age, pregnancy and other factors including obesity, altered total body water, hypoproteinaemia and various other disease states.

Elderly

Absorption is unchanged with age except by intercurrent disease and concurrent use of multiple medications.

Distribution is affected by reduced lean body mass, reduced total body water and increased fat percentage. Binding is altered by a decrease in plasma albumin and increase in α-acid glycoprotein (which increases the Vd of basic drugs).

Metabolism is slowed for most drugs, partly by a reduced hepatic blood flow and reduced capacity of the microsomal enzyme system. The ability to conjugate compounds (phase II reactions) is substantially unchanged with age. Hepatic function tends also to be diminished by other illnesses such as CCF or malnutrition. The reduction of hepatic oxidation of drugs is most apparent in drugs such as diazepam which have a long half-life and active metabolites.

Elimination by renal clearance is slowed by a progressive reduction in creatinine clearance with age. The Cockcroft-Gault equation relates clearance to age in males, the female result being multiplied by 0.85:

\[
\text{creatinine clearance (ml/min)} = \frac{(140-\text{age}) \times \text{weight (kg)}}{72 \times \text{creatinine (in mg/dl)}}
\]

(creatinine in mg/dl is 11 times the level in mmol/l)

Absorption and elimination of drugs via the lungs is also impaired in the elderly because of progressive reduction in FVC and DLCO as well as more damage from prolonged smoking.

Pharmacodynamic changes in the elderly are less important than pharmacokinetic ones. There is an increased responsiveness to some sedatives and hypnotics which may be receptor-mediated and a decrease in responsiveness to β-adrenoceptor agonists and antagonists. Many homeostatic mechanisms are impaired in the elderly: functional reserve in cardiac output to maintain blood pressure is limited with increased incidence of hypotension, glucose tolerance is often impaired and temperature regulation may also be impaired, with particular susceptibility to...
Specific examples of common drugs:

- Benzodiazepines have increased volume of distribution (if lipid soluble), reduced metabolism and clearance and possibly increased receptor sensitivity. Motor functions may be particularly impaired in the elderly.
- Narcotics show variable changes in pharmacokinetics. The major concern is that physiological reduction in respiratory capacity makes patients more susceptible to hypoventilation.
- Drugs with anticholinergic effects (including phenothiazines, butyrophenones and most antihistamines) are more likely to cause confusion or acute brain syndrome in the elderly, especially in those with dementia.

Foetus
Pharmacokinetic factors
- Lipid solubility increases placental penetration; ionized drugs do not cross the placenta easily.
- Molecules larger than 1000 Dalton cross poorly except for immunoglobulins and some hormones.
- Protein binding affects transfer. Some drugs are bound with different affinities to maternal and foetal proteins.
- Metabolism in the placenta is limited to a few oxidation reactions. The foetal liver has a reduced metabolic capacity.

Pharmacokinetic factors
- Effects on the mother are substantially the same in pregnancy, except for effects of greater circulating volume, and sometimes impaired glucose tolerance and susceptibility to cardiac failure.
- Some drug effects are specific for foetal life: steroids to accelerate lung maturation and folic acid to prevent neural tube defects.
- Some drug toxicities are predictable in foetal life: ACE inhibitors causing renal impairment and opiates causing dependence.
- Teratogenic effects are usually specific to a drug and a time of gestation: thalidomide causing phocomelia when exposure occurs in weeks 4 to 7.

Paediatric
Absorption
- Intramuscular administration is made unpredictable in neonates by small muscle mass and variable blood flow if cold.
- Oral absorption is altered by the absence of gastric acid in premature babies for several days.
- Gut motility is unpredictable in neonates, with gastric emptying commonly delayed.
- Pancreatic enzymes and bile salts are present in reduced amounts up to 4 months of age.

Distribution
- Total body water is 75% and ECF 40% of bodyweight in neonates. Diuresis in the first few days reduces the ECF compartment substantially.
- Body fat is low in premature infants, rising to 15% at term.
- Plasma protein binding is reduced in the neonate. With neonatal jaundice this effect is increased by competition of bilirubin for albumin binding sites.

Metabolism
- Hepatic metabolism of drugs by both P450 and conjugation reactions is reduced in the neonate unless enzyme-inducing drugs have been given antenatally. They reach adult levels (per kg) by about three years.

Elimination
- GFR/SA in the neonate is about 35% of adult values, rising to 50% at three weeks.
and 100% at 6 to 12 months. This substantially alters the dose requirement of drugs such as penicillins and aminoglycosides which are renally cleared.

Pharmacodynamics
Some drugs have specific effects in neonates, particularly indomethacin for closing and PGE, for maintaining patency of the ductus arteriosus.

Dosing
Dosage calculations are often based on weight or surface area. Doses in adolescents should not exceed the adult dose except in some isolated cases such as theophylline where metabolism in children may be more rapid than in adults.

Equations for scaling doses include Young’s rule: age/(age+12) and Clarks' rule: weight/70 kg, but in infants and adolescents these rules are not useful.

Obesity, dehydration, hypoproteinaemia

c. Classify drug interactions and the principles involved.

Physicochemical
- in vitro incompatibility
  - binding
  - precipitation

Pharmacokinetic
- Absorption (affecting extent and rate of absorption)
  - adsorption (cholestyramine, charcoal)
  - chelation or binding (resonium)
  - alter gastric pH (ranitidine)
  - alter motility (narcotics)
  - second gas effect (NO₂, volatile agents)
- Distribution
  - competition for protein binding (phenytoin)
  - competition for tissue binding (digoxin & quinidine)
  - direct binding (heparin & protamine)
- Metabolism
  - induction of microsomal enzymes (rifampicin, phenytoin)
  - inhibition of microsomal enzymes (cimetidine, allopurinol)
- Excretion
  - urinary pH
  - renal function in tubular secretion
  - second gas effect

Pharmacodynamic
- potentiation
  - additive or synergistic effect
  - same or different receptors or multiple points in one pathway
- antagonism
  - direct antagonism (naloxone) or partial agonism (pentazocine)
- combined toxicity
  - predictable combination of adverse effects (NSAID & gentamicin → renal impairment)
  - potentiation of adverse effects by otherwise safe drugs (ketoconazole & terfenadine → prolonged QT interval)

Pharmacokinetics 2.A.4.3 James Mitchell (November 5, 2001)
taken up by the sarcoplasmic reticulum after release, resulting in persistent contraction and thus lactic acidosis and hyperthermia (a late sign). Prevention is by taking a detailed history of anaesthetic complications, including a family history. Detection in by muscle biopsy for halothane/caffeine contraction testing or by chromosome analysis. Specific treatment is by elimination of the trigger agent: a clean anaesthetic machine, chilled intravenous fluids, and by intravenous use of dantrolene 1 mg/kg up to 10 mg/kg which inhibits Ca\(^{2+}\) release.

dantrolene
  lipid soluble hydantoin

pharmacokinetics
  low water solubility
  20% oral bioavailability
  \(V_d\) 0.5 l/kg
  clearance 0.6 ml/min/kg
  \(t\phi/\beta\) 12h
  therapeutic concentration >3 \(\mu\)g/ml
  metabolized to 5-OH dantrolene (50% potency)

pharmacodynamics
  inhibits Ca\(^{2+}\) release from sarcoplasmic reticulum
  limits excitation-contraction coupling in skeletal muscle

adverse effects
  muscle weakness
  negative inotrope
  \(\uparrow [K^+]\)
  electrolyte and volume disturbance due to water and mannitol load

indications
  malignant hyperpyrexia
  also used in
    neuroleptic malignant syndrome
    MDMA overdose, serotonin syndrome with hyperpyrexia
    muscle cramps

clinical use
  ampoules of 20 mg with 3 g mannitol, pH 9.5
  dissolved in 60 ml water \(\rightarrow\) 1 mg/3 ml
  dose 1 mg/kg up to 10 mg/kg
  = up to 30 ml/kg free water, 1.5 g/kg mannitol

Hepatic porphyria is an AD condition resulting from a defect in the HMB synthase gene. Symptoms are triggered by exposure to agents causing an increase in porphyrin synthesis, resulting in acute crampy abdominal pain, nausea, hypertension and neurological symptoms including axonal degeneration causing sensory loss peripherally and proximal motor weakness. Surgery itself can be a trigger, but many drugs are identified as precipitating attacks. These include: barbiturates, sulfonamides, phenytoin, carbamazepine, valproate, ergots, sex steroids and alcohol. Prevention is by history taking and avoidance of precipitating drugs. Between attacks, excretion of porphobilinogen and \(\delta\)-amino laevulinic acid is normal, but erythrocyte HMB synthase is low. Treatment of attacks is initially symptomatic: narcotics, phenothiazines, and benzodiazepines. Intravenous haem therapy reduces the duration of an attack.

Atypical (plasma) cholinesterase is an AR condition. The genes has been well-characterized and comes in one normal and three atypical variants: dibucaine-resistant, fluoride-resistant and silent. Patients who have neither gene normal show markedly increased duration of action of suxamethonium as it is not effectively metabolized. This results in prolonged apnoea. Some heterozygous “normal” patients also have mildly prolonged duration of apnoea. Activity is also depressed by many other chronic illnesses,
burns and in neonates. There is a rare C5 variant which results in increased plasma cholinesterase. Prevention is by history taking and avoiding suxamethonium. Treatment is by mechanical ventilation until the paralysis ceases (often up to 5 hours). The incidence of significant suxamethonium apnoea is 1:2800.

N-acetylation of isoniazid and hydralazine varies in the normal population with a bimodal distribution. Slow acetylation is an AR condition with an incidence variable by race (rare in Asians and Inuit, more common in Northern Europeans). Slow acetylators metabolize these drugs much more slowly due to low levels of normal enzyme. There are no anaesthetic consequences of this condition.

Similar conditions have been described in metabolism of other drugs, much less commonly.

Glucose-6-Phosphate Dehydrogenase deficiency is an X-linked enzyme deficiency. There are many gene defects described, the common ones being A- in 11% of blacks and variants in Eastern Mediterranean (Favism) and Chinese populations. G6PD activity falls in red cells with age, and cells with very low activity will haemolyse in the presence of an oxidant drug. Drugs inducing haemolysis include: antimalarials, sulfonamides, nitrofurantoin and many others. An acute drop in haematocrit with a rise in plasma haemoglobin and unconjugated bilirubin results from haemolysis. Because younger red cells are less susceptible, the haemolysis is usually self-limiting, even with continued exposure. Prevention is by history taking and screening for red cell G6PD (which may not be low immediately after a crisis) and avoidance of oxidant drugs. Treatment is focussed primarily on avoiding renal damage; transfusion is usually not necessary.

e. Describe immune mechanisms in anaphylactoid and anaphylactic drug reactions in general and as applied to anaesthetic drugs.

Anaphylactic (type I) hypersensitivity reactions require an initial sensitizing exposure to the allergen. This causes the synthesis of IgE which binds to the surface of mast cells and basophils by its Fc region. On re-exposure to the allergen, the Fab regions of the IgE molecules bind the allergen and become cross-linked, triggering the degranulation of mast cells (mediated by phospholipase c and Ca2+), releasing histamine, heparin, chemotactic factors and PAF and the synthesis of leukotrienes B4, C4 and D4, prostaglandins and thromboxane. These are collectively known as SRSA.

The immediate effects include vasodilatation, bronchoconstriction and an increase in capillary permeability. If localized, these effects may lead to rhinorrhoea, asthma, rash with urticaria, localized oedema or diarrhoea. If generalized, these effects lead to circulatory collapse and respiratory compromise, requiring immediate treatment, initially with adrenaline.

Type I hypersensitivity can occur with any anaesthetic drugs, but is most common with large molecules which patients are likely to have been exposed to before, especially β-lactams and cephalosporins and some anaesthetic agents, notably thiopentone and suxamethonium. A history of a localized type I reaction to a drug is a contraindication to its use. Patients with a serum IgE > 1 µg/ml are at a high risk of atopy.

Anaphylactoid reactions occur as a result of complement activation and subsequent mast cell degranulation on first exposure to the antigen. They are similar to but generally not as severe or long-lasting as anaphylactic reactions. Cremaphor (polyoxyethylated castor oil), a solubilizing agent, is noted for causing these reactions.

f. Explain alteration in drug response due to due to consequences of pathological changes such as liver disease, cardiac failure or renal failure.
A. 5 Pharmaceutical aspects

a. Define shelf life and outline factors that may influence drug potency during storage.

The period over which a drug loses 10% of its potency or its guarantee of sterility when stored according to the manufacturer’s specifications.

b. Describe methods of preserving shelf-life of drugs

Suitable method depends on the nature of the reactions which would degrade the drug.

physical
- sealed containers
- temperature
  - refrigeration or freezing to reduce the rate of degrading reactions
    - e.g. sux, atracurium, blood products
- light
  - dark or opaque containers minimize light-induced changes
    - e.g. halothane, nitroprusside
- drying
  - dried to powder to reduce reaction rates
    - e.g. thio, vec, many antibiotics

chemical
- controlled pH
  - many drugs in solution have NaOH or HCl and buffer added
- reducing or oxidizing agents in solution
  - usually reducing agents, may cause reactions (e.g. sulfites, nitrites)
- reaction with or adsorption to a carrier
  - sugar glasses in phase IIb trials for α1-antitrypsin
- controlled atmosphere (N2) or vacuum
  - thio, some antibiotics

microbiological
- pretreatment to sterilize drug
  - heat, radiation, ethylene oxide
- risk of contamination minimized by physical and chemical methods which remove water (and oxygen)
- anti-microbials
  - added to many oral agents
    - e.g. alcohol, benzalkonium chloride

c. Describe the mechanisms of action and potential toxic effects of buffers, antioxidants, anti-microbials and solubilizing agents added to drugs.

additives
buffers
- commonly NaOH, KOH, HCl used to control pH
- carbonate buffers in LA solutions, methohexitone, thio...
- phosphate buffers
- benzenesulfonic acid in atracurium
osmolal agents
- mannitol in dantrolene, vecuronium
- glucose in spinal LA solutions
stabilizing agents
- antioxidants
  - Na metabisulphite in catecholamine solutions: neurotoxicity
other agents
- thymol in halothane prevents light inactivation
- \( N_2 \) atmosphere in thiopentone

antimicrobials
- methylparabens used in multidose vials, cause hypersensitivity
- methyl- and propyl-hydroxybenzoate in topical and IV solutions
- benzalkonium chloride in nebulizer solutions
- benzyl alcohol in some water preparations

solubilizing agents
- lipid solutions
  - Cremaphor EL: polyoxyethylated castor oil, hypersensitivity
  - Intralipid: soybean oil, egg phospholipid, glycerol
  - high omega-6-fa content
- propylene glycol & alcohols solution e.g. diazepam
- polyethylene glycol in temazepam gelcaps (phlebitis if injected)

propellants
- chlorofluorocarbons in inhalers may be replaced with other agents e.g. \( N_2 \)

pharmacokinetic alteration
- binding agents: protamine in insulin
- uptake: adrenaline in LA

compliance
- flavouring, colouring etc.

d. Outline the variations in generic nomenclature of commonly used drugs.

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<td>norephedrine</td>
<td>phenylpropanolamine</td>
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<td>terpineol</td>
<td>norepinephrine</td>
<td>noradrenaline</td>
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<td>chloromethin</td>
<td>mustine</td>
<td>norethisterone</td>
<td>norethisterone</td>
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<tr>
<td>cortisol</td>
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<td>omadine</td>
<td>pyrithione</td>
</tr>
<tr>
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<td>cromoglycate</td>
<td>penicillin G</td>
<td>benzylpenicillin</td>
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<td>dextrose</td>
<td>glucose</td>
<td>penicillin V</td>
<td>phenoxyethylpenicillin</td>
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<td>cinchocaine</td>
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<td>adrenalin</td>
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<td>isoprotenerol</td>
<td>isoprenaline</td>
<td>tromethamine</td>
<td>trometamol</td>
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</tbody>
</table>

e. Define isomerism, provide a classification with examples and explain its significance.

Isomers are molecules having the same empirical formula but different structures. Chemical isomers have completely different atom to atom bonds, for example enflurane and isoflurane or edrophonium and ephedrine HCl. Stereoisomers or enantiomers have the
same bond arrangements but differ in three-dimensional structure due to the presence of chiral centres (atoms bonded to four different groups) which may exist in two mirror-image arrangements or bonds without rotational freedom such as unsaturated carbon-carbon bonds with the two carbon atoms each bonded to different groups.

Chiral centres are present in all amino-acids and many other organic compounds including sugars. They are usually designed D- or L- or d- or l- or R- or S- or (+) or (-) isomers according to their configuration or effect on the polarization of light. Unsaturated bonds are present in many lipids and other molecules and are designated cis- or trans-isomers (Z- or E-) according to whether the major functional groups on the carbon atoms involved are on the same or opposite sides.

```
<table>
<thead>
<tr>
<th>R</th>
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<tbody>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>H 2</td>
</tr>
<tr>
<td>N</td>
</tr>
<tr>
<td>C</td>
</tr>
<tr>
<td>COOH</td>
</tr>
</tbody>
</table>

H          trans-    cis-
```

a chiral carbon

Many organic compounds include multiple chiral centres (e.g. atracurium) or unsaturated bonds (e.g. retinoic acid), yielding multiple optical isomers. As the isomers are different in three dimensional structure, they often bind with different affinities to receptor sites with specific three-dimensional structure and are degraded by enzymes at different rates.

Examples (optical isomers)
- isomers equally active
- isomers have slightly different potencies and metabolism, e.g. atracurium, ropivacaine
- isomers have different actions, e.g. quinine/quinidine
- one isomer is active and drug is administered as a racemic mix, e.g. verapamil
  makes blood levels misleading (active L-verapamil is cleared more rapidly)
- one isomer is active and is administered alone, e.g. l-DOPA

**f. Describe the process by which new drugs are approved for research and clinical use in Australia and outline the phases of human drug trials.**

Safety tests in animals/tissue culture
- acute toxicity
  - LD50 in animals (2 species, 2 routes), “no effect” dose
- subacute toxicity
  - up to 6 months use in three dose ranges in 2 species
- chronic toxicity
  - 1-2 years if prolonged use is planned in humans
- specific testing
  - reproduction, carcinogenesis, mutagenicity (Ames test), investigative toxicology

Human evaluation
- phase I
  - establish dose-effect relationship in healthy volunteers or diseases volunteers
  - not blinded, establishes predictable adverse effects and pharmacokinetics
- phase II
  - small single-blind trials in diseased patients with placebo and positive controls
- phase III
  - large, usually multicentre, double-blind or crossover trials
- phase IV
  - on-going surveillance for adverse effects during marketing
  - Phases I trials often start more than 4 years after initial synthesis and phase III may
not be completed until 8 years after initial synthesis. Some drugs are made available for life-threatening or serious diseases without completion of phase III or even phase II trials, e.g. some antiretrovirals.

Australian approval is distinct from overseas approval and applies similar criteria of safety and efficacy as in the US and UK. PBS listing and approval for hospital pharmacopoeia availability depends on cost-effectiveness as well.

The detection of rare adverse effects requires more subjects than are available in phase III trials. For example, to detect the doubling in incidence of a 1/1000 adverse effect requires 18000 subjects ($\beta=0.20$, $\alpha=0.05$). Thus most rare or unpredictable adverse effects will not be detected prior to marketing.

**List the plants from which commonly used drugs are derived.**

\begin{itemize}
  \item *Claviceps purpurea*: ergotamine
  \item *Erythroxylon coca*: cocaine
  \item *Papaverum somniferum*: morphine, codeine, thebaine, papaverine etc.
  \item *Digitalis purpurea, lantana*: digoxin
  \item *Rauwolfia serpentina*: reserpine
  \item *Atropa belladonna*: atropine
  \item *Hyocyamus niger*: hyoscine
\end{itemize}
B. 1 Sedative-hypnotic drugs

a. Define and distinguish: sedation, hypnosis, anxiolysis, tolerance, REM and non-REM sleep, physical and psychological dependence.

b. Identify the major chemical classes of sedatives, hypnotics and anxiolytics.

c. Describe the pharmacodynamics of the barbiturate and non-barbiturate sedatives.

d. Describe the pharmacokinetics of commonly used barbiturates and benzodiazepines and indicate how differences between them may be applied clinically.

e. Describe individual sedative-hypnotic agents.

ethanol
- clear colourless liquid, miscible with water
- usually given orally, can be administered IV
- some is metabolized by gastric alcohol dehydrogenase (more in men)
- small $V_d = 0.7 \text{ l/kg}$
- metabolized in the liver to acetaldehyde and acetic acid
  - alcohol dehydrogenase active at low BAC ($< 0.10$)
  - microsomal oxidation at high BAC
  - limited by NAD$^+$, NADP$^+$ availability
  - zero-order kinetics (~8 g/h)
- dissolves in membranes decreasing viscosity and affecting many receptors and ion channels
  - CNS depression (many complex actions)
  - ↓ cardiac contractility, smooth muscle tone, uterine contraction, platelet aggregation
- teratogenic
- long term effects are difficult to separate from confounding variables (nutrition, smoking, social status, premorbid problems)
- interacts with other drugs acutely by reducing hepatic metabolism and with chronic use by inducing hepatic metabolism
- tolerance mainly results from cellular adaption, not increased metabolism
- cross-tolerance with other sedatives
- little therapeutic use: acute methanol poisoning, prevention of withdrawal
- dose: 10g per standard drink
  - dependent users 100-750 g/day

thiopentone
- 0.5 g in 20 ml glass ampoule
- yellow powder, sodium salt
- stabilized with anhydrous sodium carbonate 60 mg/g
- prepared with water or saline to 25 mg/ml solution
- pH 11-12. Precipitates in neutral or acid solution
- administered IV
- rapid onset of effect in CNS followed by redistribution
- hepatic metabolism
- binds GABA receptors, increasing the duration of Cl$^-$ channel opening

methohexitone
- 500 mg in 50 ml glass ampoule
- white/yellow powder, sodium salt
- stabilized with anhydrous sodium carbonate

Sedatives, hypnotics 2.B.1.1 James Mitchell (November 5, 2001)
mostly α_L and α_D isomers. β isomers increase involuntary movement.
prepared with water or saline
pH 10.6-11.6
pharmacokinetics and actions similar to thiopentone

phenobarbitone
200 mg in 1ml ampoule
30 mg tablets
the oldest anticonvulsant
pK_a = 7.4
undergoes hepatic oxidation of the C5 functional groups and conjugation with renal clearance. 25% is excreted unchanged.
t_{1/2} = 4 days
binds GABA receptors increasing Cl\(^-\) conductance, AMPA receptors blocking glutamate transmission
sedative and anticonvulsant

propofol
10 mg/ml in 20, 50 and 100 ml ampoules
white aqueous isotonic emulsion
solubilized with 2.25% glycerol, 1% soybean oil, 1% purified egg phospholipid
previously solubilized in Cremaphor EL \(\rightarrow\) anaphylaxis
pH 6.0 to 8.5
administered IV
rapid onset of effect in CNS followed by redistribution
rapid metabolism in liver (t_{1/2} \(\beta\) 0.5-1.5 h)

diazepam
Diazemuls
1 ml of 5 mg/ml glass ampoule
solubilized in soybean oil
Diazepam USP
2 ml of 5 mg/ml brown glass ampoule
clear yellow solution
dissolved in 40% propylene glycol, 10% ethyl alcohol, 5% Na benzoate

midazolam
5 ml of 1 mg/ml or 1, 3 or 10 ml of 5 mg/ml glass ampoules
clear aqueous solution
buffered to pH 3.3
precipitates in strongly alkaline solutions

clonazepam
1 mg in 1 ml glass ampoule
2.5 mg/ml oral solution
0.5 mg and 2 mg tablets
long t_{1/2} \(\beta\) \~36 h

zopiclone
7.5 mg tablets
structurally unrelated to benzodiazepines, but binds at the same site on the GABA receptor

chloral hydrate
no longer on the Australian market
prodrug metabolized to trichloroethanol
non-specific membrane stabilizer
hepatic metabolism produces trichloroacetic acid which accumulates
possibly carcinogenic
dose 0.5-1.0 g (of 100 mg/ml solution)

chlormethiazole
8 mg/ml oral solution
192 mg capsules

Sedatives, hypnotics 2.B.1.2 James Mitchell (November 5, 2001)
agents affecting CMR and CBF

<table>
<thead>
<tr>
<th></th>
<th>CBF</th>
<th>CMR</th>
<th>ICP autoregulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>N₂O</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>halothane</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>enflurane</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>isoflurane 0.5MAC</td>
<td>↓</td>
<td>↓</td>
<td>0</td>
</tr>
<tr>
<td>isoflurane 2MAC</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>barbiturates</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>benzodiazepines</td>
<td>↓</td>
<td>↓</td>
<td>0</td>
</tr>
<tr>
<td>ketamine</td>
<td>↑</td>
<td>0</td>
<td>↑</td>
</tr>
</tbody>
</table>

f. Describe the anticonvulsant and proconvulsant properties of the agents.
B. 2 Opioid agonists and antagonists

a. Provide a brief overview of the history of morphine.

300 BC juice extracted from *papaverum somniferum* described by Theophratus contains phenanthrines and isoquinolones (noscapine, papverine)
1400s repopularized in Europe
1806 morphine isolated by Sertturner
1853 syringe invented, morphine used with ether or chloroform GA
late C19 morphine-scopolamine anaesthesia tried, high mortality wave of dependence/abuse
1940s semisynthetic opioids introduced: pethidine, methadone, nalorphine balanced anaesthesia and neurolept anaesthesia introduced
1970s opioid receptors differentiated

b. Explain the structure-activity relationships of the opioid agonists and antagonists.

All L isomers
Phenolic ring, quaternary carbon, 2 more carbons, amine group (highlighted)
4.55 Å from centre of phenol to N
Substitution of a larger group than OH at C3 reduces µ activity
Alkyl group at N produces an antagonist
Br or OH at C14 produces an antagonist

phenanthrines
extracted from *papvertum somniferum*
5 rings: morphine, thebaine, codeine
substitutions
  3,6 diacetyl ↑ lipid solubility: heroin
  3 methoxy ↓ µ agonism: codeine
  6 keto, NCH₂CH=CH₂, 14OH, 7-8 saturated: naloxone

morphinans
4 rings (no ether linkage): levorphanol, dextromethorphan (has NMDA antagonist activity)

benzmorphans
3 rings (C6, 7 & 8 removed): pentazocine

phenylpiperidines
2 rings: pethidine, fentanyl, ~fentanils
5.66Å from ring to N
lipophilic chains on active N ↑ lipid solubility

peptides
endogenous opioid agonists
synthesized in endocrine and neural tissue
products all contain the same pentapeptide at the N terminal which is the opioid core
three precursors: pro-opiomelanocortin (produces hormones: ACTH, MSH, β-endorphin), pro-enkephalin and pro-dynorphin (produce neurotransmitters)
c. Explain the physiological nature and types of opioid receptors and the action of agonists, partial agonists, mixed agonist-antagonists and antagonists.

$\mu_1$
- stimulated by opiates and opioid peptides
- $\beta$-endorphin > dynorphin > enkephalins
- endogenous ligand: met-enkephalin
- exogenous agonists: morphine, fentanyl
- G protein linked: $\uparrow$ K$^+$ conductance, $\downarrow$ cAMP
  - protein kinase C activation $\uparrow$ wind-up
- supraspinal analgesia
- $\downarrow$ prolactin, ACTH release, $\uparrow$ ADH, ACh turnover, catalepsy, feeding

$\mu_2$
- stimulated by morphine
- G protein linked
- respiratory depression, $\downarrow$ gut motility, CVS depression (central)
- dopamine turnover, feeding, $\downarrow$ GH release

$\partial$
- stimulated by enkephalins
- $\beta$-endorphin = enkephalins $>$ dynorphin
- G-protein linked: $\uparrow$ K$^+$ conductance, $\downarrow$ cAMP
- spinal analgesia
- GH release

$\kappa_{1,2,3}$
- stimulated by opiates and dynorphin
- dynorphin $\gg \beta$-endorphin $\gg$ enkephalins
- endogenous ligand: dynorphin
- exogenous agonists: ketocyclazocine, pentazocine
- $\downarrow$ Ca$^{2+}$ channel conductance
- spinal analgesia
- $\downarrow$ ADH, sedation, feeding

$\varepsilon$
- stimulated by $\beta$-endorphin
- endocrine role, $\downarrow$ immune function

$\sigma$
- no longer classified as an opioid receptor
- so-called agonists turned out to be NMDA agonists
- psychotomimetic effects
- morphine-3-glucuronide is an NMDA agonist
  - $\uparrow$ pain with high dose morphine, responsive to ketamine

mixed agonist-antagonists
- nalbuphene: $\mu$ antagonist, $\kappa$ agonist
  - may reverse respiratory depression without fully reversing analgesia
- slow dissociating partial agonist
  - buprenorphine: $\mu$ partial agonist, high potency, slow dissociation

Opioids 2.B.2.2 James Mitchell (November 5, 2001)
d. Explain the pharmacokinetics of the opioids and apply them to clinical usage, including infusion kinetics, transdermal, epidural, spinal and intramuscular usage.

<table>
<thead>
<tr>
<th>Protein binding</th>
<th>Protein clearance</th>
<th>pKa</th>
<th>Lipid solubility</th>
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<tbody>
<tr>
<td>morphine</td>
<td>35%</td>
<td>1.65</td>
<td>3.0</td>
</tr>
<tr>
<td>pethidine</td>
<td>65%</td>
<td>4-11</td>
<td>3-8</td>
</tr>
<tr>
<td>fentanyl</td>
<td>80%</td>
<td>13</td>
<td>3.6</td>
</tr>
<tr>
<td>alfentanil</td>
<td>90%</td>
<td>1.6</td>
<td>1.6</td>
</tr>
<tr>
<td>sufentanil</td>
<td>92%</td>
<td>17.7</td>
<td>2.7</td>
</tr>
<tr>
<td>remifentanil</td>
<td>70%</td>
<td>6</td>
<td>10min</td>
</tr>
<tr>
<td>pentazocine</td>
<td>60%</td>
<td>3.3-5.7</td>
<td>4.3-5.6</td>
</tr>
<tr>
<td>methadone</td>
<td>90%</td>
<td>n/a</td>
<td>8-36</td>
</tr>
<tr>
<td>codeine</td>
<td>n/a</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>naloxone</td>
<td>1.5</td>
<td>1.0-2.5</td>
<td>3.6</td>
</tr>
</tbody>
</table>

Morphine is used intravenously, intramuscularly, subcutaneously, orally, intraarticular and occasionally nebulized. Its plasma levels do not correlate with clinical effect as its low lipid solubility causes slow equilibration across the blood-brain barrier. It has a high hepatic extraction ratio and so an oral bioavailability of only 30%. It is metabolized in the liver by glucuronide conjugation to morphine-3-glucuronide which is inactive and morphine-6-glucuronide which is active. These metabolites are renally cleared, so clinical effect of morphine is increased in renal failure though clearance remains constant. Metabolism is limited by hepatic blood flow.

Parenteral administration is commonly by intramuscular injection (0.1-0.2 mg/kg 3-4 hourly) or intravenous infusion for more constant plasma levels. Infusion is commonly at 1-5 mg/h in adults but a loading dose is required to achieve initial analgesia, typically 5-15 mg. Morphine is suitable for PCA. Epidural and spinal use are described but morphine is not the most suitable narcotic for this purpose as its low lipid solubility slows distribution, increasing the risk of central respiratory depression.

Pethidine is used intravenously, intramuscularly, epidurally and occasionally orally. It has an oral bioavailability of about 60%. It is metabolized in the liver to active and inactive metabolites, the most important of which is norpethidine which is a convulsant. Pethidine and its metabolites are renally cleared resulting in accumulation of metabolites in renal impairment. Its elimination half-life is prolonged in hepatic impairment.

Absorption from intramuscular injection is impaired in cold or vasoconstricted patients. When used epidurally, pethidine crosses the dura rapidly with CSF concentration peaking at about 15 minutes at the same time as plasma concentrations. It also crosses the placenta readily and has an elimination half-life in the newborn of 24 hours.

Dosing IV and IM is similar to morphine, with pethidine being about $1/10$ as potent. Epidural use is in the same dose range as IV use.

Fentanyl has a high lipid solubility and is used intravenously, epidurally and transdermally and can be used by other routes. In small doses its duration of action is determined by redistribution rather than elimination. Plasma concentrations correlate well with effect as it crosses the blood-brain barrier readily. It is metabolized in the liver by demethylation and hydroxylation to inactive metabolites which are renally cleared. A small amount may be secreted unchanged into the stomach and undergo recirculation.

Intravenous use is in two dose-ranges: 1-2 µg/kg as a coinduction or sedative agent and for brief duration analgesia and 30-100 µg/kg as an induction agent for cardiac anaesthesia alone or with N₂O. In the high dose range, its elimination half-life determines the duration of action. It can be combined with droperidol in neurolept anaesthesia.

Epidural use is common either alone or with a local anaesthetic agent. The dose range is 10-60 µg/h in adults. Fentanyl readily diffuses across the dura and also into blood.

Opioids 2.B.2.3 James Mitchell (November 5, 2001)
Its high lipid solubility allows for transdermal use via patches (S-100) which deliver 50-100 \( \mu g/h \). There is a long delay in reaching therapeutic plasma levels, so another analgesic is required to cover the first 6-8 hours. There is also a depot effect in the skin after a patch is removed. Use by intravenous infusion or intramuscular injection is uncommon as fentanyl is not well-suited to these uses because of its cost and short half-life.

Alfentanil is used intravenously. It is less lipid soluble than fentanyl but its low pKa results in most of the drug being in the unionized (basic) form at physiological pH, resulting in rapid diffusion across the blood-brain barrier. This, combined with a smaller \( V_d \) results in a more rapid onset of effect than fentanyl. Its elimination half-life is brief, so an infusion is required if it is to be used for anaesthesia.

It is metabolized in the liver to inactive metabolites by demethylation and dealkylation.

Sufentanil is pharmacokinetically similar to fentanyl.

Pentazocine is an opioid agonist(\( \kappa \))-partial agonist(\( \mu \)). It is used IM, IV and orally. It has a high extraction ratio and a bioavailability of 20%. Its hepatic metabolism is variable from patient to patient and is sensitive to hepatic impairment, with bioavailability rising to 70%. It is rarely used.

Codeine (3-methyl morphine) is used orally for analgesia and diarrhoea. It undergoes hepatic metabolism to inactive metabolites and also to morphine. Typical doses range from 8mg to 60mg q4h in adults.

Methadone is used orally for chronic pain and narcotic dependence and can be used IV. Its elimination half-life is markedly prolonged in chronic oral use. It has a low clearance by hepatic metabolism and so a low extraction ratio

Buprenorphine can be used IM, IV and sublingually.

Naloxone is an opioid receptor antagonist. It is used IM and IV for narcotic overdose. It is highly lipid soluble and has a short elimination half-life. It is metabolized in the liver by conjugation to glucuronide. Because its half-life is much shorter than most of the opioid agonists, repeat IM injection or IV infusion is required for treatment of overdose. Typical dose is 20-70 \( \mu g/kg \) IM or 5-10 \( \mu g/kg/h \) IV. Smaller doses are used to antagonize adverse effects of narcotic epidural infusions such as itch.

Naltrexone is an opioid antagonist with a lower extraction ratio than naloxone and so is used orally. It is used in an oral dose of 50 mg daily to help maintain alcohol and narcotic abstinence in dependent users who have withdrawn.

In principle, the loading dose and infusion rate of the narcotics used by IV infusion can be calculated from MEAC, \( V_d \) and clearance. In practice the dose is titrated against pain.

\[
\text{Loading dose} = \text{MEAC} \times V_d \\
\text{Infusion rate} = \text{MEAC} \times \text{clearance}
\]

e. Provide a detailed systematic description of the actions and pharmacodynamics of individual drugs: morphine, pethidine, pentazocine, diamorphine, methadone, fentanyl, alfentanil, sufentanil, codeine.

morphine pharmacokinetics above epidural, spinal use slow distribution into spinal cord (10-15 min spinal, 15-60 min epidural)
prolonged duration due to low lipid solubility (12-20 h epidural)
late respiratory depression described
conjugated to morphine-6-glucuronide (potent analgesic)
and morphine-3-glucuronide (NMDA agonist)
also sulfated and N-demethylated
pharmacodynamics
potent µ and κ agonist
actions
supraspinal
cortex
anxiolysis, sedation, inhibition of REM sleep
EEG: ↑ voltage, ↓ frequency
mood effects: euphoria, dysphoria
stiffness
µ effect from inhibition of descending inhibitory motor pathway
from caudate nucleus
brainstem
respiratory depression
↓ CO₂, O₂ sensitivity (2˚ ↑ ICP if hypercapnia develops)
↓ cough reflex
CTZ: nausea, emesis
autonomic centres
↑ vagal tone (bradycardia)
↓ sympathetic tone
analgesia
opiate receptors in periaqueductal grey, NRPG
descending inhibitory pathways in DLF
spinal
inhibit slow EPSP resulting from C fibre stimulation
most potent as preemptive analgesia
itch: from either altered threshold or direct stimulation
peripheral
analgesic activity in periphery e.g. intraarticular use
cardiovascular
direct effect on SA node to ↓ rate
haematological
direct effect on mast cells to degranulate and release histamine
gastrointestinal
smooth muscle spasm, damages anastomoses
↓ LOS tone, ↓ motility
genitourinary
↓ urine output (via ADH)
↑ detrusor and sphincter tone
endocrine (? via D₂ agonism)
↓ ACTH, prolactin, GHRH
↑ ADH
clinical use
MEAC ≈16 ng/ml
administered by all routes except rectal, transdermal and topical

pethidine
synthetic opioid developed as an anticholinergic (1939)
pharmacokinetics above
N-demethylated to norpethidine
50% analgesic potency, cerebral irritant
then hydrolyzed to normeperidinic acid
t\textsuperscript{1/2}ß 24 h in the neonate, fetal:maternal concentration ratio ≤1.0
epidural use
plasma levels peak after 10-15 min, rapid CSF penetration 15-30 min
pharmacodynamics
10% potency of morphine
\( \mu \) and \( \kappa \) agonist
local anaesthetic, type I antidysrhythmic
anticholinergic
actions
as for morphine except:
cerebral
irritation and convulsions with accumulation of norpethidine
less miosis due to anticholinergic effect
respiratory
same reduction in ventilation, but ↓ TV with little fall in rate
cardiovascular
not suitable for cardiac use because of membrane stabilizing effect
mild vasodilator
gastrointestinal
less spasm and constipation than morphine, but still ↓ motility
clinical use
MEAC \( \approx \)0.5 µg/ml
fentanyl
synthetic phenylpiperidine-related opioid
alfentanil and sufentanil differ only in potency and pharmacokinetics
pharmacokinetics
rapid redistribution and slow elimination
high hepatic extraction ratio
metabolized by N-dealkylation and hydroxylation
pharmacodynamics
potent \( \mu \) and \( \kappa \) agonist
100 times potency of morphine
actions
similar to morphine except:
cardiovascular
little effect alone, no histamine release
hypotension in large doses in conjunction with diazepam
endocrine
suppresses stress response
clinical use
MEAC 3 ng/ml
anaesthesia > 20 ng/ml
two dose ranges
coinduction 1-2 µg/kg
cardiac 30-100 µg/kg
pharmacokinetics unpredictable at intermediate doses
transdermal use occasionally
skin produces a 12-hour depot “compartment”
pentazocine
a benzomorphan
only the L-isomer is active, but it is supplied as a racemic mixture
pharmacokinetics
20% bioavailable
high extraction ratio
oxidized and glucuronidated
metabolism greatly impaired in alcoholism
pharmacodynamics
μ partial agonist, κ agonist, NMDA agonist
approximately 30% as effective as morphine as an analgesic
actions
similar to morphine except
respiratory
ceiling to μ effects: respiratory depression and supraspinal analgesia
cardiovascular
↑ sympathetic outflow, mild ↑ MAP and HR
B. 3. Pain

a. Define pain.

An unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.

Fast and slow pain: fast pain is sharp, well-localized and is conducted via A\(\delta\) afferent nerve fibres. Slow pain is dull, poorly localized and conducted via C fibres.

Somatic and visceral pain: somatic pain is conducted via spinal nerves and is localized to the site of the stimulus. Visceral pain is conducted via autonomic fibres and localizes to the dermatomal level of the organ innervated where it can produce secondary hyperalgesia. It is provoked by stretch or ischaemia and is not associated with protective reflexes.

Deep and superficial pain: superficial pain is somatic, well-localized and unpleasant. Deep pain may be somatic, but is poorly localized and is associated with nausea, sweating, muscle spasm and blood pressure changes.

Allodynia
- Pain perceived in response to a stimulus which does not usually cause pain

Analgesia
- Absence of pain in response to a normally painful stimulus

Anaesthesia dolorosa
- Pain in an area that is anaesthetic

Causalgia (CRPS II)
- Sustained burning pain, allodynia and hyperpathia after traumatic nerve injury, often accompanied by vasomotor, sudomotor and trophic changes

Dysaesthesia
- An unpleasant or painful sensation

Hyperalgia
- Increased response to a normally painful stimulus

Hyperaesthesia
- Increased sensitivity to stimuli

Hyperpathia
- A painful syndrome with increased reaction to a stimulus, especially a repetitive one, and increased threshold

Neuralgia
- Pain in the distribution of a nerve

Paraesthesia
- An abnormal sensation

b. Describe pain mediators and pain pathways and display an appreciation of the gate control theory and the concept of preemptive therapy.

receptors
- mechanosensitive
  - respond to mechanical stimuli
  - \(A\delta\) conduction (myelinated)

- mechanothermal
  - mechanical stimuli and temperatures over 43°C
  - \(A\delta\) conduction

- polymodal
  - mechanical, thermal and chemical stimuli
    - \(\text{ACh}, \text{bradykinin, histamine, PGs, K}^+\)
  - \(C\) conduction (unmyelinated)
all high threshold
do not show adaption (unlike most receptors)
sensitized by chemical mediators
dorsal horn transmission
Aδ fibres synapse in the dorsal horn Rexed laminae I (nociceptor specific) and V (wide
dynamic range)
C fibres synapse in the dorsal horn laminae I and II (substantia gelatinosa)
dorsal horn transmission displays long term potentiation resulting from repeat
stimuli
slow depolarizing response to substance P
enhanced NMDA transmission
activation of NO synthase, c-fos expression, ↑ dynorphin, ↑ NGF
which induces new neurite growth (Aδ → WDR)
transmission is sensitized by substance P even while anaesthetized,
hence preoperative local and intraoperative opioids for preemptive
analgesia
substantia gelatinosa
inhibited by Aδ and C nociceptive afferents
stimulated by Aβ mechanoreceptor afferents and descending pathways
short inhibitory interneurones project to laminae I and V, inhibiting
pain transmission (Gate Control)
spinal motor neurones
withdrawal reflex
?guarding
ascending pathways
central spinothalamic tract
posterior thalamus produces localization
medial thalamus produces unpleasant experience and autonomic response
thalamus projects to somatosensory cortex (SI and II) and cingulate gyrus
(emotional response)
also projects to nucleus reticularis paragigantocellularis
multisynaptic system
fasciculi proprii and Lissauer’s tracts project to reticular formation and
thalamus
slower transmission
periaqueductal grey matter
opiod receptors stimulate descending pathways which inhibit transmission in
the dorsal horn (transmitter may be serotonin)
hypothalamus
spinoventral tract (brainstem)
stimulation of reticular activating system
thalamic projection
Visceral afferents probably both converge on and facilitate transmission in somatic
pathways, producing referred pain. Experience influences the site of projection of
referred pain (i.e. preferentially to traumatized sites).
descending pathways
locus ceruleus
inhibitory descending projection to dorsal horn
noradrenaline inhibitory neurones
periaqueductal grey matter
input from cortex, thalamus, hypothalamus
opiod receptors
stimulates nucleus raphe magnus
nucleus raphe magnus
input from periaqueductal grey matter and nucleus reticularis
paragigantocellularis
descending projection in dorsolateral funiculus to dorsal horn
serotonin and enkephalin inhibitory neurones

transmitters

- glutamate
  - primary afferent transmitter
  - fast transmission via AMPA ((R,S)\(\alpha\)-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid) receptors & others
    \(\uparrow\) Na\(^+\), K\(^+\) conductance
  - slow potentiation via NMDA (N-methyl-D-aspartate) receptors

- Ca\(^{2+}\), Mg\(^{2+}\), Na\(^+\), K\(^+\) channels

- NMDA antagonists such as ketamine may prevent \(\uparrow\) Ca\(^{2+}\), NO production, \(c\)-fos expression, neuropeptide Y release and development of aberrant A\(\beta\) fibres which activate WDR neurones in response to mechanical stimuli, causing a pain syndrome.

- substance P, CGRP and somatostatin
  - primary afferent transmitters
  - cause slow and prolonged depolarization (LTP) via NK\(_1\) and NK\(_2\) receptors
    - phospholipase C, IP\(_3\), DAG \(\rightarrow\) \(\uparrow\) Ca\(^{2+}\) \(\rightarrow\) K\(^+\) efflux
    - messengers inhibited by some gangliosides
  - sensitizes primary nociceptors in the periphery
  - activate WDR neurones to respond to all stimuli (A\(\beta\) mechanoreceptive etc. \(\rightarrow\) “pain”)

- enkephalins, endorphins and dynorphin
  - receptors in the periaqueductal grey matter, nucleus reticularis
  - paragigantocellularis and other central sites stimulate descending inhibitory pathways from the nuleus raphe magnus
  - opioid receptors are also present in the substantia gelatinosa and may act as presynaptic inhibitors of substance P release
  - play a role in placebo analgesia and stress analgesia (antagonized by naloxone)
  - role in “resting” state is controversial

- serotonin
  - strong direct stimulation of nociceptors
  - transmitter in descending inhibitory pathways
  - inhibits substance P transmission in dorsal horn (mechanism uncertain)

- noradrenaline
  - inhibitory transmitter at dorsal horn via \(\alpha\) (clonidine analgesia)
  - injured cells may express \(\alpha\)-receptors (?pathology)
  - may stimulate dorsal ganglion afferent fibres directly in reflex sympathetic dystrophy

- NO
  - enhances dorsal column transmission (via c-fos)

- bradykinin
  - direct stimulation of nociceptors (G-linked receptor)
  - stimulates PGE\(_2\) release (and possibly other PGs) which potentiates bradykinin response

- GABA
  - inhibitory GABA\(_A\) receptors on WDR neurones
  - presynaptic GABA\(_B\) inhibition of excitatory neurotransmitter release

- glycine
  - NMDA agonist
  - blockers used for specific therapy ***

- capsaicin
  - not an endogenous transmitter
  - acts on Ca\(^{2+}\) channel linked receptors
  - stimulates substance P release acutely
depletes substance P with repeat use
destroys C fibres in the newborn
other inhibitory transmitters
somatostatin, galanin, adenosine, cholecystokinin

periphery   dorsal horn   cord pathways & higher centres

serotonin, substance P, leukotrienes, heat, pH, K+ etc.

receptors

bradykinin

PGs

NSAIDs

A\(\beta\) mechanoreceptive afferent fibres
A\(\alpha\)\(\delta\), C nociceptive afferent fibres
CGRP calcitonin gene-related peptide
DLF dorsolateral funiculus
LC locus ceruleus
NA noradrenaline
NRM nucleus raphe magnus
NRPG nucleus reticularis paragigantocellularis
NSAIDs non-steroidal anti-inflammatory drugs
op opiate receptors
PAG periaqueductal grey matter
PGs prostaglandins
SG substantia gelatinosa
SP substance P
ST spinothalamic tract

\[\alpha\] agonists, inhalational alagesics, NMDA antagonists, non-steroidal anti-inflammatory drugs, serotonergic agents and activators of adrenergic inhibition (tramadol).

Some sites of action detailed above. Details under specific drugs.

d. Describe and evaluate methods in the assessment and measurement of pain in animal models and patients.
B. 4 Non-steroidal anti-inflammatory analgesic drugs

a. Describe the prostaglandin pathway

Prostaglandins and other eicosanoids (thromboxanes, leukotrienes, lipoxins, hydroperoxyeicosatetraenoic acids etc.) are synthesized from saturated membrane phospholipids derived from dietary linoleic and linolenic acid. They are not stored, but are synthesized as required either by cleavage of phospholipids by phospholipase A2 (which can also give rise to PAF) or by phospholipase C and diacylglycerol lipase. The production of arachadonic acid is the rate-limiting step in the production of prostaglandins. Production of arachadonic acid may be stimulated either by specific receptors in some tissues or by general cell damage.

Arachadonic acid is oxidized to PGG₂ by cyclooxygenase and then reduced to PGH₁ by peroxidase. These steps are both catalyzed by prostaglandin endoperoxide synthetase. Which prostaglandins are synthesized from PGH₁ depends on the enzymes present in the tissue. In platelets thromboxane synthetase produces TXA₂, in endothelium prostacyclin synthetase produces PGI₂, in macrophages predominantly PGE₂ is formed. The subscript 2 refers to the number of saturated bonds in the fatty acid backbone of the molecule. Small quantities of prostaglandins are synthesized from dihomo-γ-linolenic acid or eicosapentanoic acid, giving one or three saturated bonds.

In lung, platelets and leukocytes, lipooxygenases convert arachadonic acid to 5-HPETE and then LTA₄, which is subsequently converted to other leukotrienes: important chemotactic factors.

Prostaglandins are metabolized either by specific uptake and inactivation in the lung (in the case of PGE₂), renal metabolism (in the case of PGI₂) or spontaneous decay to inactive substances (TXA₂ → TXB₂).

b. Classify the non-steroidal anti-inflammatory drugs

The NSAIDs are classified by chemical structure:

- salicylic acids: aspirin, diflunisal
- propionic acids: naproxen, ibuprofen, ketoprofen
- acetic acids: indomethacin, sulindac, diclofenac
- fenamates: mefenamic acid, meclofenamic acid
- oxicams: piroxicam, tenoxicam
- pyrazolones: phenylbutazone, azopropazone
- COX-II selective: celecoxib
- paracetamol

Paracetamol is an analgesic and antipyretic with no anti-inflammatory effect. It is a weak prostaglandin inhibitor. It is the most commonly used analgesic and is available without prescription.

Paracetamol

Histology

Physical: a white powder, sparingly soluble in water

Chemical:

Paracetamol

NSAIDs 2.B.4.1 James Mitchell (November 5, 2001)
structural formula above, empirical formula \( \text{C}_8\text{H}_9\text{N}_2\text{O}_2 \), a para-aminophenol derivative

Pharmacokinetics
- administered orally or rectally (variable absorption)
- IV preparation available overseas: proparacetamol
- bioavailability close to 100%
- peak concentration 30-60 min
- \( V_d \) 1 l/kg
- little protein binding (20-50%)
- plasma \( t_{1/2} \) 2-4 h
- clearance 5 ml/kg/min
- eliminated by conjugation and hydroxylation in the liver followed by renal excretion
- metabolism pathway is saturated in overdose, resulting in production of N-acetyl-p-benzoquinone which is hepatotoxic in the absence of glutathione. N-acetyl-cysteine administration within 8 hours of overdose is protective by regenerating hepatic glutathione.

Pharmacodynamics
- little effect on peripheral prostaglandin synthesis
- no antiinflammatory action
- no gastric/renal toxicity
- no antiplatelet activity
- central effect, presumably prostaglandin moderated
- analgesic
- antipyretic

Clinical uses
- dosage 10-30 mg/kg orally, less in hepatic impairment
- up to 100 mg/kg/day in children, up to 40 mg/kg PR
- duration of action around 4 hours
- analgesic of choice for mild musculoskeletal or superficial pain without an inflammatory component
- synergistic with opiates in severe pain
- antipyretic of choice in children
- no significant interactions

Adverse effects
- hepatotoxicity in overdose
- some constipation

**d. Describe the actions of aspirin on prostaglandin synthesis in high and low doses and compare it with other NSAIDs**

Class
- the prototype non-steroidal anti-inflammatory drug

History
- salicylates are present in willow bark, a traditional antipyretic described in 1763
- aspirin was synthesized in 1853 and sold commercially from 1899

Physical/Chemical
- a white powder sparingly soluble in water
- calcium salts are readily soluble
- structure above: acetylsalicylic acid
- acidic pKa (3.5)

Pharmacokinetics
- orally administered
- high bioavailability
- absorbed from stomach and small bowel, best in acidic conditions
- hydrolyzed in the liver to salicylate \( t_{1/2} \) 15 min
- salicylate is protein bound 80-90%
salicylate is conjugated with glycine in the liver
\[ t^{1/2} = 2 \text{ h at low dose, up to 20 h at high dose} \]
both are renally excreted; unchanged drug is excreted rapidly in alkaline urine

Pharmacodynamics
irreversibly acetylates cyclooxygenase
inhibits production of PGI2, thromboxanes, other PGs
impaired platelet function, analgesic, antipyretic
salicylic acid reversibly inhibits cyclooxygenase
high doses result in
PG-mediated
local gastric irritation or ulceration
CNS stimulation
seizures, hyperventilation, respiratory alkalosis
reduced GFR, Na+ and water retention, renal papillary necrosis
prolongation of labour
closure of PDA
hepatotoxicity
inner ear toxicity, tinnitus
reduced prothrombin synthesis, increasing INR
decoupling oxidative phosphorylation
metabolic acidosis, hyperthermia, dehydration
anaphylactoid reactions are most common in asthmatics
cross-reactivity with other NSAIDs is common

Clinical use

dosage
for anti-platelet activity 100 mg daily
single dose for mild pain 300-600 mg
anti-inflammatory dose 4-6 g/day

toxicity
as above, plus
protein-binding interactions, especially with warfarin
Reye's syndrome in children
marrow suppression

blood levels are closely related to toxicity
<10 mg/dl analgesic, antiplatelet
10-40 mg/dl anti-inflammatory
50-80 mg/dl tinnitus, hyperventilation
80-100 mg/dl acidosis
>100 mg/dl hypoprothrombinemia, renal failure, coma

indications
antiplatelet: IHD, carotid disease, CVA risk
analgesic: mild pain, with or without inflammatory component
synergistic with opiates

contraindications
not generally used in children
Reye's syndrome: hepatic failure associated with viral illness
bleeding risk (e.g. proliferative retinopathy, warfarin)
renal impairment or hypovolaemia
peptic ulcer disease
asthma a relative contraindication
gout (reduces uric acid excretion in low dose)

overdose management
gastric lavage & charcoal
correction of pH disturbance, dehydration or hyperthermia
alkalinized diuresis
Other NSAIDs

Inhibit cyclooxygenase reversibly, so have less prolonged antiplatelet effect and are not known to be effective at low dose.

exhibit the same adverse effects with variation according to selectivity for COX-I or COX-II. COX-II inhibition results in better selectivity for anti-inflammatory activity. Potency, metabolism, excretion and half life vary widely.

e. Describe the actions of parenterally administered NSAIDs and their side-effects.

Ketorolac

parenteral NSAID
propionic acid derivative

Pharmacokinetics

administered intramuscularly (sometimes IV)
oral bioavailability 80%
peak concentration 45 min after IM injection
99% protein bound
clearance 30 ml/kg/min
hepatic glucuronidation and renal clearance
$\text{t}_1/2$ 5h

Pharmacodynamics

similar to other NSAIDs
analgesic potency: 30 mg ketorolac $\approx$ 12 mg morphine

f. Outline the pharmacology of acetic acid derivatives and propionic acid derivatives including their side-effects.
B. 5 Intravenous anaesthetic agents

a. List the ideal properties of an intravenous induction agent.

Definition
A drug or combination of drugs which will induce anaesthesia safely and reversibly when injected in sufficient doses and which could also be used intermittently or by infusion for maintenance of anaesthesia.

Classification
- rapid acting
  - barbiturates, imidazoles, phenols, steroids, eugenols
- slower acting
  - phencyclidines, benzodiazepines, opioids, neurolept combinations

Ideal properties
- simple preparation
- compatible with other agents and IV fluids
- painless on administration
- high potency and efficacy
- predictable action within one circulation time
- minimal cardiovascular effects or other toxicity
- depression of airway reflexes for intubation
- rapid and predictable offset of effect
- rapid metabolism for minimal hangover

b. Describe the structure-activity relationship of the barbiturates.

Barbituric acid is formed by the condensation of urea and malonic acid:

\[
\begin{align*}
\text{HN} & \quad \text{HN} \\
\text{O=C} & \quad \text{C=O} \\
\text{CH}_2 & \quad \text{NH}_2 \\
\text{HOOC} & \quad \text{HOOC}
\end{align*}
\]

it is insoluble in water and has no activity in vivo. Barbiturates have two structural isomers which are in equilibrium, keto and enol forms:

\[
\begin{align*}
\text{HN} & \quad \text{C=O} \\
\text{O=C} & \quad \text{C=O} \\
\text{CH} & \quad \text{HN} \\
\text{HN} & \quad \text{C=O}
\end{align*}
\]

The barbiturates have substitutions of functional groups of barbituric acid:

\[
\begin{align*}
\text{R}_3 & \quad \text{N} \\
\text{X} & \quad \text{C} \\
\text{R}_1 & \quad \text{C=O} \\
\text{HN} & \quad \text{C=O}
\end{align*}
\]

X is oxygen (oxybarbiturates) or sulfur (thiobarbiturates). The thiobarbiturates such as thioptentone are generally more lipid-soluble and so have a more rapid onset of action. R₃ is usually hydrogen, but in the case of methohexitone a methyl group is substituted which increases convulsive effect and shortens elimination half-life. The R₁ and R₂ groups can be short alkyl or aryl chains in the hypnotic barbiturates or longer (more than 5 carbon) chains in the anticonvulsants. Branched chains give greater hypnotic than anticonvulsant effect. Phenobarbitone has phenol and ethyl groups at R₁ and R₂ and is an anticonvulsant.
c. Describe the pharmacology of propofol, thiopentone and methohexitone and the factors which influence their effects.

thiopentone

pharmacokinetics
- distribution
  - pKa 7.6
  - 85% protein bound
  - $V_{dss}$ 1-2 l/kg
- metabolism
  - $t_{1/2\alpha}$ fast 8 min, slow 60 min, $t_{1/2\beta}$ 11 h
  - clearance 3 ml/min/kg
  - rapid redistribution from VRG into muscle (30 min peak) and fat
  - slow hepatic metabolism, easily saturated in infusion

pentobarbitone is one metabolite

pharmacodynamics
- CNS
  - potentiates GABA$_\alpha$ transmission, prolongs channel opening
  - may depress excitatory transmission by inhibiting Ca$_{2+}$ transport
  - acts at reticular formation, hypothalamus and limbus
  - brief stimulatory phase before sleep
  - anticonvulsant at hypnotic doses
  - ↓ CMRO$_2$, CBF, vasoconstrictor (may cause inverse steal)
  - not analgesic

CVS
- effects depend on dose and rate of administration and filling
- venodilator: ↓ LVEDV
- myocardial depressant at high doses: ↓ SV, CO, MAP
  - but ↑ myocardial O$_2$ demand in anaesthetic doses
- not an arterial vasodilator: baroreceptor reflex ↑ SVR

respiratory
- central depressant
  - ↓ rate, ↑ $V_r$ followed by apnoea
  - ↓ CO$_2$ sensitivity
  - ↓ upper airway reflexes when deep

renal, hepatic
- minimal ↓ function

uterine
- crosses placenta readily, no effect on tone

local
- thrombophlebitis, pain, thrombosis
- intraarterial injection causes vasospasm
due to endogenous vasoconstrictor release

Intravenous anaesthetics 2.B.5.2 James Mitchell (November 5, 2001)
adverse effects
above plus anaphylaxis (1/14000), anaphylactoid
clinical use
induction of general anaesthesia around 4 mg/kg
cerebral protection (5 mg/kg + 5 mg/kg/h)
contraindicated
no IV access, no airway support equipment
respiratory obstruction (croup, epiglottitis)
allergy
porphyria
relative contraindications
cardiac disease
septicaemia, acidosis
adrenocortical insufficiency

methohexitone
pharmaceutics
500 mg in 50 ml glass ampoule
white/yellow powder, sodium salt
stabilized with anhydrous sodium carbonate
mostly αL and αD isomers. β isomers increase involuntary movement.
prepared with water or saline
pH 10.6-11.6
pharmacokinetics
pKa 7.2
70% protein bound
Vdss 1 l/kg
t1/2α fast 6 min, slow 60 min, t1/2β 2-4 h
clearance 11 ml/min/kg
pharmacodynamics
excitatory phenomena
more irritant to vessels
dose 1-1.5 mg/kg

propofol
pharmaceutics
10 mg/ml in 20, 50 and 100 ml ampoules
white aqueous isotonic emulsion
solubilized with 2.25% glycerol, 10% soybean oil, 1.2% purified egg phospholipid
previously solubilized in Cremaphor EL → anaphylaxis
pH 6.0 to 8.5
pharmacokinetics
weak organic acid, pKa 11
98% protein bound
Vdss 10 l/kg
metabolism by conjugation in liver
three compartment model
t1/2α 2 min, t1/2β 45 min, t1/2δ 4 h
pharmacodynamics
similar to thiopentone
GABA\textsubscript{\lambda} transmission effect may be its mechanism of action
CNS
excitatory effect, but anticonvulsant
? analgesic
little psychomotor effect after awakening
PNS: potentiates effect of NMJ blockers
respiratory: greater incidence of apnoea
CVS: ↓ SVR, SV, MAP

clinical use
induction 2-2.5 mg/kg (less in elderly or hypovolaemic)
maintenance 0.1-0.2 mg/kg/min
levels (µg/ml)
0.3 psychomotor effects
1.0 sleep
3 minor surgery
4 major surgery

ketamine
pharmaceutics
500 mg/10 ml, 100 mg/ml 10 ml, 2 ml vials
benzethonium chloride preservative
pH 3.5-5.5
(+ ) isomer 3-5 times more potent

pharmacokinetics
V, 3 l/kg
hepatic metabolism hydroxylation or N-demethylation, conjugation
norketamine has 20% potency
clearance 18 ml/kg/min
t 1/2α 10 min, t 1/2β 3 h

pharmacodynamics
NMDA antagonist
CNS
dissociative anaesthesia
  inhibits thalamic transmission to cortex
  ↑ CBF, ICP, IOP
  hallucinations on emergence
CVS
  ↑ sympathetic tone (central and ↓ NA uptake)
  ↑ HR, MAP, PVR
direct cardiac depressant
respiratory
  retention of airway reflexes in low dose
  ↑ secretions, bronchodilation
muscle: ↑ tone, movements, inhibits PIChE

clinical use
induction 1-2 mg/kg IV (4-6 mg/kg IM)
maintenance 5-30 µg/kg/min
analgesia 150 ng/ml
anaesthesia 1000 ng/ml

Althesin
alphaxolone and alphadolone (3α-hydroxy steroids)
not available
pharmaceutics
alphaxolone 9 mg/ml, alphadolone 3 mg/ml in Cremaphor EL
pharmacokinetics
rapid induction of anaesthesia in one circulation time
pharmacodynamics
alphaxolone is twice as potent as alphadolone
high therapeutic index (30.6)
excitatory movements common
cardiodepressant → hypotension
propanidid
pharmaceutics
eugenol derivative
50 mg/ml in Cremaphor EL
pharmacokinetics
rapidly metabolized by pseudocholinesterase
competes with suxamethonium
pharmacodynamics
excitatory movements common
marked hyperventilation in induction
hypotension, tachycardia

d. Describe the formulation of thiopentone, methohexitone, propofol, diazepam and midazolam.

Diazepam
Diazemuls
1 ml of 5 mg/ml glass ampoule
solubilized in soybean oil
Diazepam USP
2 ml of 5 mg/ml brown glass ampoule
clear yellow solution
dissolved in 40% propylene glycol, 10% ethyl alcohol, 5% Na benzoate
pH 6.6-6.9

Midazolam
5 ml of 1 mg/ml or 1, 3 or 10 ml of 5 mg/ml glass ampoules
clear aqueous solution
buffered to pH 3.3
precipitates in strongly alkaline solutions

e. Compare the pharmacokinetic and pharmacodynamic differences between thiopentone, methohexitone, midazolam, diazepam, ketamine, etomidate and the steroid anaesthetics.

Thiopentone and methohexitone are barbiturate induction agents used intravenously. Their brief duration of action results from rapid distribution from the vessel-rich group into skeletal muscle and then fat. Methohexitone is slightly less dependent on redistribution for its duration of action as its rate of hepatic metabolism and renal clearance is significantly higher.

<table>
<thead>
<tr>
<th></th>
<th>Rapid Distribution</th>
<th>Slow Distribution</th>
<th>Elimination</th>
<th>Clearance</th>
<th>V_{dist}</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( t/2 )</td>
<td>( t/2 )</td>
<td>( t/2 )</td>
<td>(ml/min/kg)</td>
<td>(l/kg)</td>
</tr>
<tr>
<td>thiopentone</td>
<td>8.5 min</td>
<td>62.7 min</td>
<td>11.6 h</td>
<td>3.4</td>
<td>2.5</td>
</tr>
<tr>
<td>methohexitone</td>
<td>5.6 min</td>
<td>58.3 min</td>
<td>3.9 h</td>
<td>10.9</td>
<td>2.2</td>
</tr>
</tbody>
</table>

Both are highly protein-bound, lipid soluble and metabolized by hepatic oxidation (and desulfuration in the case of thiopentone) to inactive and less lipid-soluble metabolites which are renally cleared. Elimination half-life is shortened in children and patients with induced liver enzymes.

Barbiturates act by depressing the reticular activating system, possibly by inhibiting the dissociation of GABA from its receptors. Tolerance develops rapidly with continuous use.

Diazepam and midazolam are benzodiazepines which are active orally, transmucosally, intravenously, and in the case of midazolam, epidurally. Midazolam is used as a sedative and coinduction agent. They are both highly lipid soluble and 96–98% protein
bound. They have similar volumes of distribution but differ in metabolism.

<table>
<thead>
<tr>
<th></th>
<th>Elimination</th>
<th>Clearance</th>
<th>$V_{\text{dist}}$</th>
<th>Oral</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$t_{1/2}$</td>
<td>(ml/min/kg)</td>
<td>(l/kg)</td>
<td>bioavailability</td>
</tr>
<tr>
<td>diazepam</td>
<td>21-37 h</td>
<td>0.2-0.5</td>
<td>1-1.5</td>
<td>94%</td>
</tr>
<tr>
<td>midazolam</td>
<td>1-4 h</td>
<td>6-8</td>
<td>1-1.5</td>
<td>50%</td>
</tr>
</tbody>
</table>

Diazepam is oxidized in the liver to desmethyldiazepam, oxazepam and temazepam all of which are active. Desmethyldiazepam has an elimination half-time of 48-96 hours, greatly prolonging the clinical effect of diazepam. The elimination half-time of diazepam increases with age and hepatic impairment to over 100 h in the elderly. The effective duration of action depends on both metabolism and initially on redistribution into fat.

Midazolam spontaneously converts to a water-soluble form at acidic pH due to a reversible ring-opening reaction and possibly due to ionization of the imidazole nitrogen. This allows preparation of a buffered (pH 3.5) water-based solution for intravenous use.

Midazolam is metabolized by hepatic microsomal enzymes to 1–hydroxymidazolam and 4–hydroxymidazolam both of which are excreted renally as glucuronide conjugates.

Benzodiazepines act by binding to a specific receptor site on GABA receptors, facilitating GABAergic transmission. In the CNS, it acts predominantly in the cortex; the concentration of GABA receptors being less in the more primitive parts of the CNS. There are GABA receptors on spinal motor interneurones, which may account for the activity of diazepam in reducing muscle tone.

Ketamine is a phencyclidine derivative used to induce dissociative anaesthesia.

<table>
<thead>
<tr>
<th></th>
<th>Elimination</th>
<th>Clearance</th>
<th>$V_{\text{dist}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$t_{1/2}$</td>
<td>(ml/min/kg)</td>
<td>(l/kg)</td>
</tr>
<tr>
<td>ketamine</td>
<td>1-2 h</td>
<td>16-18</td>
<td>2.5-3.5</td>
</tr>
<tr>
<td>etomidate</td>
<td>2-5 h</td>
<td>10-20</td>
<td>2.2-4.5</td>
</tr>
<tr>
<td>propofol</td>
<td>4 h</td>
<td>30-60</td>
<td>10</td>
</tr>
</tbody>
</table>

Ketamine is active intravenously, intramuscularly, epidurally and intrathecally. It is not significantly protein-bound. It is extremely lipid soluble and when administered IV is rapidly redistributed into the vessel-rich group including the brain, with slower redistribution to muscle and fat. It is demethylated by cytochrome p450 enzymes to norketamine (active) and hydroxylated and excreted renally as a glucuronide conjugate. Its
metabolism is slowed by the administration of halothane or diazepam. Ketamine induces the enzymes responsible for its metabolism so tolerance and dependence are seen.

Ketamine is thought to interact with opioid receptors in the CNS. Its analgesic effects exhibit cross-tolerance with opiates. It inhibits reuptake of catecholamines, causing an indirect sympathomimetic effect. It blocks glutamic acid NMDA transmission in the CNS. Its direct effect on the heart is depressant, intact sympathetic activity is required for its effect in increasing cardiac output. It enhances the activity of non-depolarizing muscle relaxants and inhibits plasma cholinesterase, prolonging the effect of suxamethonium.

Etomidate is an imidazole containing compound which can be used as an induction agent. It is water-soluble at acidic pH and is used intravenously. Its brief duration of action is a result of redistribution as with thiopentone. It is moderately lipid-soluble at physiological pH. It is 76% protein bound.

Etomidate is metabolized by hydrolysis by hepatic microsomal enzymes and plasma esterases. Its metabolism is more rapid than thiopentone. Metabolites are inactive and renally cleared.

Etomidate probably acts to increase GABA transmission. Like methohexitone lowers the seizure threshold and causes myoclonic movements. It acts to inhibit 11-ß-hydroxylase in the adrenal, reducing synthesis of cortisol and inhibiting the normal stress response. It is not used in Australia.

gamma-hydroxybutyrate
water soluble hydrocarbon
high dose (50 mg/kg for induction)
slow onset (3 min)
long duration
bradycardia, emesis and hallucinations

pregnanolone
steroid
solubilized in intralipid
rapid onset, short duration
\( t^{1/2}_\alpha \) 10 min, \( t^{1/2}_\beta \) 1 h
\( V_{ss} \) 4 l/kg
clearance 30-60 ml/kg/min
dose 0.6 mg/kg
may produce “steroid pyrogen fever”
similar thrombophlebitis to barbiturates

f. Describe the undesirable systemic effects of individual agents.

g. Describe the toxic and adverse reactions to intravenous agents.
B. 6 Inhalational anaesthetic agents

a. Describe the properties of an ideal inhalational anaesthetic agent.

preparation
- easily administered
  - boiling point above ambient temperature
  - low latent heat of vaporization
  - simple apparatus
- chemically stable
  - long shelf-life, compatible with soda-lime, metals and plastics
  - not flammable
  - cheap

pharmacokinetic
- low solubility
  - rapid onset, rapid offset, adjustable depth
- minimal metabolism
  - predictable in all age groups

pharmacodynamic
- high potency
  - allows high FiO₂
- high therapeutic index
  - analgesic

adverse actions
- minimal toxicity
- minimal unwanted effects
  - nausea, vomiting, cardiac arrhythmogenicity
- no toxicity with chronic low-level exposure of staff

b. Describe the structure-activity relationships of the volatile agents.

\[
\begin{array}{c}
\text{C}_3\text{H}_5\text{O} = \text{QH}_5 & \text{F} & \text{Br} & \text{Cl} & \text{F} & \text{H} \\
\text{Ether} & \text{F} & \text{C} - \text{C} - \text{H} & \text{H} & \text{C} - \text{C} - \text{O} - \text{C} - \text{H} \\
\text{CCl}_2=\text{CHCl} & \text{F} & \text{Cl} & \text{Cl} & \text{F} & \text{H} & \text{H} & \text{C} - \text{O} - \text{C} - \text{H} \\
\text{Trichloroethylene} & \text{F} & \text{F} & \text{F} & \text{H} & \text{F} & \text{F} & \text{F} & \text{C} & \text{F} \\
\text{Halothane} & \text{F} & \text{H} & \text{F} & \text{F} & \text{F} & \text{F} & \text{F} & \text{F} & \text{F} & \text{F} & \text{F} \\
\text{Enflurane} & \text{H} & \text{C} - \text{C} - \text{O} - \text{C} - \text{H} & \text{F} & \text{C} - \text{C} - \text{O} - \text{C} - \text{H} & \text{F} & \text{C} - \text{C} - \text{O} - \text{C} - \text{H} & \text{H} & \text{C} - \text{O} - \text{C} - \text{H} \\
\text{Isoflurane} & \text{Cl} & \text{F} & \text{F} & \text{F} & \text{F} & \text{F} & \text{F} & \text{F} & \text{F} & \text{F} & \text{F} \\
\text{Desflurane} & \text{F} & \text{F} & \text{F} & \text{F} & \text{F} & \text{F} & \text{F} & \text{F} & \text{F} & \text{F} & \text{F} \\
\text{Sevoflurane} & \text{Cl} & \text{F} & \text{F} & \text{F} & \text{F} & \text{F} & \text{F} & \text{F} & \text{F} & \text{F} & \text{F} \\
\end{array}
\]

Structure-activity relationships for the volatile anaesthetic agents apply to their physical and chemical properties and to their metabolism.

physical
- low molecular weight and non-polar structure produce low boiling point, high vapour pressure

chemical
- large number of hydrogen atoms increases flammability
- high fluorine content minimizes flammability
- CF₂H moiety can liberate CO in reaction with dry soda-lime
pharmacokinetics

fluorine content reduces solubility in blood and fat
hydrolysis of ethers is most rapid when the adjacent carbon atoms are not halogenated
hydrolysis produces a halogenated acetic acid and halogenated methanol which can release some halides
fluorine on the 1-carbon of methyl-ethyl-ethers can be liberated as F

pharmacodynamics

chlorine and hydrogen content increases potency
fluorine content reduces potency

c. Provide a brief overview of the history of nitrous oxide, cyclopropane, ether and chloroform.

1772 N₂O first prepared by Priestly
1779 Humphrey Davy suggested N₂O had anaesthetic and analgesic properties
1844 N₂O demonstrated by Horace Wells for dental extraction
1846 ether demonstrated by Morton at Massachusetts General
1847 chloroform introduced, used by Queen Victoria
1880s ethyl chloride introduced
1930s cyclopropane and trichloroethylene introduced
cyclopropane used for single-breath gas inductions (MAC 9%)
trichloroethylene (Trilene) blue coloured agent with good analgesic properties
1951 halothane synthesized
fluoxene enters clinical use
1956 halothane enters clinical use
1960 methoxyflurane enters clinical use
1963 enflurane synthesized
1965 isoflurane, desflurane synthesized
1966 enflurane enters clinical use
1968 sevoflurane synthesized
1971 isoflurane enters clinical use
1990 sevoflurane enters clinical use
1992 desflurane enters clinical use

d. Describe the preparation of nitrous oxide and Entonox and outline their physical properties.

nitrous oxide
physical properties
MW 44.02
BP -88.5°C
SG 1.53 kg/l
prepared by heating NH₄NO₃ at 245-270°C
\[ \text{NH}_4\text{NO}_3 \rightarrow \text{N}_2\text{O} + 2\text{H}_2\text{O} \]
small amounts of NH₃ and HNO₃ produced recombine to NH₂NO₃ on cooling
small amounts of NO and NO₂ are also produced
can cause methaemoglobinemia, pulmonary oedema if inspired
N₂O must be purified to remove these contaminants

Entonox™
50% O₂, 50% N₂O supplied in cylinders at 138 bar
maximum pseudo-critical temperature -5.5°C at 117 bar
separation of constituents occurs below pseudo-critical temperature
analgesic for labour and brief procedures
e. Describe the undesirable effects of nitrous oxide.

pharmaceutic
contamination in manufacture
\( \text{NO}_2, \text{NO, HNO}_3 \)

physiological
cardiovascular
haematological
\( \uparrow P_50 \) by 1.6 mmHg
inhibition of thymidylate synthetase and methionine synthetase by oxidation of cobalt ion on B\(_{12}\)
megaloblastic anaemia
neuropathy
teratogenicity

CNS
\( \uparrow \) muscle tone, rigidity especially with opiates

physical
flammability
not flammable, but will support combustion
gas spaces
partition into physiological spaces
middle ear, gut \( \rightarrow \) nausea
other spaces
expansion of pneumothorax, gas emboli, tube cuffs

hypoxia
low potency requires high FI, potential for hypoxic gas mix
rapid flow of \( \text{N}_2\text{O} \) into alveoli on ceasing administration causes diffusional hypoxia unless supplemental oxygen is inhaled

f. Describe the comparative pharmacology of halothane, enflurane, isoflurane, methoxyflurane, desflurane and sevoflurane.

<table>
<thead>
<tr>
<th></th>
<th>BP (˚C)</th>
<th>MW</th>
<th>SVP (mmHg)</th>
<th>blood: (%</th>
<th>blood: (%)</th>
<th>MAC (%)</th>
<th>metab. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{N}_2\text{O} )</td>
<td>-88.5</td>
<td>44</td>
<td>4x10(^4)</td>
<td>0.46</td>
<td>1.0</td>
<td>105</td>
<td>0.004</td>
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<tr>
<td>desflurane</td>
<td>23.5</td>
<td>168</td>
<td>669</td>
<td>0.45</td>
<td>1.3</td>
<td>6.0</td>
<td>0.02</td>
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<tr>
<td>sevoflurane</td>
<td>58.5</td>
<td>200</td>
<td>170</td>
<td>0.65</td>
<td>1.7</td>
<td>2.0</td>
<td>3.0</td>
</tr>
<tr>
<td>isoflurane</td>
<td>48.5</td>
<td>184</td>
<td>240</td>
<td>1.4</td>
<td>1.6</td>
<td>1.15</td>
<td>0.2</td>
</tr>
<tr>
<td>enfurane</td>
<td>56.5</td>
<td>184</td>
<td>172</td>
<td>1.8</td>
<td>1.5</td>
<td>1.7</td>
<td>2.4</td>
</tr>
<tr>
<td>halothane</td>
<td>50.2</td>
<td>197</td>
<td>244</td>
<td>2.4</td>
<td>1.9</td>
<td>0.75</td>
<td>20</td>
</tr>
<tr>
<td>methoxyflurane</td>
<td>105</td>
<td>165</td>
<td>22.5</td>
<td>12</td>
<td>2.0</td>
<td>0.15</td>
<td>50</td>
</tr>
<tr>
<td>ether</td>
<td>35</td>
<td>74</td>
<td>440</td>
<td>12</td>
<td>1.9</td>
<td>high</td>
<td></td>
</tr>
<tr>
<td>trichloroethylene</td>
<td>87</td>
<td>131</td>
<td>59</td>
<td>9.1</td>
<td></td>
<td>0.17</td>
<td></td>
</tr>
<tr>
<td>cyclopropane</td>
<td>-33</td>
<td>42</td>
<td>6x10(^4)</td>
<td>0.42</td>
<td>9.2</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

oil:gas partition = 150 \( \div \) MAC

g. Describe the physiological effects of the volatile agents.

CNS
anaesthesia
facts
anaesthetics act at millimolar concentrations (high)
lipid solubility increases potency for most agents
(Meyer-Overton relationship)
some stereospecificity is displayed by chiral agents
lipid fluidity changes induced by agents are very small
inhibition of intracellular Ca\(^{2+}\) release occurs
several theories
unitary vs degenerate
agents act at a single site or at multiple sites
lipid vs protein
agents act by altering lipid fluidity or binding lipophilic regions of proteins
likely explanation
binding to lipophilic protein regions (differing slightly for different agents) alters ligand-gated ion channel activity, altering some or all of ACh, GABA, NMDA, AMPA and KA transmission
analgesia
uncertain mechanism of action, probably related to anaesthetic actions
EEG ↓ frequency ↑ voltage from 0.4MAC (asleep)
I, S, D burst suppression at 1.5MAC, silence at 2MAC
H silence at 3.5MAC (impractical)
E seizure activity (↑ by low PCO\(_2\))
evoked potentials ↓ amplitude ↑ latency
CSF volume E↑ I↓
CBF loss of autoregulation → vasodilation
H from 0.6MAC
E > I from 1.0MAC
CVS
↓ contractility H, E > I, S, D
↑ RAP H, E > I
↓ SVR I, S, D > E > H (I can cause coronary steal, no tachycardia with S)
catecholamine sensitization H > I, S, D > E
respiratory
↓ hypoxic response markedly from 0.1MAC
↓ hypercapnic response: E, S > I > H
↓ TV
↑ RR up to 1MAC, then I↓ H, E↑
bronchodilation (↓ vagal tone, smooth muscle relaxation)
GIT
hepatotoxicity
all ↓ portal flow
hepatic artery flow H↓ I↑
renal
F\(^{-}\) ion toxicity (below)
E ↓ RBF and GFR
I, H, D maintain RBF and GFR
muscle
relaxant due to
↓ central outflow, ↑ blood flow, ↓ post junctional sensitivity, ↓ Ca\(^{2+}\) flux
E, I > H
trigger for malignant hyperpyrexia
H > E > I
obstetric
↓ contractility, vasodilation (↑ blood loss), depression in fetus
immune, haematological
H ↓ platelet aggregation
impair neutrophil activity
N\(_2\)O > volatiles
teratogenic

Inhalational anaesthetics
2.B.6.4
James Mitchell (November 5, 2001)
h. Describe the metabolism of the volatile agents and the role of their metabolites in toxicity.

halothane
	oxidation (most metabolism if hepatic oxygen delivery is adequate)
	→ trifluoroacetic acid, Br, Cl → conjugates of TFA
	inhibited by cimetidine, isoflurane, ischaemia
	reduction (0.1-0.5%)
	→ Br + CF₃CH₂Cl → HF + F₂C=CHCl → conjugates

toxicity
	alkane volatiles are more arrhythmogenic than ethers
	Br direct sedative
	F nephrotoxicity (but very little liberated)

dose- and hepatic blood flow-related hepatotoxicity
	mild ↑ ALT, AST
	incidence =20%
	associated with increased reductive metabolism

dose- and hepatic blood flow-related hepatotoxicity
	mild ↑ ALT, AST
	incidence =20%
	associated with increased reductive metabolism

autoimmune fulminant hepatic necrosis

1:30000
	accompanied by eosinophilia, rash
	associated with oxidative metabolites modifying hepatic proteins

could also be associated with other volatiles more rarely

fluoride ion liberation
	most severe with α-carbon fluorinated ethers
	M >> S > E >> I > D

toxic concentrations in human anaesthesia don't exceed 30 ppm

reduced by gas flow (>2 l/min recommended)

i. Describe the interaction of soda-lime with trichloroethylene, halothane and sevoflurane.

sevoflurane
	forms compound A (PIFE) on reaction with warm soda-lime
	sevoflurane → HF + FH₂C-O-C(CF₃)=CF₂ (a vinyl ether)
	other compounds formed in very small quantities

compound A causes nephrotoxicity in rats at 150-200 ppm (LD₅₀ 1000 ppm)
	normal levels in human anaesthesia don't exceed 30 ppm

reduced by gas flow (>2 l/min recommended)

halothane
	forms a vinyl compound in soda-lime

toxic compounds with soda-lime

trichloroethylene
	normal levels in high flow anaesthesia 4-6 ppm

forms toxic compounds with soda-lime

dichloroacetylene causes neurotoxicity

esp. cranial nerves V, VII, VIII

phosgene causes pulmonary toxicity

(phosgene + H₂O → 2HCl + CO₂

(never to be used with soda-lime; rarely used anyway)
B. 7 Neuromuscular blocking agents

a. Explain the physiology of neuromuscular transmission and how this may be interfered with to produce muscle relaxation.

Acetylcholine is the neurotransmitter of the NMJ. Choline is synthesized in the liver and actively taken-up by nerve cells. It is condensed with acetyl-CoA derived from the TCA cycle which is present in the cell cytoplasm. This reaction is catalyzed by choline acetyltransferase present in the nerve terminal which is inhibited by acetylcholine and acetylcholinesterase. ACh is stored in vesicles in the nerve terminal.

Vesicles are grouped in the nerve terminal away from the junctional surface and move to sites adjacent to the junction where they are bound to synapsin. The mobilization and release of vesicles is promoted by stimulation of the prejunctional nicotinic receptor and inhibited by stimulation of the prejunctional muscarinic receptor. In response to the rise in intracellular Ca$^{2+}$, protein kinase II dephosphorylates synapsin and allows vesicles to bind to synaptophysin which results in release of their contents. There is continuous slow release of the contents of vesicles from the nerve terminal, resulting in miniature end-plate potentials (MEPPs). ACh is hydrolyzed to choline and acetate by cholinesterase in the synaptic cleft. These are then reabsorbed by the nerve terminal.

The neuromuscular junction consists of a nerve terminal (of a motor neurone) adjacent to an end plate on skeletal muscle. The nerve terminal contains around 300,000 vesicles containing acetylcholine. When an action potential arrives at the nerve terminal, an influx of Ca$^{2+}$ triggers the release of the contents of around 125 vesicles of acetylcholine into the synaptic cleft. The acetylcholine diffuses rapidly to its receptors on the end plate where it opens ion channels in the muscle cell membrane, allowing a rapid influx of Na$^+$, generating an EPSP and triggering an action potential (by opening voltage-dependent channels) which propagates through the T-tubule system and causes a release of Ca$^{2+}$ from the sarcoplasmic reticulum. This intracellular Ca$^{2+}$ binds to troponin C, allowing binding of actin to tropomyosin and contraction of muscle fibrils with the hydrolysis of ATP.

The influx of Ca$^{2+}$ lasts around 50 ms in skeletal muscle. The action potential lasts only 1-5 ms and the acetylcholine is broken down within a few milliseconds by acetylcholinesterase in the subneural clefts. The low intracellular concentration of Ca$^{2+}$ is rapidly restored by active transport of the Ca$^{2+}$ back into the sarcoplasmic reticulum. A single action potential generates only a brief contraction of skeletal muscle. A sustained (tetanic) contraction requires summation of a rapid series of action potentials.

The pharmacological methods by which neuromuscular transmission is blocked include competitive blockade of the acetylcholine receptor with an antagonist (non-depolarizing block) or non-competitive blockade with an agonist which is not broken down by acetylcholinesterase (depolarizing). Non-competitive blockade works to prevent muscle contraction initially by maintaining the end plate in a depolarized state and blocking the ion channel at the receptor, thereby blocking the repeated action potentials required to produce sustained contraction (phase I block). Prolonged exposure to depolarizing blockers causes a desensitization of the end plate resulting in a phase II block similar to that caused by the non-depolarizing blockers.

Transmission can also be interfered with at other stages. Latrotoxin (Red-back spider venom) increases vesicle release, depleting ACh. Botulinum toxin inhibits vesicle release from the nerve terminal.

After blockade, transmission can be enhanced (“reversed”) by cholinesterase inhibiting drugs which increase the life of ACh in the synaptic cleft. Higher doses of these drugs inhibit transmission by causing a depolarizing block. 4–aminopyridine and tetraethylammonium block K$^+$ channels in the nerve terminal, delaying repolarization and increasing the amount of ACh released.

Open channel block is produced by depolarizing muscle relaxants but can also be produced by NDBs if a depolarizing agent is given while a high concentration of NDB is present. The NDB binds in the open channel of the ACh receptor, producing a prolonged

Relaxants 2.B.7.1 James Mitchell (November 5, 2001)
block. This is a clinical problem if a reversal agent is given while the patient is deeply paralyzed.

There is substantial redundancy in transmission at the NMJ. The quantity of ACh released and the number of nicotinic receptors are both in large excess. Normal VC and TOFC 0 is seen despite block of 75% of receptors by an NDB. Normal inspiratory force is observed with 50% blocked and sustained head lift with 33% blocked.

b. Describe the post-junctional receptor.

Nicotinic post-junctional receptors are grouped at the “shoulders” of the subneural clefts. The receptor is a cone-shaped protein consisting of five subunits which binds with two molecules of acetylcholine. The ion channel when opened admits Na⁺, K⁺ and Ca²⁺, but the main effect at the time of opening is influx of Na⁺.

The receptor is a pentamer composed of four different units (αβεδ) all of which span the cell membrane. The ACh receptor sites are on the α subunits. There is a central ion channel which opens due to conformational changes with both receptor sites are occupied by agonists.

The nicotinic receptors on nerve tissue are composed of a different combination of units (αβ) as are fetal receptors (αγδ), which are found on the muscle cell surface away from the neuromuscular junction and are also expressed in denervated muscle.

c. Outline the properties of an ideal neuromuscular blocking agent.

- Non-depolarizing action
- Rapid onset (within one circulation time)
- Short duration, suitable for infusion
- Rapid metabolism to inactive products
- Antagonized by cholinesterase inhibitors
- Actions confined to the NMJ
- Not transferred across the placenta or blood-brain barrier
- No local or systemic side-effects
- Compatibility with other drugs and solutions
- Long shelf life without refrigeration
- Cheap
- Made by chemical synthesis
- Sterilizable

d. Apprise different methods of monitoring the neuromuscular junction.

A transcutaneous nerve stimulator placed over the ulnar nerve, producing contraction of adductor pollicis is commonly used to assess the degree of neuromuscular junction block. Other sites used include the phrenic, facial, posterior tibial and lateral popliteal nerves. Other skeletal muscles have different sensitivities to neuromuscular blocking agents from the diaphragm. The ulnar nerve is the best validated.

Skin is prepared by removal of excess hair, abrasion to remove some of the stratum corneum and cleaning with alcohol. Pregelled electrodes are placed over the ulnar nerve, distally at the lateral border of FCU 1-2 cm proximal to the proximal skin crease at the wrist and proximally as close as practical to the distal electrode in the line of the nerve. The positive electrode is proximal.

An initial threshold for stimulation is established with 1 Hz stimuli: the minimum current required to produce a twitch in the thumb. This current is tripled (minimum 20 mA) to determine a supramaximal stimulus which should stimulate all fibres in the ulnar nerve.

The most common method of assessment is the “train-of-four”. A train of four impulses at 0.5 s intervals is applied to the ulnar nerve and the contraction of adductor pollicis is palpated or measured with a force transducer. The result is quantified as a count.
(TOFC) or a T4/T1 ratio (TOFR). Without a junction blocker, the four twitches are of equal strength, at TOFR \( \geq 0.7 \), spontaneous ventilation is safe. With a count of 1 or 0, intubation should be possible. Reversal should be given with a TOFC of 3 or 4, a TOFC of 1 or 2 increases the risk of inadequate reversal in recovery.

In recovery or when TOFC is 4 with little fade, double-burst stimulation of two brief 50 Hz stimuli 0.75 s apart gives a more readily palpable fade for manual monitoring of residual paralysis. Fade is due to blockade of prejunctional nicotinic receptors causing a failure of the normal increase in ACh mobilization following a stimulus.

With deep paralysis all four twitches become absent, and a post-tetanic count allows monitoring of paralysis: a 5 s 50 Hz stimulus is followed by a 3 second pause and then stimuli every second, the number before complete fade being counted. Repetitive stimuli increase synthesis and release of ACh, producing post-tetanic facilitation. Some facilitation will be present for five minutes following a PTC. To guarantee no coughing or diaphragmatic movement on intubation, a PTC of 1 or 0 is required. A PTC of 9 is equivalent to a TOFC of 1. The time from PTC 1 to TOFC 1 is documented for most relaxants (pancuronium 40 min, atracurium 9 min)

Clinical assessment of the degree of relaxation is also made by the surgeon, particularly in intraabdominal surgery and in recovery with assessment of head lift for 5 s.

e. Give a detailed account of the pharmacology of suxamethonium including its undesirable properties.

Class
depolarizing neuromuscular blocking agent, used to achieve rapid, brief paralysis of skeletal muscle.

History
This class of agent was discovered in the late 1940s by Paton & Zaimis, who initially investigated decamethonium, a similar compound without ester linkages.

Physical
The structure of suxamethonium is two ACh molecules linked through the acetate methyl groups: \((\text{CH}_3)_3\text{N}^+-(\text{CH}_2)_2-\text{O}-\text{OC-CH}_2-\text{CH}_2-\text{CO-O-(CH}_2)_2-N^+(\text{CH}_3)_3\).

Chemical
Presentation is as a 2 ml vial containing 100 mg in solution. Storage is at 4°C, with 5% loss of potency over 3 months at 20°C. It is a small polar molecule, readily soluble in water.

Pharmacokinetics
administered as IV injection
rapid distribution to ECF
rapid hydrolysis by plasma cholinesterase. 90% hydrolyzed before distribution to the NMJ. \( \rightarrow \) succinylmonocholine (+ choline) \( \rightarrow \) succinic acid + choline. 14% of succinylmonocholine is renally cleared. Spontaneously hydrolyzes slowly at physiological pH.
inactive genetic variants of plasma cholinesterase produce a greatly prolonged half life: \( t^{1/2}_\beta \) 1 h.

Pharmacodynamics
binds to post-synaptic nicotinic ACh receptors at the NMJ, resulting in the fixing open of the associated Na’ channel. This produces a brief depolarization, seen as fasciculation, particularly in the face, and then blocks transmission of normal impulses to the muscle until the suxamethonium is hydrolyzed. Fasciculation may also result from antidromic conduction. The blockade is not competitive. This is known as phase I block.
minimal affinity for preganglionic nicotinic receptors.
repeated or prolonged administration produces a state of phase II block: a more prolonged block with features similar to non-depolarizing blockade: fade on train-of-four, recovery with neostigmine administration.

Clinical use

Relaxants 2.B.7.3 James Mitchell (November 5, 2001)
dosage: 1 to 2 mg/kg IV, with a higher dose required if a NDB has been given first. Higher dose in neonates and children.
donset of action: one circulation time
duration: 3-5 minutes (except in suxamethonium apnoea)
advantages
  - rapid, complete relaxation with a standard dose
  - clinical signs of onset: fasciculations
  - brief duration
  - cheap
disadvantages
  - common
    - post operative muscle pains, common in younger patients. bradycardia from vagotonic effect
    - increased intraabdominal pressure
    - increased intraocular pressure
    - increased intracranial pressure (all prevented with NDB)
    - release of K⁺ rise of 0.5-0.7 mmol/l in normal patients
due to depolarization and trauma with fasciculation
  - extrajunctional ACh receptors
    - seen in burns, denervation, prolonged immobility
    - rise up to 9 mmol/l described
    - in muscle trauma rise of 3-4 mmol/l described
    - period of danger is quoted variously
      - burns 1-12 weeks or 1 day to 6 months
      - prevention attempted with NDB (ineffective)
      - salbutamol has some effect
    - uncommon
      - abnormal plasma cholinesterase results in very prolonged action:
        - suxamethonium apnoea
        - may trigger malignant hyperpyrexia, masseter spasm
        - development of phase II block with repeated use

Plasma cholinesterase
coded for by autosomal gene
variants
  - N normal
  - D dibucaine (cinchocaine) resistant
  - F fluoride resistant
  - S silent
  - C₅ increased activity (coded at a different locus)
  - D, F and S types have reduced (or no) activity in hydrolysing suxamethonium
  - 95% of people are NN
assays
  - direct assay of PIChE activity using benzoylcholine as the substrate
dibucaine number
    - % inhibition by 10⁻⁵ mol/l cinchocaine in vitro (low in D)
fluoride number
    - % inhibition by 5x10⁻⁵ mol/l fluoride in vitro (low in F and D)
scoline number
    - activity assay (method) high with normal hydrolysis

<table>
<thead>
<tr>
<th>genotype</th>
<th>dibucaine number</th>
<th>fluoride number</th>
<th>scoline number</th>
<th>incidence</th>
</tr>
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<tr>
<td>NN</td>
<td>80</td>
<td>60</td>
<td>90</td>
<td>95%</td>
</tr>
<tr>
<td>ND</td>
<td>60</td>
<td>50</td>
<td>65</td>
<td>4%</td>
</tr>
</tbody>
</table>
f. Describe the structure-activity relationships of the non-depolarizing muscle relaxants including the newer steroidal and benzyl-isoquinolinium muscle relaxants.

Most of the muscle relaxants bear a resemblance to acetyl choline in part of their structure. This is most obvious in suxamethonium which consists of two ACh molecules joined by their acetate methyl groups. Chain length determines specificity for neuromuscular rather than ganglionic synapses.

Most of the non-depolarizing agents can be grouped into steroids and isoquinolinium derivatives. The steroid agents include pancuronium, vecuronium, rocuronium. They each have two ACh-like regions at each end of the molecule:

This is pancuronium. Removal of the 2β-methyl group yields vecuronium. Other substitutions of the end rings give rocuronium and pipecuronium.

The isoquinolinium muscle relaxants consist of large rigid functional groups at either end of a chain resembling suxamethonium. This is atracurium. Its chiral centres are circled.

Doxacurium and mivacurium have different lengths in the central chain and extra functional groups. Not all neuromuscular blocking agents have a quaternary nitrogen.
atom nor a region resembling ACh e.g. β-erythroidine.

g. Describe the pharmacokinetics of non-depolarizing muscle relaxants and the role of prejunctional receptors as well as the effects of renal and hepatic disease.

<table>
<thead>
<tr>
<th></th>
<th>$V_d$</th>
<th>$t^{1/2}_a$</th>
<th>$t^{1/2}_b$</th>
<th>clearance</th>
<th>elimination</th>
<th>in urine</th>
<th>induction</th>
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<tbody>
<tr>
<td>atracurium</td>
<td>160</td>
<td>2.0</td>
<td>20</td>
<td>5</td>
<td>spont</td>
<td>0.5</td>
<td></td>
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<tr>
<td>cisatracurium</td>
<td>160</td>
<td>25</td>
<td>5</td>
<td>0.15</td>
<td></td>
<td></td>
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<tr>
<td>mivacurium</td>
<td>Pl ChE</td>
<td>0.16</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rocuronium</td>
<td>250</td>
<td>7.5</td>
<td>25-90</td>
<td>5</td>
<td>hepatic 15-30</td>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td>vecuronium</td>
<td>250</td>
<td>12</td>
<td>120</td>
<td>2</td>
<td>renal/hepatic 46</td>
<td>0.1</td>
<td></td>
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<tr>
<td>pancuronium</td>
<td>250</td>
<td>n/a</td>
<td>short</td>
<td>0</td>
<td>Pl ChE 0.08</td>
<td></td>
<td></td>
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<tr>
<td>suxamethonium</td>
<td>n/a</td>
<td>n/a</td>
<td>short</td>
<td>0</td>
<td>1-2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The non-depolarizing muscle relaxants are administered by intravenous injection or infusion. They are polar compounds and so have a limited $V_d$. Blood levels fall rapidly initially with redistribution.

The older agents tubocurarine, metocurine and gallamine are not metabolized, but excreted unchanged, gallamine by renal clearance and the others 50-60% by renal clearance.

The steroidal agents are hydroxylated in the 3 and 17 positions in the liver with some reduction in potency. The long-acting agents, pancuronium, doxacurium and pipecuronium are predominantly renally excreted (60-90%) while the shorter-acting agents vecuronium and rocuronium are predominantly excreted in bile (75-90%) either unchanged or as 3-hydroxy derivatives.

The isoquinolinium agents are hydrolyzed either spontaneously (atracurium) or by plasma cholinesterase (mivacurium) to inactive metabolites. The action of these agents is still affected by renal failure (which lowers plasma cholinesterase activity) and hepatic failure (due to hepatic metabolism of metabolites of atracurium).

Effective durations of action range from around 15 minutes for mivacurium, 20-35 minutes for vecuronium, rocuronium and atracurium to more than 35 minutes for pancuronium and tubocurarine.

Hepatic impairment increases the $V_d$ and $t^{1/2}_b$ (of agents undergoing hepatic metabolism or excretion) and reduces their clearance. This increases the initial dose requirement but prolongs the duration of action.

Renal impairment greatly reduces the clearance of renally cleared agents (e.g. pancuronium) and so increases the duration of action. It is also associated with a reduction in plasma cholinesterase activity and so slows metabolism of mivacurium and suxamethonium and reduces their dose requirements.

Non-depolarizing agents exert their action predominantly by acting as competitive antagonists to ACh at the nicotinic receptor site. At high doses they may also cause direct blockade of the ion channel. On the prejunctional cell membrane they block sodium channels, inhibiting the depolarization of the membrane and the release of ACh. They also block prejunctional nicotinic receptors, inhibiting the mobilization of ACh vesicles.

The factors which affect response to suxamethonium are given above: primarily factors affecting plasma cholinesterase activity and the degree of $K^+$ release with administration of suxamethonium.

**Pharmacokinetic**

adequate circulation required for distribution: determines rate of onset.

*Relaxants 2.B.7.6 James Mitchell (November 5, 2001)*
reduced $V_d$ in elderly
rate of metabolism dependent on
plasma cholinesterase for mivacurium, suxamethonium ↓ in pregnancy, burns
hepatic function for vecuronium and rocuronium ↑ metabolism with enzyme induction
elimination dependent on
renal function for many agents, especially tubocurarine and gallamine
temperature
perfusion
blood loss may be a significant contributor in some cases

Pharmacodynamic
 receptors
deficiency in myasthenia gravis
up-regulation in UMN lesions
drugs
open channel block
  aminoglycosides, Ca$^{2+}$ channel blockers, local anaesthetics, Li$^+$
closed channel block
  quinidine, tricyclics, naloxone
  Mg$^{2+}$ decreases ACh release
block antagonized by
  cholinesterase inhibitors
also increased block in
  hypothermia, acidosis, hypokalaemia, hypercalcaemia

Other
reduced motor neurone activity due to volatile anaesthetics (isoflurane >> halothane). Isoflurane also acts at the NMJ.
other drugs
diuretics, ganglion blockers

i. Describe the systemic side effects of muscle relaxants.

The adverse effects of suxamethonium are given above.
Administration of non-depolarizing muscle relaxants causes weakness and then paralysis of skeletal muscle, acting most rapidly on small, fast-twitch muscles and last on the postural muscles and diaphragm.

Cardiovascular
isoquinolinium agents other than doxacurium cause histamine release and thus vasodilation and hypotension
gallamine and pancuronium antagonize cardiac muscarinic receptors, causing an increase in heart rate
in high doses, tubocurarine causes blockade of autonomic ganglia, leading to hypotension and reduced intestinal motility

Histamine release
the obsolete agents dTC and metocurine showed strong histamine release
mivacurium causes marked histamine release
suxamethonium and atracurium cause some histamine release
causes flushing, hypotension and bronchoconstriction
B. 8 Anticholinesterase drugs

a. Classify the anticholinesterase drugs in relation to mechanism of action.

- anionic site of action
  - competitive inhibitors of binding of quaternary nitrogen of ACh
  - edrophonium
  - tetraethylammonium
- esteratic (and anionic) site of action
  - transfer acidic group onto the esteratic site (carbamate or phosphate)
  - slow dissociation (minutes to weeks)
  - carbamates
    - neostigmine
    - pyridostigmine
    - physostigmine
  - organophosphates
    - eclothiopate
    - parathion

b. Describe structure-activity relationships of these drugs.

- quaternary ammonium group
  - binds to anionic site by electrostatic force
  - reduces lipid solubility
  - poor oral bioavailability
  - don’t cross BBB
- electrophilic group
  - carbamate or phosphate
  - distance from N⁺ affects potency
  - reacts covalently with serine -OH at esteratic site
  - slow dissociation determines duration of action
- thiophosphates
  - require activation by substitution of oxygen for sulfur atom
  - very lipid soluble

\[
\text{neostigmine} \quad \text{pyridostigmine}
\]

\[
\text{edrophonium} \quad \text{eclothiopate}
\]

c. Compare and contrast the pharmacodynamics and pharmacokinetics of neostigmine, edrophonium, pyridostigmine, physostigmine and tacrine.

- absorption
  - quaternary amines have low bioavailability 10-20%
  - physostigmine and tacrine have higher bioavailability
  - lipophilic organophosphates have high bioavailability even transdermally
- distribution
  - quaternary amine reduces $V_d$ and lipid solubility
prevents penetration into CNS
metabolism and elimination
esters are hydrolysed by cholinesterase and pseudocholinesterase
quaternary amines have high renal clearance
edrophonium is conjugated with glucuronide

<table>
<thead>
<tr>
<th></th>
<th>$V_d$ (l/kg)</th>
<th>$t^{1/2}/\alpha$ (min)</th>
<th>$t^{1/2}/\beta$ (min)</th>
<th>duration (min)</th>
<th>reversing dose (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>neostigmine</td>
<td>0.7</td>
<td>3.5</td>
<td>80</td>
<td>80</td>
<td>0.04</td>
</tr>
<tr>
<td>edrophonium</td>
<td>1.1</td>
<td>7.2</td>
<td>110</td>
<td>60</td>
<td>0.5-1</td>
</tr>
<tr>
<td>pyridostigmine</td>
<td>1.1</td>
<td>6.8</td>
<td>112</td>
<td>120</td>
<td>0.2</td>
</tr>
<tr>
<td>physostigmine</td>
<td></td>
<td>25</td>
<td></td>
<td></td>
<td>0.15</td>
</tr>
<tr>
<td>tacrine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Onset of action is determined by rate of diffusion and depth of NDB blockade.
Duration of action is determined by rate of dissociation from AChE of carbamates and phosphates or by conjugation and clearance for edrophonium.
For reversal, the duration of action of neostigmine and pyridostigmine is well-matched by glycopyrrolate (5 µg/kg) and that of edrophonium by atropine (7 µg/kg).

mechanism
esteratic site agents prevent hydrolysis of ACh
$\uparrow$ ACh concentration in synaptic cleft
competitive antagonism of NDB
edrophonium
direct cholinomimetic activity
some competitive inhibition of hydrolysis of ACh

d. Outline the effects and treatment of poisoning with organophosphate compounds.
organophosphates transfer phosphate to esteratic site of AChE
hydrolysis takes weeks
prolonged $\uparrow$ in ACh at muscarinic and nicotinic synapses

effects
muscarinic (apparent first)
potent cholinomimetic effect
salivation, lacrimation, $\uparrow$ gut motility, miosis
bradycardia
bronchoconstriction
nicotinic
initial tetany, then depolarizing blockade
weakness, paralysis
minor preganglionic sympathetic actions
CNS (apparent last)
excitation, convulsions

treatment
management of acute effects
ventilation, sympathomimetics, pacing
anticonvulsants
regeneration of AChE
pralidoxime accelerates hydrolysis
blockade of autonomic effects
atropine
B. 9 Anticholinergic drugs

a. Describe the structure-activity relationship of anticholinergic drugs.

b. Compare and contrast the pharmacokinetics and pharmacodynamics of atropine, hyoscine and glycopyrrolate.

c. Describe the effects of overdoseage of anticholinergic drugs and its management.

peripheral cholinergic transmission
  muscarinic: mostly post-ganglionic parasympathetic
  nicotinic: autonomic ganglia and the neuromuscular junction

  NMJ covered in Relaxants (2.B.7)

antimuscarinic effects
  ↓ secretions (tears, saliva, bronchial, gut)
  mydriasis, cycloplegia, ↑ IOP
  ↑ heart rate
  ↓ motility, urinary retention

general structure
  natural alkaloids
    tertiary amines containing tropic acid
    l- and d- isomers, l- isomers active
    selective for muscarinic receptors
    penetrate CNS
  synthetic agents
    quaternary amines containing mandelic acid
    poor penetration of CNS
    some activity at nicotinic receptors → ganglion blockade

atropine
  derived from A. belladonna (deadly nightshade)

pharmacokinetics
  oral, rectal bioavailability 25%
  similar for ocular administration
  rapid distribution t\textsubscript{1/2α} 1min
  V\textsubscript{s} 3 l/kg
  crosses placenta
  metabolized by hydrolysis to tropine and tropic acid
  50% excreted unchanged in urine
  t\textsubscript{1/2β} 2 h

pharmacodynamics
  selective competitive muscarinic antagonist
  CNS
    stimulation at high doses
    ↑ cardioinhibitory centre, ↑ vagal tone (transient)
    ↓ CTZ transmission (weak antiemetic)
    mydriasis, cycloplegia, ↑ IOP
  CVS
    initial ↓ HR followed by ↑ due to muscarinic blockade
    little change in CO
    blocks vasodilating actions of exogenous ACh analogues
  Respiratory
    ↓ secretions, bronchodilation
  GIT
↓ LOS tone
other  ↓ sweating
clinical use
premedication 0.4-0.6 mg (largely obsolete)
prophylaxis against bradycardia
  in children at induction 10-50 µg/kg
  with neostigmine for reversal 15-20 µg/kg
treatment of bradycardia or sinus arrest 0.4-1.2 mg
adverse effects
  above, plus myocardial ischaemia due to ↑ HR
  narrow-angle glaucoma
  confusion and delirium in the elderly
hyoscine
  similar to atropine
pharmacokinetics
  bioavailability 25%
  Vd 1.5-3 l/kg
  clearance 7-15 ml/kg/min
  5% excreted unchanged in urine
  t½ 2-3 h
pharmacodynamics
  less CVS effect
  more ↓ secretions, ocular effects, antiemetic effect
clinical use
  transdermal antiemetic for motion-sickness
  0.14 mg + 5 µg/h
glycopyrrolate
  synthetic anticholinergic
pharmacokinetics
  much longer duration of action than atropine: 6-8 h
pharmacodynamics
  similar to atropine except
  less penetration into CNS
  greater potency in ↓ secretions
  less tachycardia
clinical use
  prevention of bradycardia, salivation with neostigmine: 5-6 µg/kg
other anticholinergics
  ipratropium nebulized for asthma, COAD
  benztropine, benzhexol for dystonia, Parkinsonism
  propantheline for gut, bladder spasm
  tropicamide in topical ophthalmic use
B. 10 Local anaesthetic drugs

a. Describe the structure-activity relationships of local anaesthetic drugs.

composed of lipophilic end, chain and hydrophilic end
saturated groups at hydrophilic end increase lipid solubility, decrease water solubility,
increase protein binding and potency, increase time to onset
pKₐ reduced by amide rather than ester linkage

\[
\text{procaine} \\
\text{prilocaine} \\
\text{lignocaine} \\
\text{bupivacaine}
\]

Bupivacaine is N-butylpipocelic xylidide. Mepivacaine is N-methyl~ and ropivacaine is (S) N-propyl~.
Benzocaine has no hydrophilic group and does not display frequency-dependent block.

b. Classify local anaesthetic drugs and list them under the appropriate group.

esters
cocaine (from *Erythroxylon coca*)
procaine
nesacaine
amethocaine
benzocaine
carbamoyl
cinchocaine
amides
prilocaine
lignocaine
etidocaine
mepivacaine
bupivacaine
ropivacaine
other agents with LA activity
barbiturates
pethidine
ß-blockers
phenol (6% for neurolytic block)

c. Describe the mechanism of action of local anaesthetic drugs.

diffuse through cell membrane in basic form
ionized at intracellular pH
bind to voltage-gated Na⁺ channels in the open state
channel consists of α, ß₁ and ß₂ subunits
\( \alpha \) subunit has four homologous domains which form the channel
each domain has six subunits \( S_{1-6} \)
\( S_5 \) and \( S_6 \) form the m-gate
local anaesthetics bind to \( \alpha \) domain 4 \( S_6 \) in the open and inactivated states
cause stabilization of the inactive state
bind most rapidly with repetitive firing (frequency dependence)
local anaesthetics bind to \( \alpha \) domain 4 \( S_6 \) in the open and inactivated states
cause stabilization of the inactive state
bind most rapidly with repetitive firing (frequency dependence)
lignocaine: fast dissociation
bupivacaine: slow dissociation
benzocaine: probably another mechanism
prevent channel opening
\( \uparrow \) threshold voltage, refractory period
\( \downarrow V_{\text{max}} \)
nerve
resistant to depolarization
\( B > C > A \delta - A\alpha \)
cardiac
wide QRS, long PR
\( \downarrow \) contractility
d. Explain the principles of the pharmacokinetics of local anaesthetic drugs and
apply this knowledge to use in clinical practice.

<table>
<thead>
<tr>
<th></th>
<th>pKw</th>
<th>bound (%)</th>
<th>t1/2 (h)</th>
<th>onset (h)</th>
<th>duration (h)</th>
<th>hepatic extraction</th>
<th>( V_d ) (l/kg)</th>
<th>lipid sol.</th>
</tr>
</thead>
<tbody>
<tr>
<td>lignocaine</td>
<td>7.9</td>
<td>70</td>
<td>1.6</td>
<td>fast</td>
<td>1-2</td>
<td>68%</td>
<td>1.3</td>
<td>2.9</td>
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<tr>
<td>bupivacaine</td>
<td>8.1</td>
<td>96</td>
<td>2.4</td>
<td>medium</td>
<td>2-6</td>
<td>37%</td>
<td>1.0</td>
<td>28</td>
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<tr>
<td>(S) ropivacaine</td>
<td>8.1</td>
<td>94</td>
<td>1.8</td>
<td>medium</td>
<td>4-6</td>
<td>40%</td>
<td>0.6</td>
<td>8.4</td>
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<tr>
<td>prilocaine</td>
<td>7.7</td>
<td>55</td>
<td>1.5</td>
<td>fast</td>
<td>1-2</td>
<td>high</td>
<td>2.7</td>
<td>0.9</td>
</tr>
<tr>
<td>procaine</td>
<td>8.9</td>
<td>3</td>
<td>1-10min</td>
<td>medium</td>
<td>.5-.75</td>
<td>low</td>
<td>80%</td>
<td>0.02</td>
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<tr>
<td>cocaine</td>
<td>8.6</td>
<td>1-2</td>
<td>fast</td>
<td>topical</td>
<td>80%</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>etidocaine</td>
<td>7.7</td>
<td>94</td>
<td>2.4</td>
<td>fast</td>
<td>2-6</td>
<td>73%</td>
<td>1.9</td>
<td>141</td>
</tr>
</tbody>
</table>

absorption
all weak bases \( B + H^+ \leftrightarrow BH^+ \)
pKw falls with a rise in temperature (\( \uparrow \) unionized form)
distributed as acid solution of HCl salt
unionized species diffuses readily
high pH \( \rightarrow \) rapid diffusion
hence addition of bicarbonate to solutions
intracellular pH is lower
more ionized
ionized species is pharmacologically active
systemic absorption depends on site of administration
intravascular > intercostal > tracheal > caudal > epidural > plexus > local
speed of injection increases peak level slightly (epidural and plexus)
distribution
dependent on
route
lipid solubility (\( \downarrow \) onset time), water solubility
protein binding (\( \uparrow \) duration)
PH: acidosis \( \downarrow \) diffusion
temperature
perfusion
adrenaline reduces blood flow, intensifies motor block
ropivacaine is a vasoconstrictor

Local anaesthetics 2.B.10.2 James Mitchell (November 5, 2001)
susceptibility of nerve
B > C > A

age
children: rapid tracheal uptake, slow caudal uptake

spinal
rapid uptake into spinal cord
grey > white
dorsal root > ventral
removal by partition into blood
minor spread in CSF
t1/2α
lignocaine 1 h
bupivacaine 2 compartment 30% 1 h, 70% 6 h

epidural
rapid diffusion into CSF (10-20 min)
spread into spinal nerves by 30 min
also spread into cord by diffusion into spinal arteries
sequestered in epidural fat
blood level peaks at 15-30 min

brachial plexus
penetration of nerves from outside (distal, motor) to inside (proximal, sensory)
clearance in similar sequence due to greater perfusion of outside

circulation
distribution into lung tissue smooths arterial peak after IV injection
cross placenta readily
rapid arterial injection can cause retrograde flow to cerebral circulation
bound to α1 acid glycoprotein
low level in pregnancy ↑ free fraction
high level in
renal failure (and low pH) ↓ action
post op, trauma or AMI
cancer
may result in “toxic” total plasma concentration from infusion
post-op with unchanged free concentration due to increased binding

metabolism and excretion below

**e. Explain the factors that determine the clinical effects of local anaesthetic drugs.**

**f. Describe the metabolism of local anaesthetic drugs.**

**metabolism**

esters
hydrolysed by plasma cholinesterase
both in circulation and at site of action
cocaine → benzoylecgonine → ecgonine
procaine → diethylamino ethanol + para-amino benzoic acid

amides
minimal metabolism at site of action
hepatic metabolism by hydrolysis, dealkylation and hydroxylation
perfusion limited except bupivacaine (↓ β-blockers, general anaesthesia)
metabolism in immature in the neonate t1/2β 2-3 times longer
obesity prolongs t1/2β due to slower redistribution
bupivacaine < lignocaine < etidocaine < prilocaine

lignocaine
N-deethylation → glycine xylidide (LA)
amide hydrolysis → xylidine
3' and 4' hydroxylation are minor pathways
prilocaine
   hydrolysis → o-toluidine + N-propylalanine in kidneys, liver and lung
   → methaemoglobin + 4- and 6-hydroxytoluidine
   methaemoglobin is very slowly reduced in neonates
   MetHb reduced to Hb with methylene blue 1-2 mg/kg
bupivacaine
   poorly characterized metabolism
   hydrolysis, 3'- and 4'- hydroxylation
ropivacaine
   3'-hydroxylation, glucuronidation and renal excretion (40%)
   minor N-dealkylation and 4'-hydroxylation
   t\(\frac{1}{2}\)β 1.8 h, E 0.4, clearance 6 ml/kg/min, V\(\text{d}\) 0.6 ml/kg
   t\(\frac{1}{2}\) from epidural space 4.8 h
excretion
   renal
   filtration of free fraction and tubular secretion
   1-6% excreted unchanged (increased in acidic urine)
   hepatic metabolites are renally cleared
enteral
   small amount of gastric secretion and intestinal reabsorption
coexistent disease
   cardiac failure
   ↓ V\(\text{d}\), clearance
   hepatic failure
   ↑ V\(\text{d}\), t\(\frac{1}{2}\)β, ↓ clearance
   renal failure, pulmonary disease
   little change to kinetics
drug interactions
   general anaesthesia
   ↓ hepatic blood flow, ↑ t\(\frac{1}{2}\)β
   adrenaline
   ↑ hepatic blood flow, ↓ t\(\frac{1}{2}\)β
   β-blockers
   propranolol → 40% reduction in pulmonary uptake of lignocaine
   enzyme inducing and inhibiting agents
   hepatic
   cholinesterase (for esters)

g. Describe the management of overdoseage of local anaesthetic drugs.

<table>
<thead>
<tr>
<th>Local anaesthetics</th>
<th>2.B.10.4</th>
<th>James Mitchell (November 5, 2001)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Drug</th>
<th>Safe dose (mg/kg)</th>
<th>Toxic level (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>lignocaine</td>
<td>5</td>
<td>6-8</td>
</tr>
<tr>
<td>bupivacaine</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>ropivacaine</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>prilocaine</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>procaine</td>
<td>5</td>
<td>7-10</td>
</tr>
</tbody>
</table>

“Safe dose” is for infiltration or regional block, not IV or spinal dose
40-50% higher dose for local infiltration with adrenaline
lower safe dose with ↓ protein binding, ↓ pH, ↑ HR in neonates
lower safe dose with ↓ protein binding, ↓ pH, ↑ HR in neonates

cardiac:CNS toxicity ratio is a measure of safety
  lignocaine 7:1
  bupivacaine 3.7:1 (with slow offset of action)
  central mechanism for some arrhythmias
  L-bupivacaine is less toxic

lignocaine
level (µg/ml)  effect
  2  anticonvulsant, antidysrhythmic
  4  positive inotrope, tinnitus, lightheadedness
  6  vision disturbance
  8  twitching
 10  convulsions
 15  coma
 20  respiratory arrest
 26  cardiac arrest

cardiac
  reentrant arrhythmias → VF
  refractory to DCR

brain
  tinnitus, drowsiness, convulsions, coma
  worsened by acidosis and hypercarbia due to ion trapping

local neurotoxicity
  may be due to preservatives (sodium bisulfite causes permanent damage)

management
  correction of acute disturbances
    ventilation, oxygen
    cardiac massage, DCR, bretylium/lignocaine/clonidine/amiodarone, bypass
  correction of acidosis (allows diffusion away from site of action)
  control of seizures with benzodiazepine or barbiturate
B. 11 Pharmacology of the autonomic nervous system.

a. Describe the physiological roles of the sympathetic and parasympathetic nervous systems.

**sympathetic**
- thoracolumbar outflow T₁ to L₃
- efferent: cell body in grey matter of cord, ventral root, white ramus to sympathetic chain or grey ramus to spinal nerves
- afferent: sympathetic chain, white ramus, dorsal root (body in ganglion), dorsal horn preganglionic fibres are B type myelinated nicotinic
- synapse in chain and ganglia (cervical, coeliac, mesenteric and sacral) and adrenal medulla
- postganglionic
  - adrenergic secretory cells in adrenal medulla
  - noradrenergic postganglionic fibres
    - mydriasis, distant vision accommodation, vasoconstriction/dilation, bronchodilation, inotropy, chronotropy, ↓ gut motility, ↑ renin, detrusor relaxation, trigone contraction, ejaculation, ↑ glucagon, ↑ glucose & lipid mobilization. lipolysis
  - muscarinic postganglionic fibres
    - sweating, piloerection, some vasodilation

**parasympathetic**
- craniosacral outflow (III, VII, IX, X, S₂ to S₄) 75% in vagus
- efferent: cell body in CNS, peripheral ganglia (ciliary, sphenopalatine, otic, local synapses in organs)
- preganglionic fibres are nicotinic
- postganglionic fibres are muscarinic
  - III miosis, near vision accommodation
  - VII lacrimation, submandibular gland secretion
  - IX parotid gland secretion
  - X ↑ gut secretions, ↑ motility, palmar sweating, negative inotropy & chronotropy, bronchoconstriction
  - sacral detrusor contraction, trigone relaxation, erection, defaecation

**afferent**
- minor component
  - substance P, peptide neurotransmitters including glutamate

b. Describe the physiological actions of adrenergic, cholinergic and dopaminergic receptors including their subtypes, and their molecular effects.

α and β receptors differentiated by Alquist (1948)
β subtypes identified by Lands (1967)

cotransmitters found at probably all sites of autonomic transmission
- noradrenaline ± dopamine, NO, neuropeptide Y...
- ACh ± substance P, VIP...

\(\alpha_{1A,B,C,D}\)
- G-protein linked, ↑ IP₃, DAG except possibly \(\alpha_{1A}\), which ↑ Ca²⁺ conductance
- vasoconstriction, ↑ contractility, glycolgenolysis, mydriasis, piloerection, apocrine sweating, salivation, uterine contraction, bladder neck contraction, ejaculation, detumescence

\(\alpha_{2A,B,C}\)
- G-protein linked, ↓ cAMP
- central functions (sedation, descending inhibitory pathways, ↓ CO₂ response)
platelet activation, vasoconstriction, \(\downarrow\) lipolysis, \(\downarrow\) insulin
presynaptic inhibition at postganglionic sympathetic terminals
\(\downarrow\) renin, ADH, \(\downarrow\) stress response

\(\beta_1\)
G-protein linked, \(\uparrow\) cAMP
\(\uparrow\) contractility, \(\uparrow\) HR, \(\uparrow\) conduction velocity, \(\uparrow\) diastolic relaxation
\(\uparrow\) renin

\(\beta_2\)
G-protein linked, \(\uparrow\) cAMP
bronchodilation, vasodilation, uterine relaxation, \(\uparrow\) HR
\(\uparrow\) K\(^+\) uptake by skeletal muscle, \(\uparrow\) glycogenolysis, \(\uparrow\) insulin

\(\beta_3\)
G-protein linked, \(\uparrow\) cAMP
\(\uparrow\) lipolysis

\(D_1\)
G-protein linked, \(\uparrow\) cAMP
vasodilation: renal, splanchnic, coronary, cerebral

\(D_2\)
G-protein linked, \(\downarrow\) cAMP, \(\uparrow\) K\(^+\) conductance, \(\uparrow\) Ca\(^{2+}\) conductance
\(?\) presynaptic inhibition

\(D_4\)
G-protein linked, \(\downarrow\) cAMP
possible site of action of clozapine (with 5HT\(_7\))

\(D_5\)
G-protein linked, \(\uparrow\) cAMP

\(M_1\)
G-protein linked, \(\uparrow\) IP\(_3\), DAG, Ca\(^{2+}\)
CNS neurotransmission
sympathetic postganglionic
\(\uparrow\) gut motility
presynaptic

\(M_2\)
G-protein linked, open K\(^+\) channels, \(\downarrow\) cAMP
myocardial and vascular innervation of vagus
preganglionic function (site of action of pancuronium and gallamine)

\(M_3\)
G-protein linked, \(\uparrow\) IP\(_3\), DAG, Ca\(^{2+}\)
exocrine glands, vasodilation via NO & cGMP, miosis
bronchoconstriction
\(\uparrow\) gut motility, defaecation, urination

\(N_N\)
gated ion channel, \(\uparrow\) Na\(^+\), Ca\(^{2+}\) flux
presynaptic potentiation at NMJ
CNS

\(N_M\)
gated ion channel, \(\uparrow\) Na\(^+\), Ca\(^{2+}\) flux
neuromuscular junction

c. Describe the synthesis, release and fate of adrenergic and cholinergic transmitters.

catecholamines
synthesized from tyrosine (or phenylalanine if tyrosine is unavailable)
tyrosine hydroxylase (rate limiting step, requires biopterine) →

DOPA decarboxylase (inhibited by disulfiram, requires pyridoxal phosphate) →

vesicular dopamine β-hydroxylase (requires ascorbate) →

phenylethanolamine N-methyl transferase (requires 5-adenosyl methionine) →

adrenaline or noradrenaline are metabolized by MAO and COMT to

acetylcholine

active uptake of choline from interstitial fluid, reacted with acetyl-CoA:

breakdown is by hydrolysis due to acetylcholinesterase, with recycling of choline and return of acetate to the TCAC

d. Describe the structure-activity relationships of adrenergic and cholinergic drugs

adrenergic

ligands bind in their ionized form

receptor affinity

β-OH or 3-OH required for direct activity

4-OH or > methyl group on N: ↑ β affinity, potency

> isopropyl group on N or α or 3 sidechain: β₂ selective

imidazole group: α selectivity (α₂ > α₁)

distribution, metabolism
few OH, no N+: enters CNS
> methyl on N: not a substrate for uptake 1 (no indirect action)
> methyl on N or α methyl: not a substrate for MAO
3,4 di-OH required for COMT
all bind to the receptor in the ionized form

cholinergic
  similar to ACh, all have N+ except pilocarpine
  receptor affinity
  side groups on chain: muscarinic selective
  metabolism
  no acetyl group (e.g. carbamoyl): not a substrate for AChE

e. Compare and contrast the mechanism of action and effects of sympathomimetic
and cholinomimetic agents used clinically.

f. Describe α, α, β, and β, adrenergic agonists and their clinical applications.

Endogenous (direct acting catecholamines)

adrenaline
  β > α, not α or β selective
  ↑ CO, HR, MAP, CNS activity, blood glucose
  ↓ RBF, airway resistance
  arrhythmogenic
  vasoconstrictor in local anaesthetics
  used for anaphylaxis, asystole (100 µg-1 mg),
  inotrope, nebulized for croup

noradrenaline
  α > β, >> β, not a selective
  ↑ TPR, MAP
  ↓ RBF
  used as an inotrope (5-15 µg/min)

dopamine
  D1 > β1 > α1 > β2 > α2
  ↑ CO, HR, TPR, MAP, RBF
  suppresses hypoxic drive
  used for renal "protection" (low dose), inotrope (high dose) 2-20 µg/kg/min

Exogenous catecholamines (direct acting)

isoprenaline (isopropyl noradrenaline)
  non-selective β
  ↑ HR, CO, CNS activity
  ↓ TPR, airway resistance
  arrhythmogenic
  reduces pulmonary vascular resistance
  used as an inotrope (1-5 µg/min),
  bronchodilator (obsolete)

dobutamine
  selective β1 (not dopaminergic)
  ↑ CO, HR, MAP, RBF
  used as an inotrope without
  vasoconstrictor effects

salbutamol (and terbutaline, fenoterol and
  orciprenaline)
  selective β2
  ↑ HR, CNS activity
  ↓ airway resistance, labour
used for bronchodilation (IV, oral or nebulized), chronotrope, tocolytic
dopexamine
selective D₂ (>β) agonist
Direct acting non-catecholamines
phenylephrine (and methoxamine)
selective α₁
↑ TPR, MAP (methoxamine is a more potent arteriolar constrictor)
↓ RBF
arrhythmogenic (methoxamine is mildly antidysrhythmic)
used for hypotension (20-50 µg/min IV)
topical mydriatic, nasal decongestant
clonidine
α₂ selective, imidazoline antagonist
↓ HR, CO, TPR, MAP, CNS activity
used for hypertension, reduces sympathetic outflow
sedative, reduced anaesthetic & opiate requirements
spinal/epidural analgesic (inhibits substance P release)
reduces opiate withdrawal symptoms
BRL37344
β₂ selective
↑ lipolysis
? fat-loss agent
Indirect acting non-catecholamines
ephedrine (β-OH methamphetamine)
α > β (non selective, has some direct activity)
↑ HR, CO, TPR, MAP, CNS activity
↓ RBF
used short-term for hypotension (5-25 mg IV/IM)
does not reduce uterine blood flow
abused as CNS stimulant, anorectic
amphetamine (and dexamphetamine, methamphetamine, methylphenidate)
alphamethylenephylethylamine
non selective, enter CNS rapidly, displaces noradrenaline
↑ CNS activity, HR, CO, TPR
used for ADHD (oral), widely abused orally and IV.
metaraminol
α >> β (direct and indirect), weak false transmitter
↑ TPR, MAP (reflex ↓ HR)
↓ RBF
used for hypotension (0.5-5 mg IV 40-500 µg/min)

**g. Describe the drugs used as inotropic and vasoactive agents including the phosphodiesterase inhibitors.**

phosphodiesterase inhibitors
bipyridines include milrinone, amrinone, vesarinone etc.
flosequinan is a fluoroquinolone

milrinone

*Autonomic* 2.B.11.5 James Mitchell (November 5, 2001)
pharmacokinetics
- orally active
- $t_{1/2}$ 2-3 h
- 50% renal excretion

pharmacodynamics
- selective inhibitor of phosphodiesterase III
- onset of action over 15 minutes
- $\uparrow$ intracellular cAMP in cardiac and smooth muscle
  - $\uparrow$ Ca$^{2+}$ release in cardiac muscle
  - inotrope, $\uparrow$ HR, diastolic compliance & proportion of cycle
- $\uparrow$ phosphorylation of MLCK in smooth muscle ($\downarrow$ activity)
  - $\downarrow$ MLC phosphate, $\downarrow$ contraction
  - systemic, coronary and pulmonary vasodilation
- net $\uparrow$ MAP

adverse effects
- amrinone
  - nausea, vomiting, hepatotoxicity, thrombocytopenia, arrhythmogenic
- milrinone
  - less adverse effects but same risk of arrhythmia

clinical use
- milrinone: 50 µg/kg load, 0.25-0.75 µg/kg/min infusion
- intensive monitoring required
- used for short term inotropy, especially where vasoconstriction is to be avoided

h. Outline the interactions with drugs used in the perioperative period.
B. 12 Adrenoceptor blocking agents

a. Explain the mechanisms and physiological consequences of α₁, α₂, β₁ and β₂ receptor blockade.

b. Classify α and β receptor blocking agents according to their actions, reversibility and chemical groups.

c. Describe the pharmacokinetics of α receptor blocking agents and apply this to their clinical use.

prazosin
- competitive α₁ blocker (predominantly α₁A)
- high extraction ratio, 50% bioavailable
- $t_{1/2}$ 3 h hepatic metabolism, unaffected by renal impairment
- used for hypertension, afterload reduction, urinary retention (low dose)
  - 1-10 mg o tds

terazosin
- similar to prazosin
- high bioavailability
- $t_{1/2}$ 12 h
- 5-20 mg o daily

doxazosin
- similar to prazosin
- $t_{1/2}$ 22 h
- 1-16 mg a daily

yohimbine
- competitive α₂ blocker
- used in idiopathic orthostatic hypotension (not in Australia)
- improves impotence
- more selective α₂ blockers are under development

phentolamine
- competitive non-selective α blocker
- onset of action within 2 minutes
- effective duration 10-15 minutes
- used for acute hypertension (2-5 mg IV) esp. in phaeochromocytoma surgery
- does not affect autoregulated circulations (unlike nitrates)
- also combined with papaverine in impotence
- adverse effects due to muscarinic, H₁ and H₂ agonism and reflex β stimulation

phenoxybenzamine
- non-competitive non-selective α blocker ($α_i>α₂$)
- low bioavailability
- pro-drug converted to ethylene ammonium compound
- slow onset: over 60 min to peak effect
- binds covalently to receptors
- also binds H₁, ACh and serotonin receptors
- offset of action as receptors are renewed ($t_{1/2}$ 24 h irrelevant)
- used in hypertension (phaeo) and Raynaud's syndrome
  - 10-30 mg o bd

ergot derivatives, phenothiazines and butyrophenones also have α antagonist activity

d. Describe the pharmacodynamic and pharmacokinetic features of β receptor blocking agents.

e. Describe the clinical uses of β receptor blocking agents and their side effects.
all competitive antagonists at β receptors

pharmacokinetics

<table>
<thead>
<tr>
<th>agent</th>
<th>absorbed (%)</th>
<th>bioavailability (%)</th>
<th>protein bound (%)</th>
<th>t½/β (h)</th>
<th>excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>atenolol</td>
<td>50</td>
<td>55</td>
<td>0</td>
<td>6</td>
<td>urinary</td>
</tr>
<tr>
<td>esmolol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>metoprolol</td>
<td>100</td>
<td>50</td>
<td>10</td>
<td>4</td>
<td>oxidation</td>
</tr>
<tr>
<td>pindolol</td>
<td>100</td>
<td>100</td>
<td>50</td>
<td>4</td>
<td>conj/oxid</td>
</tr>
<tr>
<td>propranolol</td>
<td>100</td>
<td>33</td>
<td>90</td>
<td>5</td>
<td>oxidation</td>
</tr>
<tr>
<td>sotalol</td>
<td>100</td>
<td>60</td>
<td>0</td>
<td>10</td>
<td>urinary</td>
</tr>
</tbody>
</table>

Agents fall into broad categories of renally cleared, hepatically metabolized and esmolol which is hydrolyzed in red cells. Elimination kinetics are correspondingly affected by renal or hepatic disease. Hepatic metabolism is also reduced in the elderly and increased in smokers. The elderly are less susceptible to β blockade, so increased plasma levels are not necessarily toxic.

pharmacodynamics

<table>
<thead>
<tr>
<th>agent</th>
<th>potency</th>
<th>selective for β₁</th>
<th>membrane stabilizing</th>
<th>partial agonist</th>
</tr>
</thead>
<tbody>
<tr>
<td>atenolol</td>
<td>1</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>esmolol</td>
<td>0.01-0.02</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>metoprolol</td>
<td>1</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>pindolol</td>
<td>6</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>propranolol</td>
<td>1</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>sotalol</td>
<td>0.3</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

β₁ selectivity is relative, at high doses β₂ antagonism is seen most display differing potencies of enantiomers membrane stabilizing (local anaesthetic) effect is independent of β blocking activity

adverse effects

predictable from β receptor functions

β₁ ↓ CO, masks hypoglycaemic symptom of tachycardia
β₂ bronchospasm, peripheral vasospasm, ↓ glucose tolerance (via ↓ insulin secretion)

clinical use

hypertension
↓ CO, ↓ renin release, central effect

IHD
↓ CO, greater ↓ in myocardial O₂ demand, proven mortality benefits
↓ HR at lower doses than ↓ contractility

thyrotoxicosis, phaeochromocytoma
symptomatic relief

SVT, AF
second line drugs for reducing AV conduction

glaucoma
↓ IOP in open-angle glaucoma (topical use)

esmolol
specific use for suppressing short-term sympathetic response e.g. at laryngoscopy and reducing tachycardia from nitroprusside infusion

Adrenoceptor blockers

2.B.12.2

James Mitchell (November 5, 2001)
B. 13 Antihypertensive drugs

a. Classify the modes of action of the antihypertensive drugs.

central sympathetic tone inhibitors
  $\alpha_2$ agonists
  $\beta$ antagonists
peripheral sympathetic antagonists
  $\alpha$ blockers
  adrenergic neurone blockers (obsolete)
vasodilators
  arteriolar
    $Ca^{2+}$ blockers
  others
  arteriolar and venous
  nitrates
ACE inhibitors
ATII1 receptor antagonists
diuretics

b. Describe the pharmacology of centrally acting agents such as clonidine and $\alpha$–methyldopa.

clonidine
  a selective $\alpha_2$ antagonist with central, spinal and peripheral actions
  available as oral, transdermal, IV, epidural and intrathecal preparations
  a weak base
pharmacokinetics
  95% bioavailable, 20% protein bound, $V_d$ 2 l/kg, $t^{1/2}$ 8-12 h
  lipid soluble, diffuses readily into the CNS
  renally cleared 50% unchanged
pharmacodynamics
  binds $\alpha_2$ receptors, imidazoline receptors
  presynaptic effect in periphery inhibits noradrenaline release
  central effect
    reduces sympathetic tone
    increases parasympathetic tone
    accentuates baroreceptor reflex
    sedative, depressant (blocked by tricyclics)
    rebound hypertension and anxiety on withdrawal
  dose 0.2-1.2 mg/d orally
$\alpha$-methyldopa
  false transmitter substrate with central $\alpha_2$ agonist effect
  administered orally
pharmacokinetics
  metabolized on the same pathway as DOPA, yielding $\alpha$-methylnoradrenaline, an $\alpha_2$ agonist
  50% bioavailable, 15% protein bound, duration of effect ~24 h
pharmacodynamics
  central effects similar to clonidine with less ↓CO
  antagonizes dopaminergic transmission
  extrapyramidal effects
  galactorrhoea
  hepatic necrosis
  Coomb's test positive in 20%
other central $\alpha_2$ agonists, guanfacine and guanabenz are similar to clonidine

c. Describe the actions of ganglion blocking agents and the pharmacology of trimetaphan.

Ganglion blocking agents include tetraethylammonium, hexamethonium, mecyamine and trimetaphan. They are all selective nicotinic-N antagonists, blocking transmission at all autonomic ganglia, the adrenal medulla and sites in the CNS (though the quaternary ammonium compounds do not penetrate the CNS readily). They are all obsolete.

trimetaphan

- competitive nicotinic antagonist acting predominantly at autonomic ganglia
- administered IV

pharmacokinetics

- rapid onset and brief action
- IV infusion allows titration of blood pressure

pharmacodynamics

- binds nicotinic receptors in autonomic ganglia
- reduces sympathetic transmission
  - marked postural hypotension
  - impotence
  - sedation
- reduces parasympathetic transmission
  - constipation
  - urinary retention
  - dry mouth
  - glaucoma, blurred vision

d. Describe the pharmacology of agents which block the release of transmitters at the adrenergic nerve ending.

guanethidine

an anti-sympathetic agent which inhibits noradrenaline release
similar to bethanecol and debrisoquin

pharmacokinetics

- variable bioavailability (3-50%), large $V_d$, $t_{1/2} \beta$, 5 days
- dose adjustment cannot be made more than fortnightly
- requires uptake 1 for action (blocked by cocaine, tricyclics)

pharmacodynamics

- transported into adrenergic neurones by uptake 1
- concentrated in noradrenaline vesicles
- displaces noradrenaline and depletes stores
- has no effect at receptors
- results in gradual onset of sympathetic blockade
  - hypotension (especially postural)
  - shock in overdose
  - impotence
  - diarrhoea
- upregulation of adrenergic receptors ↑ sensitivity

- dose starts at 10 mg/d (obsolete)

reserpine

plant-derived alkaloid from Rauwolfia serpentina formerly used as an anti-hypertensive
oral and IV preparations

pharmacokinetics

Antihypertensives 2.B.13.2 James Mitchell (November 5, 2001)
poorly elucidated, duration of action is unrelated to plasma half-life
pharmacodynamics
interferes with uptake and storage of endogenous amines in vesicles
depletes noradrenaline, dopamine and serotonin (and adrenaline)
acts both peripherally and in the CNS
mostly central effect at low doses
reduced sympathetic tone
sedation, depression
extrapyramidal effects
diarrhoea
↑ gastric acid secretion
dose 0.25 mg to 1 mg as a single dose (obsolete)

e. Appraise the use of β-receptor blocking agents, α-receptor blocking agents and calcium antagonists in the treatment of hypertension.

β-blockers
antihypertensive and antidysrhythmic drugs also used for glaucoma and sedation
classification
non-selective (propranolol), β₁ selective (metoprolol, atenolol, esmolol), α and β antagonist (labetalol)
membrane-stabilizing (propranolol, labetalol)
partial agonist (pindolol, alprenolol)
pharmacokinetics
oral, ophthalmic and IV preparations
bioavailability and binding vary from drug to drug
half-lives are mostly 3-6 h except esmolol which is short-acting and a few long-acting drugs (penbutolol, nadolol)
metabolism
responsible for variability in plasma levels in hepatic or renal disease
hepatic oxidation or conjugation
labetalol, metoprolol, propranolol, most others
renal excretion
atenolol, sotalol
hydrolysis
esmolol

<table>
<thead>
<tr>
<th></th>
<th>bioavailability</th>
<th>protein bound</th>
<th>t₁/₂β</th>
<th>metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>atenolol</td>
<td>50%</td>
<td>&lt;5%</td>
<td>6-7 h</td>
<td>renal excretion</td>
</tr>
<tr>
<td>propranolol</td>
<td>33%</td>
<td>90%</td>
<td>4-6 h</td>
<td>hepatic oxidation</td>
</tr>
<tr>
<td>metoprolol</td>
<td>50%</td>
<td>10%</td>
<td>3-4 h</td>
<td>hepatic oxidation</td>
</tr>
<tr>
<td>esmolol</td>
<td>n/a</td>
<td>50%</td>
<td>9 min</td>
<td>hydrolysis</td>
</tr>
</tbody>
</table>

pharmacodynamics
some have (class Ia) membrane stabilizing activity
competitive antagonists at β-adrenoceptors
can always be overcome with sufficient catecholamines
β₁ effects
down HR, contractility, renin secretion
β₂ effects
up airway tone, vasomotor tone
down insulin release

adverse effects
bronchospasm, asthma
cardiac failure, heart block
impaired glucose tolerance and mask hypoglycaemia
indications
hypertension
  more effective in high renin setting
  acts both by ↓ renin release and ↓ CO
angina (and cardiac/major surgery)
  ↓ CO, myocardial oxygen demand
  ↑ duration of diastole, myocardial perfusion
AMI
  proven to reduce mortality
  acutely via anti-anginal effects
  also antidysrhythmic
arrhythmia
  slow atrial rate
  slow AV conduction
  glaucoma, hyperthyroidism

Calcium channel blockers
  vasodilating and antidysrhythmic drugs

verapamil
  type I Ca^{2+} channel blocker: phenylalkylamine
  inhibits opening of both fast Na^{+} channels and slow Ca^{2+} channels
oral and IV preparations
pharmacokinetics
  10-20% bioavailable
  90% protein bound (albumin and AAG)
  hepatic metabolism
  t^1/2 β 5 h L isomer more rapidly metabolized
  slower clearance with prolonged use
pharmacodynamics
  L- (active) and D-isomers
  type Ia and IV antidysrhythmic effects at low dose
  negative inotrope at higher dose
  vasodilator
    both Ca^{2+} channel and α-antagonist effects
  weak bronchodilator
  sedative (↓ MAC)
indications
  AF, SVT: slows A-V nodal conduction
  hypertension
    improves diastolic compliance in hypertrophic cardiomyopathy
adverse actions
  complete heart block
    especially with β-blockers or halothane/enflurane
  myocardial depression
  constipation
  impaired glucose tolerance
  potentiate neuromuscular blockers and local anaesthetic effects
  causes hyperkalaemia when given with dantrolene

nifedipine
  dihydropyridine Ca^{2+} channel blocker
oral, slow release and IV preparations
pharmacokinetics
  poor absorption sublingually
  50% bioavailable (oral)
90% protein bound (albumin and AAG)
t₁/₂β 2h (slow release oral preparations available)

hepatic metabolism

pharmacodynamics
potent peripheral and weak coronary vasodilator
direct negative inotrope

site of action is dependent on pharmacokinetics

nimodipine has more cerebral effect
reflex (baroreceptor-mediated) tachycardia, ↑ CO
↑ risk of ischaemia

minimal effect on conduction

indications
hypertension
Raynaud's phenomenon

adverse actions
vasodilation
headache, flushing, peripheral oedema
constipation
hypotension

nimodipine
dihydropyridine with cerebral vasodilating activity
↓ risk of vasospasm and ischaemia in SAH
↓ Ca²⁺ entry to neurones may reduce cell death
light sensitive
administered IV 0.4-2 mg/h

diltiazem
benzothiazepine Ca²⁺ channel blocker active at both cardiac and peripheral sites
oral preparations

pharmacokinetics
40% bioavailable
80% protein bound
hepatic metabolism
t₁/₂β 4 h but complex kinetics result from enterohepatic circulation

pharmacodynamics
similar to other Ca²⁺ blockers but fairly selective for coronary vessels
improves subendocardial perfusion
some antidysrhythmic effect

indications
angina
hypertension

f. Describe the mechanism of action of vasodilators such as hydralazine, ACE inhibitors and diazoxide.

Direct vasodilators are potent in reducing blood pressure acutely, but have little effect on blood pressure when used long term. Reflex responses to arteriolar vasodilation include immediate increase in cardiac output and venous return and baroreceptor-mediated increase in sympathetic tone causing tachycardia, increased contractility and reduced venous pooling. Reduced renal perfusion pressure and sympathetic outflow results in increased renin, angiotensin II and aldosterone levels and consequent fluid retention. These effects result in a maintenance of blood pressure with increased intravascular volume and myocardial workload.

hydralazine
a directly acting arteriolar vasodilator
oral and IV preparations
pharmacokinetics
  25% bioavailability
  bimodal metabolism by hepatic acetylation
  $t_{1/2}^\beta$ 2-4 h
pharmacodynamics
  binds to vascular tissue, effect longer than $t_{1/2}^\beta$
  direct vasodilator via NO synthesis
adverse actions
  vasodilation
    headache, flushing, palpitations
  sympathetic tone
    anorexia, sweating, nausea
  sporadic
    SLE-like syndrome, neuropathy, fever
clinical use
  5 mg bolus, titrated to effect
  onset over 20 minutes
minoxidil
  oral (and topical) preparations
pharmacokinetics
  high bioavailability
  low protein binding
  prodrug: sulfate is the active metabolite (long $t_{1/2}^\beta$)
  $t_{1/2}^\beta$ 4 h
pharmacodynamics
  sulfate binds to $K^+$ channels in smooth muscle
  increased $K^+$ conductance
  hyperpolarized membrane
  direct arteriolar vasodilator
adverse effects
  major reflex increase in sympathetic tone
  pretreatment with propranolol required
  hair growth
diazoxide
  a thiazide without diuretic actions
  IV preparation
pharmacokinetics
  onset of action 5 min
  high protein binding
  metabolism uncharacterized
    some excreted unchanged
  $t_{1/2}^\beta$ ~24 h (duration of effect 4-12 h)
pharmacodynamics and effects
  as for minoxidil except without hirsuitism
ACE inhibitors
  effective in high renin hypertension (as are $\beta$-blockers)
pharmacokinetics
  most are prodrugs, deesterified in the liver
  bioavial. (%)  $t_{1/2}^\beta$ (h)  daily dose (mg)
captopril 40-70 3 15-75
enalapril 11 10-20
lisinopril 12 10-80
all renally cleared except fosinopril
pharmacodynamics

Antihypertensives  2.B.13.6  James Mitchell (November 5, 2001)
antagonize peptidyl dipeptidase
 normally converts AT I to AT II and metabolizes bradykinin
 ↓ AT II, ↑ bradykinin
 ↓ aldosterone, ↑ Na⁺ and water loss
 vasodilation

adverse effects
 cardiovascular
  initial hypotension, intraoperative hypotension
  potent effect on fetal blood pressure
 renal
  precipitate failure with or without renovascular hypertension
  K⁺ retention
 other
  dry cough (bradykinin-mediated)
  neutropenia
  altered taste, allergies

diuretics
  in B 17

g. Describe in detail the pharmacokinetics and pharmacodynamics of sodium nitroprusside and glyceryl trinitrate including their toxic side-effects.

glyceryl trinitrate
  direct vasodilator described in 1879
  explosive
  O₂N-O-CH₂-CH(O-NO₂)-CH₂-O-NO₂
pharmacokinetics
  binds to PVC, reduces predictability of dose
  prodrug metabolized by hepatic nitrate reductase, t₁/₂ 2 min
  GTN → glyceryl dinitrate + NO₂⁻
  nitrite can release NO, but glyceryl di- and mono-nitrate are the main active drugs
  NO is liberated from the nitrates by an unknown reaction which displays saturability, causing rapid tolerance
pharmacodynamics
  NO diffuses into cells, ↑ cGMP to produce effects
  smooth muscle: promotes dephosphorylation of myosin light chain
    ↓ phosphorylated myosin → relaxation
  CVS: coronary vasodilation, ↑ endocardial perfusion
  venodilation > arteriolar dilation, ↓ MAP, ↓ myocardial work
    ↓ platelet aggregation, ↑ MetHb
  respiratory: pulmonary vasodilation, bronchodilation
  GIT, uterine relaxation
clinical use
  75-150 µg/min IV, up to 500 µg/min
adverse actions
  hypotension, headache, tolerance, methaemoglobinemia

nitroprusside
  direct vasodilator
  Fe²⁺(CN)₆N⁰O • 2Na⁺
  light sensitive
pharmacokinetics
  rapid metabolism in red cells releases NO and CN⁻
  CN⁻ metabolized to thiocyanate and renally cleared (t₁/₂ 4-7 days)
  short t₁/₂: offset of action within 10 min

Antihypertensives 2.B.13.7 James Mitchell (November 5, 2001)
pharmacodynamics
vasodilator in all tissues
more arteriolar dilation than GTN
pulmonary vasodilation
loss of coronary autoregulation: potential for steal
clinical use
0.5 to 10 µg/kg/min (up to 2 µg/kg/min for sustained use)
adverse effects
cyanide toxicity if inadequate metabolism or sulfur donors
causes cellular hypoxia
treated with thiosulfate (↑ thiocyanate) or hydroxycobalamin
thiocyanate accumulation
neurological toxicity: weakness, disorientation, fits
inhibits iodide uptake: hypothyroidism
methaemoglobinaemia, hypotension, headache, tolerance
some patients are resistant or display unacceptable tachyphylaxis

h. Describe the pharmacological significance of nitric oxide, its mode of action and toxic effects.

Molecule of the Year 1992
pharmacokinetics
synthesized by nitric oxide synthetase
arginine + O₂ (+ NADPH, Ca²⁺, calmodulin) → citrulline + NO
subtypes of NO synthetase
I  brain, platelets in cytosol. Ca²⁺, calmodulin dependent
    ↑ by NMDA stimulation
    ↓ by IV induction agents
II  macrophage. Prolonged production after induction and activation
    responds to γ-interferon, cytokines, endotoxin
III  vascular endothelium. Ca²⁺, calmodulin dependent
    responds to shear, bradykinin, ACh, 5HT, hydralazine...
can be administered in inspired gas at 0.1-40 ppm
metabolism
highly reactive, spontaneous degradation with O₂ to NO₂, NO₂⁻ and NO₃⁻
strong oxidant: Hb → MetHb
t¹/₂β seconds
pharmacodynamics
vascular smooth muscle
activates guanylate cyclase, ↑ cGMP, ↑ protein kinase activity, ↓ Ca²⁺,
relaxation
macrophages
oxidizes bacterial respiratory enzymes → death
neurones
neurotransmitter via ↑ cGMP, excitatory
role in peripheral and central analgesia, pain wind-up, memory
neurotoxic in non-NO neurones
clinical use
inhaled pulmonary vasodilator
improved V/Q matching (distributed according to ventilation)
used in ARDS, neonatal hypoxic pulmonary vasoconstriction
administered in N₂ to minimize NO₂ exposure
potential for specific NOS inhibitors in septic shock
adverse actions
methaemoglobinaemia
NO₂ causes pulmonary oedema

Antihypertensives 2.B.13.8 James Mitchell (November 5, 2001)
i. Describe the pharmacology of ketanserin

ketanserin
  vasodilator, antihypertensive
  not marketed in Australia
pharmacokinetics
  $t^\text{i/β}$ 15 h
pharmacodynamics
  $5\text{HT}_1^c, 5\text{HT}_2$ antagonist
  ↓ platelet aggregation
  vasodilation
  weak $\alpha_1$ antagonist
clinical use
adverse effects
  CNS: headache, drowsiness
  CVS: ↑ QT interval, torsade de pointes
B. 14 Antidysrhythmic drugs

a. Classify antidysrhythmics by their electrophysiological actions.

Vaughan-Williams classification

I  membrane stabilizers
   all ↑ ERP, ↑ ERP/APD, all except c ↑ APD
   classified by rate of dissociation
   a  medium
      ↑ QT, QRS
      quinidine, procainamide, disopyramide
   b  fast
      ↓ QT
      lignocaine, mexiletine, tocainide
   c  slow
      ↑ PR, QT, QRS
      flecainide, encainide, others

II  β-blockers
    in Antihypertensives (2.B.13)
    ↓ HR, ↑ PR

III drugs prolonging repolarization
    ↑ APD, ↑ ERP
    ↑ QT, ↓ HR
    amiodarone, sotalol, bretylium

IV  Ca$^{2+}$ channel blockers
    in Antihypertensives (2.B.13)
    ↓ HR, ↑ PR

others
   adenosine, digoxin, alinidine, phenytoin etc.

Arrhythmia classification

abnormal impulse formation
   early afterdepolarizations
   occur in phase 3
   more likely at slow heart rates, long QT interval
   worse with class Ia, Ic and III drugs
   delayed afterdepolarizations
   occur in phase 4
   due to ↑ Ca$^{2+}$, more likely in fast heart rates
   worse with digoxin, catecholamines, ischaemia, hypercalcaemia

abnormal impulse conduction
   AV block
   three degrees
   worse with ↑ vagal tone, β-blockers, Ca$^{2+}$ channel blockers

reentry
   area of no conduction adjacent to area of one-way conduction
   circuit long enough to avoid refractory period
   source of tachyarrhythmias
   improved with either increased or decreased conduction

other abnormal conduction pathways
   Wolf-Parkinson-White
   other accessory pathways
b, c, e. Describe the pharmacodynamics and pharmacokinetics of the antidysrhythmic drugs. Describe the side effects and problems associated with the use of antidysrhythmic drugs during anaesthesia.

potassium

↑ plasma [K⁺] causes ↓ E_K and ↑ P_K
less effect on pacemaker cells (↑ V_m)

magnesium

acts on Na⁺/K⁺ ATPase, Na⁺, K⁺ and Ca²⁺ channels
mechanism of action uncertain
used in torsade and digoxin toxicity
effective in paediatric acute asthma (25-50 mg/kg of MgSO₄)

adenosine in New Developments (2.B.24)

quinidine

stereoisomer of quinine
pharmacokinetics

high bioavailability
80% protein bound (competes with digoxin)
hepatic metabolism and renal clearance
t₁/₂β 6 h
IV preparation also used for malaria
pharmacodynamics

α antagonist, antimuscarinic
may cause ↑ AV conduction
decomposition in AF or flutter due to ↑ ventricular rate
prolonged QT and APD predispose to torsade
nausea, vomiting, cinchonism, ↑ digoxin levels

procainamide

procaine with an amide instead of ester linkage
75% bioavailable
metabolized to N-acetyl procainamide (type III → torsade)
ganglion blocker
negative inotrope
long term SLE syndrome

disopyramide

50% bioavailable
t₁/₂β 6 h
potent antimuscarinic (full range of atropine effects)
negative inotrope

imipramine

class Ia activity (not used for this purpose)

amiodarone

iodine-containing tertiary amine
pharmacokinetics

high oral bioavailability
concentrated in cardiac tissue
large V_d → loading time 15-30 days
t₁/₂β weeks to months
pharmacodynamics
\( \alpha, \beta \) antagonist, \( \text{Ca}^{2+} \) channel blocker (type II and IV)
binds \( \text{Na}^+ \) channels in the inactive state (type I)
probably blocks \( \text{K}^- \) channels (type III)
effects
cardiac  
\( \uparrow \) APD, ERP, QT 
bradycardia, AV block
adverse  
corneal deposits (100%) 
pulmonary fibrosis (5-15%) 
skin discolouration (5%) 
photosensitivity (25%) 
neurological problems 
hyper- or hypo-thyroidism (5%) 
constipation (20%) 
hepatocellular necrosis
interactions  
\( \downarrow \) clearance of warfarin, theophylline, quinidine, procainamide...
clinical use  
effective in most arrhythmias including WPW (\( \downarrow \) accessory conduction)

phenytoin  
\( \text{Na}^+ \) and \( \text{Ca}^{2+} \) blocker 
\( \downarrow \) automaticity 
effective in digoxin toxicity

flecainide  
\( \text{Na}^+ \) channel blocker (type Ic) 
suppresses PVCs 
caused doubled mortality in CAST trial for asymptomatic PVCs

bretylium  
inhibits catecholamine release after initial release \( \rightarrow \) hypotension 
prolongs action potential 
previously used in resuscitation and for LA toxicity 
no longer available in Australia

sotalol  
L isomer non selective \( \beta \) blocker 
D & L isomers prolong action potential

d. Describe the pharmacological basis of the antidysrhythmic properties of lignocaine, including its pharmacokinetics.

lignocaine  
diethyl glycine xylidide 
class Ib antidysrhythmic
pharmacokinetics  
3% bioavailable orally (tocainide and mexiletine are oral congeners)  
pK\(_a\) 7.9 
70% bound to \( \alpha_1 \) acid glycoprotein 
\( t^{1/2} / \alpha \) 8 min 
\( V_d \) 1.3 l/kg 
hepatic metabolism (E = 68%)  
N deethylation, hydrolysis, 3\(^\prime\) and 4\(^\prime\) hydroxylation
clearance 15 ml/kg/min
t₁/₂β 90 min
renal excretion

pharmacodynamics
- binds S₆ α₄ domain of voltage-gated Na⁺ channel in open state
- rapid release from binding site in inactivated and resting states
- prevents Na⁺ flux
- reduces Vₘₐₓ, prolongs QRS
- binds open and inactivated Na⁺ channels
- rapid dissociation in resting state, so little effect on normal tissue
- Na⁺ channels in tissue with prolonged depolarization stay in inactive state
  → preferential binding in ischaemic or digoxin toxic tissue
- positive inotrope at low dose
- exacerbates arrhythmias in <10% (good)

clinical use
- local anaesthetic use in Local Anaesthetics (2.B.11)
- antidysrhythmic use
  - agent of choice in ventricular arrhythmias
  - loading dose: 1.5 mg/kg followed by 3x0.7 mg/kg at 10 minute intervals
  - infusion: 20-60 µg/kg/min
  - infusion rate depends on clearance (↓ in hepatic disease, CCF)

adverse effects
- level (µg/ml)
- effect
  - 2 anticonvulsant, antidysrhythmic
  - 4 positive inotrope, tinnitus, lightheadedness
  - 6 vision disturbance
  - 8 twitching
  - 10 convulsions
  - 15 coma
  - 20 respiratory arrest
  - 26 cardiac arrest

f. Describe the pharmacological basis of the use of digoxin as an antidysrhythmic and its toxic effects.

digoxin
- glycoside derived from Digitalis purpurea
- consists of lactone, steroid and sugars
- lactone and steroid are the active part (aglycone or genin)
- other similar agents: digitoxin and ouabain are not used in Australia

pharmacokinetics
- 75% bioavailable (less with certain gut flora)
- 30% protein bound
- Vₐ 6 l/kg, concentrated in heart, liver and kidney
- renal excretion unchanged
- t₁/₂β 40h

pharmacodynamics
- binds to and inhibits Na⁺/K⁺ ATPase pump
- different affinities in different tissues
- binding competes with K⁺ (↑ effect with hypokalaemia)
- less negative membrane potential
- reduced activity of Na⁺-dependent pumps (Na⁺/Ca²⁺ exchanger)

effects
- cardiac
  - ↑ intracellular Ca²⁺
\[ \downarrow \text{Na}^+ / \text{Ca}^{2+} \text{ exchange}, \uparrow \text{Ca}^{2+} \text{ entry via channels}, \uparrow \text{SR release} \]
\[ \uparrow \text{contractility, automaticity, no change in rate, } \uparrow \text{K}^+ \text{ conductance} \]
\[ \downarrow \text{AP duration} \]
\[ \text{at high Ca}^{2+} \text{ levels, delayed afterdepolarizations occur } \rightarrow \text{bigeminy} \]
\[ \uparrow \text{toxicity with hypercalcaemia, any arrhythmia} \]

- **neuro**
  - \( \uparrow \text{vagal tone at low dose: } \downarrow \text{HR} \)
  - CTZ stimulation
  - vision changes

- **GIT**
  - nausea, anorexia, vomiting, diarrhoea

- **other**
  - gynaecomastia

- **clinical use**
  - IV or oral administration

Antidysrhythmics 2.B.14.5 James Mitchell (November 5, 2001)
B. 15 Antiemetic drugs

Definitions

nausea
unpleasant sensation referred to the pharynx and upper abdomen associated with the desire to vomit.

vomiting
forceful expulsion of gastric contents via the mouth (and nose).

retching
activation of the muscles involved in vomiting without expulsion of stomach contents.

regurgitation
return of gastric contents into the mouth without effort.

Mechanism of vomiting

detectors

peripheral
visceral afferents in the vagus (vagus is 80-90% afferent fibres)
mechanoreceptors responding to stretch
chemoreceptors in enterochromaffin cells
serotonergic transmission (5HT₃)
project to CTZ and nucleus tractus solitarius (muscarinic and H₁)

central
chemoreceptor trigger zone (CTZ)
in the area postrema, caudal part of the floor of the fourth ventricle
outside the blood-brain barrier
D₂ and 5HT₃ transmission

vestibular system
in inner ear
detects movement and position of the head
cholinergic and H₁ transmission
integrated with visual and proprioceptive inputs in the cortex
project to CTZ

vision
can induce nausea alone if perception of motion does not match vestibular input
taste, smell
both directly and by association with memories
touch at the back of the pharynx
the gag reflex mediated by the glossopharyngeal nerve
cortex
memories, emotions and thought can induce or facilitate nausea
probable site of action of benzodiazepines

integration
medullary emetic centre (vomiting centre) in the brainstem
receives inputs from CTZ, cortex and nucleus tractus solitarius
predominantly muscarinic cholinergic and NK₁
operates a coordinated motor program acting on
dorsal motor vagal nucleus
nucleus ambiguus
dorsal and ventral respiratory groups
presympathetic neurones

effectors
sympathetic
cutaneous vasoconstriction, sweating, mydriasis, tachycardia
parasympathetic and enteric
  gastric relaxation, ↓ gastric secretion
  retrograde peristalsis from mid small bowel
  relaxation of oesophageal sphincters

somatic
  respiratory
diaphragm relaxed
  glottis closed, soft palate elevated

abdominal
  rectus contracts rhythmically
  flexed posture

**a. Describe the pharmacokinetics and pharmacodynamics of dopamine antagonists, anticholinergic agents and serotonin antagonists.**

**metoclopramide**
substituted benzamide:
methoxychloroprocainamide

**pharmacokinetics**
- 75% oral bioavailability
- crosses BBB
- hepatic conjugation to glucuronide and sulfate
- renal excretion 25% unchanged
- excreted in breast milk
- crosses placenta
- $t_{1/2}$ 3-5 h, more rapid redistribution

**pharmacodynamics**
- $D_2$ antagonist and $5HT_4$ agonist
- $5HT_3$ antagonist at high dose

**sites of action**
- central: CTZ
- gut: ↑ motility, LOS tone (centrally mediated)

**adverse actions**
- central $D_1$ effects: restlessness, drowsiness
- extrapyramidal effects: dystonia, akathisia
- ↑ prolactin, aldosterone secretion
- inhibits plasma cholinesterase

**clinical use**
- IV dose 0.15 mg/kg (up to 3 mg/kg in some centres)
- for prevention and treatment of PONV, chemotherapy nausea
- not effective for vestibular problems: vertigo, ENT surgery

**prochlorperazine (similar to other phenothiazines)**
- phenothiazine (7 times as potent as chlorpromazine)

**pharmacokinetics**
- high oral bioavailability
- lipid soluble
- crosses BBB

**pharmacodynamics**
- predominant $D_2$ antagonist
- also antagonist at $\alpha$-adrenergic, muscarinic, histamine and serotonin receptors

**adverse actions**
- as for all phenothiazines

**clinical use**
- oily solution for IM injection

---

*Antiemetics* 2.B.15.2 *James Mitchell (November 5, 2001)*
used IV (not approved)
effective in vertigo and ENT surgery

droperidol
  butyrophenone
  pharmacokinetics
    used IV
    90% protein bound
    crosses BBB
    $t_{1/2\beta}$ 2-3 h
  pharmacodynamics
    potent $D_2$ antagonist
    some $\alpha$-antagonist, histamine and serotonin antagonist activity
    most potent in apomorphine-induced emesis
  adverse actions
    hypotension, sedation, dysphoria
    extrapyramidal effects
    ↑ prolactin
  clinical use
    10-20 $\mu$g/kg IV in adults, 50-75 $\mu$g/kg in children (e.g. squint surgery)

ondansetron
  pharmacokinetics
    oral bioavailability $\approx$50%
    75% protein bound
    hepatic metabolism
    $t_{1/2\beta}$ 4 h
  pharmacodynamics
    specific 5HT$_3$ antagonist
    acts at gut chemoreceptors and CTZ
    potent antiemetic
  adverse actions (rare)
    headache, flushing
    hypotension, bradycardia
    involuntary movements
  clinical use
    4-8 mg IV or oral for adults
    best agent for PONV and chemotherapy nausea
    not good for opiate-induced nausea

other antiemetics in other sections
  antihistamines
  anticholinergics
  benzodiazepines
  steroids
  cannabinoids
  ephedrine
  NK$_1$ blockers in phase II trials may be better than 5HT$_3$ antagonists

b. Critically appraise the clinical useage of these drugs.

decision to use preventively depends on patient’s risk
  increased by
    school-age children, female sex, anxiety, pregnancy
    history of PONV or motion sickness
    full stomach, raised ICP
specific surgery (squints, gynae, ENT...)

choice of drug depends on likely cause
   eliminate drugs from previous anaesthetics likely to have caused PONV
   consider TIVA
spinal/epidural-induced nausea is often low CO, esp. in Caesars
   treat with posture, fluid, ephedrine
ENT surgery: prochlorperazine, droperidol affect both dopamine and serotonin
opiate induced: droperidol probably best
other: high dose metoclopramide may be as effective as ondansetron
in susceptible patients, hypnosis or acupuncture are safest
B. 16 Histamine and serotonin

da. Describe the roles of histamine and serotonin receptor subtypes.

**Histamine production**
- Histidine is decarboxylated by histidine decarboxylase in nerve cells, mast cells and basophils
- Stored in granules with acidic protein, heparin and chemotactic factors
- Metabolized by histamine N-methyl transferase
- MAO
- Release from mast cells in response to IgE crosslinking (via phospholipase C)
- Activated complement binding
- Direct drug actions: morphine, atracurium, others

**Receptors**
- **H<sub>1</sub>**
  - Act via phospholipase C
  - Bronchoconstriction, colic
  - Vascular triple response (vasodilation via NO, ↑ permeability, leukocyte activation)
  - Central neurotransmitter
  - Hypothalamus, thalamus, cerebellum and cortex
  - Temperature regulation, ADH, BP control, pain transmission

- **H<sub>2</sub>**
  - Act via adenylyl cyclase, lower affinity than H<sub>1</sub>
  - Parietal cells of the stomach ↑ acid secretion
  - Vasodilation, bronchodilation
  - Minor cardiac effects (↑ rate at SA node)

- **H<sub>3</sub>**
  - G protein-linked
  - Central & peripheral presynaptic inhibition at histamine synapses

**Serotonin production**
- From L-tryptophan
- 5-hydroxylated, decarboxylated in platelets, gut
- CNS: retina, pineal, midline raphe of pons and upper medulla, elsewhere

**Receptors**
- **5HT<sub>1A</sub>**
  - Via ↓ adenylyl cyclase
  - Central inhibitory transmission
  - Behavioural and homeostatic actions

- **5HT<sub>1B</sub>**
  - Via ↓ adenylyl cyclase
  - Central presynaptic inhibition

- **5HT<sub>1Da, Db, E and F</sub>**
  - Via ↓ adenylyl cyclase
  - Present on cerebral blood vessels
  - Cerebral vasoconstriction
5HT$_{2A}$ via ↑ phospholipase C
platelet aggregation
bronchoconstriction
gut contraction
systemic vasoconstriction or dilation
central behavioural effects

5HT$_{2B}$ via ↑ phospholipase C
contraction of gastric fundus

5HT$_{2C}$ via ↑ phospholipase C
increased CSF secretion at choroid plexus

5HT$_3$
gated ion channel
CTZ transmission
central excitation
behavioural effects
peripheral autonomic activation, nociception

5HT$_4$
via ↑ adenylyl cyclase
↑ gut motility
central excitation

5HT$_{5a, 5b, 6 \text{ and } 7}$
via ↑ adenylyl cyclase
in brain
5HT$_7$ is inhibited by clozapine

b. Describe the pharmacodynamics, pharmacokinetics and side effects of H$_2$ antagonists, serotonin agonists and antagonists and outline their applications.

H$_1$ antagonists (“antihistamines”)

many agents of different chemical classes
available in OTC preparations
most have antimuscarinic, α blocking, antiserotonergic and local anaesthetic activity
well absorbed orally, IM and IV
adverse actions
sedation or disinhibition (less with piperidines and loratidine)
clinical use
allergic rhinitis
not effective in drug reactions as reaction is sustained by other mediators
motion sickness
nausea in pregnancy (category A: chlorpheniramine)

H$_2$ antagonists

ranitidine
pharmacokinetics
30-90% bioavailable
$V_d$ 1.5 l/kg
$\tau^{1/\beta}$ 2 h
renal elimination
pharmacodynamics
competitive antagonist at H$_2$ receptors
suppresses gastric acid secretion
high dose: ↓ cardiac output, confusion
adverse effects
(cimetidine inhibits p450 enzymes, competes at androgen receptors)
ranitidine reduces gastric alcohol dehydrogenase activity
↑ alcohol bioavailability by 40%

ergotamine
alkaloid produced by Claviceps purpurea fungus in grain
pharmacodynamics
partial agonist at α and 5HT receptors peripherally and in CNS
slow dissociation
hallucinations
prolonged vasospasm, including cerebral and coronary vessels
prolonged uterine contraction
nausea, vomiting, diarrhoea
clinical use (largely replaced by similar alkaloids)
migraine (replaced by sumatriptan, dihydroergotamine)
hyperprolactinaemia (bromocriptine)
PPH (ergometrine)

sumatriptan
specific 5HT1D agonist
orally active (low bioavailability), also sc
t½ β <2 h
causes selective vasoconstriction
relieves migraine, cluster headache
may cause coronary vasospasm
injection site reaction
dose 50-100 mg o, 6 mg sc

ondansetron
specific 5HT3 antagonist
50% oral bioavailability
acts at CTZ and in gut
dose 0.1-0.2 mg/kg
potent antiemetic
may cause hypotension, headache, flushing, abnormal movement, constipation
B. 17 Diuretics

a. Outline the physiological basis of classifying diuretics, related to their site of action.

Site of action
- PCT
  - osmotic and carbonic anhydrase inhibitors (predominantly)
- loop diuretics
- cortical part of loop, DCT
- thiazides
- collecting ducts
  - potassium-sparing diuretics
  - ADH antagonists (demeclocycline, Li⁺, alcohol)

b. Describe the actions of mannitol, frusemide, thiazides, aldosterone antagonists and carbonic anhydrase inhibitors.

c. Outline the side effects of the diuretics.

d. Describe the major applications and toxicities of the thiazides, loop diuretics and potassium-sparing diuretics.

mannitol
- a sugar alcohol
- osmotically active but not metabolized

pharmacokinetics
- not absorbed orally → diarrhoea
- administered IV
- distributed throughout ECF
- not metabolized
- renal excretion by filtration

pharmacodynamics
- expands plasma volume
  - ↑ RBF, GFR
- filtered at glomerulus
- exerts osmotic pressure to prevent PCT reabsorption of Na⁺ and water
- high flow in loop “washes out” countercurrent multiplier
- produces dilute urine

adverse actions
- water loss in excess of Na⁺ loss → hypernatremia
- excess K⁺ loss, particularly if aldosterone is high

clinical use
- rapid diuresis for reduction of intracranial or intraocular pressure

frusemide
- loop diuretic
- sulfonamide derivative

pharmacokinetics
- high oral bioavailability
- 96% protein bound
- Vd 0.1 l/kg (circulation)
- t½ 1 h
- urinary filtration and secretion
- acts from tubular lumen
pharmacodynamics
- inhibits Na\(^+\), K\(^+\), 2Cl\(^-\) transporter in ascending loop
- ↓ medullary gradient
- ↓ lumen-positive potential
  - Ca\(^{2+}\), Mg\(^{2+}\), K\(^+\) loss
  - vasodilation of renal vessels and systemic veins (?mechanism)

adverse actions
cation loss
dehydration → renal failure, gout
↑ aldosterone and DCT flow → K\(^+\) and H\(^+\) loss
- hypokalaemic metabolic alkalosis
- ototoxicity
- sulfonamide allergy

clinical use
- acute pulmonary oedema (venodilation)
- hypercalcaemia
- overdose of anions: Br\(^-\), F\(^-\) and I\(^-\)

thiazides
- sulfonamide derivatives
- some have carbonic anhydrase inhibiting activity

pharmacokinetics (chlorothiazide)
- high oral bioavailability
- 95% protein bound
- \(V_d\) 0.2 l/kg
- \(t^{1/2}\), β 1.5 h
- renal excretion by organic acid mechanism

pharmacodynamics
- inhibit DCT NaCl uptake
- ↑ Ca\(^{2+}\) uptake

adverse actions
- hypokalaemic metabolic alkalosis
- hyponatraemia
- ↓ glucose tolerance, lipids
- sulfonamide allergy

clinical use
- cardiac failure
- hypercalciuria

spironolactone
- synthetic steroid

pharmacokinetics
- hepatic metabolism

pharmacodynamics
- competitive inhibitor at aldosterone receptor
- ↓ Na\(^-\) reabsorption, ↑ K\(^+\), H\(^+\) reabsorption

adverse actions
- steroid effects: gynaecomastia, prostate enlargement
- hyperkalaemia, acidosis (esp. with NSAIDs, ACE inhibitors)

amiloride

pharmacokinetics
- urinary excretion unchanged

pharmacodynamics
- inhibits Na\(^+\) transport in luminal membrane
- acts in lumen

Diuretics  2.B.17.2  James Mitchell (November 5, 2001)
adverse effects
hyperkalaemia, acidosis

acetazolamide
sulfonamide, carbonic anhydrase inhibitor

pharmacokinetics
well absorbed orally
not metabolized
weak acid actively secreted in PCT
eliminated within 12 h

pharmacodynamics
prevents secretion of H\(^+\) in PCT to reabsorb HCO\(_3\)-
results in alkaline diuresis
inhibition of carbonic anhydrase in ciliary body and choroid plexus causes reduced volume and more acidic aqueous humor and CSF

adverse effects
HCO\(_3\)- depletion and acidosis result in reduced diuretic effect
increased urinary phosphate and Ca\(^{2+}\) can cause calculi
K\(^+\) depletion due to increased luminal electronegativity
reduced urinary NH\(_4\)\(^+\) excretion in alkaline urine (reabsorbed as NH\(_3\))
exacerbates hepatic encephalopathy
↓ renal clearance can result in toxic levels in renal impairment
cross-sensitivity with other sulfonamides

clinical use
glaucoma (not for diuretic effect)
acute mountain sickness (alkalosis, ↑ ICP)
alkalinizing urine in drug overdose (e.g. salicylate)
B. 18 Drugs used in coagulation disorders

a. Classify the anticoagulants.

oral agents inhibiting vitamin K metabolism
warfarin

parenteral anticoagulants
heparin, low-molecular-weight fractions, hirudin

platelet inhibitors
aspirin, NSAIDs, dipyridamole, ticlopidine, abciximab

thrombolytics
tPA, streptokinase, urokinase

fibrinogen-depleting agents
ancrod

in vitro agents
citrate, EDTA

pro-coagulants
↑ clotting factor synthesis
vitamin K

platelet activators
DDAVP

plasminogen activation inhibitors
EACA, tranexamic acid

plasmin inhibitors
aprotinin (EACA, tranexamic acid)

b. Describe the pharmacodynamic and pharmacokinetics of heparin and low-molecular-weight heparins including their side effects.

heparin
parenteral anticoagulant
used IV and SC
derived from porcine & bovine gut and other tissues
anionic mucopolysaccharides synthesized in mast cells
MW 5000-30000
up to 50 saccharides
quantitated by anticoagulant activity
bioassay of anticoagulant effect on animal blood
1 ml sheep blood with 0.2 ml 1% CaCl₂ anticoagulated for 1 hour

pharmacokinetics
not absorbed orally
t₁/₂ of effect 0.5-3 h saturable kinetics
taken up by reticuloendothelial cells (high affinity, low capacity)
absorbed by epithelium
hepatic metabolism by heparinase
some renal clearance
administered by IV infusion (rate according to APTT) following loading dose
active subcutaneously at low dose (5000 U bd - 7500 U tds) for DVT prophylaxis
late rise in heparin levels observed after reversal with protamine

pharmacodynamics
binds to antithrombin III, greatly increasing its affinity for thrombin
thrombin activity rises rapidly from 8-13 saccharides
increases anti factor Xa activity of antithrombin III
only 5 saccharides required for Xa activity
some antiplatelet activity
adverse actions
bleeding
hypersensitivity
thrombocytopenia
dose-related in prolonged use
immune-mediated HITS
osteoporosis
alopecia

Low molecular weight heparins (dalteparin “Fragmin”, enoxaparin “Clexane”, nadroparin “Fraxiparine”, danaparoid “Orgaran”)

low molecular weight fractions of heparin produced by depolymerization
MW 2000-9000
polysaccharide with 13-22 sugars
quantitated by anti factor Xa activity
used in prophylaxis and heparin sensitivity

pharmacokinetics
90% available by subcutaneous injection
t1/2 2 h IV (3-4 h sc)

pharmacodynamics
binds antithrombin
promotes inactivation of factors IXa, Xa, XIa and kallikrein
little effect on thrombin
little platelet binding
anti factor Xa activity is not reversed by protamine

adverse actions
bleeding
hypersensitivity
osteoporosis
thrombocytopenia

hirudin
leech anticoagulant prepared by rDNA techniques
direct antithrombin activity

c. Describe the mode of action and side effects of protamine

protamine
basic protein (cationic)
derived from salmon testes

pharmacokinetics
administered slowly IV
binds heparin immediately in circulation

pharmacodynamics
binds heparin in circulation to form inactive complexes (1.3 mg protamine to 100 U heparin)
complexes are cleared by the reticuloendothelial system

adverse actions
hypotension
systemic vasodilation from rapid administration, especially via CVC
due to histamine release from cationic drug
minimized by slow injection (5 mg/min) into peripheral line
type I hypersensitivity
more common in patients with fish allergy and diabetics using protamine-containing insulin
theoretical risk in vasectomized men
anaphylactoid reactions
complement activation by heparin-protamine complexes in lungs
possible role of IgG
protamine inhibits plasma carboxypeptidase
responsible for inactivating many cytokines
increased risk if ACE is also inhibited
transient pulmonary vasoconstriction due to TXA\textsubscript{2} release
anticoagulant activity in large overdose
? mechanism

d. Describe the chemistry, mechanism of action and toxicity of the coumarin anticoagulants.

\[
\begin{align*}
\text{ONa} & \quad \text{CHCOCH} \\
\text{Warfarin} & \quad \text{O} \\
\text{Vitamin K} & \quad \text{CH}_3 \\
\end{align*}
\]

warfarin
- discovered accidentally in spoiled sweet clover silage
- oral anticoagulant of choice
- racemic mixture (L-warfarin is four times as potent as D-warfarin)

pharmacokinetics
- 100% bioavailable
- 99% protein bound
- \(V_d\) small
- \(t^{1/2}\beta\) 36 h
- hepatic metabolism

pharmacodynamics
- a competitive inhibitor of the reduction of vitamin K from epoxide to hydroquinone form
  - vitamin K hydroquinone is required for \(\gamma\)-carboxylation in the synthesis of factors II, VII, IX and X (and protein C)
  - factors II, VII, IX and X have half-lives of 60, 6, 24 and 40 h, resulting in a clinical effect from about 30 h and full effect from about 72 h
  - antagonism with vitamin K (dietary and intentionally administered)
  - can also be reversed with FFP

interactions
- pharmacokinetic
  - enzyme induction or inhibition
  - protein binding
- pharmacodynamic
  - other inhibitors of clot formation, especially NSAIDs which interact via displacement from protein binding, impaired metabolism and synergistic anti-platelet activity (phenylbutazone)
  - some patients (and rats) have a hereditary abnormality of vitamin K metabolism and are resistant to warfarin

adverse actions
- bleeding
- teratogenicity
  - warfarin crosses the placenta readily
  - \(\gamma\)-carboxylation is required in the normal synthesis of bone and other tissues in
protein C deficiency can result in hypercoagulability in some patients, with skin necrosis and multiple infarcts alopecia

The other oral anticoagulants include dicoumarol and phenindione. They have less predictable absorption and phenindione causes hepatic and renal impairment in some patients.

e. Describe the fibrinolytic pathway and mechanisms of action of thrombolytic agents.

Plasminogen is a plasma protein which is trapped in the formation of a clot. Tissue plasminogen activator (tPA) is slowly released from injured endothelium and tissues and activates plasminogen to form plasmin. Plasmin is a protease which degrades fibrin, factors V, VIII and XII, thrombin and fibrinogen, causing lysis of the clot. This typically occurs over hours to days following clot formation.

The action of plasmin is limited by circulating alpha2-antiplasmin which prevents any low levels of circulating plasmin from lysing clots.

Fibrinolytic agents include streptokinase and anisoylated plasminogen-streptokinase activator complex (derived from bacteria), urokinase (derived from the kidney) and recombinant tPA and SCU-PA. All act by binding to proactivator plasminogen which then catalyzes the formation of plasmin from plasminogen.

Streptokinase and urokinase bind to circulating as well as bound plasminogen and so result not only in clot lysis but depletion of circulating fibrinogen. APSAC binds to fibrin and is deacylated to yield active streptokinase. r-tPA and r-SCU-PA preferentially activate bound plasmin, theoretically producing more selective fibrinolysis, but in practice there is little difference between their fibrinolytic effects.

Streptokinase and APSAC differ from the human-derived agents in that they are more antigenic. An immune response typically begins within 5 days of administration and hypersensitivity reactions can result from sensitization by streptococcal infection.

Benefit from thrombolytic therapy is proven in early treatment of suitable patients with AMI. There is no proven advantage in using any one agent. Treatment for cerebral infarcts, pulmonary embolism and DVT is indicated under specific circumstances. Use in clearing clot from long-term CVCs is safe and effective.

f. Describe the action of antifibrinolytic agents such as ε-aminocaproic acid (EACA).

EACA and tranexamic acid are competitive inhibitors of plasminogen activation and have minor anti-plasmin activity. EACA is H₄N(CH₆)₅COOH.

pharmacokinetics
- high oral bioavailability
- rapid renal clearance unchanged
- Vd ~0.5 l/kg
- t₁/₂ β ~2 h

EACA dosage: 5 g over 30 minutes, 1 g/h for therapeutic plasma levels (130 mg/l)
- post-TURP: 0.25 g/h as EACA is concentrated in urine

pharmacodynamics
- binds plasminogen activator and plasmin

clinical application
- useful in the treatment of bleeding postoperatively due to primary fibrinolysis
- bleeding in DIC (secondary fibrinolysis) is greatly exacerbated by EACA
g. Describe the action and pharmacological role of anti-platelet drugs

aspirin and other NSAIDs discussed previously (2.B.4)

dipyridamole
  phosphodiesterase inhibitor
  increases platelet cAMP
  impairs adhesion and activation
  increases myocardial oxygen requirement
ticlopidine
  inhibits ADP-mediated platelet activation
  proven benefit over placebo in TIAs, unstable angina
  not demonstrated to be better than aspirin
  adverse effects
    20% nausea, diarrhoea
    5% bleeding
    1% leukopenia

abciximab
  preparation for intravascular use in PTCA
  Fab fragment directed against platelet receptors
  inhibits platelet aggregation by binding IIIa receptors

h. Describe the actions of aprotinin

  Plasma prekallikrein is activated by trypsin, factor XIIa and kallikrein itself to form
  kallikrein which activates high-molecular-weight kininogen to form bradykinin. This
  promotes activation of the intrinsic pathway and mediates a vasodilator and chemotactic
  response. Kinins act via B₁ and B₂ receptors (B for bradykinin). There are multiple B₂
  subtypes, which are G-protein linked. Bradykinin promotes tissue release of t-PA.
  Kallikrein also converts prorenin to renin, C₁ to C₁ and plasminogen to plasmin.
  Aprotinin inhibits kallikrein, reducing production of bradykinin and plasmin. It also
  inhibits plasmin’s fibrinolytic activity and reduces the inactivation of PAI by protein C.

additional

Classify and describe transfusion reactions.

haemolytic
  acute
    ABO incompatibility causes immediate intravascular haemolysis
    0.004% incidence
    recipient IgM binds to donor RBC antigens
    complement activation, CMI activation, chemotactic factors
    life-threatening: 25% mortality
      shock
      DIC
      renal failure
    usually due to clerical error
    volume dependent
    management
      cease transfusion, return to blood bank with recipient sample
      support circulation
      maintain renal function
      detect and treat DIC
      maintain ventilation
delayed

minor recipient Ab to donor antigens causes extravascular haemolysis
e.g. Rhesus
0.06%
IgG coating of RBC, haemolysis in reticuloendothelial system
gradual onset
    fever, malaise
    jaundice, haemoglobinuria
    fall in haematocrit

not haemolytic

acute

anaphylaxis
    IgA-deficient recipient Ab to donor IgA
    0.005%
    tiny volume required
    type I hypersensitivity

pulmonary oedema
    donor Ab to recipient lymphocytes
    complement activation
    rare

urticaria
    recipient Ab to donor plasma proteins or other constituents (e.g. food, drugs)
    2-3%
    type I or III hypersensitivity

fever
    recipient Ab to donor granulocytes
    1% with packed cells, 20% with platelets
    complement and recipient leukocyte activation
    treated with pethidine, steroids

delayed

purpura
    recipient antiplatelet Ab
    rare

GVH disease
    engraftment of donor lymphocytes in immunosuppressed recipient
    life threatening
B. 19 Obstetric pharmacology

a. Explain the physiological consequences of pregnancy and its pharmacological implications.

In Maternal Physiology (1.O)

b. Describe the mechanism of action and side effects of oxytocics, tocolytic agents, magnesium trisilicate and prostaglandins used in obstetrics.

α agonists
- ↑ uterine tone and contractions
- vasoconstriction

β₂ agonists
- ↓ uterine tone and contractions
- salbutamol used in large doses
  - accompanying tachycardia, excitation

ergometrine
- tonic contraction of uterus
- onset within 40 s, lasts hours
- adverse effects
  - vasoconstriction → hypertension, coronary spasm
  - emesis
- dose 0.25 mg

oxytocin
- low dose produces normal contractions, milk let-down
- high dose produces tonic contraction
- direct systemic vasodilator, pulmonary vasoconstrictor
- reflex tachycardia
- ADH-like effect on collecting ducts
- half-life of minutes

PGF₂α
- cervical relaxation, uterine contraction
- direct myometrial injection for atonic uterus in PPH
- bronchoconstrictor, vasoconstrictor in most beds
- prokinetic: nausea, vomiting, diarrhoea

PGE₂
- uterine contraction, abortion
- bronchodilation, vasodilation
- prokinetic: diarrhoea
- ↓ gastric acid secretion

magnesium salts
- trisilicate, hydroxide, other salts
  - used in antacids
- sulfate

pharmacokinetics
- normal plasma level 0.8-1.1 mmol/l
- anticonvulsant level 2-3 mmol/l
- paralysis at 7.5 mmol/l
- 99% intracellular, 25% protein bound
- eliminated by glomerular filtration and controlled reabsorption

pharmacodynamics
- reduces ACh release, desensitizes post junctional membranes

adverse effects
potentiates relaxants
↓ muscle tone in newborn

clinical use
preeclampsia: bolus 4 g followed by 1-2 g/h, monitoring levels
arrhythmia: 0.15 mmol/kg + 0.1 mmol/kg/h

c. Outline the effects on the fetus of those drugs crossing the placenta.

e. Explain the factors which influence the transfer of drugs across the placenta to the fetus.

placental transfer
Fick’s law of diffusion:

\[ J = \frac{k \Delta C A \text{Sol}}{T \sqrt{\text{MW}}} \]

where \( k \) is a constant, \( \Delta C \) is concentration gradient, \( A \) is area of interface, \( \text{Sol} \) is solubility, \( T \) is temperature and \( \text{MW} \) is molecular weight

concentration gradient
maternal and fetal plasma levels
speed of metabolism in mother and fetus
shunt past fetal liver, recirculation (e.g. alcohol)
degree of protein binding
solubility
lipid solubility
molecule size, reflection coefficient

e.g.,
examples
narcotics
rapid transfer of lipid soluble agents (pethidine etc.)
long \( t_{1/2} \) in neonate → bradycardia from pethidine
thiopentone
rapid transfer and redistribution
little effect by the time of delivery at Caesarean
propofol
demonstrated reduction in Apgar and neurobehavioural tests at >2.8 mg/kg
ketamine
increased uterine contractions, fetal depression and increased muscle tone
volatile agents
rapid transfer, higher MAC in fetus
uterine relaxation at >1.5 MAC
local anaesthetics
transfer dependent on protein binding
free fraction similar in mother and fetus (↑ protein binding → ↓ f:m ratio)
relaxants
highly polar so little transfer
f:m ratios: atracurium 0.07, vecuronium 0.11, rocuronium 0.16
B. 20 Endocrine pharmacology

a. Describe the pharmacology of insulin preparations and their use.

insulin pharmaeutics
51 amino-acid polypeptide composed of two chains linked by disulfide bonds
synthesized by β cells of the pancreas as proinsulin
proinsulin is cleaved into insulin and C-protein before secretion
endogenous production 1 unit/h plus 10-20 units/day after food
synthetic preparations were formerly bovine or porcine, now recombinant
standard solution 100 U/ml only
controlled release preparations by complexing with zinc or protamine
pharmacokinetics
zero oral bioavailability
administered by subcutaneous injection for fast or slow-release preparations
non-complexed preparations also administered IV by infusion
onset peak duration
soluble (sc) 15 min 3 h 6 h
semilente 1 h 5 h 15 h
lente 2 h 10 h 20 h
ultralente 4 h 18 h 30 h
metabolized by hydrolysis of the disulfide bonds in the liver and kidney
\[ t^{1/2} \beta \approx 3-5 \text{ min} \]
pharmacodynamics
binds specific cell-surface receptors
2α and 2β subunits, binds to α unit, β unit is a tyrosine kinase
causes a cascade of protein phosphorylations
activates GLUT 4 glucose uptake transporter in muscle and fat
↑ synthesis of fat, proteins, glycogen (↓ breakdown)
↑ K⁺ uptake
↓ ketone production
↑ growth
adverse effects
hypoglycaemia
hypersensitivity to components of insulin
worst with animal-derived
allergy to protamine
lipodystrophy at the site of injection
clinical use
for type I diabetes as replacement therapy
commonly basal long-acting plus short-acting boluses before meals
perioperatively stabilized with infusion IV plus glucose and K⁺
type II diabetes with resistance to oral therapy
much higher doses
generally normal glucose while fasting perioperatively without therapy

b. Describe the pharmacodynamics and pharmacokinetics of the oral hypoglycaemic agents with their clinical implications and side effects.

biguanides
metformin is the only agent available
pharmacokinetics
high oral bioavailability
high protein binding
renal excretion unchanged
t₁/₂β 1-2 h, effect 5-6 h

pharmacodynamics
uncertain mechanism of action
reduce fasting and post-prandial blood glucose
do not produce hypoglycaemia

adverse effects
increased lactic acidosis
nausea

sulfonylureas
pharmacokinetics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Potency</th>
<th>t₁/₂β</th>
<th>Metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>tolbutamide</td>
<td>1</td>
<td>4-10</td>
<td>hepatic</td>
</tr>
<tr>
<td>chlorpropamide</td>
<td>6</td>
<td>24-42</td>
<td>renal&gt;hepatic</td>
</tr>
<tr>
<td>glibenclamide</td>
<td>150</td>
<td>10-16</td>
<td>hepatic</td>
</tr>
<tr>
<td>glipizide</td>
<td>100</td>
<td>3-7</td>
<td>hepatic</td>
</tr>
</tbody>
</table>

pharmacodynamics
bind receptors on β cells ↓ K⁺ conductance, ↑ insulin release
this effect is opposed by thiazide diuretics (↓ glucose tolerance)
↓ glucagon secretion (mechanism uncertain)
? increase tissue sensitivity to insulin

adverse effects
hypoglycaemia
sulfonamide allergy (rash, type I)
flushing with alcohol use
chlorpropamide: ↑ ADH release and effect

c. Describe the mode of action and adverse effects of thyroid hormones and antithyroid drugs.

thyroxine

\[
\text{T}_4, \text{thyroxine, 3,5,3',5'-tetraiodothyronine}
\]

pharmacokinetics
oral bioavailability T₄ 80%, T₃ 95%
synthesized in the colloid of the thyroid follicles
I⁻ uptake and oxidation to I⁺
reaction with tyrosine residues of thyroglobulin to form MIT and DIT
condensation of MIT and DIT to form T₂ and T₃ (bound to thyroglobulin)
hydrolysis of thyroglobulin to liberate MIT, DIT, T₂ and T₃
release of T₂ (17%) and T₃ (83%), deiodination of MIT and DIT
activation of T₂ to T₃ in the periphery (t₁/₂)
inactivation of T₃ by conversion to rT₃, 3,3',5'-triiodothyronine (t₁/₂)
rapid clearance of free T₂ and rT₃
highly protein-bound to TBG, TBPA and albumin (T₄ 0.04% free, T₃ 0.4% free)
↑ binding in pregnancy
autoregulated by negative feedback of free concentration on TSH, TRH

pharmacodynamics
binds to intracellular receptors (similar to steroid, vitamin A and D receptors)
↑ RNA polymerase
↑ mitochondrial activity
  ↑ metabolic rate
  ↑ catecholamine responsiveness

clinical use
  replacement therapy
  25-100 µg/day thyroxine orally

antithyroid agents

I° uptake inhibitors
  many anions
    SCN⁻, BF₄⁻, NO₃⁻, ClO₄⁻…
  relevant only as toxic metabolites (e.g. nitroprusside), not used clinically

thioamides
  propylthiouracil, carbimazole
  contain -N-C=S moiety
  high oral bioavailability
  short plasma t½
  concentrated in thyroid, prolonging effect
  inhibit I organification, tyrosine coupling and peripheral deiodination
  can cause autoimmune syndromes and agranulocytosis
  cross the placenta

iodides
  high dose I° cause inhibition of T₄ release and deiodination
  marked rebound on withdrawal

I¹³¹
  β-ray emitter (t½, 5 days)
  ablates hyperactive thyroid

physiological antagonists
  non-selective β-blockers reduce symptoms of hyperthyroidism (e.g. propranolol)

d. Describe the glucocorticoid and mineralocorticoid activities of steroid drugs and their adverse effects.

glucocorticoids
  analogues of cortisol (hydrocortisone)

hydrocortisone
pharmacokinetics
  synthesized in the adrenal cortex from cholesterol in response to ACTH
  diurnal variation in levels
  circulates 75% bound to CBG (an α₂-globulin)
  synthetic glucocorticoids are albumin-bound
  metabolism to cortisone in kidney (20%) which has 80% potency
  inactivation in liver to multiple metabolites
  t½β 60-90 min
pharmacodynamics
  binds intracellular receptor
  promotes or inhibits gene expression
  some effects are too fast to be gene-mediated
  metabolic
    ↑ gluconeogenesis, glycogen synthesis
    ↑ muscle catabolism, bone reabsorption
    ↑ insulin synthesis, lipogenesis
  immune
    inhibit cyclooxygenase II, phospholipase A₂, IL-1 & 2 synthesis
↑ circulating neutrophils, ↓ other leukocytes
↑ susceptibility to infection

CNS
↑ ICP (minor)
↓ ACTH, TSH, FSH
psychosis, cataracts

GIT
↑ acid, pepsin secretion
↑ fat absorption
↓ Ca\(^{2+}\) absorption (oppose vitamin D)

fetus
speed maturation and surfactant production
connective tissue
acne, fine hair, striae, bruising
aseptic necrosis of the femoral head

aldosterone
mineralocorticoid synthesized in the *zona glomerulosa* of the adrenal cortex
similar to cortisol
details in *Renal Physiology (1.D)*
exogenous analogue: fludrocortisone

<table>
<thead>
<tr>
<th>antiinflammatory</th>
<th>mineralocorticoid</th>
</tr>
</thead>
<tbody>
<tr>
<td>hydrocortisone</td>
<td>1</td>
</tr>
<tr>
<td>cortisone</td>
<td>0.8</td>
</tr>
<tr>
<td>prednisolone</td>
<td>4</td>
</tr>
<tr>
<td>methylprednisolone</td>
<td>5</td>
</tr>
<tr>
<td>dexamethasone</td>
<td>30</td>
</tr>
<tr>
<td>fludrocortisone</td>
<td>10</td>
</tr>
</tbody>
</table>

e. Describe the pharmacology of glucagon.

**glucagon**
29 amino-acid protein

**pharmaceutics**
recombinant preparation
1 mg (100 U) glass ampoule with water for reconstitution

**pharmacokinetics**
synthesized by the α cells of the pancreas
rapid hydrolysis in plasma and in the liver and kidney
\( t^{1/2} \approx 3-6 \text{ min} \)
similar proteins synthesized by the gut including GLP which stimulates insulin release

**pharmacodynamics**
N-terminal binds specific cell-surface receptors
↑ cAMP
initiates cascade of protein dephosphorylation
↑ glycogenolysis, ketogenesis, gluconeogenesis
↑ insulin, catecholamine, calcitonin release
positive inotrope
↓ gut motility

**adverse effects**
nausea, vomiting

**clinical use**
acute treatment of hypoglycaemia
effect limited by hepatic glycogen stores
relaxation of gut sphincters (e.g. ERCP)

f. Describe the pharmacology of vasopressin and its analogues.

**ADH**

nonapeptide hormone synthesized in supraoptic and paraventricular nuclei
released from posterior pituitary neurones in response to
hypotension (7-10% volume change → low pressure baroreceptors)
↑ osmolarity (change of 1-2%)
overcome by volume effect
angiotensin II
sympathetic activity, stress
drugs (chlorpropamide, barbiturates, carbamazepine, clofibrate)

**pharmacokinetics**
exogenous analogue DDVAP (1-desamino-8-D-arginine vasopressin)
selective V₂ agonist used for bleeding and anti-diuretic effect
administered nasally, sc, IM and IV
$t_1/2$ 20 min renal and hepatic hydrolysis of peptide and disulfide bonds

**pharmacodynamics**

$V_1$

vasoconstrictor acting on smooth muscle

$V_2$

↓ collecting duct permeability to water (via ↑ cAMP)
results in insertion of aquaporin 2 in membrane
↑ release of VIII, and vWF ($V_2$-like receptors on endothelium)
B. 21 Gastrointestinal pharmacology

a. Describe the mode of action and comparative pharmacology of sodium citrate and magnesium trisilicate.

sodium citrate
- non-particulate antacid
- presented as 30 ml of 0.3 mol/l solution
- raises gastric pH above 3 for 2-3 hours
- given prophylactically to reduce the incidence of pneumonitis if aspiration occurs
- effectiveness depends on gastric volume, pH and motility
- most effective with low volume, poor motility
- 100% bioavailable
- citrate is metabolized by the TCAC
- represents a small alkaline load (equivalent to 27 mmol HCO₃⁻)
magnesium trisilicate
- particulate, relatively insoluble antacid
- similar to magnesium carbonate, aluminium hydroxide, others
- present in many proprietary preparations
- raises gastric pH similar to citrate
- not bioavailable, minimal absorption

b. Describe the mode of action and side effects of omeprazole.

omeprazole (and lansoprazole, pantoprazole…)
- a substituted benzimidazole
pharmacokinetics
- prodrug activated by low pH in parietal cell canaliculi
- high oral bioavailability
- plasma t½ 1-2h
- duration of effect 1-2days due to local concentration
pharmacodynamics
- direct inhibitor of H⁺, K⁺ ATP-ase in parietal cells
adverse effects
- complete suppression of acid secretion
- altered bacterial flora
- loss of barrier to infection posed by acid environment
- upregulation of gastrin secretion ( Risk of carcinoid gastrinoma)
clinical use
- 60 mg oral daily

c. Describe the mode of action and side effects of the H₂ antagonists.

ranitidine (cimetidine, famotidine, nizatidine…)
pharmacokinetics
- 30-90% bioavailable
- Vd 1.5 l/kg
- t½β 2 h
- renal elimination
pharmacodynamics
- competitive antagonist at H₂ receptors
- suppresses gastric acid secretion
- high dose: ↓ cardiac output, confusion
adverse effects
- (cimetidine inhibits p450 enzymes, competes at androgen receptors)
- ranitidine reduces gastric alcohol dehydrogenase activity
↑ alcohol bioavailability by 40%
## B. 22 Intravenous fluids

### a. Describe the composition, pH and osmolality of crystalloids and colloids used in clinical practice.

<table>
<thead>
<tr>
<th>Fluid</th>
<th>Na⁺ (mmol/l)</th>
<th>Cl⁻ (mmol/l)</th>
<th>Ca²⁺ (mmol/l)</th>
<th>Lactate (mmol/l)</th>
<th>pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.9% NaCl</td>
<td>150</td>
<td>150</td>
<td></td>
<td></td>
<td>4-7</td>
</tr>
<tr>
<td>Hartmann’s solution</td>
<td>129</td>
<td>109</td>
<td>2</td>
<td>29</td>
<td>5-7</td>
</tr>
<tr>
<td>5% dextrose</td>
<td>278</td>
<td></td>
<td></td>
<td></td>
<td>3.5-6.5</td>
</tr>
<tr>
<td>4% dextrose 1/5 normal saline</td>
<td>30</td>
<td>30</td>
<td></td>
<td>6.4</td>
<td>3.5-6.5</td>
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<tr>
<td>mannitol</td>
<td></td>
<td></td>
<td>12.5%</td>
<td>20%</td>
<td>25%</td>
</tr>
<tr>
<td>dextran</td>
<td></td>
<td></td>
<td>40 and 70 in 5% glucose or 0.9% NaCl</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### b. Evaluate their effects and fate when used in volume replacement.

- Crystalloids: 
  - t½: 20 min
  - Free water (dextrose solution): 55% ICF, 38% ISF, 7% plasma
  - ↓ total body tonicity (↓ [Na⁺]ₘ)
  - Isotonic solutions
  - 85% ISF, 15% plasma

- Colloids: 
  - Remain in circulating compartment

### c. Compare the pharmacology of colloids with crystalloids.

- Crystalloids
  - Polygeline (Haemaccel™)
  - pH 7.3±0.3

- Colloids
  - Succinylated gelatin (Gelofusine™)
  - Gelatin
  - Hetastarch

Other blood products in [Haematology (1.J)]
<table>
<thead>
<tr>
<th>Fluid</th>
<th>$t^{1/2}_{circ}$</th>
<th>$t^{1/2}_B$</th>
</tr>
</thead>
<tbody>
<tr>
<td>polygeline</td>
<td>1-2 h</td>
<td>?4-6 h</td>
</tr>
<tr>
<td>Gelofusine</td>
<td>2-3 h</td>
<td></td>
</tr>
<tr>
<td>dextran 40</td>
<td>4-6 h</td>
<td>2-6 h</td>
</tr>
<tr>
<td>dextran 70</td>
<td>12 h</td>
<td>12 h</td>
</tr>
<tr>
<td>Albumex 5</td>
<td>24 h</td>
<td>21 d</td>
</tr>
<tr>
<td>hetastarch</td>
<td>36 h</td>
<td>36 d</td>
</tr>
</tbody>
</table>

increased incidence of hypersensitivity (>1/10,000)
B. 23 Antimicrobials

a. Describe the pharmacology of antimicrobial drugs.

inhibit cell wall synthesis
  cell wall is composed of peptidoglycan
    polysaccharide and polypeptide chains
    crosslinked by transpeptidase acting on pentaglycine chains
  penicillins, cephalosporins
    β-lactams inhibit transpeptidase enzymes “PBP”s (multiple subtypes)
    cleaved by β-lactamase (plasmid-mediated resistance)
    some agents resist β-lactamase (methylillin, cefoxitin)
    some agents inhibit β-lactamase (clavulanate)
    some PBP's have low affinity for antimicrobials
  vancomycin (glycopeptide)
    prevents synthesis of peptidoglycan chains (before crosslinking)
  bacitracin
  cycloserine
    inhibits peptidoglycan synthesis (false substrate)
alter cell membrane permeability
  cell membrane has lipids characteristic of the organism
  selective detergents can disrupt the membrane
  low therapeutic index
  amphotericin B, polyenes
    active against fungi
  azoles
    inhibit fungal membrane lipid synthesis
    e.g. imidazole, ketoconazole
  polymyxins
    active against gram negatives
inhibit protein synthesis
  aminoglycosides
    attach to ribosomes
    block transcription of correct amino-acids
    disperse polysomes (groups of ribosomes)
    require active uptake into cells (aerobic metabolism dependent)
    resistance due to ↓ uptake, inactivating enzymes, deletion of receptor
  tetracyclines
    cause reversible inhibition of protein transcription, bacteriostatic
    require active uptake
  macrolides, lincomycins
    prevent polypeptide formation
    resistance due to absent binding site
  chloramphenicol
    reversibly inhibits amino-acid linking in peptide synthesis
    resistance due to inactivating enzymes
inhibit nucleic acid synthesis
  quinolones
    inhibit DNA gyrase (uncoils supercoiled DNA)
  sulfonamides
    PABA analogues inhibits folate synthesis (required for nucleotide synth.)
    p-aminosalicylic acid acts similarly in mycobacteria
    inherently resistant to PABA
  trimethoprim
    selective inhibitor of bacterial tetrahydrofolate reductase
  pyrimethamine
selective inhibitor of protozoal dihydrofolate reductase
rifampicin
inhibits RNA polymerase
resistance due to altered binding site
antiviral nucleic acid analogues
AZT, DDI, DDC etc. impair DNA transcription
penicillin
1929 described by Fleming
1940s purified by Florey & Chain
addition of other functional groups alter β-lactamase resistance and spectrum
pharmacokinetics
administered IV, IM, orally (different radicals provide oral stability)
quantitated by units ($10^6$ units = 0.6 g)
high oral bioavailability of oral preparations
elimination by renal excretion (90% active)
up to 2 g/h (saturable kinetics)
inhibited by probenecid, renal failure
hepatic metabolism for some analogues, especially halogenated
excreted in milk, sputum
spectrum
penicillin most active against gram positives
semisynthetic agents ↑ gram negative cover (ticarcillin, piperacillin)
no cover for cell-wall deficient bacteria

b. Outline the interactions between antimicrobials and anaesthetic agents.

aminoglycosides
prolong and potentiate non-depolarizing block
direct nephrotoxins
erythromycin
induced nausea and ↑ motility via motilin, receptors

c. Explain the principles of antimicrobial prophylaxis.

d. Chemotherapeutic agents

cycle specific
antimetabolites
methotrexate, citarabine, 5FU, mercaptopurine, thioguanine
most interfere with purine or pyrimidine metabolism
antibiotics
bleomycin
binds to DNA
podophyllin alkaloids
etoposide (VP-16)
inhibit topoisomerase II
plant alkaloids
vincristine, vinblastine, paclitaxel
interfere with spindle formation

cycle non-specific
alkylating agents
busulfan, cyclophosphamide, melphalan, thiotepa
metabolized intracellularly to reactive agents
metabolism (and toxicity) may be tissue-specific
donate alkyl groups to many molecules, especially guanine
result in DNA crosslinking or breakage
antibiotics
daunorubicin, doxorubicin, mitomycin
different action
cisplatin, carboplatin
probably an alkylating agent
nitrosoureas (mustards)
BCNU, CCNU
act as alkylating agents
endocrine agents
anti-oestrogens and anti-androgens
other agents
asparaginase, hydroxyurea, all-trans-retinoic acid, interferons...
b. Describe the developing pharmacology in relation to the cytokines.

cytokines
- IFN-α: antiviral, antiproliferative
- IFN-β: antiviral, antiproliferative
- IFN-γ: ↑ cytokines, leukocyte activity
- IL-1: inflammatory mediator, "endogenous pyrogen", ↑ marrow activity produced by macrophages, lymphocytes and fibroblasts
- IL-2: ↑ T cell activity, NK cells, produced by CD4 and CD8 T cells
- IL-3: multi-CSF
- IL-4: ↑ antigen-primed T and B cells, IgE, IgG1
- IL-5: ↑ eosinophils
- IL-6: ↑ plasma cells and early marrow cells, ↑ hepatic mediator synth.
- IL-7: ↑ proliferation and differentiation of early cell progenitors
- IL-8: neutrophil chemotactic factor
- IL-9: mast cell growth-enhancing factor
- IL-10: immune suppressant
- TNF (α): mobilizes Ca²⁺ from bone, similar to TNFβ
- TNFβ: antiparasitic, endotoxic shock reaction, antitumour, ↑ B cells
- GM-CSF: ↑ granulocyte, neutrophil, monocyte-macrophage and eosinophil proliferation and differentiation
- G-CSF: ↑ granulocyte proliferation and differentiation
- M-CSF: ↑ monocyte-macrophage proliferation and differentiation

Cytokines are available as pharmaceuticals through the use of recombinant DNA techniques. Most are administered as subcutaneous injections. Interferon-α is used in the treatment of some malignancies and hepatitis C. Interferon-β 1b may be effective in relapsing multiple sclerosis. Interferon-γ is used in chronic granulomatous disease. IL-2 is effective in metastatic renal cell carcinoma. Use of interleukins or interferons as vaccine adjuvants is possible but expensive.

G-CSF and GM-CSF are used to reduce the period of severe neutropenia following chemotherapy and may be used in future in other situations of poor leukocyte response.

Inhibition of the action of cytokines in conditions where they are thought to contribute to pathology is under on-going investigation. The preparations used are monoclonal antibodies against cytokines and soluble receptors (both available for IL-1 and TNF). Endogenous IL-1Ra, an IL-1 antagonist has been synthesized. These preparations are in phase III trials in patients with septic shock and may be trialled in ulcerative colitis, rheumatoid arthritis and CML.

Alteration in the endogenous production of cytokines is a mechanism of action of several established drugs.

Glucocorticoids inhibit production of IL-1 and thus IL-2 and IFN-γ. They also inhibit the production of many other inflammatory mediators, cause sequestration of lymphocytes in lymphoid tissue and impair margination of granulocytes.

Cyclosporin inhibits the gene transcription of IL-2, 3 and IFN-γ as well as other factors produced by activated T cells. It acts as a potent inhibitor of the cell-mediated immune response and is used in prevention of transplant rejection. It also prolongs the "honeymoon" period in Type I diabetes and has been trialled in rheumatoid arthritis and other autoimmune diseases. It is 20-50% bioavailable and has a t½/β of 24h with hepatic metabolism and excretion in the bile.

Tacrolimus is a macrolide antibiotic with similar actions to cyclosporin but greater potency. Sirolimus (rapamycin) binds to the same intracellular site as tacrolimus but blocks response to cytokines rather than their expression.
A<sub>1</sub>  
adenosine receptor  
G protein linked: ↓ adenylate cyclase  
actions  
   renal: afferent vasoconstriction, efferent vasodilation  
   cardiac: ↓ AV conduction, ↓ contractility  
   bronchi: constriction  
   CNS: pre- and post-synaptic inhibition (↑ K<sup>+</sup> conductance)  
      neuroprotective (↓ glutamate release)  
      ↓ dopamine release (↓ nausea)  
   benzodiazepines inhibit uptake  
agonists  
methylxanthines (as well as ↓ phosphodiesterase)  

A<sub>2</sub>  
adenosine receptor  
G protein linked: ↑ adenylate cyclase  
actions  
   platelets: ↓ aggregation  
   PNS: ↑ nociceptive afferents (?transmitter of angina)  

P<sub>2</sub>  
ATP/ADP/AMP receptors  
several subclasses (P<sub>i</sub> are adenosine receptors)  
agonists  
   ATP  
      most P<sub>2</sub> receptors are most sensitive to ATP (>ADP>AMP)  
      cotransmitter in noradrenergic and cholinergic transmission  
      especially gut relaxation, bladder contraction  
      fast transmitter in CNS and autonomic ganglia  
   ADP  
      platelet P<sub>2</sub> receptors are most sensitive to ADP  
      causes platelet aggregation (antagonized by adenosine)  
agonists  
suramin (P<sub>x</sub> only)  

Adenosine  
nucleoside which occurs naturally  
used intravenously  
pharmacokinetics  
   t<sub>1/2</sub> = 10 s  
   distribution is not relevant  
   metabolized to inosine or AMP in circulation  
pharmacodynamics  
   binds specific receptors on cardiac and smooth muscle  
   slows AV nodal conduction  
   reduces SA node discharge rate slightly (may cause asystole)  
   vasodilates  
   antagonized by methylxanthines  
   potentiated by dipyridamole (uptake inhibition)  
adverse actions  
   flushing  
   bronchoconstriction  
   hypotension, nausea, headache  
   infusion may induce gout  
use  
   6-12 mg IV bolus for SVT or VT  

New Developments  
2.B.24.2  
James Mitchell (November 5, 2001)
c. Other newish drugs.

losartan (and irbesartan)
- non-peptide angiotensin II antagonist
- oral and IV preparations

pharmacokinetics
- well-absorbed orally

pharmacodynamics
- potent competitive antagonist at the AT₁ receptor
  - AT₁ receptor is present in vascular smooth muscle and other tissues
  - G protein linked via IP₃ and DAG in vascular smooth muscle
  - may lower cholesterol (? mechanism)

adverse actions
- no bradykinin/renin/angiotensin II effects
  - cough, hormonal "escape", renal vasodilation

use
- 100 mg daily oral dose in essential hypertension
- IV bolus 25 mg in CHF
- expensive

rocuronium
- quaternary aminosteroid analogue of vecuronium
- non-depolarizing muscle relaxant

pharmacokinetics
- \( V_d = 0.2 \text{ l/kg} \)
- clearance 3.9 ml/min/kg
- \( t^{1/2} = 2 \text{ min}, \alpha 15 \text{ min}, \beta 100 \text{ min} \)
  - slightly prolonged in hepatic disease
  - shorter in children (\( t^{1/2} \beta = 50 \text{ min} \) 3-8 years)
- hepatic clearance 40% unchanged in bile
- renal clearance 15-30% unchanged

pharmacodynamics
- competitive blocker at nicotinic receptors

adverse actions
- minimal vagolytic effect in high doses (>0.9 mg/kg)
- not known to cause MH
- rare histamine release

clinical use
- \( ED_{90} = 0.3 \text{ mg/kg} \)
- induction 0.6 mg/kg
- duration of action 35 min
- supplemental 0.15 mg/kg
- infusion 5-10 \( \mu \text{g/kg/min} \)

cisatracurium
- isomer of atracurium, a benzylisoquinolinium agent
- non-depolarizing muscle relaxant

pharmacokinetics
- \( V_d = 0.15 \text{ l/kg} \)
- clearance 5 ml/kg/min
- \( t^{1/2} = 25 \text{ min} \)
- elimination largely Hoffman → laudanosine and monoquaternary acrylate
  - some hydrolysis
unaffected by age, renal or hepatic disease
metabolites have no NDB effect
metabolites are renally and hepatically cleared

pharmacodynamics
competitive antagonist at nicotinic receptors

adverse actions
uncommon histamine release

clinical use
ED₉₅ 0.05 mg/kg
induction 0.15 mg/kg
duration of action 55 min
supplemental 0.03 mg/kg
infusion 1-2 µg/kg/min

remifentanil
synthetic opioid
fentanyl derivative with ester linkage
formulated in glycine (not for intrathecal use)

pharmacokinetics
V₄₀ 25-40 l

µ agonist, equal potency to fentanyl

clinical use
load with 0.5-1 µg/kg/min, maintain 0.1-0.2 µg/kg/min
B. 25 Psychotropic agents

MAO inhibitors

MAO A
intestinal mucosa, peripheral noradrenergic nerves, placenta, liver
30% of brain MAO
highest affinity for noradrenaline, serotonin

MAO B
liver, dopaminergic neurones, platelets
70% of brain MAO
higher affinity for dopamine, tyramine, phenylethylamine

non selective
phenelzine, tranylcypromine
non competitive
inhibit both MAO A and B
cause "cheese reaction"
indirect sympathomimetics cross intestinal mucosa and liver due to lack of MAO
enter noradrenergic neurones via uptake 1
displace noradrenaline from vesicles
cytoplasmic noradrenaline is normally metabolized by MAO A but instead diffuses into synaptic cleft via uptake 1 (in reverse)

MAO A selective
moclobemide
competitive inhibitor of MAO A
minor potentiation of indirect sympathomimetics

MAO B selective
selegiline
inhibitor of MAO B
potentiates dopaminergic transmission in CNS
used in Parkinsonism

Selective serotonin reuptake inhibitors
Pharmaceutics
Chemically diverse
Prozac (fluoxetine), Zoloft (sertraline), Aropax (paroxetine), Cipramil (citalopram), Luvox (fluvoxamine), Efexor (venlafaxine) and generics
Oral preparations only

Pharmacokinetics
Oral bioavailability >90% with repeat dosing
Lower on first dose due to saturable first-pass metabolism
Highly protein bound (95%) except fluvoxamine (77%)
Large \( V_d \) (20 l/kg) due to high lipid solubility and tissue binding
\( t_{1/2} \), 15 h (fluvoxamine) to 4-7 days (fluoxetine)
Hepatic metabolism, some active metabolites (fluoxetine, sertraline)
Renal or hepatic excretion

Pharmacodynamics
Selective inhibition of presynaptic serotonin reuptake
Increased serotonin in synaptic cleft
Inhibition of serotonergic firing by presynaptic inhibitory receptor
Delayed desensitization of presynaptic receptor over two weeks
Subsequent increased serotonin release and antidepressant effect

Adverse effects
Mild inhibition of dopamine and noradrenaline uptake
Venlafaxine is a potent inhibitor of noradrenaline reuptake
Paroxetine is also antimuscarinic
Inhibition of various cytochrome p450 enzymes
  Multiple interactions
    ↑ effect of diazepam, warfarin, lipophilic β-blockers

Common symptoms
  Nausea, vomiting, diarrhoea, insomnia, agitation, tremor, headache, impotence

SIADH, hyponatraemia
Depletion of platelet serotonin, impaired aggregation

Serotonin syndrome
  ↑ serotonin in brainstem and spinal cord (5HT₁A mediated)
  Caused by combination with serotonergic drugs
    MAOI, carbamazepine, pentazocine, tricyclics, pethidine
  Confusion, agitation, coma, rigidity, myoclonus, opisthotonus, myoglobinuria,
  Autonomic instability, DIC
  May mimic neuroleptic malignant syndrome

Tricyclics
  Amitriptyline

\[
\text{Chemistry}
\]
  CH(CH₂)₂N(CH₃)₂

\[
\text{Pharmacokinetics}
\]
  Three ring nucleus
  Developed as antihistamines
  High oral bioavailability, first-pass metabolism
  Highly protein bound, high lipid solubility
  Ring hydroxylation, conjugation
  Chain demethylation \(\rightarrow\) active metabolites

\[
\text{Pharmacodynamics}
\]
  Block noradrenaline and serotonin reuptake
  Also antihistaminic, antimuscarinic, α-blocker
  Compensatory response to uptake inhibition results in delayed antidepressant effect

\[
\text{Overdose}
\]
  Clinical features
    CNS: irritability, seizures, unconsciousness, respiratory depression, fever
    PNS: urinary retention, gut paralysis
    CVS: arrhythmias, refractory SVT, VT, VF

  Management
    Activated charcoal, ABC
    Arrhythmia: lignocaine, propranolol, phenytoin, pacing
    Acidosis, decrease toxicity: \(\text{HCO}_₃^-, \text{K}^+\)
C. Statistics

a. Describe the stages in the design of a clinical trial, taking into account the: research questions and hypothesis, literature review, statistical advice, choice of study protocol, ethical issues, data collection and processing.

b. Explain concepts in statistics such as: distribution of data and frequency distributions, measures of central tendency and dispersion of data and the appropriate selection and application of non-parametric and parametric tests in statistical inference.

Data types

- Nominal
  - A list of possible results
  - E.g. death/discharge/transfer to another institution

- Ordinal
  - An ordered grouping of results on a scale with discrete points
  - E.g. ASA status, Duke’s staging

- Numerical
  - Interval
    - Equal intervals between values but no absolute zero
    - E.g. temperature in °C
  - Ratio
    - A linear scale from an absolute zero
    - E.g. mean arterial pressure

Parametric
- Data which are distributed normally

Variable
- A measurement of a sample

Parameter
- A measurement of the population

Measurement of central tendency

- Mean
  - Arithmetic
    - The average of numerical data: $\bar{X} = \frac{\sum X_i}{n}$
  - Geometric
    - The $n^{th}$ root of the product of numerical data $GM = \sqrt[n]{X_1 X_2 \ldots X_n}$ or $\ln GM = \frac{\sum \ln X_i}{n}$
- Median
  - The middle result in rank order
- Mode
  - The most common result in data on a discrete scale
  - Distributions may have more than one mode

Measurement of variability

- Range
  - The difference between largest and smallest values
  - Interquartile (25%-75%) or 5%-95% ranges are sometimes quoted
  - Suitable for ordinal or interval data
- Variance
  - $\text{var} = \frac{\sum (X - \bar{X})^2}{n}$
suitable for interval data only

standard deviation

\[ s = \sqrt{\frac{\sum (X - \bar{X})^2}{n - 1}} \]

n is used for descriptions of a sample and n-1 for descriptions of a population derived from a sample.
both variance and standard deviation are a function of the population and do not change with sample size.
comparing variances of samples is a test to see if they are from the same population: "F test"

coefficient of variation
the standard deviation as a percentage of the mean
allows comparison of the degree of variance between measurements of different quantities
independent of sample size and mean value
CV = s ÷ \bar{X}

F-test
variances of data sets can also be compared using the F-test
larger variance is divided by smaller variance
tables provide a confidence limit for the ratio obtained that the data sets are from the same population

standard error of the mean
describes the relationship between the sample mean and the population mean
SEM = s ÷ \sqrt{n}
for a normally distributed data set, the population mean has a probability of 96% of falling within 2xSEM of the sample mean
this is used to provide confidence intervals from sample data
certainty intervals are now preferred to p values
SEM falls with increasing sample size

hypothesis testing
null hypothesis (H₀)
"there is no difference between groups studied"
alternate hypothesis (H₁)
"there is a difference between groups studied"
type I error
false conclusion that H₀ is false based on sample
(spurious “significant” result)
probability of a type I error in a given study is called “α”
probability that a type I error has occurred is called “p”
type II error
false conclusion that H₀ is true based on sample
(missing a real difference)
probability of a type II error in a given study is called “β”
ß varies inversely with α, depending on study design

significance
an arbitrary decision as to the maximum p value acceptable as evidence that H₀ is false
typically 0.05 for biological studies

power
probability of finding H₀ is false given that it really is false
(finding a real difference)
power = 1 - ß
increases with sample size, α, parametric (>non-parametric) analysis

distributions
binomial

Statistics 2.C.2 James Mitchell (November 5, 2001)
describes the probability distribution for
a fixed number of independent events
with two possible outcomes of constant probability
probability of \( x \) successes each of probability \( \pi \) from \( n \) trials is
\[
P(x; n, \pi) = \binom{n}{x} \pi^x (1 - \pi)^{n-x}
\]
for large values of \( n \), this approaches normal distribution

**poisson**
describes distribution of results where an event occurs with a known frequency
(\( \lambda \)) at random intervals

**normal**
a symmetrical distribution representing the limit of the binomial distribution
as \( n \) approaches \( \infty \)

**parametric tests**
require
normal distribution
similar variance between data sets (F-test)
independent data sets

**Student’s t-test**
compares two groups from the same population to detect a difference in means
at a specified level of significance
\[
t = \frac{\bar{X}_1 - \bar{X}_2}{\sqrt{\frac{\text{SE}_{\bar{X}_1}^2 + \text{SE}_{\bar{X}_2}^2}{2}}}
\]
where
\[
\text{var}_p = \frac{\text{var}_{X_1} + \text{var}_{X_2}}{\sqrt{(n_1 - 1) + (n_2 - 1)}}
\]
in principle, \( t \) is a mean divided by a SEM
\( t \) is an expression of the spread of the SEM distribution for a given sample size
(degrees of freedom). There is a 95% probability that the population mean lies
within \( t \times \text{SEM} \) of the sample mean. \( t \) approaches 1.96 as sample size
approaches \( \infty \), and is approximated to 1.96 for \( n > 30 \).
the result \( t \) is compared with tables giving minimum values of \( t \) for specified
significance and degrees of freedom
can be performed on paired (dependent) or unpaired data, one- or two-tailed
depending on whether the alternative hypothesis postulates a direction for
change of the mean

**ANOVA (analysis of variance)**
compares the variance of multiple groups
against the “independent variable” (one-way ANOVA)
or against each other (Multiple ANOVA)
by calculating an \( F \)-ratio
\[
F = \frac{\text{between-groups variance}}{\text{within-groups variance}}
\]
this identifies the presence of a difference but not which groups cause it

**multiple comparison tests**
used to identify different groups from ANOVA
based on t-test but modified to diminish the risk of type I error
many eponymous varieties
Bonferroni, Newman-Keuls, Duncan, Dunnett, Dunn, Tukey, Scheffe,
Least significant difference etc.

**non-parametric tests**
suitable for ordinal data and data which is not normally distributed
less power than parametric tests
Wilcoxon signed ranks test ≈ paired t-test
Mann-Whitney u test ≈ 2-tailed t-test
two data sets to compare
all data are ranked 1 to \( n_1 + n_2 \) → rank sums \( R_1 \) and \( R_2 \)

*Statistics 2.C.3*  
James Mitchell (November 5, 2001)
\[ U = n_1n_2 + \frac{1}{2}(n_1(n_1 + 1)) - R \]

\( U \) is compared with values for a specified \( \alpha \) and degrees of freedom

Kruskall Wallis test = ANOVA
Friedman’s test = Multiple ANOVA
Spearman rank order \( r \)

\( \chi^2 \) test
used for nominal data
compares rates of independent events for significant difference
requires expected rates of more than 5 events in \( \geq 80\% \) of cells
(otherwise use Fisher’s Exact Test)

\[ \chi^2 = \sum \frac{(O - E)^2}{E} \]
where \( E \) is the expected number and \( O \) the observed number of events
tables of \( \chi^2 \) values for levels of significance and degrees of freedom
degrees of freedom = (interventions - 1) x (outcomes - 1)

<table>
<thead>
<tr>
<th></th>
<th>Vomiting</th>
<th>No Vomiting</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiemetic</td>
<td>10</td>
<td>90</td>
<td>100</td>
</tr>
<tr>
<td>Placebo</td>
<td>30</td>
<td>70</td>
<td>100</td>
</tr>
<tr>
<td>Total</td>
<td>40</td>
<td>160</td>
<td>200</td>
</tr>
</tbody>
</table>

\( E_{\text{vomiting}} = 20 \) in each group, \( E_{\text{no vomiting}} = 80 \) in each group
\( \chi^2 = 5 + 5 + 1.25 + 1.25 = 12.5, \text{df} = 1 \)

Yates correction for 2x2 matrices with fewer than 40 trials reduces the magnitude of \( (O - E) \) by 0.5 for each term in \( \chi^2 \)

Fisher’s exact test for small sample sizes in 2x2 matrices calculates \( p \) regardless of df using the binomial distribution

\[ p = \frac{R_1!R_2!C_1!C_2!}{n!n_1!n_2!n_{12}!n_{12}!} \]
for the example \( p=0.000248 \)
onerous to calculate for large \( n \)

McNemar’s test is used for matched data.

odds ratio
the ratio of the incidence of an outcome in an exposed group versus a control group in a case-control study
called a “risk ratio” in a prospective cohort study
a confidence interval associated with an odds ratio does not span 1 if the correlation is significant
odds ratio describes the strength of association as well as its presence

regression and correlation
regression is a mathematical description of the association between two variables
the dependent variable is plotted on the \( Y \) axis
linear regression produces a relationship \( y=ax+b \) such that
\[ \sum (Y_i - aX_i + b)^2 \] for the set of data points is minimized
correlation is a description of the tightness with which a data set matches a regression
\[ a = \frac{\sum (X_i - \bar{X})(Y_i - \bar{Y})}{\sum (X_i - \bar{X})^2} \]
\[ b = \bar{Y} - a\bar{X} \]
the coefficient of determination, \( r^2 \) expresses strength of correlation (from 0 to 1)
\[ r^2 = \frac{\sum (aX_i + b - \bar{Y})^2}{\sum (Y_i - \bar{Y})^2} \]
the correlation coefficient is \( r \) (varying from -1 to +1)
\( r^2 \) expresses the proportion of the value of the dependent variable attributable to the independent variable

Regression assumes a constant variance over the range of data. If variance is not
constant, a correction factor is added to the “least squares” calculation. Where the nature of the relationship between dependent and independent variables is known to be of a non-linear nature (e.g. dose-response), a transform can be applied to the data to render the relationship linear (e.g. Hill plot or Lineweaver-Burke plot). sequential analysis
suitable for paired subjects giving nominal results
   e.g. drug vs placebo: vomiting or no vomiting
a curve can be drawn on a graph of “number of untied pairs” versus “excess outcomes”, the boundaries of which mark statistical significance at a specified p value and H₀ demonstrated:

allows termination of a trial as soon as significance is achieved
largely obsolete technique, replaced by interim analysis (with a low p)

Ratio
the number of one of two possible results divided by that of the other
used for comparison between data sets
Rate
the number of one result divided by the total number of data points
applicable to ordinal and nominative data
c. Explain the principles of errors of statistical inference and describe techniques to minimize such errors through good study design.
d. Describe the features of a diagnostic test, including the concepts: sensitivity, specificity, positive and negative predictive value and how these are influences by the prevalence of the disease in question.
sensitivity
   a property of a test, regardless of the population tested
   the proportion of subjects having the attribute being tested for who show a positive result for the test
   e.g. proportion of hepatitis B infected patients testing positive for hepatitis B surface antigen (HBsAg)
   = true positives ÷ (true positives + false negatives)
specificity
   the proportion of subjects not having the attribute being tested for who show a negative result for the test
   e.g. proportion of patients without hepatitis B testing negative for HBsAg
   = true negatives ÷ (true negatives + false positives)
Assessment

Who is suitable for day surgery?

Routine preoperative testing

Risk assessment

Airway assessment
Who is suitable for day surgery?

Patient
- Willing to have the procedure performed and has the understanding to follow discharge instructions
- ASA 1 or 2; stable ASA 3 or 4 if the anaesthetist accepts them
- Term infants over 12 weeks or ex-prems more than 12 weeks post due date with prior anaesthetic consultation

Surgery
- Minimal risk of postoperative bleeding
- Minimal risk of postoperative airway compromise
- Postoperative pain which can be managed as an outpatient
- No special monitoring or nursing requirements
- Rapid return to normal oral intake

Social
- Responsible person available to transport the patient home in a suitable vehicle
- Responsible person at home for the first postoperative night
Preoperative screening tests (Miller Ch. 23)

History and examination are more efficient and safer than routine screening. No amount of laboratory investigation replaces a pre-anaesthetic consultation.

Young ASA 1 patients almost certainly suffer net harm from screening investigations.

Partly determined by nature of surgery
- Minimally invasive (D&C, cataract, arthroscopy)
- Moderately invasive (laparoscopic surgery, TURP, CEA)
- Highly invasive (cardiac, neuro, major laparotomy)

CXR
- Almost never indicated in asymptomatic patients
- Symptomatic or previously diagnosed pulmonary malignancy, infection
- Symptomatic congestive cardiac failure
- Exposure to tuberculosis
- Disease likely to involve the trachea: e.g. large goitre

ECG
- Asymptomatic, no risk factors: over 45 y (men) or 55 y (women)
- Major surgery, specific risk factors for IHD (smoking, diabetes, hypertension, family history, hypercholesterolaemia): threshold 5-10 y earlier
- Previous abnormal ECG more than 2 months old
- Clinical arrhythmia or symptoms suggesting arrhythmia or ischaemia

FBE
- Surgery requiring group and hold or crossmatch
- Known haematological disorder
- Clinical anaemia or significant bleeding
- Condition associated with thrombocytopenia: PET, chemotherapy

U&E
- Disease associated with renal impairment, e.g. diabetes
- Diuretic or electrolyte therapy

LFT
- Known or symptomatic hepatitis or jaundice
- Alcoholism or suspected drug abuse
- Symptomatic coagulopathy
- Suspected malignancy

Blood glucose
- Diabetes, steroid therapy
- Risk of cerebral ischaemia intraoperatively

APTT, INR
- Symptomatic abnormal bleeding
- Anticoagulant therapy
- Disease associated with coagulopathy: hepatic dysfunction, PET, SLE, ESRF, malnutrition

Urinalysis
- Probably not relevant to anaesthesia

Serology
- ßhCG
  - Possible undiagnosed pregnancy
- Hepatitis B, C, HIV
  - Established risk factors for blood-borne virus transmission and with patient counselling and consent
Risk assessment

Goldman criteria

Independent predictors of perioperative morbidity

- Age >70 y
- MI in previous 6 months
- S₃ or gallop or ↑ JVP
- Rhythm other than sinus
- Aortic stenosis
- Abnormal ABG, U&E
- Emergency thoracic or abdominal surgery

Cardiovascular risk

Dipyridamole thallium imaging
Useful in vascular patients if one or two of
  - Q waves, VEs, diabetes, age >70 y, angina (Eagle et al.)
  - Where positive result carries RR of 10 of cardiac morbidity
No risk factors → little contribution to risk assessment
Three or more → coronary angiography indicated

Ambulatory ECG
Similar predictive value to DTI
Highest risk patients often have baseline abnormalities which preclude testing

Dobutamine stress echo
Similar to DTI, possibly better predictive value

Cardiac catheterization
In PVD patients
  - 8.5% normal coronaries
  - 60% >70% stenosis

Cardiopulmonary exercise testing
Basal $\dot{V}O_2$ commonly 3.5 ml/kg/min
Postoperative $\dot{V}O_2$ requirement 5-7 ml/kg/min
  - Poor $O_2$ extraction in healing tissue, so equivalent to 8.5-11 ml/kg/min
Testing involves measuring $\dot{V}O_2$ and $\dot{V}CO_2$ over a range of exercise load
Rise together up to anaerobic threshold ($\dot{V}O_2$ at onset of anaerobic metabolism)
Onset of anaerobic metabolism causes $\dot{V}CO_2$ to rise in excess of $\dot{V}O_2$
  - AT <11 ml/kg/min moderate risk, <8 ml/kg/min high risk
Claimed RR of 42 for myocardial event in high risk patients

History
  - CABG with no symptoms: similar to never had symptoms
  - PTCA or stents: little evidence

Pulmonary risk
Airway assessment

Views of the pharynx (Mallampati)

With head in neutral position and tongue inside mouth:

   I tonsillar and pharyngeal folds visible
   II tonsillar folds and all of soft palate visible
   III part of soft palate visible
   IV hard palate only visible

Higher grade is associated with greater difficulty in intubation as are poor neck mobility, small jaw, large tongue, long narrow mouth and thyromental distance <6.5 cm.

Sensitivity and specificity of MP ≥3 as a predictor of difficult intubation (CL ≥3) is 60-70%

Combination scoring systems (including weight, TMD, mouth opening etc.) approach 95% sensitivity and specificity

Views of the cords (Cormack and Lehane)

   I cords totally visible
   II posterior part of cords visible
   III epiglottis visible but not cords
   IV epiglottis not visible

Higher grade is associated with difficulty in intubation.
Complications

Intraoperative hypotension

Anaesthesia Related Mortality in Australia 1994-96

Postoperative confusion

Pulmonary aspiration in anaesthesia

Perioperative stroke

Respiratory depression under GA

Adverse effects of laryngoscopy

Complications of, benefits of, indications for IVs, CVCs, PA catheters, arterial lines

Perioperative myocardial ischaemia

Arrest protocol

Malignant hyperthermia

Post-operative nausea and vomiting

Crisis Management in Anaesthesia
Intraoperative hypotension

Differential diagnosis

Airway and breathing
- Desaturation, hypoxia
- Pneumothorax
- High circuit pressure

Cardiac
- Arrest
- Arrhythmia with low output
- Failure
- Ischaemia or infarction
- Vagally mediated bradycardia

Circulation
- Hypovolaemia
- Obstructed venous return
- Sepsis with vasodilatation

Drugs
- Indication agents, volatile agents, vasodilators
- Incorrect dose or rate of infusion
- Regional technique: sympathetic blockade, local anaesthetic toxicity
- Anaphylaxis

Equipment
- Drug administration equipment failure
- Anaesthetic machine, syringe pumps
- Monitoring equipment failure: artifact

Fluids, electrolytes, metabolism
- Transfusion reaction, Haemaccel reaction
- Hypoglycaemia, Addisonian crisis...
- Hypothermia

Surgical
- Blood loss
- Embolism: air, fat, cement
- Obstruction to venous return
- Specific surgical complications
  - Clamp release, great vessel surgery, cardiac compression
Anaesthesia Related Mortality in Australia 1994-96

Classification

Deaths attributable wholly or partly to anaesthesia
- Under anaesthetist’s control
- Doubtful whether under anaesthetist’s control
- Combined anaesthetic and surgical factors

Deaths in which anaesthesia played no part
- Entirely due to surgical factors
- Inevitable deaths despite correct anaesthetic and surgical management
- Fortuitous deaths

Unassessable deaths
- Despite considerable data
- Due to inadequate data

1994-96

Deaths in Australia 1875 106.8 per million population
Related to anaesthesia 135 7.7 per million population
7.2% of deaths considered
15.9 per million procedures (1/63,000)

Major factors

Anaesthetic technique
- Airway 16
- Ventilation 9
- Other 48

Anaesthetic drugs
- Dosage 45
- Selection 18
- Inadequate reversal 3
- Adverse reaction 2

Preoperative
- Assessment 40
- Management 13

Anaesthetic management
- Crisis management 21
- Inadequate monitoring 12
- Equipment failure 3
- Inadequate supervision/assistance 19
- PA catheter 5

Gender
- Male 77, female 58

Age
- ≤40 y 6 (4.4%)
- >60 y 117 (86.7%)

ASA status
- 1 0
- 2 13
- 3 66
- 4 45
- 5 11

Complications 3.A.4.3 James Mitchell (October 7, 2001)
Postoperative confusion

Differential diagnosis

Respiratory failure: hypoxia
Cardiovascular
  Hypotension, arrhythmia, cardiac ischaemia, anaemia
Neurological
  Cerebral bleed, embolic event, long-standing dementia or degenerative disease particularly in unfamiliar environment and in pain
GIT
  Hepatic decompensation, gut ischaemia
Renal
  Acute renal failure, uraemia
Endocrine or metabolic
  Electrolyte disturbance, hypoglycaemia, Cushing’s syndrome, hypercalcaemia
Septic
  Infection: respiratory or urinary most characteristic
Drug-related
  Withdrawal of benzodiazepines, narcotics, alcohol, other sedatives
  Administration of sedatives, analgesics, antiemetics
  Adverse reaction to anaesthetic agents

History
Examination
  HR, BP, T, RR, SpO₂
  General examination focussing on signs of sepsis or cardiorespiratory problems
  Neurological examination for focal signs and to assess degree of confusion
Investigation
  Directed by history and examination findings
  FBE, U&E, LFT, glucose, ABG, CXR, ECG, urine dipstick
  Consider CT head if no other cause found
Management
  Correction of cause
  Acutely: supportive care, reassurance, prevention of self-harm or wandering
Pulmonary aspiration of gastric contents in anaesthesia - T. Engelhardt and N.R. Webster
BJA 1999; 83: 453-60

Pathophysiology

Particle related
Acid related
Critical pH 2.5 and volume 0.4 ml/kg may be untrue
HCl LD_{50} 1.0 ml/kg in monkeys
Process
Burn within 5 s
Neutralized by 15 s
Desquamation with 6 h
Alveolar type II cells most sensitive
Second phase: inflammatory mediators
Local effect ARDS, systemic effects

Bacterial related
Mixed aerobes and anaerobes
*Klebsiella, P. aeruginosa, E. coli, S. aureus*

Detection
No specific tests if aspiration is not witnessed and no gastric contents from ETT
Bronchoscopy, lavage, brushing may yield evidence
CXR may show signs after hours
\( {\nabla} / Q \) scanning in children

Incidence
1 in 2000-3000
Swedish study of 185385 GAs
Four fatalities
One ASA IV ICU patient, two failed intubation during resuscitation and
one kyphoscoliosis
Non fatal: 47% pneumonitis, 17% ventilation
Mayo Clinic study of 215488 GAs
Three fatalities in ASA III-IV
Obstetric patients
Incidence around 1 in 900 for Caesarean section
Negligible mortality (denominator unknown)

Prevention
No useful correlation with BMI, smoking, fasting, alcohol use, volume, pH
Fasting
Intermediate markers used in studies (volume and pH)
Drugs
Intermediate markers used
Cost-benefit analysis impossible
Likely minimal effect on morbidity or mortality
Anaesthetic technique
Rapid sequence induction recommended
Quality of cricoid pressure is variable
Overuse of the LMA has potential to increase incidence of aspiration

Treatment
Head-down, suctioning, intubation, tracheal suctioning
Ventilation with 100% oxygen
No proof for steroids or antibiotics

Conclusion
Minimal demonstrated mortality or morbidity
Changes in anaesthetic practice have probably contributed to this
No proven benefit from prophylactic measures

Complications

James Mitchell (October 7, 2001)
Perioperative stroke


**Stroke**
Rapidly developing episode of focal or global loss of cerebral function with symptoms lasting more than 24 hours or leading to death
Less than 24 hours: TIA
Peri-operative stroke commonly defined as occurring intra-operatively or within 3-30 days postoperatively

**Epidemiology**
Third most common cause of death
Annual incidence 1-2 per 1000 population
Rises with age: 3 per 1000 at 60 y, 10-25 per 1000 at 80 y
Acute mortality 15-30%, 45% independent after 1 year

**Surgery**
Incidence
- General surgery 0.2-0.7% (six times background risk)
- With previous stroke 2.9%
- Peripheral vascular surgery 1-3%
- Carotid surgery 3-5%
- Usually between 2 and 10 days postop

**Natural history**
Acute mortality 26%

**Aetiology**
- 42% emboli of cardiac origin (33% AF)
- Vascular emboli from plaque
- In situ thrombosis (hypercoagulable state)

**Risk factors**
- Hypertension, cardiac disease (AF), PVD, diabetes, age
- Carotid disease has not been established as a risk factor for periop stroke

**Prevention**
**Preoperative**
- Identify risk factors and modify if possible (e.g. revert AF, anticoagulate)
- Consider heparinization of patients on warfarin
- Delay surgery 4-6 weeks after a stroke

**Intraoperative**
- Maintain oxygen delivery
  - Normotension, maintain Hb, high PaO₂, normocapnia
- Normal blood sugar
- Avoid excessive neck rotation or extension
- Anaesthetic technique has not been shown to cause a difference

**Postoperative**
- Avoid hypotension
- Avoid dehydration and hypercoagulability
- Control anticoagulation
Respiratory depression under GA

Definition
Inadequate ventilation caused by an abnormality in control of respiration
Manifest as rising PaCO₂ or falling PaO₂

Respiratory control
Afferent
Peripheral chemoreceptors predominantly for PaO₂
Carotid bodies via IX
Aortic bodies via X
Central chemoreceptors for PaCO₂ (via CSF pH)
Lung receptors
Pulmonary stretch receptors, irritant receptors, J receptors
Other receptors
Nose and upper airway
Joint and muscle, γ afferents
Arterial baroreceptors
Pain and temperature sensation

Efferent
Central integration: cortex, hypothalamus, pons, medulla
Spinal cord: dorsolateral UMN system
Anterior horn cells: α and γ fibres
Muscles
Diaphragm, intercostals, accessory muscles

Signs
Spontaneously ventilating anaesthetized patient
↑ ETCO₂, ↓ SpO₂, ABG findings
Ventilated patient (underventilation)
Same gas changes
Mild hypercapnia: sympathetic stimulation
Profound hypoventilation
Myocardial irritability and depression, cyanosis, circulatory collapse

Causes
Anaesthetic
Drugs
Central
Induction agents, volatiles, opioids
All ↓ response to PaCO₂
Supplemental O₂ in patients reliant on hypoxic drive
Spinal cord
High block, total spinal
Peripheral nerve
LA blockade of phrenic nerve (e.g. deep cervical block)
Neuromuscular
Muscle relaxants, volatiles, Mg²⁺ etc
Physiological change
Hypothermia, hypoglycaemia
Hyperventilation

Surgical
Interruption of any part of reflex control e.g. brainstem
Mechanical disruption of thorax
Airway obstruction, pulmonary blood flow obstruction

Patient
OSA
CVA
Apnoea of newborn

Complications 3.A.4.7 James Mitchell (October 7, 2001)
Adverse effects of laryngoscopy

Mechanical
- Trauma to teeth, dental work, tongue, pharynx, epiglottis
- Compression of soft tissues: lip, gums
- Eye injury
- Cervical spine injury if preexisting instability

Physiological

Airway
- Coughing with inadequate anaesthesia
  - ↑ ICP, IOP
  - Damage if open eye injury or cerebral vascular anomaly
- Laryngospasm
- Vomiting, aspiration

Neurological
- ↑ CBF together with ↑ ICP
- May cause vagal response
- Commonly causes sympathetic response

Cardiovascular
- Usually tachycardia, hypertension
  - ↑ myocardial O₂ demand, risk of ischaemia
- Bradycardia if vagal response, more common in children

Pulmonary
- Bronchospasm

Drug-related
- Hypnotics and muscle relaxants

Failure to secure the airway
- Hypoxia, aspiration, death

Minimizing adverse effect

Patient selection
- Airway assessment
- Alternative anaesthetic techniques if laryngoscopy is likely to be problematic
- Removal of dentures

Equipment
- Suitable sized and well-maintained airway equipment
- Gentle use of laryngoscope

Drugs

Blunt airway response
- Local anaesthetic to upper airway
- Nerve blocks to IX, superior laryngeal nerve
- Prophylactic IV lignocaine, opioid

Blunt haemodynamic response
- β-blocker, clonidine, vasodilators

Reduce airway reactivity
- β₂ agonists, anticholinergics, steroids

Induction agents
- Suitable doses and adequate time for muscle relaxant to work
Complications of, benefits of, indications for IVs, CVCs, PA catheters, arterial lines.

**IV**

**Complications**
- Cannula and insertion
  - Pain of insertion
  - Vessel damage, thrombosis, haematoma, haemorrhage, local irritation
- Through the cannula
  - Infection, septicaemia
- Fluids
  - Fluid overload, incorrect fluid: electrolyte disturbance, transfusion reaction, hypothermia
- Drugs
  - Incorrect drug or dose, incorrect route of administration, administration too rapidly
  - Extravasation with vessel damage or cannula misplacement
- Dressing
  - Skin reactions, allergy

**Benefits**
- Drug administration
  - Rapid, 100% of drug delivered, more secure and reliable than oral or PR administration
  - Suitable for emergency and resuscitation drugs
- Fluids
  - In fasting patients or patient with ileus, allows hydration and electrolyte supplementation, nutrition possible

**Indications**
- Requirement for parenteral fluids or drugs where rapid effect is required
  - Volume is too large or agent unsuitable to give subcutaneously
  - Possible requirement for resuscitation drugs e.g. during mask anaesthetic

**CVC**

As for IV, plus

**Complications**
- Cannula and insertion
  - Insertion technique
    - Arterial or other vessel damage
    - Damage to nerves or other viscera (e.g. femoral insertion)
    - Pneumothorax
    - Arrhythmia related to wire or cannula irritating endocardium
    - Loss of guidewire
  - Cannula
    - Vessel wall damage: haemothorax, pericardial tamponade
    - Misplacement into cerebral or other vessels

**Benefits**
- Drug administration
  - Highly secure access
  - Suitable for irritant or hypertonic agents requiring rapid mixing
- Fluids
  - Suitable for TPN
Measurement of CVP provides information to guide fluid management

Other
Suitable for venous blood sampling, normovolaemic haemodilution
Useable for 7 days up to months depending on cannula type

Indications
Secure IV access (e.g. TIVA)
Prolonged access (e.g. chemotherapy)
Need for CVP measurement (e.g. large fluid shifts with major laparotomy)
Inadequate access elsewhere

PA catheter

As for CVC, plus

Complications
Cannula and insertion
Large sheath increases risk of vessel damage
Greater risk of arrhythmia
Potential for injury to right heart, PA, smaller pulmonary vessels
Balloon
May injure surrounding vessel
Expands with N₂O
Site of entry of gas into circulation
Through the cannula
Cardiac output boluses risk bolus injection of other agents

Benefits
Measurements
CVP, PAP, PAOP, CO, SmvO₂, SVR, PVR, MRO₂
May guide fluid and inotrope management
No proven benefit

Fluids
Sheath allows rapid infusion

Indications
Requirement for measuring PA pressures or cardiac output or SVR
  e.g. pulmonary hypertension, septic shock
Perioperative myocardial ischaemia

Epidemiology
Most common cause of perioperative (and non-periop.) death
Occurs most frequently postoperatively (peak day 3)
Symptoms obscured by surgical pain or analgesia (silent)

Myocardial oxygen balance
Demand
Heart rate
Diastolic volume (preload)
Contractility
Blood pressure (afterload)

Supply
Coronary blood flow
Diastolic duration
Coronary perfusion pressure
Coronary vessel size and patency

Oxygen content
Haematocrit
\( \text{PaO}_2 \)

Triggers
Tachycardia
Anaemia

Some evidence for maintaining Hb >90 g/l in CAD patients
Hb ≥ 70 g/l well-tolerated in normal patients

Monitoring
ECG
Subendocardial ischaemia causes ST elevation
Transmural ischaemia causes ST elevation

Criteria for ischaemia
Horizontal or downsloping ST depression ≥ 1 mm, 60-80 ms after J point
Duration ≥ 1 min
Separation from other episodes by ≥ 1 min of normal baseline

Sensitivity (intraoperative)
\( V_5 \) 75%
\( II, V_5 \) 80%
\( II, V_4, V_5 \) 96%

Advantages
Least expensive, most automated

Limitations
RBBB, LBBB, AF, LVH with strain interfere with interpretation

TOE
Segmental wall motion abnormality with ischaemia

Advantages
Most sensitive: earlier signs and more sensitive than ECG
Information about regional ischaemia, valve function, CO

Limitations
Expensive equipment and experienced operator required
Not well-tolerated without sedation

PA catheter
Rise in PAOP or change in waveform (e.g. mitral regurgitation) with ischaemia

Advantages
Information about CO

Limitations
Less sensitive than ECG or TOE
Expensive, invasive

Complications 3.A.4.11 James Mitchell (October 7, 2001)
Arrest protocol

Cardiac arrest
BLS algorithm
  Secure airway, ventilate with 100% O₂
Praecordial thump
Attach defibrillator/monitor, IV access
Assess rhythm and pulse
  VF or pulseless VT
    Defibrillate up to 3 times
      200 J, 300 J, 360 J first time
      360 J subsequent times (4 J/kg)
    CPR up to 1 min, then reassess rhythm and pulse
  non VF/VT
    CPR up to 3 min, then reassess rhythm and pulse
During CPR
  Verify electrode, paddle and ETT placement
  IV access if not present
  Adrenaline 1 mg every 3 min
  Consider atropine, K⁺, lignocaine, bicarbonate if indicated
Consider reversible causes
  Hypoxia, hypovolaemia, hypothermia, K⁺, Mg²⁺, Ca²⁺, tension pneumothorax, tamponade, drug toxicity, thromboembolism
Malignant Hyperthermia

Miller 5th Edition Chapter 27

History

1929 Ombrédanne’s syndrome: post-op hyperthermia and pallor
1960 Denborough & Lovell case report in Australia
1966 Stress-susceptible swine described
1975 Dantrolene use described in swine and trialled in humans

Epidemiology

1 in 62,000 anaesthetics with triggering agents

Aetiology

Normal excitation-contraction coupling
- ACh binds to nicotinic receptors and opens cation channels
- Na⁺ influx raises membrane potential
- Voltage-gated Na⁺ channels open: depolarization
- Voltage-gated Ca²⁺ channels in T tubules open (L-type channels or DHPR)
- Physical linkage to sarcoplasmic reticulum ryanodine receptor (Ca²⁺ channel)
- Ca²⁺ released from SR activates myofibril contraction
- Rapid reuptake of Ca²⁺ into SR and binding to calsequestrin
- Termination of contraction

MH defect
- Ry₁ coded on chromosome 19 in humans
- Multiple mutations described covering fewer than 50% of MH families
- Defects also described on chromosome 17 (Na⁺ channel, L-type Ca²⁺ channel), chromosome 7 (L-type Ca²⁺ channel), chromosome 1 (DHPR)
- Functional abnormality is complex at a molecular level
  - Increased tendency for Ca²⁺ release from SR
  - Decreased inhibition by Mg²⁺ and Ca²⁺
- Sustained high sarcoplasmic Ca²⁺ level causes sustained contraction, aerobic and glycolytic metabolism and thus rigidity, acidosis, hyperkalemia...

Risk factors

- Family history of MH
- King-Denborough syndrome, central core disease

Clinical Features

- Triggered by volatile anaesthetics or suxamethonium, but not consistently
- Rise in muscle intracellular Ca²⁺, rigidity
- Venous ↓ pH, ↓ PO₂, ↑ PCO₂, ↑ lactate, ↑ [K⁺]
- Subsequent ↑ HR, ↑ BP, ↑ T
- Temperature rise up to 1°C per 5 min
- Secondary DIC, neurological dysfunction, renal and cardiac failure and arrest
- Clinical syndrome may be indistinguishable from other causes of hypermetabolism
- Masseter spasm
  - Caused by suxamethonium
  - Present to a variable extent in most patients
  - Due to slow tonic fibres in masseters and lateral pterygoids
  - Increased risk of MH

Acute treatment

- Institution protocol
- Call for assistance
- Clean anaesthetic machine, hyperventilate with 100% O₂
- Cold fluids and packs
- Curtail surgery
- Dantrolene
  - Lipid soluble hydantoin

Pharmacokinetics
Low water solubility
20% oral bioavailability
Vd 0.5 l/kg
Clearance 0.6 ml/min/kg
t1/2 12 h
Therapeutic concentration >3 µg/ml
Metabolized to 5-OH dantrolene (50% potency)

Pharmacodynamics
Molecular action uncertain
Inhibits Ca²⁺ release from sarcoplasmic reticulum without inhibiting uptake
Limits excitation-contraction coupling in skeletal muscle

Adverse effects
Muscle weakness
Negative inotrope
↑ [K⁺]
Electrolyte and volume disturbance due to water and mannitol load

Indications
Malignant hyperpyrexia
Also used in
Neuroleptic malignant syndrome
MDMA overdose, serotonin syndrome with hyperpyrexia
Muscle cramps

Clinical use
Ampoules of 20 mg with 3 g mannitol, pH 9.5
Dissolved in 60 ml water → 1 mg/3 ml
Dose 1 mg/kg up to 10 mg/kg
= up to 30 ml/kg free water, 1.5 g/kg mannitol

Post-operative ICU, supportive treatment of other abnormalities

MH-safe anaesthesia
Safe agents
Regional (amide LA almost certainly safe)
N₂O, non-depolarizing relaxants, propofol, barbiturates, etomidate, ketamine, opioids, benzodiazepines

Follow up
Testing family members (through RMH)
Two protocols (North American and European) for muscle biopsies
Ry, testing not sufficient because of heterogeneity in humans

http://www.mhaus.org/
Postoperative nausea and vomiting (PONV)

Preoperative
    Assessment
        Detailed history of previous anaesthetic problems and nature of surgery
        Severity of PONV, duration, delay in discharge
        Examine previous anaesthetic charts if available
        Particularly if there has been a nausea-free anaesthetic
        History of drug sensitivity, particularly narcotic analgesics
    Preparation
        Minimal safe fasting time
        Preoperative hydration
        Reassurance
    Premedication
        Anxiolytic, antiemetic
        Lorazepam, ranitidine, metoclopramide
        Consider anticholinergic e.g. scopolamine (risk of dysphoria)
    Transport
        Gentle ride, sitting up
        Consider walking to theatre

Intraoperative
    Avoid GA if feasible: regional blockade
    But also avoid hypotension
    Avoid N₂O, opioids, volatile agents
        Propofol TIVA may be best choice for GA
    Avoid muscle relaxation if possible, in order to avoid neostigmine
        If neostigmine unavoidable, give slowly
    Avoid specific emetogenic drugs: e.g. ergometrine
    Give prophylactic antiemetic
        Ondansetron and dexamethasone
    Give adequate hydration
    Empty stomach and deflate insufflated gas prior to awakening

Postoperative
    Regional blockade for analgesia
    Otherwise aim for opioid-free analgesic regimen
        Paracetamol, NSAID, ketamine
    Regular antiemetic, rescue therapy available
    Continue IV hydration
Crisis Management in Anaesthesia

COVER algorithm derived by Runciman from AIMS reports (http://www.apsf.net.au/)
- Based on incident reports collected since 1988
- Performs better than the anaesthetist in 20-30% of incidents
- Performs worse in 1%
- Not always the best strategy if the cause of a problem is obvious
- Must be considered at the same time as resuscitation/ABCD

C
- Circulation
  - Pulse, BP, ECG
- Colour
  - Saturation, skin colour

O
- Oxygen flow
  - 100% O₂, increase flow
- Oxygen concentration
  - Oxygen monitor, gas analyzer

V
- Vaporizer
  - Turn off (also remember intravenous drug infusions)
- Ventilation
  - Change to manual ventilation, feel compliance and flow

E
- Endotracheal tube
  - Check position, cuff
- Eliminate machine
  - Change to Laerdal bag

R
- Recheck monitors
- Review

Causes of incidents
- 30% equipment/human interface problems
- 14% contributed to by haste
- 8% drug problems
- 8% equipment failures

Vigilance mnemonic (SCARE)
- Scan every five minutes
- Check on the unexpected
- Alert &
- Ready if a problem is suspected
- Emergency mode in a deteriorating situation
Pain

Complex Regional Pain Syndromes

Problems related to pain management

Chronic pain
Complex Regional Pain Syndromes

Reflex sympathetic dystrophy (CRPS Type I)

Continuous pain in a portion of an extremity after trauma which may include a fracture but does not involve a major nerve (causalgia), associated with sympathetic hyperactivity.

Aetiology
  Probably peripheral nervous system disorder, possible CNS component

Presentation
  Usually follows mild trauma to an extremity
  Weeks later continuous and burning pain exacerbated by movement, touch or stress
  Initial vasodilation, hyperhydrosis and oedema
  Skin atrophy, cool, red skin may be present
  Underlying bone may undergo disuse atrophy (“Sudeck’s atrophy”)
  Late vasospastic features: cool, pale, cyanosed, atrophic, Raynaud’s phenomenon, joint stiffness
  Spontaneous remission is rare

Therapy
  Pharmacological
    Sympathetic blockade with LA
    Early high-dose steroids
  Surgical
    Sympathectomy
  Physical
    Physiotherapy
  Psychological
    Depression a common complication

Causalgia (CRPS Type II)
  Similar to type I except a major nerve is injured
Problems related to pain management

respiratory
  local pain and muscle spasm ↓ ventilation
  ileus, other surgical cause → diaphragmatic splinting
  ↓ FRC, ↑ airway closure, basal collapse, shunt, infection
  “autoPEEP” with grunting respirations ↑ intrathoracic pressure
  ↑ venous stasis, ↓ venous return

cardiovascular
  ↑ sympathetic outflow
  ↑ HR, contractility, myocardial O₂ demand, risk of ischaemia
  ↑ coagulability (stress response)

GIT
  ileus exacerbated by opiates, not by epidural LA

urinary
  retention from epidural or systemic opiates

neuroendocrine
  stress response
    ↑ cortisol, aldosterone, glucagon, ADH etc.
    adaptive value uncertain

musculoskeletal
  persistent spasm → alteration in function, less effective rehabilitation

CNS
  depression, anxiety, poor sleep
  chronic pain syndromes
Chronic pain

Definition and transmission details in Pain Pharmacology (2.B.3).

Components of pain
   Noxious stimulus mediated by patient factors and modified by emotional state
   Influenced by situation and behaviour
   Stimulus-response relationship is modified at many levels
      Periphery, cord, brainstem, cortex
      Multiple stages of processing → multiple sites of therapy

Aetiology
   Usually arises from acute pain
   High-risk scenarios
      Post-herpetic, multitrauma, thoracotomy, amputation, mastectomy

Evidence-based practice
   Very little evidence, little concordance with practice
      TENS, guanethidine IVRA: proven ineffective
      Articular steroids, spinal cord stimulators: no evidence
   NSAIDs, epidural steroids, radio-frequency neurotomy, CBT: positive evidence

Management approach
   Multidisciplinary assessment usually appropriate
      Patients usually have had multiple opinions
   Coordinated plan
      Pharmacology, nerve blockade, nerve stimulation, surgery, psychology
   Medical model can relieve pain without affecting suffering or function
   CBT can improve suffering and function without change in pain

Specific therapies
   Conversion of narcotics
      Morphine
         0.1 mg IT = 30 mg IM = 100 mg po
         Acute pain (surgery) with chronic morphine use: approx. triple dose
   Neuropathic pain
      Anticonvulsants, tricyclics often effective
         Gabapentin > baclofen > valproate > phenytoin, carbamazepine
         Amitriptyline useful coanalgesic
      Calcitonin highly effective for phantom pain in first 48 hours
         3 U/kg over 30 min q8h for 3 doses, check Ca^{2+} levels
      Sympathetic blocks often effective early (stellate, coeliac, lumbar, others)
      Type I agents may be effective (lignocaine, mexiletine)
Miscellaneous anaesthesia

**Position**

**Sterilization**

**Pros and cons of anaesthetic rooms**

**Intravenous anaesthesia**
Trendelenberg Position (head-down)

Adverse effects

CVS
- ↑ CVP, ↑ HR, ↑ CO
- May precipitate failure, APO
- May cause hypotension on return to level position

Respiratory
- Abdominal contents press on diaphragm
- ↓ FRC, ↓ VC, ↓ compliance
- ↑ ventilation pressures in IPPV
- ↑ V/Q mismatch
  - PEEP may be helpful

Neurological
- Neuropraxia from pressure
  - Shoulder rests for steep Trendelenberg
  - Brachial plexus and accessory nerve
  - Stirrups in gynae laparoscopy
  - Superficial peroneal nerve

Miscellaneous 3.A.7.2 James Mitchell (October 7, 2001)
Sterilization

Why
- Prevention of disease transmission
- Medicolegal responsibilities
- Recent cases: HIV, Hep C transmission by anaesthetic techniques
- Protection of patients and staff

Crossinfection
- Requires sufficient numbers of organisms transferred from patient to patient
- Wet equipment usually harbours sufficient pathogenic organisms
- Transfer has been shown to occur in the past
  e.g. *Pseudomonas, Streptococcus* from humidifiers

High risk areas
- Equipment close to airway
- Organisms up to 1 m down tubing, mass transfer with droplets of sputum or vomitus
- Immune suppression related to anaesthesia and surgery: cellular, humoral and mechanical protection broken down.
- Some techniques limited by practicalities: airway handling and anaesthetic machine operation
- Cross infection is nonetheless rare

Risks of universal precautions
- Reassembly errors, misconnections, mechanical wear
- Latex allergy, exposure to antiseptic agents
- Cost

Sterilization techniques
- Disposable equipment: expensive, wasteful, poor quality
- Filters
- Good handling practices
- Cleaning and sterilization between cases
  - Sterilization produces known rates of elimination of all organisms
  - Disinfection is a gentler cleaning process without guaranteed sterility

Sterilization
- First step is cleaning: manual or dishwasher in a designated "dirty" area by dedicated staff
- Sterilization by heat or gas (ethylene oxide) or radiation
- Moist heat is autoclaving: for all reusable metal and plastic components
  - Cheap, quick, non-toxic
  - Specifications: commonly 134°C for 3 minutes with high pressure steam
  - Pre-wrapping in packs which can then be stored
  - Degrades: sharp edges, drugs, electrical circuits
- Dry heat
  - 150-180°C with convection for 30-60 min
  - Less blunting of needles
- Gamma radiation
  - Co^{60} emits γ rays
  - Suitable for packaged items which may be heat-labile
  - Used commercially
- Ethylene oxide used in industry for sensitive equipment
  - Cyclic ether C=\(\text{C}^\text{O}\)
  - Toxic, explosive, requires dry equipment, airing after sterilization
  - Contamination causes burns to mucous membranes

Disinfection
- By moist heat (Pasteurization) or liquid chemicals
- Pasteurization: hot water 70-90°C for specified time, drying with hot air
Suitable for more delicate equipment: laryngeal masks (can also be sterilized)
Liquid chemicals: last resort for equipment which can’t be sterilized
Cleaning surfaces, scopes
  Common agents: glutaraldehyde, 70% alcohol, sodium hypochlorite
  Requires cleaning of surfaces first, rinsing afterwards
  Fairly cheap and quick, corrosive to metals, alcohol flammable, toxic fumes

Filters
  Not 100% effective, particularly if wet
  Hygroscopic: large pore, high resistance if wet
  Hydrophobic: small pores, allow fluids to pass in small quantities, larger dead space
  Can obstruct the circuit
  Can’t be used with heated humidifiers
  Troublesome in prolonged prone cases: secretions into filter causes obstruction

Housekeeping practices
  Hand washing
    Between cases, after patient contact, before drawing up next patient’s drugs
  Gloves
    Worn for all patient contact and removed immediately afterwards with hand washing between
  Clothing
    Should be changed if dirty or between lists
  Masks
    Partly for self-protection: e.g. orthopaedics
  Placement of dirty items
    Airway equipment tray separate from drug tray
  Multiuse of ampoules
    Requires one operator and rigid procedure (if at all)
  Sharps handling
    Direct from use to sharps container

Where is cleaning done?
  Preliminary cleaning by tech in theatre
  Sterilization either in CSSD or in theatre (depending on required turnaround time)
  Verification system needs to be in place

Some things are just washed
  T-piece scavenge, laryngoscope handles, anaesthetic machine
  Some soda lime cannisters
Pros and cons of anaesthetic rooms.

Advantages
- Allows preparation of the next patient while the theatre is in use, reducing turnaround time
  - Preanaesthetic consultation (if not previously completed)
  - Insertion of lines and application of monitoring
  - Establishment of blocks
- Allows performance of minor procedures during a case
  - CVC insertion, lumbar puncture etc.
- Allows induction of anaesthesia in a less noisy and threatening environment than the OR

Disadvantages
- Requires duplication of monitoring and some equipment
  - If general anaesthesia is induced, extensive monitoring is mandated by college policy
- May require extra staffing for either sedation or general anaesthesia
  - If used for induction, transport into theatre requires a period of apnoea and inadequate monitoring

College Policy (relevant bits)
- Recommended Minimum Facilities for Safe Anaesthetic Practice in Operating Suites (T1)
  - Anaesthetic machine for each anaesthetizing location
  - Safety devices required on every machine
  - Separate emergency ventilating device
  - Suction
  - Monitoring, airway, IV... equipment
  - Availability of difficult intubation, emergency... equipment
- Sedation for Diagnostic and Minor Surgical Procedures (P9)
  - Provided that rational verbal communication to and from the patient is continuously possible during the procedure, the operator may provide the sedation and be responsible for the care of the patient.
  - Continuous pulse oximetry with alarms must be used on patients undergoing intravenous sedation.
Intravenous anaesthesia

Closed-loop control
- Drug infusion → patient → effect → monitor of effect → pharmacokinetic model
- Feasible for muscle relaxants, blood-pressure control
- “Monitor” is difficult to build for hypnotic agents
- Median EEG frequency, evoked potentials, bispectral index...
- Computed pharmacokinetic model is substituted in target-controlled infusion devices

Pharmacokinetic models
- Polyexponential model used for drug elimination
  \[ C(t) = I(t) \ast + \sum_{i=1}^{n} A_i e^{-\lambda_i t} \]
  where \( C \) is concentration, \( I \) is infused drug, \( t \) is time
  Usually not more than three compartments required
  Compartments do not necessarily represent physiological spaces

Pharmacodynamic modelling
- Relating an effect to putative biophase concentration
  \[ D_{\text{biophase}}(t) = \frac{F(E(t), P)}{C_{\text{plasma}}(t)} \]
  where \( D \) is disposition, \( E \) is effect, \( F \) is a function relating effect and other parameters \( P \) to \( C_{\text{biophase}} \).
  \( D_{\text{biophase}}(t) \) is modelled as a single term exponential equation
  \[ D_{\text{biophase}}(t) = k_{\text{eq}} e^{-k_{\text{eq}} t} \]
  So effect over time of a bolus of drug can be modelled using “time to peak effect” and \( t_{1/2}/k_{\text{eq}} \).

Application
- By deconvoluting the functions for pharmacokinetic and pharmacodynamic modelling and limiting the solutions to those involving only positive infusion rates \( (I(t) > 0) \), it is possible to derive an function for infusion rates to target a plasma concentration or end-effect

Determining target plasma levels
- An equivalent to the MAC of volatile agents for use with intravenous agents has been difficult to determine.
  - MIR is minimum infusion rate for a given effect in 50% of a population
  - Dependent on infusion duration for most agents
  - \( C_{50} \) is a steady-state plasma concentration for a given effect in 50% of a population
  - Determined as steady-state plasma levels take a long time to achieve
  - Instead commonly based on pseudo-steady-state using mathematical modelling

Plasma concentration required for a given reduction in MAC
- Determined for opioids for hypnotic and analgesic end-points
- More useful for practical application

Calculating initial bolus
- Bolus dose can be based on desired concentration and volume of distribution
- Using the \( V_d \) for the central compartment produces a dose which achieves the desired concentration only for an instant
- Using the \( V_{d_{ss}} \) gives a much larger dose with gross overshoot at the time of peak effect
- \( V_{d_{pe}} \), the calculated effective \( V_d \) at the time of peak effect, gives a resonable dose for an initial bolus
- \( V_{d_{pe}} \) for fentanyl is about 1 l/kg, propofol 0.5 l/kg, remifentanil 0.25 l/kg

Calculating infusion rate
- At \( t = \infty \), maintenance infusion rate = target conc. \times clearance
- At any earlier time, rate must be higher to account for redistribution
- Can be calculated from multicompartment distribution model
Or from nomogram based on model

**Time to recovery**

At $t = \infty$, recovery time is determined by terminal elimination half-life and total drug in body

At any earlier time, recovery is faster because of redistribution

Context-sensitive half-time is a function of infusion duration and pharmacokinetics

Describes time required for 50% decrease in plasma level

Least dependent on infusion duration for drugs with short elimination half-lives

Synergistic combinations of drugs for anaesthesia allow more rapid emergence because of lower concentrations of both drugs

*E.g.* fentanyl 1-1.5 ng/ml plus propofol 3 µg/ml provides most rapid emergence of any combination of the two drugs

**Specific drugs**

All regimens require titration to surgical stimulus

**Fentanyl**

- with volatile or propofol
  - 1.5-3 µg/kg
  - 0.01-0.04 µg/kg/min
- with N₂O
  - 5-15 µg/kg
  - 0.03-0.1 µg/kg/min

**Remifentanil**

- with volatile or propofol
  - 0.5-1 µg/kg/min
  - 0.1-0.2 µg/kg/min

**Ketamine**

- alone
  - 1-2 mg/kg
  - 30-100 µg/kg/min
- with N₂O
  - 10-50 µg/kg/min
- with propofol
  - 5-20 µg/kg/min

**Propofol**

- with opiate or N₂O
  - 1 mg/kg
  - 10,8,6 mg/kg/h (↓ every 10 min)
Monitoring

**ECG features**

**Pulse Oximetry**

**Neurological monitoring**

**Neuromuscular monitoring**

**College requirements**
ECG features

<table>
<thead>
<tr>
<th>Lead</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA</td>
<td>Right wrist</td>
</tr>
<tr>
<td>RL</td>
<td>Right ankle</td>
</tr>
<tr>
<td>LA</td>
<td>Left wrist</td>
</tr>
<tr>
<td>LL</td>
<td>Left ankle</td>
</tr>
<tr>
<td>V1</td>
<td>4th intercostal space, right of sternal border</td>
</tr>
<tr>
<td>V2</td>
<td>4th intercostal space, left of sternal border</td>
</tr>
<tr>
<td>V3</td>
<td>Between V2 and V4</td>
</tr>
<tr>
<td>V4</td>
<td>5th intercostal space, left midclavicular line</td>
</tr>
<tr>
<td>V5</td>
<td>5th intercostal space, left anterior axillary line</td>
</tr>
<tr>
<td>V6</td>
<td>5th intercostal space, left midaxillary line</td>
</tr>
</tbody>
</table>

Change ECG Response

**Hypokalemia**
- ST segment depression
- T wave flattening and inversion
- Tall U wave

**Hyperkalemia**
- Tall T wave
- PR interval prolongation
- ST segment depression
- QRS widening
- Ventricular fibrillation

**Hypocalcemia**
- Prolonged Q-T interval

**Hypercalcemia**
- Short Q-T interval
- ST segment may disappear

**Hypothermia**
- Bradycardia, prolonged PR, QRS and QT
  - Below 33°C: J wave, T inversion, 1° AVB, AF
  - Below 30°C: 3° AVB
  - Below 28°C: VF increasingly common
  - Below 20°C: asystole

**Digoxin**
- Prolonged PR, short QT, ST depression “scooped”
- Small or inverted T

ECG feature Diagnosis

- Upsloping ST depression Likely ischaemia
- Downsloping ST depression Definite ischaemia
- Inverted T wave Subendocardial ischaemia
- ST elevation Transmural ischaemia
- Q wave >0.03 s Infarction
Pulse Oximetry

Artefacts in SpO₂

- COHb, HbH  slight ↓ SpO₂ (appears as deoxyHb)
- MetHb  approaches 85%
- SulfHb  appears as MetHb on co-oximetry
- HbKöln  ↓ by 8-10%
- Dyes  ↓ variable severity
  - methylene blue > isosulfan blue > indigo carmine, indocyanine green
- Anaemia  increasing underreading with hypoxia

Venous pulsation, vasodilatation
  ↓ SpO₂ due to venous pulsation

Black henna, dark nail polish, deep pigmentation, tape, vasoconstriction
  reduced signal

HbF, HbS, Hb substitutes, fluorescein, polycythæmia, red henna, jaundice
  no effect
Neurological monitoring

EEG

Electrodes

“10-20 system”
20 electrodes in a standard arrangement
< 5 kΩ resistance
Intraoperative use usually a smaller subset

Signal

10-50 µV, 4-20 Hz
β > 13 Hz
α 8-13 Hz
θ 4-8 Hz
δ 4 Hz

Processing

Full EEG is 16-20 channels
Processed EEG
Power analysis (simple spectral analysis)
Spectral Edge Frequency 95% (95th centile frequency)
Median Frequency
Relative Delta Power (% in δ band)
Bispectral analysis
Includes phase data in analysis
Bispectral Index (BIS)
0-100, 50% unconscious at 67, 95% at 50
Validity for amnesia, unconsciousness, prevention of response to surgery depends on the anaesthetic technique

Change with anaesthesia

Standard pattern with increasing depth
Activation, frontal spindles, 1-3 Hz activity, burst suppression, silence
Produced by barbiturates, propofol, etomidate, benzodizepines (no silence), volatiles (except epileptiform activity wth enflurane)

Opioids
↓ frequency, ↑ amplitude

Ketamine
Frontal θ activity with ↑ amplitude
Higher doses, δ and β activity
No silence, slow recovery of normal pattern

N₂O
Potentiates standard agents
Alone produces frontal >30 Hz activity

Hypoxia
Slowing, silence with severe hypoxia

Hypotension
Severe hypotension required for clear effects: low frequencies

Hypothermia
Slowing, silence at 15-18˚C

Transcranial Doppler ultrasound

Principle
Continuous wave Doppler ultrasound
Applied to temples
Aligned with middle cerebral artery

Function
Display of velocity spectrum against time
Derived values for an index of cerebral blood flow and pulsatility
Detection of emboli, vasospasm
Assessment of autoregulatory function by monitoring blood flow over a range of perfusion pressures

Jugular bulb oximetry

Principle
Oximeter inserted percutaneously into internal jugular vein

Function
Measured SvO₂ of venous drainage of brain
Combined with SaO₂ allows calculation of an index of O₂ extraction
Maximal O₂ extraction suggests ischaemia

Problems
Careful calibration required
Assessment only of global perfusion
Significant variability from side to side
Bilateral placement might be necessary

Cerebral oximetry

Principle
Pulse oximeter applied to scalp

Function
Output related to scalp perfusion, no useful information about cerebral ischaemia

Evoked potentials

Applications
Cerebral injury: carotid surgery, craniotomy, CPA surgery
Spinal injury: AAA, spinal cord and column surgery
Peripheral nerve injury: parotidectomy...

Visual evoked potentials
Goggles with flashing patterns, occipital EEG
Test retina, optic nerve, chiasm, radiation, occipital cortex
Rarely used

Somatosensory evoked potentials
Transcutaneous nerve stimulation (20 Hz, 100-400 V)
EEG monitoring (frequency tuned 1-2 μV amplitude)
Measured: waveform amplitude and latency
Latency ↑ 15%, amplitude ↓ 50% suggests injury
Tests nerve, dorsal and ventrolateral tracts, cortex
Median nerve → MCA territory
Posterior tibial nerve → ACA territory

Interference
Drugs
N₂O > volatile > propofol: ↓ amplitude
opioids: minimal ↑ latency
Hypothermia: ↑ latency 1.15 ms (5%) per °C
Neuromuscular monitoring

At 60 Hz

0.05 mA  microshock current for VF
0.3-0.5 mA  threshold of perception
0.1-2.5 mA  macroshock current for VF
1-2 mA  pain
8-20 mA  “cannot let go”
Vaporizers & gas delivery

Outline hazards of anaesthetic machines

Outline arrangements of flow meters on the anaesthetic machine

Outline vaporizer arrangements on the anaesthetic machine

Classify breathing systems

Briefly outline the protocol for checking the anaesthetic machine

Vaporizers

Oxygen therapy

Gas cylinders

Suction ports
Outline hazards of anaesthetic machines.

Physical design
- Mobile and able to fall over
- Must be stable at up to 8˚ tilt

Medical gas supply
- Misconnection: pipeline, wall outlet, cylinder
- Contamination
  - Wrong gas due to backflow from mixing devices
  - Errors in gas manufacture and processing
  - Solvents or particulate matter from welding

Gas regulators
- Cooling with gas expansion may freeze valve seats
- Heating with rapid pressurization on opening gas cylinders may ignite grease
- Regulators may allow transition from pipeline to cylinder supply without alarm

Rotameters
- Bobbin & tube mismatched
  - Transposed in servicing, over- or under-read
- Gas leak
  - Test with application of soapy water
- Selective oxygen leak
  - Reason for oxygen mixing downstream
  - Can still occur with leak in flowmeter before bypass tube

Mechanical failure
- Damage to bobbin, stops, needle valve
- CO₂-related incidents
  - If CO₂ rotameter is fitted
- Contamination of flowmeter assembly
- Float not visible at top of tube
  - Flowmeter fully open but not noticed

Valves
- Resistance, obstruction, incompetence
  - Due to wear, moisture, misassembly, damage

Vaporizers
- Agent impurities, breakdown products
- Mounting problems
  - Leaks, interlock failure
- Output control problems
- Filling problems
  - Incorrect agent, overfilling, underfilling
- Free-standing vaporizers
  - Tipping, misconnection
  - Placement after oxygen flush

Thymol accumulation

Breathing systems
All systems
- Leaks
- Potential infection risk
- Humidifier disconnection or overheating
Circle system
- Valve failure
  - Rebreathing, high circuit pressure
- Absorber problems
  - Leaks, reaction with volatile agents, inhalation of dust, streaming of flow, exhaustion of soda lime
  - Condensation in circuit: inadvertent PEEP
Uncertainty in gas composition at low flows without agent monitoring
Mapleson systems
Potential for significant rebreathing at low flows

Ventilators
Hazards are model-specific
Pressure
Delivery of high airway pressures
Gas composition
Contamination of circuit gas with driver gas
Leak of circuit gas
Flow
Under- or over-ventilation
Failure to deliver adequate volume in pressure-cycled modes
Alarms
Failure to detect disconnection due to resistance in breathing system
Inadvertent inactivation
Failure or absence of power failure or “off” alarm
Potential disease transmission

Monitoring systems
Electrical safety
Patient isolation
Power backup
Alarms
Failure due to inactivation or inappropriate settings
Injury associated with monitor placement
e.g. Temperature probe epistaxis, BP cuff bruising
Misreading
Monitor misplacement or device failure
Outline arrangements of flow meters on the anaesthetic machine.

Flowmeter
A device to control and indicate flow of medical gases accurately.

Standard requirements
Flow control knob should be adjacent to flow indicator
Oxygen control knob has a characteristic profile: 8 equally spaced flutes
Oxygen flowmeter must be on the left (UK, Europe, Australia) or right (US)
Axial pressure on the knob must not greatly alter flow
Only one flow control for each gas
Oxygen must be delivered downstream in the flowmeter manifold
Mixer must not deliver <25% $O_2$
Outline vaporizer arrangements on the anaesthetic machine.

Principle
Vaporizer delivers a calibrated concentration of anaesthetic vapour into gas passing through the device
Gas is divided into bypass and vaporization chambers
   Gas in bypass chamber remains unchanged
   Gas in vaporization chamber is saturated with anaesthetic vapour
Delivery is dependent on flow, temperature and gas pressure
   Temperature compensation is integral in modern vaporizers
Output falls at high flows
Pumping effect is prevented by vaporizer design
Pressure effect is minor

Classification
   Draw-over vs plenum (plenum: uses vapour-saturated gas)
   Variable bypass vs measured flow
   Vaporization method
   Location (in-circuit vs out-of-circuit)
   Temperature compensation
   Pressure compensation
   Resistance
   Agent specificity

Position
   Historically in-circuit or out-of-circuit
   Now usually placed out-of-circuit between flowmeters and common gas outlet or replaced by electronic direct injection of vapour
   Interlock to prevent multiple vaporizers being on concurrently
      Prevents transfer of vapour from upstream to downstream vaporizer
      Reduced output of upstream agent
      Contamination of downstream vaporizer
   Contamination also minimized by placing higher SVP agent downstream

Modern plenum vaporizers
   Variable bypass, VOC, temperature compensated, backpressure resistant, high resistance, agent specific
   Most use wick vaporization except TEC6, Engstrom Elsa, Datex ADU
Models
   Ohmeda TEC series
   Penlon PPV ∑ and ∑ Elite
   Blease Datum
   Vapamasta
   Dräger 19.3
Classify breathing systems.

Rebreathing

Mapleson A
Magill
Most efficient for SV, requiring 70% of MV as FGF
3 x MV required for IPPV
Lack
Mapleson A with coaxial expiratory tubing
Mapleson B, C
Rarely used, closed bag requires high FGF
Mapleson D
Bain
Low resistance, single tube, FGF 70-80 ml/kg/min
Mapleson E
Replaced by Mapleson F (Jackson-Rees' modification)
Mapleson F
Common use for paediatric anaesthesia
FGF 2-3 times MV
Switchable devices
Several varieties for switchable A/D circuit types

Non-rebreathing valve systems
Laerdal bag
Triservice apparatus
T-piece oxygen/air inlet, drawover vaporizers, self-inflating bag, non-rebreathing valve
CO2 absorption systems
Water's to-and-fro system
Mapleson C with absorber near patient, obsolete
Circle systems
Many configurations
Commonly
  APL valve in expiratory limb before absorber
  FGF in inspiratory limb after absorber
Nomenclature depends on component arrangements
  VIC/VOC, closed/semi-closed, coaxial/not-coaxial
Advantages
  Economical of gases and vapour
  Hypocarbia easy to achieve
  Good heat and water conservation
Disadvantages
  Large number of parts, risk of faults, complex ventilator required
  Bulky, cleaning difficult
  Soda lime dust can be inhaled
  Trichloroethylene cannot be used
Briefly outline the protocol for checking the anaesthetic machine.

Level 1
- Detailed service check by manufacturer's personnel or technician
- Detailed documentation of checking and calibration
- Label visible to anaesthetist of next scheduled check
  - Gas delivery
    - Quantify and minimize leaks, exclude crossed pipelines, check valves, check O₂ failure device
  - Accuracy of vaporizers
  - Compliance with Standards

Level 2
- Anaesthetist or technician check at the start of a list
  - High pressure system
    - Cylinder and pipeline supply, cylinders off
    - Single gas test for oxygen
  - Low pressure system
    - Control valves and flowmeters
    - Hypoxic interlock device
  - Vaporizers
    - Filled, ports closed, correctly seated, no leak on or off, electricity supply
  - Precircuit leak test
  - Breathing system
    - Check connections
    - Leak test (<300 ml/min at 30 cmH₂O)
    - Check valves: one way and APL
  - Ventilator, function, leak, alarms
  - Scavenging at correct pressure
  - Spare self-inflating bag
  - Other apparatus
    - Intubation equipment, suction, gas analysis, monitoring, IV infusion, warming, humidifier, filters
  - Final check
    - Vaporizers off, purge with oxygen or air

Level 3
- Brief check before each case
- If vaporizer or breathing circuit is changed, recheck
- Recheck other apparatus
Vaporizers

Tec 6

- Separate gas and vapour circuits
- Fresh gas flow passes a fixed resistance in vaporizer
  - Pressure upstream of the resistance is “working pressure”
  - Proportional to gas flow
- Desflurane is heated to 39°C (1300 mmHg absolute)
  - Pressure downregulated to “working pressure” by differential pressure transducer, electronics and regulating valve
  - Desflurane passes through a variable resistance controlled by the concentration dial on the vaporizer
    - Desflurane output varies with working pressure and concentration selected
- Carrier gas affects working pressure
  - Lower desflurane output with N₂O
- Altitude does not affect concentration delivered (unlike variable bypass vaporizers)
  - Lower partial pressure delivered at lower ambient pressure
  - Potential for awareness
  - Vaporizer requires adjustment for ambient pressure
Oxygen therapy

Fixed performance
- High flow Venturi masks
  - O₂ flow of 6-8 l/min entrains air
  - Total flow 40-60 l/min, FiO₂ 25-60%
- Anaesthetic circuits, CPAP or PEEP machines
  - Require air-tight fit
  - Reservoir allows fixed FiO₂ (20-100%)

Variable performance
- No capacity
  - Nasal catheters
    - FiO₂ depends on flow rate and PIFR
- Small capacity
  - Simple face masks (e.g. Hudson mask)
    - O₂ flow and PIFR determine FiO₂

<table>
<thead>
<tr>
<th>O₂ flow</th>
<th>FiO₂ (approx.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>0.35</td>
</tr>
<tr>
<td>6</td>
<td>0.50</td>
</tr>
<tr>
<td>8</td>
<td>0.55</td>
</tr>
<tr>
<td>10</td>
<td>0.60</td>
</tr>
<tr>
<td>12</td>
<td>0.65</td>
</tr>
<tr>
<td>15</td>
<td>0.70</td>
</tr>
</tbody>
</table>

- Tracheostomy masks, T-piece circuit, face tent (soft bowl-shaped mask)
- Large capacity
  - Face masks with reservoir bags
    - Higher FiO₂, risk of rebreathing if disconnected
  - Head boxes, incubators, tents
Gas cylinders

Markings specified by AS2030 (1977)
Requirements

ID number
Owner’s mark
CIG, LAA, MD, NZIG
Water capacity
Mass of water required to fill cylinder at 15˚C
Test pressure
Testing station mark and date

British Tube Mills, Australia Liquid Air, Gas

Cylinders, CIG (X location, nn year), Tubemakers, Luxfer

Holdings, National Vulcan Engineering Insurance Group

Manufacturer’s mark
May be combined with testing station mark
Standards specification mark
For cylinder type e.g. AS B114 for alloy steel cylinders
Tare mass
Weight of empty cylinder without valve
Name or symbol of gas and colouring to identify contents
ISO standard

<table>
<thead>
<tr>
<th>Gas</th>
<th>Pins</th>
<th>Colour</th>
</tr>
</thead>
<tbody>
<tr>
<td>CO₂</td>
<td>1,6</td>
<td>grey</td>
</tr>
<tr>
<td>O₂</td>
<td>2,5</td>
<td>black (with white shoulder for medical O₂)</td>
</tr>
<tr>
<td>air</td>
<td>1,5</td>
<td>grey with black and white shoulder</td>
</tr>
<tr>
<td>N₂O</td>
<td>3,5</td>
<td>blue</td>
</tr>
<tr>
<td>He</td>
<td>4,6</td>
<td>brown</td>
</tr>
<tr>
<td>C₃H₆</td>
<td>3,6</td>
<td>orange</td>
</tr>
<tr>
<td>N₂</td>
<td></td>
<td>grey with black shoulder</td>
</tr>
<tr>
<td>Entonox</td>
<td>single</td>
<td>blue with blue and white shoulder</td>
</tr>
<tr>
<td>Heliox</td>
<td>4,6</td>
<td>brown with black and white shoulder</td>
</tr>
<tr>
<td>Carbogen</td>
<td>2,6</td>
<td>black with grey and white shoulder</td>
</tr>
</tbody>
</table>

Aluminium ring on neck of cylinders containing liquifiable gas

Tare weight with valve, date, test station, number and “ET” if eductor tube present

Plastic tab on some aluminium cylinders to detect excessive heat exposure
Star indicates use for dry gas only

Filling ratio
Used for liquifiable gases: N₂O, CO₂, C₃H₆
Ratio of mass of gas to water capacity at 15˚C
Specification to ensure pressure does not exceed 80% of test pressure at 65˚C
Suction ports

AS 2896, AS 2120.3

Number of ports
- OR: 4
- PACU, ICU: 3
- Delivery: 2 + 1 for baby
- Resus: 2
- Coronary care, anaesthetic room, etc.: 1

Each port
- 40 l/min free flow
- -60 kPa (-500 mmHg, -600 cmH₂O)
- Time constant ≤ 4 s

Central vacuum source
- At least two pumps with automatic switching
- Each capable of meeting peak demand
- Reservoir tank

Venturi suction
- Dry gas flow entrains gas from suction device
- Obstruction of gas flow outlet can result in high positive pressure
  - Large venturis have a safety device to prevent pressurization
- Twin-O-Vac commonly used for portable suction
  - 16 l/min or -55 kPa (using 22 l/min O₂)
  - Not up to AS 2120, but better than nothing
  - No protection against pressurization

Scavenging
- Must be separate from suction (different sleeve index)
- 30 mm or 19 mm connections
  - Usually pink 30 mm hose
- Passive
  - Simple hose from circuit to external vent (with fluid trap)
  - Able to transfer 75 l/min with acceptable back-pressure (∼0.5 cmH₂O)
  - Must be gas-tight
  - Obstruction may cause raised circuit pressure
- Active
  - Suction applied to 3 l reservoir with indicator for 20-30 l/min flow through vents
  - 30 mm tubing to circuit
  - Able to absorb 4 l bolus of exhaust without contamination of theatre
  - Multiple vents on reservoir to prevent negative circuit pressure with occlusion
Miscellaneous Equipment

Fires & Explosions

Lasers
Fires & Explosions

Explosion
Combustion fast enough to produce sound waves
Most likely with a stoichiometric combination of substances

Detonation
Combustion fast enough to produce compression waves initiating further ignition

Flammability limits
Concentrations between which combustion is supported
Lower flammability limits for volatiles (theoretical)

<table>
<thead>
<tr>
<th>Agent</th>
<th>100% O₂</th>
<th>1:4 O₂:N₂O</th>
<th>1:2 O₂:N₂O</th>
</tr>
</thead>
<tbody>
<tr>
<td>Halothane</td>
<td>3.25%</td>
<td>4.75%</td>
<td></td>
</tr>
<tr>
<td>Enflurane</td>
<td>5.2%</td>
<td>4.25%</td>
<td>5.75%</td>
</tr>
<tr>
<td>Isoflurane</td>
<td>8.75%</td>
<td>5.25%</td>
<td>7.0%</td>
</tr>
</tbody>
</table>

Flammability index
Fractional O₂ or N₂O flow in N₂ which supports sustained combustion
PVC > silicone > red rubber

Sources of ignition
- Static electricity
  Prevented with conductive flooring, earthing, high humidity
- Electrical switches
  Shielded or placed above “Five foot line”
- Diathermy
  Avoid in close proximity to airway or bowel gases
- Laser, fibreoptic light sources
- Adiabatic compression

Combustible things in theatre
- Gases and vapours
  Anaesthetic agents withdrawn
  Alcoholic prep.
  Bowel gases
- Drapes
- Papers and plastics

Miscellaneous Equipment 3.B.5.2 James Mitchell (October 7, 2001)
Lasers

Laser
Light Amplification by Stimulated Emission of Radiation
Source of coherent, monochromatic, collimated light
Lasing medium (gas, liquid or crystal) with mirrors at each end, pumping source
Delivery system
  Aperture, guide, frequency doubler if necessary
  Applicator: lenses, contact tip, diffuser
Mode of delivery
  Continuous wave, pulsed, quality-switched, mode-locked
Extinction length (EL)
  Depth of tissue for 90% absorption
Popular types
  Carbon dioxide (CO₂)
    10600 nm absorbed by water
    Used for superficial lesions (EL 0.03 mm)
  Neodymium-yttrium-aluminium garnet (Nd-YAG)
    1064 nm (near IR) absorbed by water
    High power, deep penetration (EL 3 mm)
    Addition of potassium-titanyl-phosphate (KTP) frequency doubler produces 532 nm (green) laser
  Argon (Ag)
    458-515 nm (blue green)
    Absorbed by Hb, photocoagulation
    Suitable for retinal work
  Helium-neon (HeNe)
    632 nm (red)
    Low power red laser used for aligning invisible lasers
Safe use (AS 4173, AS 2211)
Equipment design
  Control key to lock machine, warning signs, shutters, safety interlocks and emergency shut-off
Protocols
  Laser safety committee and officer
  Closed theatre with blinds and signs
  Eye protection
  Appropriately trained staff
  Eye examinations
  Drill for fire management
Anaesthetic issues
  Difficulty reading displays through tinted glasses
  Fire risk with drapes, and especially with shared airway
  Smoke plume removal to avoid inhalation or viral transmission
  Potential for gas embolism with gas-cooled lasers
Cardiology

Aortic incompetence

Mitral stenosis

Pacemaker management

Heart block management
Aortic incompetence

Aetiology
Acute
Endocarditis, aortic dissection, connective tissue disease, trauma

Pathophysiology
Acute
Sudden volume load on LV
↑ LVEDP, PAOP
Sympathetic response: ↑ HR, vasoconstriction
May cause acute decompensation and failure

Chronic
Progressive LV enlargement and hypertrophy
High compliance, high output
Late decompensation (10-20 years)

Classification
Regurgitant flow: < 3 l/min mild, 3-6 l/min moderate, > 6 l/min severe
Or by contrast findings on aortogram

Features
Tachycardia: ↓ regurgitation, LVEDV, ↑ coronary perfusion
Relatively little increase in myocardial O₂ demand until late
Volume work increases O₂ demand less than pressure work

Management
Responsive to pressors, but vasodilators may increase forward flow
Diastolic hypotension and bradycardia to be avoided (↓ coronary perfusion)
IABP contraindicated (enhances retrograde flow)

Valve replacement
Retrograde flow of pump blood may distend LV until aortic clamping
Anterograde cardioplegia may be difficult
Mitral stenosis

Aetiology
- Usually rheumatic heart disease

Clinical features
- Symptomatic early, slow progression
- Marked worsening with ↑ demand for CO (pregnancy) or development of AF

Severity
- Pressure gradient not useful (dependent on HR, CO...)
- Valve area (normal 4-6 cm$^2$)
  - Mild 1.5-2.5 cm$^2$
  - Moderate 1-1.5 cm$^2$
  - Severe <1 cm$^2$

Anaesthetic management
- Heart rate maintained low-normal in sinus rhythm
  - Bradycardia → ↓ CO due to low SV
  - Tachycardia → ↓ CO due to slow diastolic filling
  - AF → sudden decompensation, especially with rapid ventricular rate
- Maximal tolerated LAP without pulmonary oedema
- Risk of complications from PA catheter
  - Pulmonary hypertension: ↑ risk of PA rupture, unreliable PAOP
- Risk of RV failure with pulmonary hypertension
  - Septal deviation impairs LV filling
  - Prevent with NO, lowering PVR
Pacemaker management

Identification code (5 letters)
- Chamber paced: O, Atrium, Ventricle, Dual
- Chamber sensed: O, Atrium, Ventricle, Dual
- Mode of response: O, Triggered, Inhibited, Dual
- Antitachycardic function: O, Pacing, Shock, Dual
- Programmability: O, Program, Multi-program, Communicating, Rate-response

Modes

Asynchronous
- AOO, VOO, DOO: pacing regardless of underlying activity
  - Fall-back mode only as wasteful of battery and may compete with intrinsic rhythm

Single chamber demand
- AAI, VVI: single chamber pacing inhibited by intrinsic activity
- Simple single-lead pacemakers
- AAI requires intact A-V conduction
- VVI does not maintain A-V synchrony

Dual chamber
- A-V synchronous (VAT, VDD)
- A-V sequential (DVI)
- Universal (DDD)
  - Operate in AAI, VDD or DVI as required
- A-V inhibited (DDI)
  - Used where atrial tachycardia causes rapid ventricular pacing in DDD

Rate responsive
- Provide exercise response in patient who are pacemaker-dependent
- Various sensors used
  - Temperature, SvO₂, respiratory rate or minute volume, QT interval, vibration, acceleration

Antitachycardia functions
- Simple shock devices
  - Recognize sustained tachycardia
  - Deliver 25-30 J shocks up to five times
- Tiered (dual) therapy devices
  - Pacing for bradycardia
  - Overdrive pacing for atrial tachycardia
  - Low energy cardioversion for VT
  - High energy defibrillation for VF
  - Generate palpable but not dangerous voltage at the body surface

Issues
- Maintain stable heart rate and rhythm throughout surgery

Preoperative

History
- Reason for pacemaker insertion
- Symptomatic arrhythmias or IHD
- Medications
- Other illnesses
- Type of pacemaker, who manages it, last tested, history of problems
- Previous anaesthetics

Examination
- Routine, focussing on cardiorespiratory examination
- Identify location of box

Investigation
- ECG
  - Identify rhythm, presence of pacing spikes

Cardiology 3.C.1.4 James Mitchell (October 7, 2001)
Consultation
- Cardiologist to determine pacing mode, rate-responsiveness

**Rate-responsiveness and antitachycardia functions must be switched off prior to surgery**

Premedication
- Continue cardiac medications

Transport
- Avoid excess movement if movement-responsive

Preparation
- Chronotropic medications available, external pacemaker may be available
  - Atropine, isoprenaline
- Routine access and monitoring
  - Additional heart rate monitor not susceptible to diathermy interference
  - Precordial stethoscope or palpable pulse
- ECG leads short: can act as antennae
  - “Cardiac protected” theatre required

Intraoperative
- Sensing pacemakers can be affected by myopotentials, movement, diathermy

Induction
- Suxamethonium fasciculations produce myopotentials
- Excess ventilation simulates exercise in movement-responsive pacemakers
- No requirement for prophylactic antibiotics

Maintenance
- Position so that pacemaker is not a pressure area

Diathermy
- Problems
  - Direct damage to pacemaker from current
  - Microshock (VF) from current through lead
  - Inhibition of pacemaker by current if in demand mode

Precautions
- No diathermy within 15 cm of pacemaker
- Brief bursts of diathermy if interfering with pacing
- Preferably bipolar diathermy with minimal current
- Consider changing mode to asynchronous
- Diathermy current distant from and at 90˚ to pacemaker
  - Grounding plate distant, but not if head & neck surgery
- Avoidance of N₂O with a recently implanted pacemaker
  - Expanding a gas pocket around the generator can cause loss of anode contact with a unipolar generator

Maintenance
- Maintain temperature to avoid post-op shivering

Emergencies
- Use of a ring magnet
  - In VVI will set a fixed rate
  - Effect is not predictable in programmable pacemakers

“Pacemaker syndrome”
- Activation of VVI pacemaker causes hypotension
- Loss of AV synchrony or retrograde conduction causes fall in CO
- Atrial stretch causes reflex vasodilatation

Pacemaker failure
- Interference from electrical activity or muscle potentials
- Failure to capture due to electrolyte disturbance or drugs
  - Hypoxia, hypercarbia, ↑ intracellular K⁺, hypernatremia
  - Verapamil, β-blockers, quinidine

Defibrillation
- Paddles at least 12 cm from generator, orientated at 90˚ to AICD electrodes
Management of heart block

Issues
  Risk of development of AV block with bradycardia
  Is a prophylactic pacemaker required?
  Risk of associated cardiac disease

Preoperative Assessment
  Conduction defect
    Symptoms: dizziness, drop attacks, palpitations
    Cardiac examination: BP and HR, arrhythmia
    Previous investigation: conduction studies, ECG
  Stability of disease
  Associated disease
    History of Lev's or Lenegre's disease
    Fibrosis of His bundle or terminal fibres
    Cardiac surgery or His ablation
    Cardiomyopathy
    IHD
    Previous investigations: stress test, echo, coronary angiogram etc.
  Drug therapy either treating or causing block
    e.g. digoxin, propranolol, quinidine, procainamide, verapamil

General assessment
  Level of function
  Routine anaesthetic assessment

Investigation
  ECG, U&E, specific investigations as indicated

Consultation
  Discussion with treating cardiologist
  Optimize medication regimen
  Defer surgery if time is needed
  Decision whether preoperative pacing is required
    Not usually necessary unless unstable and symptomatic
    If unstable, insert transvenous pacing wire under LA

Premedication
  Continue usual cardiac drugs
  Anxiolytic, sedative premedication

Consent
  Discuss possible requirement for temporary pacing
  Anaesthetic plan
    Regional with avoidance of hypotension preferable to GA

Intraoperative Preparation
  Routine anaesthetic equipment prepared
  Drugs and equipment for rapid conversion to GA if necessary
  Chronotropes available for CHB: atropine, isoprenaline
  Transvenous or external pacing equipment available

Monitoring
  Routine, plus
  5 lead ECG monitor prior to block insertion
  Large bore IV access

Induction
  Low spinal or epidural catheter
    Depending on likely duration of surgery and stability of disease
  Preloading with fluid
Pressors drawn up

Emergencies

Heart block with nodal rhythm
Usually responsive to atropine

Heart block with ventricular escape
Usually accompanied by bradycardia, hypotension
Immediate transvenous or external pacing if available

Otherwise

- Airway control and ventilation with 100% O₂ if unconscious
- IV fluid
- Rate support with isoprenaline and atropine until
- Insertion of transvenous pacing wire
Endocrinology

Diabetes

Perioperative corticosteroid supplementation
Diabetes

Classification

Type I
- Autoimmune disease, 40-50% concordance, β-cell destruction, ? viral or environmental trigger, insulin deficiency
- Prone to diabetic ketoacidosis
- Presents at an early age
- Require insulin replacement

Type II
- 100% genetic concordance, increased in obese, insulin resistance
- Not prone to DKA, but may develop hyperglycaemic hyperosmolar coma
- Presents in middle aged or elderly (except MODY)
- Initial therapy often with diet, exercise, oral agents, later insulin

Insulin
- Synthesized in endocrine pancreas (islets of Langerhans) by β-cells
  - α-cells secrete glucagon, δ-cells secrete somatostatin, F cells secrete pancreatic polypeptide
  - Normal secretion 1 U/kg/day, peaks after meals, t¹/₂ 5 min
- Release stimulated by
  - Plasma glucose and fructose, amino acids, glucagon, gastrin, secretin, CPK, ACh, catechols via β receptors
  - GH increases insulin responsiveness
- Release inhibited by
  - Somatostatin, catechols via α-receptors

Perioperative management

Evidence
- Diabetics are at increased risk of complications
  - Due to secondary effects of diabetes (IHD, renal disease...) not due to hyperglycaemia
- Tight control of blood sugar
  - Reduces chronic complications of diabetes
  - Benefits foetus in pregnancy
    - Less macrosomia
  - Beneficial during cardiopulmonary bypass
    - More responsive to inotropes
    - Stress response produces hyperglycaemia
    - Hypothermia diminishes insulin sensitivity
  - Beneficial during cerebral ischaemia
    - Lower risk of neurological damage
- Otherwise little evidence for advantages in tight perioperative control

Major risks in the diabetic patient
- Cardiovascular: IHD, PVD, microvascular disease
- Renal impairment
- Neuropathies
- Impaired cellular immunity
- Joint collagen abnormality (jaw stiffness, poor deep wound healing)

Resuscitation of the DKA patient for emergency surgery
- Usually time for fluid replacement, electrolyte correction
- Fluid deficit 3-10 l (Saline 5-10 ml/kg plus 1-4 l/h)
- Potassium deficit 3-10 mmol/kg (KCl 10-20 mmol/l fluid)
- Insulin deficit
  - Correct K⁺ < 3 mmol/l first
  - 10 U bolus plus 5-10 U/h titrated against blood sugar
Add 5% dextrose to fluids when glucose < 15 mmol/l
Hourly ABG and glucose
   Aim for glucose 10-14 mmol/l, pH > 7.35, Na⁺ < 155 mmol/l, K⁺ 3-5 mmol/l
   Also phosphate, magnesium deficient
Classic “non-tight control” regimen
   Fast from midnight for morning surgery
   5% dextrose 125 ml/h IV from 6am
   Half normal morning dose of insulin
   Check BSL 1-4 hourly
   Sliding scale insulin from recovery until return to normal diet
“Tight” regimen
   Check fasting glucose day before surgery
   5% dextrose 50 ml/h IV
   Initial insulin IV rate (U/h) = BSL/8.3 (mmol/l) (or BSL/5.5 if on steroids)
   Titrate insulin rate to BSL 5.5-11.1 mmol/l
   Check BSL at start of surgery and every 1-2 h for 24 h
Other perioperative concerns
   Autonomic neuropathy
      ↑ gastric emptying time, risk of aspiration
      Painless myocardial ischaemia
      Signs include hypertension, lack of sweating, lack of R-R variability,
      postural hypotension, peripheral neuropathy
   Microvascular disease
      ? ↑ risk of neuropraxia with regional
Perioperative corticosteroid supplementation

Evidence
  Few patients with adrenocortical suppression have problems even without steroid cover: documented cases are rare
  Acute adrenal insufficiency is life-threatening
  Perioperative steroid cover carries minimal risks
  Primate study found no difference between physiologic and supraphysiologic doses

Physiology
  Maximum adrenal cortisol output 200-500 mg/d
  Normal 25 mg/d

Risks of supplementation
  Possible
    Minor impairment of wound healing (antagonized by vitamin A)
    Impaired immune function
    Hypertension, fluid retention, stress ulcers, psychosis
    Aseptic necrosis of head of femur

Recommended regimen
  Indicated for all patients receiving steroids within past year
  Not less than usual preoperative dose equivalent
  Hydrocortisone 200 mg/d for 70 kg adult (100 mg for minor procedures)
  Reducing 25% per day until oral steroids resumed
Haematology

Outline management of a sickle-cell patient for appendicectomy

Review of paediatric transfusion

Deep vein thrombosis
Outline management of a sickle-cell patient for appendicectomy.

Appendicectomy
Urgent operation, moderate risk

Patient factors
Sickle cell anaemia
May be trait, sickle cell disease or Hb SC or other variants
Severity of disease determined by Hb type
Hb SS
Anaemic Hb 70-80 g/l
Vaso-occlusive crises cause organ infarction
Especially spleen, renal papillae, skin (if cold), CNS
Complications
Poor spleen function, encapsulated organism susceptibility
Hepatomegaly
Impaired renal function
May cause “acute abdomen”, confused with appendicitis

Appendicitis
Causes fever, acidosis: ↑ risk of sickle crisis
Patient not fasted, commonly with an ileus: risk of aspiration

Preoperative Assessment
Usual patient assessment: clinical, baseline investigations
Severity of sickle cell disease
FBE, history, abdominal and skin examination
Resuscitation status
Needs to be warm, well-filled, supplemental oxygen

Premedication
Usually avoided as may cause hypoventilation
Oxygen by face mask, prewarming with forced-air warmer

Intraoperative
Objectives: normothermia, avoid hypoxaemia and acidosis to minimize risk of sickling
Monitoring
Usual monitoring
ECG, NIBP, SpO₂, gas analysis, airway pressure, urinary catheter, temp
Anaesthetic technique
General anaesthesia: balanced technique with muscle relaxation
Induction
Rapid sequence induction
Check equipment, difficult airway equipment available
Preoxygenation, cricoid pressure
Thiopentone (3-4 mg/kg), suxamethonium (1-1.5 mg/kg)
Reduce thiopentone dose if underfilled to avoid hypotension
Secure airway with cuffed ETT
Maintenance
Ventilate with increased FiO₂, normocapnia
Analgesia with local anaesthetic in wound plus narcotic as necessary
More likely to require transfusion if significant blood loss
Avoid hypothermia aggressively if necessary (often febrile)
Emergence
Extubation awake in lateral position
Postoperative
Maintain supplemental oxygen, keep warm
Narcotic analgesia will be required, but hypoventilation is a risk
Prompted by HIV transmission case

Transmission would have occurred once the infected unit had passed the screening process. Directed transfusion would only have caused a different child to be infected.

Risks of transfusion

Cause of death associated with transfusion (FDA, 1990)

- ABO incompatibility 50%
- Pulmonary oedema 14%
- Hepatitis C 12%
- Hepatitis B 7%
- Bacterial infection 7%
- Delayed reaction, anaphylaxis, GVHD 9%
- HIV 1%

Risk of viral transmission

- Lowest in volunteer repeat donors
- Minimized by screening questionnaire and serology

Estimate of risk of “window period” donation

- HIV 1 in 1.2 million in Australia (twice as high in US)
- Hep B 1 in 370,000
- Hep C 1 in 250,000

Risk in children

- 5% of transfusions are given to children
- 20% of paediatric transfusion is for elective surgery

Expected incidence of HIV transmission from elective paediatric surgical transfusion in Australia is 1 per 100 years.

Reducing risks

Transfuse only for specific clinical indications

Whole blood

- Massive transfusion, exchange transfusion, CPB or ECMO

Packed cells

- Under 4 months of age
  - Hb <130 g/l in neonates <24 h old or with severe pulmonary disease, cyanotic heart disease or heart failure
  - Acute loss of ≥10% of blood volume
  - Phlebotomy loss of 5-10% of blood volume
  - Hb <80 g/l with symptomatic anaemia
- Over 4 months of age
  - Operative blood loss ≥15% of blood volume
  - Post-op Hb <80 g/l with symptoms
  - Hb <130 g/l with severe pulmonary disease requiring ventilation
  - Hb <80 g/l or symptomatic Hb <100 g/l without response to medical therapy
  - Suppression of endogenous erythropoiesis in some thalassaemia and sickle-cell patients
  - Prior to renal transplant

Autologous transfusion

- Available at RCH from 40 kg up
  - 20-30 cases per year
  - 90% of elective surgery requiring transfusion is in ineligible children
- Toronto HSC from 18 kg up
  - 100 cases per year, >50% discarded

Directed transfusion

- Specific indications
  - Kidney transplant recipient preparation
  - Bone marrow transplant
Rare phenotype red cells
HLA-compatible platelet transfusion
Parent to neonate transfusion for alloimmune thrombocytopenia, neutropenia or haemolytic disease of the newborn

Other countries
UK prohibited
Canada available if parents insist
US some states prohibited, some mandate offering directed transfusion
    In California, 2-3% of donations are directed
    Early 1980s HIV risk from donor blood in CA was 1/200-1/300

Practice
88% chance of compatibility if both parents available, 72% for one parent
(84% and 50% if identical group required for cardiac surgery)
5 days notice required
31% of donations are used
More expensive than random donor transfusions

Safety
Viral markers may be slightly more prevalent in directed donations
22% of donors might modify answers to screening questions to allow donation
No studies of long-term outcomes in children
    50% of blood is transfused to patients who are dead within one year
GVHD
Near HLA-match allows lymphocyte engraftment in immunocompetent recipient
Risk 1 in 17-39,000 in Caucasians for random donor, 20 times higher if parent to child donation
TRALI
Donor neutrophil or HLA antibodies cause acute respiratory distress
May be more common in maternal plasma in the first few months after childbirth
HLA isoimmunization
Increased risk of rejection of subsequent marrow transplant

Ethical complications
Coercion of an unwilling donor, false screening declarations
    3% of donors feel forced to donate
Potentially worse therapy used based on parental desire
    No conclusive evidence that directed donation is less safe
Potential for discovering a different biological parent
False positive viral screening tests
    Positive threshold is set low for donor units
    High false positive rate, donor counselling required
Impact on volunteer donor pool
Use of finite resources
Parental desire to help their children

Cost-effectiveness recommendations (Health Ministers, 1999)
Minimize blood loss
Autologous donation should be available but should not be promoted
Acute normovolaemic haemodilution should not be encouraged
Erythropoietin and desmopressin use should not be encouraged
Cell salvage should be evaluated
Aprotinin use should be actively supported

Conclusions
No evidence to ban directed donation
Should not be encouraged because of increased cost and possible increased risk
Should be permitted in defined circumstances
Deep Vein Thrombosis

Pathogenesis

venous stasis
- no activity of muscle pump mechanism
- decreased venous return with IPPV or pneumoperitoneum
- patient position can affect venous return

vascular injury
- direct trauma
- endothelial activation due to cytokines released in surgery
  - increased tissue factor and PAI-1
  - reduced thrombomodulin

activation of coagulation
- local activation with vessel trauma
- systemic increase in coagulability with surgery or stress

known risk factors
- age > 60
- previous DVT
- major surgery
  - surgical duration
  - orthopaedic surgery to the hip or knee
  - fractured pelvis, femur or tibia
  - surgery for malignant disease
  - immobility in the perioperative period
- medical conditions
  - cardiac failure
  - sepsis
  - inflammatory bowel disease
  - myocardial infarction
  - varicose veins
  - obesity

Natural History

site
- most commonly superficial veins and deep veins of the calf
- proximal spread to involve popliteal, femoral and iliac veins
- other sites are uncommon

symptoms and signs
- calf vein DVT is usually asymptomatic
- proximal DVT causes impaired venous drainage, perivascular inflammation, symptomatic PE
- postthrombotic syndrome may occur in the long term

prognosis

untreated
- 30% of small calf DVTs will spread proximally if untreated
- proximal spread is associated with 40-50% risk of PE
- historical mortality from PE was 20%

Treated
- proximal DVT associated with 5% incidence of significant events
- recurrent DVT after treatment
  - 5-10% at one year (4% for post-surgical DVT)
  - 30% at 8 years
- risk of recurrence is greatest in DVT associated with a non-reversible cause (i.e. malignancy or coagulation disorder)
- postthrombotic syndrome
  - incidence 25% after treated DVT
caused by increased venous pressure
  incompetent valves
  outflow obstruction
  oedema, pain, venous ulceration
“thrombeneurosis”

**Prophylaxis**
proven cost-effective for high-risk patients
prevent venous stasis
  pneumatic calf compression
  calf compression is as effective as low-dose heparin in abdominal surgery
TEDS stockings
effective adjunct in the postoperative period
modulate coagulation
  low-dose heparin
cost-effective for general surgery
  reduces DVT risk by 50-70%
warfarin, adjusted dose heparin, LMWH
  LMWH is most effective in major orthopaedic surgery

low risk
  age < 40, uncomplicated surgery, mobile post-op
risks
  calf DVT 2%, proximal DVT 0.4%, fatal PE <0.02%
prophylaxis
  early mobilization

moderate risk
  age > 40, medical risk factors, immobility (e.g. leg fracture)
risks
  calf DVT 10-20%, proximal DVT 2-4%, fatal PE 0.2-0.5%
prophylaxis
  low dose heparin or pneumatic calf compression

high risk
  high risk surgery, previous DVT
risks
  calf DVT 40-70%, proximal DVT 10-20%, fatal PE 1-5%
prophylaxis
  LMWH or warfarin or adjusted dose heparin
neurosurgery, ophthalmic surgery
  if anticoagulation is contraindicated, pneumatic compression and stockings are safe

**Diagnosis**
venography
  gold-standard for diagnosis
  operator dependent
  may be misleading in recurrent DVT
venous ultrasound
  operator dependent
  inadequate resolution for calf veins
impedance plethysmography
  fails to detect calf thrombi
predictive value of tests is greatly influenced by clinical probability
Ultrasound Clinical Likelihood Management

<table>
<thead>
<tr>
<th>Ultrasound result</th>
<th>Clinical probability</th>
<th>Likelihood of DVT</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>positive</td>
<td>high</td>
<td>100%</td>
<td>treat</td>
</tr>
<tr>
<td>positive</td>
<td>intermediate</td>
<td>96%</td>
<td>treat</td>
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<tr>
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<td>low</td>
<td>63%</td>
<td>venography</td>
</tr>
<tr>
<td>negative</td>
<td>high</td>
<td>24%</td>
<td>venography or retest</td>
</tr>
<tr>
<td>negative</td>
<td>intermediate</td>
<td>5%</td>
<td>retest</td>
</tr>
<tr>
<td>negative</td>
<td>low</td>
<td>&lt;1%</td>
<td>no treatment</td>
</tr>
</tbody>
</table>

diagnosis of pulmonary embolism
clinical features are non-specific
  shortness of breath (increased dead space)
  pain, haemoptysis, sudden death
diagnostic tests
  pulmonary angiography
gold-standard test
highly invasive
ventilation/perfusion scan
interpreted in combination with clinical impression
“high probability” scan result means
  PE in 96% of patients with high clinical suspicion
  PE in 85% with intermediate clinical suspicion
  PE in 50% with low clinical suspicion
“low probability” scan means
  PE in <6% with low clinical suspicion
testing for the presence of a DVT may determine management
ECG
significant negative predictive value if other pathology (e.g. pericarditis, infarction)
may show right heart strain
CXR
useful positive diagnostic signs are uncommon
may show effusion, infarction, regional oligaemia, prominent pulmonary vessels at the hilum
ABG
non-specific
may show hypoxaemia, hypocarbia in large PE in an awake patient

Treatment
anticoagulation
heparin
promotes inhibition of thrombin and factor Xa via AT-III
high concentrations required to affect clot-bound thrombin
warfarin
inhibits synthesis of factors requiring γ-carboxylation
  thrombin, VII, IX, X
usual regimen
therapeutic heparin, followed by
warfarin to INR 2-3 for 3-6 months
shorter duration is more appropriate if there is no on-going predisposing factor
patients with a thrombotic condition (e.g. antiphospholipid antibody) may require lifetime therapy
overlap period should be about 4 days as INR rises as factor VII level falls (t½ 7 h) but full anticoagulant effect requires a fall in factor II (t½
sc LMWH may be an alternative to IV heparin thrombolysis usually contraindicated in the postoperative period surgery caval interruption intracaval devices thrombectomy

**Pregnancy**

*diagnosis* leg pain and swelling are frequent without DVT venography, V/Q scanning are relatively contraindicated

*management* heparin is safe in pregnancy warfarin is teratogenic at 6-12 weeks and contraindicated at term women on prophylactic warfarin are changed to heparin or LMWH before 6 weeks gestation (or before conception) heparin is ceased at the onset of labour

**Children**

DVT is relatively rare highest risk surgery has <1% incidence of clinical DVT 80% of neonatal and 40% of childhood DVTs are associated with CVCs

**Perioperative management of anticoagulants**

“low” risk patients on warfarin risk of thromboembolism from AF or prosthetic valves without anticoagulation is about 10% per year ceasing warfarin 4-5 days before surgery should carry <0.1% risk of thromboembolism

“high” risk patients on warfarin (e.g. recurrent thromboembolism) reduction in INR to 1.5 for surgery replacement of warfarin with heparin ceased 4-6 hours before surgery recommenced 12 hours after surgery
Metabolic

Hypothermia

Obesity
Hypothermia

Definition
Body temperature below normal
Normal 36.7-37.0˚C
Mild 34-36.5˚C, moderate 27-34˚C, deep 17-27˚C, profound <17˚C

Mild hypothermia

Benefits
Cerebral and myocardial protection, ↓ risk of MH, ↓ MAC requirement

Risks
↑ O₂ demand during cooling, myocardial ischaemia, arrhythmia, impaired immunity, pharmacokinetic changes, discomfort

Effects in detail
Regulation in Thermoregulation (1.L)

Neurological
↓ CBF, CMRO₂ (7% per °C), EEG activity, MAC requirement, IOP
Neuroprotection via ↓ neurotransmitter release, membrane stabilization, effects on response to ischaemia
Impaired conscious state at 33˚C, coma at 30˚C (dilated pupils)
↑ neuromuscular blockade
via ↓ axonal depolarization, ↑ ACh release, ↓ excitation-contraction coupling
↓ TOFC (causing overestimate of paralysis)

CVS
↑ myocardial O₂ demand if shivering, ↓ CO if anaesthetized
severe: arrhythmias, ↓ HR, O₂ consumption
contractility and SV relatively preserved
vasoconstriction, poor peripheral perfusion, ↑ SVR, CVP
ECG
SB, ↑ PR, wide QRS, prolonged QT
<32˚C: J wave in II, V₆, then anterior leads
nodal rhythms, PVCs, AV block, fibrillation

Respiratory
↑ VO₂ with shivering (up to 300%)
↑ PVR, V/Q mismatch, impaired hypoxic vasoconstriction
↓ ventilatory drive, ↓ bronchial tone, ↑ dead space
↑ gas solubility

Renal
↓ RBF, GFR directly due to ↑ sympathetic tone, ↓ CO
Cold diuresis due to ↓ Na⁺ reabsorption

Hepatic, GIT
↓ blood flow, metabolic and excretory functions
↓ gut motility

Haematological
↓ platelet function, ↑ visceral sequestration
↓ coagulation, ↑ fibrinolysis
↑ haematocrit, rouleaux formation, left shift of Hb-O₂ dissociation curve

Endocrine and metabolic
↓ BMR 5-7% per °C if not shivering (↓ PCO₂, ↑ glucose)
Metabolic acidosis, pH and PCO₂ changes (α-stat)
Acute rise in K⁺ with rewarming
↓ insulin, insulin resistance, hyperglycaemia with ↑ sympathetic tone
↑ thyroid hormone secretion (long term)

Pharmacokinetic
↓ metabolism and excretion (hepatic and renal)
↑ protein binding, ↓ $V_d$ of circulating compartment
Obesity

Definition
BMI (height in m ÷ weight in kg squared)
> 25 overweight, > 30 obese
Waist-hip ratio
0.8 ideal, > 1.0 overweight

Risks
↑ perioperative morbidity and mortality, average hospital stay

Associated diseases
Respiratory
↓ FRC, ↑ closing capacity
Hypoventilation, OSA
Cardiovascular
↑ CO 0.1 l/min/kg fat
HT, LVH
Cor pulmonale
Other
Diabetes, cholelithiasis, cirrhosis
30% overweight → 40% ↑ in IHD mortality, 50% ↑ in CVA mortality

Anaesthetic risks
Reduced physiological reserve
↑ difficult intubation
↓ FRC, ↑ ventilatory pressures
↑ fasting gastric volume
75% have > 25 ml, pH < 2.5 at 140 kg
Pressure areas
Monitoring difficulties, vascular access
Larger fat compartment in pharmacokinetics

Postoperative risks
Postoperative hypoxia
Wound infection
DVT, PE
Neurology

Brain death

Tests

EEG in Monitoring 3.B.2

Neuromuscular disorders and anaesthesia
Brain death
Coma GCS < 8, potential for recovery
Persistent coma
Persistent vegetative state: brainstem function intact
Brain death: brainstem function lost (no spontaneous ventilation)
Death: “Irreversible cessation of circulatory and respiratory functions or irreversible cessation of all functions of the entire brain, including the brainstem.”

Diagnostic criteria of brain death
Deep coma
confirm clearance of depressant drugs
normal body temperature
no gross electrolyte or metabolic disturbance
Apnoea
no relaxants, opioids or other depressants
raised PaCO₂, normal PaO₂
Irreversible structure brain damage
Procedure
Pupillary response to light absent
Corneal touch reflex absent
Vestibulo-ocular reflexes absent
20 ml ice cold water in ear canals, no eye movement
Facial motor response to trigeminal distribution pain absent
Gag and cough reflexes absent
Apnoea in the presence of PaCO₂ > 60 mmHg, pH < 7.30
Two examinations at least 2 h apart by separate qualified doctors
Angiography required if no diagnosis or tests incomplete (e.g. eye injury)
Modified criteria < 1 year of age due to greater recovery potential
Tests

Flicker fusion test
  Increasing frequency of flashing light
  Frequency at which light appears steady is recorded
  Used to assess degree of hypotension producing significant cerebral ischaemia
Neuromuscular disorders and anaesthesia

Literature
- Little high-quality evidence
- Many case reports, few series
- Small numbers for all conditions except myasthenia gravis (thymectomy)

General concerns
Pre-op assessment
- Weakness
  - Respiratory failure
  - Upper airway maintenance
  - Assessment of need for back-up ventilated bed
  - Decreased fitness and exercise tolerance
  - Possible myocardial involvement
  - Documentation of functional state before anaesthesia
Deformity
- Airway assessment
- Likely ease of intubation
- Positioning
Investigations
- Respiratory function testing
- Blood gas analysis
- ECG, echocardiography if indicated

Intra-op management
- Risk of aspiration
- Decision regarding need for muscle relaxants
- Altered sensitivity to relaxants, need for NMJ monitoring
- Variable distribution of weakness makes relaxant monitoring unreliable
- Appropriate management of steroids or other drugs

Post-op
- Careful monitoring of recovery to adequate tidal volume
- Monitoring for respiratory failure post-extubation
- Possible ICU ventilation

Motor neurone disorders

Multiple Sclerosis
Aetiology
- Unknown, environmental and genetic associations
- Patchy demyelination in the CNS
Features
- Signs
  - Typical onset in females 20-40 years of age
  - Variation in severity over minutes to years
  - Common involvement of optic nerve and oculomotor pathways
  - Exacerbated by
    - Parturition, elevated temperature, other stresses
  - Progression to motor weakness of limbs
Investigations
- MRI shows “plaques”
- Abnormal sensory evoked potentials
- CSF IgG and myelin basic protein elevated
Treatment
- Steroids, ACTH, immunosuppressants used with some effect

Anaesthetic considerations
Hyperthermia may cause exacerbation of weakness
Induction agents, volatiles, relaxants (including suxamethonium) all known to be safe
  Relaxants may exacerbate weakness directly
Regional
  Possible increased permeability of blood-brain barrier
  Increased risk of CNS toxicity from local anaesthetics
  Possible increased risk of histotoxicity from spinal local anaesthetic
  Not supported by clinical data

Guillain-Barré syndrome
Aetiology
  Cell-mediated autoimmune response
  Causes demyelination of peripheral nerves
  Commonly post-viral (herpes viruses, influenza, para-'flu, HIV)
  Possibly post-vaccination (TB, tetanus, typhoid)
Features
  Signs
    Progressive motor weakness or more than one limb
    Areflexia or hyporeflexia
    Symmetrical and progressive
    Results in flaccid paralysis
    Mild sensory involvement, mostly vibration and proprioception
    Cranial nerve involvement in 45%
    Autonomic dysfunction
      Circulatory instability: hypo- and hyper-tension
      Bradycardia, tachyarrhythmias
      Ileus, urinary retention
Investigations
  CSF: low WCC, high protein
  Abnormal nerve conduction studies
Timecourse
  Recovery 2-4 weeks after onset
Treatment
  Plasma exchange proven effective
  Immunoglobulin therapy is as effective, but more relapses
  Steroids commonly used but unproven
  Supportive management: ventilation etc.
Anaesthetic considerations
  Increased aspiration risk with bulbar palsy
  Respiratory muscle weakness
  Circulatory instability on induction
    Exaggerated response to pressors and vasodilators
  Suxamethonium contraindicated

Motor neurone disease
Aetiology
  Some inherited, most sporadic (amyotrophic lateral sclerosis)
  Progressive degeneration of upper and lower motor neurones
Features
  Signs
    Sensory and autonomic pathways spared
    Cerebral function largely spared
    Several patterns of progression
      Cranial vs somatic
      Upper vs lower
Similar to post-polio syndrome

Investigations
None specific
EMG shows denervation

Anaesthetic considerations
Upper airway and respiratory muscle weakness
Lack of specific treatment raises ethical problems
Suxamethonium contraindicated due to potassium release

Neuromuscular junction disorders

Myasthenia gravis

Aetiology
Autoantibodies (IgG) to α-subunit of ACh receptors on skeletal muscle
Thymic abnormalities in 75% of patients
Associated with other autoimmune diseases
Hypothyroidism, RA, SLE, pernicious anaemia

Neonatal variants
Children of myasthenic mothers
Transient weakness from maternal IgG

Hereditary myasthenia
No autoantibodies, structurally abnormal receptors

Paraneoplastic variant (Eaton-Lambert syndrome)
Autoantibodies against voltage-gated Ca^{2+} channels
Decreased ACh release from nerve terminals
Association with autonomic dysfunction, reduced gastric motility
Predominantly limb involvement
Little bulbar involvement

Features

Signs
Ocular involvement first: ptosis and diplopia
Commonly bulbar weakness
Asymmetrical trunk and limb involvement

Investigations
Edrophonium (Tensilon™) test
1 mg-6 mg edrophonium, 0.6mg atropine
Autoantibody assay
False positives in RA and some family of affected patients
False negative immediately after anaesthesia

Treatment
Anticholinesterase drugs
Pyridostigmine 60 mg qid (up to 750 mg/day)
Plasma exchange
Immunoglobulin (unknown mechanism)
High dose corticosteroids
Azathioprine, cyclophosphamide, cyclosporin
Thymectomy after medical optimization gives the best results

Anaesthetic considerations
Decision to continue anticholinesterase drugs depends on severity
Anticholinergic agents may be required to cover bowel anastomoses
Myasthenic crisis (acute exacerbation)
Described worsening with local anaesthetics, muscle relaxants, narcotics, ether, aminoglycosides
Weakness can also be due to anticholinesterase overdose
Regional anaesthesia is well tolerated
General anaesthesia
Propofol plus opioid, or 
Volatile only 
Produces 50% twitch fade at 1.0 MAC
Suxamethonium is safe 
Possibly decreased sensitivity
Decreased metabolism if on high anticholinesterase dose
High incidence of phase II block at normal dose
Non-depolarizing agents are usually avoided
Increased sensitivity, difficulty reversing

**Muscle disorders**

**Myotonia dystrophia**

**Aetiology**
Disorder of relaxation of skeletal muscle (AD 19q)
Slow reuptake of Ca²⁺ into sarcoplasmic reticulum
Multiple tissues affected
Myotonia congenita variant present from birth
Paramyotonia variant manifest only with cold

**Features**

**Signs**
Weakness with myotonia
Involving pharyngeal muscles as well as limbs and face
Cataracts
Frontal balding
Variable intellectual disability, somnolence
Cardiomyopathy, conduction abnormalities
Testicular failure
Reduced gastric motility

**Investigations**
ECG increased PR interval, atrial flutter, other arrhythmias
RFT marked reduction in maximal expiratory pressure, small reduction in VC

**Treatment**
Myotonia can be treated with phenytoin, but is not usually a problem
Atrophy is not treatable

**Anaesthetic considerations**
Prolonged contraction in response to depolarizing relaxants
Suxamethonium absolutely contraindicated
Also triggered by propranolol, clofibrate, K⁺
Prolonged contraction with shivering
Aim to maintain normothermia
Relative contraindication to volatiles
Myotonia provoked by mechanical stimulus and diathermy
Increased risk of apnoea with sedative drugs
Myotonia antagonized only by intramuscular local anaesthetic
Some relief with quinine, procainamide or phenytoin
Non-depolarizing relaxants are effective at normal doses
Reversal appears to be safe despite theoretical risk of myotonia
Intravenous regional anaesthesia should be effective

**Muscular dystrophy**

**Aetiology**
Familial
Duchenne (X-linked), Limb girdle (AR), Facioscapulohumeral (AD)

Atrophy of skeletal muscle with fatty infiltration and fibrosis

*Neurology* 3.C.6.7 *James Mitchell (October 7, 2001)*
Features
  Signs
  Progressive limb weakness
  Diaphragm function relatively preserved
  Late cardiomyopathy, arrhythmias, mitral valve prolapse
  Kyphoscoliosis with respiratory compromise common

Investigations
  CK typically elevated
  ECG abnormalities (RSR' in V1, deep Q in lateral V leads, arrhythmias)
  RFT VC<30% predicted indicated high risk with GA

Anaesthetic considerations
  Progressive disease so earlier operation is preferable
  Increased incidence of malignant hyperthermia
  Suxamethonium contraindicated due to potassium release
  Decreased margin of safety with non-depolarizing relaxants
  Gastroparesis reported pre- and post-operatively
  Increased risk of aspiration with bulbar weakness
  Avoid tachycardia as increased risk of arrhythmia
  Rhabdomyolysis and renal failure

Malignant hyperthermia in Complications 3.A.4

Neuroleptic malignant syndrome
Management of anaesthesia for a teenager with cystic fibrosis
Management of anaesthesia for a teenager with cystic fibrosis

Cystic fibrosis
- AR inherited condition: 1/2500 Caucasians
- Chromosome 7 mutation, multiple abnormalities described
- Expressed as defective Cl channels
  - High Cl- concentration in secretions, increased viscosity
  - Sweat Cl- > 60 mmol/l
  - Resultant respiratory, pancreatic, biliary dysfunction

Clinical problems
- Respiratory
  - Impaired clearance of secretions, mucociliary dysfunction
  - Chronic infection, bronchiectasis, dyspnoea, excessive sputum
  - Air-trapping due to mucous plugging: COAD-like picture
  - Nasal polyps, chronic sinusitis
- Complications
  - Respiratory failure: cyanosis, CO₂ retention
  - Haemoptysis, pneumothorax, cor pulmonale

- GIT
  - Pancreatic exocrine failure
    - Malabsorption, malnutrition without enzyme supplementation
    - Chronic pancreatitis, acute exacerbations
    - Secondary endocrine failure: diabetes mellitus
  - Bile secretion impaired
    - Fat and fat-soluble vitamin malabsorption
    - Later cirrhosis and portal hypertension

- Psychological
  - Many admissions and procedures
  - Chronic illness, medicalization
  - Longer survival resulting in more adult presentations

Assessment
- Routine, plus
- History related to CF
  - Admissions, current therapy, respiratory disease, diabetic control
  - Previous anaesthesia
- Examination
  - General appearance, respiratory, cardiac focus
  - Signs of respiratory failure, right heart failure
- Investigation
  - CXR, RFT, ABG
  - FBE, U&E, LFT, glucose
  - Recent cultures of sputum

Optimize
- Consult with treating physician to achieve best respiratory function
- Bronchodilators, saline nebs, antibiotics, physiotherapy

Technique
- Regional avoids the need for intubation and risk of worsening infection
- If GA required by nature of surgery, regional analgesia may result in better respiratory function postoperatively
- Airway
  - Humidified gases, nebulized saline may be of benefit
  - Frequent suctioning
  - Avoid nasal intubation
- Ventilation
  - As for COAD: long I:E, minimize airway pressures, slow rate
Increased FiO₂
Vigilance for pneumothorax
Circulation
  Consider invasive monitoring if cor pulmonale: arterial line ± PA catheter
Other considerations
  Management of diabetes: fasting, glucose monitoring
  Choice of drugs suitable for impaired hepatic function
Postoperative
  Level of care determined by severity of disease and extent of surgery
  Active physiotherapy and early mobilization
Smoking
Miscellaneous medicine

Short case history

Short case examination

Anaesthesia and connective tissue disease
Short case history

General history
Presenting symptoms
History of the presenting illness
Symptoms: duration, site and radiation, character, severity, onset, aggravating and relieving factors, associated symptoms, treatment
Past history
Social history
Family history
Systems review
Cardiovascular, respiratory, gastrointestinal, hepatobiliary, haematological, genitourinary, musculoskeletal, neurological, endocrine

Cardiovascular history
Symptoms
Chest pain (nature, stable or unstable), dyspnoea (exertional, postural, nocturnal), ankle swelling, palpitations, syncope, claudication, fatigue
Risk factors
Family history, smoking, hypertension, hypercholesterolaemia, diabetes, obesity, sex and age
Past history
Angina, AMI, rheumatic fever, chorea, preeclampsia, investigations
Treatment
Drugs, revascularization
Social history
Work, exercise tolerance, smoking
Family history

Respiratory history
Symptoms
Cough, sputum, haemoptysis, dyspnoea, wheeze, chest pain, sinusitis, hoarseness, night sweats
Past history
Pneumonia, tuberculosis, bronchitis, allergies
Treatment
Steroids, bronchodilators, antibiotics
Social history
Occupation, hobbies (exposures), smoking, alcohol
Family history
Tuberculosis, asthma, emphysema (e.g. cystic fibrosis)

Gastrointestinal history
Symptoms
Pain, nausea, vomiting, bleeding, reflux, dysphagia, appetite and weight change, diarrhoea, constipation, mouth ulcers, fever
Past history
Peptic ulcer, colitis, carcinoma
Treatment
Steroids, NSAIDs, antibiotics, diet
Social history
Alcohol, smoking, travel, occupation
Family history
Bowel cancer, IBD, coeliac disease, polyposis coli

Hepatobiliary history
Symptoms
Jaundice, dark urine, pale stools, fever, pruritus
Past history
Jaundice, surgery, hepatitis, transfusion, blood-borne virus risks
Treatment
Drugs, especially sex steroids and other hepatotoxic drugs

Social history
Alcohol, viral exposure (travel, contacts, sex, occupation, drug use)

Family history
Genetic disease (Wilson’s disease, haemochromatosis…), family contacts

Haematological history
Symptoms
Blood loss, bruising, infection, gland enlargement, bone pain, symptoms of anaemia, paraesthesia, rash

Past history
Gastric surgery, colitis, malabsorption, rheumatoid arthritis, uraemia, transfusion

Treatment
Anticoagulants, immunosuppressants, anticonvulsants

Social history
Diet, alcohol

Family history
Genetic disease (haemophilia, thalassaemia, sickle cell, pernicious anaemia, haemolytic anaemia)

Genitourinary history
Symptoms
Infection
Dysuria, frequency, urgency, fever, loin pain, urethral discharge
Renal failure
Anuria, nocturia, polyuria, anorexia, vomiting, fatigue, hiccough, itch, bruising, oedema
Obstruction
Reduced stream, hesitancy, dribbling

Menses
Onset, regularity, last period, dysmenorrhoea, menorrhagia, parity, discharge

Past history
Infections, stones, surgery, proteinuria, nephritis, diabetes, gout, hypertension, preeclampsia

Social history
Analgesic use

Family history
Polycystic kidneys

Musculoskeletal history
Symptoms
Pain, stiffness, swelling, loss of function, nodules, dry eyes or mouth, red eyes, rash, fever, fatigue, weight loss, mucosal ulcers, Raynaud's

Past history
Trauma, infection, IBD

Treatment
Physiotherapy, analgesics, NSAIDs, steroids, DMDs, surgery

Social history
Home arrangements, work, carer, STDs

Family history
Arthritis, gout, psoriasis, IBD

Neurological history
Symptoms
Headache, pain, paraesthesia, anaesthesia, weakness, disturbance of sphincter control, special senses, loss of consciousness, dizziness, ataxia, tremor, speech disturbance

Risk factors for stroke

Miscellaneous medicine 3.C.10.3 James Mitchell (October 7, 2001)
Hypertension, family history, smoking

Past history
Meningitis, head or spinal injury, convulsions, operations, STDs

Treatment
Anticonvulsants, anti-Parkinsonian agents, steroids, antihypertensives

Social history
Alcohol, drugs, work, travel

Family history
Neurological disease, consanguinity

Endocrine history

Symptoms
Hyperthyroid
Goitre, heat intolerance, weight loss, increased appetite, palpitations, sweating, anxiety, diarrhoea

Hypothyroid
Goitre, cold intolerance, lethargy, eyelid swelling, hoarse voice, constipation, coarse skin

Diabetes
Polyuria, polydipsia, thirst, blurred vision, weakness, infections

Past history
Thyroid surgery, irradiation, diabetic complications, hypertension

Treatment
Iodine, antithyroid drugs, hormone replacement (thyroxine, steroids, insulin...)

Social history
Impotence

Family history
Thyroid disease, diabetes, endocrine adenomatosis
Short case examination

General
- Position
  - Patient supine in bed, examined from right side
  - Fully exposed (with consideration to modesty)
- Overview
  - Facies, skin colour, hair, body habitus, hydration
  - HR, BP, temperature

Cardiovascular
- Position
  - Supine at 45° on pillows
- General appearance
  - Pallor, dyspnoea, fatigue, cachexia
  - Characteristic appearance (Marfan’s, Down’s…)
- Hands
  - Clubbing, nailbeds, finger pulps
- Pulse
  - Rate, rhythm, character and volume, radiofemoral delay
- Blood pressure, postural effects
- Face
  - Sclerae (pallor, jaundice), mitral facies, mouth (arched palate)
- Neck
  - Carotid pulse, JVP (level, waveform, Kussmaul’s sign, hepatojugular reflex)
- Praecordium
  - Inspection: scars, pacemaker, apex beat (5 ICS, 1 cm medial to MCL)
  - Palpation: apex beat size and character, left sternal heave, palpable P2, thrill
  - Auscultation
    - Bell at apex: mitral stenosis or S3
    - Diaphragm at apex: Mitral regurgitation or S4
    - 5L ICS (tricuspid)
    - 2L ICS (pulmonary)
    - 2R ICS (aortic)
    - Carotids or axilla as indicated
    - Sit forward
    - Inspiration: right-sided murmurs louder
    -Expiration: left-sided murmurs louder (esp. AI)
    - Valsalva: HOCM louder or MVP earlier (↓ LV volume)
    - Squatting: murmurs except HOCM, MVP louder (↑ LV volume, CO)

Back
- Lung bases, sacral oedema

Abdomen
- Hepatomegaly, splenomegaly, ascites

Legs
- Femoral pulses and auscultation
- Distal pulses and oedema
- Buerger’s test: pallor on elevation (poor perfusion), cyanosis on dependence
- DVT, PVD signs
- Varicose veins

Other
- Urinalysis, fundoscopy

Respiratory
- Position
  - Sitting
- General
  - Sputum mug, cough, rate and depth of respiration, accessory muscle use

Miscellaneous medicine 3.C.10.5 James Mitchell (October 7, 2001)
Hands
  Colour (cyanosis, tar), clubbing, wasting, tenderness (HPO), pulse, tremor

Chest
  Inspect
    Shape (kyphosis), scars
  Palpate
    Expansion, nodes, fremitus, breasts
  Percuss, auscultate (breath sounds, resonance, adventitious sounds)
  Pemberton’s sign
  Cardiac examination if indicated
    JVP, pulmonary hypertension...

Face
  Horner’s syndrome, jaundice, pallor, cyanosis
  Hoarseness
  Tracheal deviation

Other
  Tests: FET, PEFR, counting tests
  Signs of malignancy elsewhere
  Temperature
Anaesthesia and Connective Tissue Diseases

Ankylosing Spondylitis

Epidemiology
- 0.5 to 4 per 1000
- male:female 10:1
- HLA-B27 related
- onset between 15 and 40

Pathology and Clinical Findings
- progressive inflammatory synovitis
- sacroiliac, intervertebral, costovertebral, hip, shoulder and other joints
- fibrosis and ossification, especially of the *annulus fibrosus*
- "bamboo spine"
- may impinge spinal cord, nerve roots, vertebral arteries
- aortic root involvement may cause aortic incompetence (3%)
- fibrosis of the AV bundle may cause conduction defects
- pulmonary fibrosis, especially upper lobe, can cause massive haemoptysis
- uveitis in 20-30%

Treatment
- symptomatic treatment with NSAIDs
- no disease-modifying therapy

Anaesthetic Considerations
- may present with
  - orthopaedic procedures (joint replacement, spinal wedge resection)
  - NSAID-associated gastric ulcer disease
  - aortic incompetence, haemoptysis
- spine involvement limits neck mobility
- may be difficult intubation
- high incidence of cervical fractures with minimal trauma
- fixed neck flexion may preclude cryothyroididotomy or tracheostomy
- TMJ involvement limits mouth-opening in 10%
- cricoarytenoid arthritis rarely causes vocal cord fixation
- costovertebral involvement limits chest expansion
- increased incidence of post-op pulmonary complications
- external cardiac massage is often ineffective
- neuraxial anaesthesia has an increased failure rate

Can J Anaesth 1996 case series:
- 3 of 13 of spinals and 3 of 3 of epidurals unsuccessful
- case report analysis suggests epidural haematoma is more likely

Anaesthetic Management
- investigation
  - radiological and clinical assessment of cervical spine and airway
  - ECG
- induction
  - likely difficult intubation
  - cervical manipulation may be dangerous
  - awake fibreoptic intubation or avoidance of intubation may be safest
  - diaphragmatic splinting postoperatively is more likely to cause respiratory failure
- regional
  - spinal or epidural is likely to be even more difficult than GA

Rheumatoid Arthritis

Epidemiology
- approx. 1% of population
- female:male 3:1
prevalence increases with age
onset usually between 35 and 50
associated with HLA-DR4 in some populations

Pathology and Clinical Findings

aetiology uncertain

persistent inflammatory synovitis with symmetric polyarthritis
cartilage destruction and bone erosion
pain and stiffness usually worst in the morning

joints affected
most commonly pip, mcp, wrist, knee, elbow
most other synovial joints
axial involvement limited to cervical spine
atlanto-axial subluxation

TMJ and cricoarytenoid joints may be involved
articular swelling may cause nerve entrapment
 median, ulnar, radial interosseos br., anterior tibial

extraarticular involvement
rheumatoid nodules in 25%
vasculitis can cause several complications
 polynuropathy, skin necrosis, distal gangrene, visceral infarction, renal
 impairment
pleuropulmonary nodules and pulmonary fibrosis
pericarditis and pericardial effusion (present in 50% but subclinical)
episcleritis and scleritis (1%)
increased incidence of dysphagia

Treatment
disease-modifying
gold: thrombocytopenia, granulocytopenia, proteinuria
D-penicillamine: thrombocytopenia, granulocytopenia, proteinuria
hydroxychloroquine: retinopathy

symptomatic
simple analgesics
NSAIDs
corticosteroids

immunosuppressants
azathioprine, cyclophosphamide: marrow suppression, ?malignancy
methotrexate: abnormal LFTs

surgery
synovectomy, joint replacement, nerve releases

Anaesthetic Considerations
cervical spine
cervical spine instability in 25%, usually atlanto-axial
most asymptomatic
case reports of spinal cord damage in relaxed patients
occipito-cervical fusion increases the incidence of lower instability

larynx
odontoid migration is associated with laryngeal displacement
 usually anteriorly and to the left

mouth opening
limited by TMJ involvement
more common in juvenile arthritis

cardiac function
pericardial effusion and valve involvement

pulmonary fibrosis

drug-related complications

Anaesthetic Management
investigation
clinical and x-ray assessment of cervical spine in flexion and extension
investigation for drug complications (FBE, U&E)
RFT if pulmonary involvement

induction
- cervical collar if unstable
- intubation with fibroptic scope or laryngeal mask
- cryocoarytenoid involvement may necessitate a smaller tube

**Progressive Systemic Sclerosis ("Scleroderma"), CREST syndrome**

**Epidemiology**
- Female > male
- Onset 30-50 years
- Variation in severity over time

**Pathology and Clinical Findings**
- Increased production of normal collagen
  - Cutaneous, gastrointestinal, cardiac, renal, other organs
  - Possibly due to endothelial damage in small vessels causing an inflammatory response, antinuclear antibodies are usually present
- Cutaneous
  - Taut, shiny skin tethered to underlying tissue
  - Contractures of joints and the mouth may occur (bird-like facial appearance)
- Peripheral vascular spasm causes Raynaud's phenomenon
- Gastrointestinal
  - Involve the upper third of the oesophagus
  - Remainder of the small bowel affected
  - Diverticulae in large bowel
  - Dysphagia and dysmotility, malabsorption
- Pulmonary
  - Vascular involvement may cause pulmonary hypertension
  - Interstitial fibrosis usually lower 2/3
- Cardiac
  - Fibrosis of myocardium and conducting system (56%)
  - Fibrinous pericarditis, effusion (28%)
- Renal
  - Cortical infarction and glomerulosclerosis in >50%
  - Temperature-sensitive vasospasm
- Symmetric polyarthritis
- Hypothyroidism due to fibrosis

**Treatment**
- D-penicillamine, aspirin used without evidence, vasodilators for Raynaud's (and avoidance of cold)
- Symptomatic H2 blockers, antihypertensives may delay renal failure

**Anaesthetic Considerations**
- Periphery
  - Difficult venous access
  - Increased risk of fingertip ischaemia or ulceration
  - Telangiectasia may bleed
- Airway
  - Mouth contractures
  - Increased reflux risk
- Cardiovascular
  - Hypertension, LV failure, arrhythmias
  - Cold-induced vasospasm
- Pulmonary
constrictive chest wall, alveolitis
regional
case reports of prolonged sensory loss after local anaesthetic

Anaesthetic Management
investigation
assessment of airway and any contractures
assessment of pulmonary function
CXR may show prominent PA in pulmonary hypertension
pre-op
warming, possible need for CVC or cut-down for IV access
increased risk of distal ischaemia with arterial cannulation
induction
protection from reflux risk

Systemic Lupus Erythematosis
Epidemiology
15 to 50 per 100,000
female: male 10:1
onset 20-50 years
racial differences in prevalence
association with multiple autoantibodies and HLA types
Pathology and Clinical Findings
type III immune complex disease
aetiology uncertain
drug-induced variant from hydralazine or procainamide
abnormal immune activation against self antigens
skin
“butterfly” rash, photosensitivity, vasculitis, ulceration, alopecia
arthritis
painful pip and mcp joints, tenosynovitis
ischaemic necrosis of bone
renal
immune complex deposition causes glomerulosclerosis
may cause renal failure requiring dialysis
neurological
CNS involvement, ?personality changes, psychosis, fitting
neuropathies, including cranial nerves
vascular, haematological
thrombotic tendency (Lupus anticoagulant)
binds phospholipids in prothrombin-activator complex
persistent vasculitis predisposes to coronary and peripheral vascular disease
commonly require anticoagulant prophylaxis
may develop anti-VIII or IX antibodies, causing bleeding
thrombocytopenia is common
cardiac
pericarditis, myocarditis are uncommon
endocarditis can involve mitral or aortic valves, causing incompetence
pulmonary
pleural effusions are common, infiltrates are most commonly infective
gastrointestinal
vasculitis may cause gut ischaemia or perforation
eyes
retinal vasculitis, infarcts, blindness
pregnancy
normal fertility, increased spontaneous abortion rate
SLE commonly exacerbated from first trimester

Miscellaneous medicine 3.C.10.10 James Mitchell (October 7, 2001)
neonates may display complete heart block or discoid lupus rash

Treatment
- 30% mortality over 10 years from diagnosis, related to severity
- symptomatic treatment of inflammation with NSAIDs
- rash may respond to hydroxychloroquine
- severe disease responds to high-dose corticosteroids
- immunosuppressants sometimes used: azathioprine, cyclophosphamide, chlorambucil

Anaesthetic Considerations
- pulmonary involvement may cause restrictive lung deficit
- thrombotic tendency, but abnormally prolonged APTT with Lupus anticoagulant
- commonly thrombocytopenic
- commonly present during pregnancy

Anaesthetic Management
- investigation
  - RFT for pulmonary disease
  - assessment of cardiac involvement and renal function
  - coagulation testing, platelet count
  - test for Lupus anticoagulant

- regional
  - difficult risk-benefit assessment for epidural analgesia in labour
Cardiac surgery

Management of pericardial tamponade post bypass surgery

Preparation for going onto and coming off cardiopulmonary bypass

Post-bypass bleeding

Patient assessment for cardiac surgery

Anaesthesia for cardiac surgery

Priorities in valve disease

Doses

Anaesthesia in the post-transplant patient
Management of pericardial tamponade post bypass surgery

Issues
- Emergency complication of bypass surgery requiring immediate surgical consultation
- Simultaneous diagnosis and management
- Accumulation of blood in enclosed pericardial space limits atrial and ventricular filling

Features
- Fall in cardiac output
- Hypotension, narrow pulse pressure
- High filling pressures
  - ↑ PAOP, CVP
- Failure of mediastinal drainage
  - Large volume drainage early followed by clots

Management
- ABCDE priorities
  - Secure airway, ventilate with 100% O₂
  - Support circulation
    - High filling pressures, tachycardia
- Surgical intervention
  - Remove clot from pericardium in theatre if there is time for transfer

Anaesthesia
- Reanaesthetizing post-bypass patient

Preparation
- Routine check of anaesthetic machine and equipment
- Pressor and dilator drugs, heparin for bypass
- Check Hb, platelets, coagulation status, acid-base status
- Notify blood bank
- Haemodynamic support
  - IV fluid, pacing to 90-140 min⁻¹
  - Continue inotropes from ICU

Monitoring
- Invasive monitoring (arterial and PA catheter) usually in situ
- TOE may give useful information about tamponade and ventricular function

Induction
- Fentanyl 10-20 µg/kg, pancuronium
  - Consider sux if reintubation required (may be difficult)
- Small dose of thiopentone or ketamine

Maintenance
- High degree of vigilance for complications, arrhythmias
- May require going onto bypass
- Monitoring of Hb, ABG, coagulation

Postoperative
- Return to ICU intubated and ventilated

Cardiac surgery 3.D.1.2 James Mitchell (October 7, 2001)
Preparation for going onto and coming off cardiopulmonary bypass

Check list for bypass

Before cannulation

Anticoagulation
- Heparin dose 300-400 U/kg
- ACT > 300 s

Haemodynamics
- Systolic BP < 100 mmHg
- ECG recorded
- CVP adequate for caval cannulation

Ventilation
- Compliance recorded
- ABG and acid-base satisfactory

Before running on CPB

Anaesthesia and paralysis confirmed
- CPB circuit has no bubbles, correctly connected and clamps off
- IV fluid ceased and urine recorded

First minutes of CPB

- Adequate flows and pressures
- Obvious oxygenation of aortic cannula blood
- Cease ventilation when arrested
- Continue ABG, ACT measurement

During CPB

Anticoagulation
- Maintain ACT > 400 s
- Inspect circuit and reservoir for fibrin

ABG, acid-base
- ABG normal (α stat)
- $\text{PvO}_2 > 40 \text{ mmHg}$, $\text{SvO}_2 > 60\%$
- Hct 18-22%

Haemodynamics
- MAP 40-90 mmHg, PAP < 15 mmHg, CVP < 0
- Quiescent ECG

Temperature
- Monitor hypothermia and rewarming

Neurological
- Facial oedema, pupils, EEG (if monitored), paralysis

Renal
- UO > 1 ml/kg/h, no haemolysis

Pump
- Pressure and flow appropriate
- Venous return appropriate
- Fluid balance

Coming off CPB

Rewarming
- Neurological unresponsiveness
- Adequate ACT, normal ABG, pH, electrolytes
- Vasodilation for even rewarming
- Defibrillation ± pacing

Prior to coming off
- ABG, Hct, K+
- Core and peripheral temperatures
- Suitable rhythm
- Controlled MAP
- Filling, vasodilation, CVP, PAP
Reinflate lungs, Valsalva
Vent arterial air, verify with TOE

Weaning CPB
Preload
  CVP, PAOP
  Filling and vasodilation
Ventricular function
  dP/dt on arterial trace
  CO, TOE
  Inotropes if indicated
Return of reservoir blood ± haemodilution blood

After discontinuation
Protamine to normalize ACT
Correction of coagulopathy, thrombocytopenia if indicated
Haemodynamic management (pacing, filling, inotropes, vasodilation)
Maintenance of anaesthesia
Preparation for ICU transfer
Post-bypass bleeding

Issues
Postoperative patient with multiple possible causes of impaired haemostasis
Usually in ICU setting
May be an emergency depending on severity: simultaneous diagnosis and management

Priorities
ABCDE if necessary (tamponade, rapid bleed)
Aim for haemodynamic stability, assessment, correction of abnormalities
In practice, treatment may be empirical in order to achieve stability

Assessment
History
Medical problems (e.g. renal failure, hepatic dysfunction)
Preoperative drug therapy (e.g. aspirin, warfarin)
Operative detail: duration of CPB, transfusion requirement
Examination
Rate, source and nature of bleeding (general vs localized, arterial vs haemoserous)
Relation to position if drain tube losses only
Tests
ACT prior to leaving theatre
APTT, INR, platelets
DIC screen
Thromboelastography

Management
Surgical haemostasis
Reversal of residual heparinization
Replacement of platelets and desmopressin
Replacement of clotting factors
Prevention of secondary fibrinolysis, DIC
Patient assessment for cardiac surgery

Epidemiology
  IHD in 20% of adult surgical patients, 70% of vascular patients
  Perioperative AMI has 15-70% mortality

Cardiovascular
  History, examination
  Angina, exercise tolerance, dyspnoea, palpitations
  Hypertension
  Medication, previous procedures
  Other vascular disease: aneurysms, carotid or peripheral disease
  Signs of cardiac failure or valve dysfunction

ECG, exercise ECG
  HR and BP at which ischaemia was evident
  Leads which showed ischaemia best
  Evidence of ventricular dysfunction

Echocardiography
  Condition of aorta and coronaries, LV function, valve function
  Regional wall motion abnormalities
  Stress echo has good discriminatory power

Coronary angiogram
  Static test, no indication of exercise ischaemia
  Location of lesions → ECG leads to monitor
  Results of previous revascularization procedures
  LVgram indicates LV function (not best test)

Radionuclide angiography
  Perfusion defects ± stress, ventricular ejection

Cardiac catheter
  Valve function and gradients, ventricular pressure, output
  Quantification of shunts

Other tests
  FBE, U&E, LFT, XM, ABG (sometimes at induction)
  Of questionable value: clotting, urinalysis

Noncardiac disease of interest
  Condition should be optimized before elective surgery

Endocrine
  Obesity, thyroid dysfunction, adrenal dysfunction, phaeo
  Diabetes
    Autonomic lability, silent ischaemia, slowed gastric emptying

Haematological
  Anaemia, coagulopathy, haemolytic conditions

Respiratory
  Smoking, asthma, COAD, infection, pulmonary embolism

Other
  Renal failure, cirrhosis, peptic ulcer disease, drug dependence, connective tissue diseases

Medications
  Decision to continue or cease in consultation with cardiologist
    Continue
      Antianginals, β-blockers, antidysrhythmics, most antihypertensives
    Usually continue
      Aspirin, Ca²⁺ channel blockers, digoxin, most other agents
    Maybe cease
      ACE inhibitors (worsen hypotension)
    Usually cease
      Diuretics, oral hypoglycaemics (substitute insulin)
Other preparation
Consent
Height, weight, BSA
Washing, shaving, fasting
Anaesthesia for cardiac surgery

Premedication
Anxiolytic and sedative, avoid hypotension and marked hypercarbia
- Diazepam 0.1-0.2 mg/kg plus morphine 0.1 mg/kg
  or lorazepam and fentanyl, or Omnopon and scopolamine
Reduced risk of ischaemia
- Nitrate, β-blocker, clonidine

Monitoring
Routine
- SpO₂, ECG with ST analysis, arterial line, PA catheter (CVC in some units),
  temperature (core and peripheral), IDC with burette, large peripheral IV
- All in place before induction
- Priorities: volume status and contractility assessment to guide therapy
If indicated
- Oesophageal stethoscope can monitor HR, breathing without interference
- PA catheter (unless routine) for CO, PAOP
- TOE
- Cerebral function monitor for deep hypothermia
Bedside tests
- ABG, Na⁺, K⁺, Hb, glucose, ACT (? thromboelastography)
Induction
Traditional
- Fentanyl 10-30 µg/kg, pancuronium 0.1 mg/kg, propofol minimum
  required dose
Additional drugs
- Antibiotics, ε-aminocaproic acid or aprotinin, Mg²⁺
- Heparin pre-bypass
- Pressors and vasodilators as required
“Fast track”
- Propofol, isoflurane, fentanyl or remifentanil
- Requires normothermia, haemodynamic stability and coagulation at end
  of case
Thoracic epidural
- Improved analgesia, ↓ stress response
- Risks unknown, may be no better than β-blockade
Off-bypass CAGS
- Conventional anaesthetic, grafts performed on beating heart
- Requires low CO, low O₂ demand during grafting as coronary vessel is
  occluded
  - Fill, posture head down, reduce heart rate
Maintenance
- Usually air, O₂, isoflurane ± propofol infusion for bypass
Bypass
- Going onto and coming off bypass
- Venous return usually from SVC and IVC
- Total or partial bypass
- Additional input from sucker and LV vent if present
- Reservoir in bypass machine
- Oxygenator (membrane or bubble)
- Heat exchanger
- Pump (usually non-occlusive roller)
- Bubble catcher and filter
- Arterial infusion usually ascending aorta
  - Output commonly set at typical CO for patient (=5 l/min)
  - MAP set by dilator/pressor infusion (=70 mmHg)
Management of pH, PCO₂
No temperature correction (alpha-stat) is conventional

Postoperative
Transfer to ICU
   Oxygen and means of ventilation
   Continuous monitoring (ECG, SpO₂, BP), pacemaker if necessary
   Infusion devices for drugs
   Assistance for emergencies
   Sedative, analgesic and resuscitation drugs
   Advance notice to ICU

Analgesia
   Narcotic infusion, PCA, oral adjuvant agents
<table>
<thead>
<tr>
<th>Category</th>
<th>Drug</th>
<th>Bolus</th>
<th>Infusion</th>
<th>Prepare</th>
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</thead>
<tbody>
<tr>
<td><strong>Pressors</strong></td>
<td>Methoxamine</td>
<td>2-100 mg</td>
<td></td>
<td>10 mg in 20 ml</td>
</tr>
<tr>
<td></td>
<td>Phenylephrine</td>
<td>50-100 µg</td>
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<td></td>
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<tr>
<td></td>
<td>Metaraminol</td>
<td>0.1-2 mg</td>
<td>40-500 µg/min</td>
<td>10 mg in 20 ml</td>
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<td></td>
<td>Ephedrine</td>
<td>5-30 mg</td>
<td></td>
<td>30 mg in 6 ml</td>
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<tr>
<td></td>
<td>Noradrenaline</td>
<td>1-10 µg</td>
<td>1-60 µg/min</td>
<td>1.5 mg in 25 ml</td>
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<td><strong>Inotropes</strong></td>
<td>Dobutamine</td>
<td>2-20 µg/kg/min</td>
<td>3·BW mg in 50 ml</td>
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<td></td>
<td>Dopamine</td>
<td>2-15 µg/kg/min</td>
<td>3·BW mg in 50 ml</td>
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<td>Isoprenaline</td>
<td>1-5 µg</td>
<td>0.5-5 µg/min</td>
<td>200 µg in 20 ml</td>
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<td>Adrenaline</td>
<td>2-50 µg</td>
<td>1-60 µg/min</td>
<td>1.5 mg in 25 ml</td>
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<td>Milrinone</td>
<td>50-75 µg/kg</td>
<td>0.4-0.8 µg/kg/min</td>
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<td></td>
<td>CaCl₂</td>
<td>0.25-1 g</td>
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<td></td>
<td>Glucagon</td>
<td>3-10 mg</td>
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<tr>
<td><strong>Vasodilators</strong></td>
<td>GTN</td>
<td></td>
<td>50-500 µg/min</td>
<td>15 mg in 25 ml</td>
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<td>SNP</td>
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<td>0.2-8 µg/kg/min</td>
<td>50 mg in 500 ml</td>
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<td>Phentolamine</td>
<td>1 mg</td>
<td>0.5-7 µg/kg/min</td>
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<tr>
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<td>PGE₁</td>
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<td>0.05-0.5 µg/kg/min</td>
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<tr>
<td></td>
<td>Hydralazine</td>
<td>5 mg</td>
<td>&lt;40 mg/h</td>
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</tbody>
</table>
Priorities in valve disease

Mitral stenosis
- Severity by valve area: normal 4-6 cm², mild 1.5-2.5 cm², moderate 1-1.5 cm², severe ≤1 cm²
- Sinus rhythm and normal heart rate are vital for output
- Maximize LA pressure without pulmonary oedema
- ↑ risks with PA catheter in pulmonary hypertension
- Pulmonary HT may cause RV failure

Mitral regurgitation
- Severity by regurgitant fraction: >0.6 severe
- Heart rate normal to high
- Low SVR increases forward flow (limited by hypotension)
- Maintain contractility without high preload (dilates LV)
- Risk of ventricular rupture coming off bypass
  - Loss of chorda tendinae bracing ventricle and ↑ pressure work
- IABP may be helpful

Aortic regurgitation
- LV volume overload, gradual hypertrophy, sudden decompensation
- Severity by regurgitant volume: mild 1-3 l/min, moderate 3-5 l/min, severe >6 l/min
- Tachycardia reduces LV distension
- Low SVR increases forward flow (limited by hypotension)
- Contractility usually impaired
- Aortic cross-clamp or LV vent may be required
- Antegrade cardioplegia may be impossible
- IABP contraindicated

Aortic stenosis
- Severity by valve area (<1 cm² severe) or pressure gradient
- High LVEDP (PAOP) to fill non-compliant ventricle
- Sinus rhythm a high priority, normal heart rate
- Myocardial O₂ balance is impaired by LV hypertrophy and low aortic root pressure
- Vasodilation may severely impair coronary and cerebral perfusion

HOCM
- Dynamic functional aortic outflow obstruction due to septal hypertrophy
- Obstruction improves with reduced pressure gradient
  - Vasoconstriction, β-blockade, myocardial depressants
- Maintain high preload
- High incidence of arrhythmia
Anaesthesia in the post-transplant patient (BJA 1991; 67: 772-778)

Transplant types
Heart, heart-lung, single lung

Complications
Arrhythmia: including fatal VT, sign of rejection
Infection related to immunosuppression
CMV, HSV, pneumonia with *Pneumocystis carinii*
Neoplasia related to immunosuppression
Depression, anxiety, thought disorder
May lead to rejection due to medication non-compliance
Coronary vessel disease
Common (46% at 2 years) without pain (denervated)
Presents with lethargy and dyspnoea
Routine screening angiography and biopsies for rejection
Lung rejection
Symptoms similar to infection: desturation, fever, leukocytosis, opacification

Anaesthesia issues
Denervated heart
Rate 90-100 /min, no vagal or sympathetic response
Normal response to circulating catecholamines
No rate response to baroreceptors, Valsalva, carotid sinus, hypovolaemia, light anaesthesia
Dependent on intrinsic regulation of cardiac output
Preload dependent \(\rightarrow\) stroke volume
Must maintain filling pressure

Cardiac pharmacology
Little effect from cholinergic agents: atropine, neostigmine, suxamethonium
\(\beta\) adrenergic agents and glucagon remain effective
Antidysrhythmics and DC reversion remain effective

Denervated lung
Relatively normal respiratory pattern and maintenance of gases
\(\text{PCO}_2\) response may be blunted
No cough in response to irritation of bronchi
Extubate awake, encourage active physio

Uneven \(\mathbb{V}/Q\) distribution
Bronchoconstriction can occur

Usual drug regimen
Immunosuppression
Must be continued perioperatively
Steroid requires supplementation
Azathioprine
Cyclosporin: nephrotoxicity, hepatotoxicity, hypertension, ↑ NDB effect

Evaluation
Consult with treating unit
Routine preoperative assessment

Technique
GA or regional **provided filling maintained**
Meticulous aseptic technique
Routine prophylactic antibiotics (? also for line insertion)
Isoprenaline for bradycardia (not atropine)
Minimize lines, avoid right IJV (used for biopsies)
Vigorous physio post-op
Vascular

Carotid endarterectomy

Preoperative assessment of a patient for carotid endarterectomy

Abdominal aortic aneurysm

Thoracic aortic aneurysms
Carotid endarterectomy

Indication
Symptomatic carotid disease > 70% occlusion: proven benefit in long-term stroke rate
Asymptomatic disease > 50-60% occlusion: reduces ipsilateral stroke rate

Perioperative morbidity
Stroke 3-5%, most postoperatively (> 50% after 4 hours post-op)
Risk factors: previous stroke, poor BP control post-op
AMI 0-4%

Preparation
Cardiac investigation indicated only for unstable angina, recent MI or decompensated CCF
70% of patients have silent IHD, diagnosis does not alter management
Relative priority of CAGS is undetermined

Anaesthetic management

Objectives
Cardiac and neurological protection from ischaemia
Cardiovascular stability
Early postoperative neurological examination

Monitoring
Routine plus ST segment monitoring, arterial line, large IV
Arterial line in arm with highest BP on examination
CVC generally avoided

GA
Fairly routine
Consider propofol “book-end” technique for rapid awakening
O₂, N₂O, isoflurane maintenance
Ready availability of pressors and nitrates for BP control
Continued BP control with emergence and post-op
Maintain normocapnia and normoglycaemia
Cerebral protection: high dose barbiturates for burst-suppression

Regional
Deep and superficial cervical plexus block
Exclude contraindications, monitor, IV access, assistant
Detail of technique

Advantages
Continuous functional neurological monitoring
High level of patient acceptance: 92% would have again
Possible lower risk of perioperative stroke
Possible lower risk of cardiopulmonary complications
Less BP lability intra- and post-operatively
No instability on “wake-up”

Disadvantages
High plasma levels of LA
Phrenic nerve block
Higher catecholamine levels, ? more tachycardia

Clamping
Order: ICA, CCA, ECA
Observe neurological findings for 2-3 minutes (regional) or BP, stump pressure, other monitors (GA)

Unclamping
Order: ICA (flush), clamp ICA, ECA, CCA, ICA

Postoperative complications

Neurological complications
Usually due to intraoperative embolization or hypoperfusion or endarterectomy site embolization or thrombosis
Some due to intracerebral haemorrhage (0.4-2%) or hyperperfusion
Rate strongly correlates with surgical technique

Hypertension, hypotension
  Usually due to carotid sinus baroreceptor dysfunction but hypoventilation,
pain, bladder distension should be excluded
  Treated aggressively to minimize risk of cerebral or myocardial injury

Nerve injury
  Commonly recurrent laryngeal, superior laryngeal, hypoglossal or marginal
  mandibular

Wound haematoma requires prompt drainage if airway compromised
Preoperative assessment of a patient for carotid endarterectomy.

Surgery
  Elective, high risk
  1-2% mortality, 4-10% morbidity
Issues
  Access to airway
  Cerebral protection
Assessment
  Identify myself and patient, confirm procedure, explain role
History
  CVS
    Symptoms of cerebrovascular disease
    Hypertension, usual BP as basis for intraoperative aim
    Coronary vascular disease
      MI, angina, SOB, symptoms of failure
    Peripheral vascular disease symptoms
    NYHA functional classification
  Respiratory disease
    Commonly smokers, COAD
  Other illnesses
    Diabetes, renal impairment
Examination
  Focussed on cardiac and respiratory complications
  Document neurological status
Medications
  Decision whether to continue or withhold
  Commonly on multiple medications
    Antiplatelet, β-blockers, diuretics, ACEI, others
Investigation
  ECG: high incidence of IHD
  U&E, FBE
  If IHD, consider echo, thallium scan or angiography
    Carotid disease is generally treated before CAGS
    But other revascularization options may be considered
Overall
  Diseases unstable or stable, optimized or not
  Plan for risk minimization
Consult
  Appropriate referral for optimization of function
Consent
  Anaesthetic plan: GA or regional
    Regional requires detailed explanation in advance
  Risks
    General: allergy, aspiration, blood transfusion, cardiac event, dental injury, death, awareness
    Specific: stroke risk
Postoperative plan
  Ward or HDU
  Analgesia
Premedicate
  Aiming for normotension, normocapnia, anxiolysis
  Usual antihypertensives, antiplatelet drugs as per surgeon’s instructions
  Anxiolytic: temazepam
Abdominal aortic aneurysm

Natural history
Progressive enlargement and rupture
5 y rupture rate
- 4-7 cm: 25%
- 7-10 cm: 45%
- >10 cm: 60%

Risk of rupture rises with diameter and rate of expansion
Greater than risk of surgery at ≥5 cm or ↑ ≥0.5 cm in 6 months

Preoperative
Assessment
Similar to endarterectomy

Intraoperative
Monitoring
Routine, plus arterial line, multiple large IVs, CVC or Swan sheath
Cell-saver for large anticipated blood loss
Consider nasopharyngeal airway placement prior to heparinization if extubation planned

Induction
GA with minimized BP rise, epidural catheter or Spinal or CSE for endoluminal repair

Crossclamping
Effects depend on level of clamping, collateral circulation and physiological reserve
Little effect from infrarenal clamp, major changes with thoracic clamp

Haemodynamic
↑ SVR (direct): ↑ BP, ↓ ejection fraction, ↓ CO, ↑ LVEDV,
↑ contractility, ↑ coronary flow
reflex ↑ sympathetic tone: ↑ SVR, ↑ venous return, ↑ PAOP & CVP,
↑ LVEDV, ↑ CO (if good myocardial function)
If coronary stenosis: segmental wall motion abnormality, ischaemia or LV failure
Wall motion abnormalities in 40% of infrarenal and 90% of supracoeliac clamps

Metabolic
Distal ischaemia: ↓ VO₂, ↓ CO₂ excretion, ↑ SvO₂, ↑ catecholamines
Metabolic acidosis, if ventilated: respiratory alkalosis

Intervention
Afterload reduction
SNP, volatiles, amrinone, epidural, remifentanil
Preload reduction
GTN, epidural, shunt or left heart bypass
Renal protection
Mannitol, dopamine, fluids
Suprarenal clamp → 90% reduction in RBF
Infrarenal clamp → 40% reduction in RBF

Unclamping
Haemodynamic
↓ SVR, ↓ CVP, ↓ CO, ↓ BP, ↓ contractility
Metabolic
↑ VO₂, ↓ SvO₂, ↑ lactate, PGs, activated complement, myocardial depressants
Intervention
↓ vasodilators & volatiles, IV filling, pressors
Reapply crossclamp if unacceptable hypotension

Emergence
Extubate on table if stable: normothermia, normal ABG, no massive transfusion
Thoracic aortic aneurysms

Classification
DeBakey
I    thoracoabdominal
II   ascending and arch
III  descending ± abdominal

Crawford I-IV

Risk with surgery
Mortality 5-15%
Paraplegia 5-40%
ARF 3-30%
All depending on extent of aneurysm

Issues
Planned technique
Extracorporeal circulation
One-lung ventilation
Monitoring
Spinal cord function
Protection
Spinal cord, renal, cerebral, myocardial

Preoperative
Assessment
As any vascular or thoracic patient, plus anatomical detail of aneurysm
Respiratory function if OLV planned

Intraoperative
Monitoring
Routine, plus
IV access: 8.5 Fr x 3 (PA catheter and 2 rapid infusers)
Arterial line in right radial ± femoral if femoral bypass
Temperature (core and periphery), TOE, SSEPs
Induction
Minimizing hypertension with cardiac-type induction
Left-sided DLT for left lung deflation (minimizes risk of occluding RUL)
Maintenance
Bypass
Full bypass with flow into ascending aorta
Partial bypass with flow LA → femoral artery
Passive shunt around clamped aorta
No bypass “clamp and run”
Clamp duration
30 min   10% paraplegia
60 min   90% paraplegia
Deep hypothermic circulatory arrest (DHCA) for arch aneurysms
± cold oxygenated retrograde cerebral perfusion
Spinal protection
CSF drainage, hypothermia, intrathecal papaverine
Renal protection
Dopamine, mannitol, fluid loading, frusemide
Myocardial protection
Clamping and unclamping: compensate for haemodynamic changes with vasoactive drugs
Emergence
Change DLT for single-lumen tube with changing catheter
Transfer ventilated to ICU

Vascular  3.D.2.7  James Mitchell (October 7, 2001)
Neurosurgery

- Positioning for neurosurgery
- Venous air embolism
- Problems associated with raised ICP
- Transsphenoidal surgery for acromegaly
- Paediatric neurosurgery
- Surgery following subarachnoid haemorrhage
- Awake craniotomy
Positioning for neurosurgery

General considerations
- Usually prolonged surgery
- Careful identification of pressure areas
- Avoidance of traction on nerves
- Thromboembolic precautions

Supine
- Used for frontal, temporal or parietal access
- Extreme of head rotation may cause venous obstruction, carotid dissection
- Slight head-up usually desirable for venous drainage
- Hip and knee flexion reduces back strain: beach-chair position

Semilateral (“Jannetta”)
- Used for retromastoid procedures
- Table tilted 10-20˚, shoulder roll, head rotation
- Avoid extreme head rotation

Lateral
- Used for posterior parietal and occipital access
- Axillary roll to prevent brachial plexus injury
- Stabilization with vacuum bean-bag or lateral rests (potential pressure areas)

Prone
- Used for spinal, occipital, cranial suture and posterior fossa procedures
- For cervical spine and posterior fossa usually head-up and neck flexed
- Requires planning for turning
  - Secure airway and lines, 100% O₂, removal of most monitoring
  - Unstable cervical spine may require awake intubation and positioning
  - Facial support much not cause eye compression and retinal ischaemia
  - Other pressure areas: elbows, breasts, iliac crests, genitalia, knees, toes
  - Avoid pressure on abdomen: ↑ PAW, IVC obstruction
  - Neck flexion may cause compression of base of tongue and pharynx
    - Especially with instrumentation: ETT, TOE

Sitting
- Used for some posterior fossa and cervical spine surgery
- Possibly greater dangers than alternative positions
  - Hypotension, cerebral ischaemia (↓ venous return, ↓ CPP)
  - Perfusion pressure should be measured at ear level
  - Lightly anaesthetized patients may compensate with ↑ SVR, ↓ CO
  - Volume loading and pressors to maintain CPP ≥60 mmHg
  - TEDs stockings or calf compression devices
  - Tongue and pharynx compression or spinal injury from neck flexion
  - Pressure areas: buttocks, potential brachial plexus distraction
  - Venous air embolism ± paradoxical embolism
  - Pneumocephalus
    - May be worsened by N₂O diffusion after dural closure
    - Cease N₂O with dural closure
    - PA catheter tip may be in West’s zone 1 (alveolar pressure > PA pressure)
  - Surgery in this position may involve the brainstem
    - Haemodynamic, respiratory, homeostatic disturbance
Some advantages
- Better venous and CSF drainage, possibly better access
Venous air embolism

Incidence
- Depends on procedure, position and method of detection
  - Sitting position posterior fossa surgery with TOE: 76%
  - Less for other positions, surgery and monitors

Aetiology
- Open vessels at lower than ambient pressure
  - Cerebral sinuses, emissary veins, diploic vessels in head-up position
  - Gas under pressure in ventricles, subdural space
  - Gas under pressure in non-neurosurgical procedures: laparoscopy, hysteroscopy, gas-cooled lasers

Detection
- High sensitivity
  - TOE, praecordial Doppler (right sternal edge 3rd-6th intercostal spaces)
- Lower sensitivity, indication of severity and recovery
  - ETCO₂, PAP
- Low sensitivity, indication of incipient arrest
  - BP, ECG, SpO₂

Management
- ABC
- Prevent further air entry
  - Notify surgeon, flood field
  - Jugular compression, lower head
- Manage intravascular air
  - 100% O₂, cease N₂O, cease PEEP
  - Aspirate right heart catheter if present
  - Circulatory support: fluid, pressors, chest compression
- Head-down right lateral position theoretically advantageous
  - Not feasible in most neurosurgery, no evidence for efficacy

Paradoxical embolism
- Requires PFO (25% prevalence) and transient RAP > LAP
- PFO may be detected by TOE after induction

RAP to LAP gradient
- Transiently positive during cardiac cycle
- Increased by PEEP, greatest with release of Valsalva manoeuvre
- Reduced by fluid loading
Problems associated with raised ICP

ICP

Intracranial pressure
Usually measured with LP in lateral position or intraventricular catheter
Used to calculate cerebral perfusion pressure
CPP = MAP - greater of JVP and ICP
Rises with intracranial expansile mass
Monro-Kellie Doctrine: volume of cranium is constant
Initial compensation by reduced venous blood volume
Then rapidly rising ICP, ↑ capillary pressure increases cerebral oedema
CBF becomes pressure-passive
Potential for herniation through tentorium

Cerebral blood flow (CBF)
Autoregulated under normal conditions
CPP 60-160 mmHg
Affected by PaO₂, PaCO₂, cerebral metabolic activity (CMRO₂)

Surgery
To relieve intracranial pressure
Craniotomy, resection of lesion, drainage of haematoma
Incidental
Trauma patient with head injury and other injuries
Chronic intracranial hypertension

Assessment
Routine, plus
Neurological findings
Headache, nausea, vomiting, visual disturbance, cranial nerve lesions, irritability and confusion
Intracranial pathology: malignancy, haemorrhage
Timecourse of symptoms
Cardiorespiratory history
Usual blood pressure (baseline for autoregulation of CBF)
Specific diseases
Diabetes, pituitary dysfunction, trauma
Medications
Steroids, anticonvulsants, antihypertensives, mannitol, frusemide
Airway assessment, risk of aspiration
Usual investigations plus imaging

Preoperative
Premedication
Avoid hypercapnia, so no opiates
Usual machine and equipment checking
Monitoring
Routine, plus
ECG arrhythmias common
Arterial line, CVC or long line
IDC, temperature

Intraoperative
Induction
Most agents suitable except ketamine
Barbiturates, propofol reduce CMRO₂, CBF and ICP
Non-depolarizing relaxants safe
Histamine release should be avoided
Suxamethonium relatively contraindicated
ICP rise is small and blocked by pre-dosing with NDB
Lignocaine 1.5 mg/kg may reduce ICP rise at intubation
Protect eyes and face
Use armoured tube

Maintenance
Continuous deep muscle relaxation
TIVA or inhalational techniques
All agents except ketamine cause ↓ CMR, ↓ CBF in parallel
High concentration of volatiles impair autoregulation (H >> E > I, S, D)
N₂O is a cerebral vasodilator alone (↑ CBF, ↓ CMRO₂)
Probably safe in balanced techniques
Propofol TIVA is probably best

Techniques to reduce ICP (in consultation with surgeon)
Cellular
Surgical resection
ICF, ECF
Osmotic diuretics (mannitol 0.25-2 g/kg)
Limited by serum osmolarity ≤320 mOsm/l
May cause rebound swelling, hypovolaemia, hypotension
Loop diuretics
↓ ECF and impair idiogenic osmole formation
May reduce rebound swelling
Fluid restriction
Steroids
↓ ICP over 48-72 h, may worsen outcome overall

CSF
Surgical drainage

Blood
Head-up position (also reduces perfusion pressure)
Lower CMR (with intact autoregulation)
Barbiturates, anticonvulsants, hypothermia
Acute hyperventilation (controversial)
Transient response, risk of ischaemia, rebound on cessation
Avoid agents which impair autoregulation
High dose volatiles, vasodilators
Avoid coughing, straining or high PAW → venous pressure
Hypotension for vascular lesions
Worsens cerebral perfusion
Once the head is open, CPP is a higher priority
Support MAP

Neuroprotection
Drugs: barbiturates
Hypothermia
Transsphenoidal surgery in acromegaly.

Acromegaly

Excessive growth hormone secretion
>99% due to pituitary adenomas
Gradual onset of clinical features
  Pre-puberty: pituitary giantism, ↑ linear growth plus adult features
  Adult
    Continued growth of facial, hand and foot bones
    Hypertrophy of soft tissues, viscera, skin tags, mucosal polyps
    Cardiomyopathy, hypertension, IHD
    Diabetes
    Proximal myopathy
    Local effects
      Failure of other pituitary secretion: LH, FSH, ACTH…
      Headache
      Bitemporal hemianopia
   Usually diagnosed in 3rd or 4th decade
   Medical therapy with bromocriptine, octreotide, radiation
   Surgical excision usually curative

Surgery

Elective, moderate risk
Performed through the nose or an incision under the upper lip
Shared airway, commonly soiled by surgery

Preoperative

Assessment
  Routine, plus
  Features of acromegaly
    Airway compromise: large tongue and jaw, nasal polyps, mucosal folds,
    recurrent laryngeal nerve palsy
    Cardiorespiratory complications
  Other disease complications
    Diabetes, IHD
  Pituitary tumours
    Commonly secrete prolactin, occasionally GH, ACTH or TSH
    Compress normal tissue with loss of other hormone secretion
    Supplement hypoadrenalism (hyponatraemia, hypovolaemia) or
    hypothyroidism

Investigation
  Routine bloods, glucose, crossmatch
  Imaging of the head may give information about the airway

Premedication
  Important if fibreoptic intubation planned

Intraoperative

Monitoring
  Routine plus arterial line, but 50% positive Allen test
  Large IV

Induction
  Large mask required, mask ventilation may be difficult
  Oral intubation, consider awake FOB if likely to be very difficult
  Small tube due to incidence of subglottic narrowing
  Armoured tube plus throat pack

Positioning
  May be heavy, nerve hypertrophy increases risk to ulnar nerve
  Head-up reduces bleeding but may cause air embolism

Maintenance
Neuro-type balanced technique
Vigilance for complications
  Disconnection
  Dissection into cavernous sinus with haemorrhage
  Pressure on face or eyes
  Antiemetic
Emergence
  Clear blood or CSF from airway
  Aim to minimize coughing
Postoperative
  Ward care
  Attention to complications
    Diabetes insipidus (usually transient)
    Panhypopituitarism
  Analgesia
    Oral ± IM narcotic
Paediatric neurosurgery

Positions
- supine, prone, sitting, lateral/park bench, knee-chest
- purpose: surgical access, physiological effect (ICP, bleeding control)
- considerations:
  - airway: usually IPPV with oral ETT
  - raises CVP, ICP
  - compensate with head-up, minimize airway P using deep paralysis, long inspiratory time, improve compliance with position (e.g. pressure off abdomen)
  - SV occasionally in brainstem surgery, still ETT
- access
  - monitoring
  - pressure areas: especially eyes
  - specific complications
    - air embolism in sitting position
      - diagnosis by TOE, fall in CO₂, fall in SpO₂, calibrate arterial pressure at head level for hypotension
      - manage Valsalva, 100% O₂, flood field, neck tourniquet, aspirate CVC

Control of ICP
- Monroe Kellie doctrine
  - volume of cranium is constant
  - true after closure of sutures
- physiologic control
  - normal 5-15 cmCSF
  - remains constant due to redistribution of CSF and venous blood volume
  - rises sharply after critical point in elastance curve as intracranial "mass" expands

Physiologic interventions
- positioning
  - head up reduces both ICP and CPP
- hypovolaemia, hypotension
- PCO₂
  - fall causes transient fall in ICP due to vasoconstriction
  - not used below 30 mmHg as may impair CPP
  - effect is transient
- opening the cranium: surgery

Pharmacologic interventions
- reducing mass effect
  - steroids reduce reactive oedema
- diuretic agents
  - mannitol (acute volume-expanding effect)
  - frusemide
  - IDC required
  - can also reduce MAP
- agents to reduce CBF, CMRO₂
  - general anaesthesia, barbiturates
- avoiding agents which raise ICP
  - high PCO₂, Valsalva, coughing
- drugs: suxamethonium (but commonly indicated in trauma etc.)
agents which impair autoregulation: volatiles

Protection of the patient
positioning
  pressure areas, joint hyperextension or malposition
vascular compromise
neuropraxia
temperature
  conservation and warming
neuroprotection
drugs
  maintain cerebral autoregulation, reducing CMRO₂
barbiturates, volatiles, propofol
hypothermia
Surgery following subarachnoid haemorrhage

Subarachnoid haemorrhage
Aetiology, natural history
Rupture of arterial aneurysm or bleed from AVM
40% immediate major morbidity or mortality
30% major morbidity or mortality after surgery

Grading

<table>
<thead>
<tr>
<th>Grade</th>
<th>GCS</th>
<th>ICP (cmH₂O)</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>15</td>
<td>&lt;10</td>
<td>2%</td>
</tr>
<tr>
<td>II</td>
<td>13-14 without motor deficit</td>
<td>&lt;10</td>
<td>5%</td>
</tr>
<tr>
<td>III</td>
<td>13-14 with motor deficit</td>
<td>15-20</td>
<td>5%</td>
</tr>
<tr>
<td>IV</td>
<td>7-12</td>
<td>&gt;25</td>
<td>35%</td>
</tr>
<tr>
<td>V</td>
<td>3-6</td>
<td>&gt;25</td>
<td>50%</td>
</tr>
</tbody>
</table>

Surgical management
Operation before 72 h or after 14 days (reduced risk of vasospasm)
Ischaemia managed with fluid loading and hypertension
Nimodipine
Believed to reduce vasospasm, probably cell protection
Requires CVC administration
May cause hypotension

Anaesthetic priorities
Avoid acute hypertension
Intraoperative brain “relaxation”
Maintain high-normal CPP
Preparation for BP manipulation at clipping or rupture

Preoperative
Assessment
Routine, plus
Neurological assessment
Complications of SAH
SIADH or salt-wasting (hyponatraemia, hypovolaemia, high urine Na⁺)
Vasospasm related to clot around Circle of Willis
ECG abnormalities: T inversion, QT prolongation, ST depression, U waves
No correlation with LV function
No specific therapy unless ischaemic pattern

Premedication
No sedation (may raise PCO₂)

Monitoring
Routine, plus
Arterial line, long line for central venous access, large bore IV, IDC, temperature, nerve stimulator

Intraoperative
Induction
Aim to minimize BP rise
Rebleeding at induction (1%) is usually fatal
Vasodilator and pressor agents drawn up
Topical anaesthesia to airway
Lignocaine, β-blocker, narcotic to smooth intubation
Suxamethonium probably safe

BP manipulation
Air, O₂, propofol probably causes least cerebral vasodilation in “tight” cases
Volatile, N₂O probably safe for elective cases
Maintain low-normal PCO₂, check on ABG
Blunting response to pinning (as for intubation)
Maintained planned CPP (e.g. 70 mmHg)
Induced hypotension for uncontrolled bleeding: SNP fastest agent
Induced hypertension for temporary occlusion: metaraminol or phenylephrine
ICP manipulation
Hypocapnia controversial
Lumbar CSF drain, mannitol may be requested by surgeon
Cerebral protection
Propofol commonly used
Thiopentone proven effective but delays awakening so not common
Consider bolus 5 mg/kg for temporary occlusion
Mild hypothermia 32-34˚C
AVM surgery
“Perfusion pressure breakthrough”
Closure of AVM and loss of shunt causes sudden increase in perfusion of adjacent brain which has always been vasodilated
Failure of autoregulation response causes rapid oedema of brain
Other considerations
EEG monitoring, angiography with femoral access
Emergence
Avoidance of hypertension, coughing
Consider extubation deep if fasted
Postoperative
Maintain slight head-up position or as required by surgeons
Close monitoring of haemodynamic and neurological status
ICU or HDU level of care
Awake craniotomy

Surgery
Usually for an epileptogenic focus in the temporal lobe

Preoperative
Assessment
Routine, plus
- Detailed history of epilepsy
  - Nature of aura and seizures for intraoperative recognition
  - Medication and complications

Investigation
- Wada test
  - Unilateral carotid injection of sodium amytal
  - Determines lateralization of speech, short term memory

Videotelemetry
- Continuous EEG with subdural, parenchymal or foramen ovale electrodes to localize focus of seizures

Premedication
- Anticonvulsant agents avoided (benzodiazepines)

Monitoring
Routine, plus
- Gas analysis to confirm airway patency
- Continuous neurological assessment
- Careful attention to patient comfort and warming

Intraoperative
Sedation, analgesia
- Must allow patient responsiveness during cortical stimulation
- Must not inhibit seizure activity

Drug regimens
- Local anaesthetic block and infiltration for pins and incision
- Droperidol 2.5-7.5 mg plus narcotic
  - alfentanil 5-10 µg/kg plus 0.25-0.5 µg/kg/min, or
  - fentanyl 0.7 µg/kg plus 0.7 µg/kg/h
- Propofol infusion or PCA plus narcotic
- If provoking agent is required for seizures, methohexitone 0.3 mg/kg
- For seizure termination if necessary, thiopentone 1 mg/kg

Surgery
- Usually prolonged
- Pin placement (if necessary) and craniotomy are painful
- Brain parenchyma is insensate
- Airway access may be difficult, especially if head is pinned
Orthopaedics

Total hip replacement

Other orthopaedic surgery

Tourniquets

Anaesthesia for a patient with unstable cervical spine fracture for fixation
Total hip replacement

Surgery
Ranges in complexity from simple cementless arthroplasty to re-do with bone grafting, revision of acetabular protrusion etc.
Moderate to high risk

Issues
Choice of anaesthetic technique
Positioning
Blood loss
Cement
Thromboprophylaxis

Preoperative
Assessment
Patient
Typically old patient, may have multi-system disease
Exercise tolerance difficult to assess if limited by hip pain
Discussion of anaesthetic technique
Surgery
Complexity and likelihood of blood loss
Suitability or desire for autologous predonation
Likely requirement for haemodilution, cell-saver

Monitoring
Simple surgery
Routine SpO₂, ECG, NIBP, large IV
Complex surgery, GA, induced hypotension
Temperature, IDC, arterial line, CVC

Intraoperative
Spinal or CSE
Lumbar placement
Plain (hypobaric) bupivacaine if lateral position
3-4 ml 0.5% spinal dose
GA
Relaxant technique if complex procedure
Consider use of induced hypotension
Reduces blood loss 30-50% (as does spinal)
Either
Intraoperative forced-air warming, avoid hypothermia

Position
Commonly lateral
\( V/Q \) mismatch in ventilated patients
Pressure on dependent brachial plexus, axillary artery
Lateral rest may press on femoral canal
Pressure necrosis more likely with hypotension

Reaming and cementing
Sudden profound hypotension, hypoxaemia or arrest may follow reaming or cemented prosthesis insertion
Associated with \( \uparrow \) PA pressure
 Possibly due to methyl methacrylate or fat, air and marrow emboli
May be delayed by femoral vein obstruction with leg position

Postoperative
Analgesia
Epidural not commonly used because of incidence of urinary retention
Systemic narcotic plus paracetamol and NSAID (if not contraindicated)
Level of care
Usually ward unless high-risk

Orthopaedics
3.D.4.2
James Mitchell (October 7, 2001)
Other orthopaedic surgery

Total knee replacement

Surgery
  Unilateral or bilateral
  Higher incidence of complications if bilateral and HDU care may be required
  Commonly done below a tourniquet
Issues
  Cement associated hypotension with femoral component
  Blood loss
    Tourniquet
    Antifibrinolytics (ε-aminocaproic acid)
  Postoperative analgesia
    Epidural catheter
    Femoral catheter
    Spinal morphine
    Femoral, sciatic, obturator blocks

Spinal surgery

Surgery
  Major surgery, commonly in prone position
Issues
  Patient deformity and respiratory or neuromuscular disease
  Positioning
  Spinal cord monitoring: SSEP, wake-up test
  Blood loss and conservation techniques
  Duration, temperature conservation
Tourniquets

Inflation

Local
Folds or lines under tourniquet may cause bruising or pressure necrosis of skin

Metabolic
By 8 min mitochondrial PO$_2$ approaches 0
Anaerobic metabolism
↓ ATP, NAD$^+$, CP, ↓ pH
Release of myoglobin, K$, intracellular enzymes, thromboxane
Tissue oedema develops after 60 min
Tissue temperature approaches room temperature

Haemodynamic
Exsanguination ↑ CVP, PAP
Inflation ↑ SVR, BP
45-60 min hypertension “tourniquet pain” unresponsive to anaesthesia
Not prevented by axial blockade
May be prevented or delayed by plexus blockade

Neurological
Conduction ceases by 30 min
Neuropraxia may be due to ischaemia or shear forces
Prevented by periodic deflation

Release
Metabolic
Rapid washout of metabolic products and equilibration of temperature
↓ core temperature, SvO$_2$ falls to 20%, ↑ PCO$_2$

Haemodynamic
Direct: ↓ SVR, ↓ CVP
Metabolites: marked vasodilation, myocardial depression
Potential embolisation of distal venous clot or debris
Anaesthesia for a patient with unstable cervical spine fracture for fixation.

Halo traction
   Emergency surgery in a trauma patient at high risk of catastrophic neurological injury

Issues
   Cervical immobilization
   Other injuries
   Minimizing anaesthetic intervention

Preoperative
   Assessment
      Routine, plus
      Trauma patient
         ABC priorities
         Conscious state, and fluctuation
         Other injuries, particularly head and airway
         Careful airway assessment
      Neurological state
         Documentation of any defect

Optimization
   Urgency of surgery usually does not allow much time
   Cervical spine immobilization
      Hard collar, sand bags, spinal board

Premedication
   None
   Detailed explanation of procedure

Transport
   Supine on spinal board
   Transfers on board or lifting frame
   Log-rolling for turning

Intraoperative
   Preferred anaesthetic technique is local infiltration for bolts and no sedation
   Monitoring and access
      Large bore IV access, routine monitors
   Induction
      Drugs available for induction of general anaesthesia
      Emergency drugs for CVS support
      Difficult airway equipment available
      GA only if unmanageable otherwise
         Aim to minimize cervical spine movement
         In-line immobilization for laryngoscopy or use of FOB or Fastrach or Bullard if appropriate

Postoperative
   Traction frame bed or body-harness
   Minimal analgesia required
Management of airway fire in laser microlaryngoscopy

Pharyngeal pouch

Local anaesthetic for tonsillectomy
Management of airway fire in laser microlaryngoscopy. How can this be avoided.

Laser microlaryngoscopy

High energy laser (CO₂ or Nd-YAG) used along side the ETT
0.5%-1.5% incidence of airway fire
Usually laser igniting ETT or swabs

Minimizing risk

Surgeon
- Control of laser direction and operation
- Non-reflective instruments
- Moistened swabs
- Copious sterile water on setup
- Fire drill should be agreed or rehearsed

Choice of ETT
- Metal tube: Mallinkrodt “Laser Flex”
- Metal coated silicone tube: Xomed “Laser Shield”
- Metal tape coating on regular tube
  - Flammability silicone < rubber < PVC
  - Toxic debris silicone > PVC > rubber
- Cuff is still vulnerable
  - Fill with saline ± methylene blue
  - Second cuff on Laser Flex
  - Distal placement of cuff (out of sight)
- Place moist swabs on wires above cuff
- Metal can be ignited or cut by Nd-YAG laser
- Consider jet ventilation or oscillator

Airway gases
- Minimize use of oxidant gases
  - Minimal required FiO₂
  - No N₂O
  - Helium retards ignition
- Air available for ventilation in case of fire

Maintenance
- Immobility required: deep anaesthesia or paralysis
- High level of vigilance for fire
- Good communication with surgeon

Managing fire
- Remove source of fire and extinguish with water
- Stop ventilation, turn off O₂
- Mask ventilate with air, then 100% O₂ once fire is extinguished
- Laryngoscopy and rigid bronchoscopy to remove debris
- Lavage and fibreoptic bronchoscopy if indicated by airway injury
- Common pattern is worst injury at the surgical site and little distal injury
- If severe injury
  - Maintain ventilation
  - Consider low tracheostomy
  - IV corticosteroids may be helpful
  - CXR, ABG with co-oximetry for smoke inhalation assessment
Outline management of anaesthesia for resection of pharyngeal pouch.

Surgery
- Elective, moderate risk
- High risk of aspiration
- Close to major structures in neck

Assessment
- Routine plus
  - History
    - Dysphagia, regurgitation and aspiration of food
      - Positional or on waking
  - Examination
    - Complications of lesion
      - Malnutrition, pneumonia
  - Investigations
    - Imaging of pouch: contrast studies, CT

Preoperative
- Premedication to reduce aspiration risk: H₂ blocker

Monitoring
- Routine plus
  - Arterial line, CVC
  - Epidural if thoracic incision

Induction
- Rapid sequence induction with cricoid pressure
- Pharynx may need to be suctioned
- Avoid high-pressure mask ventilation
- Risks distension ± rupture of pouch
- Consider cervical plexus block if neck incision

Maintenance
- Usually supine with head turned to side
- If lateral, increased risk of pressure areas
- No nasogastric before surgery
  - May pass into pouch

Emergence
- Aim for extubation when awake
- Usually do not require HDU care
Local anaesthetic for tonsillectomy

Anatomy
Tonsil innervated by branches of glossopharyngeal n. which runs along stylopharyngeus and anterior palatal arch

Technique
Initial topical anaesthesia to pharyngeal arches with lignocaine
Tongue depressed with spatula
Infiltration of posterior palatal arch, then anterior palatal arch (IX n.)
Tonsil grasped with forceps and drawn medially
Tonsillar attachment infiltrated
Careful aspiration at all points because of proximity of ICA

Local anaesthetic
Lignocaine 0.5% 10-15 ml each side
Thoracic surgery

Anaesthetic management of bronchopleural fistula

Outline your approach to tracheal stenosis surgery

Preparation for lung surgery

One lung ventilation

Mediastinoscopy
Anaesthetic management of bronchopleural fistula

Bronchopleural fistula
Communication from major bronchus to pleural space
Commonly associated with pneumonectomy, trauma, abscess or empyema
Relevant complications
Pus may contaminate other lung
Associated injuries with trauma

Surgery
Usually semi-elective
Resuturing of bronchial stump, muscle flap to stump, drainage of abscess
High risk surgery requiring GA and one-lung ventilation
If incidental surgery, GA may be avoided, regional preferred
Positioning still important to avoid soiling

Patient
Commonly debilitated, may have coexistent medical problems
Respiratory function assessed
Clinical, spirometry, ABGs
Routine assessment for thoracic surgery
Consideration of epidural

Decision to proceed
Respiratory function optimized
Chest drain inserted to avoid tension pneumothorax and drain pleural collection

Induction
Objectives
Maintain oxygenation and ventilation, avoid tension pneumothorax
Avoid soiling good lung
Protection of lung requires DLT, bronchial lumen to good side
Small leak without infection may be manageable with single-lumen ETT
Paediatric patients are typically too small for DLT or FOB ⇒ blocker or endobronchial intubation
Fistula reduces effectiveness of mask IPPV, so spontaneous ventilation
Ideally awake DLT intubation
Topical local anaesthetic to airway
Position head-up and bad side down
Sedation for intubation
Alternatively spontaneously ventilating GA with DLT insertion when deep
Verification of DLT position with differential ventilation or FOB

Maintenance
IPPV to healthy lung
Lung with fistula may benefit from small V̇̇, ventilation or CPAP below critical pressure for fistula or HFJV

Emergence
Avoid high airway pressures if fistula has been repaired
Hand ventilation or SIMV

Postoperative
Epidural analgesia
HDU monitoring post-op
High incidence of arrhythmia post-thoracotomy
Outline your approach to tracheal stenosis surgery.

**Surgery**
- Elective, high risk
- Cervical level: neck incision
- More distal stenosis: thoracotomy or sternotomy

**Stenosis**
- Extrinsic compression e.g. goitre
  - Usually tracheomalacia: soft tracheal stenosis
  - May be easily splinted with ETT
  - Surgery may not involve opening trachea
- Scarring
  - Usually firm fibrous stenosis

**Assessment**
- Routine plus
  - History
    - Symptoms of airway compromise: positional dyspnoea, sleeping position
  - Examination
    - Respiratory examination: upper airway sounds
  - Investigations
    - Pulse oximetry, ABG if obvious compromise
    - Spirometry: may be only slightly blunted by significant stenosis
    - Tomography or CT: define anatomy

**Preoperative**
- Sedative premedication may worsen function as may anxiety
- Aspiration prophylaxis: H₂ blocker
- Anticholinergic to reduce secretions

**Monitoring**
- Routine plus
  - Left radial arterial line (compression of innominate artery during surgery)

**Induction**
- Technique depends on degree of stenosis and airway control
- Mild, flexible stenosis with little compromise
  - Conventional IV induction
- Tracheostomy in situ
  - IV induction and armoured tube in tracheostomy
  - Replacement by surgeon with sterile tube
- Critical stenosis
  - Inhalational induction with potent volatile agent in 100% O₂
  - May take 20 min to achieve anaesthesia
  - e.g. sevoflurane in O₂ plus BP support if required

**Intraoperative**
- Rigid bronchoscopy should delineate degree of stenosis
- Allow decision about method of ventilation
- Ventilation options
  - Conventional IPPV
    - Armoured ETT or DLT passing stenosis: sterile or non-sterile
    - Reinforced ETT above stenosis, sterile tube across surgical field
  - Jet ventilation using small catheter
  - Cardiopulmonary bypass
  - Deep hypothermic arrest
- Head is usually in flexion at the end of the surgery, may be sutured chin-to-chest

**Emergence**
- Aim for extubation to minimize tension on tracheal anastomoses
  - Spontaneous ventilation, suctioning, extubation either deep to minimize coughing or light with adequate narcotics

*Thoracics* 3.D.7.3 *James Mitchell (October 7, 2001)*
Fibreoptic scope available in case of need for reintubation
Preparation for lung surgery

Assessment

Associated disease: IHD, PVD, COAD

History

Exposures (smoking, occupation)

Symptoms

Bronchopulmonary, extrapulmonary

Intrathoracic, extrathoracic

Metastatic, non-metastatic

Examination

Investigation

FBE, U&E, enzymes

CXR, CT

Pulmonary function testing

Whole lung: ABG, spirometry, diffusing capacity

Single lung: V/Q testing, split function testing

Simulation: occlusion of main stem bronchus or pulmonary artery

Exercise testing

Risk factors for poor outcome

PaCO₂ >45 mmHg, MBC or FEV₁ <50% predicted, RV >50% of VC, raised PVR (>190 dyne.s.cm⁻²)

Requirements for surgery

Predicted postop: FEV₁ >0.85 l, PAP <40 mmHg, PaCO₂ <60 mmHg, PaO₂ >45 mmHg

Preparation

Optimize respiratory function

Cease smoking, bronchodilate, treat infection, mobilize sputum, educate for physio

Optimize associated diseases

Intraoperative

Monitoring

Tiered approach

Routine

FiO₂, O₂ fail, SpO₂, gas analysis, NIBP, ECG, airway P, disconnect, nerve stimulator, temperature

Sick patient or major procedure

Arterial line, gases, spirometry and derived measurements, CVC

Sick patient and major procedure

PA catheter and derived measurements, SVO₂ and derived measurements

Lateral position

Placement of PA catheter may need to be verified on II (if in deflated lung, CO and SVO₂ measures are inaccurate)
One lung ventilation

Physiology
Hypoxic pulmonary vasoconstriction
PVR is locally responsive to $\text{PO}_2$
Reduced shunt fraction in lung which is partially hypoxic
Most effective in reducing fall in $\text{PaO}_2$ when 30-70% of lung is hypoxic
Inhibited by some agents
Volatiles inhibit HPV \textit{in vitro} but not significantly in humans
No intravenous anaesthetics inhibit HPV
Direct arterial dilators inhibit HPV (SNP, GTN, Ca$^{2+}$ antagonists, $\beta$ agonists), though aminophylline and hydralazine may be safe

Distribution of blood flow
Lateral positioning reduced lung blood flow by 10% of CO
Non-ventilation reduces lung blood flow by 50% due to HPV
1 MAC of isoflurane inhibits HPV to 40% reduction in flow
The inhibition of HPV by volatiles is difficult to detect in practice
No significant difference from TIVA

Position | Left | Right |
---|---|---|
Upright or supine | 45% | 55% |
Right lateral | 35% | 65% |
OLV | 18% | 82% |
+1 MAC iso | 21% | 79% |
Left lateral | 55% | 45% |
OLV | 77% | 23% |
+1 MAC iso | 73% | 27% |

Anaesthetic technique
Recommendations
High $\text{FiO}_2$, precludes $\text{N}_2\text{O}$ use
Potent volatile or propofol reduces airway reactivity
Narcotic analgesia or thoracic epidural diminishes hypnotic requirement

Intubation
Response blunted with adequate anaesthesia, narcotic and lignocaine

Indications for DLT
Absolute
Lung isolation for bronchopleural fistula, bullous disease, bleeding, infection, bronchopulmonary lavage
Conducting airway surgery or trauma
VATS

Relative
Surgical exposure: aortic, lung, mediastinal, oesophageal, vertebral surgery
Differential lung ventilation following unilateral massive PE thrombectomy or with unilateral lung disease

DLT insertion
Types
Carlens left with hook
Robertshaw left or right
26, 28, 35, 37, 39 or 41 Fr (4.0 to 6.5 mm lumen diameter)
Left side most commonly used unless proximal left main lesion

Protocol
Check cuffs and connections
Conventional laryngoscopy
Tip passed with curvature concave-forward
Rotated if hook present so hook passes anteriorly through larynx
Rotated so tip points to side to be endobronchially intubated and
head turned to opposite side
Advanced until resistance is met (typically at 29 cm + 1 cm per 10 cm height over 170 cm)
Tracheal cuff inflated and bilateral lung ventilation verified
  If unilateral, may be in too far, withdraw until bilateral
Bronchial cuff inflated, bronchial lumen ventilated
  If bilateral lung inflation ± leak from tracheal lumen, tube is not advanced far enough
  If lower lobe inflation only, tube is advanced too far
  If right lung isolation, tube is in right bronchus
  Verify lung isolation
Tracheal lumen ventilated
  If no apparent ventilation, tube may be too far advanced in either bronchus or entirely in the trachea so deflate bronchial cuff and ventilate to determine position
  Verify lung isolation
Verify position with tracheal lumen fibreoptic bronchoscopy, particularly with right-sided tubes to verify upper lobe bronchus position relative to cuff
Verify isolation again after patient positioning
Other methods to verify position
  X-ray, differential capnography or flow-volume loops, surgical palpation
  Underwater bubble test to verify total lung isolation
Other lung isolation techniques
  Univent, bronchial blockers
  Place with FOB assistance

Ventilation
Principles
  Maintain two-lung ventilation as long as possible
  High FiO₂
  Initial OLV Vₐ of 10 ml/kg
  Titrate ventilation to normal PaCO₂
Strategy to maximize HPV in non-ventilated lung
  Avoid vasodilation in non-ventilated lung due to Systemic vasodilators, ↑ PA pressure, ↑ PVO₂, ↓ PCO₂
  Avoid vasoconstriction in ventilated lung due to Hypoxia, ↓ PA pressure, ↑ PCO₂, high PEEP
Managing falling PaO₂
  Low PEEP to ventilated lung
  CPAP with 100% O₂ to non-ventilated lung
  Intermittent two-lung ventilation
  Early PA clamping if lung resection
Other options
  HFPPV, HFJV
    Lower mean airway pressures
    Less movement
  Low flow apnoeic ventilation
    Theoretically feasible for up to 20 minutes
    High PaCO₂ and severe respiratory acidosis
Mediastinoscopy

Surgery
  Suprasternal notch incision
  Blunt dissection anterior to trachea, posterior to aortic arch down to carina

Intraoperative
  Monitoring
    Routine, plus
    Right radial arterial line (for great vessel compression) and left NIBP
    Large bore IV access in arm and leg (in case of SVC disruption)
  Induction
    Conventional relaxant GA (reduced risk of air embolus)
    Reinforced ETT
  Maintenance
    Extreme vigilance required
    Head-up position reduces bleeding but increases risk of air embolus

Complications
  Massive haemorrhage requiring sternotomy
    Have rapid infusion device available and blood crossmatched
    Venous disruption may cause air embolus and require lower limb access for drug administration
  Pneumothorax
    Common postoperatively, usually small
  Recurrent laryngeal nerve injury
    50% permanent
  Compression of aortic arch branches
    Especially right innominate: cerebral ischaemia
    Detect with right arm arterial line or pulse oximeter
  Autonomic reflexes
    Especially bradycardia, hypotension

Postoperative
  CXR to detect pneumothorax
  Repeat mediastinoscopy is usually impossible due to scarring
Upper GI surgery

Management of a 60yo for laparoscopic cholecystectomy

Outline basic management of liver transplant surgery

Anaesthesia with portal hypertension for shunt insertion
Management of a 60yo for laparoscopic cholecystectomy.

Laparoscopy
  Intraperitoneal insufflation with gas through a paraumbilical Veress needle
  Pressure 12-15 mmHg
  Usually CO₂ used

Surgery
  Elective, moderate risk

Preoperative
  Assessment
    Routine, plus
    Respiratory compromise: lung disease, obesity, smoking
    Reflux risk, airway assessment, assess need for RSI
    Cardiac function
    Autonomic dysfunction e.g. diabetes

  Premedication
    H₂ antagonist, anxiolytic

Intraoperative
  Monitoring
    Routine: SpO₂, ECG, NIBP, gas analysis
    Arterial line if very obese
    Large IV

  Induction
    Routine IV induction, balanced technique unless RSI indicated

  Maintenance
    Volatile, O₂, air or N₂O.
    N₂O may worsen complications of gas embolus
    Narcotic analgesia, local anaesthetic in port sites
    High PIP may be required during pneumoperitoneum
    High degree of vigilance for signs of gas embolism

Complications
  Trocar insertion and insufflation
    Injury to bowel, bladder, large vessels
    Insufflation of CO₂ intravascularly

  Pneumoperitoneum
    CO₂ absorption
    Fall in cardiac output
    Difficulty in ventilation

  Usual surgical risks
    Haemorrhage, bile leak, damage to nearby structures
    Change to open procedure

Emergence
  Routine, extubation in lateral position

Postoperative
  Analgesia
    Local, oral agents, IM narcotic
    Consider epidural if opened

  Ward level of care
Outline basic management of liver transplant surgery

Surgery
High risk, semi-urgent procedure
Requires tertiary hospital with special expertise

Issues
Perioperative management of hepatic failure
Coagulopathy and potential for haemorrhage
Massive transfusion and fluid requirements
Hypothermia, hyperkalaemia, acidosis
Often paediatric patient
Prolonged anaesthesia

Preoperative
Assessment
Complications of liver failure
Electrolyte, acid base, glucose, fluid homeostasis disordered
Coagulopathy
Encephalopathy
Other complications of primary cause of liver failure
Blood-borne virus, haemochromatosis (diabetes)
Crigger-Najjar syndrome (avoid barbiturates)
Budd-Chiari syndrome (may need anticoagulant prophylaxis)
Drug toxicity

Premedication
Aspiration prophylaxis, no sedation with encephalopathy

Transport
May be coming from ICU

Monitoring and access
Emergency drugs drawn up
Rapid infusor, cell saver, blood warmer, humidifier, patient warmer prepared
Large bore IV access x 2, PA catheter, arterial line
Thromboelastograph

Induction
Increased risk of aspiration with ascites, risk of haematemesis, delayed gastric
emptying may require RSI or FOB

Positioning
Care for pressure areas, prolonged laparotomy

Maintenance
Relaxant GA, balanced technique
Air:oxygen:isoflurane does not compromise splanchnic blood flow
N₂O avoided as it worsens bowel distension and gas emboli
Increased dose requirement but prolonged action from NDB

Preanhepatic phase
Major risks are haemorrhage and coagulopathy
Oliguria treated with adequate filling, diuretic, dopamine

Anhepatic phase (hours)
Portal vein, IVC, hepatic artery clamped, biliary drain
Diaphragm retracted: impairs venous return, reduces lung compliance
Renal venous congestion, oliguria
Risk of hyperkalaemia, citrate toxicity from transfusion
Calcium, magnesium, water infused to maintain usual hyponatraemia

Neohepatic phase
Vascular anastomoses
Immunosuppression with cyclosporin, azathioprine, prednisolone
Haemorrhage, coagulopathy still risks
Flushing cold hyperkalaemic fluid out of liver
Treat hypothermia, hyperkalaemia, acidosis

Emergence
  ICU transfer, intubated
  Risks of pneumonia, ARDS, anastomotic leaks, other infection
Anaesthesia with portal hypertension for shunt insertion.

Major abdominal surgery in a high-risk patient.

Preoperative Assessment

Complications

Cardiac

↑ CO, ↓ SVR, ↑ SvO₂, BP and HR unchanged
Cardiomyopathy, arrhythmias
↓ responsiveness to α agonists
↓ renal blood flow

Respiratory

↑ 2,3 DPG causing right shift of Hb-O₂ dissociation curve
Vasodilators (VIP, glucagon, ferritin) cause pulmonary shunting,
↓ pulmonary vascular response to hypoxia
Ascites may splint diaphragm (closing volume > FRC)
↓ colloid oncotic pressure may predispose to pulmonary oedema

Haematological

↑ plasma volume, ↓ Hb (bleeding, B12 deficiency), ↓ albumen
Factor deficiencies: VII, V, X, fibrinogen
DIC may complicate surgery

Endocrine

Impaired glucose tolerance (↑ glucagon, ↑ GH, insulin resistance)
Feminization of male patients

Other

Encephalopathy
Renal failure (hepatorenal syndrome, ATN)
Altered pharmacodynamics
Varices, haemorrhage

Decide whether further optimization is possible

Treatment of complications
Vitamin K or FFP, platelets if required

Specific therapy
Vasopressin: preportal vasoconstriction
Also coronary, arteriolar vasoconstriction
Somatostatin: ↓ glucagon, gut activity, mesenteric blood flow
Propranolol: ↓ CO, splanchnic vasoconstriction, ↓ renin
Rebound bleeds with discontinuation

Investigation
FBE, U&E, LFT, clotting, XM, ABG
ECG, CXR if in failure

Premedication
Minimal if at risk of encephalopathy
↑ sensitivity to benzodiazepines
Antacid or H₂-blocker for ↑ reflux risk

Intraoperative

Monitoring and access
Large bore IV access (consider multiple)
Routine monitoring, plus
CVC, arterial line, IDC, temperature
Blood and fluid warmer available
ABG, Hb and glucose measurement available

Anaesthetic technique
High mortality in patient in hepatic failure
Surgery is the major determinant of hepatic damage, not anaesthesia

General anaesthesia
- Rapid sequence induction if recent bleeding or full stomach suspected
- Avoidance of hepatotoxic drugs (e.g. halothane)
- Some evidence of ↑ enzymes with ketamine, thiopentone and N₂O
- ↓ protein binding, so ↓ dose of bound drugs such as thiopentone
- Aim to maintain hepatic O₂ delivery: BP, Hb, PaO₂

Epidural analgesia
- Contraindicated in coagulopathy or thrombocytopenia
- Stress response reduces hepatic blood flow
- Allows minimization of other anaesthetic drugs

Formation of shunt: flow from portal vein to IVC
- ↑ IVC flow
- ↓ hepatic blood flow causes release of glucagon, VIP (vasodilators)
- ↓ portal resistance, ↓ SVR
- reflex ↑ SV, ↑ CO

Postoperative
- HDU or ICU care may be needed
- Epidural analgesia or judicious opioids
- Careful fluid management
General surgery

Thyroid surgery

Physiological response to pneumoperitoneum
Thyroid surgery

Preoperative
Assessment
Routine, plus
Thyrotoxicosis symptoms
- Anxiety, tremor, heat intolerance, fatigue, weight loss
- TFT, Ca\textsuperscript{2+}, FBE, U&E, ECG, CXR, CT if indicated
Complications
- Goitre, atrial fibrillation, SVC obstruction
- Airway compromise, stridor, tracheomalacia
- Eye complications of Graves’ disease
Treatment
- Antithyroid drugs, radioactive iodine
- Complications of therapy: marrow suppression
- Other therapy: \(\beta\)-blockers
Determine fitness for surgery
- Euthyroid, little risk of thyroid storm
- Airway and vascular compromise determined and manageable
Preparation, premedication, transport
Routine

Intraoperative
Monitoring, access
Routine
Induction
Routine relaxant technique
- Tube placement commonly armoured tube with circuit over head
  - Care with positioning, secure connections, eye protection
Positioning
Supine with shoulder roll
Maintenance
- Balanced technique, IPPV
- Poor access to head and airway
Emergence
- Request from surgeon to check vocal cord movement
  - Often will not change surgical management
  - Requires deep extubation when reversed and laryngoscopy

Postoperative
Airway distress
- Upper airway obstruction due to soft tissues and reduced muscle tone
- Laryngospasm, bilateral cord paralysis
- Inadequate reversal
- Wound haematoma
- Laryngeal oedema
- Tracheomalacia
- Anaphylaxis
Hypocalcaemia due to hypoparathyroidism
- May be early (1-3 hours), more commonly 1-3 days
Physiological response to pneumoperitoneum

Intraabdominal pressure 10-12 cmH₂O

CVS
  Venous pooling in legs, IVC compression → ↑ RVR, ↓ venous return
  ↑ vascular resistance of intraabdominal organs → ↑ SVR

Respiratory
  ↓ compliance, ↑ intrathoracic pressure on IPPV

Neuroendocrine
  ↑ ADH, catecholamines, renin, angiotensin II
  ↑ sympathetic tone

Net effect
  ↓ CO, ↑ MAP
  Minimized by filling, head-down position, α₂-agonists

Regional effects
  Venous stasis in legs → DVT
  PCO₂ causes vasodilation if ventilation is not increased (↑ ICP)
  Arrhythmia: bradycardia due to peritoneal manipulation
Miscellaneous surgery

Outline management of a 20 year old man who is intoxicated for ORIF # mandible

Outline management of anaesthesia for cataract extraction

Ophthalmic anaesthesia

Penetrating eye injury
Outline management of a 20 year old man who is intoxicated for ORIF # mandible.

Issues
- Semiurgent surgery in an intoxicated and non-fasted patient
- Trauma patient with possible associated injuries and airway compromise
- Shared airway surgery with likely bleeding
- Possibility of wiring the jaw closed with associated airway access compromised

Assessment
- Routine anaesthetic assessment, plus
  - History of trauma, associated injuries
    - Jaw mobility, limited by pain or mechanical obstruction
- Intoxication
  - Drugs used, BAC measurement
  - Competence to consent
  - Complications of drugs
    - Full stomach, specific effects of other drugs: narcotics, amphetamines
  - Difficulty of detecting altered conscious state from head injury
  - Legal concerns if a driver: BAC sample handling dictated by law

Examination
- Mouth opening, careful airway assessment

Investigations
- Trauma x-rays
- Jaw x-rays or OPG
- Routine bloods, G&H

Decision on timing of surgery
- Often not necessary to proceed before patient is sober and fasted

Plan for anaesthesia
- Rapid sequence or awake nasal FOB if not fasted and surgery cannot be deferred
- Otherwise plan for GA with nasal intubation when fasted

Premedication
- Routine antacid and/or anxiolytic

Consent
- Discussion of plan with patient, especially if awake FOB planned

Intraoperative

Preparation
- Routine equipment check, suction
- Availability of difficult intubation equipment

Access and monitoring
- Routine: ECG, SpO₂, NIBP etc.
- IV access

Induction
- Good jaw mobility: conventional induction, nasal Rae
- Potentially difficult: awake nasal FOB
- Nasal lignocaine, phenylephrine
- Topical lignocaine to airway for awake FOB
- Throat pack insertion

Maintenance
- Conventional balanced technique
- Remember to remove throat pack if jaw if to be left wired
- Analgesia supplemented with local infiltration or nerve block
- Prophylactic antiemetic
Emergence
Usually mandible plated and mobile
Remove throat pack, suction, inspect larynx for blood
Awake extubation in lateral position
Consider suctioning of ETT tube in nasopharynx and nose
Jaw wired
Fully awake extubation required
Equipment on hand to cut wiring
Drugs and equipment for emergency reintubation
Pull tube through cords and leave as nasopharyngeal airway

Postoperative
Analgesia
Usually PCA or intermittent narcotic plus oral adjuvant analgesics
Level of care
PACU and normal surgical ward
Outline management of anaesthesia for cataract extraction.

Elective surgery with minimal physiological impact usually performed on elderly patients.

Issues
- Population with high incidence of concurrent disease
- Commonly a brief operation with high turnover

Preoperative
Assessment
- Routine, plus
- Cataract
  - Nature of surgery (intracapsular vs extracapsular)
  - Previous cataract surgery
  - Primary disease e.g. diabetes
- Retrobulbar or peribulbar blockade
  - Axial length
  - Assessment of orbit and ease of access to retrobulbar space
- Coexistent disease
  - Particularly cardiac disease, respiratory disease
  - Persistent cough, tremor, claustraphobia may make regional unfeasible

Premedication
- Minimal as sudden waking may be associated with movement

Intraoperative
Monitoring and access
- IV access
- Routine monitoring: HR and SpO₂ required during block
  - ECG, NIBP, SpO₂, E₄CO₂ on Hudson mask
Block
- Deep intraconal (“retrobulbar”) vs peribulbar vs topical plus infiltration
  - My practice
    - Topical oxybuprocaine (benoxinate)
    - Sterile solution 2% lignocaine, 0.4% bupivacaine, 15 U/ml Hyalase
    - Aseptic technique
      - Medial canthus direct posteriorly 30g 12 mm 2.5 ml full depth
      - Inferotemporal percutaneous 27g 32 mm 3.5 ml
      - hub at level of limbus
      - Slow injection with periodic aspiration
      - Gentle massage, assessment of IOP and orbital pressure
      - Honan’s balloon if required by surgeon
      - Supplementation for intact movement or sensation according to distribution and surgical requirements
      - Facial nerve block usually not required

Issues intraoperatively
- Maintain communication
- Atropine available for bradycardia
- Surgeon may supplement with sub-Tenon’s injection if required

Postoperative
- Usually good analgesia from block
Ophthalmic anaesthesia

Anatomy

Layers
- Connective tissue globe: conjunctiva, sclera
- Retina: nerve tissue
- Choroid: vascular

Humour: aqueous and vitreous

Size: A-scan typically 20-24mm
- High myopes may be > 25mm: increased risk with retrobulbar block

Muscles: 4 recti, 2 obliques, orbicularis oculi, levator palpebrae

Nerves
- Motor: III MR, IO, IR, SR
- IV: SO
- VI: LR
- Sensory: conjunctive nasociliary V,
- Parasympathetic: short ciliary br of III
- Sympathetic: ciliary ganglion to V and carotid plexus

Physiology

IOP: 10-15 cmH₂O
- Varies with volume of aqueous and blood in the globe and muscle tone causing extrinsic pressure
- CVP transmitted readily to IOP
- Rises with coughing, vomiting, head-down, IPPV
- Suxamethonium causes a small rise
- Induction agents: reduce IOP
- Dizolamide, acetazolamide: reduce aqueous secretion

Atropine IV causes little mydriasis, little risk with closed-angle glaucoma

Complications of pressure changes
- Rise: reduced perfusion pressure, exuding of contents if an open eye
- Fall (removal of contents): potential for retinal detachment

Oculocardiac reflex: afferent V short ciliary n., ciliary ganglion, ophthalmic, reticular formation, efferent X
- Bradycardia, standstill, nausea and vomiting
- Can be elicited by other stimuli like NGT, faciomaxillary surgery
- Classically eye traction or pressure (sometimes retrobulbar block, face mask pressure).
- Does not require an intact eye: e.g. prosthesis fitting.
- Management: tell surgeon to stop, deepen anaesthesia, prophylactic atropine or treatment.
- Fatigues with repeated stimulation

Nausea and vomiting
- Most common with squint surgery, vitreoretinal surgery
- Usually post-recovery, continues up to 24 hours
- Raises IOP, delays discharge
- Cause: visual change after squint surgery causes "motion-sickness"
- Oculogastric reflex: vagal effect

Prevention
- General: hydration, low nausea anaesthetic (no opiates, N₂O...), antiemetics
- Premedication with benzodiazepine (esp. lorazepam)
- Midazolam blocks adenosine reuptake in area postrema (required for dopamine synthesis)
- Other concerns: drug interactions, coexisting disease (esp. diabetes)

Vitreoretinal surgery

Miscellaneous Surgery 3.D.10.5 James Mitchell (October 7, 2001)
Often with poorly controlled diabetes or else ex-prem babies
Long cases, poor airway access
Immobility required
May have gas or oil: no N₂O while gas still present

Open eye injury
Need to know
  Degree of injury: salvageable eye? Take care with IOP.
  Urgency: clean vs dirty injury. Clean: wait until fasted
  Dirty: RSI required
Children: LA cream for IV, sedative premedication
Minimize IOP rise with big induction agent dose, fentanyl, topical local to airway

EUA for glaucoma
  Measurements require an anaesthetic which doesn't alter IOP much
  Halothane: reduces IOP
  Kids usually have multiple anaesthetics

NLD probe
  Simple mask anaesthetic
  Some babies have a mucocoele: aspiration of pus

Sub Tenon block
  painless, fast onset, good motor block, no needle in retrobulbar space
  catheter passed subconjunctivally
  look up and out, nick conj fascia, probe around globe to post attachment of Tenon fascia
Outline management of anaesthesia for a penetrating eye injury

Issues
  - Emergency surgery, usually a trauma patient with a full stomach
  - Avoidance of rise in IOP with potential expulsion of globe contents

Assessment
  - Routine, plus
  - Trauma
    - Associated injuries, ABCDE, fasting status
  - Eye
    - Nature of injury, acuity

Preoperative
  - Premedication
    - Antacid, H\textsubscript{2} blocker, prokinetic

Intraoperative
  - Monitoring and access
    - Routine: IV, ECG, Sp\textsubscript{O}\textsubscript{2}, NIBP, gas analysis, disconnect etc.
  - Induction
    - Modified RSI
      - Preoxygenation
      - Predosing with lignocaine, remifentanil, β-blocker IV
      - Induction with thiopentone or propofol
  - Relaxation options
    - Suxamethonium
      - Predose with NDB followed by suxamethonium
    - High dose NDB (e.g. rocuronium)
  - Trade-off between risk of coughing and ↑ IOP with sux

Maintenance
  - Lower IOP
    - Mild hyperventilation, β-blocker, acetazolamide, mannitol, hypotension
  - Monitor muscle relaxation to prevent coughing
  - Prophylaxis: antibiotics, tetanus

Emergence
  - Prevention of coughing/vomiting and protection of airway are conflicting priorities
  - Extubate awake in lateral position
  - Give narcotic and antiemetic before emergence
Cardiac disease in pregnancy
Management of post-partum haemorrhage for EUA
Management of 160kg female for Caesarean section
Justify an epidural test dose in obstetrics and contraindications to epidural for LUSCS
Outline management of a 32 week pregnant woman who fits at home
Outline differences between spinal and epidural for LUSCS
Management of a term female with moderate aortic stenosis for elective Caesarean section
Anaesthesia for LUSCS
Perinatal and Maternal Mortality 1997
Analgesia in Labour
Tocolysis
Antenatal class
Foetal monitoring
Trauma in pregnancy
Doses
Case scenarios
Cardiac disease in pregnancy

Cardiac stresses
- pregnancy, labour, surgery (LUSCS), blood loss
- cardiac disease may worsen in pregnancy

Anaesthetic interventions
- Major regional blockade
  - Objective is to minimize physiological disturbance
  - Choice of drug: opioid vs local anaesthetic
  - Titration of drug to minimize high block
  - Volume loading to maintain preload
  - Posturing to maintain preload
  - Use of vasopressors

  Degree of concern
  - Normal patient
  - Disease will improve with block e.g. AR
  - Disease will worsen with block e.g. AS

  Monitoring
  - Routine
  - HDU
  - ICU

  Blockade for analgesia is safer than for anaesthesia

General anaesthesia
- Objective is to minimize physiological disturbance
- Modified RSI
  - e.g. more fentanyl, less thiopentone
- Cardiac induction
  - may compromise safe airway

General management of cardiac disease in pregnancy
- Workup
  - Nature of defect
  - Severity e.g. NYHA grading
  - Optimization e.g. valve replacement, medical therapy
  - Assessment of likely outcome
  - Counselling patient re termination

- Objectives
  - Survive to viability and early Caesarean (e.g. 32/40)
  - Aim for normal labour with monitoring

- Anaesthetic plan
  - Regional suitable for analgesia or anaesthesia?
  - GA preferred?
  - Technique, level of care pre- and post-op
Management of post-partum haemorrhage for EUA.

Post-partum haemorrhage
>600 ml blood loss from birth canal from third stage to 24 h post-delivery

Surgery
High risk, emergency surgery
Causes: uterine atony, retained products, vaginal or uterine laceration

Preop
Assessment
Determine reason for EUA
Define risk of procedure
Patient
Concurrent disease e.g. PE
Resuscitation status
Bloods, crossmatch, Hb

Anaesthesia
Epidural in situ?
IV access
Fluid management
Regional versus GA
Determined by urgency, haemodynamic stability, patient preference

Premedication
Effervescent ranitidine
O₂ by mask
Syntocinon infusion to continue

Induction
Rapid Sequence for GA
Equipment, suction, drugs
Preoxygenation
Cricoid, thiopentone, suxamethonium
ETT
Spinal or epidural or CSE

Maintenance
Reduced MAC requirement, volatiles cause uterine relaxation
Low volatile use unless uterine relaxation required
Physiological hypocapnia
Surgical issues
Haemorrhage, coagulopathy, warming of infusions
Oxytocic agents
Uterine relaxants: volatiles, GTN

Extubation
When awake and protecting airway

Postop
Ward/HDU/ICU as indicated
Management of 160kg female for Caesarean section.

Surgery
  Elective, urgent or emergency
  Determines opportunity for optimization

Risk factors
  Term pregnancy
    Airway: oedema, vascularity, risk of difficult intubation, risk of aspiration
    Ventilation: ↓ FRC, ↑ O₂ requirement
    Circulatory: ↑ CO, ↑ blood volume, ACC

Surgery
  Haemorrhage
  Embolism: amniotic fluid, air

Obesity
  Airway difficulty
  ↑ gastric volume, ↓ pH
  ↑ O₂ requirement
  Difficulty ventilating
  Difficult access for IV, blocks

Preoperative
  Assessment
    Pregnancy, complications
    Concurrent disease
    Medications, allergies...

  Premedication
    Non-particulate antacid, sodium citrate: ↑ gastric pH
    H₂ antagonist, metoclopramide: ↑ pH, ↑ motility

Intraoperative
  Positioning
    Supine with left lateral tilt 15˚
    Avoid aorto-caval compression

  Monitoring
    ECG, SpO₂, NIBP on frequent cycle and manual BP cuff
    Arterial pressure if likely to be unstable
    CTG or doppler prior to positioning for surgery
    Supplemental O₂ for all mothers

Regional
  Advantages
    Avoids need to intubate potentially difficult airway
    Spinal may be as fast as GA in experienced hands
    Preemptive analgesia, reduced postoperative analgesic requirement
    Allows greater experience of birth, partner present
    Often preferred by patient

  Disadvantages
    May delay surgery, especially epidural
    Spinal is of fixed duration, lacks flexibility

  Complications
    Failed block, hypotension, local anaesthetic toxicity, neuropraxia,
    PDPH
    Minimized with careful technique: fluid loading, pressors...
    Obese patient may require longer needle, ↑ technical difficulty, CSE is
    not possible with long epidural needle

Epidural
  Lumbar epidural catheter
  Suitable for urgent procedure if
    Haemodynamically stable, block established
Bolus lignocaine 2% with adrenaline and bicarbonate, 5ml aliquots to T4
Additional epidural narcotic (fentanyl 100 µg or pethidine 50 mg)
improves analgesia
May be combined with spinal (CSE)
May be supplemented intraoperatively

Spinal
L2-3 or L3-4
Fine pencil-point needle 26g minimizes PDPH
Hyperbaric bupivacaine 0.5% 2.2-2.5 ml
Fentanyl 10-20 µg
Posture for block to T4
Test block with cold or painful stimulus

General
Advantages
Reliable and rapid onset of anaesthesia
Greater control of airway, ventilation and haemodynamics

Disadvantages
Potential for failed intubation, aspiration
Major causes of anaesthetic-related death in pregnancy
Greater post-operative narcotic requirement
Neonatal depression from volatiles, N₂O and induction drugs

Rapid sequence induction
Required in all pregnant women after early second trimester or with
other indications
Suction and difficult airway equipment must be at hand
Preoxygenation: 100% O₂ by mask to denitrogenate FRC
Cricoid pressure
Thiopentone (4 mg/kg), suxamethonium (1.5 mg/kg) may be less in
obese, correct towards LBM
Laryngoscopy, cuffed ETT

Maintenance
O₂/N₂O/isoflurane: FiO₂ ≥ 50%, isoflurane ≤ 1 MAC
Higher FiO₂ and PIP required with obese patient
↑ sensitivity to non-depolarizing relaxants, esp. with Mg²⁺
Relaxants do not cross placenta significantly
Minimal narcotics prior to delivery, then morphine 0.2-0.5 mg/kg

Post-delivery
Oxytocics
Oxytocin 5-20 U plus infusion
Ergometrine 0.25-0.5 mg IV or IM if continued bleeding

Emergence
Extubation when awake and protecting airway

Postoperative
Analgesia, antiemetics
Appropriate review
Justify an epidural test dose in obstetrics and contraindications to epidural for LUSCS.

Test dose

Purpose
- Determine incorrect placement of epidural catheter
  - Intravascular or subarachnoid or subdural
- Aspiration is a useful test if positive: blood or CSF, but may be falsely negative

Procedure
- After placement of the catheter, 3 ml of local anaesthetic solution (typically bupivacaine 0.25% or lignocaine 1%) containing adrenaline 5 µg/ml is administered
- The heart rate is observed for a rapid rise of 20-30 bpm in response to intravascular adrenaline
- The degree of sensory and motor blockade is observed after 3-5 min for a dense spinal block as high as T10

Rationale
- The potential morbidity from incorrect placement of an epidural bolus dose can be severe
  - Bupivacaine 25-75 mg or lignocaine 200-400 mg administered intravascularly can cause fitting due to neurotoxicity and cardiac arrest due to Type I antidysrhythmic effect
  - The same dose given subarachnoid may cause a total spinal requiring urgent intubation and ventilation
- The cost or risk associated with a test dose is small: a 3-5 min delay in establishing a block
- The test is not 100% sensitive or specific, especially in labouring women in whom the heart rate is typically high and variable, but it is the best readily available and rapid test
- Contrast epidurography may be a better test, but involves fluoroscopy, requiring a radiation dose, and substantial delay and cost

Absolute contraindications
- Refusal by a competent patient
- Infection at the site of potential insertion
- Hypovolaemic shock
- Coagulopathy, severe thrombocytopenia
- Intellectual disability or other reason for being unable to cooperate

Relative contraindications
- Urgency of surgery, delay in establishing block may be 20 minutes
- Unstable neurological disease
- Cardiovascular disease requiring maintenance of SVR e.g. severe aortic stenosis
- Treatment with anticoagulants, aspirin or other NSAIDs
- Disease likely to cause technical difficulty or failure e.g. ankylosing spondylitis
Outline management of a 32 week pregnant woman who fits at home.

Immediate management

**ABCDE**
- Lateral position, clear airway
- Expired air resuscitation if not breathing, oxygen when available
- External cardiac massage if no output
  - Requires supine position with left lateral uterine displacement
- Summon assistance: ambulance

**Aetiology**

- Eclampsia
- Organic brain problem
  - Idiopathic epilepsy
  - Arteriovenous malformation
  - Tumour
- Trauma
- Metabolic disturbance
  - Drug withdrawal
  - Uraemia, hypoglycaemia, hyponatraemia etc.

**General management**

Once patient is well-oxygenated, fit is terminated and she is transported to a suitable hospital, the cause of the fit needs to be determined

Unless another cause is found, the aetiology is assumed to be eclampsia

**Eclampsia**

**Immediate management**

- ABCDE as above
- Mg$^{2+}$ 2-4 g IV may terminate fit

**Incidence**

- Preeclampsia 30 per 1000 births
  - Most common in young primigravidas
- Eclampsia 0.4 per 1000 births
  - 44% fit before delivery
  - 37% during delivery
  - 19% after delivery

**Management**

- Definitive management is delivery of the foetus and placenta
- Examine and test for complications
  - Hypertension, proteinuria, thrombocytopenia, hepatic dysfunction
  - Growth-retarded or distressed foetus
- Monitoring
  - Fetal well-being: CTG
  - Mother: NIBP or IABP, urinary catheter, possibly CVC or PA catheter
  - Best managed in HDU or labour ward if adequately equipped
- Magnesium
  - Anticonvulsant, vasodilator, tocolytic, bronchodilator, ↓ renin, ↓ ACE, ↓ platelet activity, ↓ prostacyclin release
- Antihypertensives
  - Hydralazine, α-methyldopa, clonidine, prazosin, labetalol, nifedipine, nitrates
- Fetal management and delivery
  - Best done by experienced obstetrician

**Epilepsy**

**Immediate management**
Fits usually self-limiting
Administer oxygen
Fit can be terminated with barbiturate or benzodiazepine if prolonged
Incidence 50 per 100,000
Pregnancy
May increase frequency of fits
  Possibly due to increased clearance and altered distribution of drugs,
electrolyte changes
Antiepileptic medication may be teratogenic
  Phenytoin → cleft lip and palate, cardiac lesions, digital hypoplasia
Increased incidence of preeclampsia, complications and intervention
Management
  Careful monitoring of blood levels of anticonvulsant and adjustment of dose
Outline differences between spinal and epidural for LUSCS

Requirement
Both
Surgical anaesthesia to T4
Adequate duration for surgery

Anatomy, technique
Both
Lumbar technique midline or paramedian
Sitting or lateral position

Epidural
Probably safer in lateral position (less risk of dural puncture)
Tuohy needle 16g-19g used to approach epidural space
Space identified with LOR to air or saline
Catheter passed into space or single dose of anaesthetic given
Test for incorrect placement with aspiration and test dose of adrenaline-containing solution

Spinal
Commonly easier in sitting position
Pencil point needle 25g-27g used to enter subarachnoid space
Space identified with “pop” through dura and return of CSF
Single dose of anaesthetic
Clearer confirmation of correct placement of drug

Indications, contraindications
Safe techniques for elective and urgent LUSCS
Spinal usually faster to get the case started
Epidural can be fast if block already established
Both thought to be safer than GA (no conclusive evidence)
Coagulopathy or thrombocytopenia: both contraindicated, but epidural more strongly
Haemodynamic compromise e.g. aortic or mitral stenosis
Relative contraindication to regional
Fall in SVR more rapid and uncontrolled with spinal
May be safer to use graduated epidural

Drugs used
Epidural
Local anaesthetic: lignocaine 2%, ropivacaine 0.5-1%, bupivacaine 0.5%
Dose up to 20ml of 2% lignocaine
Addition of fentanyl or pethidine or morphine

Spinal
Local anaesthetic: bupivacaine 0.5%, cinchocaine (obsolete)
Dose typically 2.2-2.5ml of hyperbaric bupivacaine 0.5%
Addition of fentanyl 10-20 µg or morphine 100-200 µg

Reliability, duration
Spinal a more reliable technique
Clearer end-point
Denser block
Fixed duration, typically 45-60 min of good surgical anaesthesia

Epidural
May be patchy, unilateral
Intraoperative supplementation allows longer duration

Complications, risks
Both
Major risks of anaesthetic
Failed block, inadequate block, headache, infection, neuropraxia, drug toxicity, hypotension

Obstetrics 3.E.1.9 James Mitchell (October 7, 2001)
Major risks of surgery
Haemorrhage, embolism, nausea, vomiting, infection probably unaffected by anaesthetic technique

Spinal
Less risk of failure, headache, local anaesthetic toxicity
Minor risk of respiratory depression with intrathecal morphine

Epidural
Larger dose of local anaesthetic, possible intravascular injection so greater risk of toxicity
Management of a term female with moderate aortic stenosis for elective Caesarean section

Surgery
Elective, moderate risk

Preoperative
Assessment
Routine anaesthetic assessment
Obstetric issues
Size, obesity
Airway compromise
Obstetric complications, e.g. preeclampsia
Crossmatch

Aortic stenosis
Severity moderate

History
Symptoms of severity
Exercise limitation, dyspnoea, angina, drop attacks

Examination
BP, pulse character
Murmur, radiation
Signs of failure: creps, oedema

Investigations
CXR, ECG, echocardiographic findings required
Catheter study results if performed

Optimize condition
Consult with cardiologist, obstetrician
Symptoms often worsen with pregnancy, fall in SVR
Treat failure
Valvuloplasty if indicated

Premedication
Ranitidine or antacid
Benzodiazepine if anxiolytic required

Transport
Left lateral position
Supplemental O₂

Intraoperative
Monitoring and access
Large bore IV access
Routine monitoring, plus
Arterial line
If severe consider PA catheter or TOE

Induction
Position with 15° left lateral tilt and uterine displacement
Preload with fluid
Prepare resuscitation drugs
Vasoconstrictor agents: metaraminol, phenylephrine

Regional
Graduated epidural
L2-3 or 3-4 catheter
Incremental boluses of lignocaine plus fentanyl to block to T4
Maintain contractility, HR and BP with pressors and fluid

General
Preoxygenation, cricoid pressure
Narcotic plus midazolam titrated to unconsciousness
Relaxation with suxamethonium
Oral intubation
Pressors as needed to maintain BP

Maintenance
   General
      Remifentanil infusion or
      N₂O, O₂, low concentration volatile
      Slow administration of required syntocinon to prevent hypotension
      Expect neonate to require resuscitation: naloxone ± ventilation
      Aggressive replacement of volume loss

Emergence
   Awake extubation in lateral position
   May be delayed by high narcotic dose

Postoperative
   HDU or ICU care
   Continue ECG, arterial BP monitoring
   Analgesia with morphine PCA plus NSAID and paracetamol
Anaesthesia for LUSCS

Rate 62000/year Vic

Indications
- Distress 20%
- Malpresentation 15-20%
- FTP 40%
- Previous Caesar 30%

Maternal death rate 1/10000

Technique
- Regional vs GA vs local
  - Urgency, patient choice, anaesthetic opinion, indication for LUSCS
  - Complications of pregnancy (PE, placenta praevia…)
  - Classify as needs of: mother, baby, obstetrician

GA
- Advantages
  - Rapid, reliable, good conditions, safer in unstable conditions or coagulopathy, familiar to patients
- Disadvantages
  - Requirement for airway control, awareness, fetal depression, increased analgesic requirement, ↓ breast feeding at 6 months, no participation in birth

Regional
- Advantages
  - Participation, no airway problems, ↓ analgesic requirement, better Apgar at 1 minute
- Disadvantages
  - Limited duration, ? more hypotension, inadequate block, PDPH, neurological complications, total spinal, difficult conversion to GA, LA toxicity from IV injection

Assessing block
- T4-T6 required for surgery
  - consider resiting epidural or CSE for poor block

Contraindications
- Refusal, thrombocytopenia, coagulopathy, conditions markedly worsened by afterload reduction (e.g. AS), urgency of induction

Premedication
- Possibility of conversion to GA, so non-particulate antacid immediately before, H₂ blocker or metoclopramide premedication

Complications
- Hypotension
  - prevent with fluid load (0.5-1 l), left lateral tilt, suitable spinal dose or titrated epidural, early use of ephedrine, close monitoring of BP and symptoms of hypotension
  - High block, inadequate block

Supplemental oxygen
- ↑ materal and foetal PO₂, given during block in case of hypotension before uterine incision: load with O₂ before reduced placental perfusion

Doses
- in recipes

GA
- Complications
- Aspiration, failed intubation management, aortocaval compression,
- Priorities
  - Maintain oxygenation, adequate ventilation (PCO₂ 32-34), minimize incision to delivery time, avoid depressant drugs

Obstetrics 3.E.1.13 James Mitchell (October 7, 2001)
Initial gas mixture: 50:50 + 0.5 MAC volatile (initial overpressure)
Reduced anaesthetic requirements (25-40% MAC reduction)
Reduced FRC $\rightarrow$ rapid hypoxia and rapid equilibration of anaesthetic gases
Awareness most likely: intubation and incision
Perinatal Mortality 1997

Declining birth rate (p. 8)
62000 in 1997, similar number of births since 1962, but rate has fallen from 21.1 per 1000 population to 13.4

Declining perinatal deaths (p. 5)
429 deaths, 6.9 per 1000 births
269 stillborn, 160 before 28 days post-delivery
Rates are lower using WHO criteria (4.3 per 1000 births)
count infants ≥1000g or 28 weeks rather than 500g or 22 weeks

Preventable causes of perinatal death (p. 13)
Mostly related to obstetric practice
Some anaesthetic relevance
Initiate management of maternal illness prior to transfer (e.g. controlling hypertension or treating preeclampsia)
Avoid surgery unless mandatory
Discourage smoking in pregnancy

Maternal Mortality 1997

Older population of mothers (p. 30)
Median age increased from 27 in 1984 to 30 in 1997
Perinatal mortality rate increases with maternal age (p. 29)

Method of delivery has changed (p. 34)
1984 16% forceps, 15% Caesarean
1997 10% forceps, 20% Caesarean

Duration of hospital stay has fallen (p. 38)
1985 84% stayed ≥5 days
1997 42% stayed ≥5 days

Maternal death (p. 72)
Rate continues to fall from 0.66 per 1000 births in 1953 to 0.08 in 1997
Only five deaths reported
36yo G₄P₂ 29/40 massive PE with history of DVT
35yo P₄ 41/40 vaginal haemorrhage, Caesar, *failed intubation*
32yo P₁ 24/40 obese asthmatic hypertensive smoker, arrhythmia
32yo P₂ 34/40 hypertensive, SAH in doctor’s rooms
26yo P₀ recurrent glioma
Analgesia in Labour

Schema for examining analgesic techniques

Evidence
- Basic science
- Clinical

Efficacy

Costs

Complications
- Mother
- Baby

Monitoring requirement

Technique, skill

Effect on obstetric outcome

Analgesic options

Psychological
- Education, visualization…

Pharmacological
- Systemic: N₂O, pethidine
- Regional: epidural, spinal, nerve blocks

Indications for early epidural

Preeclampsia without severe thrombocytopenia
Serious contraindication to GA
- Failed intubation, morbid obesity
- Trial of scar
- Twins
- Poor cardiac reserve
- Likely Caesarean section

Indications for GA in labour ward
- Stuck second twin or shoulder dystocia without an epidural

Difficulties in pregnancy with epidural
- More likely to be fat, oedematous
- Increased lordosis, difficulty positioning
- Contractions increase risk of movement or bloody tap (?10%)
- Reduced volume of epidural space and increased sensitivity to LA
- Raised CO, low SVR before block
- Remote location
- ↑O₂ consumption, ineffective CPR in pregnancy if complicated

Contraindications

Risk/benefit consideration
- Usual technique
- Modified technique

Fever
- Generalized sepsis vs local vs febrile due to labour alone
- Epidural abscess is rare even in septic patients
- Modification of technique
- More likely to use α agonist for hypotension
- Close observation of neurological status post-procedure

Thrombocytopenia
- <80 usually contraindicated
- >100 usually safe unless other contraindication
- 80-100 consider other options: systemic analgesia, GA for Caesar, spinal with 27g needle

Hypovolaemia

Valvular heart disease
- Modified technique usually suitable
Gradual development of block
Closer monitoring
Tocolysis

Preterm labour
  Preterm delivery (before 37 weeks) incidence 7%
  Increased risk of respiratory distress, hypothermia, hypoglycaemia, jaundice

Risk factors
  Young, low body weight, low socioeconomic class, unsupported, smokers
  Previous preterm delivery, early bleeding, heart disease, cervical incompetence, multiple pregnancy, premature rupture of membranes

Causes
  Medical induction
  Infection
    Streptococci, mycoplasma, fusiform bacilli
    ↑ IL-1β, IL-6, TNFα → PG production → labour
    Risk might be reduced with antibiotics for Gardnerella vaginosis

Ruptured membranes
  Multiple pregnancy
    Rising incidence with IVF, GIFT etc.
    1985-95: twins 10 to 14 per 1000 births, triplets 0.14 to 0.44
  Polyhydramnios, intrauterine death, fetal abnormality, uterine abnormality, cervical incompetence

Diagnosis
  Cervical dilatation too late for treatment
  Fetal fibronectin in vaginal mucus unreliable
  Diagnosis is clinical, 30-40% false positive

Management
  Tocolytic drugs
    Effective for less than 48 hours
    Time for transfer or steroids
    Greatest gains in 25-30 week gestations
  β-agonists
    Salbutamol 100 µg bolus
  MgSO₄
    Muscle weakness
  Nitrates
    GTN best acute agent (first report 1986)
      200-600 µg dose IV
      Onset 90 s, duration 3-5 min
      Surprisingly little hypotension
  Indomethacin
    Causes DA closure after 34 weeks → pulmonary hypertension
  Ca²⁺ channel blockers
    Nifedipine → hypotension, uteroplacental flow dysfunction
  In trials
    Atosiban (oxytocin blocker), nimesulide (COX-II inhibitor)
  Obsolete
    Alcohol, isoxsuprine, amyl nitrite
  Contraindications
  Antibiotics for ruptured membranes (unproven)
  Steroids to prevent neonatal respiratory distress
  Mode of delivery depends on presentation
  Delivery should be in a centre with NICU

Other uterine relaxants
  Volatile agents (and cyclopropane)
  MAC equipotent
Indications

Tocolysis (above)

Manipulative delivery
  Malpresentation, breech, second twin, abnormal uterine anatomy

Manual removal of placenta

Acute uterine inversion
  Pain, bleeding, vagal discharge, air embolism, venous congestion and difficulty reducing

Acute hypertonus
  Drug-induced, following axial blockade

Intrauterine surgery
Antenatal class

Analgesia in labour

Historical perspective
e.g. Queen Victoria and chloroform

Potential benefit of analgesia in labour
Maternal distress
Possible tocolytic effect of endogenous catecholamines

Epidemiology
Caesarean section rate 20-25%
Epidural analgesia in primiparas ≈50%

Analgesic options
Psychological
Visualization, relaxation
Simple physical
Position, heat, massage
Pharmacological
Systemic
Oral analgesics
Narcotics, N₂O
Regional
Epidural
Spinal
CSE

For various techniques
Basic mechanism
Safety, efficacy
Advantages, disadvantages
Complications

Anaesthesia for Caesarean section
General
Indications
Advantages, disadvantages
Regional
Spinal vs epidural
Advantages, disadvantages
Post-operative analgesia
Foetal monitoring

Antenatal
   Noninvasive
      Simple
         Auscultation for foetal heart
         Palpation of uterus, fundal height (cm above symphysis pubis = gestational age - 20)
         Kick chart
   Complex
      Ultrasound
         Head and abdominal circumference
         Amniotic fluid index
         Anatomical anomalies
         Doppler flows in umbilical arteries
      Cardiotocography
         Biophysical profile
            Scoring system derived from movements (limb and breathing), tone, AFI and CTG
   Invasive
      Amniocentesis
      Chorionic villous sampling
      Lecithin/sphingomyelin ratio
         (oestriol)

Intrapartum
   Noninvasive
      Foetal heart rate monitoring (auscultation or CTG)
      Examination of liquor for meconium
   Invasive
      Foetal scalp electrode for CTG
      Foetal scalp pH (sensitive for stress)
      Vibroacoustic stimulation
Trauma in pregnancy (also in Trauma)

Primary survey

A
Difficult airway, ↑ risk of aspiration

B
↑ VO₂, ↓ PCO₂, risk of hypoxia, fetal consideration

C
Resting tachycardia, expanded blood volume, altered resting BP, vasodilated
Potential for aortocaval compression
Blood loss related to pregnancy
Abdominal assessment difficult e.g. retroperitoneal haemorrhage
Pelvic fracture causes greater bleeding with enlarged vessels
Coagulation altered, physiological anaemia, thrombocytopenia

Tests

Bloods: ↑ WCC, ↓ Hb, plt, ↓ PCO₂
ECG: LAD
Abdo: Altered US assessment, risk with DPL
Imaging: consider radiation dose
Additional assessment of fetus: CTG, consultation with obstetrician

Obstetric management
Resuscitation of mother is first priority
Suitable hospital for trauma
Management of fetus determined by mother’s stability, fetal/placental well-being,
uterine damage
Options
Expectant, delivery, Caesarean
Monitoring and frequent reassessment is important

Presentations

Arrest
ABC resuscitation, left lateral tilt, CPR may be ineffective
Caesarean if failed resuscitation at 4 min
Even if fetus is non-viable, improves CPR effectiveness

Major uterine injury
Rupture: pain, hypovolaemia, fetal distress or death, vaginal or IDC bleeding
Emergency laparotomy

Minor trauma, mother and baby apparently okay
↑ risk of premature labour, fetal distress
Monitoring with CTG, expectant management
If minor abruption
Risk of DIC: monitor fibrinogen, possible AFE
Fetomaternal haemorrhage: Kleihauer, anti-D if indicated
Doses

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>PGF$_{2\alpha}$</td>
<td>5 mg (1 amp) in 20 ml, 1-2 ml up to 20 ml in myometrium</td>
</tr>
<tr>
<td>Mg$_{2}^{2+}$</td>
<td>4 g bolus (30 min) 1-2 g/h 6 h'ly levels</td>
</tr>
<tr>
<td>Ergometrine</td>
<td>250 µg IV, 250 µg IM</td>
</tr>
</tbody>
</table>
Case scenarios

1. Inadequate perineal cover from epidural
   - LA bolus 5 ml 0.25% bupivacaine
     ± pethidine 25-50 mg
     ± clonidine 30-50 µg
   - still failed: lignocaine 2% or bupivacaine 0.5% to block motor and sensory
   - Caudal an option in theory (risk of toxicity and foetal injection)

2. Head at spines requests analgesia
   - CSE: 0.5 ml 0.5% bupivacaine, 25 µg fentanyl intrathecal
     epidural infusion to start after ≈30 min

3. LUSCS with L3-4 epidural in situ top-up 15 ml 2% lignocaine, 50 µg fentanyl, block at T8
   - bolus 5ml lig.
   - still no block: resite epidural to ≈T12-L1

4. Inadequate perineal block with LUSCS open on table
   - Wait, bolus epidural, narcotic, N₂O, clonidine, ketamine
   - Lignocaine 0.5% applied by surgeon to bladder, pelvis

5. Late decelerations, emergency GA LUSCS. RSI, can't see cords
   - Ventilate?
     Yes: introducer, bougie, Fastrach, FOB, wake-up → regional
     No: help!, airway position, BURP position, different blade (straight, McCoy),
     ventilation is a higher priority than intubation, two hands on mask, Guedel,
     LMA, COPA, Combitube, cricothyroid puncture
   - Cricothyroid puncture
     14G Jelco with syringe, aspirate air, attach 3 way tap, O₂ tubing, Sanders
     injector (50 psi initially), airway to improve exhalation
   - Cricothyroidotomy

6. Post delivery, 14 hour labour, PPH 600 ml, BP 70 mmHg, HR 110 bpm, no IV access
   - Acute resuscitation: ABC
   - Supplemental O₂, large bore IV access, rapid fluid replacement
   - Blood specimen for crossmatch, FBE
   - Obstetric management of haemorrhage
     - Remove placenta, rub fundus, oxytocin, ergometrine, PGF₂α, aortic
       compression, theatre
   - Anaesthesia in theatre
     - RSI with reduced doses, reduced volatile (uterine relaxant)
     - Rapid IV infusion: Level 1 or warmer with pump set
     - Scale up monitoring when time available: arterial line, CVC
     - Early access to blood products: packed cells, platelets, FFP likely to be needed

7. 39 weeks BP 155/95 mmHg, protein +, oedema, 95 kg, req. analgesia in labour at 4 cm
   - FBE, clotting, U&E, LFT, G&H, uric a., IDC (UO), CTG

Obstetrics 3.E.1.24 James Mitchell (October 7, 2001)
Mg²⁺ bolus 4 g over 30 min, 1-2 g/h, 6 h'ly levels
Add hydralazine if still hypertensive after an hour 5 mg bolus, infusion
Aim 120-140/70-90 mmHg
If plt ≥80 and clotting normal, epidural preferred with patient discussion of risks
Paediatrics

**Neonatal anaesthesia**

**Burns management**

**Outline airway problems in choanal atresia, Pierre-Robin syndrome, laryngomalacia**

**Outline your approach to paediatric bronchoscopy**

**Management of anaesthesia for teenage scoliosis surgery patient**

**Outline the management of anaesthesia for tracheoesophageal fistula surgery**

**Paediatric respiratory failure**

**Common sizes and doses**
Neonatal anaesthesia

Neonate

birth to 28d, more usefully up to 44w post conception

Anaesthesia

poorer outcomes with anaesthesia by non-experts
increasing numbers coming to theatre as they survive more commonly

Physiology

CVS
rate dependint CO
transitional circulation
caused by hypoxia, acidosis, hypercapnia, cold
treat with 100% O₂, hyperventilate
little sympathetic tone
HbF, p50 17 mmHg
higher haematocrit (depends on cord-clamping time)

blood volume 90ml/kg
inefficient myocardium due to poorly organized myofibrils
preferential blood supply of highest pO₂ to coronary, cerebral circulation

Respiratory

large head, short neck
small diameter airway
different laryngeal angle, anterior larynx
edentulous, but tooth buds can be damaged on intubation

short trachea
mouth breathing
increased MV
compliant chest wall, horizontal ribs
noncompliant lungs
prone to apnoea, sensitive to sedative drugs

Homeostasis

temperature maintenance
high SA to volume ratio
thin skin, rapid evaporative loss
little fat
no shivering, but non-shivering thermogenesis
poor vasoconstriction
thermoneutral zone

temperature requiring minimal O₂ consumption to maintain temperture

neonate 28-32°C at term, higher for prems

maintaining temperature in anaesthesia extremely important

Fluids

increased body water
high evaporative losses
reduced renal function
low GFR, poor concentrating ability
requirements
day 1-2 40-60ml/kg/24h (more for prems up to 200ml/kg/d)
10% dextrose plus Na⁺ 2mmol/kg/d, K⁺ 2-3mmol/kg/d, Ca²⁺, Mg²⁺ as required
continue glucose intraop (or glucose component of TPN)

lowered renal threshold for glucose
risk related to Ca²⁺ administration: burns if extravasates

Diseases

HMD
lack of surfactant prior to 34w, later in IDM
increased work of breathing, ground glass x-ray
respiratory distress, cyanosis, tracheal tug, grunting
prevention
   reduce risk of prematurity, steroids prior to delivery, tocolytics
treatment
   oxygen, CPAP, intubation, ventilation: IPPV, HFJV, oscillation,
surfactant, PLV
complications
   pneumothorax, IVH, ?NEC, chronic lung disease
Oxygen toxicity
   retinopathy of prematurity
     high pO2, vasoconstriction, neovascularization, haemorrhage, scarring,
     retinal detachment
     rare after 30w, PaO2<80 mmHg, <4 h
Pulmonary O2 toxicity
   free radical generation by high FiO2, worse with IPPV, high FiO2, aim for
   FiO2<60%, endothelial damage
IVH
   brain lesion associated with prematurity
   neonates: fragile vessels around ventricles: haemorrhage with rise in BP, also
   periventricular leukomalacia: ischaemia (watershed area in hypotension) with
   venous haemorrhage
   high risk at the time of intubation or volume expansion
   graded by extent, detected by u/s through fontanelle
   good prognosis unless very large
   older babies: cortical lesions more common
Apnoea
   More common with prematurity
   central, obstructive or mixed
   monitoring post anaesthetic up to 45w post conceptual in term babies here
   up to 60w in some units or with ex-prems

![Graph showing the probability of apnoea against post-conceptual age (w) and gestation at birth (w).]

NEC
   abdominal distension, tram tracking, acidosis
Anaesthesia
Assessment
   routine plus prematurity, associated abnormalities, recent course (ventilation,
   glucose..)
Transfer
   do case in neonates if sick, ?transfer to major hospital
Induction in theatre
   temperature monitoring and maintenance
IV usually not too hard: little fat, some veins invariant
intubation different: view and tube manipulation
monitoring: standard plus ECG, T, SpO₂ x 2
laryngoscopy: straight or curved blade, pick up epiglottis or not
tube size, need for leak, PCV, taping technique, nasal vs oral

Maintenance
ventilation PCV 5-20 cmH₂O 20/min, 10 l/min flow
positioning: flexible, need for head support, lying on wires etc., access usually poor, improved with hand up, oximeter lead available, tubing for IV access fluids: Albumex 4 (no evidence), continue dextrose
maintenance plus losses: e.g. open abdomen 10 ml/kg/h

Exubtation
awake

Recovery location
depends on procedure and institution

Regional
no long-term studies, morph infusion OK, paracetamol effective, little use of NSAIDs

Fasting time
clear fluids 2h breast 3h formula 4h solids 5h
Burns Management

First aid
- Remove burning debris, extinguish flames, remove from area of smoke
- ABCDE management
- Transfer to hospital

Primary survey
- ABCDE
  - Location and severity of burns
    - Rule of 9s for area burned, modified for children
  - Special areas
    - Face, mouth, airway
    - Eyes
- Associated injuries
  - Inhalational injury
    - More likely if facial burns
  - Cause of injury: smoke, toxic fumes, hot steam
  - Smoke inhalation
    - May have high COHb, give supplemental oxygen
    - Lung injury may produce respiratory distress syndrome
  - Airway burn
    - Develop oedema due to injury
    - Intubate early to secure airway
- Other injuries
  - Electrical burns, chemical burns, blast injury etc.
  - Circumferential burns may require escharotomy

Obtain IV access
- Large bore in non-burned area
- May need to be CVC or temporary intraosseous cannula
- Take baseline bloods
- Start hydration
  - Hartmann's solution
    - Maintenance (4/2/1 ml/kg formula), plus
    - Fasting time, plus
    - Burn losses 2-4 ml/kg/% burn over 24 hours
    - half in 8 hours
  - If young, may require glucose
  - Severe burns are often given some colloid
- Monitor urine output to assess hydration
  - ≥0.75-1 ml/kg/h desired
- Give IV analgesia
  - Titrated doses of morphine IV
  - Reduced dose requirement due to fluid depletion and centralized circulation
- Maintain normothermia
  - Warm environment
  - Warmed fluids
- Involve surgical/burns unit for on-going management

Later issues
- Infection
  - Prophylactic antibiotics vary by institution
  - Silver sulfadiazine dressings
- Nutrition
  - Commonly require NGT or IV supplementation
  - Particularly Zn, ω3 fatty acids

Anaesthesia
Surgery
- Commonly debridement and grafting
- Multiple procedures over weeks or months
- Commonly start about 5 days after injury

Preoperative
- Routine, plus
- Careful airway assessment
- Investigation
  - U+E to assess renal function
  - FBE, coagulation
  - Crossmatch for all debridements

Induction
- Good IV access required
- Commonly spontaneous ventilation with LMA
- Induction with
  - Thiopentone or propofol commonly
  - Ketamine: less fall in cardiac output than other IV agents
  - Halothane: vasodilator, myocardial depressant, ↓ platelet function
    - but still commonly used
- Muscle relaxation
  - Often not required
  - Increased number of post-junctional receptors
    - Decreased sensitivity to non-depolarizing agents
    - Increased K⁺ rise with suxamethonium
      - Unsafe from around 1 week to 12 weeks (or healed)
      - Lower dose useable (in theory)

Analgesia
- IV narcotic
- Nerve blocks for donor sites
  - Posterior cutaneous nerve of thigh
    - 1/4 of the way from ischial tuberosity to greater trochanter
      - In gluteal fold, LOR before reaching muscle or on withdrawal
  - Lateral cutaneous nerve of thigh
    - 2 cm inferior to ASIS between internal oblique and ilium
  - Femoral nerve
    - Lateral to femoral artery in the groin
      - 2 pops on insertion of 45° bevel needle
  - Sciatic nerve
    - Intersection of biceps femoris and sciatic nerve in leg
      - Nerve passes from midpoint of ischial tuberosity and greater trochanter to popliteal fossa
      - Muscle passes from ischial tuberosity to head of fibula
Outline airway problems in choanal atresia, Pierre Robin syndrome, laryngomalacia.

Choanal atresia
- Congenital atresia of the passage from nose into pharynx
- Unilateral or bilateral
- Membranous, cartilaginous or bony

Presentation
- Often detected at birth
- Respiratory difficulty and hypoxia as neonates are obligate nose breathers
- Tested for by occlusion of each nostril or passage of cannula

Immediate management
- Oral airway
- Supplemental oxygen
- Infants are typically pink and well-oxygenated when crying but hypoxic when feeding or asleep

Pierre Robin syndrome
- Congenital anomaly of the jaw, tongue and palate
- Cause uncertain
- Micro- or retro-gnathia, glossoptosis, cleft or arched palate (lip intact)

Presentation
- Obvious deformity at birth
- Commonly respiratory obstruction when supine
- May lead to cor pulmonale if untreated

Anaesthetic problems
- Usually difficult intubation
- Difficulty usually reduced with age as mandible grows
- May require gas induction and fibreoptic intubation
- Assistant retracting tongue may be helpful

Laryngomalacia
- Infantile larynx
- Normal variant laryngeal anatomy
- Unusually soft cartilaginous structures
- Epiglottis and surrounding structures cause dynamic obstruction

Presentation
- Stridor developing soon after birth
- Absent with quiet breathing
- Increasingly noisy with distress
- Resolves over first 6 months of life

Anaesthetic problems
- Increased risk of difficult intubation
- Due to floppy laryngeal structures obscuring view
- Difficulty with stridor after extubation
Outline your approach to paediatric bronchoscopy.

Rigid bronchoscopy

Surgery

- Elective for investigation of masses, respiratory symptoms
- Semi-urgent for removal of foreign bodies
- Emergency for massive haemoptysis, acute obstruction
- May be moderate or high risk
- Shared airway

Preoperative

Anaesthetic assessment

- Routine, plus
- Careful assessment of mouth opening and potential for dental injury
- Respiratory function testing if adult and compromised

Assessment of indication for bronchoscopy

- Respiratory compromise
- Complications of disease e.g. cachexia from tumour

Premedication

- Anxiolytic, amnestic agent e.g. benzodiazepine
- Anticholinergic to reduce secretions

Induction

Preparation of the airway

- Local anaesthetic
  - Topical spray or nebulized lignocaine
  - Transtracheal lignocaine
  - Nerve blocks: glossopharyngeal and superior laryngeal
- Dental guard

Monitoring

- Routine: SpO₂, ECG, NIBP
- Plus arterial line if debilitated
- Secure IV access for TIVA

Induction

- Propofol plus short-acting relaxant (rocuronium or suxamethonium)
- Fentanyl to blunt haemodynamic response to bronchoscopy

Ventilation

- Jet insufflation through scope
  - Requires special equipment
  - No anaesthetic agent delivered so requires TIVA
  - Permissive hypercapnea limits duration of procedure
    - ↑ risk of arrhythmias
  - Risk of barotrauma if scope occluded
- IPPV through scope
  - T-piece circuit
  - Allows delivery of volatile agent
  - Intermittent ventilation as scope must be occluded
    - So high FiO₂ to allow for apnoea
  - Requires good communication with surgeon
- HFJV
  - Spontaneous ventilation without relaxant

Maintenance

- Intermittent boluses of IV anaesthetic agent and relaxant or infusion
- Extreme vigilance for ventilatory compromise

Emergence

- May require intubation and suctioning after procedure until awakening and muscle relaxant reversal
Lateral position
  Risk of haemoptysis after resection or biopsy

Postoperative
  Usually little analgesia required
  Supplemental oxygen and saturation monitoring

Particular considerations in paediatric bronchoscopy
  Patient population
    Commonly performed for foreign body aspiration
    Usually fibreoptic scope is not an option
    Often semi-urgent
    Higher metabolic rate, low FRC
    Rapid onset of hypoxia
    Particularly good communication with surgeon required
  Airways
    Smaller calibre and softer tissue
    Increased risk of perforation or bleeding
    Increased risk of laryngospasm during emergence
Management of anaesthesia for a teenage scoliosis patient

Surgery
Elective, high risk surgery
Usually in teenage females
Extensive thoracotomy, potential for massive blood loss, hypothermia
Posterior and anterior approaches
May have coexisting neuromuscular disease
Secondary respiratory or cardiovascular compromise
Increased incidence of MH in this patient population

Preoperative
Assessment
Routine history and examination, plus
Scoliosis
Airway assessment vital
Degree, mobility
Complications
Respiratory function testing, restrictive deficit
Exercise tolerance

Investigations
FBE, XM, RFT, ABG
Autologous blood donation or directed donation

Consent
Discussion of risks
Possible need to wake intraoperatively to test neurological function

Premedication
Oral benzodiazepine with regard to respiratory function

Transport
Routine

Intraoperative
Monitoring and access
Usual emergency equipment, plus
Difficult airway equipment
Rapid infusion equipment available
Cell saver if indicated
Routine monitoring, plus
Arterial line, temperature probe, IDC
SSEP or MEP monitor
Availability of ABG and Hb measurements

Induction
Intubation required
Thoracotomy and commonly prone
Prepare for difficult airway if likely
Consider spontaneously breathing induction or awake FOB if required
Otherwise routine IV induction
Short-acting muscle relaxant if MEP required

Maintenance
Position
Pressure care may be difficult if severe scoliosis
Often prone, avoid abdominal pressure causing vertebral vein engorgement

Ventilation
N₂O, O₂, low isoflurane dose
± propofol for intraoperative awakening
Controlled hyperventilation to cause vasoconstriction
One lung often retracted for surgical access: OLV

Paediatric Anaesthesia 3.F.10 James Mitchell (October 7, 2001)
Circulation
May be large blood loss
Maintain normotension for cord perfusion
   Fluid loading and pressors
Analgesia
   Consider spinal or caudal morphine either by surgeon or pre-incision
   Fentanyl bolus plus infusion
Emergence
   Awake extubation, lateral position
   May require ICU ventilation if severe respiratory compromise
   Aim for early assessment of neurological function
   Consider propofol “bookend”
   Supplmental O₂
   Postoperative CXR and FBE
   Prolonged immobilization in supine position
   Chest physiotherapy, ?DVT prophylaxis
Outline the management of anaesthesia for tracheooesophageal fistula surgery.

Tracheooesophageal fistula
1/3000 live births
Abnormal communication between oesophagus and trachea
Usually associated with oesophageal atresia
Classified by topology
85% distal TOF with proximal blind oesophagus
10% oesophageal atresia with no TOF
4% patent oesophagus with TOF (often diagnosed late)
Diagnosed shortly after birth
Associated with polyhydramnios
Failure to pass orogastric tube
Failure to feed or aspiration with feeding
Surgical management
IV hydration
Laparotomy, feeding gastrostomy, determination of “gap”
Thoracotomy, fistula closure, oesophageal repair
Surgery
Urgent, high risk
Preoperative
Assessment
History
Post-conceptual age, gestational problems
Family history
Diseases of prematurity
VATER abnormalities
Vascular (cardiac), vertebral, atresia in GI tract, TOF, renal, radial abnormalities
Examination
Cardiac, respiratory, general
15-25% incidence of cardiac defects
Aspiration common
Investigation
XM, FBE, U&E or gases
CXR
Contrast studies
Echocardiogram
Optimization
Hydration, antibiotics for pneumonia, treatment of lung disease
Premedication
Atropine, paracetamol, antibiotics
Intraoperative
Monitoring
Routine: ECG, NIBP, SpO₂, gas analysis, IDC
Consider arterial line if unstable or blood gases required
Temp probe not in oesophagus
Induction
Aim to avoid mask IPPV which causes gastric distension
Bradycardia and diaphragmatic splinting
Aspirate gastrostomy and leave open
Topical LA to airway
Inhalational induction, spontaneously breathing intubation, or
Rapid IV induction
ETT placement beyond level of TOF, may be at carina
Maintenance

Position
- Laparotomy at 45˚ head-up
- Thoracotomy in left lateral position unless right aortic arch (5%)
Warming to maintain temperature
High FiO₂ with potent volatile agent
Hand ventilation often required
- ETT may migrate into fistula with positioning
- Low lung compliance
- Gas leak through fistula
- Retraction of right lung for access
- Retraction on mediastinum may cause tracheal occlusion
Analgesia with LA in wound or intercostal blocks
Close attention to blood loss and fluid management

Emergence
- Aim for extubation if stable
- Less stress on tracheal sutures than IPPV
- Avoid neck extension: stresses anastomosis

Postoperative
- NICU or neonatal unit level of care
- SpO₂ monitoring
- Morphine infusion for analgesia
Complications
- Pneumonia, anastomotic leak, tracheomalacia, fistula, reflux, stricture
Paediatric respiratory failure

Definition

- \( \text{PO}_2 < 60 \text{ mmHg}, \text{PCO}_2 > 55 \text{ mmHg}, \text{RR} > 35 \) at BTPS, \( \text{FiO}_2 0.21 \), worse than normal function
- Type 1 ventilation failure, acidic pH (raised \( \text{PCO}_2 \))
- Type 2 oxygenation failure, normal pH

Diagnosis

- Very broad range of clinical symptoms, essentially subjective
- Apnoea
- Increased work of breathing, other clinical features
- Tachypnoea, but rate highly variable and not different between well and ill populations
- Cyanosis
- ABG criteria

Susceptibility of children

- Less reserve, higher BMR for size
- Small airways, less adherent mucosa, readily occluded by oedema
- Narrow subcricoid level, airways cause 20% of resistance
- Short horizontal ribs, little increase in AP chest diameter
- Soft chest wall, poor inspiratory pressure generation
- Type I muscle fibres, easily fatigued
- Less alveoli, continued budding to age 1y
- Few pores of Kohn, more variation in time constants
- Increased susceptibility to infection, poor cellular immunity, no memory IgG response
- Birth injuries: asphyxia, aspiration, RDS of newborn

Differences from adults

- Adults recover slowly if at all (80% mortality)
- Children require only brief ventilation (3-4 days), good outcomes (5-6% mortality)
- Most deaths in neonates

Analysis

- Cost per year independent life saved
  - Neonate $1500, child $170, adult $1950
- Cost per survivor
  - Neonate $95500, child $11500, adult $27850
- Cost per patient intubated
  - $28650, $8600, $9750

Causes of respiratory failure in children

- Epiglottitis
  - Marked decline due to haemophilus influenzae B vaccination
- Croup
  - Nebulized adrenaline 0.5 ml/kg of 1:1000 or 0.05 ml/kg of racemic (1:88)
  - Steroids
  - Bronchiolitis
  - Asthma

Treatment

- Ventilation
  - HFPPV
    - 60-100 /min 3-4 ml/kg small dead space
    - pressure generator with "chopper"
HFJV
similar to Sanders jet ventilator
3-5 ml/kg intermittent
Trial evidence suggests benefit in neonates by intermediate indicators

HFOV
3-15 /sec alternates between positive and negative pressure
less than dead space ventilation
rescue ventilation
set rate, Δ P, mean airway pressure (FiO₂, usually .9-1.0)
CO₂ elimination better with high Δ P, low frequency
Mechanism of ventilation
  Pendelluft: differing time constants
  Assymetric velocity profiles: wave interference between in and
  out flow at joints
  Taylor dispersion: wave diffusion at joints?
  Molecular diffusion: simple diffusion
Trial (HIFI) showed no benefit, but done in centres inexperienced with
HFOV. Increased IVH, PVL rate. Less risk of long term disease, fibrosis,
ECMO etc.
Surfactant and NO can be delivered
Conventional ventilation is usually the first strategy as HFJV and HFOV are
not available in obstetric hospitals

ECMO
Available if failed ventilation, correctable disease, 80% expected mortality
Physiological indices also determine entry
Anticoagulation problems
Femoro-femoral or femoro-atrial
Ventilation for lung recruitment
Common sizes and doses

Weight
- Birth 3-4 kg
- 1 y 10 kg
- age x 2 + 9 up to 9 y
- age x 3 from 9 y

ETT size
- Prem 2.5 mm
- Term 3-3.5 mm 9 cm at lips
- age ÷ 4 + 4 ≤ age + 10 cm at lips (or age ÷ 2 + 12)

Induction (single agent unpremedicated elective)
- Thiopentone 7 mg/kg
- Propofol 4 mg/kg
- Ketamine 2 mg/kg
- Suxamethonium 1.5-2 mg/kg
- Atracurium 0.5 mg/kg
- Atropine 10-20 µg/kg
- Morphine 0.1-0.2 mg/kg
- Fentanyl 1-3 µg/kg
- β-lactams 20 mg/kg
- Metronidazole 15 mg/kg
- Gentamicin 6 mg/kg (less <1 y)

Reversal
- Neostigmine 50 µg/kg
- Atropine 24 µg/kg

Resuscitation
- Adrenaline 10 µg/kg up to 100 µg/kg
- Calcium 0.1-0.15 mmol/kg (0.2 ml/kg CaCl₂, 0.5 ml/kg Ca gluconate)
- DCR 2-4 J/kg (1 J/kg for atrial arrhythmia)

Hypotension
- Nitroprusside 50 mg/500 ml 0-20 ml/h (=0-33 µg/min, 0-10 µg/kg/min)
Thoracic anatomy

Autonomic nervous system
Autonomic nervous system

Division by direction
  Visceral efferent
    Preganglionic myelinated, postganglionic unmyelinated
    Synapse in ganglia
  Visceral afferent
    Similar to somatic afferent
    Cell body in CNS, peripheral processes travel with autonomic and somatic fibres

Division by outflow
  Sympathetic
    Thoracolumbar outflow: T1-L3
    Synapse in sympathetic trunk ganglia or other ganglia near CNS
    Preganglionic cholinergic, postganglionic predominantly noradrenergic (also adrenergic, cholinergic sudomotor and purinergic)
  Parasympathetic
    Craniosacral outflow: III, VII, IX, X, S2-4
    Synapse adjacent to end-organs
      Cranial nerve parasympathetic ganglia are traversed by other fibres but contain only parasympathetic synapses

Parasympathetic anatomy

  III
  Edinger-Westphal nuclei → oculomotor n. → n. to inferior oblique → ciliary ganglion → short ciliary mn. → ciliary muscle and sphincter pupillae

  VII
  Superior salivatory nucleus → nervus intermedius → facial n. → chorda tympani → lingual n. → submandibular ganglion → submandibular and sublingual glands
  Geniculate ganglion → greater petrosal n. → pterygopalatine ganglion → zygomatic and lacrimal nerves to lacrimal gland and nasal and palatine branches to nasal mucosa

  XI
  Inferior salivatory nucleus → glossopharyngeal nerve → tympanic plexus → lesser petrosal n. → otic ganglion → auriculotemporal n. → parotid gland and oral mucosa

  X
  Dorsal nucleus of vagus → vagus n. → minute ganglia in respiratory tract, heart, kidneys and gastrointestinal viscera from oesophagus to mid transverse colon. Most vagal fibres are afferent, there is a very large ratio of postganglionic to preganglionic efferent fibres.

  S2-4
  Anterior rami → sacral spinal nerves → pelvic viscera and pelvic plexus → bladder, erectile tissue, gonads, uterus and uterine tubes, hindgut from mid transverse colon to rectum

Sympathetic anatomy
  Preganglionic efferent
    Lateral column cell body → ventral root → white ramus communicans → sympathetic trunk → synapse in trunk or other ganglia or adrenal
  Postganglionic
    May ascend or descend in the trunk, rejoin all spinal nerves via grey rami communicantes or leave in direct branches to vessels or viscera

Distribution
  Cranial
    Internal carotid plexus arises from superior cervical ganglion and
cerebral arteries and ophthalmic artery

Cervical
Sympathetic chain condenses usually into three ganglia on each side: superior (C2-3), middle (C6) and cervicothoracic (stellate, T1) cervical ganglia

Cardiac plexus
Derived from T1-4 (and X) via cervical and thoracic ganglia
Surrounds heart, great vessels and coronaries

Pulmonary plexuses

Coeliac plexus
Two ganglia opposite T12-L1 with large condensation of autonomic fibres
Gives rise to phrenic, splenic, hepatic, left gastric, intermesenteric, suprarenal, renal, gonadal, superior and inferior mesenteric plexuses which accompany arteries to their target organs

Superior hypogastric plexus
Inferior hypogastric plexus
Supplies hindgut, ureter, bladder, gonads, sex organs

Somatic levels of visceral afferents

<table>
<thead>
<tr>
<th>Organ</th>
<th>Sympathetic</th>
<th>Parasympathetic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td>T1-5</td>
<td>X</td>
</tr>
<tr>
<td>Lungs</td>
<td>T2-4</td>
<td>X</td>
</tr>
<tr>
<td>Oesophagus</td>
<td>T5-6</td>
<td>X</td>
</tr>
<tr>
<td>Stomach</td>
<td>T6-10</td>
<td>X</td>
</tr>
<tr>
<td>Liver, gallbladder</td>
<td>T6-10</td>
<td>X</td>
</tr>
<tr>
<td>Pancreas, spleen</td>
<td>T6-10</td>
<td>X</td>
</tr>
<tr>
<td>Small bowel</td>
<td>T9-10</td>
<td>X</td>
</tr>
<tr>
<td>Large bowel</td>
<td>T11-12</td>
<td>X to mid transverse</td>
</tr>
<tr>
<td>Kidney, ureter</td>
<td>T10-L2</td>
<td>X, S2-4</td>
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<tr>
<td>Adrenal</td>
<td>T8-L1</td>
<td>none</td>
</tr>
<tr>
<td>Gonads</td>
<td>T10-11</td>
<td>S2-4</td>
</tr>
<tr>
<td>Bladder</td>
<td>T11-L2</td>
<td>S2-4</td>
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<tr>
<td>Prostate</td>
<td>T11-L1</td>
<td>S2-4</td>
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<tr>
<td>Uterus</td>
<td>T10-L1</td>
<td>S2-4</td>
</tr>
</tbody>
</table>
Anatomy

nose

bones
external: nasal processes of frontal bones, nasal bones, frontal processes of maxillae
internal: ethmoid, sphenoid, occipital, pterygoid, palatine, maxilla, conchae, vomer

arteries
facial: lateral nasal branch and others
superior labial: septal and alar branches
ophthalmic: dorsal nasal and anterior and posterior ethmoidal branches
maxillary: nasal branch of infraorbital branch, sphenopalatine branch

innervation
special sensory
smell (I) through cribriform plate
sensory
external
V¹ via anterior ethmoidal and external nasal branches of the nasociliary nerve to bridge and tip
V² via nasal branches of infraorbital nerve
internal
external nasal and infraorbital branches to vestibule
septum: V¹ anterior ethmoidal branch anterosuperiorly, V² nasopalatine branch from pterygopalatine ganglion
posteroinferiorly
lateral wall: V¹ anterior ethmoidal, V² anterior superior alveolar branch, posterior and inferior nasal branches and greater palatine nerves from pterygopalatine ganglion

motor: VII to muscles of facial expression

mouth

innervation
special sense
VII to palate via greater petrosal nerve
VII chorda tympani to lingual nerve supply anterior 2/3 of tongue
IX to posterior 1/3
sensory
V² and V³ via infraorbital, superior alveolar, nasopalatine, greater and lesser palatine, buccal, lingual, inferior alveolar and mental nerves
IX to posterior parts

motor
VII to muscles of facial expression
V³ to tensor veli palatini and muscles of mastication
IX, X and XI via pharyngeal plexus to palatoglossus
XII to tongue and floor of mouth
Larynx

Skeleton

Hyoid bone above, firmly attached by 3 thyrohyoid ligaments and thyrohyoid membrane

Three unpaired midline cartilages

Thyroid cartilage
  Two laminae, fused in midline
  Superior border attached to hyoid
  Posterior borders attached to stylopharyngeus and palatopharyngeus
  External surface attached to sternothyroid, thyrohyoid and inferior constrictor muscles
  Inferior synovial joint with cricoid posteriorly and lateral and median cricothyroid ligaments
  Internally attached to stem of epiglottis, vocal and vestibular ligaments and thyroarytenoid, thyroepiglottic and vocalis muscles

Cricoid cartilage
  Complete ring of cartilage at level of C6
  Attached to thyroid cartilage above
  Inferior attachment to trachea
  Posterior insertion of oesophageal muscle
  Posterolateral origin of posterior cricoarytenoid muscle
  Lateral and anterior origin of cricothyroid and inferior constrictor
  Superior edge origin of lateral cricoarytenoid muscle and posteriorly articulation with arytenoid cartilages

Epiglottis
  Leaf-shaped elastic cartilage
  Inserts into thyroid cartilage
  Anterior attachment to hyoepiglottic ligament
  Median and lateral glossoepiglottic folds attach to tongue
  Lateral aryepiglottic folds

Three paired cartilages

Arytenoids
  Tetrahedral cartilages
  Anterior vocal process attaches to vocal ligament
  Lateral muscular process attaches to posterior and lateral cricoarytenoid muscles
  Posterior surface attaches to transverse arytenoid muscle (to other arytenoid)
  Anterolateral attachment to vocalis and thyroarytenoid muscle
  Rotates to open or close vocal cords

Cuneiforms
  Corniculatcs
  Contained in aryepiglottic folds

Muscles

Extrinsic
  Move the larynx

Intrinsic
  Sphincter muscles
  Transverse and oblique arytenoid, and aryepiglottic muscles bring the opening of the larynx closed

Muscles of vocal folds
  Tensing of vocal cords by cricothyroid
  Slackening of vocal folds by thyroarytenoid and vocalis muscles
  Adduction of vocal folds by lateral cricoarytenoid and transverse arytenoid muscles
Abduction of vocal cords by posterior cricoarytenoid muscles
All supplied by recurrent laryngeal nerve except cricothyroid (external laryngeal nerve). Fibres from XI travelling in X.

**Sensory innervation**
- X internal laryngeal nerve above vocal cords
- X recurrent laryngeal nerve below vocal cords
Miscellaneous

Somatic levels of visceral afferents
Somatic levels of visceral afferents

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<tr>
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<td>X</td>
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<td>Lungs</td>
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<td>Oesophagus</td>
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<tr>
<td>Stomach</td>
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<td>X</td>
</tr>
<tr>
<td>Liver, gallbladder</td>
<td>T6-10</td>
<td>X</td>
</tr>
<tr>
<td>Pancreas, spleen</td>
<td>T6-10</td>
<td>X</td>
</tr>
<tr>
<td>Small bowel</td>
<td>T9-10</td>
<td>X</td>
</tr>
<tr>
<td>Large bowel</td>
<td>T11-12</td>
<td>X to mid transverse</td>
</tr>
<tr>
<td>Kidney, ureter</td>
<td>T10-L2</td>
<td>X, S2-4</td>
</tr>
<tr>
<td>Adrenal</td>
<td>T8-L1</td>
<td>none</td>
</tr>
<tr>
<td>Gonads</td>
<td>T10-11</td>
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</tr>
<tr>
<td>Bladder</td>
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<td>Prostate</td>
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Regional

Abdomen and pelvis

Lower limb
- Lumbar and lumbosacral plexus
- Femoral block, three-in-one block
- Sciatic block
- Ankle block
- Other lower limb blocks

Spine and thorax
- Intercostal block
- Paravertebral block
- Blood patch

Upper limb
- Brachial plexus
- Interscalene
- Supraclavicular block
- Axillary
- Elbow
- Wrist

Head
- Complications of retrobulbar and peribulbar eye blocks
- Ear
- Nose
- Trigeminal nerve
- Other head and neck

Neck
- Cervical plexus
- Airway

Recipes for regional anaesthesia
Lumbar and lumbosacral plexus

Lumbar plexus
Four roots: ventral rami of L1-4
L1 divides into superior and inferior branches
Superior: ilioinguinal and iliohypogastric nn.
Inferior: joins L2 to form genitofemoral n.
L2-3 give branches to form lateral femoral cutaneous n.
L2-4 give branches to form femoral and obturator nn.

Iliohypogastric nerve
Runs superior to iliac crest between internal oblique and transversus abdominis
Motor to abdominal wall
Sensory branches: lateral (hip) and anterior cutaneous (suprapubic)

Ilioinguinal nerve
Immediately inferior to iliohypogastric
Traverses inguinal canal
Cutaneous branches to upper inner thigh and root of penis or labia majora

Genitofemoral nerve
Genital branch traversus inguinal canal and supplies cremaster and lateral scrotal skin
Femoral branch arises medially and passes under inguinal ligament with external iliac a., passes through saphenous opening and supplies skin over femoral triangle

Lateral femoral cutaneous nerve
Passes under lateral part of inguinal ligament, deep to fascia lata
Supplies skin of lateral thigh from greater trochanter to above knee

Obturator nerve
Runs on the medial and posterior aspect of psoas, though the obturator canal
Supplies adductors, hip and knee joints and skin over medial thigh just above knee

Femoral nerve
below

Lumbosacral plexus
Five roots: ventral rami of L4-S3
Collateral branches to gluteal region, pudendal plexus and hip joint
Anterior and posterior terminal branches
Form posterior cutaneous nerve of thigh
Anterior branches form tibial portion of sciatic nerve
Posterior branches form common peroneal portion of sciatic nerve

Psoas compartment block

Anatomy
Lumbar nerve roots run in compartment posterior to psoas muscle

Needle placement
Patient in lateral position, knees to chest, sedation required
15 cm needle inserted 5 cm lateral and 3 cm inferior to L4 spinous process
Strikes L5 transverse process
Redirected slightly superiorly and advanced until loss of resistance at 12±2 cm

Local anaesthetic
20 ml air to dilate space
30 ml of dilute solution

Indications
Analgesia or anaesthesia in region of femoral, obturator and lateral cutaneous n.
Femoral nerve block, three-in-one block

Anatomy

Femoral nerve arises from L2-4 roots in lumbar plexus
- Runs deep to psoas, comes lateral to psoas tendon at level of inguinal ligament
- Lies lateral to femoral artery below inguinal ligament
  - Different fascial plane: deep to fascia lata and fascia iliaca
- Divides into superficial and deep bundles
  - Superficial supplies anterior thigh and sartorius
  - Deep supplies quadriceps, knee joint, gives rise to saphenous nerve

Obturator nerve arises from L2-4
Lateral cutaneous nerve of thigh arises from L2-3

Needle placement

Patient supine
- Short-bevel needle inserted 1-2 cm below inguinal ligament 1-1.5 cm lateral to femoral artery
- Two “pops” or paraesthesia elicited or nerve stimulator used to determine depth

Local anaesthetic

Femoral nerve only
- 10-20 ml of 0.5% bupivacaine

Three-in-one
- 30 ml of solution (may need to be more dilute than 0.5% to avoid toxic dose)
  - Distal pressure over nerve causes solution to flow proximally
  - Proximal spread to lumbar plexus anaesthetizes obturator and lateral cutaneous nerve of thigh

Indications

Three-in-one may be combined with sciatic block for most leg surgery
- Ideal for muscle biopsy in MH testing
- Useful for knee examination and surgery
- Analgesia for femoral fractures

Complications

Vascular
- Femoral artery or vein injury, haematoma

Neurological
- Neuropraxia, sympathetic block to leg

Common to all blocks
- Local anaesthetic toxicity (esp. combined with sciatic block)
- Poor effect
- Infection
Sciatic block

Classic approach of Labat
- Lateral position, upper heel on lower knee
- Line from greater trochanter to PSIS marks upper border of piriformis
- Bisector of this line extended 3 cm inferiorly marks injection site
  or intersection with line from greater trochanter to sacral cornu
  or intersection with line from midpoint of line from PSIS to ischial tuberosity
  to greater trochanter

Advance 6-8 cm until bone is contacted
Geometric grid approach searching for paraesthesia or using nerve stimulator

Anterior approach of Labat
- Supine anatomical position
- Line of inguinal ligament identified
- Medial trisector extended inferiorly
- Intersection with a line parallel to inguinal ligament running through greater trochanter identified
- Needle advanced slightly laterally strikes lesser trochanter
- Walk medially off femur and identify LOR 4.5-6 cm beyond (or use nerve stimulator)

Lithotomy approach
- Lithotomy position with full hip flexion
- Needle advanced through midpoint perpendicular to skin
- LOR or nerve stimulator or paraesthesia determine depth

Lateral approach
- Supine position
- Needle inserted 3 cm distal to greater trochanter at posterior border of femur
- Advanced immediately behind femur 8-12 cm total depth
- Nerve stimulator or paraesthesia used to determine depth

Prone (Ian McKenzie’s) approach
- Prone position
- Line from ischial tuberosity to head of fibula marks biceps femoris
- Line from midpoint between ischial tuberosity and greater trochanter to middle of popliteal fossa marks course of sciatic (tibial) nerve
- Needle inserted at intersection of lines
- LOR deep to biceps femoris
Ankle block

Saphenous n
Blocks postero-medial part of dorsum of foot
Superficial infiltration around long saphenous vein anterosuperior to medial malleolus

Tibial n
Needle entry medial to Achilles tendon or lateral to posterior tibial artery at upper border of medial malleolus
Determine depth with paraesthesia, nerve stimulator or 1 cm superficial to tibia
Alternatively infiltration either side of artery behind medial malleolus
Blocks sole, plantar surface of digits

Deep peroneal n
Needle entry between extensor hallucis longus and tibialis anterior tendons or lateral to anterior tibial artery
Blocks first web space and short toe extensors

Superficial peroneal n
Superficial infiltration from lateral border of tibia to upper part of lateral malleolus
Blocks dorsum of foot and toes except first web space

Sural n
Superficial infiltration from Achilles tendon to lateral malleolus
Blocks lateral side of foot and fifth digit
Other lower limb blocks

Lateral femoral cutaneous nerve

Anatomy
L2-3 ventral roots
Emerges at lateral border of psoas inferior to ilioinguinal nerve
Runs between iliac fascia and iliacus
Emerges inferomedial to ASIS from under inguinal ligament
Crosses origin of sartorius and runs deep to fascia lata, dividing into anterior and posterior branches
Supplies skin over lateral thigh

Needle placement
Patient supine
Short bevel needle inserted 2 cm inferior and 2 cm medial to ASIS
Pop felt on passing though fascia lata

Local anaesthetic
10-15 ml placed deep and superficial to fascia lata
Dilute solution required if multiple blocks are to be performed

Indications
Combined with sciatic, femoral and obturator blocks for leg surgery

Obturator nerve

Anatomy
L2-4 nerve roots
Emerges medial to psoas at pelvic brim
Runs around pelvis behind iliac vessels and ureter
Enters obturator canal superior and anterior to obturator vessels
Divides in canal into anterior and posterior branches
Anterior branch supplies anterior adductors, hip joint and medial thigh
Posterior branch supplies deep adductors and knee joint

Needle placement
Patient supine, legs slightly abducted
Point 1.5 cm lateral and 1.5 cm inferior to pubic tubercle identified
Needle inserted AP, contacts superior pubic ramus at 1.5-4 cm depth
Walked laterally into obturator canal and advanced 2-3 cm

Local anaesthetic
10-15 ml of dilute solution while advancing and withdrawing

Complications
Intravascular injection in obturator vessels, haematoma

Tibial and common peroneal nerves in the popliteal fossa

Anatomy
Sciatic nerve divides at apex of popliteal fossa
Tibial nerve continues lateral to vessels inferiorly between heads of gastrocnemius
Common peroneal nerve accompanies biceps femoris tendon laterally, passes around head of fibula and divides into superficial and deep branches

Needle placement
Patient prone or lateral
Margins of popliteal fossa identified: semimembranosus, biceps femoris and gastrocnemius
Point identified 1 cm lateral to midline of fossa and 5 cm superior to skin crease
Needle inserted angled 45°-60° anterosuperiorly, paraesthesia sought
Local anaesthetic
  30-40 ml of dilute solution
Indication
  Foot and ankle surgery
  Saphenous nerve territory not covered (femoral origin)
Blood patch

Technique
  Timing
    Probably less effective in first 24 hours
    Must wait until block is completely resolved
  Volume
    No clear evidence that large volumes are better
    Commonly 10-20 ml
  Bed rest
    Two hours is better than 30 min or one hour

Indications
  Moderate to severe PDPH
  Prophylactic on catheter withdrawal after dural tap on insertion (controversial)

Contraindications
  Needle placement
    Coagulopathy, sepsis, local infection, anatomical abnormality
  Autologous blood injection
    Sepsis
    No adverse sequelae in HIV infection
    Raised ICP: increased further by injection

Complications of PDPH
  Cranial nerve palsies unaltered
  Hearing loss and tinnitus markedly improved
  Seizures uncommon, no evidence of effect
  Intracranial bleed and ↑ ICP: contraindication

Effectiveness
  >90% initial relief
  60-75% persistent relief after large needle puncture

Mechanism of action
  Pressure effect from injection
  Brief for crystalloids, minutes to hours for blood
  “Plug” effect from sealing dural tear

Effect on subsequent epidural
  Increased risk of dural puncture and poor block

Prophylactic use
  Saline 40-60 ml reduces need for blood patch
Intercostal block

Anatomy

Intercostal nerve arises from T1-T11 nerve roots, T12 is similar (subcostal)

Branches

Grey *ramus communicans* from sympathetic chain

Posterior cutaneous branch arises beyond vertebral foramen and supplies paravertebral muscles and skin

Lateral cutaneous branch arises anterior to midaxillary line and supplies skin of lateral aspect of chest

Anterior cutaneous branch pierces *pectoralis major or rectus abdominis* and supplies breasts and anterior chest and abdominal wall

T1-3 give branches to axillary plexus and intercostobrachial nerve

T12 gives branches to iliohypogastric and ilioinguinal nerves

Nerve lies deep to internal and external intercostal muscles, superficial to *intercostalis intimis* and pleura

Neurovascular bundle lies immediately inferior to rib and consists of vein, artery and nerve from superior to inferior

Needle placement

Sitting, lateral or prone positions

Identify line of lateral margin of paravertebral muscles (6-8 cm lateral to midline)

Count ribs to identify correct level

Apply traction superiorly to skin, insert needle over rib

Allow skin to retract inferiorly and walk needle off inferior edge of rib

Inserted another 2-5 mm with aspiration

Local anaesthetic

Long-acting agent with adrenaline

2-5 ml of solution per nerve

Care with total dose as absorption is fairly rapid

Indications

Anaesthesia

- Chest drain insertion, gastrostomy insertion
- Other minor thoracic or abdominal procedures

Analgesia

- Fractured ribs
- Thoracotomy or laparotomy as adjuvant technique

Complications

Pneumothorax

- Rare despite risks of entering pleura as the needle used is small
- Managed conservatively

Local anaesthetic toxicity

- Minimize with adrenaline-containing solution

Paravertebral block

Anatomy

Similar to intercostal block but placement 2 cm lateral to midline

Needle placement

- Needle inserted postero-anteriorly onto transverse process
- Walked off top or bottom of process and inserted 1 cm
- “Hanging drop” can be used
- Inject at every level or else rely on spread between levels

Local anaesthetic

- Divide total dose between number of levels

Indications

- Breast surgery, other surgery requiring unilateral block
Brachial plexus

Five nerve roots
- C5-8 branches to *longus colli* and *scaleni*
- C5-7 branch to long thoracic n.
- C5 contributes to phrenic n. and dorsal scapular n.

Three trunks
- Form between *scalenus medius* and *scalenus anterior*
- Superior, middle and inferior
- Superior gives off suprascapular n.
- Inferior gives off first intercostal n.
- Divide into ventral and dorsal divisions at lateral edge of first rib

Six divisions
- Dorsal divisions supply extensors
- Ventral divisions supply flexors
- Form cords on entering the axilla

Three cords
- Lateral, posterior and medial
- Axillary artery lies between
- Posterior gives off five extensor branches
  - Two major: radial and axillary nn.
  - Three minor: thoracodorsal and two subscapular nn.
- Lateral gives off three branches
  - Two major: musculocutaneous n. and half of median n.
  - One minor: lateral pectoral n.
- Medial gives off five branches
  - Two major: ulnar and half of median n.
  - Three minor: medial pectoral and medial cutaneous nn. of arm and forearm
Interscalene block

Anatomy
Trunks of brachial plexus cross first rib behind *scalenus anterior* and subclavian artery at the level of C6

Needle placement
Patient supine with head turned away
Interscalene groove is palpable at the level of cricoid cartilage or Chassaignac’s tubercle
Needle inserted with slight postero-inferior angulation
Walked posteriorly in C6 plane if required to elicit paraesthesia or twitches

Local anaesthetic
30-40 ml of lignocaine 2% or bupivacaine 0.5%

Indications
Most reliable from C4-C7
Shoulder surgery, reduction of dislocated shoulder
Supplementation required for hand or forearm surgery
More caudal needle placement to cover C8-T1/ulnar distribution

Complications
Phrenic nerve block common
Subarachnoid or epidural injection
Intravascular injection (subclavian or vertebral artery)
Pneumothorax
Supraclavicular block

Anatomy
- Plexus lies inferior to mid-clavicle
- Subclavian artery is anterior and medial to the plexus
- Both pass over the first rib together

Needle placement

Classical approach
- Relatively difficult to describe and teach
- Patient supine, arm at side, head turned away
- Interscapular roll and inferior displacement of the shoulder can make it easier
- Interscalene groove identified by palpation posterior to sternocleidomastoid
- Subclavian artery is often palpable behind clavicle
- Needle inserted 2 cm behind midpoint of the clavicle or immediately posterior to the artery
  - Lateral end of clavicle is medial to the acromion
  - Directed inferiorly with slight posteromedial angulation
- Paraesthesia or nerve-stimulator indicates location at the plexus
- If no paraesthesia is elicited, the superior surface of the first rib is usually contacted
- Walking anteriorly along the rib surface should result in paraesthesia

“Plumb-bob” approach
- Patient supine, head turned away
- Lateral margin of insertion of sternocleidomastiod into clavicle identified
- Needle inserted directly anteroposterior
- Angled superiorly and then inferiorly until paraesthesia elicited

Sternocleidomastoid approach
- 10 cm needle inserted at junction of clavicular and sternal heads of sternocleidomastoid
- Directed posterolaterally aiming at posterior of midpoint of clavicle
- Nerve stimulator indicates plexus

Local anaesthetic
- 15-25 ml of lignocaine, bupivacaine or ropivacaine
- Periodic aspiration

Indications
- Most reliable from C5-T1
- Most upper limb surgery
  - Proximal block: compact plexus, above most branches, small volume required
  - Shoulder surgery may require supplemental cervical plexus block for overlying skin

Complications
- Pneumothorax
  - 0.5-6.0% in different series
  - Usually small and managed conservatively
- Phrenic nerve block
  - 40-60%, usually asymptomatic
- Stellate ganglion block
  - Increased incidence with volume of anaesthetic
  - Up to 90% with 50 ml of solution
  - Horner’s syndrome

Vascular injury
- Local anaesthetic toxicity
Axillary

Anatomy

- Brachial plexus has formed terminal branches in the axilla
- Musculocutaneous lies in coracobrachialis
- Median, ulnar and radial nerves lie in close relation to the axillary artery from superficial to deep
- Fascial septa divide the branches of the plexus at this level

Needle placement

- Patient supine with arm abducted to 90°, externally rotated and flexed 90° at the elbow
- Course of the axillary artery determined by palpation
- Skin wheal and needle insertion adjacent to artery
- Paraesthesia or twitching elicited in appropriate nerves
- Alternatively LA deposited in all quadrants around artery
- Infiltration in mass of coracobrachialis to block musculocutaneous n.

Local anaesthetic

- 20-30 ml of lignocaine or bupivacaine with adrenaline
- Hyaluronidase, bicarbonate for more rapid spread (but less duration)

Indications

- Most reliable from C7-T1
- Best for distal limb surgery (hand or forearm)
- Suitable for indwelling catheter placement

Complications

- Intravascular injection (axillary artery or vein)
- Haematoma and plexus compression
Elbow

Median
Anatomy
Lies medial to brachial a. where it emerges medial to biceps tendon
Needle placement
Arm supinated and extended at the elbow
Plane of epicondyles of humerus identified
Brachial artery palpated
Needle insertion immediately medial to artery
Local anaesthetic
3-5 ml of lignocaine 1% or bupivacaine 0.25%

Radial
Anatomy
Pierces lateral intermuscular septum above the elbow
Lies between brachialis and brachioradialis
Needle placement
Position and level as for median nerve
Point 2 cm lateral to biceps tendon
Local anaesthetic
Fan-like injection of 4-6 ml

Ulnar
Anatomy
Nerve runs behind medial epicondyle
In groove between epicondyle and olecranon
Needle placement
Elbow in full flexion
Epicondyle identified
Needle inserted 1 cm proximal to epicondyle (not in groove)
Local anaesthetic
3-5 ml lignocaine 1% or bupivacaine 0.25%

Medial cutaneous nerve of forearm
Anatomy
Continuation of musculocutaneous nerve
Ramifies superficially over medial forearm
Needle placement
Infiltration in a band across medial forearm one third of the way from elbow to wrist

Indications
Supplementation of brachial plexus block with inadequate cover
Not commonly used alone
Wrist

Median
- **Anatomy**
  - Lies deep to and between FCR and palmaris longus tendons
  - Inside carpal tunnel
- **Needle placement**
  - Line from ulnar styloid to distal tip of radius identified
  - Needle inserted on this line between FCR and palmaris longus
  - Flexor retinaculum penetrated
- **Local anaesthetic**
  - 3-5 ml, plain solution probably advisable

Radial
- **Anatomy**
  - Already divided into terminal branches at the wrist
  - Spread over radial and dorsal aspect of the wrist
- **Needle placement**
  - Infiltration over anatomical snuff-box and further medially
  - Superficial to EPL
- **Local anaesthetic**
  - 5-6 ml

Ulnar
- **Anatomy**
  - Lies lateral to FCU and medial to ulnar a.
  - Has already given off palmar cutaneous and dorsal braches
  - Divides into deep motor and superficial sensory braches at the level of pisiform
- **Needle placement**
  - Approach from anterior or medial aspect just proximal to pisiform
  - Medial approach allows infiltration to all branches from one puncture
- **Local anaesthetic**
  - 3-5 ml plus infiltration

**Indications**
- Supplementation of brachial plexus block with inadequate cover
- Not commonly used alone
Complications of retrobulbar and peribulbar eye blocks

Complications of any block
  Needle
    Local pain
  Drug
    Systemic local anaesthetic toxicity
    Allergy, anaphylaxis
  Technique
    Failure of aseptic technique: cellulitis, ophthalmitis, meningitis
    Failure of block: pain intraoperatively or postoperatively

Complications of eye blocks
  Vessels
    Retrobulbar haemorrhage, retinal vascular occlusion, optic nerve trauma, late optic atrophy
      Variable presentation: arterial vs venous haemorrhage
      More common with large needle insertion in vascular areas e.g. superonasal
      Microvascular disease increases risk of ischaemia e.g. diabetes
      Manage with local pressure, IOP measurement, IOP reduction measures, surgical decompression if necessary
      Haemorrhage within the optic nerve sheath results in rapid ocular venous congestion
      Intravascular injection
        Retrograde flow with rapid injection
        Injection of antibiotics or steroids by the surgeon can also be intravascular, causing embolism
  Nerve
    Optic nerve injection
      Injury to III, IV or VI uncommon
      Other cranial nerve block related to facial nerve block at stylomastoid foramen
        Vagus, glossopharyngeal block
        Swallowing difficulty, respiratory obstruction
    Brainstem anaesthesia
      Associated with long, sharp needles
      Onset over 2 to 20 minutes, lasts up to three hours
      Symptoms highly variable: unconsciousness to isolated nerves or nuclei blocked
      Contralateral eye signs one of the earliest markers
    Atonic pupil
      One case related to ciliary ganglion needle damage
      More commonly direct trauma
      Test with pilocarpine
  Muscle
    Extraocular muscle dysfunction
      Block duration up to 48 h with bupivacaine or ropivacaine
      Longer duration suggests nerve or muscle damage
      Most commonly intramuscular injection which resolves over weeks
      Persistent ptosis
        Common in cataract patients regardless of surgery
        May be intramuscular injection or bridle suture damage
        Extraocular muscle injection may cause muscle rupture and diplopia
Globe

Ocular penetration and perforation
More common in long eyes
High myopes for retinal surgery or radial keratotomy
Prevention
Known axial length, open eye during needle placement, avoiding
displacement of the globe into the path of the needle
Commonly accompanied by pain, retinal detachment, haemorrhage
Corneal injury
Careful attention to padding and taping the anaesthetic eye
Ischaemia related to Honan's balloon or other compression device
Suprachoroidal haemorrhage
Related to hypertension
May be secondary to coughing or full bladder
Sympathetic ophthalmia

Reflex
Oculocardiac reflex
Bradycardia after injection
May persist longer than during surgery
Most common in children and young adults
Treat with atropine or glycopyrrolate
Ear

Anatomy
  Cervical plexus branches greater auricular and lesser occipital supply posterior surface of auricle and lower third of anterior surface
  Greater auricular also supplies posterior part of external canal
  Auriculotemporal branch of mandibular division of trigeminal nerve supplies superior two thirds of anterior surface
  Auriculotemporal also supplies superior part of external canal
  Auricular branch of vagus supplies inferior part of external canal
  Tympanic branch of glossopharyngeal and facial nerve supplies drum

Needle placement
  Superficial cervical plexus block or infiltrate over mastoid for cervical plexus branches
  Infiltrate at posterior aspect of zygoma for auriculotemporal block
  Canal supply from exterior blocked by infiltration at junction of bony and cartilaginous parts
  Drum anaesthetized with topical lignocaine spray 4-10%
Nose

Anatomy

Trigeminal nerve, ophthalmic division (V₁), nasociliary nerve, anterior ethmoidal and external nasal branches to bridge and tip and superior and anterior parts of septum and lateral wall

Trigeminal nerve, maxillary division (V₂), infraorbital nerve, nasal branches to remainder of external nose

V₂ pterygopalatine ganglion, nasopalatine branch to posterior and inferior septum

V₂ anterior superior alveolar branch to anterior and inferior lateral wall

V₂ pterygopalatine ganglion, posterior and inferior nasal branches to posterior and superior lateral wall

V₂ pterygopalatine ganglion, greater palatine nerve to posterior and inferior lateral wall

Needle placement

External nose: supraorbital notch & medially, infraorbital foramen, junction of nasal bone and cartilage all infiltrated

Cavity

Topical or soaked cotton bud applied to anterior ethmoidal by inserting along the line of the external nose until it reaches a superior limit

Same applied to sphenopalatine ganglion by insertion at 20°-30° to horizontal

Floor anaesthetized with topical local
Trigeminal nerve

Ganglion

Anatomy
Ganglion is intracranial in Meckel's cave, a reflection of dura
Closely related to superior orbital fissure, foramen rotundum, and foramen ovale through which branches leave the skull
Foramen ovale is in the horizontal plane of zygoma, vertical plane of mandibular notch, dorsolateral to pterygoid process

Needle placement
Skin wheal at anterior border of masseter, 3 cm lateral to corner of mouth, opposite second upper molar
10 cm needle advanced in plane of the pupil, superiorly, medially and posteriorly
Contact with inferior surface of greater wing of sphenoid at 4.5-6 cm
Walked posteriorly along sphenoid until enters foramen ovale, 1-1.5 cm beyond first bony contact

Local anaesthetic
1-3 ml of any solution injected in small aliquots with aspiration

Indications
Facial neuralgias
Major facial surgery in patient unable to receive GA

Complications
Technically difficult
Subarachnoid injection of LA
Unconsciousness reported with 0.25 ml of 1% lignocaine
Local pain, haematoma formation

Maxillary nerve

Anatomy
Leaves the cranium though the foramen rotundum, deep to the pterygoid plate
Passes through the pterygopalatine fossa
Enters the floor of the orbit through the inferior orbital fissure
Emerges throught the infraorbital foramen

Needle placement
Skin wheal over mandibular notch
8 cm needle inserted superomedially through mandibular notch
 Strikes lateral pterygoid plate at 5 cm depth
Walked off anterior margin of lateral pterygoid plate into pterygopalatine fossa
Inserted 1 cm into pterygopalatine fossa

Local anaesthetic
5 ml of any solution

Indications
Facial neuralgia

Complications
Vascular region of insertion → haematoma formation
Close proximity to infraorbital fissure
Disturbance of eye movement or vision
“Black eye” from haematoma formation

Mandibular nerve

Anatomy
Leaves the cranium through the foramen ovale, posterior to lateral pterygoid plate
Divides into anterior and posterior divisions
Anterior division is motor supply to muscles of mastication, sensory to buccal branch
Posterior division is motor to *** sensory: auriculotemporal, lingual and inferior alveolar nerves

Needle placement
- Skin wheal over mandibular notch
- 8 cm needle inserted superomedially through mandibular notch
- Strikes lateral pterygoid plate at 5 cm depth
- Walked posteriorly off lateral pterygoid plate
- Advanced only 0.5 cm to avoid superior constrictor, pharynx

Local anaesthetic
- 5 ml of any solution

Indications
- Facial neuralgia
- Dental work (usually transmucosal approach)

Complications
- Haematoma
- Injury to the superior constrictor, entering the pharynx
Other head and neck

Greater occipital nerve

Anatomy
- Greater occipital n. is the dorsal ramus of C2
- Emerges over atlas, deep to cervical musculature
- Becomes subcutaneous near superior nuchal line
- Immediately medial to occipital a.
- Supplies sensation to posterior scalp to vertex

Needle placement
- Patient sitting with neck flexed
- Superior nuchal line from occipital protuberance to mastoid
- Nerve lies approximately at medial 1/3 point, near artery
- Infiltration of 3-5 ml around artery

Indications
- Occipital tension headache, diagnostic aid

Complications
- Low risk block
Cervical plexus

Anatomy
- Formed by ventral rami of C1-4
- Direct motor branches to prevertebral muscles
- Cutaneous branches form “superficial” plexus
  - Lesser occipital, greater auricular, transverse cervical and supraclavicular nerves
  - Emerge from behind the midpoint of sternocleidomastoid
- *Ansa cervicalis* innervates infrahyoid and geniohyoid muscles
- Phrenic nerve (C3-5) is central sensory and sole motor supply to diaphragm
  - Emerges lateral to *scalenus anterior* and enters the thorax medial to it
- Contribution to CN XI motor supply to sternocleidomastoid and trapezius

Needle placement
- **Deep**
  - Patient in supine position with head turned away
  - Line drawn 1 cm posterior to line from mastoid to Chassaignac’s tubercle (transverse process of C6)
  - C2 transverse process palpable 1.5 cm inferior to mastoid
  - C3 and C4 transverse processes identified relative to C2 and C6
  - Needles placed on transverse processes of C2-4
    - Withdrawn 1-2 mm off bone
    - Caudal angulation to reduce chance of entering foramina
    - Aspiration to check for vertebral artery puncture
- **Superficial**
  - Short bevelled needle inserted posterior to midpoint of sternocleidomastoid
  - Injection immediately deep to superficial cervical fascia
  - Infiltration along posterior border of sternocleidomastoid superiorly and inferiorly
- **Local anaesthetic**
  - **Deep**
    - 15-20 ml of lignocaine 1.5% or ropivacaine 0.75%
  - **Superficial**
    - 15 ml of lignocaine 1.5% or ropivacaine 0.75%
- **Indications**
  - Carotid endarterectomy, lymph node biopsy, plastic surgery to neck
- **Complications**
  - **Deep**
    - Phrenic nerve block, hypoventilation
    - Vertebral artery injection, convulsions
    - Dural sheath injection, total spinal
  - **Superficial**
    - External or internal jugular vein injection

Stellate ganglion

Anatomy
- Cervical sympathetic trunk is a continuation of the thoracic sympathetics
- Lies anterior to cervical transverse processes
- Composed of three ganglia
  - Superior cervical ganglion opposite C1
  - Middle cervical ganglion opposite C6
  - Stellate ganglion opposite C7-T1
  - Commonly closely related to subclavian and vertebral arteries

Needle placement
- Patient supine with neck extended

Regional

3.H.23

James Mitchell (October 7, 2001)
Chassaignac’s tubercle identified (at level of cricoid cartilage)
Firm palpation medial to carotid artery either side of C6 transverse process
Short needle inserted onto transverse process of C6 directly A-P
Withdrawal 1-2 mm before injection
Local anaesthetic
  5-10 ml of 0.25% bupivacaine with adrenaline
  Frequent aspiration
Indications
  Complex regional pain syndrome of upper limb
  Poor perfusion of upper limb
Complications
  Vertebral artery injection, convulsions
  Blockade of recurrent laryngeal or phrenic nerves
Airway

Principles

Trigeminal
- Nasopharynx down to soft palate
- Maxillary division

Glossopharyngeal
- Soft palate to epiglottis
- Pharyngeal nerves to pharyngeal mucosa
- Tonsillar nerves to tonsils and soft palate
- Posterior third of tongue

Vagus
- Below epiglottis
- Superior laryngeal nerve arises from inferior ganglion of vagus
  - Crosses cornu of hyoid and divides into internal and external laryngeal branches
  - Internal branch penetrated thyrohyoid membrane and innervates mucosa from epiglottis to cords
  - External branch supplies cricothyroid m.
- Vagus gives off recurrent laryngeal nerve below aorta (L) or subclavian a. (R)
  - Penetrates cricothyroid membrane laterally and innervates the mucosa below the cords and muscles of the larynx

Glossopharyngeal nerve

Anatomy
- Exits the skull through the jugular foramen lateral to X, ICA and IJV, anterior to XII and XI
- Descends in the carotid sheath, passes between ICA and ECA before branching
- Branches lie submucosally posterior to tonsil, deep to posterior tonsillar pillar

Needle placement

Intraoral route
- Mouth opened with laryngoscope, topical anaesthesia to tongue and tonsil
- 9 cm curved needle inserted submucosally in caudal part of posterior tonsillar pillar
- Careful aspiration for blood (ICA is adjacent)

Peristyloid route
- Patient supine, head in neutral position
- Line from mastoid to angle of jaw identified
- Skin wheal at midpoint of line, styloid may be palpable
- Short needle inserted medially to contact styloid
- Walked off posterior aspect of styloid
- Careful aspiration of blood (IJV and ICA)

Local anaesthetic
- 5-7 ml of lignocaine 0.5%

Indications
- Awake intubation

Complications
- Intravascular injection, convulsions

Superior laryngeal nerve (internal br.)

Anatomy
- Leaves the vagal trunk above the hyoid
- Crosses the cornu of the hyoid
- Penetrates the thyrohyoid membrane inferior to the hyoid
- Accompanied by superior laryngeal artery and vein
Needle placement
   Patient supine with neck extended
   Hyoid displaced toward side of block
   Skin wheal over greater cornu
   Needle inserted medially to make contact with greater cornu
   Walked inferiorly off cornu and advanced 2-3 mm
      Should lie between thyrohyoid membrane and laryngeal mucosa
Local anaesthetic
   3-4 ml of lignocaine 0.5%
Indications
   Awake intubation
Complications
   Entering the larynx, coughing with injection
   Intravascular injection is uncommon

Translaryngeal block
   Needle placement
      Needle or IV cannula inserted in midline through cricothyroid membrane until
      air is aspirated
Local anaesthetic
   3-4 ml of lignocaine 4% topical solution rapidly injected and needle withdrawn
   before coughing
Recipes for regional anaesthesia

Eye block (Royal Victorian Eye and Ear Hospital)
- lignocaine 10% 2 ml
- bupivacaine 0.5% or ropivacaine 1.0% 7 ml
- hyalase 150 U in 1 ml bupivacaine 0.5% or ropivacaine 1.0%
- oxybuprocaine topical to conjunctiva
  - 30g 12 mm medial canthus 2-3 ml
  - 27g 32 mm inferotemporal 3-4 ml

Bier's
- prilocaine 0.6% 40 ml
- prilocaine 0.5% 0.5 ml/kg (2.5-3.0 mg/kg)
- lignocaine 2-3 mg/kg

Interscalene
- 15-20 ml

Supraclavicular to Axillary
- 30-40 ml

Cervical
- lignocaine 1.5% with adrenaline
- + ropivacaine
- superficial 15 ml
- deep 5-7 ml x 3

Caudal (Royal Children’s Hospital)
- bupivacaine 0.25% 0.5-1 ml/kg
- bupivacaine 0.5% 0.5 ml/kg up to 20ml
- add clonidine 2 µg/kg

Spinal
- LUSCS (Mercy Hospital for Women)
  - bupivacaine 0.5% heavy 2.2 ml (2.2-2.5)
  - fentanyl 15 µg or morphine 100 µg

Manual removal (MHW)
- bupivacaine 0.5% plain 1.2 ml (1.2-2)
- fentanyl 15 µg

Neonatal for hernia repair (RCH)
- bupivacaine 0.5% plain 0.2 ml/kg, min 0.4ml

THJR
- bupivacaine 0.5% plain 3-4 ml
  - D Williams: bupivacaine 0.5% plain 2 ml, midazolam 2 mg, morphine 250 µg

Knee scope, ESWL, other short procedures
- procaine 2% 5 ml

CSE
- Labour (MHW)
  - bupivacaine 0.5% plain 0.5 ml
  - fentanyl 25 µg

Epidural
- Labour (MHW)
  - bupivacaine 0.25% 6-10 ml
  - fentanyl 100 µg
  - plus infusion 0.1% bupivacaine, 2 µg/ml fentanyl 10 ml/h

Labour PCEA (MHW)
- bupivacaine 0.125%, fentanyl 5 µg/ml 15 ml + 5 ml if inadequate at 15 min
- bupivacaine 0.625%, fentanyl 2 µg/ml 5 ml bolus, 10 min lockout

LUSCS (MHW)
- lignocaine 2% up to 20ml
- fentanyl 100 µg or pethidine 50 mg or morphine 3-4 mg

Paediatric (RCH)
bupivacaine 0.125% = 0.25 ml/kg/h
± fentanyl or clonidine 2 µg/ml
Initial Assessment and Management

Airway and Ventilatory Management

Shock

Thoracic Trauma

Abdominal Trauma

Head Trauma

Spine and Spinal Cord Trauma

Musculoskeletal Trauma

Injures Due To Burns And Cold

Paediatric Trauma

Trauma in Women

Transfer to Definitive Care
Initial Assessment and Management

Preparation

Pre-hospital

Minimize scene time

Priorities

Airway maintenance
Control external bleeding and shock
Immobilization
Immediate transport to the closest appropriate facility
Obtain information for hand over

Criteria for transfer to trauma centre

GCS <14, RR <10 or >29, systolic <90 mmHg, RTS <11, PTS <9
Flail chest, >2 proximal long bone fractures, amputation proximal
to wrist or ankle, penetrating trauma proximal to elbow or knee,
limb paralysis, pelvic fracture, trauma with burns

Consider trauma centre for

Ejection from car, death in same compartment, pedestrian thrown
or run over, high speed crash, extrication time >20 min, fall >6 m,
roll over, pedestrian struck at >8 km/h, motorcycle crash at
>32 km/h or with separation of bike and rider
Age <5 or >55, pregnancy, immunosuppression, cardiac or
respiratory disease, diabetes, cirrhosis, morbid obesity,
coagulopathy

In hospital

Resuscitation area
Airway equipment, warm IV solutions, monitoring
Means to summon medical help, means to summon diagnostic
services
Transfer agreement with trauma centre
Universal precautions to be observed

Triage

Revised Trauma Score

Respiratory rate

>29 4
10-29 3
6-9 2
1-5 1
0 0

Systolic BP

>89 4
76-89 3
50-75 2
1-49 1
0 0

GCS

13-15 4
9-12 3
6-8 2
4-5 1
<4 0
Paediatric Trauma Score

Weight
<20 kg 2
10-20 kg 1
<10 kg -1

Airway
Normal 2
O₂ 1
Intubated -1

Systolic BP
>90 2
50-90 1
<50 -1

Consciousness
Awake 2
Any LOC 1
Coma -1

Fracture
None 2
Single closed 1
More / open -1

Skin
Intact 2
Lac. <7 cm 1
More -1

Score >8 should have zero mortality.

Priorities
Multiple casualties are treated in order of severity.
Mass casualties (exceeding capacity of available facilities) are treated in order of probability of survival with least expenditure of resources.

Primary Survey
Examination and management take place simultaneously

Airway maintenance with cervical spine protection
Assess patency of the airway: fractures, foreign bodies
Establish a patent airway
Definitive airway is usually required if GCS ≤ 8
Cervical spine must be immobilized in any multi-system trauma
Deterioration of conscious state may demand reassessment of airway

Breathing and ventilation
Requires function of lungs, chest wall and diaphragm
Examine the chest for acute causes of impaired ventilation
   Tension pneumothorax, open pneumothorax, flail chest with pulmonary contusion, massive haemothorax
Intubation may worsen pneumothorax
Chest x-ray is required as soon after intubation as practical
Circulation and haemorrhage control
- Haemorrhage is the commonest cause of post-injury death treatable in hospital
- Volume status is assessed by conscious state, skin colour and pulse rate and strength
- Hypotension is caused by hypovolaemia until proved otherwise
- Bleeding is controlled by local pressure
- Occult haemorrhage occurs into the chest or abdomen, retroperitoneum following pelvic fracture or soft tissues following long bone fracture
- Blood pressure is not a good indicator of volume status

Disability (neurologic evaluation)
- Rapid assessment of GCS or AVPU status
- Impaired consciousness after correction of hypoxia and hypovolaemia is usually due to CNS trauma
- Drugs may confuse examination findings
- Frequent reassessment is required

Exposure and environmental control
- Complete exposure is required for examination
- Prevention of hypothermia is required, using warming blankets, warmed IV fluids and early control of haemorrhage

Resuscitation
Airway
- Definitive airway if there is doubt about the patient’s ability to maintain an airway
- Application of a hard collar for cervical spine immobilization
Breathing and ventilation
- All patients should receive supplemental oxygen
Circulation
- Two large IVs should be inserted
- Blood taken for crossmatch, baseline bloods and pregnancy test
- IV fluid administration, initially warmed Hartmann’s 2-3 l
- Hypovolaemic shock is treated with operative intervention to stop bleeding and continued fluid resuscitation, not pressors, steroids or bicarbonate

Adjuncts to primary survey and resuscitation
ECG monitoring
- Signs of cardiac injury, pulseless electrical activity, hypoxia or hypoperfusion
Urinary and gastric catheters
- Urine output provides an indication of volume status
- Catheter should not be inserted if the urethra might be injured
  - Blood at meatus, perineal ecchymoses, blood in scrotum, high riding prostate, pelvic fracture
- Gastric catheter reduces the risk of regurgitation and aspiration, but does not eliminate it
- Nasogastric insertion is contraindicated if the cribriform plate might be disrupted
Other monitoring
- Ventilatory rate and ABGs
- CO₂ confirmation of ETT placement
- Pulse oximetry
- Blood pressure
Diagnostic studies
CXR and pelvis x-ray can guide resuscitation but must not cause delay
Lateral cervical spine x-ray is useful if it shows an injury
Further tests during secondary survey
Consider need for transfer
However life saving interventions should start at the time the problem is identified
Secondary survey
Begins when resuscitation is underway and vital signs are normalizing
History
Allergies, medications, past illnesses or pregnancy, last meal, events related to the injury (mnemonic: AMPLE)
Physical examination
Head
Complete examination for soft tissue or bony injury
Eye examination for acuity, pupils, hyphaema, penetrating injury, contact lenses, lens dislocation, muscle entrapment
Facial bones for fractures
Cervical spine and neck
Head or face injury implies cervical spine injury until it is excluded
Penetrating injuries should be explored in theatre
Cervical spine injury should be excluded as soon as convenient and hard collar removed
Chest
Inspection and palpation of the entire thorax
Auscultation for heart sounds and breath sounds
Bony or soft tissue injury makes visceral injury likely
Children have a more compliant chest wall which may hide deeper injuries
Abdomen
Specific diagnosis is not as important as recognizing that an injury exists
Repeat examination for changing signs may be necessary
If injury is suspected
Ultrasound or lavage
CT if stable
Perineum
Inspection, PR, PV, urinary catheter
Musculoskeletal
Limbs must be inspected and palpated
Pelvis integrity should be assessed
The back must be examined
Soft tissue injury may be difficult to detect in an unconscious patient
Neurological
Assess conscious state (and reassess)
Examine for peripheral signs of nerve or cord injury
Prevent abrupt rises in ICP in head-injured patients
Specialized diagnostic tests (as indicated)

X-rays
  CXR, pelvis, cervical spine, thoracolumbar spine, sites of injury

CT
  Head (±MRI), chest, abdomen, spine

Contrast studies
  Urography, angiography

Ultrasound
  Abdomen, gynaecological, transoesophageal

Endoscopy
  Bronchoscopy, gastroscopy

Tests requiring transport demand a stable patient

Reevaluation

  Continuous monitoring of vital signs
    ECG, BP, SpO₂, conscious state, urinary output, ABG, E₄CO₂

Analgesia

Definitive care

  Surgical intervention
  Transfer to an appropriate facility

Documentation

  Essential for continuity of medical care and evidence in case of medicolegal problems
  A dedicated record-taker is needed in the resuscitation setting
  Consent should be obtained before procedures if possible
  If criminal involvement is likely, evidence must be preserved
Airway and Ventilatory Management

Airway
Problems
Maxillofacial trauma, neck trauma, laryngeal trauma
Signs
Talking patient: airway is patent and not compromised
Agitation, obtundation, cyanosis, rib retraction, accessory muscle use
Noisy breathing, stridor, hoarseness, confusion (hypoxia)
Palpable larynx and trachea

Ventilation
Problems
Airway patency, chest and lung integrity, innervation, CNS function
Signs
Chest movement
Breath sounds
Oximetry

Management
All require protection of cervical spine if injury is suspected
Airway maintenance
Chin lift, jaw thrust, Guedel airway, nasopharyngeal airway
Definitive airway
“A tube present in the trachea with the cuff inflated, the tube connected
to some form of oxygen-enriched assisted ventilation, and the airway
secured in place with tape.”
Orotracheal, nasotracheal, surgical options
Indications
Apnoea, inability to maintain a patent airway, protection from
aspiration, impending or potential airway compromise, closed head
injury (GCS ≤8), inadequate oxygenation with face mask
ventilation
Intubation
Method depends on practitioner’s experience, usually orotracheal
Cervical immobilization, preoxygenation, cricoid pressure, drugs (if
required), laryngoscopy, ETT placement, auscultation, CO₂ analysis, CXR
Nasotracheal intubation is only used in spontaneously breathing patient
Induction agents typically suxamethonium and benzo.
Surgical Airway
Needle cricothyroidotomy
12g or 14g cannula inserted through cricothyroid membrane
Intermittent jet O₂ insufflation (1 s on 4 s off)
Contraindicated in glottic obstruction (→ barotrauma)
Provides 30-45 minutes oxygenation (limited by PCO₂)
Surgical cricothyroidotomy
Palpate thyroid notch and sternal notch, find cricothyroid
Local anaesthetic if required, prepare skin
Stabilize trachea with one hand, transverse incision through skin
and cricothyroid membrane
Insert scalpel handle or artery and dilate opening
Insert cuffed tube (5-6 mm), inflate cuff and check ventilation
Secure tube
Oxygenation
All patients require supplemental oxygen
Oximetry should be used where available
unreliable with poor peripheral perfusion, anaemia, abnormal Hb

Ventilation
Bag-valve-mask is best performed with two operators
Ventilation is required during prolonged attempts at intubation
Pressure-limited ventilation is required post-intubation
Shock

Assessment
Signs
- Peripheral vasoconstriction, tachycardia, narrowed pulse pressure
- Hypotension is a late sign (>30% volume loss)
- Haemoglobin is not a measure of volume status

Causes
- Haemorrhagic
  - Present in most patients with multiple injuries, responds to filling
- Non-haemorrhagic
  - Cardiogenic, tension pneumothorax, neurogenic, septic

Haemorrhagic shock
- Haemorrhage is the acute loss of circulating blood volume
- Normal blood volume is 70 ml/kg in adults (80-90 ml/kg in children)

Classification
- Class I
  - Loss up to 15% of blood volume
  - Usually fully compensated
  - Recovers by transcapillary refill within 24 hours
- Class II
  - 15%-30% blood volume lost
  - Tachycardia, tachypnoea, reduced pulse pressure, anxiety
  - Urine output 20-30 ml/h
  - Responsive to crystalloid filling
- Class III
  - 30%-40% blood volume lost
  - Marked tachycardia, tachypnoea, hypotension, mental changes
  - Urine output low 5-15 ml/h
  - Will require transfusion
- Class IV
  - More than 40% blood volume lost
  - Immediately life-threatening
  - Minimal urine output
  - Requires immediate transfusion and usually surgery

Soft-tissue haematoma may consume litres of blood.

Management

Examination
- ABCDE
- Gastric decompression
- Urinary catheter insertion

Vascular access
- Large peripheral IVs initially (16g or 14g short)
- Cut-down if required depending on level of experience
- Intraosseous infusion if under 6 years and no other access
- CVC insertion is not the best choice for rapid infusion
- Blood taken for crossmatch, investigations including ßhCG, ABG

Initial fluid therapy
- 20 ml/kg Hartmann's as a bolus
- Further therapy guided by response to initial bolus and on-going losses

Response
- Urine output, conscious state, peripheral perfusion, CVP
Evaluation of resuscitation

Normalization or improvement of HR, BP and pulse pressure
Urine output >0.5 ml/kg/h (1 ml/kg/h in children, 2 ml/kg/h in infants)
CVP or PAOP or CO (if PA catheter inserted)
ABG
  Initial respiratory alkalosis followed by metabolic acidosis
  Persistent metabolic acidosis if peripheral perfusion is inadequate

Response to initial therapy

Rapid response
  Haemodynamic normalization with bolus fluid

Transient response
  Deterioration following initial response to bolus fluid indicates
  inadequate resuscitation or ongoing losses
  Likely requirement for transfusion and surgery

Minimal or no response
  Likely exsanguinating haemorrhage requiring surgery, or
  Non-haemorrhagic cause for shock
  Differentiate using CVP or echocardiography

Choice of fluid

Blood
  Usually packed cells
  Used to replace oxygen carrying capacity
  Not the first choice for volume replacement
  Type-specific or O negative can be used in extreme urgency
  Component therapy for coagulopathy as indicated by pathology tests

Crystalloids
  Hartmann’s or normal saline
  Heated to 39°C

Special considerations

Use of vasopressors is contraindicated in haemorrhagic shock
  ↑ SVR, ↓ CO → “death spiral”

Elderly have reduced physiological reserve
Tachycardia may be a poor sign if on β-blockers or pacemaker or in athletes
Hypothermia may prevent a response to fluid
Always suspect ongoing haemorrhage if response is poor
Under-resuscitation is far more common than fluid overload
CVP can guide fluid therapy
Thoracic Trauma

Primary Survey

Airway
Assess air movement at nose and mouth, inspect oropharynx, observe for intercostal retraction
Laryngeal injury or posterior dislocation of sternoclavicular joint can obstruct the airway

Breathing
Expose chest, observe, palpate and auscultate
Tension pneumothorax
Decompress with large Jelco in second intercostal space in midclavicular line followed by chest tube in the fifth intercostal space between the midaxillary and anterior axillary lines
Open pneumothorax
Flap-valve dressing, surgical closure and chest tube

Flail chest
Underlying pulmonary contusion is usually the major concern
Administer oxygen, limit IV fluids unless shock is present, analgesia
May require intubation and ventilation

Circulation
Assess pulse, blood pressure, JVP
Monitor ECG and SpO₂
Massive haemothorax
Rapid accumulation of more than 1500 ml in the chest cavity, usually manifest as shock with absent breath sounds and dullness on one side of the chest
Rapid IV fluid administration, decompression with a chest tube, thoracotomy likely if >1500 ml or >200 ml/h evacuated or persistent transfusion requirement or penetrating injury medial to nipple or scapula
Cardiac tamponade
15-20 ml in pericardial space is enough to cause haemodynamic compromise
Difficult to diagnose acutely, echocardiography may help
IV fluid may produce transient improvement
Pericardiocentesis may be performed without definitive diagnosis
Open pericardiectomy may be required to evacuate clot and inspect the heart

Resuscitative thoracotomy
May be helpful in penetrating chest injury with pulseless electrical activity
Only performed by an appropriate surgeon

Secondary survey
Further examination
Upright CXR, ABG, SpO₂, ECG
Simple pneumothorax
Decreased breath sounds, resonant percussion
Chest tube inserted in fifth intercostal space, underwater seal drain,
CXR to confirm lung re-expansion all required before IPPV or air transport.
Haemothorax
Usually due to laceration of intercostal or internal thoracic arteries, bleeding is usually self-limiting
Chest tube allows drainage of blood and monitoring ongoing loss
Thoracotomy for severe bleeding

Pulmonary contusion
Most common potentially lethal chest injury, gradual respiratory failure
\[ P_{O_2} > 65 \text{ mmHg or } SpO_2 < 90\% \] demands intubation and ventilation
Repeated assessment of ABG, ECG and SpO\(_2\)

Tracheobronchial tree injuries
Most injuries are within 2.5 cm of the carina and cause death at the scene
Haemoptysis, subcutaneous emphysema or tension pneumothorax
Large air leak after chest tube insertion, two chest tubes may be required
Diagnosis confirmed at bronchoscopy, may require double lumen tube, may require urgent surgical repair

Blunt cardiac injury
Pain, hypotension with ↑ CVP, wall motion abnormality, conduction abnormalities (PVCs, ST, AF, RBBB, ST∆)
Treatment of arrhythmia as indicated, ECG monitoring

Traumatic aortic disruption
Common cause of death after severe deceleration injury
Survivors to hospital have contained haematoma
Signs on CXR: widened mediastinum, obliterated aortic knob, tracheal deviation to right, no space between aorta and PA, depressed left main bronchus, deviation of oesophagus to right, widened paratracheal stripe, widened paraspinal interfaces, apical cap, left haemothorax, fractures of first or second rib or scapula
Diagnosed at angiography or TOE

Traumatic diaphragmatic injury
Commonly missed, may be diagnosed on CXR with NGT or contrast, or by drainage from chest tube of DPL fluid, or at thoracoscopy or laparotomy
Treated by direct repair

Mediastinal traversing wounds
Penetrating injury crossing from one hemithorax to the other or with metallic fragment lodged in the mediastinum
50% unstable, 20% mortality
Early surgical consultation
Injury to great vessels, tracheobronchial tree, oesophagus, heart, spinal cord and lung must be considered
Chest tubes may be required bilaterally, early operation if unstable
Stable patients require angiography, contrast swallow, gastroscopy, bronchoscopy, CT or echocardiography

Associated problems
Subcutaneous emphysema
Crush injury
Rib, sternum and scapula fractures
Rib 1-3 protected by upper limb; fracture suggests great vessel injury
Rib 4-9 most commonly injured, require greater force in the young
Rib 10-12 fracture suggest hepatic or splenic injury
Analgesia is required for good ventilation

Trauma & Resuscitation 3.J.1.12 James Mitchell (October 7, 2001)
Blunt oesophageal rupture
Due to forced expulsion of gastric contents with oesophageal tearing or instrumentation
May present as left pneumothorax without rib fracture, particulate matter in chest tube
Required operative repair to prevent mediastinitis and sepsis

CXR examination
Confirm ID of film
Trachea and bronchi
Interstitial or pleural air, pneumomediastinum, pneumothorax, subcutaneous or interstitial emphysema, pneumoperitoneum
Pleural space and lung parenchyma
Lung infiltrate, consolidation or haemothorax
Mediastinum
Altered cardiac silhouette, signs of aortic rupture (above)
Diaphragm
Elevation, disruption, obscured, mass above or air below
Bony thorax
Clavicle, scapula, ribs, sternum fractures or dislocation
Soft tissues
Tubes and lines
Abdominal Trauma

Assessment

History
- Mechanism of injury: e.g. vehicle crash, speed, direction, position in car etc. or weapon and range in penetrating trauma
- Location of pain and referral of pain

Examination
- Inspection
  - Including posterior abdomen and chest and perineum
- Auscultation, percussion
- Palpation
  - Guarding, pregnancy
- Evaluation and local exploration of penetrating wounds
  - Dependent on surgical experience
  - 25%-33% of anterior stab wounds do not penetrate peritoneum
- Assess pelvic stability
- Perineal, penile/vaginal and rectal examination
  - Signs of pelvic fracture or urethral injury
- Gluteal examination

Intubation
- Insertion of NGT, urethral catheter (if no indication of injury)

Blood and urine sampling

Imaging
- Screening x-rays: cervical spine, CXR, pelvis
- Supine and erect AXR (lateral decubitus if can’t be sat up)
- Contrast studies
  - Urethrography, cystography if injury suspected
  - IVP only if contrast CT unavailable
  - GI contrast studies if injury suspected and patient stable

Special investigation
- Diagnostic peritoneal lavage
  - 98% sensitive for intraperitoneal bleeding
- Indications
  - Haemodynamically abnormal, multiple blunt injuries
  - Altered conscious state
  - Spinal cord injury
  - Equivocal abdominal examination
  - Prolonged “loss of contact” with abdomen expected (e.g. CT)
  - CT or US not available
- Relative contraindications
  - Previous surgery, morbid obesity, cirrhosis, coagulopathy
- Lavage catheter inserted and aspirated
  - If no aspirate, 1000 ml Hartmann’s used for lavage
  - Positive if ≥100,000 RBC/mm³, ≥500WBC/mm³ or gram stain +ve
- Ultrasound
  - As good as DPL or CT in experienced hands
  - Gives views of pericardium, hepatorenal fossa, splenorenal fossa, pelvis
  - Repeat scan at 30 minutes to detect slow bleeding
- Computed tomography
  - Time-consuming, only for stable patients
  - Most specific test for injury
  - Will miss some diaphragmatic, bowel and pancreas injuries
Special investigation in penetrating trauma
  Lower chest wounds
    Serial examination and imaging, laparoscopy, thoracoscopy
  Anterior abdominal stab wounds
    Serial examination or DPL help to detect asymptomatic penetration of peritoneum
  Back or flank stab wounds
    Serial examination or contrast CT or DPL plus follow up beyond 24 hours if asymptomatic

Indications for laparotomy
  Blunt trauma with
    Positive DPL or ultrasound
    Hypotension despite resuscitation
  Peritonitis
  Penetrating trauma with
    Hypotension
    Bleeding from GI or urogenital tract
    Gunshot wounds
  Evisceration
    AXR with free air, diaphragmatic defect or retroperitoneal air
    CT with ruptured viscus, injury to bladder, renal pedicle or other viscus

Pelvic fractures
  Classification
    Anteroposterior compression injury
      Commonly sacral fracture or dislocation
      Haemorrhage from posterior venous or internal iliac vessels
    Lateral compression injury
      Pubis commonly injures bladder or urethra
      Haemorrhage less common
    High energy shear force injury
      Disrupts sacrospinous and sacrotuberous ligaments
      Major instability
  Assessment
    Inspection for bruising, lacerations, urethral injury, PR
    Manual test of mechanical stability
    X-ray
  Management
    Exsanguination
      ABCDE, PASG, operate if open or DPL positive, post-op fixation
      Angiography if unstable and DPL negative
    Stable following resuscitation and unstable fracture
      ABCDE, PASG, operate if DPL positive, post-op fixation,
      angiography if still unstable
    Normal BP
      ABCDE, PASG if hypotension develops, treat other injuries, fix
  DPL technique
    Urinary catheter, NGT
    Prep, local below umbilicus
    Vertical incision to fascia, peritoneal incision (alternatively Seldinger tech.)
    Insert catheter, advance into pelvis
    Aspirate, irrigate, agitate, drain after 5-10 min
    Send sample for RBC, WBC counts and gram stain
Head Trauma

Classification
Mechanism: blunt or penetrating (dura)
Severity: by GCS: severe 3-8, moderate 9-13, mild 14-15

Morphology
Usually determined at CT scan
Skull fractures
Vault: linear or stellate, open or closed, depressed or not
Basilar: with or without CSF leak, VII nerve palsy

Intracranial lesions
Focal
Extradural haematoma
9% of comatose head injuries
Lenticular lesion, usually arterial
Subdural haematoma
30% of severe head injuries
Cover entire hemisphere, usually venous
Intracerebral haematoma or contusions
Usually frontal and temporal and associated with subdural

Diffuse “concussion”
Mild, classical and diffuse axonal injury

Management
Mild
80% of head-injury presentations
All require CT scan if any LOC, amnesia or headache
Skull x-rays only for penetrating injury
Usual cervical spine x-rays, blood tests etc.
Avoid narcotics
12 hours of observation (can be at home) even if normal CT
Discharged only if asymptomatic, uninjured, living nearby and in the company of a responsible adult

Moderate
10% of head-injury presentations
10 - 20% will deteriorate

History
Examination
Investigations
CT head (40% abnormal), baseline bloods
Surgery if indicated (8% on CT scan)
Admission for observation
Repeated examination and CT if any deterioration
Severe

10% of head-injury presentations

ABCDE

Hypotension and hypoxia are associated with 75% mortality

Require rapid resuscitation

- Early intubation, moderate hyperventilation (PCO₂ 25-35 mmHg)
- Maintenance of cerebral perfusion pressure
- Management of other injuries as indicated
- Priority of CT versus DPL/US depends on response to fluid resuscitation: poor response → DPL/US first

High incidence of other injuries

- Long bone or pelvic fracture 32%
- Mandible or maxillary fracture 22%
- Major chest injury 23%
- Thus detailed secondary survey

Neurologic examination

- GCS and pupils at least prior to relaxation
- Serial examinations over time, recording best responses on each side

Diagnostic procedures

- Emergency CT scan unless precluded by instability
- Looking for lesions and midline shift

Medical management of head injury

36% mortality for severe head injury

- IV fluids: maintain euvolaemia with saline or Hartmann’s (not glucose)
- Maintain perfusion pressure ≥70 mmHg
- Moderate hyperventilation: PCO₂ 25-35 mmHg
- Mannitol for oedema if normotensive
- Frusemide and anticonvulsants with surgical consultation
- Steroids and barbiturates probably not beneficial

Surgical management

- Scalp laceration without underlying fracture
  - Closed after shaving and irrigation
- Depressed fracture
  - Elevated surgically if depressed more than the skull thickness
- Mass lesions
  - Transfer to neurosurgical unit
  - Emergency burr holes by a non-specialist are rarely justified
Spine and Spinal Cord Trauma

Epidemiology
450 spinal injuries per year in Australia, 2% mortality

Level of injury
- C4-7 48%
- T3-6 13%
- T10-12 18%
- other 21%

Classification of injury

Level
The most caudal segment with normal sensory and motor function

Dermatomes
- C5 deltoid
- C6 wrist extension
- C7 elbow extension
- C8 middle finger flexion
- T1 finger abduction
- L2 Hip flexion
- L3 Knee extension
- L4 Ankle dorsiflexion
- L5 Toe extension
- S1 Ankle plantar flexion

Differs from bony level of injury

Severity
- Complete, incomplete

Cord syndromes

Central cord
- Anterior spinal artery compromise
- Usually cervical extension injury
- Upper limb weakness > lower limb

Anterior cord
- Anterior spinal artery infarction
- Pain and temperature sensation loss, paraplegia
- Intact vibration, proprioception

Brown-Sequard
- Cord hemisection
- Ipsilateral motor and vibration/proprioception loss
- Contralateral pain and temperature loss two segments lower

Morphology
- Fracture, fracture dislocation, SCIWORA, penetrating injury
- Stable or unstable (all assumed to be unstable)

X-ray evaluation

Cervical spine
- Must see BOS to T1
- May require lateral and swimmer's views: 85% sensitivity for fractures
- Addition of AP and open-mouth views: 92% sensitivity
- Addition of oblique views: slight ↑ in sensitivity
- CT scan if unable to see low vertebrae or injury suspected
- 10% of cervical spine fractures have a second vertebral fracture
- To detect spinal cord compression: MRI or CT myelography

Thoracic and lumbar spine
- AP views routine
- Lateral or CT if injury suspected
Management

Rules for cervical spine

Paraplegia or quadriplegia suggests cervical instability.
Alert, normal and pain-free patients can be cleared if full-range voluntary movement is pain-free.
Alert, normal patients in pain need lateral, AP and open-mouth films. If a flexion lateral film is also of good quality and clear there is no need for CT.
Unconscious or confused or uncommunicative patients require AP, lateral and, if possible, open-mouth films before assessment by a surgeon before being cleared.
If there is doubt, the collar should be left on.
Neurosurgical or orthopaedic referral is required for all suspected injuries.
Paralyzed patients should be removed from a backboard as soon as practicable.
Never force the neck.
If operation is required prior to clearing the neck, the collar should be left on.
Assess the cervical spine x-rays for

- Bony deformity
- Fracture of the vertebral body or processes
- Loss of alignment
- Increased distance between spinous processes
- Narrowing of the canal
- Increased prevertebral soft-tissue shadow

Immobilization

A semirigid collar does not ensure immobilization.
A collar, backboard, tape and straps should be applied before definitive transfer.
Sedation, paralysis and intubation may be required to maintain immobilization.
Two-handed technique for cricoid may reduce cervical spine movement

Steroids

Not used in Australia for spinal cord injury
Musculoskeletal Trauma

Primary survey
- Occur in 85% of trauma patients
- Major importance in primary survey is haemorrhage
  - Control with local pressure
- Fracture immobilization
  - Aim to reduce fracture, minimize pain and bleeding
  - Not more important than ABCDE
- X-rays
  - Obtained when convenient
  - AP pelvis is indicated early in multi-trauma

Secondary survey
- History
  - Detail of mechanism of injury: time, force...
  - Environment: temperature, poison, fragments, contamination
  - Preinjury status: AMPLE...
  - Prehospital observations
- Physical examination
  - Complete exposure
  - Detection of life-threatening, limb-threatening and other injuries
  - Systematic examination: skin, neuromuscular, circulation, skeletal and ligamentous
    - Look, feel, pulses/circulation, x-ray
- Potentially life-threatening extremity injuries
  - Major pelvic disruption with haemorrhage
    - Falls, motorcycle or pedestrian accidents are associated with ring-opening injuries: sacroiliac disruption and major haemorrhage
    - Motorcar accidents are associated with lateral force injuries with genitourinary injury and less incidence of haemorrhage
  - Signs
    - Progressive swelling or bruising
    - Failure to respond to fluid resuscitation
    - Signs of urethral injury
    - Mechanical instability
    - X-ray findings
  - Management
    - Haemorrhage control with immobilization ± PASG
    - Rapid fluid resuscitation
    - Early surgical consultation
  - Major arterial haemorrhage
    - Penetrating or blunt injury with fracture or dislocation
    - Signs of ischaemia or haematoma
  - Management
    - Direct pressure
    - Fluid resuscitation
    - Surgical consultation
  - Crush syndrome
    - Prolonged crush injury to muscle causes rhabdomyolysis
    - Signs: dark urine, hypovolaemia, acidosis, hyperkalaemia, hypocalcaemia, DIC
    - Management fluid loading, osmotic diuresis, urinary alkalinization
Limb-threatening injuries

Open fractures and joint injuries
- Communication between external environment and bone
- Management sterile dressing, examination of soft-tissue, circulatory and neurological involvement, surgical consultation
- Tetanus prophylaxis

Vascular injuries, traumatic amputation
- Suggested by circulatory insufficiency associated with limb trauma
- May result from circumferential dressings or casts
- Urgent surgical revascularization
- Replantation is indicated only in isolated limb injuries, not in patients requiring intensive resuscitation
  - Amputated part is washed in Hartmann’s, wrapped in penicillin-soaked gauze and transported on crushed ice

Compartment syndrome
- Caused by injury within a closed fascial space or external compression
- Compartment pressure exceeds perfusion pressure
- High risk: tibial and forearm fractures, tight dressings or casts, severe crush injuries, interstitial oedema due to reperfusion, increased capillary permeability or exercise

Signs
- Unexpectedly severe pain, worse with stretching
- Dysfunction of nerves in the compartment
- Tense swelling
- Weakness and loss of pulses are late signs
- Compartment pressure >35-45 mmHg

Management
- Removal of dressings or casts
- Fasciotomy if no improvement over 30-60 min.

Neurologic injury secondary to fracture dislocation
- Assessment of nerve function requires a cooperative patient
- Documentation of progression of disability and repeat examination is important, especially after reduction manoeuvres (table below)

Other extremity injuries

Contusions and lacerations
- Examine for associated injury
- Superficial injury from crushing or degloving may be minor
- Tetanus risk increased: >6 h old, abraded, >1 cm deep, due to burn, cold or missile, contaminated

Joint injuries
- May not be associated with fractures
- Hyperextension or hyperflexion soft tissue injury
- Examine for associated nerve or vessel damage
- Immobilize

Fractures
- Usually associated with soft tissue injury
- Clinical examination to make diagnosis, accompanied by x-rays in two planes
- Joint above the injury must also be x-rayed
- Examine for associated nerve or vessel injury
- Immobilize
<table>
<thead>
<tr>
<th>Nerve</th>
<th>Motor</th>
<th>Sensation</th>
<th>Injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ulnar</td>
<td>Index finger abduction</td>
<td>Little finger</td>
<td>Elbow injury</td>
</tr>
<tr>
<td>Median (distal)</td>
<td>Thenar opposition</td>
<td>Index finger</td>
<td>Wrist dislocation</td>
</tr>
<tr>
<td>Median (anterior interosseous)</td>
<td>Index tip flexion</td>
<td></td>
<td>Supracondylar fracture of humerus</td>
</tr>
<tr>
<td>Musculocutaneous</td>
<td>Elbow flexion</td>
<td>Lateral forearm</td>
<td>Anterior shoulder dislocation</td>
</tr>
<tr>
<td>Radial</td>
<td>Thumb, finger MCP extension</td>
<td>1st dorsal web space</td>
<td>Distal humeral shaft, anterior shoulder dislocation</td>
</tr>
<tr>
<td>Axillary</td>
<td>Deltoid</td>
<td>Lateral shoulder</td>
<td>Anterior shoulder dislocation, proximal humerus fracture</td>
</tr>
<tr>
<td>Femoral</td>
<td>Knee extension</td>
<td>Anterior knee</td>
<td>Pubic rami fractures</td>
</tr>
<tr>
<td>Obturator</td>
<td>Hip adduction</td>
<td>Medial thigh</td>
<td>Obturator ring fractures</td>
</tr>
<tr>
<td>Posterior tibial</td>
<td>Toe flexion</td>
<td>Sole of foot</td>
<td>Knee dislocation</td>
</tr>
<tr>
<td>Superficial peroneal</td>
<td>Ankle eversion</td>
<td>Lateral dorsum of foot</td>
<td>Fibular neck fracture, knee dislocation</td>
</tr>
<tr>
<td>Deep peroneal</td>
<td>Ankle/toe dorsiflexion</td>
<td>Dorsal 1st to 2nd web space</td>
<td>Fibular neck fracture, compartment syndrome</td>
</tr>
<tr>
<td>Sciatic</td>
<td>Plantar flexion</td>
<td>Foot</td>
<td>Posterior hip dislocation</td>
</tr>
<tr>
<td>Superior gluteal</td>
<td>Hip adduction</td>
<td></td>
<td>Acetabular fracture</td>
</tr>
<tr>
<td>Inferior gluteal</td>
<td>Gluteus maximus hip extension</td>
<td></td>
<td>Acetabular fracture</td>
</tr>
</tbody>
</table>

**Physical Examination**

**Look**
- Age, sex
- Wounds, deformity, position
- Colour of extremities
- Spontaneous activity: evidence of pain or paraplegia
- Urine colour

**Feel**
- Palpate pelvis for instability
- Peripheral pulses and capillary refill
- Muscle compartment palpation
- Joint stability
- Neurological examination: sensory and motor
Injures Due To Burns And Cold

Immediate management

ABCDE

Airway
Immediate intubation if inhalational injury likely
Facial burns, eyebrows or nasal hair singed, acute inflammation or carbon deposits in mouth, carbonaceous sputum, history of confinement in burning environment, explosion with burns to head or torso, COHb > 10%

Stop the burning process
Remove all clothing, chemical residue
Rinse with water

Intravenous access
Required if burns > 20% of BSA
Large bore, upper limb preferable, unburned area preferable

Assessment

History
AMPLE history, tetanus status

Examination

Area burned
“Rule of nines” for adults, modified for children
Adult: head, arm, half of leg, quarter of torso = 9%
Infant: head = 18%, half of leg = 7%
Palm excluding fingers = 1%

Depth of burn
First degree
Erythema, pain, no blisters e.g. sunburn
Second degree, partial thickness
Red or mottled, blisters, weeping, hypersensitive
Third degree, full thickness
Dark and leathery, painless, dry

“Major” burns
>10% full thickness or >25% partial or inhalational injury

Stabilization

Airway
Early intubation if any suggestion of inhalational injury

Breathing
Injury mechanisms
Thermal injury
Upper airway oedema, obstruction
Inhalation of smoke and toxins
Tracheobronchitis, oedema, pneumonia
CO poisoning
< 20% COHb asymptomatic
20-30% headache and nausea
30-40% confusion
40-60% coma
> 60% death
Treat with high FiO2 (hyperbaric if pregnant)

Circulation
IV access and IDC required for management
Aim for urine output 1 ml/kg/h in children, 30-50 ml/h in adults
Initial fluids
Hartmann’s 2-4 ml/kg/%burn over 24 h
Half given in 8 hours, half in next 16
Plus acute losses and fasting requirements
Adjust according to urine output, vital signs

Examination
Document extent and depth of burns
Assess for associated injuries
Weigh patient

Investigations
FBE, XM, ABG (COHb), glucose, U&E, βhCG if indicated

Adjuncts to initial management
Assessment of limbs with circumferential injury for circulatory compromise, escharotomy if necessary
NGT insertion for gastric stasis and nausea initially
Later may be required for hyperalimentation
Analgesia with IV narcotic or ketamine
Small graduated doses, as circulation is centralized in shock
May worsen hypotension, hypoxia if not adequately resuscitated
Dress burns with clean linen
Prevent hypothermia

Special burns
Chemical injury
Alkali, acid or petrochemical burns
Alkali burns are generally the most serious
Remove all traces of chemical and irrigate
Burns to the eye may require continuous irrigation

Electrical burns
Frequently small entry and exit burns with extensive deep tissue injury underlying
Rhabdomyolysis common
Manage the same except
High index of suspicion of rhabdomyolysis, cardiac injury
ECG monitor, urine colour observation
Osmotic diuresis ± alkalinization of urine
Paediatric Trauma
Trauma in Women

Alterations in pregnancy

Uterus
- Intrapelvic until week 12, thick-walled, embryo well cushioned
- At umbilicus by week 20
- At costal margin at week 34-36, thin-walled, vulnerable to injury
- Protects bowel from blunt trauma
- High risk of placental abruption with trauma

CVS
- ↑ blood volume, ↓ Hb, ↑ WCC (15-25,000 mm⁻³), ↓ albumin (22-28 g/l)
- ↑ CO (by 1-1.5 l/min), ↑ HR (10-15/min), ↓ BP (5-15 mmHg), ECG LAD

Resp
- ↑ MV, ↓ PCO₂, ↓ RV, FRC

Other
- ↑ gastric emptying time
- ↑ RBF, GFR, uterine compression of ureters
- ↑ pituitary size
- ligamentous laxity

Assessment and management

Primary survey and resuscitation

Mother
- Usual ABCDE
- Except left lateral tilt with uterine displacement unless spinal injury suspected
- Vigorous fluid resuscitation to prevent uterine vasoconstriction and fetal hypoxia
- Indicated x-rays must be performed, risk to fetus is low

Fetus
- Good maternal resuscitation is good fetal management
- Assessment by abdominal examination
  - Signs of uterine rupture
  - Signs of abruption
  - Fetal heart sounds, ultrasound, CTG

Secondary survey
- Usual, including DPL or ultrasound
- Except DPL must be above the umbilicus
- Additional attention to uterine contraction, obstetric pelvic examination
- Admission and fetal monitoring is required for even minor injuries

Specific conditions

Uterine rupture
- Massive haemorrhage and shock if severe
- Abnormal fetal position, extended limbs, free intraperitoneal air
- Laparotomy required if rupture suspected

Abruption
- Leading cause of fetal death after trauma
- Vaginal bleeding, pain, uterine rigidity, shock
- 30% show no external bleeding

Amniotic fluid embolism
- Hypotension, hypoxia, DIC

Fetomaternal haemorrhage
- Fetal anaemia and death
- Maternal isoimmunisation (use anti-D even if Kleihauer negative)

Perimortem Caesarean section
Transfer to Definitive Care
Remote anaesthesia

Anaesthesia in a hyperbaric chamber

Anaesthesia in a dental surgery

Problems in transporting patients
Anaesthesia in a hyperbaric chamber

Hyperbaric chamber
- Increased atmospheric pressure, usually up to 3 atm
  - Commonly chamber contains air, but oxygen headboxes or masks are used to deliver high FiO₂

Indications
- CO poisoning, gas embolism, decompression illness
- Acute infections, sports injuries
- Maintenance of oxygen transport in anaemia
- Increased arterial oxygenation in anaesthesia

Physiological effects
- Increased barometric pressure
  - Pressure reversal of anaesthesia requires much higher pressures
- Increased partial pressure of oxygen, risk of toxicity

Practical use
- Limited duration
- Oxygen toxicity
- Decompression obligation
- Monitoring difficulty
- Patient discomfort

Equilibration
- Middle ear and lung

Equipment
- Increased fire hazard so minimal use of electrical devices
- Monitors usually placed outside chamber with long cables
  - Pressure devices need adjustment
  - Catheter balloons need deflation prior to compression or decompression (e.g. Swan)
  - Blood gas assessment is complicated by decompression of sample
- Defibrillation is hazardous
- IV giving set air-fluid level changes with pressure change
- Anaesthetic machine
  - Flow meters under read
  - Vaporizers deliver same partial pressure but reduced vol%
  - Special ventilators required

Anaesthesia
- Trials in
  - Carotid, caesarean, lung lavage
Would you anaesthetize in a dental surgery?

College Policy T5 (1995)

Principles of anaesthetic care
  Suitable medical practitioner
  Medical preanaesthetic consultation
  Compliant monitoring
  Anaesthetist has discretion to cancel cases

Staffing
  Assistant to the anaesthetist
  Assistance for positioning
  Technical assistance for equipment service

Equipment
  Anaesthetic machine for each anaesthetizing location
    Calibrated vaporizers
    Suitable breathing systems
    Paediatric breathing systems if children are being anaesthetized
  Safety devices
    Indexed gas connection, oxygen reserve supply, oxygen failure warning device, oxygen analyzer, anti-hypoxic interlock, pressure relief valve, non-slip common gas outlet connection, scavenging
  Separate ventilating device with independent oxygen supply
  Compliant suction equipment
  Other equipment
    Gloves, masks, eye protection etc.
    Stethoscope, sphygmomanometer, compliant monitoring
    Range of face masks, airways, ETTs and connectors
    Two laryngoscopes and a range of blades
    Introducers, syringe, clamps, Magill’s forceps, tapes, scissors, lube, throat pack
    Tourniquets, IV equipment, sharps container
    Regional equipment
    Defibrillator

Environment
  Good lighting
  Emergency lighting
  Telephone or intercom
  Refrigerator
  Environmental temperature control
  Chair which allows rapid head-down or horizontal positioning

Drugs
  Anaesthetic agents
    Emergency drugs for initial management of
      Anaphylaxis, arrhythmias, cardiac arrest, pulmonary oedema, hypotension, hypertension, bronchospasm, respiratory depression, hypoglycaemia, hyperglycaemia, adrenal dysfunction, malignant hyperpyrexia (dantrolene at nearby hospital), coagulopathy
  Mechanism for checking use-by dates

Maintenance
  Routines for checking equipment
  Twice yearly service of anaesthetic machine with documentation
  Protocol for checking the anaesthetic machine

Recovery
  Compliant recovery room
  Contingency plan for emergency transfer to hospital care
Problems in transporting patients.

Assistance
   Two staff minimum for patient transport
   One to resuscitate, one to get help
   At least one must be familiar with the route and destination

Airway and breathing
   If intubated, the ETT must be well-secured
   Ventilation
      Apnoeic for short periods (e.g. induction room to OR)
      Self-inflating bag
      Gas-powered ventilator (e.g. Dräger Oxylog)
      Battery-powered ventilator (e.g. some Siemens models, Dräger Julian)
   Portable oxygen source adequate for expected duration of transport
   Portable suction
   N$_2$O and anaesthetic vapours usually not available
      Vaporizers do not operate correctly when shaken

Circulation
   External pacing device must have adequate battery power and leads secure
   Intravenous infusions must have adequate length and be well-secured
      Best attached to bed
   Warming devices will not operate without AC power
   Circulatory support devices must have adequate tubing length and battery power
      and triggering not subject to interference (e.g. IABP, LVAD)

Monitoring
   SpO$_2$, ECG, NIBP or invasive pressure usually available
      Adequate lead length and battery power required
   Gas analysis, complex monitors usually not available
   Vibration in transport may interfere with all monitors
      Greater dependence on clinical signs: pulse, colour, chest movement
      Conflicts with need to keep patient covered and warm

Drugs and equipment
   Awake patient
      Emergency induction drugs and airway equipment
   Maintenance of anaesthetized patient
      Sedative or hypnotic agents
         e.g. midazolam, morphine, thiopentone, propofol
      Relaxants
         longer-acting agents preferred
   Emergency drugs
      Resuscitation drugs, pressors
      Specific agents depending on patient’s condition
         e.g. anticonvulsants, vasodilators

Other
   Surgical drains
      Chest drains clamped or placed so as to ensure no “backflow”

College Policy: Minimum Standards for Transport of the Critically Ill (P23)

Administrative guidelines
   Central coordination to minimize delays
   Clear determination of responsibility
   Appropriate documentation
   Quality assurance mechanism

Categories of transport
   Prehospital, interhospital (emergency and semi-elective), intrahospital
Staffing

Prehospital: appropriate ambulance service personnel
Interhospital: experienced medical, nursing, technical and ambulance staff
Specifically trained personnel for neonatal and infant transport
Intrahospital: appropriate medical and nursing personnel

Transport
Vehicle determined by availability, urgency, distance, conditions
Requirements for safety, space, gases and energy, access, lighting, temperature control, restraints, noise and vibration, speed, communication, pressurization, headsets for auditory alarms
Special issues with aircraft: pressure, space, motion, noise
Fundamental requirement for stable vital signs, secure airway, secure IV, secure catheters and appropriate monitoring before departure

Equipment
Regard to size, weight, durability, battery life, restraint
Respiratory
Oxygen, airways, masks, nebulizer, self-inflating bag with PEEP, suction, ventilator with pressure and disconnect alarms, intubation set, cricothyroidotomy set, pleural drainage set

Circulatory
Monitor, defibrillator, pacer, oximeter, anaeroid sphygmomanometer, cannulae, fluids, pump set, infusion pumps, arterial pressure transducer, syringes, needles, MAST

Other
NGT, IDC, Cophenylcaine, instruments, sutures, dressings, prep, gloves, insulation, thermometer, splints

Drugs
Resuscitation drugs for all likely emergencies
Arrest, hypotension, hypertension, arrhythmia, APO, anaphylaxis, bronchospasm, hypoglycaemia, hyperglycaemia, raised ICP, uterine atony, adrenal dysfunction, narcotic depression, convulsions, agitation, pain, vomiting, electrolyte disturbance

Monitoring
Appropriate to the situation
Clinical monitoring is fundamental
Circulation: pulse and BP
Respiration: frequent assessment
Oxygenation: observation and pulse oximetry
Minimum standards
O2 supply failure alarm, pulse oximeter, disconnect or ventilator failure alarm, high airway pressure alarm, ECG
Policies

E1 Registrar Posts
TE3 Supervision of Trainees
TE4 Regional Education Officers
TE5 Supervisors of Training
E6 Duties of an Anaesthetist
TE7 Secretarial Services
TE9 Quality Assurance
TE11 Formal Project
E13 Provisional Fellowship Year
E14 In-Training Assessment
TE15 Certificate in Pain Management
TE16 Pain Management Centres Offering Training
TE17 Advisors of Candidates
EX1 Examination Illness
T1 Minimum Facilities in Operating Suites
T3 Minimum Facilities in Radiology
(T4 Minimum Facilities in ECT)
T5 Minimum Facilities in Dental Surgeries
T6 Minimum Facilities in Delivery Suites
P1 Training for GP Anaesthetists
P2 Privileges
PS3 Major Regional Anaesthesia
P4 Recovery
(P5 Care of Patients made Unconscious)
P6 Anaesthesia Record
PS7 Preanaesthetic Consultation
PS8 Assistant for the Anaesthetist
P9 Sedation
PS10 Handover of an Anaesthetic
P11 Bypass
PS12 Smoking
P13 Autologous Blood
PS14 Epidural Anaesthesia in Obstetrics
P15 Day Surgery
P16 Standards of Practice

PS17 Bronchoscopy
P18 Monitoring
P19 Monitored Anaesthetic Care
P20 Postoperative Responsibilities
P21 Sedation for Dental Procedures
P22 Patients’ Rights and Responsibilities
P23 Transport of Critically Ill
P24 Sedation for Endoscopy
(P25 Pain Management Centres Offering the CPM)
PS26 Providing Information about Anaesthesia
P27 Standards for Extracorporeal Perfusion
P28 Infection Control
PS29 Children in Non-Paediatric Centres
PS31 Checking the Anaesthetic Machine
PS33 Minimum Facilities in ECT
PS36 Sedation for Eye Surgery under Regional
PS37 Regional and Allied Health Practitioners
PS38 End of Life Decisions
PS39 Intrahospital Transport of Critically Ill
PS40 Relationships with the Healthcare Industry
IC1 Standards for ICU
IC2 Duties of an ICU Specialist in a Training Hospital
IC3 Training Posts in ICU
IC4 Supervision of ICU Trainees
IC5 Education Officer in ICU
IC6 Supervisor of Training in ICU
IC7 Secretarial Services to ICU
IC8 Quality Care
IC9 Ethics and Patients’ Rights and Responsibilities
IC11 In-Training Assessment in ICU

3.K.4.1 James Mitchell (October 7, 2001)
**E1 Registrar Posts**

- 3-15 months ICU
- No more than 4 years in one hospital
- At least one consultant per trainee
- Access to library, journals, texts, computers

**TE3 Supervision of Trainees**

Four levels of supervision
1. One consultant to one trainee
2. One to two
3. Consultant available within the hospital
4. Consultant exclusively rostered and available from home

General requirements
- Level 1 and 2 for ≥25% of work in first four years
- Level 4 for ≤30% of work in first four years
- Out of hours work 25-50% of work in first four years
- Supervisor must attend if asked to
- Level 1 supervision in an unfamiliar area

**First year**
- Level 1 supervision for at least 3 months
- Level 1 or 2 for most in-hours cases
- Supervisor notified of all out-of-hours cases, 25% to be level 1 or 2

**Second year**
- Level 1 or 2 for about half of in-hours cases
- Level 1 or 2 for at least 20% of out-of-hours cases

**Third year**
- Level 3 for many in-hours cases
- Level 1 for cardiac, obstetric, major paediatric work

**Fourth year**
- Level 3 for previously encountered work

**PFY**
- Consultation and supervision available at all times

**E6 The Duties of an Anaesthetist**

**Clinical**
- Providing anaesthesia and other consultative services
- Preoperative assessment and postoperative care
- Supervising trainees and other staff
- Supervising recovery
- Supervising day surgery anaesthesia areas
- Maintaining an acute pain service
- Associating with a pain management service
- Acute resuscitation for emergencies
- Management of ICU patients
- Consultative service in preoperative assessment and management
- Supervising cardiopulmonary bypass

**Other**
- Administrative duties in the Department and Hospital
- Educational activities for doctors, trainees, nurses, students, the public
- Peer review and quality improvement activities
- Continuing medical education
- Professional associations
- Research and reviews

*Policies 3.K.4.2  James Mitchell (October 7, 2001)*
Contributing to hospital or health committees
Activities to safeguard the wellbeing of colleagues

TE9 Quality Assurance

“An organized process that assesses and evaluates health services to improve practice or quality of care.”

Process
Planning, implementation, review cycle
Setting standards

Activities
Assess Department structure and performance relative to other Departments or ANZCA policies
With regard to staff, physical facilities, management and education
Criteria-based audit
Clinical indicators, periop mortality or morbidity, ICU stats, utilization
Formulation of guidelines or protocols
Critical incident review
Risk management
Peer reviews
Patient surveys

T1 Minimum Facilities for Safe Anaesthetic Practice in Operating Suites

T2, T5, PS33 (Radiology, Dental, ECT) similar
T6 (Delivery Suite) similar with addition of paediatrician, specifications for delivery room

Principles
Anaesthesia should be administered by appropriately trained doctors
Every patient should have a preanaesthetic consultation with a doctor trained in anaesthesia
Appropriate monitoring must occur during anaesthesia

Staffing
In addition to surgical staff
An assistant to the anaesthetist
Assistance for positioning
Technical assistance

Anaesthetic equipment
Anaesthetic machine: O₂, N₂O, volatiles, breathing circuits (adult, paediatric), air if necessary
Safety devices: indexed gas supply, O₂ reserve, O₂ failure warning, pressure relief valve, O₂ analyzer, antihypoxic device, non-slip CGO
Separate ventilating device
Suction, scavenging
Monitoring, IV, airway, regional equipment
Difficult intubation equipment, rapid infusion device, warming, chest drain, defib.

Other equipment
Appropriate lighting, emergency lighting, telephone or intercom, refrigerator, airconditioning, trolleys

Drugs
Usual anaesthetic drugs
Drugs required to manage complications

Cleaning and servicing procedures
Recovery area

PS3 Major Regional Anaesthesia

Policies 3.K.4.3 James Mitchell (October 7, 2001)
Principles
Administered only by appropriately trained doctors
The anaesthetist must not also be the operator
Informed consent required
Monitoring requirements as for any anaesthetic
Anaesthetist must be present until the block is stable or procedure complete

Epidural catheters
IV access required
Catheter clearly labelled “Epidural”
Management as prescribed by anaesthetist
Protocols for management of complications
Protocol for monitoring for complications
Observations must be charted
Catheter removal and condition must be documented
Management may be delegated to a nurse or APS
With specific training and experience

P4 Recovery

Principles
Specific area, close to theatre, trained staff able to contact anaesthetist

Design
Part of the operating suite, accessible in street clothes
9 m² per bed with access to patient’s head
1.5 spaces per theatre
Each bay
  O₂, suction, SpO₂, sphygmomanometer, stethoscope, thermometer,
  power, lighting, emergency lighting, space for monitors
Nurses station, drugs, linen, utility room, scrub area, x-ray box
Clock with second hand
Telephone and emergency alarm, emergency power

Equipment
Present
Ventilating device per two spaces, intubation drugs and equipment,
resuscitation drugs, IV equipment, analgesics, syringes and needles,
ECG per three spaces
Available
12-lead ECG, invasive pressure monitor, gas analyzer, defibrillator,
nerve stimulator, bronchoscope
Warming cupboard, refrigerator, procedure light, surgical tray, blood
gases, x-ray

Trolleys
Firm base and mattress, tilt 15° up and down, manoeuvrable, brakes, able to
sit patient up, removable side rails, IV pole, mountings for monitors and
transport equipment

Staff
Trained recovery staff present at all times
Flexible ratio: up to 1 to 3, but 1 to 1 for unconscious patients

Management
Written protocols for management
Routine for checking equipment and drugs
Appropriate recording of consciousness, SpO₂, RR, HR, BP, temp.
Established criteria for discharge
Anaesthetist responsibilities
  Accompany patient until handed over, provide written and verbal
orders, specify O₂ therapy, remain nearby until patient is safe to be left, supervise recovery and authorize discharge or delegate the discharge decision

P6 Minimum Requirements for the Anaesthesia Record

Basic information
- Name, hospital, UR, age, gender, weight
- Date of preop consult and operation
- Anaesthetist’s name (also supervisor’s name and level of supervision)
- Surgeon’s name and procedure planned and performed

Prior to anaesthesia
- Preop assessment and ASA status
- General medical history, drug therapy, allergies
- Previous anaesthesia and surgery
- Airway, dental and reflux assessment
- Investigations
- Premed
- Documentation of anaesthetic plan discussed

Anaesthesia
- Drugs used, including by the surgeon
- Anaesthetic technique and any problems
- Time of events, observations and interventions
- Airway instrumentation and problems
- Details of vascular access and fluids given
- Blood loss
- Position
- Monitoring
- Other interventions

Post anaesthesia
- Observations and events as required in recovery standards
- Plan for pain management, fluid therapy, O₂ therapy
- Clinical indicators and QA markers
- Post-anaesthetic visit

PS7 The Pre-Anaesthesia Consultation

Principles
- Performed by the anaesthetist administering the anaesthetic even if already performed by someone else or questionnaire
- Appropriate time before surgery and in privacy
- Not to be modified except for the welfare of the patient (emergencies)

Including
- Identification and introduction
- Concise medical history and examination, investigations indicated
- Consultation if required
- General discussion of anaesthetic management significant to the patient
- Informed consent
- Ordering premedication
- Written summary

PS8 Assistant for the Anaesthetist

Principles
- A trained assistant is essential
- Present for preparation and induction until no longer required
Available at short notice during maintenance
Present for conclusion of anaesthesia
Required for anaesthesia or sedation
Equipment as required by other policies

Deployment
Number and status of assistants determined by nature and workload of anaesthesia
Assistant is exclusively responsible to the anaesthetist while assisting
The assistant is essential: staffing and rostering must allow for one

Education
Must have attended a suitable training course
EN or RN in clinical work or VCE required
Content
Lecture course of at least 150 hours with significant anaesthetic input
Practical instruction by anaesthetists with a log book kept
Completion of assignments, internal assessment and examinations
Duration
Three years full-time if no previous hospital experience
Two years full-time for EN or equivalent
One year full-time for RN
May be part-time
Regular continuing education

P9 Sedation for Minor Procedures

Equipment and care must conform to requirements for anaesthesia in other policies
Consultation, record, monitoring, recovery
Principles
Preanaesthetic assessment required
Serious medical condition or possible airway compromise mandates constant presence of the anaesthetist
Practitioner administering sedation must understand drugs, potential complications and effect of patient illness on drug action
Single operator sedation is permissible only if rational verbal communication is maintained with the patient, otherwise an anaesthetist must be present
Facilities
Tiltable table, space and drugs for resuscitation, suction, lighting, oxygen, ventilation equipment, pulse oximeter, defibrillator

PS10 Handover of responsibility

Transfer
Satisfied of competence of relieving anaesthetist
Reliever willing to take over responsibility
Patient details: past history, present condition
Anaesthetic details: drugs, lines, airway, fluids, events, likely problems
Plan for further management if permanent handover
Compliant anaesthetic record
Check anaesthetic machine, lines and monitoring
Notification to surgeon (and supervising anaesthetist if a trainee)

Relief
Patient stable and likely to remain so
Facts relevant to safe management explained to reliever
Reliever not to substantially change management unless an emergency
Anaesthetist available to return at short notice
P11 Cardiopulmonary bypass

Principles

A medical practitioner must take responsibility for CPB
Must be trained in CPB techniques
Should be assisted by a clinical perfusionist or technician
Should assess the patient pre-op and follow post-op
Must communicate with practitioners with overlapping responsibility

PS12 Smoking

Smoking is addictive and can damage the health of smokers and those around them
Benefits of ceasing

↓ COHb t/2 4 h, so 12 h cessation significantly improves O₂ carriage
Polycythaemia and ↑ viscosity reverse in days
Nicotine ↑ HR, BP, peripheral vasoconstriction, improved within 12-24 h
↑ mucus, ↓ ciliary clearance improve over 6 weeks
Small airway function improves over 1-6 months
Chest infection rate reduced at 2 months, normal at 6 months
Immune response normalizes over 6 months
Increased analgesic requirements normalize over 6-8 weeks
Complication rate higher in plastic and reconstructive surgery
Impaired microcirculation

P13 Autologous blood

Standard label with unique identifier on unit
Signature and name of person collecting blood
Label with patient name, UR, date and time of collection attached
If stored for more than 6 hours, must be stored as for homologous blood
Checking prior to infusion as for homologous blood

PS14 Regional in obstetrics

Epidural or spinal to be performed by practitioner experienced in the techniques
Mother must be under care of an obstetrician
Anaesthetist

Ensures the mother is informed of risks
Is available to supervise management of the blockade
Is competent to deal with complications of block
Provides full instructions for management
Techniques must be recorded in mother’s notes
A trained assistant is required for performing a block
Further epidural doses may be given by nurses or other doctors
When prescribed by the anaesthetist with appropriate written instructions
When competent to give the bolus and to monitor the mother and fetus
When skilled staff are available to manage complications
Care during infusion

Monitoring for mother and fetus, assessment of block and adverse effects,
management of the labour
Handover as for any anaesthetic
IV cannula must be present throughout
PCEA must be explained to mother and nursing staff
Removal of catheter must be documented

P15 Periop care of day cases

Policies 3.K.4.7 James Mitchell (October 7, 2001)
Suitability for day surgery

Surgery
- Minimal risk of postop haemorrhage, airway compromise
- Pain controllable with outpatient techniques
- No special nursing requirements
- Rapid return to normal oral intake

Patients
- Willingness and understanding to follow postop instructions
- ASA I or II, or stable III and IV with anaesthetic consultation
- Term infants over 3 months or ex-prems over 60 weeks PCA

Support
- Responsible person to take the patient home and be present overnight

Decision ultimately rests with the anaesthetist

Preparation
- Preanaesthetic consultation may be assisted by questionnaire or nurse
- Prior referral in case of doubt as to suitability
- Written patient information on process as day case and fasting requirements

Recovery
- Compliant recovery room
- Reclining seating area for after recovery
  - Nursing supervision, oxygen, suction, resuscitation equipment

Discharge
- Wheelchair, car and ambulance access

Criteria
- Obs stable for 1 h, orientated, adequate analgesia, able to dress and walk, no nausea or vomiting or dizziness, tolerating oral fluids, minimal bleeding, has voided
- Responsible adult for transport, discharge authorized by surgeon and anaesthetist, written instructions and emergency contact information, 24 hours of analgesic drugs
- Telephone follow up next day

PS17 Endoscopy of the airways

Principles
- Procedure supervised by an experienced practitioner
- Preoperative assessment may indicate the need for a second practitioner
- Informed consent should be obtained
- Equipment must be checked
- Local, sedation or GA may be required
  - Sedation or GA require a second practitioner
- Pulse oximetry and other compliant monitoring
- Reliable venous access
- Supplemental O2, before, during and after bronchoscopy
- Compliant recovery
- Record of administration of sedation

Facilities
- Tilttable table
- Space and drugs for resuscitation
- Suction, lighting, oxygen, ventilation equipment, pulse oximeter, sphygmomanometer, ECG and defibrillator
- Reversal agents for benzos and opiates

Discharge as for day surgery

P18 Monitoring during anaesthesia

Policies 3.K.4.8 James Mitchell (October 7, 2001)
Personnel
Appropriately trained doctor present from induction to recovery room
Responsibility only for anaesthesia

Patient monitoring
Pulse and BP at frequent and clinically appropriate intervals
Ventilation monitored continuously, directly and indirectly
Oximetry interpreted with clinical observation
Adequate lighting to assess colour

Equipment
Must be in use
O₂ failure, O₂ analyzer, pulse oximeter
Disconnect alarm if mechanically ventilated
Must be available
ECG, temperature, capnograph, nerve stimulator, agent analysis

P19 Monitored Care

For procedures under local anaesthesia or sedation or in situations such as IV contrast in possibly sensitive patients.
Preanaesthetic consultation, monitoring, sedation, recovery, anaesthetic record, facilities as specified in other policies.

P20 Postoperative responsibilities

Shared responsibility with surgeon for
Monitoring, analgesia, fluids, respiratory therapy
Responsibilities in recovery
Handover when stable
Availability for management of problems, or covered by another anaesthetist
Safe criteria for discharge to ward
On-going adequate care after recovery
Suitability for day surgery if discharged home
Quality assurance
Recognition, management and documentation of adverse events
On-going audit of anaesthesia care
Inform patient of any matters relevant to future anaesthetics

P21 Sedation for Dental Procedures

As in P9 plus
Dental practitioners administering sedation must be appropriately trained
Dosage and administration of drugs
Management of complications: resuscitation, CPR
Equipment
Chair able to be laid flat, space for resuscitation, lighting
Monitoring: BP, SpO₂ for IV sedation
Resuscitation: suction, oxygen, means of ventilation, drugs
N₂O, O₂ sedation
Minimum flow of 2.5 l/min O₂, minimum 30% O₂
Maximum flow 7-10 l/min N₂O
Flow meters, O₂ failure device, non-return valve, at least 2 cm diameter tubing, nose-piece incorporating air dilution valve, O₂ flush, scavenging to maintain N₂O below 25-50 ppm
Installation and regular servicing by qualified personnel
IV sedation
SpO₂ required, IV access which will remain patent throughout, reversal drugs
Recovery
Adequately equipped and staffed, plan for transfer to medical care if needed

P22 Patients’ Rights and Responsibilities

Rights
To be treated with skill, consideration and dignity regardless of age, gender,
race, religion, disabilities, health and legal status
To know the identity and status of attending staff and refuse the presence of
others during treatment
To be informed of proposed care and alternatives, side-effects and risks
To refuse proposed treatment without prejudice to alternative strategies
provided the implications are understood by all involved
To be provided anaesthesia by an anaesthetist after written consent
To request a second opinion without prejudice
To know of any involvement in teaching or research and to understand that
non-involvement will not prejudice treatment
To know that all aspects of care will remain confidential
To know the broad financial implications of therapy
To the presence and support of next of kin, partner or friend when practicable
To expect decisions to be made on their behalf after discussion with next of kin
should they be unable to communicate
To be informed of any matters which may affect anaesthesia in the future

Responsibilities
To inform staff of all relevant medical history including the possibility of
infectious disease
To comply with agreed treatment or inform staff of their intention not to
comply
To consider participation in teaching and research which may improve the care
of others in the future
To consider their ability to meet their financial obligations in relation to care

P23 Transport of the Critically Ill

Administration
24-hour coordinated transport by road and aircraft
Delay minimized by central coordination and communication
Transfer should not be delayed by waiting to identify a receiving unit
Reliable communication between sending and receiving hospitals and transfer
team
Clear determination of responsibility and hand-over
Documentation of condition before and during transport, therapy and history
On-going quality assurance activities
Classification
Prehospital, interhospital, intrahospital
Staffing
Team of staff familiar with transport
Ambulance officers
Nursing and medical staff
Special expertise for neonatal and paediatric transport
Vehicle
Choice determined by urgency, location, availability, nature of illness
Requirements
Safety, space, power and gas supply, access, lighting, air-conditioning,
restraints, noise and vibration, speed, communication system,
pressurization

Equipment
- Determined by patient condition and expected duration
- Attention to battery life and restraint in vehicle

Respiratory equipment
- Airways, masks, nebulizer, self-inflating bag, suction, ventilator with alarms, sets for intubation, cricothyroidotomy and chest drain

Circulatory equipment
- Monitor-defibrillator, oximeter, sphygmomanometer, IV equipment, arterial transducer, pacemaker, MAST

Other
- NGT, IDC, dressings, sutures, instruments, splints, blankets, termperature monitor

Drugs
- As required to manage resuscitation and likely emergencies as well as sedatives and relaxants
- Ensure all lines and ETT are well-secured prior to transport

Monitoring
- Similar to intraoperative requirements

**PS26 Providing Information about Anaesthesia**

Principles
- Information is to be provided in such a way that the patient and relatives are able to understand
- Where options exist, they should be outlined together with advantages and disadvantages
- The patient should be made aware of the financial implications of the service

Presentation
- Basic information should be provided, even if the patient requests no information. If information is refused it should not be forced on the patient, but the refusal recorded in the notes.
- Questions should be encouraged and answered
- An interpreter should be used when necessary
- Where blood products may be required, their advantages, risks and alternatives should be discussed

Risks
- Known risks should be disclosed for common, mild adverse effects and rare but serious ones.
- Uncertainty in risk and difficulty in applying population risks to an individual should be explained

Emergencies
- No discussion of risks may be possible. Attempts should be made to provide information to the family as soon as possible.

Incompetent patients
- An explanation appropriate to the patient’s understanding should be given.
- Appropriate consent should be sought from a guardian or next-of-kin.

**P28 Infection Control**

Cleaning and disinfection as per AS 4187-1994

Handwashing
- Before handling a new patient or equipment for a new patient
- After leaving a patient
- Whenever contaminated
- Gloves to be worn whenever hands may contact blood, saliva or any bodily...
Invasive procedures

IV
  Wash hands, wear gloves, disinfect skin, ensure tip and cannula remain sterile

CVC
  Full aseptic technique (mask, gown and gloves), skin preparation, sterile drapes

Regional anaesthesia
  Peripheral blocks: as for IV
  Axial block or catheter insertion: as for CVC

Anaesthetic apparatus
  Disposable items should not be reused
  ETTs and airways to remain sterile until inserted
  Face masks and upper airway instruments (laryngoscopes) to be disinfected
  Circuit to be disinfected or protected with a filter
  Sampling lines can be reused but returned gas must pass through a viral filter
  CO₂ absorber and valves to be disinfected regularly and protected with a filter
  Ventilator to be disinfected regularly
  Fibreoptics to be cleaned as per AS

Drugs for injection
  Multi-dose ampoules only used where all doses drawn up before first is given
  Single-dose ampoules should be used for only one patient

For immune-suppressed patients, more stringent practices may be required

PS29 Paediatric Anaesthesia in the Non-specialist Hospital

Non-paediatric centres treating children should have a policy on management of children

Factors
  Age (and prematurity), medical and nursing staff experience and familiarity

Equipment
  Airway, IV, monitoring, temperature maintenance equipment suitable for children
  A separate ward area

Policy
  Criteria for transfer to a specialist centre
    e.g. neonates, PCA <52 weeks, history of apnoea, ASA 3 or worse

PS37 Regional and Allied Health Practitioners

Practitioners such as dentists, podiatrists and nurses may administer local anaesthetic

Requirements
  Training in the use of LA, pharmacology, complications and their management
  Certified competence in CPR
  Patients should not be denied a GA when indicated
  Arrangements for transfer of care if required

PS38 End of Life Decisions

ANZCA’s mission statement is “To serve the community by fostering safety and quality patient care in anaesthesia, intensive care and pain medicine”.

ANZCA supports Policies 3.K.4.12 James Mitchell (October 7, 2001)
Provision of adequate pain relief in terminal illness, even though it may shorten the patient’s life, where the intention is relief of pain and not the death of the patient
Relief of pain in non-terminal illness to restore quality of life and minimize the risk of suicide
The right of competent patients to refuse treatment, even though it may be life-saving
The right of Fellows and patients to their individual beliefs

ANZCA does not support
The application of therapies which offer no benefit to the patient
The application of therapies in which the primary intent is the death of the patient

PS39 Intrahospital Transport of Critically Ill

Principles
Hospital must have a protocol for transport
Benefits of interventions requiring transport must outweigh risks of transport

Equipment
Dedicated durable trolley capable of fitting in lifts and through doorways
Suitable for the intervention area (e.g. MRI), gas, suction and electricity available at destination
No equipment placed on the patient
Basic monitoring: ECG, HR, BP, SpO₂
Desirable monitoring: ETCO₂, MV,
Basic equipment: defibrillator, suction, self-inflating bag if on ventilator, spare batteries, airway equipment
Basic drugs: analgesics, sedatives, relaxants, resuscitation drugs

Policy
Checking of transport equipment
QA process for evaluation of transport

Staff
Designated nurse, orderly and doctor familiar with equipment and emergency management

Departure check
Notify destination
Check monitors and alarm limits, ventilator and alarms, self-inflating bag, suction, gas cylinders and spare cylinder, batteries and spare battery, emergency equipment and drugs, patient films and notes
Check patient: paralyze and sedate if indicated, replace near-empty infusions, check airway, ventilation, alarms, drains, lines, monitors, security on trolley, haemodynamic stability

In transit
Best route planned, lifts held in advance, communication facilities in transit
Vigilance in monitoring, documentation of interventions

Arrival
Check fixed gas, suction, electrical and monitoring equipment
Transfer to fixed equipment and recheck patient
Formal handover of care if required

IC1 Minimum Standards for Intensive Care Units

Level 1
Provides immediate resuscitation, short-term cardiorespiratory support, and monitor and prevent complications in “at risk” patients
Suitable for uncomplicated myocardial ischaemia, post-surgical, unstable
medical and short-term ventilated patients
Should have
Access to emergency, theatre, imaging, laboratory and physiotherapy services
Policies for admission, discharge and referral
Supervision by a suitably qualified doctor, consultant support always available and 24-hour resident cover
1:1 nurse:patient ratio for critically ill patients
Programs for education, orientation and audit
Technical and clerical support with adequate office space

Level 2
In addition
Ventilatory support, invasive monitoring and dialysis support
Designated medical director who is an intensivist
Medical staff present at all times
Nursing staff to have ICU certification
Access to a nurse educator
Isolation
Formal audit

Level 3
In addition
The widest level of care: all aspects of intensive care medicine
Greater than 1:1 nurse:patient ratio for complex patients
Formal nursing education program and nurse educator
Medical education programs
Research program

Physical facilities
20 m² per bed
One washbasin per two beds
One single room per seven beds with own washbasin
Adequate service outlets
Level 3: 3 O₂, 2 air, 3 suction, 16 power per bed, compliant with standards
Lighting, air-conditioning, windows, privacy