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Analgesics and opioids

OP01 [Mar96] With regards to pethidine's physical properties: A. It has an octanol coefficient of 10 B. It has a pKa of 8.4 C. ? D. ? E. ?	Most likely B [From Stoelting table p 93] pKa 8.5 Protein binding 70% Cl 1020ml/min Vd 305L Octanol:water coefficient 30 - 32 Elimination half time 3-5hrs Unionized % at normal pH 7%
OP02 [Mar96] Which factor does NOT predispose to bradycardia with fentanyl in doses of 50 mcg/kg? A. Calcium channel antagonist B. Beta-blocker C. Benzodiazepines D. ? E. Slow injection of drug	E Bradycardia is more prominent with fentanyl than morphine (careful in infants) Factors predisposing to bradycardia/asystole during opioid induction * presence of beta and/or calcium channel blockade * premedication or concomitant use of benzodiazepines * rapid administration * muscle relaxants with little or no vagolytic properties * vagotonic muscle relaxants (e.g. suxamethonium) * added vagal stimuli (e.g. laryngoscopy)
OP03 [Mar96] [Mar99] [Jul99] [Feb00] [Apr01] Naloxone: A. Is not an antagonist of agonist-antagonist drugs B. Is not an antagonist at ?mu & sigma receptors C. Causes pulmonary oedema D. Can cause hypotension in experimental shock animal models E. May cause an abrupt increase in sympathetic tone	C, E Naloxone is a nonselective antagonist of all 3 opioid receptors. Side effects include increased sympathetic outflow, tachycardia, hypertension, pulmonary oedema and arrhythmias. [Stoelting p121]
OP03b [Mar97] Naloxone: A. Is effective at antagonising a full agonist but not a partial agonist B. Causes pulmonary oedema C. ? D. ?	B as above
OP04 [Mar96] [Jul99] {Diagram of numbered structure of morphine} Which substitutions correct? A. N17 substitution gives antagonist activity B. C6 methylation produces codeine C. Glucuronidation occurs at C2 D. Diacetylation decreases lipid solubility	A - substitution CH3 for CH2CHCH2 gives naloxone  Morphine C3 methylation produces codeine Glucuronidation occurs at C3 and C6 (ie gives M6G and M3G) Diacetylation increases lipid solubility

Also remembered as: Morphine base structure with questions about substitutions A. C3 and C6 increase lipid solubility B. Acetyl group on ?C3 gives heroine C. N- substitution gives antagonist D. C5 glucuronidation site E. C3 methyl gives codeine	C A - probably true: C3 and C6 acetylation (ie -OH swapped for -OCO.CH3) gives heroin that is more soluble B - false, needs C3 and C6 C - true, as above + N subsitutions result in nalorphine, nalbuphine, butorphanol and naloxone D false E True
OP05 [Mar96] [Jul98] [Jul00] Pethidine in doses of 2 to 2.5 mg/kg causes all of the following EXCEPT: A. Bradycardia B. Decreased systemic vascular resistance C. ?Normal arterial BP / ?decreased BP D. Increased cardiac output	A D also possible in large doses (see below) Interferes with compensatory sympathetic nervous system reflexes and causes orthostatic hypotension, vasodilation, decreased SVR. Rarely causes bradycardia, may increase heart rate (modest atropine-like properties). Large doses of pethidine result in decreases in myocardial contractility. [stoelting p104]
OP06 [Mar96] Regarding the clearance of morphine: A. Affected by cirrhosis B. Affected by hepatic blood flow C. Shows low hepatic extraction ratio D. ? E. ?	B "Renal metabolism makes a significant contribution to the to the total metabolism of morphine, which offers a possible explanation for the absence of any decrease in systemic clearance of morphine in patients with hepatic cirrhosis or during the anhepatic phase of liver transplant" [Stoelting p95] High hepatic extraction ratio 0.6-0.8 "If hepatic extraction ratio is high (>0.7), the clearance of the drug will depend on hepatic blood flow" [Stoelting p13]
OP07 [Jul97] [Mar99] [Jul99] [Jul00] [Feb04] [Jul04] Fentanyl: A. With pKa 8.4 is 90% ionised at physiological pH B. Has an octanol coefficient of 10 C. Is 1,000 times more potent than morphine D. Has first-pass lung uptake reduced to 20% by propranolol E. Has up to 50% uptake in the lung F. Elimination half-life < 2 hour G. Carried on albumin mostly H. Carried on alpha-1 acid glycoprotein mostly I. Can cause hypertension with MAOI J. Alfentanil acts faster as it has a higher unionised, unbound fraction	A, G A - pKa is 8.4, 91% ionized at pH 7.4 B -Octanol coefficient 600-900 C - 75-125 x more potent than morphine D ? E 75% uptake into lungs F. Elimination half-time 3-6hrs G/H. Albumin tends to bind acidic and neutral drugs, a1-acid glycoprotein tends to bind basic drugs, non-specific binding to other plasma proteins occurs to a much smaller extent but albumin is much more abundant [Goodman & Gillman online] I. PETHIDINE causes interactions with MAO J. Alfentanil does have a higher unionized fraction, but has a lower unbound fraction stoelting says pulmonary first pass uptake is substantially ↓ in patients treated chronically with propranolol: as a result, 2-4 times as much injected fentanyl enters the systemic circulation in the time period immediately after injection (reflects ability of one basic lipophilic amine to inhibit the pulmonary uptake of a second basic lipophilic amine)
OP08 [Jul97] An opioid which can not be used for TIVA: A. Morphine B. Pethidine C. Fentanyl D. Sufentanil E. Alfentanil	B Faunce p245 - Pethidine not used in TIVA due to negative inotropism and histamine release as well as its active metabolite, norpethidine, which can cause seizures in large doses

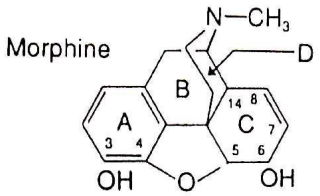
OP09 [Mar98] Nalbuphine: A. Works at mu receptor only B. Has same side effects as pentazocine C. ? D. ?	None. Is an agoinst-antagonist opioid. Equal potency as an analgesic as morphine, 1/4 potency of nalorphine as antagonist. Selective for mu (antagonist), and delta & kappa (agonist) [Rang, Dale, Ritter, 4th ed, p593] Incidence of dysphoria is less than that with pentazocine, and in contrast to pentazocine, it doesn't increase BP, PAP, HR, atrial filling pressure. [Stoelting p 119]
OP10 [Mar98] Pethidine A. 100mg is equal to 10mg morphine in effect B. Increases heart rate C. No effect on cardiac output D. Is preferred to morphine for analgesia E. ?	A, B Pethidine is 1/10 as potent as morphine. It may increase heart rate (some atropine-like qualities) In large doses, decreases myocardial contractility. [Stoelting p103-4]
OP10b [Mar98] Pethidine produces: A. Miosis B. More severe hypotension with comparable dose of morphine C. More biliary spasm than morphine D. ?	B Tends to cause mydriasis, not miosis (mild atropine like actions) "Hypotension after meperidine injection is more frequent and more profound than after comparable doses of morphine" "Biliary tract spasm is less after mepridine injection than after morphine injection" [Stoelting p104]
OP11 [Mar98] TIVA with morphine causes the following EXCEPT: A. Mydriasis B. Muscle rigidity C. Respiratory depression D. ?	A
OP12 [Mar98] [Jul98] [Jul02] [Mar03] Codeine: A. Substitution at C6 position of morphine B. 10% of codeine is metabolised to diacetyl morphine C. IM 100mg is equivalent to 10 mg morphine D. Methyl substitution at the ?C5/?C6 position of morphine E. Can be safely given IV because causes no histamine release F. Has higher first pass effect than morphine	C Methyl substitution at C3 10% of codeine is demethylated to morphine, any remaining is demethylated to inactive norcodeine. 100-120mg (depends on source) IM codeine equivalent to 10mg morphine. Administration of codeine IV is not recommended because histamine-induced hypotension is likely The presence of this methyl group limits first-pass hepatic metabolism and accounts for the efficacy of codeine when administered orally.
OP13 [Jul98] Morphine metabolism: A. Principally metabolised to morphine-6-glucuronide B. Metabolites have shorter half-life C. Found in extrahepatic sites D. Metabolites freely cross the blood-brain barrier E. ?All have analgesic effect / ? Are 30% renally excreted F. In neonates, predominantly by sulphation G. In adults, mostly to morphine-3-glucuronide	C, F, G 75-85% M3G, 5-10% M6G. M3G longer half-time. Renal metabolism makes a significant contribution to total metabolism of morphine. Metabolites have limited ability to cross BBB. M6G analgesic effect, M3G not analgesic & may cause more adverse effects. Metabolites are principally renally excreted & only 10% biliary excretion. [Stoelting p95] Because of low conjugating capacity in neonates, morphine-like drugs much longer duration of action [Rang 4th ed p598] Sulfation is an important pathway for elimination of morphine in neonates [Evers & Maze, 2004 p69]

OP14 [Jul98] Buprenorphine: A. Effective orally B. ? C. ?	?A if the other options are bad due to sublingual route None Agonist-antagonist, more potent than morphine (0.3mg equivalent to 10mg morphine) Affinity 50x that of morphine, slower dissociation from receptors, can provoke opioid withdrawal. Well absorbed but undergoes significant first-pass metabolism so not given orally. [Sasada & Smith p51]
OP15 [Mar99] [Feb00] [Jul02] Sufentanil: A. 30 times as potent as fentanyl B. < 7% excreted unchanged in urine C. Greater protein binding than fentanyl D. Half-life of elimination between fentanyl & alfentanil E. Predominantly bound by ?albumin/ ? alpha1-acid glycoprotein	C, D & E if was AAG 5-10x potency of fentanyl <1% of sufentanil appears unchanged in urine (high lipid solubility - reabsorbed in renal tubules) Fentanyl 84% bound, sufentanil 93% bound (this is the most bound opioid) Half-time ~3hrs, fentanyl ~5hrs, alfent ~1.5hrs. "Binding to a1-acid glycoprotein constitutes a principal proportion of the total plasma protein binding of sufentanil" [Stoelting p93 & 109]
OP16 [Mar99] [Jul00] Pethidine is the traditionally favoured opioid in obstetrics because: A. Norpethidine does not cross the placenta B. Does not undergo ion trapping C. Causes less neonatal depression D. It does not cross the placenta E. It is thought to cause less respiratory depression in the neonate.	C and E Pethidine readily crosses the placenta (highly lipid soluble) With a pKa of 8.5, it is prone to ion trapping in the foetus Placental transfer of an active metabolite, norpethidine with a longer elimination half-life has also been implicated. Was popular in labour as was thought to cause less neonatal respiratory depression, now disproven.
OP17 [Mar99] Pethidine: A. Better bioavailability than codeine B. ? C. ? D. ?	None Pethidine has a high hepatic extraction ratio and undergoes significant first pass metabolism, so bioavailability ~50%. Codeine bioavailability 60-70% [Sasada & Smith]
OP18 [Jul99] Pethidine: A. Norpethidine metabolite B. Pethidine 6-glucuronide C. ?	A Metabolised extensively via demethylation to norpethidine and pethidinic acid. [Stoelting p103]
OP19 [Jul00] Alfentanil is more lipid soluble than fentanyl because: A. Has a pKa of 8.4 & is 90% unionized at physiological pH B. ?"n-Octanol coefficient is [some five digit num] [Jul96] [Mar98] [Jul04]." C. ? D. ?	None Alfentanil has a pKa of 6.5, so is 90% unionized at physiological pH. Fentanyl has a pKa of 8.4 and is 9% unionized at physiological pH. The Octanol coefficient for fentanyl is ~900 and for alfentanil 130. [Stoelting p93]
OP19b [Jul01] [Jul04] Alfentanil works faster than fentanyl because: A. More lipid soluble B. Higher concentration unbound, unionised at physiological pH C. Decreased protein binding D. Larger volume of distribution E. ?	None of these (faster action because more unionized & given in higher concentrations as is less potent) [Stoelting p93] Fentanyl is more lipid soluble than alfentanil (as per octanol coefficient) Fentanyl 84% protein bound, alfentanil 89% protein bound. Alfentanil is more unionized at physiological pH. Vd fentanyl 335L, Vd alfentanil 27L
OP20 [Jul00] [Apr01] Methadone: A. Phenanthrene derivative B. ?metabolism C. Peak plasma levels at 3 hours D. Used in chronic cancer pain due to non addictive potential E. ?d & l isomers	E, D and arguably C as well Structural formula bears no obvious chemical relationship to that of morphine. It is it's own class (the "methadone series") along with dextropropoxyphene. [Rang, 4th ed, p591] Reaches peak concentrations at ~4hrs. Used in chronic pain because of **low abuse potential** and additional NMDA receptor antagonist activity. It is racemic: L-methadone analgesic 8-50x as potent as D isomer, but D isomer has antitussive and NMDA effects [Goodman & Gillman online]

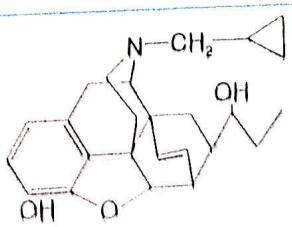
OP21 [Apr01] Tramadol: A. Has beta blocking properties B. Blocks noradrenaline reuptake C. Has greater opioid activity than morphine (OR: As potent a mu agonist as morphine) D. Is directly inhibited by yohimbine E. Only the +ve enantiomer is active	B Tramadol is racemic mixture of 2 enantiomers, (-) inhibits noradrenaline uptake and the (+) inhibits 5HT reuptake. 5-10x less potent than morphine. Yohimbine is a selective antagonist at presynaptic alpha2 receptors, leading to enhanced release of noradrenaline from nerve endings. [Stoelting p 177 +322]
OP22 [Jul01] The most unlikely thing to occur with morphine administered in recovery is: A. Constipation B. Respiratory depression C. Sedation D. Nausea and vomiting E. Physical dependance F. Pruritis	E This should take longer to develop, others are all immediate side effects.
OP23 -Deleted	
OP24 [Jul01] Extrahepatic de-esterfication of Remifentanil A Occurs in RBC B By Plasma Cholinesterase C NOT in incubated blood D Has (?mean) clearance less than 1L/min E Has an active metabolite Alt options: C. Hydrolysis does not occur in vitro in incubated blood E. The drug is hydrolysed to an active metabolite which undergoes further hydrolysis (Q75 Jul01)	E Metabolised (hydrolysed) by nonspecific plasma and tissue esterases (not red cell esterase) It does not appear to be a substrate for pseudocholinesterase. HOWEVER: in vitro where no tissue esterases are present, red cells only hydrolyze remifentanil more rapidly than whole blood where some of the remifentanil is bound & buffered. This is unlikely to translate to an in vivo effect and abnormal pseudocholinesterase is NOT thought to be a problem. Clearance nearly 3L/min The principal metabolite, remifentanil acid, is 300-4600x less potent than remifentanil. This and other inactive metabolites undergo renal excretion. (BUT I don't think the active metabolite is further metabolised, it is excreted as it is).
OP25 [Jul01] The following are metabolites of morphine except: A. Morphine-6-glucuronide B. Morphine-3-glucuronide C. Normorphone D. Codeine E. Hydromorphine	E
OP26 [Jul01] Fentanyl given at dose of 50-150 mcg/kg: A. Causes potent cardiac depression B. Does not cause muscle rigidity C. Has an elimination half-time of more than 3 hours D. Not enough to relieve the stress response to surgery E. Preserve cardiac output	C High dose! Can cause cardiac depression (bradycardia - may cause hypotension and reduced cardiac output), rigidity, and can significantly reduce or even eliminate the metabolic stress response to surgery. [Peck & Hill p145] However, lacks direct myocardial depressant effects [Stoelting p106] Elimination half-time 3-6hrs [Stoelting p93]
OP27 [Jul04] Prolonged duration of action of morphine in renal failure is due to A. Morphine 3-glucuronide B. Morphine 6-glucuronide C. Metabolism of morphine D. ? E. ?	B

OP28 [Jul-06] Which is NOT a side effect of morphine: A. Seizures B. Mydriasis C. Respiratory depression D. Histamine release E. ?	B

Morphine analogues



Drug	Substituents			
	3	6	N	14
Morphine	—OH	—OH	$—CH_3$	—H
Diamorphine (heroin)	$—OCO \cdot CH_3$	$—OCO \cdot CH_3$	$—CH_3$	—H
Codeine	$—OCH_3$	—OH	$—CH_3$	—H
Levorphanol	—OH	—H	$—CH_3$	—H (lacks —O— at C_4–C_5)
Dihydrocodeine	$—OCH_3$	—OH	$—CH_3$	—H (lacks double bond C_7–C_8)
Nalorphine	—OH	—OH	$—CH_2CH=CH_2$	—H
Nalbuphine	—OH	—OH	$—CH_2$—cyclobutyl	—OH (lacks double bond C_7–C_8)
Butorphanol	—OH	—H	$—CH_2$—cyclobutyl	—H (lacks —O— at C_4–C_5 and double bond C_7–C_8)
Naloxone	—OH	=O	$—CH_2CH=CH_2$	—HO (lacks double bond C_7–C_8)
Buprenorphine				



Anticholinergics and antimuscarinics

All answers from Stoelting chapter 10

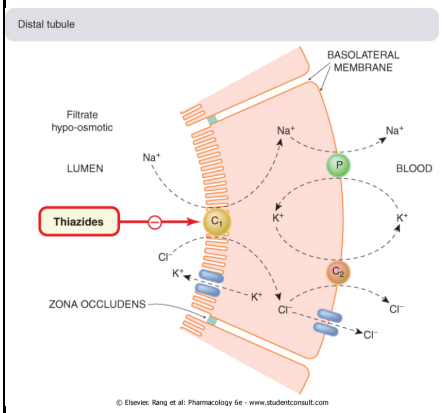
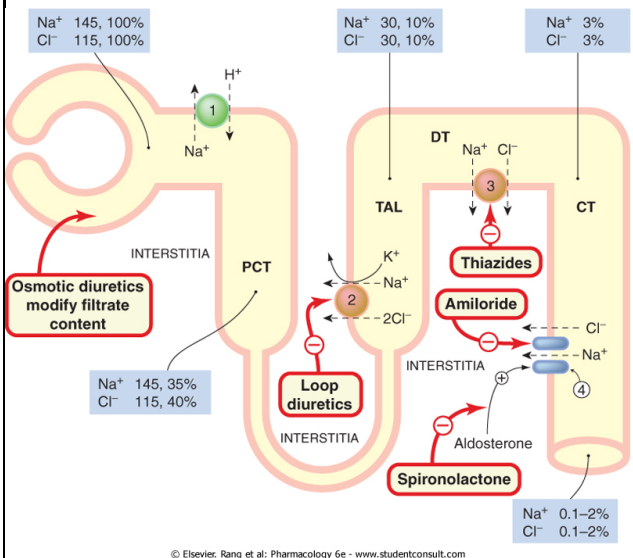
AH01 [Jul97] [Mar98] [Jul98] [Mar99] [Jul99] Glycopyrrolate: A. Has mandelic acid rather than tropic acid B. Tertiary amine C. ? D. ? (See also MB08)	A - Naturally occurring anticholinergics (atropine and scopolamine) are esters formed by the combination of tropic or mandelic acid and an organic base (tropine, scopine, or an N-methylated derivative of tropine). - Synthetic anticholinergic drugs like glycopyrrolate contain mandelic acid rather than tropic acid. - Structurally, these drugs resemble cocaine. - Glycopyrrolate increases metabolic oxygen consumption (atropine no change, scopolamine decreases it) - Glycopyrrolate is a synthetic quaternary amine
AH02 [Jul98] [Mar99] [Jul00] Hyoscine: A. ? B. Quaternary ammonium compound C. ? D. Causes mdriasis E. Causes confusion in the elderly	D and E Hyoscine = scopolamine - Tertiary ammonium compound - can cross blood brain barrier and cause sedation and confusion, particularly in elderly - more potent antisialagogue - topical anticholinergics to eye cause mydriasis and cycloplegia but atropine typically used even though IM scopolamine is more potent. IV atropine/glycopyrrolate dont have this effect
AH03 [Jul99] [Feb00] Scopolamine d & l isomers: A. d is active B. Provided as racaemic product C. Doesn't cause central effects D. ?	B “Atropine and scopolamine comprise mixtures of equal parts of dextrorotatory and levorotatory isomers, but the anticholinergic effects are due to the levorotatory from.” Can cross BBB and cause central effects

AH04 [Jul00] Atropine: A. ? B. Increases anatomical & alveolar dead space C. ? D. ?	B – the resulting relaxation decreases airway resistance and increases dead space, as well as the effect vagal activity has in HPV - Antagonism of ACh effects on airway smooth muscle present predominantly in large and medium sized airways. - decreases airway resistance - increase dead space by about 1/3, but this effect depends largely on the degree of preexisting bronchomotor tone - glycopyrrolate is equally effective bronchodilator
AH05 [Jul01] [Mar03] Atropine & glycopyrrolate: A. Both are naturally occurring B. Cause confusion in the elderly C. ? D. ? E. ?	?B Neither Atropine natural, glyco semisynthetic Glyco is tertiary and cannot cross BBB to cause confusion. Look at the q on the day but Stoelting says that glyco has been associated with central anticholinergic syndrome even though it is less likely
AH06 [Jul04] Which of the following is the most toxic effect of atropine in children? A. Hypotension B. Tachycardia C. Hyperthermia D. Hypertension	C "Small children are particularly vulnerable to drug-induced increases in body temperature, with 'atropine fever' occurring occasionally in this age group after administration of even a therapeutic dose of anticholinergic drug." Although the best choice would be central effects: "fatal events include seizures, coma and medullary ventilatory centre paralysis" [Stoelting p274]
AH07 [Apr07] The nerve agent sarin: A. should not be treated with anticholinesterase if there is tachycardia B. something about pyridostigmine C. symptoms can include fasciculations and paralysis D. *something about pralidoxime unblocking the receptor (a red herring teaser)* E. ?	C This is a organophosphate anticholinesterase. Pralidoxime is a acetylcholinesterase reactivator.

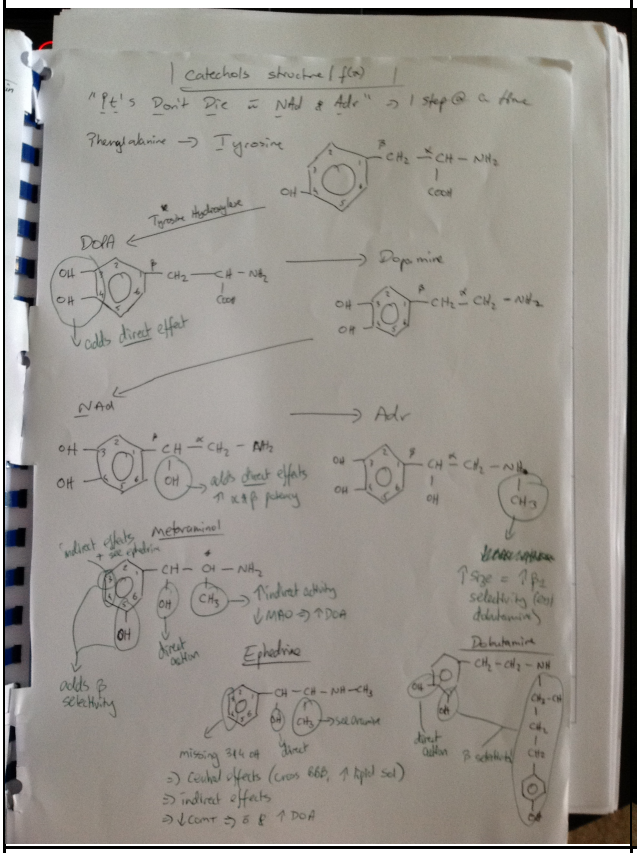
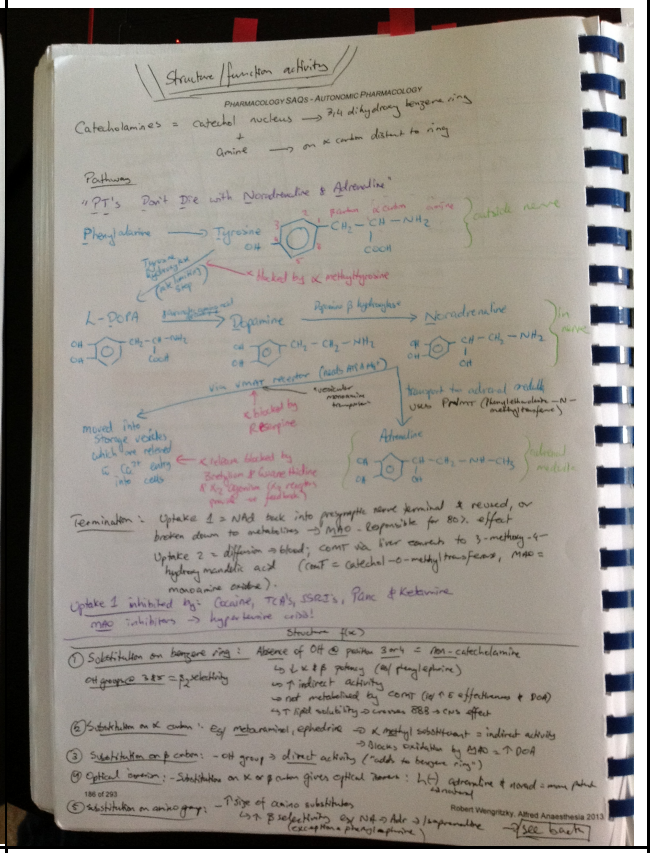
Cardiovascular

CD01 Milrinone: A Decreases pulmonary vascular resistance B Increases systemic vascular resistance C Is poorly absorbed when given orally D Chronic use causes thrombocytopenia	A Milrinone is a peripheral vascular dilator, so decrease vascular resistance. It is absorbed, but increases mortality when given orally. Thrombocytopenia occurs with amrinone, but is rare with milrinone Milrinone is a selective phosphodiesterase III inhibitor, ↑cAMP, ↑stimulation of protein kinases that increase inward calcium. This produces positive inotropic effects. It also ↑cGMP which ↓Ca2+ causing smooth muscle relaxation in the lungs and peripherally, ↓PVR and SVR. It has minimal effects on heart rate and myocardial O2 consumption. Stoelting p317
CD01a Milrinone causes: A Chronic use causes thrombocytopenia B Pulmonary vasoconstriction C Not effective orally D ? E ?	None are true! See above.
CD01b Milrinone: A Cannot be given orally B Is a phosphodiesterase III inhibitor that decreases cyclic AMP C Decreases peripheral vascular resistance D Increase pulmonary vascular resistance	C PDIII inhibitor, but function is to reduce degradation of cAMP (ie increase it). Others see above
CD01c Milrinone: A Is structurally related to thyroid hormone B Is arrhythmogenic C Has its effects via cAMP mediated increase in intracellular Ca2+ D Increases myocardial oxygen consumption	C B & C are true, but arrhythmias are rare, so perhaps C more true? A Can't find anything on structural relation to thyroid hormone. D Minimal effects on HR & myocardial oxygen consumption, but can be a problem in acute phase of AMI
CD02 Sodium nitrate used in cyanide toxicity: A Increases methaemoglobinaemia B To produce increased hepatic sulphydryl groups C Increases conversion to cyanocobalamin D Displaces cyanide from haemoglobin E Enhances oxidative phosphorylation	A (?also E, but indirectly) Converts Hb to meth-Hb (has a higher affinity for cyanide). Sodium Thiosulphate is usually the sulphur donor. By binding to form cyanometh-Hb, should allow more oxygen to pass to cells for oxidative phosphorylation.
CD03 Ephedrine: A. Is resistant to metabolism by MAO - Is metabolised by COMT - Action is totally indirect - Acts via direct & indirect beta effect - Action is purely alpha agonist	D ?A Ephedrine indirectly (via norad) and directly acts on α and β. It is resistant to metabolism to MAO in the gut (but some is metabolised by MAO in the liver) and COMT as it does not have the hydroxyl group on C3. Stoelting p302 IV administration results in increases in systolic and diastolic blood pressure, heart rate and cardiac output. Renal and splanchnic blood flows are decreased whereas coronary and skeletal blood flows are increased.
CD03(i) Ephedrine: A Has direct alpha actions only B Has direct beta actions only C Has indirect (alpha) actions only D ? E Has both indirect & direct actions on alpha & beta receptors	E see above
CD03a(ii) Ephedrine - α 1 & 2 and β 1 & 2 & 3 - More alpha than beta - Indirect this and direct that... - Direct this and indirect that...	D? Predominantly A1, B1 and B2 (used as chronic oral medication because of bronchodilating effects)
CD03b Ephedrine: A ?increases/?decreases skeletal muscle blood flow B Acts only by indirect effects C Not metabolised by GIT MAO D Not metabolised by COMT E Increase renal blood flow	C & D true A true if increased Increase blood flow to skeletal & cardiac muscle, decreased flow to renal and splanchnic flow.

CD03c Ephedrine has: A Direct agonist on alpha receptors B Direct and indirect effects on α & β C Indirect actions on alpha receptors D Direct actions on beta receptors E Indirect actions on beta receptors	B all are true but B is most true.
CD04 The principle (?urinary) metabolite of adrenaline is: - Normetanephrine - Metanephrine - 3,4-dihydroxy-mandelic acid - 3-methoxy, 4-hydroxymandelic acid - 3-methoxy, 4-hydroxy phenylalanine	D Principle metabolite in urine is D. Also produced for adrenaline is B & for noradrenaline is A. Uptake into organs accounts for more offset of action than excretion Diffusion away ≈ 20% ↓Metabolised by COMT (liver) Normetanephrine Reuptake into nerve terminal ≈ 80% ↓Metabolised by MAO ↓ Dihydroxymandelic acid Recycled

CD05 Thiazide diuretics: A. Work mainly on PCT B. Not effective if severely sodium depleted C. Action is independent of acid-base balance D. Increase GFR immediately E. Decrease BP by decreasing contractility F. Cause hypoglycaemia G. Interferes with kidney concentrating mechanisms H. Causes hypocalcaemia I. Used to treat hypercalcaemia J. Potentiate hyperglycaemia K. Are effective as antihypertensives by decreasing cardiac output L. Cause hypernatraemia M. Washes out the medullary concentration gradient.	C, J true B - decreased effect Note H & I true in Stoelting, false in Goodman & Gillman Thiazides produce diuresis by inhibiting reabsorption of Na & Cl. Used in HTN, oedema, diabetes insipidus, tx hypercalcaemia. Principle action in ascending loop of Henle, some action in proximal & distal. Result in loss of Na, Cl, HCO3 with associated loss of K (if enhanced distal delivery of Na & H2O). HTN rx due to decreased ECF which often leads to decreased CO, but sustained effect due to ↓SVR & peripheral vasodilation (takes weeks to develop, due to loss of Na). Side effects: ↓K/Cl - metabolic alkalosis, ↓Na/Mg - kaliuresis + side effects of electrolyte disturbance, hyperglycamia (unknown mechanism), hyperuricemia  
CD05b Thiazide diuretics A. Increase calcium excretion in the urine B. Decreased efficacy in sodium depletion C. Main side of action is the proximal tubule D. Cause equivalent amount of diuresis to frusemide E. ?	B A arguably true from Stoelting but B less controversial. Faunce says increased Ca reabsorption in DCT
CD06 Sodium nitroprusside in healthy pt: A Decreases venous more than arterial resistance B Has no effect on control of pulmonary vascular resistance C Decreases cerebral blood flow D Causes uterine relaxation E Does not inhibit hypoxic pulmonary vasoconstriction	D Causes venous and arterial relaxation, decreases SVR & PVR (so inhibit HPV), increased cerebral blood flow. Inhibits spontaneous contractions of the non-pregnant human uterus

CD07 Which one of the following statements about clonidine is correct? A Increase MAC requirements B Cause transient hypertension with IV administration C With IV bolus cause hyper- then hypo- tension D Causes hypotension immediately E Is not (?administered/absorbed) transdermally	B, C (C is better answer) Decreases MAC requirement. Is available in patch form. Has transient alpha 1, then alpha 2 action on IV admin Clonidine is a centrally acting partial α2 adrenergic agonist (220:1 α1:α2). Stoelting p340.
CD08 Regarding digoxin: A. The aglycone portion causes the cardiac effects B. The glycone portion causes the cardiac effects C. & D. ?	A Cardiac glycosides consist of 2 parts: - aglycone (steroid & lactone ring): intrinsic cardiac activity - glycone (attached sugar residues): responsible for pharmacokinetics (eg tissue uptake) Both are required for drug to be clinically useful.
CD09 Digoxin: A. Decreases ventricular response to vagal stimulation in AF B. Decreases myocardial oxygen consumption C. Increases the R-T interval D. Decreases AV conduction	D Inotropic action results from increased intracellular Ca+ - increase phase 4 slope (ie increase rate of automaticity), especially if K+ is low. Inhibits Na/K/ATPase pump → ↑ intracellular Ca++ and +ve iontropic effect → ↑ contractility & automaticity & force of contraction. Indirect but prominent vagotonic effect - sensitisation of baroreceptors & activation of vagal nuclei resulting in inhibition of Ca++ currents in the AV node and activation of acetylcholine mediated K+ currents in the atrium. Thus ↓ SA node discharge, slow AV, ↑ refractory period. At therapeutic concentration: PR prolonged, ST depressed, T flattened, QT shortened
CD10 Which of the following ECG changes would be most likely in digoxin toxicity? A Increased PR interval B Increased QT interval C Peaked T waves D ST elevation E Ventricular extrasystoles	E and A No unequivocal features on ECG confirm toxicity, but [toxic] typically cause atrial or venticular dysrhythmias and delayed conduction through AV node. Atrial tachycardia with block is the most common cardiac dysrhythmia attributed to dig toxicity. Also see junctional bradycardia, ventricular bigeminy, 2nd/3rd degree heart [Goodman and Gillman] Although digitalis intoxication can cause virtually any arrhythmia, certain types of arrhythmias are characteristic. Arrhythmias that should raise a strong suspicion of digitalis intoxication are those in which DAD-related tachycardias occur along with impairment of sinus node or AV nodal function. Atrial tachycardia with AV block is classic, but ventricular bigeminy (sinus beats alternating with beats of ventricular origin), "bidirectional" ventricular tachycardia (a very rare entity), AV junctional tachycardias, and various degrees of AV block also can occur. With severe intoxication (e.g., with suicidal ingestion), severe hyperkalemia owing to poisoning of Na^+,K^+-ATPase and profound bradyarrhythmias, which may be unresponsive to pacing therapy, are seen. ECG effects are: 1. Prolonged P-R intervals due to delayed conduction of the AV node 2. Shortened QTc intervals because of more rapid ventricular depolarisation 3. ST segment depression 4. Diminished amplitude or inversion of T waves. Stoelting p314
CD10b Digoxin toxicity A Inverted T waves B Prolonged PR C Xanthopsia D Prolonged PT interval	C B See above **Xanthopsia refers to the predominance of yellow in vision due to a yellowing of the optic media of the eye. The most common cause is digoxin toxicity and the development of cataracts which can cause a yellow filtering effect. Wikipedia.**
CD11 Regarding digoxin overdose/toxicity: A. Serum level >2.1ng/ml is toxic B. ? C. Causes a long PR interval D. Cause xanthopsia (OR causes yellow vision) E. Causes a long QT interval and bigeminy	D or C Therapeutic range 0.5-2.5, definate toxicity >3ng/ml Xantopsia is a side effect in some texts (rather than toxicity) but a toxicity in others QT shortened

CD12 Clonidine: A Elimination half-life of 3 hrs (??or 3-6hrs) B Excreted 50% unchanged in urine (or 50% renally excreted) C Oral bioavailability 50% D Cannot be absorbed topically E Is highly protein bound	B (up to 65% excreted unchanged in urine) Clonidine is a centrally acting selective alpha2 agonist. $t_{1/2}$ 6-10hrs Oral bioavailability 100% Comes in patches Very lipid soluble, Vd 1.7-2.5L/kg, 20% protein bound
CD13 deleted (same as CD05)	
CD14 Adenosine: A Slows conduction velocity and increases refractory period B Is metabolised in plasma C Decreases urate levels D Methylxanthines increase response	None. Acts on A1 receptors (Gi protein) coupled to K+ channels in SVT tissue causing AV nodal block. Slows conduction velocity and increases PR interval. Sasada. It shortens the action potential. Stoelting p385 Adenosine is a naturally occurring purine nucleoside used to dx &tx SVT. Metabolised in RBC & vascular endothelium ($t_{1/2}$ <10sec) Uric acid levels may ↑ 10-20% Methylxanthines such as theophylline and caffeine block adenosine receptors so larger than usual doses are required to produce an effect. Adenosine is potentiated in patients taking dipyridamole is an adenosine uptake inhibitor. Goodman & Gillman
CD15 Catecholamine substitution: A Alpha carbon CH2 substitution give beta selectivity B Beta-hydroxy substitution gives increased affinity C D-dobutamine antagonist, L-Dobutamine agonist D ?	C and B (C most correct) Dobutamine isomers: both are beta agonists, opposite effects at alpha1 (levo dobutamine is the alpha1 agonist) [Stoelting p300] Substitution at alpha carbon blocks oxidation by MAO and prolongs the action of these drugs, particularly the noncatecholamines (eg ephedrine, amphetamine). Substitution of beta hydroxyl group will mean it loses it direct action (ie becomes indirectly acting)
	
CD16 Esmolol A Active at beta1 & beta2 receptors B Half-life <2mins C Has methanol as metabolite D Is metabolised by (?acetyl/?plasma) cholinesterase E Is excreted unchanged in the urine F Is a non-selective beta1 receptor antagonist	C Negative inotrope & chronotrope used in acute supraventricular dysrhythmias (AF/flutter), HTN, AMI. Competitive BBlocker, relatively selective for B1. Little/no intrinsic sympathomimetic activity. Vd 3.43L/kg, 56% protein bound, $t_{1/2}$ 9.2mins, metabolism by red cell esterases to methanol & acid metabolite with weak beta antagonism, Cl 285 ml/min/kg, <1% excreted unchanged in urine

CD16b Esmolol: A Is a non-selective beta antagonist B Has intrinsic sympathomimetic activity C Does not have membrane stabilising activity D ?	C On Peck & Hill table 13.2 - no membrane stabilising activity. Others as above
CD17 Mannitol: A Less sodium delivered to distal tubule B Hypotonic medulla C Increased sodium loss D Urine osmolality > plasma osmolality E increased sodium reabsorption/?causes hypernatraemia F ?MW greater than 600 G Washes out the medullary interstitial gradient	C, G (both correct, different options different years) Osmotic diuretic. Low MW (182 daltons) - freely filtered at glomerulus & not reabsorbed. Increases osmolality of glomerular filtrate & tubular fluid - osmotic effect. Renal blood flow increased, rate of renin secretion decreases. Mannitol washes out medulla interstitial gradient (isotonic medulla) - decreased ability to concentrate urine. Na & K may fall (more delivered at lower concentration) & urea may increase
CD17b Osmotic diuretics: A Include mannitol and the dextrans B Wash out the medullary osmotic gradient C Cause sodium retention D E Have a molecular weight >600 daltons	B Mannitol & urea are osmotic diuretics.
CD18 Guanethidine: A Causes sedation as a side effect B Postural hypotension occurs C Decreases reuptake of catechols presynaptically D ?	B Guanethidine was an antiHTN - postganglionic adrenergic blocking agent. Uptake & storage via norad pump & vesicles - replaces norad storage & blocks release Sophie is right - the uptake is POSTsynaptic and NOT presynaptic [Katzung and Longnecker's] Side effects include expansion of intravascular volume, necessitating its use with a diuretic, as well as orthostatic and exercise-induced hypotension, diarrhea, and sexual dysfunction. Tricyclic antidepressants, amphetamines, chlorpromazine, and ephedrine may interfere with its effectiveness by their effects on guanethidine's uptake mechanism. Guanethidine is contraindicated in patients with pheochromocytomas and should not be given to those receiving monoamine oxidase (MAO) inhibitors.
CD18b Guanethidine: A Acts primarily at?/on? the CNS B Produces anti-hypertensive effects primarily by presynaptic inhibiting release of noradrenaline C Highly lipid soluble D Mental depression is a troublesome side effect E Orthostatic hypotension is not a prominent side effect	B Poorly lipid soluble Doesn't cross BBB
CD19 Labetalol: A Alpha agonist and beta agonist B Alpha agonist and beta antagonist C Alpha antagonist and beta antagonist D Is a more potent alpha blocker than phenoxybenzamine E Alpha > beta effect	C Racemic with 4 isomers: 2 inactive, 1 alpha blocker, 1 beta blocker. Alpha blocking weak. Labetalol is a selective α1 and nonselective β antagonist. Presynaptic α2 receptors are spared such that noradrenaline can inhibit further release via negative feedback. Labetalol is 1/10 to 1/5 as potent as phentolamine in blocking α receptors and is 1/4-1/3 as propranolol in blocking β receptors. Stoelting p335.
CD20 Frusemide: A 30% plasma protein binding B ??% absorption C Elimination half-life less than 1 hr D Promotes active secretion E Affects the uricosuric effect of probenecid F Effects not decreased until large decrease in GFR G Causes a diuresis which is dependent on GFR over a wide range	C true, G true, E [C is best answer & direct quote from stoelting] Loop diuretic, inhibits Na reabsorption in PT & ALH - reduces tonicity of renal medulla. No active secretion. 60-70% absorbed orally, bioavailability 43-71%, 90+% protein bound, Vd 0.11-0.13 L/kg, 50-80% excreted unchanged in urine, rest appears in the bile & faeces. Cl 2.2ml/kg/min, elimination$_{1/2}$ <1hr. Uricosuric drugs are substances that increase excretion of uric acid. Frusemide impairs the naturetic effect of probenecid. Responsiveness is directly related to the GFR over a wide range
CD20a Frusemide: A Has 30% (?35%) protein binding B Has an elimination half-life <1hr C 90% excreted in bile D Increases rate of secretion in the renal tubules	B As above
CD20b Frusemide does NOT cause: A Hyponatraemia B Hypokalaemia C Hypouricaemia D Hypomagnesemia E Hypocalcaemia	C Causes hypokalaemia, hyponatraemia, hypocalcaemia, hypomagnesaemia, metabolic acidosis. Causes minimal hyperuricaemia

CD21 The antiarrhythmic effect of lignocaine: A Because it increases the refractoriness in cardiac muscle B Therapeutic level 2-5ng/ml C ?	A - yes by slowing phase IV In low concentration, ↓rate of phase IV depolarisation, duration of action potential, effective refractory period & conduction velocity Therapeutic level 1-5mcg/ml [Stoelting]
CD22 The effects of beta blocker - the following is not true A Relax uterine muscle B Increased AV conduction C Decreased lipolysis D Increased SVR E. Mask hypoglycaemia F. Negative inotropy G. Opposing effects of insulin H. Lipolysis	B, G, H (multiple years worth of questions) D is true: "Blockade of β2 receptors ↑PVR and CVR due to ref: propranolol" in Stoelting p326 and Sasada. Non-selective β blockers may impeded LV ejection due to unopposed α1 adrenergic peripheral vasoconstriction. B the most false hence the most correct! Non-selective B-blockers eg propranolol cause initial B2 block and initial increase in SVR.
CD23 Phentolamine; A Is a selective alpha-1 antagonist B Binds covalently to the alpha receptor C Causes bradycardia D Is a selective alpha-2 antagonist E Increases cardiac output	E Competitive alpha blocker, nonselective but has alpha1>2, some beta agonism & serotoninergic activity. Phenoxybenzamine binds covalently. Decreased BP & reflex tachycardia. Positive inotropy related to indirect effect of alpha2 block & norad release.
CD24 A non-selective beta-blocker with a low extraction ratio, long half-life and ISA: A Atenolol B Propranolol C Metoprolol D Labetalol E ?	None – pindolol is correct, Next best is D Atenolol & metoprolol B1 selective Propranolo & labetalol nonselective ISA = intrinsic sympathetomimetic action, ie agoinsm and antagonism. Propranolol, atenolol, metoprolol - no ISA (pure antagonist) Labetalol may have some ISA & some alpha1 antagonism . ISA in oxprenolol, pindolol, penbutolol, acebutolol Pindolol is the correct answer. Non Selective. FPM 10%. 3-4 hrs. Partial agonist activity.
CD24b Which ONE of the following is water soluble, half life 6-8hrs, ("and something else")? A Esmolol B Metoprolol C Propranolol D? E Atenolol	E Esmolol half life 8mins Metoprolol halflife 3-4hrs Propranolol halflife 2-3hrs Atenolol halflife 6-8hrs & has renal removal (water soluble)
CD24c Which one of the following selective BB has a low extraction ration & is predominantly ... A Propranolol B Esmolol C Atenolol D Metoprolol	C Hepatic extraction ratio: Propranolol 75%, esmolol -, atenolol 10%, metoprolol 60%
CD24d A beta1 selective antagonist, predominantly excreted in urine & halflife 6-8 hrs A Sotalol B Esmolol C Atenolol D Propranolol E Metoprolol	C
CD26 Sotalol: A Non-selective beta-blocker B Contraindicated in long QT C Increases K+ conductance D Used in the tx of torsades E Class II antiarrhythmic drug F Is a selective B1 antagonist G Blocks K+ channels.	A, B, E, G (asked multiple years) Sotalol is used for sustained VT, VF, atrial arrhythmia. Non-selective B antagonist at low dose. Class II & III activity. At higher dose prolongs cardiac action potential. Not recommended in asthma, LVdysfn & conduction abnormalities (eg long QT, can cause torsades). Renal excretion, no protein binding, not metabolised, doesn't x BBB
CD27 Trimetaphan A Crosses the blood-brain barrier B Incompatible with thiopentone C ?	B Trimethaphan is a peripheral vasodilator & ganglionic blocker previously used for controlled HTN (now replaced by SNP & GTN). Quaternary ammonium - doesn't x BBB Is incompatible with thio

CD28 Diazoxide A Has diuretic activity B Opens ATP-dependent K channels C Not absorbed orally D ?	B Benzothiadiazine derivative, related chemically to thiazide diuretics. Used for acute BP mx. Causes Na & H2O retention (unlike thiazides). Has been given orally to tx hypoglycaemia (drug-induced alpha agonist-like inhibition of insulin release) It causes fluid retention despite structural similarity to thiazides, and it is use orally – 50mg tablets, bioavailability of 80% (PHW)
CD29 Phenylephrine: A Metabolised by COMT B Causes mydriasis C Metabolised by MAO D Effects last (?same time as/?longer than) noradrenaline E Acts by indirect method only	B (most correct), C (correct with topical adminstration), D also correct (depending on wording of actual options – effects last longer than NAd) Synthetic noncatecholamine, stimulates principally alpha1 by direct effect & small indirect (norad release) No catechol so not metabolised by COMT. Much longer duration of action than the catecholamines
CD30 Regarding hydrallazine: A Fast acetylators have shorter half lives than slow acetylators B Acts via SNS mechanism C Slow acetylators decrease half-life D Has diuretic action E Clearance >50ml/kg/min	A Phthalazine derivative that activates (by uncertain mechanism) guanylate cyclase to produce vascular relaxation. ↓BP by relax vasc smooth muscle. Induces reflex increase in SNS. Acetylation is major route of metabolism. Rapid acetylators have bioavail 30%, slow acetylators have bioavail 50% & gain higher conc in chronic oral dosing. Causes Na & H2O retention. Duration of action 2-6hrs Elimination 1/2life avg 3hrs, 87% protein-bound, Vd 4.2L/kg, Cl 23ml/kg/min (Sasada & Smith) to 50ml/kg/min
CD31 Which ONE of the following beta-blockers is selective for beta-1 receptors? (No other details)	
CD32 Which of the follow statements about hydrallazine is (?true/false): A Acts via alpha 1 receptors B/C/D? E Has a duration of action of 1-2 hours	A False - mechanism not certain but probably direct activation of guanylate cyclase and increase in cGMP - leading to decreased in intracellular Ca++ and vasodilation. E False - duration of effect 2-6hrs
CD33 Concerning dobutamine A Levo has alpha 1 antagonist and beta agonist effects B Levo has partial alpha agonist effects and beta effects C is a pure beta agonist D ?	B Dobutamine is a synthetic catecholamine that acts as a selective B1 agonist. Both isomers of dobutamine are B agonists, whereas at alpha1 receptors these isomers exert opposing agonist (levo) and antagonist (dextro) effects
CD34 Adenosine A Causes AV block via action at A1 receptors B Causes bronchoconstriction via A2 receptors C Causes renal vasodilation D Causes profound depression of the SA node E Decreases AV transmission	A & E Effects of adenosine via A1, A2 & A3 receptors (A = adenosine NOT alpha). All are GPCR. A1: block AV conduction, bronchoconstriction, inhibition of transmitter release at many CNS & PNS synapses A2: vasodilation except kidney (which gets vasoconstriction), inhibits platelet aggregation, stimulates nociceptive neurons, A3: release mast cells mediators SA & AV node by A1 (adenosine1) receptors - opening of K channels - hyperpolarisation & decrease in diastolic depolarization & negative chronotropy.
CD35 Mechanism of action of hydralazine: A Selective cerebral, coronary, renal vasodilator B Alpha agonist C None of the above D ?	C Cerebral, coronary, renal & splanchnic circulations have more pronounced vasodilatory effects but does cause generalised vasodilation
CD36 [Jul00] [Jul04] Clonidine: A. Causes hypertension and tachycardia B. Causes bradycardia C. A single dose given orally is significantly less effective then an intravenous dose D. Counteracts the hypertensive response in phaeochromocytoma E. ?	B [Stoelting + Peck/Hill/Williams] Hypotension. May have bradycardia (suppression of endogenous catecholamine release). CO initially decreased then returns to normal. Rapidly & almost completely absorbed orally, bioavailability nearly 100%. Decrease the plasma concentration of catecholamines in normal patients but not in the presence of phaechromocytoma.
CD36b [Jul04] Clonidine can cause these, except A. Bradycardia B. Apnoea C. Sedation D. ?	B In contrast to opioids, doesn't cause significant respiratory depression

CD37 [Jul00] [Jul04] The first sign of sodium nitroprusside toxicity is: A. Cyanide toxicity B. Tachyphylaxis C. Hypotension D. ? (see also [[CD02, [[CD06)	B Cyanide toxicity should be suspected in any patient who is resistant to the hypotensive effects of the drug despite maximum infusion rates, or a previously responsive patient who becomes unresponseive to the systemic blood pressure-lowering effects (tachyphylaxis). [Stoelting p 356] Also causes increased mixed venous PO2, metabolic acidosis, CNS dysfunction.
CD38 [Apr01] Dexmedetomidine: A. Alpha-1 antagonist B. ? C. Decrease in intraocular pressure D. Partial alpha2 agonist E. Less selective than clonidine	C Selective alpha 2 agonists (a2 1600:1 a1), more selective than clonidine (200:1). Considered to be a full agonist at a2 (clonidine is considered a partial agonist). Has been demonstrated to decrease intraocular pressure [BJA article 1992, 68 (6): 570]
CD39 [Jul01] [Jul04] Amiloride: A. Potassium sparing antidiuretic which blocks the aldosterone receptor B. Blocks luminal sodium channels in the collecting tubules C. Increases potassium excretion. D. Is metabolised by the liver. E. Has a short elimination half time.	B Amiloride is a K+ sparing diuretic that acts directly on renal tubular transport mechanisms in DCT & CD independent of aldosterone. Diuresis characterized by increase in urinary excretion of Na+, Cl-, HCO3- & increase urinary pH. May have no increase or decrease in K+ excretion in urine. Is incompletely absorbed, is not metabolised, elimination half-time 18hrs. [Stoelting 4th ed p492 + Katzung 9th ed p250]
CD40 [Jul01] With regard to sodium nitrite in cyanide (CN) toxicity: A. Causes MetHb B. Used to create more hydrocobalamin C. Used to displace CN from Hb D. Creates more sulfhydryl groups	A Nitrites (sodium or amyl nitrite) are used to convert oxyhaemglobin to methaemoglobin which has a higher affinity for CN. Sodium thiosulphate provides additional sulphydryl groups, B12 is sometimes used for hydrocobalamin, dicobalt edetate chelates CN- [Peck/Hill/Williams 3rd ed, p248]
CD41 [Jul01] Methylxanthines: A. (Something about Ca^{++} currents) B. (Something about K^{+} currents) C. Inhibit adenosine receptors D. Decrease plasma glucose level E. Cause diuresis by acting on renal tubules F. Physically addictive	C most correct E correct ? A correct Methylxanthines are represented by caffeine, theophylline & theobromine. Effects: CNS stimulant, diuresis, increase myocardial contractility, relax smooth muscle (esp airway). MOA: antagonism of receptor-mediated effects of adenosine. [Stoelting 4th ed, p593] Caffeine inhibits ADH secretion - diuresis. Soph's additional: Methylxanthines: uncertain mechanism of action. ?via PDE inhibition. CVS effects via inhibition of presynaptic adenosine receptors à increased catecholamine release. At higher concentrations ?Ca influx due to increase in cAMP via PDE inhibition. They are also weak diuretics – via increased GFR and reduced tubular Na reabsorption (Katzung). I think that C is most correct, although ? A correct, ?E correct ?F correct. Fairly sure B and D incorrect.
CD42 [Feb04] [Jul04] Which is the initial drug to use in the treatment of ventricular fibrillation? A. Amiodarone B. Lignocaine C. Adrenaline D. Magnesium E. Sotalol	C Adrenaline then amiodarone [Australian resuscitation council website www.resus.org.au]
CD43 [Feb04] All are side effects of Thiazides except: A. Hypokalaemia B. Hypernatraemia C. Impaired carbohydrate tolerance D. Pancreatitis	B Thiazide side effects include hypokalaemic, hypochloraemic metabolic alkalosis, hypomagnesaemia, hyponatraemia. May have effects from these (arrhythmias, weakness, ileus). May cause hyperglycaemia (aggrevate DM), hyperuricaemia (exacerbate gout). Bendrofluazide may precipitate pancreatitis. [Stoelting 4th ed, p487 + Peck 3rd ed, p307]
CD44 [Feb04] Why do you give adrenaline for VF? A. To coarsen fine VF B. To improve coronary blood flow C. Increase chronotropy	B Adrenaline administered in cardiac arrest to cause peripheral vasoconstriction & may facilitate defibrillation by improving myocardial blood flow during CPR. [Australian resuscitation council website www.resus.org.au]

CD45 [Feb04] Nitroprusside toxicity: A. Treat with ??? B.	Dicobalt edetate: chelates CN- ions Sodium thiosulfate: provides sulfhydryl groups to facilitate conversion of CN- to SCN (which is 100 times less toxic than CN- but still toxic esp if it accumulates) Nitrites (sodium nitrite/amyl nitrite): conversion of oxyHb to metHb, which has a higher affinity for CN- than cytochrome oxidase Vitamin B12 can be used as prophylaxis (but not in acute setting), complexes CN- to cyanocobalamin [Peck 3e pp248-249] • Treatment: 1. Sodium bicarbonate to correct acidosis 2. Sodium thiosulfate 150mg/kg to act as sulphur donor 3. Sodium nitrite which converts Hb - MetHb 4. Dicobalt edetate or Vit B12a which chelates cyanide
CD46 [Jul04] Which of the following is a sign of SNP toxicity? A. Tachyphylaxis B. Decreased mixed venous PO2 C. Sudden decrease in arterial PO2 D. ?Hypotension	A see question 37
CD47 [Jul04] Dihydropyridine Ca channel blocker causes peripheral oedema due to A. vasodilator causing redistribution of ECF B. has a mild antidiuretic effect, and therefore easily treatable with diuretic C. salt and water retention due to hypotension D.	A Dihydropyrimidines include nifedipine, nicardipine, nimodipine, felodipine & amlodipine. They have an affinity for peripheral arterioles. Dihydropyridines not uncommonly cause ankle swelling, possibly because arteriolar dilatation increases capillary pressure, especially in the feet where venous pressure is greatest when standing. [Rang 4th ed, p276]
CD48 [Jul04] Isoprenaline A. can be used as a substitute to Metaraminol for treatment of hypotension B. used extensively to treat ischaemic heart disease C. cause decrease SVR D. cause bradycardia E. ?	C Isoprenaline = Isoproterenol (US term) Is the most potent activator at B1 & B2 receptors. In clinical doses is devoid of alpha action. Metabolism by COMT in liver rapid - requires continuous infusion. Clinical uses: heart block, bradydisarrhythmias, bronchodilator. Effects: ↑HR, ↑cardiac contractility, ↑cardiac automaticity, ↓SVR → net effect ↑CO that is usually sufficient to increase SBP but may ↓MAP & ↓DBP → may ↓coronary flow (poor perfusion pressure) & compromise pt with coronary disease (causes increased demand at same time due to tachycardia). [Stoelting 4th ed, p301]
CD49 Which one of the following is NOT an adverse effect of amiodarone? A. Pulmonary fibrosis B. Photosensitive rash C. Corneal microdeposits D. cardiomyopathy E. thyrotoxicosis	D Causes bradycardia/heart block/arrhythmias but is not known to cause cardiomyopathy. Others are potential side effects. [Stoelting 4th ed, p382]
CD50 The beta blocker with the greatest oral bioavailability is: A. Atenolol B. Metoprolol C. Sotalol D. Labetalol E. Carvedilol Others: ??Propranolol ??Esmolol	C Bioavailability % Pindolol 90 Sotalol 85 Timolol/metoprolol 50 Atenolol 45 Oxprenolol/acebutolol 40 Propranolol/Carvedilol 30 Labetalol 25 Esmolol 0 [Peck 3rd ed, p222 + Katzung 11th ed p157]
CD51 Dexmedetomidine A. MAC sparing for isoflurane by maximal 30% B. can cause bradycardia & sinus arrest C. increases CBF D. ? E. ?	B Highly selective a2 agonist (1600:1) In humans, Isoflurane MAC decreased 35-48% by dexmedetomidine (0.3-0.6ng/ml). In high doses, can be used as TIVA. Severe bradycardia may follow administration & cardiac arrest has been reported. [Stoelting 4th ed, p344]

CD52 [Jul08] Acetazolamide: A. maximum increase in urine pH 8 hours after oral dose B. maximum safe dose causes complete absence of HCO3 reabsorption C. maximum safe dose decreases HCO3 reabsorption (?to) 45% D. causes hypochloraemic acidosis E. is a potassium sparing diuretic	C Acetazolamide is a carbonic anhydrase inhibitor - binds avidly to CA enzyme, noncompetitive inhibition principally in PT. Excretion of H+ ions is diminished & loss of bicarb is increased. Cl- is retained by kidneys to offset bicarb losses. K+ excreted in exchange for Na+ in DT (as H+ not available). Net effect is hyperchloraemic metabolic acidosis. Max safe dose inhibits 85% of HCO3- reabsorption at PCT, but 45% inhibition for whole kidney (continued HCO3 reabsoprtion by CA independent mechanism) [Stoelting, 4th ed, p494 + Katzung 11th ed, p256]
CD53 [Mar09] Acetazolamide A. Structurally related to procainamide and may have anti-arrhythmic activity at high doses B. Something about metabolism C. ? D. ?	None of these Procainamide has similar effects to quinidine but is less vagolytic. Other effects: inhibit formation of aqueous humour (for glaucoma), inhibit formation of CSF, inhibits seizure activity, helps in management of familial periodic paralysis [Stoelting, 4th ed, p494]
CD54 [Mar09] Pharmacokinetics of amiodarone: A. Oral bioavailability is reliable B. Doses must be reduced in renal and hepatic failure C. Omission of 1 or 2 doses can lead to severe consequences D. Metabolism is via ?hydroxylation/demethylation? E. ?Increases/?decreases refractory period	E if is increases Poorly absorbed from the GIT, oral bioavailability 50-70%. Hepatic metabolism produces desethylamiodarone (some anti-arrhythmic activity). It is excreted by lachrymal glands, skin & biliary tract. (Little renal excretion) Elimination half life very long 20-100days (could probably miss several doses). MOA: Blocks K+ channels, slows rate of repolarisation - increases duration of action potential. The refractory period is also increased. [Peck 3rd ed, p239
CD55 Sympathomimetics: A. Phenylephrine acts only on alpha receptors B. Metaraminol acts only on alpha receptors C. Methoxamine in high doses acts on beta receptors D. Pseudoephedrine is an isomer of ephedrine E. ?	A Phenylephrine is only an alpha agonist. Metaraminol has alpha and beta. Methoxamine is only alpha. [Stoelting, 4th ed, chapter 12]
CD56 Whice ONE of the following is True about vasopressin? A. Slowly metabolized by renal peptidase B. Does not cause coronary vasoconstriction C. Causes mesenteric vasoconstriction D. Increases plasma level of factor VIII E. Is an orally active derivative of ADH	C Vasopressin is an exogenous preparation of ADH. Marked splachnic vasoconstriction - can be used in bleeding oesophageal varicies in pt with liver cirrhosis & portal hypotension. Even in small doses may produce selective vasoconstriction of coronary arteries - manifests as angina. Does not increase plasma concentrations of Factor VIII, von Willebrand factor antigen of ristocetin co-factor. May cause platelet aggregation via V1 receptors. Rapid renal and hepatic metabolism [Stoelting, 4th ed, p473]
CD57 Clonidine: A. Dry mouth and agitation are very common side effects B. Half life is 24-48 hours C. ? D. Can cause severe hypertension if withdrawn abruptly after long term therapy with large doses E. Therapeutic dose is 2-5mg per day	D Dry mouth may occur with neuroaxial treatment but is rare, agitation only in super high doses. Elimination half-time 9-12hrs Abrupt discontinuation of clonidine may result in rebound hypertension. The usual adult daily dose is 0.2-0.3mg orally. [Stoelting, 4th ed, p340-344]
CD58 Beta adrenergic receptor antagonists A. Seldom causes inhibition of lipolyisis B. Causes inhibition of gluconeogenesis caused by adrenergic stimulation following hypoglycaemia C. Does not mask the signs of hypoglycaemia D Sudden cessation is not associated with rebound effects E. There is no evidence of cardiac protection for high risk patients pre-operatively	B BBlockers - selective competitive inhibition, reversible. Non-selective BBs may obtund the normal blood sugar response to exercise & hypoglycaemia. May mask normal symptoms of hypoglycaemia. Lipid metabolism may be altered - increased triglycerides & reduced high density lipoproteins. May get up-regulation of receptors with prolonged use (risk of rebound HTN) POISE study indicates some cardioprotection in high risk patients (possibly higher risk of stroke, controversial methodology) [Peck, 3rd ed, p223]
CD59 Labetalol: A. Beta and alpha antagomisn with partial agonist activity at alpha 2 receptors B. Beta and alpha 1 antagonist C. Alpha agonist and beta 1 antagonist D. ? E. ?	B Combined blockade: specific to a1 receptors, non specific at b receptors. [Peck, 3rd ed, p 226]

CD60 GTN is helpful myocardial infarction by: A. Decreasing left ventricular pressure and mean arteriolar pressure B. Producing methaemoglobinaemia C. improving coronary blood flow by dilating the small arterioles D. ? E. ?	A Organic nitrates act principally on venous capacitance vessels and large coronary arteries to produce peripheral pooling of blood and decreased cardiac ventricular wall tension. Methaemoglobinaemia is via nitrites but is used in cyanide toxicity, not AMI. [Stoelting, 4th ed, p361] I think the problem with C is that it is the option is small arterioles but the major target of GTN is the LARGE arteries/arterioles
CD61 Which of the following could cause significant adverse reactions with the MAO-i selegiline? A. Dopamine B. Phenylephrine C. Ephedrine D. Metaraminol E. None of the above	E Selegiline is a 2nd gen MAOI. It is highly selective & irreversible inhibitor of MAO-B, used for antiparkinson effect (weak alone, moderate when adjunct to carbidopa-levodopa). MAO-B enzyme activity is one of the principle catabolic pathways for dopamine in CNS. In contrast to nonspecific MAOIs, does not result in life-threatening potentiation of the efects of catecholamines when administered concurrently with centrally active amine. Metabolism of noradrenaline in peripheral nerve endings is not altered by selegiline. [Stoelting, 4th ed, p584] A consequence of MAOB in the brain is reduction in overall catabolism of DA, which may reduced the formation of potentially toxic free radicals: ? neuroprotective effect. Potential interactions with pethidine & serotonergic drugs (esp TCA) [Goodman & Gilman, chapter 22] Soph's addit: I agree with you Bron. The selective MAOI have the other MAO (either B or A) to metabolise these drugs. Their administration with selegiline should not cause hypertensive crisis. Maybe we should check this one with an anaesthetist??
CD62 Mannitol: A. Causes loss of medullary tonicity B. Urine hyperosmolar compared to plasma C. Site of action is PCT and DCT D. Tubular fluid is isotonic in descending loop of Henle	A Osmotic diuretic. Completely filtered at the glomeruli & none reabsorbed. Increase in renal medullary blood flow removes NaCl and urea from renal medulla, thus reducing medullary tonicity. Under some circumstances, prostaglandins may contribute to renal vasodilation & medullary washout induced by osmotic diuretics. Act both in PT and LOH, the latter being the primary site of action. [Goodman & Gilman, chapter 25]
CD63 Clonidine side effects A. Sedation B. Nausea and vomiting C. ? D. ? E. delirium	A best of causes B best if "all except" Could argue anxiogenic & delerium in high doses. Unlike opioids, does not produce depression of ventilation, pruritus, nausea, vomiting or delayed gastric emptying. Urinary retention is uncommon. Clonidine effects (good and bad): - Antihypertensive - sedation - decrease MAC - analgesic - treatment of withdrawal - xerostomia - protection against perioperative MI - Attenuate response to surgical stimuli - inhibits thermoregulatory control - retention of water and sodium - skin rashes - impotence - rebound hypertension [Stoelting, 4th ed, p340-344]

Endocrine pharm

EN01 [Mar96] [Jul97] Chlorpropamide: A. Inhibits ADH secretion B. Has a short duration of action (? Half-life < 12]] hrs) C. Increases glucose entry into cells D. Is prolonged in renal failure	**ANSWER: D best, C possible** A Yes as per PHW, No as per Goodman B NO – long t½ C Yes – sulphonylureas increase insulin release from pancreas à increases glucose entry into cells D – Yes (see below and as per Goodman) PHW: Chlorpropamide is a sulphonylurea with duration of action 27-72hrs. It is partially reliant on renal elimination . This combined with long t½ put elderly at high risk hypoglycaemia. It can cause facial flushing/vomiting following alcohol and may rarely enhance ADH secretion à hyponatraemia.
EN02 [Jul97] [Jul01] Sulphonylureas: A. High incidence of lactic acidosis B. Good in patients with depleted insulin stores C. Metformin & phenformin are examples D. Increased glucose utilisation in the peripheries E. Are related to sulphonamides Jul 01 version: With regards to sulfonylureas: A. Work effectively if Insulin stores depleted B. Cause a lactic acidosis C. Tolbutamide, (something else), phenylformin are examples (? Spelling) D. Highly protein bound E. ?	**ANSWER:** **02: E** **01 version: D** . Stoelting: Sulphonylureas work by increases release of insulin from pancreas (no role in insulin deplete). The don't increase utilisation of glucose, they simply increase insulin to increase glucose UPTAKE but not usage. They are derivatives of sulphonamides. They are weakly acidic and are highly protein bound (90-98%) principally to albumin. (Metformin and phenformin are biguanides). High risk of lactic acidaemia with biguanides
EN03 [Jul01] Glipizide is: A. A biguanide B. Half life 4-6hrs C. Causes metabolic acidosis /lactic acidosis D. Not contraindicated in hepatic failure E. Highly bound to albumin F. Is ineffective in patients with low insulin stores	**ANSWER: B, E or F best** Stoelting: Glipizide is a sulphonylurea with t ½ 4-7hrs. It stimulates insulin secretion causing increased glucose uptake and suppression of hepatic glucose output. Liver metabolism is extensive (inactive metabolites, caution in liver failure). Sulphonylureas are highly protein bound and are ineffective in patients with low insulin stores. Glipizide has mild diuretic effect.

General pharm

GP01. A drug is given at a dose of 50 mg/kg to a 70 kg man. The plasma concentration after giving it is 10 mg/ml. The elimination half-life is 8 hours. Clearance would be: A. 1.3 l/h B. 3 l/hr C. 0.03 l/hr D. 125 l/hr	C Vd = dose/conc Cl = 0.69x3 x Vd / $t_{1/2}$ **Vd** = dose / concentraion = 3500 mg/10 mg/ml = 350 ml **Clearance** = 0.693 x Vd / t1/2 = 0.693 x 350 ml / 8 hrs = 30 ml / hr = 0.03 L / hr Therefore answer C is correct
GP02. A drug is given orally and 95% absorbed. Only 25% reaches the general circulation due to hepatic first pass metabolism. If hepatic blood flow is 1500ml/min, the hepatic clearance is: 400 ml/min ? 1100ml/min ? 1425 ml/min	C HER = ([inflow] - [outflow]) / [inflow] Hep Cl = HER x Q Hepatic clearance = Hepatic blood flow (QH) x Hepatic extraction ratio (EH) = 1500 x ([0.95 – 0.25]/0.95) = 1105 mls/min
GP03 Histamine release (no other details)	Histamine is low MW, natural hydrophilic amine. Acts via GPCR + is important mediator of inflammation in allergy (released in antigen-ab reactions/drugs). Mast cells & basophils contain histamine. Does not easily cross blood-brain (minimal CNS effect). H1 receptor - smooth muscle contraction/pruritis/sneeze. H2- gastric acid secretion/incr HR. H3 in heart
GP04. Rectal administration of drugs: Gives predictable blood levels From lower 1/3rd avoids first pass & upper 2/3rds doesn't None undergoes first pass metabolism All of it undergoes first pass metabolism	B - true because of different drainages of anus. Variable absorption & metabolism depending on where it was administered to.
GP05. LD50 is: Median lethal dose Determined in phase I clinical trial Determined from log-dose response curve Dose causing death in 50% of animals within ?1/?4 hours Half the mean lethal dose Best expressed as a ratio of lethal dose in 50% of	A LD50 is median lethal dose. Testing in phase 0. (Phase 1 is normal human volunteers). Determined from quantal dose-response curves. F is the therapeutic index.

animals to effective dose in 50%	
GP06 Which ONE of the following crosses the blood-brain barrier? A. GABA Propranolol Suxamethonium Edrophonium Dopamine	B From Stoelting: BBlockers cross BBB to produce side effects Sux - charged & doesn't x, but has indirect effect on brain fn Edrophonium - quaternary amine Dopamine & GABA cannot cross
GP07 With regard to drug-receptor binding: A competitive antagonist has no intrinsic activity A partial agonist has less receptor affinity than a full agonist KD is maximal intrinsic efficacy	A Affinity is how avidly binds the receptor, not the response produced. KD is the equilibrium dissociation constant. The affinity constant is the reciprocal of KD.
GP07b A partial agonist: Always antagonises a full agonist Can never be used to antagonise a full agonist Has a dose response curve similar to that of a full agonist in the presence of a non-competitive antagonist. D?	C May antagonise a full agonist (depends on how may receptors are occupied by each)
GP08 Placental transfer of drugs: Increases in late pregnancy Increases late because of decreased albumin Do not cross if MW >600 daltons Lipid soluble drugs diffuse through placenta depending on concentration gradient Increased diffusion if greater plasma protein binding in fetus	E A The placenta is more permeable in early pregnancy B No C False - drugs 100-500 cross easily, 500-1000 cross with difficulty, >1000 will not cross D – No. Rate of diffusion is more dependent on conc gradient E - true - high protein binding in fetus ↑ drug transfer across placenta (lower conc difference – Fick's law!)
GP09 Regarding pharmacokinetics: ? Half-life is inversely proportional to clearance ? Half life is proportional to steady state B&D	E ? B correct - Cl = 0.693 x Vd / Cl D True in zero order kinetics. Steady state maintenance dose = clearance x plasma conc (and therefore E)
GP10 An ether bond: A Formed from condensation of 2 alcohols B Hydroxyl group on middle bond C. ?	A A ROH + R'OH = H20 + R-O-R' B wrong: an ether bond is a link between 2 carbon-containing groups R-O-R'.

GP11 The NMDA receptor Ketamine is an agonist Requires glycine as a modulating protein to have its effect Mg2+ blocks the receptor Is not permeable to calcium	C wrong, antagonist wrong - amino acid true false - permeable to Ca, Na, K
GP12 Activated charcoal: Should be given with sorbitol Is not effective against theophylline Should be given with ipecac Should be given in a drug:charcoal ratio of 1:10	D Sorbitol causes vomiting & diarrhoea - may not be desired (same as ipecac) Not effective against corrosive agents, alcohols, misc (boric acid, iron, lithium), and petroleum products. (Avoid CAMP BAIL - where BAIL covers misc ones)
GP13 Therapeutic index A Easy to determine in humans B ? C ? D ? E Derived from the LD50/ED50	E Not determined in humans - done in animals
GP14 A basic drug with a pKa of 8.7 A ? B ? C will be predominantly ionised at plasma pH	C "Bases ionised Below, Acids ionised Above"
GP15 Oxygen toxicity A Causes convulsions at less than 100kPa B Causes lipid peroxidation at less than 100kPa	B - can cause toxicity if this is not superacute exposure Need kPa >200 for CNS toxicity
GP16 With regard to log/dose response curves: A The response is fairly linear of the 20%-80% range B The dose is fairly linear over the 20%-80% range C The ED50 & slope are characteristic for each drug D & E ?	A – that's why they're created! For easier comparison
GP18 With regards to diffusion through a membrane: A Directly proportional to thickness B Inversely proportional to thickness C Inversely proportional to surface area	B Diffusion = (Area x pressure gradient x solubility) / (thickness x MW)

D Inversely proportional to concentration difference E ?	
GP19 Which of the following act via ligand gated channel? A Metaclopramide B Phenylephrine C Morphine D Vecuronium E Salbutamol	D Metaclopramide at 5HT3 GPCR, phenylephrine at alpha1 Gq, morphine at mu GPCR, vecuronium acts on nicotinic ACh receptor, salbutamol B2 receptor
GP20 Zero order kinetics means: A & B ? C Drug elimination at a constant rate regardless of dose D Elimination half time will vary according to dose E ?	C C is zero order, D is first order
GP21 All exist as racemic mixtures except: A Thiopentone B Lignocaine C Bupivucaine D Isoflurane E Enflurane	B Lignocaine is achiral and does not have enantiomeric forms, others all chiral compounds.
GP22 Clearance of a drug with a high hepatic extraction will be A Decreased in shock B Increased in high output states	Both are true! Possibly A is “more true” - shock always decreases hepatic flow, high output usually increases hepatic flow. If HER is high, clearance of drug depends on blood flow, whereas changes in enzyme activity will have little effect
GP23 Chemoreceptor trigger zone A Contains 5HT3 and D2 receptors B Not involved in inner ear mediated nausea C ?	A Chemoreceptor trigger zone receptors for 5HT3, histamine, muscarinic, D2, opioids. Motion can stimulate equilibrium receptors in inner ear which may also stimulate chemoreceptor trigger zone
GP24 Glutamate A Dissociates slowly from the NMDA receptor B does not act at AMPA and kainite receptors	A Excitatory transmitter, binds NMDA & AMPA & kainate, does dissociate slowly from NMDA receptor

C Inhibitory neurotransmitter in CNS D ?	
GP25 Regarding pharmacokinetics in pregnancy: A Paracetamol uptake increased B Increased sensitivity and faster onset with thiopentone C hepatic clearance decreased by decreased protein binding	B - true Uptake/absorption fairly unchanged, decreased protein binding increases hepatic clearance.
GP26 Which is an antagonist at the NMDA receptor? A Dexamethasone B Dextropropoxyphene C Dexmedetomidine D Dextromethorphan E Dexmethamphetamine	D - marketed primarily as an antitussive, is an antagonist of the glutamatergic NMDA receptor. A synthetic glucocorticosteroid B centrally acting synthetic opioid C full alpha 2 agonist D sympathomimetic
GP27 Comparing dexamethasone and hydrocortisone: A Both are endogenous hormones B Dexamethasone has 8x potency of hydrocortisone C Both have mineralocorticoid activity D Dexamethasone is the only water-soluble compound	D Dexa - synthetic, 25x potency of hydrocort, very little mineralocorticoid Hydrocort needs additives to make H2O soluble
GP28 A drug has a hepatic extraction ratio of 0.7 and is 30% absorbed, what is the bioavailability? A 0.3 B 0.7 C 0.21 D 0.09 E 0.03	D Oral bioavailability = fraction of drug reaching systemic circulation compared with same iv dose = fraction absorbed x fraction remaining after hepatic extraction F = fx(1-ER) Or F = Cls / Clo (Cls = systemic clearance, Clo = oral clearance) = 0.3 x (1 - 0.7)
GP29 Which of the following drugs cannot cross the BBB? A Ondansetron B Scopolamine	E Ondans cross to act on central 5HT4. Scopolamine is an anticholinergic with a tertiary amine structure (like atropine).

C Metaclopramide D Droperidol E Domperidone	Metaclop acts on central 5HT3, droperidol acts via central D2 blockade. Domperidone - peripheral D2 blockade
GP30 With regard to LD50 A Is the mean lethal dose in animals B Something about probit's relation to standard deviation C Animals are given increasing doses of a drug until they die D ? E Something about log concentrations being plotted against something using probits to linearize the data for humans	C Given increasing doses of 14 days or until 50% of the animals die A is wrong as it is the **median** lethal dose
GP30b Which is true for LD50? A Probit score of 5 means it is 5 SD away from the median B Mean lethal dose C Calculated from graded dose-response curves D Calculated from quantal dose-response curves E Animals are given increasing doses of a drug until they die	D and E D quantal dose response curve sound right as we re looking at population % effect to drug (ED50or LD50 in this case) as opposed to graded dose response curves which look at an individual response eg muscle relaxants and 95% reduction in twitch height (EC50). [goodman]
GP31 Which is not a ligand gated channel? A Alpha2 receptor B 5HT3 receptor C Nicotinic cholinergic receptor D GABA receptor E NMDA receptor	A - it is GPCR -> note this question probably asking which is not linked to ion channel directly (ionotropic)? Since a receptor is something that binds a ligand by definition **Ion channels**: gated / ungated **Gated**: ligand / voltage / 2nd messenger / mechano **Receptors**: ionotropic, metabotropic, nuclear **Ionotropic** receptors are directly linked to ion channels **Metabotropic** receptors act via second messengers **G-proteins** (assoc with GPCR) mainly affect second messangers (metabotropic) but can also directly affect ion channels eg Kir (ionotropic) **Adrenoreceptors** are metabotropic **5-HT3** receptors are ionotropic (all the others are metabotropic) **Nicotinic** receptors are ionotropic (unlike muscarinic which are metabotropic) **GABAa** receptor is ionotropic (but GABAb is metabotropic) **NMDA** receptor is ionotropic (but also voltage sensitive)
GP32 G proteins:	B

A. Always have 3 subunits B. Alpha subunit has intrinsic GTPase activity C. One G protein only attached to one G protein coupled receptor D. Spans membrane 7 times	A – small G proteins have only alpha subunit C - ?true D – no, this is the receptor
GP33 [Aug11] When is the safest time to give a drug to a lactating mother? A. 3 - 4 hours before breastfeeding B. Immediately before breastfeeding C. Immediately after breastfeeding D. 30 - 60 minutes after breastfeeding E. Either A or D	E "If the nursing mother must take medications and the drug is a relatively safe one, she should optimally take it 30-60 minutes after nursing and 3-4 hours before the next feeding." *-from Katzung 11th ed, Ch59*
GP34 [Aug11] Which of the following drugs has low first pass metabolism A. Lignocaine B. Morphine C. Metoclopramide D. Midazolam E. Aspirin	E – Aspirin Notable drugs that experience a significant 1st pass effect are imipramine, morphine, propranolol, buprenorphine, diazepam, midazolam, metoclopramide, demerol, cimetidine and lignocaine Aspirin has oral bioavailability of 70%
GP35 [Aug11] All are secreted by the proximal tubule in the kidney except: A. Diazepam B. Morphine C. Probenicid D. Penicillin E. Frusemide	**A - Diazepam is not.** B - Morphine is C - Probenicid is D - Penicillin - main mechanism of clearance E - Frusemide - is part of it's mechanism of action
GP36 [Aug11] Elimination coefficient Units (Repeat) A. ? B. mcg/ml C. mg/ml D. ? E. ?	Neither, see below

GP36b [Feb12] The units of rate constant k are? A. mg/min B. mcg/kg/min C. min D min^{-1} E. ml^{-1}	D Assuming first order kinetics though. Answer is always time $^{-1}$
GP37 [Aug11] Which drug reversibly inhibits platelet aggregation?* Repeat* A. clopidogrel B. warfarin C. [[heparin] D. diclofenac E. aspirin	**Answer: diclofenac** Aspirin covalently, ie. irreversibly binds to cox-1 **Diclofenac reversibly binds to cox-1** clopidogrel binds irreversibly to platelet ADP receptors, thus inhibiting ADP activation of the GPIIb/IIIa complex Heparin does not affect platelet function- is involved in clotting cascade Warfarin does not affect platelet function - is involved in clotting cascade
[[GP37]b [Feb08] Which of the following causes reversible inhibition of platelet function? A. aspirin B. heparin C. warfarin D. diclofenac E. clopidogrel GP37c Which one causes reversible impairment of platelet function? A. Aspirin B. diclofenac C. clopidogrel D. heparin E. warfarin	**Answer: diclofenac** Aspirin covalently, ie. irreversibly binds to cox-1 **Diclofenac reversibly binds to cox-1** clopidogrel binds irreversibly to platelet ADP receptors, thus inhibiting ADP activation of the GPIIb/IIIa complex Heparin does not affect platelet function- is involved in clotting cascade Warfarin does not affect platelet function - is involved in clotting cascade

Haem pharm

MD03 [Mar96] [Jul97] [Jul98] Regarding the plasma half-life of heparin: 7A. Clearance affected by warfarin B. Depends on site of injection C. Less for low MW heparins D. Depends on dose given MD03b [Jul97] Heparin: A. Has a half life dependent on dose B. Inactivates factors XII, XI, X, IX C. ? D. ? (see also [[MD49)	**Answer** **Part 1: D** **Part 2: A** - LWMH have longer t ½ elimination - Heaprins t ½ elim depends on dose given (increasing dose → increases t ½ elim) - Acts via enhancing activity of anti-thrombin III thereby inhibiting thrombin and ACTIVATED factors X, XII, XI, IX (answer suggest inactivated factors) - Also inhibits platelet function
MD05 [Mar96] Aspirin: A. At low doses inhibits prostacyclin B. Reversibly inhibits lipoxygenase C. Irreversibly inhibits cycloxygenase D. Can cause asthmatic reactions	**Answer: C + D** Aspirin: At low doses it inhibits the synthesis of PGI (not PGI itself). It irreversibly binds to and inhibits COX via acetylation (ipoxygenase pathway intact). Can trigger asthma: incraesed production of leukotrienes → bronchospasm +/- hypotension.
MD10 [Mar97] [Jul02] Thrombocytopaenia is a side-effect of which ONE of the following: A. Busulphan B. Cis-platin C. Methotrexate D. All of the above E. ?	**Answer: D** All are cytotoxic drugs and therefore effect cells with rapid turnover (platelets). Busulfan: prolonged thrombocytopenia Cisplatin: transient thrombocytopenia Methotrexate: occurs at 5-7/7 post administration, then rapid recovery.
MD21 [Jul98] [Jul99] [Mar02] Streptokinase: A. Acts on circulating plasmin B. When administered IV causes increased blood pressure? C. Is significantly more efficacious in preventing mortality if given within 1 hour of onset of chest pain, compared with being given within 3-6 hours? D. Is significantly more effective in preventing death from MI when used in combination with aspirin? E. Is not useful in treatment of lower limb DVT?	**ANSWER: D (also C)** **Wrong: A,B,E** Streptokinase is a protein produced by B-haemolytic streptococci. It is not an enzyme and does not convert plasminogen to plasmin by proteolytic cleavage. Instead it binds non-covalently to **plasminogen**, converting it to a plasminogen-activator complex that acts on other plasminogen molecules to generate plasmin. T ½ elim 23 minutes. Infusion can **decrease SVR** and cause **hypotension**. It is not fibrin specific and can produce systemic thrombolytic state. Can also stimulate antibody production and subsequent allergic reactions/fever. Anti-streptococcal antibodies induce amnestic response that makes repeated treatment difficult or impossible for months to years after initial treatment. Only marker of efficacy is thrombin time (if not prolonged in few hours of starting treatment not going to work due to high titre of antistrep antibodies). GISSI Study: 47% reduction mortality if given within 1hr onset chest pain (17% if at 6hrs). ISIS: 53% reduction mortality if streptokinase + aspirin within 4 hours (35% streptokinase alone).
MD25 [Mar99] Phenylbutazone: A. Interferes with heparin metabolism B. Increases warfarin plasma concentration C. Decreases warfarin plasma concentration D. Reduces the elimination of warfarin July 2000 version: Phenylbutazone's effect on the coagulation system are due to: A. Binding to albumen, displacing warfarin B. Inhibiting warfarin metabolism C. ? some interaction with aspirin D. ? effect on platelets	**ANSWER:** **Part 1: B** **Part 2: A (?better than C)** **Phenylbutazone** is an anti-inflammatory drug used in acute **gout** + **rheumatoid** arthritis. Toxicity so do not use for >7days. Absorbed rapidly + completely from GIT. **Protein** binding **98%**. **Metabolism** in **liver** extensive glucuronidation, hydroxylation to **active** metabolites (oxyphenbutazone). Excreted in urine. T ½ elim = 50-100hrs. SE are not uncommon: anaemia, agranulocytosis, N/V, epigastric discomfort, rahses. Na retention due to its direct action on renal tubules. **Displaces** other highly protein bound **drugs** such as warfarin, OHG, sulfonamides. Displaces thyroid hormone from protein binding sites complicates TFT interpretation. It also decreases uptake of iodine by thyroid gland. Increased **bleeding** if phenylbutazone is co-administed with warfarin or **aspirin**.
MD27 [Jul98] [Jul99] [Jul00] Aspirin: A. Greatest absorption is from the stomach B. Peak plasma level is achieved in 30]] minutes C. Has cross-reactivity with all NSAIDs D. Half-life 4 hours July 2000 version: Aspirin: A. Plasma half-life 4 hrs B. Peak plasma concentration within 10mins of oral	**ANSWER** **Part 1: C** **Part 2: F** Aspirin (acetylsalicylic acid): irreversibly acetylates COX → decreased synthesis and release of prostaglandins. Relatively weak inhibitor of renal prostaglandin synthesis. Does not interact with opioid receptors and has little effect on histamin/5HT release. Rapidly hydrolysed to salicylic acid which inhibits PG synthesis in a non-acetylation way. Rapidly **absorbed** mainly from **small intestines**, lesser extent in stomach. Rate of

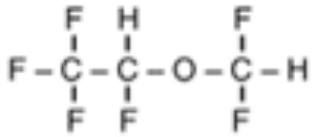
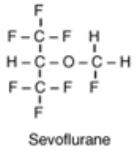
administration C. Requires conversion to salicylic acid for activity D. ? is more ?? than salicylic acid E. Better absorption if food in stomach F. Cross reactive sensitivity with all NSAIDs	absorption depends on dissolution rates of the administered tablet and gastric emptying time. If gastric pH increased → more drug is ionised → decreased rate of absorption. **Food slows** absorption. Peak plasma levels occur in 1 hour. Aspirin in effervescent preparations have more rapid absorption high plasma concs, less GI irritation. Has cross-reactivity with all NSAIDs. Metabolism: rapidly hydrolysed in liver to salicylic acid (active). Salicylic acid is also metabolism in liver via glycine conjugation → renal excretion (renal excretion increased in alkaline urine). T ½ elim = 15-20mins aspirin, 2-3hrs salicylic acid. Peak plasma concentration of aspirin must be shorter than its t ½ elim (ie <15-20 mins). Peak plasma salicylic acid conc 1-2hrs.
MD29 [Mar99] [Feb00] Warfarin affects: A. Factor XIII B. Protein S (? or Protein C) C. ?	**ANSWER: B** Warfarin acts by inhibiting the enzymes vitamin K epoxide reductase and vitamin K reductase. This prevents the formation of the reduced formed of vitamin K which acts as a cofactor in the gamma-carboxylation of glutamic acid residues in clotting factors 2,7,9,10 as well as anticoagulant protein C and S. Gamma-carboxylation is necessary for biological activity of these factors as it confers the calcium binding properties that are essential for their catalytic action. Inhibition by warfarin is COMPETITIVE.
MD46 [Apr01] Aspirin overdose A.Causes metabolic & respiratory acidosis B. Causes metabolic & respiratory alkalosis C. Causes metabolic alkalosis & respiratory acidosis D. Causes metabolic acidosis & respiratory alkalosis	**ANSWER: D** Stoelting: Aspirin causes metabolic acidosis likely due to uncoupling of oxidative phosphorylation and tendency towards anaerobic metabolism → lactic acidaemia and reduced renal elimination of strong acids. Also has direct effect on respiratory centre → respiratory alkalosis.
MD49 [Apr01] [Jul01] [Jul02] [Jul04] Low molecular weight heparin A.Has better bioavailability B. Molecular weight 1/10 that of normal heparin C. More protein bound than heparin D. ? E. ?	**ANSWER: A** Stoelting: Unfractionated heaprin is a mizure of low and high molecular weight acid mucopolysaccharides 3,000-60,000 Da. LMWH are dervied from UFH by chemical depolymerisation to fragments approximately **1/3 the size** of heparin. LMWH has **better bioavailability** than UFH. LMWH is **less protein** bound than UFH.
MD50 [Apr01] [Jul01] [Mar03] [Jul04] Desmopressin A Increases factor X B Increases factor V C Causes sustained severe hypertension D Can be used to improve haemostasis in haemophilia E Increases factor VIII activity F. ?v2B receptors?	**ANSWER: D + E** Stoelting: Desmopressin (dDAVP) is a synthetic analogue of AVP with intense antidiuretic (V2) effect and decreased pressor (V1) effect. Via V2 effects it also causes endothelial cells to release vWF, tissue type plasminogen activator and PGs. Used in diabetes insipidus to decrease UO and to promote release of vWF and FVIII in patients with Type 1 VW disease, **mild-moderate** haemophilia A and thrombocytopenia. SE: hypertension, nausea, and hypotension (decreased SVR with IV administration). DDAVP t ½ elim = 2.5-4.4 hrs is MIMS: 'high doses of desmopressin acetate produce marked and sustained increases of factor VIII coagulant activity (VIII:C) as well as of von Willebrand Factor (vWF). At the same time plasminogen factor is released."
MD63 Regarding warfarin? A. Affects platelet function B. Increases the action of vitamin K epoxide reductase C. ?More effective when given as an intravenous dose D. Doesn't cross the placenta E. Peak effect 36-72 hours following dose	E A Affects platelet function - false B Increases the action of vitamin K epoxide reductase - false - it inhibits it preventing formation of Vit K and therefore factors II, VII, XI & X> C ?More effective when given as an intravenous dose - false ' *oral bioavailability of 100% (Sassada and Smith 4th ed)* D Doesn't cross the placenta. - false - it is teratogenic so must cross the placenta. *"Extensive protein binding prevents diffusion into erythrocytes, cerebrospinal fluid and breast milk. Warfarin however does cross the placenta and produces exaggeratedeffects in the fetus, who has limited avility to synthesize clotting factors." (steolting 4th ed page 513)* **E Peak effect 36-72 hours following dose - true** *(see stoelting 4th ed page 512*

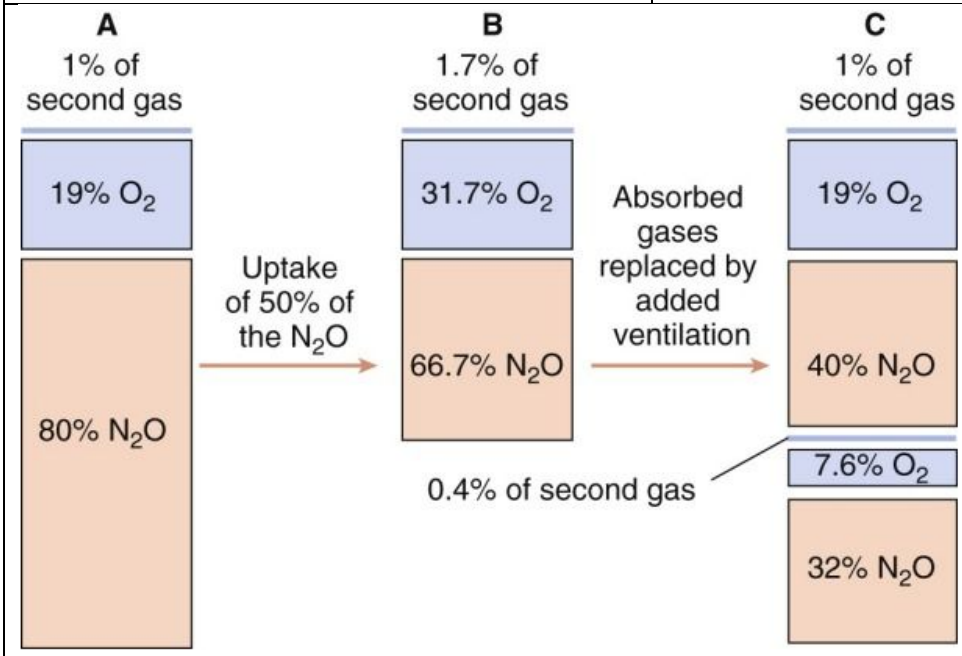
	table 27.1)

Inhalational agents

IN01 [Mar96] Which compound(s) is/are broken down in soda-lime? A. Nitrous oxide B. Halothane C. Sevoflurane D. Desflurane E. All of the above	Probably C best as it has breakdown A-E more readily than the others can form CO etc (Halothane stable up to 40 degrees, Desflurane stable to 80 degrees) B C D - Agents with the CHF2 moiety (desflurane > enflurane > isoflurane >> halothane = sevoflurane) produce carbon monoxide - Halothane: difluorovinyl compound (BCDFE) = nephrotoxic in rats, less reactive than compound A - Sevolfurane: compounds A-E, can form carbon monoxide if temperature >70°C in dry Baralyme, also produces formaldehyde gas and heat
IN02 [Mar96] Regarding nitrous oxide at 70%: A. Synthetised from ? & N2 at 273C B. Decreases muscle blood flow by 30% C. Decreases cerebral autoregulation 24% D. ?	C *Peck, Hill and Williams:* - Nitrous oxide is manufactured by heating ammonium nitrate to 250 °C - Unless the temperature is carefully controlled, N2O may contain contaminants - These are actively removed by passage through scrubbers, water and caustic soda *Stoelting:* - Nitrous oxide does not change SVR - Nitrous oxide increases CBF
IN02b [Jul97] Nitrous Oxide: A. ?Increases/decreases CBF B. Is an effective oxidant C. Is made by heating nitrogen and oxygen in an iron retort D. Decreases pulmonary artery pressure in neonates	A (Increases) B D correct if nitric oxide *Stoelting:* - Nitrous oxide will support combustion, also oxidises the cobalt ion of B12 - Sympathetic stimulation → ↑ PVR: exaggerated in pulmonary HT and neonates and may ↑ R→ L shunt in congenital heart disease  Nitrous Oxide
IN03 [Mar96] [Jul96] [Jul97] [Jul98] [Jul99] The following drugs are (potent) triggers for malignant hyperthermia EXCEPT: A. Decamethonium B. Suxamethonium C. Isoflurane D. Halothane E. Calcium F. Sevoflurane G. Tubocurarine H. Nitrous oxide (Different options on different papers)	E G H *Miller's:* - MH is elicited by the administration of triggering anaesthetic agents, such as a volatile anaesthetic or a depolarizing neuromuscular blocking agent - Decamethonium = depolarising - Tubocurarine = non-depolarising *Stoelting:* When compared with volatile anaesthetics, nitrous oxide is a weak trigger for malignant hyperthermia
IN04 [Mar96] [Mar03] IPPV with isoflurane at 1 MAC results in: A. Depresses cardiovascular reflexes more than halothane B. Causes decreased conduction velocity C. Maintains cerebral autoregulation D. Equal respiratory depression to enflurane E. Reduction in cardiac output by 25% F. Increased vasodilatation	C F *Stoelting:* - HR ↔ with halothane (depression of baroreceptor reflex and ↓ SA node dpeolarisation) but ↑ with the others - Autoregulation is maintained at 1 MAC isoflurane but not halothane

	- Both halothane and isoflurane slow the rate of SA node discharge and prolong His-Puerkinje and ventricular conduction times, also prolongs QTC - Isoflurane produces a dose dependent ↑ RR up to 1 MAC only (unlike the other volatiles), does not alter cardiac output, and ↓s SVR
IN05 [Mar96] [Mar98] The effect of increased cardiac output on Pa versus time for volatile agents is: A. No effect B. Decrease slope C. Decrease then increase slope D. Increase then decrease slope	B *Peck, Hill and Williams:* A high cardiac output will maintain a concentration between the alveolus and the pulmonary blood so that PA rises slowly
IN06 [Mar96] [Jul97] [Apr01] Nitrous oxide (N2O): A. Supports combustion B. Is flammable C. Causes muscle rigidity D. In tissues is slower to reabsorb than oxygen E. Has a partition coefficient of 0.76 F. All of the above G. Is formed by heating oxygen & nitrogen H. Induces methionine synthetase I. Oxidises the cobalt in vitamin B12	A I C (only if you're in a hyperbaric chamber) *Stoelting:* - Although nitrous oxide is non-flammable, it will support combustion - Does not relax skeletal muscles, and in doses of >1 MAC (delivered in a hyperbaric chamber), it may produce skeletal muscle rigidity - Does not potentiate the effects of neuromuscular blocking drugs - Low blood solubility (B:G 0.46), lowest fat solubility (O:G 1.4) → quicker reabsorption from tissues - Oxidises the cobalt atom in B12 such that the activity of B12 enzymes (methionine and thymidylate synthetise) is ↓
IN06b [Mar98] [Jul98] Nitrous oxide: A. Has MW of 42 B. Critical temperature 32 C C. Formed by using iron as a catalyst D. Does not support combustion E. ?? has saturated vapour pressure of 24]] kPa F. Produced using ammonium sulphate in an iron retort G. Boiling point 32C H. ??. . . ammonium nitrate . . . copper vessel ?? (Multiple options as this represents 2 separate N2O questions on Mar98 paper)	? C or H (probably H?) *Barash:* It *was* made by heating ammonium nitrate in the presence of iron filings *Stoelting:* MW = 44 *Davis and Kenny:* - Critical temperature = temperature above which a substance cannot be liquefied no matter how much pressure is applied - Critical temperature of nitrous oxide is 36.5°C (compared with oxygen, -119°C: this is why at 20°C, nitrous oxide in a cylinder is liquid but oxygen is a gas) *Miller's:* - When a volatile liquid is in a closed container, molecules escape from the liquid phase to the vapour phase until the number of molecules in the vapour phase is constant: these molecules in the vapour phase bombard the wall of the container and create a pressure known as the saturated vapour pressure (↑ with temperature) - Boiling point = temperature at which vapour pressure equals atmospheric pressure *Cross:* - SVP of nitrous oxide at 20°C is 5200 kPa
IN07 [Mar97] [Mar03] Desflurane A. Takes 5 minutes to reach equilibrium B. Is fastest to approach equilibrium of any inhaled anaesthetic agent C. Is a fluorinated diethyl ether D. ?	None correct technically although B correct if not comparing against N2O or Xenon *Miller:* - Possible to achieve equilibration within 15 minutes of exposure to a constant end-tidal anaesthetic concentration - Desflurane is a fluorinated methyl ethyl ether - Nitrous (second gas effect) and xenon (B:G 0.115) are faster to reach equilibrium but desflurane is the fastest volatile (lowest B:G 0.42)

	 Desflurane
IN08 [Mar97] [Jul97] Regarding sevoflurane: A. The vapour pressure is less than enflurane B. The vapour pressure is greater than isoflurane C. Cardiovascular side effects are similar to isoflurane D. Molecular weight less then isoflurane E. Boiling point greater than enflurane	A E *Stoelting:* - Vapour pressure = 170 mmHg (lowest) versus 172 for enflurane and 240 for isoflurane - Molecular weight = 200 (highest) versus 184 for isoflurane - Boiling point = 58.5°C (highest) versus 48.5°C for enflurane - Re: CV effects, desflurane most closely resembles isoflurane, whereas sevoflurane has characteristics of both isoflurane and halothane **Isoflurane** / **Sevoflurane** HR: ↑ / Only ↑ if >1.5 MAC Cardiac output: ↔ / ↓ at 1-1.5 MAC then ↔ at 2 MAC RAP: ↑ / ↔
IN08b [Jul97] [Feb00] Sevoflurane: A. Is a methylethyl ether B. Is odourless C. Is stable in soda lime at 37 degrees D. Has a boiling point higher than enflurane E. Has a molecular weight lower than desflurane	D *Stoelting:* - Sevoflurane is a fluorinated methyl isopropyl ether - Non-pungent, minimal odour - Breaks down in the presence of the strong bases present in carbon dioxide absorbents to form compounds that are toxic in animals (compound A: nephrotoxin in rats) - Highest boiling point (58.5 °C) - Highest molecular weight (200)  Sevoflurane
IN08c [Jul98] [Jul99] Sevoflurane: A. Molecular weight greater then enflurane B. MAC less than enflurane C. Contains Cl & F D. SVP > enflurane	A *Stoelting:* - MAC of sevoflurane is 1.8%, MAC of enflurane is 1.63% - Lowest SVP (170 mmHg; 20°C)
IN09 [Mar97] [Jul98] [Jul00] Uptake of N2O when breathing 70%: A. More than one litre absorbed in the first minute B. Equilibrium (?90%) is achieved in 3mins C. Absorb 10 litres ?at time of ?90% equilibration / ?in first 3 mins D. At steady state, uptake is 200mls/min E. Produces surgical anaesthesia	A B also true if 90% (FA/FI reaches 90% at 3 min) *Miller:* - Uptake = product of blood solubility, cardiac output, and alveolar-to-venous anaesthetic partial pressure difference - For N2O uptake: $Uptake = 0.46 \times 5 \times .7 = 1.6L$ *Stoelting:* Absorb up to **10** L during the first **10**-15 minutes, reflecting its administration at inhaled concentrations of 60-70%
IN10 [Mar97] [Jul98] [Mar99] [Jul01] [Jul04] N2O causes the second gas effect because: A. It is relatively insoluble B. Reaches equilibrium faster than the more soluble second gas C. Larger volume D. Its high concentration	D **A.** N_2O is relatively insoluble when compared with other potent inhaled anaesthetics with a blood:gas partition coefficient of 0.47. It should be noted however that desflurane has an even lower blood:gas coefficient of 0.42 and hence is *more insoluble*. Desflurane does not cause the second gas effect and so it is not the low solubility that is responsible for the second gas effect. A low blood gas coefficient is important solely in determining a *rapid* achievement of an alveolar and brain partial pressure of the drug. **B.** The lower the blood:gas partition coefficient then the faster a gas will reach equilibrium as already stated in (A) above. This does not

	contribute to the second gas effect. **C.** The large volume uptake of N_2O is an important contributing factor in creation of the 2nd gas effect (see (D) below). The reason that large volumes of N_2O are absorbed from the alveoli is due to the high concentration of nitrous oxide that is inspired and the initial steep concentration gradient that is generated, during or soon after induction. Due to this sequence of events, option D appears to be technically "more correct" as the high inhaled concentration *precedes* the uptake of large volumes of N2O from the alveoli. **D.** The relatively low potency of N_2O ensures that effective administration requires concentrations of 40-70%. The high concentrations that are administered result in the uptake of a large volume of gas (in the initial phases). This initial large uptake (as much as 1-2L/min) has 2 effects: 1. The gases remaining in the alveoli are concentrated (including the remaining N2O) 2. *Negative* pressure is created which draws bronchial and tracheal gas into the alveolar space to replace it. It is these 2 effects which together accelerate the rate of rise in alveolar partial pressure of the 2nd gas. Nitrous oxide is distinguished by the fact that it is the only inhaled anaesthetic to be administered in such high concentrations hence D appears to be the correct answer.
	
IN11 [Jul97] Desflurane: A. Is non-irritant to the airways B. Is more/less potent than sevoflurane C. Has a higher molecular weight than ?isoflurane/?enflurane D. Is a chlorinated methyl ethyl ether	B: Less potent *Stoelting:* - Desflurane has a pungent odour - It is less potent than sevoflurane (desflurane MAC 6.6% versus sevoflurane MAC 1.8%) - It has the lowest MW of all the volatiles (desflurane MW 168 versus isoflurane/enflurane 184) - It is a fluorinated methyl ethyl ester
IN12 [Jul97] [Apr01] Effects of volatile agents include: A. Halothane increases hepatic artery and portal blood flow B. Isoflurane causes hypotension by reducing cardiac output C. ? D. ?	None correct *Stoelting:* - In contrast to isoflurane, halothane acts as a vasoconstrictor on the hepatic circulation - Halothane, isoflurane, desflurane, and sevoflurane produce similar and dose-dependent decreases in MAP - With halothane, this is due to a decrease in myocardial contractility and cardiac output - With isoflurane, desflurane, and sevoflurane, this is due to a decrease in SVR
IN12b [Feb04] Volatile agents:	B

<table>
<tr><td>A. Halothane causes less cerebral vasodilation than enflurane
B. Isoflurance causes less cerebral vasodilation than halothane</td><td>
Stoelting:
- Volatile anaesthetics produce dose-dependent increases in CBF
- Magnitude is dependent on the balance between intrinsic vasodilatory actions and vasoconstriction secondary to flow-metabolism uncoupling

Miller:
- Halothane produces the greatest cerebral vasodilation
- Sevoflurane produces the least</td></tr>
<tr><td>IN13 [Jul97] [Jul98] [Jul99] [Apr01] Problems with MAC:
A. Large interspecies variability
B. Affected by temperature and other factors
C. Affected by obesity
D. ?</td><td>B

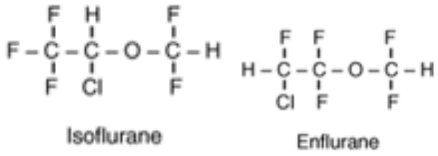
Stoelting:
- MAC = alveolar concentration of an inhaled anaesthetic at 1 atmosphere that prevents movement in 50% of patients in response to a standardised stimulus (e.g. surgical incision)
- MAC is an anaesthetic 50% effective dose (ED50)
- A unique feature is its consistency varying only 10-15% among individuals</td></tr>
<tr><td>IN13b [Mar96] [Jul98] [Feb00] [Jul01] MAC:
A. Is decreased in the elderly
B. Is unchanged throughout pregnancy
C. Increases in hypothermia
D. ?Decreased/?increased with hyper/hypo-kalaemia
E. ?</td><td>A

<table><tr><th>↑ MAC</th><th>↓ MAC</th></tr><tr><td>↓ age: peaks at <u>6</u> months</td><td>- ↑ age: <u>6</u>% per decade
- Pregnancy
- Postpartum</td></tr><tr><td>↑ temperature</td><td>↓ temperature: <u>4</u>-5% per degree</td></tr><tr><td>↑ Na</td><td>↓ Na</td></tr><tr><td>- ↑ catecholamines
- Acute amphetamine use
- Sympathomimetic use
- Cyclosporine</td><td>- ↓ catecholamines
- Chronic amphetamine use
- α2 agonists
- Preoperative medication (opioids, benzodiazepines)
- Lignocaine
- Lithium</td></tr><tr><td>- Chronic ETOH use
↑ pheomelanin (red hair)</td><td>- Acute ETOH use
- PaO2 < <u>4</u>0 mmHg
- BP < <u>4</u>0 mmHg
- Cardiopulmonary bypass</td></tr></table>
No change in MAC
• Gender
• Duration of anaesthesia
• ↕ PaCO2
• ↕ thyroid (controversial)
• Anaesthetic metabolism
• ↕ K
• ↕ pH</td></tr>
<tr><td>Alt version (Jul 01) All the factors decrease MAC except:
A. Pregnancy
B. Hyperthermia
C. Hypothermia
D. Hypoxia
E. ?</td><td>B</td></tr>
<tr><td>IN13c [Mar99] [Apr01] [Jul01] MAC:
A. Highest between ages 2 to 5 yrs
B. Increases with pregnancy
C. MAC BAR is concentration at which 95% do not move
D. Is 0.2% halothane in 70% N2O
E. ?</td><td>?D (correct number 0.29 – 0.2 in ballpark?)

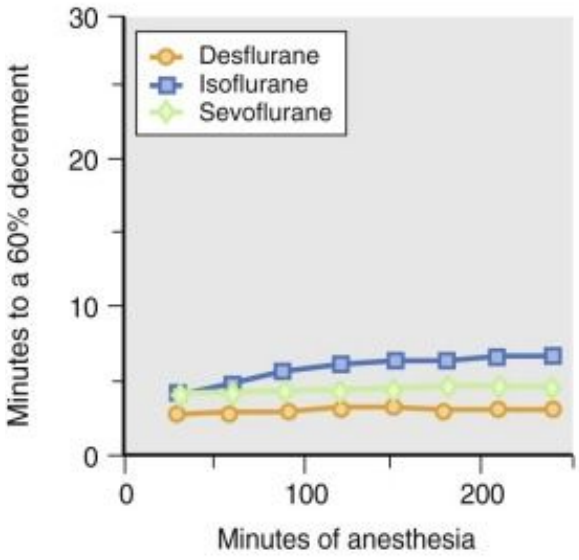
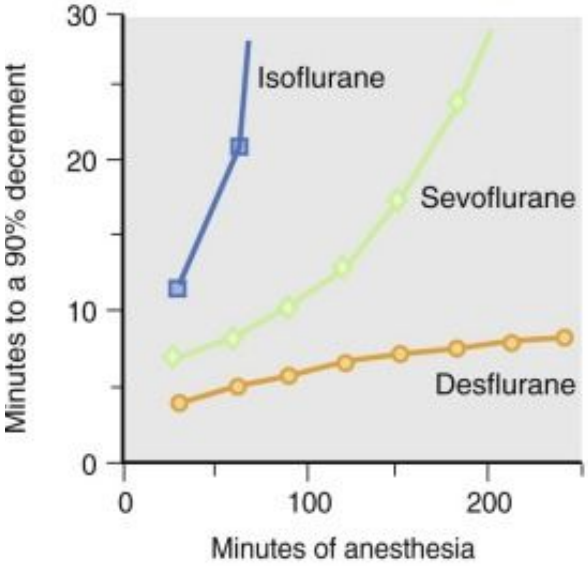
MAC BAR = blocks an adrenergic response to skin incision

Sasada
MAC of halothane is 0.75 (0.29 in the presence of 70% N2O)

Derivation (MAC is additive):
- MAC of N2O is 104%, so 70% N2O = 0.67 (or 2/3) MAC
- MAC of halothane is 0.75, so 1/3 MAC = 0.25</td></tr>
<tr><td>Jul 01 version: With regards to MAC:
A. The MAC of Halothane with 70%N2O is 0.29
B. Concentration at which 95% of patients don't move after a surgical stimulus
C. MAC- BAR ??
D. Decreased by increased CO2
E. ?</td><td>A</td></tr>
<tr><td>IN14 [Mar98] [Mar99] Systemic vascular resistance is LEAST changed with:</td><td>E</td></tr>
</table>

A. Isoflurane B. Sevoflurane C. Desflurane D. Enflurane E. Halothane	*Stoelting:* - Isoflurane, desflurane, and sevoflurane, but not halothane, decreases SVR - Thus, although these four volatile anaesthetics decrease systemic blood pressure comparably, only halothane does so principally by decreasing cardiac output - Nitrous oxide does not change SVR
IN15 [Mar98] [Jul98] [Mar99] MAC awake during emergence when patient will respond to command: A. 0.1 B. 0.2 C. 0.3 D. 0.5 E. ?0.7 ?0.8	C *Miller:* MAC-awake = 1/3 to 1/4 MAC (significantly higher for nitrous oxide)
IN16 [Jul98] [Jul99] Isoflurane & enflurane are: A. Structural isomers B. Enantiomers C. Diastereomers D. Optical isomers E. Configurational isomers	A - Structural isomers = same chemical formulae but different atomic bond structure - Stereoisomers = same chemical formulae and atomic bond structure, but different 3D configuration - Enantiomers = optical isomers = stereoisomers that have 1 chiral centre - Diastereoisomers = stereoisomers that have >1 chiral centre or which are subject to geometric isomerism - Geometric = cis-trans isomers = stereoisomers that differ in their groups attached to two atoms linked by a double bond or ring  Isoflurane Enflurane
IN17 [Mar96] [Jul96] Sevoflurane: A. Is broken down in the body to Compound A which has been shown to be toxic to rats B. Has a blood: gas partition coefficient of 2.3 C. Is a irritant causing coughing on induction D. Has a boiling point of 24]] degrees centigrade E. Has Cl & F atoms in its structure F. None of the above	F *Stoelting:* - Trifluoromethyl vinyl ether (compound A) is produced in CO2 absorbents - Blood: gas partition coefficient of sevoflurane = 0.69, resembling that of desflurane, ensuring prompt induction of anaesthesia and recovery after discontinuation of the anaesthetic - Nonpungent, minimal odour, bronchodilation similar in degree to isoflurane, and the least degree of airway irritation, making it acceptable for inhalation induction - 3-5% metabolised to inorganic fluoride and hexafluoroisopropanol - Boiling point 58.5 (highest)
IN18 [Mar99] [Feb00] With isoflurane anaesthesia, MAC awake is: A. 0.1% vol B. 0.3% vol C. 0.5% vol D. 0.5% vol E. 1% vol	B $MAC\ awake \approx \frac{1.17}{4} to \frac{1.17}{3} = 0.29\ to\ 0.4$
IN19 [Mar99] [Jul04] Isoflurane: A. Is a halogenated methyl ethyl ether B. Higher boiling point than sevoflurane C. No odour D. Enantiomer of enflurane	A *Stoelting:* - Halogenated methyl ethyl ether - Pungent, ethereal odour - Boiling point lower than sevoflurane (48.5 versus 58.5, sevoflurane is the highest!) - Structural isomer of enflurane
IN20 [Mar99] MAC of halothane with 70% N2O is: A. 0.25% B. 0.5% C. 0.75% D. 1.0%	A Derivation (MAC is additive): - MAC of N2O is 104%, so 70% N2O = 0.67 (or 2/3) MAC - MAC of halothane is 0.75, so 1/3 MAC = 0.25 *Sasada* MAC of halothane is 0.75 (0.29 in the presence of 70% N2O)
IN21 [Mar99] All reduce MAC except: A. Aminopyridine	A

B. hypothermia C. pregnancy D. hypoxia	*Goodman and Gilman:* 4-aminopyridine is a widely used in vitro blocker of K+ channels
IN22 [Jul98] N2O is NOT relatively contra-indicated with: A. Pneumothorax B. Ear surgery C. Postop nausea & vomiting D. Renal failure	D *Stoelting:* B:G of N2O is 34 times greater than that of N2 (0.46 versus 0.014), therefore it leaves the blood to enter an air-filled cavity 34 times more rapidly than N2 can leave the cavity to enter blood, increasing the volume or pressure of an air-filled cavity
IN23 [Jul99] [Jul02] [Mar03] [Jul04] Which of the following does NOT affect the speed of induction with a volatile agent? A. FRC B. Obesity C. pCO2 D. Cardiac output E. Body mass F. MAC	E F - ↓ FRC = small volume with which to dilute the inspired gas → ↑ rise in the alveolar to inspired concentration ratio - Obesity → ↓ FRC - ↓ PaCO2 → ↓ CBF → ↓ anaesthetic delivery to the brain - ↓ cardiac output, as with shock , → ↓ uptake to oppose input → ↑ rise in the alveolar to inspired concentration ratio - ↑ cardiac output → ↑ uptake → ↓ rise in the alveolar to inspired concentration ratio (occurs faster than expected because of preferential perfusion to VRG)
Alt version: Regarding the time constant for volatile anaesthetic uptake in the lungs A. Affected by agent concentration B. Affected by obesity C. Not affected by FRC D. Affected by restrictive lung disease	D Time constant for lung = FRC/VA Time constant for circuit = Circuit capacity/FGF Input (delivery) is affected by: - Inspired partial pressure (concentration and second gas effects) - Alveolar ventilation (spontaneous versus controlled breathing) - Anaesthetic apparatus (solubility in the rubber or plastic) - FRC (alveolar ventilation to FRC ratio = 5:1 in neonates compared with 1.5:1 in adults) Uptake (loss) is affected by: - Blood: gas partition coefficient (anaesthetic agent, haematocrit, lipid content, age) - Cardiac output (age, R → L shunt) - Alveolar-to-venous anaesthetic partial pressure gradient (tissue uptake: determined by tissue solubility, blood flow, and arterial-to-tissue anaesthetic partial pressure difference) - Metabolism and non-pulmonary excretion (percutaneous loss)
IN24 [Feb00] 22g of Nitrous oxide at STP occupies a volume of: A. 3.6 L B. 11.2 L C. 22]] L (? or 22.4 L) D. 44.1 L	B *Davis and Kenny:* - Avogadro's hypothesis = equal volumes of gases at the same temperature and pressure contain equal numbers of molecules - Mole = quantity of a substance containing the same number of particles as there are atoms in 0.012 kg of carbon 12 = 6.022×10^{23} - One mole of any gas at STP occupies 22.4 L, so 44 g of N2O, 2 g of H2 or 32 g of O2 or 44 g of CO2 occupy 22.4 L at STP
IN25 [Jul00] [Mar03] [Jul04] Wash in (? washout) of volatile anaesthetics is reduced in neonates because: A. Reduced FRC B. Increased cardiac index C. Decreased plasma protein levels? D. (Something about blood:gas partition coefficients being different in neonate)	B and D - Alveolar ventilation to FRC ratio = 5:1 in neonates compared with 1.5:1 in adults → neonates have a ↑ rise of the alveolar to inspired concentration ratio - ↑ cardiac output per kilogram in neonates acts to ↑ uptake, but they have relatively greater perfusion of VRG tissues → ↑ rise in the alveolar to inspired concentration ratio - Neonates have ↓ solubility of halothane, enflurane and isoflurane → ↑ rise in the alveolar to inspired concentration ratio (sevoflurane or desflurane ↔)
Alt version which probably is the same question remembered differently: The washout of inhalational anaesthetics A.. Increases with elimination by the liver B.. Related considerably with the duration of anaesthesia C. Increases in the neonates compared to an adult	All true (although be careful how the terms are defined on the day) - Metabolism decreases wash out (but not wash in!) but applies significantly to obsolete anaesthetics like halothane - The continued passage of anaesthetic from blood to the MG and FG speeds the rate of ↓ in the PA: depends on the solubility of the anaesthetic and the duration of anaesthesia

	 *If a 60% decrement is needed, there is little difference between isoflurane, sevoflurane, and desflurane*  *If 90% of the anaesthetic must be eliminated, awakening from both sevoflurane and isoflurane will be delayed more and more as the duration of anaesthesia increases (isoflurane > sevoflurane), but awakening from desflurane will be minimally affected*
IN26 [Jul01] With regard to compound A: A. Increased production in Baralyme compared to sodalime B. More likely in children C. Sevofluranes metabolites cause hepatotoxicity D. Sevoflurane is METABOLISED to Compound A in the liver E. ?	A *Stoelting:* - CO2 absorbents containing potassium and sodium hydroxide react with sevoflurane and eliminate hydrogen fluoride from its isopropyl moiety to form breakdown products - The degradation product produced in greatest amounts is trifluoromethyl vinyl ether (compound A) - Compound A is a dose-dependent nephrotoxin in rats and can be fatal - Increased production with Baralyme, probably as a result of higher absorbent temperatures - The rationale for using at least 2L/min FGF with sevoflurane is to minimise the concentration of compound A
IN27 [Jul01] Concerning the effects of various volatile agents on cerebral blood flow under conditions of 1 MAC and normocarbia: A. Halothane produces greater increase than enflurane B. Isoflurane produces greater increase than enflurane C. Any change produced depends upon cerebral metabolic rate D. Change in CBF is due to change in cardiac output E.	A *Miller:* The order of cerebral vasodilating potency is halothane >> enflurane > desflurane = isoflurane > sevoflurane

IN28 [Jul01] Which of the following drugs is NOT associated with EEG epileptiform activity A. Propofol B. Enflurane C. ? D. ? E. ?	A *Stoelting:* - Enflurane can produce seizure activity on EEG and tonic-clonic twitching - Desflurane, sevoflurane and isoflurane, do not produce evidence of convulsive activity on the EEG - There are reports of paediatric patients with epilepsy and healthy adults who developed EEG evidence of seizure activity with sevoflurane
IN29 [Jul04] Which does not increase risk of increased carboxyhaemoglobin in blood during anaesthesia? A. Dry absorbent B. Baralyme C. Low flows D. Desflurane E. Halothane	E *Stoelting:* - CO formation reflects the degredation of volatile anaesthetics that contain a CHF2 moiety - Desflurane>enflurane>isoflurane - Halothane and sevoflurane do not possess a vinyl group, so carbon monoxide production is less likely - Increased production with: (a) dryness of the CO2 absorbent: hydration prevents formation (b) high temperatures of the CO2 absorbent: occurs during low fresh gas flows and increased metabolic CO2 production (c) prolonged high fresh gas flows that cause desiccation (dryness) of the CO2 absorbent (d) type of CO2 absorbent - CO formation may still occur with sevoflurane in the presence of a dessicated Co2 absorbent especially when an exothermic reaction between the volatile anaesthetic and desiccated absorbent occurs
IN30 [Jul04] The concentration effect for N20 is due to A. Increased conc of N20 B. Faster eqilibrium of N20 than the second soluble second gas C. ? D. ?	A *Stoelting:* - Concentration effect = the higher the PI, the more rapidly the PA approaches the PI - Is the impact of PI on the rate of rise of the PA of an inhaled anaesthetic - Results from a concentrating effect and an augmentation of tracheal inflow

Intravenous agents

IV01 [Mar96] [Mar97] [Jul97] Propofol: A. Has a pKa of 7 B. Has a pH of 11 C. Causes hypotension due to myocardial depression Has 98% protein binding E. ?	D pH 7 (6.5-8) pKa 11 Hypotension due to reduced SVR Elimination half time 0.5-1.5 hrs, CSHT <40mins, Vd 3.5-4.5L/kg, Cl 30-60ml/kg/min, 98% protein bound
IV02 [Mar96] [Jul97] [Apr01] Thiopentone causes a decrease in BP by: A. Direct decrease in myocardial contractility B. Fall in systemic vascular resistance C. Decrease in venous tone D. Does not usually cause an increase in heart rate.	B & C 5mg/kg thio produces no myocardial depression, minimal depression with higher doses. The mild and transient decrease in systemic blood pressure that accompanies induction of anaesthesia with barbituates is principally due to peripheral vasodilation, reflecting depression of the medullary vasomotor centre and decreased sympathetic outflow from the CNS. The resulting dilatation of peripheral capacitence vessels leads to pooling of blood, decreased venous return and the potential for decreases in cardiac output and blood pressure. pStoeling p134 Carotid-sinus baroreceptor-mediated compensatory tachycardia.
IV03 [Mar96] [Jul96] [Jul97] [Mar99] Ketamine: A. Is a direct inotrope B. Causes bronchodilatation C. Less likely to see emergence delirium (?psychotomimetic effects) in ?older/?younger females D. Reduces pharyngeal secretions E. Leaves airway reflexes reliably intact (See IV17 for another Ketamine Q)	B Ketamine produces anticholinergic symptoms (emergence delirium, bronchodilation, sympathomimetic action). Possibility of emergence delirium limits the clinical usefulness. Emergence more likely in young females, previous psych, rapid/high dose. Has direct myocardial depression and indirect activation by central stimulation of sympathetics. Doesn't produce significant depression of airway reflexes. Increases salivary & tracheobronchial mucous gland secretion
IV04 [Mar96] [Apr01] With regards the action of midazolam: A. Ring closure occurs immediately on injection B. ? C. ?	A In vial, has a pH of 3.5 (pKa 6.15), is ionised & open ring structure. At pH >4, ring closes
IV05 [Jul97] [Mar99] [Jul99] [Apr01] Propofol depresses cardiac output predominantly by: A. Direct depression of myocardial contractility B. Decreased SVR C. ? D. ?	B Propofol decreases systemic BP...these decreases in BP are often accompanied by corresponding changes in cardiac output and systemic vascular resistance. A negative inotropic effect may result from ↓ in intracellular calcium availability 2° to inhibition of trans-sarcolemmal Ca influx
IV06 [Jul97] [Apr01] Methohexitone: A. Has a molecular weight of 285 B. Has a melting point of 158 degrees C. A 2.5% solution is isotonic D. Is yellow E. Has 4 isomers	E MW 262 B/C ? White powder becomes clear & colourless liquid. 4 optically active isomers, but clinical prepartion usually contained only 2.
IV06b [Mar02] Methohexitone A. Is a oxythiobarbiturate B. Breakdown is principally by splitting of ring C. "Longer duration than thio/ or maybe greater protein binding compared to thio??" D. ? E. ?	None of these Methohexitone is a methylated oxybarbitone. Shorter duration of action than thio (higher metabolism & rapid distribution). Metabolism is by side-chain oxidation
IV07 [Mar98] Benzodiazepine binding site on GABA receptor is: A. Near Cl- channel B. Inside the channel C. Outside the channel D. On the alpha subunit	D Benzo site Ɣ/α GABA site α/β GA site β
IV08 [Mar98] [Jul01] The drug with the largest volume of distribution at steady state is: A. Propofol B. Midazolam C. Etomidate D. Thiopentone E. Methohexitone	A Propofol Vd 3.5-4.5 L/kg Midaz Vd 1-1.5 L/kg Etomidate 3.0 L/kg Thiopentone 2.5 L/kg Methohexitone 2.0 L/kg

IV09 [Jul98] [Jul04] GABA: A. Is the principal inhibitory neurotransmitter in the spinal cord B. Barbiturates decrease the dissociation time between GABA and its receptor C. ??A & B types?? D. ? (see also IV18)	B Decreases the dissociation time so increases the association time. Glycine is the principle inhibitory neurotransmitter in the spine, GABA in the brain. GABA receptors have types A, B and nonA/nonB
IV10 [Mar96] Propofol is structurally related to: A. Althesin B. Etomidate C. Ketamine D. ? E. None of the above	E Propofol is a 2,6-diisopropylphenol Althesin is alphalaxone & alphadolone in cremophor EL Etomidate is an imidazole derivative & an ester Ketamine is a phencyclidine derivatibe
IV11 [Mar99] [Feb00] Midazolam: A. Water soluble at physiological pH B. Undergoes oxidative metabolism C. More lipophilic than lorazepam D. Causes hypotension E. Has a pKa of 7.4 (or ? 8.1) F. Causes retrograde amnesia	C/D most true, B some truth Water soluble at pH <4 Undergoes hydroxylation & conjugation - a form of oxidative metabolism Midaz is more lipophilic than loraz Can cause hypotension due to decrease in peripheral vascular resistance pKa 6.15 Anterograde amnesia
IV12 [Jul98] Thiopentone: A. Is the sulphur analogue of phenobarbitone B. Has higher protein binding than its oxy analogue C. ? 6% sodium bicarbonate D. Isotonic at 2.5% concentration	B Thio is sulphur analogue of PENTObarbitone. Protein binding of barbiturates parallels lipid solubility, thios bound greater than oxys. 6% sodium carbonate (not bicarbonate) 2.5 is not isotonic, just less chance of necrosis/tissue damage
IV13 [Jul98] Propofol clearance is significantly increased in: A. Elderly B. Metabolic acidosis C. Pregnancy D. ? (See also IN13b)	C Elderly have less hepatic blood flow and less enzyme activity. Pregnancy has higher cardiac output, relatively less albumin
IV14 [Feb00] [Jul04] Thiopentone: A. 100% reabsorbed in renal tubule B. Does not cross the placenta in significant amounts due to high plasma protein binding C. ??accumulate in the foetus	None of these (but A best choice) Very highly reabsorbed and <1% excreted unchanged in urine (but not 100% reabsorbed) Barbiturates used for IV induction of anaesthesia readily cross placenta but concentrations in fetal plasma < maternal due to Cl by fetal liver
IV15 [Jul00] Thiopentone: A. ? Tachyphylaxis if multiple administration in short period B. ??	A Acute tolerance to barbiturates occurs earlier than does barbiturate-induced induction of microsomal enzymes. Barbiturates induce hepatic enzymes after 2-7 days
IV16 [Jul00] Propofol: A. 10% eliminated unchanged B. Undergoes oxidative metabolism C. Clearance depends on hepatic blood flow D. No effect / chronic liver disease E. ?	D B true too - hydroxypropofol [stoelting p156] C some truth <0.3% is excreted unchanged in urine. Hepatic metabolism resulting in glucuronide & sulphate metabolites, may also undergo ring hydroxylation which is then glucuronidated or sulfated. There is no evidence of impaired elimination in patients with cirrhosis of the liver. Propofol can reduce its own metabolism by reduced hepatic flow but some extra hepatic metabolism takes place.

Reconstructed IV17: Ketamine: A. Direct acting negative isotope B. ?Indirectly acts on sympathetic nervous system peripherally C. Directly on the sympathetic ganglia D. Is a competitive antagonist at NMDA receptors E. Directly stimulates alpha and beta receptors Alt version of IV17: Ketamine: A. Is a negative isotope ("it was isotope and not inotrope") B. ? C. Directly stimulates autonomic ganglia D. Is a competitive antagonist at NMDA receptors E. Directly stimulates alpha and beta receptors? Comments: Both independently submitted versions of this MCQ contained a comment that one of the options was 'negative isotope' - ??? Using the information contained in these 2 submitted versions, we can attempt to reconstruct the whole question as below. However, the question still does not look right: for example 3 options say 'directly' and only one says 'indirect' & the other does not use either term, so by 'frequency analysis', this suggests that one of A, C or E is correct. The problem with this is the College has in recent times been going through their whole MCQ Bank trying to eliminate this type of "design problem" where you can guess or narrow in towards the answer by looking at the frequency of numbers or words in the different options. Reconstructed **IV17**: Ketamine: A. Direct acting negative isotope B. ?Indirectly acts on sympathetic nervous system peripherally C. Directly on the sympathetic ganglia D. Is a competitive antagonist at NMDA receptors E. Directly stimulates alpha and beta receptors IV17a [Jul04] Ketamine: A. Is a NON-competitive antagonist at NMDA receptors B. ?Direct acting negative inotrope C. ?Indirectly acts on sympathetic nervous system peripherally D. ?Directly on the sympathetic ganglia E. ?Directly stimulates alpha and beta receptors	B Not an isotope - this is an atom of particular chemical element that has different numbers of neutrons (eg carbon 12,13&14). Noncompetitive antagonist at NMDA. Direct negative cardiac inotropy (Ca & Na voltage-gated channels) & central sympathetic stimulation - overall SNS picture. Actually, I believe the answer would be "Indirectly acts on SNS peripherally". Goodman and Gilman 11th ed. - "CVS effects are indirect and are most likely mediated by inhibition of both central and peripheral catecholamine reuptake. Ketamine has direct negative inotropic and vasodilating activiy, but these effects usually are overwhelmed by the indirect sympathomimetic action." It is likely that ketamine's action is to inhibit norepinephrine uptake at the neuroeffector junction rather than to augment norepinephrine release. - Mechanism of the positive inotropic effect of ketamine in isolated ferret ventricular papillary muscle. Cook et. al. Anesthesiology [1991, 74(5):880-8] 17a = A
IV18 [Jul01] With regard to GABA receptors: (OR: Which of the following is INCORRECT about GABA neurotransmission:) A. GABA-A found all over the body B. Is an excitatory transmitter in 20% of CNS synapses C. GABA-B is predominately post-synaptic D. GABA receptor located in spinal cord, medulla and rest in Cortex. E. Is metabolised by deamination F. Is metabolised by transamination by ?GABA transaminase G. Stimulated by benzodiazepines H. Opposes action of glycine (Above is a composite of options from two GABA questions which were on the Jul 01]] paper.)	F true D true but care Re: wording as GABAc also exists in retina G true at high doses only GABA in CNS, only trace elsewhere, inhibitory transmitter. GABAb presynaptic and postsynaptic but preferentially presynaptic. GABA present in cerebral cortex, basal ganglia, cerebellum and spinal cord. GABA is formed from glutamate by action of glutamic acid decarboxylase (GAD) and is destroyed by a transamination reaction catalysed by GABA-transaminase (GAD-T). Benzos modulate - they increase frequency of opening in presence of GABA but cannot themselves stimulate. Glycine is another inhibitory neurotransmitter (found principally in spinal cord)

IV19 [Jul01] Propofol A. Causes decreased hepatic blood flow to influence its own clearance B. Relatively low clearance in Children C. Has a high rate of transfer from the peripheral to the central compartment on ceasing an infusion D. Has clinically significant metabolites E. Elimination halflife of 5 minutes	D most true A? May cause decreased hepatic blood flow to influence its own Cl. High Cl in children. Short CSHT due to C. Metabolites active – 4 hydroxypropofol has about 1/3 hypnotic activity of propofol. Elimination half time 0.5-1.5hrs Straight from Miller: "This longer elimination half-life indicates a deep compartment with limited perfusion, which results in a slow return of propofol back to the central compartment." Suggests that C is false. I think that short CSHT is due to rapid metabolism rather than transfer between compartments…
[[IV20 [Mar02] Which one of the following induction agents does NOT exert its main effect via the GABA receptor? A. Ketamine B. Thiopentone C. Propofol D. Midazolam E. Methohexitone	A Ketamine has only weak actions at GABAa receptors. Rest thought to have main actions at GABA
IV21 [Feb04] Sodium carbonate added to Thiopentone: A. As a bacteriostatic agent B. To neutralise Thiopentones acidity C. To increase ionised portion D. Enhances activity	C Thiopental is formulated as a sodium salt. Contains sodium carbonate (Na2CO3, 6% by weight) and nitrogen in place of air. These 2 measures are designed to improve solubility. $Na_2CO_3 + H_2O = NaHCO_3 + Na^+ + OH^-$ a strongly alkaline solution, enol form favouring water solubility
IV22 [Jul04] Which agent does not cause increased heart rate on induction of anaesthesia? A. Thiopentone B. Etomidate C. Propofol D. Ketamine E. Methohexitone	C best (B also true) Etomidate causes minimal changes in heart rate. Propofol characteristically causes a decrease in SBP without a compensatory increase in HR. Propofol can cause profound bradycardia/asystole.
IV23 [Jul04] Benzodiazepine receptor has A. Two glycine binding sites B. ?	None of these Benzo receptor is on GABA receptor and only has one binding site for benzo but two for GABA.
IV24 [Jul04] Midazolam A. Bioavailability 10% B. Bioavailability 50% C. Elimination t1/2 30]] min D. Elimination t1/2 30]] hours E. ?	B Bioavailability is 50% Elimination half-life 1-4hrs.
IV25 Ketamine is not usually used as a sole TIVA agent because: A. It causes profound analgesia but insuffient hypnosis for procedure B. It causes emergence phenomena in up to 30% of patients when given as an infusion C. It is too water soluble (*or something like that*) compared to propofol D. Half life is 80 mins E. ?	B A = false, used in field anaesthesia B = true, but not necessarily with infusion. Stoetling lists this as limiting factor C = false, more water soluble and therefore doesn't require a lipid emulsion carrier (an advantage over propofol) D = false, half life 2.5hrs

IV26 The amount of thiopentone remaining in brain 30 mins after administration: A. 10% B. 20% C. 30% D. E. 40%	A **Stoelting**: "Thiopental, thiamylal, and methohexital undergo maximal brain uptake within 30 seconds (rapid effect site equilibration), accounting for the prompt onset of CNS depression. The brain receives about 10% of the total dose in the first 30 to 40 seconds. This maximal brain concentration is followed by a decrease over the next 5 minutes to one-half the initial peak concentration, due to redistribution of the drug from the brain to other tissues. Indeed redistribution is the principal mechanism, accounting for early awakening after a single IV dose of these drugs. **After about 30 minutes, the barbiturate has been further redistributed and as little as 10% remains in the brain.**"
IV27 Thiopentone is: A. anti-analgesic in sub-therapeutic doses B. ? C. ? D. ? E. ?	None "small does of barbiturates seem to lower the pain threshold, accounting for the clinical impression that these drugs are anti-analgesic. Therefore barbiturates cannot be relied on to produce sedation in the presence of pain. Nevertheless, the concept that barbiturates are anti-analgesic has **never** been confirmed" (Stoelting 4th ed p132)
IV28 Propofol is preferred to thiopentone in TIVA because: A Low therapeutic index B T1/2 keo C high clearance D. ? something about lipid solubility E. ?	C The rapid clearance of propofol is the key determinant in its non cumulative nature (short CSHT) and hence its usefulness as a TIVA agent. Drug $t½_{keo}$ (min)for thiopentone is 1.17mins vs Propofol at 3.5 mins. hence more rapid onset time for thiopentone. a small $t1/2_{keo}$ is useful, but not the source of benefit for propofol over thio, which accumulates very rapidly.
IV29 Comparing thiopentone to propofol: A. Resistance to infection thiopentone > propofol B. t½keo propofol = thiopentone C. Effect site conc thiopentone faster than propofol D. Pain on infection thio > prop (**or**: propofol > thiopentone) E. ?	C = best, A = true D = true if prop > thio The truth of the following statements is listed, but beware the negative / positive wording of the question WRT which is the best answer: A. Resistance to infection thio > prop - **true** , propofol supports bacterial growth (soy bean oil protein and egg lecithin- yummy for bugs cf. Thio - pH 10.5) B. $t½_{keo}$ prop = thio - **false** $t½_{keo}$ prop = 3.5mins; thio = 1.17 (hence quicker time to sleep with thiopentone) C. Effect site conc thio faster than prop - **true** see answer B D. Pain on infection thio > prop - **false** or D. was Pain on injection prop>thio - **true**
IV30 [Feb13] Propofol: A. Has a chiral centre B. Does NOT need a dose reduction in the elderly C. Has active metabolites D. Clearance affected in cirrhosis E. ?	C

IV31 [Feb13] Five minutes after giving thiopentone, the amount remaining in brain is: A. 5% B. 10% C. 30% D. 50% E. 100% V31b [Alt Version] Percentage of thiopentone dose remaining in the brain *FIVE* minutes after a bolus dose: (*definitely 5 not 30 mins as previously recalled/asked*) a) 0.2% b) 0.5% c) 20% d) 35% e) 50%	31 = D 31b = E See also IV26 which is the same question but says amount after **30 minutes**. Not sure which is the correctly remembered time but there is a exact reference for the 30 min MCQ. Just a bit above the part referenced in IV26: "The brain receives about 10% of the total dose of thiopental in the first 30 to 40 seconds. This maximal brain concentration is followed by a decrease over the next 5 minutes to **one-half** the initial peak concentration, due to redistribution of the drug..." -Stoelting
IV32 Addition of sodium carbonate to thiopentone: A - Confers a yellow colour B - Increases lipophilicity?? C - provides CO_2 D - E - Bacteriostatic	None are true (unless B actually stated increases hydrophilicity?) Thiopental is formulated as a sodium salt. Contains sodium carbonate (Na2CO3, 6% by weight) and nitrogen in place of air. These 2 measures are designed to improve solubility. $Na_2CO_3 + H_2O = NaHCO_3 + Na^+ + OH^-$ a strongly alkaline solution, enol form favouring water solubility The yellow color is due to the presence of the sulphur molecule
IV33 With regards to the structure of barbiturate drugs: *(Refer to Stoelting 4E p127)* a) b) Oxygen substitution at the 1- position increases ?half-life c) Phenol substitution at the 5- position increases anticonvulsant activity	C Keto-enol tautomerization (enol form ionized form at ph 11, keto form unionized at ph 7.4) Sulphur at position 2 produces more lipid solubility, rapid onset, greater hypnotic potency but shorter duration of action (eg/ thiopentone) Phenyl group at position 5 produces anticonvulsant property (eg/ phenobarbitone) Hypnotic activity is introduced into the barbituric acid molecule by the addition of side chains, especially if at least one of them is branched, in position 5 The length of the side chains in the 5 position influences both the potency and the duration of action of the barbituric acid derivatives; more potent with longer side chains in position 5 (eg/ phenobarbital) Addition of methyl group at C1 produces rapid onset of action and short duration of action, but excitatory effects (eg/ methohexital)
IV34 Propofol clearance *(There were two questions on it - can't recall both so I've put what I can recall from them together)* a) Decreased in hepatic failure b) Decreased in renal failure c) Increased in children d) Decreased in cirrhosis	C Propofol has a high Vd and Cl in children, and a decreased one in elderly Clearance of propofol is higher than the hepatic blood flow which suggests extrahepatic sites (lung and kidney) and so decreased clearance is less of an issue in hepatic failure and the drug can be used in cirrhosis/liver/renal disease
IV35 Ketamine: A decreases ICP / CBF B acts via opioid receptors C decreases salivation D airway reflexes E ?	?D A – incorrect; 60% increase in CBF, ICP and CMRO2 B – main action as non competitive NMDA antagonist, also has minor actions at opioid, monoaminergic, muscarinic and Ca^{2+} channels C – increases salivary and bronchial secretions D – relative sparing of upper airway reflexes

Local anasthetics

LA01 [Mar96] [Mar97] [Jul97] [Mar99] [Jul01] Lignocaine has a pKa of 7.9 At pH 6.9, the percentage ionised is: A. 1% (or 5%) B. 10% C. 50% D. 90% E. 99% (Also remembered as: With a pKa of 7.9, what percent of lignocaine is ionised at intracellular pH?)	D pH = pKa + log([B]/[BH+]) (for an acid pH = pKA + log [A-]/[AH]) 6.9 = 7.9 + log ([B]/[BH+]) -1 = log ([B]/[BH+]) 0.1 = [B]/[BH+] so base unionized = 10% of the base ionized. % ionized is ~91% and unionized is ~9% Rules of thumb: If pka – pH = 0 => 50% ionized If pka – pH = 0.5 => 75% ionized If pka – pH >1 => >95% ionized Can also use following formula: % ionized = $100/(1+10^{x(ph-pka)})$ where x =-1 if acid and 1 if base ⇨ 100/1.1 = ~90
LA02 [Mar96] [Jul04] Cocaine: A. Blocks reuptake of dopamine and noradrenaline B. Central effects are due to noradrenaline C. Crosses lipid soluble membranes because its pKa is 2.8 D. Is not metabolised by plasma pseudocholinesterase E. Rapidly absorbed by nasal mucosa	A Cocaine blocks uptake 1 and MAO and also stimulates CNS - blocks reuptake of noradrenaline & dopamine. Euphoric properties are due primarily to inhibition of dopamine reuptake. pKa 8.6 Unlike other esters, it undergoes hepatic hydrolysis as well as plasma. "Cocaine inhibits the neuronal membrane transporters for catecholamines, thereby potentiating the effect of NA at alpha-adrenergic receptors in the vasculature, resulting in vasoconstriction and reduced cocaine absorption in vascular beds where alpha adrenergic effects predominate" [Goodman and Gillman online chapter 20] Stoelting p187: Cocaine is metabolised by plasma and liver cholinesterases to water-soluble metabolites that are excreted in urine
LA03 [Mar96] [Mar03] Ropivacaine: A. Produces greater motor block than bupivacaine B. Is prepared as the R enantiomer C. Is less lipid soluble than lignocaine D. Has the same cardiotoxicity as lignocaine	None Lower lipid solubility = reduced ability to penetrate thicker motor nerves = less motor block. S-enantomer More lipid soluble than lignocaine More cardiotoxic than lignocaine (less than bupivacaine)
LA03b [Mar97] [Feb00] Ropivacaine A. Is a pure R isomer B. Is an isomer of bupivacaine C. Provides more motor block than bupivacaine D. Has more toxicity than bupivacaine E. Has similar physico-chemical properties to bupivacaine	E? Same pKa 8.1, similar protein binding (B 95%, R 94%), same slow onset, same duration of action 240-480mins, same relative potency of 4. Different lipid solubility (B > R), different Vd (B 73L, R 59L), Cl slightly different (B 0.47L/min, R 0.44L/min)
LA03c [Mar98] [Jul98] Ropivacaine differs from bupivacaine mainly by: A. More motor blockade than bupivacaine B. Mainly affecting A beta rather than A delta fibres C. Lower cardiac toxicity than bupivacaine D. ? E. None of the above	C B. Mainly affecting A beta rather than A delta fibres – No. Both types of pain fibres A-delta and nonmyelinated C fibers are blocked by similar concentrations of local anaesthetics despite the differences in diameters of these fibers. Preganglionic β fibres ar more readily blocked by LAs than any other fibre, even though they are myelinated. Stoelting p183
LA04 [Mar96] [Mar99] Bupivacaine: A. Is an aminoester local anaesthetic B. Is formed by substituting butyl for methyl on amino group of mepivacaine C. ?Less/more toxic than tetracaine D. Adrenaline solution contains sodium metabisulphite E. Equipotent to etidocaine in causing motor block	B, D Amide local anaesthetic. Formed from mepivacaine by subsitution of a butyl group for methyl group. Bupivacine replacing tetracaine as smaller doses can be used, B > T faster onset and LESS toxicity. [Goodman & Gillman online] but website says MORE toxic CNS in Evers & Maze Sodium bisulfite (strong acid) may be added to local-adrenaline solutions to prevent oxidative decomposition of adrenaline. Etidocaine: very rapid onset, prolonged duration of action and profound sensory and motor blockade (only useful when muscle relaxation required for surgery)

LA05 [Jul97] With regard to molecular weight of local anaesthetics, which is the correct sequence? A. Cinchocaine > bupivacaine > lignocaine > prilocaine B. Bupivacaine > lignocaine > cinchocaine > prilocaine C. Bupivacaine > lignocaine > prilocaine > cinchocaine D. Prilocaine > bupivacaine > cinchocaine > lignocaine E. Lignocaine>bupivacaine>prilocaine>cinchocaine (see also LA09, LA10)	A Molecular weights for the above local anaesthetics are as follows: - Cinochocaine: MW 343 (C20.H3.0.Cl.N3.O2) - Bupivacaine: MW 288.4 (C18.H28.N2.O) - Lignocaine: MW 234.3 (C14.H22.N2.O) - Prilocaine: MW 220.3 (C13.H20.N2.O) Also found as: Prilocaine = 220 Lignocaine = 234 Procaine = 236 Ropivacaine = 274 (ie Bupivacaine minus a CH_2) Bupivacaine = 288 Cinchocaine = 343
LA06 [Jul97] [Jul04] Lignocaine works by: A. Altering Na^+ permeability B. Altering membrane structure C. Reduced Ca^{++} permeability D. Increased K^+ permeability E. Ca^{++} binding to tropomyosin	A
LA07 [Jul97] Lignocaine: A. Has ?% uptake in lung B. Is 24% ionised at physiological pH C. Reduces Na^+ conductance (?) D. ?	C? The lungs are capable of extracting local anaesthetics such as lignocaine, bupivacaine and prilocaine from the circulation. Not sure about %. MCQ website answer 25% 25% UNionized at physiological pH 7.4
LA08 [Jul97] Lignocaine: A. Has active metabolites B. Metabolism faster in females because of progesterone C. Metabolism is independent of liver blood flow D. ?	A Some of metabolic products have antiarrhythmic properties while other may potentiate lignocaine-induced seizures. Clearance is reduced in the presence of hepatic or cardiac failure.
LA09 [Mar98] [Feb00] Protein binding of local anaesthetics (in decreasing order): A. Procaine > bupivacaine > lignocaine > prilocaine B. Bupivacaine > lignocaine > prilocaine > procaine C. Prilocaine > bupivacaine > lignocaine > prilocaine D. Lignocaine > bupivacaine > prilocaine > procaine E. Bupivacaine > lignocaine > procaine > prilocaine F. Bupivacaine>procaine>lignocaine>prilocaine	B Protein binding: Cocaine 95 Bupivaciane 95 Ropivacaine 94 Mepivacaine 77 Amethocaine 75 Lignocaine 70 Prilocaine 55 Procaine 6
LA10 [Mar98] Local anaesthetics are metabolized in the following order: A. Bupivacaine>ropivacaine>lignocaine>prilocaine>procaine B to E. (The above in different orders)	Answer = Procaine > Prilocaine > Lignocaine > ropivacaine > bupivacaine Ester anaesthetics quickest Prilocaine more rapid Lignocaine & mepivacaine intermediate Etidocaine, bupivacain and ropivacaine slowest Ropivacaine higher clearance and shorter half life than bupivacaine [Stoelting p 185-6] t1/2β Bupivacaine = 210 mins Ropivacaine = 108 mins Lignocaine = 96 mins Prilocaine = 96 mins Procaine = 6 mins

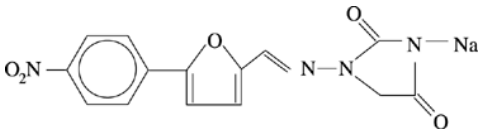
LA11 [Mar98] Saxitoxin site on sodium channel is: A. Inside channel B. Outside channel C. On membrane outside D. ?	B Saxitoxin is a toxin produced by algae, humans usually get this after eating contaminated shellfish. Both saxitoxin and tetrodotoxin specifically block the outer mouth of the pore of Na+ channels in the membranes of excitable cells [Goodman & Gillman online, chapter 20]
LA12 [Jul98] The site of action of benzocaine is: A. Same site as saxitoxin B. Inside Na+ channel /OR: At the channel mouth C. At axoplasmic end of Na^+ channel D. At Ca++ channel E. In the cell membrane	E "Certain local anaesthetics (eg benzocaine) are only present in the body as uncharged, tertiary bases, and must therefore act in a different way. They are believed to cause conduction blockade by "membrane expansion" (ie by causing swelling of the lipoprotein matrix of the Na+ channel. To some extent, other local anaesthetics, which are partly present in the neurilemma as the uncharged base may act in this manner." - from Calvey & Williams "Principles and Practice of Pharmacology for Anaesthetists" 4th ed 2001, p152-3
LA13 [Jul98] EMLA cream contains: A. Soluble in water at >16 degrees C B. 20% ionised at pH ?? C. 80% ionised at pH ??.. OR: Base contains 80% local anaesthetic D. ?? amount of ionised drug E. All of the above	None without information on pHs ? mostly un-ionised as a cream/oil EMLA = eutectic mixture of local anaesthetics 2.5% lignocaine, 2.5% prilocaine. Low melting point: oil at room temperature while the individual components would be crystalline solids. [http://www.drugs.com/pro/emla.html]
LA14 [Mar99] [Mar03] What factor (?does not) influence the peak plasma levels after epidural injection of local anaesthetic? A. Vasoconstrictor B. Natural vasoconstrictor activity of the drug C. Hepatic clearance D. Renal clearance	D Vasoconstrictors definately effect plasma. Hepatic clearance very important in amides (esterases in plasma for esters) [Stoelting p1885] ? renal best option as little drug is excreted unchanged from kidney
LA15 [Mar99] [Mar03] Which ONE of the following is an amide? A. Tetracaine B. Procainamide C. Procaine D. Prilocaine E. Cinchocaine	D, E, B Procainamide is an analogue of the local anaesthetic procaine [Stoeltingp376] procainamide is the AMIDE analogue of procaine, hence the name!
LA15b [Jul01] The following are all amides except: A. Bupivicaine B. Prilocaine C. Etidocaine D. Tetracaine E. Dibucaine	D
LA16 [Jul99] Lignocaine: A. Anti-arrhythmic effect - ??Na channel /open & inactivated state B. Prolongs QRS C. ? D. ?	? A – reduces phase 0 slope and peak of AP B is also correct (in large doses). Stoelting 191: Excessive plasma concentrations of lidocaine may slow conduction of cardiac impulses through the heart, manifesting as prolongation of the PR interval and QRS complex
LA17 [Jul99] [Feb00] [Jul00] [Jul01] [Jul03] A solution of local anaesthetic contains 1:100,000 adrenaline. How much adrenaline has been added? A. 0.01% B. 0.1% C. 10 mcg/ml D. 100 mcg/ml E. 1000 mcg/ml	C 10mcg/ml = 0.001%
LA18 [Feb00] Regarding the addition of adrenaline to a local anaesthetic administered epidurally, which of the following is NOT true? A. Significantly prolongs the duration of action of bupivacaine B. Causes tissue acidosis at the site of injection C. Causes vasoconstriction D. ?	B Careful – this question says which is NOT true! B is not true as the dose is only 5mcg/ml which is unlikely to cause significant tissue ischaemia! "The duration of surgical epidural anaesthesia is not greatly prolonged when epinephrine is combined with prilocaine, bupivacaine or etidocaine, but does result in a significant increase in the duration of epidural blockade produced by agents such as lignocaine" [Longnecker's online, chapter 44]

LA19 [Jul00] [Jul01] Regarding local anaesthetic plasma protein binding A. Is predominantly by albumin B. Is predominantly by alpha-1 acid glycoprotein C. Is greater for tetracaine than for bupivacaine D. Neonates have a greater number of binding sites E. Plasma binding is directly proportional to local anaesthetic concentration. (Comment: wording in option E was 'plasma binding' & not 'plasma protein binding')	A, ? B Alpha-1 acid glycoprotein binds local anaesthetic with high affinity although albumin binds a greater quantity due to its relative abundance. [Peck p167] Bupivacaine 95% bound, tetracaine 76% bound. Protein binding is increased by pregnancy, myocardial infarction, renal failure, post-operatively and in infancy = reduced free fraction of drug. [Peck p168] Percentage bound inversely proportional to concentration. Neonates have less alpha1 acid glycoprotein Neonates have more risk of toxicity cos of decreased protein binding from decreased alpha 1 glycoprotein. They also have decreased hepatic clearance. So D incorrect.
LA20 [Jul01] For a local anaesthetic agent at a given concentration: A. Effect is NOT dependent on resting membrane potential B. Faster onset with increasing frequency of stimulation of nerve C. Unionised form blocks the surface receptor D. Agent blocks the channel in the activated state E. Faster onset with more negative resting membrane potential.	B
LA21 [Feb04] Lignocaine A. Over 50% unionised at pH 7.4 ?? B. Decreased metabolism with GA ?? C. ? D. ? E. ?	? B pKa 7.9, so at pH 7.4 it has 75% ionized. If hepatic blood flow was reduced due to GA, may then have decreased metabolism.
LA22 [Mar09] Levobupivacaine is different from bupivacaine in: A. Increased hydrophobicity of the aromatic ring B. Increased hydrophilicity of amine group C. Addition of a methyl group to the hydrophilic amine ring D. ? E. ?	None of these
LA23[Mar09] A toxic dose of bupivacaine is given and results in seizure and ventricular fibrillation. Which is most correct in order of priority: A. Amiodarone, diazepam, ventilate with 100% O2, defibrillation B. Ventilate with 100% O2, external cardiac compressions, diazepam, defibrillation C. Diazepam, defibrillation, vetilate with 100% oxygen, cardiac compression D. Ventilate with 100% oxygen, defibrillate, external cardiac compressions, adrenaline E. External cardiac compressions, defibrillation, amiodarone, ventilate with 100% oxygen	D or E Tricky seeing as the guidelines have changed to CAB! I think should be compressions, 100% O2, DCR, adrenaline and intralipid but open to suggestions! Most probably D
LA24 [Mar09] Cocaine A. Overdose rarely causes convulsions B. Central effects are due to high dopamine levels C. Metabolism is dependent on plasma pseudocholinesterase D. ? E. ?	B

Miscellaneous pharm

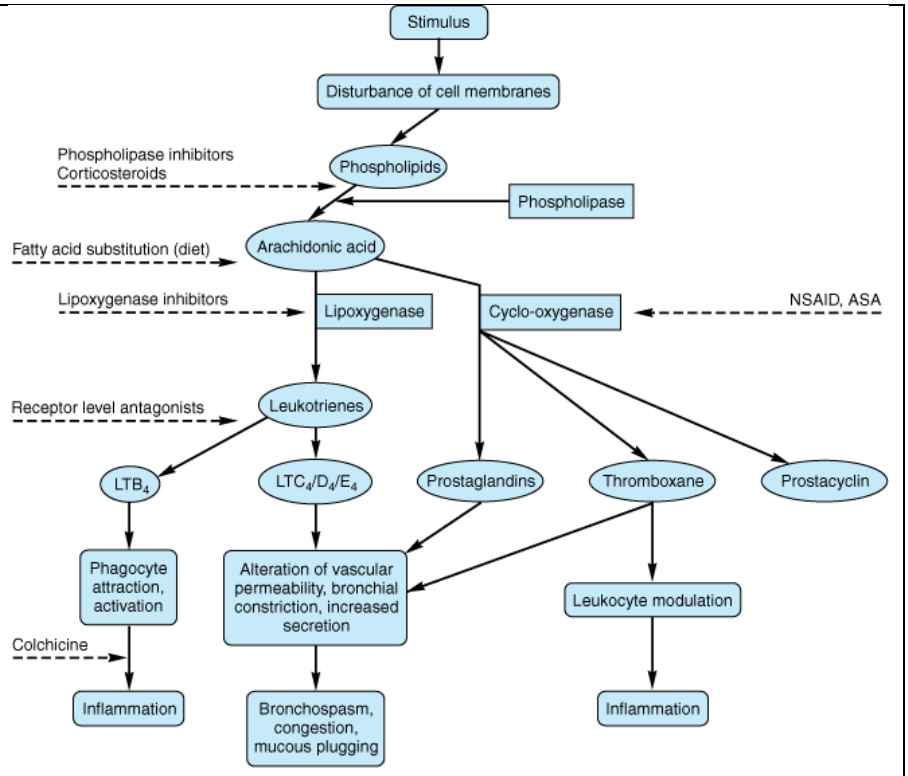
MD01 [Mar96] [Jul97] [Mar03] Oxytocin: A. Synthetised in posterior pituitary B. Poorly absorbed orally C. Metabolised by oxytocinase in the liver D. Bolus dose will increase central venous pressure E. Bolus dose will increase systemic vascular resistance F. Metabolised by the liver and kidney (see also EM15) MD01b [Mar99] [Jul99] Oxytocin: A. Has diuretic effect B. Partially depolarises uterine muscle / ?effect on membrane threshold C. Causes emesis D. Increases threshold of receptors for depolarisation E. Hypertension MD01c [Feb00] Oxytocin: A. Ringed octapeptide B. Effects on uterus antagonized by beta agonists C. ADH like effect D. ?	**Answer:** **Part 1: B** **Part 2: ?B (wording dependent) + C** **Part 3: B or C (partly correct)** **OXYTOCIN:** - Nonapeptide, synthesised in hypothalamus, released from posterior pituitary - USES: induction labour, counteract uterine hypotonicity - polypeptide, rapidly digested by peptidases in GIT → poorly oral abosrption - metabolised in fat + muscle + placenta tissue by oxytocinae/insulin-regulated aminopeptidase - high doses cause vascular smooth muscle relaxation → lower SVR → low BP → reflexive tachycardia + increased CO - in the past, oxytocin preparations were often contaminated by ergot alkaloids → exaggerated hypertensive response in those previously treated with sympathomimetic - modern synthetic preparations are PURE oxytocin (same as physiological structure) and don't have this risk - MIMS: nausea/vomiting common SE - it has an ADH-like effect (anti-diuresis) → H2O intoxication - acts on preganant uterus by lowering the threshold for depolarisation in uterine smooth muscle (Stoelting) - Salbutamol is a tocolytic → will antagonsise the effects oxytocin
MD02 [Mar96] [Mar97] [Jul97] [Jul98] [Jul99] [Feb00] Cisapride: A. Will increase gastric motility in the presence of atropine B. Can be used to treat opioid induced gastric stasis C. Decreases/increases lower oesophageal sphincter tone (?due to atropine) D. Decreases gastric pH E. Increases gastric volume F. Blocks histamine receptors G. Agonist at D2 receptors	**Answer**: B; C (**increases** LOS tone) **Cisapride**: GI prokinetic drug, stimulates gastric emptying, increases lower oesophageal sphincter tone, enchances motility of small + large intestine via enhance release of Ach from nerve endings in myenteric plexus + GI mucosa (agonist at M2 and 5HT4 receptors). Other uses: GORD, mild oesophagitis. Administration of cisparide before antagonism of NMB with atropine/neostigmine will not prevent the ability of atropine to decrease lower oesophageal sphincter tone. Opioid induced gastric stasis can be reversed by cisapride (Stoelting).
MD04 [Mar96] [Jul99] [Apr01] Paracetamol: A. Has an active metabolite B. Interferes with renal blood flow C. Does NOT cause gastric irritation D. Causes methaemoglobinaemia E. Maximum adult dose 4g Apr 2001 version: Paracetamol: A. Frequently causes dyspepsia (?gastric irritation) B. Acid-base abnormalities common with overdose C. Maximum dose 4 grams in adult D. ? E. ? MD04b [Jul98] [Mar99] [Feb00] [Jul04] Paracetamol: A. Is a powerful anti-inflammatory agent B. Should never be given in a dose > 20 mg/kg to children C. Increased risk of hepatic necrosis in chronic alcoholics D. Sulphate conjugation is major metabolic pathway E. pKa 3.5 F. ?Glutathione conjugation	**Answer** **Part 1: C, E** **Part 2: C** **Part 3: C & D** **Part 4: C** **Part 5: NIL** **Part 6: ?A** **PARACETAMOL (Stoelting)** - Weak COX1/2 inhibitor in peripheral tissues (anti-inflammatory effects are weak-Stoelting) - Adult daily dose 4g - NB single dose 15g paracetamol hepatotoxic - pKa 9.5 - Unlike salicylates, paracteamol does not produce gastric irritaion, alter platelet aggregation or antagonise effects of uricosuric drugs (Stoelting) - Metabolism in liver to INACTIVE metabolites - 80% metabolised by hepatic micorsomal enzymes and converted to glucuronide > sulfate metabolites - 5% excreted unchange - 15% metabolised to N-acetyl-p-benzoquinone (this is the hepatotoxic metabolite causing centrilobular necrosis – normally scavanged by glutathione but overdose = exhaustion of supplies) - metabolite p-aminophenol is concentrated in renal papillae → accumulate → ?cause of papillary necrosis → analgesic-induced nephropathy - long term renal toxicity of NSAIDs may be due to persisten inhibition of PG synthesis → medullary synthesis - phenacetin: old analgesic, contained paracetamol and genetically determined differences in metabolism → other metabolites formed which can result in methaemoglobinaemia +

Alt version remembered from Feb 2000: Paracetamol: A. Has analgesic, antipyretic and anti-inflammatory effects B. Is metabolised to BENZOQUINONIMINE which is inactivated by conjugation to glutathione C. Dose should not exceed 4000mg/day in an adult D. Gastric irritation is common July 2004 Paracetamol: A. Has analgesic, antipyretic and anti-inflammatory effects B. Is metabolised to N-methyl-p-benzoisopuinonimine conjugated to glutathione C. Toxic dose is 10 times the normal ?daily dose? D. pKa 3.5 E. ? MD04c [Jul00] Paracetamol: A. Minimum toxic dose 8-12G/day in an adult B.-E. ?	haemolysis (eg G6PD deficiency) - **NOT** with current paracetamol preparations
MD06 [Mar97] [Jul97] [Jul99] [Feb00] Serotonin (5-HT) is most common in: A. Platelets B. Enterochromaffin cells C. Cerebral cortex (?neurones) D. Pineal gland E. GIT F. Mast cells	**Answer: B, E** Stoelting: 5HT: widely distributed autocoid (vasoactive substance) – has impact various circulations (), neutotransmitter in emesis and pain. About 90% of the body's stores of 5HT are in the enterochromaffin cells of the GIT, the remainder in the CNS and platelets.
MD07 [Mar97] [Jul97] [Jul98] [Mar99] [Feb00] Mannitol: A. Metabolised in the liver B. Half-life is proportional to GFR C. Increases Na+ D. Excretion is dependent on GFR E. Urine will be hyperosmolar compared to plasma F. Absorbed orally G. Isotonic H. Clearance dependent on GFR (see also [[CD17) MD07b [Feb04] Mannitol: A. is a sugar and is not metabolised B. does not increase delivery of sodium to distal tubule	**Answer:** **Part 1: D, H best answers (Na+ where?) (?E)** **Part 2: A (B increased Na delivery)** Stoelting Stucturally it is a 6carbon sugar that does not undergo metabolism. It is not absorbed by GI (hence need to use IV). It does not enter cells – only means of clearance from plasma is via glomerular filtration. Mannitol is completely filtered at glomeruli, and none of the filitered drug is subsequently reabsorbed in renal tubules. Hence manniotl increases the osmolarity of renal tubular fluid and prevents reabsorption of water. Sodium is diluted in the retained water in the tutubles causing less reabsorption of sodium. As such there is an osmotic effect of diuresis of sodium, cholirde and bicarbonate ions. Urinary pH does not change. T ½ is **inverseley** proportional to clearance.
MD08 [Mar97] [Jul97] [Mar99] [Mar03] [Jul04] Gastric drugs: Which is true? A. Sucralfate is a mixture of sulphated sucrose and bismuth that sits in the ulcer B. Gastrin & acetylcholine directly & indirectly inhibit H+ secretion C. Misoprostil decreases gastric acid and causes marked constipation D. Pirenzipine is less effective than H2 blockers E. Omeprazole reversibly inhibits proton pump	**Answer: D** Sucralfate: mixture of sulphated sucrose and **aluminium hydroxide.** Adheres to gastric ulcer to fomr cytoprotective barrier against pepsin penetration. No advangated of H2 blockers. Gastrin/ACh directly **enhance H+ secretion** Misoprostol decreases gastric acid and causes **diarrhoea**. Pirenzipine is less effective than H2 blockers Omeprazole **irreversibly** blocks proton pump
MD09 [Mar97] [Feb00] A decrease in renal function might be expected with: A. Gentamicin B. Cis-platin C. Busulphan D. Methotrexate E. All of the above	**ANSWER: E** Gentamicin nephrotoxicity: 5-25% if given gent for >3-5days. Cisplatin nephrotoxicity can be avoided if adequate pre-hydration and diuresis. Busulfan: main effects are myelosuppresion, N/V/D, impotence/steriligy, Addison-like syndrome, venoocclusive disease. On Mims: increase Cr/Ur, dysuria, oliguria, haematuria, moderate renal insufficiency.

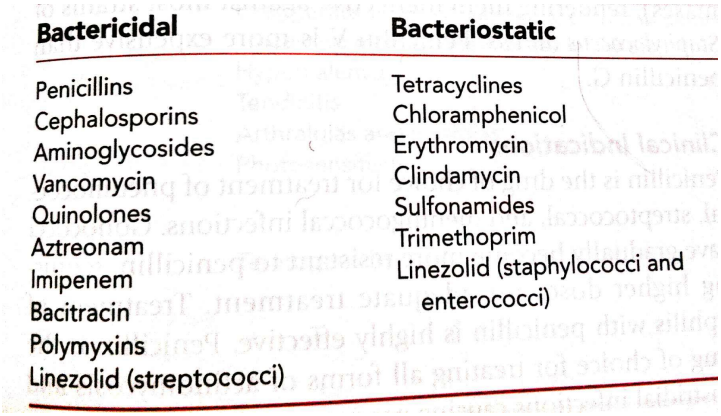
MD11 [Jul97] [Jul98] [Jul99] Theophylline levels increased with: A. Smoking B. Phenytoin C. Cimetidine D. ?	**Answer: C** Theophylline: - T ½ decreased in smokers (hence theophylline levels decreased). - Increased clearance of theophylline with concurrent phenytoin. - Cimetidine: inhibits CYP450, increase levels of substrates such as theophylline (GG)
MD13 [Jul97] [Feb00] When a ligand binds to a receptor linked to a G-protein: A. There is a fall in cAMP B. The signal is amplified 108 times	**Answer: ?B** The alternative wording was when a B agonist binds to a g-protein. Things pointed out: ligand binds to receptor coupled with g-protein, not g-protein itself. There is an amplified response (the degree of which is uncertain). If B-agonist, all B-receptors are G-s which stimulates adenylyl cyclase → increase cAMP.
MD14 [Jul97] [Apr01] Dantrolene: A. Is a benzyl-isoquinoline derivative B. Undergoes oxidative and reductive metabolism C. Inhibits sodium channel activation D. Causes a marked reduction in contractility E. Not effective as prophylaxis because of poor oral bioavailability F. Acts via ryanodine receptor Alt version: Dantrolene: A. Benzylisoquinolonium B. Undergoes hepatic and renal metabolism C. Profound myocardial depression D. Poor oral bioavailability	**Answer:** **First part: Incorrect = A,C,?D (contractility of what?),E. Correct: B,F (?F best)** **Alt version: Incorrect = A,B,C,D ??**  **Dantrolene** (hydantoin derivative) produces smooth muscle relaxation by inhibiting calcium release from sarcoplasmic reticulum into cytosol via **ryanodine** receptors and inositol triophosphate channels. It may also stabilise membranes. Uses: treatment and prevention of MH, treatment of skeletal muscle spasticity. Prophylaxis: oral dose. MH = 2mg/kg IV repeated up to 10mg/kg Unlike NMBD dantrolene cannot decrease contractile activity by >80%. Therapeutic doses has **little/no effect** on **cardiac**/smooth muscle. **Diruesis** (**mannitol** added to powder to make it isotonic). Highly lipophilic → low H2O solubility. 70% of oral administered dose is absorbed. IV preparation is alkaline → phlebitis. Extravasation → tissue necrosis. Metabolised in **liver to** active 5-hydroxydantrolene which has 30-50% activity. <1% unchanged in urine. T ½ elim: 5-8hrs. SE: skeletal muscle weakness (difficulty spont vent/risk aspiration), N/D/blurred vision, uterine atony, hperkalaemia, hepatitis (can be fatal), pleural effusion. Krause et al. (2004). Dantrolene – A review of its pharmacology, therapeutic use and new developments. *Anaesthesia*. Volume 59 Page 364, April.
MD15 [Jul97] Omeprazole: A. Irreversibly inhibits the parietal cell B. Acts at apical membrane of parietal side C. Acts at the basolateral membrane of the parietal	**Answer: B** Stoelting/Mims: Omperazole is a substitute benzimidazole that acts as a prodrug theat becomes a **PPI**. Weak base, concentrated in seceretory canaliculi of gastric parietal cells. Here it is protonated to its active form which **reversibly** inhibits the enzyme **pump** (H-K-ATPase) – not the parietal cell. Initial dose only works on proton pumps present at luminal surface (as new pumps made/inserted into membrane, need more doses of omeprazole to block them). Inhibits H+ secretion more than H2-receptor antagonists.
MD16 [Mar98] Diclofenac: A. Plasma protein binding is ....% B. Percent absorption . . % C. Mechanism of action via increase in endorphins D. ?	**Answer: A if 99%** Diclofenac is a proprionic acid derivative (along with ibuprofen, naproxen). Analgesia, anti-pyretic, antiinflammatory effects. Inhibits COX and decreases PG production. 99% Plasma protein bound. Drug producf information states that it is well absorbed, but 50% 1st pass metabolism. It is eliminated by metabolism to glucuronide, hydroxy and sulfate conjugates followed by excretion in bile and urine. Rapid elimination (90% clearance within 3-4rs). <1% excreted unchanged in urine
MD17 [Mar98] [Apr01] [Jul04] Regarding phenytoin A. Acts via blockade of Na channels and	**Answer: possibly A (Incorrect: B,C)** **Phenytoin**:

via effect on K channels B. Weak base with pKa 8.3 C. Has active metabolites D. ? E. ?	Protoypte of the hydantoins and is effective for treatment of partial/generalised seizures. High therapuetic index. Regualtes **Na** and possibly **Ca** ion **transport** across **neuronal** cell membranes. **Membrane stabilising** effect on cerebral cortex. Also acts on 2nd messengers eg calmodulin, cyclic nucleotides. (Stoelting). *NB Sassada/Smith: "stabilising activity is via slowing inward Na and Ca influx during depolarisation in excitable tissue. It also delays outward K efflux."* **Weak acid, pKa 8.3**. Maintained in aqueous solution as a sodium salt. **90% protein** bound (**albumin**). Poor water solubility → slow and variable GI absorption (30-70%). Therapeutic [plasma] = 10-20mcg/mL. **Hepatic metabolism**: **98**% to **inactive** metabolites via microsomal enzymes (glucuronide → urine). Only 2% excreted unchanged in urine.
MD18 [Mar98] [Mar99] [Feb00] [Apr01] [Jul02] [Mar03] Which ONE of the following decrease gastric pH? A. Omeprazole B. Famotidine C. Calcium salts D. Misoprostil E. PGE2 July 2000, 2002 and 2003 version : Which ONE of the following decreases gastric acid secretion?: A. ? B. Misoprostil C. Cisapride D. Na citrate E. Metoclopramide Apr 2001 version: Decrease gastric pH: A. Calcium salts B. H2 antagonists (?ranitidine) C. Omeprazole D. Pirenzipine E. PGE2	**Answer: NB watch pH vs acid secretion (opposite directions)** **Part 1: C** **Part 2: B** **Part 3: A** Omeprazole, famotidine, misoprostal and PGE2 all increase the pH of gastric acid. Calcium salts: potentially via Ca-dependent pathway stimulating H/K/ATPase.
MD19 [Jul98] [Mar99] [Feb00] [Jul01] [Jul04] NSAIDs: A. Exhibit no selectivity for COX 1 & 2 B. Exert renal effects other than effect on afferent arterioles C. Cause renal toxicity separate to inhibition of prostaglandins D. Aspirin & ketorolac irreversibly bind COX1 & 2 E. Directly cause gastrointestinal ulceration Alt version: NSAIDs: A. All inhibit COX 1 B. Aspirin and ketoralac inhibit COX irreversibly C. They can cause renal toxicity by mechanisms other than alterations in renal blood flow by PG mediators.	**ANSWER** **Part 1: B,C** **Part 2: C** A: No- NSAIDs do exhibit selectivity. B: Yes- NSAIDs usually cause nephrotoxicity via inhibition of PG synthesis in medulla → ischaemia. But can also be via tubulointerstitial nephritis. C: Yes D: No: aspirin irreversibly binds but ketorolac does not E: GIT effects indirect by inhibition of PG syntehsis as a result of COX1 inhibition. A: No B: No C: Yes
MD20 [Jul98] [Mar99] [Feb06] Irreversible cardiomyopathy can be due to: (OR: Which of the following causes dose-dependent cardiac toxicity?) A. Vincristine B. Bleomycin C. Danorubicin D. Asparaginase E. Cyclophosphamide F. All of the above	**ANSWER: C** Cardiomyopathy is a **unique** characteristic of **anthracycline antibiotics** (danorubicin, doxorubicin, idarubicin) Vincristine = neurolgoical toxicity (ischaemic cardiac toxicity rare) Bleomycin = cutaneous + pulmonary toxicity (coronary artery disease has been reported) Asparaginase = toxicity via antigenicty as foregin protein Cyclophosphamide = N/V/ulceration/skin pigmentation, pulmonary fibrosis NB 5FU and its prodrugs are associated with coronary vasospasm.
MD22 [Mar99] [Apr01] [Mar03] Gastric lavage: A. Not useful if more than one hour has elapsed B. In children, use normal saline instead of water	**Answer: B** Goodman Gilman: Can use gastric lavage up to **24hrs** after ingestion. Use **saline** instead of H2O in **kids** due to risk of water intoxication. Should be performed in **left lateral** position. Can be performed in unconscious person if **airway** protected. Do **not** use if **corrosive** poision.

C. Contraindicated if poison corrosive D. Is performed in the right lateral position E. Should not be performed in the unconscious	*(Comment: The restriction in unconscious patients is they should be intubated for airway protection)*
MD23 [Mar99] [Apr01] Long term prednisolone 20mg/day will result in: A. Increased lymphocyte count B. Increased capillary permeability C. Metabolic alkalosis D. ??glucose	**ANSWER: C or D** An analogue of cortisol. 5mg equipotent to 20mg cortisol. Has dual glucocorticoid and mineralocorticoid effects hence can be used as sole agent in adrenocortical insufficiency. All corticosteroids increase WCC but increase it is a **neutrophilia** and relative **decrease** in **lymphocytes**, eosinophils and monocytes. They inhibit the use of glucose in peripheral tissues → **hyperglycaemia**. Can cause hypokalaemia **metabolic alkalosis** with mineralocorticoid actions on distal **renal tubules**. **Drug** / **Equivalent Dose (mg)** Cortisol 20 Cortisone 25 Prednisolone 5 Prednisone 5 Methylprednisolone 4 Betamethasone 0.75 Dexamethasone 0.75 Fludrocortisone 2
MD24 [Mar99] NSAIDs cause gastric side-effects by: A. Direct effects on mucosa B. Indirect effects C. ?	**ANSWER: B** NSAIDS inhibit COX → decreased prostaglandins → indirect gastric SE's via: 1. Decreased mucosal blood flow 2. Decreased protective mucous/HCO3 layer 3. Increased gastric acid production
MD26 [Jul98] [Jul99] With respect to prednisone: A. [[Prednisone] is converted to active prednisolone in the gut B. Prednisone 5mg is equivalent to 100mg cortisol C. Betamethasone has equivalent mineralocorticoid activity D. Methylprednisolone ? Alternative version of options A & E: A. Prednisone is converted to prednisolone after absorption from the gut. E. Betamethasone has adrenocorticoid and mineralocorticoid activity	**ANSWER** **Part 1: ?D (rest wrong)** **Part 2: A** Prednisone is an analogue of cortisone, rapidly **converted** to **prednisolone after abosprtion** from GIT. Anti-inflammatory effects. See chart from before: Prednisone 5mg = Cortisol 20mg. **Betamethasone lacks** the **mineralocorticoid** activities of cotisol.
MD27 [Jul98] [Jul99] [Jul00] Aspirin: A. Greatest absorption is from the stomach B. Peak plasma level is achieved in 30]] minutes C. Has cross-reactivity with all NSAIDs D. Half-life 4 hours July 2000 version: Aspirin: A. Plasma half-life 4 hrs B. Peak plasma concentration within 10mins of oral administration C. Requires conversion to salicylic acid for activity D. ? is more ?? than salicylic acid E. Better absorption if food in stomach F. Cross reactive sensitivity with all NSAIDs	**ANSWER** **Part 1: C** **Part 2: F** Aspirin (acetylsalicylic acid): irreversibly acetylates COX → decreased synthesis and release of prostaglandins. Relatively weak inhibitor of renal prostaglandin synthesis. Does not interact with opioid receptors and has little effect on histamin/5HT release. Rapidly hydrolysed to salicylic acid which inhibits PG synthesis in a non-acetylation way. Rapidly **absorbed** mainly from **small intestines**, lesser extent in stomach. Rate of absorption depends on dissolution rates of the administered tablet and gastric emptying time. If gastric pH increased → more drug is ionised → decreased rate of absorption. **Food slows** absorption. Aspirin in effervescent preparations have more rapid absorption high plasma concs, less GI irritation. Has cross-reactivity with all NSAIDs. Metabolism: rapidly hydrolysed in liver to salicylic acid (active). Salicylic acid is also metabolism in liver via glycine conjugation → renal excretion (renal excretion increased in alkaline urine). T ½ elim = 15-20mins aspirin, 2-3hrs salicylic acid. Peak plasma concentration of aspirin must be shorter than its t ½ elim (ie <15-20 mins). Peak plasma salicylic acid conc 1-2hrs.

	 Source: Katzung BG: *Basic & Clinical Pharmacology*, 10th Edition: http://www.accessmedicine.com
MD28 [Jul98] [Mar03] Organophosphates: A. Phosphorylate the esteratic site B. Phosphorylate the anionic site C. ? D. ? (See also MB11, MB27)	**ANSWER: A** Organophosphates phosphorylate the ESTERATIC site of acetylcholinesterase.
MD29 [Mar99] [Feb00] Warfarin affects: A. Factor XIII B. Protein S (? or Protein C) C. ?	**ANSWER: B** Warfarin acts by inhibiting the enzymes vitamin K epoxide reductase and vitamin K reductase. This prevents the formation of the reduced formed of vitamin K which acts as a cofactor in the gamma-carboxylation of glutamic acid residues in clotting factors 2,7,9,10 as well as anticoagulant protein C and S. Gamma-carboxylation is necessary for biological activity of these factors as it confers the calcium binding properties that are essential for their catalytic action. Inhibition by warfarin is COMPETITIVE.
MD30 [Jul99] [Feb00] Bleomycin A. Related to nitrogen mustard B. Can cause agranulocytosis (or: frequently causes myelosuppression) C. Causes pulmonary toxicity in 90% of patients D. Is an alkylating agent E. Causes pulmonary oxygen toxicity due to production of superoxide radicals	**ANSWER: E** Bleomycin is a mixture of cytotoxic glycopeptide antibiotics silated from a strain of Streptomyces verticillus. It causes pulmonary toxicity in about 4% of patients. It probably induces lung toxicity through the induction of O2 radicals, with recruitment of WCC + fibroblasts augmenting the early inflammatory and later fibrotic reactions. It is not an alkylating agent, nor is it related to nitrogen mustard. Bleomycin and vincristine differet from other chemotherapeutic agents (do NOT cause myelosuppression.
MD31 [Jul99] Which drug causes the most anaphylaxis? A. Suxamethonium B. High potency non-depolarisers C. ? D. ?	**ANSWER: Probably A – B only in one french study** Rocuronium in French study (but less potent drug). *FRCA UK: The antigen is the quaternary ammonium group which is found in other drugs, food, cosmetics and hair products. Therefore a reaction can occur without previous exposure to the agent. Most common precipitants in decreasing order vecuronium, atracurium, suxamethonium, pancuronium, rocuronium, mivacurium.* **Vs the French:** "The muscle relaxants most often involved in anaphylaxis in France in 1997-1998 are, in decreasing order of the numb r of cases reported: rocuronium, suxamethonium, atracurium, vecoronium. The relation between the number of patients having had a reaction to each of these agents and the number of patients treated with them is the highest for

	rocuronium and suxamethonium, the lowest for atracurium, with vecuronium situated inbetween." Reducing the risk of anaphylaxis during anaesthesia: guidelines for clinical practice. P.M. Mertes et al, for ENDA** and theEAACI interest group on drug hypersensitivity. J Invest Allergol Clin Immunol 2005; Vol. 15(2): 91-101
MD32 [Jul99] [Jul04] Syrup of Ipecac: A. Is not effective in phenothiazine overdose B. Has peripheral irritant and direct CTZ action C. The syrup is more potent than the fluid D. ?	**ANSWER: B** G+G and Wiki: Ipecac: derived from the dried rhizome and roots of ipecacuanha plant. It induces vomiting. May be effective when anti-emetic drugs such as phenothiazines (chlorpromazine, promethazine) have been ingested. It is a local irritation on GI tract and has effect on CTZ. Fluid is 14x more potent than syrup.
MD33 [Feb00] Regarding antiemetics which drug has anti-5HT3, anti-H1 and anti-D2 actions: A. Ondansetron B. Scopolamine C. Domperidone D. Droperidol E. Prochlorperazine F. Chlorpromazne Alternative versions: • Which of the following anti-emetics have D2, ACh, 5 HT-3 antagonist effects? • Which drug is a D2 antagonist, H1 antagonist and 5HT3 receptor antagonist?	**ANSWER**: E Ondansetron: specific to **5HT3** receptors (nil action at dopamine, histamine, adrenergic, cholinergic) Scopolamine: antichlolinergic – sedation, amnesia, potent antisialogogue Domperidone: specific dopamine antagonist (peripheral action = prokinetic) Droperidol: butyrophenone (like haloperidol). It inhibits D2 receptors in CTZ in medulla. Does no help labrynthine-nausea. Chlorpromazine: phenothiazine, block D2 receptor in CTZ Propchlorperazine: phenothiazine, antagonist at D2 receptor in CTZ, muscarinic, alpha ½, H1, 5HT receptors
MD34 [Jul99] [Feb00] With regard to **nitric** oxide A. It is anaesthetic at high concentration B. May improve V:Q mismatch C. Is a liquid in the cylinder, gas at room temperature D. ?	**ANSWER: B (why we use it in ICU)** Debate as to whether question should be about nitrous oxide (in that case A + C correct) NO is synthesised from L-argnine by family of enzymes 'NO synthestases.' Diffused from producing cells into target cells where activates guanylate cylcase → increase cGMP → vasodilatation. T ½ <5secs. Avidly bound and inactivated by haemoglobin. NO actually appears to be involved in excitatory neurotransmission by CNS (NO synthase inhibition seems to suppress excitation transmission mediated by NMDA).
MD35 [Feb00] [Jul01] Ethanol A. About 35% excreted via the lungs B. Concentration falls at a fixed rate with respect to time C. Only 60% is metabolised, the remainder being excreted in expired air D. Is excreted at a rate independent of the plasma concentration E. Constant elimination independent of plasma concentration F. Elimination is not dependant upon amount absorbed from GIT	**ANSWER: E, B** Ethanol: 90-98% metabolised, mainly via liver. Zero order kinetics (constant amount metabolised per time).
MD36 [Feb00] Which drugs cause convulsant activity? A. Cocaine B. Lithium C. Norpethidine D. Enflurane E. All of the above	**ANSWER: E** All of them do! (G+G)
MD37 [Feb00] Metoclopramide A. Increases gastric emptying faster with an oral dose than an IV dose B. Causes diarrhoea in children C. Is a dopamine agonist D. ?	**ANSWER: B** Metoclopramide is a dopmaine receptor ANTAGonist. Onset of action of oral 30-60 mins vs 1-3mins for IV. Diarrhoea is a known side effect in children.
MD38 [Feb00] [Jul00] Physostigmine A. Causes (? excitatory activity / ?alerting response) on the EEG B. Doesn't cross the blood brain barrier C. Doesn't cause sedation	**ANSWER: C ?A** *Stoelting*: Phytostigmine is a lipid soluble **tertiary** amine **anticholinesterase** which **crosses** the **BBB** and hence can antagonise the CNS SE's of some drugs. It works by increasing concentrations of Ach in brain, making more neurotransmitters available to interact with cholinergic receptors. Its duration of action is shorter c/w anticholinergic drugs so may need repeat doses. Works at many receptors

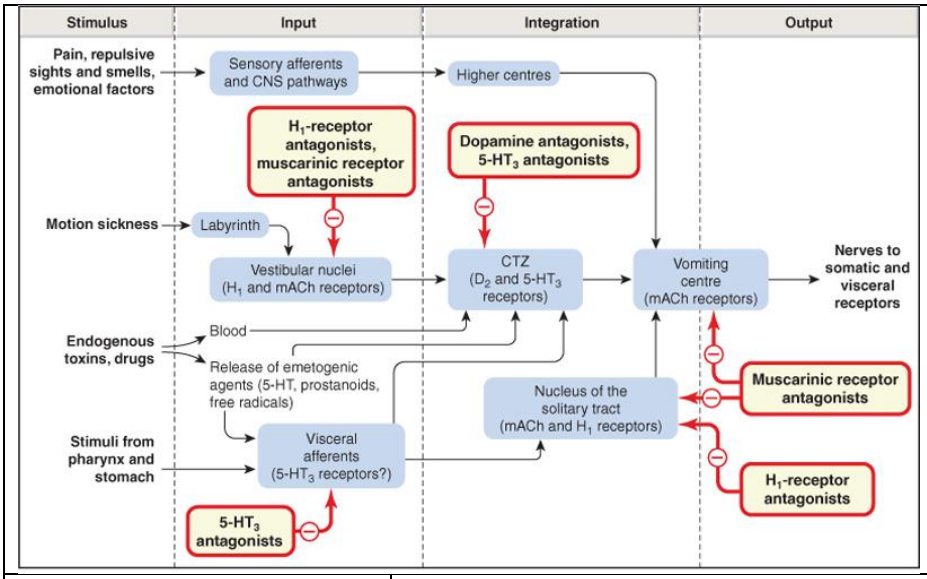
D. Only has its effects at nicotinic receptors E. Causes amnesia F. Causes excitatory activity on the EEG G: Is/isn't a quaternary ammonium that does/doesn't cross BBB	(antagonises the effects of opioids). *G+G/Katzung*: 'in low concentrations they can cause diffuse activation on the EEG'
MD39 [Jul00] Drugs filtered and secreted in the PCT include: A. Penicillin B. Probenecid C. Chlorothiazide D. ? Also remembered as: Which basic drug is secreted by the kidney for excretion? A. Procainamide B. Probenecid C. Penicillin D. Acetazolamide	**ANSWER** **Part 1: A,B and C** **Part 2: A – rest are all acids** Stoelting: Penicillin (acidic drug) excreted by kidneys (10% glomerular filtration, 90% tubular secretion). Probenecid (acidic drug) is filtered at glomerulus, secreted in proximal tubule and reabsorbed in distal tubule). Chlorothiazide (acidic drug) thiazide diuretic. Main action is at cortical portin of ascending LOH but also has minor action in DCT and PCT. Procainamide: analogue of LA procaine (also basic). Renal excretion 40-60%, rest hepatic metabolism. Acetazolamide: (?weak acid) non-competitive inhibition of enzyme activity in PCT. Excreted unchanged by kidneys.
MD40 [Jul00] Which of the following is bacteriostatic only? A. Penicillin B. Gentamicin C. Vancomycin D. Trimetophan E. ?Cefoxitin /?cefuroxime (see also [[MD40)	**ANSWER: D**  Penicillin, Gentamicin, Vancomycin, cephalosporins are bactericidal. Trimethoprim is bacteriostatic. Trimet**o**phan: WTF? Trimeth**a**phan is a peripheral vasodilator. Antimicrobial agents are classified based on chemical structure and proposed mechanism of action, as follows: (1) agents that inhibit synthesis of bacterial cell walls, including the -lactam class (e.g., penicillins, cephalosporins, and carbapenems) and dissimilar agents such as cycloserine, vancomycin, and bacitracin; **BACTERIOCIDAL** (2) agents that act directly on the cell membrane of the microorganism, increasing permeability and leading to leakage of intracellular compounds, including detergents such as polymyxin; polyene antifungal agents (e.g., nystatin and amphotericin B) which bind to cell-wall sterols; and the lipopeptide daptomycin (Carpenter and Chambers, 2004); **BACTERIOCIDAL** (3) agents that disrupt function of 30S or 50S ribosomal subunits to reversibly inhibit protein synthesis, which generally are bacteriostatic (e.g., chloramphenicol, the tetracyclines, erythromycin, clindamycin, streptogramins, and linezolid); **BACTERIOSTATIC** (4) agents that bind to the 30S ribosomal subunit and alter protein synthesis, which generally are bactericidal (e.g., the aminoglycosides); **BACTERIOCIDAL** (5) agents that affect bacterial nucleic acid metabolism, such as the rifamycins (e.g., rifampin and rifabutin), which inhibit RNA polymerase, and the quinolones, which inhibit topoisomerases; and **BACTERIOCIDAL**

	(6) the antimetabolites, including trimethoprim and the sulfonamides, which block essential enzymes of folate metabolism. **BACTERIOSTATIC** There are several classes of antiviral agents, including: (1) nucleic acid analogs, such as acyclovir or ganciclovir, which selectively inhibit viral DNA polymerase, and zidovudine or lamivudine, which inhibit HIV reverse transcriptase; (2) non-nucleoside HIV reverse transcriptase inhibitors, such as nevirapine or efavirenz; (3) inhibitors of other essential viral enzymes, e.g., inhibitors of HIV protease or influenza neuraminidase; and (4) fusion inhibitors such as enfuvirtide. Additional categories likely will emerge as more complex mechanisms are elucidated. The precise mechanism of action of some antimicrobial agents still is unknown. GOODMAN & GILLMAN
MD41 [Jul00] With respect to serotonergic receptor action, which ONE of the following is true? A. Sumiatriptan is a 5HT1 antagonist B. Ondansetron is a 5HT3 agonist C. ?Serotonin is a 5HT3 agonist D. Metoclopramide is a 5HT4 agonist E. ?	**ANSWER: C! also D** G+G: Sumitriptan: 5HT1 agonist Ondansetron: 5HT3 ANTagonist Metoclopramide: 5HT3 ANTagonist and partial 5HT4 agonist. Serotonin: 5HT agonist

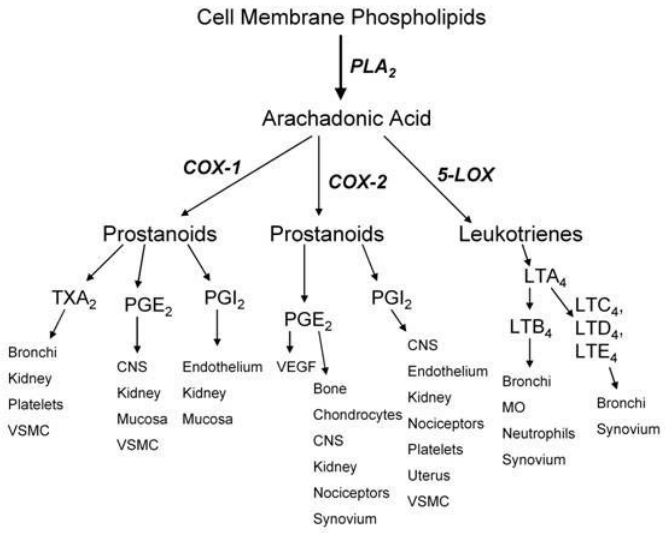
Receptor	Location	Main effects	Second messenger	Agonists	Antagonists
1A	CNS	Neuronal inhibition Behavioural effects: sleep, feeding, thermoregulation, anxiety	↓cAMP	5-CT 8-OH-DPAT Buspirone (PA)	Spiperone Methiothepin Ergotamine (PA)
1B	CNS Vascular smooth muscle	Presynaptic inhibition Behavioural effects Pulmonary vasoconstriction	↓cAMP	5-CT Ergotamine (PA)	Methiothepin
1D	CNS Blood vessels	Cerebral vasoconstriction Behavioural effects: locomotion	↓cAMP	5-CT Sumatriptan	Methiothepin Ergotamine (PA)
2A	CNS PNS Smooth muscle Platelets	Neuronal excitation Behavioural effects Smooth muscle contraction (gut, bronchi, etc.) Platelet aggregation Vasoconstriction/vasodilatation	↑IP_3/DAG	α-Me-5-HT LSD (CNS) LSD (periphery)	Ketanserin Cyproheptadine Pizotifen (non-selective) Methysergide
2B	Gastric fundus	Contraction	↑IP_3/DAG	α-Me-5-HT	-
2C	CNS Choroid plexus	Cerebrospinal fluid secretion	↑IP_3/DAG	α-Me-5-HT LSD	Methysergide
3	PNS CNS	Neuronal excitation (autonomic, nociceptive neurons) Emesis Behavioural effects: anxiety	None-ligand-gated cation channel	2-Me-5-HT Chlorophenyl-biguanide	Ondansetron Tropisetron Granisetron
4	PNS (GI tract) CNS	Neuronal excitation GI motility	↑cAMP	5-Methoxy-tryptamine Metoclopramide Tegaserod	Various experimental compounds (e.g. GR113808, SB207266)
5	CNS	Not known	Not known	Not known	Not known
6	CNS	Not known	Not known	Not known	Not known
7	CNS GI tract Blood vessels	Not known	↑cAMP	5-CT LSD No selective agonists	Various 5-HT_2 antagonists No selective antagonists

2-Me-5-HT, 2-methyl-5-hydroxytrypamine; 5-CT, 5-carboxamidotryptamine; 8-OH-DPAT, 8-hydroxy-2-(di-***n***-propylamino) tetraline; CNS, central nervous system; DAG, diacylglycerol; GI, gastrointestinal; IP_3, inositol trisphosphate; LSD, lysergic acid diethylamide; PA, partial agonist; PNS, peripheral nervous system; α-Me-5-HT, α-methyl 5-hydroxytrypamine.

MD42 [Jul00] Acetazolamide: A. ? secreted by the renal tubules B. ? diuresis C. ? develop tachyphylaxis	**ANSWER: A,B,C** Carbonic anhydrase inhibitor, weak diuretic effect, rapid development of tachyphylaxis, is secreted by renal tubules.
MD43 [Jul00] Best antiemetic for motion sickness: A. Metoclopramide B. Ondansetron C. ? D. ? E. Hyoscine	**ANSWER: E** Think about it in terms of inputs to CTZ/vomiting centre: Want to block H1 or muscarinic Ach receptors in vestibular nuclei, which then feed into CTZ (D2 and 5HT3 receptors). A: Metoclopramide antagonism of dopamine-agonist effects on CTZ theoretically contributes to anti-emetic effect. B: definitely NOT as per Stoelting E: **Scopolamine** is L-hyoscine. Competitive inhibition at muscarinic Ach receptors. Used in motion sickness. NB: other drugs used for motion sickness: 1. **Cyclizine** (H1 antagonist, muscarinic (M1,2,3) ACh antagonist). 2. **Promethazine**: reversible competitive inhibition of H1 histaminergic receptors, plus antidopaminergic, anticholinergic, antiserotonergic effects



MD44 [Jul00] Complications of salbutamol used in asthma treatment include the following EXCEPT: A. Tachycardia B. Decreased V/Q mismatch C. Tremors D. Pulmonary oedema E. Hyperkalaemia	**ANSWER: E best answer** re **B:** short term worsened (increased) V/Q mismatch but longer term/supplemental O2: improved V/Q mismatch (decreased). re: **D**: there are case reports about B agonists causing pulmonary oedema when used as tocolytic. **Salbutamol** (aka albuterol) SE's: tachycardia (B2 vasodilatation + reflex tachycardia plus some B1 effects), tremor (direct B2 stimulation in skeletal muscle), hypokalaemia. Inhibition of hypoxic pulmonary vasoconstriction can cause transient drop in arterial oxygenation (can be avoided with supplemental O2). Also get hyperglycaemia, hypomagnesaemia, lactic acidosis (excessive glycogenolysis and lipolysis from B2 receptor activation).
MD45 [Apr01] (Antibiotic sensitivities against certain bacteria) A. Penicillin and …? B. Amoxycillin and …staph +? C. Flucloxacillin and G +ve? D. ?cephalosporin and …?	**ANSWER: unclear!** **PENICILLINS:** 1. **Narrow spectrum penicillins** are mainly active against gram +ve organisms, but are inavtivated by beta-lactamases. Include: Benzylpenicillin, procaine penicillin (IMI preparation and provides blood evels for 24hrs), benzathine penicillin (IMI and provides low levels of benzylpen for 4 weeks), phenoxymethylpenicillin (penV, po formulation) 2. **Narrow spectrum penicillins** with antistaphylococcal activity - stable to beta lactamases produced by Staphylococci. Includes diclox, fluclox and methicillin. 3. **Moderate spectrum penicillins** also called the aminopenicillins, incl. amoxycillin and ampicillin - have greater activity than benzylpenicillin against some gram negative organisms e.g. E Coli, H infl. But they are destroyed by beta lactamase producing strains. Drugs of choice for enterococcal infections. 4. **Broad spectrum penicillins (beta-lactamase inhibitor combinations)**. Beta lactamase inhibitors Incl clavulanate, sulbactam, and tazobactam inhibit the enzymes produced by staph aureus, bacteroides fragilis, e. coli, klebsiella, neisseria gonorrhoea and h.infl.. They extend the spectre of activity of amoxycillin and, ticarcillin and piperacillin when in combination. 5. **Broad spectrum penicillins with antipseudomonal activity**. Ticarcillin and piperacillin are the only pen with activity against pseudomonas aeruginosa **CEPHALOSPORINS:** A. **Moderate spectrum** . Cephalexin, cephalothin and cephazolin. Active against strep and staph incl beta lactamase prod staph. Inactive against enterococci or listeria . Gram -ve activity against ecoli, and kleb sp. Inactive against many gram -ve aerobes. B. **Moderate spectrum** with anti haemophilus activity - cefuroxime and cefaclor C. **Moderate spectrum** with anti anaerobic activity cefoxitin treats bacteroides fragilis. D. **Broad spectrum** cefoxitime and ceftriaxone covers the majority of commnity acquired g -ve rods. E. **Broad spectrum cephalosporins and antipseudomonal activity** - ceftazidime and cefepime covers majority of enteric gram -ve rod organisms, incl pseud aeruginosa *Therapeutic Guidlines*
MD46 [Apr01] Aspirin overdose A.Causes metabolic & respiratory acidosis B. Causes metabolic & respiratory alkalosis C. Causes metabolic alkalosis &	**ANSWER: D** Stoelting: Aspirin causes metabolic acidosis likely due to uncoupling of oxidative phosphorylation and tendency towards anaerobic metabolism → lactic acidaemia and reduced renal elimination of strong acids. Also has direct effect on respiratory centre → respiratory alkalosis.

respiratory acidosis D. Causes metabolic acidosis & respiratory alkalosis	
MD47 [Apr01] Atropine overdose in neonates A. Causes hyperpyrexia B. ??	**ANSWER: A** Katzung Atropine Overdose: 1. Hyperthermia in paediatric population (loss of sweating) 2. Central cholinergic syndrome in elderly 3. Tachycardia/tachyarrhythmias 4. Blurred vision, loss of balance, miosis 5. Initial bradycardia at low doses (?weak partial agonist effect).
MD49 [Apr01] [Jul01] [Jul02] [Jul04] Low molecular weight heparin A.Has better bioavailability B. Molecular weight 1/10 that of normal heparin C. More protein bound than heparin D. ? E. ?	**ANSWER: A** Stoelting: Unfractionated heaprin is a mizure of low and high molecular weight acid mucopolysaccharides 3,000-60,000 Da. LMWH are dervied from UFH by chemical depolymerisation to fragments approximately **1/3 the size** of heparin. LMWH has **better bioavailability** than UFH. LMWH is **less protein** bound than UFH.
MD51 [Jul01] An intravenous infusion of 8.4% sodium bicarbonate to a healthy adult may cause: A. Hypotonicity B. Intracellular Acidosis C. Ionized Hypercalcaemia D. ?Respiratory Alkalosis E. Rebound Metabolic Acidosis MD51b [Feb04] Bicarbonate A. Complications include intracellular acidosis B. 100ml of 8.4% NaCO3 has 200 milliosmoles C. ?	**ANSWER** **Part 1: B** **Part 2: A** Uses: correction metabolic acidosis, alkalinisation urine, antacid. Dose for correction metabolic acidosis: Dose (mmol) = (base deficit x body weight)/3 → administer ½ this dose then reassess acid base status. 8.4% NaHCO3: molecular weight is 84 (8.4g/100mL). Hyperosmolar (2000 mOsm/kg = 7x plasma osmolality). SE: metabolic **alkalosis** if overenthusiastic administration, hyperNa^+, hyperK^+, hypoCa^{2+}. Paradoxical intracellular acidosis occuring following bicarbonate administration due to CO2 production, and this seems to be one of the arguments against its use. It also causes hypocalcaemia. See Current Opinion in Critical Care. 14(4):379-383, August 2008.
MD52 [Jul01] [Jul04] Cyclo-oxygenase-1 (COX-1) isoenzyme: A. Is increased by inflamation B. Is ?predominant mode of action of indomethacin C. Is increased by lipopolysaccaride D. Is NOT involved in gastric mucosal protection E. Is increased by cytokines	**ANSWER: B is best** A technically correct C can't find anything, D/E wrong Stoelting: COX 1 consitutively expressed, only slightly up-regulated in response to inflammatory hormones. COX-2 is inducible and mediates inflammation, fever, pain, carcinogenesis. **COX 1** in gastric mucosa, renal parenchyma and platelets. Provides protective role in gastric mucosa. **COX 2**: induced by cytokines, growth factors, tumour promoters. Faunce: Indomethacin has 50x greater effect on COX 1 than COX 2. 
MD53 [Jul01] Caffeine A. Is a CNS depressant	**ANSWER: B is best** Possibly E (but ? weak diuretic)

B. Causes cerebral vasoconstriction C. Reduces the acidity of gastric fluid secretion (or: Not a gastric irritant) D. Reduces plasma glucose level E. Is a potent diuretic. F. Has been shown to be dependence producing G. Does not show an improvement in psychomotor function	Possibly F Caffeine is a methylxanthine derive PDE inhibitor. CNS stimulant. CNS vasoconstrictor. Increases BSLs. Causes secretion of acidic gastric acid. USES: neonatal apnoea of prematurity, post-dural puncture headache.
MD54 [Jul02] Which of the following drug interactions is mediated by serotonin? A. ? B. ? C. ? D: Pethidine & Tranylcypromine E. ?	**ANSWER: D** Tranylcypromine is non-selective irreversible MAOI. Pethidine reduces 5HT uptake from nerve endings causing excessive central 5HT activity (Yentis, Peck).
MD55 [Feb04] Metabolism of which drug is decreased in pseudocholinesterase activity: A. Mivacurium B. Cocaine C. Procaine D. Remifentanil E. Esmolol	**ANSWER: A, C** Likely question meant psuedocholinesterase deficiency.
MD56 [Jul04] What drugs affecting ganglia ? A. Hexamethonium, B. ?carbachol C. ?	**ANSWER: A + B** Hexamethonium is an autonomic ganlion blocker. Carbachol is a cholinergic agonist and stimulates PNS (muscarinic>nicotinic). Has high level of nicotinic activity, particularly on autonomic ganglia, which may reflect drug-induced endogenous Ach release from the terminals of cholinergic fibres.
MD57 [Jul04] Which of these agents does not reduce uterine contractions? A. Nifedipine B. Gycerol trinitrate C. Indomethicin D. Isoprenaline E. Phenytoin	**ANSWER: E** Nifidipine, GTN and isoprenaline are all tocolytics. Indomethacin is a tocolytic used in pre-term labour. Phenytoin is not a tocolytic (Shah and Kelly)
MD58 [Jul04] Which of the following is the MOST COMMON side effect of oxytocin? A. Hypotension B. ADH effect C. Supraventricular tachycardia D. Histamine release	**ANSWER: A** Stoelting: Direct relaxant effec on smooth muscle → hypotension. Slight AVP effect in high doses. SVT not common. Histamine release not mentioned in main texts (Yentis: can cause nausea, rash, allergic reactions).
MD59 [Jul04] Cause of hypotension during iv Vancomycin administration A. ? B. ? C. ?	**ANSWER: N/A** Stoelting: give over 60 mins in order to minimise the occurrence of drug-induced histamine release and hypotension.
MD60 Which of the following is a non particulate antacid A. Aluminium hydroxide B. Sodium citrate C. Magnesium hydroxide D. Cimetidine E. ?	**ANSWER: B** Sodium citrate is a non-particulate antacid. Compared with particulate antacids, non-particulate antacids: ▪ Are less likely to cause a foreign body reaction if aspirated. ▪ Mix with gastric fluid more completely.
MD61 Mechanism of action of ondansetron? A - blocks ligand gated ion channel - True, blocks non selective cation channel - only 5HT3 subtype are ion channels, others are GPCR	**ANSWER: A**

B peripheral blockade 5HT3 - false - central and peripheral action - CTZ and vagal afferents / myenteric plexus C blockade 5HT4 - false - low affinity D increases amount of serotonin in CTZ - false I think, but only rough lack of confirmatory information	
MD62 Which of the following is true regarding action on platelets? A. Non-selective COX inhibitors act irreversibly - false B. Clopidogrel acts reversibly C. ? D. Abciximab acts reversibly E. ?	**ANSWER: D**
MD72 Vancomycin: A. Is less sensitive than penicillin for methicillin sensitive Staphylococci B. ? C. Something like "*equal sensitivity for both gram positive and negative bacteria*" D. Can be used orally in outpatient E. Half life of ?12 hours and not removed by haemodialysis	**ANSWER: A** **A - true** *"vancomycin is not as effective as an antistaphylococcal penicillin for treatment of serious infections such as endocarditis caused by methicillin-susceptible strains."* (Katzung 11th ed page 787) B ? C - false - with the exception of flavobacterium it is active only agains gram-positivies particularly staph - katzung 11th ed page 786 D - false - only used orally for GIT infections - e.g. pseudomembranous colitis etc... not conditions amenable to outpatient care ("no" oral bioavailability.) E - false - dr wiki lists a t½β of 4- 11 hours in normal adults and 6-11 days in anephric patients. Also:*"roughly 50% of vancomycin is removed during a standard haemodialysis run when using a modern high flux membrane)* [1]

Muscle pharmacology

MB01 [Mar96] [Jul97] With regard to tetanic stimulation by a nerve stimulator:

A. Used to determine residual curarisation

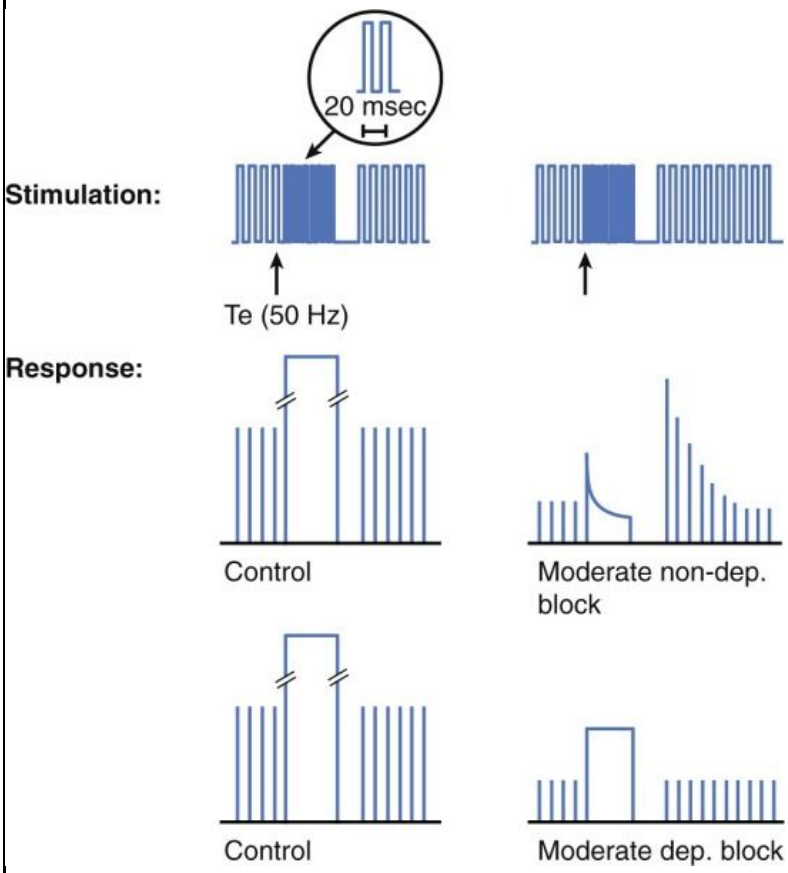
B. Degree of fade is independent of stimulus duration

C. Degree of fade is dependent on stimulus intensity

D. Used to check depth of anaesthesia

A

Miller's:



- Tetanic stimulation consists of very rapid delivery of electrical stimuli

- The most commonly used pattern in clinical practice is *50-Hz stimulation for 5 seconds*

- During normal neuromuscular transmission and a pure depolarising block, the muscle response to 50-Hz tetanic stimulation for 5 seconds is sustained

- Traditionally, tetanic stimulation has been used to evaluate residual neuromuscular blockade but is too painful to use in an unanesthetised patient

- Except in connection with PTC, tetanic stimulation has very little place in everyday clinical anaesthesia

- If the response to nerve stimulation is recorded, all the information required can be obtained from the response to TOF nerve stimulation

Fade

- During a nondepolarising block and a phase II block after succinylcholine, the response will not be sustained (i.e. fade occurs)

- At the start of tetanic stimulation, large amounts of acetylcholine are released from immediately available stores in the nerve terminal

- As these stores become depleted, the rate of acetylcholine release ↓s until equilibrium between mobilisation and synthesis of acetylcholine is achieved

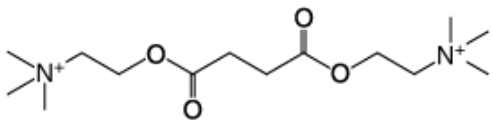
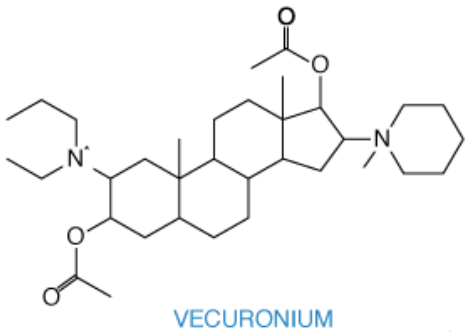
	- Despite this equilibrium, the muscle response caused by tetanic stimulation of the nerve is maintained because the acetylcholine released is many times greater than the amount necessary to evoke a response - When the "margin of safety" at the postsynaptic membrane (i.e. the number of free cholinergic receptors) is reduced by nondepolarising neuromuscular blocking drugs, a reduction in twitch height is seen with a fade during repetitive stimulation - In addition to this postsynaptic block, nondepolarising neuromuscular blocking drugs may also block presynaptic neuronal-type acetylcholine receptors, leading to impaired mobilisation of acetylcholine within the nerve terminal - This substantially contributes to fade in the response to tetanic (and TOF) stimulation - Although the degree of fade depends primarily on the degree of neuromuscular blockade, fade also depends on the frequency and the length of stimulation and on how often tetanic stimuli are applied Nerve stimulators must generate a supramaximal stimulus (60-80mA) to ensure all the composite nerve fibres are depolarised. The duration of stimulus is 0.1msec. 5 main patterns: 1. Single twitch at frequency of 0.1 Hz (or 1 every 10 seconds). 2. Tetanic stimulation - Individual stimulus are applied at a frequency of 50-100Hz for 5 sec. - In the presence of partial NDMR the tetanic stimulation fades with time due to blockade of presynaptic nicotinic receptors preventing positive feedback. - Partial DMR does not exhibit fade. 3. Post tetanic potentiation and count - Stimuli of 1 Hz started 3 seconds after tetanic stimulation. - Number of twitches inversely related to depth of block - Best used when degree of blockade is > 95% or when single twitch or TOF is unable to evoke muscle twitches. - 1 = intense block; 3 = less intense; 8 = surgical block - Partial DMR does not exhibit post tetanic stimulation. 4. Train of four - Four stimuli delivered at 2Hz. - When T4 has decreased by 25%, T1 starts to decrease and corresponds to 75-80% receptor occupancy. - T4 disappears when T1 is approximately 25% of its original height. - Partial DMR produces a TOF ratio > 0.7. 5. Double burst stimulation - 2 burst of stimulation consisting of three 50hz stimuli separated by 0.75 sec. When the magnitude of two stimuli are equal clinically, significant residual NMJ blockade does not exist.
MB02 [Mar96] [Apr01] Hyperkalaemia with suxamethonium is associated with: A. Abdominal infection B. Parkinson's disease C. Meningomyelocoele D. Cerebral palsy E. Myotonic dystrophy	A - best E – especially if question states "muscular dystrophy" *Stoelting:* - Hyperkalaemia may occur in patients with clinically recognised muscular dystrophy (Duchenne, Becker), unhealed third-degree burns, denervation leading to skeletal muscle atrophy, severe skeletal muscle trauma, and upper motor neuron lesions - Severe abdominal infections have been associated with potassium release - Potential for excessive potassium release after denervation may develop within 96 hours and may persist up to 6 months or longer - No evidence of hyperkalaemia in Parkinson disease, cerebral palsy, myelomeningocoele, or in those undergoing cerebral aneurysm surgery - Pretreatment with a subparalysing dose of non-depolarising neuromuscular blocking drug does not influence the magnitude of potassium release - Preexisting hyperkalaemia (>5.5 mEq/L) as associated with renal failure and in the absence of skeletal

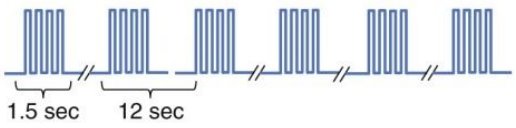
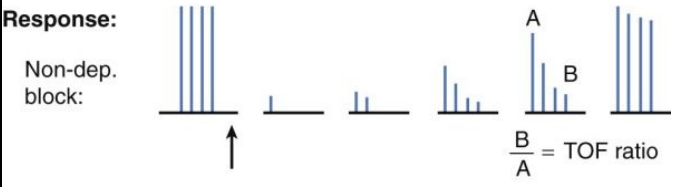
	muscle paralysis is not associated with an ↑ risk of acute potassium release following intubating doses of succinylcholine - A small percentage of the male paediatric population may present for a surgery with an occult myopathy: some clinicians avoid succinylcholine in this population when an equally acceptable response can be achieved with a nondepolarising neuromuscular blocking drug - Proliferation of extrajunctional cholinergic receptors providing more sites for potassium to leak outward from cells during depolarisation is the presumed explanation in patients with denervation injury *Miller's:* - Succinylcholine in a healthy patient for an elective operation ↑s potassium by ~0.5 mEq/L: due to the depolarising action of the relaxant → activation of acetylcholine channels → movement of sodium into the cells with movement of potassium out of the cells - This is well tolerated by most individuals and generally does not cause dysrhythmias - Severe hyperkalemia may occur in patients with severe metabolic acidosis and hypovolaemia: in this situation, the potassium *originates from the gastrointestinal tract*, not from muscle - After immobilisation, burn injury causes upregulation of both foetal (α2βγδ) and mature (α2βεδ), nAChRs: this is associated with resistance to nondepolarising neuromuscular blockers and ↑ sensitivity to succinylcholine - Causes of nAChR upregulation: spinal cord injury, stroke, burns, immobility, prolonged exposure to neuromuscular blockers, MS, Guillain-Barré, muscular dystrophies - Causes of nAChR downregulation: myasthenia gravis, anticholinesterase poisoning, organophosphate poisoning - General considerations for myotonic dystrophy are similar to those for other muscular dystrophies
MB03 [Mar96] [Jul96] [Jul97] [Mar98] [Mar99] [Jul99] [Feb00] Which of the following is NOT metabolised by plasma cholinesterase? A. Procaine B. Cocaine C. Dibucaine D. Suxamethonium E. Esmolol F. Mivacurium	C E *Stoelting:* - Ester local anaesthetics (procaine, tetracaine, chloroprocaine) undergo hydrolysis by plasma cholinesterase (AKA pseudocholinesterase, butyrylcholinesterase), principally in the plasma and to a lesser extent in the liver - Exception is cocaine, which undergoes significant metabolism in the liver by esterases with slight plasma metabolism - Amide local anaesthetics undergo metabolism by microsomal enzymes, primarily in the liver - Dibucaine is metabolised in the liver and is the most slowly eliminated of all the amide derivatives - Dibucaine inhibits the activity of normal plasma cholinesterase by ~80%, compared with only ~20% inhibition of the activity of atypical enzyme - The brief duration of succinylcholine (3-5 minutes) is principally due to its hydrolysis by plasma cholinesterase - Mivacurium consists of three stereoisomers: hydrolysis of the cis-trans and trans-trans isomers by plasma cholinesterase is responsible for the short duration of action, whereas the cis-cis isomer, which lacks significant neuromuscular blocking effects, does not depend on this and is cleared at a rate closer to that of the intermediate-acting neuromuscular blocking drugs - Duration to return to >25% control twitch height = 12-20 minutes - The duration of action of mivacurium is ↑ in patients with atypical plasma cholinesterase

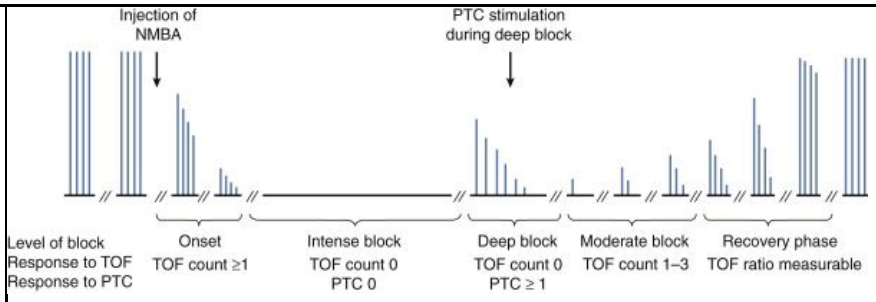
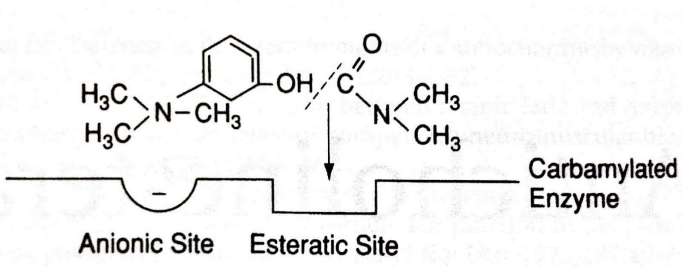
	Goodman and Gilman's: - Esmolol contains an ester linkage, and is hydrolysed rapidly by RBC esterases
MB03b [Mar98] [Apr01] Which of the following is metabolised by plasma cholinesterase? A. Remifentanil B. Procaine C. Esmolol D. ? E. All of the above	B – Procaine is metabolised by plasma cholinesterase to PABA *Stoelting:* - Remifentanil is unique among the opioids in undergoing metabolism by **nonspecific** plasma and tissue esterases to inactive metabolites which undergo renal excretion - Does not appear to be a substrate for pseudocholinesterase, and thus its clearance should not be affected by cholinesterase deficiency or anticholinergics
MB03c [Jul98] [Feb00] Esterases metabolise all EXCEPT: A. Remifentanil B. Dibucaine C. Pyridostigmine D. ?	B C – duration of action of 3-6hrs and metabolised in liver and excreted in urine
MB03d [Feb04] Which drug has a significantly prolonged duration of action in plasma cholinesterase deficiency? A. Remifentanil B. Procaine C. Mivacurium D. Rocuronium E. Cocaine	C *Miller's:* - When butyrylcholinesterase activity is severely deficient, the duration of action of mivacurium is prolonged for up to several hours
MB04 [Mar96] [Jul02] The action of nondepolarising neuromuscular blocking agents is PROLONGED by: A. Respiratory acidosis B. Increased temperature C. Increased calcium D. Increased potassium E. Decreased magnesium	A *Miller's:* - <u>Acidosis, hypokalemia, hypothermia, and medications</u> (e.g. aminoglycosides, verapamil, magnesium sulphate) potentiate residual neuromuscular blockade and render pharmacologic antagonism more difficult - Both metabolic and respiratory acidosis may ↑ blockade from a nondepolarising neuromuscular blocker, but only respiratory acidosis prevents adequate antagonism - The probability of achieving adequate antagonism of nondepolarising neuromuscular blockade in the presence of significant respiratory acidosis ($PaCO_2$ >50 mmHg) is low, therefore, attempts to antagonise residual blockade may fail if a patient hypoventilates - Administration of narcotics to relieve pain may, by producing hypoventilation, ↑ the likelihood of this adverse event - <u>Calcium</u> triggers the release of acetylcholine from the motor nerve terminal and enhances excitation-contraction coupling in muscle; ↑ing calcium concentrations ↓s sensitivity to blockade - <u>Verapamil</u> will potentiate nondepolarising neuromuscular blocking drugs and may render achieving adequate reversal difficult

	- Magnesium sulphate, given for preeclampsia, potentiates the neuromuscular blockade induced by nondepolarising neuromuscular blockers: mechanisms probably involve both prejunctional and postjunctional effects
MB05 [Mar96] Agents prolonging nondepolarising NMBA by desensitising the post-junctional membrane : A. Phenytoin B. Halothane C. Lignocaine D. Verapamil	C *Stoelting:* - Drugs that enhance non-depolarising blockade include volatile anaesthetics, aminoglycosides, local anaesthetics, antiarrhythmics, frusemide, magnesium and lithium - Chronic anticonvulsant use (phenytoin, carbamazepine) → pharmacodynamic resistance in adults but pharmacokinetic changes in children (↑ hepatic clearance of vecuronium) - Volatile anaesthetics most likely act by depression of the CNS → ↓ tone of skeletal muscles (*may* ↓ the sensitivity of postjunctional membranes to depolarisation; ↑ skeletal muscle blood flow delivering more drug to the NMJ is important only for isoflurane) - Local anaesthetics interfere with the prejunctional release of acetylcholine, stabilise postjunctional membranes and directly depress skeletal muscle fibres; in addition, esters compete with other drugs for plasma cholinesterase → ↑ effects from succinylcholine - Calcium channel blockers ↓ presynaptic release of acetylcholine because calcium ions are necessary for the release of acetylcholine at the neuromuscular junction; the local anaesthetic effects of verapamil and diltiazem, reflecting inhibition of sodium ion flux via fast sodium channels, may also contribute to the potentiation of neuromuscular blocking drugs
MB06 [Mar96] [Jul98] Which drugs (?competitively) inhibit acetylcholinesterase? A. Neostigmine B. Pyridostigmine C. Physostigmine D. Edrophonium E. All of the above	E *Stoelting:* - Anticholinesterase drugs as represented by edrophonium, neostigmine, and pyridostigmine facilitate the speed of recovery from nondepolarising neuromuscular blocking drugs - Another anticholinesterase drug, phytostigmine, may be administered to produce nonspecific antagonism of the CNS effects of certain drugs - The treatment of patients with myasthenia gravis or glaucoma may include administration of these drugs
MB06b [Jul00] [Apr01] The activity of plasma cholinesterase is decreased by the following drugs except: A. Neostigmine B. Organophosphates C. THA D. Metoclopramide E. Cimetidine	E *Stoelting:* - Neostigmine, but not edrophonium causes a profound ↓ in plasma cholinesterase activity - Potent anticholinesterase drugs used in insecticides and occasionally in the treatment of glaucoma and myasthenia gravis, as well as chemotherapeutic drugs (nitrogen mustard and cyclophosphamide), may ↓ plasma cholinesterase activity - The duration of action of succinylcholine after injecting metoclopramide is ↑, presumably reflecting inhibition of plasma cholinesterase by metoclopramide Note question below - answer says metaclopramide decreases activity - Plasma cholinesterase activity is not altered by cimetidine *Katzung:* - Tetrahydroaminoacridine (THA), a long-acting cholinesterase inhibitor and muscarinic modulator, was the

	first drug shown to have any benefit in Alzheimer's disease
MB06c [Jul04] Which decrease plasmacholinesterase activity? (remembered options from 2 questions) A. Hepatic disease B. Cyclophosphamide C. Six weeks post partum D. Hyperthyroidism E. Obesity F. Cytotoxic drugs G. Pregnancy H. Dibucaine number of 20	A B D F G H *Stoelting:* - Liver disease must be severe before ↓s in plasma cholinesterase production sufficient to prolong succinylcholine induced neuromuscular blockade occur - ↑ oestrogen levels e.g. term parturients are associated with ↓ plasma cholinesterase activity, but the duration of paralysis from succinylcholine is not ↑ (due to ↑ volume of distribution at term) - In obese patients there is an ↑ in plasma cholinesterase activity so that succinylcholine requirements may ↑ - In myasthenia gravis, there is a ↓ in functional acetylcholine end-plate receptors → ↓ response to acetylcholine - Resistance to succinylcholine has been observed in juvenile hyaline fibromatosis - ~1 in 3,200 patients is homozygous for an atypical plasma cholinesterase enzyme variant and has a dibucaine number of 20 *Miller's:* - Factors which ↓ butyrylcholinesterase activity include liver disease, advanced age, malnutrition, pregnancy, burns, oral contraceptives, monoamine oxidase inhibitors, cytotoxic drugs, neoplastic disease, anticholinesterase drugs and metoclopramide - The histamine type 2 receptor antagonists have no effect on butyrylcholinesterase activity or the duration of succinylcholine's effect
MB07 [Mar97] [Jul98] [Jul99] [Feb00] [Apr01] Regarding vecuronium: A. It accumulates in renal failure B. Is a benzylisoquinolinium C. Is a bisquaternary amine D. Is more lipid soluble than pancuronium E. Is predominantly renally excreted	A and D *Stoelting:* - Monoquaternary aminosteroid nondepolarising neuromuscular blocking drug - Is pancuronium without the quaternary methyl group → ↓ acetylcholine-like character → 20-fold ↓ vagolytic properties compared with pancuronium - Monoquaternary structure → ↑ lipid solubility compared with pancuronium - Unstable in solution so supplied as a lyophilised powder that must be dissolved in sterile water before use - Mostly hepatic metabolism (deacetylation to active metabolites; facilitated by its ↑ lipid solubility) but also renal excretion - ↑ elimination half time of 3-desacetylvecuronium in renal failure, (reflecting ↓ clearance) → persistent paralysis after prolonged infusion
MB08 [Jul97] [Jul98] [Mar99] [Jul02] [Mar03] In reversing neuromuscular blockade, which of the following combinations is best matched	C

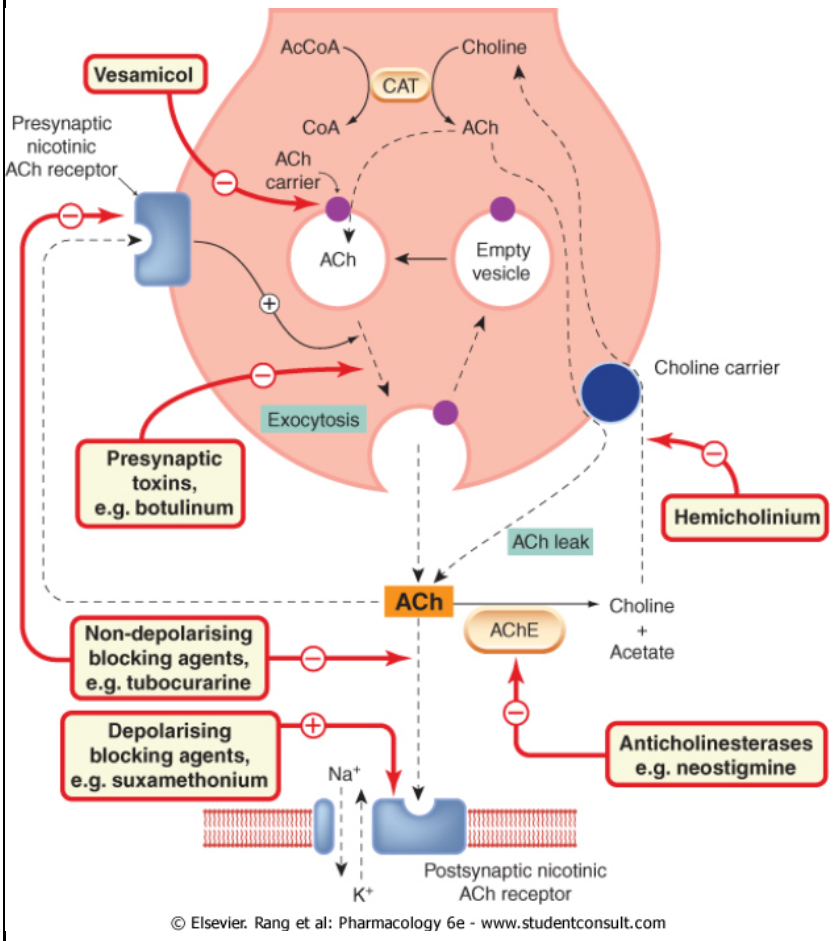
with respect to time of onset? A. Atropine & neostigmine B. Atropine & glycopyrrolate C. Atropine & edrophonium D. Atropine & physostigmine E. Glycopyrrolate and edrophonium (Comment: Option B is an unusual distractor for this question but it has been confirmed by a couple of people that this is the way it is on the paper)	*Stoelting:* Anticholinesterase drugs: - Edrophonium: 1-2 minutes - Neostigmine: 7-11 minutes - Pyridostigmine: 16 minutes Anticholinergic drugs: - Atropine: 1 minute - Glycopyrrolate: 2-3 minutes
MB09 [Jul97] [Jul98] [Mar99] [Jul99] [Jul00] [Mar03] Plasma cholinesterase: A. Metabolises dibucaine B. Metabolises esmolol C. Hydrolyses mivacurium at 80% the rate of suxamethonium D. Is unaffected by neostigmine	C *Stoelting:* - Dibucaine inhibits the activity of normal plasma cholinesterase by ~80%, compared with only ~20% inhibition of the activity of atypical enzyme *Miller's:* - Mivacurium is metabolised by butyrylcholinesterase at 70% to 88% the rate of succinylcholine
MB09b [Jul01] [Jul04] Suxamethonium A. Bigger molecule than vecuronium B. Needs to occupy 80% of nicotinic receptors to get effect C. Resistant to hydrolysis by acetylcholinesterase D. ??Is an antagonist at nicotinic receptors E. Increasing dose produces similar block	C *Goodman and Gilman's:* The competitive agents (e.g. tubocurarine, benzylisoquinolines, ammonio steroids) are relatively bulky, rigid molecules, whereas the depolarising agents (e.g., decamethonium and succinylcholine) have more flexible structures that enable free bond rotations  SUCCINYLCHOLINE  VECURONIUM PANCURONIUM: addition of CH_3 at N^+

	Stoelting: - Succinylcholine attaches to one or both of the α subunits of nicotinic acetylcholine receptors and mimics the action of acetylcholine (partial agonist), depolarising the postjunctional membrane - Neuromuscular blockade develops because a depolarised postjunctional membrane cannot respond to subsequent release of acetylcholine - Depolarising neuromuscular blockade = phase I block - The brief duration of succinylcholine (3-5 minutes) is principally due to its hydrolysis by plasma cholinesterase - Because plasma cholinesterase is not present in large amounts at the NMJ, termination of block is by diffusion into ECF, therefore plasma cholinesterase influences the duration of succinylcholine by controlling the amount hydrolysed *before* reaching the NMJ - ↓ing the intubating dose from 1 mg/kg to 0.6 mg/kg IV ↓s the duration of twitch depression by >90 seconds and is still associated with acceptable intubating conditions - A single large dose (>2 mg/kg), repeated dose or prolonged infusion may → postjunctional membranes that do not respond normally to acetylcholine even when the postjunctional membranes have become repolarised (desensitisation neuromuscular blockade = phase II block); mechanism unknown - Neuromuscular transmission of nondepolarising neuromuscular blocking drugs fails when >80% of receptors are blocked
MB10 [Jul97] [Jul98] With regard to the nerve stimulator in competitive blockade: A. Fade is dependent on stimulating frequency B. TOFC of four is a sign of adequate reversal C. ? D. ?	A *Miller's:* - Although the degree of fade depends primarily on the degree of neuromuscular blockade, fade also depends on the frequency and the length of stimulation and on how often tetanic stimuli are applied - Antagonism with cholinesterase inhibitors should not be initiated before at least two responses are observed - In TOF nerve stimulation, *four supramaximal stimuli are given every 0.5 second (2 Hz)* - The TOF ratio must exceed 0.8 to exclude clinically important residual neuromuscular blockade **Stimulation:**  **Response:**  

	
MB11 [Jul97] Anticholinesterase agents A. Carbamates duration of action is related to the time required for dissociation from the anionic site. B. Carbamates act by acetylation of the esteratic site. C. ? (See also [[MB11b, [[MD28)	None correct *Stoelting:* - Carbamate esters e.g. physostigmine, neostigmine and pyridostigmine act as competitive substrate substitutes for acetylcholine in the enzyme's normal interaction with acetylcholinesterase - Produce reversible inhibition of acetylcholinesterase by formation of a <u>carbamyl ester complex</u> at the <u>esteratic site</u> of the enzyme - This carbamylated acetylcholinesterase cannot hydrolyse acetylcholine until the carbamate-enzyme bond dissociates - Carbamylated acetylcholinesterase has a half time of 15-30 minutes 
MB11b [Jul00] [Apr01] [Jul02] [Jul04] Carbamylation of acetylcholinesterase: (Jul02: Phosphorylation of acetylcholinesterase:) A. Ionic bonding at anionic site B. Ionic bonding at esteratic site C. Covalent bonding at anionic site D. Covalent bonding at esteratic site E. None of above (see also MB27 for similar Q)	D *Katzung:* - Carbamate esters e.g. neostigmine, physostigmine, pyridostigmine form <u>covalent bonds</u> - Organophosphates produce a <u>covalent phosphorus-enzyme bond</u> that is extremely stable - Quaternary alcohols e.g. edrophonium reversibly bind <u>electrostatically</u> and by <u>hydrogen bonds</u> *Stoelting:* - Carbamate esters: esteratic site - Organophosphates: esteratic site (echothiophate also interacts with the anionic site) - Quaternary alcohols: electrostatic bond at anionic site and hydrogen bond at esteratic site
MB12 [dgj] [Jul00] [Jul02] [Jul04] Mivacurium: A. Is metabolised at 80% the rate of suxamethonium B. Takes 15 mins from ED95 dose to recovery of 95%	A E not clinically significant prolongation

twitch height C. Has an ED95 of 1.5 mg/kg D. Trigger for malignant hyperthermia E. ? Duration of action is increased in renal failure	*Stoelting:* - Benzylisoquinolinium nondepolarising neuromuscular blocking drug - Consists of three stereoisomers: hydrolysis of the cis-trans and trans-trans isomers by plasma cholinesterase is responsible for the short duration of action, whereas the cis-cis isomer, which lacks significant neuromuscular blocking effects, does not depend on this and is cleared at a rate closer to that of the intermediate-acting neuromuscular blocking drugs - Duration to return to >25% control twitch height = 12-20 minutes - Renal excretion = minor pathway for clearance - Clinically insignificant prolongation in anephric patients - ED95 (measure of potency, is the dose needed to produce 95% suppression of the single-twitch response in the presence of nitrous oxide-barbituate-opioid anaesthesia) = 80 µg/kg - Onset = 2-3 minutes *Miller's:* - Mivacurium is metabolised by butyrylcholinesterase at 70% to 88% the rate of succinylcholine - MH is elicited by the administration of triggering anaesthetic agents, such as a volatile anaesthetic or a depolarising neuromuscular blocking agent
July 2000 version: Mivacurium: A. Twice the ED95 dose is 1.5mg/kg B. is metabolised at 80 to 90% the rate of suxamethonium C. After 2 x ED95 dose 95% return of twitch height after 15mins	B *Stoelting:* - 2 x ED95 (dose of nondepolarising muscle relaxant recommended to facilitate intubation) = 0.15 mg/kg - The greater the concentration of mivacurium, the more rapid is its breakdown, and unlike the response seen with other neuromuscular-blocking drugs, ↑ing the dose has only a small impact on the duration
July 2002]] version included the following options: C. Does not usually require reversal D. Duration of action may be prolonged by anti-cholinesterases	C *Stoelting:* - Spontaneous recovery from mivacurium is rapid, and the need for pharmacologic antagonism has been questioned - Neostigmine ↓s plasma cholinesterase activity; nevertheless, moderate levels of mivacurium-induced neuromuscular blockade are antagonised readily by anticholinesterases
July 2006 Mivacurium A. Is not made up of different isomers B. Metabolised at 75-85% rate of suxamethonium C. Has a Half life of 30 minutes D. Is antagonised less by edrophonium than nestigmine	B *Stoelting:* - Edrophonium produces more rapid antagonism of deep mivacurium-induced neuromuscular blockade than does neostigmine - Elimination half life = 1-3 minutes
MB12b [Jul00] Mivacurium administered at a dose of 2	B

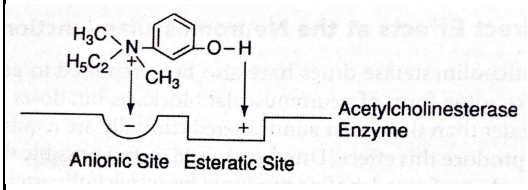
times the ED95 dose produces relaxation for: A. 10 mins B. 15 mins C. 20 mins D. 25 mins E. None of the above	*Stoelting:* - Duration to return to >25% control twitch height = 12-20 minutes *Miller's:* Classification of nondepolarising neuromuscular blockers according to duration of action (time to T1 = 25% of control) after twice the ED95… <u>Steroidal compounds</u> - Long acting (>50 min): pancuronium - Intermediate acting (20-50 min): vecuronium, rocuronium <u>Benzylisoquinolinium compounds</u> - Long acting (>50 min): d-tubocurarine - Intermediate acting (20-50 min): atracurium, cisatracurium - Short acting (15-20 min): mivacurium
MB13 [Mar98] [Jul99] [Jul01] The Recovery Index 25% to 75% is 7 minutes for which drug? A. Vecuronium B. Rocuronium C. Mivacurium D. Suxamethonium	C *Stoelting:* - Recovery index = time from 25% return of single twitch height to 75% return of single twitch height - Clinical duration = time from injection to recovery of TOF ratio to >=0.7 or >=0.9 *Sasada and Smith:* Mean recovery indices… - Mivacurium = 6.6 min - Vecuronium = 14-30 min - Rocuronium = 8-17 min - Sux = 3-5 min
Also recalled as: A muscle relaxant is administered at twice ED95 for a short dental case. Return of normal TOF ratio occurred at 7minutes. The muscle relaxant used was: A. Suxamethonium B. Vecuronium C. Atracurium D. Rocuronium	A (poor wording: TOFR is normal with suxamethonium unless phase II block) *Stoelting:* Duration of return to train of four >0.9… - Mivacurium: ~30 min - Atracurium, vecuronium, rocuronium: ~60 min - Cisatracurium: ~90 min - Pancuronium: >120 min

E. Mivacurium	
MB14 [Mar98] [Jul00] [Mar03] Release of acetylcholine at the motor endplate: A. ?? gentamicin B. Botulinum toxin works by ?? C. ? D. ?	Both inhibit *Stoelting:* - Antibiotics <u>may</u> exert effects on the prejunctional membranes similar to those exerted by magnesium → ↓ release of acetylcholine → ↑ neuromuscular blockade produced by neuromuscular blocking drugs *Rang and Dale:*  *Power and Kam:* - The anaerobic bacterium Clostridium botulinum produces an exotoxin which inhibits acetylcholine release from cholinergic nerves → GI and urinary dysfunction, blurred vision, and paralysis which spares limb but affects respiratory muscles
July 2000 version: Release of acetylcholine at motor endplate: A. Hemicholinium directly interferes with releae B. Only in response to action potential C. Decreased by aminoglycosides / ??	D better answer C *may* be correct *Rang and Dale:* - The rate-limiting process in the <u>synthesis</u> of ACh in the presynaptic nerve terminals is the transport of choline into the nerve terminal

prejunctional effect D. Is Ca2+ dependent process E. Always causes an action potential	- Hemicholinium blocks this transport and thereby inhibits ACh synthesis - It is useful as an experimental tool but has no clinical applications - Its blocking effect on transmission develops slowly, as the existing stores of ACh become depleted *Stoelting:* - In the absence of action potentials, quanta of acetylcholine are released randomly, producing miniature endplate potentials of <1 mV that are insufficient to trigger depolarisation of the skeletal muscle membrane - Release of acetylcholine is a calcium-dependent process and is triggered by ↑s in the concentration of free calcium ions in nerve terminals
MB15 [Mar98] Gentamicin potentiates non-depolarising neuromuscular block by: A. Interfere with Ca++ influx for exocytosis B. ? C. ?	A *Rang and Dale:* - Acetylcholine release by a nerve impulse involves the entry of Ca2+ into the nerve terminal; the ↑ in [Ca2+]i stimulates exocytosis and ↑s the rate of quantal release - Agents that inhibit Ca2+ entry include Mg2+ and aminoglycosides, which occasionally produce muscle paralysis as an unwanted side effect when used clinically
MB16 [Jul98] [Mar99] [Feb00] [Jul01] [Mar03] Rocuronium: A. Monoquaternary at physiological pH B. More lipid soluble than pancuronium C. 30% metabolised (?deacetylated) in the liver D. Rapid onset is due to its high potency E. Fastest onset is with 2 times ED95 dose F. Is bisquaternary	A *Stoelting:* - Monoquaternary aminosteroid nondepolarising neuromuscular drug - ED95 = 0.3 mg/kg - Onset = 1-2 minutes - Duration = 20-35 minutes - Structurally resembles vecuronium except for the presence of a hydroxyl group rather than an acetyl group on the A ring of the steroid nucleus - Largely excreted unchanged in the bile - Deacetylation does not occur - Some renal excretion occurs - May have ↑ duration in renal failure and liver disease - Lack of potency compared with vecuronium is important in its rapid onset: ↑ number of molecules → ↑ number of molecules available to diffuse into the NMJ - Onset of maximum single-twitch depression after 3-4 x ED95 resembles onset of action of succinylcholine 1 mg/kg: is the only nondepolarising drug that may serve as an alternative to succinylcholine when the rapid onset of neuromuscular blockade is needed to facilitate tracheal intubation and succinylcholine is CI
MB17 [Mar96] Plasma cholinesterase is inhibited 80% by 10 -5 molar dibucaine: A. In late pregnancy B. ? C. ?	A *Stoelting:* - High oestrogen levels, as observed in parturients at term, are associated with up to 40% decreases in plasma cholinesterase activity - Dibucaine, a local anaesthetic with an amide linkage, inhibits the activity of normal plasma cholinesterase

	enzyme by 80%, compared with 20% inhibition of the activity of atypical enzyme - A dibucaine number of 80 confirms the presence of normal plasma cholinesterase enzyme - The dibucaine number reflects *quality* of cholinesterase enzyme (ability to hydrolyse succinylcholine), not the quantity of enzyme e.g. normal in liver disease, anticholinesterase drugs *Miller's:* - Although the dibucaine number indicates the genetic makeup of an individual with respect to butyrylcholinesterase, it does not measure the concentration of the enzyme in plasma, nor does it indicate the efficiency of the enzyme in hydrolysing a substrate such as succinylcholine or mivacurium - Both of the latter factors are determined by measuring butyrylcholinesterase activity, which may be influenced by genotype
MB18 [Mar99] Which of the following do NOT prolong neuromuscular blockade? A. Volatile anaesthetics B. Antibiotics C. Phenytoin D. Beta-blockers E. Hyperthermia (see also MB26)	E *Stoelting:* **Prolonged non-depolarising neuromuscular blockade…** *Drugs:* - Volatile anaesthetics most likely act by depression of the CNS → ↓ tone of skeletal muscles (*may* ↓ the sensitivity of postjunctional membranes to depolarisation; ↑ skeletal muscle blood flow delivering more drug to the NMJ is important only for isoflurane) - Aminoglycosides → ↓ presynaptic release of acetylcholine - Local anaesthetics interfere with the prejunctional release of acetylcholine, stabilise postjunctional membranes and directly depress skeletal muscle fibres; in addition, esters compete with other drugs for plasma cholinesterase → ↑ effects from succinylcholine - Antiarrhythmics e.g. lignocaine, quinidine - Frusemide 1 mg/kg inhibits cAMP production → ↓ prejunctional output of acetylcholine - Magnesium and lithium ↑ non-depolarising and depolarising block - Cyclosporine - Calcium channel blockers ↓ presynaptic release of acetylcholine because calcium ions are necessary for the release of acetylcholine at the neuromuscular junction; the local anaesthetic effects of verapamil and diltiazem, reflecting inhibition of sodium ion flux via fast sodium channels, may also contribute to the potentiation of neuromuscular blocking drugs - Corticosteroids: ↑ blockade in combination with vecuronium may reflect pharmacologic denervation of nicotinic acetylcholine receptors and contribute to *critical illness polyneuropathy* - Combinations in non-depolarising neuromuscular blocking drugs → different degree of block from the degree produced by either drug alone *Non-drugs:* - Females have ↓ skeletal muscle mass - Hypothermia → ↓ clearance, slowed effect site equilibration, ↑ sensitivity of NMJ - Hypokalaemia → ↑ transmembrane potential → hyperpolarisation → resistance to depolarising neuromuscular drugs and ↑ sensitivity to non-depolarising neuromuscular drugs **Decreased non-depolarising neuromuscular blockade…**

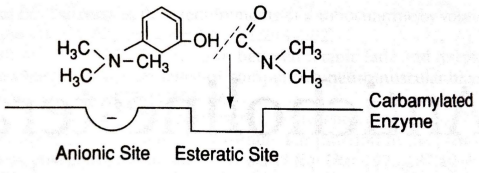
	Drugs: - Chronic anticonvulsant use (phenytoin, carbamazepine) → pharmacodynamic resistance in adults but pharmacokinetic changes in children (↑ hepatic clearance of vecuronium) - Azathioprine antagonises non-depolarising neuromuscular blockade (PDE inhibition) but augments depolarising blockade produced by succinylcholine - Frusemide in ↑ doses may inhibit phosphodiesterase → ↑ cAMP available → antagonism of nondepolarising neuromuscular blocking drugs *Non-drugs:* - Hyperkalaemia → ↓ RMP and thus partially depolarises cell membranes → ↑ effects of depolarising neuromuscular drugs and opposes the action of non-depolarising neuromuscular drugs - Burn injury: >30% burns → altered affinity of nicotinic acetylcholine receptors → *resistance* to nondepolarising neuromuscular drugs - Paresis or hemiplegia → proliferation of extrajunctional nicotinic acetylcholine receptors → *resistance* to neuromuscular blocking drugs - Males have ↑ skeletal muscle mass **Other altered responses** - Ephedrine → ↑ cardiac output and skeletal muscle blood flow → more rapid delivery to neuromuscular junction → ↓ onset time - Esmolol → ↓ cardiac output and skeletal muscle blood flow → slower delivery to neuromuscular junction → ↑ onset time - Allergic reactions: drugs with single quaternary ammonium groups (pancuronium, vecuronium, rocuronium) less likely to cause allergic reactions than succinylcholine; anaphylactic reactions after first exposure may reflect sensitisation from prior contact with cosmetics or soaps with quaternary ammonium groups; females > males
MB19 [Jul98] Malignant hyperthermia causes: A. Hypertension B. Whole body rigidity C. Tachyphylaxis with a suxamethonium infusion D. ?	B *Miller's:* - Rigidity after induction with succinylcholine - Unexplained sinus tachycardia or ventricular arrhythmias - Tachypnoea if spontaneous ventilation is present - Unexplained ↓ O2 saturation (because of ↓ venous O2 saturation) - ↑ end-tidal Pco2 with adequate ventilation (and in most cases unchanged ventilation) - Unexpected metabolic and respiratory acidosis - Central venous desaturation - ↑ body temperature > 38.8°C with no obvious cause
MB20 [Jul99] [Jul01] Edrophonium: A. Longer half life than neostigmine B. Onset slower than neostigmine	A D E

C. ?Pyridostigmine D. Binds to anionic site of cholinesterase E. Relieves symptoms of myaesthenia gravis F. ? Is reliable in reversing a Phase 2 block	*Stoelting:* - Quaternary ammonium anticholinesterase that lacks a carbamyl group - More *rapid* onset of action than neostigmine and pyridostigmine, whereas the *duration of action of these three anticholinesterase drugs is similar* - Mild muscarinic effects compared with longer-acting anticholinesterase drugs - Uses: antagonise the effects of non-depolarising neuromuscular blocking drugs, symptomatic treatment of myasthenia gravis and cholinergic crisis, and evaluate the presence of dual blockade produced by succinylcholine - Electrostatic bond at anionic site and hydrogen bond at esteratic site - Because a true chemical (covalent) bond is not formed, acetylcholine can easily compete with edrophonium for access to acetylcholinesterase  - Onset times: edrophonium rapid (1-2 minutes), neostigmine intermediate (7-11 minutes), pyridostigmine delayed (16 minutes) - Half lives: edrophonium and pyridogstigmine 110 minutes, neostigmine 80 minutes - Reversal of phase II block with succinylcholine can be reversed with neostigmine or edrophonium; reversal of phase II block in patients with atypical plasma cholinesterase may not be reliable
MB20b [Apr01] ("Edrophonium Q about elimination half times and metabolism") A. ? B. ?	*Stoelting:* - The duration of action of anticholinesterases is governed largely by the rate of their disappearance from the plasma e.g. the half life of the carbamylated enzyme (15-30 minutes) is much shorter than the elimination half times of the anticholinesterase drugs - Although edrophonium in the past has been considered a short acting drug, controlled studies in anaesthetised patients have documented that the duration of action of edrophonium does not differ from that of neostigmine - Anticholinesterase drugs are actively secreted into the lumens of the renal tubules - Renal clearance accounts for ~50% of the elimination of neostigmine and ~75% of the elimination of edrophonium and pyridostigmine - In renal failure, elimination half times ↑ > non-depolarising neuromuscular drugs, making recurarisation unlikely - In the absence of renal function, hepatic metabolism accounts for 50% of a dose of neostigmine, 30% of a dose of edrophonium, and 25% of a dose of pyridostigmine
MB21 [Jul99] . .? . . with return of ¾ TOF ratio: A. ? B. ? C. ? D. ? E. ?Neostigmine may prolong the action of Mivacurium	E *Stoelting:* - Neostigmine profoundly ↓s plasma cholinesterase activity and could thus interfere with the normal rapid spontaneous recovery from mivacurium-induced neuromuscular blockade - Nevertheless, moderate levels of mivacurium-induced neuromuscular blockade are antagonised readily by anticholinesterases such as neostigmine
MB22 [Jul99] [Apr01]	C

Atracurium: A. Has an active metabolite B. Ester metabolism is a minor pathway of elimination C. Metabolism is by Hofmann elimination which is pH dependent ('Did not include temperature') D. ? E. ?	*Stoelting:* - Bisquaternary benzylisoquinolinium non-depolarising neuromuscular blocking drug - ED95 = 0.2 mg/kg - Onset = 3-5 minutes - Duration = 20-35 minutes - Site of action, like other non-depolarising neuromuscular blocking drugs, is on presynaptic and postsynaptic cholinergic receptors - May also directly interfere with the passage of ions through channels of nicotinic cholinergic receptors - Was designed specifically to undergo spontaneous degradation (Hofmann elimination) - A second and simultaneously occurring route of metabolism is hydrolysis by nonspecific plasma esterases - Laudanosine = major metabolite of both pathways, is not active at the NMJ but may, in high concentrations, cause CNS stimulation in animals - Ester hydrolysis accounts for ~2/3 of degraded atracurium, whereas Hofmann elimination provides a "safety net", especially in patients with impaired hepatic and/or renal function - Adjusting the pH of the commercial solution to 3.25-3.65 ↓s in vitro degradation: should not be mixed with alkaline drugs (e.g. barbituates) or exposed to solutions with more alkaline pHs - In contrast, cisatracurium undergoes degradation principally by Hofmann elimination; nonspecific plasma esterases do not seem to be involved
MB23 [Feb00] [Jul04] What muscle relaxant has an active metabolite with a half-life twice that of the parent compound? A. Rocuronium B. Vecuronium C. Pancuronium D. Atracurium or Cisatracurium E. None of the above F. Mivacurium	B *Stoelting:* <u>Rocuronium</u> - Majority excreted unchanged in the bile - Some eliminated renally - Prolonged duration in hepatic and renal failure <u>Vecuronium</u> - Hepatic metabolism and renal excretion - The 3 desacetylvecuronium metabolite is half as potent as the parent compound - Accumulation of this metabolite may contribute to prolonged effects, especially with repeated does administered to patients with renal dysfunction <u>Pancuronium</u> - Mostly eliminated unchanged in the urine - Some undergoes hepatic deacetylation - 3-desacetylpancuronium = 50% potency, whereas the other metabolites have minimal activity - Prolonged duration in hepatic and renal failure

	Mivaurium - Metabolites are presumed to be inactive at the NMJ *Miller's:* - 3-desacetylvecuronium has slower plasma clearance and a longer duration of action than vecuronium - The 3-OH metabolite of pancuronium is the most potent and is the only one present in detectable concentrations in plasma: has pharmacokinetics and a duration of action similar to those of pancuronium
MB23b [Jul04] Which of these NDNMB has a metabolite that's 50-70% as active as its parent drug A. Atracurium B. Vecuronium C. Rocuronium D. dTC E. None of the above	B *Miller's:* - d-tubocurine has a long duration, undergoes no metabolism, and is primarily eliminated by the kidneys with a small amount by the liver; causes moderate histamine release
MB24 [Feb00] Succinylcholine can cause: A. Bradycardia B. Histamine release C. Tachycardia D. Hypertension E. All of the above	E *Stoelting:* - Mimics effects of acetylcholine at cardiac muscarinic cholinergic receptors → sinus bradycardia, junctional rhythm, sinus arrest especially with second dose; suggests the role of metabolites (succinylmonocholine, choline) - Mimics effects of acetylcholine at autonomic ganglia → ganglionic stimulation → ↑ HR, ↑ BP - Causes slight histamine release (like atracurium, mivacurium)
MB25 [Feb00] Neostigmine reversal of nondepolarising neuromuscular block A. Not affected by enflurane at 2 MAC B. Varies depending on use of NDNMA by bolus or infusion C. Is/isn't affected by age D. ?	C: is affected by age *Stoelting:* - Occurs more rapidly and the dose required is less in infants and children: likely due to pharmacodynamic reasons rather than pharmacokinetic - Prolonged duration in elderly patients: due to ↓ ECF volume and ↓ clearance; pharmacodynamics are not altered - In contrast, edrophonium unchanged in infants and elderly, supporting the concepts that these drugs antagonise neuromuscular blockade by different mechanisms - Continued administration of a volatile anaesthetic may delay drug-assisted antagonism of nondepolarising muscle relaxants - The speed and extent to which neuromuscular blockade is reversed is influenced by the intensity of the block at the time of reversal and the drug being reversed
MB26 [Feb00] Which of the following is associated with a decrease in duration or effect of nondepolarising neuromuscular blocking	D *Miller's:*

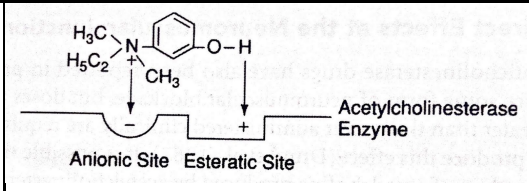
drugs: A. Volatile anaesthetic alkanes B. Volatile anaesthetic ethers C. Aminoglycoside antibiotics D. Aminopyridine derivatives E. Local anaesthetic esters (see also MB18)	- The calcium current can be prolonged by potassium channel blockers (e.g., 4-aminopyridine), which ↓ the efflux of potassium out of the nerve - An effect of ↑ing calcium in the nerve ending is also in post-tetanic potentiation: calcium enters the nerve with every stimulus, but because it cannot be excreted as quickly as the nerve is stimulated, it accumulates - A stimulus applied to the nerve during this time causes the release of ↑ amounts of acetylcholine → antagonises the relaxant → ↑ size of the twitch *Stoelting:* - Drugs that enhance non-depolarising blockade include volatile anaesthetics, aminoglycosides, local anaesthetics, antiarrhythmics, frusemide, magnesium and lithium - Volatile anaesthetics most likely act by depression of the CNS → ↓ tone of skeletal muscles (*may* ↓ the sensitivity of postjunctional membranes to depolarisation; ↑ skeletal muscle blood flow delivering more drug to the NMJ is important only for isoflurane) - Aminoglycosides → ↓ presynaptic release of acetylcholine - Local anaesthetics interfere with the prejunctional release of acetylcholine, stabilise postjunctional membranes and directly depress skeletal muscle fibres; in addition, esters compete with other drugs for plasma cholinesterase → ↑ effects from succinylcholine
Alt version: Which of the following decreases the duration/depth of neuromuscular blockade? A. Enflurane at 2 MAC B. Aminoglycosides C. Bolus doses versus infusion D. Aminopyridines	D
MB26b [Jul01] Neuromuscular blockade NOT prolonged by: A. Hyperthermia B. Gentamicin C. Volatile agents D. Hypothermia E. ?	A *Miller's:* - Acidosis, hypokalemia, hypothermia, and medications (e.g. aminoglycosides, verapamil, magnesium sulphate) potentiate residual neuromuscular blockade and render pharmacologic antagonism more difficult
MB27 [Jul00] [Apr01] [Jul04] Neostigmine's mechanism of action: A. Binds covalently to esteric site on AChEsterase B. Binds electrostatically to esteric site on AChEsterase C. Binds to anionic site D. Forms complex with AChEsterase with a shorter half life than acetylcholine E. ("Some other long winded explanation requiring 30 seconds to read and	A *Katzung:* - Carbamate esters e.g. neostigmine, physostigmine, pyridostigmine form covalent bonds - Organophosphates produce a covalent phosphorus-enzyme bond that is extremely stable - Quaternary alcohols e.g. edrophonium reversibly bind electrostatically and by hydrogen bonds *Stoelting:* - Carbamate esters: esteratic site

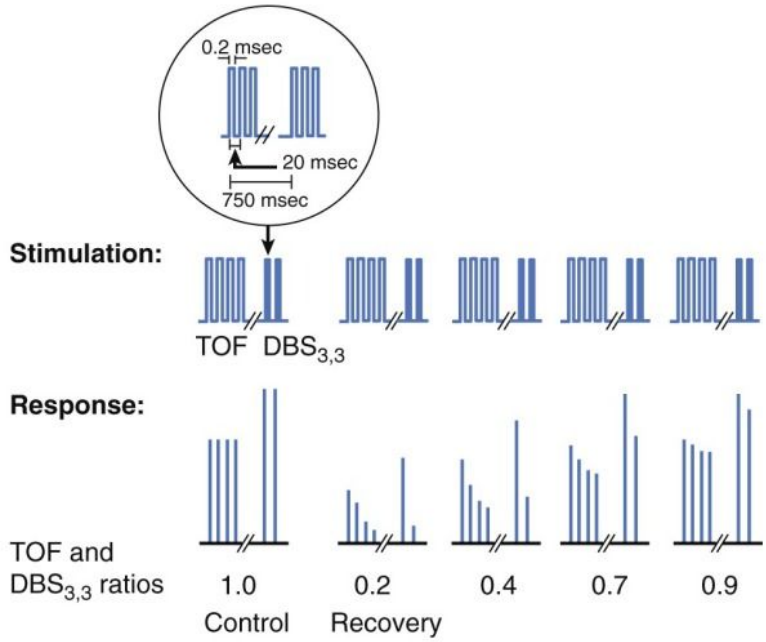
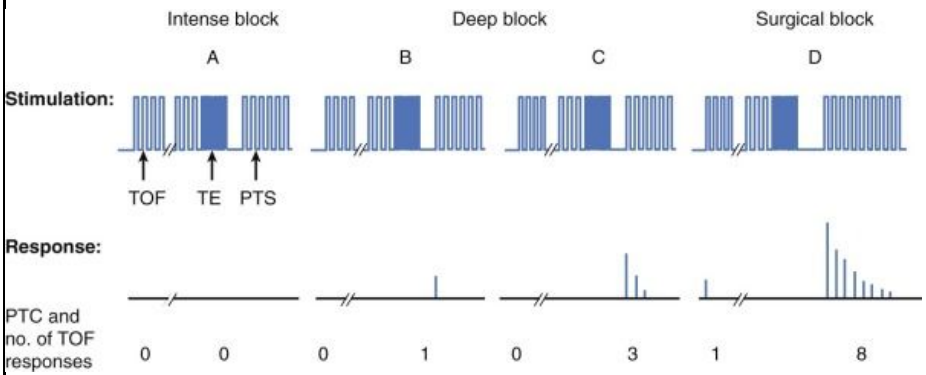
impossible to remember.")	- Organophosphates: esteratic site (echothiophate also interacts with the anionic site) - Quaternary alcohols: electrostatic bond at anionic site and hydrogen bond at esteratic site - Carbamylated acetylcholinesterase has a half time of 15-30 minutes - In contrast, acetylcholinesterase is responsible for the rapid hydrolysis (<15 ms) of acetylcholine to acetic acid and choline, which prevents sustained depolarisation of the NMJ 
MB28 [Jul00] With depolarising neuromuscular blocker: A: Is competitively antagonised by NDMR B: ("Something about tetany & fade") C. ? D. ? E: Shows post tetanic potentiation	B: does not cause *Stoelting:* - The prior administration of succinylcholine 1 mg/kg ↑s the magnitude of twitch response suppression produced by the subsequently administered non-depolarising neuromuscular blocking drug, even when evidence of neuromuscular blockade produced by succinylcholine has waned - This is unexpected, because the sequence of succinylcholine following a non-depolarising neuromuscular blocking drug should be antagonistic - Presumably, postjunctional membranes remain desensitised by succinylcholine - Despite the initial enhancement, the subsequent duration of atracurium or vecuronium is *not* prolonged Characteristics of phase I block: - ↓ contraction in response to single twitch stimulation - ↓ amplitude but sustained response to continuous response to continuous stimulation - TOF ratio > 0.7 - Absence of posttetanic facilitation - Augmentation of neuromuscular blockade after administration of an anticholinesterase drug - Onset accompanied by fasciculations that reflect the generalised depolarisation of postjunctional membranes
MB29 [Jul00] Rocuronium administered in 2 times the ED95 dose: A. Rapid onset, short duration B. Rapid onset, Intermediate duration C. Slow onset, intermediate duration D. Slow onset, long duration E. ("some other combination.")	B *Stoelting:* - Monoquaternary aminosteroid nondepolarising neuromuscular drug - ED95 = 0.3 mg/kg - Onset = 1-2 minutes - Duration = 20-35 minutes - Structurally resembles vecuronium except for the presence of a hydroxyl group rather than an acetyl group on the A ring of the steroid nucleus - Lack of potency compared with vecuronium is important in its rapid onset: ↑ number of molecules → ↑ number of molecules available to diffuse into the NMJ

	- Large doses, as needed to mimic the onset of action of succinylcholine (3-4 x ED95), produce a duration of action that resembles the long-acting non-depolarising neuromuscular blocking drug pancuronium *Miller's:* Classification of nondepolarising neuromuscular blockers according to duration of action (time to T1 = 25% of control) after twice the ED95… <u>Steroidal compounds</u> - Long acting (>50 min): pancuronium - Intermediate acting (20-50 min): vecuronium, rocuronium <u>Benzylisoquinolinium compounds</u> - Long acting (>50 min): d-tubocurarine - Intermediate acting (20-50 min): atracurium, cisatracurium - Short acting (15-20 min): mivacurium
MB30 [Apr01] Anticholinesterase drugs A. ? B. ? C. Used in treatment of Glaucoma D. ?	C *Stoelting:* Uses of anticholinesterase drugs… - Antagonist-assisted reversal of neuromuscular blockade produced by non-depolarising neuromuscular blocking drugs - Treatment of the CNS effects produced by certain drugs (physostigmine for central anticholinergic syndrome, but shorter duration than anticholinergic drugs: might need to repeat) - Treatment of myasthenia gravis (neostigmine, pyridostigmine) - Treatment of glaucoma (topical administration ↓s resistance to outflow of aqueous humour but ↑s risk of cataracts so short-acting miotic drugs used initially, with introduction of long acting drugs if short acting drugs are ineffective) - Treatment of paralytic ileus and atony of the urinary bladder - Mild to moderate Alzheimers disease (donepezil = Aricept, rivastigmine = Exelon, galantamine = Reminyl) - Diagnosis and management of paroxysmal SVT (edrophonium) - Postoperative analgesia (neuraxial neostigmine) - Postoperative shivering (physostigmine)
MB31 [Apr01] Neostigmine: A. Tertiary ammonium compound B. ? no, quaternary C. ?	B *Stoelting:* - Anticholinesterase drugs containing a quaternary ammonium group (edrophonium, neostigmine, pyridostigmine) are poorly lipid soluble and thus do not easily penetrate lipid cell membrane barriers such as the GIT or BBB - Lipid soluble drugs, such as tertiary amines (physostigmine) and organophosphates, are readily absorbed from the GIT or across mucous membranes and have predictable effects on the CNS

MB32 [Jul01] [Jul04] The dibucaine number for a normal person is: A. 20 B. 40 C. 60 D. 80 E. 100	D *Stoelting:* - Dibucaine inhibits the activity of normal plasma cholinesterase by ~80%, compared with only ~20% inhibition of the activity of atypical enzyme
MB33 [Jul01] Muscle relaxants are less likely to cause anaphylaxis if: A. Injected slowly B. Suxamethonium is the most common cause C. H1 and H2 blockers prevent anaphylaxis D. Always fatal E. ?	B *Stoelting:* - Drugs with single quaternary ammonium groups (pancuronium, vecuronium, rocuronium) less likely to cause allergic reactions than succinylcholine - Anaphylactic reactions after first exposure may reflect sensitisation from prior contact with cosmetics or soaps with quaternary ammonium groups - Females > males - Regarding atracurium and histamine release: slow administration or pretreatment with H1 and H2 receptor antagonists does not evoke circulatory changes (↑ HR, ↓ BP) despite similar ↑s in plasma concentrations of histamine *Miller's:* - Steroidal compounds (e.g. rocuronium, vecuronium, pancuronium) result in no significant histamine release - Anaphylactic reactions are mediated through immune responses involving immunoglobulin E antibodies fixed to mast cells - Anaphylactoid reactions are not immune mediated and represent exaggerated pharmacologic responses in very rare and very sensitive individuals
MB34 [Jul01] Laudanosine: A. ? B. ? C. ? D. ?	*Stoelting:* - Major metabolite of atracurium and cisatracurium metabolism (less with cisatracurium) - Depends primarily on the liver for clearance; some excreted in the urine - Is not active at the NMJ - Animal studies: CNS stimulant, ↑s MAC, causes peripheral vasodilation - Unlikely that atracurium administration will result in plasma concentrations of laudanosine capable of producing CNS or CV effects
MB35 [q[All of the following result in prolongation of Vecuronium block except: A. Concomitant insulin and dextrose infusion B. Prior suxamethonium blockade	B *Miller's:* - Acidosis, hypokalemia, hypothermia, and medications (e.g. aminoglycosides, verapamil, magnesium sulphate) potentiate residual neuromuscular blockade and render pharmacologic antagonism more difficult *Stoelting:*

	- The prior administration of succinylcholine 1 mg/kg ↑s the magnitude of twitch response suppression produced by the subsequently administered non-depolarising neuromuscular blocking drug, even when evidence of neuromuscular blockade produced by succinylcholine has waned - This is unexpected, because the sequence of succinylcholine following a non-depolarising neuromuscular blocking drug should be antagonistic - Presumably, postjunctional membranes remain desensitised by succinylcholine - Despite the initial enhancement, the subsequent duration of atracurium or vecuronium is *not* prolonged
MB36 [Feb04] Post-suxamethonium myalgia: A. Preceeded by transient myoglobinuria B. More common in the elderly C. Can be prevented by pre-treatment with 0.04 mg/kg of D-tubocurarine "pre-curarisation" D. Is invariably associated with increased intra-ocular pressure E. Is associated with hypokalaemia	C *Stoelting:* - Particularly prominent in the skeletal muscles of the neck, back, and abdomen - Especially in young adults undergoing minor surgical procedures that permit early ambulation - Myalgia localised to neck muscles may be perceived as a pharyngitis by the patient and attributed to intubation by the anaesthetist - Speculated to be due to unsynchronised contractions of skeletal muscle fibres associated with generalised depolarisation produced by succinylcholine - Prevention of clinically visible succinylcholine-induced skeletal muscle contractions with prior administration of a nonparalysing dose of dTc ↓s the incidence of myalgia - Surprisingly, use of vecuronium in place of succinylcholine does not ↓ the occurrence of myalgia in patients undergoing laparoscopy - Myoglobinuria rarely occurs in adults but may occur in children (reflects skeletal muscle damage associated with fasciculations) - Sustained opening of receptor ion channels and resulting depolarisation of postjunctional membranes is associated with leakage of potassium ions from the interior of cells sufficient to produce a 0.5 mEq/L ↑ in serum potassium - ↑s intraocular pressure, *not* due to contraction of extraocular muscles; cytoplegic actions and ↑ choroidal blood volume and ↑ CVP are likely to contribute
MB37 [Feb04] Regarding anticholinesterases: A. Pyridostigmine is a tertiary amine B. Quaternary ammonium anticholinesterases have a larger volume of distribution than non-depolarising muscle relaxants C. Edrophonium has a slower onset of action than neostigmine D. Neostigmine has a longer duration of action than pyridostigmine E. Edrophonium binds covalently to the esteratic site of acetylcholine	B *Stoelting:* - Anticholinesterase drugs containing a quaternary ammonium group (edrophonium, neostigmine, pyridostigmine) are poorly lipid soluble and thus do not easily penetrate lipid cell membrane barriers such as the GIT or BBB - Lipid soluble drugs, such as tertiary amines (physostigmine) and organophosphates, are readily absorbed from the GIT or across mucous membranes and have predictable effects on the CNS - The large volume of distribution of quaternary ammonium anticholinesterase drugs (edrophonium and pyridostigmine 1 L/kg, neostigmine 0.7 L/kg) compared with non-depolarising neuromuscular drugs is surprising because these drugs would not be expected to cross lipid membranes easily: presumably, this reflects tissue storage in organs such as the liver and kidneys - Onset times: edrophonium rapid (1-2 minutes), neostigmine intermediate (7-11 minutes), pyridostigmine delayed (16 minutes) - Duration of action of edrophonium, neostigmine and pyridostigmine is similar - Edrophonium produces reversible inhibition of acetylcholinesterase by an electrostatic bond at the anionic site and hydrogen bond at the esteratic site - Because a true chemical (covalent) bond is not formed, acetylcholine can easily compete with edrophonium for access to acetylcholinesterase

	
MB37b [Jul04] Regarding Antiacetylcholinesterase A. Given orally to treat glaucoma B. Edrophonium is a long acting AChE inhibitor C. Physostigmine is quarternary ammonium D. ?	None correct *Stoelting:* - Topical administration ↓s resistance to outflow of aqueous humour but ↑s risk of cataracts so short-acting miotic drugs used initially, with introduction of long acting drugs if short acting drugs are ineffective - Duration of action of edrophonium, neostigmine and pyridostigmine is similar - Anticholinesterase drugs containing a quaternary ammonium group (edrophonium, neostigmine, pyridostigmine) are poorly lipid soluble and thus do not easily penetrate lipid cell membrane barriers such as the GIT or BBB - Lipid soluble drugs, such as tertiary amines (physostigmine) and organophosphates, are readily absorbed from the GIT or across mucous membranes and have predictable effects on the CNS
MB38 [Jul04] Which is the best indicator of adequate reversal? A. TOF Count of 4 B. No fade on DBS C. No fade to 200 Hz tetanus D. Head lift?? E. Evidence of post-tetanic facilitation	B *Miller's:* - It is difficult and often impossible to exclude with certainty clinically significant residual curarisation by clinical evaluation of recovery of neuromuscular function - Unreliable clinical tests of postoperative neuromuscular recovery: sustained eye opening, tongue protrusion, arm lift to the opposite shoulder, normal tidal volume, normal vital capacity, maximum inspiratory pressure < 40 cmH2O - Most reliable: sustained head lift for 5 seconds, sustained leg lift for 5 seconds, sustained handgrip for 5 seconds, sustained "tongue depressor test", maximum inspiratory pressure >=40 cmH2O - In non-paralysed muscle, the response to double burst stimulation is two short muscle contractions of equal strength - In a partly paralysed muscle, the second response is weaker than the first (i.e., the response fades) - Tactile evaluation of the response to DBS is superior to tactile evaluation of the response to TOF stimulation - However, absence of fade in the manually evaluated response to DBS (and TOF) does not exclude residual neuromuscular blockade

	 - It is possible to quantify intense neuromuscular blockade by applying tetanic stimulation (50 Hz for 5 seconds) and observing the post-tetanic response to single-twitch stimulation given at 1 Hz starting 3 seconds after the end of tetanic stimulation 
MB38b [Jul04] Residual curarization is best evaluated with: A. TOF 1:4 > 50% B. Equal twitch height on DBS C. ?Degree of fade is independent on stimulus intensity D. ?Used to check depth of anaesthesia E. ?	B
MB39 [Jul07] Sugammadex binds most avidly to: A. Pancuronium B. Rocuronium C. Vecuronium	B *Miller's:* - Sugammadex is the first selective relaxant binding agent (su refers to sugar, and gammadex refers to the structural molecule gamma-cyclodextrin) - Is a modified γ-cyclodextrin

D. Atracurium E. Cisatracurium	- Their 3D structure resembles a doughnut - The structure has a hydrophobic cavity and a hydrophilic exterior because of the presence of polar hydroxyl groups - Exerts its effect by forming very tight complexes in a 1:1 ratio with steroidal neuromuscular blocking agents (rocuronium > vecuronium ≫ pancuronium) - Hydrophobic interactions trap the drug in the cyclodextrin cavity (the "doughnut hole"), resulting in the formation of a water-soluble guest-host complex - The stability of the rocuronium-sugammadex complex is the end result of an interplay of intermolecular forces (van der Waals forces), including thermodynamic (hydrogen bonds) and hydrophobic interactions - Has no effect on acetylcholinesterase or any receptor system in the body, eliminating the need for anticholinergic drugs and their undesirable side effects - Because of the soluble nature of the rocuronium-cyclodextrin complex, urinary excretion of the complex is the major route of elimination of rocuronium - Efficacy does not rely on renal excretion of the cyclodextrin-relaxant complex - Ineffective against succinylcholine and benzylisoquinolinium neuromuscular blockers such as mivacurium, atracurium, and cisatracurium because it cannot form inclusion complexes with these drugs - Therefore, if neuromuscular blockade must be reestablished after using sugammadex, one of the benzylisoquinolinium neuromuscular blockers should be considered

Psychotherapeutics

PS01 [Mar96] [Jul98] [Jul01] [Jul02] Benzodiazepines: A. Are all lipid soluble (OR: None are water-soluble) B. Are all renally excreted unchanged C. Causes retrograde amnesia D. Lorazepam is more lipophilic than midazolam E. Block GABA receptors F. Have high therapeutic index	F A is possible depending on wording Lipid solubility depends on pKa and pH - most are water soluble at very low pH. Many undergo hepatic metabolism. Cause anterograde amnesia Lorazepam is less lipophilic than midazolam, accounting for its slower onset of action (~5 mins) Bind to the GABAa receptor at the gamma/alpha site. Are relatively safe in OD A ? Stoelting page 141: "All are highly lipid soluble and highly bound to plasma proteins, especially albumin"…
PS02 [Mar97] [Jul97] [Jul99] [Mar03] Which is TRUE regarding monoamine oxidase inhibitors (MAOI)? A. Should/must be ceased for two weeks prior to general anaesthesia B. Cause hypotension and sedation in combination with pethidine C. Inhibit activity of indirect sympathomimetics D. Ingested tyramine causes hypertension due to indirect effects E. Includes doxepin and amitriptyline	D Dietary tyramine & other monoamines can enter the systemic circulation and be taken up by SNS nerve endings - this can result in elicit of massive release of endogenous catecholamines & hyperadrenergic crisis, resembling pheo. Old advice to cease prior to surgery. Should increase the activity of sympathomimetics metabolised by MAO. Doxepin & amitriptyline are TCAs. Pethidine & MAOI may cause type 1 (agitation, headache, rigidity, hyperpyrexia) or type 2 (hypotension, ventilatory depression, coma) response [Peck/Hill/Williams p277, Stoelting p407]

PS03 [Jul97] [Jul98] [Jul00] [Jul01] Neuroleptic malignant syndrome: A. Occurs only with chronic use B. 80% (60%) mortality C. ?Treated /? not treated with dantrolene D. Can be caused by acute withdrawal of L-Dopa therapy E. Is treated with bromocriptine	C and E A - Can occur with acute use. B - NMS has a mortality to 20% - most commonly from ventilatory failure, cardiac failure/arrhythmia, renal failure, thromboembolism. The syndrome typically develops over 24-72hrs, characterized by hyperthermia, generalised hypertonicity, instability of ANS, fluctuating consciousness. Neuroleptic malignant syndrome occurs in 0.5-1% of all patients treated with antipsychotic drugs. Mortality is about 10%. Risk factors are: 1. 2 weeks of starting a neuroleptic agent 2. Rapid rise in dose 3. Withdrawal or reduction of L-dopa or dopamine agonist therapy in patients with Parkinson's disease 4. Dehydration 5. Intercurrent illness Thought to be due to: 1. Dopamine receptor blockade 2. Genetically reduced function of dopamine receptor D2 Syndrome characterised by: 1. Fever 2. Encephalopathy 3. Vitals – unstable manifesting as alterations in systemic blood pressure, tachycardia, and cardiac dysrhythmias. 4. Elevated enzymes – Creatine Kinase (from muscle damage) 5. Rigidity of muscles Treatment is: 1. Stopping the neuroleptic agent 2. Immediate supportive care. 3. Extrapyramidal symptoms can be treated with antiparkinsonian medications (bromocriptine – dopamine agonist) 4. Muscle relaxation achieved with diazepam or dantrolene Differential is: 1. Malignant hyperthermia 2. Central anticholinergic syndrome Differentiating feature is the ability of NDMRs to produce flaccid paralysis in patients experiencing NMS.

PS04 [Jul97] Inhibitors of monoamine oxidase A
A. Allow tyramine to enter the circulation from the gut
B. ?
C. ?
D. ?

A
MAOI act by forming a stable, irreversible complex with MAO enzyme and thereby preventing breakdown of neurotransmitters. MAO-A is found in the GIT & liver where it acts to metabolize bioactive amines such as tyramine. Dietary tyramine & other monoamines can enter the systemic circulation and be taken up by SNS nerve endings - this can result in elicit of massive release of endogenous catecholamines & hyperadrenergic crisis, resembling pheo. MAO-B inhibitors (selegiline) do not require tyramine-free diet. [Stoelting, 4th ed, p406]

PS05 [Jul97] [Feb00] Benzodiazepines:
A. Have no analgesic effect
B. Have an antanalgesic effect
C. Have an analgesic effect
D. Have dose-related analgesic and antanalgesic effects

A

Miller's says that benzodiazepines lack analgesic properties and must be used with other anaesthetic drugs to provide sufficient analgesia.

Nothing in Katzung

PS06 [Jul98] [Jul99] [Mar03] [Jul04] The benzodiazepine with the longest elimination half-life is:
A. Diazepam
B. Oxazepam
C. Temazepam
D. Midazolam
E. Lorazepam
F. Flunitrazepam

A
Elimination half-times:
Diazepam 21-37
Oxazepam 5-15hrs
Temazepam 15hr
Midazolam 1-4hrs
Lorazepam 10-20hr
Flunitrazepam 20-30hrs

[Stoelting, 4th ed, chapter 5]

Table 37-1. Characteristics of benzodiazepines in humans

Drug(s)	Half-life of parent compound (h)	Active metabolite	Half-life of metabolite (h)	Overall duration of action	Main use(s)
Triazolam,[a] midazolam	2-4	Hydroxylated derivative	2	Ultrashort (< 6 h)	Hypnotic Midazolam used as intravenous anaesthetic
Zolpidem[b]	2	No	-	Ultrashort (~ 4 h)	Hypnotic
Lorazepam, oxazepam, temazepam, lormetazepam	8-12	No	-	Short (12-18 h)	Anxiolytic, hypnotic
Alprazolam	6-12	Hydroxylated derivative	6	Medium (24 h)	Anxiolytic, antidepressant
Nitrazepam	16-40	No	-	Medium	Hypnotic, anxiolytic
Diazepam, chlordiazepoxide	20-40	Nordazepam	60	Long (24-48 h)	Anxiolytic, muscle relaxant Diazepam used intravenously as anticonvulsant
Flurazepam	1	Desmethyl-flurazepam	60	Long	Anxiolytic
Clonazepam	50	No	-	Long	Anticonvulsant, anxiolytic (especially mania)

[a] Triazolam has been withdrawn from use in the UK on account of side effects.
[b] Zolpidem is not a benzodiazepine but acts at the same site. Zopiclone is similar.

PS07 [Jul98] Fluoxetine: A. Inhibits noradrenaline & adrenaline uptake B. Inhibits serotonin uptake C. ? D.	B Fluoxetine in an SSRI - inhibits reuptake of 5HT
PS08 [Mar99] [Jul00] Flumazenil: A. Formulated In propylene glycol in commercial preparation B. Inverse agonist C: Is slowly metabolised making resedation unlikely D. Does not reliably reverse sedation and resp depression (in large agonist dose ?) E. Is a partial agonist at mu opioid receptors Option D has also been remembered as: D. May significantly reverse evidence of sedation whilst hypoxia or hypercapnia persist D. Reliably reverses the sedating effects of benzodiazepines but marked respiratory depression still can occur	B – only inverse agonist in clinical use (Kam lecture) Option D alternates are both correct too Flumazenil is a 1,4-imidazobenzodiazepine derivative. It is specifically and exclusive benzodiazepine antagonists with a high affinity for BZD receptors, where it exerts minimal agonist activity. Metabolism is by hepatic microsomal enzymes to inactive metabolites. Duration of action is 30-60mins and supplemental doses may be required. Generally, total doses of 0.3-0.6mg IV have been adequate to decrease the degree of sedation to the required extent where as total doses of 0.4-1.0mg IV are usually sufficient to completely abolish the effect of a therapeutic dose of benzodiazepine. [Stoelting, 4th, p152] Mims states: Active. Flumazenil. Inactive. Disodium edetate, acetic acid, sodium chloride, sodium hydroxide in water for injections adjusted to pH 4.0.
PS09 [Mar99] Diazepam: A. Half-life of 5 to 10 hours B. Metabolised to oxazepam & temazepam /?desmethyldiazepam C. ? D. ?	B Elimination 1/2 time 21-37hrs. Vd 1-1.5L/kg (lipid soluble & extensive uptake) Protein binding 96-98% Cl 0.2-0.5ml/kg/min Diazepam metabolism: hepatic, oxidative pathway of N-demethylation. The 2 principle metabolites are desmethyldiazepam & oxazepam, with a lesser amount metabolised to temazepam [Stoelting, p147]
PS10 [Mar99] [Jul99] Droperidol: A. Substituted phenothiazine B. Reliably produces mental tranquility C. Does not act (directly) on CTZ D. Alpha-blockade with hypotension is not a problem with 2mg dose E. Slows alpha rhythm on EEG (Note: Mar 99 paper had 2 questions on droperidol)	E Droperidol is a butyrophenones. Structurally resembles & evokes pharmacologic effects similar to phenothiazines & thioxanthenes. CNS - outwardly calming but pts sometimes describe intensly dysphoric experience when drug has worn off, akathisia, extrapyramidal reactions in 1% (dopamine antagonist) and rarely involving laryngospasm, cerebral vasoconstrictor and reduced cerebral blood flow, but CMRO2 not greatly altered (may be undesirable), reticular activating system not depressed, alpha rhythm persists on EEG. No amnesia/anticonvulsant activity. CVS - can decrease BP due to CNS effects & anti-alpha actions - usually this is minimal. SVR & PVR only modestly & transient decrease. Myocardial contractility not altered. Anti-dysrhythmic & protects against adrenaline-induced dysrhythmias (? mechanism), but may cause prolonged QT & torsades due to delayed ventricular repolarization. RESP - augments response to hypoxaemia (useful premed in resp disease) GIT - powerful antiemetic agent as a result of inhibition of dopamine2 receptors in chemoreceptor trigger zone of the medulla Millers says that the EEG in conscious patients shows some reduction in frequency, with occasional slowing.

PS11 [Mar99] Monoamine oxidase inhibitors (MAOI): A. Moclobemide is a reversible inhibitor B. Interacts with tyramine to cause hypertension C. Interacts with pethidine to cause hypothermia D. ?	A B not true as doesn't interact with tyramine so much as stop its metabolism. Moclobemide is a new generation MAOI that selectively and reversibly inhibits only MAOA. Causes less potentiation of tyramine than older generation (phenelzine, isocarboxazid, tranylcypromine). Pethidine & MAOI may cause type 1 (agitation, headache, rigidity, hyperpyrexia) or type 2 (hypotension, ventilatory depression, coma) response [Peck/Hill/Williams p277, Stoelting p407] ? B is incorrect… it doesn't interact with tyramine so much as stop its metabolism.
PS11b [Feb04] Monoamine oxidase inhibitors A. Mobenclamide is a reversible type B inhibitor B. Prevent hepatic metabolism of tyramine enabling it to enter the circulation and act as an indirect agonist ??	B Reversible MAOA inhibitor. MAOA is found in GIT & liver where it acts to metabolize bioactive amines such as tyramine. Dietry tyramine entering systemic circulation can be taken up by sympathetic nerve endings & elicits massive release of endogenous catecholamines.
PS12 [Jul99] [Apr01] Metabolites of diazepam, all EXCEPT: A. Temazepam B. Oxazepam C. Desmethyldiazepam D. Lorazepam	D see q9
PS13 [Jul00] With respect to action of midazolam: A. Acts on GABA-B receptors B. increases duration of opening of Cl – channels C. ? competes with barbiturates for receptor site on GABA receptor D. Metabolism is decreased by cimetidine E. Decreases chloride conductance F. Interacts with the B1 subunit of GABA	D and B GABAa binders Modulates actions of GABA at the receptor - more frequent opening of the Cl channel. Separate binding site to barbiturates. Acts on the benzo site of GABA receptor (alpha-gamma) Metabolism is by p450 CYP3A4 to 1-hydroxymidazolam (1/2 the activity) then conjugated to 1-hydroxymidazolam glucuronide and cleared by the kidneys. Metabolism is slowed in presence of cimetidine, erythromycin, calcium channel blockers, antifungal drugs (other 3A drugs) [Stoelting 5th chapter]
PS14 [Jul00] Benzodiazepines - which statement is true ? A. ? B. Midazolam has ?active / ?inactive metabolites C. ? D. All depend on hepatic clearance	B true if active D true Midazolam does have active and inactive metabolities. "Aging & liver disease affect glucuronidation less than oxidative metabolic pathways. In this regard, lorazepam, oxazepam & temazepam are metabolised only by glururonidation & have no active metabolites. For this reason, these BZD may be selected in elderly patients over other BZD" [Stoelting p142] - so I'd take this to mean that all have some hepatic metabolism.

PS15 [Jul00] [Mar03] [Jul04] Tricyclic antidepressants: A. Do not cause sedation B. Formed from modification of the phenothiazine ring C. Avoid anti-cholinergic effects compared to other anti-depressants D. Does not decrease reuptake of 5HT ?at 5HT3 R E. Decrease CNS amine levels	B Do cause sedation - may be desirable for management of agitated patients. The structure of TCAs resembles that of local anaesthetics and phenothiazines. Imipramine, which is the prototype TCA, differs from phenothizine only in the replacement of the sulfur atom with an ethylene linkage to produce a 7-membered central ring. Anticholinergic effects of TCAs are prominent, especially at high doses. TCAs act at several transporters and receptors, but their antidepressant effect is likely produced by blocking reuptake of serotonin &/or norad at presynaptic terminals. [Stoelting p402]
PS16 [Jul00] Diazepam 0.1 mg/kg given orally, the percent absorption is: A. 100% B. 94% C. ? D. ?	A Bioavailability is 86-100% [Sasada & Smith p101] Oral bioavailability 90% [Faunce, p231] Katzung says that all benzos are absorbed completely. Bioavailability refers also not only absorption, but also to what goes on in the liver. E.g. midazolam is 100% absorbed but only 50% bioavailability cos of liver metabolism.
PS17 [Feb04] Clinical uses of Diazepam include: A. Anticonvulsant B. Skeletal muscle relaxation C. Treatment of Delerium Tremens D. Induction of anaesthesia E. All of the above	E
PS18 Midazolam: A. open ring structure above pH 4. B. poor oral bioavailability so less than 50% reaches systemic circulation C. has approximately the same affinity for GABA receptor which is similar to diazepam D. ? E. ?	B A – open and ionized at ph > 4 C = false – has 2x affinity

PS19 You are about to anaesthetise someone taking a MAOI (*tranylcypramine I think*) Which drug is least likely to be problematic? A. Ephedrine B. Tramadol C. Etomidate D. Phenylephrine E. ?Metaraminol ?F. Pethidine	D A - false - Ephedrine has indirect and direct sympathomimetic actions - potential to cause hypertensive crisis B - false - Tramadol has serotenergic actions - potential to cause serotonin syndrome C - false - Etomidate is associated with epileptiform EEG ? bad - used for ECT in patients on MAOI D - **True - Phenyleprhine has direct actions only therefore "no" risk of a hypertensive crisis** E - false - Metaraminol has indirect and direct sympathomimetic actions - potential to cause hypertensive crisis ?F - false - Pethidine - potential to cause serotonin syndrome
PS20 Feb13 Flumazenil: A. ? B. ? C. Predictably reverses the respiratory depression caused by benzodiazepine overdose D. ? E. ?	C