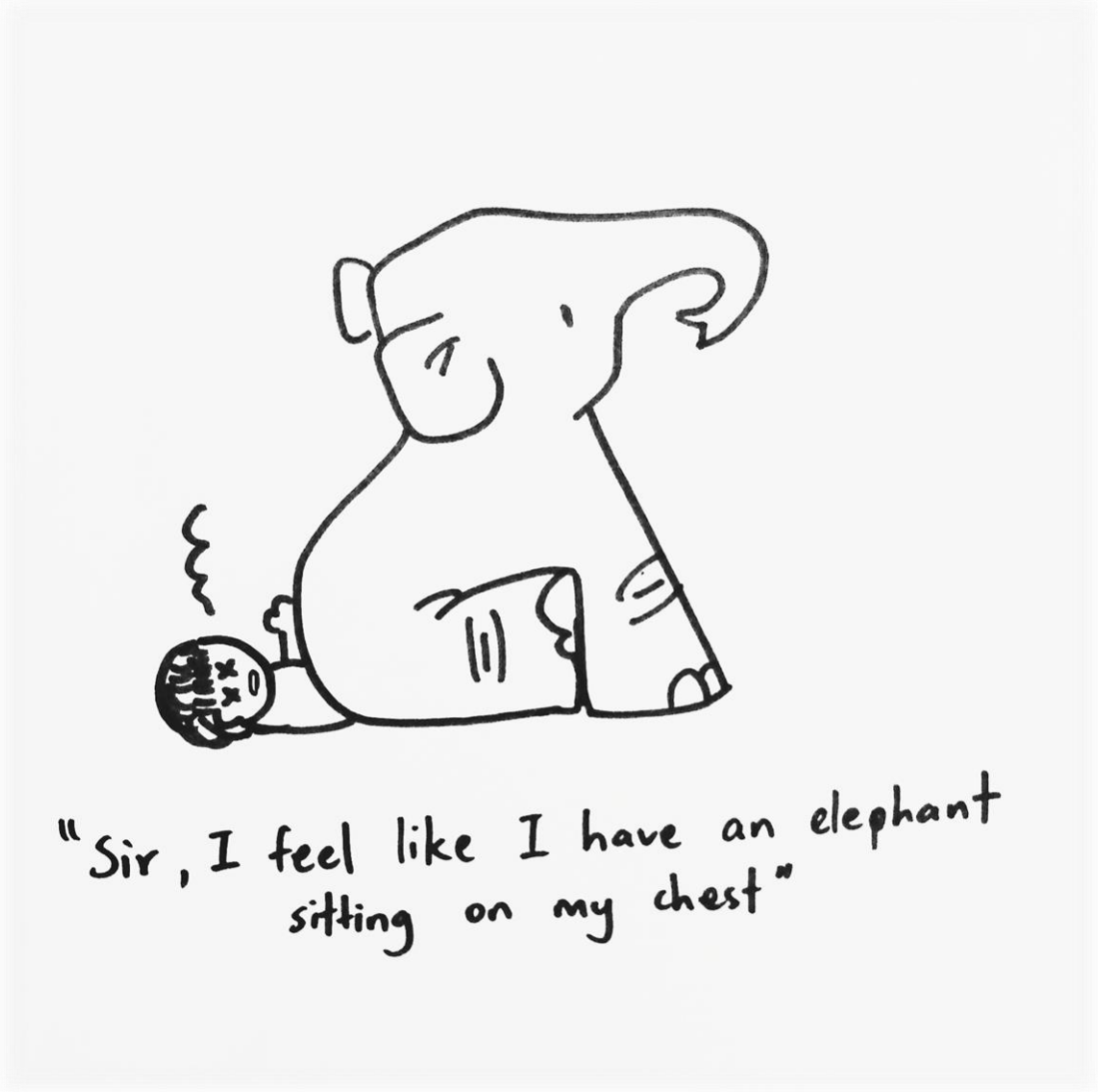

PHASE I INTEGRATED CLINICAL CASES

"Thinking through Pathophysiology"

Discussions for Mentors AY 2017/2018
Version 1.5

PREFACE

Dear M1s,

Welcome to your first year of the exciting and enriching course that is medicine. Year 1 is a really busy year with a lot of new things to learn and changes to adapt to, and we can sometimes get lost in the details of Physiology and Anatomy and lose sight of the big picture and the reason why we need to learn all this stuff in the first place. As seniors, we believe that the best way to make year 1 relevant and connected to the coming years is really to see the basics come to life in real patients. We hope that this casebook will give you adequate opportunity and exposure to organize your knowledge and understand why certain patients present to us the way they do.

The cases are organized in blocks of increasing difficulty and arranged to match what you're learning with each physiology block, so do take each session as an opportunity to tidy up, consolidate and clarify doubts before moving on to different systems. With the kind help and support of your M2 seniors and the faculty, we sincerely hope that these cases will excite your interest to learn medicine and be beneficial to you in preparation for year 2.

We would like to thank the following people for the invaluable contributions to this effort:

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Please contact us if you spot any errors or would like to add more cases for the Phase I Integrated Clinical Cases!

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CASE 1 | ABDOMINAL DISCOMFORT

You are a third year medical student doing your first rotation – on the way to becoming the doctor you envisioned yourself to be when entering medical school. You've been tasked to 'clerk' (that is, take a history and perform a physical examination on) an interest patient by the friendly medical officer in your team.

The patient is Mr. Wan Tu Tok, a boisterous 46 year old Chinese man working as a teacher in a special needs school. Mr. Wan recounts his contact with the healthcare system: more than a year ago he began experiencing vague abdominal discomfort accompanied by bloatedness and slight nausea, which was relieved by meals. He found himself progressively less able to concentrate at work due to the increasing abdominal discomfort. It was then that he visited his general practitioner, who prescribed a proton pump inhibitor (PPI).

Q1. What are the two key cell types in the stomach responsible for digestion? What are their respective functions?

They are the parietal cells and chief cells. **Parietal cells** have two key functions: firstly to secrete gastric acid (hydrochloric acid) by its H+/K+ ATPase at its luminal surface, and secondly to secrete intrinsic factor which is essential for the absorption of vitamin B12 in the ileum. **Chief cells** secrete the proenzyme pepsinogen into the gastric lumen. Pepsinogen is an inactive zymogen; it is converted to its active form pepsin which catalyses protein degradation into peptides, in the presence of an acidic environmental that is created by parietal cells.

Q2. How is the secretion of gastric acid (HCl) physiologically regulated? What hormones and neurotransmitters are involved?

Upregulation:
HCl secretion by parietal cells is upregulated by three ligands: acetylcholine (binding to the muscarinic M3 receptor on parietal cells), gastrin (to the CCK-B receptor) and histamine (to the histamine H2 receptor). **Acetylcholine** is released by parasympathetic output from the vagus nerve in response to a meal, during the cephalic and gastric phases of digestion. The ACh binds directly to parietal cell receptors to stimulate HCl secretion. ACh also binds to receptors on G cells in the gastric antrum, to promote release of the hormone **gastrin** that binds to parietal cell receptors to further upregulate HCl secretion. Finally, both acetylcholine and gastrin are capable of stimulating the enterochromaffin-like (ECL) cells in the stomach to release **histamine**, which is the most important stimulus for parietal cells to secrete HCl. The upregulation of HCl secretion is therefore via a hormonal cascade that begins with ACh release.

Downregulation:
There are also mechanisms to downregulate gastric acid secretion. The most important one is the binding of **prostaglandins** to receptors on parietal cells, which in turn reduced its HCl secretion into the gastric lumen. This is an important counter-regulatory mechanism to finely control the pH of the gastric lumen for appropriate activation of pepsinogen. Somatostatin also downregulates acid secretion.

Q3. The proton pump inhibitor prescribed by Mr. Wan's GP inhibits the gastric H+/K+ pump, to reduce the acidity of the stomach. PPIs are typically better at relieving symptoms compared to another class of drugs known as H2 blockers, which block histamine receptors in the stomach. Based on your understanding, why are PPIs more effective than H2 blockers?

PPIs **block the common end-point** – the parietal cell luminal H+/K+ pump – of the above-described upregulatory mechanisms, since all three ligands (ACh, gastrin and histamine) control secretion of gastric acid by this ATPase pump. In contrast, H2 blockers merely block one of the three pathways (histamine), leaving the other two pathways active.

Mr. Wan tells you about how his symptoms failed to resolve for many months, even after the highest doses of PPIs were prescribed by his GP. He also speaks of a particularly fatty diarrhea ('steatorrhea') he experienced around that time, together with a loss of weight from about 65kg to 60kg. It was then that a decision was made for a specialist appointment by his astute GP.

An oesophagogastroduodenoscopy (a procedure involving a camera to visualise the oesophagus all the way to the proximal duodenum) was performed; from the hospital's record system you note that multiple giant bleeding ulcers were visualised in all four parts of the duodenum. You realise this is highly unusual, as it suggests that gastric acid secretion was overwhelmingly massive that large amounts of intraluminal acid extensively damaged the small intestine mucosa. A full blood count also showed low hemoglobin – indicative of anemia.

Q4. Which large artery would be prone to erosion by ulceration at the posterior wall of the D1 duodenum? What other anatomic structures are closely associated with the D1 duodenum?

Erosion of the **gastroduodenal artery** (a branch of the common hepatic artery, which arises from the celiac trunk) is most classically described. This artery traverses posterior to the 1st part of the duodenum.

Anteriorly, the D1 duodenum is related to the gallbladder and quadrate lobe of the liver. Posteriorly, it is related to the gastroduodenal artery, common bile duct and portal vein. Superiorly is the foramen of Winslow (epiploic foramen). Inferiorly is the head and neck of the pancreas.

You reflect that steatorrhea is a result of fat malabsorption, and realise that it could be attributed to the inactivation of pancreatic enzymes by the excessive HCl secretion.

Q5. Apart from pancreatic enzymes, what other substances are essential for lipid digestion? Detail the process of lipid digestion all the way to the eventual absorption of lipids into the bloodstream.

Bile salts are also extremely important for lipid digestion. Due to their amphipathic nature, they function to emulsify fats (i.e. break them down into smaller particles) in the small intestine. Emulsification into micelles firstly increases surface area for pancreatic lipases and colipases to act on, and secondly promotes the transport of degraded triglycerides (fatty acids and monoacylglycerol) through the brush border together with the bile salts.

The fatty acids and monoacylglycerol are re-esterified into triglycerides within enterocytes. The lipids are released initially into the **lymphatic system** (not the bloodstream!) as **chylomicrons**. They only enter the blood circulation where the lymphatic drainage empties into the venous circulation, such as by the thoracic duct.

Q6. Which vitamin deficiencies may result from longstanding fat malabsorption? Briefly, how might these deficiencies present?

Chronic fat malabsorption may result in deficiencies of the **fat-soluble vitamins A, D, E & K**. This is because the normal lipid digestion mechanism is required for these vitamins to be transport across the brush border as part of the micelles (as described above) and into the body.

The often-described pathologies when the above vitamins are deficient are:

Vitamin A: night blindness (it is an essential component of retinal epithelium)
Vitamin D: rickets in children, osteomalacia in adults (it is responsible for maintaining body supplies of calcium and phosphate, and their incorporation into bone)
Vitamin E: hemolytic anemia & neuropathy (it is an antioxidant that prevents free-radical damage)
Vitamin K: coagulopathy with raised PTT and PT (it is required for activation of four coagulation factors: II, VII, IX and X)

Note that in reality, fat-soluble vitamins are able to partition into lipid-rich compartments of the body such as adipocytes. Therefore body stores of the fat-soluble vitamins are typically not low, and it is harder to develop a deficiency.

In view of Mr. Wan's anemia, you review his iron panel and folate, B12 levels via the hospital electronic records. You recall that iron, folate and B12 are essential precursors of red blood cell synthesis – iron is a component of the heme group in hemoglobin, whereas folate and B12 are needed for cell division.

The summary of his laboratory findings are as follows:

Serum Iron	LOW
Serum Transferrin	HIGH
Transferrin Saturation	LOW
Serum Ferritin	BORDERLINE LOW
Folate (Vitamin B9)	NORMAL
Vitamin B12	LOW

Q7. Which locations in the gut are primarily responsible for absorbing the following substances essential for RBC production?

Iron	:	**duodenum**
Folate	:	**jejunum**
Vitamin B12	:	**ileum**

Q8. Following the absorption of iron, how is iron normally transported around and stored in the body?

Iron is absorbed in its reduced ferrous (2+) state. Upon entering the blood, iron is oxidized to its ferric (3+) state and transported whilst binding to the serum protein **transferrin**. The ferric iron is then unloaded into peripheral tissues such as the liver and macrophages, where the iron is stored as intracellular **ferritin** and hemosiderin.

Q9. With the physiology of iron in mind, does Mr. Wan have adequate stores of iron according to his laboratory results?

No. He is iron-deficient. We can tell because serum iron and ferritin are low, which indicates that both extracellular (serum iron) and intracellular (ferritin) stores of iron are reduced. The protein transferrin is present in increased concentrations because of a negative feedback loop; the lower the iron stores, the greater the quantity of transferrin synthesised to retain and "trap" as much iron in the blood as possible.

Q10. Normally, how is vitamin B12 stabilised prior to its eventual absorption in the distal gut?

Vitamin B12 is stabilised by binding to the protein **intrinsic factor (IF)**, which is secreted by the parietal cells of the stomach. *(Note however, that IF is neither secreted nor regulated in parallel with HCl secretion by parietal cells!)* IF is absolutely essential for the eventual absorption of B12 in the ileum.

Q11. Propose what might account for the derangements in Mr. Wan's iron panel and vitamin B12 levels.

The **iron deficiency** can be attributed to chronic bleeding from the multiple ulcer sites in Mr. Wan's duodenum. As iron is lost via the gut when excreted in fecal matter in the form of hemoglobin, bodily iron stores are slowly depleted over time.

B12 malabsorption may be attributed to the sub-optimal ileal absorption of the B12-IF complex secondary to a drop in intraluminal pH. Recall that proteins function optimally within narrow ranges of pH values. B12 deficiency is not directly attributed to the fatty diarrhea, because the B vitamins are all water-soluble and can be absorbed independently from lipids.

Mr. Wan, obviously well-educated about his disease, continues to enthusiastically talk about his workup. He tells you about a hormone test that was performed in the hospital; the electronic hospital records tell you that it was a fasting gastrin test:

Serum gastrin (fasting) VERY HIGH

Q12. Considering the mechanism of negative feedback, what physiologic stimuli might cause gastrin levels to be elevated?

Gastrin secretion from the G cells of the gastric antrum can be triggered by **Gastrin-releasing peptide** from vagal stimulation, as discussed above. On top of this, gastrin is known to be secreted in response to direct **stomach distention** and **alkalinisation** of its lumen – both of these happen when food enters the stomach! (alkalinisation occurs because food neutralises the acidic pH of the stomach)

Because of Mr. Wan's high fasting gastrin levels and fasting hyperacidity, a gastrinoma (gastrin-secreting tumour) was suspected. Other physiologic causes of hypergastinemia were ruled out.

Imaging studies localised a significantly-sized tumour to Mr. Mai's head of pancreas. Fortunately for him, no metastases were detected. Screening for other associated conditions such as a pheochromocytoma was also negative. A resection of his pancreas was therefore planned.

Q13. What endocrine deficiencies may result from pancreatic resection? Where are the cells that secrete these hormones located?

Perhaps the most significant endocrine derangement is that of **insulin deficiency**, as the endocrine component of the pancreas is responsible for secreting insulin (amongst other hormones) in addition to its role as an exocrine GI organ. This will manifest as diabetes mellitus – first as impaired fasting glucose and impaired glucose tolerance (i.e. when sugar levels are high, but not within diabetic range), and subsequently as full-blown **secondary diabetes mellitus**. Insulin is secreted by **β cells in the Islets of Langerhans**, which are found most abundantly in the tail of the pancreas.

Mr. Mai continues telling you about his hopes that the surgery will go well, so that he can return to school and continue educating his students as soon as possible. He verbalises his hopes for his family to stay strong as well.

You thank him for the past half hour you spent talking to him, and wish him well for his surgery.

Unfortunately over the next few days, your team medical officer was scheduled to rotate to another department before he was able to clear a timeslot to hear your presentation ☹

Ah well. Life as an M3 student goes on.

CASE 2 | CHEST DISCOMFORT

Mr. Sim Chong Peh is a 45 year-old Chinese taxi driver who has hypertension, hyperlipidemia and moderate obesity. He experiences occasional chest discomfort during his weekly badminton sessions with his family or when climbing multiple flights of stairs, which is relieved by resting.

Q1. What are the risk factors for coronary artery disease (CAD) that Mr. Sim has?

[Q1 and 2 are strictly speaking not part of the M1 syllabus, so it's okay if they don't know, but early exposure to important medical topics always helps ☺]

Mr Sim's risk factors can be divided into non-modifiable and modifiable:

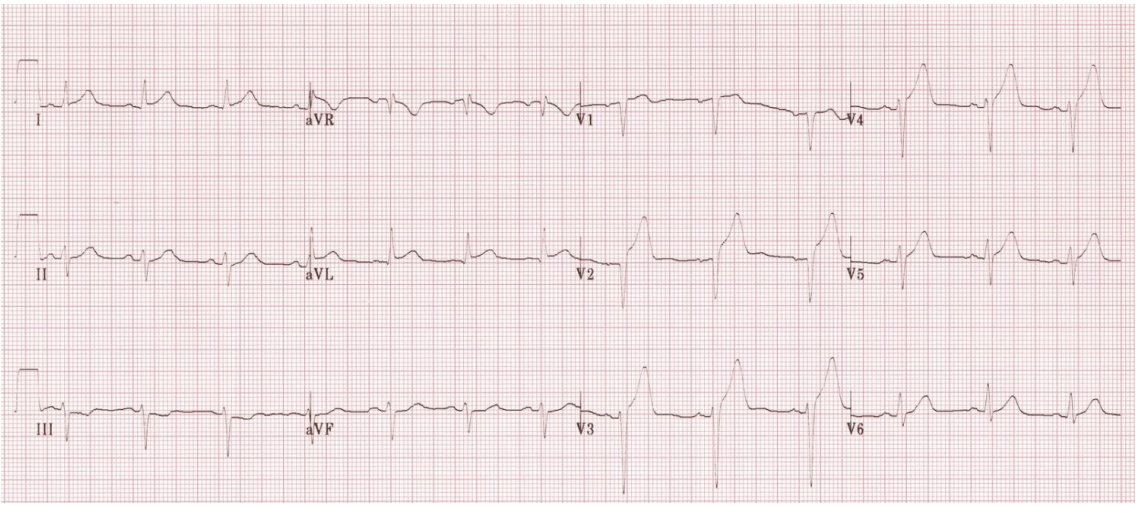
Non-modifiable: Male gender
Modifiable: Hypertension, hyperlipidemia, obesity, sedentary occupation (taxi driver)

Q2. Can you name additional 3 more risk factors for developing CAD?

Any 3 among the following:

Non-modifiable: Old age, family history of premature CAD, past medical history of stroke or peripheral vascular disease
Modifiable: Smoking, alcohol, diabetes mellitus, stress

One day, while having lunch at a food court with his wife, Mr. Sim suddenly felt a tight crushing sensation in his chest, radiating to his left arm and jaw. This was accompanied by profuse sweating and a nauseous feeling. Mr. Sim's wife noticed that his face had turned pale and he was also very breathless. She called 995 and was subsequently transferred to the hospital by the paramedics. At the hospital, an ECG was done for Mr. Sim:



Q3. What is Mr. Sim's diagnosis, based on his symptoms? (Let's ignore the above ECG temporarily)

He is experiencing an **acute myocardial infarction**.

Let's explain the physiologic basis behind the symptoms experienced by Mr. Sim, specifically:

Q4. Diffuse non-localising chest pain

Mr Sim's chest pain is a direct result of myocardial ischemia, i.e. insufficient blood flow. The heart is a **visceral organ**; therefore its **stimuli for pain are different from those of a somatic organ such as the skin**. The major pain stimuli for visceral organs are threefold: (1) ischemia (as is the case here), (2) stretching and (3) inflammation.

Visceral pain is characterised by poor localisation on the body surface. This is in contrast to, for instance, a pin prick on the skin that is easily localised.

Q5. Radiation of pain to arm and jaw

Radiation is a consequence of **referred pain from the heart**. There are a number of proposed mechanisms for referred pain, one of which is the convergent-projection theory which proposes that visceral afferent fibres (from the heart for example) converge to the same spinal nerve as somatic afferents that innervate the skin at specific dermatomes. Hence, **visceral pain from an organ will be felt at the corresponding somatic dermatomes that converge to the same spinal segment**.

Pain from visceral organs typically travels retrograde towards the spinal cord via sympathetic fibres, with the exception of organs below the pelvic pain line. Sympathetic innervation of the heart that normally serves to increase contractility, heart rate and so forth is derived from the C7-T4 spinal segments (there will be variations quoted between different anatomy textbooks). Hence pain from the myocardium is reflected in those dermatomes. **The entirety of T1 and part of T2 dermatomes are contained at the medial aspect of the arm, which explains radiation to those segments.**

Q6. Sweating and nausea

Sweating is a result of **sympathetic stimulation to sweat glands in the skin**, which can be explained by **increased sympathetic discharge by the body**. There is a transient fall in Mr Sim's cardiac output following a drop in contractility due to ischemic injury to his myocardium. As contractility falls, stroke volume decreases (SV is a function of preload, contractility and afterload) and so does the cardiac output (CO = SV x HR) and eventually blood pressure (BP = CO x SVR). The physiologic response to a transient drop in blood pressure is adrenergic stimulation to the heart and peripheral arterioles – which also affects his sweat glands.

Nausea is a result of a visceral nociceptive stimulus, which in this case is myocardial ischemia (recall the 3 main nociceptive stimuli from above).

Q7. Paleness and breathlessness

His pale appearance ("pallor") is a result of the adrenergic stimulation to peripheral arterioles (via alpha 1 receptors) that causes peripheral vasoconstriction to maintain cardiac output.

In this scenario, the myocardial insult has probably been too acute and extensive for complete compensation by sympathetic stimulation. As a consequence, there is pulmonary congestion from the backward accumulation of blood due to left ventricle impairment from the acute myocardial infarction. This gives rise to **shortness of breath**.

Back to the above ECG…

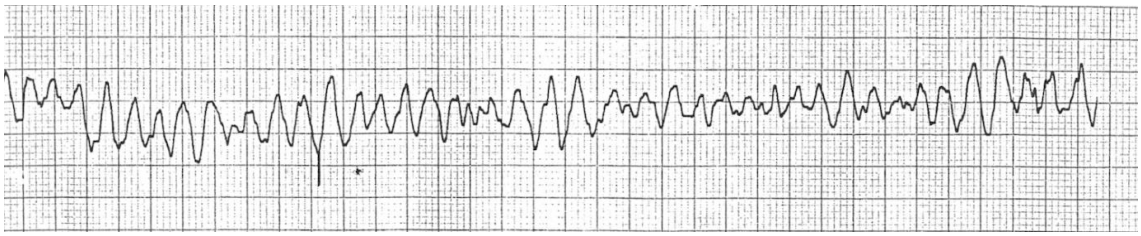
Q8. What did the above ECG show?

He is suffering from an **anterolateral** ST-elevation myocardial infarction (STEMI).

His ST segments – the portion of the ECG between the QRS complex and T wave – in leads V1 to V6, I & aVL are raised with respect to the baseline. ST segment is, as its name suggests, suggestive of a STEMI. These leads overlie the **anterior** (V1 to V4) and **lateral** (V5, V6, I, aVL) surfaces of the left ventricle, hence the localization of the infarct to the anterolateral aspect of the heart.

Additionally, the T waves in leads V2 to V6 are peaked and tall (these are termed "hyperacute T waves") with especially deep Q waves in leads V1 & V2 ("pathologic Q waves").

10 minutes after reaching the hospital, the cardiac monitor attached to Mr. Sim started to beep very loudly. Mr. Sim became unresponsive and his blood pressure was undetectable. His ECG shown on the cardiac monitor was:



Q9. What has happened to Mr. Sim? Give the ECG diagnosis and clinical diagnosis.

Mr Sim's ECG shows **ventricular fibrillation**. Clinically, he has gone into **cardiogenic shock**.

Q10. Physiologically speaking, why did he become unresponsive with undetectable blood pressure?

Ventricular fibrillation is a potentially fatal condition whereby uncoordinated contraction of individual ventricular myocytes results in an **inability of the heart to act as an effective pump**. Recall that the pump mechanism demands coordinated contraction of individual myocytes to eject blood from the ventricle. As a result his **cardiac output is virtually zero**, i.e. no fresh blood is being circulated around his blood vessels! As BP = cardiac output (CO) x systemic vascular resistance (SVR), such a drastic and acute fall in cardiac output will send his blood pressure plunging. This is obviously

disastrous because hypoperfusion to vital organs (most notably the brain) can result in irreversible injury within minutes.
Electrical defibrillation was commenced, and after successful resuscitation by the medical team, Mr. Sim was transferred to the cardiac catheterization laboratory for immediate percutaneous coronary intervention to relieve the acute blockage in the coronary artery. He was subsequently warded in the coronary care unit (CCU).

At the CCU, Mr. Sim was examined by the medical officer and a medical student, who both noted the following findings on physical examination: normal first and second heart sound, with a pan-systolic murmur heard loudest at the apex of the heart. Inspiratory lung crepitations were also heard. The MO explained to the medical student, that the findings were consistent with mitral regurgitation and acute pulmonary edema.

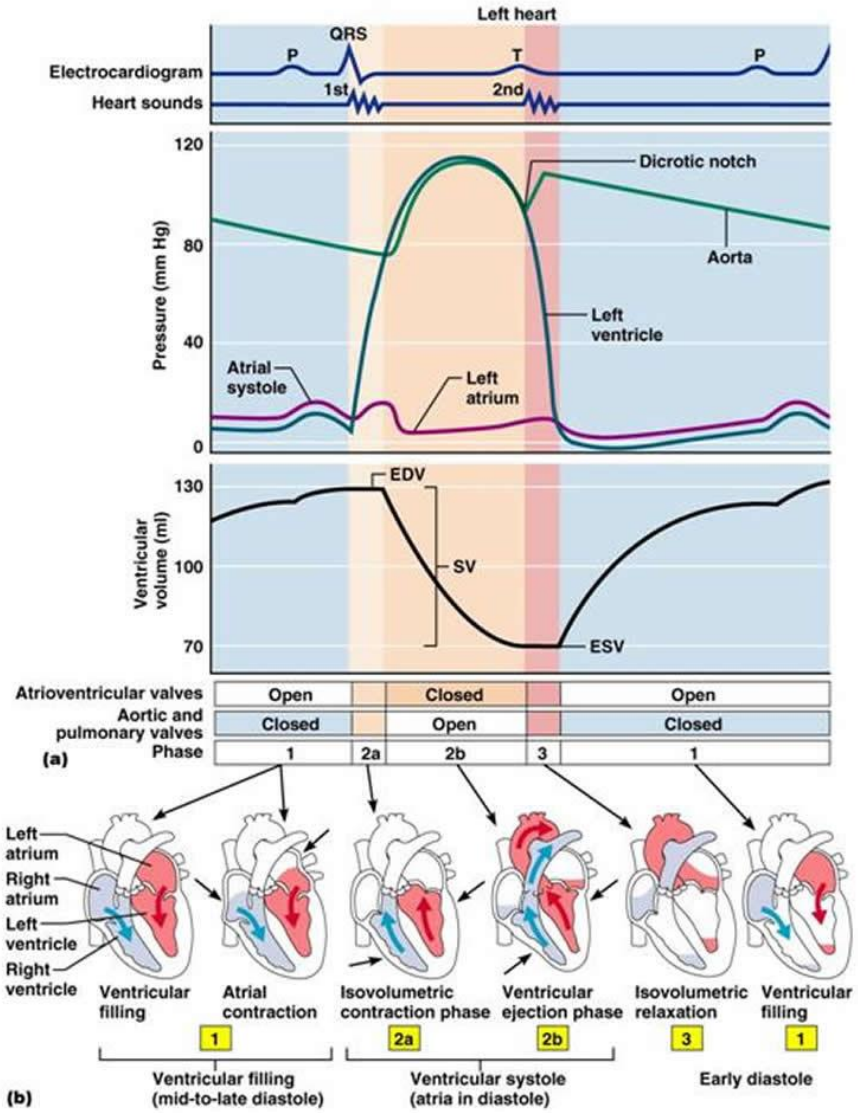
With regard to the mitral regurgitation…

Q11. What was the cause?

Mitral regurgitation is the result of the acute myocardial infarction, with resultant ischemia, necrosis and **rupture of the papillary muscle**. This resulted in an incompetent (leaky) mitral valve which lets blood flow backwards from the left ventricle to left atrium during systole, although it is supposed to remain shut.

Q12. How did the mitral regurgitation result in a systolic murmur, and not a diastolic one?

The closure of the mitral valve occurs at the very start of systole, for left ventricular pressure to increase rapidly when the ventricular myocardium contracts against closed mitral and aortic valves in a normal heart. However, with a "leaky" mitral valve, the **rapid rise in left ventricular pressure is transmitted backwards to the left atrium in early systole**. The turbulent flow of blood through the defective mitral valve gives rise to the murmur. It is hence logical that this **murmur will be heard all the way until systole is complete, as the ventricle continually contracts against its pool of blood that backflows into the left atrium**. Recall the different phases of the cardiac cycle, which is divided into systole and diastole. The often-quoted diagram is as follows:



http://classes.midlandstech.edu/carterp/Courses/bio211/chap18/chap18.html

The first defining event of systole is the closure of the atrioventricular valves (mitral & tricuspid), which gives the S1 heart sound. The continued contraction of the ventricle causes a sharp rise in intraventricular pressure that eventually opens the semilunar valves (aortic & pulmonary) that rapidly ejects blood from the ventricles. As intraventricular pressure falls from the ejection of blood into the aorta and pulmonary artery, the intraventricular pressure eventually dips below the diastolic blood pressure. When this happens, the semilunar valves close – this gives the S2 heart sound and defines the end of systole. In early diastole, the ventricles relax against closed AV and semilunar valves. The AV valves eventually open, causing rapid filling of blood from atria into ventricles. The last event in diastole is the contraction of the atria, which pumps the remaining blood from atria into the ventricles. A new cycle of systole then begins, starting with closure of the AV valves.

Q13. The potential complications of the mitral regurgitation include: left atrial enlargement, pulmonary hypertension and right heart failure. How would these complications arise?

Left atrial dilatation is due to a remodeling process of the left atrium, from retrograde ejection of blood from the left ventricle into the atrium even during systole, to increase the containing capacity of the left atrium.

Pulmonary hypertension is, as with the acute pulmonary edema explained above, a consequence of backpressure buildup from the left heart towards the pulmonary circulation from left heart failure. Chronic fluid overload of the pulmonary circulation causes remodelling to contain the backpressure buildup.

Right heart failure would result from chronic contraction of the right ventricle against an increased afterload, a consequence of pulmonary hypertension, that results in physiologic decompensation over time. The most common cause of right heart failure is left heart failure.

Q14. Explain how Mr. Sim developed pulmonary edema, using the Starling forces. What are the complications of pulmonary edema?

The acute myocardial infarction has resulted in impaired myocardial contractility, resulting in increased backpressure buildup from the left heart into the pulmonary circulation. In addition, with mitral regurgitation, there is an increased backflow of blood into the pulmonary circulation. These factors **increase the hydrostatic pressure within pulmonary capillaries**, which by Starling forces, causes an acute increase in fluid movement from the intravascular compartment into the pulmonary interstitium – explaining his pulmonary edema.

Mr. Sim was given supplementary oxygen support, and he was also treated with inotropic agents (to increase cardiac contractility) and furosemide in-patient. His echocardiography results on Day 5 of admission showed regional wall motion abnormality (reduced movement of one portion of the heart compared to the other), moderate mitral regurgitation, left ventricular apical thrombus and an ejection fraction of 35% (normal EF: 55% and above). In view of the thrombus formation, Mr. Sim was started on heparin.

Q15. What do you think resulted in the thrombus formation in the heart? Briefly describe, using your knowledge regarding the normal mechanisms in blood clot formation.

There is a tendency towards thrombosis, because of the hypokinetic segment of the left ventricle that has infarcted.

A blood clot is formed from two processes: platelet plug formation & the coagulation cascade. To facilitate recall: the first step in platelet plug formation is activation of the platelets, by their binding to either a damaged endothelial surface (by platelet's GP Ia/IIa) or von Willebrand factor (via GP Ib/V/IX). Activation of the platelets is the second step, mediated by ADP binding to the ADP receptor on the platelet surface. Finally aggregation occurs, facilitated by GP IIb/IIIa that binds to fibrinogen.

The coagulation cascade is meant to stabilize the initial platelet plug formed, and is activated by two pathways: the intrinsic and extrinsic pathways which both result in the conversion of fibrinogen binding the platelets together to a more-stable fibrin that becomes cross-linked. Normally these hemostatic processes are inhibited by continuous laminar flow of blood, because the platelets and coagulation factors do not adhere to their target surfaces for a sufficiently long period of time for any significant platelet plug to form (they're continually swept away by bloodflow!). In a hypokinetic segment of myocardium, however, blood stasis occurs which allows for a thrombus to form.

Q16. Using your knowledge of anatomy, if the ventricular thrombus dislodges from the heart, what are the potential complications?

The main complication is **embolism**, where the thrombus is dislodged from the ventricular lumen and is swept into the systemic circulation. It can then lodge itself in smaller arteries, where is obstructs the downstream flow of blood. End-organ hypoperfusion causes ischemic injury, which at worst results in death of the organ. Clinically important embolic destinations include:

Brain, resulting in an ischemic stroke.
Lower limb arteries, resulting in acute limb ischemia.

Q17. Explain how heparin is effective in treating the thrombus.

The mechanism of heparin is such that it **activates AT III**, which cleaves coagulation factors II, VII, IX, X, XI and XII and therefore **slows down the rate of both intrinsic and extrinsic pathways** of the coagulation cascade. This buys additional time for the above anti-thrombotic mechanisms to lyse the thrombus.

Q18. How does ejection fraction affect cardiac output? What is the clinical significance of knowing the ejection fraction of the heart?

The **ejection fraction** is formally defined as the stroke volume divided by left ventricular end-diastolic volume. In simpler terms, it is the percentage of blood that is ejected from the left ventricle during each cycle of systole. Recall that cardiac output (CO) = heart rate (HR) x stroke volume (SV). Stroke volume is a function of three components: preload, contractility and afterload. With a reduction in ejection fraction, there will thus be a reduction in ejection fraction.

Its **clinical significance** lies in that it is a proxy for myocardial function of the left ventricle. A decrease in ejection fraction is an indicator of left heart systolic failure, as it shows that the role of the left ventricle as a pump has been compromised. The normal EF value is at least 55%.

Mr. Sim was subsequently discharged from the hospital 3 days later. He was converted to warfarin instead of heparin treatment, and was also prescribed antihypertensive, lipid lowering agent, dual antiplatelet agents and referred for outpatient cardiac rehabilitation. He was given a 2 weeks clinic appointment to see his cardiologist for monitoring of his condition.

Q19. What are the possible long-term outcomes for Mr. Sim?

[Again, not required for M1s to know for exam purposes, but for early exposure.]

In the long run, complications result from weakening of the ventricular myocardium:
- Congestive heart failure
- Ventricular aneurysm
- Embolism of the ventricular thrombus
-Recurrent ventricular thrombosis
- Recurrent myocardial infarction

Source of ECGs: http://www.lifeinthefastlane.com/ecg-library

CASE 3 | EXERCISE INTOLERANCE

Mr. Mai Cheong Suah is a 51-year-old Chinese male. He has been smoking cigarettes since his army days, starting from "a few packs every day" when he picked the habit up, although he has managed to cut down to a one or two packs per day owing to financial constraints.

Mr. Mai works in the food catering industry. He and his team of men provide manual labour to set up buffets around Singapore; this mainly involves setting up the buffet line at event venues, which entails carrying heavy tables, chairs, food items and the drink containers around. Over the past two years, though, he noticed himself needing to stop and catch his breath much more frequently during such event setups. Whilst he once prided himself in being able to "tank" an entire event setup alone in his younger days, his 51-year-old self now wonders if this decrease in stamina is simply part of growing old. Regardless, he now has a team of younger men under him, on whom he increasingly relies for most of the manual work.

You have recently gotten to know Mr. Mai as a medical student in charge of catering food for a school event. In waiting for the buffet setup Mr. Mai, aware of your university major, talks to you about his condition as he is increasingly concerned about its impact on his job. On further questioning, he reveals he has been coughing intermittently for the past few years with significant phlegm production – enough to warrant clearing his throat onto the roadside every now and then. You wonder if he has Chronic Obstructive Pulmonary Disease (COPD).

COPD is classified as an "obstructive" lung disease. There are three important pathological components of COPD in reaction to prolonged exposure to cigarette smoke: chronic bronchitis (hypersecretion of mucus in airways), chronic bronchiolitis (inflammatory small airways thickening) & emphysema (progressive destruction of elastic alveolar walls).

Q1. For each chronic bronchitis & emphysema, separately consider how the (a) airflow within the airways and (b) exchange of gas at the alveolar-capillary membrane are affected.

	Chronic bronchitis	Emphysema
(a) Airflow within airways	There is significant airflow limitation, due to hypersecretion of mucus in both the large and small airways, with mucus plugging, inflammatory edema and fibrosis of the bronchiolar wall. Intermittent bronchospasm can also be present.	Destruction of elastic tissue in lung parenchyma results in decreased elastic recoil, resulting ineffective expiration of air.

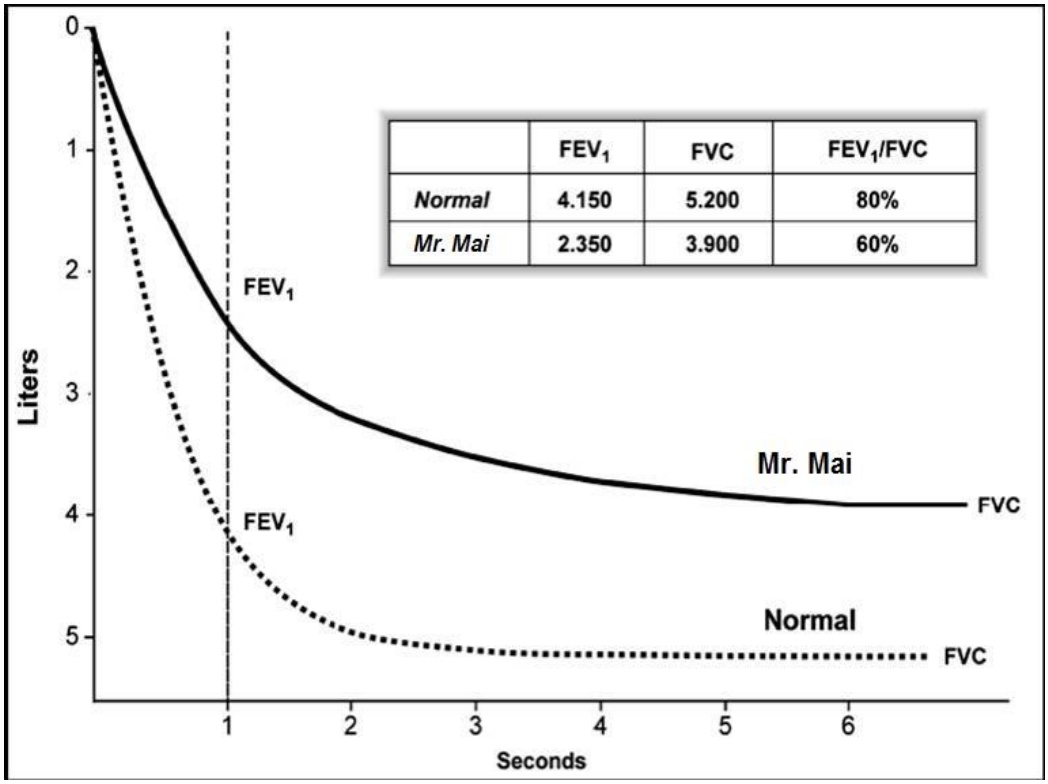
(b) Gas exchange at alveolar-capillary membrane	There is no significant limitation in gas exchange with bronchitis alone, but chronic bronchitis is often associated with coexistent emphysema, which can limit gas exchange.	There is a marked loss of alveolar wall, which greatly decreases the surface area for gas exchange and hence the diffusing capacity of the lung.

Q2. COPD patients with predominant chronic bronchitis or emphysema are sometimes described as being "blue bloaters" or "pink puffers" respectively. Explain these terms and comment on the degree of respiratory failure present in these patients.

Pink Puffers are COPD patients with predominantly **emphysema**, so the main problem is ineffective gas exchange because of the loss of elastic recoil and loss of alveolar surface area. The loss of elastic recoil can be compensated for by "puffing" by pursed-lip breathing; pursing your lips will increase the expiratory intra-airway pressure (just like how pinching the end of a hose increases the backstream water pressure) to expel air from the airways to the external environment. Therefore, they are still "pink" because they are only mildly hypoxemic due to less severe air trapping and minimal carbon dioxide retention. These patients typically have type 1 respiratory failure i.e. hypoxemic but not hypercapnic.

Blue Bloaters are COPD patients with predominantly **chronic bronchitis**, so the key problem is airflow limitation (as discussed above) with trapping of "stale air" within alveoli that have been plugged by mucus which increases dead space within lungs, giving a pathologic **V/Q mismatch**. There is minimal impact on gas exchange at the level of alveoli. They are blue because compensatory mechanisms such as hyperventilation cannot compensate for this V/Q mismatch; they become markedly hypoxemic which results in large amounts of circulating deoxyhemoglobin that result in the bluish discoloration. They have a "bloated" appearance because they are often barrel-chested from the air trapping and poor ability to compensate. These patients typically have type 2 respiratory failure i.e. hypoxemic and hypercapnic.

There are a number of parameters we can use clinically to assess lung function. The forced expiratory volume in 1 second/forced vital capacity ratio (FEV1/FVC) is an assessment of the degree of obstruction in airways. The diffusion capacity of carbon monoxide (DLCO) assesses the capacity for gaseous exchange at the alveolar-capillary interface.



	FEV_1	FVC	FEV_1/FVC
Normal	4.150	5.200	80%
Mr. Mai	2.350	3.900	60%

Q3. Shown here is Mr. Mai's FEV1/FVC curve. His DLCO (a measurement of total diffusion capacity) is at 50% of normal predicted. Explain (a) Mr. Mai's derangements in all the above parameters and (b) how they might differ in a patient with "restrictive" lung disease.

(a) Mr Mai's **FEV1/FVC is lower than the normal predicted value** (<0.80). This is indicative of an obstructive airway disease, where FEV1 is lowered to a greater extent compared to FVC hence decreasing the ratio. In normal people, most of the air is expired within the first second. This amount of air, however, takes longer to exhale in patients with obstructive lung diseases, thereby resulting in a lowered FEV1. **DLCO is reduced**, due to the emphysematous process which destroys the interalveolar septae, hence reducing surface area for gaseous exchange at the level of the alveoli.

(b) Restrictive lung disease is characterized by reduction in lung compliance and increase in elastic recoil from fibrosis, resulting in an inability to expand the lung, and a reduction in total lung capacity and FVC. There is no airflow obstruction, and thus FEV1 would not be affected. **FEV1/FVC will be normal or increased**. **DLCO would be normal** as well, as there is no change in the surface for gaseous exchange.

You advise him to seek medical help from a qualified doctor, which he refuses to heed because of his inherent dislike to approach healthcare professionals in a daunting clinical setting. It is not until many years later that you, as a Medical Officer in the Emergency Department, with another medical student by your side encounter Mr. Mai again. He rehashes the same story of progressive worsening of his exercise tolerance over many years. However following a recent "flu" he caught over the past few days, his symptoms have dramatically worsened, and now experiences shortness of breath even at rest which made him seek medical attention. He also noticed that he has been catching the "flu" more frequently. You take a look at Mr. Mai.

With your knowledge of physiology, explain the following observations.

Q4. His "barrel chest", that appears larger compared to the thorax of a normal person

Barrel chest (an increase in anterior-postero diameter of the chest) is indicative of **hyperinflation of the lungs**. This is due to obstruction of the airways, causing entrapment of the air in the alveoli, and an increase in residual volume of the lung. Air trapping occurs during expiration, when the positive intrathoracic pressure leads to the collapse of airways that have already been narrowed from mucus hypersecretion. This does not occur during inspiration because the negative intrathoracic pressure keeps the airways patent.

Q5. His pursed-lip breathing

Pursed-lip breathing helps to **increase expiratory intra-airway pressure**, which firstly inhibits expiratory airway collapse and secondly helps to compensate for the loss of elastic recoil by destroyed lung tissue. Recall that in COPD, there is an increase in airway resistance, which markedly increases the work of breathing. Compressive forces during expiration compresses not just the alveolar, but also the bronchioles, which also adds to increasing the airway resistance during expiration.

Q6. A bluish appearance to his lips

The patient is cyanosed, with an **excess of deoxygenated hemoglobin** in the circulation. Cyanosis is usually visible when there is >5grams of deoxygenated hemoglobin in 100mL of blood. Mr Mai has severe COPD, with a marked reduction in the diffusing capacity of his lungs, resulting in a reduced ability of the lungs to oxygenate the blood.

Q7. Increased respiratory rate, pulse rate and use of other muscles (e.g. the sternocleidomastoid) to breathe, with his hands on his lap

These are results of both physiological as well as conscious compensation for respiratory failure.

The increased respiratory rate and pulse rate reflect the physiological compensatory mechanisms to **improve oxygen delivery to peripheral tissues.**

The use of other muscles and the placing on hands on laps reflect Mr Mai's attempt to maintain airflow to his lungs despite them already being hyperinflated. Additional effort is required for further inspiration of air given the large residual volume in COPD. This **increased work of breathing** results in the recruitment of accessory respiratory muscles. The placing of Mr Mai's hands on his laps helps to stabilize and fix the arms, scapulae and clavicles. This optimizes the mechanical action of the respiratory muscles to bring about greater chest expansion and more effective inspiration.

Q8. Suggest possible reasons for the increasing frequency of Mr. Mai's "flu".

These are infective exacerbations of COPD. Mr. Mai may be at **greater risk of infection** due to depressed ciliary function, increased mucus secretion, chronic irritation and inflammation of the epithelial surfaces, all of which are known effects of smoking. Because of reduced reserve lung physiologic capacity, similar insults may now manifest more easily as respiratory compromise or failure.

Being the good doctor that you are, you complete the rest of your physical examination and note the presence of wheezes with decreased air entry bilaterally and a prolonged expiratory phase when listening to his chest with your stethoscope.

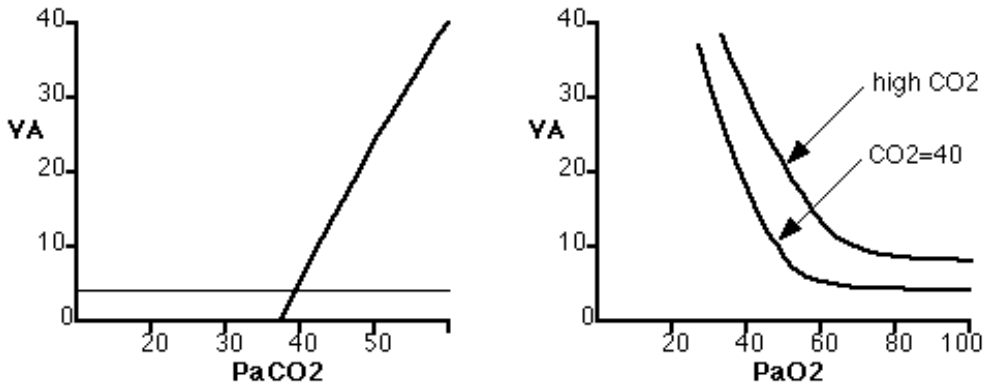
The medical student attached to your clinic suggests administering 100% oxygen to Mr. Mai. However, with your years of clinical experience, you decide this is a bad idea, and instead administer oxygen at a lower dose. You explain to the medical student that COPD patients rely on oxygen, instead of carbon dioxide, as the main drive behind their respiratory rate.

Q9. In a normal person, how is the rate of ventilation regulated? Is oxygen or carbon dioxide normally the primary driver of a person's respiratory rate?

An individual's ventilatory drive is a function of three dissolved substances in the blood: **(1) CO_2, (2) oxygen and (3) H^+ ions**. Two sets of chemoreceptors are present to detect these substances. The **central chemoreceptors in the medulla are sensitive only to CO_2** – CO_2 crosses the blood brain barrier where it dissolves to form carbonic

acid and dissociates to form H^+ in the CSF, which is detected by central chemoreceptors. However, **peripheral receptors, located at the aortic and carotid bodies, sense all 3 substances with O_2 being the main substance detected**. All chemoreceptors will communicate information to the respiratory centre in the medulla to alter one's breathing rate.

Respiratory rate is increased by high [CO_2], lower [O_2] and increased [H^+]. **The main driver of a person's respiration, however, is the increased concentration of carbon dioxide**. This is because of the nature of the body's response to CO_2 and O_2:



http://www.anaesthesia.med.usyd.edu.au/resources/lectures/ventilation_clt/ventilation.html

When [CO_2] rises, minute ventilation rises linearly. However when [O_2] falls, the change in minute ventilation is minimal until pO_2 has significantly dropped to <60mmHg! Therefore at physiologic conditions, the body is more responsive to [CO_2] in the blood. This is unless a patient has become severely hypoxemic, in which case the hypoxemia plays a significant role in the respiratory drive as well.

Q10. Consider the effect of administering 100% oxygen to Mr. Mai. What physiological consequences are there to this decision?

The major adverse effect is that administering 100% O_2 is likely to restore his O_2 saturation back to "normal", causing a cessation in respiratory drive and consequent inability to compensate for his pre-existing respiratory failure.

In chronic CO_2 retention, the respiratory acidosis eventually becomes compensated by an increase in bicarbonate, resulting in a lower concentration of H^+ ions for the same level of CO_2 in the blood. This **blunts the compensatory response by the central chemoreceptors and causes the regulation of respiratory drive to become dependent on O_2 levels instead**. By giving 100% O_2, saturation is likely to be restored to normal levels (>97%), further reducing respiratory drive and leaving the patient with no means of compensation for the hypoxemia and hypercarbia.

There are also minor reasons against administering oxygen. For instance, lung oxygenation is known to cause pulmonary vasodilation as a normal physiologic response to shunt blood towards well-ventilated portions of the lung. However in COPD patients, mucus plugging and V/Q mismatch are already present so the above may worsen V/Q mismatch further. Also, the Haldane effect is weakened by a higher pO_2; this in summary means that the blood is less able to carry CO_2 when it is well-oxygenated, contributing further to CO_2 retention within the blood and worsening of hypercarbia.

Q11. You also considered the option of putting Mr. Mai on positive pressure ventilation. How might this help?

This works by the same principle as pursed-lips breathing and helps prevent airway collapse by providing **positive intraluminal pressure to overcome the positive intrathoracic pressure**. Maintaining airway patency alleviates the problem of air trapping and improves tidal volume and reduces residual volume, achieving better overall ventilation.

You make the choice to admit Mr. Mai to an inpatient setting, where he is formally diagnosed with COPD and started on therapy, and is counselled to stop smoking.

A few years down the road, Mr. Mai returns to the Emergency Department on your shift. This time, he complains of an acute-onset stabbing left-sided chest pain that began about an hour ago. This was accompanied by an onset of shortness of breath at rest too. Worried it may be a "heart attack", he called for a taxi to fetch him to the hospital.

You note a shift in his trachea towards the right side, as well as an apex beat at the left lower sternal edge. There was a visible decrease in chest expansion on the left side after Mr. Mai removed his shirt, together with hyperresonance on percussion and almost no breath sounds on the left. His blood pressure was also low. You recognise this as a tension pneumothorax.

Using your understanding of the anatomy of the thorax, explain the following.

Q12. Tracheal deviation towards the right, with a shift in his apex beat in the same direction

The heart is a component of the mediastinum, with the trachea above it extending into the neck. The shift of both structures towards the right suggests that the pneumothorax on the left has become large enough to **exert significant pressure on these midline structures, to shift them to the contralateral side**.

Q13. Hyperresonance on percussion with markedly decreased breath sounds on the left side

The degree of resonance is directly proportional to the amount of air in the lungs. An analogy would be tapping a hollow structure; structures with more air in them tend to produce a more "hollow" (i.e. resonant) sound.

The lungs are the largest organ in the left-sided thoracic cavity. A lung consists of mainly two things: (1) air and (2) parenchyma; the percussion note that doctors hear upon striking the chest is formed because of a balance between these two things that make up lung tissue. With a left pneumothorax, there is an **increased proportion of air in the left-sided thoracic cavity and decreased lung tissue (as the ipsilateral lung collapses)**, so the percussion note will appear to be hyperresonant.

Q14. Low blood pressure

In tension pneumothorax, there is a mediastinal shift resulting in compression of the major veins (SVC and IVC) and disruption of venous return to the heart. This **reduction in preload** leads to a decrease in cardiac output and eventual fall in blood pressure. Respiratory and cardiac arrest may occur if patient is not attended to in time.

Q15. Explain the acute onset of his shortness of breath. How is this different from the progressive dyspnea and decrease in exercise tolerance Mr. Mai first experienced when he was diagnosed with COPD?

A pneumothorax is an acute process; the collapse of the ipsilateral lung can take place in a matter of minutes to hours if left untreated. The potential loss of half the body's healthy lung tissue in such a short span of time allows for **little time for any physiologic compensation to occur**, so the symptoms of a pneumothorax will be felt very quickly.

On the other hand, COPD is a chronic disease. It takes decades for the pathophysiologic processes underlying COPD to exert their influence and produce a sufficient degree of alveolar hypoventilation and impaired diffusion, to become symptomatic. Compensatory mechanisms kick in – for instance, the so-called "pursed-lip breathing" – to allow for better alveolar ventilation during that period of time. It is only when these compensatory mechanisms are no longer able to sustain a sufficient level of gaseous exchange that symptoms will be felt many years later.

Q16. Why might a COPD patient be predisposed to a pneumothorax?

Some patients with emphysema develop bullae (aka air bubbles!) in their lungs. This is because **destruction of the interalveolar septa allows the air spaces to coalesce and form large pockets of air in the lungs**. The walls of these bullae are relatively weak, due to the underlying chronic destructive process of emphysema. Rupture of these bullae allows air to enter the pleural cavity from the lungs – giving rise to a pneumothorax.

Mr. Mai is once again admitted. Following the resolution of his tension pneumothorax, the House Officer overseeing his care notes some pitting edema bilaterally over his shins, together with a raised jugular pressure and signs suggestive of ascites. There was also a parasternal heave. You realise you have missed these signs owing to the urgent nature of Mr. Mai's tension pneumothorax. These signs are suggestive of right heart failure.

Q17. Right heart failure secondary to lung pathology, also known as cor pulmonale, may result from longstanding unresolved lung pathologies. Consider the physiology explaining how poor alveolar ventilation in the long-term may result in the development of right heart failure.

It is the normal physiologic response of the pulmonary capillary beds to constrict in response to hypoxia of the part of the lung it perfuses. In the context of COPD, **because alveolar ventilation is poor throughout all lung tissue, there is generalised vasoconstriction of all pulmonary capillaries**. Recall that resistance is inversely proportional to diameter to the power of 4 – any amount of vasoconstriction will significantly increase the resistance of the pulmonary vasculature! This increases the afterload against which the right ventricle has to pump. Over time, there is decompensation of the right ventricle, giving rise to right heart failure.

While this vasoconstriction may seem counter-productive (even deleterious!) in the context of diffuse lung pathologies like COPD, consider the physiologic role of this response. When a specific portion of any lung tissue is poorly oxygenated, say due to a lobar pneumonia, it makes physiologic sense to divert blood away from that poorly oxygenated part of the lung. This is because blood can be shunted towards healthy lung tissue for optimal gas exchange, instead of being "wasted" by passing through diseased lung tissue where gas exchange is poor.

On further history taking, it is realised that Mr. Mai has not been compliant with his discharge plans, in particular smoking cessation, resulting in a worsening of his COPD. After being scared by this acute pneumothorax episode, Mr. Mai vowed to quit smoking for good on further counselling by his primary team.

CASE 4 | RIGHT UPPER QUADRANT PAIN

You are the house officer in the general medicine ward clerking the new admissions for the day's ward rounds. A new 23 year old patient, Mr Koh Kane, has been admitted from the emergency department the night before for a complaint of fever and vague right upper quadrant pain.

As you are asking him about his symptoms, you notice needle-track marks on his right antecubital fossa and you begin to suspect that Mr Koh may be an intravenous drug abuser. With some difficulty, you manage to obtain a positive history of intravenous drug abuse, and that he has been sharing needles with some of his friends. Mr Koh also complains that he has had some vomiting and loss of appetite when the symptoms came on several days ago.

On examining his abdomen, you find that he has a diffusely enlarged and slightly tender liver, suggestive of acute liver inflammation.

A hepatitis panel sent off by the emergency department also comes back positive for acute hepatitis B infection. Putting together the clinical risk factor of intravenous drug use as well as the acute symptoms, you decide that Mr Koh has contracted acute hepatitis B.

Q1. Given that the liver does not actually have pain fibres, why might Mr Koh be in pain?

The liver itself does not have pain fibres, but **the capsule** surrounding the liver is **sensitive to stretch**. Acute hepatitis causes the liver to swell, which stretches the capsule and produces pain.

Q2. Why is his pain poorly localized in the right upper quadrant?

The liver is **viscera** and thus experiences **visceral pain**. One of the features of visceral pain is poor localization, and patients may describe the pain as more dull or squeezing in nature.

Mr Koh makes an uncomplicated recovery in the hospital. Knowing the risk of chronic hepatitis B leading to liver cirrhosis and cancer, you advise Mr Koh to quit his drug abusing habits and come regularly for follow up with gastroenterology.

The years go by and you grow from a wee young house officer into a confident and compassionate gastroenterology consultant. A group of enthusiastic medical students that you are taking for tutorial request that you run through with them a case they recently clerked, a request you are more than happy to accede to.

They bring you to the bedside of a vaguely familiar man who you gradually recognize as Mr Koh. As the medical students present the case to you, you realise that Mr Koh completely ignored your advice and defaulted on all his followup appointments. As a result, he has developed liver cirrhosis and is gradually dipping further and further into liver failure.

Q3. What are the functions of the liver?

The functions of the liver can be broken down into 5 basic components

1. Synthetic Function
2. Excretory Function
3. Homeostatic/Metabolic Function
4. Anatomic Function
5. Immunologic Function

Synthetic Function

The synthetic function of the liver mainly concerns **protein synthesis** and **coagulation factor synthesis**

While the liver does make a whole host of proteins, the one that we deal with clinically is usually albumin. Albumin acts to increase the plasma oncotic pressure, thus retaining fluid intravascularly. (Remember starling's forces are basically a balance between hydrostatic pressure and oncotic pressure)

Coagulation factor synthesis is also a major component of liver function. With the exceptions of fator 8 and von willebrand factor, the rest of the factors are synthesized by the liver. Factor 7 has the shortest half-life (3-6h) and will thus decrease first in acute liver failure.

Excretory Function

The excretory function of the liver refers to its ability **to break down toxic substances**, make them **water soluble** and **secrete them into the bile**.

Bilirubin is a breakdown product of the heme that is released from red blood cells when they die. It is made water soluble by conjugation with glucuronide in the liver, then excreted into the bile where it undergoes enterohepatic circulation. A failure to excrete bilirubin causes jaundice, because bilirubin has a yellowish tinge.

Nitrogenous waste, of which ammonia is the major component, is also removed from the body through the urea cycle. The urea cycle converts ammonia, a fairly centrally toxic substance, into urea, which is less toxic to the body (though by no means perfectly safe! High urea in renal failure patients leads to uremia, which can kill patients).

Estrogen is also deactivated in the liver, and tends to build up in liver failure patients. This leads to signs of hyperestrogenism such as palmar erythema, spider naevi, gynecomastia, loss of axillary hair and testicular atrophy.

Drugs are both deactivated (inactive metabolite) and activated (active metabolite) by the liver depending on the specific drug being metabolized. All drugs that are absorbed through the GI tract enter the portal circulation and go through the liver for metabolizing first (first pass effect). Thus, some drugs accumulate and become toxic in liver failure patients.

Homeostatic/Metabolic Function

The liver plays a crucial role in maintaining **blood glucose** and **body temperature** due to its high metabolic function.

Hepatic stores of glycogen are generated when a person is well fed, and consumed to maintain blood glucose when a person is fasting. The liver also converts circulating lactate back into glucose (cori cycle), which helps to maintain blood glucose levels during periods of exercise.

The high metabolic activity of the liver also contributes to thermogenesis, helping the body to maintain temperature homeostasis. Body temperature is actually a clinically used measure of transplanted liver function.

Other important metabolic functions of the liver include the synthesis of lipoproteins, ketogenesis and amino acid metabolism.

Anatomic Function

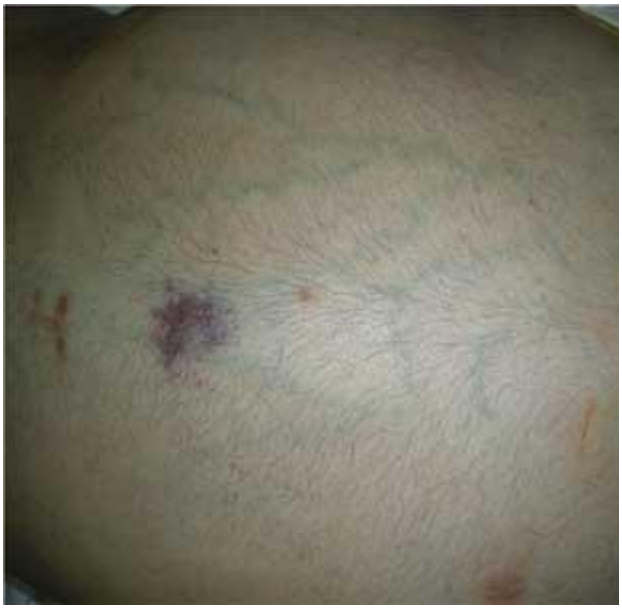
The liver acts as a conduit for blood from the portal circulation to reach the systemic circulation. This keeps the portal circulation at low pressure and reduces the blood flow through the portosystemic shunts.

Immunologic Function

All blood from the gastrointestinal tract passes through the liver before it reaches the systemic circulation. This blood flows through the liver sinusoids, and the parasinusoidal kupffer cells (macrophages) respond to toxins and bacteria to prevent them from entering the systemic circulation.

The liver also acts a secondary hematopoietic organ and can help to make red blood cells when the bone marrow fails or when red blood cells are rapidly broken down.

You run through Mr Koh's history and discover that he has been admitted this time round because he had an episode of vomiting large amounts of blood. You also notice that his abdomen looks like this



Q4. What do you see on this patient's abdomen? What is this a sign of?

This is superficial abdominal vein dilatation, a sign called Caput Medusae (head of the medusa). It indicates that blood is being shunted from the portal venous system into the systemic circulation through pathways other than the liver. It is thus a sign of portal hypertension and can be seen as liver cirrhosis progresses and the orderly architecture of the liver is replaced by fibrous tissue.

The observant M1 may also note that the abdomen appears distended and there are some bruises over the abdomen, findings which are not uncommon in liver cirrhosis.

Q5. Why might this patient be more prone to bleeding from the upper GI tract? Are there other manifestations of portal hypertension?

Superficial abdominal veins aside, the other clinically significant portocaval anastomoses that allow blood to flow from the portal venous system back to the systemic circulation are located in the lower third of the esophagus and the rectum. When dilated, they are known as esophageal and rectal varices respectively.

The dilated veins of the esophagus are particularly prone to trauma and bleeding, particularly because liver cirrhosis patients are already coagulopathic to begin with. Esophageal varices can bleed extremely large amounts of blood and can be rapidly life threatening.

Other signs of portal hypertension might include ascites, which is a combined effect of the hypoalbuminemia and the back-pressure, as well as splenomegaly.

You continue with the physical exam for this patient and point out some of the physical signs below

Ecchymosis in the arm

Q6. Why might a patient with liver failure develop this?

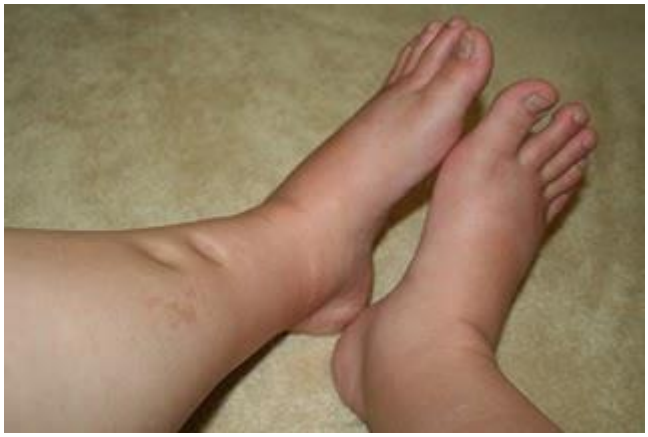
As mentioned earlier, the liver synthesizes most of the coagulation factors in the body. Liver failure patients thus gradually become more and more coagulopathic as the synthetic function of the liver decreases. This coagulopathy manifests itself as easy bruising, which is seen as ecchymosis on areas prone to trauma (eg. Limbs)

Q7. Cutaneous bleeding is usually not very worrisome, but bleeding in other parts of the body might be more problematic. Where else is he at risk of dangerous bleeding?

The main dangers of bleeding are **large volumes of blood loss** and **bleeding in the brain**.

Bleeding in the GI tract (noted earlier) is of particular significance because of the large amounts of blood that can be lost from it. GI bleeds are probably the most common sites of massive bleeding outside of a trauma situation.

Bleeding in the brain raises the intracranial pressure because the skull is a rigid space that cannot expand to accommodate the extra volume. This compresses the cerebral cortex and also pushes the brainstem out the foramen magnum, a process known as coning. This can be rapidly fatal because the cardiorespiratory centres in the medulla are compressed.



Pitting Edema (Limb swelling that leaves an indentation when you press on it)

Q8. Using what you understand of starling forces, why might there be pitting edema in a liver failure patient?

Recall starling's **hydrostatic** and **oncotic pressures** that regulate fluid movement between the intravascular and extravascular space. A high capillary hydrostatic pressure favors movement extravascularly, whereas a high capillary oncotic pressure favors movement intravascularly.

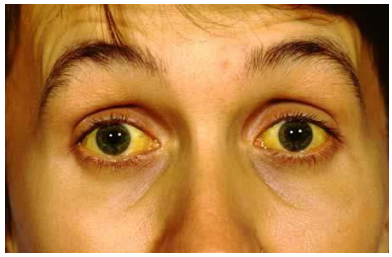
Liver cirrhosis patients have problems producing albumin, which decreases the capillary oncotic pressures and thus promotes fluid extravasation. This tends to happen in areas where capillary hydrostatic pressures are high (dependent portions of the body), so fluid tends to accumulate in the lower limbs first.

The extravasation of fluid causes the patient to be intravascularly dry and thus slightly hypotensive. The kidney's response to this is to retain salt and water, which perpetuates the development of edema. Treatment of edema in liver cirrhosis patients is thus a tricky job, because the patient is intravascularly dry but at the same time has too much total body water.

The pitting nature of the edema tells us that the edema is not due to lymphatic obstruction. What happens when you press on the edematous limb is that the fluid drains out through the lymphatic system, thus leaving the "pit" where the fluid used to be. If the edema was due to lymphatic obstruction, no pit would be left because no fluid is drained.

Q9. Where else might you expect to see swelling and fluid accumulation?

As noted earlier, fluid collection in the abdomen is also common due to the portal hypertension that develops in liver cirrhosis. As the disease progresses, the upper limbs may also become edematous.



Scleral Icterus (Jaundice)

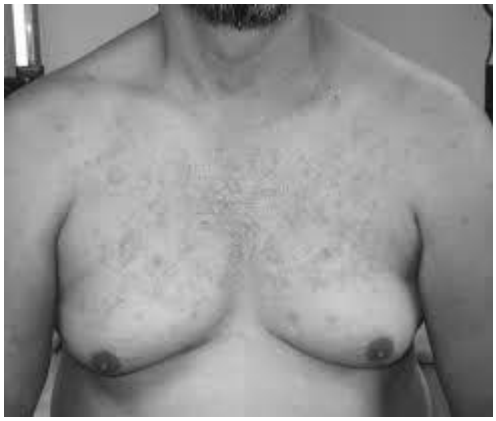
Q10. What substance, when accumulated in the blood, causes this?

The yellowish pigmentation of **bilirubin** is best seen against the whites of the eyes (the sclera), though in severe cases can be seen as a yellowish discoloration of the skin. When manifested in the skin, the jaundice progresses from the head, then to the thorax, abdomen and finally the lower limbs. In neonates, the lowest point of the jaundice can be used to estimate roughly how high the bilirubin level is.

Q11. What is the liver's normal method of getting rid of this substance? Why can't it be excreted unchanged?

Bilirubin is not regularly very water soluble. It must be conjugated with glucuronic acid in the liver to form conjugated bilirubin (bilirubin glucuronide), which is considerably more water soluble. This is then excreted into the bile and into the GI tract.

When conjugated bilirubin reaches the large intestine, it gets oxidized by colonic bacteria to urobilinogen, urobilin and stercobilin. Urobilin and stercobilin are excreted in the feces and give it its brown colour, whereas some urobilinogen is reabsorbed and excreted in the urine, which gives urine its yellow colour.



Gynecomastia (Male breast tissue development)

Q12. Failure of the liver to deactivate what hormone might cause this?

Failure of the liver to deactivate estrogen results in gynecomastia, palmar erythema, spider naevi, loss of axillary hair and testicular atrophy in male patients with liver cirrhosis.

After demonstrating these and other physical signs of liver failure, you remind your students of a potentially life threatening complication of liver failure known as hepatic encephalopathy.

This develops when there is a buildup of nitrogenous waste in the blood, which crosses the blood brain barrier and results in confusion, coma and even death.

Q13. How does the body get rid of waste nitrogenous compounds? Why might they accumulate in liver failure?

The body's means of removing waste nitrogenous compounds is through the urea cycle, which takes place in the liver. The urea cycle converts ammonia, a fairly toxic compound, into urea, a relatively less toxic compound. This is then excreted in the urine.

Liver cirrhosis patients gradually lose their ability to excrete ammonia as well, which can precipitate hepatic encephalopathy.

Having concluded your tutorial, you thank Mr Koh for his time and patience with you and your students and wish him a speedy recovery.

Images from: http://www.czytelniamedyczna.pl/4732,caput-medusae-in-alcoholic-liver-disease-case-report.html

http://medicalpicturesinfo.com/icterus/

http://library.med.utah.edu/WebPath/jpeg3/SKIN075.jpg

http://www.turner-white.com/pdf/hp_jul03_stigmata.pdf

http://diseaseslab.com/wp-content/uploads/2015/08/pitting-edema-5.j
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CASE 5 | WEIGHT GAIN

A 40 year old woman comes into your clinic complaining of weight gain, weakness, constipation and feeling cold for the past 2 months. The weight gain puzzles her because she says she recently hasn't felt like eating much. Her husband, who is with her in clinic, complains that she has been very lethargic recently and seems to be less focused than usual. Her voice has also become somewhat hoarse.

On examination, she appears to be pale and her skin has a peaches and cream appearance. Her hair seems unusually thin and dry. Though her reflexes are intact, you find that they take a while longer to relax after contracting than normal. Her skin is cool to the touch and feels dry.

Vitals
Heart rate: 50
Respiratory rate: 18
Blood pressure: 110/70
Temperature: 36.0
Oxygen saturation: 98% on room air

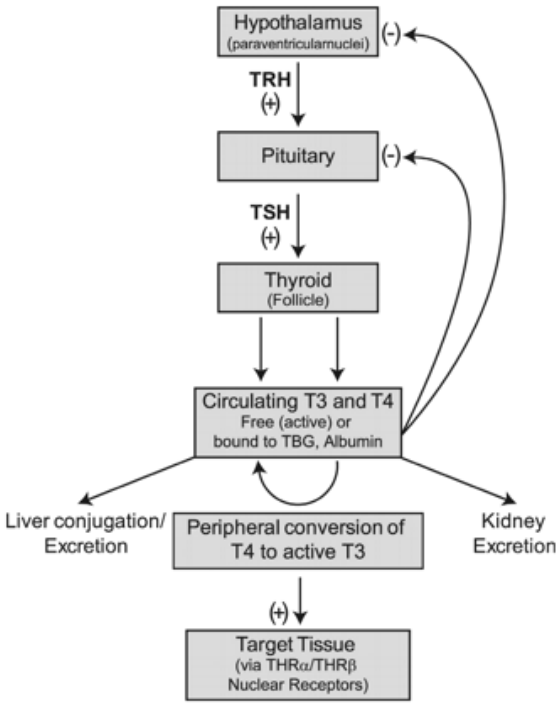
Q1. What hormones are secreted by the thyroid gland? What are their functions?

Triiodothyronine (T3) and tetraiodothyronine (T4/thyroxine) are the hormones present in the blood. Broadly, thyroid hormones function mainly to increase the basal metabolic rate and potentiate beta adrenergic stimulation.

Adrenergic Potentiation	Increased basal metabolic rate	Others
- Heart: Tachycardia, arrhythmias, hypertension/ hypotension (hypo if heart is beating too fast to fill in diastole, or if systemically very vasodilated) - Brain: Anxiety, restlessness - Hands: Tremors - General: Excessive sweating	- Weight loss - Polyphagia/Increased appetite - Heat intolerance - Proximal myopathy (due to altered protein metabolism) - Vasodilation due to buildup of metabolites - Diarrhea	- Maintain lipid metabolism (hypothyroidism causes hyperlipidemia) - Normal brain growth in infants, and normal bone growth in children. - Maintain menstrual cycle (hypothyroidism tends to cause menorrhagia, hyperthyroidism tends to cause oligomenorrhea) - Skin changes (peaches and cream appearance with thin hair in

		hypothyroid)

Q2. How is the secretion of thyroid hormones regulated?



http://labmed.ascpjournals.org/content/41/6/338.figures-only

Q3. What is this patient's clinical thyroid status and why? What tests would you order to confirm this suspicion?

This patient is clinically hypothyroid. The clinical features of hypothyroidism are due to a decreased basal metabolism rate and decreased adrenergic stimulus.

Decreased adrenergic stimulus in this patient	Decreased basal metabolic rate in this patient	Others
- Bradycardia - Mental slowness - Dry skin	- Weight Gain - Weakness - Constipation - Feeling cold with cold peripheries - Lethargy - Weakness	- Peaches and cream skin changes - Slow relaxing reflexes

You order a thyroid function test and it comes back as follows:

TSH: 0.8mIU/L (0.4-4.0)
Free T4: 0.5ng/L (0.8-1.8)

Free T3: 1.8pg/mL (2.3-4.2)

Q4. What is this patient's biochemical thyroid status?

This patient is biochemically **hypothyroid** (low T3 & T4, with not-high TSH).

[Emphasise on the importance of 'not-high' TSH versus 'low TSH'! As long as TSH is low or normal, it shows the hypothalamus-pituitary is inadequately compensating.]

Q5. From the thyroid panel, what is the anatomic location of the lesion?

The low TSH suggests that this is a central hypothyroidism, which implies either a **pituitary** or a **hypothalamic** dysfunction.

Clinically, TSH is actually the most sensitive test for peripheral hypothyroidism (not T3/T4).

Q6. What other signs and symptoms of her thyroid status did she not present with?

Signs and symptoms can be divided into those based on thyroid physiology, and those based on thyroid anatomy.

Physiologically, some other possible signs that she has not presented with are **hyperlipidemia** and **menorrhagia**; refer to the given list in Q1. Other signs and symptoms may be those caused by deficits in other pituitary hormones.

Anatomically, goitre is unlikely in central hypothyroidism because goitres grow under TSH stimulation, which happens in primary hypothyroidism.

EXTENSION

If she comes in with myxedemic coma (which is incredibly rare), the features are then due to severe slowing of practically the whole body due to lack of thyroxine. Peripheries become puffy with non-pitting edema due to mucin deposition (myxedema), along with marked hypothermia, bradycardia and decreased consciousness. Hypoventilation due to central respiratory depression and muscle weakness are possible, and cardiac failure (due to decreased contractility and heart rate), pleural and pericardial effusions are other features one might notice.

As you are concluding the consult, she mentions that she has had 3 near-misses at the road recently. The first time round, she was turning a corner side by side with a bus and ended up side-swiping the bus. The second time, she nearly knocked down a motorcyclist overtaking her on the right. Most recently, she nearly got into an accident

while trying to filter into the left lane because she could not see a car in her left blind spot.

She also says that she has not been pregnant or given birth recently, yet she has not had her period for the last 9 months. She attributes this to early menopause, but she does note that for some reason, she has been having white breast discharge recently.

Q7. Is this new information consistent with the suspected anatomical location of the lesion? Explain the physiology behind these symptoms.

This sounds like **bitemporal hemianopia** (bilateral loss of peripheries of vision), suggestive of a lesion at the optic chiasm. The pituitary gland sits practically in the middle of the optic chiasm, so any enlargement of the pituitary may compress and cause bitemporal hemianopia.

The **amenorrhea and concomitant galactorrhea** suggest that there is at least 1 other hormone that is deranged: Excess prolactin suppresses the release of FSH and LH and also can account for the lactation. Hyperprolactinemia can result from either an interruption of the pituitary stalk (remember that prolactin secretion is suppressed by dopamine from the hypothalamus), or a prolactin secreting tumour itself.

Q8. What are some signs on physical exam that might corroborate with this suspicion?

Loss of temporal visual fields on visual field confrontation.

Q9. What other hormonal deficiencies might you expect? What abnormalities would these deficiencies cause?

The anterior pituitary synthesises six hormones: growth hormone, prolactin, TSH, ACTH, FSH and LH. All of these may be deficient in disease involving the anterior pituitary; involvement of the posterior pituitary tends to be very rare in anterior pituitary disease. The hormones tend to derange in the order of gonadotropins (FSH, LH) first, growth hormone after that, then ACTH, then finally TSH. Basically, the not-so-critical hormones go first, and the metabolically-essential hormones go last. Prolactinomas are a common cause of anterior pituitary disease, so prolactin may be high rather than low.

GH deficiency

This is usually asymptomatic in adults. There may be some nonspecific loss of energy that improves with growth hormone replacement. Lean body mass and bone mineral

density decrease somewhat, and there is an increased overall risk for cardiovascular disease.

FSH/LH deficiency

In children, these manifest as delayed puberty. Late bone fusion means that these children grow to be extra tall (eunuchoid proportion) but don't usually get a growth spurt. In male adults, symptoms tend to relate to decreased libido and erectile dysfunction. Secondary sexual characteristics typically do not regress once developed. In female adults, this manifests as anovulation/amenorrhea. Once again, secondary sexual characteristic typically do not regress.

ACTH deficiency

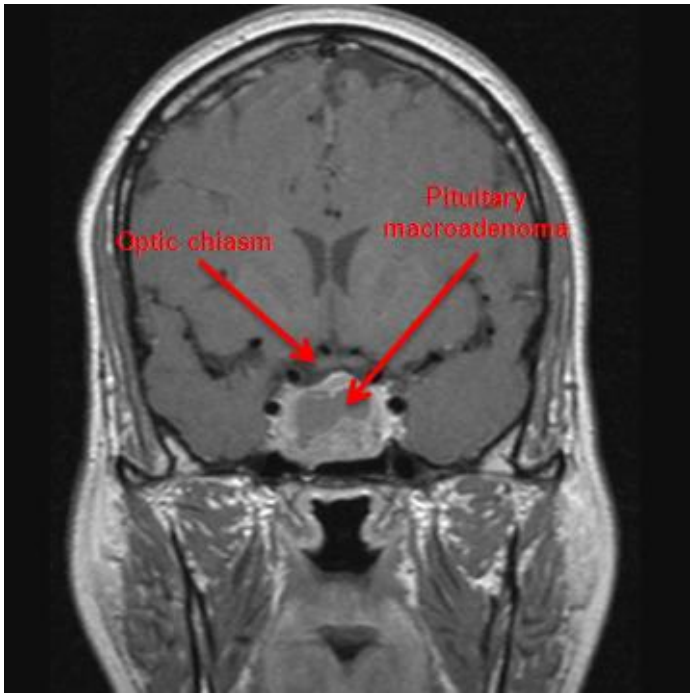
ACTH deficient patients have a deficiency in glucocorticoids (which also have some mineralocorticoid effect). As such, they typically are asymptomatic until periods of acute stress, or if the deficiency is extremely severe. Symptoms of glucocorticoid deficiency include fatigue, weight loss, decreased appetite, hypotension, hyponatremia (due to both mineralocorticoid deficiency and hypotension-induced ADH secretion), hyperkalemia and mild metabolic acidosis. Hypoglycemia may be seen, more commonly after fasting and in acute stress states rather than at rest.

Acutely stressed patients with both glucocorticoid and mineralocorticoid deficiency present with shock due mainly to lack of mineralocorticoids. Lack of glucocorticoid potentiation of the sympathetic nervous system appears to play a minor role compared to the fluid-maintaining effect of mineralocorticoids. As such, patients with central causes of adrenal insufficiency do not usually go into adrenal crisis. Hypoglycemia may also be noted during acute stress states in glucocorticoid-deficient patients

TSH deficiency

TSH deficiency presents itself clinically as T3/T4 deficiency, the features of which were outlined above.

You suspect that there may be a pituitary tumor of some sort causing the endocrine and visual disturbances. To search for the tumor, you order an MRI of her brain. At the same time, you order other blood tests to help you workup the endocrine disturbances. They return as follows:



Prolactin Test
Serum Prolactin: 12000mU/L (43-617)

Electrolyte Panel
Sodium: 133mEq/L (135-145)
Potassium: 4.2mEq/L (3.5-5.0)
Bicarbonate: 24mEq/L (22-26)
Chloride: 98mEq/L (95-105)

Arterial Blood Gas
pH: 7.4 (7.35-7.45)
PaCO2: 40mmHg (35-45)

Serum Glucose
Serum Glucose: 3.4mmol/L (<4 is considered hypoglycemic)

Q10. Given that you suspect this patient might have deficiencies of other pituitary hormones and you have an MRI confirming a pituitary tumor, interpret these lab results.

This is a prolactinoma compressing the optic chiasm, giving rise to her visual symptoms. The sodium and glucose are mildly low because of the **adrenal insufficiency**, but the electrolytes are otherwise normal – as expected because there is no acute stress state. Prolactinomas classically have serum prolactin that ranges in the 5 digits.

Q11. Summarise her pituitary hormone status.

She is deficient in TSH (confirmed with blood test), ACTH (would be good to get a short synacthen* test to prove that this is indeed ACTH deficiency), FSH/LH (anovulatory), growth hormone status unknown (should do IGF-1). She is also hyperprolactinemic.

*A note on the short synacthen test: This is a test for measuring adrenal reserve of cortisol. Baseline cortisol is measured first, then a dose of synthetic ACTH (syn-ACTH-en) is given intravenously. Half an hour later, cortisol levels are again measured. If the cortisol increases a lot, the adrenal glands are fine and the problem is either at the pituitary or the hypothalamus. If the cortisol level doesn't increase a lot, the problem is with the adrenal gland.

Q12. What treatments might be appropriate for her?

It is worth knowing that **dopamine is the inhibitor from the hypothalamus to the anterior pituitary for prolactin release**. As such, dopamine agonists like cabergoline or bromocriptine are first line in treatment of prolactinomas. They help suppress prolactin release and thus shrink the tumor.

Second line would be either radiotherapy or surgical resection. Since such a procedure is very invasive (involving entering the cranial cavity!), the above medical options are naturally the first choice.

You recognize that this is a prolactin secreting macroadenoma causing deficiencies of all other anterior pituitary hormones and compressing the optic chiasm. She is unlucky in this respect because most prolactinomas in women are microadenomas, and it's usually men that get macroadenomas. Nonetheless, you treat her with cabergoline (a synthetic dopamine agonist) with the intention of shrinking the tumor and restoring normal pituitary function.

3 years later, she returns to the clinic for follow-up. Repeat blood tests show that her electrolytes and glucose have normalized. Her visual fields are intact, and her menstrual cycle is regular. Her weight and appetite have returned to normal, and you note that her energy and presence of mind have greatly improved.

You give yourself a pat on the back as you reassure her that she is responding well.

Image from: http://bestpractice.bmj.com/best-practice/monograph/363/resources/image/bp/3.html

CASE 6 | VOMITING

You are the house officer on call at the accident and emergency. Mr. Gerald Eng is a 65 year old Chinese gentleman who walks in with a 1 day history of vomiting, fever and abdominal pain. He complains that he vomits out everything that he tries to eat and drink. He says that his urine output has also decreased in the last 6 hours, and that he feels quite thirsty.

On examination, he is alert and reasonably comfortable. His blood pressure is 125/85mmHg, heart rate is 110bpm, respiratory rate is 12/min and temperature is 38.3°C.

Blood Test Results
Sodium: 135mEq/L (135-145)
Potassium: 3.3mEq/L (3.5-5.0)
Bicarbonate: 33mEq/L (22-26)
Chloride: 93mEq/L (95-105)
pH: 7.47 (7.35-7.45)
$PaCO_2$: 46mmHg (35-45)

Your consultant on call with you diagnoses him to have acute gastroenteritis.

Let's interpret and explain the blood test results, in light of what has been happening to Mr. Eng. The above results are part of what is referred to as a "Urea, Electrolytes & Creatinine (UECr)" panel and "Arterial Blood Gas (ABG)" in the wards.

Q1. What mechanisms does the body have to maintain a normal pH?

Blood. The bicarbonate buffer system is the most important; it helps resist pH change extracellularly in the blood. The phosphate buffer system is important only for intracellular buffering, because extracellular phosphate concentrations are negligible.

Respiratory. Peripheral chemoreceptors are sensitive to H^+, pCO_2 and pO_2, whereas central chemoreceptors only sense pCO_2 (To be physiologically accurate, it is CO_2 which crosses the blood brain barrier and is converted to H^+ and HCO_3^-; the H^+ is then sensed by chemoreceptors). High H^+ and CO_2 both stimulate increased respiratory rate to blow off the acidic CO_2 from the blood, and the inverse is true as well. People generally do not hypoventilate significantly when alkalotic though.

Renal. Renal reabsorption of bicarbonate depends on active secretion of H^+ ions, which in turn depends on the action of carbonic anhydrase in the renal tubular cells. In the proximal convoluted tubule, filtered bicarbonate within the tubule is reclaimed by

the secretion of H^+ ions. By the distal convoluted tubule, bicarbonate is usually fully reclaimed and the secretion of H^+ ions thus acidifies the urine. When the body is alkalotic, the amount of bicarbonate flowing through the nephron is more than can be "titrated" with H^+, so the excess bicarbonate remains in the tubule and is excreted in the urine. The converse is true in acidosis; in the PCT luminal H^+ is titrated against tubular HCO_3^- thus "reclaiming" bicarbonate the body already has, and in the distal tubule there is no longer any HCO_3^- to be reclaimed. Hence, any H^+ excreted is lost and thus causes the luminal pH to drop below 7.

Other mechanisms. Other mechanisms such as secretion of NH_3 from glutamate are more relevant in acidosis, but may be discussed for completeness sake.

Q2. What mechanisms does the body have to maintain potassium homeostasis?

Potassium homeostasis is maintained via 2 main mechanisms: (1) control of ICF/ECF potassium shifting and (2) control of renal excretion of potassium.

ICF/ECF potassium shifts. Potassium is mainly stored intracellularly in the body. As such, intracellular space acts as a reservoir for potassium in the same sense that bone is a reservoir for calcium. The sodium-potassium ATPase is activated by insulin and by catecholamines, causing intracellular shift of potassium (and thus lowering blood potassium concentrations). There is also an H^+/K^+ exchanger, which shifts H^+ intracellularly in exchange for pushing K^+ extracellularly. Thus, acidotic states cause hyperkalemia, and alkalotic states cause hypokalemia.

Renal excretion. Potassium balance is also regulated by aldosterone, which causes increased secretion of H^+ and K^+ in the distal convoluted tubule and collecting ducts. Aldosterone secretion is controlled in part by blood K^+ concentrations, so this is one of the mechanisms for homeostasis.

Q3. Name this patient's acid-base status.

Metabolic alkalosis with respiratory compensation.

Q4. Why is the potassium low?

Vomiting itself loses K^+ because of the mechanism of gastric acid secretion. K^+ is swapped with H^+ eventually, but it is actually first to be secreted into the gastric juices.

Metabolic alkalosis due to H^+ loss also encourages intracellular shift of potassium as mentioned above. Note that although the serum potassium is only slightly low, the total body deficit may be fairly significant.

Aldosterone secretion is increased when hypovolemic to maintain blood pressure. This, however, causes H^+ and K^+ secretion into the tubules, perpetuating the alkalosis and hypokalemia. Aldosterone secretion is probably a minor mechanism in this case because the hypovolemia reduces flow at the distal convoluted tubule and collecting tubules.

Q5. Why is the chloride low?

Vomiting purges chloride from the body because gastric acid (HCl) is lost, hence causing a hypochloremic hypokalemic metabolic alkalosis. *[This is the typical description of metabolic status in vomiting, and M1s should know this description and be able to explain it.]*

Charge balancing is another way to explain this phenomenon. As the bicarbonate levels rise, they must electrically "displace" some other negative ions (chloride) to maintain electrical neutrality.

Q6. Why is the bicarbonate high?

This indicates a metabolic alkalosis, because of loss of H^+ in the gastric acid (HCl).

Let's think about the body's physiological response to dehydration.

Q7. What problems are caused by dehydration, in terms of blood pressure and osmolarity?

Blood pressure drops when severely dehydrated due to intravascular volume depletion that overcomes the sympathetic nervous system's ability to compensate. Dehydration will lower ventricular filling (i.e. preload) and thus cause a decrease in stroke volume. A drop in stroke volume lowers cardiac output because CO = SV x HR. From the formula BP = CO x TPR, it can be deduced that blood pressure will drop. *[While not necessary at M1 level, some of the consequences of this drop in BP could include acute kidney injury. If the hypotension is severe enough, shock and end-organ dysfunction can develop.]*

Osmolarity increases because as the body becomes more dehydrated, blood becomes increasingly hyperosmolar due to the water loss causing hemoconcentration.

Q8. What is the cardiovascular response to dehydration?

Recall the formula BP = CO x TPR. It follows that both (1) cardiac output and (2) total peripheral resistance need to be maintained in order to maintain blood pressure, which most importantly perfuses the brain.

The sympathetic nervous system is activated when the baroreceptors sense falling blood pressure, causing an increase in heart rate and contractility to improve **cardiac output**. The sympathetic response also causes peripheral vasoconstriction to increase **total peripheral resistance**, causing the extremities to feel cold.

Q9. What is the renal response to fluid loss?

The **renin-angiotensin-aldosterone system (RAAS)** is activated when the juxtaglomerular cells sense a decrease in GFR by 3 mechanisms. Firstly, decreased blood pressure directly decreases stretching of the afferent arteriole. Secondly, the macula densa in the distal convoluted tubule also senses this decrease in GFR indirectly by decreased sodium delivery, causing paracrine activation of the juxtaglomerular cells. Thirdly, adrenergic input to the kidneys in response to hypovolemia and stress also directly stimulates renin release.

The above mechanisms cause an increased secretion of renin by the JG cells. Renin is an enzyme which converts angiotensinogen to angiotensin I, which is then converted in the lungs by ACE to angiotensin II. Angiotensin II then causes release of aldosterone by the cells of the zona glomerulosa in the adrenal glands.

The hormones angiotensin II and aldosterone both cause resorption of sodium and water (isotonic fluid) in the kidneys. Angiotensin II is also a potent vasoconstrictor to maintain peripheral vasoconstriction, and a potent dipsinogen, which helps to replace intravascular volume. Angiotensin II also stimulates ADH secretion from the posterior pituitary, which further promotes water retention by its action in the collecting tubules.

And now back to Mr. Eng…

Q10. In light of the laboratory findings, do you agree with your consultant's diagnosis?

This is a very general question. Re-emphasise the fact that vomiting typically gives a hypochloremic hypokalemic alkalosis as a result of both acid (HCl) as well as extracellular fluid loss. If you see things other than this on the blood work, consider

alternative pathologies. For example, acidosis might indicate that the vomit is coming from the intestines rather than the stomach, which may suggest an intestinal obstruction.

Tip: The answer to the above question when asked by your consultant in the wards is more often than not: yes.

Q11. What might be a reasonable treatment plan for Mr. Eng?

As we have discussed in the above questions, the main problem is twofold: (1) volume contraction and (2) electrolyte imbalance that has occurred as a result of the vomiting.

Ordinarily we can fix both issues by getting the patient to **drink Oral Rehydration Solutions (ORS)** which are a mixture of sodium chloride, potassium chloride and glucose. However, Mr. Eng is actively vomiting out everything that goes in, so drinking ORS is not a viable solution. Putting Mr. Eng on a **normal saline (NaCl) and potassium IV drip** will deal with the issue and bypass the upset stomach.

Administering an **anti-emetic (anti vomiting agent)** will mean he gets to eat and drink sooner and thus get off the drip and prevent complications such as infection at the drip site and discomfort to the patient.

Not much can be done about the alkalosis directly, but when the volume status normalises and the vomiting stops, the kidney is remarkably efficient at bringing the acid-base status back to normal.

With the diagnosis made, you confidently begin treating him with a normal saline drip containing potassium. To help him keep fluids down, you also give him an injection of prochlorperazine (an anti-emetic). He makes an uneventful recovery and is discharged once the drip can be stopped and he can tolerate oral fluids well.

CASE 7 | MORE VOMITING

You find yourself – for better or for worse – in the ED again, this time as a medical officer. A 65 year old man by the name of Mr. Ding Kong An is rushed in the emergency department by ambulance. His son is with him, and says that his father had been having vomiting, diarrhea, fever and abdominal pain for the past 24 hours. He has a history of type 2 diabetes mellitus, but has forgotten to take his insulin injections for the past 24 hours as well. The son also says that Mr. Ding has been getting progressively more agitated and drowsier over the past 12 hours.

On examination, Mr. Ding is breathing deeply and rapidly, and he appears to be drowsy. His blood pressure is 90/60, heart rate 140, temperature 38.5°C, respiratory rate 28, oxygen saturation 98% on room air.

Blood Results
Sodium: 133mEq/L (135-145)
Potassium: 5.2mEq/L (3.5-5.0)
Bicarbonate: 12mEq/L (22-26)
Chloride: 91mEq/L (95-105)
pH: 7.25 (7.35-7.45)
PaCO2: 31mmHg (35-45)
Serum Glucose: 22mmol/L (under 7.8 if 2hours postprandial)

His serum ketones are markedly elevated, and a dipstick shows high amounts of glucose and ketones in his urine.

Q1. What are the metabolic functions of insulin, cortisol and adrenaline? When are these hormones secreted?

The function of **insulin** is to signal a 'well-fed' state by allowing uptake and storage of blood glucose by cells. Muscles and adipose tissue require insulin for glucose uptake via the GLUT4 receptor, and subsequent storage by glycolysis, glycogenesis, fatty acid synthesis and protein synthesis by intracellular enzyme activation again by insulin's intracellular signaling effects such as via cAMP. Note that the liver (GLUT2) and brain (GLUT3) do not require insulin. Insulin is secreted by the beta cells in the pancreas in response to high blood glucose levels.

Cortisol is a glucocorticoid. It has multiple roles in the body. Firstly, its increases glucose levels in the blood (counter-regulatory to insulin); if elevated for a prolonged time, cortisol can also cause lipolysis and proteolysis by a catabolic effect and redistribute fat from peripheral to central tissues. Secondly, it is enables the body to

cope with physiologic stresses, by a multifactorial mechanism. Thirdly, it potentiates the body's response to catecholamines like adrenaline. Fourthly, it is immunosuppressive and anti-inflammatory. Although the following is not a key function, it is worth noting that cortisol has some mineralocorticoid activity and can thus lead to fluid retention, because both cortisol and aldosterone are cholesterol-derived enzymes from the adrenal cortex and bind to similar intracellular receptors. Cortisol is secreted in response to physiological and psychological stress, in order to make sure there is enough glucose in the blood for use by relevant organs and also to maintain blood pressure to perfuse these organs.

Adrenaline is a catecholamine, which mediates the effects of the sympathetic nervous system. Its effects are multisystemic and organ-dependent.

- Heart: Tachycardia (aka positive chronotropy) and increased contractility (aka positive inotropy) via β1 receptors
- Lungs: Bronchodilation via β2 receptors
- Brain: Anxiety, sensation of hunger (released in response to hypoglycemia)
- Liver: Increased gluconeogenesis and glycolysis to increase blood glucose levels
- Blood Vessels: Vasodilation (β2 action) or vasoconstriction (α1 action). Adrenaline has a mixed effect, but the net effect seems to be peripheral vasoconstriction, i.e. α1 effect
- GIT: Decreased motility (α2 action)
- Note that while sweating is typically associated with a sympathetic response, innervation to sweat glands is actually by acetylcholine muscarinic receptors, and not adrenergic receptors!

Adrenaline is secreted in response to physiological and psychological stress, similar to cortisol.

Q2. Why might the serum glucose and ketones be high?

The glucose in the urine is suggestive of a high serum glucose, which is confirmed by blood investigations. 2 factors are likely to be the cause:

Firstly, this patient is likely to be **insulin deficient from missing his insulin injection**. This makes it harder for the glucose to shift intracellularly and raises the serum glucose. This alone, however, is rarely enough to precipitate DKA symptoms.

The second reason is that this patient is **acutely ill**. As a response to this stress, **cortisol and adrenaline are high**, causing further insulin resistance and raising the blood glucose to dangerously high levels.

The high serum ketones happens because the body can no longer use glucose for energy. Ketone bodies such as β-hydroxybutyrate and acetoacetate derived from fatty acids are a 'backup' source of energy which are used in place of glucose in this patient.

Q3. Why are there glucose and ketones in this patient's urine?

Glucose appears in the urine when it **exceeds the transport maximum of glucose transporters in the renal tubules**. This implies that the serum glucose level is abnormally high (normal serum glucose is far less than the transport maximum).
Ketones are not resorbed by the renal tubules. Their presence in the urine means that the serum ketone level is abnormally high.

You take a look at the laboratory results and calculate the anion gap. The formula for the anion gap is $[Na^+]$ - $[HCO_3^-]$ - $[Cl^-]$. Conceptually, this represents the quantity of anions in the serum that is not accounted for by the typical physiologic anions of chloride and bicarbonate.

Q4. Offer an explanation of the acid-base status of the patient, and calculate the anion gap. What do you think accounts for this anion gap?

The anion gap is used to evaluate the cause of metabolic acidosis in patients. Sodium is the major positive ion in the blood, while bicarbonate and chloride are the major negative ions. For every H^+ ion released into the blood which causes HCO_3^- to decrease, there is an anion that must be present to balance the charge from that H^+. **If the anion that does this is not Cl^-, it will be reflected as a larger anion gap.**

The normal gap is 8 to 12; **this patient's gap is 16**. This patient has a high anion gap metabolic acidosis. This suggests that there are 'hidden' acids in his body that are not accounted for. In light of the positive urine ketones, the likely explanation is that the body is undergoing ketogenesis, as ketones are acids. *[Not required to know at M1, but other common causes of high anion gap metabolic acidosis follow the acronym KULT (Ketoacidosis, Uremia, Lactic acidosis, Toxins)]*

Why is this patient in ketoacidosis? The answer probably lies in the fact that he's an insulin dependent diabetic who didn't take his insulin *[Note: type 2 diabetics can have pancreatic burnout later in the disease course that causes insulin deficiency on top of insulin resistance]*. The acute illness (gastroenteritis) causes a spike in his counterregulatory hormone levels which are not opposed by insulin because his body currently lacks insulin. The lack of insulin results in 2 things.

Firstly, blood glucose levels rise extremely high because hormones like cortisol raise blood glucose levels unopposed, causing the osmotic diuresis that makes him dehydrated. Secondly, the lack of insulin prevents many organs particularly muscle from using glucose as an energy source (via GLUT 4). Hence, the body will have to turn to ketoacids as an alternative energy source, resulting in ketoacidosis. Tachypnea is present in this patient in order to try and compensate for the metabolic acidosis, and drowsiness/altered mental status is a common presentation of acidosis.

Q5. Why is this patient hyponatremic and hyperkalemic?

There are multiple mechanisms for **hyponatremia** in this patient:

(1) Due to high glucose, serum osmolarity rises. This glucose and rise in osmolarity exerts an osmotic effect, **causing free water to shift from the intracellular to the intravascular compartment**. This is an attempt to normalize serum osmolarity. Sodium appears low because it has been "diluted" by this extra water.

(2) If dehydration is severe (>10% of body weight), **ADH secretion kicks in**. Now recall that ADH is secreted in response to (i) hyperosmolarity, and (ii) hypovolemia, with (ii) over-riding (i) when intravascular volume and perfusion is at risk. Hence, ADH is secreted to improve intravascular volume, at the cost of decreasing osmolarity and hence sodium (since sodium is the main constituent of osmolarity).

The **hyperkalemia** arises due to a few mechanisms as well:

(1) The increase in extracellular fluid osmolality due to glucose drags intracellular fluid out of the cell, thus concentrating the potassium within the cell. The increased concentration then causes potassium to diffuse out of the cell and into the blood. The movement of fluid from intracellular to extracellular space also drags with it some amount of potassium (solvent drag).

(2) Insulin as a hormone increases the activity of the Na/K ATP-ase, which acts to shift potassium intracellularly. In conditions of insulin resistance, insulin's effect of shifting potassium intracellularly is diminished, resulting in higher extracellular potassium levels.

(3) In an acidotic state, H^+/K^+ exchangers attempt to shunt H^+ ions intracellularly, by pumping K^+ ions into the extravascular volume.

The fluid loss may also be at a degree that it can cause the potassium to be more concentrated.

Don't be fooled by the high potassium though! This patient actually has a total body deficit of potassium because of massive renal losses owing to osmotic diuresis due to glucose (remember that potassium resorption in the kidney is flow-dependent). It's just that the impaired regulation mechanisms and the dehydration make it look high.

Please note that RAAS does not control osmolarity (common misconception). Osmolarity is under ADH control and volume is under RAAS control. Even though RAAS causes greater sodium reabsorption, this is followed by water reabsorption and hence no change in osmolarity. It is only the action of ADH that causes free water (without sodium) reabsorption. Despite all this, note that the body actually doesn't have enough of these ions.

Q6. Interpret and explain the vital signs in this patient.

This patient is febrile, tachycardic, tachypneic and in shock.

Given the high serum and urinary glucose, it seems like this patient is losing fluid due to osmotic diuresis. This **fluid loss has gone to the extent of causing shock, the compensatory response of which is tachycardia**. Even with a heart rate of 140, the BP is still very low, suggesting that the patient is unable to compensate.

The **tachypnea likely reflects compensation for the metabolic acidosis and some degree of tissue hypoperfusion** due to the low BP (the saturations can still be normal in this case).

The fever reflects a likely infectious etiology, gastroenteritis in this case.

Recognising that the patient is in diabetic ketoacidosis, he is treated with IV insulin and IV normal saline that is mixed with potassium. Sometime after treatment, his vitals are:

Blood pressure: 120/80
Heart rate: 90
Temperature: 38.5°C
Respiratory rate: 20
Oxygen saturation: 98% on room air

Blood Results
Sodium: 138mEq/L (135-145)
Potassium: 4.0mEq/L (3.5-5.0)
Bicarbonate: 24mEq/L (22-26)
Chloride: 106mEq/L (95-105)
pH: 7.40 (7.35-7.45)
PaCO2: 40mmHg (35-45)
Serum Glucose: 6.8mmol/L (under 7.8 postprandial)

Serum and urine ketones are negative, and dipstick no longer shows urinary glucose.

Mr. Ding has become alert and comfortable at rest, though he still complains of the fever and resolving diarrhea.

Q7. What will happen if he is only treated with insulin and nothing else?

Serum glucose will drop, as insulin drives glucose into cells. Ketones should resolve but this takes time; hence the practice is that once glucose falls to ~12-14mmol/L,

insulin infusion is halved and a dextrose drip started, instead of stopping insulin completely as that would cause DKA to return.

Potassium will fall because insulin drives potassium into cells by activating the Na/K ATPase, and because of resolution of ketoacidosis. This fall may be quite precipitous without potassium replacement; excessively low potassium can be dangerous (may cause weakness, arrhythmias), hence the need for potassium replacement. He initially has a high potassium but this is deceptive because he has lost a lot of electrolytes through diuresis, diarrhoea, and vomiting - serum K is high, but total body K is likely to be low, which needs replacement.

Furthermore, if only insulin is given, **nothing is being done for his fluid depletion** (due to diuresis and vomiting). The average fluid deficit is 5-7L in DKA. He is likely to remain fluid depleted. This manifests as clinical signs, tachycardia, and even hypotension.

Q8. How does IV normal saline with potassium make a difference?

Potassium replacement helps to restore total body potassium and prevents K from falling as insulin is given, as discussed above. IV normal saline restores fluid volume. Sodium levels are also likely to return to normal because rehydration with normal saline (Na = 154 mmol/L, higher than serum sodium) tends to raise the low sodium towards its normal value. Also as glucose shifts into cells, serum osmolarity falls; with rehydration, sodium homeostasis occurs through ADH action.

See above, the normal saline replaces the fluid deficit (5-7L on average in DKA, 8-10 in HHS), and the potassium replacement will prevent hypokalemia

Q9. What advice might you give him and his family regarding the insulin therapy when he next falls sick?

He **should not stop insulin therapy** as this leads to unopposed counterregulatory hormone action.

Insulin requirements may fall due to poor oral intake (appetite tends to fall when one is sick!) causing risk of hypoglycemia, or rise due to infective state causing risk of hyperglycemia.

Therefore while injections should continue, the dose may differ; **it is best to titrate insulin injections against fingerprick glucose**. We can advise the patient to call his doctor or care coordinator if unsure.

CASE 8 | WEAKNESS

You are a third year medical student doing your Neurology rotation in Internal Medicine. Your consultant has asked you to speak to and examine Mr Lee, a patient who has been warded for weakness.

Mr Lee is a 72 year old gentleman who tells you that his weakness started about a week ago. He was sweeping the floor at home one night when he suddenly felt his left arm become very weak, forcing him to drop the broom and take a break. At that time, his wife also noticed that his left lip was drooping and so drove him to the emergency department for workup.

You proceed to examine Mr Lee and find the following:

- *No significant wasting noted*
- *Left upper limb hypertonia*
- *Left upper limb power 3/5 for all movements*
- *Hyperreflexia of left biceps, triceps and brachioradialis reflexes*
- *Left upper limb numbness*
- *Right upper limb exam normal*
- *Lower limbs exam normal*

Q1. Compare and contrast the features of an Upper Motor Neuron lesion against those of a Lower Motor Neuron lesion.

	UMN	LMN
Wasting	Mild	Prominent
Fasciculations	Not present	Present
Tone	Increased	Decreased
Reflexes	Hyperreflexic	Hyporeflexic
Power	Upper limb Flexors stronger Lower limb Extensors stronger	

Upper motor neuron lesions remove the inhibitory-excitatory control of the lower motor neurons in the spinal cord. Because the muscles are still innervated and there's unopposed stimulus from the lower motor neuron, muscles tend not to be very wasted (lack of denervation atrophy) and the tone is higher. Reflexes are also unsupressed and so tend to be hyperreflexic.

Power is a soft sign, but the classic upper motor neuron pattern of weakness is stronger upper limb flexors and stronger lower limb extensors. This is known as decorticate posturing.

Q2. Is this patient's lesion Upper or Lower motor neuron? Where (Anatomically) could it be?

The hypertonia, hyperreflexia and lack of wasting suggests an upper motor neuron lesion. This means that the lesion must be at least at the level of the spinal cord, or above (in the brainstem, subcortex or cortex).

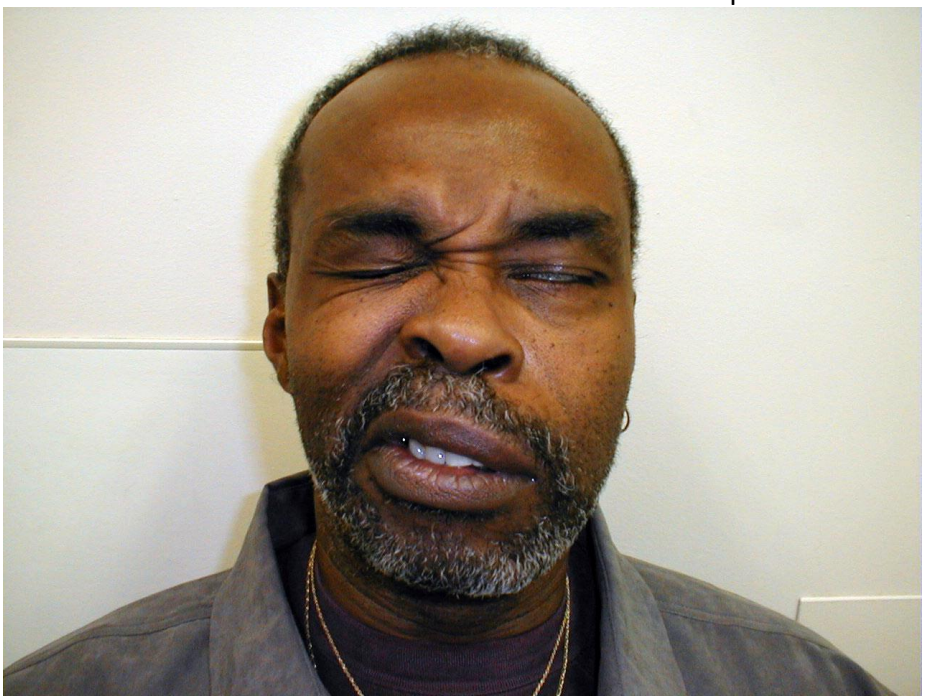
Q3. What patterns of involvement might help you decide between the possible anatomical areas listed in Q2?

Spinal cord lesions tend to have a fairly clear sensory level and tend to produce bilateral symmetrical upper motor neuron signs. There should not be any involvement of the cranial nerves, and there may be lower motor neuron signs at the level of the lesion.

Brainstem lesions classically give crossed signs; that is, the face is weak on the side of the lesion whereas the body is weak on the opposite side. This is because the motor pathways have not yet decussated in the brainstem, but the cranial nerve nuclei that arise within the brainstem innervate the ipsilateral face.

Subcortical and cortical lesions are sometimes hard to differentiate. The weakness is usually one sided, with the face and limbs involved on the same side. A cortical lesion may produce cortical signs (eg. Visual field defect, hemineglect, apraxia, aphasia etc.), but they may be quite subtle and hard for students to pick up.

You also note that Mr Lee's smile seems to be crooked as in the picture below



Q4. Describe the facial asymmetry that you see when Mr Lee smiles (Ignore the racial discrepancy). What does this indicate that the patient has?

There is drooping of the left lip with loss of nasolabial fold. Ideally, there would be full closure of the left eye and symmetrical forehead creases.

(My apologies, I really can't seem to find a good UMN 7th nerve. This patient actually looks like he has some weakness of closing the left eye and the forehead creases are poorly seen. Please take time to explain to your M1s that this is not the best picture available)

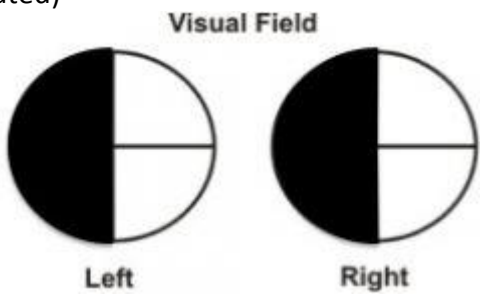
The pattern of lower face involvement with upper face sparing indicates an upper motor neuron lesion, likely in the contralateral brain.

Q5. Putting together the limb and facial findings, which part of the brain may be affected in Mr Lee?

This patient has what is known as a brachiofacial pattern of weakness, which suggests either a Middle Cerebral Artery (MCA) stroke or a subcortical stroke of the internal capsule (which carries motor fibres from the cortex and condenses them down into a more compact anatomical area).

Recall that the motor homunculus of the brain represents the lower limbs medially and the face laterally in the motor and sensory cortex. The middle cerebral artery supplies the lateral aspect of the cortex, while the anterior cerebral artery supplies the medial aspect of the cortex. An MCA stroke will hence affect the face and upper limbs preferentially over the lower limbs, as in this case.

As you are finishing the examination and preparing to leave, Mr Lee mentions that he seems to have developed problems with his vision ever since the start of his symptoms. You examine his visual fields and find that he has problems seeing things on the left side (as illustrated)



Q6. Is this finding consistent with your diagnosis in Q5? Why might the patient have developed this?

This is a left homonymous hemianopia, which is consistent with a lesion of the right optic tract, right optic radiation or the right occipital lobe (though there will usually be macular sparing).

This is consistent with a middle cerebral artery infarction which involves both loops of the optic radiation. Meyer's loop runs in the temporal lobe and carries the superior quadrantic visual field. Baum's loop runs in the parietal lobe and carries the inferior quadrantic visual field. If both of them are lesioned (as in a large MCA stroke), a contralateral homonymous hemianopia may develop.

Piecing together the signs and symptoms, you decide that Mr Lee has suffered from a Middle Cerebral Artery infarction. You discuss the case with your consultant, review the MRI findings and happily find that your diagnosis is correct. The road to recovery for Mr Lee will now involve controlling his vascular risk factors (the same ones that

cause a myocardial infarction) and starting him on physiotherapy to improve his physical function.

Images from:
https://meded.ucsd.edu/clinicalmed/neuro2.htm
http://fce-study.netdna-ssl.com/images/upload-flashcards/back/0/3/34230595_m.jpg

CASE 9 | MORE WEAKNESS

While doing your rehabilitation posting in Family Medicine, you meet Mr. Sim in the ward of a community hospital. A man of about 40 years old, Mr. Sim tells you of the fateful night many weeks ago that landed him here.

An active member of a local gang, Mr. Sim has seen his fair share of gang fights and bears the scars on his arms and legs to prove it. One night about 3 weeks ago, he was involved in a fight and was stabbed from behind by a member of the opposing gang using a parang. Shortly after being stabbed, Mr. Sim felt his leg go weak and he collapsed to the ground. He was diagnosed with a spinal cord injury in the emergency department.

One surgery and a week of hospitalization later, Mr. Sim has been transferred to the community hospital to continue with his physiotherapy program. You perform a physical examination on him and find the following:

- *No significant wasting*
- *Right lower limb hypertonia*
- *Right lower limb hyperreflexia*
- *Right lower limb power 2/5 for all movements*
- *Loss of fine touch, proprioception and vibration on right lower limb*
- *Loss of temperature and pain sensation on left lower limb*
- *Left lower limb power and reflexes normal*
- *Abdominal and upper limb examination normal*

Q1. What ascending tracts run in the spinal cord? At what levels do they decussate?

The spinothalamic tract runs anterolaterally in the spinal cord and decussates at the level (or slightly above) the spinal segment (eg. L5's spinothalamic tract decussates at the level of L3 to L5).

The dorsal column medial lemniscus runs in the posterior aspect of the spinal cord and decussates at the inferior medulla

The spinocerebellar tract run in the lateral portion of the spinal cord and generally do not decussate.

Q2. What modalities are each of the tracts in Q1 responsible for?

The spinothalamic tract is responsible for carrying pain, temperature and crude touch sensation

The dorsal column medial lemniscus is responsible for carrying vibration, fine touch and conscious proprioception

The spinocerebellar tract is responsible for carrying subconscious proprioception

Q3. What major descending tract runs in the spinal cord? At what level does it decussate?

The corticospinal (pyramidal) tract descends in the spinal cord and controls motor functions. It decussates at the level of the medulla.

Q4. Knowing the anatomy of the spinal cord and the neurological deficits, what structures might the parang have cut through? What is this syndrome known as?

The deficits are as follows:
Left sided spinothalamic tract
Right sided DCML
Right sided corticospinal tract

This patient has Brown Sequard Syndrome, a hemi-cord transection. Given that pretty much the whole of the lower limb is involved, the parang probably cut through the right sided spinal cord at the level of L1 or higher. The spinothalamic fibres supplying the left sided lower limb have decussated to the right, so transection on the right gives rise to a left sided pain and temperature sensation deficit. The DCML has not yet decussated and so still supplies the right sided lower limb when it is transected. The Corticospinal tract has already decussated in its descent from the brain, so it supplies the right sided lower limb as well when it is transected.

Q5. (Enrichment) What other cord syndromes have you heard of? How does spinal cord anatomy make sense of the signs and symptoms of these syndromes?

Some other spinal cord syndromes are:
1) Complete cord transection – there is usually a clear sensory level and bilateral symmetrically involved limbs. This need not be traumatic, there are inflammatory causes of complete cord transection as well
2) Central cord syndrome – The central area of the cord is lesioned, so the deficits preferentially affect the upper limbs. This usually manifests as a cape-like distribution of sensory loss and a weakness that only involves the upper limbs

3) Anterior cord syndrome – This involves the anterior and lateral aspects of the spinal cord and tends to spare the DCML. Findings are a loss of motor and spinothalamic sensory function with a sparing of the DCML bilaterally below the level of the lesion
4) Posterior cord syndrome – This tends to preferentially affect the DCML running posteriorly in the spinal cord, sparing the motor and spinothalamic pathways. In essence, it's the reverse of anterior cord syndrome.

CASE 10 | WOMANLY WOES

Madam Tan, a 50 year old married lady with 2 children presents to the General practitioner for increasingly irregular menstrual periods over the past 1 year. She complains of feeling very hot and sweating occasionally even in the cold room, especially at night when she is trying to sleep. These episodes usually last for about 1 minute and she feels highly distressed by this.

Her periods started at 12 years old, and has been normal throughout her life until recently. She had her first child at 30 years old and her second child at 32 years old.

Q1. What four hormones are involved in the menstrual cycle and how do their levels change throughout the course of the menstrual cycle?

FSH, LH, Estrogen & Progesterone

Q2. What do each of these hormones do?

FSH - At the time of menstruation, FSH initiates follicular growth, specifically affecting granulosa cells. This causes the increase in production of aromatase, which converts androgens to estrogen. Adipose tissue also produces aromatase, which peripherally produces estrogen. Thus women with higher weight post menopause are at lower risk of menopausal complications. FSH also induces follicles in the ovaries to mature, until there is usually only one mature follicle.

LH – LH is released from the anterior pituitary gland and works on the Theca cells. Theca cells produce androgens, which are then converted to estrogen in the granulosa cells. LH Spike causes ovulation, causing the release of the ovum from the follicle. This causes the follicle to become the corpus leutium.

Estrogen – This hormone is produced by the granulosa cells, under the influence of FSH. Estrogen causes the proliferation of the uterus lining. Low levels of Estrogen has a negative feedback pituitary gland to reduce production of FSH and LH. High levels of Estrogen causes positive feedback on the pituitary gland to increase the production of LH. This LH surge causes ovulation.

Progesterone – This hormone is produced by the Corpus leutium (other places include adrenal glands and placenta). This helps to maintain the lining of the uterus, in preparation for implantation.

Q3. Describe the phases in the uterus lining throughout the menstrual cycle.

The uterine cycle has three phases: menses, proliferative, secretory.

Menstruation is the first phase of the uterine cycle. Regular menstruation that lasts for a few days (usually 3 to 5 days, but anywhere from 2 to 7 days is considered

normal). The average blood loss during menstruation is 35 milliliters with 10–80 ml considered normal. An enzyme called plasmin inhibits clotting in the menstrual fluid.

Painful cramping in the abdomen, back, or upper thighs is common during the first few days of menstruation.

The proliferative phase is the second phase of the uterine cycle when estrogen causes the lining of the uterus to grow, or proliferate, during this time. As they mature, the ovarian follicles secrete increasing amounts of estradiol, and estrogen. The estrogens initiate the formation of a new layer of endometrium in the uterus, histologically identified as the proliferative endometrium.

The secretory phase is the final phase of the uterine cycle and it corresponds to the luteal phase of the ovarian cycle. During the secretory phase, the corpus luteum produces progesterone, which plays a vital role in making the endometrium receptive to implantation of the blastocyst and supportive of the early pregnancy, by increasing blood flow and uterine secretions and reducing the contractility of the smooth muscle in the uterus; it also has the side effect of raising the woman's basal body temperature.

Q4. What are some possible causes of Madam Tan's symptoms?

Symptoms of irregular periods + hot flushes + sweating:
1) Peri-menopause (if asked, clarify that Madam Tan is not yet menopausal because she is still having periods. The definition of menopause requires 12 months of no periods – a retrospective diagnosis)
2) Hyperthyroidism
Other causes of irregular periods:
3) Hypothalamus → Stress, Excessive weight loss/gain, Anorexia, Excessive exercise
4) Pituitary → Prolactinoma

The GP diagnosed her as being peri-menopausal. Madam Tan is very worried about this, and wants to find out what that means and what are the possible complications.

Q5. Explain what menopause is and how that would affect her hormonal levels (in terms of the hypothalamic-pituitary-ovary axis).

Menopause refers to the phase of a woman's life where she no longer gets menstrual periods. It is a retrospective diagnosis and is defined as 12 consecutive months of lack of menstrual periods. With age, a woman's reserve of ovarian follicles are depleted and the fall in ovarian follicular activity leads to a fall in estrogen levels. With a lack of negative feedback, FSH levels rise and remain high.

Q6. The complications of menopause arise due to changes in the female hormone levels. List the complications of menopause.

Short-term complications:

- Vasomotor symptoms (hot flushes, night sweats) Exact pathophysiology is not well known but a fall in circulating estrogen levels is thought to disrupt the body's natural thermostat in the hypothalamus, leading to cutaneous vasodilatation and heat loss.

Long-term complications:

- Osteoporosis → Estrogen acts as an anti-resorptive agent on trabecular bone and a fall in estrogen levels after menopause results in increased resorption of bone and a decrease in bone mineral density, predisposing the elderly woman to osteoporotic fractures