Sample Oral Questions

This file contains sample which have been presented to candidates for the Part 2 FRCPath oral examination in Clinical Biochemistry. Candidates are given half an hour to prepare their answers to a management problem and a laboratory scenario or clinical case.

After each case, the notes for the examiners have been provided by the examiner who set the question. These are not intended to be exhaustive but provide some background for the case. More importantly, they provide some insight for candidates into what the examiners are looking for.

Questions for all candidates

Question 1

You are a fairly recently appointed head of Chemical Pathology in a district general hospital.

Since arriving you have implemented major changes in equipment and working practices. Results for almost all tests can be available within an hour or so of the sample arriving in the laboratory (depending only on how many other samples arrive at the same time), at any time of the day or night.

What difference, if any will this make to the way you clinically validate results?

Question 1: Notes for Examiners

As with most management questions, there is no definitive right answer to this one - at least, not until NICE tells us there is.

However, candidates should realise that there is a balance to be struck between holding back results for clinical validation and the amount of time they are prepared to spend validating. Factors which may influence this balance include:

- What happens to the results once they are clinically validated (eg. immediate electronic transmission to wards and GPs *vs* printing and sending out on the next working day).
- The number of people in the Department who are appropriately trained and qualified in clinical validation. (Might this include technical staff following established protocols?).
- The presence of modem links to permit clinical validation from home in the evenings and at weekends. (Should staff who do this receive additional remuneration?).
- The clinical needs of any specialist clinical units the DGH may house.

Whatever the local solution, two points seem clear:

- There is little point in improving analytical turnaround times to this extent if the results are all held back for clinical validation on the next working day.
- Releasing all results with no clinical validation stage raises some interesting questions about the role of the consultant chemical pathologist/clinical scientist.

Question 2

You are Head of Chemical Pathology Services in a large District General Hospital. Your Clinical Director is approached by the local Mental Health Trust who wish to discuss long term support for their urine drugs of abuse (DOA) screening service.

The current situation in the Mental Health Trust is:

- they have a workload of 250 samples/week (200 from day clinics; 50 from inpatients.
- they currently analyse all samples on site in the Drug Dependency Unit using nursing staff trained by the instrument company.
- they have a recently procured dedicated immunoassay system (throughput 50 samples/hr) and have entered into a favourable 3 year reagent rental contract covering service, support and training.
- they require a Monday-Friday with same day results for IP samples and next day results for clinical samples.
- they feel unable to support the above situation indefinitely and are worried about 'quality issues'.
- they wish to negotiate MLSO staffing for their on-site analysis and associated quality support from Chemical Pathology.

The Directorate supports the above in principle and you are asked to advise the Business Manager on the key issues in respect of any future Service Level Agreement with the Mental Health Trust. In doing this:

1. What further information would you require about the current situation?

2. What would be the key cost elements in the proposed 'staff quality' package?

3. What quality standards might be incorporated into the agreement and how could they be monitored?

Question 2: Notes for Examiners

1. Extra information on current situation could include:

   - DOA profile required
   - Policy for any confirmatory analyses (if required)
   - Peaks and troughs of workload
   - Transport arrangements
   - Report validation procedures
   - Mode of transmission of reports
   - Standard of 'laboratory' facilities in the Drug Dependency Unit.

2. Cost Elements could include:

   - MLSO staffing:
     - state registered staff will be needed (working unsupervised)
     - workload suggests half-day commitment on M-F basis is necessary
     - cost of 0.5 wte MLSO 1 is approximately 8K pa + on-costs
   - Quality Support:
     - QC materials and documentation (if not in reagent contract)
     - EQAS participation costs
   - Requirement for consultant advice (if any)
   - Financial agreement for accommodating growth/reduction in workload

3. Quality Standards and Monitoring

   Important to realise that both parties can incorporate these.

   User (Mental Health Trust) may include:
   - Provider laboratory CPA status
   - Turn around times (how define??) – including any requirement for urgent analysis
   - EQAS performance

   Provider (Pathology) may include:
   - Minimum acceptable ID for samples and request forms
   - Deadline for sample delivery (to meet agreed TAT)

   Monitoring Arrangements
   - Monthly Report (activity; standards compliance etc.)
   - Audit of specific aspects as necessary

Candidates may well wish to propose a longer term strategy of performing the work in the central laboratory rather than a POCT exercise.

In making their response, candidates should show an awareness of the guidelines of the Joint Working Party or Quality Assurance (POC Testing) and the CPA standard requiring compliance with these.

Question 3

You receive a call from the 'Customer Services Manager' of your hospital saying that she has received a formal written complaint from the parents of a child being treated by the oncology firm. It concerns the clinical chemistry laboratory and she needs some information.

The gist of their complaint is that their son had to remain in hospital for an additional night because the result for a specimen sent to the laboratory, for a Methotrexate analysis, was not received in the late afternoon, when they had been promised it, but the following day. The medical staff had told them that the specimen, which had been taken in the early morning, would be analysed that day and that if the result was within their acceptable target range, as they expected, their son would be discharged. The lateness of the result had caused great distress to both the child and the parents together with the added inconvenience of an extra night at the hospital and the additional expense.

Methotrexate analyses are not performed by your laboratory but sent to a neighbouring hospital about 5 miles away, usually by taxi. Your preliminary investigation reveals that the specimen was received by your specimen reception at 09.15h on the morning in question but had not been sent to the referral laboratory. It had been discovered in a refrigerator in the late afternoon after a phone call from the requesting doctor who was trying to obtain the result. The specimen had been sent for analysis the following morning, and the result was within the target range.

What further information would you require to investigate the complaining in more depth?

What steps would you take to ensure that the same problem did not happen again?

You will be expected to draft a letter on behalf of the Chief Executive, who replies to all of the formal complaints received by the hospital. How will you word this letter?

Question 3: Notes for Examiners

1. Further information

- ƒ What was the standard procedure for sending Methotrexate specimens away?
- ƒ Was there a written protocol?
- ƒ Who had the responsibility for sending the specimen?
- ƒ Why had the specimen not been sent away?
  - ¾ Too busy
  - ¾ Inexperienced staff
  - ¾ Poor training
  - ¾ Etc
- ƒ Was the area being supervised?
- ƒ Why was it placed in the refrigerator?
- ƒ At the end of the investigation, what actually did go wrong?

2. Preventing a repeat of the problem

- ƒ Ensure correct training for all who undertake specimen reception.
- ƒ Written procedures for all specimens sent away.
- ƒ Adequate supervision for this crucial area.
- ƒ Reminder to all staff of the vital nature of the work in specimen reception.
- ƒ Sharing of the complaint with all staff, avoiding a 'who's to blame' approach.

3. Chief Executive's letter

- ƒ Apologise for the error, since the laboratory was to blame.
- ƒ Explain in outline what went wrong.
- ƒ Give mitigating circumstances if there were any.
- ƒ Explain that procedures have been put in place to prevent it happening again.
- ƒ Offer to talk to the parents or show them around the laboratory.

There are many avenues that can be explored with this case.

- ƒ Methotrexate treatment and regimes.
- ƒ 'No blame' culture vs. the witch-hunt.
- ƒ The response of the individual who made the mistake.
- ƒ The likelihood of the mistake happening again.
- ƒ Errors often being a combination of circumstances.
- ƒ Completing an 'incident report'.
- ƒ Who should perform the investigation?
- ƒ Learning from mistakes.
- ƒ Etc.

Question 4

You are three months into your Consultant appointment at a large District General Hospital. Thus you are perceived by your Clinical Director to be 'new blood' and are asked to be one of two Pathology representatives (the other is a Consultant Histopathologist) on the Trust's established General Practitioner (GP) Liaison Group. This meets every two months to review clinical and support services provision by the Trust.

After two meetings it is clear that there is general dissatisfaction with the Pathology services and Chemical Pathology seems to be singled out for much non-specific criticism. ('Too slow' and 'unhelpful' are familiar comments from the more vociferous GP's).

In subsequent discussion with the Clinical Director you express your concerns and 'volunteer' to conduct a formal review of user satisfaction among the GP's as the basis for changes in service provision.

In planning this exercise:
What approaches to gathering the required information would you consider and why? From your experience, what do you feel will be the key aspects of the services to GP's on which you will need to seek opinion?

Question 4: Notes for Examiners

It is likely that we would all have slightly different approaches to this problem but candidates might consider the following points:

Approaches to Gathering Information

Background
Existence of any current service agreement and standards.
Previous audits (if any) of service to GP's
Formal log of complaints from GP's (general or discipline specific)

New Information
Audit of current service
Questionnaire – validity? Design?
Visits to selected GP's (possibly with questionnaire)
Views of laboratory staff

Aspects of Service for User Opinion/Level of Satisfaction

May include:
Access ('opening hours')
Request form design (personalised; multidisciplinary)
Phlebotomy Services (?domiciliary visits)
Turnaround times
Transport of Samples and Reports
Availability of Consultant advice
Electronic Data Interchange
POCT Support
Management data on Pathology usage by practice
CPA Status (awareness!)
Participation in Clinical Audit

Pathology handbook/Information sheets/CD (covering much of the above information)

Some of the above will require an overall opinion, others (eg. consultant advice) may require discipline specific information.

Question 5

You are informed by the Laboratory Manager that the Trust is suffering long 'trolley waits' and is reorganising its Medical Admissions Unit (MAU) to enable better patient management. A Nurse Consultant has recently been appointed as part of this initiative. She has stated it is necessary for MAU to have a "machine that does D-Dimers and Troponins" to enable early discharge.

Develop your view of this information. What are the implications for patients, the Trust and the laboratory?

The Medical Policy Board decides that it needs the laboratory perspective. You are asked to attend one of their monthly meetings to inform them prior to their making a decision. Draft your submission highlighting the points to be made.

Question 5: Notes for Examiners

While a number of approaches are possible reflecting local practice the essential components of the candidate response should focus around recent National (MDA guidance) and publications on the utility (or otherwise) of such testing.

The candidate should be aware that:

- The Medical Devices Agency have issued guidance on point of care testing (POCT) which informs current practice.
- There are cross-discipline issues and they need to liase with their Haematology colleagues.
- The need to tactfully approach the Nurse Consultant as the information is indirect.
- Clinical decisions are ultimately the responsibility of the Medical Consultants and they therefore need to elicit their views. They need to obtain their perspective of the MAU.
- Issues such as turnaround time and IT (patient records, contiguity, the electronic patient record) are high relevant.
- The impact on the laboratory service of supporting POCT training, maintenance and supervision.
- The economics of the proposal (at different levels: direct cost, impact on unit, impact on Trust, societal implication)
- The need for a concise response setting out the position adopted incorporating timeliness, cost, staffing and training implications.
- The need for the use of management structures to effect input.
- Risk and Clinical Governance issues underpin such decisions.

Question 6

As the newly appointed head of clinical biochemistry you are called to see your clinical director. The contract for your main endocrine immunoassay analyser system is due for renewal in a year's time. Under pressure to make cost savings, the Pathology Directorate decides to take this opportunity to amalgamate the immunoassay functions of all the departments. As a result of a "process re-engineering study", the director has taken the irrevocable decision to undertake all the immunoassays formerly performed in the separate departments of haematology, clinical biochemistry, immunology, virology and microbiology in one laboratory area on the minimum number of new analysers. You are charged with drawing up a specification for the clinical chemistry analytical performance and implementing the changes. Indicate how you will deal with this within the time frame. What important elements must be retained to ensure service quality is not compromised by the new arrangements?

Question 6: Notes for Examiners

In a sense this is a gift to anyone who has had a part in change management, or works in immunoassay. However, candidates need to be able to see the bigger picture and work logically, even if they have never met the situation suggested in this scenario. There are a number of aspects to this question.

Specifying and selecting analytical system within time frame.

Need to draw up specification – workload, turnaround, speed of analysis, minimum volume, analytical performance (CV, EQA data, calibration frequency, etc), random access, add on tests, stats, assay list (which Troponin, hCG specificity) etc, etc.
Needs to be tendered through European Journal advert (for candidates from EEC!).
Timeframe should include allowance for seeing systems in hospitals, testing system etc. Need for redundancy in number of analysers to avoid downtime (?critical assays – troponins, hCG, etc).
Need to produce test script to test responses to tender against specification. How to deal with special tests – eg. IGF, GH, vitamin D, bone markers, rarer steroids etc not on standard platforms.
Need to define show-stoppers in terms of what is impossible (eg. workload incompatible with proposed configuration, (unable to perform stat hCG or Troponin for example.

Suitability of cross-discipline platforms

Compatibility of sample types.
Any precautions for high risk work (virology, etc) in mixed samples.
Ability to work random access or pseudo-batch.
Best of breed for all disciplines possible?

Arrangements for cross-discipline working

Working practices in each department, (eg. add-on-tests, follow-up tests).
Numbering systems and booking samples in.
Grade and training of staff operating analysers.
QC and calibration practices.
Sample storage (eg. paired sera for virology).
Authorising results from analyser and finished reports – different practices in different departments.

Implementing the change

(This is the key) – need for clear leadership and management structure for both implementing change and running new section.
Perhaps need to question idea of changing laboratory practices and analysers at the same time (forced to by resources but better not both at once).
Dedicated, experienced leadership essential at BMS and senior management level.
Training needs.
Visiting successful combined laboratories eg. The Netherlands, USA.
Communication, communication, communication!

Questions for medical candidates

Question 1

A 47 year old man presented to his GP with eruptive xanthomata over his elbows and hips. The GP arranged for fasting lipids to be measured:

Cholesterol	17.4 mmol/L
Triglyceride	28.8 mmol/L
HDL Cholesterol	0.5 mmol/L

He was referred to the local Lipid Clinic, and in the course of investigation for secondary causes of hyperlipidaemia he was found to have abnormal thyroid function tests:

Free T4	3 pmol/L	(10-24)
TSH	0.91 mIU/L	(0.5-6.0)

His identical twin brother was also screened and found to have very similar lipid and thyroid function test results.

How would you investigate these patients and what recommendations would you make about their management?

Question 1: Notes for Examiners

There are two aspects to this problem: the mixed hyperlipidaemia (which is reasonably straightforward) and the odd thyroid function tests (which we have still not explained satisfactorily).

Candidates should be aware of secondary causes of hyperlipidaemia and of the need to try lifestyle changes before considering pharmacological treatment. In fact both of these patients were still living with their mother and consuming a fairly unhealthy diet. Their weekly beer intake was around 14 pints each and they were not taking much exercise. They were advised accordingly and complied enthusiastically, so that drug treatment for the hyperlipidaemia was unnecessary. The xanthomata present in the first twin had virtually disappeared when I last saw him.

It is important to treat patients and not laboratory tests, so I would expect candidates to want more clinical information with regard to endocrine status. Neither man appeared to be hypothyroid. The only unusual points in their past medical history is that they both had Perthes disease as infants and they were considered to be ‘educationally subnormal’ and were educated in a special school. However, they both have engaging personalities and are both able to hold down jobs. They appear fit and well and have normal secondary sexual characteristics.

The first question thus seems to be are the thyroid results correct?

The TFTs were consistently abnormal using the in-house assay (Bayer Immuno 1), even when the samples were no longer lipaemic. Tests for heterophile antibody interference were negative. The Free T4s and TSHs were confirmed in another lab by a different commercial assay, and the Free T4 was also found to be low by an equilibrium dialysis method.

The TFT results seem to be genuine, so a pituitary cause seems to the next most likely explanation, even in the absence of any clinical evidence. Baseline pituitary hormones have all been normal, and response to intravenous Synacthen was also normal. This is as far as we have got to date – please note down any pertinent ideas from good candidates!

Question 2

Routine checking of the overnight emergency results reveals the following results obtained from an 80 year old woman admitted the previous evening. The clinical details are "? Obstruction".

Na	115	mmol/L	
K	2.8	mmol/L	
Urea	12.9	mmol/L	
Creatinine	81	umol/L	
ALT	26	IU/L	(9-52)
Alkaline Phosphatase	64	IU/L	(36-125)
Total Protein	67	g/L	
Albumin	42	g/L	
Bilirubin	18	umol/L	
Calcium	2.39	mmol/L	
Glucose	7.2	mmol/L	

A TSH had also been requested.

On contacting the ward, you discover the patient has a four week history of abdominal pain and has suffered from profuse vomiting for a week. She was admitted because she had become confused. The houseman had diagnosed SIADH, possibly secondary to gastric carcinoma and had put the patient on fluid restriction but the Registrar is not so sure and asks for your help.

How would you investigate this patient and what suggestions would you make about management?

Question 2: Notes for Examiners

I would expect the candidates to want to know her fluid status (put on Dextrose, saline 1L over 16 hours but had not yet passed urine, clinically rather flat but not markedly dehydrated).

The clinical picture is one of gastric outlet obstruction, which had been recognised by the medical team. They thought she might have a gastric carcinoma and this was causing SIADH and hence the fluid restriction therapy. However, this was unlikely as adenocarcinomas tend not to be associated with SIADH and her results suggested a degree of dehydration with a high albumin and urea for someone who had not been eating for weeks. Further, she has other reasons for low potassium concentration, from alkalosis due to loss of gastric acid and her drug therapy could cause the hypernatraemia. Finally if we accept she was significantly dehydrated, then she may have elevated ADH due to volume contraction from prolonged fluid loss enhancing water retention and causing relative hyponatraemia.

I would expect the candidate to:

1. Recognise this is unlikely to be SIADH and violates most of the principles underlying the definition of SIADH.
2. Suggest that the original therapy (fluid restriction) is potentially dangerous in a patient who has had significant fluid loss.
3. Be able to discuss the pathophysiology of the electrolyte response to prolonged vomiting.
4. Recognise the effects of drugs (and ask about them).
5. Recognise the need to suggest therapeutic changes to medical colleagues diplomatically!

I recommended checking her urine osmolality and sodium loss on a stat urine as I was sure she would be conserving it as much as possible given her drug therapy. I suggested she needed N saline with potassium IV to maintain her urine output and slowly raise her sodium. Fluid restriction was not indicated in a patient who was vomiting. If she had untoward sodium loss I would have measured a cortisol although this was not a typical picture of Addison's crisis and I checked the TSH as hypothyroidism could have complicated the picture.

Her TSH was normal. We never received a urine sample and her electrolytes approached normal in a couple of days on IV fluids alone, although her sodium has remained slightly low (they have now stopped her drugs so it may rise further). Her albumin dropped to 32 g/L once adequately hydrated emphasising her original fluid deficit may have been more than was apparent clinically. The gastroscopy showed severe erosive duodenitis but no malignancy and she stopped vomiting once her oral intake was stopped. She is now awaiting rehabilitation although it may be delayed as she slipped in the bathroom and banged her head!

Question 3

You are the most senior person in the laboratory when, at 5.15 pm on a Monday evening, the MLSO in your automated section brings you the following results on a 26 year old woman on a gynaecology ward.

Serum		
Sodium	108	mmol/L
Potassium	4.2	mmol/L
Urea	21	mmol/L
Creatinine	130	umol/L
Glucose	6.2	mmol/L
TSH	<0.1	mIU/L
Free T4	>50	pmol/L

You find the request form: the clinical details are 'hyperemesis gravidarum, agitated'. The patient administration system records that she was admitted late that morning.

What action do you take?

Question 3: Notes for Examiners

This woman was admitted in July, under the circumstances described. There are a whole host of possible answers that we could consider acceptable but clearly candidates must appreciate first that this woman is gravely ill and second that she may not be in the best place. I rang the Gynae SHO whose bleep number was on the form and explained that (a) this woman was thyrotoxic (b) severely hyponatraemic and thus (c) should be referred immediately to the physicians with a view to further management in the ITU.

Having established this, the candidate could then be invited to discuss the principles of management: it might be, for example, that the physicians were busy in A&E and would be unable to see her for an hour. In that case, it could reasonably be expected that the Chemical Pathologist should initiate immediate treatment . If that is the case he or she must go and see the patient (I hope that they would want to anyway).

Although from the history the probability is that the hyponatraemia is secondary to vomiting and inadequate sodium intake, the candidate should think about whether the lab can measure her cortisol urgently.

Details of management will depend on clinical assessment of course and candidates should be able to consider the principles which are straightforward, eg. cessation of any hypotonic fluid, very careful provision of hypertonic saline with regular biochemical, physiological and neurological monitoring, drugs to control vomiting (and fitting if necessary) for the hyponatraemia and anti-thyroid drugs, iodine, dexamethasone and beta-blockade for the thyrotoxicosis (if confirmed clinically).

The discussion might then lead to the dangers of severe hyponatraemia and its treatment, and/or the nature of thyrotoxic crisis – often of very sudden onset, precipitated by intercurrent illness, vomiting, etc. in a patient who may not have been diagnosed as hyperthyroid before.

Question 4

A 24 year old woman weighting 60 kg is admitted to hospital with an acute abdomen. She is diagnosed as having superior mesenteric artery thrombosis. Attempts to restore perfusion are in vain and she develops irreversible bowel ischaemia, necessitating resection of the small gut from a point 20 cm distal to the duodenal-jejunal junction, to a point 50 cm proximal to the ileocaecal junction, with construction of the jejunoileal anastomosis.

You will be asked to advise on her immediate and longer-term management from the point of view of maintaining fluid and electrolyte balance, and ensuring maintenance of her (previously good) nutritional status.

You may further be asked how this management would differ from that of a patient who has had a jejunostomy constructed.

Question 4: Notes for Examiners

These notes are fairly comprehensive – but general principles more important than detail.

Note that this patient does not have a jejunostomy. Preservation of the colon allows considerable absorption of fluid and although IV fluid supplementation will be required until bowel sounds return, it may not be required long term. The preservation of the ileocaecal value is also significant, as it may delay transit and increase the time for absorption of fluid (an nutrients) in the small gut. Nevertheless, diarrhoea is often a problem, and patient's oral free fluid intake should be limited; drugs such as Loperamide (to reduce intestinal mobility) may be helpful.

With less than 50 cm of jejunum, this patient is likely to require long term parenteral nutrition, but it is important to introduce early enteral feeding as much as can be tolerated. This helps to preserve the integrity of the gut and promotes adaptation in the ileum.

Malabsorption is usually a continuing problem, and nutrient intake must take account of this. A diet high in polysaccharides is recommended. These undergo fermentation in the colon to short chain fatty acids, which provide a valuable source of energy (NB hazard of D-lactic acidosis). A high fat intake will cause steatorrhoea, reducing transit time and water and mineral absorption in the colon but medium chain fatty acids can be reabsorbed from the colon. Diarrhoea and steatorrhoea may significantly reduce the amount of food/enteral supplements that a patient is willing to consume.

Oxalate urinary calculi are a recognised hazard and the diet should be low in oxalate. Vitamin supplementation is usually required.

In patients with a jejunostomy, the major early problem is fluid loss. Intravenous replacement is always required – stoma output can be up to 8L/24h and is exacerbated if oral fluids containing inadequate sodium are given. The concentration of sodium in oral fluid should be 100-120 mmol/L and the addition of glucose facilitates sodium and water uptake. Loperamide and drugs to reduce secretion (Omeprazole, Octreotide) are often useful. Magnesium supplementation is usually required, potassium supplementation may be.

Long term parenteral nutritional support is always required with less than 75 cm of jejunum, but in addition to whatever enteral intake is possible. Patients with up to 200 cm jejunum usually require enteral supplementation (eg. overnight gastrostomy/ nasogastric) but can usually manage without parenteral support. Enteral supplements should be iso-osmolar and high in salt – note that elemental diets are usually the opposite – hyperosmolar, low salt, and may exacerbate fluid loss. Vitamin B12 supplementation is essential.

Question 5: For Medically Qualified Candidates

A man you discharged some years ago is referred by the GP back to your lipid clinic:

	Referral 1	Referral 2
Age	57	68
Presentation	Mixed hyperlipidaemia discovered during blood donation 13 years previously. Been on diet and Clofibrate in the past, but no treatment at present.	Lipid medication changed to Simvastatin a few months ago: lipids now worse.
Exercise tolerance	Walks for miles without ill effect. Occasional chest tightness and difficulty breathing brought on by jarring movements and eased by leaning forward.	Still a keen walker, but has noticed some chest tightness and 'fizziness' in his left arm when walking uphill during a monthly 8 mile hike with friends.
Past medical history	Has had attacks of gout in the past	Recent urological investigations after passing small blood clot in urine; no pathology found.
Medications	Nil at present.	Nifedipine m/r 30 mg bd Simvastatin 40 mg nocte
Smoking history	Non-smoker from age 18.	Non-smoker from age 18.
Alcohol intake	Six units per week.	One bottle of red wine per week.
Family history	Mother died of stroke at 65 after 4 year history of angina. Father has gout. One brother has peripheral vascular disease and hypertension. Sons of 29 and 27 not investigated.	As before, plus: elder brother died of MI at 68; younger brother of 65 had MI last year; sister of 60 on treatment for hypertension. Sons of 40 and 38 not investigated.
On examination	Well. No signs of lipid deposition. BMI 28.7.	Well, apart from a small amount of bilateral pitting ankle oedema. BMI 31.2.
BP mm/Hg	190/110	170/110 (140/82 earlier in the day on own BP meter!).
Fasting lipids (mmol/L): Cholesterol Triglyceride HDL cholesterol	 11.3 8.6 0.6	 7.8 16.0 0.7
Fasting plasma glucose mmol/L	5.5	9.6

On the first occasion he was discharged on Bezafibrate 400 mg nocte and Nifedipine 30 mg bd. His lipids then were cholesterol 6.5 mmol/L, triglycerides 3.9 mmol/L, HDL 0.8 mmol/L and LDL 3.9 mmol/L, his BMI was 27.8 and his blood pressure 144/84

How would you investigate and manage this patient now?

If the first referral was being made now, would your investigation and management be any different to what it was 11 years ago?

Question 5: Notes for Examiners

This clinical scenario is taken from a real case and should be familiar territory for anyone who has worked in a lipid clinic. However, there is a lot of material here, so it is important for candidates to prioritise their responses. I think the aspects to focus on first are as follows.

How would you investigate and manage this patient now?

The clinical history is suggestive of angina and needs further investigation. He had a positive exercise test, positive coronary angiography and is awaiting CABG.

Glucose: his fasting plasma glucose is in the diabetic range, although this was the first raised glucose on record and he was asymptomatic. Further biochemical evidence was sought (and readily obtained) to support the diagnosis. A dietitian gave appropriate dietary advice.

Lipids: the Simvastatin is clearly not keeping his lipids within ideal limits. It was stopped and he started Fenofibrate 267 mg nocte. After a couple of month he had managed to reduce his BMI to 29.4 and the combination of this and the Fenofibrate improved his lipids to:

Cholesterol	5.7 mmol/L
Triglyceride	3.3 mmol/L
HDL	0.9 mmol/L
LDL	3.3 mmol/L

This is encouraging, but in view of his very high risk, a small dose (10 mg) of Simvastatin was added back in (with appropriate warnings etc.), with further improvement in the profile (non-fasting cholesterol 4.8 mmol/L).

Blood pressure etc: Nifedipine may have been implicated in his ankle oedema.
Currently on:

Ramipril	2.5 mg daily	
Atenolol	50 mg daily	
Nicorandil	10 mg bd	
Lansoprazole	30 mg daily	
Aspirin	75 mg daily	
Nitrolingual spray	prn	plus lipid lowering drugs.

Family: his two sons should clearly be encouraged to have their lipids and other risk factors checked.

If the first referral was being made now, would your investigation and management be any different to what it was 11 years ago?

The way we assess risk, the evidence in favour of the benefits of risk factor management, the drugs available and the targets of treatment have all changed over the years, so it is not unreasonable to ask this question. It is more difficult for the author to be objective about his own practice! However, some possible topics for discussion are:

Should the patient have had an exercise test at the first referral?

The lipids at discharge are not as good as current practice would wish.

I have heard it argued that everyone with raised triglycerides should have a glucose tolerance test, irrespective of their fasting glucose. The rationale for this is that one would

be more likely to treat their hyperlipidaemia if the 2-hour glucose were raised. Since this patient was treated anyway, it does not seem an important consideration here.

The two sons should have had a CHD risk factor assessment before now.

There are other biochemical markers of CHD risk that could have been checked, although I am not convinced that the results would have made any difference to his management.

No one seems to have taken much interest in the management of his gout.

(NB. All the usual tests for secondary causes of hyperlipidaemia were negative).

Question 6

52 year old male bus driver presented with a 6 month history of increasing weakness.
He was previously healthy.
Weakness severe enough to require help.
He also complained of diarrhoea on and off for the past 4 months.
He also complained of generalised bone pain.
He is a non-smoker, does not drink alcohol.
Examination unremarkable except for muscle weakness – worse in proximal and lower limbs.

Investigations

Renal function tests – normal.
Liver function tests – normal.
FBC – normal.
Calcium 2.28 (2.15-2.55) mmol/L
Phosphate 0.40 (0.80-1.30) mmol/L
ALP 376 (<126) IU/L

What further investigations would you recommend?

ALP isoenzyme studies showed ALP to be predominately of bone origin
TmP/GFR 0.23 (0.7-1.3) mmol/L
Serum PTH 25 (10-65) ng/L
Serum 250HD 82 (50-150) nmol/L

How do you interpret these results?

Suggest a possible diagnosis.

What advice would you give regarding the management of this patient?

Question 6: Information for Examiners

What further investigations would you recommend?

First confirm the low phosphate to exclude a transient decrease in phosphate due to transcellular shift. Persistent low phosphate can cause muscle weakness.
Next step is to exclude vitamin D deficiency.
With a history of diarrhoea a malabsorption syndrome needs to be considered.
Faecal fat measurement was done and it was found to be normal.
Vitamin B12 and folate and full blood count were all normal.
Measurement of serum 250HD and PTH and renal tubular reabsorption of phosphate are necessary.

How do you interpret these results?

Low TmP/GFR indicates reduced reabsorption of phosphate.
In vitamin D deficiency secondary hyperparathyroidism will cause low TmP/GFR and low serum phosphate. Serum PTH and 250HD are within the reference range and this makes vitamin D deficiency unlikely.

Suggest possible diagnosis.

Inherited hypophosphataemic disorder is unlikely – age and recent onset .
Oncogenic osteomalacia is the most likely diagnosis.

What advice would you give regarding the management of this patient?

Attempts to find the tumour were made and these were initially unsuccessful.
Treatment: Calcitriol and phosphate supplements. These improved symptoms and serum phosphate increased to 0.7 mmol/L.

Questions for Clinical Scientists

Question 1

'What action would you take when you discover that, due to a mechanical failure on a large automated analyser involving specimen sequencing, 100 sets of general clinical biochemistry results have been reported against the incorrect patient identities?'

The results had left the laboratory 36 hours previously and were from patients on medical and surgical wards, and patients seen in outpatients, renal clinics and by general practitioners.

Question 1: Notes for Examiners

The suggested action might be along the following lines:

1. Inform all staff receiving requests for results over the phone, of the extent of the problem, including the specimen accession numbers involved, and instruct them to explain that these results are being rechecked. Where urgent clarification is need recommend specimen recollection.
2. Identify correct results either by reanalysis or, where possible, reliable correction of mismatched specimen and patient identity.
3. For each patient, compare correct with erroneous results, any previous results and the source of the request.
4. Based on this information, 'triage' reports into those requiring immediate action because of patient status and the magnitude or significance of the discrepancy. (eg. preop/post op, time taken for report to reach user, such as computer report or hard copy).
5. Attempt to contact medical staff and nursing staff concerned for high priority patients identified above.
6. Amend computer database (both Lab and Hospital) with correct results. There is an issue of transparency here so that accusations of a 'cover up' cannot be laid.
7. Issue amended hard copy reports with an explanatory comment regarding previous erroneous results.
8. Investigate and document the circumstances of the incident following the local policy for 'Incident reporting'.
9. In addition to reviewing the mechanical failure and taking steps to prevent a repetition, investigate how procedures for analytical validation and clinical credibility failed to identify the error earlier.

Question 2

After many years of using a traditional wet chemistry analyser to provide the bulk of your analyses, you are about to replace this with a modern discretionary analyser. The old analyser required very frequent calibration; the manufacturers claim that each assay which is run on the new analyser will only require calibration at intervals of 3 to 6 months.

Outline the internal quality control system you think appropriate to maintain the quality of analyses on the new analyser.

Question 2: Notes for Examiners

Every candidate should know that classical internal QC techniques are designed to detect unacceptably large changes in bias caused by calibration or reagent changes. In essence, such techniques rely on deciding whether a QC signal (usually the result given by a QC sample) lies within or outside a pre-set limit, which is usually a line drawn on a 'QC chart' (at for example 3 SD away from the mean), often refined by further rules such as those proposed by Westgard. The response to a result lying outside the limit is to re-calibrate and possibly to change the reagents.

Every candidate should realise that the QC problems with modern analysers are different. They are not about sudden stepwise changes in bias. They are about very slow changes in bias with time (drift), about periods of deteriorating precision associated with less than optimal analyser performance, and about occasional fliers. Candidates should realise that classical QC techniques are inappropriate to these problems.

A more appropriate QC system must include:

1. Checking whether bias is acceptable after calibration (eg. by comparison of QC results or patient sample results before and after calibration).

2. Monitoring very small bias changes over time, to decide the point at which re-calibration is necessary.

A good candidate should point out that it is difficult to detect fliers, and this can usually only be done by comparing results with previous results on that patient (delta checks) or by comparing results with clinical information and/or with that is credible. The appropriate response is of course to repeat the analysis.

An extremely good candidate may mention the problem of periods of increased imprecision. There are several ways to look at this – the number of patient results falling outside the reference range is often a good guide. The appropriate response to worsening imprecision is to check instrument maintenance; and if necessary call the manufacturers in.

It may also be possible to push a good candidate into a discussion of what constitutes acceptable performance, both for bias (particularly for hormone analyses) and for imprecision (should be based on biological variation). Classical QC tends to be directed towards technical achievability, not biochemical desirability.

Question 3

You are telephoned at home at 11.45 pm by a House Officer in the Accident and Emergency Department, who would like an urgent blood ethanol measured on a 17 year old boy. He has been involved in a road traffic accident, and the House Officer explains that the boy's parents are anxious to know the result.

What do you do?

Question 3: Notes for Examiners

This is a difficult real-life problem, and there are three distinct issues.

1. Medical
   In my view, the only medical justification for measuring ethanol in this case would be if the patient had an altered state of consciousness, which could be related to ethanol or could be related to a head injury. Knowledge of the ethanol concentration could therefore affect subsequent medical assessment and treatment. If so, this is a justified demand which could well be urgent. Without an altered state of consciousness, there is no justification for measuring ethanol for medical reasons in this case.

2. Legal

   I think there are two main legal issues.

   a. Confidentiality
      1. The Victoria Gillick case established that even children of 15 have the right to medical confidentiality. The House Officer must be told that any results, particularly an ethanol result, should only be given to the parents if the patient agrees. Where there is reason to believe that a crime has been committed, the police may obtain authorisation to see medical records or seize samples – authorisation may be given by for example a Coroner, a Judge, etc.
   b. Assault
      A blood sample which is potentially to be used for non-medical purposes can only be taken from a patient if the patient agrees (or if unconsciousness, his next of kin or other representative). I am unsure to what extent the parents of a minor can give consent if the minor himself disagrees.

3. Ethical

   This is particularly difficult.

   I personally believe that we should neither help nor hinder the police. However, where there is reason to believe that a crime may have been committed, then there is a public duty to ensure that as far as possible any relevant evidence is retained. In this case, there are three main scenarios.

   a. The patient is the driver of a motor vehicle. Potentially, a sample for blood ethanol measurement could be instrumental in showing if he had driven while over the statutory limit.
   b. The patient is a pedestrian who was hit by a motor vehicle. The sample could then be important evidence in a charge of dangerous driving by the driver of the vehicle.
   c. The patient was a passenger in a motor vehicle. In this case, his blood ethanol is likely to be irrelevant to any crime which may have been committed.

   My own feeling is that if (a) or (b) apply, one should make an effort to obtain an appropriate sample for blood ethanol measurement (although probably not to measure it). However, to stay within the law, consent for this sample must be obtained from the patient or his representative. It will be necessary to point out that in the event of a crime, the result could help the prosecution or help the defence.

Question 4

You are contacted by a GP who wants to discuss the creatinine result on a full biochemical profile on a 53 year old lady, and would like advice on further tests.

Na	141	mmol/L	Alkaline phosphatase	148	U/L (RR<150)
K	3.9	mmol/L	Total Protein	69	g/L
Urea	6.8	mmol/L	Albumin	39	g/L
Creatinine	250	umol/L	Bilirubin	7	umol/L
Calcium	2.20	mmol/L	AST	27	U/L (RR<50)
Phosphate	0.69	mmol/L			

The clinical details given at the time were “Routine screen”. You note a previous creatinine one month ago was 213 umol/L and that haematinics taken at that time were normal. In his introduction the GP reveals that the lady had non-specific malaise with vague back and loin pain but had no previous medical problems and had rarely bothered the surgery. One month ago a haemoglobin of 9.7 g/dL with normochronic normocytic picture and ESR of 62 mm/h had prompted the haematinic request and three faecal occult bloods were normal.

What information do you require from the GP and what further tests would you undertake on this sample or suggest in the future?

Question 4: Notes for Examiners

This is a real case from last year. The lady obviously had some nephropathy but the absence of a raised urea in the face of quite abnormal creatinine was very odd. The first things I checked with the GP were that they had checked her BP and urinalysis – ie. was this diabetic or hypertensive nephropathy. Her BP was normal and he thought urinalysis was negative.

I then asked about drugs, concerned about a drug induced nephritis – she was using an NSAID (I forget which) but not regularly. However I would want to try and draw out the association of NSAID with nephritis and raised creatinine.

I was concerned at the time about some fliers on our creatinine method (Vitros dry slide) and sent it for analysis a different way (Olympus – Jaffe). It came back identical.

I think it would be reasonable to suggest asking for a urine protein and MSU in view of her symptoms in order to eliminate chronic nephritis but we never got to that stage as we got the diagnosis on the sample we had.

I was then left with endogenous causes of nephropathy of which there are 3 easily eliminated ones – myoglobin (no muscle symptoms except the vague back pain which could have been renal), uric acid (but urea is usually elevated and no joint pains) and myeloma proteins. I asked for a CK, forgot about uric acid, and despite the normal protein requested an electrophoresis.

Electrophoresis showed a strong band which typed as free kappa light chains only with immune paresis. This explains the lack of dipstick proteinuria and normal globulins. The normal calcium was a good prognostic point (but the only one – her low urea was actually a bad sign as it indicated massive anabolic activity and aggressive low grade disease). Had we got round to measuring urine protein she had grams of pure Bence Jones protein in her urine when worked up elsewhere by the haematologists.

This lady has an aggressive Bence Jones myeloma. She has had marrow ablation and a transplant but has a very poor prognosis of less than 5 years survival.

Question 5

You have received a letter from NEQAS pointing out your poor performance in your plasma urate assay. The letter states that your results have been very variable, with major biases being seen either side of your method mean on different samples. Some recent NEQAS returns are included in the following table.

Return Number	Method Mean	Your Result
101	105	133
102	257	265
103	98	129
104	555	434
105	200	211
106	425	357

Can you think of some possible explanations for these differences and explain how you would investigate further?

Question 5: Notes for Examiners

From the NEQAS data it could be supposed that there may be a calibration problem, with either the method group or your particular assay. It appears for high results your laboratory is reporting results that are too low, and for low results your laboratory is reporting results that are too high. At concentrations of urate of approximately 240-260 umol/L your laboratory agrees with the consensus mean.

Possible actions:

- Establish whether the correct results had been sent in.
- Establish whether the laboratory has been put into the correct method group.
- Establish from the NEQAS return whether the method mean is different to the other reported method means.
- Check your internal QC charts to check the precision, to see the amount of acceptable variation you may expect for a serum urate assay (CV's ~ 1-3%), ie. can the results be explained by analytical variation. Do the charts show any variation over the measuring range for urate?
- Establish whether your laboratory performs the assay as per protocol, or whether you use different calibrators, single-, multi-point, force-, do not force through zero.
- The outcomes of these questions could lead you to think whether your laboratory is "right" or "wrong". It would be wrong to presume that the method mean is actually the correct answer. Further action could range from doing some simple experiments to contacting the company and NEQAS to discuss the problem.
- Simple experiments could include "spiking" a sample with a known concentration of urate (the candidates should think about how they would spike a sample with a high concentration of urate), double diluting serum/control with saline (once again what effects could this have, eg. matrix problems).
- Time and money permitting you could check your method against an authenticated standard, or get your friendly expert to measure some sample by isotope dilution MS.

You never know sometimes you can be right and they can be wrong!

Question 6

How would you assess a Laboratory's performance?

Question 6: Notes for Examiners

Candidates should be able to come up with a range of answers, those sticking just to QC and EQA should be encouraged to think wider.

EQA performance
- Analytical
- Clinical Comments

CPA

Error rates - Types of error (is it even measured?)
- Clerical
- Analytical
- Clinical Authorisation

Good risk management with follow up of mistakes and near-misses

Turnaround times

Clinical Audit participation

How many calls to the duty biochemist are made per day
(Personal opinion is that if high indicates good use of Lab expertise, but open to argument)

Laboratory initiated and collaborative research
- Publications
- Research funding

Teaching
- Biomedical Scientists
- Clinical Scientists
- Junior medical staff/medical students (if teaching hospital)

Feedback from users (CPA are particularly interested in this)

Others?