The Anaesthesia Science Viva Book

Simon Bricker

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Clinical science as applied to anaesthesia, intensive therapy and chronic pain

A guide to the oral questions

Simon Bricker **MA, MBChB, FRCA**
Examiner in the Final FRCA
Consultant Anaesthetist
The Countess of Chester Hospital
Chester, UK

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Preface

The Final FRCA examination has a daunting syllabus which is tested by a multiple choice paper, by written short answer questions, and by two oral examinations, one in clinical anaesthesia, and a second in applied basic clinical science. This book is intended to give you some insight into how the clinical science viva works, along with some general guidance as to how to improve your chances of passing. More importantly it aims to provide you with a wide range of potential questions which contain, nonetheless, a manageable amount of information.

The introduction explains the format of the viva, outlines how the questions are constructed, conducted and marked, and offers some advice about technique. The questions then which follow, which are typical of those which have appeared, are divided broadly into the four areas which the examination is designed to cover, namely applied anatomy, physiology, pharmacology and clinical measurement. One section, entitled 'Miscellaneous Science and Medicine' includes a number of subjects which do not fall readily into any of the other categories.

You may notice that there is some overlap in content with the companion volume, 'Short Answer Questions in Anaesthesia'. Where this has happened I have reworked the answers both to give more detail and to focus the topic more specifically towards the oral part of the examination, but a degree of duplication in one or two of the questions is inevitable.

The answers have been constructed to provide you with enough information to pass the viva, but as I have had to be selective in the detail that has been included they cannot claim to be complete accounts of the subjects. This means that in some areas you may notice various omissions, but none I hope so egregious that your chances of success will be ruined. Each of the questions is prefaced by a short commentary on the relevance (or otherwise) of the subject that is being asked. There follows the body of the answer to the likely areas of questioning. This is presented mainly in the form of bulleted, but detailed points, which include supporting explanation. These are written in text rather than as lists, because I felt that this format would make the book easier to read. If some of the questions seem long, then it is either because the background information is complex, or because they contain enough material for more than one viva topic.

Even in a structured examination a viva may take an unforeseen course, and so the answers also include some possible directions which the questioning might follow. Although each one is intended to provide details more than sufficient to allow you to pass, in many cases they are simplified, and it is always possible that some examiners may ask part of the question in more depth than can be covered in a book of this size. There are 150 specimen questions in this book, and on the day of the examination you will be asked only four. Odds of about 40 to 1 or less do not provide a huge incentive for study, but I should hope that some of the material would be relevant to your anaesthetic practice. The material that you do find of little clinical relevance may at least prove of some future use as in due course you guide less experienced colleagues through the FRCA.

I promised my family that I would never again succumb to the temptation of writing a book. I lied. To my wife and three boys, therefore, my love and thanks for all their patience and support.

Simon Bricker
2004

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Advice on answering clinical science viva questions

The clinical science viva

The format of the current Final FRCA (Fellow of Royal College of Anaesthetists) examination has changed little since its inception in 1996, and the clinical science viva is intended still to test *the understanding of basic science to the practice of anaesthesia, intensive therapy and pain management*, with the proviso that *it is accepted that candidates will not have acquired a detailed knowledge of every topic during the period of recognised training*. To which some past candidates might respond testily that you could have fooled them, sometimes given their bitter perception that they had been examined almost to destruction on scientific minutiae.

This perception has been acknowledged recently by the college, which as a result is encouraging its examiners to emphasise the clinical application of the underlying science, rather than concentrating on those details which were meant to have been tested in the Primary FRCA examination. The basic science bias does, nonetheless, persist, if for no other reason than that many examiners are reluctant to dilute the rigour of what for most candidates will be the last examination in anaesthesia that they will ever take. This recognition on the part of the college, however, does mean that many of the clinical science questions will have two parts, namely the underlying science and its application. A question on anatomy, for example, may be completed by a discussion of relevant nerve blocks; and a discussion of magnetic resonance imaging (MRI) or lasers is likely to be followed by questions related to safety. The proportion allocated to the two parts of the question may well depend on the examiner's own interest and knowledge of the subject, but you will not be able to depend on your clinical expertise alone to get you through the viva. If there is doubt about your performance, the examiners are more likely to refer back to your knowledge of the facts of the underlying science, rather than to what may just be your clinical opinion.

The viva lasts 30 minutes, during which time you will be asked questions on four different and unrelated subjects. The time spent on each question should be similar, between 7 and 8 minutes.

The marking system

In common with all parts of the FRCA examination a 'close-marking' system is used. This means that instead of being given a numerical mark a candidate is awarded one

of the four grades, which range from '1' to '2+'. A '1' represents a poor fail and '1+' a fail; a '2' is a pass and a '2+' is an outstanding pass. One of the reasons for the close-marking system is to force examiners to make the definite choice between a pass and a fail, which a numerical marking system might otherwise allow them to avoid. A '1' mark in any part of the examination means that the candidate has been judged either to be potentially dangerous, or to be too ignorant of the fundamentals of anaesthetic practice to pass, even should their other marks include three '2+'s. A '2+' represents an outstanding pass, which is indicative of a potential prizewinner. A prize may be considered if a candidate achieves a '2+' in each of the four parts of the examination at their first attempt. For most candidates, therefore, the '1' and the '2+' marks are largely theoretical: what is much more important for them is the distinction between a '1+' and a '2'.

How the viva is marked

You will be aware that the FRCA is a structured examination. The material on which candidates are to be tested is now made available to the examiners in the week prior to the examination, but in random order. Previously they had access to the questions only on the day. At the examination itself the questions are allocated to sessions, such as *Monday 1*, and the sheet will include the four topics on which the candidates are to be examined during the first session of the vivas. The questions are changed after each session to avoid any possibility of later candidates obtaining unfair advantage. Each pair of examiners will decide between themselves which two questions of the four they are going to ask. That broadly is the extent of the choice that they are able to make, because the scope of each question is limited both by the guidance answer and by the relatively short time available for each topic. The first examiner will spend 7 or 8 minutes on the first subject before changing to the second. At the first bell, the other examiner will repeat the process. The examiner who is not asking questions will usually be making detailed notes, which will help to inform the marking process. At the end of the viva each examiner records an independent mark before conferring. It is usual for each question to be marked using the close-marking system, and it is from these marks that the final mark is agreed. The decision to confer a pass or fail will rest mainly on how well you have conveyed the scientific knowledge that was asked of you. But if you really are a borderline case then it is *probable* that clinical aspects of your performance will decide your fate. Should you have been weak on some of the basic science but have been reassuringly confident about clinical management then it may just tip the balance in your favour. The examiners try to look at each of the four topics separately before marking the viva as a whole. Do not, therefore, lose all heart if you feel that you have answered a question particularly badly. Try and leave it behind you, because your other answers may be able to redeem it, and you should not forget that all four questions are totally unrelated.

Appearance and affect

You cannot fail the Final FRCA because of your appearance or poor dress sense, and most examiners will be able to recollect candidates whose personal presentation could at the least be described as unconventional. At worst, however, an unkempt or casual appearance may convey the subliminal impression that you are unprofessional, and at best it is likely to be a distraction. It is sensible to wear something neutral and reasonably smart, which above all is comfortable and which you have worn before. The examinations areas can be hot, particularly in summer, and there is no need to increase your already high stress levels by forcing yourself into a three-piece suit or other outfit that sees the light of day only for weddings and funerals.

You also cannot fail the FRCA because of inappropriate behaviour alone. Examiners are well aware of the stress that candidates are enduring, and many will make every

attempt to put you at your ease. They are also likely to assume that aggressive or facile responses are a manifestation of that stress and will make allowances accordingly. On one occasion, for instance, an aggressive candidate almost shouted *For God's sake don't ask me that – I've never even thought about it,* before ending her viva by saying *Thank heaven that's over – and thanks for nothing*. Other candidates, in contrast, can be very facile. Take the individual, for example, who replied to a particular question by responding that *I'll probably know the answer when you tell it me,* or another who was asked about etomidate, and who took what might be called the Bertie Wooster approach to vivas by riposting *It blocks the 1,2 hydroxy-whatsit, oh I don't know, I think you give the stuff and the atom bings off.* Examiners up to a point will be indulgent, but the overall impression that you are creating will not be reassuring, and if an inappropriate manner is accompanied by a weak performance then you will stand little chance of being given the benefit of the doubt. Take issue with examiners, by all means: it is stimulating for both sides to develop a considered discussion of a topic, but avoid getting into an argument, because the odds are not stacked in your favour.

There are rare occasions, perhaps not surprisingly given that a viva is a human interaction, when a candidate or examiner may take an immediate dislike to the other. If as a candidate, you find your examiner thoroughly disagreeable, then you will have to accept it philosophically and not let it show. The rules of this particular enterprise are not written to your advantage, and if you are angered or irritated by your questioner then you are very unlikely to perform at your best. What if it is the other way round, and the examiner, for whatever reason, takes an instant dislike to you? You need not worry. The examiner will be aware of the potential loss of objectivity and will therefore try hard not to let any hostility influence the marking process. In practice they are likely to overcompensate and mark more leniently than otherwise they might. It would probably be unwise, however, deliberately to be obnoxious in the hope of achieving this effect.

Oral questions

On average you will have about 7 minutes on the topic. Should a question have somewhat limited scope, or if your knowledge is thin, you may spend only 5 or 6 minutes or so discussing it before moving on for the final 9 or 10 minutes to a more substantial subject. As explained above, these vivas are structured and the examiners have no choice of question. Although it would be logical, given the avowed purpose of the clinical science viva, to subdivide the questions into anaesthesia, intensive therapy and pain management, in practice they do not fit readily into these categories. In the past, the four questions could be somewhat random: more recently it has become usual to have one question which relates to applied anatomy, one to physiology, one to pharmacology and one to physics, clinical measurement, equipment and statistics. This classification is not absolute: topics such as jaundice or latex allergy do not fit strictly into any one of these groups, but it does indicate the broad division of the available questions. The structured nature of the examination minimises the likelihood of an examiner being able to question you in excessive depth on a subject which happens to be their area of special interest or expertise. It also increases the probability of an examiner having to ask questions about a subject in which they do not even have a current generalist interest. The sub-speciality interests of examiners clearly change as retiring examiners are replaced, but at any one time only about 15–20% will have an interest in intensive care medicine, in paediatric anaesthesia or in neuroanaesthesia, and an even smaller number will work in chronic pain management. Thus a paediatric cardiac anaesthetist may find himself asking questions about adult ophthalmic applied anatomy, a neuroanaesthetist questions about neonatal fluid requirements, or an obstetric anaesthetist questions relating to intensive therapy ventilatory strategies. These examiners will not necessarily be ignorant of these topics, but it is certainly possible that your own clinical experience

will be more recent and better informed than theirs. This should give you confidence, and you should not let the stress of the examination situation override it. Many candidates will have had direct experience, for example, of the technique of percutaneous tracheostomy in intensive care. Unless your examiner is an intensivist, it is possible, if not probable, that he or she has performed not even one, and so your own clinical experience in this area is already much wider than theirs. Draw confidence from this, and do not be intimidated. The examiner guidance may well say, for instance, that the approach should be through the first and second tracheal rings, whereas you may be well aware of the increasing tendency to site the tracheostomy lower. If you do get the sense that the examiner is unhappy with your answer mainly because it does not accord with what is written on the sheet, then have the confidence to explain the current thinking. Do not be argumentative, but simply offer your considered reasoning of the issue. This is likely to increase your own credibility while somewhat denting theirs. So if you have recently seen an innovative technique used in the operating theatre, in the chronic pain clinic or in the intensive care unit then cite it in discussion.

The other consequence of the format of the structured viva is that it may lack fluency. It is partly a reflection of the examining technique. Some examiners simply introduce the question before initiating a discussion with only occasional reference to their paperwork. This is usually because they are familiar with the material, and can allow the viva to run a more spontaneous course because they have confidence enough in their own ability to assess the answers. An examiner who is less comfortable with the topic and who is less certain of the criteria against which the answers are to be judged, is likely to spend much more time referring to the answer sheet. Alternatively, of course, they might just be particularly pedantic in their interpretation of how a structured viva should be conducted. You may get a clue as to which of these you are facing by the way that they introduce the topic. One type of examiner may start by saying something like, *I imagine that you spend some of your time on call covering intensive care? Well, let's spend this first part of the viva discussing ways of supporting the circulation, in particular by the use of inotropes*. This kind of examiner is trying to put you more at ease by framing the question in a clinical context with which you will be familiar, while also emphasising the clinical application of the subject under discussion. The second type of examiner may simply look down at the sheet and intone *What is an inotrope?* This second examiner is likely to want facts, and ideally the facts that are listed on the answer paper. He or she clearly has not realised that you are not telepathic. If, however, you do have some confidence both in your knowledge and in your clinical experience you may be able to get them on the defensive. Remember that such an examiner may never have used dopexamine or enoximone, and if you sense a slight uncertainty which confirms that suspicion, then expound as freely as they will let you. Remember also that this may be the limit of the manipulation that you will be able to employ.

What you may be able to do, however, is to pace the viva. The clinical science questions broadly have two parts, namely the basic science and its application. In general the underlying science represents the core aspect, because there may often be less to discuss about the direct clinical implications. The examiner may then have to move away into diffuse topics that may be only distantly related to the main question. Take, for example, the humidification of inspired gases or the anatomy of the inguinal region. The questions about the measurement of humidity and different methods of humidification will occupy much more time than the discussion of the clinical benefits. Equally the anatomy of the nerves supplying the lower abdominal wall will take longer to discuss than the description of a field block. There is a danger, therefore, that if you complete the first part too rapidly then the viva may drift away from the core topic and meander round subjects that will neither gain nor lose you much credit. The overall impression, however, may be that your knowledge about the main subject was sketchy. To an extent, therefore, you will have to gauge what is the key area of

questioning and concentrate on supplying as many details as you can muster. This applies particularly to anatomy. If you are able to give a detailed account, which defers your proceeding to the supplementary questions, then so be it. You will have passed on the question that you were asked, and it is the examiner's responsibility to move the viva onto other areas if he or she so wishes. As an extreme example of this process, there was one sitting of the examination in which a candidate who was in full flow about a topic was interrupted by a newly appointed examiner, who having recognised that the individual was very knowledgeable wished to move onto another area. The candidate paused, looked him in the eye and announced *No, thank you, but I would like to finish,* before talking almost until the bell sounded. He passed. Embark on that brave strategy only if you have substantial and justified confidence in your abilities, because usually you will be unable to manipulate the viva and it will not work.

What you can do, however, is refine your viva technique to improve the overall impression that you create. Take, for example, two imaginary candidates who have been asked about the Poiseuille–Hagen equation. The examiner initiates the questioning in an interchange which may go as follows:

Examiner: Does this have any clinical relevance?
Candidate: Yes.
Examiner: Can you give me some examples?
Candidate: It affects fluid flow through tubes.
Examiner: In what ways?
Candidate: If you increase the driving pressure, then you increase the flow.
Examiner: Anything else?
Candidate: If you increase the viscosity of the fluid then the flow will decrease.
Examiner: Are there any other important factors?
Candidate: The diameter of the tube is important.
Examiner: In what way?
Candidate: If you double the diameter then the flow will increase by sixteen times.
Examiner: In what clinical situations may this be of importance?
Candidate: In giving fluids.
Examiner: Can you think of any others?
Candidate: Airway obstruction in children.

The interchange with the second candidate begins in the same way, but thereafter is somewhat different.

Examiner: Does this have any clinical relevance?
Candidate: The Poiseuille–Hagen equation strictly speaking applies only to Newtonian or ideal fluids, but in practice it still has both cardiovascular and respiratory implications. The relationship means that gas or liquid flow through a tube is inversely proportional to the length and viscosity of the fluid, and is directly proportional to the pressure gradient down the tube and, crucially, to the fourth power of its diameter. This means, for example, that major fluid resuscitation will be much more effective if a pressure infusor is used to deliver low-viscosity fluid through a short, wide-bore cannula. The equation is also relevant in conditions of airway obstruction. This is of particular importance in young children whose small airways may be further narrowed by inflammation and oedema, and in whom gas flow may be critically impaired.

You will notice that the first candidate actually has given the examiners much the same information as did the second. The difference lies in the fact that each of their rather abbreviated answers was prompted, and he or she gave no real sense of any mastery of the subject. The second candidate, in contrast, required no prompting, but demonstrated instead an orderly and logical approach that conveyed the impression of obvious familiarity with, and understanding of the topic.

Only the occasional candidate achieves the fluency of the second example, whereas rather more candidates behave like the first, and require a little help. Yet if you do have some knowledge of the subject asked, you can train yourself, with practice, to deliver the information both with more facility and with more enthusiasm. This applies particularly to the clinical areas of the viva. If you are asked, for instance, how you approach weaning an intensive care patient from a ventilator, you could say that *I would follow the unit protocol and would begin by …*, or alternatively you could start by commenting that *This can be a really difficult problem, particularly after prolonged ventilation or in those with pre-existing lung disease, but in general I would….* If you take the first approach it will look as though you have read the information in a book; if you take the second it will appear as if weaning patients from intermittent positive-pressure ventilation (IPPV) is a challenge with which you are enthusiastically familiar. Your overall performance will be more impressive for it.

The viva on each subject lasts less than 8 minutes. The examiners will take about 20–30% of this total time in framing the questions. That leaves you, therefore, with only about 5 or 6 minutes during which you have to talk. Were you to read out steadily, fluently and without hesitation one of the average length answers in this book, it would probably take you twice that long. There are few candidates, moreover, who are able to answer viva questions as rapidly as they can read. You should find this reassuring, because it means that you cannot be expected to convey more than a proportion of the information that appears in each of the specimen questions.

Why do they have to ask these kinds of questions?

When your examiner looks up with an air of benign amusement from the question paper and invites you to discuss *Cytochrome P450* or *Chirality*, your initial instinct may be to leap across the table to transfix them with your free Royal College examinations' pencil. Some examiners, at least, will ask these questions with at least a hint of apology, which may raise your spirits marginally as you sense that these individuals might be on your side. Other examiners will be completely bereft of irony.

The difference between them should be obvious, but it might be of interest, if little consolation, were you to be aware of some of the reasons why such questions can arise.

A brief history of anaesthesia's inferiority complex

Anaesthesia had its humble origins in mid-nineteenth century dentistry, and although hospital-based anaesthesia did become more sophisticated, in the early twentieth century simple anaesthesia in the UK was still being delivered by some individuals who were not medically qualified. There were even some who did not have so much as a rudimentary general education. In contrast, however, physicians and surgeons of that era had a high social and intellectual standing that had been established for centuries. As the speciality of anaesthesia evolved over the succeeding decades of the twentieth century, it continued to enjoy only very modest status. There were, however, some politically astute individuals who recognised the potential perils of anaesthetic humility and who thought it unwise to succumb to anaesthesia's inferiority complex. In particular they recognised the truth that anaesthetists could achieve equality of status with surgeons only if they had a qualification that was equivalent to the Fellowship of the Royal College of Surgeons, the FRCS. It was this realisation which explained the early two-part examinations, first the Diploma of Anaesthesia, and then the FFARCS (Fellow of the Faculty of Anaesthetists of the Royal College of Surgeons) which was the immediate forerunner of the FRCA. These examinations were modelled on the FRCS, had a low pass mark in the region of 25–30%, and which by including in the syllabus detailed anatomy and pathology, created the precedent for rigour in the basic sciences.

This establishment of a difficult anaesthetic examination with a low pass rate did in fact play a crucial role in the development of the speciality. When you are tempted, therefore, to curse the college for erecting the hurdles of the Primary and Final FRCA, you can at least reflect that the difficulty of these examinations may in some oblique way ensure that you get paid the same as your colleagues in surgery and medicine. Anaesthesia has a reputation for having among the most difficult post-graduate examinations and, superficial though this may sound, it does remain one of the ways in which the speciality safeguards its standing.

Did this attempt to mirror the FRCS take the process too far? At times it can certainly seem so, and you may have to console yourself with the familiar, yet no less true observation that *Examinations are formidable even to the best prepared … for the greatest fool may ask more than the wisest man can answer* (Reverend Charles C. Colton 1780–1832). A more recent perspective has been provided by a distinguished professor of medicine and scientist from Oxford. During his valedictory speech to the faculty, he commented that in 30 years of clinical medicine his intimate knowledge of the Krebs' cycle had influenced his management … *of not one single patient*. Some, but not all, examiners agree with the wisdom of that view, and do not accept that a detailed knowledge of scientific minutiae is necessary for the safe and effective practice of clinical anaesthesia. It may be obvious at your viva into which category the examiner falls.

Strategies for answering clinical science questions

Anatomy

Some candidates demonstrate a very detailed knowledge of areas of human anatomy, which allows them to embark on a thorough description of all the relevant structures and their immediate relations. Others have a more modest working knowledge, and there is a final group which includes candidates who are able to demonstrate only that they have a very vague idea of where these structures lie. You will know as soon as the question is asked which of these types you most closely match. One strategy for passing questions on applied anatomy is simply to learn it, or at least develop enough confidence to be able to launch into a rapid account of the area in question. The speed of delivery is important. There are not many examiners who will be able to recall the precise anatomical details that are found in the specimen questions in this book. This means that they will probably have to make repeated reference to their guidance sheet in order to check that what you are saying is true. If they were to ask you to clarify more than one or two of your descriptions then much of the time in the viva would be lost. There is a tendency, therefore, for the examiner to listen to what you are saying, rather than making frequent interruptions. At the end of your account he or she may simply judge their overall impression of its accuracy. Confident presentation may, in this instance, allow you to mask gaps in your knowledge.

What if you are the candidate whose recollection of an area is vague? Your chances of success in the question will depend on whether it is what could be termed 'theoretical anatomy' or is 'practical anatomy'. The coronary arterial and venous circulation is an example of theoretical anatomy. Certainly it is important, and of course it is true that anaesthesia may influence it, but it remains a visual construct, which we neither see nor feel. One tactic, which may salvage something from this part of the viva, is to move swiftly to the functional anatomy of the circulation. *The main importance for anaesthetists of the right and left coronary circulations*, you could state loftily, *lies in the way that we can influence oxygen supply and demand*. The examiner will take you back to check that you indeed are ignorant of the anatomy, but you will at least have initiated the physiological discussion which is the second part of the question and which, in any case, is generally of greater interest to anaesthetists, both candidates and examiners alike. Other examples of theoretical anatomy are the cerebral circulation and the blood supply to the spinal cord.

Questions on 'practical anatomy' should be rather easier to handle, because they relate to areas such as the internal jugular vein and the brachial plexus; detailed knowledge of which is of direct and self-evident importance. You can also reinforce this knowledge by disciplining yourself to visualise the relevant structures each time that you perform or observe one of these procedures. If you rehearse in your mind the nerves that are being blocked for an awake carotid endarterectomy as you see it being done, or describe the anatomy of the sacrum to a less experienced colleague to whom you are teaching a caudal block, it will not be long before the details are secure without recourse to yet more evening study. You can, in other words, revise for the Final FRCA during the course of your daily work. This does not, of course, apply only to anatomy, but is true of other areas of the examination as well.

The examiner may ask you if you have performed a particular procedure, or may even give you a question that allows you to discuss, for example, an upper or lower limb block of your choosing. In respect of practical procedures that you claim to have undertaken, you should be aware that the threshold for a pass shifts upwards. If you say that you regularly perform caudal blocks in children or interscalene blocks in adults, but then show that your knowledge either of the anatomy or of the appropriate drug doses is at best hazy, then you will almost certainly fail the viva with a '1+'. You will incur a '1', if your answer is judged to be dangerous. In examination anaesthesia as in real-life anaesthesia, whenever you are in any doubt you should choose the safest option. Better in both situations to admit that you have done very few caudal or interscalene blocks, and that you would seek experienced help.

Anatomy questions finally, do lend themselves readily to diagrammatic answers. Many candidates seem to benefit from being allowed to describe the anatomy while they draw: producing the diagram acts as a stimulus to recollection. It is worth practising this technique because the number of anatomy topics is relatively restricted and it is almost certain that one of them will appear as a question.

Physiology

Anatomy, pharmacology and physics are all large scientific disciplines, yet in the context of the Final FRCA their scope is restricted, and the areas of specific relevance to anaesthetic practice are finite. Physiology, in contrast, is very wide ranging, and questions appear which are related to all the systems, including renal, gastrointestinal and endocrine.

The questions in the clinical science viva are not weighted formally, and so in theory a question about the nephron or the functional anatomy of the liver will be treated just the same as one about respiratory function or cardiovascular compensatory mechanisms. You will not, of course, be asked more than one such topic, and so examiners do not find themselves having to argue about the merits of a particular candidate who knew everything about bile salts but nothing about functional residual capacity. What you might find them discussing, however, is the candidate who knew little about the physiology subject, but who performed well in most of the other areas. If the physiology topic is one that might be considered a core area, such as respiratory or cardiovascular function, then that candidate's chances of passing the viva diminish. If, however, the topic is one that is rather more peripheral, then the examiners are more likely to make allowances. What this means, in practice, is that you should concentrate your study more on areas such as respiratory and cardiovascular physiology, than on hepatic and gastrointestinal function. It is not that you will not get asked a question on these latter, but you will disadvantage yourself much more by ignorance of the former.

Pharmacology

The number of core anaesthetic drugs is limited. The sum of the regularly used induction agents, neuromuscular blockers, volatiles, analgesic drugs and local anaesthetics exceeds barely 20. The pharmacology of these substances is almost by definition

applied science, and so you will find examiners much less forgiving of deficiencies in anaesthetic pharmacological knowledge than they would be of ignorance of lasers or medical statistics. You may feel somewhat aggrieved if the viva concentrates on gamma amino butyric acid (GABA) and *N*-methyl-D-aspartate (NMDA) receptor theory, but you should recognise that there is only so far that such a topic can be pursued, and you should be able to acknowledge finally that questioning about the scientific foundation of your everyday anaesthetic practice is a legitimate area of enquiry. Given the restricted numbers of drugs, however, it should not be an insuperable task to acquire the necessary amount of information. Some of the questions can be straightforward and lend themselves readily to a structured answer that you can adapt across the range of anaesthetic drugs. One such question, for instance, may ask you to enumerate the properties of an ideal volatile agent, and to compare desflurane and sevoflurane against that ideal. You will see that this same question could be asked of local anaesthetics, neuromuscular blockers, inotropes, anti-emetics and any number of classes of agents. You will also need to have some understanding of subjects such as pharmacokinetics and receptor theory. Much of the knowledge that you may have acquired in working for the Primary FRCA will stand you in good stead for this part of the Final FRCA.

Clinical measurement and equipment

You might have hoped to have left most of the physics and clinical measurement behind, but as also applies to pharmacology questions, much of the work that you did for the Primary FRCA will also be helpful for the Final FRCA. Some final examiners are mesmerised by the physics involved in some of the questions that appear: others find it less beguiling. If you are examined by one of the former group then expect to be asked to define, for example, the SI units that are appropriate to the particular question, and do not worry if you get so immersed in the science that you never reach its clinical application. At the other extreme lie the examiners who take the view that complex anaesthetic devices are essentially black boxes whose inner workings can safely be left a mystery. In this case the viva will follow a rather different course, and it is probable that the emphasis will be more on clinical uses and on sources of error in interpretation of the information that is delivered. You will need, therefore, to be prepared for both. But even examiners who have considerable enthusiasm for this subject will recognise that there is only so far that it can be reasonably taken. The detailed physics underlying MRI, for example, is too formidable to be covered in a viva such as this. If you can articulate the basic principles of the topic, whether it is MRI scanning or defibrillation, and if you can demonstrate that you are aware of its clinical and safety implications, then in most cases that should be enough to ensure you a pass.

Statistics

There are doctors who have an intuitive gift for statistics, which is a subject that they find very straightforward. Included among such doctors are some examiners and some candidates, and they do not, therefore, understand the collective groan that goes up when the prospect emerges either of having to ask or to answer a question on medical statistics. The fact remains, however, that the topic is unpopular with the majority of anaesthetists. Yet paradoxically this may be of some benefit to those who are uncomfortable with the concepts. Is a pair of examiners really going to fail a candidate on the basis of statistical ignorance alone? That would be a decision much harder to justify than were it to be based on a poor performance in a question about respiratory physiology or anaesthetic pharmacology. Most examiners, moreover, are conditioned by their own experience of asking about statistics to expect less than brilliant answers. What this means in practice is twofold. First, that the questions are not

especially demanding, and second, that as long as you are able to enunciate some basic principles and definitions then you are more likely to get a bare pass than you would were you to offer the same level of information about, say, the anatomy of the epidural space. So as a minimum make sure, for example, that you know the difference between parametric and non-parametric data and tests, between paired and unpaired *t*-tests, and about the null hypothesis. Be prepared to discuss briefly the principles which underlie meta-analysis and be familiar with the results of at least one meta-analysis which is of clinical importance.

Prioritising the questions

When you are contemplating the syllabus for the Final FRCA you may, understandably, feel daunted by the requirement to know about what seems like a vast range of disparate subjects. It may be helpful for you to give different priority to these, so that you do not spend a disproportionate amount of time learning dispiriting detail about topics in which you may have little interest. You need to visualise, therefore, a situation in which at the end of your viva one examiner has awarded you a '2', whereas the other has given you a '1+'. At this point they will confer in order to arrive at a final mark. They will not be seeking to fail you, but they need to determine which side of the pass–fail border you are destined to fall. To that end they will probably go through each of the viva questions that you have been asked. The deciding factor is often a question that has been answered very poorly, and you have to imagine them saying *He (or she) did all right on questions A and B, not so well on C, but knew almost nothing about D.* It is Question 'D' that may determine your fate. If it is on the internal jugular vein, on propofol or on pulse oximetry, then quite reasonably you are more likely to fail, because these are core areas of anaesthetic practice. If, on the other hand, question 'D' was on the fuel cell, on plasma proteins or on immunology, then the examiners may be more forgiving, reasoning that these subjects are less central to the practice of safe clinical anaesthesia. It may be that you are so well organised and so self-disciplined that you will be able to cover every area with equal enthusiasm. If, however, you have to make some choices about how to apportion your time, you may decide that you will have to spend less of it on some subjects. So when you are working through the topics during your preparation for the examination, imagine that each one potentially is your question 'D' and into which category it might fall. If you believe that it might be peripheral to clinical practice then do not ignore it completely, but concentrate your efforts on more mainstream areas.

2

Anatomy and its applications

The internal jugular vein

Commentary

Outside the intensive therapy unit, the right internal jugular vein is probably the first site of choice for central venous cannulation. It is readily accessible and has a comparatively low complication rate. The ability to cannulate the vessel is a core skill.

The viva

You will be asked to describe its anatomy.

- The internal jugular vein originates at the jugular foramen in the skull (the foramen drains the sigmoid sinus) and is a continuation of the jugular bulb.
- It follows a relatively straight course in the neck to terminate behind the sterno-clavicular joint where it joins the subclavian vein.
- Throughout its course it lies with the carotid artery and the vagus nerve within the carotid sheath, but it does change position in relation to the artery. Initially it lies posteriorly before moving laterally and then anterolaterally.
- The vein is superficial in the upper part of the neck before it descends deep to the sterno-cleidomastoid muscle. In the neck the structures through which a cannulating needle passes are skin and subcutaneous tissue, the platysma muscle, sterno-cleidomastoid (in the lower neck) and the loose fascia of the carotid sheath.
- Anterior to the vein at the top of its course lie the internal carotid artery and the vagus nerve.
- Posterior to the vein are (from above downwards): the lateral part of C_1, prevertebral fascia and vertebral muscles, the cervical transverse processes, the sympathetic chain, and at the root of the neck, the dome of the pleura. On the left side the jugular vein lies anterior to the thoracic duct.
- Medial to the vein are the carotid arteries (internal and common), and four cranial nerves: the ninth (glossopharyngeal, IX), the tenth (vagus, X), the eleventh (accessory, XI) and the twelfth (hypoglossal, XII).

Direction the viva may take

You may be asked briefly to describe a technique for venous cannulation.

- You will have had experience of this technique. Describe the one with which you are most familiar.
- As an example: the high approach. (This is a so-called landmark technique, as opposed to one which is guided by the use of ultrasound.) A fine 'seeking' needle (25G or similar) is inserted at the level of the superior border of the thyroid cartilage (at about C_4) and on the medial border of sterno-cleidomastoid.
- The needle is directed caudally at an angle of 30° in the direction of the ipsilateral nipple. The vein is usually quite superficial, although this will depend on the body habitus of the patient.
- Once the vein is located, the Seldinger technique (catheter over guide wire) can be used to establish definitive central access.

Further direction the viva could take

You may be asked finally about the complications associated with the technique and how these may be avoided.

- **Complications:** Some of these can be minimised by the use of an ultrasound-guided needle. The National Institute of Clinical Excellence (NICE) report of September 2002 recommended the routine use of ultrasound for locating the internal jugular vein. Evidence to support its use for other sites is not yet robust.
- **Pneumothorax (and haemothorax):** The risk is minimised by using a high approach, which avoids the dome of the pleura.
- **Intrapleural placement:** Here too the risk is minimised by using a high approach which avoids the pleura. A check X-ray will prevent inadvertent intrapleural infusion.
- **Air embolism:** Positioning the patient head down during insertion decreases the risk.
- **Cardiac dysrhythmias:** These may occur should the guide wire or catheter be inserted as far as the heart.
- **Carotid artery puncture or cannulation:** The risk is reduced if the artery is palpated continuously throughout cannulation, and it is minimised by the use of an ultrasound-guided needle.
- **Thoracic duct injury (chylothorax):** The thoracic duct cannot be damaged if the left side is not used. Otherwise the risk is minimised by using a high approach.
- **Infection:** Central line infection can be disastrous. Significant infection is said to occur in around 12% of insertions, although the rate of bacterial colonisation is likely to be higher. The risks are reduced by scrupulous aseptic technique as well as meticulous aftercare. See *Central venous pressure and cannulation*, page 141.

The cerebral circulation

Commentary

This is a standard question, but is one which contains a lot of anatomical detail. It may be helpful to practice drawing a simple explanatory diagram. The viva may also touch on the physiological aspects of cerebral perfusion or briefly on the subject of intracranial pressure.

The viva

You will be asked about the arterial supply to, and the venous drainage of the brain.

Arterial supply

- The brain is supplied by four major vessels: two internal carotid arteries which provide around two-thirds of the arterial supply, and the two vertebral arteries which deliver the remaining third.
- The vertebral arteries give off the posterior inferior cerebellar arteries, before joining to form the basilar artery. This also provides the anterior inferior cerebellar, and the superior cerebellar arteries.
- The basilar artery then gives off the two posterior cerebral arteries, which supply the medial side of the temporal lobe and the occipital lobe.
- The artery then anastomoses with the carotid arteries via two posterior communicating arteries.
- The internal carotid arteries meanwhile, give rise to the middle cerebral arteries, which supply the lateral parts of the cerebral hemispheres. They also provide much of the supply to the internal capsule, through which pass a large number of cortical afferent and efferent fibres.
- The carotids also give rise to the anterior cerebral arteries, which are connected by the anterior communicating artery, and which supply the medial and superior aspects of the hemispheres.
- The three arterial stems (basilar and carotid arteries), linked by the anterior and posterior communicating arteries, comprise the arterial circle of Willis.

Venous system

- The cerebral and cerebellar cortices, which are relatively superficial structures, drain into the dural sinuses. These venous sinuses lie between the two layers of the cranial dura mater. The superior sagittal sinus lies along the attached edge of the falx cerebri dividing the hemispheres, and drains usually into the right transverse sinus. The inferior sagittal sinus lies along the free edge of the falx, and drains via the straight sinus into the left transverse sinus. (The straight sinus lies in the tentorium cerebelli.) The transverse sinuses merge into the sigmoid sinuses before emerging from the cranium as the internal jugular veins.
- Deeper cranial structures drain via the two internal cerebral veins, which join to form the great cerebral vein (of Galen). This also drains into the inferior sagittal sinus.
- The cavernous sinuses lie on either side of the pituitary fossa and drain eventually into the transverse sinuses.

Direction the viva may take

The direct anaesthetic implications of the anatomy described above are modest. You may be asked about cerebral perfusion (see *Cerebral blood flow*, page 127) or intracranial pressure (see *(Raised) intracranial pressure*, page 124), although these are both complete topics in themselves. Below are some miscellaneous facts, which may prove useful during the discussion.

- The circle of Willis provides very effective collateral blood supply in the presence of arterial occlusion. Three out of four of the main arteries can be occluded, as

long as the process is gradual, without producing cerebral ischaemia. The normal intracranial blood volume is around 150 ml.

- The middle cerebral artery has been described as 'the artery of cerebral haemorrhage'. This is mainly because it supplies the internal capsule, where a large number of important cortical afferent and efferent fibres congregate.
- The superficial areas of the cerebral (and cerebellar) cortex drain to the venous sinuses via thin-walled veins. These are vulnerable to rupture, with the formation of subdural haematomata, particularly in the elderly in whom there is a loss of brain mass.
- Other potential intracranial catastrophes include cavernous sinus thrombosis, sagittal sinus thrombosis and cortical vein thrombosis (CVT). CVT is associated with pregnancy, and is reported as occurring in between 1 in 3000 and 1 in 6000 deliveries. If this figure is accurate then CVT is being under-diagnosed, because very few obstetric anaesthetists encounter the one or two cases a year that this incidence would suggest.

Anatomy of the orbit

Commentary

Questions on the eye seem to be disproportionately common in the Final FRCA, despite the fact that alternative forms of local anaesthesia are now widespread. Sub-Tenon's block and topical instillation of local anaesthetic drops are supplanting traditional retrobulbar and peribulbar anaesthesia, which are fast losing relevance for anaesthetists. The abiding attraction for examiners may lie in the fact that considerable anatomical detail is concentrated in a small well-circumscribed area. Although the viva will end up discussing local anaesthetic blocks, anatomy remains the core part of this question. There is more information below than overall you will need, but it is included in case at some stage of the questioning you are asked for further detail.

The viva

You may be asked simply to describe the anatomy of the orbit, or you may be invited to concentrate on one aspect, such the extraocular muscles.

- The bony orbit has been described variously as a pyramid whose apex is directed inwards and upwards, as a cone, and as a pear whose stem points towards the optic canal. Its roof is comprised of the orbital plate of the frontal bone, with the anterior cranial fossa above, while its floor is formed by the zygoma and the maxilla, with the maxillary sinus beneath. Its medial wall is formed by parts of the maxilla, lacrimal bone, ethmoid and sphenoid, and beyond it lie the ethmoid air cells and the nasal cavity. The zygoma and the greater wing of the sphenoid make up its lateral wall.
- It contains the globe, together with the muscles, nerves and blood vessels that subserve the normal functions of the eye.
- The normal globe has an axial length of around 24 mm (this is measured in the anteroposterior diameter). An eye longer than 26 mm is usually myopic. Its outer layer comprises sclera and cornea, the middle vascular layer contains the choroid, the ciliary body and the iris, and the innermost layer is made up of neural tissue in the form of the retina.
- The movements of the globe are controlled by the six extraocular striated muscles. The four recti (lateral, medial, superior and inferior) originate from the annulus of Zinn, the tendinous ring which encircles the optic foramen, and insert beyond the equator of the globe. The lateral and medial recti have two heads. The superior oblique muscle originates above and medial to the annulus, curves round the trochlea (which acts like a pulley) before inserting behind the equator and beneath the superior rectus. The inferior oblique originates from the lacrimal bone and inserts posterolaterally on the globe, having passed beneath the inferior rectus muscle.
- **Motor innervation:** The lateral rectus is supplied by the sixth cranial nerve, the abducens and the superior oblique is supplied by the fourth, the trochlear. The remaining muscles are supplied by the third cranial nerve, the oculomotor. (This also supplies levator palpebrae superioris, which elevates the eyelid.)
- **Autonomic innervation:** Sympathetic innervation is by the long and short ciliary nerves via the superior cervical ganglion. Nerve impulses dilate the pupil via the dilators of the iris. Parasympathetic innervation is by the short post-ganglionic ciliary nerves via the ciliary ganglion. The pre-ganglionic supply comes from the oculomotor nerve, and its impulses constrict the pupil.
- **Sensory supply:** This is derived mainly from the ophthalmic branch of the fifth cranial nerve, the trigeminal (V), although branches of the maxillary division make some contribution to lateral structures and to the nasolacrimal apparatus. There are a large number of sensory nerves for such an anatomically confined area. The examiner is unlikely to dwell on these in any detail, but in summary the innervation that may have relevance for ocular surgery can be outlined as

follows. The ophthalmic division V^1, branches into the frontal nerve, which then subdivides into the supratrochlear nerves (medial upper conjunctiva), the supraorbital nerve (upper conjunctiva) and the long ciliary nerve (cornea, iris and ciliary muscle). V^1 also forms the nasociliary nerve, which in turn branches into the infratrochlear nerve (inner canthus and lacrimal sac), and the long sensory root to the ciliary ganglion (thence to the cornea and iris). The lacrimal branch of V^1 supplies the rest of the conjunctiva.

- **Foramina:** The orbit contains nine fissures and foramina, of which three are particularly important: the optic foramen (canal), and the superior and inferior orbital fissures.
- **Optic canal:** The optic nerve traverses the optic foramen together with the ophthalmic artery.
- **Superior orbital fissure:** Through this fissure run the oculomotor, trochlear and abducens nerves to the extraocular muscles, together with the frontal, nasociliary and lacrimal nerves, and the superior and inferior ophthalmic veins. The oculomotor, abducens and nasociliary nerves traverse the lower part of the fissure and enter the muscular cone between the two heads of the lateral rectus. The trochlear, frontal and lacrimal nerves remain outside the cone.
- **Inferior orbital fissure:** Through the inferior fissure run the zygomatic and infraorbital nerves (branches of V^2), the infraorbital artery and the inferior ophthalmic vein.

Direction the viva may take

You will be asked about methods of anaesthetising the eye.

- **Topical:** The anterior structures can be anaesthetised using topical amethocaine 0.5% or 1.0%, oxybuprocaine 0.4% and proxymetacaine 0.5%. Topical anaesthesia is simple and (mostly) safe and effective, although the lack of akinesia of the eye and eyelids means that the surgeon has to control eye movement via the intraocular instruments. Anaesthesia can be supplemented by the addition of lignocaine to the irrigation fluid, or by further instillation of drops. The use of drops, however, is associated with corneal oedema, and excessive doses may worsen this problem.
- **Retrobulbar block:** This is performed by a single injection, which is made either percutaneously or transconjunctivally. The axial length of the eye gives a guide to needle depth and if the transconjunctival approach is used a 25-mm needle is amply long enough to reach the retrobulbar muscular cone. The injection is made at the junction of the lateral and middle thirds of the orbital margin in the inferotemporal quadrant. Complications include retrobulbar haemorrhage, penetration of the globe, damage to the optic nerve or ophthalmic vessels, and central spread of local anaesthetic. Retrobulbar block is very effective, but these potential complications have led a number of ophthalmic surgeons and anaesthetists to abandon it in favour of other techniques.
- **Peribulbar block:** This has been cited as a safe and effective alternative to retrobular block, but it too is not without its problems. Larger volumes of local anaesthetic are required (8–10 ml rather than 3–4 ml) which increases the intra-orbital pressure and causes periorbital chemosis. The onset of block is also considerably slower and the failure rate higher. The risk of scleral perforation is not removed because the technique requires one inferotemporal and one superonasal injection, both of which are directed beyond the equator of the globe. Some practitioners include a third injection, made at the extreme medial side of the palpebral fissure.
- **Sub-Tenon's block:** The popularity of this technique has increased recently, because it is viewed as safer than either of the sharp needle approaches. It is, however, more invasive, in that a modest amount of surgical dissection is

necessary. After topical anaesthesia to the conjunctiva the patient is asked to look upwards and outwards (in the direction of the person performing the block). This improves access to the inferonasal quadrant where the injection is made, as posterior as possible. A fold of conjunctiva is drawn upwards with forceps. A small nick at the base of this fold with surgical scissors usually opens the sub-Tenon's fascia. A blunt cannula is then inserted gently into this space and guided backwards following the contour of the globe. Injection of 4–5 ml of local anaesthetic solution will provide analgesia and adequate akinesia. The globe can in theory be perforated, but the complication is sufficiently rare for sub-Tenon's block to be considered suitable for administration by trained, but non-medical practitioners.

The trigeminal nerve

Commentary

The applied anatomy of the trigeminal nerve is relevant mainly for those working in the management of chronic pain. Trigeminal neuralgia, however, is described classically as one of the most severe pains in human experience, one which is said to have driven some patients even to suicide. It is a dramatic condition, and one that is amenable to a range of treatments. You should have some familiarity with it.

The viva

You will be asked to describe the anatomy of the trigeminal nerve.

- The trigeminal (fifth cranial nerve) is the largest of the 12, and provides the sensory supply to the face, nose and mouth as well as much of the scalp. Its motor branches include the supply to the muscles of mastication.
- It has a single motor nucleus and three sensory nuclei in the brain. The motor nucleus is in the upper pons, and lying lateral to it is the principal sensory nucleus, which subserves touch sensation. The mesencephalic nucleus is sited in the midbrain and subserves proprioception. Pain and temperature sensation are subserved by the nucleus of the spinal tract of the trigeminal nerve. This lies deep to a tract of descending fibres, which run from the pons to the substantia gelatinosa of the spinal cord.
- Sensory fibres pass through the trigeminal (Gasserian) ganglion. It is crescent shaped (hence its alternative description as the semilunar ganglion), and lies within an invagination of dura mater near the apex of the petrous temporal bone, and at the posterior extremity of the zygomatic arch. The motor fibres of the trigeminal nerve pass below the ganglion.
- From this ganglion pass the three divisions of the nerve: the ophthalmic (V^1), which is the smallest of the three, the maxillary (V^2) and the mandibular (V^3).
- **Ophthalmic division:** This passes along the lateral wall of the cavernous sinus before dividing just before the superior orbital fissure into the lacrimal, nasociliary and frontal branches. The frontal branch divides further into the supraorbital and supratrochlear nerves.
- **Maxillary division:** This runs below the ophthalmic division before leaving the base of the skull via the foramen rotundum. It crosses the pterygopalatine fossa, giving off superior alveolar dental nerves, zygomatic nerves and sphenopalatine nerves before entering the infraorbital canal and emerging through the infraorbital foramen as the infraorbital nerve.
- **Mandibular division:** This is the largest of the three branches and is the only one to have both motor and sensory components. Its large sensory root passes through the foramen ovale to join with the smaller motor root, which runs beneath the ganglion. Its branches include the sensory lingual, auriculotemporal and buccal nerves; the inferior dental nerve, which is mixed motor and sensory; and motor nerves, the masseteric and lateral pterygoid, to the muscles of mastication.

Direction the viva may take

You may be asked about trigeminal neuralgia.

- Trigeminal neuralgia is a neuropathic pain with a reputation as one of the worst pains in human experience.
- **Pathogenesis:** This remains speculative. It may be caused centrally, with abnormal neurones in the pons exhibiting spontaneous and uncontrolled discharge in the nerve. It may also be due to peripheral factors; either demyelination (in younger patients trigeminal neuralgia may be a first symptom of multiple sclerosis), or compression by abnormal blood vessels in the posterior fossa.

- **Clinical features:** The peak onset of the condition is in the middle age. The pain commonly is intermittent, lancinating and extremely severe. Attacks are spasmodic and last only for seconds. Patients are pain free in the interim, but episodes may be very frequent. Pain is limited usually to one (occasionally two) of the branches of the trigeminal nerve, which supply sensation to the face. It occurs least commonly in the ophthalmic division, which accounts for only around 5% of cases, and more frequently in the maxillary or mandibular divisions. The distribution is always unilateral. Paroxysmal pain can be precipitated by trigger points around the face reacting to the lightest of stimuli, such as a light breeze or touch, and by actions such as chewing or shaving.

Further direction the viva could take

You may be asked briefly to discuss methods of treatment.

- **Pharmacological**
  - *Carbamazepine*: This is effective in more than 90% of cases of true trigeminal neuralgia (100 mg b.d. up to maintenance of 600–1200 mg day^{-1}). The full blood count must be monitored, because the drug can cause bone marrow suppression.
  - *Phenytoin*: This is effective in a smaller proportion (around 60%) and can be given intravenously for acute intractable pain (the starting dose is 300–500 mg day^{-1}).
  - *Baclofen*: This is an antispasmodic gamma-amino butyric acid (GABA) analogue, which binds to $GABA_B$ receptors (the dose is up to 80 mg day^{-1}).
  - *Gabapentin*: This is a GABA analogue, which does not, however, act on GABA receptors. Its mechanism of action is unclear. It is an anticonvulsant, which is also used increasingly to treat neuropathic pain. The dose is titrated against response to a maximum of 1800 mg daily.
- **Destructive**
  - *Radiofrequency ablation*: A needle is passed percutaneously and under X-ray control through the foramen ovale to the trigeminal ganglion. The entry point of the needle is below the posterior third of the zygoma. Chemical ablation may also be used. This technique can be complicated by anaesthesia dolorosa, in which the patient loses not only the pain, but also most of the sensation to that side of the face, which feels dead and 'woody'.
- **Surgical decompression**
  - This is the most invasive therapeutic technique because it requires exploration of the posterior fossa to identify the aberrant vessel(s), which are compressing the nerve near its emergence from the pons.

Sensory nerve supply to the face

Commentary

The major sensory supply to the face is easy to describe, it is the numerous terminal branches that may give you more difficulty. The examiner equally may not immediately be intimate with the 25 or more named nerves which originate from the trigeminal, and so your detailed knowledge needs extend only to those branches which can be blocked with local anaesthetic to allow minor surgery on the face or to provide post-operative analgesia.

The viva

You will be asked to describe the sensory innervation of the face.

- The sensory supply to the face is provided mainly by the three divisions of the fifth cranial nerve, the trigeminal. (As the largest cranial nerve it also supplies much of the scalp, the mouth, teeth and the nasal cavity.) The skin over the parotid gland and the angle of the mandible is supplied by the greater auricular nerve, which arises from the ventral rami of the second and third cervical nerves.
- At the trigeminal (Gasserian) ganglion the nerve separates into the ophthalmic (V^1), the maxillary (V^2) and the mandibular (V^3) divisions.
  - *Ophthalmic*: The ophthalmic nerve supplies the skin of the nose, the forehead, eyelids and the scalp. (It also supplies the globe, the lacrimal apparatus and the conjunctiva.) The nerve divides just before the superior orbital fissure into the lacrimal, nasociliary and frontal branches. The large frontal branch divides further into the supraorbital and supratrochlear nerves. The supraorbital nerve supplies the skin of the forehead and scalp sometimes as far back as the lambdoid suture. The supratrochlear nerve supplies part of the upper eyelid and the skin of the lower part of the forehead near the midline. The lacrimal nerve supplies the skin adjacent to the medial canthus of the eye, while the nasociliary nerve and its branches supply the skin of the nose down as far as the alae nasae.
  - *Maxillary*: This runs below the ophthalmic branch before leaving the base of the skull via the foramen rotundum to divide into its various branches. The zygomatic nerve divides further on the lateral wall of the orbit into a zygomatico-temporal branch which supplies the skin of the temple, and a zygomatico-facial branch which supplies the skin over the cheekbones. The maxillary nerve proper crosses the pterygopalatine fossa to enter the infraorbital canal from which it emerges through the infraorbital foramen as the infraorbital nerve. This supplies the skin of the lower eyelid, of the cheek and upper lip.
  - *Mandibular*: Its large sensory root passes through the foramen ovale with branches that include the auriculotemporal, lingual and buccal nerves. The auriculotemporal nerve emerges from behind the temporo-mandibular joint to supply the skin over the tragus and meatus of the ear as well as the skin over the temporal region. The mandibular division also provides the inferior dental nerve, and one of its terminal branches, the mental nerve, emerges through the mental foramen in the mandible to supply the skin of the chin and lower lip.

Direction the viva may take

You will be asked how you could provide local anaesthesia for superficial surgery on the face.

- The supraorbital and supratrochlear nerves can be blocked a few millimetres above the supraorbital ridge. If the injection is made too close to the eyebrow it

increases the risk of periorbital haematoma. Alternatively, a single insertion point can be used in the midbrow region to allow bilateral blocks.

- The infratrochlear nerve can be blocked by a needle directed along the medial wall of the orbit via an insertion site about 1 cm above the inner canthus.
- The infraorbital nerve can be blocked as it exits the infraorbital foramen, which lies about 1.5 cm (a finger's breadth) below the inferior orbital margin in line with the pupil. The nerve can also be blocked by an intra-oral approach, injecting above the canine (3rd) tooth.
- The mental foramen, conveniently, is also in line with the pupil and can be blocked in the mid-point of the mandible (although the height of the foramen varies with age, being nearer the alveolar margin in the elderly).
- The superficial branches of the zygomatic nerve can be blocked by subcutaneous infiltration, or by injection at their sites of emergence from the zygoma.
- The auriculotemporal nerve is blocked over the posterior aspect of the zygoma, and the greater auricular nerve by infiltration over the mastoid process behind the ear.
- Relatively small volumes of 3–5 ml of local anaesthetic will usually be sufficient to block all these nerves described.

Further direction the viva could take

The viva could continue with the subject of the trigeminal nerve and trigeminal neuralgia.

- See *The trigeminal nerve*, page 18.

Local anaesthesia for carotid endarterectomy

Commentary

A multicentre trial of the merits of local anaesthesia versus general anaesthesia for carotid endarterectomy makes this a topical and practical question (at least at the time of writing). Carotid surgery in patients who are awake is both challenging and interesting and you will find it much easier to give a credible account if you have been able to see, or better still perform, some of the blocks that are required.

The viva

You will be asked to describe the local anaesthetic blocks that are performed for this procedure.

- The nerves which supply the lateral aspect of the neck all derive from the ventral rami of the second, third and fourth cervical spinal nerves ($C_{2,3,4}$). The first cervical nerve has no sensory distribution to skin.
- **Superficial cervical plexus anatomy:** The cutaneous supply to the anterolateral aspect of the neck is via the anterior primary rami of C_2, C_3 and C_4. These nerves emerge from the posterior border of the sterno-cleidomastoid muscle midway between the mastoid and the sternum. The accessory nerve is immediately superior at this point. The lesser occipital nerve (the first branch) supplies the skin of the upper and posterior ear, the greater auricular nerve (the second branch) supplies the lower third of the ear and the skin over the angle of the mandible, the anterior cutaneous nerve (the third branch) supplies the skin from the chin down to the suprasternal notch, and the supraclavicular nerves (the fourth branch) supply the skin over the lower neck, clavicle and upper chest.
- **Superficial cervical plexus block:** All these nerves can be blocked at the mid-point of the sterno-cleidomastoid by infiltrating up to 20 ml of local anaesthetic solution between the skin and the muscle. The external jugular vein crosses the muscle at this point and can be a useful landmark.
- **Deep cervical plexus anatomy:** The ventral ramus of the second nerve emerges from between the vertebral arches of the atlas and axis and runs forward between their transverse processes to exit between longus capitis and levator scapulae. The ventral ramus of the third nerve exits the intervertebral foramen lying in a sulcus in the transverse process, and emerges between the longus capitis and scalenus medius muscles. The ventral ramus of the fourth and remaining cervical nerves appear between the scalenus anterior and the scalenus medius.
- **Deep cervical plexus block:** Deep cervical plexus block in effect is a paravertebral block of C_2, C_3 and C_4. Needles are inserted at each of the three levels, using as landmarks a line between the mastoid process and the prominent tubercle of the sixth cervical vertebra (which is palpable as Chassaignac's tubercle at the level of the cricoid cartilage). The C_2 transverse process is approximately one finger's breadth below the mastoid process along this line; with C_3 and C_4 following at similar intervals caudad. After encountering the transverse process 5–8 ml of local anaesthetic can be injected with due precautions. As there is little resistance to the spread of solutions through the paravertebral space in the cervical region, adequate anaesthesia can also be obtained using a single-needle technique and a larger volume (15–20 ml) at a single level, usually C_3.

Direction the viva may take

You could be asked briefly about the complications of the blocks, which may be linked to a discussion about the benefits of the technique.

- **Complications:** Superficial cervical plexus block risks mainly what can be described as generic complications of local anaesthesia, namely intravascular

injection and systemic toxicity. The complications of deep cervical block are much the same as those associated with interscalene block, which is not surprising given the anatomical similarities, and include injection into the vertebral artery, extension of the block either extradurally or intrathecally, phrenic nerve block and cervical sympathetic block, which will manifest as Horner's syndrome (miosis, ptosis, anhydrosis and enophthalmos). The recurrent laryngeal nerve may also be affected with resultant hoarseness.

- **Advantages of endarterectomy under local anaesthesia:** Normal cerebration depends on adequate cerebral perfusion, and in the awake patient it is very obvious whether or not this is being preserved. There is no interference with cerebral autoregulation, and the requirement for vasoactive drugs is less. Proponents for the technique claim lower morbidity and mortality, but robust outcome data must await the results of the trial.
- **Disadvantages of endarterectomy under local anaesthesia:** Cerebral oxygen consumption does not fall (cerebral metabolic rate for oxygen, $CMRO_2$, decreases under general anaesthesia) and a higher pulse and blood pressure during surgery results in higher myocardial oxygen demand than otherwise would be the case. It does also mean, however, that cerebral perfusion pressure is higher. Cooperation can on occasion be a problem: immobility during extended surgery may be very uncomfortable for the patient, and should their cerebration be obtunded by ischaemia they may become restless and agitated. The nerve blocks may sometimes prove inadequate as surgery proceeds, but local supplementation by the surgeon can circumvent this problem.

The larynx

Commentary

You will read in some texts that the competent anaesthetist should know as much about the anatomy of the larynx as any otorhinolaryngologist. Examiners do not necessarily make the same assumption, because in reality the clinical applications of such detailed knowledge are relatively restricted. You will, however, be expected to give a reasonably assured account of the main anatomical features. The account below should provide you with more than enough information, although necessarily it is much simplified.

The viva

You will be asked to describe the anatomy of the larynx.

- Laryngeal reflexes are very powerful, a fact which confirms the crucial role of the larynx in protecting the airway from contamination. The larynx has also evolved into an organ of phonation.
- It extends from the base of the tongue above, to the trachea below, and in the adult male it lies opposite the third to sixth cervical vertebrae. In the adult female and in children it lies higher.
- The larynx comprises a number of articulating cartilages, which are joined by ligaments and which are subject to the action of various muscles, which move these cartilages in relation to each other.
- The cartilaginous framework comprises the thyroid, cricoid and arytenoid cartilages. The smaller corniculate and cuneiform cartilages contribute little to this structure.
- The thyroid cartilage comprises two quadrilateral laminae which are fused anteriorly to form the laryngeal prominence. It articulates inferiorly with the cricoid. The thyroid notch lies at the level of C_4.
- The cricoid cartilage is a continuous ring with a narrow anterior arch and a deeper posterior lamina. It articulates on each side with the inferior cornu of the thyroid cartilage and with the base of the arytenoid cartilage.
- Each of the paired arytenoid cartilages is pyramidal in shape. The smooth concave base articulates with the cricoid cartilage. The lateral angle, or muscular process, projects backwards, while the anterior angle, or vocal process, projects forwards. The apex articulates with the corniculate cartilage.
- The two corniculate cartilages are small nodules which are sometimes fused with the arytenoids and which lie in the posterior aryepiglottic folds of mucous membrane. The two cuneiform cartilages lie anterior to the corniculate cartilages, also within the aryepiglottic fold.
- There are a number of intrinsic and extrinsic ligaments. Those of anaesthetic interest include the thyrohyoid membrane, which joins the upper border of the thyroid cartilage to the hyoid bone, and the cricothyroid ligament between the cricoid and thyroid cartilages.
- The vocal cords (also known as the vocal folds) are opalescent folds of mucous membrane which extend from the anterior vocal processes of the arytenoid cartilages as far as the middle of the angle of the thyroid cartilage. The vestibular folds, or false cords, lie lateral to the cords and comprise thicker folds of mucous membrane which also extend from the thyroid cartilage to the arytenoids.
- There are a number of extrinsic and intrinsic muscles of the larynx. The extrinsic sternothyroid, thyrohyoid and inferior constrictor of the pharynx attach the larynx to adjacent structures. The intrinsic muscles are of more immediate interest to the anaesthetist because they control the opening of the cords during inspiration, the closure of the cords and laryngeal inlet during swallowing, and the tension of the cords during speech.
- Abduction of the cords is performed by the posterior cricoarytenoid muscles.

- Adduction of the cords is performed by the lateral cricoarytenoids and the unpaired interarytenoid muscle.
- The main tensors of the vocal cords are the cricothyroid muscles.
- The main relaxors of the vocal cords are the thyroarytenoid muscles.
- All the muscles of the larynx, with one exception, are innervated by the recurrent laryngeal nerve. The exception is the cricothyroid muscle, which is supplied by the external branch of the superior laryngeal nerve.

Direction the viva may take

You may be asked about the clinical relevance of this information.

- It is important to be able to recognise structures that are seen at laryngoscopy. The anaesthetist will see beyond the elevated epiglottis the false and the true vocal cords. Posteriorly will be seen the arytenoid cartilages (together with the bulges of the corniculate and cuneiform cartilages). Between the cords is the laryngeal inlet, or rima glottidis, beyond which may be visible the upper rings of the trachea.
- The arytenoids can be dislocated or subluxed during tracheal intubation or laryngeal mask insertion. This will interfere with the function of some of the intrinsic muscles and may compromise the airway. The cricoarytenoid joint may also be affected by systemic inflammatory arthropathies, particularly rheumatoid arthritis, and by the tissue changes associated with acromegaly.
- The anatomy of the cricoid cartilage is relevant both for rapid sequence induction of anaesthesia, and also for emergency access to the airway. See *Surface anatomy of the neck*, page 32.
- It is important to be able to recognise the airway signs of injury to the recurrent laryngeal nerve. See *Innervation of the larynx*, page 26.

Innervation of the larynx

Commentary

The innervation of the larynx is another area that is regarded as core anatomy, and it does have immediate relevance for awake fibreoptic intubation. The other traditional question about the laryngeal nerves relates to the consequences of injury, and although anaesthetists see this very rarely, you may find yourself being questioned as though it were an everyday occurrence.

The viva

You will be asked to describe the innervation of the larynx.

Sensory innervation

- The sensory innervation of the larynx is via the vagus (10th cranial nerve), which divides into the superior laryngeal nerve and the recurrent laryngeal nerve. The superior branch divides thereafter into internal and external laryngeal nerves.
- The internal laryngeal nerve innervates the inferior surface of the epiglottis and the supraglottic region as far as the mucous membrane above the vocal folds.
- The recurrent laryngeal nerve provides the sensory supply to the laryngeal mucosa below the vocal cords.

Motor innervation

- The recurrent laryngeal nerve supplies all the intrinsic muscles of the larynx, with the exception of the cricothyroid muscle. This is supplied from the external branch of the superior laryngeal nerve.
- The right recurrent laryngeal nerve leaves the vagus to loop beneath the subclavian artery, before ascending to the larynx in the groove between the oesophagus and the trachea.
- The left recurrent laryngeal nerve passes beneath the arch of the aorta and similarly ascends in the groove between oesophagus and trachea.

Direction the viva may take

You may be asked to describe how you would provide anaesthesia for an awake fibreoptic intubation.

Nebulised lignocaine

- Nebulised local anaesthetic will provide adequate surface anaesthesia of the airway, although the procedure takes some time and patients may find it claustrophobic and uncomfortable.

Topical anaesthetic

- The nasal mucosa can be anaesthetised with local anaesthetic plus vasoconstrictor to minimise risk of bleeding. Topical cocaine can be used to a maximum dose of $1.5\,mg\,kg^{-1}$. If oral intubation is planned the tongue and posterior pharynx can be anaesthetised using lignocaine 4% or a lignocaine 10% metered pump which delivers 10 mg with each spray.

'Spray as you go' technique

- This is another simple method of anaesthetising the airway, in which local anaesthetic (usually lignocaine 4%) is introduced under direct vision via the injector channel in the fibreoptic endoscope.

Supplemental nerve blocks

- **Glossopharyngeal nerve:** This provides sensory innervation to the oral pharynx, the supraglottic area, the base of tongue and the vallecula. It can be blocked by submucosal infiltration behind the tonsillar pillars.

- **Superior laryngeal nerve:** This can be anaesthetised by bilateral injections which can be performed either by walking off the greater cornua of the hyoid to penetrate the thyrohyoid membrane, or by walking off the superior alae of the thyroid cartilage.
- **Recurrent laryngeal nerve:** This nerve is commonly blocked even if a 'spray as you go' technique has been used to anaesthetise the remainder of the airway. It is blocked via a transtracheal injection that is made through the cricothyroid membrane during inspiration. The inevitable cough distributes the solution (typically 4 ml of lignocaine 4%), more widely.

Further direction the viva could take

You may be asked about the clinical consequences of injury to the laryngeal nerves.

- The external branch of the superior laryngeal nerve supplies the cricothyroid muscle, which tenses the vocal cords. Damage will be followed by hoarseness. If the injury is unilateral this hoarseness will be temporary, because in time the other cricothyroid muscle will compensate. If it is bilateral the hoarseness will be permanent.
- The recurrent laryngeal nerve supplies all those muscles which control the opening and closing of the laryngeal inlet.
- Partial paralysis affects the abductor muscles more than the adductors and so with unilateral injury the corresponding vocal cord is paralysed. This also results in hoarseness.
- If both nerves are damaged then both cords oppose or even overlap each other in the midline. This leads to inspiratory stridor and has the potential to cause total respiratory obstruction.
- If one or both nerves are transected, the vocal cord(s) adopt the cadaveric position in which they lie partially abducted and through which airflow is much less compromised. Phonation, however, may be reduced to a whisper.

The anatomy of the trachea and bronchi

Commentary

Anatomy of these areas is of self-evident importance both in anaesthesia and intensive care. You may be given the opportunity to describe every bronchopulmonary segment, but because the terminology is cumbersome, with considerable duplication, it is more likely, once you have demonstrated that you know the key points (such as the origin of the right upper lobe bronchus), that the viva will move onto more applied clinical aspects.

The viva

You will be asked to describe the anatomy.

- **Trachea:** The trachea is a tube of cartilage with a membranous lining which is continuous inferiorly with the larynx. The trachea proper is 10–11 cm long, and extends downwards from the cricoid cartilage at the level of the sixth cervical vertebra, as far as the sixth thoracic vertebra (in full inspiration). It then divides into left and right main bronchi. Its diameter in the adult is around 20 mm. In the first year of life its diameter is 3 mm or less, and increases thereafter by about 1 mm $year^{-1}$ of age until it attains adult dimensions. It comprises 16–20 C-shaped cartilages attached vertically by fibro-elastic connective tissue, which helps explain the mobility of the structure. Through most of its course the trachea lies in the midline although at the bifurcation it is displaced slightly rightwards by the arch of the aorta.
- **Anterior relations:** In the upper part of the neck these are confined to skin and fascia, with the isthmus of the thyroid overlying the second to fourth tracheal rings. In its lower cervical course the trachea is partly overlain by the sternohyoid and sternothyroid muscles, and by the jugular arch connecting the anterior jugular veins. In its thoracic course the manubrium sterni lies anteriorly, as do the remnants of the thymus, the inferior thyroid veins and the brachiocephalic artery.
- **Posterior relations:** Posteriorly lies the oesophagus, and in grooves between trachea and oesophagus run the recurrent laryngeal nerves.
- **Lateral relations:** In the upper neck it is related to the lobes of the thyroid and to the carotid sheath. In its lower course it is related on the right to the lung and pleura, to the brachiocephalic artery and veins, to the azygos vein and to the superior vena cava. On the left it is related to the arch of the aorta and the left common carotid and subclavian arteries.
- **The right and left main bronchi:** The main bronchi are formed at about the level of T_5. The right is shorter (3 cm long), wider and angled more vertically than the left, which means that foreign bodies and tracheal tubes are more likely to enter its orifice than the left. The left main bronchus is more obliquely placed and is some 5 cm in length. Important relations on the right are the pulmonary artery which lies first below and then anterior to it, with the azygos vein above; while on the left side the main bronchus lies below the arch of the aorta with the descending aorta behind and the left pulmonary artery lying in front. In children the angles of the bronchi at the carina are equal.
- **Bronchopulmonary segments – right lung:** Within about 2.5 cm of the bifurcation the right main bronchus gives off the right upper lobe bronchus (which divides in turn within 1 cm into apical, anterior and posterior segments). It is this right upper lobe bronchus that is most at risk from inadvertent occlusion by a tracheal tube or a right-sided double-lumen endobronchial tube. The right main then gives off the middle lobe bronchus, which is directed downwards and forwards (before bifurcating into medial and lateral lobes). Just below the origin of the middle lobe bronchus and opposite to it, is the bronchus of the apical segment of the lower lobe. This directs posteriorly, before dividing

into superior, anterior basal and lateral basal segments. The medial, anterior, lateral and posterior basal segments arise in due course from the main stem of the lower lobe bronchus, which continues in its downward direction.

- **Bronchopulmonary segments – left lung:** The longer left main bronchus gives off the left upper lobe bronchus after about 5 cm, and this then divides into a superior division from which arise apical, posterior and anterior segments of the upper lobe, and a lingular bronchus from which arise the superior and inferior lingular segments. The anatomy of the left lower lobe is similar to the right, in that the left lower lobe bronchus gives off superior, anterior basal, lateral basal and posterior basal segments. The medial basal bronchopulmonary segment usually arises in common with the anterior basal, however, which means technically that there are only four rather than five bronchopulmonary segments on the left.

Direction the viva may take

You may be asked whether this anatomy allows you to predict which parts of the lung may be contaminated following an episode of aspiration.

- **Pulmonary aspiration of gastric contents:** The anatomy of the lobes and bronchopulmonary segments influences zonal contamination should pulmonary aspiration occur. If the patient is supine it is more likely that the apical segments of the lower lobes will be affected because of the direct posterior projection of the bronchus of the apical segment. If they are in the lateral position then aspiration is more likely to affect the upper lobes. If prone, the right middle lobe and lingula will be the site of the problem because of their downward and forward orientation, and if the patient is sitting, it will be the posterior or lateral basal segments of the lower lobes that are contaminated.

Further direction the viva could take

You may be asked about double-lumen tubes

- **Double-lumen endobronchial tubes:** These are used when one lung needs to be isolated so that the other can be collapsed to allow surgery. Such procedures include pulmonary resection, oesophago-gastrectomy, surgery on the thoracic aorta, anterior spinal fixation and thorascopic sympathectomy. A left-sided tube is almost always favoured because this avoids the risk of occluding inadvertently the origin of the right upper lobe bronchus. Problems with malpositioned tubes are an important cause of mortality and morbidity (see *One-lung anaesthesia*, page 107). A double-lumen tube is positioned correctly when the upper surface of the bronchial cuff lies immediately distal to the bifurcation of the carina. The position of the tube should be checked endoscopically.

The stellate ganglion

Commentary

Stellate ganglion block is a common procedure in the chronic pain clinic, is simple to perform, and has significant potential complications. You may well not have carried out this block yourself, but as one of several procedures in the neck undertaken by anaesthetists (others include interscalene block, deep cervical plexus block and internal jugular cannulation), its anatomy is of some relevance.

The viva

You will be asked to describe the anatomy.

- The cervical sympathetic chain lies either side of the vertebral column in the fascial space: posterior lies the fascia over the prevertebral muscles, anteriorly is the carotid sheath.
- The area where the inferior cervical and the first thoracic ganglia meet, either in close proximity or fusion, is referred to as the stellate ganglion.
- The ganglion extends from the neck of the first rib where its lower part is covered anteriorly by the dome of the pleura, to the transverse process of C_7 where anterior lies the vertebral artery. By the level of C_6 the vertebral artery has moved posteriorly into the foramen transversarium pending its ascent into the skull.
- Much of the sympathetic nerve supply to the head and neck as well as to the upper extremity synapses in or near the stellate ganglion.
- Sympathetic pre-ganglionic fibres leave the cord from segments as widely separated as T_1–T_6 and although many converge in or around the stellate ganglion, some may bypass it. For this reason large volumes of local anaesthetic solution may be needed to fill the space in front of the prevertebral fascia down to T_4, but this will produce reliable sympathetic blockade of the head, neck and upper limb. It is more accurately described as a 'cervicothoracic block'.

Direction the viva may take

You will probably be asked about a technique of stellate ganglion block, and then about its indications.

- **Technique:** Two approaches are described; the anterior (sometimes called the 'paratracheal' anterior) approach and the paratracheal approach.
  - *Anterior approach*: The trachea and carotid pulse are gently retracted to allow identification of the most prominent cervical transverse process (the Chassaignac tubercle) at C_6, the level of the cricoid cartilage.
  - A lower approach to the ganglion's actual location at C_7 risks both pneumothorax and vertebral artery puncture.
  - The carotid sheath is moved laterally, and the trachea medially, before a 25–30 mm × 23–25G needle is directed perpendicularly down on to the tubercle.
  - Once it has encountered bone, the needle is withdrawn 4–5 mm. If this is not done there is a higher incidence of upper limb somatic blockade.
  - Local anaesthetic in low concentration and high volume is injected (such as lignocaine 0.5% or bupivacaine 0.125% × 15–20 ml).
  - *Paratracheal approach*: The needle insertion is two fingerbreadths lateral to the suprasternal notch and two fingerbreadths superior to the clavicle. This identifies the transverse process of C_7, immediately below Chassaignac's tubercle at C_6, at the level of the cricoid cartilage.
  - The sterno-cleidomastoid and carotid sheath are moved laterally before the needle is directed perpendicularly down onto the transverse process.
  - Once it has encountered bone the needle is withdrawn 0.5–1.0 cm.

- Local anaesthetic in low concentration and high volume is injected as above.
- This lower approach risks pneumothorax as well as vertebral artery puncture.

Further direction the viva could take

You might then be asked indications for the block, and the viva may concentrate on its use following inadvertent intra-arterial injection, this being one of the classic anaesthetic indications. Very few of the other indications listed are likely to lie within your current experience.

- You could start by commenting that the evidence base for the therapeutic use of stellate ganglion blocks is not strong, but the technique has a long tradition of use in the management of chronic pain.
- **Indications:** These include any condition requiring sympathetic block of the head, neck and upper limb.
  - *Neuropathic pain conditions*: Complex regional pain syndromes types 1 and 2, post-herpetic neuralgia of head and neck, shoulder–hand syndrome (following cerebrovascular accident (CVA) or ischaemia), phantom limb pain and pain associated with upper limb denervation.
  - *Ischaemic conditions*: Thrombosis or microembolism, vasospastic disorders (e.g. Raynaud's disease), scleroderma, frostbite and inadvertent intra-arterial injection. See *Arterial supply of the hand*, page 45.
  - *Angina pectoris*: Severe refractory chest pain due to coronary ischaemia.
  - *Miscellaneous*: Hyperhydrosis and treatment of pain associated with Paget's disease of bone.

If you have got this far, you may be asked finally about complications.

- **Complications:** These include local trauma and haematoma (which may compress the airway if severe); recurrent laryngeal nerve block, which causes hoarseness; brachial plexus block, because via the anterior approach only a layer of fascia separates the plexus and the ganglion which is anterior to it; carotid or vertebral arterial puncture and possible intravascular injection (with the paratracheal lower approach); intrathecal injection; pneumothorax (if the approach is too low) and deep cervical plexus block (if the approach is too high).

Surface anatomy of the neck (*with particular reference to percutaneous tracheostomy and cricothyroidotomy*)

Commentary

If these procedures are performed incorrectly the results can be disastrous. The applied anatomy is not complex but you should give a simple authoritative account of the techniques, particularly in relation to the potentially life-saving manoeuvre of cricothyroidotomy. If the techniques that you describe put the patient at risk then you will fail this question and probably the viva.

The viva

This question is specific, and so you will be asked to describe the surface anatomy of the neck.

It does not matter particularly how you approach the answer; one way is to outline the anatomy from above downwards.

- The hyoid bone lies at the level of the third cervical vertebra (C_3). Lying just above and behind is the epiglottis.
- The bifurcation of the common carotid artery is at the level of the fourth cervical vertebra (C_4), slightly above the notch of the thyroid cartilage.
- The larynx lies opposite the fourth, fifth and sixth cervical vertebrae (C_4, C_5 and C_6).
- The cricoid cartilage is at the level of the sixth cervical vertebra (C_6).
- The trachea extends from the sixth cervical vertebra (C_6) down as far as the fifth or sixth thoracic vertebra (T_5 and T_6) at end-inspiration.
- The suprasternal notch is located at the level of the second and third thoracic vertebrae (T_2 and T_3).

Direction the viva may take

You may be asked further about the anatomy relevant to the two clinical techniques (of percutaneous tracheostomy and cricothyroidotomy), which have different indications but broadly similar complications.

- The trachea comprises 16–20 C-shaped cartilages, which lie anteriorly in the neck covered by skin and the superficial and deep fascial layers. The second, third and fourth rings are covered by the isthmus of the thyroid. The great vessels of the neck lie laterally, and so identification of the midline is crucial.
- The cricothyroid membrane spans the inferior border of the thyroid cartilage and the superior border of the cricoid cartilage, and immediately overlies the subglottic region of the larynx. It is covered anteriorly by skin and by superficial and deep fascia. Immediately lateral are the sterno-cleidomastoid muscle, the sternothyroid and the sternohyoid muscles and the carotid sheath.

Percutaneous tracheostomy

- This is an elective, not an emergency procedure, which in the context of intensive care has become a well-established alternative to definitive surgical tracheostomy. Its indications are the same as for formal tracheostomy in the critically ill: typically to simplify airway management in a patient who otherwise would face the problems of long-term tracheal intubation.
- There are variations in approach, but all are based on a modified Seldinger technique for placing a tracheostomy tube.
- A typical technique is described as follows:
  - Guided by the surface anatomy as described above, a skin incision is made to allow a needle and guide wire to be placed through the fibro-elastic tissue that joins the tracheal rings.

— The isthmus of the thyroid gland covers the second to fourth tracheal rings. A higher approach through the subcricoid membrane, or between the first and second tracheal rings does avoid the thyroid isthmus but is associated with greater incidence of tracheal stenosis. It is for this reason that many intensivists now prefer a low approach, below the second or even third ring.
— The diameter of the hole is enlarged with progressively larger dilators to the point at which it will accept a definitive tracheostomy tube.
— It is usual for a second anaesthetist to monitor this procedure from within the trachea, by using a fibreoptic bronchoscope. The posterior wall of the trachea may be so ragged and friable that it can easily be perforated.

Further direction the viva could take

You may be asked to compare percutaneous tracheostomy with cricothyroidotomy.

- Both the techniques bypass the normal translaryngeal route to secure the airway, but the circumstances and urgency of their use differ considerably. Percutaneous tracheostomy is an elective procedure, whereas cricothyroidotomy is an emergency procedure, which is usually invoked only when all other attempts to secure a definitive airway have failed and when critical hypoxia is imminent.
- The cricothyroid membrane is used for emergency access because it is readily identifiable and because it is relatively avascular.
- The patient is positioned with the neck extended to allow identification of the membrane. After stabilisation of the overlying skin, which can be quite lax, a small vertical incision in the skin is followed by a transverse incision in the membrane. A spreader or scalpel handle is used to open the airway, after which an appropriate tube can be inserted under direct vision. The purpose-made devices typically have an internal diameter of 4 mm.

You may be asked finally to comment on complications.

- Haemorrhage (immediate or delayed); the creation of false passage; tracheal or oesophageal perforation; barotrauma; subcutaneous emphysema; failure and accidental decannulation.
- Subglottic stenosis is a cause of serious morbidity; it is more common after cricothyroidotomy than after percutaneous tracheostomy.

The brachial plexus

Commentary

An understanding of the anatomy of the brachial plexus is the key to successful regional anaesthesia of the upper limb. The anatomy is detailed, but is not so complex that it cannot be incorporated into a 7 or 8 min viva question. It is a clinically important area of anatomy and it is asked frequently. It is worth learning a schematic diagram of the plexus, because it makes it much easier to explain it to the examiners.

The viva

You will be asked about the formation of the brachial plexus.

- The plexus forms in the neck from the anterior primary rami of C_5, C_6, C_7, C_8 and T_1.
- These five roots merge in the posterior triangle of the neck to form three trunks.
- C_5 and C_6 form the upper, and C_7 the middle trunk (above the subclavian artery). C_8 and T_1 form the lower trunk (posterior to the subclavian artery).
- At the lateral border of the first rib the three trunks each divide into anterior and posterior divisions.
- The three posterior divisions form the posterior cord (described according to its relationship with the axillary artery), from which derives the radial nerve. (Also the axillary, thoracodorsal and upper and lower subscapular nerves.)
- The anterior divisions of upper and middle trunks form the lateral cord, from which derive the median nerve (lateral head) and the musculocutaneous nerve. (Also the lateral pectoral nerve.)
- The anterior division of the lower trunk continues as the medial cord, from which derive the ulnar nerve and the median nerve (medial head). (Also the medial cutaneous nerves of arm and forearm and the medial pectoral nerve.)

Direction the viva may take

You will be asked about brachial plexus block. It is probable that you will be asked to describe an approach of your choosing. Choose a block that you have actually performed.

- **Interscalene block**
  - Interscalene local anaesthesia blocks the anterior primary rami of the nerves of C_5, C_6, C_7, C_8 and T_1, before they merge in the posterior triangle to form the trunks of the brachial plexus.
  - The cervical nerves leave the intervertebral foramina, and pass caudad and laterally between the scalenus anterior and the scalenus medius muscles. The nerves are enclosed within a fascial compartment which comprises the posterior fascia of the anterior scalene muscle, and the anterior fascia of the middle scalene muscle.
  - The patient should lie supine with the head turned slightly away from the side of injection and with the arm by the side (gently pulled down if necessary to depress the shoulder).
  - After standard aseptic preparation, the interscalene groove between scalenus anterior and medius should be identified at the level of the cricoid cartilage (C_6).
  - If the awake patient is asked to lift the head off the pillow (which tenses the sterno-cleidomastoid muscles) or to give a sniff, the groove becomes more evident. In the anaesthetised patient identification is helped by the fact that in more than 90% of subjects the external jugular vein overlies the groove at this level.
  - The groove and the roots beyond are superficial and in most cases a stimulating needle no longer than 30 mm is needed. The needle should be

held perpendicular to the skin in all planes as it is directed medially, posteriorly and caudally (inwards, backwards and downwards, respectively) towards the transverse process of C_6 (Chaisssaignac's tubercle).
  - Once muscle stimulation is apparent in the required distribution (usually shoulder movements mediated by C_5 and C_6) 30–40 ml of solution may be injected after aspiration and with all due precautions. In common with most plexus blocks into fascial compartments, large volumes of appropriately dilute solutions may be needed to obtain adequate analgesia of all the nerves involved.
  - Interscalene block is particularly useful for shoulder surgery. It can be used to provide analgesia for more distal structures in the upper limb, but it does not provide reliable block of C_8 and T_1 and so ulnar sparing is frequent (some reports quote 30–40%).
  - It commonly blocks the phrenic nerve and so should be used cautiously in those with respiratory disease. Bilateral blocks should not be performed.
  - *Complications*: These include intravascular injection (particularly into the vertebral artery), central spread via inadvertent dural puncture leading to a total spinal, phrenic nerve palsy (which almost invariably accompanies an effective block), Horner's syndrome (cervical sympathetic block, which is usually innocuous), vagal and recurrent laryngeal nerve block which may cause hoarseness, but is usually benign, and pneumothorax. (There are also the generic complications such as systemic toxicity and neurapraxia.)
- **Supraclavicular block**
  - This block provides analgesia for most of the upper limb. The three trunks are in close arrangement and the block is reliable. It can also be used for shoulder surgery, although the interscalene approach is usually preferred.
  - The three trunks lie on the first rib, between the insertion of the scalenus anterior and scalenus medius muscles, and immediately posterior to the subclavian artery (the pulsations of which can provide a landmark).
  - The trunks cross the rib at about the mid-point of the clavicle.
  - A number of approaches have been described: if you are familiar with one of them then explain it. In essence the aim of the technique is to direct the needle down onto the first rib, and to contact the brachial plexus where it lies cephaloposterior to the subclavian artery.
  - Once muscle stimulation is apparent in the appropriate distribution, 20–40 ml of appropriate local anaesthetic solution (such as laevobupivacaine 0.25–0.5%) may be injected after aspiration and with the usual precautions. If localisation is accurate, then the smaller volumes will be effective.
  - *Complications*: These include pneumothorax (the incidence may be 0.5–1.0% even in experienced hands, and may take up to 24 h to develop), intravascular injection or puncture (subclavian artery or vein), phrenic nerve palsy (in 40–60%), Horner's syndrome in 70–90% (cervical sympathetic block) and neuritis (plus generic complications as above).
- **Subclavian perivascular or infraclavicular block** (several variations have been described).
  - In effect this is an approach to the axillary sheath from a proximal direction, although the blocks provides analgesia similar to that offered by the supraclavicular approach. The subclavian perivascular block is actually made through a needle inserted above the clavicle. Unlike the other techniques these alone reliably block the intercostobrachial nerve. These blocks are not widely used in the UK and unfamiliarity with their details will not disadvantage you.

- **Axillary block**
  - This has fewer complications than other approaches, is generally effective and is a popular technique.
  - The block provides good analgesia for surgery below the elbow. The musculocutaneous nerve may leave the axillary sheath proximal to the site of injection, in which event supplemental analgesia may be needed by blocking the nerve between brachioradialis and the lateral epicondyle at the elbow. This nerve innervates a substantial part of the radial side of the forearm, and so local anaesthetic sparing of this area is not purely academic.
  - The arm is abducted to 90° (hyperabduction may abolish the arterial pulsation). The advancing needle is directed at an angle of about 45° to the skin as far proximally as possible. In practice this often means injecting at the lateral border of pectoralis major.
  - Once a twitch is elicited, the entire volume of local anaesthetic solution can be injected (after aspiration). It takes just over 40 ml to fill the axillary sheath as far as the coracoid process in adults, and in theory complete block of all three cords will follow circumferential spread round the sheath. Some anaesthetists prefer to identify the major nerves of the upper limb separately, and block each one in turn.
  - An alternative approach uses axillary arterial puncture as an end point. Following transfixion of the vessel, the needle is either advanced or withdrawn until aspiration is negative. The widespread use of nerve stimulators has made this technique less respectable than once it was.

Further direction the viva could take

It is important that you understand the indications for these different approaches (for instance, interscalene block for shoulder surgery; axillary block for a fasciectomy involving the fifth finger) and that you are aware of their limitations and complications. You may be asked, therefore, to compare and contrast the blocks.

The ulnar nerve

Commentary

This is a well-circumscribed area of anatomy, which is of interest not only because the ulnar nerve can be blocked to provide surgical anaesthesia, but also because it is vulnerable to damage during general anaesthesia.

The viva

You will be asked about the anatomy of the ulnar nerve.

- The ulnar nerve arises from the brachial plexus. (This is formed from the anterior primary rami of C_5, C_6, C_7, C_8 and T_1. These roots merge in the posterior triangle of the neck to form three trunks: C_5 and C_6 form the upper, C_7 the middle trunk, and C_8 and T_1 form the lower trunk. At the lateral border of the first rib the three trunks each divide into anterior and posterior divisions.)
- The anterior division of the lower trunk continues as the medial cord, from which derives the ulnar nerve. Its fibres originate mainly from C_8 and T_1, although it may also receive a contribution from C_7.
- It passes through the extensor compartment of the upper arm, lying medial to the axillary and brachial arteries. It then continues medially on the anterior aspect of the medial head of triceps to pass beneath the medial epicondyle of the humerus, where it lies in the ulnar groove.
- It enters the forearm between the two heads of flexor carpi ulnaris. In the upper part of the forearm it lies deep to this muscle and separated from the ulnar artery. In the distal forearm it lies lateral to flexor carpi ulnaris and near to the medial side of the artery.
- About 5 cm above the wrist it gives off a dorsal branch before continuing into the hand lateral to the pisiform bone and above the flexor retinaculum.
- The ulnar nerve provides the motor supply to flexor carpi ulnaris, to the medial part of flexor digitorum profundus, and to the hypothenar muscles. It also supplies all the small muscles of the hand apart from the lateral two lumbricals and the three muscles of the thenar eminence (abductor pollicis brevis, opponens pollicis and part of flexor pollicis brevis). The deep head of flexor pollicis is supplied by the ulnar nerve.
- It supplies sensation to the elbow joint but gives off no branches in the upper arm. It supplies the skin over the hypothenar eminence and over the fifth finger as well as over the medial part of the fourth finger.

Direction the viva may take

You may be asked about the indications for, and techniques of, ulnar nerve blockade.

- Indications for ulnar block follow from knowledge of its anatomy, and its main use is to provide analgesia for procedures on the medial, ulnar side of the hand and forearm. Digital nerve blocks are an easy and reliable method of providing anaesthesia for finger surgery, and so ulnar block is reserved usually for more proximal operations such as palmar fasciectomy. It is commonly performed jointly with blocks of the other major nerves of the arm.
- The nerve can be blocked at a number of sites:
  - — *At the brachial plexus*: See *The brachial plexus*, page 34.
  - — *At mid-humeral level*: A line is drawn between the upper border of pectoralis major in the axilla and the mid-point of the flexor crease of the elbow. A parallel line is drawn along the middle of the humerus about 1 cm medial to it, and via a single injection point at this mid-point all three major nerves of the forearm can be reached with a 50-mm stimulator needle.
  - — *At the elbow*: The nerve can be blocked with about 5 ml of solution injected 2–3 cm proximal to the ulnar groove. Injection into the actual fibrous sheath

at the elbow is thought to be associated with a high incidence of residual neuritis.

— *At the wrist*: The nerve lies beneath the tendon of flexor carpi ulnaris, proximal to the pisiform bone, and medial and deep to the ulnar artery. An approach from the ulnar side of the tendon (3–5 ml of solution injected at a depth of around 1.5 cm) is less likely to encounter the artery, and will also block the cutaneous branches.

Further direction the viva could take

You may be asked about the potential for ulnar nerve damage and the clinical signs of such damage.

- **Damage:** Even when the arm is lying in the neutral position by the side of the anaesthetised patient it is vulnerable to pressure, either from arm supports or from the table itself. It has become routine practice to protect the elbow with padding, and it has become equally routine to blame anaesthesia for any ulnar nerve damage. This is despite the fact that ulnar nerve palsy has been reported even when every precaution has been taken. The nerve is also vulnerable to stretch and so the upper arm should not be displaced posteriorly, nor abducted to greater than 90°.
- **Symptoms and signs of injury:** Apart from the sensory loss and paraesthesia of which the patient will complain, ulnar nerve injury is associated with the classic *main en griffe*, or claw hand. This is because the extensors of the fingers and the long flexors of the hand act unopposed. If the nerve is transected at the elbow the clawing is less marked. This so-called 'ulnar paradox' occurs because flexor digitorum profundus is also paralysed.

The radial nerve

Commentary

The radial nerve is one of the three main nerves of the upper limb, and comprises another well-defined area of anatomy. Upper limb surgery and trauma is common, and radial nerve block is a reliable means of producing useful analgesia. The nerve has a relatively large number of terminal branches whose detailed anatomy is beyond the scope of this viva, but you will need to know the effects of blocking the radial nerve proximal to its main divisions.

The viva

You will be asked about the anatomy of the radial nerve.

- The radial nerve arises from the brachial plexus. (This is formed from the anterior primary rami of C_5, C_6, C_7, C_8 and T_1. These roots merge in the posterior triangle of the neck to form three trunks: C_5 and C_6 form the upper, C_7 the middle trunk, and C_8 and T_1 form the lower trunk. At the lateral border of the first rib the three trunks each divide into anterior and posterior divisions.)
- The three posterior divisions form the posterior cord (described according to its relationship with the axillary artery), from which derives the radial nerve. Its fibres originate, therefore, from C_5, C_6, C_7, C_8 and T_1, and it is the largest branch of the brachial plexus.
- The radial nerve descends beneath the axillary artery and passes between the long and medial heads of the triceps muscle into the posterior compartment of the arm. It then passes obliquely behind the humerus where it lies in a shallow spiral groove.
- In the lower third of the humerus it enters the anterior compartment of the upper arm, descending into the forearm between brachialis medially and brachioradialis laterally. At the lateral epicondyle of the humerus it divides into its terminal deep and superficial branches.
- It is motor in the upper arm to triceps, in the lower arm to brachialis, brachioradialis and to the extensor muscles of the wrist and hand.
- The area of sensory innervation that is of particular anaesthetic relevance includes much of the dorsum of the hand, and the radial side of the forearm. (The ulnar nerve supplies the skin over the distal phalanges, the fifth finger and medial side of the fourth finger and over the fifth and fourth metacarpals.) The radial nerve also supplies cutaneous sensation to the posterior aspect of the forearm and to the skin over the dorsal base of the thumb. (The musculocutaneous nerve supplies much of the radial surface of the forearm.)

Direction the viva may take

You may be asked about the indications for, and techniques of, radial nerve blockade.

- Its main use is in conjunction with other blocks to provide analgesia for procedures on the lateral, radial side of the hand and forearm. Digital nerve blocks provide reliable anaesthesia for finger surgery, but radial block can be used for procedures on the base of the thumb and, in combination with musculocutaneous block, to allow the creation of forearm arterio-venous fistulae for dialysis.
- The nerve can be blocked at various sites:
  - — *At the brachial plexus*: See *The brachial plexus*, page 34.
  - — *At mid-humeral level*: A line is drawn between the upper border of pectoralis major in the axilla and the mid-point of the flexor crease of the elbow. A parallel line is drawn along the middle of the humerus about 1 cm medial to it, and via a single injection point at this mid-point all three major nerves of the forearm can be reached with a 50-mm stimulator needle.

— *At the elbow*: The nerve can be blocked as it traverses the anterior aspect of the lateral epicondyle of the humerus. The needle is inserted some 2 cm lateral to the biceps tendon and directed towards the bone. Up to 10 ml of solution can be injected in a fanwise direction as the needle is withdrawn. The musculocutaneous nerve can also be blocked at the elbow between the biceps and brachioradialis muscles.
— *At the wrist*: Nerve block at the wrist is effectively a superficial field block of the terminal sensory branches. Local anaesthetic solution can be injected along the lateral border of the radial artery, extending dorsally to include the area delineated by the extensor tendons of the thumb.

Further direction the viva could take

You may be asked about the potential for radial nerve damage and the clinical signs of such damage.

- **Damage:** The radial nerve is subject to various types of injury and may be damaged by compression against the upper humerus, as in the so-called 'Saturday night or crutch palsy'. The pressure exerted by an arterial tourniquet can also damage the nerve by the same mechanism. Its close relation to the humerus makes it vulnerable to damage in mid-humeral fractures, and the posterior interosseous branch may be traumatised in injuries to the head of the radius.
- **Symptoms and signs of injury:** Overlap of innervation means that sensory loss and paraesthesia may be confined to a relatively small area on the dorsum of the hand. Otherwise radial nerve injury typically is associated with wrist drop due to paralysis of the extensor muscles. If the damage to the nerve has occurred below the elbow then the functional preservation of extensor carpi radialis longus will minimise this effect.

The median nerve

Commentary

This is the third of the main nerves of the upper limb, and comprises another well-defined area of anatomy. As with the questions on the ulnar and radial nerves, you will be expected to outline the anatomy and to discuss the relevant local anaesthetic blocks.

The viva

You will be asked about the anatomy of the median nerve.

- The median nerve arises from the brachial plexus. (This is formed from the anterior primary rami of C_5, C_6, C_7, C_8 and T_1. These roots merge in the posterior triangle of the neck to form three trunks: C_5 and C_6 form the upper, C_7 the middle trunk, and C_8 and T_1 form the lower trunk. At the lateral border of the first rib the three trunks each divide into anterior and posterior divisions.)
- The anterior divisions of the upper and middle trunks form the lateral cord, from which derive the lateral head of the median nerve.
- The anterior division of the lower trunk continues as the medial cord, from which derives the medial head of the median nerve. Its fibres originate, therefore, from C_5, C_6, C_7, C_8 and T_1.
- The nerve passes into the arm lying lateral to the brachial artery which it then crosses to descend on its medial side to the antecubital fossa, where it is protected by the bicipital aponeurosis.
- It passes down into the forearm between the bellies of the deep and superficial flexors of the fingers (flexor digitorum profundus and superficialis) and at the wrist lies lateral to or just beneath the tendon of palmaris longus, and medial to flexor carpi radialis.
- It enters the hand beneath the flexor retinaculum before dividing into a leash of terminal branches.
- It is motor in the forearm to several of the superficial flexors (excluding flexor carpi ulnaris) and in the hand to muscles of the thenar emininence: abductor pollicis brevis, part of flexor pollicis brevis and the opponens pollicis. Its anterior interosseous branch also supplies flexor pollicis longus, pronator quadratus and part of flexor digitorum profundus.
- The cutaneous innervation extends to the radial aspect of the palm, and the palmar surface of the radial 3½ digits, together with their dorsal tips as far as the first interphalangeal joint.

Direction the viva may take

You may be asked about the indications for, and techniques of, median nerve blockade.

- Its main use is the provision of analgesia for procedures on the radial palm. The fingers and distal thumb can readily be anaesthetised using digital nerve blocks, but median nerve block is useful for procedures such as carpal tunnel release and palmar fasciectomy.
- The nerve can be blocked at various sites:
  - — *At the brachial plexus*: See *The brachial plexus*, page 34.
  - — *At mid-humeral level*: A line is drawn between the upper border of pectoralis major in the axilla and the mid-point of the flexor crease of the elbow. A parallel line is drawn along the middle of the humerus about 1 cm medial to it, and via a single injection point at this mid-point all three major nerves of the forearm can be reached with a 50-mm stimulator needle.
  - — *At the elbow*: The nerve can be blocked immediately medial to the brachial artery as it crosses the intercondylar line. The needle is directed perpendicularly and should find the nerve within 1–2 cm.

— *At the wrist*: The nerve lies in the midline on the radial border of the palmaris longus tendon. The needle is directed perpendicularly some 2 cm proximal to the distal flexor crease of the wrist. The nerve is superficial and lies beneath the deep fascia at a depth of 1 cm or less.

Further direction the viva could take

You may be asked about the potential for median nerve damage and the clinical signs of such injury.

- **Damage:** The median nerve is most vulnerable to trauma at the wrist, although it can be injured in supracondylar humeral fractures and following injury to the distal radius. The most common lesion occurs as a result of compression of the nerve in the carpal tunnel.
- **Symptoms and signs of injury:** Trauma at the wrist will paralyse the thenar muscles and cause significant sensory loss. More proximal injury leads to weak wrist flexion, loss of pronation, and loss of flexion of the thumb, index and middle fingers. Atrophic changes and wasting of the thenar eminence will flatten the contours of the hand.

The antecubital fossa

Commentary

By analogy with the femoral triangle, the anatomy of the antecubital fossa is straightforward, and it too lends itself readily to simple diagrams. A transverse sketch is a simple way of showing that you are aware of the important anatomical relations. Alternatively you may find yourself automatically demonstrating on your own arm: this can be an effective technique which may make the anatomy easier to learn. Questioning may extend to practical clinical matters such as inadvertent intra-arterial injection, nerve blocks at the elbow and the insertion of long lines. Non-medical staff who undergo training in venepuncture and cannulation are required to learn the detailed anatomy of this area, and so the FRCA examiners will expect no less.

The viva

You will be asked to describe the anatomy.

- The antecubital, or cubital fossa, is a triangular intermuscular depression on the anterior surface of the elbow joint.
- The base of the triangle is formed by the line which joins the medial and lateral epicondyles of the humerus.
- The lateral side of the triangle is formed by the medial edge of the brachioradialis muscle, while the medial side is formed by the lateral border of the pronator teres.
- The floor consists of the brachialis and supinator muscles.
- The roof (from above down) comprises skin, subcutaneous tissue, and the deep fascia, which includes the bicipital aponeurosis.
- Within the fossa lie the tendon of the biceps muscle and the terminal part of the brachial artery, which lies in the centre of the fossa prior to its division into the radial and ulnar arteries opposite the neck of the radius. It also contains the associated veins and the median and radial nerves.
- The anatomy of the superficial veins varies greatly, but that of a typical subject can be described as follows.
  - *Cephalic vein*: The cephalic vein drains the radial side of the forearm, and ascends over the lateral side of the fossa to lie in a groove along the lateral edge of the biceps. At the lower border of pectoralis major it moves deeper to lie between pectoralis major and deltoid before penetrating the clavipectoral fascia to join the axillary vein.
  - *Basilic vein*: The basilic vein drains the ulnar side of the forearm and rises along the medial border of biceps to pierce the deep fascia in the middle upper arm before going on to form the axillary vein.
  - *Median cubital vein*: The median cubital vein originates from the cephalic vein distal to the lateral epicondyle, and then runs upwards and medially across the antecubital fossa to join the basilic vein above the elbow.

Direction the viva may take

You are likely to be asked about the clinical relevance of the anatomy.

- The antecubital fossa is the most common site for venepuncture as well as being a site for venous cannulation. One potential hazard is inadvertent puncture or injection into the brachial artery. The danger of this happening is lessened by the presence of the bicipital aponeurosis, which is an extension of the medial lower border of the muscle and tendon of biceps. It passes downwards and medially to merge with the deep fascia at the origin of the forearm flexor muscles, separating as it does so, the brachial artery from the median cubital vein. (This is the reason why historically it was known as the 'grâce à Dieu fascia'.)

- The lateral cutaneous nerve of the forearm crosses the fascia of the roof of the fossa, and although it lies deep to the cephalic vein may still be vulnerable to damage from a needle or a cannula.
- Long lines can be inserted via the antecubital veins, which offer a safer route to the central veins. Although cannulation at the elbow may be simple, the acute curve at the clavipectoral fascia may prevent a long venous catheter from gaining access to the central venous circulation.

Further direction the viva could take

You may be asked how you would recognise and manage inadvertent intra-arterial injection, and about nerve blocks at this site.

- This is detailed in *Arterial supply of the hand*, on page 45. An anomalous ulnar artery which lies superficially just below the median cubital vein is present in 2% of the population, and so it is not only accidental injection into the brachial artery of which anaesthetists must be aware.
- Nerve blocks at the elbow are described in *The radial nerve*, page 39, *The median nerve*, page 41, and *The ulnar nerve*, page 37.

Arterial supply of the hand

Commentary

This is a straightforward area of anatomy which in the modified Allen test has an obvious clinical application, albeit one whose value is disputed. If you impart the basic information too rapidly then you will find yourself discussing arterial pressure waveforms and damping. That may suit you, but if you would prefer to stay with the anatomy then it will be worth refreshing your memory of some of the relevant muscles and tendons. This in any event will make your knowledge of anatomy appear much more substantial.

The viva

You will be asked the basic anatomy of the arterial supply.

- The hand is supplied by the radial and ulnar arteries.
- **Radial artery:** In the distal forearm the radial artery lies between flexor carpi radialis and brachioradialis. The tendons of these muscles comprise the landmarks between which the artery is palpated at the wrist.
  - Beyond the radial pulse the artery supplies a branch which contributes to the superficial palmar arch.
  - The main arterial branch continues over the scaphoid and beneath the extensor and abductor tendons of the thumb (extensor pollicis longus and brevis, and abductor pollicis longus), and passes between the first and second metacarpal bones to contribute to the deep palmar arch.
- **Ulnar artery:** In the distal forearm the ulnar artery lies superficially between the tendons of flexor carpi ulnaris and flexor digitorum superficialis.
  - It crosses beneath the flexor retinaculum to complete the superficial palmar arch. The ulnar arterial component is much more significant than the radial.
  - The deep branch enters the palm where it forms an anastomosis with the radial artery to complete the deep palmar arch.
  - The superficial palmar arch then gives off further branches including dorsal metacarpal and dorsal digital arteries. The deep palmar arch similarly branches to form palmar metacarpal and palmar digital arteries.

Direction the viva may take

You will probably be asked about the clinical relevance of this arterial supply.

- Both arteries can be cannulated in order to allow direct intra-arterial measurement of blood pressure, but anaesthetists prefer to be confident that the circulation of the hand will not be jeopardised. The traditional method for assessing the adequacy of radial or ulnar arterial flow is the modified Allen test. After compression of both arteries at the wrist, the patient is asked to blanch the palm by clenching and then opening the hand. On releasing the compression of one or other of the arteries, depending on which is chosen as the site of cannulation, the palm should reperfuse, demonstrating thereby the adequacy of flow. Seven seconds or less is considered normal; longer than 15 s is abnormal. Although the test continues to be used widely it has a poor predictive value. Ischaemic complications have been reported following a normal Allen test and vice versa.

Further direction the viva could take

This topic is not large, and so you may exhaust it fairly quickly. You will be assessed mainly on the core information above, but there a number of directions the viva could take. You may be asked about intra-arterial injection or about indications for, and direct methods of measuring arterial pressure. There is unlikely to be enough time to explore this latter subject in any depth.

- **Intra-arterial injection:** Accidental injection occurs when an artery is wrongly identified as a vein, or when an intra-arterial catheter is mistaken for a venous cannula. Drugs that have been so injected include anaesthetic induction agents, phenytoin, benzodiazepines and antibiotics. In the awake patient severe pain in the hand is a cardinal feature. In the anaesthetised or sedated patient there may be ischaemic colour changes in the distal limb, which because of arterial spasm may be pale, mottled or cyanosed. Thrombosis may follow. The degree of damage depends on the substance injected. Thiopentone causes substantial damage because at body pH it precipitates into crystals, which occlude small arterial vessels and provoke intense vasospasm mediated via local noradrenaline (norepinephrine) release. Propofol, in contrast, seems relatively innocuous. Any such injection should be treated as for the worst-case scenario, because clinical experience of intra-arterial injection of many drugs is limited.
- **Management:** After the injection of 500–1000 heparin units to reduce thrombosis risk, warm NaCl 0.9% can be given to dilute the substance. Arterial spasm can be treated with papaverine 40–80 mg, prostacyclin at rate of 1 $\mu g\,min^{-1}$, tolazoline (which is a noradrenaline antagonist) and phenoxybenzamine (which is an α_1-antagonist). Sound though the recommendation may be, these drugs may well not be immediately available, and this advice may be impractical. Dexamethasone 8 mg given immediately may reduce arterial oedema. Perfusion can be enhanced by sympatholysis, either by a stellate ganglion block (which is quick to perform) or via a brachial plexus block, using a catheter technique to provide analgesia and a continuous block. Maintenance anticoagulation is recommended for up to 14 days, and hyperbaric oxygen has also been suggested as a means of minimising final ischaemic damage.
- **Intra-arterial monitoring:** See *Intra-arterial blood pressure measurement*, page 263.

Intercostal nerves

Commentary

This area of anatomy was of more direct relevance before thoracic epidural anaesthesia, paravertebral injection and intrapleural catheterisation were more commonly employed as analgesic techniques. Intercostal nerve blocks were used to provide analgesia for subcostal surgical incisions and to treat the pain of fractured ribs. The topic, however, continues to be asked, but because the list of indications for intercostal block is shrinking, the viva will concentrate on the anatomy and on the distribution of injected drugs more than on clinical techniques of nerve blockade.

The viva

You will be asked the anatomy of an intercostal nerve.

- The intercostal nerves are the ventral somatic rami of the spinal nerves from T_1 to T_{11}. T_{12} is a subcostal nerve which is not closely associated with its corresponding rib, and which in addition links with fibres from the first lumbar nerve. T_1, T_2 and occasionally T_3, are also atypical, in that some of their fibres join with fibres of the brachial plexus, as well as contributing to the formation of the intercostobrachial nerve.
- The typical intercostal nerve exits the intervertebral foramen to lie initially between the posterior intercostal membrane and the pleura. Thereafter the nerve lies between the internal and the innermost (intercostalis intimis) intercostal muscles.
- Each nerve lies in the neurovascular bundle comprising the artery, vein and inferiorly the nerve, which runs in a groove beneath each rib. The overhanging external edge of the rib protects this bundle from direct trauma. The groove is also invested in the fascia of the external and internal intercostal muscles.
- The groove is well defined until it reaches the mid-axillary line, at which point the nerve divides.
- Motor filaments supply the intercostal, the transversus thoracis and the serratus posterior muscles. The lower intercostal nerves also supply motor fibres to the abdominal muscles.
- Sensory branches supply the overlying skin as well as supplying the parietal pleura and the costal part of the diaphragm.
- The first sensory branch arises as the posterior cutaneous branch, which supplies the skin and muscles of the paravertebral area.
- The second sensory branch arises as the lateral cutaneous branch after the division of the nerve at around the mid-axillary line. The terminal fibres of this branch supply the skin and subcutaneous tissue of much of the chest and abdominal walls.
- The third and final sensory branch arises as the anterior cutaneous branch which is the continuation of the main intercostal nerve, and which supplies the skin and subcutaneous tissue of the anterior chest and abdominal walls.

Direction the viva may take

You may be asked about indications for, and the technique of, intercostal block. You may never have seen this block performed, and it will come as no surprise to your examiners if you admit as much. Your account, therefore, may be theoretical, but it must be safe.

- Intercostal nerve block can provide effective analgesia for upwards of 12 h. Historically it was used for analgesia following subcostal and loin incisions (for gall bladder and renal surgery), after thoracotomy and to provide analgesia for fractured ribs. Only the last indication now applies, and even here the technique has been supplanted by intrapleural and epidural block. It has been

used to alleviate the discomfort of herpes zoster. A block of T_{10}, T_{11} and T_{12} provides effective analgesia following appendicectomy, but it is rarely utilised for this purpose, possibly because in the UK relatively inexperienced trainees give the majority of anaesthetics for this operation.

- Technique of intercostal block
  - The intercostal injection is made usually at the angle of the rib, before the nerve divides.
  - The skin of the back is tensed gently in a cranial direction before a needle and syringe is advanced to encounter the lower surface of the appropriate rib. The skin tension is then released. This helps the needle move to its correct position.
  - The needle is then carefully 'walked off' the inferior surface, before being directed a further 2–3 mm inwards to pierce the fascia of the innermost intercostal muscle (the posterior intercostal membrane) and enter the subcostal groove.
  - Following injection of 3 or 4 ml of solution, for example bupivacaine 0.25–0.5% with adrenaline, the needle is withdrawn to rest on the posterior surface of the rib. The next space can then be located in the same way without risking inadvertent injection in the same space. This can easily happen in individuals even of modest size, and is common in the obese.
- Complications include pneumothorax (incidence of less than 1%), respiratory embarrassment in patients with any diaphragmatic impairment, and systemic toxicity if a large number of nerves are blocked. The rich vascular supply of the area means that systemic absorption following intercostal block exceeds that from almost any other site.

Further direction the viva could take

You may be asked what happens to local anaesthetic once it has been injected.

- Contrast studies have confirmed that local anaesthetic spreads not only along the rib but also can track medially as far as the sympathetic chain. It also extends to several dermatomes above and below the site of injection, probably via direct sub-pleural spread. The intercostal, sub-pleural and paravertebral spaces are all in anatomic continuity, and so it is not surprising that injection of sufficient volume may lead to spread throughout all three.

The diaphragm

Commentary

The diaphragm is an important anatomical area for anaesthetists although it acts mainly as a radiographical marker for other disease processes. A raised hemidiaphragm, for example, may indicate pulmonary or abdominal pathology, while gas under the diaphragm is pathognomonic of visceral perforation. So even though primary diaphragmatic problems are rare, the examiners will expect you to demonstrate knowledge of the anatomy that allows you to use it as an indicator for these other conditions.

The viva

You will be asked to describe the basic anatomy of the structure.

- **Diaphragm:** The diaphragm (from the Greek words for 'across' and 'partition') is the dome-shaped muscular and fibrous partition which separates the abdominal from the thoracic viscera.
- **Vertebral part:** The vertebral part of the diaphragm originates from the right and left crura, which arise from the front of the vertebral bodies of L_1–L_3 and L_1–L_2, respectively, and from the arcuate ligaments. The median ligament is a fibrous band which links the crura; the medial ligament is a tendinous arch arising as a thickening of the fascia of the psoas major muscle; the lateral ligament arises as another thickening of fascia, in this case from the quadratus lumborum muscle.
- **Costal part:** The costal part of the diaphragm arises from the six lowest ribs and their costal cartilages.
- **Sternal part:** The sternal part comprises two small attachments from the xiphisternum.
- **Central tendon:** The muscle fibres converge into the central tendon, which is a tough aponeurosis near the centre of the dome of the diaphragm and which is merged above with the connective tissue of the pericardium.
- **Foramina:** There are three important openings in the diaphragm. Through a foramen at the level of T_8 pass the inferior vena cava and right phrenic nerve. Through an aperture at the level of T_{10} pass the oesophagus and vagus nerves. Through the final opening at the level of T_{12} pass the aorta, the thoracic duct and the azygos vein.
- **Motor supply:** Motor innervation is supplied by the phrenic nerve (mainly C_4 but with contributions from C_3 and C_5) and whose long thoracic course reflects the descent of the diaphragm during fetal development.
- **Sensory supply:** The central part of the diaphragm is innervated by the sensory afferents of the phrenic nerve: hence the tendency for sub-diaphragmatic pain to be referred to the shoulder tip, which shares the sensory innervation of C_5. The peripheral area of the diaphragm is innervated by the lower intercostal nerves.

Direction the viva may take

There are a number of miscellaneous areas of clinical relevance about which you could be asked.

- **Position on chest X-ray:** After forced expiration the right cupola (which is higher than the left because of the upward pressure of the liver) is level anteriorly with the fourth costal cartilage, and level posteriorly with the eighth rib. During quiet respiration the diaphragm moves only about 1.5 cm but this excursion can increase to 10 cm or more with deep inspiration.
- **The cardio-oesophageal sphincter:** The fibres of the crura that surround the cardio-oesophageal junction exert a pinchcock effect on the oesophagus which contributes to the prevention of gastro-oesophageal reflux. Laxity of this oesophageal hiatus is associated with hiatus hernia in which the lower

oesophagus and stomach slide into the chest, causing symptoms of dyspepsia and reflux. (This is a sliding hernia; the much less common rolling hernia occurs when the fundus of the stomach rolls up through the hiatus in front of the oesophagus which remains intra-abdominal. Patients have dyspepsia but no reflux.) You should be prepared to detail your management of anaesthesia in a patient with hiatus hernia. This commonly would involve a precise clinical history seeking the symptoms and characteristics of oesophageal reflux, which if positive would mandate rapid sequence induction following administration of agents to reduce gastric acidity.

- **Phrenic nerve palsy:** This may be caused by disease, or may be iatrogenic, associated for example with a successful interscalene nerve block. On a plain chest X-ray the affected hemidiaphragm will be raised (other causes include pregnancy, ascites, obesity, intra-abdominal malignancy and lobar collapse) while fluoroscopy will reveal paradoxical upward movement during inspiration. During quiet breathing some 75% of respiratory function is diaphragmatic, although when the minute volume is high, around 60% of the tidal volume is provided by the accessory muscles. The phrenic nerve can be paced by stimuli applied where it lies on the scalenus anterior muscle in the neck.
- **Spinal cord injury:** Cord lesions at the level of C_2 and C_3 cause respiratory tetraplegia. Injuries at C_4 and below permit some phrenic nerve function, but vital capacity is reduced to about 25% of normal. Damage below C_6 allows full diaphragmatic function.
- **Neuromuscular block:** The diaphragm is among the muscles most resistant to muscle relaxants. Post-operative respiration may therefore be adequate even though the patient subjectively may feel profoundly weak.
- **Diaphragmatic hernia:** These may be congenital, occurring *in utero* (the incidence is 1 in 4000 live births) and preventing the proper development of the lung, or traumatic. Surgical repair in the neonate requires tertiary paediatric centre expertise, details of which you will not be expected to furnish. Traumatic herniation may be associated with immediate symptoms, but equally there are cases in which the abnormality has been diagnosed years after an injury from which the patient has been asymptomatic.

Innervation of the inguinal region

Commentary

This in essence is a straightforward question about field block for inguinal hernia repair based on anatomical knowledge. If you provide reasonably comprehensive anatomical details it will prevent the viva moving away from the core topic into more vaguely related areas such as local anaesthetic toxicity.

The viva

You will be asked to describe the nerve supply to the inguinal region.

- **Supply:** The skin over the lower abdomen is supplied by the first and second nerves of the lumbar plexus, L_1 and L_2, together with a contribution from the subcostal nerve, T_{12}.
- **Iliohypogastric nerve:** This arises from L_1, emerges from the lateral border of the psoas muscle, and passes obliquely behind the kidney to perforate the posterior part of the transversus abdominis muscle above the iliac crest. It lies then between transversus and the internal oblique where it divides. Its anterior cutaneous branch runs forward between those muscles before passing through the internal oblique about 2 cm medial to the anterior superior iliac spine. It pierces the aponeurosis of the external oblique muscle about 3 cm above the external inguinal ring and supplies sensation to suprapubic skin.
- **Ilioinguinal nerve:** This also arises from L_1, emerging from the lateral border of the psoas muscle and passing below the larger iliohypogastric nerve to perforate the posterior part of the transversus abdominis muscle near the anterior iliac crest. It lies below the internal oblique, before piercing it to traverse the inguinal canal accompanied by the spermatic cord. It exits the external inguinal ring to supply the skin of the upper thigh, the skin over the root of the penis or the mons pubis, and the skin of the scrotum or labia.
- **Genitofemoral nerve:** This arises from L_1 and L_2, emerging on the abdominal surface of the psoas muscle opposite the third or fourth lumbar vertebra. It runs down on the body of the psoas muscle, retroperitoneally, and divides above the inguinal ligament into genital and femoral branches. The genital branch enters the inguinal canal via the deep inguinal ring to supply the cremaster muscle and to send some fine terminal branches to innervate scrotal skin. (In the female it accompanies the broad ligament and contributes to cutaneous sensation of the mons and labia.) The femoral branch passes behind the inguinal ligament to enter the femoral sheath, lateral to the artery, before perforating the sheath and fascia lata anteriorly to supply the skin over the upper femoral triangle.

Direction the viva may take

You will be asked how you would perform a field block for inguinal herniorrhaphy. There are various techniques described: choose the one with which you are most familiar.

- Reliable anaesthesia for inguinal hernia repair is not always easy to achieve, and if the operation is done with the patient awake it is common for surgeons to infiltrate considerable volumes of supplemental local anaesthetic. Field block is, however, useful for post-operative analgesia.
- All three nerves need to be blocked, and subsequent infiltration may also be required over the skin incision itself, depending on its extent, and at the internal ring.
- A short bevelled needle is advanced via a point approximately 2 cm medial and 2 cm caudal to the anterior superior iliac spine. This blunter needle will better appreciate the resistance offered by the external oblique aponeurosis, which is penetrated often with a definite click. Injection of around 5 ml of local

anaesthetic should be sufficient to block the iliohypogastric nerve at this point. If the needle is then advanced through the internal oblique muscle for about 1–2 cm the same volume should block the ilioinguinal nerve which at this point lies below the muscle. The genitofemoral nerve is approached via an injection made from the pubic tubercle and extending fanwise from the midline to the external inguinal ring.

- Alternative techniques include the fanwise injection of large volume low-concentration solutions in and between the oblique muscles (plus genitofemoral nerve block as above), lumbar plexus and lumbar paravertebral blocks. These latter two techniques are used infrequently.

Further direction the viva could take

You may be asked about the potential for local anaesthetic toxicity. See *Local anaesthetic toxicity*, page 165.

Blood supply to the spinal cord

Commentary

This is another area of 'theoretical' anatomy. Its main clinical relevance lies in the potential for catastrophic neurological damage secondary to ischaemia. For most anaesthetists, thankfully, this also is theoretical, but the required knowledge may allow you one day to astound colleagues as you alone correctly diagnose an anterior spinal artery syndrome.

The viva

You will be asked to describe the arterial blood supply to the cord.

- The spinal cord is supplied by paired posterior arteries and a single anterior artery, together with a series of smaller feeder radicular arteries.
- The two posterior arteries arise from the posterior inferior cerebellar arteries. These descend to the posterior nerve roots, to which they lie medially, and give off penetrating vessels to the posterior white columns and the rest of the posterior grey columns.
- The anterior spinal artery is a single midline artery, which is formed between the pyramids of the medulla oblongata from terminal branches of the vertebral arteries. It descends the cord in the midline in the anterior median fissure, giving off numerous circumferential vessels. The central branches of the artery supply up to two-thirds of the cross-sectional area of the cord.
- The anterior and two posterior arteries are fed by a variable number of smaller radicular arteries which approach the spinal cord along both ventral and dorsal nerve roots. These arteries, whose number may vary from about 25 to 40, arise from the spinal branches of the subclavian artery, the aorta and the iliac arteries inferiorly.
- In the cervical and upper thoracic regions the anterior spinal artery begins with contributions from the vertebrals, and then receives feeders from the subclavian, the thyrocostal and the costocervical arteries. From the level of T_4 down to T_9 the feeding branches of the intercostal arteries are relatively small.
- The three main arteries are also supplied by a few of the spinal branches of the vertebral, deep cervical, ascending cervical, posterior intercostal, lumbar and lateral sacral arteries. Only about six or seven of these make any significant contribution to the anterior artery, and a similar number supply the posterior arteries (but not at the same level). These feeding arteries terminate in a series of short lengths which anastomose across the midline from posterior to anterior. The posterior radicular arteries are larger than the anterior.
- The largest of the feeder arteries is the radicularis magna, or anterior radicular artery of Adamkiewicz. This originates from the aorta at a variable level, and supplies the low thoracic and lumbar regions of the cord. It enters, on the left in 80% of subjects, through any one of the intervertebral foramina between T_8 and L_3. In a small number of patients (around 15%), the artery of Adamkiewicz originates high on the aorta, at the level of T_5, in which event the contribution of iliac tributaries to the lumbar cord enlarges. This renders the conus medullaris vulnerable should there be subsequent damage to this iliac supply, for example, by ligation during pelvic surgery.
- This anatomical arrangement ensures an adequate blood supply across three large and discrete areas of the cord: the cervical, the upper thoracic and the thoracolumbar. There is, however, a much poorer vertical anastomosis between the cervical, thoracic and lumbar areas, and at these watershed zones, particularly at T_4/T_5, the spinal cord is particularly vulnerable to ischaemia.

Direction the viva may take

You may be asked about the clinical situations in which cord damage may arise.

- This may occur following profound hypotension from any cause, including subarachnoid and extradural anaesthesia. It has been described specifically following hypotension secondary to coeliac plexus block.
- It may result from aortic surgery, particularly for repair of aneurysms of the thoracic aorta, although the incidence in elective procedures is quoted as less than 5%. Risk factors, predictably, are those which worsen ischaemia: the pre-morbid state of the patient's circulation, the patient's age, the duration of aortic cross-clamp time and the difficulty of the surgical procedure.

Further direction the viva could take

You may be asked about anterior spinal artery syndrome.

- This describes the situation in which critical ischaemia of the anterior part of the spinal cord leads to loss of the corticospinal and vestibulospinal tracts, which are motor, and the spinothalamic tracts, which subserve deep touch and pressure sensation. This results in a lesion that is primarily motor below the level of cord damage. Vibration sense, light touch and proprioception are mediated via the posterior columns and these remain undamaged.

The autonomic nervous system

Commentary

This potentially is a large question, which were you to address it in even moderate detail, would exceed the time available. The account below is simplified, but it should prove adequate for the question. Once you have outlined the anatomy the viva could go in a number of directions. You may be asked about sympathetic blocks, about autonomic neuropathy, about vagal reflexes or about sympathetically maintained pain. There is unlikely to be time to explore these topics in any depth, but you will be expected to convey at least the headline details.

The viva

You may be asked to describe the anatomy of the autonomic nervous system, or you may be invited to discuss it with the help of an unlabelled line drawing which may be provided for you.

Sympathetic division

- Pre-ganglionic myelinated efferents from the hypothalamus, medulla oblongata and spinal cord leave the cord with the ventral nerve roots of the first thoracic nerve down to the second, third and in some subjects the fourth lumbar spinal nerves (T_1 to L_2–L_4).
- These efferents pass via the white rami communicantes to synapse in the sympathetic ganglia lying in the paravertebral sympathetic trunk, which is closely related throughout its length to the spinal column.
- They synapse with post-ganglionic neurones, usually non-myelinated, some of which pass directly to viscera. Others pass back via the grey rami communicantes to rejoin the spinal nerves with which they travel to their effector sites. A number of pre-ganglionic fibres (from T_5 and below) synapse in collateral ganglia, which are close to the viscera that they innervate. These collateral ganglia include the coeliac ganglion (receiving fibres from the greater and lesser splanchnic nerves) and the superior and inferior mesenteric ganglia. The adrenal medulla is innervated directly by pre-ganglionic fibres via the splanchnic nerves, which pass without relay through the coeliac ganglion.
- The sympathetic supply to the head originates from three structures: the superior cervical ganglion, the middle cervical ganglion and the stellate ganglion.
- Distribution of the sympathetic supply to the viscera occurs via a series of sympathetic plexuses. The main three are the cardiac, the coeliac and the hypogastric plexuses.
- The anatomy of the sympathetic division is such that it can function better as a mass unit. The parasympathetic division, in contrast, comprises relatively independent components.

Parasympathetic division

- The parasympathetic nervous system has a cranial and a sacral outflow. The cranial efferents originate in the brain stem and travel with the third (oculomotor), seventh (facial) and ninth (glossopharyngeal) cranial nerves. These pass via the ciliary, sphenopalatine, submaxillary and otic ganglia to subserve parasympathetic function in the head. The most important cranial efferent is the tenth (vagus) cranial nerve, which supplies the thoracic and abdominal viscera. Its fibres synapse with short post-ganglionic neurones that are on or near the effector organs.
- The sacral outflow originates from the second, third and fourth sacral spinal nerves to supply the pelvic viscera. As with the vagus nerve, the fibres synapse with short post-ganglionic neurones that are close to the effector organs.

Autonomic afferents

- These autonomic afferents mediate the afferent arc of autonomic reflexes, and conduct visceral pain stimuli. The vagus has a substantial visceral afferent component whose importance is well recognised by anaesthetists who have to deal commonly with vagally mediated bradycardia or laryngeal spasm. Sympathetic afferent fibres are also involved in the transmission of visceral pain impulses, including those originating from the myocardium. This is the rationale for using stellate ganglion block to treat refractory angina pectoris. Sympathetic afferents are also involved in sympathetically maintained pain states, such as the complex regional pain syndrome. There is usually no direct communication between afferent neurones and sympathetic post-ganglionic fibres, but following injury there does occur some form of sympathetic–afferent coupling.

Neurotransmitters

- **Sympathetic:** Acetylcholine is the neurotransmitter at sympathetic pre-ganglionic fibres (at nicotinic receptors). Noradrenaline (norepinephrine) is the neurotransmitter at most post-ganglionic fibres, apart from those to sweat glands and to some vasodilator fibres in skeletal muscle.
- **Parasympathetic:** Acetylcholine is the neurotransmitter throughout the parasympathetic division, acting at nicotinic receptors in autonomic ganglia and at muscarinic post-ganglionic receptors thereafter.

Direction the viva may take

You may be asked about autonomic blocks. Some of these are described in *The lumbar sympathetic chain*, page 58, *The stellate ganglion*, page 30 and *The coeliac plexus*, page 60.

- The segmental sympathetic supply to the head and neck is from T_1–T_5; to the upper limb from T_2–T_5; to the lower limb T_{10}–L_2; and to the heart T_1–T_5. Chemical or surgical sympathectomy has been used to improve the blood supply in vasospastic or atherosclerotic disorders of the peripheral circulation, to control hyperhydrosis, and to treat pain associated with myocardial ischaemia.

Further direction the viva could take

Diverse supplementary topics could include autonomic neuropathy, vagal reflexes or sympathetically maintained pain.

- **Autonomic neuropathy:** This may be associated with conditions, such as diabetes, chronic alcoholism, nutritional deficiency, Guillain–Barré syndrome, Parkinson's disease and acquired immunodeficiency syndrome (AIDS). Rarely it is seen as primary condition in the Shy–Drager syndrome or familial dysautonomia. Its clinical features include disordered cardiovascular responses and orthostatic hypotension, the absence of sinus arrhythmia and inability to compensate during the Valsalva manoeuvre. Patients may complain of flushing, erratic temperature control with night sweats, episodic diarrhoea and nocturnal diuresis. The normal response to hypoglycaemia is lost as are normal diurnal rhythms.
- **Vagal reflexes:** The word 'vagus' comes from the Latin, meaning 'wandering'. Had it been derived instead from Greek, then the nerve would have been called the 'plankton'. It distributes widely, and sources of stimulation that can lead to bradycardia and sometimes to asystolic cardiac arrest include the dura, the zygoma, the extraocular muscles, particularly the medial rectus, the carotid sinus, the pharynx, the glottis, the bronchial tree, the heart, the mesentery and peritoneum, the bladder and urethra, the testis, and the rectum and anus. The Brewer–Luckhardt reflex describes laryngospasm that is provoked by a distant stimulus. Vagal reflexes can be attenuated by the use of an anticholinergic such

as atropine, but in low doses this can stimulate the vagus before it blocks it (the Bezold–Jarisch reflex).

- **Sympathetically maintained pain:** In some pain syndromes it appears that efferent noradrenergic sympathetic activity and circulating catecholamines have a role in maintaining chronic pain. There is usually no communication between sympathetic efferent and afferent fibres, but following nerve injury it is apparent that modulation of nociceptive impulses can occur not only at the site of injury, but also in distal undamaged fibres and the dorsal root ganglion itself.

The lumbar sympathetic chain

Commentary

The anatomy of this area is not detailed and so the viva is likely to move on quite quickly to clinical aspects of the subject. Lumbar sympathectomy is a procedure which is undertaken mainly by chronic pain specialists, and so you may well not have seen it done. The same may apply to psoas compartment (lumbar plexus) block, which you may also be invited to discuss. If you are struggling for facts then do not guess, but instead fall back on the anatomy. If you are able to show that you could work out a safe theoretical approach by virtue of your anatomical knowledge then you are likely to pass, even though the practical details may be incomplete.

The viva

You will be asked to describe the anatomy of the lumbar sympathetic chain and how you would perform a lumbar sympathetic block.

- The sympathetic outflow originates in the hypothalamus, medulla and spinal cord as pre-ganglionic myelinated efferents. These exit the cord with the ventral nerve roots of the first thoracic nerve down to the second, third and in some subjects the fourth lumbar spinal nerves (T_1 to L_2–L_4). These efferents pass via the white rami communicantes to synapse in the sympathetic ganglia of the paravertebral sympathetic trunk, which is closely related to the spinal column throughout its length.
- The lumbar part of the sympathetic trunk lies in a fascial plane on the anterolateral aspect of the vertebral bodies. Posterolaterally is the fascia of the sheath of psoas major, and anterolaterally is peritoneum. On the left side the anterior relation is the aorta, while on the right it is the inferior vena cava.
- **Technique:** Several techniques have been described. Choose the one with which you are familiar, but if you have never seen this procedure performed then you can cite the account which follows as the 'traditional approach'. The block should always be undertaken with the help of an image intensifier. With the patient in the lateral position and after infiltration of the skin, a 120-mm needle is inserted 8–10 cm from the midline at the lateral margin of the erector spinae muscle and at the level of the L_2 spinous process (the procedure is repeated at L_3 and L_4). The needle is then directed inward and medially at an angle of 45° towards the vertebral body. As soon as the needle encounters bone it is partly withdrawn prior to reinsertion at a steeper angle, which will allow the needle (with the bevel facing towards the vertebra) to slide past the vertebral body and through the psoas fascia to lie close to the sympathetic chain. After aspiration checks for blood (the aorta is on the left, the inferior vena cava on the right) a small volume of contrast medium is injected. Correct placement is indicated by localised linear spread along the vertebral column. If the needle is lying within the psoas compartment then the contrast will track away from the vertebral body. Local anaesthetic is then injected, or if a permanent block is sought either absolute alcohol, or a dilute solution of phenol (5%) can be used.

Direction the viva may take

You may be asked the indications for, and complications of, lumbar sympathectomy.

- **Indications:** The block is performed to improve the circulation of the lower limb, the most common cause of which is peripheral vascular disease. It is also used to treat syndromes in which sympathetically maintained pain is a feature, such as the complex regional pain syndrome, and for phantom limb and other neuropathic pain. It has been used to alleviate renal colic, and to manage chronic urogenital pain.

- **Complications:** These include puncture of the aorta or inferior vena cava, inadvertent subarachnoid injection, profound hypotension, genitofemoral nerve neuritis (occurring in 5–10% of patients and presenting as pain in the groin), injury to somatic nerves (1%) and perforation of the intervertebral disc. Some of these complications are associated with mechanical damage caused by the advancing needle, others by the substance that is injected. L_1 genitofemoral neuralgia, for example, is much more common after alcohol has been used. Ureteric strictures have also been reported following the use of alcohol and phenol.

Further direction the viva could take

You may be asked to contrast lumbar sympathetic block with lumbar plexus block.

- The lumbar plexus is formed from the anterior primary rami of the first four lumbar nerves, together with a small contribution from the twelfth thoracic nerve. After emerging from the intervertebral foramina the nerves lie just within the substance of the psoas major muscle (and within its sheath). The nerves formed by the plexus include the femoral, the obturator, the iliohypogastric, ilioinguinal, genitofemoral and the lateral cutaneous nerve of the thigh. All except the obturator nerve emerge laterally in the plane between the psoas and quadratus lumborum. The obturator nerve issues medially before descending beneath the iliac vessels.
- Lumbar plexus block (sometimes called psoas compartment block) can provide effective analgesia (as well as motor block) to much of the groin and upper leg. It should, therefore, offer a useful alternative to field block for inguinal herniorrhaphy, and to '3-in-1' blocks for proximal hip surgery (cannulated and dynamic hip screws, DHSs). The analgesia afforded by the block is rarely dense enough to allow surgery without general anaesthesia, and nerves such as the femoral and obturator can as readily be blocked at more distal sites.
- **Technique:** Various approaches have been described. With the patient in the lateral position with the side to be blocked uppermost, a needle is directed perpendicular to the skin to encounter the transverse process of L_3. This site is chosen because the process is longer and wider than those of the other lumbar vertebrae. The needle is then walked off superiorly, penetrating first the fascia of quadratus lumborum and then that of the psoas sheath. Some anaesthetists use a nerve stimulator, although as the fibres of the plexus are separated and embedded within the body of the muscle this technique may not always succeed. An alternative is to use a Tuohy epidural needle with a loss of resistance device attached. The loss of resistance as the needle penetrates the sheath is not dissimilar to that which occurs when the epidural space is entered. The advantage of this approach is that an epidural catheter can be inserted in order to provide continuous analgesia. It also allows verification of placement, because an injection of contrast medium will outline the borders of the psoas compartment should the catheter be in the correct place. A single bolus injection may require 20–40 ml of local anaesthetic in order to achieve a satisfactory block.

The coeliac plexus

Commentary

You are unlikely to have had much, if any, direct experience of the coeliac plexus. Coeliac plexus block is no longer a procedure that can be undertaken blind without imaging, and its indications are limited to severe intractable pain. This question, however, remains a perennial favourite despite the fact that most examiners expect only theoretical knowledge. You will, however, need to know the anatomy reasonably well, because even the most sympathetic examiner has no choice but to pursue the topic. There is nowhere else to go and the 7 or 8 min otherwise will seem interminable.

The viva

You will be asked about the anatomy.

- The coeliac plexus is most commonly the target for anaesthetists who are treating malignant visceral pain.
- It is the largest sympathetic plexus and lies anterior to the abdominal aorta where as a dense network of nerve fibres it surrounds the root of the coeliac artery at the level of L_1.
- It is a bilateral structure. There are two ganglia, right and left, which are closely related to the crura of the diaphragm.
- The plexus receives the greater splanchnic nerve (fibres from T_5–T_9 or T_{10}), and the lesser splanchnic nerve (fibres from T_9/T_{10} or T_{10}/T_{11}).
- The plexus also receives some filaments bilaterally both from the vagus and the phrenic nerves.
- Superiorly lie the crura of the diaphragm; posteriorly is the abdominal aorta; laterally are the adrenal glands in the superior poles of left and right kidneys. The important anterior relation is the pancreas.

Direction the viva may take

You are likely to be asked about indications for coeliac plexus block.

- **Therapeutic block:** The plexus can be blocked in conjunction with intercostal nerves in order to provide analgesia for intra-abdominal surgery. This technique does not have many enthusiasts. More commonly it is used for the relief of malignant pain, typically that due to carcinoma of the pancreas. Neurolytic blocks give good analgesia in up to 90% of patients, although the effect may only last for a number of months.
- **Non-malignant pain:** The most common such condition is chronic pancreatitis. Many clinicians are reluctant to use coeliac plexus block in such patients both because of the risks of paraplegia (1–2 per 1000 due to acute ischaemia at the watershed area of the cord), and because its effective duration is limited. Coeliac plexus block for non-malignant visceral pain is also generally less successful, with only around 60–70% of patients reporting good pain relief.
- **Diagnostic block:** Coeliac plexus block using local anaesthetic alone can be used for diagnostic purposes, and for attempting to break a sympathetically mediated acute pain cycle.

Further direction the viva could take

You may then be asked how you might perform a block. Remember that the examiner's knowledge may be as theoretical as yours and that your collective experience may be small. You are unlikely to be picked up on small details as long as your overall account is plausible and safe. If your examiner does happen to work in chronic pain management they should not allow their specialist knowledge to influence the standard that is expected of you.

- **Technique**
  - The patient lies prone.
  - The spinous process of T_{12} forms the apex of a flattened triangle whose base is a line joining the 12th ribs, and which ends 7–8 cm from the midline.
  - A 10–15-cm 20G needle (depending on the size of the patient) is directed medially and rostrally along the lines of this triangle, and towards the lateral border of the body of the first lumbar vertebra.
  - When the needle encounters the vertebral body it is withdrawn almost to skin before redirection so that it can be walked off the anterolateral side of the vertebra to advance a further 2–3 cm.
  - The diffuse nature of the para-aortic plexus means that 20–25 ml of local anaesthetic will be required on each side. Neurolytic agents should be injected only under X-ray control, after needle placement has been confirmed by contrast media.
  - All neurolytic drugs lead to indiscriminate neural destruction. Alcohol (50–100%) is usually preferred to phenol (5–8%) for coeliac plexus block. It can be very painful on injection, but does not cause the vascular injury that is associated with phenol (which is a potential problem for a block such as this which is para-aortic). Transient intoxication may occur in the elderly.
  - The duration of effective action may be limited to 1–6 months. The neuritis that can accompany the regeneration of nerves may be as severe as the original symptoms.

If there is time, the questions will include complications of the block.

- **Complications:** These include hypotension (it is a sympathetic block), anterior spinal artery syndrome, subarachnoid, epidural and intrapsoas injection, intravascular injection (the aorta is very accessible on the left, the inferior vena cava is less vulnerable on the right), retroperitoneal haemorrhage, and visceral puncture, most commonly of the kidney. The neurolytic agent may also spread unpredictably, causing paresis, paralysis and dysaesthesia.

Myocardial blood supply

Commentary

This is functional, rather than practical anatomy. There is considerable overlap in the arterial supply to areas of the myocardium, and so it is not always possible to diagnose the site of coronary artery occlusion from electrocardiographical or echocardiographical changes. After you have been asked about the anatomy, which you may find easier to explain with the help of a diagram, the viva is likely to move on to the physiology of coronary perfusion.

The viva

You will be asked to describe the arterial supply and venous drainage of the heart.

- **Arterial supply:** The heart is supplied by the right and left coronary arteries: these originate from the ascending aorta (anterior and posterior aortic sinuses, located just above the cusps of the aortic valve).
- The right coronary artery passes between the pulmonary trunk and the right atrial appendage to descend in the anterior atrio-ventricular groove.
- It gives off atrial and ventricular short branches to supply those structures.
- At the inferior border of the heart it effectively divides into the marginal branch which travels along the right ventricle towards the apex and the inferior interventricular artery which continues in the groove of the same name to anastomose with the circumflex artery (the corresponding branch of the left coronary artery). This anastomosis is variable.
- **Right main coronary or its branches:** These supply the right ventricle and right atrium, part of the interventricular septum, the sino-atrial node (in 65%), the bundle of His, the atrio-ventricular node (80%) and the conducting system (80%). It also supplies a small diaphragmatic part of the left ventricle.
- The left coronary artery is larger than the right, and after arising from the posterior aortic sinus, passes between the left atrial appendage and the pulmonary trunk.
- It divides shortly into the anterior interventricular (also known as the left anterior descending, LAD) artery, which passes down the interventricular groove giving off anterior ventricular branches, and into the circumflex artery. This continues in the atrio-ventricular groove to anastomose with the inferior interventricular artery as above.
- **Left coronary artery or its branches:** These supply the left ventricle and left atrium, part of the interventricular septum, the sino-atrial node (in 35%), the atrio-ventricular node (20%) and the conducting system (20%).
- The innermost part of the endocardium receives oxygen directly from the blood within the ventricle.
- **Venous drainage:** As much as a third of cardiac venous blood drains directly into the cardiac chambers via the venae cordis minimae (a network of small veins). The remainder is drained by larger veins, which tend to accompany the coronary arteries.
- Most of the remaining venous blood drains into the right atrium via the coronary sinus, which is located to the left of the opening of the inferior vena cava, and which lies in the posterior atrio-ventricular groove.
- The main veins which drain into the sinus are:
  - the *great cardiac vein*, which lies in the anterior interventricular groove (and accompanies the LAD);
  - the *middle cardiac vein*, which lies in the inferior interventricular groove containing the anastomosis between the inferior interventricular and the circumflex arteries;
  - the *small cardiac vein* accompanying the marginal branch of the right coronary artery;

— the *oblique vein* on the posterior surface of the left atrium;
— the *anterior cardiac vein*, which lies with the right coronary artery in the anterior atrio-ventricular groove and which drains directly into the right atrium.

Direction the viva may take

You may be asked about the physiology of coronary perfusion.

- At rest about 250 ml min^{-1}, or 5% of the cardiac output is supplied to the myocardium through the coronary arteries. This can increase by up to five times during vigorous exercise.
- Flow is governed by the driving pressure. In the presence of a fixed coronary stenosis this pressure gradient is crucial. In the absence of a stenotic lesion the main variable that determines flow is the calibre of the blood vessels. Vasodilatation occurs mainly in response to the presence of local metabolites, such as hydrogen ions, adenosine, potassium, phosphate, carbon dioxide and prostaglandins. Autonomic control of vascular tone is present but is a negligible influence in comparison.
- Myocardial tissue has a high oxygen extraction ratio (80%), which limits its capacity for anaerobic metabolism. Increased oxygen demand, therefore, has to be met by an increase in coronary perfusion.
- During systole the sub-endocardial pressure in the left ventricle exceeds that in the outer part of the myocardium, and so in the main, arterial flow occurs through the arteries only in diastole. There is, however, some flow to the outer areas of the left ventricle throughout the cardiac cycle. In the right side of the heart, which is a lower pressure system, coronary perfusion persists throughout systole and diastole. At an average heart rate of 72 beats per minute, about 0.3 s will be spent in systole and 0.5 in diastole. High heart rates can compromise ventricular perfusion as well as ventricular filling.

Further direction the viva could take

You may be asked about the factors that determine the balance between myocardial oxygen supply and demand.

- **Supply**
  — Coronary blood flow (as discussed above).
  — Oxygen content of blood (dependent on haemoglobin concentration and oxygen saturation).
  — The position of the oxygen–haemoglobin dissociation curve.
- **Demand**
  — Systolic arterial pressure (afterload).
  — Left ventricular end-diastolic pressure (preload).
  — Myocardial contractility.
  — Heart rate.

Anatomy relevant to subarachnoid (spinal) block

Commentary

Everyone taking the Final FRCA examination will have performed spinal anaesthesia. The technique is regaining popularity, particularly in obstetrics, and together with epidural analgesia is a central area of anaesthetic practice. Ignorance of its main aspects potentially can put patients at grave harm, and so you will be expected to demonstrate that your knowledge is sound.

The viva

You will be asked the basic anatomy.

- The subarachnoid space is defined by its relation to the arachnoid mater, which is one of the three meningeal layers.
- **Meningeal layers:** There is continuity between the cranial and spinal meninges. The spinal subarachnoid space communicates freely with the ventricular system of the brain.
- **Dura mater:** This is the strongest of the meningeal coverings and consists of fibro-elastic connective tissue. The cranial dura has two layers: an outer endosteal layer which lines the skull, and a meningeal layer which invests the brain. These two layers are closely applied, except where they separate to accommodate the large venous sinuses. At the spinal level the endosteal layer continues down the vertebral canal as a lining of periosteum. The inner layer continues downwards as the spinal dura. The width of the dura varies with the spinal level: in the lumbar region it is between 0.3 and 0.5 mm thick, and it becomes progressively thicker towards the cervical region where it can be three times as large. The spinal dura also provides a cuff for nerve roots, which thins as each nerve approaches the intervertebral foramen.
- **Arachnoid mater:** This is a fine non-vascular membrane, which is closely applied to the dura. The subdural space between these two layers is a potential capillary space, containing a small amount of lubricant serous fluid. It is widest in the cervical region, and laterally, adjacent to the nerve roots themselves.
- **Pia mater:** This is a fine vascular membrane, which invests the spinal cord itself. Its lateral projections form the dentate ligament, which attach to the dura and support the cord. The filum terminale is the terminal extension of the pia mater which runs from the end of the spinal cord to attach to coccygeal periosteum. It is not purely vestigial: it stabilises and anchors the cord within the cerebrospinal fluid (CSF), and tethers the dura within the lower part of the epidural space.
- **Subarachnoid space:** This contains CSF, the spinal cord and associated structures, and the anterior and posterior roots of the 31 pairs of spinal nerves. The subarachnoid space extends laterally as far as the dorsal root ganglion.
- **CSF:** This is an ultrafiltrate of plasma, which is found in the spinal and cranial subarachnoid spaces, and within the cerebral ventricles. It is formed by secretion and ultrafiltration from the choroid arterial plexus in the lateral third ventricles and the fourth ventricle. Its rate of production is constant at around 0.4 ml min^{-1} (500 ml day^{-1}). Its specific gravity at body temperature ranges from 1.003 to 1.009 (mean 1.006). The total volume in adults is between 120 and 150 ml; 25–35 ml of which is found in the spinal subarachnoid space, most of which is distal to the cord, in the area of the cauda equina. The PCO_2 is higher than that of blood, and the pH of CSF is slightly below arterial pH at 7.32. Electrolyte concentrations are similar (but not identical) to plasma. The protein concentration is less, but levels are not uniform. These demonstrate a gradient between the ventricles, where the concentration is low, and the lumbar region where they are highest. The mean protein concentration is 23–28 mg dl^{-1}.
- The adult spine has a number of natural curves, the high points of which (in the supine position) are the fifth cervical and the second or third lumbar (C_5 and

L_2/L_3) vertebrae, and the low points of which are the fifth and sixth thoracic and the second sacral (T_5/T_6 and S_2) vertebrae. This has relevance for the spread of intrathecal hyperbaric solutions.

Direction the viva may take

You may be asked what surface landmarks govern your approach to a particular vertebral level.

- The spinal cord in the adult ends at the level of the intervertebral disc at L_1/L_2. There is some variation and in up to 10% of subjects the cord may end as high as T_{12}/L_1 or as low as L_2/L_3. (In the neonate the cord ends at the lower border of L_3.) It is very important, therefore, to identify the vertebral level as accurately as you are able.
- A line drawn between the highest points of the iliac crests (the intercristal or Touffier's line) passes across either the spinous process of L_4 or the L_4/L_5 interspace. This is the technique that is most commonly used by anaesthetists. It can, however, be difficult to identify this point clinically, which is why neurosurgeons operating on the back identify the level radiologically prior to operation. Anaesthetists must aware of this potential for inaccuracy, because a spinal needle which is advanced too high, or is advanced without finesse, risks penetrating the conus medullaris with permanent neurological deficit.
- The lowest rib (which is palpable only in very thin subjects) is at the level of T_{12}.
- The first spinous process which is clearly palpable is C_7, which is the vertebra prominens (although the spinous process of T_1 below it, is actually more prominent still).
- The inferior angle of the scapula in the neutral position is at the level of T_7/T_8.

Further direction the viva could take

There are various ways in which a viva on spinal anaesthesia may develop. You may be asked about complications, but this is relatively straightforward, and so it is more likely that you will be asked the factors that influence intrathecal spread, about which there are common misconceptions.

- **Drug dose:** The prime determinant of spread is the mass of drug. The greater the amount of drug, the higher and more prolonged the block. The volume is of minimal importance. The injection of bupivacaine 15 mg in 15 ml (0.1%) will achieve a block of similar height to that obtained after injection of bupivacaine 15 mg in 3 ml (0.5%).
- **Level of injection:** In the supine patient with a normal spine the maximum height of the lumbar lordosis is at L_2/L_3. Less local anaesthetic will move rostrally if the injection is made below that level. In practice the final block height is similar, except it that it takes longer to achieve.
- **Baricity of drug:** Plain solutions of local anaesthetic are isobaric relative to CSF at room temperature (mean CSF specific density is 1.006). At body temperature they become slightly hypobaric. Hyperbaric ('heavy') solutions are made so by the addition of glucose ('heavy' bupivacaine contains glucose 8%). In the supine patient with a normal spine, hyperbaric solutions tend to pool in the thoracic kyphosis at T_5/T_6, and produce blocks which generally are higher but which are claimed to be more predictable than those produced by isobaric solutions. Solutions which pool in the lumbosacral area may have a relatively enhanced effect because the nerves of the cauda equina have large surface area and only a thin layer of pia mater. This appears to increase their sensitivity to local anaesthetic.
- **Patient position:** This is linked to 'baricity'. If the patient is in the decubitus position the curves of the spine have no influence. Trendelenberg positioning clearly will increase the rostral spread of a hyperbaric solution.

- **Patient height:** There may be reduced cephalad spread in taller subjects: the relationship is not reliable enough to allow any prediction.
- **Patient age:** There may be increased cephalad spread with advancing age, although again the block height cannot reliably be predicted.
- **Pregnancy (and multiple pregnancy):** Term pregnancy is said to be associated with greater block height, which is made higher still with multiple pregnancy. The mechanism may relate to the relative smaller volume of the dural sheath because of encroachment in the epidural space by the engorged venous plexus.
- **Needle direction and speed of injection:** Rostral facing injection or forceful injection shortens the onset time but does not influence the final height of block.
- **Barbotage, weight of patient, gender of patient, adjuvant drugs, vasoconstrictors:** None of these factors has any significant effect on block height.

The extradural space

Commentary

This is a key subject for anaesthetists. In many hospitals the numbers of epidurals that are now inserted for surgical analgesia exceed those that are given to relieve the pain of labour. Thus quite detailed knowledge will be expected: you will be required to demonstrate a good three-dimensional grasp of the anatomy as well as being aware of all the material complications.

The viva

You will be asked first to describe the basic anatomy of the area.

- The extradural (epidural) space is the area surrounding the dural sheath as it lies within the vertebral canal.
- It extends from the foramen magnum superiorly (where the dura is fused to the skull) to the sacral hiatus inferiorly.
- It is traversed by the dural sheath, whose thickness in the lumbar region is about 0.3–0.5 mm, and which comprises the membranes of the dura and arachnoid maters, the subarachnoid space containing CSF, the spinal nerves of the cauda equina and the filum terminale. The filum terminale is an extension of the pia mater, which runs from the conus medullaris to the coccyx.
- Anteriorly the epidural space is bounded by the bodies of the vertebrae and by the intervertebral discs, over which lies the posterior longitudinal ligament.
- Laterally it is bounded by the pedicles and the intervertebral foramina.
- Posteriorly it is bounded by the laminae of the neural arches.
- **Ligamenta flava:** There are two ligaments which meet in the midline and which connect the laminae of adjacent vertebrae. Each extends from the lower part of the anterior surface of the lamina above to the posterior surface of and upper margin of the lamina below. Their fibres run in a perpendicular direction, but when viewed in the sagittal plane the ligaments are triangular in shape with the apex of the triangle formed at the upper lamina.
- At the level of a typical lumbar vertebra, for example L_4, the space contains the spinal nerves, each of which is invested with a cuff of dura, with loosely packed fat, areolar connective tissue, lymphatics and blood vessels. These vessels include the rich valveless vertebral venous plexus of Batson.
- The depth of the posterior epidural space (between the ligamenta flava and the dura) varies with the vertebral level. In the mid-cervical region it is only 1.0–1.5 mm wide, and at T_6 it is deeper at around 2.5–3.0 mm. The greatest depth is at the L_2 interspace in males, in whom this is about 6.0 mm.

Direction the viva may take

You may be asked to discuss the complications. The list is long, and so once you have volunteered as many complications that you can recall, it is probable that the viva will concentrate on the recognition and management of one or two of them.

Complications associated with the procedure

- These include: inadvertent dural puncture and subsequent post-dural puncture headache (PDPH) (incidence of 0.5%); failure (1%); unilateral or patchy block (5–10%); inadvertent subdural block (0.1%); intravascular injection; retention of a fragment of needle or catheter; epidural haematoma. The risk of permanent neurological sequelae is very small. The incidence is quoted at 1 in 10,000 epidurals, but many of these complications are relatively minor, comprising for example, little more than a patch of residual numbness. There is no evidence that routine epidurals lead to chronic back pain.

Complications associated with drugs that are injected

- These include: hypotension due to sympathetic block; a total spinal or high spinal block; evidence of systemic toxicity of local anaesthetic; urinary retention; pruritus, nausea and vomiting (usually associated with extradural opiate); respiratory depression. There are many case reports of accidental injection of the wrong solution. Numerous substances have been administered in this way, including various antibiotics, solutions of total parenteral nutrition and thiopentone. The influence of obstetric epidurals on labour and labour outcome remains contentious.

Further direction the viva could take

You may be asked about your diagnosis and management of some of the more common, or complex complications.

PDPH

- **Diagnosis:** The incidence of inadvertent dural puncture should not exceed 0.5%, and the incidence is usually quoted at between 0.5% and 1.0%. The incidence of PDPH is highest in obstetric patients, over 80% of whom will develop symptoms. These are due probably to traction on intracranial pain-sensitive structures such as the tentorium and blood vessels. The headache results from the failure of the choroid plexus to produce sufficient CSF to compensate for the loss through the breach in the dura. The onset is variable, with the headache commonly starting after about 12–24 h. It can occur earlier or later. The headache may be frontal or occipital rather than global, but typically it is postural and relieved by recumbency or abdominal pressure. It may also be associated with photophobia, visual disturbance, neck and shoulder stiffness, and tinnitus. If the patient also complains of anorexia, nausea and vomiting, this is an indication that there is significant sagging of intracranial contents with pressure on the brain stem at the foramen magnum. The patient may feel systemically very unwell. The presentation is not always typical.
- **Management of severe PDPH:** Assuming the failure of initial conservative treatment, advising recumbence when headache supervenes and simple analgesia, management may move on to other treatments. Cerebral vasoconstrictors such as caffeine and sumatriptan may improve symptoms, but they will not address the cause. Patients are instructed frequently to overhydrate. This has no influence on CSF production. The only agents which may increase it are corticosteroids. Adrenocorticotrophic hormone (ACTH) analogues such as tetracosactrin ('synacthen') are used by some anaesthetists, but their benefits are anecdotal. The only technique that is likely to provide immediate relief is an extradural blood patch (EBP). This will abolish symptoms in almost all patients but in at least 30% of mothers the procedure will need to be repeated. EBP has been associated with the development of chronic low back pain, and this risk must be weighed against those of persistent long-term headache, or of neurological disaster (such as subdural haemorrhage) which has been reported in PDPH left neglected.

Inadvertent subdural block

- A catheter or needle may deposit solution in the subdural space between the dura and arachnoid mater. Radiologists maintain that during myelography there is a 1% incidence of subdural injection. It is much less commonly diagnosed in clinical anaesthesia. Some authorities cite an incidence of 1 in 1000.
- Subdural block is often patchy, it may be extensive and unilateral, may extend very high (the subdural space extends into the cranium), and it often spares the sacral roots. The dura and arachnoid are more densely adherent to each other anteriorly, and so there may be a relative sparing of motor fibres. Sympathetic

block may be minimal and analgesia may be delayed. Horner's syndrome may be apparent.

- The use of a multi-holed catheter may further confuse the picture, because it is theoretically possible for the catheter to lie partly within the epidural and partly within the subdural space. Slow injection will favour emergence of the solution from the proximal epidural holes: more vigorous injection will favour dispersal through the distal subdural hole.

High block or total spinal

- Examiners may address a question about total spinal anaesthesia by asking you to describe what happens as the block ascends. A high block or developing total spinal is characterised by the development of paraesthesia and weakness of the upper limbs, respiratory embarrassment due to intercostal paralysis, a weak voice, and cough and sensory loss over the skin of the neck and eventually the jaw. If the block is a total spinal, then apnoea and unconsciousness will supervene. It is always said that a high sympathetic block will lead to hypotension and bradycardia due to local anaesthetic effects on the cardiac accelerator fibres (T_1–T_4). In practice the cardiovascular changes are by no means always so predictable. High blocks regress quickly, whereas it might be some hours before a total spinal has worn off to the point at which comfortable respiration will be possible. Until this happens anaesthesia must be maintained so as to prevent awareness.

The sacrum

Commentary

Caudal (sacral extradural) anaesthesia is a popular technique, particularly in children in whom it can provide analgesia similar to that provided by a low lumbar epidural. In contrast to other neuraxial blocks it requires no equipment other than a needle, syringe and/or intravenous cannula, and is simple to perform. This is a core area of anatomy applied to anaesthetic practice.

The viva

You will be asked to describe the basic anatomy. (Do not be disconcerted if an examiner asks you in passing if you know the origin of the name: ignorance of etymology is not a criterion for failure.)

- The sacrum was believed by the ancients to be the site of the soul, the bone which was the last to decompose, and thus the one around which the new body would form. Hence it was called the 'sacred bone'.
- It is a triangular-shaped bone that articulates superiorly with the fifth lumbar vertebra, inferiorly with the coccyx and laterally with the ilia.
- The dorsal roof comprises the fused laminae of the five sacral vertebrae and is convex dorsally (the curve is variable between sexes and races).
- In the midline there is a median crest, which represents the sacral spinous processes.
- Lateral to this is the intermediate sacral crest with a row of four tubercles, which represent the articular processes. The S_5 processes are remnants only and form the cornua, which are the main landmarks for identifying the sacral hiatus.
- At S_5 this failure of development of the spinous processes and laminae results in a hiatus in the roof of the canal. It is this sacral hiatus which allows access to the extradural space. It is covered by the sacro-coccygeal membrane.
- Along the lateral border are anterior and posterior foramina which are the sacral equivalent of intervertebral foramina of higher levels, and through which the sacral nerve roots pass.
- In addition to the dura superiorly, the canal contains areolar connective tissue, fat, the sacral nerves, lymphatics, the filum terminale (which is an extension of the pia mater originating from the conus medullaris at the end of the spinal cord and which extends to the coccyx) and a rich venous plexus.

Direction the viva may take

You may be asked how you would perform a caudal block.

- Access to the canal is via the sacral hiatus at the level of the fifth sacral vertebra through the sacro-coccygeal membrane. In up to 7% of subjects fusion has taken place and so access is impossible. (Some authorities believe this to be an overestimate.)
- **Identification:** There are several ways of identifying the hiatus:
  - The sacral hiatus is at the apex of an equilateral triangle completed by the posterior superior iliac spines.
  - If the tip of index finger palpates the coccyx, the mid-point of the middle interphalangeal joint of the finger identifies (in an 'average' adult) the hiatus.
  - With the hips flexed at 90° a line extended along the mid-point of the thigh will end at the hiatus.
  - Palpation of the midline sacral crest caudally until the cornua are identified is useful only in lean subjects in whom the anatomy is not obscured by a sacral fat pad.
- **Drug doses:** In adults a typical dose would be laevobupivacaine 0.5% × 20 ml. In children various formulae have been elaborated in order to achieve blocks of adequate height. A commonly used regimen is that described by Armitage

(1979): 0.5 ml kg^{-1} of (laevo)bupivacaine 0.25% for sacral block (circumcision, hypospadias and anal procedures), 1.0 ml kg^{-1} for low thoracic block (for inguinal herniotomy) and 1.25 ml kg^{-1} for higher thoracic block up to T_8 (for orchidopexy). The addition of clonidine 2.0 μg kg^{-1} will double the duration of effective analgesia, while ketamine 0.5 mg kg^{-1} (preservative-free) will increase it by four times.

- The 'whoosh' and 'swoosh' tests have been described as methods of verifying accurate needle placement. In the 'whoosh' test a small volume of air (2 ml) is injected while listening with a stethoscope over the lumbar spine. Some anaesthetists first deposit a small volume of fluid in the space first; correct needle placement is confirmed by definite crepitus. The injection of air into the extradural space has well-recognised disadavantages: the subsequent block may be patchy, and air embolism has been reported. The 'swoosh' test is similar in principle, except that auscultation is performed as the local anaesthetic itself is being injected.

Further direction the viva could take

You may then be asked about differences in the performance and behaviour of caudal blocks between adults and children.

- **Anatomical differences:** The dura mater usually ends at the level of S_2 in adults (although it can descend to within about 5 cm of the hiatus in some subjects). At birth the dura is as low as S_4, but by around 2 years of age it ascends to adult levels.
- The sacral hiatus is easier to locate in children because it is not overlain by the sacral fat pad that develops in adults.
- **Physiological differences:** The spread of solution in the sacral extradural space is influenced in adults by total volume, speed of injection and posture (one study has reported that higher levels are reached if the patient is 15° head up).
- There is good correlation in children between spread of a given dose and age. There is poor correlation between spread and weight and/or height.
- The sacral extradural space in children offers lower resistance to longitudinal spread than the adult. Epidural fat in children has a loose and wide-meshed texture, whereas in adults it becomes more densely packed and fibrous. There is less fibrous connective tissue in the sacral epidural space than in adults and this combination of factors means that local anaesthetic spread is greater.
- In children it is possible to direct a 20G 51-mm cannula rostrally to escape the sacral space altogether and allow what is in effect a lower lumbar epidural block. Generous volumes can be employed, therefore, if a high block is required. High blocks are much more difficult to achieve in adults.
- Complications such as intrathecal injection are more likely in children less than 2 years of age. Otherwise the incidence both of intrathecal and intravascular injection does not differ from that seen in adults.
- **Sympathetic effects:** Children up to and beyond the age of 6 years show cardiovascular stability in the face of blocks that would cause sympathetic blockade and hypotension in adults. This is probably due to some delay in the maturation of the autonomic nervous system.

You may also at any stage be asked about complications of the block.

- **Complications:** These include failure, intravascular injection (false-negative aspiration may occur in 10% or more of cases, as negative pressure collapses the vein), intra-osseous injection in young children, and dural and subdural puncture (which is characterised by an extensive, patchy block of slow onset). There are also the potential complications associated with the particular drugs injected (local anaesthetics, opiates, clonidine and ketamine).

The femoral triangle

Commentary

The anatomy of the femoral triangle is straightforward. It lends itself readily to simple diagrams: the first of the triangle itself, the second a transverse view to demonstrate that you realise that the nerve lies in a fascial compartment quite separate from the femoral sheath. The question may then move on to the structures of significance to the anaesthetist, namely the femoral nerve, the femoral vein and the femoral artery.

The viva

You will be asked first to describe the anatomy.

- The triangle is bounded superiorly by the inguinal ligament (which curves from the anterior superior iliac spine to the pubic tubercle).
- Its lateral border is formed by the sartorius ('The tailor's muscle' which runs across the thigh from its origin at the anterior superior iliac spine to the medial side of the upper tibia. It is the longest muscle in the body.)
- Its medial border is formed by the adductor longus muscle (whose insertion is at the superior ramus of the pubis and which has a linear attachment to the linea aspera on the posterior aspect of the femur).
- Its roof is formed by areolar tissue, fascia lata, subcutaneous tissue and skin.
- Its floor is a trough comprised of the iliacus, psoas and pectineus muscles.
- Within the triangle lie the femoral canal, containing lymphatics, and immediately lateral to it, the femoral sheath, containing the femoral vein (medial) and femoral artery (lateral).
- Outside the femoral sheath and lying lateral to it is the femoral nerve. The nerve is invested in the fascia of the iliacus muscle (fascia iliaca), which separates it from the femoral sheath. Above this is the fascia of the tensor fascia lata muscle. The distance by which it is separated is variable. It may bear a close relation to the pulsation of the femoral artery or may be 1–2 cm or more lateral to it. It can also be separated from the femoral sheath by a small part of the psoas muscle.

Direction the viva may take

You will probably be asked about the structures within the triangle that are of relevance to anaesthetists.

- **Femoral vein:** This is useful for central venous access (if other sites are unsuitable) and for siting large-bore cannulae for haemo-diafiltration. It is the central vein of choice in infants and young children. It is also the site of access for insertion of vena caval filters.
- **Femoral artery:** This is used for arterial sampling and monitoring (again if other sites are unsuitable). The artery also provides access for angiography, and for the insertion of intra-aortic balloon pump catheters.
- **Femoral nerve:** Relevant for peripheral nerve block. If there is sufficient time remaining it is likely that the second part of the viva will concentrate on this procedure. See *The femoral nerve*, page 73.

The femoral nerve

Commentary

The applied anatomy of the femoral nerve is not straightforward because it can be variable. Peripheral femoral nerve block is popular and useful, and so this is a core area of anatomical information. Take heart from the fact that this popularity is relatively recent, and so unless your examiners have an interest in anaesthesia for orthopaedic surgery, their experience of this block may be rather less than yours.

The viva

You will be asked first to describe the anatomy.

- The femoral nerve originates from the anterior primary rami of L_2, L_3 and L_4, and enters the anterior thigh beneath the inguinal ligament (which runs from the anterior superior iliac spine to the pubic tubercle).
- The femoral sheath is formed from an extension of the extraperitoneal fascia and contains the femoral vein (medially) and artery (laterally). It does not contain the femoral nerve.
- The nerve is invested in the fascia of the iliacus muscle (fascia iliaca), which separates it from the femoral sheath. Above this is the fascia lata.
- The distance by which it is separated from the vessel is variable. It may bear a close relation to the pulsation of the femoral artery or may be 1–2 cm or even more lateral to it. It can also be separated from the femoral sheath by a part of the psoas muscle.
- The nerve usually starts to divide into its terminal branches at the base of the femoral triangle. In some subjects this division can start above the inguinal ligament.
- It divides into a leash of nerves which supply the muscles of the thigh. One of the main divisions continues as the saphenous nerve, which passes medially across the knee to provide sensory innervation as far as the medial aspect of the ankle and rear foot.

Direction the viva may take

The second part of the question is likely to be about femoral nerve and '3-in-1' nerve blocks. It may touch briefly on the use of peripheral nerve stimulators. See *Peripheral nerve location using a stimulator*, page 225.

- It is common for anaesthetists to assume that the femoral nerve is a straightforward block to perform and that the '3-in-1' block provides useful analgesia for hip surgery. Neither is necessarily true: the anatomy of the femoral nerve is variable, and the benefits of '3-in-1' block are unreliable.
- **Supply:** The nerve supplies the shaft of the femur, the muscles and skin of the anterior thigh as far as the knee, and via the saphenous nerve, the medial side of the lower leg as far as an area surrounding the medial malleolus.
- **Indications:** These include the provision of analgesia for fractured shaft of femur (which is usually very effective, particularly if an in-dwelling catheter technique is used), peri-operative analgesia for knee surgery (which is most effective if it used in conjunction with sciatic and obturator nerve blocks) and peri-operative analgesia for hip surgery (usually as part of a '3-in-1' block).
- **'3-in-1' block:** This describes a single injection, which aims to block the *femoral* nerve, the *obturator* nerve and the *lateral cutaneous* nerve of the thigh. A larger volume of local anaesthetic is used, and during injection firm distal pressure is applied. In theory this spreads the local anaesthetic rostrally back up into the psoas compartment so that all three nerves are blocked. The obturator nerve supplies the adductor muscles of the hip, part of the hip joint, skin on the medial side of the thigh and part of the knee joint. The lateral cutaneous nerve supplies

skin over the anterolateral thigh as far as the knee, and the over the lateral thigh from the greater trochanter down to the level of mid-thigh.

- **Efficacy:** The '3-in-1' block can be effective for cannulated hip screws and sometimes for DHSs, but as its anatomy demonstrates, in many cases it will not provide reliable analgesia for cutaneous sensation above the level of the greater trochanter, which is the site of incision for much hip surgery. It has been described, perhaps unfairly, as *a nerve block in search of an operation*.
- **Technique of femoral and '3-in-1' nerve block:** The success of these blocks is increased greatly by the use of a nerve stimulator. A plexus or block needle is inserted at an angle of about 45° and directed rostrally just below the inguinal ligament and lateral to the pulsation of the femoral artery. There may be two 'pops' or 'clicks' as the advancing needle penetrates first the fascia lata and then the fascia iliaca. Movement of the patella (quadriceps femoris) is the best indicator of correct placement (at around 0.5 mA). The mass of drug injected will depend on whether or not other nerves such as the sciatic and obturator are being blocked at the same time, but the general dose range is 15–20 ml of 0.5% laevobupivacaine for a femoral nerve block, and 30 ml or more for a '3-in-1' block.

The sciatic nerve

Commentary

The sciatic nerve is the largest peripheral nerve in the body and it is accessible from a number of sites. Sciatic nerve block provides good analgesia for much lower limb surgery, and the variety of possible approaches provides an appropriate test of applied anatomy. As always with questions which include practical procedures, it will help greatly the credibility of your answer if you can convince the examiner that you have undertaken some of these blocks. You will not, however, be expected to be familiar with every single approach.

The viva

You will be asked to describe the anatomy.

- The sciatic nerve arises from the sacral plexus, which is formed by the union of the L_4, L_5, S_1, S_2 and S_3 nerve roots, and which lies separated from the anterior sacrum by the piriformis muscle.
- The nerve, which is the largest in the body, is about 2 cm in diameter as it exits the pelvis posteriorly via the greater sciatic notch.
- It continues its descent into the thigh between the ischial tuberosity and the greater trochanter, and then lies behind the femur before dividing in the popliteal fossa into the common peroneal and the posterior tibial nerves.
- The sciatic nerve provides a sensory supply to much of the lower leg via its main terminal branches (the tibial and common peroneal).
- It supplies the knee joint (via articular branches), and almost all of the structures below the knee.
- It does not, however, supply a variable, but extensive cutaneous area over the medial side of the knee, lower leg and ankle, and medial side of the foot around the medial malleolus. This is supplied by the saphenous nerve (from the femoral).

Direction the viva may take

You may be asked to describe one method of blocking the sciatic nerve.

- **Posterior approach**
  - The patient lies in the supine position with upper leg flexed to 90° at hip and knee.
  - A line is drawn from the greater trochanter to the ischial tuberosity. The nerve can be located just medial to the mid-point of this line at a depth of around 6 cm. The depth clearly varies with the size of the patient. The needle is inserted at right angles to the skin, attached to a nerve stimulator. A twitch in the lower limb (usually dorsiflexion of the foot) elicited at about 0.5 mA is a sign of accurate placement, and 20 ml laevobupivacaine 0.5% is injected. The stimulator technique and drug dose apply to the other proximal approaches to the sciatic nerve.
- **Posterior (classic approach of Labat)**
  - The patient lies in the decubitus position with the upper leg flexed to 90° at hip and knee.
  - A line is drawn from the greater trochanter to the posterior superior iliac spine. From the mid-point of this line a perpendicular is dropped 3–5 cm. The needle is inserted vertically to the skin and the nerve is sought at around 6–8 cm. Alternatively a line can be drawn from the greater trochanter to the sacral hiatus and the injection made at its mid-point.
- **Anterior approach**
  - The nerve emerges from the greater sciatic foramen and lies between the ischial tuberosity and the greater trochanter of the femur. Before it passes

down behind the bone it is accessible medial to the femur and just below the lesser trochanter.
  - The patient lies supine and a line is drawn from the anterior superior iliac spine to the pubic tubercle.
  - A line parallel to it is drawn from the greater trochanter. At the junction of the medial third and lateral two-thirds of the upper line, a perpendicular is dropped to meet the lower.
  - At this junction a long (150-mm) needle is inserted vertical to the skin until it contacts the medial shaft of the femur. It is then redirected medially to slide off the femur before advancing another 5 cm or so to encounter the nerve in the region of the lesser trochanter.
  - It is worth noting that in a proportion of patients (about 15%) the sciatic nerve lies immediately posterior to the femur at this point and is therefore inaccessible to the anterior approach.
- **Lateral approach**
  - The patient lies supine. A long needle is inserted 3 cm distal to the most prominent part of the greater trochanter and seeks the nerve as it descends behind the femur. This approach is not commonly used in the UK.
- **Popliteal fossa block**
  - The sciatic nerve can be blocked in the popliteal fossa before it divides into its tibial and common peroneal branches.
  - The patient lies lateral or prone and the proximal flexor skin crease of the knee is identified.
  - A line is drawn vertically for about 7 cm from the mid-point of the skin crease, and the injection is made about 1 cm lateral to this point.
  - If dorsiflexion is elicited it may be the common peroneal nerve alone that is being stimulated, and the sciatic nerve may have already branched. Plantar flexion or inversion of the foot indicates successful location of the posterior tibial nerve.
  - *Drug dose*: 10–20 ml laevobupivacaine 0.5%

You may also be asked for the indications for sciatic nerve blockade.

- Sciatic nerve block alone will provide reliable analgesia for surgical procedures which involve the forefoot, the sole of the foot and the lateral side of the foot and ankle. In conjunction with femoral and with obturator nerve block it provides good analgesia for major knee surgery.

Ankle block

Commentary

This is a predictable question about applied anatomy. The ankle block does not necessarily provide the best analgesia for forefoot surgery, but the fact that five separate nerves need to be identified makes it a good topic for anatomical discussion. Your examiners may not have much practical experience of this block themselves, unless they happen to work with a lower limb surgeon, so give yourself an advantage by getting to observe, or perform, some ankle blocks so that you will have recent practical experience on which you can draw.

The viva

You will be asked about the anatomy and how you would block each nerve.

- The ankle block is an effective means of providing prolonged analgesia for the forefoot. Five nerves need to be blocked before local anaesthesia is complete. Concentrations may need to be reduced, for example if the patient is frail, or if the procedure is bilateral.
- **Saphenous nerve:** This supplies a variable portion of the medial border of the foot and ankle. It is a terminal branch of the femoral nerve and is anaesthetised immediately anterior to the medial malleolus where it is superficial, close to the saphenous vein. It is blocked with subcutaneous local anaesthetic, for example, laevobupivacaine 0.5% × 5 ml.
- **Posterior tibial nerve:** This supplies the plantar surface of the foot. This is a branch of the sciatic nerve (which divides into tibial and common peroneal branches in the popliteal fossa) and is blocked behind the medial malleolus where it lies posterior to the posterior tibial artery. The needle is gently directed perpendicular to the skin until it encounters bone, and then withdrawn 1–2 mm prior to injection of 3–5 ml laevobupivacaine 0.5%, on either side of the artery.
- **Deep peroneal nerve:** This supplies only a small area of skin on the dorsum of the foot between the first and second toes. It passes beneath the extensor retinaculum at the front of the ankle joint and is most readily blocked between the tendons of extensor hallucis longus and extensor digitorum longus where it lies lateral to the dorsalis pedis artery. It is blocked with a total of 3–5 ml laevobupivacaine 0.5% either side of the artery and deep to the fascia.
- **Sural nerve:** This supplies sensation to the fifth toe and the lateral border of the foot. It is a branch of the tibial nerve: at the level of the ankle it lies superficially behind the lateral malleolus. Subcutaneous infiltration of laevobupivacaine 0.5% × 5 ml between the lateral malleolus and the tendo Achilles usually provides effective analgesia.
- **Superficial peroneal nerve:** This supplies much of the dorsum of the foot (excepting the small area supplied by the deep peroneal nerve, and the lateral foot which is supplied by the sural nerve). It is a branch of the common peroneal nerve, which divides further into terminal branches at the level of the malleoli. It is blocked with a ring of superficial infiltration, laevobupivacaine 0.5% × 10 ml, between the anterior tibia and the lateral malleolus.

Direction the viva may take

You are likely to be asked about indications and complications.

- **Indications:** These include forefoot surgery, typically Keller's procedure, metatarsal osteotomy, excision of neuromas and foreign body removal.
- **Complications:** These are largely generic, so include local anaesthetic toxicity (you may need to modify the concentrations quoted above to reduce the total dose), nerve and vessel damage, intravascular and intraneural injection.

As this is only a short list, you may be asked how else you might provide local analgesia for foot surgery (which can be disproportionately painful).

- **Possible local anaesthetic techniques:** These include subarachnoid (spinal) block, lumbar extradural (epidural) block, sacral extradural (caudal) block, sciatic nerve block at the hip, sciatic nerve block in the popliteal fossa, intra-osseous nerve block (for procedures in the distal foot which cannot be done under digital nerve (ring) block, intravenous regional anaesthesia (Bier's block) which needs high compression pressures and high volumes to obtain satisfactory analgesia, and local infiltration (this is unlikely to be satisfactory, but is included for completeness).

3

Physiology

Pneumothorax

Commentary

Pneumothorax is an important complication in anaesthesia and trauma. This viva will concentrate more on the precise mechanisms by which pneumothoraces occur rather than on details of recognition and management. A pneumothorax can develop rapidly into a life-threatening emergency and so you must ensure that your management is competent. This may be the factor that decides whether you pass or fail, should your performance in the remainder of the viva have been borderline.

The viva

You will be asked how pneumothoraces may arise.

- By definition, a pneumothorax exists when there is air in the pleural space.
- At the end of expiration there is no pressure differential between intra-alveolar and atmospheric pressure. However, the intrapleural, or transpulmonary pressure is subatmospheric, and the slight negative pressure of around 4–6 cmH_2O (caused by the opposing elastic recoil of the lung and the chest wall) keeps the lungs expanded. This pressure differential also opposes the tendency of the thoracic wall to move outwards.
- When air gains access to the intrapleural space the negative transpulmonary pressure is lost and the stretched lung collapses while the chest wall moves outwards.
- Air can gain access to the intrapleural space via a breach in the parietal or visceral pleura (or both), or via the mediastinal pleura as a consequence of intrapulmonary alveolar rupture. Gas insufflated into the abdomen under pressure may enter the interpleural space via the mediastinal pleura.

Damage to the parietal pleura

- This may occur as a result of open penetrating chest trauma, as a result of oesophageal, tracheal or mediastinal perforation, or during operative procedures such as nephrectomy, tracheostomy and laparoscopy. It may also follow surgery to the thoracic spine.

Damage to the visceral pleura

- This is commonly iatrogenic and can be caused by needle punctures or vascular cannulation. It may follow attempted subclavian and internal jugular puncture,

and is also a well-recognised complication of some nerve blocks. These include supraclavicular, interscalene, intercostal and paravertebral blocks.

Intra-pulmonary alveolar rupture

- Gas escapes from the alveolus, dissects towards the hilum and ruptures the mediastinal pleura. Causes include barotrauma from mechanical ventilation (due to excessive pressures) or high pressure gas delivery systems (injectors), and chronic obstructive pulmonary disease with bullous emphysema. It is also caused by blast injury. It may also occur in asthmatics and in patients in whom the alveolar septa are weakened or distorted by infection, collagen vascular disease or connective tissue disorders, such as Ehlers–Danlos and Marfan's syndromes. Severe hypovolaemia has also been implicated as a risk factor for the same reason.

Direction the viva may take

You may be asked to list some of the common causes of pneumothorax, and explain how you would confirm the diagnosis.

Causes

- You may have already cited some of these in your explanation of the mechanisms.
- **Traumatic:** Penetrating injury, rib fracture and blast injury.
- **Iatrogenic (surgical):** During nephrectomy, spinal surgery, tracheostomy (especially in children), laparoscopy, or as consequence of oesophageal or mediastinal perforation.
- **Iatrogenic (anaesthetic):** During attempted central venous puncture and various nerve blocks. Barotrauma from mechanical ventilation at excessive pressures, from high pressure gas injector systems or in patients with bullae.
- **Miscellaneous:** May occur if the alveolar septa are weakened, as described above. It is associated with many diseases, including asthma. Recurring catamenial pneumothorax is a spontaneous pneumothorax, usually right-sided, which occurs in phase with the menstrual cycle. (By all means impress the examiners with this information, but do not cite it first.)

Diagnosis of pneumothorax in the awake patient

- Typical features (which are not invariable and which will depend on the size of the pneumothorax and whether or not it is expanding) include chest pain, referred shoulder tip pain, cough, dyspnoea, tachypnoea and tachycardia. There may be reduced movement of the affected hemithorax, hyperresonance on percussion, diminished breath sounds, decreased vocal fremitus, and sometimes a postive coin test (*bruit d'airain*), or Hamman's sign ('crunching' sound of air in the mediastinum). Chest X-ray will confirm the clinical diagnosis.
- If the pneumothorax is expanding under tension the clinical signs are more dramatic, because mediastinal compression by the expanding mass decreases venous return, impairs ventricular function and reduces cardiac output. Patients will complain of dyspnoea; clinical signs include tachypnoea and eventual cyanosis. Cardiovascular compromise will manifest as tachycardia, hypotension and, ultimately, cardiac arrest. There may be tracheal deviation and subcutaneous emphysema. Tension pneumothorax can be bilateral.

Diagnosis of pneumothorax in the anaesthetised patient

- Initial signs may be non-specific, with hypotension and tachycardia, others include diminished unilateral chest movement, wheeze, hyperresonance, decreased breath sounds and increased airway pressure. There may be tracheal deviation and elevated central venous pressure (CVP) (if it is being monitored).

Cyanosis, dysrhythmias and circulatory collapse may supervene. If the diagnosis is suspected confirmation should never await chest X-ray.

Further direction the viva could take

There may be time for the examiners to ask about management.

- **Management:** Discontinue nitrous oxide (in the anaesthetised patient) and give 100% oxygen. Immediate management is decompression via needle thoracocentesis followed rapidly by insertion of a definitive chest drain (intravenous cannulae are too small to provide continued effective decompression).
- **Underwater seal drain:** Air from the pneumothorax drains underwater via a submerged tube in a sealed bottle and is then vented to atmosphere. The depth of water is important: if it is too shallow air may be entrained back into the drainage tube, if it is too deep the pressure may be too great to blow off the pneumothorax gas. The typical depth is 3–5 cm.

Fluid therapy

Commentary

The optimum choice of fluids for many different clinical circumstances remains confusing and contentious, and you will not be expected to resolve the various controversies. Volume restoration, however, is such an important part of anaesthetic practice that you will be expected to demonstrate both an understanding of the fluid compartments of the body, as well as a logical appreciation of the characteristics of the different replacement fluids.

The viva

You may be asked first about the distribution of fluids within the body.

- **Normal body fluid compartments:** Of the total body weight in males, 60% is water. In females, who have a higher proportion of body fat, it is 50–55%. These proportions change with age: total body water (TBW), as a percentage of body weight may be 80% in the neonate and 50% in the elderly. Two-thirds of TBW is intracellular water (ICW), the remaining third is extracellular fluid (ECF), which can be divided further into interstitial fluid (ISF) and the intravascular volume. There is a small volume of residual transcellular fluid which has been secreted but which remains separated from plasma, for example as cerebrospinal fluid (CSF) or intraocular fluid.

Direction the viva may take

You may then be asked how fluids can be lost from these compartments.

- **Blood loss:** This is straightforward. Intravascular volume may be depleted directly by trauma or during surgery. It may occur pre-operatively, for example following the rupture of a varicose venous ulcer or an arterial aneurysm.
- **Pure dehydration:** Pure dehydration implies a loss of water alone, without electrolytes. This may be caused by prolonged lack of fluid intake, protracted pre-operative fasting and as a result of any condition that may prevent swallowing. Dehydration depletes all the fluid compartments, and is corrected by a solution that equilibrates across all three, namely glucose 5%. Even in these situations there are always some electrolyte losses.
- **Dehydration:** In the context of clinical medicine, most water deficits are also accompanied by electrolyte losses. The causes are numerous and include inappropriate diuretic therapy, diarrhoea and vomiting, intestinal obstruction, pre-operative bowel preparation, diabetes mellitus (and insipidus) and pyrexia.
- **Peri-operative fluid losses:** These include the fluid deficits accrued as a result of pre-operative fasting, and/or pre-operative pathology, together with intra-operative haemorrhage and what are termed 'third space' losses. This refers to fluid that is sequestered at the site of injury. Losses are variable, but during the course of a long laparotomy through a large abdominal incision, may need replacement by a balanced salt solution at a rate of up to 15 ml $kg^{-1}h^{-1}$.

Further direction the viva could take

You will be asked which fluids you would use to restore volaemic status.

- **Crystalloids**
  - *Definition*: A crystalloid solution is defined chemically as one containing a water-soluble crystalline substance capable of diffusion through a semi-permeable membrane.
  - Crystalloids can be infused rapidly in large volumes, are readily available and are cheap. Disadvantages include their short duration in the circulation, with only about 50% of the infused volume remaining in the intravascular compartment at 20 min. This increases the potential for

overinfusion, circulatory overload and pulmonary oedema. Crystalloids have no oxygen-carrying capacity.
- — *Normal saline (NaCl 0.9%)*: This contains 154 mmol l^{-1} each of sodium and chloride and is isotonic. The excess of chloride ions means that if large volumes are infused a hyperchloraemic acidosis may supervene. This can be a particular problem in children.
- — *Hartmann's (compound sodium lactate)*: This is a balanced salt solution whose composition approximates that of ECF. The lactate in Hartmann's is gluconeogenic and so the solution should not be used in diabetics.
- — *Glucose 5%*: This is effectively a means of giving free water. Isotonic glucose solutions are appropriate for resuscitation of the intracellular compartment, but will have minimal impact on intravascular volumes because they will equilibrate throughout the 42 l of water in the body's fluid compartments. Fluids which contain glucose have no place in acute fluid resuscitation.

- **Colloids**
  - — *Definition*: A colloid is defined chemically as a dispersion, or suspension of finely divided particles in a continuous medium. It is not, therefore, a solution. A butterfly's wing is a colloid, as; more prosaically are foam rubber and fog.
  - — Colloids theoretically are more effective than crystalloids in resuscitation, but the evidence to support their superiority is equivocal. All contain NaCl 0.9%, and Haemaccel contains small amounts of potassium and calcium. Blood is also a colloid, but by convention is treated separately.
  - — *Gelatins*: Gelatins (Gelofusine and Haemaccel) contain modified gelatin of molecular weight of between 30,000 and 35,000 Da, and have an effective half-life within the circulation of 3 h. They carry a small risk of allergic reactions and have no oxygen-carrying capacity.
  - — *Starches*: These consist of amylopectin that is etherified with hydroxyethyl groups. They comprise a wide range of molecular weights and remain within the circulation for much longer, with an effective intravascular half-life of 24 h. Smaller molecular weight particles (less than 50,000) are excreted renally, but the average molecular weight of hetastarch is 450,000 and so much of it remains in the body. Some of the starch molecules are taken up by the reticuloendothelial system and may persist for over a year. Intractable pruritus has been reported as a complication of their use. Preparations include hetastarch, hexastarch and pentastarch.
  - — *Dextrans*: These polysaccharides are classified according to their molecular weight, 40, 70 and 110 $\times$ 10^3. They also remain within the circulation for longer than crystalloids with an effective half-life of 3 h and upwards, but they have enjoyed only fitful popularity in the UK. They can also precipitate allergic reactions, may interfere with blood cross-matching (Dextran 70) and can cause renal problems (Dextran 40).
  - — *Human albumin solution (HAS)*: This previously was supplied as plasma protein fraction (PPF) and has an intravascular half-life of 24 h. It is derived from pooled human plasma but is sterile. There remains uncertainty about prion diseases, vanishingly small though the risk may be, and there is controversy about its role in resuscitation. Some argue that if albumin crosses damaged cerebral and pulmonary capillary membranes, its use will only worsen outcome.
- **Blood:** Blood is also a colloid, but it is convenient to discuss it separately. In acute blood loss fresh whole blood is arguably the ideal replacement: it has oxygen-carrying capacity and expands the intravascular volume. Red cell concentrates, such as SAG-M, supply oxygen carriage, but are not ideal intravascular expanders when given alone, as each unit has a volume of around 300 ml or less. Blood is the most physiological solution, but homologous

transfusion has numerous potential disadvantages which must be set against the urgency of optimal intravascular resuscitation. Autologous transfusion is ideal but is impractical in unexpected major blood loss. Blood is also an expensive commodity.

You may finally be asked about alternative solutions that potentially may be of clinical value.

- **Perfluorocarbons:** These are inert, halogenated compounds which have the capacity to carry oxygen in solution according to Henry's Law (the amount of gas that is dissolved in a liquid at a given temperature is proportional to the partial pressure in the gas in equilibrium with the solution). Older preparations, such as Fluosol DA20, had limited usefulness because of the requirement for high inspired oxygen concentrations, their relative inefficiency of oxygen carriage and the potential for adverse reactions. Newer compounds, such as perfluoro-octobromide, allow the carriage of oxygen equivalent to a haemoglobin concentration of up to $7\,g\,dl^{-1}$, and show more clinical promise.
- **Stroma-free haemoglobin solutions:** Free haemoglobin is able to carry and deliver oxygen molecules, but in order to minimise the risk of toxicity it must be stroma free (with no residual red cell debris). It has higher affinity for oxygen than red cell haemoglobin (the P_{50} is 1.6 kPa compared to 3.6 kPa for red cell haemoglobin), and this marked leftward shift of the oxygen–haemoglobin dissociation curve (OHDC) reduces oxygen delivery to tissues. The molecules are also rapidly degraded in the body, may impair the immune response and can cause renal failure.
- **Micro-encapsulated haemoglobin:** Haemoglobin can be enclosed within artificial microspheres of diameter around 1 μm and which retain 2,3-diphosphoglycerate (2,3-DPG) inside the membrane. Such solutions are experimental.

Compensatory responses to blood loss

Commentary

This is a standard, but fundamental question about applied physiology. You need, above all, to be reassuringly confident about your handling of any of the clinical scenarios with which you may be presented. In addition it must be clear that your management is rational, based both on an understanding of the homeostatic mechanisms involved as well as familiarity with the characteristics of the fluids that you may give.

The viva

You will be asked about the normal compensatory responses to the loss of intravascular volume.

- The function of the circulation is to distribute the cardiac output to tissues sufficient to meet their metabolic demands. Any progressive loss of circulating volume is accompanied by a redistribution of flow aimed to ensure that the brain and myocardium continue to receive oxygenated blood.
- As blood loss continues, the decreases in venous return, right atrial pressure and cardiac output activate baroreceptor reflexes (mediated by stretch sensitive receptors in the carotid sinus and aortic arch). This is an immediate response. The decreased afferent input to the medullary cardiovascular centres inhibits parasympathetic and enhances sympathetic activity.
- There follows an increase in cardiac output together with alterations in the resistance of vascular beds in an attempt to maintain tissue perfusion. These changes are mediated via direct sympathetic innervation, and by circulating humoral vasopressors such as adrenaline, angiotensin, noradrenaline and vasopressin, and by local tissue mediators including hydrogen ions, potassium, adenosine and nitric oxide (NO). (The renal vasculature is especially sensitive.) Hypovolaemia encourages movement of fluid into capillaries: the decreased capillary hydrostatic pressure favouring absorption of ISF with a resultant increase in plasma volume and restoration of arterial pressure towards normal (Starling forces). These mechanisms are particularly efficient in situations in which blood loss is slow and progressive.
- The hypothalamo-pituitary-adrenal (HPA) response is also important, although it is slower. Reduced renal blood flow stimulates intra-renal baroreceptors which mediate renin release from the juxta-glomerular apparatus. Renin converts circulating angiotensinogen to angiotensin I from which angiotensin II (ATII) is formed in the lung. ATII is a potent arteriolar vasoconstrictor that stimulates aldosterone release from the adrenal cortex, and arginine vasopressin (antidiuretic hormone, ADH) release from the posterior pituitary. ADH release is also stimulated by atrial receptors, which respond to the decrease in extracellular volume. These changes enhance sodium and water reabsorption at the distal renal tubule as the body attempts to conserve fluid. Sympathetic stimulation also mediates secretion of catecholamines and cortisol.

Direction the viva may take

You may be asked why major blood loss is associated with a metabolic acidosis.

- Decreased tissue perfusion causes a progressive decline in aerobic metabolism, which is accompanied by a compensatory increase in anaerobic metabolism. This shift to anaerobic metabolism results in a decrease in energy production and the development of a metabolic acidosis. In the aerobic tricarboxylic acid (TCA) cycle, the hydrogen ions which are produced are carried by NADH and $NADH_2$ to the electron transport chain in which the final acceptor is molecular oxygen, which is then converted to water. In the absence of molecular oxygen the final acceptor is missing and so NADH accumulates. The lack of NAD^+ effectively

blocks the TCA cycle and so pyruvate (CH_3—C═O—COOH) also accumulates (at the 'entrance' to the cycle). NADH and pyruvate react to form lactate (CH_3—HCOH—COOH) and NAD^+. The lactate then diffuses out of the cell to accumulate as lactic acid; NAD^+ meanwhile allows anaerobic glycolysis to proceed.

Further direction the viva could take

You are unlikely to be asked about the clinical features of hypovolaemia: unless your performance has been very shaky the examiners will take as read your ability to recognise a patient who is losing blood. Symptoms and signs of blood loss, however, may briefly be discussed in the context of responses to resuscitation, as you are asked about your fluid management.

- **Summary:** Redistribution of blood flow is responsible for the typical pallor, cold peripheries, peripheral cyanosis and oliguria. Sympathetic stimulation explains the tachycardia, and the increase in respiratory rate. Carotid chemoreceptors also stimulate ventilation in response to changes in P_aO_2, P_aCO_2 and pH. Systolic blood pressure is a relatively crude index which may show little change until substantial volumes have been lost. The pulse pressure may be more useful, as blood loss continues it narrows and the mean arterial pressure (MAP) may actually increase. This occurs because diastolic blood pressure is under the influence of catecholamines, which rise in response to haemorrhage. Capillary refill time is a simple and effective measure. A delay of more than 2 s is abnormal, and trends can be used to gauge the effectiveness of fluid resuscitation. Changes in mental state, such as confusion, indicate cerebral hypoxaemia and hypoperfusion.
- **Fluid resuscitation:** See *Fluid therapy*, page 82.

Circulatory changes at birth

Commentary

This is not an area of clinical practice that involves anaesthetists very directly. Although congenital heart disease is common, occurring in approximately 1 in 250 live births, most lesions are identified early and the problems are referred on to specialist paediatric cardiac teams. Patients do occasionally present later in life, but it is the applied pathophysiology itself which seems to be of particular interest to examiners, who will want to discover whether or not you understand the principles of rational management.

The viva

The first part of this viva will concentrate on the fetal and neonatal circulations.

Circulatory changes at birth

- In utero the right and left hearts pump in parallel. There are connections between the systemic and pulmonary circulations via the ductus arteriosus (which links the pulmonary artery to the aorta) and the foramen ovale (which is a communication between the left and right atria). The pulmonary circulation has high resistance and the right and left ventricular (LV) pressures are equal, although the right ventricle (RV) ejects 66% of the combined ventricular output.
- With clamping of the umbilical cord there is a sudden rise in systemic vascular resistance (SVR) and aortic pressure.
- Respiration expands the lungs, and pulmonary vascular resistance (PVR) decreases in response to expansion, respiratory movements, increased pH and increased oxygenation. (PVR continues to decrease with recruitment of small arteries, and the reduction over weeks of pulmonary vascular smooth muscle.) Pulmonary blood flow increases. Enhanced pulmonary venous return into the left atrium raises the left atrial pressure above the right, and the foramen ovale closes by a flap valve effect. It is a functional closure which can be reversed if there is a sudden increase in right atrial pressure.
- The increase in left-sided, and fall in right-sided pressures decrease, or even reverse, shunting through the ductus arteriosus.
- The ductus closes in response to oxygen, prostaglandins, bradykinin and acetylcholine. The process takes up to 14 days to complete. It can be accelerated should the duct remain patent, by giving a prostaglandin antagonist such as indomethacin. In duct-dependent congenital cardiac disease it is important that the duct should be prevented from closing. Alprostadil (prostaglandin E_1) is the agent of choice. The dose in neonates, should the examiner pursue it this far, is 50–100 $ng\,kg^{-1}min^{-1}$ titrated against effect.

Direction the viva may take

The practical application of this information may lie in the rational management of children, and later adults, with uncorrected lesions. It is unusual to encounter adults with cyanotic congenital heart disease.

Acyanotic congenital heart disease

- The main problem in acyanotic heart disease is pulmonary hypertension, which develops as the circulation attempts to 'protect' itself from high pulmonary blood flows caused by intracardiac left to right shunting (for example, through a septal defect) by developing hypertrophy of the media of vascular smooth muscle.
- With progressive disease the resistances in the left and right circulations become finely balanced so that an increase in PVR or a decrease in SVR may reverse the shunt (from left to right, to right to left). This is Eisenmenger's syndrome.

- **Principles of anaesthesia:** Rises in PVR or falls in SVR must be avoided.
  - *PVR*: The resistance in the hyper-reactive pulmonary vascular tree is increased by hypoxia, hypercapnia, acidosis, nitrous oxide and catecholamine release.
  - *SVR*: This is decreased by various factors, including drug-induced vasodilatation and pyrexia.
- LV function is also impaired by chronic hypoxia and by increased pulmonary venous return. Mechanical efficiency may also be impaired by the loss of some of the stroke volume (SV) through a VSD.
- There is a risk of paradoxical emboli and bacterial endocarditis (as with any cardiac structural abnormality).

Cyanotic congenital heart disease

- This will be identified more commonly in children, and exists when there is:
  - Right to left shunt with pulmonary oligaemia, as in the Tetrad of Fallot (VSD, overriding aorta, pulmonary stenosis and RVH).
  - Parallel left and right circulations (transposition of the great arteries).
  - Mixing of oxygenated and deoxygenated blood without decreased pulmonary blood flow (double outlet RV, single ventricle, total anomalous pulmonary venous drainage (TAPVD), truncus arteriosus).
- The chronic hypoxia stimulates polycythaemia. This leads to suboptimal rheology which worsens with dehydration (sludging and thrombosis is possible), and a significant risk of CVA at a haematocrit of greater than 65%.
- There is a risk of paradoxical emboli, and so it is vital to avoid injection of any air. In-line filters should be used.
- There is a risk of bacterial endocarditis (as above).
- If there is pulmonary oligaemia, inhalation induction will be slower.

Further direction the viva could take

The examiner may ask why you have described the condition as the 'Tetrad', rather than the 'tetralogy' of Fallot. This will be your opportunity to widen their education.

- A 'tetralogy' is any series of four related literary or dramatic compositions, just as a 'trilogy' is a set of three. A 'tetrad' is a group of four, as a triad is a group of three. The condition associated with Fallot may be dramatic, but it is not a composition, and whoever named it, you can state airily, was disappointingly imprecise in their use of language.

Post-operative nausea and vomiting

Commentary

Post-operative nausea and vomiting (PONV) is a common problem and this is a standard question, which can follow a fairly predictable course. It combines physiology and pharmacology and you will be expected to demonstrate that you understand the underlying physiological principles and that you can recognise patients who are at risk. You may also be asked about treatment, although this in itself is a large subject. If the examiner wants to cover all three areas then time constraints mean that the questioning will be relatively superficial. Do not be surprised, however, if instead you are examined in more depth on one or other aspects of this substantial topic.

The viva

You will be asked about the neural pathways which mediate nausea and vomiting.

Neural pathways

- Nausea and vomiting are reflexes. The afferent and efferent pathways by which they are mediated are linked to a central integrator: the vomiting centre, which is an anatomically ill-defined area located in the medulla oblongata.
- **The vomiting centre:** The vomiting centre receives afferents from a large number of sources including the cerebral cortex, the viscera and the chemoreceptor trigger zone (CTZ).
  - — *Cortical afferents*: Nausea and vomiting may be provoked by pain, fear and anxiety, as well as by association and by other psychological factors. It may also be precipitated by visual and olfactory stimuli. Cortical stimulation of the vomiting centre may also result from organic disturbance such as raised or lowered intracranial pressure (ICP), hypoxia (of which nausea is a sensitive early sign), and the vascular derangement that accompanies migraine.
  - — *Visceral afferents*: The vomiting centre responds to stimuli such as peritoneal irritation, as well as a variety of visceral disorders including inflammation, distension and ischaemia. Obvious causes include intestinal obstruction or perforation, gastric stasis and gastric irritation. Cardiac pain is also a potent stimulus to vomiting.
  - — *CTZ afferents*: See below.
- **The CTZ:** This is also located in the medulla, in the area postrema on the floor of the fourth ventricle. It lies outside the blood–brain barrier, and receives afferents from various sources.
  - — *Vestibular afferents*: Inputs are received from the vestibular apparatus via the cerebellum.
  - — *Drug effects*: Numerous drugs exert a direct action on the CTZ. These include opiates (which also sensitise the vestibular apparatus to motion), cytotoxic drugs, cardiac glycosides, volatile anaesthetic agents and many others, including drugs which have sympathomimetic actions.

Direction the viva may take

You may then be asked which groups of patients are particularly at risk of PONV. The answer lends itself readily to some form of classification, an example of which is found below.

- **Factors related to patients:** The incidence of PONV in females exceeds by two to four times that seen in males. It is also more marked during the second half of the menstrual cycle. It is greater in obese subjects, in the young, and if ambulation after surgery is premature. A positive history of PONV increases its likelihood threefold. Smoking appears to exert a protective effect.
- **Factors related to surgery:** Intra-abdominal, intracranial, middle ear and squint surgery are all associated with a higher incidence of PONV, as are laparoscopic

and gynaecological procedures. Moderate to severe post-operative pain can also be a potent precipitant.

- **Factors related to anaesthesia:** Opiates and all inhalational agents, including nitrous oxide, predispose patients to PONV. The same applies to agents with sympathomimetic actions such as ketamine. Hypoxaemia is a stimulus to vomiting.
- **Factors related to disease:** The list of potential causes is long and includes intestinal obstruction, hypoglycaemia, hypoxia, uraemia and hypotension.

Further direction the viva could take

It is likely that you will also be asked about the management of PONV. The main emphasis will be on pharmacology and the sites of actions of the agents that you suggest.

- **Drug treatment:** The pharmacology is considered in *Drugs used in the treatment of nausea and vomiting*, page 160.
- Overall management includes prevention by avoidance of emetic drugs (including nitrous oxide in severe cases), and even by the use of alternative techniques such as acupressure on the P_6 acupuncture point at the wrist. Mention these only at the end, for completeness, the examiner otherwise may think that you are stalling for time.

Obesity

Commentary

This topic is a perennial favourite: possibly because the nation is getter fatting, with some 20% of adults being classified as obese. There is potentially much to cover in the time available but this is a topic on which it is quite difficult to fail. There is a lot of information to convey, but much of it is relatively soft, and there is little in the subject for the examiner to use as a discriminator. You will, nonetheless, be expected to address those areas where safety is crucial: the risk of regurgitation and aspiration, perioperative respiratory problems and prophylaxis against venous thromboembolism.

The viva

You may be asked to classify the degrees of obesity, before describing the physiological and anaesthetic implications.

- **Classification:** The most widely used method of classifying obesity is the body mass index (BMI), which is determined by the weight (kg) divided by the square of the height (m^2). A BMI of 18–25 is normal, 26–30 is overweight, 31–35 is obese, and over 35 is morbidly obese. There has recently been introduced the further category of 'super obesity' into which fall patients with a BMI greater than 50.
- **Ideal weight:** There are simple empirical formulae to approximate a patient's 'ideal' weight. One such estimates the optimum weight by subtracting from the height in centimetres 105 (for women) and 100 (for men).
- **Mortality:** The morbidly obese individual has only a 1 in 7 chance of reaching a normal life expectancy and their mortality for all forms of surgery averages twice that of the non-obese population. Problems affect most systems.
- **Cardiovascular:** Hypertension is found in 50–60% of subjects, and is severe in 5–10%. There is increased blood volume with increased cardiac work. Although adipose tissue is relatively avascular, it has been calculated that each additional 1 kg of fat contains 0.6 km of blood vessels. (This piece of peculiar information may at least momentarily entertain your examiner.) There is an increased incidence of coronary artery disease and cardiomyopathy. The risk of deep venous thrombosis and pulmonary embolus doubles. Obese patients have less water per unit of body weight, they tolerate hypovolaemia badly and they may also compensate poorly for changes of position during anaesthesia.
- **Respiratory problems:** The increased adipose tissue of the neck and upper chest may increase problems with tracheal intubation as well as making it much more difficult to maintain the airway with a facemask. The work of breathing is increased due to the mass effect of chest weight, which reduces chest wall compliance. Spontaneous respiration is restricted, and the large abdominal mass can cause diaphragmatic splinting. There is a reduction in the functional residual capacity (FRC) together with an increase in closing volume. Other lung volumes decrease (total lung capacity, inspiratory capacity and expiratory reserve volume), and there is also an increase in pulmonary 'shunting' with mild hypercapnia and peri-operative hypoxia. Equilibration with inhaled volatile anaesthetic agents may be slow. Some 5% of obese subjects have obstructive sleep apnoea. Seriously obese patients may hypoventilate, and manifest the 'Pickwickian syndrome', comprising obesity, somnolence, polycythaemia, pulmonary hypertension and right heart failure. (This is named not after Mr. Pickwick in Dickens' *The Pickwick Papers*, but after the fat boy Joe.)
- **Gastrointestinal system:** Obesity predisposes to hiatus hernia, gastro-oesophageal reflux with potential pulmonary aspiration of gastric contents, and cholelithiasis.
- **Endocrine:** There is a fivefold increase in the likelihood of developing diabetes mellitus. There is an increase in plasma insulin levels which is linked to high calorie intake, but binding to cell receptors decreases (insulin resistance).

- **Miscellaneous physical and technical problems:** These patients are difficult to move, to lift and to nurse. Venepuncture is difficult, and all practical procedures, including local and regional anaesthetic blocks, can be technically demanding. The accurate estimation of drug dosage is problematic, and non-invasive arterial pressure monitoring may be inaccurate. Surgeons as well as anaesthetists face technical problems and the duration of surgery frequently is prolonged.

The physiology of ageing

Commentary

This subject, like obesity, is another question which is quite difficult to fail. In this topic also, there is a lot of information that can be conveyed, but much of it is predictable and again there may be little in the subject for the examiner to use as a discriminator. It will help if you can quote some numerical data: it may appear otherwise that you are simply recounting the obvious fact that every physiological variable deteriorates. An alternative strategy is to make clear that you are focusing your answer on the areas of higher anaesthetic priority.

The viva

You will be asked about changes in physiology with increasing age.

This lends itself to a systems-based approach.

- **General points:** Progressive and global decline in physiological function is measurable after about the fourth decade of life, and more rapid deterioration occurs when patients reach their 70s.
- **Central nervous system:** There is progressive structural change with cerebral atrophy (the weight of the brain decreases by over 10%), a decrease in neurotransmitter concentrations, diminished cerebral blood flow (CBF) and a fall in oxygen consumption. MAC decreases with age both for general and for local anaesthesia. It declines by about 5% per decade after the age of 40 years, and if this curve is extrapolated it reaches zero at the age of 137. There may be some increase in receptor sensitivity, for example to benzodiazepines, while the effect of opiates may be enhanced because of decreased protein binding.
- **Autonomic nervous system:** There is a gradual functional decline as evinced by orthostatic hypotension due to impairment of baroreceptor function. This occurs in 25% of subjects older than 65 years. Temperature control is impaired, and heat generation is reduced by the decline in basal metabolic rate (BMR). The frail and elderly may also have less subcutaneous fat for insulation.
- **Cardiovascular system:** There is gradual functional decline: cardiac output decreases (by 20% at age 60) with decreases in heart rate (HR), SV and myocardial contractility. A decline in receptor numbers means that there is decreased sensitivity to inotropes. The risk of pulmonary thromboembolism is increased, both because of age itself, and because of the nature of the surgery for which elderly patients may present, particularly orthopaedic fractures and intra-abdominal procedures. Anaemia is common.
- **Respiratory system:** There is a progressive decline with age. The closing volume equals FRC in the upright position at around the age of 65 years but encroaches on FRC by age 44 if supine. Increased V/Q mismatch leads to a widening of the alveolar–arterial oxygen gradient ($A–aDO_2$), there is decreased sensitivity to hypoxia and hypercapnia, and there is a decrease in lung compliance.
- **The airway:** Elderly patients are likely to be edentulous with mandibles that are osteoporotic. Oropharyngeal muscle tone is lax, and cervical spondylosis and osteoarthritis are common problems.
- **Gastrointestinal system:** Elderly subjects have slower gastric emptying, parietal cell function is impaired, and hiatus hernia and gastro-oesophageal reflux are more common.
- **Renal system:** Renal blood flow diminishes and glomerular filtration rate (GFR) is decreased by 30–45% in the elderly. Renal concentrating function is diminished, fluid handling is impaired, and pre-operative dehydration is more likely.
- **Drugs:** Hepatic and renal function decline with a decrease in the clearance of drugs, protein binding is reduced and receptor sensitivity alters. It is increased for central nervous system (CNS) depressants, but decreased for inotropes and for β-adrenoceptor blockers.

Direction the viva may take

You may be asked to outline factors of particular relevance to anaesthesia.

- **Co-existing disease is common:** The list potentially is very long and includes ischaemic heart disease, hypertension, chronic airways disease, cerebrovascular disease, osteoarthritis, diabetes mellitus, dementia (which has an incidence of 20% in those age over 80 years), Parkinson's disease, physical frailty, malnutrition, polypharmacy and sensory impairment.
- **Surgical mortality is high:** About 15% of the population of the UK is aged over 65, and the population is continuing to age. This is a group in whom surgery is more common, and in whom mortality is higher. In the 1999 CEPOD report which looked at the extremes of age, 75% of reported cases of mortality were aged over 70 years and the overall mortality rate was 10%.

The 'stress response' to surgery

Commentary

The stress response to injury is a subject of continued, although perhaps diminishing interest to anaesthetists, if not to examiners. There is no consensus about the desirability of abolishing it, but considerable research effort has been expended in studying the attenuating effects of general and regional anaesthesia. Much remains speculative and so the subject eludes focus. You will be able to give the impression of knowing sufficiently about the topic if you have grasped the overall picture and can reproduce some of the key words, and it should not be difficult to provide a broad overview.

The viva

You will be asked for a definition of the stress response followed by an outline of its important features.

- The 'stress response' is the term used to describe the widespread metabolic and hormonal changes which occur in response to trauma, including surgical trauma. It is a complex neuroendocrine response whose net effect is to increase catabolism and release endogenous fuel stores, while conserving body fluids. In evolutionary terms it is a natural mechanism which increases an injured animal's chances of survival.
- The degree of catabolism is related to the severity of the surgical insult or traumatic injury. In practice the plasma concentrations of most substances increase, and it is unlikely that the examiner will ask you specifically about a single hormone. If this does happen, and you do not immediately know the answer, or suspect that it is a trick question, then try to answer it from first principles. Do not be concerned if your reply does not seem that logical: it is not clear, for example, why thyroid hormone should rise little, if at all, while prolactin concentrations should increase.

Endocrine response

- **Autonomic nervous system – sympathoadrenal response:** This is mediated via the hypothalamus with the stimulation of adrenal medullary catecholamines. There is also increased pre-synaptic norepinephrine release. This leads predictably to cardiovascular stimulation with tachycardia and peripheral vasoconstriction. The renin–angiotensin system stimulates aldosterone release leading to sodium and water retention.
- **HPA axis:** Hypothalamic-releasing factors respond to major surgical trauma by stimulating the anterior pituitary. This in turn leads to increases in adrenocorticotrophic hormone (ACTH), which stimulates adrenal glucocorticoid release, and somatotrophin (growth hormone). This enhances protein synthesis and inhibits breakdown, stimulates lipolysis and antagonises insulin. Prolactin release is also evident, although this is to little obvious purpose. The other anterior pituitary hormones, including thyroid hormone, change little. The posterior pituitary produces increased amounts of arginine vasopressin (ADH).
- **Cortisol:** Release from the adrenal cortex after stimulation by ACTH may increase fourfold, and this leads to intense catabolism in which there is protein breakdown, increased gluconeogenesis and lipolysis, with inhibition of glucose utilisation. Cortisol is anti-inflammatory: it inhibits leucocyte migration into damaged areas and inhibits synthesis of various inflammatory mediators including prostaglandins.
- **Insulin:** This is the major anabolic hormone of which there is a relative peri-operative deficiency. Its effects are unable to match the catabolic response.

- **Inflammatory response:** This comprises the release of cytokines (interleukins (IL), tumour necrosis factor and interferons) and the development of an 'acute phase response'.

Direction the viva may take

You may be asked about the significance of the stress response for anaesthesia, whether or not anaesthetists should modify it, and the techniques that can be used.

Modification of the response by anaesthesia

- Catabolism provides endogenous fuel from carbohydrate, fatty acids and amino acids, with the loss of body nitrogen. The process is accompanied by sodium and water retention. As an evolutionary process this may have conferred a survival benefit, but this must apply less in the context of modern surgery and anaesthesia. In the elderly surgical population with patients with significant co-morbidity, the stress response may have obvious adverse effects. Whether or not anaesthetists should be trying to ablate the response, however, remains contentious.
- **Opiates:** These suppress hypothalamic and pituitary secretion, and high dose opiates may attenuate the response substantially, but at the cost of profound sedation and respiratory depression.
- **Etomidate:** This drug is an effective inhibitor of cortisol and aldosterone synthesis via its inhibition of the 11-β- and 17-α-hydroxylase steps of steroid synthesis. It might be logical to use it deliberately to attenuate the response, although this has never been done, presumably because of anxieties about an agent whose use as an infusion in intensive care patients was associated with increased mortality.
- **Benzodiazepines:** These also inhibit cortisol production, probably via a central effect.
- **α-2-agonists:** These attenuate the sympathoadrenal responses, and lead indirectly to a decrease in cortisol production.
- **Regional anaesthesia:** This is of continued interest, because it has been demonstrated that extensive extradural block ablates the adrenocortical and glycaemic responses to surgery. It may be more difficult to achieve in upper gastrointestinal tract and thoracic surgery, but there is increasing acceptance of the claim that targeted and sustained regional anaesthesia has beneficial effect on surgical outcome. This, however, may be related as much to earlier ambulation and improvements in respiratory function as to the abolition of the stress response itself.

The glucocorticoid response to surgery

Commentary

The stress response to injury may be important in patients who are receiving corticosteroids. The traditional concern relates to the danger of precipitating an Addisonian crisis in patients whose HPA axis is suppressed. Many clinicians believe that these anxieties are over-stated. Certainly there is now little justification for the use of potentially dangerous supraphysiological replacement regimens.

The viva

The viva may be introduced by a question about the problems of anaesthetising patients who are being treated with steroids (glucocorticoids). It will go on to the normal steroid response to surgery.

- Patients who are receiving corticosteroids are often assumed to have suppression of the HPA axis. This occurs via a feedback inhibition of hypothalamic and pituitary function.
- This adrenal suppression means that patients cannot mount a normal steroid response to surgery, and may develop an Addisonian crisis in the post-operative period. This is characterised by cardiovascular instability and electrolyte derangement. Patients have hypotension, which may be refractory to routine treatment, and can be hypokalaemic, hyponatraemic and hypoglycaemic.

Steroid response to surgery

- **Sympathoadrenal response:** This is an autonomic response which is mediated via the hypothalamus, and which results in an increase in medullary catecholamines. There is also an increase in the pre-synaptic release of noradrenaline. Aldosterone release is stimulated by the renin–angiotensin system, leading to sodium and water retention.
- **HPA axis response:** Hypothalamic-releasing factors stimulate the anterior pituitary, with resultant increases in ACTH via corticotrophin-releasing hormone (CRH).
- **Cortisol production:** ACTH stimulates adrenal glucocorticoid release. This is mediated by a specific cell-surface receptor, with G-protein activation, adenyl cyclase stimulation and increased intracellular cyclic adenosine monophosphate (cAMP). The effects of cortisol are catabolic, with protein breakdown, gluconeogenesis, inhibition of glucose utilisation and lipolysis. The hormone is also anti-inflammatory, inhibiting leucocyte migration into damaged areas and decreasing the synthesis of inflammatory mediators such as prostaglandins.
- **Cortisol output:** This varies according to the degree of surgical stress. There is normally a maximal rise at 4–6 h with peak cortisol usually subsiding within 24 h. After major surgery it may be sustained for up to 72 h. Normal blood levels are around 200 nmol l^{-1}, but the increase following surgery may range from 800 to more than 1500 nmol l^{-1}. Normal 24 h cortisol output is around 150 mg: minor surgery such as hernia repair will stimulate extra production of less than 50 mg in 24 h, whereas following thoracotomy or laparotomy between 75 and 100 mg will be released.

Direction the viva may take

You will be asked to describe your approach to peri-operative steroid replacement.

- Ideally a replacement regimen should be based on laboratory evaluation of the HPA axis (by conducting short synacthen or insulin tolerance tests if possible) and an assessment of the likely degree of surgical stress. Corticosteroid supplementation minimises the risk of peri-operative cardiovascular instability.
- Patients who are taking prednisolone less than 10 mg daily (or the equivalent) have a normal response to HPA testing and require no supplementation. Patients

who have previously been taking an HPA suppressant dose, but have discontinued this within 3 months from surgery should be assumed to have residual suppression. They should be tested wherever possible, because exogenous steroid supplementation is not innocuous. Patients on high dose immunosuppressant doses must continue these peri-operatively.

- If taking more than 10 mg prednisolone daily and undergoing minor to moderate surgery:
  - Continue the usual dose pre-operatively.
  - Give hydrocortisone 25 mg intravenously at induction.
  - Prescribe hydrocortisone 100 mg in first 24 h (by continuous infusion).
- If taking more than 10 mg daily and undergoing major surgery:
  - Continue the usual dose pre-operatively.
  - Give hydrocortisone 25 mg intravenously at induction.
  - Prescribe hydrocortisone 100 mg day^{-1} for 48–72 h (by continuous infusion).

Further direction the viva could take

You may be asked finally about the dangers of supraphysiological doses of exogenous corticosteroids. Complications of steroid therapy make for a long list, although this question relates to problems related to acute administration.

- **Complications of acute therapy:** Excess catabolism, hyperglycaemia, immunosuppression, peptic ulceration, delayed wound healing, myopathy (which can occur acutely), steroid psychosis (which is related to sudden large increases in blood level), fluid retention and electrolyte disturbance, including hypokalaemia.

If there remains time you may be asked to fill it with a list of the numerous complications related to long-term treatment.

- **Complications of chronic therapy:** In addition to the above these include immunosuppression, hypertension, increased skin fragility, posterior subcapsular cataract formation, osteoporosis, hypocalcaemia due to reduced gastrointestinal absorption, negative nitrogen balance and Cushing's syndrome.

Oxygen delivery

Commentary

An organism survives by means of effective oxygen delivery to mitochondria. There has been considerable interest in the concept of optimising oxygen flux both in critically ill patients and in those undergoing major surgery. The examiners will not necessarily expect you to elucidate the finer points of the debate, but they will require an understanding of the basic principles which will allow you to deduce how the important variables can be influenced to increase oxygen delivery.

The viva

You may be asked (in passing) where oxygen is utilised, before being asked what factors determine oxygen delivery.

- Oxygen is required for energy generation in mitochondria via the process of oxidative phosphorylation.
- Oxygen delivery (oxygen flux) to the tissues is governed by cardiac output (HR × SV) and arterial oxygen content. Content is determined by:

  [Haemoglobin concentration] × [% saturation] × [1.31]

  1.31 is the oxygen-carrying capacity of haemoglobin. The theoretical figure of 1.39, which was based on a more exact determination of the molecular weight of haemoglobin, has been superseded by this figure of $1.306\,ml\,g^{-1}$, derived from direct measurements of oxygen capacity and haemoglobin concentration. Dissolved oxygen ($0.003\,ml\,dl^{-1}\,mmHg^{-1}$) is small and effectively can be ignored, unless hyperbaric therapy is contemplated.
- The formal equation relates delivery to cardiac index (cardiac output/body surface area (BSA)) and so is given by:

  Oxygen flux = [HR × SV ($l\,min^{-1}$)/BSA] × [SaO_2%]/[100] × [[Hb] ($g\,l^{-1}$) × 1.31]

Direction the viva may take

The questioning is likely to concentrate on the value of this variable and how it might be optimised.

- Oxygen delivery is a sensitive index of dysfunction because it incorporates several factors that influence utilisation, all of which are amenable to manipulation. It does, however, require invasive monitoring via a pulmonary artery catheter. Optimisation of oxygen delivery is a logical process.
- **Cardiac output:** Its prime determinants are HR and SV, which itself is affected by several factors including venous return and myocardial contractility. It can be improved by optimising volaemic status to enhance venous return. The treatment aim should be to achieve a pulmonary artery occlusion pressure (PAOP) of around 12 mmHg. PAOP is a better index of left ventricular end diastolic pressure (LVEDP) and volume than CVP. LV contractility can be enhanced by the use of inotropes such as dobutamine, dopexamine, adrenaline, or enoximone.
- **Oxygen saturation:** This may be improved by enhancing cardiac performance as above. It will also be influenced by primary pulmonary factors affecting gas exchange, some of which may be amenable to treatment. Conditions that can be improved include chest infections, atelectasis and bronchoconstriction. Supplemental oxygen will increase P_aO_2.
- **Haemoglobin concentration:** The oxygen delivery equation confirms the importance of haemoglobin: given a cardiac index of $5\,l\,min^{-1}$ and an SaO_2 of 100%, oxygen delivery at a [Hb] of $10\,g\,dl^{-1}$ is $655\,ml\,min^{-1}$; at $15\,g\,dl^{-1}$ it rises to $983\,ml\,min^{-1}$. It is clear; therefore that oxygen flux can significantly be

improved if a low haemoglobin is increased by transfusion. 'Low' in the context of anaesthesia and intensive therapy does not, of course, mean 10 g dl^{-1}.
An oxygen delivery of 655 ml min^{-1} is more than adequate, and few intensivists would wish to transfuse a patient at this level.

- **Dissolved oxygen:** At atmospheric pressure, breathing air, the oxygen solubility coefficient (0.003 ml dl^{-1} $mmHg^{-1}$) means that dissolved oxygen content is around 0.26 ml dl^{-1}. If a subject breathes 100% oxygen this increases to 1.7 ml dl^{-1} and at 3 atmospheres (atm) in a hyperbaric chamber it reaches 5.6 ml dl^{-1}. At this level dissolved oxygen can make a significant contribution to delivery to the tissues.
- **Summary of an optimisation regimen:** In the context of major surgery, optimisation could be summarised as follows:
  - Admission to ITU for invasive PA monitoring.
  - Fluid therapy (crystalloid, colloid or blood) to maintain PAOP at 12 mmHg.
  - Blood to increase haematocrit to 37–40%.
  - Supplemental oxygen to maximise SaO_2.
  - Inotropes to optimise LV output.
  - Manipulation of the above to ensure delivery of >600 ml min^{-1} m^{-2}.

Oxygen–haemoglobin dissociation curve

Commentary

This is a standard and predictable question relating to respiratory physiology, and will be viewed by most examiners as representing core knowledge that is basic to an understanding of respiratory physiology and monitoring. You will be expected, therefore, to answer it with some ease. You are almost certain to be invited to draw the curve, so make sure that you can do this with some facility, so as to reinforce the impression of complete familiarity with the subject.

The viva

- **The OHDC:** This defines the relationship between the partial pressure of oxygen and the percentage saturation of oxygen. In solutions of blood substitutes, such as perfluorocarbons, this curve is linear, with saturation being directly proportional to partial pressure. With haemoglobin containing solutions, however, the curve is sigmoid shaped. This is because as haemoglobin binds each of its four molecules of oxygen its affinity for the next increases. Haemoglobin exists in two forms, an 'R' or 'relaxed' state in which the affinity for oxygen is high, and a 'T' or 'tense' state in which affinity for oxygen is low. As haemoglobin takes up oxygen this effects an allosteric change in the structure of the molecule, which increases affinity and enhances uptake with each of the combination steps.
- **Shifts in the OHDC:** The curve can be displaced in either direction along the *x* axis; movement that is usually quantified in terms of the P_{50}, which is the partial pressure of oxygen at which haemoglobin is 50% saturated. This is normally 3.5 kPa. The P_{50} is decreased (leftward shift) by alkalosis, by reduced PCO_2, by hypothermia, and by reduced concentrations of 2,3-DPG. The curve for fetal haemoglobin (HbF) lies to the left of that for adult haemoglobin (HbA). A shift to the right is associated with acidosis, by increased PCO_2, by pyrexia, by anaemia and by increases in 2,3-DPG. In most instances a shift to the right is accompanied by increased tissue oxygenation. A better reflection of this is the venous PO_2 which can be determined from the curve, assuming an arterio-venous saturation difference of 25%. At low PO_2 levels however (on the steep part of the curve) hypoxia may outweigh the benefits of decreased affinity and increased tissue off-loading. Under these circumstances a rightward shift is actually deleterious for tissue oxygenation. At high altitude with the critical reduction in arterial PO_2, the curve shifts to the left.
- **Haldane effect:** The deoxygenation of blood increases its ability to transport carbon dioxide (CO_2). In the pulmonary capillary oxygenation increases CO_2 release, while in peripheral blood deoxygenation increases uptake. The double Haldane effect applies in the uteroplacental circulation, in which maternal CO_2 uptake increases while fetal CO_2 affinity decreases, thereby enhancing the transfer of CO_2 from fetal to maternal blood.
- **Bohr effect:** This describes the change in the affinity of oxygen for haemoglobin which is associated with changes in pH. In perfused tissues CO_2 enters the red cells to form carbonic acid and hydrogen ions ($CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^-$). The increase in H^+ shifts the curve to the right, decreases the affinity of oxygen and increases oxygen delivery to the tissues. In the pulmonary capillaries the process is reversed, with the leftward shift of the curve enhancing oxygen uptake. The double Bohr effect is a mechanism which increases fetal oxygenation. Maternal uptake of fetal CO_2 shifts the maternal curve to the right and the fetal curve to the left. The simultaneous and opposite changes in pH move the curves in opposite directions and enhance fetal oxygenation.
- **Carboxyhaemoglobin and methaemoglobin:** Other ligands can combine with the iron in haemoglobin, the most important of which is carbon monoxide (CO).

Its affinity for haemoglobin is 300 times that of oxygen, and not only does it reduce the percentage saturation of oxygen proportionately, but it also shifts the curve to the left. In methaemoglobinaemia the iron is oxidised from the ferrous (Fe^{2+}) to the ferric (Fe^{3+}) form, in which state it is unable to combine with oxygen. This happens when haemoglobin acts as a natural scavenger of NO, when a subject inhales NO or when they receive certain drugs, including prilocaine and nitrates.

- **2,3-DPG:** This is an organic phosphate which exerts a conformational change on the beta chain of the haemoglobin molecule which decreases oxygen affinity. Deoxyhaemoglobin bonds specifically with 2,3-DPG to maintain the 'T' (low affinity) state. Changes in 2,3-DPG levels do alter the P_{50}, but the clinical significance of this seems to be small. It is true that concentrations of 2,3-DPG in stored blood are depleted (and are reduced to zero after 2 weeks) and that it can take up to 48 h before pre-transfusion levels are restored. There is, however, little evidence that massive transfusion is associated with severe tissue hypoxia, and this is borne out by clinical experience with such patients.
- **Abnormal haemoglobins:** Fetal haemoglobin is abnormal only if it persists into adult life, as in thalasssaemia. (It comprises two α- and two γ-chains, instead of the two α- and two β-chains in the normal adult.) Haemoglobin S (HbS), which is found in sickle cell disease, is formed by the simple substitution of valine for glutamic acid in position six on the β-chains. The P_{50} is lower than normal and the 'standard' OHDC for HbS is shifted leftwards. The anaemia that is associated with the condition then shifts the curve to the right. There are other haemoglobinopathies, including HbC and HbD (mild haemolytic anaemia without sickling), Hb E, Hb Chesapeake and Hb Kansas. You should not be expected to know about these in detail: they are rare conditions which almost every anaesthetist would wish to look up in a textbook of uncommon diseases should they encounter a case in clinical practice.

Hyperbaric oxygen

Commentary

This topic may seem to be one that is clinically orientated, but in fact it allows an exploration of some basic respiratory physiology. During the discussion you will have to make clear, for example, that you appreciate the difference between oxygen saturation, oxygen partial pressure and oxygen content. Be prepared to cite some figures to demonstrate that you understand the principles.

The viva

You will be asked about the principles underlying hyperbaric oxygen therapy (HBOT). You might wish to start discussing HBOT straightaway, but the first two paragraphs below give some background which explains the rationale for its use.

- **Predicted P_aO_2 from F_iO_2:** There is a useful formula that predicts the partial pressure of oxygen in arterial blood (P_aO_2) by multiplying the inspired oxygen percentage by 0.66. A young adult in good health and breathing room air, therefore, will have a P_aO_2 of $20.93 \times 0.66 = 13.3$ kPa (100 mmHg). Vigorous hyperventilation can increase this to around 16 kPa, but further rises are possible only by enriching the inspired oxygen concentration. From the empirical formula above it can be seen that the maximum P_aO_2 that can be achieved by breathing 100% oxygen is around 66 kPa. (In practice it may be slightly higher.)
- **Saturation, partial pressure and content:** At oxygen partial pressure of 13.3 kPa haemoglobin is almost 100% saturated. Further increases in inspired oxygen (F_iO_2) can therefore increase the oxygen saturation (SpO_2) only marginally, although the P_aO_2 will rise substantially. The sigmoid shape of the OHDC, moreover, means that oxygen will start to be released to the tissues only when the P_aO_2 is around 13.3 kPa. It is also important to note that although the increase in P_aO_2 is very high, the rise in oxygen content is relatively modest. If a subject changes from breathing room air to breathing 100% oxygen at barometric pressure, the arterial oxygen content rises from around 19 to only 21 ml dl^{-1}. In practice the venous oxygen content is probably more significant because this reflects more reliably the minimum tissue PO_2. In the situation above the venous arterial content rises from about 14 to 16 ml dl^{-1}. This is the same as the arterial rise, because the arterio-venous oxygen difference remains constant.
- **Hyperbaric oxygenation:** This is an example of an application of Henry's Law, which states that the number of molecules (in this case oxygen) which dissolve in the solvent (plasma) is directly proportional to the partial pressure of the gas at the surface of the liquid. It is the only means whereby very high arterial P_aO_2 values (greater than 80 kPa) can be obtained. Thus at 2 atm the P_aO_2 will be 175 kPa. However, even at these levels the venous content will only be of the order of 18 ml dl^{-1}, and it is not until the blood is exposed to oxygen at 3 atm of pressure, at which the arterial content is 25.5 dl^{-1} and the venous content 20.5 ml dl^{-1}, that all the tissue requirements can be met by dissolved oxygen. Content is determined by the product of the [Hb] $\times$ [% saturation] $\times$ [1.31] (oxygen-carrying capacity of Hb) plus dissolved oxygen. Dissolved oxygen (0.003 ml dl^{-1} $mmHg^{-1}$) is small and is usually ignored, except under these hyperbaric conditions when it assumes great importance.

Direction the viva may take

You will probably be asked about the indications for HBOT. Many claims of benefit have been made: few have been supported by evidence. Cite them, by all means, but not before you have discussed the mainstream indications, beginning with any that you may have encountered in clinical practice.

- **Decompression sickness:** Recreational divers use compressed air mixtures which they breathe at hyperbaric pressures: each 10 m of descent increasing the pressure by 1 atm. At depth the tissues become supersaturated with nitrogen. If the diver ascends too rapidly the partial pressure of nitrogen in tissues exceeds the ambient pressure, and so the gas forms bubbles in the circulation and elsewhere. Most remains in the venous side of the circulation to be filtered out by the lung, but some may gain access to the arterial (and hence the cerebral) circulations via hitherto innocuous shunts. Hyperbaric treatment mimics controlled ascent from depth, and this allows the nitrogen to wash out exponentially without causing symptoms.
- **Infection:** The evidence supports the use of HBOT as part of the management of patients with bacterial infections. The main indications are for anaerobic bacterial infections, particularly with clostridia, osteomyelitis and necrotising soft tissue infections. Oxygen-derived free radicals are bactericidal.
- **CO poisoning:** The half-life of CO while breathing 100% oxygen is reduced to an hour. This is reduced further to about 20 min in a hyperbaric chamber, but unless the chamber is on site, the transfer time alone will make this benefit negligible. CO is, however, a cellular toxin, which appears to inhibit cellular respiration via cytochrome A_3, as well as impairing the function of neutrophils. The rationale for hyperbaric treatment rests on the presumption, as yet unproven, that it attenuates these toxic effects.
- **Delayed wound healing:** HBOT may be of benefit to patients in whom wound healing is delayed by ischaemia. Its theoretical role in the treatment of thermal injury has not been supported by recent studies. Angiogenesis is however stimulated at hyperbaric pressure, by a mechanism that is unclear.
- **Anaemic hypoxia:** Jehovah's witnesses, and others in whom very low haemoglobin concentrations have compromised oxygen delivery to tissues have been managed successfully using hyperbaric oxygen.
- **Soft tissue injuries:** Early treatment has been used in elite sportsmen to treat soft tissue injuries and some fractures.
- **Multiple sclerosis:** Hyperbaric therapy for this disease still has its enthusiasts, despite the many controlled trials that have shown no benefit.

Further direction the viva could take

You may be asked about the potential complications of hyperbaric therapy.

The main problem relates to oxygen toxicity. See *Oxygen toxicity*, page 105.

Oxygen toxicity

Commentary

One of the most basic principles of anaesthesia and intensive care is the maintenance of oxygenation, and so it is paradoxical that a molecule which is essential to life can, under certain circumstances be lethal. It is important that anaesthetists realise that oxygen potentially is toxic, and the viva is testing your recognition of that reality. It is a relatively sharply focused question and you will have to know some of the details in order to acquit yourself well.

The viva

You will be asked what are the main problems associated with continued administration of supplemental oxygen.

Adverse effects at atmospheric pressure

- **Oxygen toxicity:** The major problem is dose-related direct toxicity. Dose–time curves have been constructed to allow the recommendation that 100% should be administered for no longer than 12 h at atmospheric pressure; 80% for no longer than 24 h and 60% for no longer than 36 h. An F_IO_2 of 0.5 can be maintained indefinitely.
- **Pulmonary pathology:** Oxygen causes pathological changes, which begin with tracheobronchitis, neutrophil recruitment and the release of inflammatory mediators. Surfactant production is impaired, pulmonary interstitial oedema appears, followed after around 1 week of exposure, by the development of pulmonary fibrosis. Toxicity also accelerates lung injury in the critically ill. In patients receiving certain cytotoxic drugs, particularly bleomycin and mitomycin C, ARDS and respiratory failure may supervene after 'normal' doses of oxygen.
- **Mechanism of toxicity:** This is complex and not fully elucidated, however it is suggested that oxygen interferes with basic metabolic pathways and enzyme systems. It is known that hyperoxia increases production of highly oxidative, partially reduced metabolites of oxygen. These include not only hydrogen peroxide but also oxygen-derived free radicals (superoxide and hydroxyl radicals and singlet oxygen). The hydroxyl free radical is the most reactive and dangerous of these species. These substances appear particularly to affect enzyme systems which contain sulphydryl groups.
- **Defence mechanisms:** Up to a partial pressure of oxygen of about 60 kPa, a number of endogenous antioxidant enzymes are effective. These include catalase, superoxide dismutase and glutathione peroxidase.

Toxic effects under hyperbaric conditions

- This toxicity presents the major limitation of HBOT. It is dose-dependent and affects not only the lung, but also the CNS, the visual system, and probably the myocardium, liver and renal tract.
- **Pulmonary toxicity:** Oxygen at 2 atm produces symptoms in healthy volunteers at 8–10 h together with a quantifiable decrease in vital capacity (VC), which starts as early as 4 h. It persists after exposure ceases.
- **CNS:** Oxygen at 2 atm is associated with nausea, facial twitching and numbness, olfactory and gustatory disturbance. Tonic–clonic seizures may then supervene without any prodrome, although some subjects report a premonitory aura.
- **Eyes:** Hyperoxia may be associated in adults with narrowing of the visual fields and myopia.

Direction the viva may take

You may then be asked under what other circumstances oxygen may have adverse effects.

- **Paediatrics:** Neonates and infants of post-conceptual age less than 44 weeks may develop retrolental fibroplasia, if they are allowed to maintain a P_aO_2 greater than 10.6 kPa (80 mmHg) for longer than 3 h. In practice this means keeping the oxygen saturation (SpO_2) in these babies at around 90%. The condition is almost certainly multifactorial.
- **Absorption atelectasis:** This is an adverse effect of therapy.
- **Hypoventilation:** Oxygen concentrations higher than 24% may suppress respiration in patients who are reliant on hypoxaemic ventilatory drive. This is another adverse effect of therapy. It is a phenomenon that seems to worry physicians much more than anaesthetists, most of whom have seen it only rarely.

Further direction the viva could take

You may finally be asked to describe the clinical features of toxicity.

Symptoms

- Initial symptoms include retrosternal discomfort, carinal irritation and coughing. This becomes more severe with time, with a burning pain that is accompanied by the urge to breathe deeply and to cough. As exposure continues symptoms progress to severe dyspnoea with paroxysmal coughing.
- CNS symptoms may supervene as described above: nausea, facial twitching and numbness, disturbances of taste and smell. Convulsions may supervene, preceded by a premonitory aura.

One-lung anaesthesia

Commentary

Introduction to this topic may be via a question about desaturation during thoracic surgery or double-lumen tube placement, but the viva is likely to end up as a discussion about one lung anaesthesia. This is a technique that is used mainly for complex and specialist procedures, but the physiological changes that ensue are of particular anaesthetic relevance, which make it an attractive science-based clinical topic. The examiners will not expect you necessarily to have had very much direct experience, but as this is a standard and predictable question you will be expected to demonstrate that you understand the basic principles.

The viva

You will be asked initially about the indications for, and the basic physiology of, one lung anaesthesia.

- The indications for single lung anaesthesia (during which one lung is deliberately collapsed to facilitate surgical exposure) include pulmonary, oesophageal and spinal surgery. It may be necessary during surgery on the thoracic aorta, and is also used for relatively minor procedures such as transthoracic cervical sympathectomy and pleurodesis.

Physiological changes

- For the duration of anaesthesia the surgical side is uppermost, and the non-ventilated upper lung is usually described as the non-dependent lung.
- When ventilation is interrupted the remaining blood flow takes no part in gas exchange, creating ventilation–perfusion mismatch and a shunt, which contributes to hypoxia.
- The shunt is partly reduced because gravity favours flow to the dependent lung, and because surgical compression and retraction may further decrease blood flow to the non-ventilated lung.
- The shunt will further reduce if non-dependent blood vessels are ligated surgically, and will largely disappear if the pulmonary artery is clamped prior to pneumonectomy.
- Hypoxic pulmonary vasoconstriction (HPV) decreases by around 50% the flow to the non-dependent lung, and may reduce the shunt from 50% down to 30% (which nonetheless is still significant).
- The dependent lung loses volume because of compression, but hypoxic vasoconstriction, should it occur, may compensate partially by diverting some blood to the non-dependent lung.
- Secretions may pool in the dependent lung but suction removal via a double-lumen tube may be very difficult.

Direction the viva may take

You may be asked how you adjust ventilatory settings when the lung is collapsed.

- The ventilator settings are similar to those used for double lung ventilation with tidal volumes of around 10–12 ml kg^{-1}. Higher volumes increase both mean airways (P_{aw}) and vascular resistance, with the result that more blood may flow to the non-ventilated lung and increase shunt. Lower volumes are likely to lead to pulmonary atelectasis.
- Although shunt is not substantially improved by supplemental oxygen, many anaesthetists routinely increase the F_IO_2 to 0.8–1.0.
- The respiratory rate is adjusted to keep the end-tidal carbon dioxide ($ETCO_2$) at around 5–6% or 40 mmHg.

Further direction the viva could take

You may then be asked how you would manage an episode of hypoxia.

- Pre-existing disease, either pulmonary or cardiac, may be an important contributory factor.
- You should check the F_IO_2 and increase it if necessary. This may not help if significant shunt is the problem, but it is probably the swiftest intervention that you can make.
- You should check the tidal volume and other ventilator indices. Again these are interventions that can be made rapidly. The $ETCO_2$ should be maintained at 5–6% because hypocapnia may decrease HPV, although small increases in tidal volume can help oxygenation.
- The double-lumen tube position should then be checked with a fibreoptic bronchoscope. Displacement to a suboptimal position is very common, particularly if the patient has been moved.
- If oxygenation still does not improve, then continuous positive airways pressure (CPAP) of around 5 cmH_2O can be added to the upper lung, but you will have to warn the surgeon that the lung may partially re-expand. Alternatively oxygen can be insufflated in the upper lung, but many anaesthetists do this routinely from the start of surgery.
- You can also add around 5 cmH_2O of positive end-expiratory pressure (PEEP) to the lower lung, which may increase volume in potentially atelectatic areas. This manoeuvre may, however, increase vascular resistance and divert blood to the non-ventilated upper lung.
- Both CPAP and PEEP can be increased in small increments.
- If none of these interventions is successful, intermittent inflation can be tried, or it may finally be necessary to revert to full double lung ventilation (with lung retraction which will allow surgery to continue).

At some stage during the viva you may be asked about the problems of using double-lumen tubes.

- Difficulties with double-lumen tubes are probably the most important cause of mortality and morbidity associated with one-lung anaesthesia. In the 1998 National Confidential Enquiry into Peri-operative Deaths (NCEPOD), which looked at oesophagogastrectomy, problems with double-lumen tubes were implicated in 30% of peri-operative deaths. Studies have confirmed that critical malpositioning occurs in over 25% of cases and general misplacements complicate over 80% of uses.
- This is not surprising: the anatomy may be distorted by tumour or effusion, and the tubes are bulky and more complex to insert, requiring rotation within the airway of between 90° and 180°.
- Complications include failure to achieve adequate lung separation and one lung ventilation, prolonged surgical retraction and associated pulmonary trauma, occlusion of a major bronchus with lobar collapse and secondary infection, contamination of the dependent lung by infected secretions from the upper lung and trauma during insertion.
- A double-lumen tube is positioned correctly when the upper surface of the bronchial cuff lies immediately distal to the bifurcation of the carina. This tube position can be assessed clinically, but this may be unreliable. The average depth of insertion for a patient of height 170 cm is 29 cm, and the distance alters by 1 cm for every 10 cm change in height. This distance from the incisors can be used as an approximate guide. Auscultation of the lung fields during clamping and release can be performed, although findings may be equivocal if access to the chest wall is limited because surgery has begun. Oximetry and capnography will not give specific enough information about where the tube is sited.
- The tube position should therefore be checked using a fibreoptic bronchoscope.

Physiological changes of late pregnancy relevant to general anaesthesia

Commentary

This is not meant to be a question about general anaesthesia for Caesarean section, but as few other surgical procedures are performed at or around term, then it will be a difficult subject to avoid. The examiners, however, initially will try to do so, which will free you to take a standard systems approach to the subject.

The viva

You will be asked about the changes in late pregnancy pertinent to general anaesthesia. A discussion of the various systems is an appropriate start.

- **Cardiovascular system:** During pregnancy there is a total weight gain that averages 12 kg. Half of this is accounted for by an increase in plasma volume and ISF. Plasma volume increases by up to 40% and TBW by around 7–8 l. This volume loading is associated with mild cardiac dilatation, and so heart murmurs (for example that of mitral regurgitation) are common. Cardiac output increases by 40–45% to near maximal at 32 weeks gestation. The resting HR increases by 15% and tachydysrhythmias are more common. The ECG shows left axis deviation due to mechanical displacement by the gravid uterus, and minor T wave and ST segment changes may be seen. Blood pressure falls, with the diastolic drop of 10–15 mmHg making a bigger contribution than the systolic, and there is a decrease in SVR. There is reduced sensitivity to circulating vasopressors, although it appears that the uterine circulation may be more sensitive to these than is the systemic.
  - *Aortocaval compression (supine hypotension syndrome)*: This is of particular clinical relevance. Compression by the gravid uterus of the great vessels affects mainly venous return, but it can also compromise aortic flow. Symptoms of decreased venous return occur in at least 10–15% of mothers. The problem is attenuated by the use of a wedge, but in some cases full lateral tilt is needed to prevent hypotension. The uteroplacental unit does not autoregulate and so blood flow is crucially dependent on the pressure gradient.
  - *Anaesthetic implications*:
    - There must be careful positioning to avoid aortocaval compression.
    - Cardiac output and systemic blood pressure must be maintained to ensure continued perfusion of the uteroplacental unit, but the anaesthetist must be equally aware of the consequences of fluid loading a mother who is already waterlogged.
- **Respiratory system:** Some of the data is contentious and much is based on older studies of small numbers of subjects, which are unlikely ever to be repeated. There is an increase in minute volume by 40% at term, but from early pregnancy progesterone induced hyperventilation reduces P_aCO_2 by around 1 kPa. This is associated with a mild respiratory alkalosis. This would shift the OHDC downwards and to the left, were it not for an increase in maternal 2,3-DPG which offsets the effect. Increased metabolic demand for oxygen increases by around 50% along with an increase in the work of breathing and a decrease in both chest wall and lung compliance. The increased demand for oxygen is more than compensated by the increase in cardiac output and so there is a small rise in P_aO_2 of about 1 kPa. There are anatomical changes which influence the upper airway: general fluid retention and oedema of pregnancy may complicate laryngoscopy and intubation. With regard to pulmonary volumes, the most important change is the 20% decrease in FRC, which by the third trimester may fall in the supine position to half its predicted value.

- *Anaesthetic implications*:
  - The FRC must be filled with oxygen prior to induction to minimise risk of desaturation. This can be achieved either by pre-oxygenating the mother for 3 min with 100% oxygen, or by asking that she take three VC breaths. Slight head-up position will reduce encroachment of the closing volume on the FRC.
  - The reduced FRC means further that the onset of effect of volatile anaesthetic agents will be more rapid.
  - Relative hyperventilation and low normal P_aCO_2 should be maintained, although it is not until the P_aCO_2 falls below about 2.7–3.3 kPa (20–25 mmHg) that uterine blood flow is compromised.
  - The congested and more oedematous upper airway may be traumatised during instrumentation. A smaller tracheal tube (7.0) may be required.

- **Gastrointestinal system:** By the third trimester some 70% of mothers have symptoms of gastro-oesophageal reflux and heartburn. Oesophageal barrier pressure decreases with the loss of lower oesophageal sphincter tone, and there is also a fall in intestinal transit time and some duodenal gastric reflux. Gastric emptying itself, however, is not delayed in late pregnancy. Gastric residual volumes are increased, as is placental gastrin secretion. Whether this translates into maternal gastric hyperacidity remains disputed.
  - *Anaesthetic implications*: The airway must be protected against the risk of pulmonary aspiration of gastric contents by antacid prophylaxis (H_2 antagonists, proton pump inhibitors and sodium citrate). Effective cricoid pressure applied during a rapid sequence induction is also essential.
- **CNS:** Under the influence of progesterone and endogenous β-endorphins, the minimum alveolar concentration (MAC) of anaesthetic agents decreases by about one-third, and there is an increased sensitivity to all drugs which act centrally. (Requirements for local anaesthetics also decrease, which may be related to an increased availability of free drug and to hormonally enhanced neural sensitivity.)
  - *Anaesthetic implications*: Reduction in the doses of anaesthetic agents, sedatives and analgesics may be possible. Inter patient variability, however, is so great that it would be unwise to assume that anaesthetic awareness or severe post-operative pain are less likely.
- **Musculoskeletal system:** Pregnancy increases ligamentous laxity due to the rises in the hormones progesterone and relaxin. There is also an increased lumbar lordosis which helps to accommodate the enlarging uterus.
  - *Anaesthetic implications*: Scrupulous positioning of the patient with appropriate supports and protection may minimise the risk of post-operative backache or other joint problems.
- **Haematological**: Pregnancy is a hypercoagulable state. There is an increase in all clotting factors, except for Factor XI, and fibrinolysis is impaired by a plasminogen inhibitor that is derived from the placenta.
  - *Anaesthetic implications*:
    - Should a mother have additional risk factors predisposing to venous thrombosis, then prophylactic measures should be instituted. These may include the use of low molecular weight heparin.
- **Metabolic:** There is a 30% fall in the levels of plasma cholinesterase.
  - *Anaesthetic implications*: This fall has the greatest implications for those patients with atypical cholinesterases. It is often claimed that this decrease does not produce a clinically important increase in the duration of suxamethonium. Clinical experience would suggest, however, that the actions of suxamethonium are prolonged in many pregnant patients.
- **Drug handling:** Increased renal blood flow and glomerular filtration enhances the clearance of renally excreted drugs. The reduction in maternal albumin may

increase the amount of free drug present in plasma, with consequent enhancement of its effects.

Direction the viva may take

Discussion of the factors above is likely to take up most of the time available. If you have covered many of the points above then the viva may move to a discussion about the management of a mother who insists on a general anaesthetic for an elective Caesarean section. This raises some wider issues such as the autonomy of the patient to choose a technique that carries greater risk than the alternative, and the problems of informed consent. You will probably not be able to explore these very far, but it might be advisable to give such issues some thought, if for no other reason than this is a situation that arises on every labour ward in the country.

Non-obstetric surgery in the pregnant patient

Commentary

It is not uncommon for pregnant women to require surgery for non-obstetric reasons such as acute appendicitis, torsion of ovarian cysts and trauma. There are implications both for mother and fetus of which anaesthetists should be aware, but the questions in the viva will be predictable. For a mother whose pregnancy is well advanced the anaesthetic considerations are those which apply to Caesarean section under general anaesthesia. For a mother in the first trimester the main concerns relate to teratogenesis.

The viva

You will be asked about the implications of anaesthetising a pregnant woman for non-obstetric surgery.

- Non-obstetric surgery is required in 0.5–2.0% of women (the incidence varies with the survey). Acute appendicitis occurs 1 in 2000 confinements, and other surgical procedures include ovarian cystectomy and cervical cerclage. Maternal trauma may also necessitate surgery. The anaesthetic considerations vary according to gestational age.

General principles

- Maternal safety considerations are as for any general anaesthetic. In respect of the fetus, the timing of surgery should be such as to maximise fetal viability. The techniques that are used should minimise the risks of teratogenesis or the onset of premature labour, and prevent uterine hypoxia or hypoperfusion. The same principles apply to post-operative analgesia and fluid and oxygen therapy.

First trimester

- The major concerns are of teratogenesis and of spontaneous abortion. There is very little evidence that any of the long established anaesthetic agents are teratogenic in humans. The teratogenic effects of nitrous oxide have been demonstrated only in rats.

Later pregnancy

- From about the third trimester of pregnancy the anaesthetic considerations are little different from those which apply to Caesarean section. As fetal delivery is not imminent, however, there is less concern about giving drugs such as opiates, which might otherwise cause neonatal respiratory depression.
- The general physiological changes are described elsewhere (see *Physiological changes of pregnancy*, page 109) but to save you returning frequently to the previous question, the factors and their implications for anaesthesia are summarised again as follows.
- **Cardiovascular system:** The relevant changes include a 40% increase in plasma volume, a 40% increase in cardiac output and a fall in blood pressure and SVR. Aortocaval compression causes symptoms of decreased venous return (supine hypotension) in 10–15% of mothers.
  - *Anaesthetic considerations*: These include careful positioning to avoid aortocaval compression, together with maintenance of cardiac output and systemic blood pressure to ensure continued perfusion of the uteroplacental unit.
- **Respiratory system:** The main changes include a 40% increase in minute volume at term, and mild respiratory alkalosis associated with a 1 kPa reduction in P_aCO_2. The leftward shift of the OHDC is offset by an increase in maternal 2,3-DPG. There is a 50% increase in oxygen demand, an increase in the work of breathing and a decrease in both chest wall and lung compliance. The FRC is

reduced by 20%, and by the third trimester may fall in the supine position to half its predicted value. The general fluid retention and oedema of pregnancy may complicate laryngoscopy and intubation.
  - *Anaesthetic considerations*: Mothers must be pre-oxygenated prior to induction to minimise risk of desaturation. (By breathing 100% oxygen for 3 min or by taking three VC breaths.) The congested upper airway may be traumatised during instrumentation and so a smaller tracheal tube should be used. Reduced FRC means that the onset of volatile anaesthetic agent effects will be more rapid. Relative hyperventilation and low normal $P_{a}CO_2$ should be maintained.
- **Gastrointestinal system:** By the third trimester some 70% of mothers have symptoms of gastro-oesophageal reflux and heartburn. Oesophageal barrier pressure decreases with the loss of lower oesophageal sphincter tone, and there is also a fall in intestinal transit time and some duodenal gastric reflux. Gastric emptying is not delayed in late pregnancy. Gastric residual volumes are increased, as is placental gastrin secretion. Whether this results in maternal gastric hyperacidity is disputed.
  - *Anaesthetic considerations*: The airway must be protected against the risk of pulmonary aspiration of gastric contents by antacid prophylaxis (H_2 antagonists, proton pump inhibitors and sodium citrate). Effective cricoid pressure applied during a rapid sequence induction is essential.
- **CNS:** Under the influence of progesterone and endogenous β-endorphins, the MAC of anaesthetic agents decreases by about one-third, and there is an increased sensitivity to all drugs which act centrally. Requirements for local anaesthetics also decrease, possibly due to increased free drug and enhanced neural sensitivity.
  - *Anaesthetic considerations*: A reduction in the doses of anaesthetic agents, sedatives and analgesics may be possible, but anaesthetists should remain alert to the possibility of awareness during general anaesthesia or of pain and visceral discomfort during regional anaesthesia.
- **Musculoskeletal system:** Pregnancy increases ligamentous laxity due to the rises in the hormones progesterone and relaxin.
  - *Anaesthetic considerations*: Careful positioning of the patient with appropriate supports and protection may minimise the risk of post-operative backache or other joint problems.
- **Haematological:** Pregnancy is a hypercoagulable state. All clotting factors (except XI) are increased, and fibrinolysis is impaired by a plasminogen inhibitor is derived from the placenta.
  - *Anaesthetic considerations*: Prophylactic measures may be necessary in any mother with factors which predispose further to venous thrombosis.
- **Metabolic:** There is a 30% fall in the levels of plasma cholinesterase.
  - *Anaesthetic considerations*: Clinical experience suggests that the actions of suxamethonium are prolonged in many pregnant patients.
- **Renal:** There is increased blood flow and glomerular filtration.
  - *Anaesthetic considerations*: Pre-operative evaluation of renal function as 'normal' may underestimate a small degree of renal impairment, which may be important if drugs such as non-steroidal anti-inflammatory drugs are used for post-operative analgesia.

Direction the viva may take

You may be asked what you would tell a mother about the risks of damage to the baby.

- **Teratogenesis:** Major organogenesis is completed by the 8th week of pregnancy, and although the risk of other malformations persists briefly beyond that period, you could reassure a mother who was 10 weeks into pregnancy that the risks

were negligible. Were she to require an anaesthetic in very early pregnancy, you could explain that you would use agents whose risks of causing fetal defects were extremely small. In practice this would mean using the older agents which have been in long established use.

- **Spontaneous abortion:** The increased risk of miscarriage is also very small, and probably bears no relation to anaesthesia. It is more likely that direct surgical stimulation might provoke premature uterine activity, but in practice this is unusual, even after pelvic surgery. The exception is following cervical cerclage, but in this case it should be the obstetric team rather than the anaesthetist who explains the risks and benefits.

Further direction the viva could take

You may be asked about factors which affect the transfer of drugs across the placenta to the fetus.

- The placenta in effect is a lipid bilayer. Some nutrients cross this membrane by active transport processes, but drugs cross only by passive diffusion.
- Small hydrophilic molecules (up to a molecular weight of around 100) will diffuse across the placenta, but transfer of larger compounds that are poorly lipid soluble depends largely on the concentration gradient (according to Fick's law of diffusion), on the permeability and on the area available for transfer. Permeability is inversely proportional to molecular weight.
- Lipophilic substances will cross the placenta according to flow-dependent transfer, that is according to the rate at which they are delivered to the placental circulation.
- Transfer depends on the diffusion gradient, and this in turn is affected by the degree of protein binding and ionisation on either side of the membrane. Local anaesthetics, for example, may concentrate on the fetal side of the circulation, due to ion-trapping. The relative fetal acidaemia increases the proportion of drug in the ionised form, thereby reducing its transfer back across the placental membrane. The same is true of pethidine.

Adrenaline (*epinephrine*)

Commentary

Epinephrine, or adrenaline as most clinicians still prefer to call it, is a key drug in anaesthesia, intensive care and resuscitation. The questioning will include some clinical aspects of its use, but these are rooted firmly in the basic physiology of the compound and so it is this with which you must be familiar.

The viva

You may be asked an open-ended question about adrenaline, or you may be asked more specifically about its effects on one or other systems of the body.

- Adrenaline is one of the body's principal catecholamines (a catechol is a benzene ring with two adjacent hydroxyl groups) which is produced via a short biosynthetic pathway in the adrenal medulla, from where it is secreted. Phenylalanine undergoes two hydroxylation steps to form first tyrosine, and then dihydroxyphenylalanine (dopa). Dopa is decarboxylated to form dopamine, which is hydroxylated to produce noradrenaline. Methylation of noradrenaline produces adrenaline.
- Adrenaline is inactivated by oxidative deamination (monoamine oxidase) and methylation (catechol-*O*-methyltransferase, COMT). COMT is much the more significant pathway.
- Unlike noradrenaline, which is responsible for maintaining normal sympathetic tone, it is not a 'routine' neurotransmitter, but is released instead in response to physiological crisis.
- Adrenaline has effects at both α- and β-adrenoceptors, of which there are several subclasses: α_1, α_2 (each with a further three subtypes) and β_1, β_2 and β_3.
- These adrenoceptors are G-protein coupled, and are associated with different second messenger systems. α_1-effects are mediated via phospholipase C, and α_2-effects via a decrease in cAMP. β-effects are all mediated via an increase in cAMP.
- **Cardiovascular effects:** In lower doses the β_1-effects predominate, but there is still a rise in systolic blood pressure due to the increase in cardiac output. Even at low blood concentrations (the normal level is around 25 pg ml^{-1}) there is still a β-receptor mediated fall in diastolic pressure, and so the pulse pressure widens with only a small rise in MAP. α_2-vasodilatation in skeletal muscle and in the liver also counteracts any rise in peripheral vascular resistance. There is an α_1-mediated increase in the force and rate of myocardial contraction, coupled with an increase in SV secondary to enhanced venous return. Cardiac output increases. Direct myocardial stimulation is partially opposed by inhibitory baroreceptor reflexes which act to modify the rises in blood pressure. The transplanted heart, therefore, which is denervated, shows a more exaggerated response to circulating adrenaline than otherwise would be the case. The same is true if the actions of the vagus nerve have been blocked by high doses of atropine, or if ganglion-blocking drugs have been given. In both normal and denervated hearts the excitability of myocardial cell membranes is enhanced. As the dose of adrenaline increases so both α- and β-effects are seen, while at high doses α_1-vasoconstriction predominates. Adrenaline may also cause α_1-mediated vasoconstriction in the main coronary arteries, which is offset by β_2-mediated vasodilatation in the smaller vessels. From an evolutionary point of view it would be curious were the net effects of adrenaline to compromise the coronary circulation, although the evidence for that proposition remains elusive.
- **Respiratory effects:** Adrenaline is a potent bronchodilator, acting via β_2-receptors to inhibit smooth muscle contraction in the airways.
- **Metabolic effects:** Adrenaline increases oxygen consumption by up to 30%. Blood glucose rises both because of increased glycogenolysis in muscle and liver, and also because of decreased insulin secretion. This is an α_2-effect.

- **CNS effects:** In higher doses adrenaline is a cerebral stimulant which causes arousal. If administered intrathecally adrenaline acts on α_2-receptors to produce analgesia.
- **Gastrointestinal effects:** Smooth muscle of the gastrointestinal tract relaxes, although the sphincters contract (α_1-effect).

Direction the viva may take

You will probably be asked about the indications for its use.

Indications

- **Cardiac resuscitation:** Adrenaline is the main drug in the cardiac arrest algorithms. Its main action is to constrict the peripheral circulation into which the (diminished) cardiac output produced by external cardiac compression is being delivered. The standard dose in adults is 1 mg (10 ml of 1 in 10,000).
- **Circulatory support:** Its use to support the failing circulation is popular in some intensive therapy units. It is given by continuous infusion via a central vein at a rate of 0.05–2.0 $\mu g\,kg^{-1}\,min^{-1}$.
- **Bronchodilatation:** It can be used in acute severe and refractory asthma in a dose range similar to that used for circulatory support.
- **Anaphylaxis:** Adrenaline is the drug of first choice. The drug is given either by deep intramuscular injection in a dose of 500 μg (0.5 ml of 1 in 1000), or by intravenous injection at a rate of 100 $\mu g\,min^{-1}$ until the patient responds.
- **Upper airway obstruction:** Nebulised adrenaline can reduce upper airways oedema, due for example, to croup in children or allergic reactions in adults. 1–2 mg diluted with saline can be used in adults, while children may receive 400 $\mu g\,kg^{-1}$ up to a maximum dose of 5 mg.
- **Vasoconstriction:** Adrenaline can be added to solutions of local anaesthetic to reduce local bleeding, to prolong the duration of action and to reduce the rapidity with which the drug is absorbed. Surgeons may use pre-prepared solutions containing adrenaline 1 in 80,000 up to 1 in 200,000, but they may also prepare their own mixtures for use, for example, in plastic surgical procedures in which large areas of subcutaneous tissue are infiltrated. It is important to be aware of how much adrenaline is being given in these circumstances. The total dose should not exceed 500 μg. (Solutions of 1 in 1000 contain 1000 $\mu g\,ml^{-1}$; 1 in 10,000 contain 100 $\mu g\,ml^{-1}$; 1 in 80,000 contain 12.5 $\mu g\,ml^{-1}$; 1 in 100,000 contain 10 $\mu g\,ml^{-1}$; and 1 in 200,000 contain 5 $\mu g\,ml^{-1}$.) Some surgeons may also use vasoconstrictors such as cocaine (in nasal surgery) and phenylephrine. The pressor effect of these drug combinations can be extremely hazardous.

Further direction the viva could take

You may be asked about potential problems.

- **Ischaemic necrosis:** Injection of adrenaline containing solutions into digits or appendages may jeopardise the blood supply.
- **Cardiac dysrhythmias:** Adrenaline appears to increase the automaticity of the ventricular conducting system. The ECG may show runs of ventricular premature beats, leading in the worst case to ventricular fibrillation. This effect is enhanced by hypercapnia, by hypoxia and by acidosis. In conjunction with the use of some volatile agents, particularly halothane, this could be a fatal combination, although the newer agents seem to be much safer in this regard.
- **Cardiac disease:** Adrenaline should be infiltrated with caution in those patients who have pre-existing hypertension or ischaemic heart disease. The combination of adrenaline and monoamine oxidase inhibitors (MAOIs) may also be hazardous.
- **Alternative vasopressors:** These include agents such as felypressin (Octapressin), which is a vasopressin (ADH) analogue. This is a potent local vasoconstrictor which is less likely to provoke cardiac dysrhythmia.

5-Hydroxytryptamine (*serotonin*)

Commentary

This is a basic science topic that you might expect to encounter in the Primary FRCA rather than the Final. Although serotonin does mediate a large number of physiological functions via a family of receptors and subtypes, the direct anaesthetic applications nonetheless are quite limited. Much remains to be elucidated about the receptor types, which as always will relieve the pressure on you to deliver precise factual answers. You cannot, for example, be expected to know details of 5-HT_6 and 5-HT_7 receptors when their functions remain unclear. You might even succeed in bluffing your way through part of this question. At a recent sitting of the exam a candidate approached this subject with as much confidence as if serotonin had been the subject of his MD thesis. So when he announced resolutely that there were at least 27 5-HT receptors (rather than the 14 that have so far been characterised) the uneasy examiner felt that he had no choice but to let him proceed. If you adopt this stategy only to find alas that serotonin actually was the subject of the examiner's MD thesis then it is easy enough to retreat with the excuse that you must have confused it with some other receptor subset. The examiner will not pursue you, because to do so would mean that they were using their specialist knowledge to unfair advantage.

The viva

As there is no immediate clinical direction for the viva to follow, it is likely that you will simply be asked to tell the examiner about 5-HT.

- 5-hydroxytryptamine (5-HT, or serotonin) is one of four aminergic neurotransmitters (the others being dopamine, noradrenaline and histamine), which has its highest CNS concentrations in the midbrain. This at 1% is a tiny proportion of total body 5-HT, the remainder of which is found peripherally. It is most abundant in the enterochromaffin cells in the walls of the stomach and the small bowel, and it is found also in platelets. In the gastrointestinal myenteric plexus it functions as an excitatory neurotransmitter.
- It is synthesised by hydroxylation and decarboxylation of tryptophan (an essential amino acid the dietary intake of which can influence 5-HT levels), and is metabolised by monoamine oxidase. It is stored in cytoplasmic vesicles. Reuptake is the primary mechanism whereby the compound is recovered following release.
- There are numerous receptor subtypes, further examples of which continue to be characterised. Currently there are 5-HT_1 (with subtypes 1_A–1_F), 5-HT_2 (with subtypes 2_A–2_C), 5-HT_3, 5-HT_4, 5-HT_5 (with subtypes 5_A–5_B), 5-HT_6 and 5-HT_7 receptors, totalling 14. All of them apart from 5-HT_3 receptors are coupled to G proteins. The effects of the 5-HT_3 receptor are mediated via a rapid sodium/potassium ligand-gated ion channel. The receptors variously are pre- and post-synaptic depending on subtype.
- The receptors appear to mediate a large number of different, and sometimes contradictory effects.
  - — *CNS*: These include mood and affect, arousal, circadian rhythms, and CSF production. Serotonergic pathways are similar to noradrenergic systems which inhibit some dorsal horn pain tracts. Discharge in the dorsal raphe nucleus precipitates migraine. 5-HT influences autonomic function, including temperature and blood pressure.
  - — *Cardiovascular system*: 5-HT causes platelet aggregation and can mediate both vasoconstriction and vasodilatation. Intravenous serotonin causes a fall in blood pressure due to arteriolar vasodilatation, which is preceded by an initial rise. In blood vessels 5-HT_{2A} receptors mediate vasoconstriction. (5-HT_1 agonism leads to constriction of larger intracranial vessels.) Other 5-HT receptors, however, cause vasodilatation which is mediated via the

release of NO, and by the inhibition of noradrenaline release from sympathetic nerve terminals.
— *Respiratory system*: 5-HT causes contraction of bronchial smooth muscle.
— *Gastrointestinal system*: 5-HT increases gastrointestinal secretion and peristalsis. It is also involved with nausea and vomiting.
— *Genitourinary system*: 5-HT increases uterine muscle tone.

Direction the viva may take

The above gives an overview of the diverse functions of serotonin. You may be asked about some of the receptor subtypes, mainly because there is some evidence relating to the site of action of various drugs.

- Many, but not all 5-HT_1 receptors are inhibitory in effect. 5-HT_{1A} receptors are the main target of drugs used to treat depression, thus drugs such as fluoxetine ('Prozac') are selective serotonin uptake inhibitors (SSRIs) at these sites. Buspirone, which is a 5-HT_{1A} agonist, is used as an anxiolytic. Sumatriptan and related drugs are 5-HT_{1D} agonists which are effective treatments for migraine, 5-HT_1 receptors mediating intracranial vasoconstriction.
- 5-HT_2 receptors appear to exert excitatory post-synaptic effects and are abundant in the cortex and the limbic system (the hallucinogen LSD is a potent agonist). Platelet aggregation and smooth muscle contraction is mediated by 5-HT_{2A} receptors, and CSF production by 5-HT_{2C}. Gastrointestinal secretion and peristalsis is enhanced by a 5-HT_2 stimulatory effect on smooth muscle. 5-HT_{2A} receptors mediate vascular smooth muscle contraction and vasoconstriction. Methysergide, which is an ergot alkaloid used to treat refractory migraine as well as diarrhoea associated with carcinoid syndrome, is a 5-HT_{2A} and $_{2C}$ antagonist. (The use of this drug is limited by its well-recognised potential to cause devastating endocardial, valvular and retroperitoneal fibrosis.)
- 5-HT_3 excitatory ionotropic receptors in the area postrema mediate nausea and vomiting. They are also excitatory to enteric neurones. Ondansetron and granisetron are effective 5-HT_3 antagonists.
- 5-HT_4 receptors are found in the gut, and centrally in the striatum of the brain. They may have a pre-synaptic facilitatory effect on acetylcholine release, and so may be involved in cognitive function. They are also excitatory to enteric neurones. Metoclopramide is a 5-HT_4 agonist.
- The remaining receptor types have functions which remain incompletely understood. 5-HT_5 and 5-HT_6 receptors in the limbic system appear to be involved with the control of mood, and 5-HT_6 receptors in particular have a high affinity for antidepressants. 5-HT_7 receptors may have some role in sleep and arousal.

Further direction the viva could take

Most examiners will not wish to dwell in detail on receptor subtypes, other than to discover whether you know the sites of action of anaesthetic related drugs. You may then be asked about clinical disorders of 5-HT function, and in particular, about the carcinoid syndrome.

- Disorders include migraine (often treated with 5-HT_{1D} agonists), depression (commonly treated with SSRIs) and anxiety (sometimes treated with a 5-HT_{1A} agonist). Excessive doses of tramadol may manifest with extreme serotonergic effects. See *Drug overdose: prescribed and therapeutic drugs*, page 187.
- **Carcinoid syndrome:** Carcinoid syndrome occurs as a result of enterochromaffin tumours which secrete not only 5-HT but other neuropeptides such as substance P and vasoactive intestinal polypeptide (VIP), as well as prostaglandins, histamine and bradykinin. More than 80% of these tumours originate in the gut and so symptoms do not appear until they metastasise to the liver. Prior to

metastasis these substances are degraded to inactive metabolites. Once they gain direct access to the circulation, either from primary sites in the lung or from metastases, then the problems of flushing, hypotension, tachycardia, wheeze, abdominal cramps and diarrhoea may supervene. Endocardial and valvular fibrosis (which affects the right-side of the heart more frequently than the left) may also complicate the condition, as may pellagra. This is due to nicotinamide (vitamin B2) deficiency, which is caused by the excessive consumption of dietary tryptophan by the tumour. The symptoms of carcinoid are due not solely to serotonin secretion, but those which are mediated via 5-HT can be treated with the 5-HT_2 antagonist cyproheptadine. Octreotide, which is a long acting somatostatin analogue which suppresses 5-HT and other hormone secretion, can also be used.

Plasma proteins

Commentary

This is a rather non-specific topic which could branch off into unpredictable directions for which you may not be prepared. A reliable strategy, therefore, may be to dwell on the core subject in as much descriptive detail as you can muster, so as to avoid being asked, say, about the functions of one of the many hormones that are transported by plasma proteins, or about the immunology of γ-globulins.

The viva

You will be asked about the proteins that are normally present in plasma.

- Plasma is the non-cellular component of the intravascular space and comprises around 3500 ml in a 70 kg adult male, and accounts for about 5% of total body weight.
- Among the considerable quantity of ions, inorganic and organic molecules (including electrolytes, urea, creatinine, fats, amino acids, sugars, metals, vitamins and enzymes) are a large number of plasma proteins. These comprise albumin, the globulins and fibrinogen.
- **Albumin:** Albumin has a molecular weight of around 69,000 and is quantitatively the most important with a plasma concentration of $5\,g\,dl^{-1}$ ($35\,g\,l^{-1}$ in blood). Albumin makes the greatest contribution (20 mmHg) to the plasma oncotic pressure, and is a versatile carrier protein for numerous substances, including bilirubin, calcium, metals, fatty and amino acids, enzymes, hormones and drugs. It is synthesised in the liver at a rate of $0.2\,g\,kg^{-1}\,day^{-1}$.
- **Globulins:** The globulin fraction is divided further into α_1-, α_2-, β_1-, β_2- and γ -subtypes. Their molecular weights average around 200,000 but they are quantitatively less significant with a plasma concentration of $1.5\,g\,dl^{-1}$ ($10\,g\,l^{-1}$ in blood). They contribute about 5 mmHg to plasma oncotic pressure. The α- and β-fractions are synthesised in the liver and include coagulation factors, transport proteins such as α_1-acid glycoprotein (which binds bupivicaine, for example) and precursors such as angiotensinogen. They also include steroid and thyroid hormone binding globulin, as well as acute phase proteins, such as C-reactive protein. Complement is a series of plasma proteins which are also produced in the liver.
- **γ-globulins:** The γ-globulins are antibodies which are synthesised in plasma cells. There are five different classes: immunoglobulin G or IgG, which is the most abundant and which together with IgM is responsible for complement fixation, IgA which is a secretory antibody, IgD which mediates the recognition of antigens by lymphocytes and IgE which is found on the cell membranes of mast cells and which mediates the classic anaphylactic Type 1 hypersensitivity reaction.
- **Fibrinogen:** This is a large molecule of molecular weight variously quoted as between 340,000 and 500,000, which has a plasma concentration of $0.5\,g\,dl^{-1}$ ($3.5\,g\,l^{-1}$ in blood), contributing about 1 mmHg to plasma oncotic pressure. It is a crucial part of the final coagulation common pathway. (It is Factor I.)
- **Other functions:** Plasma proteins are weakly ionised due to their carboxyl (—COOH) and amino (—NH) groups, which dissociate to form anions at body pH. This gives them a buffering capacity which amounts to about 5% of the total. (Some texts quote 15%.)

Direction the viva may take

The examiner may choose one or more aspects and relate them to anaesthesia or intensive care. This means that the viva ceases to be as tightly structured, and the fact that one examiner might question you about immunological function while another might choose coagulation will undermine their ability to mark you as rigorously on

this section of the viva. You should, nonetheless, be prepared to say something sensible about the following topics:

- Coagulation. See *Drugs affecting coagulation*, page 209.
- Immunological function. See *Immunology (and drug reactions)*, page 325.
- Oncotic pressure. See *Osmosis*, page 279.
- Disease states that are associated with abnormalities of plasma proteins, such as liver dysfunction causing hypoalbuminaemia or multiple myeloma.
- Buffers.

Thyroid function

Commentary

This viva may end up with a discussion of the anaesthetic implications of thyroid disease, but you will not get there without having had to explain the basic physiology of thyroid function. Even if details of the biochemistry elude you, at least ensure that you can outline the effects of thyroxine.

The viva

You will be asked about the normal functions of the thyroid gland and thyroid hormone.

- **The gland:** The thyroid gland produces thyroid hormone, which is an iodine-containing amino acid that is central to metabolism. In essence, it maintains the metabolic rate that is optimal for normal cellular function.
- **Production:** The production of thyroxine first involves iodide trapping within the gland by a process of active transport. Iodide is rapidly oxidised to iodine prior to the iodination of tyrosine with the formation of diiodotyrosine (DIT). Two molecules of DIT condense to form T_4. Thyroxine is then stored in the colloid of the thyroid bound in a peptide linkage as part of the large thyroglobulin molecule. It then undergoes proteolysis and release into the circulation. Most of the hormone is released in the form of T_4 with only about 5% secreted as T_3. Once in the circulation about one third of T_4 is converted to T_3.
- **Secretion:** Secretion is controlled by the thyroid-stimulating hormone (TSH) of the anterior pituitary, which in turn is regulated by thyrotropin-releasing hormone (TRH) from the hypothalamus. The process is subject to negative feedback control by thyroid hormones which act at both pituitary and hypothalamus. The proteolysis of stored thyroid hormone is inhibited by iodide.
- **Binding:** Carriage in the circulation is via binding to albumin and throxine-binding globulin (TBG). TBG has very high affinity and so most circulating T_4 is bound. T_3 is bound equally by TBG and by albumin. Free T_3 and T_4 concentrations in plasma are very low.
- **Functions:** In summary, thyroid hormones stimulate oxygen consumption, act as a regulator of carbohydrate and lipid metabolism, and have an important role in normal growth and maturation. The hormones enter cells and T_3 binds to thyroid receptors in the nuclei. T_3 acts more rapidly and is 3–5 times more potent than T_4. The hormone-receptor complex then binds to DNA and changes the expression of a variety of different genes that code for enzymes that regulate cell function. Thyroxine is calorigenic, increasing the oxygen consumption of almost all metabolically active tissues. (Exceptions include the brain, anterior pituitary, testes, uterus, lymph nodes and spleen.) T_4 actually depresses pituitary oxygen consumption, presumably via a negative feedback mechanism. It increases the force and rate of myocardial contraction, increases the number and affinity of β-adrenergic receptors and enhances the cardiac response to circulating catecholamines. As a catabolic hormone it increase lipolysis and stimulates the formation of low-density lipoprotein receptors. It increases protein breakdown in muscle, and enhances carbohydrate absorption from the gut.

Direction the viva may take

You are likely to be asked about the anaesthetic implications of thyroid disease. Overt thyrotoxicosis and myxoedema are rare, but anaesthetic mismanagement of either condition may be disastrous. So even though the viva may have concentrated on basic endocrinology, make sure that you know the principles of clinical management.

- **Airway problems:** All forms of thyroid disease may be associated with large goitres, which may extend retrosternally and cause airway problems.

- **Hyperthyroidism:** The clinical features are well known and are predictable from knowledge of the actions of the hormone. Excess thyroid hormone hyperstimulates almost all metabolically active tissue. The cardiovascular system is of particular interest to the anaesthetist, because severe cases may have cardiac dysrhythmias and heart failure. The cardinal principle underlying the anaesthetic management of thyrotoxic patients is to render them euthyroid prior to surgery. One approach is to do this over 2–3 months using propylthiouracil. This decreases thyroid synthesis and inhibits the peripheral conversion of T_4 to T_3. Carbimazole can be used as an alternative. This also decreases synthesis of thyroid hormone, possibly by inhibiting iodination of tyrosine residues in thryroglobulin. For 10 days or so prior to surgery patients are also given potassium iodide to reduce the vascularity of the gland. An alternative, and less time-consuming option is to control the manifestations of thyroid overstimulation using β-adrenoceptor blockers for 2–3 weeks pre-operatively, together with potassium iodide as above. Emergency surgery carries the risk of a thyrotoxic crisis, also known as 'thyroid storm', in which there is a sudden further extreme surge of metabolic stimulation, with hyperpyrexia, diaphoresis, tachycardia and dysrhythmias. Intravenous β-blockade using propranol (or esmolol if there is concern that the patient is in cardiac failure), together with intravenous potassium iodide should allow adequate control. Larger doses of anaesthetic agents may be required to compensate for their more rapid distribution and metabolism.
- **Hypothyroidism:** Hypothyroid patients, in contrast, need much smaller doses of anaesthetic drugs. The BMR is greatly reduced, and with it cardiac reserve. Uncorrected myxoedema may be associated with amyloidosis, with accompanying cardiac and renal impairment. The opposite of thyroid storm is myxoedema coma, which is characterised by obtunded cerebration, marked hypothermia, alveolar hypoventilation and bradycardia. Correction of hypothyroidism is usually undertaken slowly, giving oral thyroxine, although intravenous T_3 can be used in the emergency situation. This risks provoking myocardial ischaemia and should be avoided if possible. T_4 can be given, but its conversion to T_3 under these circumstances is greatly depressed.

Further direction the viva could take

You may be asked, almost as an aside, why patients with thyrotoxicosis develop proptosis, and why hypothyroidism is known as myxoedema. It will have (almost) no bearing on whether you pass or fail, but there is no point in becoming unnecessarily dejected by not knowing the answer to the final question of the section.

- Skin contains various proteins combined with polysaccharides, hyaluronic acid and chondroitin sulphuric acid. In hypothyroidism these complexes accumulate, and so promote water retention along with a characteristic coarsening of the skin, which becomes puffy. When treated with thyroid hormone these complexes are metabolised with resolution of the 'myx'-oedema.
- Exophthalmos is a characteristic of auto-immune Graves' disease and is due to swelling of the muscles and connective tissues of the orbit, which leads to proptosis. This effect is due not to thyroid hormone, but to an autoimmune attack on the tissues by cytotoxic antibodies. These are formed in response to antigens that are common to the eye muscles and to the thyroid.

(Raised) intracranial pressure

Commentary

There are several variations on this question about ICP. The viva may concentrate on ICP itself or branch off to include the concept of cerebral–perfusion pressure (CPP), or the protection of the brain against hypoxic or ischaemic brain injury. The diagnosis and rational management of raised ICP are important and so you will need to know about basic underlying mechanisms.

The viva

You will be asked about the factors that may influence ICP.

- The skull of an adult is in effect a rigid box which contains brain tissue, blood and CSF. The brain itself has minimal compressibility and so there is very limited scope for compensation. An increase in the volume of one component invariably results in an increase in ICP unless the volume of another component decreases. (This is the Monroe–Kellie hypothesis.) These intracranial contents comprise brain tissue (1400–1500 g), blood (100–150 ml), CSF (110–120 ml) and ECF (less than 100 ml).
- Rises in ICP from the normal 10–12 mmHg are significant because of their potential impact upon cerebral perfusion. The CPP is determined by MAP minus the sum of the CVP and the ICP. CPP = MAP − (CVP + ICP).
- **Mass lesions:** ICP is raised by mass lesions which increase the volume of brain, bone, or meninges. These include tumours of all three structures, as well as infection (with abscess formation).
- **Impaired drainage:** ICP is also raised by conditions which impede drainage of CSF (which is produced at 0.4–0.5 ml min^{-1}) and thus increase its intracranial volume. These include congenital and acquired hydrocephalus, which may also be associated with trauma, tumour or infection. A blocked ventricular shunt is another important cause.
- **Volume increases:** ICP is raised by conditions which increase non-CSF fluid volume. Intracranial aneurysm, arterio-venous malformation and trauma are all relatively common causes of subarachnoid or subdural haemorrhage. ICP is raised by cerebral oedema, which itself has many causes including trauma, infection, metabolic dysfunction (such as hepatic encephalopathy or Reye's syndrome), hypoxia, venous obstruction and increased hydrostatic pressure (such as is caused by a steep or prolonged Trendelenberg position on the operating table). It may be idiopathic, as in benign intracranial hypertension. This is a clinical entity defined by an ICP greater than 15 mmHg (but which can reach three times that figure) in the presence of normal CSF composition, normal conscious level and with no evident pathological process. It may be due to an increase in intracranial venous pressure which is offset by ICP and CSF pressure increases which restore the required gradient for CSF absorption into the venous system. Some cases can be managed with corticosteroids, diuretics and azetazolamide, but severe cases may require the insertion of a lumbo-peritoneal shunt.
- **Pathophysiology:** In the presence of raised ICP, CPP is given by MAP − ICP. Perfusion will be maintained until CPP starts to fall below 50 mmHg, with the onset of critical ischaemia at 30–40 mmHg. There may also be focal ischaemia in the region of a mass lesion. Raised ICP attenuates cerebral autoregulation to the point at which it is lost completely, after which CBF follows MAP passively.

Direction the viva may take

You may be asked about the clinical features of raised ICP and its management.

- **Symptoms:** These depend on whether the ICP rise is acute or chronic. Typically patients complain of headache, nausea and vomiting. These symptoms are worse

in the morning both because of increased hydrostatic pressure effects and because the $PaCO_2$ may be raised. Patients may have changes in level of consciousness and visual disturbances (see below).

- **Signs:** Patients may exhibit neurological signs caused by brain distortion or by one of the brain herniation syndromes (see below), including pupillary changes and failure of upward gaze. There may be papilloedema, hypertension, bradycardia and abnormal respiration. These last constitute Cushing's triad.
- **Cerebral herniation:** Several syndromes have been described.
  - — *Central herniation*: In this situation (which is the most important), the raised ICP forces the brain downwards through the foramen magnum as the cerebellar tonsils herniate and compress the medulla. This is known colloquially as 'coning'.
  - — *Cingulate herniation*: The cingulate gyrus and part of hemisphere are displaced beneath the falx cerebri, to affect primarily the anterior cerebral vessels.
  - — *Uncal herniation*: The uncus (which is part of the hippocampal gyrus) herniates through, and is then compressed against the tentorium.

Specific clinical signs (ICP can rise without these)

- **Cushing's reflex:** The triad comprises hypertension, bradycardia and abnormal respiration. This is a late and ominous sign that coning is imminent, as the carotid body receptors attempt to mediate an increase in perfusion pressure that is doomed to fail.
- **Pupillary signs:** These may follow uncal compression or kinking of the oculomotor nerve by distorted vessels. There is ipsilateral pupillary dilation followed by motor paralysis of the extraocular muscles (excluding the superior oblique and lateral rectus muscles which are supplied by the fourth and sixth cranial nerves respectively).
- **Eye signs:** The lateral rectus is also affected because of the displacement of the sixth cranial nerve (abducens) which has a long intracranial course. As it leaves the posterior margin of the pons it is crossed by the anterior inferior cerebellar artery. Displacement of the cerebellum may distort these vessels such that they compress the abducens nerve. The clinical effect of such compression is failure of lateral gaze.

Management

- A moderate head up position will reduce venous pressure without unduly affecting the MAP (provided there is no physical constriction to drainage by artefacts such as tracheal tube tapes). Moderate hypocapnia will reduce ICP, but the benefit is relatively short-lived, and there is a risk of rebound hyperaemia. Mannitol 20% in a dose of $0.5\,g\,kg^{-1}$ has a marked, but transient effect. It may shift the patient down the intracranial compliance curve and gain sufficient time for definitive treatment before a catastrophic rise in ICP, but it too is associated with rebound hypertension. If the blood–brain barrier is affected, mannitol may also cross into brain parenchyma and exert a reverse osmotic effect. High dose dexamethasone reduces oedema secondary to intracranial tumours, but has no effect on raised ICP following trauma. It is important to avoid hyperthermia, which will increase $CMRO_2$ and CBF. Hypothermia has the opposite effect and may confer some benefit.
- ICP can be measured by subdural or extradural transducers or via an intraventricular catheter. All these methods are invasive, requiring a burr hole, but they allow quantification of CPP.

Further direction the viva could take

You may be asked finally about CSF. (This could form a question on its own, and would be linked to the topic of post-dural puncture headache and its management. See *The extradural space*, page 67.)

- **Formation:** Its total volume is around 150 ml, about 80% of which is intracranial. Most of the extracranial (spinal) CSF is found distal to the conus medullaris. CSF is formed by the choroid arterial plexuses either by secretion or by the quantitatively much less significant process of ultrafiltration. It is produced in the lateral, the third and the fourth ventricles, at a rate of around 0.5 ml min^{-1} or 500–600 ml day^{-1}. The rate of production is constant and is not related to ICP unless it is sufficiently high to compromise CPP and reduce blood flow to the choroid plexus.
- **Circulation:** It passes through the cerebral aqueduct to the fourth ventricle and thence through the midline foramen of Magendie and the two lateral foramina of Luschka to communicate with the subarachnoid space of the brain and spinal cord. It is either absorbed directly into cerebral venules (10%) or absorbed by the arachnoid villi (90%).
- **Functions:** It has a cushioning effect which protects the brain from injury. Supported by CSF the effective cerebral weight is only 50 g. It can partly buffer increases in ICP by translocation of CSF from the intracranial to the extracranial subarachnoid space.
- **Composition:** It has a higher PCO_2 than plasma and a lower pH of 7.33. The mean specific gravity is 1.006 with a range of 1.003–1.009. Its protein content is low (0.2 g l^{-1}) so buffering capacity is negligible. Glucose concentration is lower than plasma. Sodium and chloride are higher, while potassium is lower (40%). This is because the formation of CSF requires the active transport of Na^+, Cl^- and K^+ into the ventricles. Further Na^+ is then added in exchange for K^+ (mediated by Na^+/K^+ ATP-ase). The influx is maintained by the further exchange of H^+ and HCO_3^- for Na^+ and Cl^-. H^+ and HCO_3^- are generated from H_2CO_3 in a reaction that is catalysed by carbonic anhydrase.
- **Factors affecting rate of production:** Acetazolamide, which is a carbonic anhydrase inhibitor, may reduce CSF production by as much as 50%. High dose diuretics also reduce it by affecting the sodium transport process. Corticosteroids may increase production, but not consistently enough to make them a reliable treatment for post-dural puncture headache.

Cerebral blood flow

Commentary

This is a standard question which has obvious relevance for general anaesthesia, for head injury, for techniques such as induced hypotension and for anaesthesia in patients with hypertensive disorders, including pre-eclampsia.

The viva

You will be asked about the factors which influence CBF.

- The brain weighs 2% of the human organism yet receives 15% of the cardiac output. The intracranial contents consist of brain tissue (approximately 1400–1500 g), blood (100–150 ml), CSF (110–120 ml) and ECF (less than 100 ml).
- **Normal CBF:** Normal CBF is 50 ml 100 g^{-1} of brain tissue per minute, and is determined by the CPP. The CPP = MAP − (CVP + ICP). The normal CPP is 70–80 mmHg. Blood flow to grey matter is more than twice that to white matter.
- **Autoregulation:** Over a wide range of MAP, typically between 50 and 150 mmHg, autoregulation maintains normal flow. The process is not instantaneous, and may take some seconds to complete. The classic cerebral autoregulation curve is an oversimplification: there is not a neat linear relationship between MAP and CBF at each end of the curve, and changes in perfusion pressure may be regional. Chronic hypertension shifts the autoregulatory curve to the right; drug-induced hypotension shifts it to the left. The mechanisms which underlie autoregulation are primarily myogenic, modulated by stretch receptors in vascular smooth muscle, and metabolic, in which hydrogen ions and substances such as NO and adenosine accumulate in the tissues at low flow and mediate vasodilatation.
- **P_aCO_2:** There is a linear relationship between $P_{a}CO_2$ and CBF in the range of partial pressures from 3.5 to 10.0 kPa. Below 3.5 kPa cerebral vasoconstriction leads to tissue hypoxia (with subsequent reflex vasodilatation): at around 10.0–12.0 kPa there is a ceiling at which blood flow is maximal (at around 120 ml 100 g^{-1} min^{-1}).
- **P_aO_2:** Decreases in the partial pressure of oxygen below 8 kPa are associated with sharp increase in CBF up to around 110 ml 100 g^{-1} min^{-1}. At 4.0 kPa CBF is doubled. Hyperoxia is associated with decreases in CBF.
- **Temperature:** Changes in temperature are associated with altered requirements for cerebral oxygen (the cerebral metabolic rate for oxygen, $CMRO_2$). Each 1°C change in temperature is accompanied by a 7% alteration in $CMRO_2$.
- **$CMRO_2$:** CBF is linked to $CMRO_2$ by a mechanism that has not fully been elucidated. There is a short lag time of 1–2 min.
- **Rheology:** Lower plasma viscosity is associated with enhanced capillary flow, although there is a balance between optimal rheology and oxygen delivery. A haematocrit above 50% risks intravascular sludging and a reduction in CBF, while a haematocrit below 30% is associated with decreased oxygen flux.
- **ICP:** The formula for CPP confirms that CBF is compromised by increases in ICP from its normal 10–12 mmHg. See *(Raised) intracranial pressure*, page 124.

Direction the viva may take

You may be asked how you would measure cerebral flow.

- **Kety–Schmidt method:** This is an application of the Fick principle, which states that flow is equal to the amount of a substance taken up or excreted by an organ, divided by the arterio-venous concentration difference. (Hence CBF = quantity of substance taken up by the brain/A–V difference.) Nitrous oxide is used as the diffusible tracer. The subject breathes 10% N_2O for 10 min, during which time paired peripheral arterial and jugular venous bulb samples are taken. At the end

of 10 min the concentrations are equal, at which point the venous concentration is the same as brain. The speed at which the arterial and venous curves equilibrate is a measure of nitrous oxide delivery to the brain. The technique is invasive and gives only a global measure of flow. It is not a technique for clinical use.

- **Transcranial Doppler ultrasonography:** This gives a measure of the velocity of red cells flowing through large cerebral arteries, most commonly the middle cerebral, and can be used in clinical practice. The velocity can give an index of flow provided that the diameter of the artery is determined independently, and provided this diameter changes little (as is the case with the major cerebral arteries).
- **Positron emission tomography (PET):** This (research) technique monitors the uptake by different areas of the brain of 2-deoxyglucose, which is labelled with a positron emitter.
- **Scintillography and SPECT scanning:** These techniques use radioactive xenon to trace regional blood flow, with or without enhancement by computed tomography (CT) or magnetic resonance (MR) imaging.

Further direction the viva could take

You may be asked what effect anaesthesia has on CBF.

- **Intravenous induction agents:** All except for ketamine reduce $CMRO_2$ and as a result CBF falls in tandem. Autoregulation is not affected. Ketamine increases MAP which leads to a rise in blood flow.
- **Volatile anaesthetic agents:** These uncouple CBF and $CMRO_2$. They reduce $CMRO_2$ but are associated with a rise in CBF secondary to their capacity to vasodilate the cerebral circulation and abolish autoregulation. The response to changes in P_aCO_2 is unchanged. This action is dose-dependent but can partly be offset by the vasoconstrictor effect of hyperventilation. Autoregulation is abolished by 1.5 MAC of all the agents bar sevoflurane. This has only 30% of the vasodilatory potential of isoflurane and does not impair autoregulation. Nitrous oxide increases CBF by increasing the $CMRO_2$, while also affecting autoregulatory mechanisms.
- **Opiates:** Opiates have little direct effect, but CBF will rise in response to CO_2 retention should respiratory drive be depressed.
- **Arterial pressure:** Chronic hypertension shifts the autoregulatory curve to the right, while drug-induced hypotension shifts it to the left. If autoregulation is attenuated by the use of volatile anaesthetics then CBF and ICP will rise in parallel with an increase in MAP.
- **Venous pressure:** Any of the many factors which increase venous pressure such as position, coughing, straining against a ventilator, impeded drainage from the head and neck, volume overload, or the use of IPPV and PEEP, will all decrease CPP and reduce CBF.
- **Steal and inverse steal:** There will be focal areas of injured brain in which autoregulation is lost, while elsewhere it is retained. Cerebral vasodilation may further compromise these areas by diverting blood away, while conversely the vasoconstriction associated with hyperventilation may divert blood from normal to damaged brain, where vasoconstrictor responses have been lost. These effects describe respectively cerebral steal and inverse steal.

Hypoxic pulmonary vasoconstriction

Commentary

HPV is just one of the factors that influences ventilation–perfusion relationships in the lung, but it may alone form the subject of a question. Inasmuch as anaesthetists rarely intervene actively to exploit the mechanism it remains theoretical, but because it is influenced by anaesthesia and because it has relevance for special situations such as one-lung anaesthesia, it is of continued interest to examiners.

The viva

You will be asked to describe the phenomenon of HPV.

- **Definition:** HPV is a mechanism that diverts blood flow away from areas of the lung where the alveolar oxygen tension is low; shunting it to better ventilated zones and improving the ventilation–perfusion ratio. (Elsewhere in the circulatory system hypoxia always results in the vasodilatation of vascular beds.)
- **Significance:** HPV is of little importance in health, but it is more significant in disease. It explains, for example, the upper lobe diversion characteristic of LV failure, as blood in the congested and hypoxaemic lower parts of the lung is diverted away. It is significant during one-lung anaesthesia.
- **Response:** The response occurs via the constriction of small arterioles. This is not neurally mediated. It is seen, for example, in denervated lungs (following transplantation). Nor is it mediated by humoral vasoconstrictors, but by pulmonary mixed venous oxygenation and, much more importantly, by alveolar oxygenation. Larger blood vessels may be affected globally, as in the fetal pulmonary circulation, in which the low P_AO_2 reduces pulmonary blood flow to about 15% of the cardiac output.
- **Onset:** Its onset is within seconds of the decrease in P_AO_2, and lobar blood flow may halve within minutes from its value during normoxia. The phenomenon is biphasic, with the vascular resistance returning almost to baseline before the onset of a second phase of slower and sustained vasoconstriction that reaches a plateau at 40 min.
- **Mediators:** The mechanisms have not fully been elucidated. The pulmonary vasculature is maintained in a state of active vasodilatation to which NO may contribute, and so suppression of endothelial NO production will lead to vasoconstriction. In addition, hypoxia stimulates production of endothelin, which is a vasoconstrictor peptide. It is also known that pulmonary blood vessels have oxygen-sensitive potassium channels, such that the membrane potential alters in response to hypoxia with opening of calcium channels and smooth muscle contraction. This phenomenon is not seen in the systemic vasculature.
- **Influences:** Acidosis and hypercarbia potentiate HPV, while alkalosis either attenuates or abolishes it and causes pulmonary vasodilatation.

Direction the viva may take

You may be asked about the influence of anaesthesia on HPV.

- **Anaesthesia:** All inhalational anaesthetics inhibit HPV. The effect is dose-dependent and is similar for all the agents apart from nitrous oxide, whose action is less potent. The dose–response curve is of typical sigmoid shape; the ED_{50} is just under 2 MAC, and the ED_{90} is around 3 MAC. At 1.3 MAC HPV is diminished by around 30%. Intravenous induction agents have little effect.
- **Oxygen:** A high F_iO_2 may inhibit HPV by maintaining higher P_AO_2 even in underventilated alveoli.
- **Cardiac output:** Any factor which depresses cardiac output will reduce mixed venous PO_2 and so may enhance HPV.

- **Drug effects:** Drugs such as calcium channel blockers, sodium nitroprusside (SNP), glyceryl trinitrate (GTN), bronchodilators, NO and dobutamine attenuate HPV. It is potentiated by cyclo-oxygenase inhibitors, propranolol and by the respiratory stimulant almitrine. (This is not used in the UK, but acts by stimulating carotid body chemoreceptors. It also enhances the effect of HPV in situations in which it is deficient.)

Further direction the viva could take

- You may be asked about other factors which influence PVR, or about means of optimising ventilation–perfusion ratios in critical illness.

Pulmonary oedema

Commentary

Pulmonary oedema is common in critical care, if less so in anaesthesia. This viva explores your understanding of the various forces that allow its development as well as your ability to apply that knowledge to its rational management.

The viva

You will be asked what factors contribute to the formation of oedema by movement of fluid across capillary membranes.

- Fluid flux across the capillary into the interstitium and thence into the alveolus is governed by Starling's hypothesis for capillary fluid exchanges.
- **Starling equation:** Fluid flux = $\kappa(p_{cap} - p_{is}) - \Sigma(\pi_{cap} - \pi_{is})$
- **κ:** This is the capillary filtration coefficient, a proportionality constant which is a measure of the ease with which fluid traverses the endothelial boundary. It is the product of the area of capillary wall, and its permeability to water. 'Leaky' capillaries have a high filtration coefficient.
- **p_{cap}** and **p_{is}:** These are the capillary and interstitial hydrostatic pressures respectively.
- **Σ (also written sometimes as σ or δ):** This is the reflection (or reflectance) coefficient, which is an indication of the permeability of the capillary barrier (acting as a semi-permeable membrane) to solute. A coefficient of 1 indicates total 'reflection', with no solute passing into the interstitium. A coefficient of zero indicates that the capillary wall allows free passage of solute.
- **π_{cap}** and **π_{is}:** These are the capillary and interstitial oncotic pressures respectively.
- The net sum of the four forces is usually outwards, with the extravasated fluid being cleared by the lymphatics. This is despite the lower hydrostatic pressures in the pulmonary circulation. The normal clearance rate of 10–20 ml h^{-1} (in the lungs) can increase to 200 ml h^{-1} before the system is overwhelmed.
- The oncotic pressure is the contribution made to total osmolality by colloids. (Hence the alternative term 'colloid osmotic pressure'.) The plasma oncotic pressure, at 25–28 mmHg, is only about 0.5% that of total plasma osmotic pressure, but is significant because from the equation above it can be seen that it is the only force whose effect is to retain fluid within the pulmonary capillary.

Direction the viva may take

You will be asked to explain how the different types of pulmonary oedema may arise.

- **Increased capillary hydrostatic pressure (p_{cap}):** This is common and explains the formation of pulmonary oedema as a consequence of LV failure, fluid overload, mitral stenosis and any other condition that may cause pulmonary venous hypertension. Hydrostatic pressure is clearly greater in the dependent parts of the lung. Neurogenic pulmonary oedema may be due to a sudden increase in hydrostatic pressure in response to a catecholamine surge.
- **Decreased interstitial pressure (p_{is}):** If interstitial pressure becomes acutely negative, pulmonary oedema may develop as the lymphatics are overwhelmed. This can occur with upper airway obstruction during which very high negative intra-thoracic pressures may be generated, creating a gradient which favours transudation.
- **Decreased capillary oncotic pressure (π_{cap}):** This commonly worsens oedema that is due to another primary cause. Hypoproteinaemia, hypoalbuminaemia, haemodilution, liver failure and the nephrotic syndrome are all conditions which will decrease the gradient between the oncotic pressure and the pulmonary capillary occlusion (or 'wedge') pressure. If this gradient does not exceed 4 mmHg, then oedema formation is inevitable. Albumin makes a substantial

contribution to COP, and if the plasma albumin concentration × 0.57 does not exceed PCWP, then pulmonary oedema will supervene.

- **Decreased reflection coefficient (Σ):** Capillary endothelial damage may reduce Σ to zero, so that protein will diffuse freely across the wall such that no effective oncotic pressure can be exerted. This form of capillary leak characterises the acute respiratory distress syndrome (ARDS). Capillary injury will also increase permeability to water, with a rise in the filtration coefficient, κ.
- **Decreased lymphatic clearance:** This is uncommon, but will accompany any disease process which obliterates lymphatic vessels. Examples include severe fibrosing lung disease, silicosis and lymphangitis carcinomatosis (lymphangitis obliterans).
- **Idiopathic:** Other causes of pulmonary oedema include ascent to altitude and rapid lung re-expansion after collapse. The mechanisms are uncertain.

Further direction the viva could take

You may be asked to outline how you can apply these principles to the rational management of pulmonary oedema.

- Hydrostatic pulmonary oedema is treated by reducing left atrial pressure. This can be achieved by offloading the LV using nitrates or ACE inhibitors to improve myocardial function. The emergency treatment of acute LV failure commonly involves intravenous diamorphine and diuretic. These probably alleviate symptoms by the same mechanism. Myocardial contractility can be enhanced using positive inotropes.
- Decreased capillary oncotic pressure is usually contributory rather than primary. In theory the restoration of the COP by giving albumin should be beneficial, but this is rarely done. Plasma albumin concentrations in the critically ill can be maintained only if the patient's condition begins to improve.
- Increased alveolar pressure. PEEP is now believed to increase the capacity of the interstitium to hold fluid. (The pulmonary interstitium can accommodate 500 ml with an increase in pressure of only 1.5 mmHg.) PEEP also increases alveolar recruitment.

The neuromuscular junction

Commentary

If you are asked about the neuromuscular junction it is almost inevitable that the viva will include questions about neuromuscular blockers and the assessment of neuromuscular blockade. If, on the other hand, you are asked about either of the two latter topics you may not be required to discuss the neuromuscular junction in any detail. It is for this reason that the account below is somewhat simplified.

The viva

You will be asked about the generation of a muscle action potential.

- Acetylcholine (ACh) is formed in the motor nerve terminal (by the acetylation of choline, catalysed by choline-*O*-acetyltransferase). Much of the synthesised ACh is stored in vesicles.
- ACh release is triggered by the motor nerve action potential. In response to depolarisation, voltage-gated channels permit an inward flux of calcium which stimulates release into the junctional gap. (This itself is complex, involving the activation of a number of improbably named proteins which facilitate the process: synaptotagmin, syntaxins, synaptophysin and synaptobrevin. Synaptobrevin is of passing interest because it is inhibited by botulinum toxin which thereby prevents ACh release and muscle contraction.)
- Pre-junctional nicotinic cholinergic receptors modulate further ACh mobilisation and release via a positive feedback mechanism.
- ACh acts at the post-junctional nicotinic receptor, whose structure has been fully identified. It consists of five glycoprotein subunits characterised as α (2), β, δ and ϵ which form a central ionophore (ion channel). Binding of one molecule of ACh to one of the two α units facilitates the binding of a second, during which the receptor undergoes an evanescent conformational change and the ionophore opens. A net influx of sodium ions then depolarises the muscle cell membrane.
- The ACh in the cleft will interact with an α unit only once before being broken down within 100 μs by the acetylcholinesterase in the junctional folds of the muscle membrane.

Direction the viva may take

You may be asked about the action of neuromuscular blocking agents. (For more details about specific agents see *Neuromuscular blocking drugs*, page 214, and *Suxamethonium*, page 216.)

- **Structures:** All are quaternary amines, whose potency is increased if the molecule contains two quaternary ammonium radicals. (Pancuronium is bisquaternary whereas vecuronium is monoquaternary.)
- **Depolarising block:** Suxamethonium is the only therapeutic depolarising neuromuscular blocker, but agonists at nicotinic cholinergic receptors can have a similar effect. Anticholinesterases given in the absence of non-depolarising block, for example, may themselves cause blockade. Following depolarisation of the muscle membrane suxamethonium remains bound to the receptor for some minutes, during which time muscle action potentials are prevented.
- **Phase II block:** This is a post-junctional non-depolarising ion channel block which accompanies the prolonged action or accumulation of suxamethonium. The block is also characterised by impairment of pre-junctional acetylcholine release. This probably explains why anticholinesterases may reverse the block, although the advice to do so is not universal.
- **Non-depolarising block:** Non-depolarising blockers are competitive inhibitors of ACh at the post-junctional nicotinic receptors. They bind to one or both of the α units to prevent ACh access, but they induce no conformational change in the

receptor. Receptor occupancy needs to be at least 80%, depending on the surgery that is planned, and it is important to recognise that the sensitivity of muscle groups is very different. The pattern appears to be the same across all mammalian species such that the muscles of facial expression, including the ocular muscles, and the muscles of the distal limb (including the tail) are much more sensitive than the diaphragm. Thus only 20% receptor blockade is sufficient to paralyse the tibialis anterior muscle, whereas the diaphragm requires 90%.

Further direction the viva could take

You are likely to be asked to describe how neuromuscular block may be assessed.

- **Clinical signs:** Grip strength, the generation of a tidal volume of between 15 and 20 ml kg^{-1} and the ability to keep the head lifted from the pillow for 5 s are cited as useful indicators of recovery from neuromuscular block.
- **Nerve stimulators:** The degree of block can be assessed using a battery operated nerve stimulator that is capable of delivering different patterns of square wave pulses of uniform amplitude. The stimulus that is delivered should be supramaximal to ensure recruitment of all the muscle fibres. The stimulus is usually transcutaneous.
- **Single twitch:** A decrease in twitch height will be apparent only after 75% or more receptors are blocked, so this is of limited use in monitoring non-depolarising block. It can be used for assessing block due to depolarising relaxants (which do not exhibit fade or post-tetanic facilitation).
- **Train-of-four (TOF):** Four identical stimuli are delivered at 2 Hz and repeated every 10 s. The number of twitches observed corresponds approximately to the percentage receptor blockade. (0 twitches = 100% blockade, 1 twitch = 90%, 2 twitches = 80%, 3 twitches = 75% and 4 twitches = <75%.) The ratio of twitch heights can be quantified to give an objective measure of block. The T_4:T_1 ratio must be 90% before it can be assumed that protective airway reflexes are intact.
- **Double burst stimulation (DBS):** Two tetanic bursts at 50 Hz and separated by 750 ms are applied every 20 ms. The muscle response is detectable as two twitches which show a more exaggerated fade than that of the TOF. It is more sensitive at detecting residual block, which makes it of particular value at the end of surgery.
- **Tetanic stimulation:** Stimuli of 50 or 100 Hz for 5 s may produce fade in situations when the twitch response after TOF or DBS has returned to normal. It is therefore a more sensitive means of detecting low levels of receptor blockade. It cannot be used in the conscious patient who may be aware of marked residual discomfort even if the stimulus has been applied during anaesthesia.
- **Post-tetanic count (PTC):** A tetanic stimulus as above is followed by single stimuli at 1 s intervals. Tetany triggers supranormal ACh release (post-tetanic facilitation) which transiently overcomes the neuromuscular blockade. The twitches which result comprise the PTC. The technique is used to monitor significant degrees of block (for example in neurosurgery during which any patient movement could be disastrous), and a PTC of less than 5 indicates profound block. A PTC of greater than 15 approximates to two twitches following TOF stimulation, at which point pharmacological reversal should be possible.
- **Mechanomyography, electromyography and acceleromyography:** These methods allow much more accurate methods of measuring neuromuscular blockade during onset and offset of effect. Such accuracy is not necessary during routine clinical practice and these instruments are used mainly in research. Details of their function will not be expected of you.

Nitric oxide

Commentary

At the last count there were approaching 5000 research publications on this ubiquitous molecule, whose importance has been recognised only since the 1980s. Much as you might wish to share your exploration of this enormous body of work, the 8 min of the viva will not allow it, and a broad overview is all that can reasonably be expected. Although it appears to mediate such a large number of functions its direct implications for anaesthesia are disappointingly modest. You will, however, need to know some of the basic details of its synthesis and chemistry, as well as those areas of anaesthetic practice and pharmacology for which nitric oxide (NO) does has some relevance.

The viva

You may be asked to describe NO and its functions.

- **NO:** NO is a free radical gas which is formed in a reaction between molecular oxygen and L-arginine. The reaction is catalysed by NO synthetase (NOS) and leads to the formation of NO and citrulline.
- **NOS isoforms (iNOS, eNOS and nNOS):** There are three NOS isoforms. The single inducible form, iNOS, is expressed in response to pathological stimulation in a variety of cells, including macrophages, neutrophils and endothelial cells. It is induced by several chemical mediators such as IL, γ-interferon and tumour necrosis factor. The two constitutive forms are eNOS, which is present in endothelium (and some other cells such as cardiac myocytes and platelets), and nNOS, which is present in neurones. The activity of the constitutive isoforms of NOS is governed by intracellular calcium-calmodulin, whereas iNOS is calcium independent. The quantity of NO generated by iNOS exceeds by about a thousand times that which is formed by the constitutive enzymes.
- **Actions:** NO appears to be a central signalling molecule, which modulates many aspects of physiological function. As endothelium-derived relaxing factor (EDRF) it regulates blood pressure and regional blood flow, as well as limiting platelet aggregation. As a neurotransmitter it may have a role centrally in memory, consciousness and CNS plasticity. Its peripheral roles include gastric emptying. An absence of nNOS is characteristic of infants with hypertrophic pyloric stenosis. It has a non-specific role in the immune system, and by mechanisms such as the inactivation of haem-containing enzymes and nitrosylation of nucleic acids can destroy pathogens and tumour cells.
- **Cardiovascular effects:** NO is a small lipophilic molecule which diffuses rapidly across cell membranes to combine with thiol groups to form nitrosothiol compounds. NO binds to the iron moiety to activate soluble guanylyl cyclase. This enzyme catalyses the formation of cyclic guanosine monophosphate (cGMP) with the activation of protein kinases, protein phosphorylation and finally the relaxation of vascular smooth muscle.
- **Inactivation:** NO is a free radical gas that has a half-life measured in seconds (variously quoted as 0.50–1.0 s up to 5 s). It is inactivated after forming complexes with haemoglobin, and with other haem-containing molecules. The affinity of haem for NO is more than 10,000 greater than its affinity for oxygen. NO is also inactivated by a series of oxidation reactions that produce nitrate. This is then excreted renally.

Direction the viva may take

You are likely to be asked about the anaesthetic relevance of this molecule.

- **Vasodilators:** The nitrovasodilators such as GTN and SNP act by producing exogenous NO in a reaction mediated by glutathione-S-transferase and cytochrome p450. Vascular smooth muscle is constantly in state of NO-mediated

vasodilatation, NO being formed in response to shear stresses in the vessel wall, but the venous circulation has a lower basal release. This is the reason why drugs such as GTN and SNP are more effective dilators of the venous rather than the arterial circulation. NO deficiency may contribute to hypertension or organ ischaemia.

- **Interactions with volatile anaesthetics:** Volatile agents inhibit NO synthetase and so reduce NO production from endothelial cells. The end effect of volatile administration is not vasoconstriction, however, because NO inhibition is offset by direct mechanisms which influence vascular smooth muscle tone. It has been argued, although not universally accepted, that NOS inhibition by volatiles may decrease MAC, that NO influences conscious level, and that it may have a role as one of the mediators of general anaesthesia.
- **Inhaled NO:** The half-life of NO is very short and so when the gas is inhaled it acts to reduce PVR without exerting any systemic effects. It may therefore be of use in patients with intrapulmonary shunts typical of conditions such as ARDS. Systemic administration causes indiscriminate pulmonary vasodilatation, which can only worsen the ventilation–perfusion mismatch. Inhaled NO, in contrast, is delivered to better-recruited alveoli where it dilates the associated pulmonary vessels and reduces shunt fraction. It is also a bronchodilator. In theory its use should benefit patients with impaired right heart function and those with pulmonary hypertension. Clinical experience is probably greatest in the treatment of neonates with respiratory distress syndrome. Although it has also been used to treat ARDS there is no evidence that it is superior to other strategies such as prone ventilation, and difficulties with safe delivery systems have also limited its use.
- **Delivery:** This can be problematic because at concentrations greater than around 100 parts per million (ppm) the free radical gas is highly reactive and toxic. It is stored in nitrogen in a concentration of 1000 ppm, and has been given in doses that range from 250 parts per billion up to 80 ppm.

Control of breathing

Commentary

This question has many potential complexities, but there will be insufficient time to cover these in any detail. However, because the control of breathing is an important part of anaesthetic practice you should try to convey the impression that you could talk about various aspects at length, if only you were given the opportunity.

The viva

You will be asked to describe the factors that control breathing.

- **Overview:** The control of breathing is coordinated by centres within the CNS, by receptors in respiratory muscles and the lung, and by specialised chemoreceptors such as the carotid bodies.
- **Respiratory centre:** A brainstem 'respiratory centre' mediates automatic rhythmic breathing, which is influenced by physical and chemical reflexes. Breathing is a complex activity, which can be interrupted by coughing, vomiting, sneezing, hiccoughing and swallowing. It is also subject to voluntary control from the cerebral cortex to allow activities such as singing, reading (during which the cortex computes the appropriate size of breath for the proposed segment), speech and vigorous exercise (during which expiration may be almost entirely an active process).
- **Inputs:** The 'centre' is in the medulla, where the respiratory pattern is generated and where the voluntary and involuntary impulses are coordinated. It contains receptors for excitatory neurotransmitters such as glutamate (whose activity is inhibited by opiates) and inhibitory neurotransmitters such as GABA and glycine. The centre receives a large number of afferents from the cortex, from the vagus, from the hypothalamus and from the pons. An area in the upper pons, the pontine respiratory group (formerly known as the pneumotaxic centre), contributes to fine control of respiratory rhythm by influencing the medullary neurones, which comprise two main groups.
- **Dorsal respiratory neurones:** These are primarily inspiratory, and are responsible for the basic ventilatory rhythm.
- **Ventral neurones:** These are predominantly expiratory.
- **Reciprocal innervation:** As activity increases in one or other of these groups of neurones, so inhibitory impulses are relayed from the other, resulting eventually in the reversal of the respiratory phase.
- **Central chemoreceptors:** These lie on the anterolateral surface of the medulla, and are acutely sensitive to alterations in H^+ ion concentration. A rise in P_aCO_2 increases CSF PCO_2, cerebral tissue PCO_2 and jugular venous PCO_2 (which all exceed P_aCO_2 by about 1.3 kPa or 10 mmHg). This rise in CSF PCO_2 decreases CSF pH. This acidosis stimulates chemosensitive areas by a mechanism that has not precisely been elucidated. Respiratory acidosis stimulates greater ventilatory change than metabolic acidosis, despite the same blood pH, because the blood–brain barrier is permeable to CO_2 but not to H^+ ions. Over a period of hours this CSF acidosis is corrected by the bicarbonate shift.
- **Peripheral chemoreceptors:** These are located in the carotid bodies, which are small structures, of volume of only around 6 mm^3, which are found close to the bifurcation of the common carotid artery, and in the aortic bodies along the aortic arch. Afferents from the carotid bodies travel via the glossopharyngeal nerve, while those from the aortic bodies travel via the vagus. These are sensitive primarily to hypoxia, but as sensors of arterial gas partial pressures are less sensitive to a decline in oxygen content. This means that they mediate minimal respiratory stimulation in patients who are anaemic, or when there is carboxyhaemoglobinaemia. Their response time is of the order of 1–3 s. They are stimulated minimally by an increased CO_2. Acidaemia stimulates respiration,

regardless of whether its cause is metabolic or respiratory. This rapid response is mediated via the peripheral chemoreceptors. Pyrexia is another stimulus mediated via the peripheral chemoreceptors, and which also enhances the responses to hypercapnia and hyoxia. Hypoperfusion is also a stimulant, presumably due to 'stagnant' hypoxia. Peripheral chemoreceptor stimulation may also mediate increases in bronchiolar tone, adrenal secretion, hypertension and bradycardia. Aortic body stimulation has a proportionately greater effect on the circulation. (The nerves to the carotid bodies may be lost during carotid end-arterectomy. The subsequent loss of hypoxic ventilatory drive is not in most circumstances significant.)

- **Mechanoreceptors:** Mechanical as well as chemical stimulation of pulmonary receptors leads to afferent input to the respiratory centre by the vagus nerve. Their importance remains contentious, since patients with denervated transplanted lungs or with (experimental) bilateral vagal block demonstrate normal ventilatory patterns. The inflation reflex comprises the inhibition of inspiration in response to an increased transmural pressure gradient with sustained inflation. In the deflation reflex, inspiration is augmented via a reflex excitatory effect in response to the decrease in lung volume.

Direction the viva may take

You may be asked about the ventilation–response curves that can be drawn following changes in P_aCO_2 and P_aO_2.

- ***P_aCO_2*/ventilation–response curve:** In response to an increase in P_aCO_2 there is an increase in respiratory rate and depth. This response is linear over the range of usual clinical values, although the slope varies. There is interindividual variation and the slope is also altered by disease, drugs and hormonal changes. The minute volume for a given increase in P_aCO_2 is influenced by the P_aO_2, so that a lower P_aO_2 shifts the line up and to the left, leading to a greater increase in minute ventilation.
- ***P_aO_2*/ventilation–response curve:** This curve is a rectangular hyperbola, asymptotic to the ventilation at high P_aO_2 (when there is zero hypoxic drive) and to the P_aO_2 at which theoretically ventilation becomes infinite at around 4.3 kPa. The response is easier to gauge if it is linear, and a graph of ventilation plotted against oxygen saturation is linear down to about 70%.

Further direction the viva could take

You may be asked about the influence of anaesthesia on these mechanisms.

- **Anaesthetics:** All anaesthetic agents have a depressant effect on the initial ventilatory response to hypoxia by the peripheral chemoreceptors. They also depress the response to increases in P_aCO_2 (shifting the line of the CO_2 response curve down and to the right).
- **Hypoxia:** Hypoxia has a direct depressant effect on the respiratory centre. Should the medulla be subjected to severe ischaemic or hypoxic hypoxia, then apnoea will result.
- **Opiates:** Their powerful central respiratory depressant action at the medulla is well known.
- **Respiratory stimulants:** Drugs such as doxapram and almitrine act at peripheral chemoreceptors. The mechanism of action remains unclear, but their effects may be mediated via products of their own metabolism.

Apnoea and hypoventilation

Commentary

Questions about breathing and gas exchange can come from different angles, and so you may be asked what happens during apnoea (either obstructed or non-obstructed) and about the consequences of hypoventilation. Neither of these patterns of respiration is uncommon in anaesthetic practice and so you will be expected to explain them with some clarity.

The viva

You will be asked what happens to arterial blood gases during apnoea.

P_aO_2

- **Obstructed apnoea:** The basal requirement for oxygen is around 250 ml min^{-1}. The FRC in an adult is about 2000–2500 ml (21% of which is oxygen). Under normal circumstances, therefore, if a patient obstructs when breathing air, the oxygen reserves will be exhausted in about 2 min, and the partial pressure will fall from the normal 13 kPa down to about 5 kPa. The lung volume also falls, by the difference between the oxygen uptake and CO_2 output (which ceases).
- **Non-obstructed apnoea:** If the airway is patent the lung volume does not fall because ambient gas is drawn into the lungs by mass movement down the trachea. If the ambient gas is room air then hypoxia will occur almost as swiftly as it does in obstructed apnoea. If, however, the ambient gas is 100% oxygen then it will take about 100 min before hypoxia will supervene. (This assumes that the patient has effectively been pre-oxygenated by breathing 100% oxygen prior to becoming apnoeic.)
- **Rate of oxygen desaturation:** This depends on the alveolar oxygen (P_AO_2), the FRC and the oxygen consumption.
  - — *Oxygen reserves*: These are mainly in the alveoli. The circulating oxygen is sufficient to maintain metabolism for only 2–3 min, and there is no real 'storage' capacity. Efficient pre-oxygenation (either for 3–5 min or with three VC breaths) will replace alveolar air with 100% oxygen. If nitrogen washout has been completed then 8–10 min may elapse before desaturation starts to take place.
  - — *Lung volume*: The volume of the FRC decreases in pregnancy, in the obese and with some forms of pulmonary disease. FRC is decreased or is exceeded by closing capacity in the children up to the age of 6 years and adults (in the supine position) over the age of 44 years.
  - — *Oxygen consumption*: This is increased by any rise in metabolic rate such as is seen in children, in pregnancy, thyroid disease, sepsis and pyrexia. It is decreased by hypothermia, myxoedema and a range of drugs, including anaesthetic agents.

P_aCO_2

- **P_aCO_2:** During apnoea CO_2 elimination stops and arterial CO_2 rises, at a rate of between 0.4 and 0.8 kPa min^{-1}. (In patients in whom the metabolic rate may be low, as in a patient undergoing tests for brain stem death, this rate of rise may be slower.) The body stores of CO_2 total around 120 l (compared with 1.5 l of oxygen). In non-obstructed apnoea the CO_2 still rises, because elimination via convection or diffusion is opposed by the mass inward movement of ambient gas.
- **Effect on oxygenation:** As the P_aCO_2 and P_ACO_2 rise the P_AO_2 falls, by an amount that can be quantified by the alveolar gas equation, which states that the $P_AO_2 = P_IO_2 - P_ACO_2/RQ$. (The P_IO_2 is obtained by multiplying the inspired oxygen fraction by the atmospheric pressure and subtracting the saturated vapour pressure of water, 47 mmHg or 6.3 kPa.

$P_IO_2 = F_IO_2 \times$ BPatm − SVP H_2O.) This means that if a patient who is breathing room air has a P_ACO_2 of 12 kPa, their P_AO_2 will fall to only 5 kPa.

Direction the viva may take

You may be asked about hypoventilation.

- The relations of alveolar gas tensions to alveolar ventilation are described by rectangular hyperbolas (concave upwards for eliminated gases such as CO_2 and concave downwards for gases that are taken up by the lung, such as oxygen).
- In the case of the P_ACO_2 this relationship (which is given by the equation: $P_ACO_2 = CO_2$ output/alveolar ventilation) means that if the alveolar ventilation halves the P_ACO_2 will double. From the alveolar air equation above this makes it inevitable that a hypoventilating patient who is breathing air will become hypoxic.
- Oxygen enrichment to 30% will increase the P_AO_2 by almost 9 kPa, thereby restoring it almost to normal (while having no effect on the P_ACO_2).

Further direction the viva could take

You may be asked if this information has any further clinical implications or applications.

- **Respiratory failure:** Supplemental oxygen will ensure that oxygen saturations remain high even in the presence of a high P_ACO_2. This may mask ventilatory failure.
- **Apnoeic oxygenation:** This technique is used during the apnoea test for brain stem death testing, when P_aCO_2 must rise to 6.6 kPa or above. Oxygenation can be achieved by simple insufflation. It can also be used during airway endoscopy and at critical points of complex upper airway surgery. The rise in P_aCO_2, however, is inevitable, and should it reach too high a level will lead to a respiratory acidosis and exert negative inotropic effects on the myocardium (at around 9.0 kPa). It also influences CBF, which increases in a linear fashion by around 7.5 ml 100 g^{-1} min^{-1} for each 1 kPa rise from baseline, to maximal at 10.5 kPa, above which no further vasodilatation is possible. CO_2 narcosis will occur at a P_aCO_2 of around 12 kPa in non-habituated individuals.

Central venous pressure and cannulation

Commentary

Central venous catheters are used widely in critical care and in major anaesthetic cases, and so although the underpinning principles are not complex, questions on the topic reappear. You will be expected to understand how to interpret measurements and the normal waveform, to know how to insert the devices and to be familiar with most of the long list of potential complications.

The viva

As an introduction to the subject you will probably be invited to list the indications for central venous catheterisation before being asked to discuss CVP measurement.

- **Indications:** CVP catheters are used for the monitoring of CVP, for the insertion of pulmonary artery catheters, and to provide access for haemofiltration and transvenous cardiac pacing. Central venous lines also allow the administration of drugs that cannot be given peripherally, such as intropes and cytotoxic agents, and the infusion of total parenteral nutrition (TPN). It is suggested that they can be used to aspirate air from the right side of the heart after massive air embolism, although very few anaesthetists have ever used them for this purpose.
- **Function of CVP monitoring – intravascular volume:** The CVP is the hydrostatic pressure generated by the blood within the right atrium (RA) or the great veins of the thorax. It provides an indication of volaemic status because the capacitance system, including all the large veins of the thorax, abdomen and proximal extremities, forms a large compliant reservoir for around two-thirds of the total blood volume. Hypovolaemia may be actual or effective, due for example to subarachnoid block or sepsis, in which loss of venoconstrictor tone or venodilation decreases venous return and reduces CVP.
  A single reading may be unhelpful, whereas trends are more useful, particularly when combined with fluid challenges.
- **Function of CVP monitoring – RV function:** CVP measurements also provide an indication of right ventricular (RV) function. Any impairment of RV function will be reflected by the higher filling pressures that are needed to maintain the same SV.
- **Normal values:** The normal range is 0–8 mmHg, measured at the level of the tricuspid valve. The tip of the catheter should lie just above the RA in the superior vena cava.
- **CVP decreases:** If the blood volume is unchanged then the CVP will alter with changes in cardiac output . It will fall as the cardiac output rises because the rate at which blood is removed from the venous reservoir also increases. This reflects the essentially passive volume–pressure characteristics of the venous vascular system. The major cause of a fall in CVP is depletion of effective intravascular volume. (Raising the transducer will lead to an apparent fall in CVP.)
- **CVP increases:** Potential causes for an increase in CVP include a fall in cardiac output (the converse of the effect described above). Ventilatory modes may also cause the increase which is seen with IPPV, PEEP and CPAP. The CVP rises in response to volume overload, if there is RV failure, pulmonary embolus, cardiac tamponade or tension pneumothorax. Rarer causes include obstruction of the superior vena cava (assuming that the catheter tip lies proximally), and portal hypertension leading to inferior vena caval backpressure. Moving the reference point and lowering the transducer will also lead to an apparent increase.

The normal pressure waveform

- This comprises three upstrokes (the 'a', 'c' and 'v' waves) and two descents (the 'x' and 'y') that relate to the cardiac cycle.
- **'a' wave:** This occurs at the end of diastole and is due to increased **a**trial pressure as the atrium contracts (occurs at end-diastole).

- **'x' (or 'x'') descent:** This reflects the fall in atrial pressure as the atrium relaxes.
- **'c' wave:** This supervenes before full atrial relaxation, and is due to the bulging of the closed tricuspid valve into the atrium at the start of isovolumetric right ventricular contraction.
- **'x' descent:** This is a continuation of the 'x'' descent (interrupted by the 'c' wave) and represents the pressure drop as the ventricle and valve 'screw' downwards at the end of systole.
- **'v' wave:** This is the increase in right atrial pressure as it is filled by the venous return against a closed tricuspid valve.
- **'y' descent:** This reflects the drop in pressure as the RV relaxes, the tricuspid valve opens, and the atrium empties into the ventricle.
- Any event that alters the normal relationship between the events above, will alter the shape of the waveform. For example, in atrial fibrillation the 'a' wave is lost; in tricuspid incompetence a giant 'v' wave replaces the 'c' wave, the 'x' descent and the 'v' wave. 'Cannon' waves are seen when there is atrial contraction against a closed tricuspid valve (as occurs at a regular interval if there is a junctional rhythm, or at an irregular interval if there is complete atrioventricular conduction block).
- **Complications of insertion:** These are numerous and include arterial puncture (carotid and subclavian), haemorrhage, air embolism, cardiac dysrhythmias, pneumothorax, haemothorax, chylothorax, neurapraxia, cardiac tamponade and thoracic duct injury. Anatomically proximate structures such as the oesophagus and trachea can also be damaged. Parts of catheters or entire guide wires can embolise into the circulation. Complications associated with catheter insertion can be reduced by using ultrasound guidance. Endocarditis and cardiac rupture have been reported. Venous thrombosis is common, but the risk may be reduced by the use of heparin-bonded catheters. Infection is a problem, and occurs in up to 12% of placements. Its risk is reduced by full aseptic precautions, by the use of antiseptic and antibiotic coated catheters (in high risk patients), and by using the subclavian approach. There is no definite evidence of benefit for tunnelling, for prophylactic line changes or for the use of prophylactic antibiotics.

Direction the viva may take

You may be asked what information a CVP reading provides about LV function.

- The right atrial pressure reflects the right ventricular end diastolic pressure (RVEDP) and it is frequently assumed that this also reflects LVEDP. This is not strictly true, even in health, because the RV ejects into a low pressure system and so the normal RV function curve (in which SV is plotted against filling pressure) is steeper than the LV curve. This means that for a given fluid load the increase in SV of each ventricle is identical, but the rise in filling pressure in the LV exceeds that in the right. This discrepancy is accentuated by LV dysfunction, and under these circumstances, accurate diagnostic information has to be obtained by other means.

Further direction the viva could take

CVP measurements are sometimes recorded as negative values. You may be asked to explain how this can happen.

- If the CVP is measured from the accurate reference point of the tricuspid valve then a sustained negative intravascular pressure is impossible. Certainly the negative intra-thoracic pressure during inspiration will be transmitted to the central veins, and if there is respiratory obstruction this negative pressure will be high. It will, however, be transient. If a mean CVP reading is consistently negative it can only be because the transducer has been placed above the level of the RA.

Physiology of the infant and neonate

Commentary

The scope for asking basic science questions that are related to paediatric practice is quite restricted, and so topics tend to be limited to aspects of infant anatomy and physiology. Physiology is probably asked more commonly than anatomy because it is inherently more complex. Questions about a single physiological function would be unlikely to fill the time available, and so the discussion tends to be more wide ranging. This means that examiners will expect breadth rather than depth of knowledge in this specialist area.

The viva

You are likely to be asked to describe the physiological characteristics of the infant (defined as a child aged between 1 month and 1 year). Make reference to the neonate, by all means, because the youngest children exemplify the differences between paediatric and adult practice. An approach based on systems has become almost invariable.

Surface area to mass ratio

- The smaller the child the larger is the ratio of surface area to mass, so that in the neonate it is 2.5 times that of the adult. This difference explains many of the physiological characteristics.

Cardiovascular system

- The need to maintain body temperature via heat production results in a higher BMR and higher tissue oxygen consumption, which at 7 ml $kg^{-1}min^{-1}$ is twice that of an adult.
- Cardiac output, which at birth is 200 ml $kg^{-1}min^{-1}$ (100 ml $kg^{-1}min^{-1}$ in the adult) increases predominantly by an increase in HR rather than SV.
- Blood volume is 80 ml kg^{-1} at term, and 75 ml kg^{-1} at age 2. The haemoglobin concentration at birth is 16–18 g dl^{-1} (80% HbF) dropping to 10 g dl^{-1} at 3 months and rising to 12–14 g dl^{-1} at 1 year.
- Infants demonstrate increased sensitivity to vagal stimulation. The limbs are smaller in relation to the body, so there is less reserve blood volume to mobilise from the periphery.

Respiratory system

- Alveoli at birth number 20–50 million, and they are structurally underdeveloped. By 18 months they total 300 million, and thereafter grow in size rather than number. The FRC is small and desaturation occurs quicker.
- The high BMR is associated with a high respiratory rate. Respiratory compensation occurs via an increase in respiratory frequency more than increases in tidal volume. Infant ribs are more horizontal and so are mechanically less efficient. The compliant chest wall is unable effectively to oppose the action of the diaphragm to maintain the FRC. Respiration is predominantly diaphragmatic and the intercostal and accessory muscles are relatively weak, being deficient in Type 1 muscle fibres until around the age of 2 years. (Tidal ventilation is 7 ml kg^{-1}, as in older children and adults.) Infants respond to hypoxia with bradypnoea rather than tachypnoea.
- Decreased compliance (because of poorly developed elastic tissue) means that ventilatory units have short time constants, so alveolar ventilation is maintained at the expense of a high respiratory rate, high work of breathing and high oxygen consumption (15% of the total).
- Closing capacity exceeds FRC (up to the age of 6 years) and infants generate physiological CPAP (of around 4 cmH_2O) by partial adduction of the cords

during expiration. The 'grunting' of a premature neonate in respiratory difficulty is an exaggeration of this mechanism.
- Pre-term infants are at risk of sudden apnoeic episodes (defined as cessation of breathing for 15 s or more). This applies up to around 60 weeks of post-conceptual age, and is a manifestation of poor maturation of ventilatory control.

Temperature control
- Thermoregulation is immature in the infant. A large surface area is associated with increased heat loss, and neonates are especially vulnerable to rapid hypothermia. Infants aged less than 3 months do not shiver, but generate heat via non-shivering thermogenesis from brown fat, which comprises up to 6% of the body weight of the term fetus. Heat is generated by the catecholamine-mediated metabolism of fatty acids.

Renal system
- Infant kidneys have a reduced GFR (which at 65 ml min^{-1} is half that of the adult), diminished tubular function and sodium excretion and a decreased concentrating ability. Sodium loss is inevitable and there is limited ability either to conserve or excrete water, so infants tolerate hypovolaemia or over-transfusion badly. The excretory load is mitigated partially by the 50% of the nitrogen that is incorporated into growing tissue. Renal function is mature at about 2 years of age.

Central nervous system
- Neurological development continues in the early years of life with the completion of myelination of the brain and spinal cord. The sympathetic nervous system is also incompletely developed which explains the tolerance of central neuraxial blockade. The blood–brain barrier is immature, which increases the neonate's, and to a lesser extent the infant's sensitivity to opiates and other CNS depressants. By 6 months of age the response to morphine is probably the same as in adults.

Gastrointestinal system
- The incidence of neonatal gastro-oesophageal reflux is high (coordination of swallowing with respiration does not mature until around 4–5 months) but this rarely proves to be a problem in clinical practice.

Drug effects
- A combination of factors influences the response of the neonate and infant to drugs. CNS depressants may have enhanced effects both because the blood–brain barrier is less effective and because CBF accounts for a greater proportion of the cardiac output. TBW is higher and so water-soluble drugs have a larger volume of distribution and may require higher initial doses. (Suxamethonium is an example.) Fat-soluble drugs may have a longer clinical effect because lower stores of body fat decrease redistribution. Plasma protein levels are lower and so free diffusible drug levels may be higher. Enzymatic function, particularly that associated with hepatic phase II conjugation reactions, is also immature. This may delay metabolism and excretion of drugs.

Direction the viva may take
- The examiners may take any one of the systems discussed and ask you how it might influence your anaesthetic technique. Theoretical rather than practical knowledge will be expected, because they will assume that you probably will not have anaesthetised children as young as this.

Compliance

Commentary

Compliance is an important concept with clear implications for ventilatory management of patients, and this particular viva should divide quite evenly between the basic science and its clinical application. Make sure that you are able to draw the pressure–volume curves because they will inform the discussion of both parts.

The viva

You will be asked to define what is meant by 'compliance'.

- **Definition:** Compliance is defined by the change in lung volume per unit change in pressure. It has two components: the compliance of the lung itself, and the compliance of the chest wall. Lung compliance is determined both by the elastic properties of pulmonary connective tissue and by the surface tension at the fluid/air interface within alveoli. Both normal lung compliance and normal chest wall compliance are 1.5–2.0 kPa^{-1} (150–200 $ml\,cmH_2O^{-1}$). Total compliance is about 1.0 kPa^{-1} (100 $ml\,cmH_2O^{-1}$), and is determined from the sum of the reciprocals of the two values.
- **Static compliance:** A pressure–volume curve is obtained by applying distending pressures to the lung and measuring the increase in lung volume. The measurements are made when there is no gas flow. (The patient expires in measured increments and the intrapleural pressure at each step is estimated via oesophageal pressure.)
- **Dynamic compliance:** A pressure–volume curve is plotted continuously throughout the respiratory cycle.
- **Hysteresis:** The inspiratory and expiratory pressure–volume curves are not identical, which gives rise to a hysteresis loop. Hysteresis describes the process in which a measurement (or electrical signal) differs according to whether the value is rising or falling. It usually implies an absorption of energy, for example due to friction, as in this case. The area of the hysteresis loop represents the energy lost as elastic tissues stretch and then recoil (viscous losses) and as airway resistance is overcome (frictional losses).
- **Specific compliance:** Compliance is related to lung volume, and this potential distortion can be removed by using specific compliance, which is defined as compliance divided by the FRC. This correction for different lung volumes demonstrates, for instance, that the lungs of a healthy neonate have the same specific compliance as those of a healthy adult.
- **Factors which alter compliance:** ARDS and pulmonary oedema decrease respiratory compliance by reducing lung compliance. Restrictive conditions such as ankylosing spondylitis or circumferential thoracic burns reduce it by decreasing the compliance of the chest wall. Compliance is also decreased if the FRC is either higher or lower than normal. At high lung volumes tissues are stretched near their elastic limit, while at low volumes greater pressures are required to recruit alveoli. In acute asthma, therefore, patients are ventilating at a high FRC, at which the compliance is lower and the work of breathing correspondingly greater. Compliance is also affected by posture, being maximal in the standing position. Morbid or super obesity may reduce compliance both via a reduction in FRC and a decrease in chest wall compliance due to the cuirass of adipose tissue. Age has no influence.

Direction the viva may take

You may be asked about how different types of ventilator respond to a decrease in compliance.

- **Constant-pressure generators:** These ventilators generate an increase in airway pressure which produces inspiratory flow, whose rate depends on the

compliance and resistance of the whole system (patient and breathing circuit). The sudden initial mouth-alveoli pressure gradient produces high flow into the lungs, which then decreases exponentially as the lungs fill and the gradient narrows. In lungs with low compliance the alveolar pressure increases much more rapidly, the pressure differential reduces and inspiratory flow declines.

- **Constant-flow generators:** These ventilators produce an incremental increase in flow rate to generate a tidal volume that is a product of the flow rate and the inspiratory time. The pressure of the driving source is much greater than that in the airways, and so flow into the lungs is not affected by sudden decreases in pulmonary compliance or increases in airway resistance. The delivery of an unchanged tidal volume in the face of decreased compliance will, however, be associated with a more rapid increase in alveolar pressure and a higher airways pressure.

Further direction the viva could take

Anaesthetic interest in compliance relates particularly to the ventilatory management of patients with acute lung disease. You may be asked about your approach to a patient with severely reduced compliance, such as that typically associated with ARDS.

- Pressure–volume curves are useful but they may oversimplify what is happening in the lung. Accurate dynamic compliance curves can be difficult to generate in diseased lungs, but more importantly the final curve represents the total rather than the separate lung units whose individual compliance may be very different. In ARDS a third of the lung, typically, remains normal.
- The aim of ventilation is optimise oxygenation without incurring further lung damage. This damage has been attributed more to volutrauma, with overdistension of alveoli, than to barotrauma *per se*. The excessive shearing forces that can be generated during recruitment and derecruitment of alveoli appear to exacerbate the process not only by reducing surfactant but also by producing further cytokines.
- With reference to the static pressure–volume curve, the distending pressure should be kept below the upper inflection point so as to avoid over expansion, but above the lower inflection point so as to avoid derecruitment of alveoli. This is usually achieved using pressure-controlled ventilation on the steep linear part of the curve midway between the two points. Pressure-controlled ventilation reduces the peak airway pressure for a given mean airway pressure and minimises intrinsic PEEP.

You may be asked what else you might do to improve gas exchange in a patient with severe ARDS.

- **Inverse ratio ventilation:** Changing the I : E ratio from 1 : 2 to 2 : 1 or even 3 : 1 will increase the inspiratory time sufficiently to allow ventilation of lung units with prolonged time constants.
- **Non-conventional IPPV:** High frequency jet ventilation and high frequency oscillation can be used in an attempt to minimise peak airways pressures. Differential lung ventilation down a double-lumen tracheal tube may also have a place if the pulmonary characteristics are very dissimilar.
- **Prone ventilation:** This improves shunt and P_AO_2, because the pleural pressure gradient becomes more uniform. This maneouvre is as effective as inhaled NO at improving oxygen saturation.

Nutrition

Commentary

Nutrition has become a separate science, and in many hospitals there are specific teams which manage the needs both of the peri-operative surgical patient as well as the critically ill. You will nevertheless be expected to know something about it because nutrition is a topic that reappears in the examination. You will not have to know specific details of trace element or vitamin concentrations, but you can anticipate a broad discussion of the effects of starvation, of the indications for nutritional support, of the major components of feeds, and the place of enteral and parenteral routes of administration.

The viva

You may be asked to start by describing normal nutritional requirements and then the physiological changes that are associated with starvation.

- **Nutritional requirements – energy:** Basal expenditure can be judged from the Harris–Benedict equation (which links weight, height and age) or from nomograms. Kilocalorie needs range from around 30 kcal kg^{-1} in the non-stressed ambulatory state to 60 kcal kg^{-1} in sepsis or following major trauma. In severe burns, which exemplify an extreme catabolic state, patients may require 80 kcal kg^{-1}.
- **Nutritional requirements – protein:** This can be estimated empirically. Demands may range from 0.5–1.0 g kg^{-1} in the non-stressed state to 2.5 g kg^{-1} under conditions of extreme stress.
- **Assessment of nitrogen balance:** Each gram of nitrogen is equivalent to 6.2 g of protein or 30 g of muscle. In catabolic states patients are in negative balance. Losses can be determined over each 24 h period by measuring urinary urea and incorporating the value into a formula, a typical example of which is: 24 h nitrogen loss = (urinary urea mmol $24\,h^{-1} \times 0.028$) + 4. 0.028 is a factor that converts urea in millimoles to grams of nitrogen, and 4 g is the approximate total lost daily in faeces, skin, hair and urine as non-urea nitrogen.
- **Nutritional requirements – fluids:** A simple formula for basal requirements in a temperate climate is 100 ml kg^{-1} for the first 10 kg body weight, 50 ml kg^{-1} for the next 10 kg and then 20 ml kg^{-1} thereafter. To this total must be added the various losses as appropriate. (This formula can also be used to approximate normal kilocalorie requirements.)
- **Starvation:** Hepatic glycogen stores are depleted within 24–48 h, after which adipose tissue is the source of fatty acids for use as an energy substrate. A small number of cell types, among which are erythrocytes and cells in the renal medulla, can utilise only glucose, and this has to be provided via amino acids that are produced from protein breakdown. The CNS normally depends on glucose, but can function using ketones as an energy substrate. During prolonged fasting there is an obligatory protein loss of at least 20 g daily. (Catabolism is a form of accelerated starvation with glycogenolysis, lipolysis and proteolysis.)

Direction the viva may take

You may be asked about the indications for nutritional support in the surgical or in the critically ill patient, and about the routes by which it can be given.

- **Indications for nutritional support:** Cachectic patients with a pre-operative weight loss of 15% or more, or who have effectively been starved for over 10 days (because of dysphagia, for example) have improved outcomes if they receive nutritional support before surgery. There are numerous other indications including malabsorption due to small bowel resection, small bowel fistulae, radiation enteritis, intractable diarrhoea and vomiting and hyperemesis gravidarum.

- **Parenteral nutrition:** TPN may be necessary in specific cases, such as short bowel syndrome, but under most circumstances enteral feeding is preferred. Complications associated with the parenteral route include all those associated with central venous catheterisation, as well as the problems of impaired gastrointestinal structure and function, a loss of normal bowel flora with increased bacterial translocation, hepatic steatosis and acalculous cholecystitis. Infection is a significant risk and TPN has the added disadvantage of high cost.
- **Enteral nutrition:** In contrast, enteral feeding improves splanchnic blood flow, better maintains gastrointestinal tract integrity and is associated with greater nitrogen retention and enhanced weight gain. It also improves immune defences by increasing the secretion of IgA.
- **Calorie sources:** Carbohydrate (glucose) and protein (amino acids) provide 4 kcal of energy per gram, fat provides 9 $kcal\,g^{-1}$. (Alcohol provides 7 $kcal\,g^{-1}$.) Glucose-rich solutions are associated with hyperglycaemia and fatty infiltration of the liver, with excess CO_2 production which increases the respiratory quotient (RQ) to unity, with hyperinsulinaemia and fluid retention, hypophosphataemia causing reduced tissue oxygenation and with decreased immune function. Lipid administration (10% or 20% emulsion) reduces reliance on glucose as a calorie source with its attendant problems and provides essential fatty acids. Hyperlipidaemia can complicate its administration. Protein is given in the form of crystalline amino acids.
- **Additives:** These include extra electrolytes, where appropriate, together with phosphate and magnesium, trace elements including zinc, copper, manganese, chromium and selenium, and the full range of fat-soluble and water-soluble vitamins.
- **Other supplements:** Glutamine appears to improve energy utilisation and protein synthesis in skeletal muscle as well as enhancing both gut immunity and lymphocyte function. Arginine also improves lymphocyte function as well as influencing wound healing. Omega-3 fatty acids may modulate the inflammatory response to trauma and in sepsis.

4

Pharmacology

Chirality

Commentary

The science of chirality is somewhat indigestible, and you might well feel aggrieved were this to be the only pharmacology that you were given the opportunity to discuss in the examination. The introduction of laevobupivacaine and ropicaine, however, has given this subject some topical relevance, and so even if you cannot unravel the nomenclature convincingly, you will have to be prepared to talk about drugs which can be prepared as pure enantiomers. If you are struggling for facts it may help if you remember that in the case of the newer drugs, 'R' also stands for 'risky' and 'S' stands for 'safe'.

The viva

You will be asked to explain chirality.

- 'Chirality' is derived from the Greek, means *having handedness*, and defines a particular type of stereoisomerism. Right and left hands are mirror images of each other but cannot be superimposed when the palms are facing in the same direction. There are many drugs, including anaesthetic and related agents, which exist as right- and left-handed forms that are mirror images but which cannot be superimposed. These particular isomers are known as 'enantiomers' (substances of opposite shape), and this form of stereoisomerism is dependent on the presence of one more chiral centres, which typically comprise a carbon atom with four groups attached. These enantiomers have the capacity to rotate polarised light, and so are also known as optical isomers. Their physicochemical properties otherwise are identical. Confusion can arise because of the differing nomenclature that has been used to describe chiral substances.
- One convention describes optical activity: enantiomers that rotate plane polarised light to the right are described as (+). This is the same as (dextro) or (d). Enantiomers that rotate plane polarised light to the left are described as (−), which is the same as (laevo or levo) or (l).
- Another convention, which largely is historical, is based on the configuration of a molecule in relation to (+) glutaraldehyde, which arbitrarily was assigned a 'D' (not 'd') configuration. Compounds were denoted 'D' or 'L' according to comparison with the model substance, and the optical direction added where appropriate. It is recommended that this method of description be limited to stereoisomers of amino acids and carbohydrates.
- The currently accepted convention is that which assigns a sequence of priority to the four atoms or groups attached to the chiral centre. The molecule is described

as though it were being viewed from the front with the smallest group extending away from the viewer. If the arrangement of the largest to the smallest groups is clockwise, then the enantiomer is designated 'R' for *rectus*. If the arrangement is anticlockwise it is designated 'S' for *sinister*. The optical direction is then added to complete the description. This gives, for example, S(+) prilocaine, and R(+) tramadol. Drug manufacturers have contributed to residual confusion about nomenclature by calling S(−) bupivacaine 'laevobupivacaine', whereas logic dictates that it should have been called 'sinister bupivacaine'.

Direction the viva may take

You will be asked about its relevance for anaesthesia.

- Chiral drugs that are found in nature are usually single enantiomers, because they are synthesised enzymatically in reactions that are stereospecific. Such drugs include adrenaline (epinephrine), atropine, cocaine, ephedrine, hyoscine, morphine and noradrenaline (norepinephrine). All are laevorotatory and have the designation (l).
- Most synthetic chiral drugs are racemic mixtures, and in the case of the examples above, are less potent than the pure enantiomers because the d-forms are much less active. This is not surprising, because drug receptor sites are likely to contain chiral amino acids which are stereoselective.
- The clinical behaviour of the enantiomers, and in particular their toxicity, is related to the chiral form, which is of particular relevance to a number of anaesthetic-related compounds.
- **Local anaesthetics**
  - *Bupivacaine*: The S(−)-enantiomer has less affinity for, and dissociates quicker from myocardial sodium channels. The risk of cardiovascular and central nervous system (CNS) toxicity is reduced. The S(−)-enantiomer also exerts some vasoconstrictor activity.
  - *Ropivacaine*: This is the pure S(−)-enantiomer of propivacaine and this also is associated with a safer cardiovascular profile in overdose.
  - *Prilocaine*: The S(+)-enantiomer is a stronger vasoconstrictor and is metabolised more slowly than the R(−)-form which therefore produces higher concentrations of *o*-toluidine and a greater risk of methaemoglobinaemia.
  - *Lignocaine*: This is achiral.
- **Intravenous induction agents**
  - *Ketamine*: The S(+)-enantiomer has a greater affinity for its main binding site (the *N*-methyl-D-aspartate, NMDA receptor) and is up to four times as potent as the R(−) form. Its administration is also associated with fewer emergence and psychotomimetic phenomena, and it is now available (in Germany only) as a commercial preparation.
  - *Etomidate*: This presented as the pure R(+)-enantiomer; 'R' in this case standing for 'required effect' rather than 'risk'.
- **Volatile anaesthetic agents**
  - *Isoflurane, enflurane, desflurane and halothane*: These are all chiral compounds that show some stereoselectivity in action. This selectivity is too modest to warrant their production as pure enantiomers.
  - *Sevoflurane*: This agent is achiral.
- **Analgesics**
  - *Tramadol*: Tramadol is a racemic mixture of R(+) and S(−)-enantiomers. The (+)-enantiomer appears to have relatively low activity at μ-receptors, but the higher affinity of its main M1 metabolite results in a sixfold increase in analgesic potency. (The μ-effects in humans are not very impressive.) The S(−)-enantiomer acts to inhibit the re-uptake of noradrenaline and 5-HT within the CNS.

Nitrous oxide

Commentary

Not that long ago there were some candidates for the then equivalent of the Final FRCA who were very discomfited by a written question on the 'pharmacology of nitrous oxide' (N_2O). This was hardly surprising, because few anaesthetists then had much interest in the drug and it was ignored largely as being simply a carrier gas with modest analgesic properties. This perception did the complex pharmacology of the drug a disservice, and there followed an upsurge of interest, both in its potential toxicity as well as in its mechanisms of action. This interest appears now to be waning, but given the continued and ubiquitous use of N_2O, it remains a core anaesthetic agent about which quite detailed knowledge will be expected.

The viva

The pharmacology and toxicology are reasonably complex and so the topic may be introduced via a question about the place of N_2O in modern anaesthetic practice.

Advantages

- It is a useful carrier gas for more potent anaesthetic agents.
- It has a rapid onset and equilibration, due to its very low blood/gas partition coefficient of 0.47.
- The onset or induction of anaesthesia is accelerated via the second gas effect, in which the rapid uptake of N_2O from the alveoli increases the alveolar concentration of other agents.
- It is a potent analgesic (this is usually underestimated). The drug acts partly at opioid receptors and transiently has the potency of morphine. This is not surprising given data showing that entonox (N_2O/O_2) affords better pain relief during labour (effective analgesia in around 50% of mothers) than pethidine (effective analgesia in about 35%).
- It is a weak anaesthetic (MAC^{50} is 105%), but in combination with its analgesic actions, it does decrease the mean alveolar concentration (MAC) of other inhalational agents.

Disadvantages

- **Effect on air-filled spaces:** The diffusing capacity of N_2O relative to nitrogen is high (25 ×).
  - — *In non-compliant air-filled spaces*: Pressure increases (in the middle ear, in nasal sinuses, and in the eye if it has been filled with gas such as SF_6 after vitreo-retinal surgery). The pressure change is related arithmetically to the alveolar partial pressure of N_2O; so that the administration of 50% N_2O leads to a pressure increase of 0.5 atmospheres (atm).
  - — *In compliant air-filled spaces*: Volume increases (significant for pneumothoraces, bullae, bowel, air embolus, cuffs of tracheal tubes). After 4 h of 66% N_2O the volume of the bowel increases by 200%. The volume change is related geometrically to alveolar partial pressure of N_2O; the % increase is given by the final % N_2O divided by (1.0 − FiN_2O). So at 50% the volume increase is 50/0.5 = 100%. At 75% a pneumothorax will triple in size after 30 min of N_2O administration.
- **Bone marrow toxicity and neurotoxicity:** See below.
- **Emesis:** This is probably due to a combination of its sympathomimetic and opioid effects, together with the effects of bowel distension.
- **Second gas effect:** This results in diffusion hypoxia (which is of modest clinical relevance: it lasts less than 10 min and can be overcome with supplemental oxygen).

- **Respiratory depression:** There is an increase in respiratory rate to offset decreased tidal volume: this is common to all volatile agents, and is not a particular problem.
- **Cardiovascular system**
  - N_2O acts as a direct negative inotrope and chronotrope.
  - Cardiac contractility is decreased if cardiac function already impaired; its use exacerbates ischaemic change in any situation in which myocardial oxygen supply is exceeded by demand.
  - It is an indirect stimulant (via its sympathomimetic action).
  - It increases pulmonary vascular resistance in the presence of pre-existing pulmonary hypertension.
- **Greenhouse effect**
  - N_2O is a greenhouse gas: anaesthesia contributes about 1% of the global total.

Direction the viva may take

You may then be asked about mechanisms of action and its potential toxicity. Much is speculative and so a broad overview should be adequate.

Anaesthesia

- **Gamma amino butyric acid$_A$, GABA$_A$ (mainly inhibitory) and NMDA (mainly excitatory) receptors in the CNS:** N_2O appears to have no effect on $GABA_A$ receptors but does strongly inhibit NMDA-activated currents. There is concern that NMDA antagonists can be neurotoxic: which is a potential problem if N_2O is used alone under hyperbaric conditions. If $GABA_A$ agonist agents or facilitators (such as benzodiazepines) are used as in addition, they may exert a protective effect to offset this damage.
- **Dopamine receptors:** N_2O is stimulatory to dopaminergic neurones; this may mediate release of endogenous opioid peptides. This would explain why the effects of N_2O are partly antagonised by naloxone.

Analgesia

- **Opioid peptide release:** This occurs in the peri-aqueductal grey matter of the midbrain, and stimulates descending noradrenergic pathways which modulate pain processing via noradrenaline release. Noradrenaline acts at α_2-receptors in the dorsal horn.
- **Other theories:** N_2O may activate a supraspinal descending pain inhibition system with an increase in encephalinergic interneurones in the substantia gelatinosa of the cord. These endogenous encephalins inhibit transmission via substance P-dependent synapses.

Toxicity

- **Bone marrow toxicity and neurotoxicity**
  - A biochemical lesion in the liver (methionine synthetase inhibition) is demonstrable after only 40 min of N_2O administration.
  - N_2O oxidises the cobalt atom in vitamin B_{12} (cyanocobalamin) from Co^+ to Co^{2+} in a very simple reaction: vitamin B_{12}, however, is a co-factor for the enzyme methionine synthetase.
  - Methionine synthetase catalyses the transfer of a methyl group in a linked methyl-transferase reaction. The methylation of homocysteine forms methionine, while the demethylation of CH_3-tetrahydrofolate leads to the formation of tetrahydrofolate.
  - Inhibition of methionine synthesis, therefore, prevents the production of methionine and tetrahydrofolate. Methionine is a precursor of *S*-adenosyl methionine (SAM). SAM is incorporated into myelin, and its absence leads to subacute combined systems degeneration of the cord in chronic B_{12}

deficiency, and to dorsal column function impairment acutely (from experimental data after 48 h of N_2O 20% administration). Tetrahydrofolate is an important substrate involved in nucleotide and DNA synthesis (hence the development of megaloblastic anaemia in folate and B_{12} deficiency).
  - The administration of methionine and folinic acid will provide substrates to allow biosynthesis to continue below the level of the enzyme block.
- **Teratogenicity**
  - The mechanisms above plus its other actions are believed to contribute to possible teratogenicity: α_1-adrenoceptor agonism is associated with disorders of left/right body axis development (such as situs inversus). The association is not strong: almost 25 million administrations of the drug take place in the USA annually without obvious sequelae.

If you have exhausted the information above then you will be heading for a '2+', and so you might as well be equipped with a few final miscellaneous facts.

- *Malignant hyperpyrexia (MH)*: There is one definite case report, so N_2O is a weak trigger.
- Hyperbaric N_2O is excitatory leading to a threefold increase in respiratory rate, diaphoresis and cardiovascular α-adrenergic stimulation. At increased pressure N_2O becomes an anaesthetic (MAC is 105%) but it also causes CNS-mediated muscle rigidity and catatonic jerking.

Propofol

Commentary

Propofol is the most commonly used agent for induction of anaesthesia in the UK. It is used also in total intravenous anaesthesia (TIVA) and for sedation in intensive care. This makes it a central anaesthetic agent and so you will not be surprised that detailed knowledge will be expected. Having said that, however, the structured nature of the viva will constrain the examiners from concentrating in excessive detail on any one aspect of the topic.

The viva

The viva is likely to start simply with an invitation to discuss propofol.

- **Chemistry:** Propofol is a substituted stable phenolic compound: 2,6-di-isopropylphenol. It is highly lipid soluble and water insoluble, and is presented as either a 1% or 2% emulsion in soya bean oil. Other constituents include egg phosphatide and glycerol. It is a weak organic acid with a p*K*a of 11.
- **Mechanism of action:** In common with many other drugs which produce general anaesthesia, the mechanism of action is not fully elucidated. It appears to enhance inhibitory synaptic transmission by activation of the Cl^- channel on the β_1-subunit of the GABA receptor. It also inhibits the NMDA subtype of the glutamate receptor.
- **Clinical uses:** Propofol is used for the induction of anaesthesia in adults and children, for the maintenance of anaesthesia, for sedation in intensive care, and for sedation during procedures under local or regional anaesthesia. It has an anti-emetic action and can be given by very low-dose infusion to chemotherapy patients.
- **Dose and routes of administration:** The drug is used only intravenously. A dose of 1–2 mg kg^{-1} will usually induce anaesthesia in adults. Children may require twice this dose. Infusion rates for TIVA vary greatly, but typically would range between 4 and 12 mg $kg^{-1}h^{-1}$. Propofol is an effective anti-emetic when given at a rate of 1 mg $kg^{-1}h^{-1}$.
- **Onset and duration of action:** An induction dose of propofol will lead to rapid loss of consciousness (within a minute). Rapid redistribution to peripheral tissues (distribution half-life ($t_{1/2}$) is 1–2 min) leads to rapid awakening. The elimination $t_{1/2}$ is quoted at between 5 and 12 h.

Main effects and side effects

- **CNS:** Propofol causes CNS depression and induction of anaesthesia. It may be associated with excitatory effects and dystonic movements, particularly in children. The electroencephalogram (EEG) displays initial activation followed by dose-related depression. The data sheet states that it is contraindicated in patients with epilepsy, although this has been disputed.
- **Cardiovascular system:** Systemic vascular resistance (SVR) falls yet it is unusual to see compensatory tachycardia. A relative bradycardia is common and the blood pressure (BP) will fall. Propofol is a myocardial depressant.
- **Respiratory system:** Propofol is a respiratory depressant, which also suppresses laryngeal reflexes. Without this attribute it is very unlikely that the use of the laryngeal mask airway would have become so well established.
- **Gastrointestinal system:** The drug is anti-emetic.
- **Other side effects:** Propofol causes pain on injection. A newer preparation, propofol-lipuro, appears to have reduced this problem by including medium chain triglycerides in the formulation. There is a risk of hyperlipidaemia in intensive care patients who have received prolonged infusions. Its data sheet states that it should not be used in pregnancy.

- **Pharmacokinetics:** Propofol is highly protein bound (98%) and has a large volume of distribution ($4\,l\,kg^{-1}$). Distribution $t_{1/2}$ is 1–2 min and the elimination $t_{1/2}$ is 5–12 h. Its metabolism is mainly hepatic with the production of inactive metabolites and conjugates which are excreted in urine.
- **Miscellaneous:** Propofol is not a trigger for MH and it may also be used safely in patients with porphyria. It does not release histamine and adverse reactions are very rare.

Direction the viva may take

The examiners are unlikely to take this viva very much further, because although once more there is a lot of information to convey, each aspect of the pharmacology is not enough on its own to fill the allotted time. It should not, therefore, be a difficult viva to pass.

Ketamine

Commentary

Ketamine is unique among anaesthetic agents in that by causing 'dissociative anaesthesia' a single dose can produce profound analgesia, amnesia and anaesthesia. It is also of interest because its pharmacology has been elucidated probably more clearly than that of other induction agents. It finds its way into the examination more frequently than its clinical use might deserve, but investigation of the S(+) isomer as an agent with fewer side effects has renewed the drug's promise.

The viva

When the subject of a viva is a single drug, the questioning is often open ended, and the examiner may simply say 'Tell me about ketamine.' If this does happen it will help if you have a structured approach. The candidates' particular templates are usually obvious, especially when they use an opening statement such as: *Ketamine is a clear, colourless liquid of pH 3.5 which is presented in concentrations of….* It is preferable if you can show some enthusiasm for the subject, by starting instead, for instance, by saying that *Ketamine is an interesting anaesthetic and analgesic drug which might be used much more frequently were it not for its psychotomimetic side effects.* The examiner is more likely to conclude that this is a drug that you have used and have thought about, rather than a drug that you have memorised from the data sheet compendium.

- **Chemistry:** Ketamine is a cyclohexanone derivative of phencyclidine (PCP). This is an anaesthetic agent used in veterinary practice and which is also a drug of abuse ('Angel dust'). It is water soluble and is presented in three different concentrations. It is an acidic solution of pH 3.5–5.5. Most formulations now contain preservative, which precludes its use in central neural blockade, although preservative-free preparations can be obtained. It is presented as a racemic mixture of two enantiomers.
- **Mechanism of action:** Ketamine is an NMDA receptor antagonist. The NMDA receptor is an L-glutamate receptor in the CNS, glutamate being the major excitatory neurotransmitter in the brain. The receptor incorporates a cation channel to which ketamine binds. Ketamine also has effects on opioid receptors; acting as a partial μ (OP3) antagonist and as a partial agonist at κ (OP2) and δ (OP1) receptors. (Note that the nomenclature of opioid receptors is undergoing change.) It may therefore exert its analgesic effects after intrathecal or extradural injection at spinal κ-receptors.
- **Clinical uses:** Ketamine can be used for the induction of anaesthesia in adults and children, for so-called 'field' anaesthesia as a single anaesthetic agent outside the hospital setting, for bronchodilatation in severe refractory asthma, and for sedo-analgesia during procedures performed under local or regional anaesthesia. It is also finding increasing use in the treatment of intractable chronic and neuropathic pain.
- **Dose and routes of administration:** The drug can be administered via intravenous, intramuscular, oral and rectal routes. It has been used extradurally and intrathecally. The addition of $0.5\,mg\,kg^{-1}$ to a sacral extradural block in children with local anaesthetic will increase the duration of action fourfold. An intravenous dose of $1–2\,mg\,kg^{-1}$ will induce anaesthesia. The intramuscular dose is $5–10\,mg\,kg^{-1}$. Subhypnotic doses are usually up to $0.5\,mg\,kg^{-1}$.
- **Onset and duration of action:** An induction dose of ketamine does not lead to hypnosis within one arm–brain circulation time. Consciousness will be lost after 1–2 min but the patient may continue to move and to make incoherent noises. Intramuscular administration will take 10–15 min to take effect. The duration of action is between 10 and 40 min.

Main effects and side effects

- **CNS:** Dissociative anaesthesia. Afferent input is not affected but central processing at thalamocortical and limbic levels is distorted. Anecdotally it is reported that ketamine is much less effective in brain-damaged patients. The drug produces profound analgesia as well as amnesia. The drug increases intracranial pressure (ICP) and $CMRO_2$.
- **Cardiovascular system:** Ketamine is sympathomimetic and increases levels of circulating catecholamines. On isolated myocardium, however, it acts as a depressant. Indirect effects result in tachycardia, increases in cardiac output (CO) and BP, and a rise in myocardial oxygen consumption.
- **Respiratory system:** Ketamine is a respiratory stimulant. It is also said to preserve laryngeal reflexes and tone in the upper airway. It antagonises the effects of acetylcholine (ACh) and 5-hydroxytryptamine (5-HT) on the bronchial tree and causes clinically useful bronchodilatation.
- **Gastrointestinal system:** Salivation increases. As with most anaesthetic agents with sympathomimetic actions the incidence of nausea and vomiting is increased.
- **Other effects:** The use of ketamine has been limited by its CNS side effects. It is associated both with an emergence delirium and also with dysphoria and hallucinations. Emergence delirium is a state of disorientation in which patients may react violently to minor stimuli such as light and sound. The psychotomimetic effects are a separate phenomenon, which can become manifest many hours after apparent recovery from anaesthesia. Benzodiazepines may attenuate the problem.
- **Pharmacokinetics:** Ketamine is weakly protein bound (25%). Metabolism is hepatic; demethylation produces the active metabolite norketamine, which has one-third the potency of the parent compound. Further metabolism produces conjugates, which are excreted in urine.
- **Miscellaneous:** There is increasing interest in the use of the S(+)-enantiomer which is 3–4 times as potent as the R(−)-enantiomer, and which is associated with shorter recovery times and with fewer psychotomimetic reactions.

Direction the viva may take

Examiners may divert briefly to explore concepts such as the NMDA receptor and chirality, but the bulk of the viva will be on the basic information detailed above.

Etomidate

Commentary

Etomidate is no longer an induction agent that is used very widely, but it has two properties which make it of interest to examiners. The first is its purported cardiovascular stability when compared with other agents; the second is its potent inhibition of steroidogenesis. It is probable that the viva would emphasise these two aspects of its action.

The viva

Even though the questioning will be heading towards cardiovascular stability and steroid synthesis it is likely to start with the basic pharmacology of the drug itself.

- **Chemistry:** Etomidate is a carboxylated imidazole. It is water soluble but has been formulated in propylene glycol 35% to improve the stability of the solution. A newer preparation presents it in a lipid formulation containing medium chain triglycerides. It is a pure R(+)-enantiomer.
- **Mechanism of action:** As with many other drugs which produce general anaesthesia, the mechanism of action is not fully understood. Like other induction agents such as thiopentone and propofol, it also appears to enhance the inhibitory synaptic transmission by activation of the Cl^-channel on the β_1-subunit of the GABA receptor.
- **Clinical uses:** Etomidate is used to induce general anaesthesia for the induction of anaesthesia in adults and children. It cannot be used for the maintenance of anaesthesia or for sedation in intensive care, because of its effects on steroid metabolism (for which see below).
- **Dose and routes of administration:** The drug is used only intravenously. The dose is 0.2–0.3 mg kg^{-1}.
- **Onset and duration of action:** An induction dose of etomidate will lead to rapid loss of consciousness (within a minute). Its rapid redistribution to peripheral tissues leads to rapid recovery of consciousness.

Main effects and side effects

- **CNS:** Etomidate causes CNS depression and induction of anaesthesia. It may be associated with marked myoclonus. The EEG displays no epileptiform activity. Cerebral blood flow (CBF) and ICP are decreased.
- **Cardiovascular system:** Etomidate is associated with minimal changes in SVR or heart rate (HR). It has minimal myocardial-depressant effects and CO is largely unchanged. It is these characteristics that make the drug popular for induction of anaesthesia in patients with limited circulatory or cardiac reserve.
- **Respiratory system:** Etomidate has some respiratory-depressant effects, but these are transient and much less marked than is seen with barbiturates or propofol. It does not inhibit hypoxic pulmonary vasoconstriction.
- **Gastrointestinal system:** The drug is emetic and is associated with a high incidence of nausea and vomiting.
- **Other side effects:** Etomidate causes pain on injection, although the newer preparation, etomidate-lipuro, may attenuate this problem.
- **Pharmacokinetics:** Propofol is 75% protein bound and has a volume of distribution of 2.0–4.5 l kg^{-1}. The distribution half-life ($t_{1/2\alpha}$) is 2–4 min and the elimination half-life ($t_{1/2\beta}$) is 1–4 h. It is metabolised by ester hydrolysis and *N*-dealkylation in the liver to inactive compounds which are excreted renally.
- **Miscellaneous:** Etomidate does not release histamine and the incidence of hypersensitivity reactions is extremely low (fewer than 1 in 50,000). It is not a trigger for MH. During continuous infusion it has been shown to increase levels of δ-ALA synthetase and so in theory may be unsuitable for patients with porphyria.

- **Adrenocortical suppression:** Etomidate is an inhibitor of steroidogenesis in the adrenal cortex. Its imidazole structure (a ring comprising three carbon and two nitrogen atoms) allows it to combine with cytochrome P450 to block cortisol production. Specifically it blocks two enzymes, 17-α-hydroxylase and 11-β-hydroxylase, which catalyse at least six of the reactions in the biosynthetic pathways from cholesterol to hydrocortisone (cortisol). The mineralocorticoid and glucocorticoid pathways are linked, and etomidate inhibits both the formation of corticosterone, which is a precursor of aldosterone, as well as hydrocortisone. You will not be expected to know these pathways in any detail, but the enzyme inhibition does explain why etomidate is one of the most potent inhibitors of steroid production that has so far been synthesised.

Direction the viva may take

You may be asked about the clinical relevance of this information.

- **Cardiovascular stability:** This property makes it the intravenous induction agent of choice in patients who have actual or effective hypovolaemia, or who have ischaemic heart disease or cardiac dysfunction.
- **Immunosuppression:** The immunosuppressant effects of etomidate were unmasked by studies in which mortality in intensive care patients was demonstrably higher in those who had been sedated with a continuous infusion. It has since been shown that impaired adrenocortical function will follow even a single induction dose, and that although the enzyme inhibition is reversible, it may still persist for up to 8 h.

Drugs used in the treatment of nausea and vomiting

Commentary

Post-operative nausea is a core problem in anaesthesia. The effective prescription of anti-emetics requires some knowledge about their diverse sites of action. This viva may be combined with general questions about the physiology of vomiting. See *Post-operative nausea and vomiting*, page 89.

The viva

You will be asked about the applied pharmacology, with particular reference to the sites of action of the drugs that you cite.

- Nausea and vomiting are mediated by a number of sites with different receptors. This means that if necessary these symptoms can be treated by 'balanced anti-emesis' using drugs of differing actions. Although some drugs act at more than one receptor, their anti-emetic actions usually predominate at one.
- **Vestibular nuclei and the labyrinth**
  - These contain histamine (H_1) and muscarinic ACh (M_3) receptors.
  - Drugs acting at this site include: cyclizine, promethazine (H_1-antagonists); hyoscine, atropine and glycopyrrolate (anticholinergic M_3-antagonists).
- **Visceral afferents**
  - These are mediated by serotinin (5-HT_3) receptors in the gut wall and myenteric plexus.
  - Drugs acting at this site include ondansetron, granisetron and tropisetron (selective 5-HT_3-antagonists).
- **Vomiting centre (VC)**
  - This contains primarily muscarinic ACh (M_3) and some histamine (H_1) receptors. It may also contain μ-opioid receptors.
  - Drugs acting at this site are the same as those which affect the vestibular apparatus: cyclizine, promethazine (H_1-antagonists); hyoscine, atropine and glycopyrrolate (anticholinergic M_3-antagonists).
- **Chemoreceptor trigger zone (CTZ)**
  - Impulses from the CTZ to the VC appear to be mediated mainly via dopamine (D_2) and serotonin (5-HT_3) receptors. It may also contain δ-opioid receptors. In addition, substance P, which is a slow excitatory neurotransmitter, may have a role by acting at neurokinin-1 (NK_1) receptors. NK_1-receptors are abundant in the brain stem where emetic afferents converge.
  - Drugs acting at this site include metoclopramide, domperidone (D_2-antagonists); prochlorperazine, trifluoperazine (D_2-antagonists); haloperidol and previously droperidol, which is no longer available (D_2-antagonists); and vofopitant (NK_1-antagonist).
- **Drugs of uncertain sites of action**
  - *Cannabinoids*: Synthetic derivatives such as nabilone appear to antagonise the emetic effects of drugs which stimulate the CTZ. Since the cannabinoid effects can themselves be antagonised by naloxone, it is postulated that opioid receptors are involved in their actions. An endogenous cannabinoid CB_1-receptor which modulates neurotransmitter release has been identified.
  - *Corticosteroids*: High-dose steroids, such as dexamethasone or methyl prednisolone act as anti-emetics by mechanisms that are unclear.
  - *Propofol*: This has effective activity which has been used to treat cytotoxic-induced emesis. It would appear, therefore, to act at the CTZ.

Direction the viva may take

You may be asked about significant side effects of the anti-emetics that you prescribe.

- **Antimuscarinic drugs:** (atropine, hyoscine and glycopyrrolate) All are potent antisialogogues, and so a dry mouth is almost invariable. Hyoscine is sedative.
- **Antidopaminergic drugs:** (metoclopramide, prochloperazine and haloperidol) These may cause extra-pyramidal and dystonic effects which are due to a preponderance of the antidopaminergic stimulatory actions over anticholinergic inhibitory actions in other parts of the CNS. The phenothiazines may also cause sedation.
- **Antiserotoninergic drugs:** (ondansetron and granisetron) Their side effect profile is good, although headache has been reported as a complication of treatment in 3–5% of patients.
- **Cannabinoids:** (nabilone and dronabinol) Sedation is common, and the drugs may sometimes exert psychotomimetic effects similar to those induced by the parent compounds. Dry mouth and postural hypotension may also occur.
- **Corticosteroids:** (methyl prednisolone and dexamethasone) The list of acute side effects includes steroid psychosis, which is related to sudden increase in plasma levels of corticoids, and metabolic disturbance including hyperglycaemia, fluid retention and hypokalaemia. Short courses of high-dose steroids may cause peptic ulceration.

Local anaesthetic actions

Commentary

Questions about local anaesthesia are popular, because the subject can switch readily between basic science and its clinical implications. If you give thorough and detailed explanations in response to the early questions then you will impress the examiners without having to provide much further information. If your knowledge is sketchy then the viva will probably proceed to clinical aspects, including toxicity, but you must remember that this structured question relates mainly to mechanisms of action.

The viva

You will be asked about the mechanism of action of local anaesthetics.

- **Definition:** A local anaesthetic agent is defined as a compound which produces temporary blockade of neuronal transmission when applied to a nerve axon.
- **Drugs:** Numerous drugs share this characteristic with conventional local anaesthetics. They include anticonvulsants, many antidysrhythmics including bretylium and β-adrenoceptor blockers, some phenothiazines and some antihistamines, as well as drugs such as pethidine. None is used as a local anaesthetic, but all have a similar mechanism of action. The range of local anaesthetic agents that is used in the UK is small, and is restricted largely to lignocaine, bupivacaine, prilocaine, and to a lesser extent, ropivacaine.
- **Normal action potential:** Local anaesthetic action is best described in the context of a normal nerve action potential. The axon maintains a voltage differential of 60–90 mV across the nerve membrane. At rest the membrane is relatively impermeable to the influx of sodium (Na^+) ions, and is selectively permeable to potassium (K^+) ions. In the resting cell membrane this selective permeability allows a small net efflux of K^+ ions, which leaves the axoplasm electrically negative (polarised). At rest, Na^+ ions tend to flow into the axon: both because the inside is electrically negative and because of the concentration gradient. This resting membrane potential is maintained by the Na^+/K^+ pump, which continually extrudes Na^+ from within the cell in exchange for net uptake of K^+, using adenosine triphosphate (ATP) as an energy source. When specific sodium channels in the axonal membrane are opened there is a selective permeability to Na^+ ions, and the membrane depolarises. Repolarisation takes place when voltage-dependent K^+ channels open and permit a large efflux of K^+. As the membrane becomes less negative, more Na^+ channels open, and open more rapidly: more Na^+ ions enter the cell and depolarisation is further accelerated.
- **Impulse propagation:** The impulse is propagated by the spread of inward current through the conducting medium of the axoplasm to adjacent inactive regions. Inward currents from all the active nodes integrate as they spread, ensuring that impulse propagation will continue.
- **Local anaesthetic action:** These mainly block the function of the sodium channels, which exist in 'open', 'resting' and 'inactivated' conformational states. Local anaesthetic affinity is higher when the channel is in the open or inactivated state. The drugs exert no effect on cellular integrity or metabolism, but when a sufficient concentration is reached in the perfusing solution, depolarisation does not occur in response to an electrical stimulus. Na^+ influx is blocked, although repolarisation associated with K^+ efflux is unaffected. The agents in their cationic ionised form block the sodium channels on the inside of the axoplasm. External perfusion has no effect: the uncharged form must penetrate the cell wall before dissociating. The nerve blockade is concentration dependent and ends when the local anaesthetic concentration falls below a critical minimum level. Local anaesthetics work by stabilising the axonal membrane, and will stabilise all excitable membranes, including those of skeletal, smooth and cardiac muscle. Local anaesthetics also block some potassium ion channels, broaden the action

potential and enhance binding by maintaining the sodium channel in the open or inactivated state.

Direction the viva may take

It is almost inevitable that you will be asked about p*K*a.

- **p*K*a:** Local anaesthetics exist in equilibrium between ionised and non-ionised forms. The ratio of the two states is given by the Henderson–Hasselbalch equation (originally derived to describe the pH changes resulting from the addition of H^+ or OH^- ions to any buffer system). The *K*a is the dissociation constant which governs the position of equilibrium between the charged and uncharged forms. By analogy to pH, the p*K*a is the negative logarithm of that constant. Rearranging the equation $pH = pKa + \log[HCO_3^-]/[H_2CO_3]$ gives: p*K*a = pH − log[base]/[conjugate acid]. This is the same as saying [base]/[conjugate acid] = 1.0, so the dissociation constant, or p*K*a, is the pH at which equal amounts of drug are present in the charged and uncharged state.
- **Clinical implications:** A p*K*a of 7.4 indicates that at body pH there are equal numbers of molecules in the charged and uncharged forms. Most local anaesthetics, however, have p*K*a values higher than body pH, and the further away the dissociation constant is from body pH the more molecules that exist in the ionised form. The pH scale is logarithmic: hence if a drug has a p*K*a of 8.4 it is 1 pH unit (that is a 10-fold H^+ concentration) away from body pH. At 7.4 there is a 10 : 1 ratio, that is the drug is 90% ionised and 10% non-ionised. At p*K*a 9.4 the difference is 100-fold, so at body pH of 7.4, 99% of the drug will be charged. Uncharged base is necessary for tissue penetration: hence drugs with lower p*K*a usually have a more rapid onset of action. Thus lignocaine and prilocaine (p*K*a: 7.7) have a shorter latency than bupivacaine (p*K*a: 8.1). This dominance of the non-diffusible cation also explains the reason why local anaesthetics are much less effective in the presence of inflamed and acidotic tissue. Note, however, that p*K*a is not the only factor involved. Concentration and intrinsic potency are also important. Drugs also have to penetrate a perineural membrane of connective tissue, and this property has not been well quantified, thus chloroprocaine (popular in the USA) has one of the fastest onsets of action of all local anaesthetics, despite having a p*K*a of 9.1.

Further direction the viva could take

You may be asked about other factors that may influence local anaesthetic action.

- **Structure–activity relationships of local anaesthetics:** Their site of action is a protein structure in the Na^+ channel. The affinity of the drug to the channel, which determines the duration of action, is related to the length of the aliphatic (open carbon) chains on the compound. For example, bupivacaine is structurally identical to the local anaesthetic mepivacaine (which is used in dentistry), apart from the fact that it has a butyl (C_4H_9), rather than a methyl (CH_3) side chain. This simple substitution increases lipid solubility almost 20 times, and increases protein binding from 77% to 96%. The quoted durations of action are 100 and 175 min, respectively.
- **Lipid solubility:** As with general anaesthetics this is a prime determinant of intrinsic anaesthetic potency. With local anaesthetics, however, there appears to be a ceiling effect. Above a partition coefficient of 4 there is no observed increase in potency. The esters procaine and chloroprocaine have low lipid solubility, and so are delivered in high 2–3% concentrations. Amethocaine and bupivacaine have high lipid solubility and produce effective anaesthesia at 0.25%.
- **Frequency dependence:** You will be doing well if you get as far as discussing this phenomenon. Drug entry into the sodium channels occurs when the channel is open during the period of membrane depolarisation. Nerves conduct at

different frequencies: pain and sensory fibres conduct at high frequency whereas motor impulses are at a lower frequency. This means that the sodium channels are open more times per second. Some drugs – lignocaine, bupivacaine and probably ropivacaine – appear to produce a more rapid and more dense blockade in these sensory nerves of higher frequency. This is not true of a drug, such as etidocaine, which is associated with a much more profound motor block. You may be asked about toxicity. See *Local anaesthetic toxicity*, page 165.

Local anaesthetic toxicity

Commentary

Local anaesthetic techniques such as combined sciatic, femoral and obturator nerve blocks for knee surgery are becoming increasingly popular. The use of large drug doses for these nerve and other plexus blocks means that local anaesthetic toxicity is not merely an academic possibility. In this viva you need above all to reassure the examiners that your practice is safe. If your answers indicate that you might put the patient at risk then you will receive at best a '1+', no matter how good your performance in the other three questions might have been.

The viva

You will be asked about the factors that predispose a patient to local anaesthetic toxicity.

- **Site of injection:** The primary influences are the vascularity of the anatomical site of injection, and the presence locally of tissue such as fat, which may bind local anaesthetics. There is a spectrum of absorption, which is greatest after intercostal and paracervical block, and thereafter, in descending order, sacral extradural (caudal) block, lumbar and thoracic extradural block, brachial plexus block, sciatic and femoral nerve block, and subcutaneous infiltration. Absorption from this last site is so delayed that some authors have described using doses that far exceed recommended maxima. Lignocaine 35 mg kg^{-1}, for example, has been used during tumescent liposuction.
- **Drug dosage and concentration:** It is not only the peak level, but it is also the rate of rise that may contribute to local anaesthetic toxicity. The total mass of drug may also be less important than its concentration: a dilute solution of the same dose is associated with lower peak levels. You may be asked what are the maximum doses that can be used. As factors such as the rate of injection and the site of administration have such a substantial influence on blood levels, there is little logic to the maximum doses of local anaesthetics that usually are cited. If you are asked this question, then preface your answer by all means with a comment to that effect. The commonly quoted maximum doses are: lignocaine 3.0 mg kg^{-1}, 7.0 mg $kg^{-1}$with adrenaline; bupivacaine 2.0 mg kg^{-1}; prilocaine 400 mg total dose (600 mg with adrenaline); and ropivacaine 150 mg total dose, with or without adrenaline.
- **Vasoconstrictors:** The use of vasoconstrictors lowers the maximum blood concentrations, but does not prolong the time to peak. There is also a complex interrelation with the inherent vasoactivity of local anaesthetics, all of which, apart from cocaine, a potent vasoconstrictor, demonstrate biphasic activity. At very low concentrations all enhance vascular smooth muscle activity and cause vasoconstriction. At clinical doses they demonstrate vasodilator activity that is dose dependent and which varies for each drug. Racemic bupivacaine is a vasoconstrictor at low concentrations and is a less effective vasodilator than laevobupivacaine 0.75%. Lignocaine also constricts at low concentrations but dilates at clinical levels. Increased blood flow increases vascular uptake and decreases duration of action.
- **Binding:** Local anaesthetics bind mainly to α_1-acid glycoprotein, which is a high-affinity low-capacity site, and to a lesser extent to low-affinity high-capacity sites on albumin. The binding decreases as pH decreases, and so toxicity is increased by hypoxia and acidosis. A decrease in intracellular pH will lead to increased ionisation within the axoplasm and ion-trapping. The convulsive threshold is inversely related to arterial PCO_2.
- **Pulmonary sequestration:** High blood levels may be attenuated by temporary sequestration of local anaesthetic within the lung. A high lung : blood partition coefficient encourages some uptake by the lung, and because the extravascular

pH of lung is lower than that of plasma this encourages ion-trapping. Prilocaine is sequestered more effectively than bupivacaine, whose uptake in turn is greater than that of lignocaine.

- **Allergic reactions:** Genuine allergy to amides is extremely rare, but it can be a problem with esters. Allergic reactions are commonly due to *p*-aminobenzoic acid (PABA), which is a product of the metabolism of ester local anaesthetics such as procaine, benzocaine, chloroprocaine and amethocaine.
- **Toxicity:** The cardiovascular and CNS toxicity that may be seen are common to all local anaesthetic agents, and are predictable in light of the known mechanism of action of these drugs. Local anaesthetics work by stabilising the axonal membrane, and will stabilise all excitable membranes, including those of skeletal, smooth and cardiac muscle. See *Local anaesthetic actions*, page 162.
- **CNS:** As the blood concentrations increase, an initial excitation gives way to generalised CNS depression with respiratory depression and arrest. The excitatory phase is due to the selective blockade of inhibitory pathways in the cortex. Convulsive activity supervenes when bupivacaine concentrations reach 2–4 $\mu g\,ml^{-1}$ and lignocaine levels reach 10–12 $\mu g\,ml^{-1}$.
- **Cardiovascular effects:** These are complex and vary between the agents. Lignocaine can be used as a primary treatment for ventricular dysrhythmias. It decreases the maximum rate of depolarisation, but does not alter the resting membrane potential. In cardiac tissue, depolarisation is related to sodium influx through fast channels and calcium influx through slow channels. The slow channels are responsible for the spontaneous depolarisation of the sino-atrial (SA) node. Cardiac conduction slows with increasing blood levels, and this is manifest by an increased PR interval and duration of the QRS complex (ventricular depolarisation). High doses depress SA node pacemaker activity, perhaps by inhibiting the slow calcium channels, and they also depress atrio-ventricular (AV) nodal conduction. In addition, local anaesthetics exert a dose-dependent negatively inotropic action on the myocardium. This effect relates directly to the potency of the agents. Bupivacaine is more dangerous than lignocaine in overdose, by predisposing patients to dysrhythmias and ventricular fibrillation (VF). The underlying mechanism for this effect is not known, but it appears to cause a unidirectional block with re-entrant tachydysrhythmias. Bupivacaine markedly reduces the rapid phase of depolarisation, and recovery from this block is much slower than with lignocaine. The drug binds avidly to myocardial cells; there is a decrease in the rate of depolarisation and action potential duration, with subsequent conduction block and electrical inexcitability.
- **Myotoxicity:** Local anaesthetics will damage muscle into which they are injected directly. Skeletal muscle is a regenerating tissue and so this is not usually a clinical problem, although persistent diplopia has been reported following the use of bupivaciane 0.75% concentrations for retrobulbar ophthalmic block.
- **Prilocaine toxicity:** Prilocaine is held to be one of the safest local anaesthetics. Its use in high doses may, however, lead to methaemoglobinaemia. Prilocaine has a slightly different structure in the aromatic moiety in that it has only one methyl group on the aromatic ring (unlike the 2,6-xylidine ring in the other amides). This makes the toluidine ring less stable and more rapidly metabolised to *o*-toluidine, which is responsible for methaemoglobinaemia.

Direction the viva may take

You are likely to be asked about the clinical presentation and management of suspected toxicity.

- **Clinical features:** The patient may complain of circumoral tingling and paraesthesia, light-headedness and dizziness. They may have visual and

auditory disturbance manifested by difficulty in focusing and tinnitus. They may be disorientated. The objective signs are usually excitatory, with shivering, twitching, tremors in the face and extremities preceding full grand mal convulsions. Cardiac dysrhythmias may be obvious on electrocardiograph (ECG) monitoring.

- **Management: supportive**
  - The patient can be managed using the standard approach to **A**irway, **B**reathing and **C**irculation, with interventions as appropriate to the clinical state of the patient.
- **Management: specific measures**
  - *Cardiac dysrhythmias*: If bupivacaine has been used, then resuscitation may be very prolonged. Amiodarone ($5\,mg\,kg^{-1}$) is the drug of choice for most dysrhythmias, apart from VF. If the VF is refractory to direct current (DC), then bretylium ($5\,mg\,kg^{-1}$) is the agent most likely to aid eventual reversion to sinus rhythm.
  - *Grand mal convulsions*: These can be treated either with a specific anticonvulsant drug such as phenytoin, in a starting dose of $15\,mg\,kg^{-1}$, or with a drug such as thiopentone which has effective anticonvulsant activity. Small bolus doses of 50 mg should suppress a fit that has been induced by local anaesthetic toxicity, but if necessary an infusion of $1–3\,mg\,kg\,h^{-1}$ can be started. Diazemuls or midazolam can also be used to abort convulsive activity.
  - *Methaemoglobinaemia*: Treatment is with methylene blue, $1\,mg\,kg^{-1}$.

Alkalisation of local anaesthetics

Commentary

This technique is of clinical interest because it is used to shorten the latency of onset of effective anaesthesia, and is particularly useful in the context of extending an epidural block for urgent operative delivery. It is of interest to FRCA examiners because it allows candidates to demonstrate their understanding of the basic mechanisms of local anaesthetic action.

The viva

You will be asked why it might be useful to add alkali to a local anaesthetic.

- **Basic chemistry:** All local anaesthetics are chemical descendants of cocaine and comprise a lipophilic, aromatic portion, which is joined via an ester or amide linkage to a hydrophilic, tertiary amine chain. The presence of the amino group means that they are weak bases, existing in solution partly as the free base, and partly as the cation, as the conjugate acid. When the acid HA dissociates to H^+ and A^- the anion A^- is a base because it serves as a proton receptor in the reverse reaction. The special relationship of base A^- to the acid HA is acknowledged by calling it the conjugate base of the acid.
- **Drug action:** The axoplasmic part of the sodium channel is blocked by the ionised part of the local anaesthetic molecule, but a charged moiety will not traverse the lipid and connective tissue membranes. It is only when existing in the uncharged form that the drug can gain access to the axoplasm.
- **Equilibrium:** Drugs exist in rapid equilibrium between the non-ionised (N:) and the ionised species (NH^+). Both ionised and non-ionised drug forms can inhibit Na^+ channels, but access to the axoplasm is via the uncharged species. Once within the axoplasm the local anaesthetic becomes protonated. The ratio of the two forms is given by the Henderson–Hasselbalch equation, which in this context can be written as p*K*a = pH − log[base]/[conjugate acid]. The *K*a is the dissociation constant which governs the position of equilibrium between the base and acid. By analogy to pH, the p*K*a is the negative logarithm of that constant. When p*K*a = pH, the charged and uncharged forms are present in equal concentrations. Local anaesthetics have p*K*a values higher than body pH, and the further away the dissociation constant is from body pH the more molecules that exist in the ionised form. The pH scale is logarithmic: hence if a drug has a p*K*a of 8.4 it is 1 pH unit, that is a 10-fold H^+ concentration, away from body pH, at which the drug will be 90% ionised and 10% non-ionised.
- **Presentation:** Most local anaesthetics are poorly water-soluble weak bases that are usually presented as aqueous solutions of the hydrochloride salts of the tertiary amine. The tertiary amine is the base. They are therefore prepared as the water-soluble salt of an acid, usually the hydrochloride, which is stable in solution.
- **Alkalisation:** The addition of bicarbonate will raise the pH of the weakly acidic solution nearer the p*K*a. Addition of 1.0 ml $NaHCO_3$ 8.4% to 10.0 ml of lignocaine 2%, will raise its pH from 6.5 to 7.2. This means that more drug will exist in the non-ionised form so penetration will be more rapid.
- **Carbonation:** This is a variation on alkalisation, and is based on a similar principle but with a different site of action. Most local anaesthetics are marketed as hydrochloride salts; it is, however, possible to combine the base form with carbonic acid to form the carbonate salt rather than the hydrochloric acid. The H_2CO_3 is in equilibrium with dissolved CO_2. After infiltration of the drug, it is believed that the increased amount of CO_2 moves into the axoplasm, where it increases the levels of the weak carbonic acid. This lowers the intracellular pH and thereby favours cation production. In clinical practice this theoretical promise has not been realised.

- **Clinical uses:** Alkalisation is particularly useful in decreasing the onset time of a block when speed may be of the essence. The commonest example is when an epidural block that has been used for labour analgesia needs to be extended for surgical delivery.

Direction the viva may take

If you have exhausted the core material above then you will have to be prepared for the viva to take a potentially variable course. Further aspects of local anaesthesia about which you may be asked include:

- **Inflammatory modulation:** The inflammatory response is initiated partly by G-coupled-receptor proteins. Local anaesthetics have recently been shown to interact with some of these proteins to modify the physiological response.
- **Protein binding:** This influences the duration of action of a compound. (For fuller details see *Mechanisms of action of general anaesthetics*, page 287.)
- **Lipid solubility:** As with general anaesthetics this is a prime determinant of intrinsic anaesthetic potency. Lignocaine has low lipid solubility, whereas that of bupivacaine is high. For fuller details see *Mechanisms of action of general anaesthetics*, page 287.
- **Newer preparations:** The duration of action may be prolonged by the use of lipid emulsions (which increase the non-ionised proportion and release active drug more slowly), suspensions, liposomes (which are amphipathic lipid molecules encapsulating local anaesthetic) and polymer microspheres. You will not be expected to know about these in any detail.
- **Adjuncts to local anaesthetics:** You may be asked what adjuvant drugs may be added to local anaesthetics in order to enhance their action. See *Spinal adjuncts to local anaesthetics*, page 199.

Bupivacaine and ropivacaine (compared)

Commentary

While a discussion about local anaesthetics logically would include all the agents that currently are used, in practice it is quite difficult to focus such a viva effectively. It is much easier to compare only two agents, which in turn is more interesting than concentrating on only one. You might conceivably be asked to talk solely about either bupivacaine or ropivacaine, but it is almost certain that some comparative information will still be required. Make sure that your knowledge of bupivacaine is thorough, because this is a drug that you will have used frequently.

The viva

You will be asked to compare bupivacaine and ropivacaine.

- **Definitions:** Bupivacaine and ropivacaine are local anaesthetics which produce a reversible block of neuronal transmission, and which are synthetic derivatives of cocaine. Both possess the same three essential functional units, namely a hydrophilic chain joined by an amide linkage to a lipophilic aromatic moiety.
- **Structures:** The parent compound of bupivacaine is mepivacaine, which has a single methyl group attached to the tertiary amine. Bupivacaine is identical apart from a butyl (C_4H_9) side chain. The structure of ropivacaine (which is effectively a derivative of bupivacaine, and which is prepared as the pure S-enantiomer of propivacaine) differs only in that there is a shorter propyl (C_3H_7) substituent on the piperidine nitrogen atom.
- **Protein binding:** Structural differences change the properties of the molecule. The affinity of local anaesthetics for the sodium channel is related to the length of the aliphatic chains. Affinity determines duration of action: hence ropivacaine, with its shorter propyl chain has a duration of action of 150 min as compared with 175 min for bupivacaine. Both the drugs are around 96% protein bound.
- **Lipid solubility:** Longer side chains also increase influence lipid solubility, which is a determinant of potency. Highly lipid-soluble agents such as bupivacaine are highly concentrated in local tissue and dislodge slowly. As measured by partition coefficients bupivacaine is twice as soluble as ropivacaine, and is more potent.
- **Dissociation constants:** Both the drugs have a p*K*a of 8.1, which means that their onset times are similar.
- **Toxicity:** Ropivacaine was developed as a safer alternative to bupivacaine. Its myocardial and CNS toxicity has been quoted as being 25% less than racemic bupivacaine. The cardiovascular and CNS toxicity of bupivacaine, however, is a function of the R(+)-enantiomer. The S(−)-enantiomer has less affinity for, and dissociates faster, from myocardial sodium channels. Animal studies confirm a fourfold decrease in the incidence of ventricular dysrhythmias and VF. Symptoms of CNS toxicity in human volunteers such as tinnitus, circumoral numbness, apprehension, and agitation are also less with infusions of the S(−)-enantiomer. This enantiomer is now available as L-bupivacaine ('Chirocaine'), and would appear to be no more dangerous than ropivacaine.
- **Vasoactivity:** All local anaesthetics apart from the potent vasoconstrictor cocaine show biphasic activity, being vasodilators at high concentrations and vasoconstrictors at low. The vasoconstriction at low concentrations appears to be associated particularly with the S-enantiomers. Ropivacaine probably exerts greater vasoconstrictor activity than bupivacaine, thereby reducing its potential toxicity and increasing the duration of action. As already discussed, however, it is no less toxic and has a shorter duration of action, so this vasoconstrictor activity probably confers little benefit over laevobupivacaine.
- **Sensory–motor dissociation:** This refers to the capacity of a local anaesthetic preferentially to block sensory nerves while sparing motor nerves. It is of

particular advantage when the drugs are used in continuous epidurals for labour and for surgical analgesia. Selective block is a genuine phenomenon: etidocaine, for example, demonstrates more potent motor than sensory block. Etidocaine is highly lipid soluble and penetrates better than bupivacaine into the large myelinated A-α-motor fibres. It also penetrates into the cord itself to provide long-tract anaesthesia. But what of the claim that ropivacaine exhibits greater sensory–motor dissociation than other local anaesthetics? This claim has been based largely on studies that have used doses that are supramaximal for sensory block, at which the greater motor-blocking effect of bupivacaine is obvious. If the doses are reduced, then little motor block will be evident with either drug, but the differences in sensory block will be revealed. It is well known that this group of local anaesthetics demonstrates preferential sensory block: the purported superiority of ropivacaine is in fact illusory, and is based on the fact that it is simply a less potent drug.

- **Frequency dependence:** This is another factor which helps to explain true sensory–motor dissociation. Drug entry into the sodium channels occurs when the channel is open during the period of membrane depolarisation. Nerves conduct at different frequencies: pain and sensory fibres conduct at high frequency whereas motor impulses are at a lower frequency. This means that the sodium channels are open more times per second. Lignocaine, bupivacaine and ropivacaine produce a more rapid and denser block in these sensory nerves of higher frequency. This is not true of drugs such as etidocaine, which is associated with a much more profound motor block.

Induced hypotension

Commentary

This question has been around since before the current examiners were themselves examined, and it is seen as a predictable and standard topic. You should be aware of the applied pharmacology, of the indications for the technique and of its potential complications.

The viva

You will be asked about the intravenous drugs that can be used to induce hypotension.

- The subject lends itself readily to a structured approach. You can, for example, talk either about their physiological sites of action or organise your answer according to the groups of drugs that are available. This is almost, but not quite the same thing: labetalol, for instance, is a hypotensive drug with more than one site of action.
- The prime determinants of arterial BP are CO (HR and stroke volume) and SVR. Drugs used to induce hypotension can affect one or more of these variables.

Drugs which affect SVR

α-adrenoceptor blockers

- **Phentolamine:** This is a non-selective α-antagonist (the ratio of $\alpha_1 : \alpha_2$-effects is 3 : 1), which also has weak β-sympathomimetic action. It decreases BP by reducing peripheral resistance due to its peripheral α_1-vasoconstrictor blockade and mild β-sympathomimetic vasodilatation. The α_2-blockade increases noradrenaline (norepinephrine) release. The dose is 1–5 mg, titrated against response and repeated as necessary. The drug has a rapid onset of 1–2 min, and has an effective duration of action of around 15–20 min.

Peripheral vasodilators

- **Glyceryl trinitrate (GTN) nitroglycerine:** Its hypotensive action is mediated via nitric oxide (NO). NO activates guanylate cyclase, which increases cyclic guanosine triphosphate (cGMP) within cells. This in turn decreases available intracellular Ca^{2+}. The drug causes venous vasodilatation more than arteriolar, and hence it decreases venous return and preload. Myocardial oxygen demand is reduced because of the decrease in ventricular wall tension. GTN has a rapid onset (1–2 min) and offset (3–5 min) which can allow precise control of BP. A typical infusion regimen would be to start at around $0.5\,\mu g\,kg^{-1}\,min^{-1}$, titrated against response. There is no rebound hypertension when the infusion is discontinued. The drug increases CBF and ICP. Tolerance to the effects of GTN may develop, which may partially be prevented by intermittent dosing.
- **Sodium nitroprusside (SNP):** SNP is another nitrovasodilator which mediates hypotension via the action of NO. In contrast to GTN it causes both arterial and venous dilatation, leading to hypotension and a compensatory reflex tachycardia. The drug has a complex metabolism that results in the production of free cyanide (CN^-), which by binding irreversibly to cytochrome oxidase in mitochondria is potentially very toxic, causing tissue hypoxia and acidosis. Toxicity is manifest when blood levels exceed $8\,\mu g\,ml^{-1}$. The maximum infusion rate is $1.5\,\mu g\,kg^{-1}\,min^{-1}$, and the total dose must not exceed $1.5\,mg\,kg^{-1}$. Treatment of toxicity is with sodium thiosulphate 50% (20–25 ml intravenously over 5 min) and/or cobalt edetate 1.5% (20 ml rapidly). SNP also increases CBF and ICP. Coronary blood flow is also increased. The rapid onset (1–2 min) and offset (3–5 min) of effect allows good control of BP, although patients may demonstrate rebound hypertension when the infusion is stopped. Tachyphylaxis

may be seen in some patients, the mechanism underlying which is uncertain. The solution is unstable and so the giving set must be protected from light.

Ganglion blockers

- **Trimetaphan:** This acts as an antagonist at the nicotinic receptors of both sympathetic and parasympathetic autonomic ganglia, but it has no effect at the nicotinic receptors of neuromuscular junction. It has some α-blocking actions and is a direct vasodilator of peripheral vessels. It is a potent histamine releaser, which contributes to its hypotensive action. Reflex tachycardia is common, and this may present a problem during surgery which mandates a quiet circulation. Trimetaphan also antagonises hypoxic pulmonary vasoconstriction. The drug is given by infusion at a rate of 20–50 $\mu g\,kg^{-1}\,min^{-1}$.

Direct vasodilators

- **Hydralazine:** This produces hypotension by direct vasodilatation together with a weak α-antagonist action. This is mediated via an increase in cGMP and decrease in available intracellular Ca^{2+}. The tone of arterioles is affected more than venules. A reflex tachycardia is common. It is less easy to titrate the dose against effect and the drug finds its main use in the control of hypertension in pregnancy. The maximum infusion rate is $10\,mg\,h^{-1}$.

Drugs which affect CO

- **β-adrenoceptor blockers:** There are many examples; all are competitive anatagonists, but their selectivity for receptors is variable. Selective β_1-antagonism clearly is a useful characteristic. Their influence on BP is due probably to decreased CO via a decreased HR, together with some inhibition of the renin–angiotensin system. Unopposed α_1-vasoconstriction may compromise the peripheral circulation without causing hypertension.
- **Drugs in use**
  - *Atenolol*: This is a selective β_1-antagonist except in high doses. It is long acting with a $t_{1/2}$ of around 7 h. It is given more commonly as a bolus (over 20 min) of $150\,\mu g\,kg^{-1}$ for cardiac dysrhythmias than to induce hypotension.
  - *Esmolol*: This is a relatively selective β_1-antagonist. It is ultra-short acting, with a $t_{1/2}$ of around 9 min. It is rapidly metabolised by non-specific ester hydrolysis. Its infusion dose is 50–200 $\mu g\,kg^{-1}\,min^{-1}$.
  - *Labetalol*: This acts both as α- and β-antagonist (in a ratio of 1 : 7), which mediates a decrease in SVR without reflex tachycardia. It is a popular drug in anaesthetic, obstetric anaesthetic and intensive therapy use. Its elimination $t_{1/2}$ is 4–6 h. It can be given as a bolus of 50 mg intravenously, or at a rate of 1–2 $mg\,kg^{-1}\,h^{-1}$.
  - *Propanolol*: This is a non-selective β-antagonist which is usually given as a bolus of 1 mg, repeated to a maximum of 5 mg (in a patient who is anaesthetised).

α_2-adrenoceptor agonists

- **Clonidine:** This is an α-agonist with affinity for α_2-receptors some 200 times greater than that for α_1. Its hypotensive effects are mediated via a reduction in central sympathetic outflow and by stimulation of presynaptic α_2-receptors which inhibit noradrenaline release into the synaptic cleft. It also possesses analgesic and sedative actions. Its elimination $t_{1/2}$ is too long at around 14 h to allow its use for fine control of acutely raised BP, but it can be a useful adjunct in low doses.

Direction the viva may take

You will probably be asked to discuss the indications for, and dangers of, induced hypotension.

- **Indications:** An old adage avows that induced hypotension should be used only to make the impossible possible, and not the possible easy. There was a time when surgeons largely were oblivious to that injunction, and induced hypotension had many indications, particularly for neurosurgical and procedures in the head and neck. The indications have now shrunk to the point at which the technique is confined to a very few, very specialised surgical procedures, one example of which is the removal of choroidal tumours of the eye.
- **Dangers and complications:** These relate, predictably, to the consequences of hypoperfusion in key parts of the circulation. Precipitate falls in BP may lead to cerebrovascular accidents and to myocardial ischaemia. Drug-induced hypotension usually shifts the autoregulatory curve to the left, and confers thereby a degree of protection. In patients who are previously hypertensive, however, the curve is shifted to the right, making them more vulnerable to catastrophic drops in perfusion of essential areas. You should be able to draw the curve of cerebral autoregulation to demonstrate these shifts.
- **Exacerbating influences:** The effects of induced hypotension will be enhanced by factors such as hypovolaemia, the use of other drugs with hypotensive actions such as volatile anaesthetic agents, the reduction in venous return associated with intermittent positive-pressure ventilation, and drugs which release histamine. The head-up position may also further diminish effective cerebral perfusion.

Hypotension and its management

Commentary

This may end up largely as a viva about drugs to treat hypotension, but it will be introduced from first principles. Vasopressors are the logical treatment for falls in BP that have been induced pharmacologically, but they also find deployment in a variety of clinical scenarios in which patients are hypotensive. You will be expected to know about this class of drugs and to be able to demonstrate judgement in their use.

The viva

You will be asked to describe the prime determinants of arterial BP.

- Systemic BP is determined by cardiac output (CO), which is the product of heart rate (HR) and stroke volume, multiplied by systemic vascular resistance (SVR). (BP = CO × SVR)
- Hypotension may result from an inadequately compensated decrease in any one or more of these variables.

Direction the viva may take

You may be asked to follow this logical beginning by detailing the causes and management of acute hypotension. You can preface your answer by explaining, for example, that a fall in vascular resistance may be compensated by reflex tachycardia, but that initially it is useful nonetheless to analyse them in isolation.

*Reduction in HR: causes and management (BP = **HR** × SV × SVR)*

- **Hypoxia:** This will cause a bradycardia at a late stage, but it must not be missed.
- **Vagal stimulation:** Profound bradycardia may follow traction on extraocular muscles, anal or cervical dilatation, visceral traction, and sometimes, instrumentation of the airway.
- **Drugs:** Medication with drugs such as β-adrenoceptor blockers and digoxin may be responsible. Anaesthetic drugs may also contribute. Volatile agents in high concentrations, or halothane in normal concentrations, suxamethonium, opioids, and anticholinesterases can all be associated with bradycardia. Low doses of atropine may provoke a paradoxical bradycardia (the Bezold–Jarisch reflex).
- **Cardiac disease:** The commonest cause is ischaemic change affecting the conducting system.
- **Metabolic:** Acute hyperkalaemia may hyperpolarise the myocardial cell membrane with a resulting fall in HR.
- **Spinal anaesthesia:** In theory, the block of the cardiac accelerator fibres from T_1 to T_4 should be associated with bradycardia. In practice this is often not seen.

Management

- First of all diagnose the cause, and if it is amenable to treatment then act accordingly. Is it hypoxia? Treat immediately. Is it surgical stimulus? If so then stop traction on the extraocular muscles or the mesentery. If drug treatment is required the most effective immediate first-line drug is an anticholinergic agent, usually atropine or glycopyrrolate. Neither is a treatment for hypoxia.

*Reduction in stroke volume (BP = HR × **SV** × SVR)*

- The commonest cause is reduced venous return. This may be due to an actual reduction in circulating volume because of blood loss or dehydration, or to an effective reduction in circulating caused by sympathetic block.
- SV may also be diminished because the ventricle is failing.

Management

- As before it is important to diagnose the cause, and if it is amenable to treatment then act accordingly. Is it hypovolaemia? Resuscitate with the appropriate fluid. Is position contributing? Revert to recumbency or the head-down position; ensure lateral uterine displacement in the later stages of pregnancy. Beware aortocaval compression by the intra-abdominal mass that is not a gravid uterus. Is it a failing ventricle? Consider using inotropes to support ventricular function.

*Reduction in SVR (BP = HR × SV × **SVR**)*

- The commonest cause of inadvertent profound hypotension is probably that which is induced by the sympathetic block associated with spinal or epidural anaesthesia.
- In the context of intensive care medicine the commonest cause is sepsis.

Management

- The rational management of hypotension that has been induced pharmacologically is to treat it pharmacologically. The reduced SVR associated with sepsis is different, but it still is usually managed with a combination of vasopressor, fluids and inotropes.

Further direction the viva could take

You will be asked about the range of drugs that is available to treat hypotension.

Ephedrine

- **Pharmacology:** Ephedrine is a naturally occurring compound (from the Chinese plant *Ma Huang*), which is now synthesised for medical use. It is a sympathomimetic drug which acts both directly and indirectly, and which has both α- and β-effects. It also inhibits the breakdown of noradrenaline (norepinephrine) by monoamine oxidase. This mixture of effects mean that its main influence on BP is via an increase in CO. Its α_1-effects mediate peripheral vasoconstriction, while the β_1-effects are positive inotropy and chronotropy, and the β_2-effects are bronchodilatation (and vasodilatation). The bolus dose is 3–5 mg titrated against response and repeated as necessary. The drug has a rapid onset of action with a duration of action that is said to be around 60 min, but in practice appears to be less. Noradrenaline depletion due to its indirect action leads to tachyphylaxis.
  - *Clinical usage*: It traditionally has been favoured in obstetric anaesthesia because it does not cause α_1-mediated vasoconstriction in the uteroplacental circulation. The fetal EEG, however, does show excitation for about 6 h after administration. Ephedrine increases myocardial oxygen demand and so should be used in caution in patients with a pre-existing tachycardia or with cardiac disease. It is also dysrhythmogenic. It is an effective bronchodilator.

Phenylephrine

- **Pharmacology:** Phenylephrine is an α_1-agonist with mainly direct actions. It also possesses some weak β-activity. Its primary influence on BP is via α_1-vasoconstriction with an increase in peripheral resistance. The dose is 50–100 μg titrated against response and repeated as necessary. Onset is rapid and its duration of action is often shorter than the 60 min that is claimed.
  - *Clinical usage*: It is an effective vasopressor which is especially popular in some cardiac units. It may also be used in obstetric anaesthesia despite traditional avoidance of all pressor drugs apart from ephedrine. Phenylephrine has no more deleterious effects on neonatal cord pH than ephedrine and it raises the BP more effectively. It is not dysrhythmogenic,

but it can cause a reflex bradycardia, which may require treatment with atropine or glycopyrrolate. It can be useful in patients in whom a tachycardia should be avoided.

Methoxamine

- This vasopressor was primarily a direct-acting α_1-agonist, with some minor indirect and β-adrenoceptor-blocking actions. It is no longer manufactured, although there are a few residual supplies which shortly will be exhausted.

Metaraminol

- **Pharmacology:** Metaraminol is a sympathomimetic with both direct and indirect actions and α- and β-effects (α-effects predominate). Its influence on BP is via α_1-vasoconstriction and increase in CO with increased coronary blood flow. The dose is 1–2 mg titrated against response and repeated as necessary. The onset of action is rapid (1–3 min) and duration of action around 20–25 min.
  - *Clinical usage*: It is a potent and effective vasopressor, which is particularly useful for the treatment of hypotension due to sympathetic blockade.

Noradrenaline (norepinephrine)

- **Pharmacology:** Noradrenaline is an exogenous and endogenous catecholamine. It is a powerful α_1-agonist with weaker β-effects. Its vasopressor effect is mediated via α_1-vasoconstriction and the increase in peripheral resistance. It is administered by intravenous infusion ($0.05–0.2\,\mu g\,kg^{-1}\,min^{-1}$) and titrated against the desired level of arterial pressure. Its onset and offset of action are rapid.
  - *Clinical usage*: Noradrenaline is used more commonly in intensive care medicine than in anaesthesia, particularly to treat the low SVR associated with sepsis. Sudden discontinuation of an infusion may be accompanied by rebound severe hypotension. This explains the occasional requirement for the drug following removal of a noradrenaline-secreting phaeochromocytoma. Reflex bradycardia is common.

Adrenaline (epinephrine)

- **Pharmacology:** Adrenaline is also an exogenous and endogenous catecholamine, which acts both as an α_1- and β-agonist. In low doses β-mediated vasodilatation predominates, but the BP rises because of the increase in CO. In high doses adrenaline causes α_1-vasoconstriction. It is given either as a bolus (in the case of circulatory arrest) or as an intravenous infusion in the same dose range as noradrenaline ($0.05–0.2\,\mu g\,kg^{-1}\,min^{-1}$).
  - *Clinical usage*: The use of adrenaline as a vasopressor is effectively limited to catastrophic circulatory collapse and cardiac arrest.

Magnesium sulphate

Commentary

When this topic was first asked in the Final FRCA it caused some consternation among candidates who were then unaware both of its physiological importance and of its wide range of clinical applications. These are now much better recognised, and you will be expected to have a broad appreciation of the significance of this drug.

The viva

You will be asked to describe its basic pharmacology and physiology.

- **Mode of action:** Many processes are dependent on magnesium (Mg^{2+}) including the production and functioning of ATP (to which it is chelated) and the biosynthesis of DNA and RNA. It has an essential role in the regulation of most cellular functions.
  - It acts as a natural calcium (Ca^{2+}) antagonist. High extracellular Mg^{2+} leads to an increase in intracellular Mg^{2+}, which in turn inhibits Ca^{2+} influx through Ca^{2+} channels. It is this non-competitive inhibition that appears to mediate many of its effects. It also competes with calcium for binding sites on sarcoplasmic reticulum thereby inhibiting its release.
  - High concentrations inhibit both the pre-synaptic release of ACh and as well as post-junctional potentials.
  - Mg^{2+} also has an antiadrenergic action: release at all synaptic junctions is decreased, and it inhibits the release of catecholamines.
- **Physiology:** Magnesium is the fourth most abundant cation in the body, as well as being the second most important intracellular cation. It activates at least 300 enzyme systems. It affects the activity of neurones, of myocardial and skeletal muscle fibres, and of the myocardial conduction system. It also influences vasomotor tone and hormone receptor binding.

Effects on systems

Central and peripheral nervous systems

- Magnesium penetrates the blood–brain barrier poorly, but it nevertheless depresses the CNS and is sedating. It acts as a cerebral vasodilator, and it interferes with the release of neurotransmitters at all synaptic junctions. Deep tendon reflexes are lost at a blood concentration of 10 $mmol\,l^{-1}$. High Mg^{2+} levels do not, as once was thought, potentiate the action of depolarising muscle relaxants. Predictably, however, they do decrease the onset time and reduce the dose requirements of non-depolarising relaxants.

Cardiovascular

- It mediates a reduction of vascular tone via direct vasodilatation. It also causes sympathetic block and the inhibition of catecholamine release. Magnesium decreases cardiac conduction and diminishes myocardial contractile force. This intrinsic slowing is opposed partly by vagolytic action.

Respiratory

- Magnesium has no effect on respiratory drive, but it may weaken respiratory muscles.

Uterus

- It is a powerful tocolytic, which has implications for mothers who are being treated with the drug to control hypertensive disease of pregnancy prior to delivery.

Renal

- Magnesium acts as a vasodilator and diuretic.

Direction the viva may take

The viva is likely to move onto clinical indications for its use.

Therapeutic uses

- **Pre-eclampsia and eclampsia:** Magnesium sulphate decreases SVR and is used to reduce CNS excitability. Its use in the UK to preempt eclamptic convulsions is not yet as widespread as in the USA.
- **Acute dysrhythmias:** It is effective at abolishing tachydysrhythmias: particularly ventricular, and those induced by adrenaline, digitalis and bupivacaine. The ECG of hypermagnesaemia shows a widening QRS complex with a prolonged P–Q interval.
- **Hypomagnesaemia:** This may have nutritional (normal intake 12 mmol day^{-1}) and endocrine causes. It may also be caused by malabsorption and is associated with critical illness.
- **Tetanus:** This disease is now rare in the UK, but $MgSO_4$ by infusion is the primary treatment for the muscle spasm and autonomic instability caused by this condition.
- **Epilepsy:** It can be used in status epilepticus.
- **Respiratory:** Magnesium sulphate is an effective bronchodilator that can be used in severe refractory asthma.

Further direction the viva could take

You may at some stage be asked about magnesium toxicity.

- Many of these toxic effects are predictable from its known actions.
  - The normal blood level is 0.7–1.0 mmol l^{-1}, the therapeutic level is 4.0–8.0 mmol l^{-1}.
  - Respiratory paralysis supervenes at around 15.0 mmol l^{-1}.
  - Cardiac dysrhythmias. At blood levels of 15.0 mmol l^{-1} SA and AV block is complete, and cardiac arrest will supervene at 25.0 mmol l^{-1}.
  - Magnesium crosses the placenta rapidly, and so it may exert similar effects in the neonate, which may exhibit hypotonia and apnoea.

Drugs used to treat diabetes mellitus

Commentary

Diabetes is common and the main clinical interest for anaesthetists lies in the maintenance of effective glucose homoeostasis. This is not, however, the focus of this question, which concentrates more on an understanding of intermediary metabolism. The range of drugs is expanding, but you will not be asked in any detail about newer agents such as the meglitinides and glitazones. You will, on the other hand, be expected to know about insulin and something about the well-established biguanides and sulphonylureas.

The viva

You will be asked about the range of drugs that is available. You can preface your answer with a brief account of the two types of diabetes.

- *Type 1*, or insulin-dependent diabetes mellitus, is due to an absolute deficiency of insulin. Its aetiology probably includes an auto-immune process. *Type 2*, or non-insulin-dependent diabetes, is due to a relative deficiency of insulin. This comprises either insulin resistance, reduced insulin secretion from the β-cells in the pancreatic islets of Langerhans, or both.

Insulin

- This is a major anabolic hormone, which controls intermediary and not solely carbohydrate metabolism.
  - — *Carbohydrate*: It stimulates glycogen synthesis and inhibits glycogenolysis in the liver, while also increasing glucose uptake and utilisation in muscle.
  - — *Fat*: It increases lipid synthesis (fatty acids and triglycerides) and inhibits lipolysis.
  - — *Protein*: It enhances protein synthesis (hence its abuse among bodybuilders), by enhancing amino acid uptake by muscle. It decreases protein catabolism.
- **Mechanism of action:** The hormone binds to a specific insulin receptor on the cell membrane. This consists of a large transmembrane glycoprotein complex, comprising two α-extracellular-binding sites and two β-intracellular and transmembrane proteins.
- **Insulin preparations:** There are numerous formulations whose purpose is to help diabetics maintain constant blood glucose levels throughout the day. Soluble insulin (such as human 'Actrapid') works rapidly but its action is evanescent. Longer-acting preparations are made by precipitating insulin with substances such as zinc and protamine, to form an insoluble depot compound from which insulin is more slowly absorbed. Insulin glargine is a modified insulin analogue which because of slow absorption, provides a basal insulin supply to mirror the normal physiological state. Other forms of insulin can then be given according to the patient's particular requirements.

Oral hypoglycaemic agents

Biguanides

- **Drugs:** The only biguanide in routine clinical use is metformin.
- **Mechanism of action:** Biguanides increase glucose uptake and utilisation in skeletal muscle while decreasing hepatic gluconeogenesis. They also reduce the plasma concentrations of low-density and very-low-density lipoproteins (LDL and VLDL, respectively). They may, rarely, cause a severe lactic acidosis, particularly in patients with impaired renal function. The underlying mechanism of action of these agents has not fully been elucidated, but they act only in the presence of residual endogenous insulin.

- **Pharmacokinetics:** Metformin has an elimination $t_{1/2}$ of 3 h. It is excreted renally and so will accumulate if renal function is compromised, as frequently is the case in diabetics.

Sulphonylureas

- **Drugs:** These include chlorpropamide (now largely obselete), tolbutamide, and the second-generation sulphonylureas, glibenclamide and glipazide.
  - — *Mechanism of action*: Sulphonylureas promote insulin secretion from β-cells after binding to high-affinity receptors on the cell membrane. They block an ATP-sensitive potassium channel thereby allowing membrane depolarisation, calcium influx and insulin release. They can cause prolonged and severe hypoglycaemia, particularly in the presence of other drugs, such as non-steroidal anti-inflammatory drugs (NSAIDs) which can compete for metabolising enzymes and alter plasma protein binding.
  - — *Pharmacokinetics*: Tolbutamide has a shorter $t_{1/2}$ (6–12 h) and duration of action (4 h) than glibenclamide ($t_{1/2}$ 18–24 h and duration 10 h) or glipazide ($t_{1/2}$ 16–24 h and duration 7 h). Some of these drugs, such as glibenclamide, have active metabolites, and these, like the parent compound, are excreted by the kidney. Renal impairment mandates caution with their use.

α-glucosidase inhibitors

- **Drugs:** The only drug of this class that is available is acarbose.
  - — *Mechanism of action*: Acarbose inhibits intestinal α-glucosidase, which delays the breakdown and absorption of carbohydrates (sugars and starch). Its inhibitory action is maximal against sucrase.
  - — *Pharmacokinetics*: Most of the drug remains within the gut, with only about 1–2% being absorbed systemically. Duration of action, therefore, will vary greatly according to intestinal transit times.

Glitazones (thiazolidinediones)

- **Drugs:** The agents available are pioglitazone and rosiglitazone.
  - — *Mechanism of action*: The drugs reduce peripheral insulin resistance, enhance glucose uptake by muscle and decrease hepatic gluconeogenesis. Their mechanism of action is complex, but they are agonists at the nuclear PPAR γ-receptor which mediates lipogenesis and uptake both of glucose and of free-fatty acids. The drugs were developed after a glitazone that was being investigated as a lipid-lowering agent demonstrated a hypoglycaemic effect. These current drugs also lower LDL concentrations. They increase plasma volume and some weight gain is common. Their onset of action develops over weeks and they should not be used as single component therapy.
  - — *Pharmacokinetics*: Time-to-peak action is 2 h and the $t_{1/2}$ for both is around 7 h. Both drugs have active metabolites: weakly active in the case of rosiglitazone, but with a long $t_{1/2}$ of 150 h, more active in the case of pioglitazone, but with a shorter $t_{1/2}$ of 24 h.

Meglitinides

- **Drugs:** These are analogous in action to the sulphonylureas. The two that have been developed are nateglinide (licensed only for use in combination with metformin) and repaglinide.
  - — *Mechanism of action*: These also promote insulin secretion from β-cells by blocking the ATP-sensitive potassium channel in the cell membrane. The drugs are less potent than the sulphonylureas.

— *Pharmacokinetics*: The time-to-peak effect is short at about 55 min and they also have a rapid $t_{1/2}$ of around 3 h. Inadvertent hypoglycaemia is therefore less likely with their use.

Direction the viva may take

You may be asked about diabetic ketoacidosis.

- See *Diabetic ketoacidosis*, page 318.

Drugs which relax the uterus

Commentary

Tocolysis is indicated either to inhibit premature labour in an attempt to save a threatened fetus, or to attenuate uterine contractions which are compromising fetal oxygenation. There is no placental blood flow during a contraction, and in a case of fetal distress in which the decision has been made to proceed to operative delivery; it is logical to try to relax the uterus. Anaesthetists are involved frequently with mothers in these situations and so you should know about the principles of management. There are a number of drugs which exert a tocolytic effect: ensure that you are familiar with at least the one that you have seen used most frequently.

The viva

You will be asked to describe the classes of drugs which relax the uterus.

β_2-adrenoceptor agonists

- **Drugs:** These include ritodrine, salbutamol and terbutaline. The use of ritodrine as a tocolytic is no longer recommended.
- **Mechanism of action:** The smooth muscle of the myometrium contains numerous β_2-receptors. β_2-agonists bind to these specific adrenergic receptors which lie on the outer membrane of myometrial cells. This stimulation activates adenyl cyclase with the formation of cyclic adenosine monophosphate (cAMP), the second messenger which in smooth muscle mediates relaxation. (The process is complex, but there is always the risk that some examiners may ask for more detail. Smooth muscle contraction depends on the interaction of actin and myosin, an energy-dependent process that is reliant on the hydrolysis of ATP. The interaction of the myofilaments is dependent also on the phosphorylation of myosin by myosin light-chain kinase. This enzyme is activated by calmodulin, which requires intracellular calcium ions for its activation. Increased cAMP decreases intracellular calcium and thereby inhibits myosin light-chain kinase.)
- **Effects:** Their selectivity is limited and all these drugs have some β_1- as well as β_2-activity. Hypotension, tachycardia and chest pain can complicate their use, as can tachydysrhythmias. Pulmonary oedema has been reported, to which associated high infusion rates may contribute. Patients may become agitated and tremulous. β_2-agonism stimulates glucagon release and hepatic glycogenolysis which lead to hyperglycaemia. Increased insulin secretion occurs both in response to this rise in blood glucose as well as to direct β_2-stimulation. While this maintains glucose homoeostasis the net effect is to lower serum potassium, which moves into cells. β_2-agonists cross the placenta, increase fetal HR and can also cause hyperglycaemia and hyperinsulaemia followed by hypoglycaemia.

Magnesium sulphate

- $MgSO_4$ is an effective tocolytic (see *Magnesium sulphate*, page **178**).

Calcium channel blockers

- **Drugs:** The only drug that is used as a tocolytic is nifedipine.
- **Mechanism of action:** Nifedipine blocks voltage-dependent calcium channels and also antagonises the release of calcium from sarcoplasmic reticulum.

Oxytocin antagonists

- **Drugs:** Atosiban ('Tractocile') is the only available drug of this type.
- **Mechanism of action:** It is a specific oxytocin antagonist, which has an effect on the pregnant uterus that is similar to ritodrine but with a better side effect profile. Atosiban inhibits the second-messenger release of free intracellular calcium which mediates uterine contraction. The drug can be used in conjunction with other tocolytic agents.

Nitrates

- **Drugs:** GTN is the only nitrate used for tocolysis.
- **Mechanism of action:** Effects are mediated via NO (see *Nitric oxide*, page 135), which relaxes smooth muscle. It is synthesised in the uterus and helps to maintain uteroplacental blood flow. Exogenous GTN is effective transdermally, sublingually or by intravenous infusion. The drug may cause hypotension as well as pulmonary oedema consequent upon an increase in vascular permeability. It may be less effective after 34-week gestation.

Miscellaneous

- Other tocolytics include ethanol (ethyl alcohol), which is effective, but which may cause maternal intoxication, hypotension and hyperglycaemia. Significant side effects also limit the use of diazoxide, which otherwise is another effective agent. Volatile anaesthetic agents cause a dose-dependent relaxation of uterine smooth muscle.

Direction the viva may take

You may be asked about the clinical situations in which you, as an anaesthetist rather than as an obstetrician, might use these drugs.

- To stop uterine contractions in a situation in which fetal distress mandates urgent operative delivery. One dramatic example of this is cord prolapse, in which the pressure of the presenting part on the umbilical cord may cut off the fetal blood supply. A less common, but potentially more calamitous complication, is that of acute uterine inversion.

Drugs which stimulate the uterus

Commentary

Successive reports of the confidential enquiry into maternal mortality have confirmed that uterine atony is the most important cause of fatal postpartum haemorrhage. A knowledge of the range of drugs that is available is therefore of obvious importance. The list, however, is not very long, and so the viva may well move onto a discussion about postpartum haemorrhage in general.

The viva

You will be asked to describe the drugs which stimulate the uterus.

You could begin your answer by outlining the normal contractile mechanisms of the gravid uterus.

- **Uterine activity:** Uterine smooth muscle demonstrates considerable spontaneous electrical and contractile activity. Gap junctions between myometrial cells enhance the spread of electrical activity, and these junctions increase during pregnancy to provide a low-resistance pathway. Depolarisation takes place in response to the influx of sodium ions, while the availability of calcium ions enhances the response of uterine smooth muscle. These cross the cell membrane to stimulate further release of calcium from the sarcoplasmic reticulum. The uterus contains both α_1-adrenergic (excitatory) and β_2-adrenergic (inhibitory) receptors, as well as serotoninergic and specific excitatory receptors for oxytocin. These receptors increase in number in late pregnancy.

Oxytocins

- **Drugs:** The main drug in use is syntocinon. This is an oxytocin analogue which is largely free from the arginine vasopressin effects of the endogenous compound.
- **Mechanism of action:** It acts via specific excitatory receptors, as above.
- **Effects:** In the presence of oestrogen, oxytocins stimulate both the force and frequency of uterine contraction. It also has vasodilator properties which decrease systolic and diastolic pressures, and which provoke a reflex tachycardia. It also appears to have amnesic properties (as demonstrated by experimental injection into the cerebral ventricles). Its elimination $t_{1/2}$ is between 5 and 12 min. Problems associated with its use include hypotension and pulmonary oedema.

Ergot alkaloids

- **Drugs:** *Ergometrine* is one of the powerful ergot alkaloids derived from the fungus *Claviceps purpurea*.
- **Mechanism of action:** It acts via α_1-adrenergic and also serotoninergic myometrial receptors, but the precise mechanism whereby it mediates its oxytocic effect is not fully understood.
- **Effects:** It causes uterine contraction. On the already contracted uterus it has little effect, but it is a potent oxytocic if the postpartum uterus is relaxed. Ergometrine also increases BP via arterial and venous constriction. It can cause coronary vasospasm sufficient to provoke angina pectoris. It is emetic, probably through a direct dopaminergic effect on the CTZ.

Compound preparations

- **Drugs:** The main compound preparation is syntometrine, which is a mixture of syntocinon (5 units) and ergometrine (500 μg).
- **Mechanism of action:** The drugs act in combination as above.

- **Effects:** It causes uterine contraction. The opposing cardiovascular effects of the two drugs in combination minimise the separate cardiovascular effects of each. The drug is also less emetic than ergometrine alone.

Prostaglandins

- **Drugs:** The main prostaglandin that is used to counteract uterine atony is 15-methyl $PGF_{2\alpha}$ (carboprost, 'Hemabate'). PGE_2 (dinoprostone, 'Prostin') is used for induction and augmentation of labour.
- **Mechanism of action:** Endogenous prostaglandins are usually synthesised and inactivated locally, in the tissue in which they are active. PGE_2 and $PGF_{2\alpha}$ mediate strong uterine contractions. The uterus becomes more sensitive to their effects as pregnancy progresses.
- **Effects:** Exogenous prostaglandins stimulate smooth muscle, hence diarrhoea and vomiting can be troublesome side effects. $PGF_{2\alpha}$ is also a potent constrictor of bronchiolar smooth muscle. In addition this synthetic preparation has hypothalamic effects which may lead to pyrexia. Flushing and hypotension are common. Carboprost is most effective when it is injected directly into the myometrium, after which its onset of effect is less than 5 min.

Direction the viva may take

Anaesthetists use these drugs routinely at Caesarean section and may well be involved with the further management of mothers whose deliveries are complicated by postpartum haemorrhage. It is likely that the viva may move to a general discussion of this subject. See *Postpartum haemorrhage*, page 313.

Drug overdose: prescribed and therapeutic drugs

Commentary

Patients take overdoses of numerous different drugs. The clinical features of drug poisoning may result from exaggeration of their normal effects or from the direct toxicity of the parent compound and its metabolites. Effective management of drug overdose, therefore, in some cases of poisoning, depends on an understanding of the mechanism of action of the substances that have been ingested.

The viva

You will be asked first about the drugs that are most commonly taken in overdose. It is probable that you will also be asked to give a brief outline of your emergency management. The examiner will not be interested in a generic 'Airway, Breathing, Circulation' approach, but will want specific details where appropriate.

- **Antidepressants:**
  - The main classes of drugs are the tricyclic antidepressants (TCAs) such as amitriptyline and imipramine, and the selective serotonin re-uptake inhibitors (SSRIs) such as fluoxetine ('Prozac') and paroxetine ('Seroxat').
    - *Mechanism of action*: TCAs are tertiary amines and are related chemically to phenothiazines. Their main effect is to block the re-uptake of amines, primarily noradrenaline and 5-HT, by inhibiting competitively the binding site of a transport protein. They have minimal influence on dopaminergic synapses, but do affect muscarinic ACh and histamine receptors.
  - SSRIs are relatively selective for 5-HT uptake, have fewer anticholinergic side effects than TCAs and are safer in overdose. They can cause a 'serotonin syndrome' if used in combination with drugs such as monoamine oxidase inhibitors (MAOIs). Its features include hyperthermia, muscular rigidity and cardiovascular collapse.
    - *Features of overdose*: The major problems are cardiovascular and neurological. Ventricular dysrhythmias are common and are associated particularly with Q–T interval prolongation. In high doses they appear to block a specific cardiac potassium channel (the HERG channel). VF may supervene. Other potential dysrythymias include heart block and ventricular tachycardia. CNS effects include agitation and excitability, grand mal convulsions and coma. The muscarinic effects resemble those of atropine poisoning with flushing, dry mouth, mydriasis and gastrointestinal stasis. Features of poisoning with SSRIs are analogous, but generally are less severe.
    - *Management*: This is largely supportive. Benzodiazepines may abort convulsions. Any cardiac dysrhythmias should be treated only with extreme caution, if at all, because the combination of effects can be fatal. Magnesium is probably the least dangerous treatment, although intravenous lignocaine and amiodarone have also been used. ECG monitoring is mandatory for at least 24 h after ingestion. Induced alkalosis (plasma pH greater than 7.5) by the use of hyperventilation and intravenous $NaHCO_3$ may reduce the amount of free drug that is present.
- **Paracetamol:** This is a ubiquitous simple analgesic.
  - *Mechanism of action*: Paracetamol probably acts as an inhibitor of central prostaglandin synthesis, although its precise subcellular mechanism of action remains unclear. Evidence about any peripheral anti-inflammatory action is conflicting. It is rapidly absorbed from the small intestine. Its therapeutic index is narrow because the liver enzymes which catalyse the normal conjugation pathways rapidly become saturated. The alternative

metabolic pathway via mixed function oxidases produces the metabolite *N*-acetyl-*p*-benzoquinine imine, which is toxic to cells both of the liver and of the renal tubules. This metabolite normally is conjugated with glutathione, but will accumulate when glutathione stores are depleted to cause centrilobular hepatic necrosis and renal tubular damage.
  - *Features of overdose*: Nausea and vomiting occur early, symptoms and signs of hepatic failure appear later.
  - *Management*: Definitive early treatment is with agents that will replenish glutathione stores and prevent hepatic damage. Methionine, which is a glutathione precursor, can be given orally, although the more common treatment is intravenous *N*-acetylcysteine. Fulminant hepatic failure can be treated only by hepatic transplantation.

- **Benzodiazepines**
  - These anxiolytics and hypnotics, of which there are over 20 available for clinical use, are common prescription drugs. Typical examples are temazepam, diazepam and clonazepam. (Midazolam is a drug whose use is restricted largely to hospital.)
  - *Mechanism of action*: Benzodiazepines facilitate the opening of GABA-activated chloride channels and thereby enhance fast inhibitory synaptic transmission within the CNS. They bind to a separate receptor, which effects an allosteric change that increases the affinity of GABA for the $GABA_A$ receptor.
  - *Features of overdose*: These drugs are relatively safe in overdose because taken alone they cause profound sedation but without respiratory depression, haemodynamic instability or secondary toxicity. In combination with other CNS depressants, however, they may be associated with marked respiratory depression.
  - *Management*: Flumazenil ('Anexate') is a specific benzodiazepine anatagonist which displaces benzodiazepines from the binding sites and reverses their effects. The effective duration of action of flumazenil is shorter than that of many of the drugs which it antagonises, and so the dose (typically up to 500 μg intravenously) may need to be repeated. The incautious use of flumazenil may also unmask convulsions due, for example, to TCAs, otherwise suppressed by the benzodiazepine overdose.

- **Tramadol**
  - This is a synthetic piperidine analogue of codeine. It is an oral analgesic which is used for moderate pain, but which is not associated with drug dependence or abuse. It is not, therefore, a controlled substance.
  - *Mechanism of action*: Tramadol is a racemic mixture of R(+) and S(−)-enantiomers. The R(+)-enantiomer appears to have relatively low activity at μ-receptors, but the higher affinity of its main M1 metabolite results in a sixfold increase in analgesic potency. The μ-effects in humans are not very impressive. The S(−)-enantiomer acts to inhibit the re-uptake of norepinephrine and 5-HT within the CNS.
  - *Features of overdose*: Although activity at μ-opioid receptors is weak, after overdose patients may demonstrate typical features of sedation and respiratory depression. Of greater interest are the signs of a serotonin syndrome, which include agitation, tachycardia and hypertension, diaphoresis and muscular rigidity. Patients may also be hyperthermic and show other signs of deranged autonomic function. Disseminated intravascular coagulation has been reported, as has rhabdomyolysis and renal failure. Grand mal convulsions may supervene.
  - *Management*: In general the treatment of a tramadol overdose is supportive. Naloxone can be used to treat the opioid side effects, but the optimal

management of a serotonin syndrome remains uncertain. The 5-HT_{2A} antagonist cyproheptadine has been used, as have drugs such as dantrolene, propranolol and diazepam.

- **Alcohol**
  - This is included because alcohol ingestion frequently complicates overdose with other drugs. TCAs, for example, appear dangerously to enhance the depressant effects of acute alcohol intake.
  - *Mechanism of action*: Ethanol facilitates the opening of GABA-activated chloride channels to increase fast inhibitory synaptic transmission within the CNS. It also acts to inhibit the NMDA receptor.
  - *Features of overdose*: Disinhibition is followed by CNS depression. The features of acute intoxication are too well known to warrant detailing here. An important complication that must not be missed, however, is the effect of acute alcohol on glucose metabolism. Subjects who have recently ingested large volumes of alcohol are at risk of profound hypoglycaemia. The metabolism of alcohol to acetaldehyde is catalysed by alcohol dehydrogenase, in a reaction which produces NADH from NAD^+. This effectively depletes NAD^+, which is important co-factor in the gluconeogenetic conversion of lactate to pyruvate.
  - *Management*: The metabolism of alcohol follows zero-order kinetics and management is supportive.

Recreational drugs and drugs of abuse

Commentary

The abuse of recreational drugs is common, and patients may present either because of an adverse reaction or because, often unwittingly, they have taken or been given, an overdose. It can be difficult to identify exactly what substances are affecting an individual, however, because street drugs have no quality control. These adulterated compounds, moreover, are commonly taken in combination. But as is the case with prescribed drugs, an understanding of their mechanisms of action helps the rational management of overdose.

The viva

You are likely to be asked about the common drugs of abuse. There are some niche drugs, such as 'GHB' (gamma-hydroxybutyrate) and 'Special K' (ketamine), but the general pattern of drug abuse relates to methadone and heroin (diamorphine), cocaine, ecstasy (3,4-methylenedioxy methamphetamine (MDMA)) and, of course, alcohol. It is also probable that you will be asked to comment on your emergency management. As with overdoses of therapeutic drugs, the examiners will be less interested in your generic management than in your ability to apply appropriate pharmacological knowledge.

- **Opiates:** Methadone and heroin are the main opiates of abuse.
  - *Mechanisms of action*: There are three main opioid receptor subtypes: μ(mu), κ (kappa) and δ (delta), which are also referred to, respectively, as OP3, OP2 and OP1 receptors. Opiates have a number of effect at the cellular level: they inhibit intracellular adenyl cyclase via G-protein coupling, they hyperpolarise cell membranes by facilitating the opening of potassium channels, and inhibit neurotransmitter release by decreasing the function of calcium channels. μ-receptors are believed to mediate not only analgesic effects, but also respiratory depression. κ-receptors have more spinal and peripheral than central analgesic effects, as do the δ-receptors. (The σ (sigma) receptor is not considered to be a true opioid receptor, but mediates psychotomimetic effects both of opiates and of other types of psychoactive agents.)
  - *Features of overdose*: The features of opiate overdose are well known. The life-threatening complication of opiate overdose is profound central respiratory depression. Patients may be sedated, comatose and bradypnoeic. Hypotension is common, and this may be associated both with tachycardia and bradycardia. The other numerous effects of opiates are of much less relative importance. Methadone has a similar spectrum of action to diamorphine, although it is less euphoriant and less sedative. It has a much longer elimination $t_{1/2}$ (more than 24 h.)
  - *Management*: The specific opiate antagonist naloxone is the initial drug of choice. The intravenous dose is higher than is used for typical post-operative respiratory depression being 0.8–2.0 mg, repeated after 2–3 min to a maximum of 10 mg. If there has been no response by this stage then the diagnosis should be reviewed.
- **Cocaine**
  - *Mechanism of action*: Cocaine is an indirect sympathomimetic which blocks the pre-synaptic re-uptake of noradrenaline (norepinephrine). It also exerts central dopaminergic and serotonergic effects.
  - *Features of overdose*: These include agitation and disorientation, together with other features of sympathetic hyper-stimulation. Hypertension, hyperpyrexia, convulsions and coma may all be evident. The drug increases myocardial oxygen demand and causes coronary vasospasm. VF may supervene.

  - *Management*: It would be logical to treat the sympathetic overactivity with α- and β-adrenoceptor blockers, although some authorities dispute the place of β-blockers because of their unopposed α-effects on the circulation. These can be offset by using, for example, phentolamine (5 mg intravenously, repeated as necessary). Otherwise the management of cocaine poisoning is supportive.
- **MDMA (ecstasy):** This is a popular recreational drug, which has caused well-publicised deaths among a small number of young people. These deaths are not necessarily related to overdose, although because the drug is illegal, information about quantity, quality and formulation is almost impossible to obtain. The clinical features may, therefore, be due to an idiosyncratic reaction.
  - *Mechanism of action*: MDMA is related structurally both to methamphetamine and to mescalin, which is a potent hallucinogen. Amphetamines are centrally acting sympathomimetics which appear to stimulate central aminergic pathways, particularly those mediated by dopamine and norepinephrine. They inhibit re-uptake of neurotransmitter, stimulate its pre-synaptic release, and act as direct agonists at post-synaptic receptors. These effects occur peripherally as well as centrally. MDMA also acts as an agonist at 5-HT_2-receptors to produce psychotomimetic effects. This may also be partly responsible for the hyperthermia that may be evident.
  - *Features of overdose*: 'Ecstasy' use is associated with the club scene and so patients may present having been dancing violently in a hot environment without taking adequate isotonic fluid. They may be delirious or unconscious, with grand mal convulsions. They are frequently diaphoretic and febrile. This hypermetabolic state is associated with a metabolic acidosis, and also with rhabdomyolysis. Disseminated intravascular coagulation rapidly may supervene, followed by multi-organ failure.
  - *Management*: Patients may require full intensive care management, including renal support if indicated. Dantrolene (1 mg kg^{-1} initially) has been used to control hyperpyrexia, although support for its use is not universal.
- **Alcohol**
  - Alcohol may be taken alone in overdose, or as part of a cocktail of substances.
  - See *Drug overdose*: *prescribed and therapeutic drugs* page 187.
- **Cannabis:** Overdose of cannabis is not a common problem, given that most individuals in the UK smoke the drug, rather than ingesting it. Nor is acute excess directly life threatening. A brief account is included for completeness in the event that the examiners may raise the topic.
  - *Mechanism of action*: Central cannabinoid receptors (CB_1 subtype) exert an inhibitory effect on nociceptive afferents and on transmission via the dorsal horn. Like opiates they are typical G-protein-linked receptors, which inhibit adenyl cyclase, hyperpolarise cell membranes by facilitating the opening of potassium channels, and decrease neurotransmitter release via calcium channel inhibition. Tetrahydrocannabinol (THC) is analgesic, sedating, anti-emetic, antispasmodic, euphoriant, anxiolytic and bronchodilatory.
  - *Features of acute excess*: The main features are sedation and confusion, although the drug can also cause vasodilatation and tachycardia. Paranoid delusions of the kind that may be seen with hallucinogenic drugs are rare.
  - *Management*: Unless patients have complicated cannabis use by concurrent ingestion of other substances they will require only modest supportive therapy.

Clonidine

Commentary

Clonidine is an old drug, which has been used in the treatment of hypertension and of migraine, in angina, as an anxiolytic, as a treatment for glaucoma and as a nasal decongestant. It has also been used in conditions as diverse as neuropathic pain and attention-deficit hyperactivity disorder (ADHD). Anaesthesia has found new uses for the agent whose actions cannot totally be explained in terms of agonism at α_2-adrenoceptors. It is an interesting drug, and so it would be preferable if you can convey some of your enthusiasm via direct experience of its use.

The viva

The question is likely to be open ended, and will start with an invitation to talk about clonidine.

- Clonidine is an agonist at α_2-adrenoceptors. It has some minor activity at α_1-receptors (the ratio of $\alpha_1 : \alpha_2$ is 1 : 200) and because it is an imidazoline derivative also acts at imidazole receptors. Two subtypes have so far been identified, the I_1- and I_2-receptors, which are located centrally and appear to mediate sedation and hypnosis. Clonidine is associated with a decease in intracellular cAMP via a G_i-protein receptor.
- It acts at pre-synaptic α_2-receptors, both centrally and peripherally, to inhibit the release of noradrenaline. α_2-receptors in the hypothalamus are inhibitory to the vasomotor outflow. Clonidine also acts post-synaptically in the adrenal medulla.
- It acts in addition at peripheral post-junctional α_2-receptors to mediate slow onset vasoconstriction of long duration, to which its activity at α_1-receptors may contribute. This may explain why an intravenous dose may be associated with a transient rise in arterial BP.

Direction the viva may take

You are likely to be asked about the use of clonidine in clinical anaesthesia.

- **Stress and pressor responses:** Clonidine can be used (in a dose of $5\,\mu g\,kg^{-1}$) to attenuate both the endocrine stress response to surgery and the pressor responses to laryngoscopy and tracheal intubation.
- **Adjunct to anaesthesia and analgesia:** A dose of $1–2\,\mu g\,kg^{-1}$ intravenously can be given during anaesthesia to reduce the MAC of inhaled volatile agents and to reduce the requirement for systemic analgesics.
- **Hypotensive anaesthesia:** $1–2\,\mu g\,kg^{-1}$ intravenously can produce modest and sustained hypotension which may improve operating conditions during which bleeding would otherwise mask the surgical field.
- **Antisialogogue effect:** A side effect of clonidine administration is reduced salivary secretion: this property can be utilised in the peri-operative period.
- **Alcohol withdrawal:** Clonidine inhibits the exaggerated release of sympathomimetic neurotransmitters during acute alcohol withdrawal. It has also been used to attenuate the symptoms of opiate withdrawal.
- **Sedation and anxiolysis:** It has both sedative and anxiolytic actions, but is not commonly used alone for these properties.
- **Chronic pain:** Clonidine has been used for the treatment of neuropathic pain.
- **Adjuvant use in regional anaesthesia:** There appear to be no α_2-receptors on the axons of peripheral nerves, although the addition of clonidine to local anaesthetic does increase modestly the duration of action of the block. It produces a small decrement of nerve conduction at high concentrations, affecting preferentially on C-fibres. Neuraxial clonidine, in contrast, does extend the block. The addition of $2\,\mu g\,kg^{-1}$ to local anaesthetic solutions for sacral extradural (caudal) block will double the duration of effective analgesia. The

same is true of clonidine given intrathecally. The side effects are those of sedation, dry mouth, and it is said, refractory hypotension, although this is not an obvious problem in clinical practice. Intrathecal α_2-agonists achieve analgesia partly through cholinergic activation: hence the brief interest in using spinal neostigmine as an adjunct.

Further direction the viva could take

You may be asked to compare clonidine with dexmedetomidine.

- The drugs act in a similar way. Dexmedetomidine, which is the R isomer of metetomidine, has the advantage of being a more selective α_2-agonist than clonidine, and it has more pronounced effects on central α-receptors. It has yet to become available in the UK because it awaits a licence for use in humans.

Design of a clinical trial for a new analgesic drug

Commentary

Drugs are at the core of the speciality of anaesthesia, and so you should not find it unreasonable should you be asked about the broad principles that underpin randomised-controlled clinical trials. The subject is not too difficult, and you should be able to work out the important aspects of this kind of research even if you do not have the information readily to hand. It is inevitable that statistics will form part of the discussion, however much you might wish to defer it. You will always do well to start simply when the subject of statistics arises, because a demonstration that you understand the basic concepts will usually be sufficient to get you through.

The viva

You will be asked to describe how you would design a clinical trial for a new drug, typically an anaesthetic or analgesic agent.

- A clinical trial for a new agent is carried out during phase II or III of the drug's development. (Pre-clinical development involves animal studies into aspects such as safety, efficacy and mutagenicity. Phase I involves small group studies of fewer than 100 healthy volunteers, looking at pharmacokinetics, pharmacodynamics and adverse effects. Phase II recruits larger numbers of patients, typically 200–300, in which the findings of the phase I studies are refined. Phase III involves still larger numbers of patients, usually in the thousands, who are entered into definitive randomised-controlled clinical trials. Phase IV occurs after the drug has been licensed for use, and involves post-marketing surveillance of its effects in much greater numbers of individuals.)
- **Ethics committee approval:** No clinical trial can proceed without the approval of an appropriately constituted ethics committee, which will include lay people among its members. These committees are increasingly rigorous, and in essence they seek to preserve the full protection of the rights of every potential participant. Individuals must receive full information about every aspect of the trial before they consent, and must be free to withdraw at any stage without compromising their future care. Committees will scrutinise intensely any trial in which financial inducements are involved.
- **Trial design:** The best-designed clinical trials seek to answer a single simple question: in this case, whether the new analgesic is superior to established treatments. It is essential to have a control in the study, which in this instance would be an analgesic in clinical use that was of proven efficacy. Trial design must therefore involve defining end points for efficacy, and must also ensure that data relating to adverse effects are collected. The use of placebos in trials of analgesics is considered to be unethical, and so the drugs in all limbs of the trial will be pharmacologically active.
- **Subject selection:** It is important that the groups are matched as far as possible. Such matching should include age, gender, American Society of Anesthesiologists (ASA) status and racial characteristics. Exclusion criteria must also be established. If the drug is to be used for treatment of chronic pain then the trial can be a double-blind (see below) crossover trial in which the patient can act as his or her own control. Sufficient time must elapse between administrations of the two drugs to ensure that the first one that the patient has received is no longer exerting any effect.
- **Sample size:** The conclusions of any trial can be erroneous. The study can determine either that there is a difference between treatments when none exists, or it can determine that there is no difference between treatments when a difference does in fact exist. The first (false-positive) conclusion is known as a Type 1 error. The second (false-negative) conclusion is a Type 2 error. The probability of avoiding a Type 2 error and missing a significant difference

between treatments is known as the power of the trial. In other words, the power of a study is its ability to reveal a difference of a particular size. The power calculation allows the investigator to determine the sample size necessary to demonstrate this difference. It is calculated from 1-β, where β is the Type 2 error. Trials are usually designed with a power of 80% ($\beta = 0.2$) or better 90% ($\beta = 0.1$). The investigators must also decide the magnitude of the difference that is sought.

- **Randomisation:** Randomisation of patients to one or other limbs of the trial is intended to remove bias. The bias may be unconscious or hidden. Patients may not have been allocated randomly to an operating list, for example, and so assigning alternate patients to trial groups might be unreliable. Simple methods, such as tossing a coin, are valid, although it is more common to use computer-generated randomisation.
- **Blinding:** It is ideal for the trial to be double blind, so that neither the patient nor the investigator knows to which group they have been assigned. This is of particular importance when the outcome data are subjective, as in a comparison of analgesic drugs or techniques.
- **Data collection:** Obvious considerations apply to the scrupulous collection of data. Inherent variation can be avoided by minimising the number of investigators involved in the process.
- **Statistical evaluation:** The appropriate statistical tests must be chosen for the question that is being asked. In this case the null hypothesis is that there is no difference between new analgesic A and established analgesic B. The tests of statistical significance aim to define whether the null hypothesis has been disproved, in other words that there is a difference between drugs A and B, and at what level of probability. The investigators must also decide whether the data are continuous and normally distributed, in which case a parametric test is appropriate. If the data do not follow a normal distribution then a non-parametric test should be used. The evaluation of an analgesic would almost certainly involve the use of visual analogue scales, about which statisticians may disagree. Some argue that response to pain is a biological variable with a normal distribution; others contend that the data are not normally distributed and that non-parametric tests should be used.
- **Clinical and statistical significance:** Trial data will be cited according to the strength of its statistical significance, although clinical significance is the more important. The bigger the sample size the more likely it is that a small effect will be statistically significant, even though clinically its impact may be negligible.

Inhalational agents: comparison with the ideal

Commentary

This is a standard introduction to a discussion of the agents that are available. After you have outlined the desirable characteristics of your ideal agent you will be asked how one or more of the drugs in current use compare. The way that this question is structured means that the subject tends to be discussed at a quite superficial level, although you will need to be prepared to explain some of the concepts in somewhat more detail. Be aware of the important purported differences in their effects on systems, but recognise also that comparisons have been established via studies of dissimilar methodology and have sometimes yielded conflicting results. This means that you cannot be expected to discuss detailed comparative information.

The viva

You will be asked first to describe the properties of an ideal volatile anaesthetic agent. You will also be asked, either as you describe each property or subsequently, to compare one or more of the currently available agents against this ideal. (In the interests of completeness, xenon is mentioned intermittently in the account below. There is, however, much less commonly available information about this agent, and the examiners will be very interested if you have actually encountered it.)

There is no right answer to this question, so do not worry if initially your mind goes blank. You can start with the common sense observation that a drug needs to be safe and effective, with minimal metabolism, and the examiner will prompt you thereafter to the areas that he or she wishes to explore.

Characteristics of the ideal inhalational agent might include the following:

- **Safety:** The ideal agent would be safe by virtue of its specificity for the nervous system. It would, in other words, allow a controlled state of insensibility in which all other physiological indices such as cerebral and myocardial blood flow remained unchanged. No such agent exists, and so patients receiving inhalational agents may be at potential risk from the secondary, undesirable effects of an agent, from directly toxic effects, or from toxic products of metabolism.
- **Secondary effects**
  - *Respiratory*: The potential to cause airways irritation is discussed below. All the drugs are respiratory depressants, and cause a typical decrease in tidal volume with an increase in respiratory rate. They are effective bronchodilators.
  - *Cardiovascular*: All the halogenated agents have cardiovascular effects, but none so marked as to preclude their clinical use.
    - Halothane, however, is the most dysrhythmogenic. It causes a dose-related fall in mean arterial pressure (MAP) and it may also cause bradycardia, junctional rhythms and ventricular premature beats. It sensitises the myocardium to catecholamines, particularly in the presence of acidosis and hypercapnia.
    - Enflurane similarly causes dose-related cardiovascular depression, but is not dysrhythymogenic. Isoflurane leads to a dose-dependent reduction in SVR and coronary vascular vasodilatation. HR increases and CO and cardiac contractility are maintained.
    - Isoflurane was believed to cause a coronary steal syndrome in which coronary vasodilatation diverted blood away from stenotic vessels. Controlled trials, however, have suggested that is no worse than any other volatile in this regard.
    - The actions of desflurane are similar: SVR and MAP fall, HR rises and CO is maintained.

  - Sevoflurane also leads to dose-dependent cardiovascular depression, with decreases in MAP, SVR and contractility. The HR, however, does not increase and the agent causes less coronary vasodilatation than isoflurane.
  - *CNS:* All the halogenated agents increase CBF, which can cause a rise in ICP that in some circumstances may be deleterious. Sevoflurane preserves cerebral autoregulation better than the other agents. Desflurane in contrast abolishes autoregulation at 1.5 MAC. At 1 MAC isoflurane and sevoflurane are associated with minimal change in CBF and ICP. Enflurane is associated with abnormal epileptiform activity in the EEG particularly if its administration is accompanied by hypocapnia.
  - *Uterus*: All the agents, apart from N_2O, cause dose-related uterine relaxation.
  - *MH*: All the halogenated agents are reported triggers for MH, although halothane is the most potent in this regard.
- **Toxicity**
  - N_2O depresses bone marrow function via its oxidation of the cobalt atom in the vitamin B_{12} complex (see *Nitrous oxide*, page 151). Sevoflurane may produce the potentially, but not demonstrably toxic compound A (see below), as well as free-fluoride ions. Enflurane also produces fluoride ions, while halothane is implicated in post-exposure hepatic dysfunction (see below).
- **Efficacy:** The agent, by definition, has to be able to induce and maintain a state of anaesthesia, and all the halogenated agents produce dose-dependent narcosis. Some are more 'potent' than others, in the sense that their effects are produced at lower concentrations, but clinically it is of little relevance. According to this criterion for example, halothane is almost nine times as potent as desflurane. A much more significant property is the blood solubility, as quantified by the blood-gas partition coefficient. The less soluble the agent the lower the amount required to produce a given partial pressure and the more rapid the onset of action. In ascending order, therefore, the agents can be ranked: xenon, whose blood-gas partition coefficient is only 0.17, desflurane (0.42), N_2O (0.47), sevoflurane (0.68), isoflurane (1.4), enflurane (1.9) and halothane (2.3). 'Potency' in respect of inhalational agents is in effect defined by the minimum alveolar concentration, at which 50% of the population will not display reflex movement in response to a standard surgical stimulus. This is the MAC_{50}, but the MAC_{95} (the prevention of movement in 95% of subjects) is more useful.
- **Non-irritant:** This is a desirable feature in any agent that is inhaled. Sevoflurane is non-irritant to the upper airway and bronchi, and inhalational induction can be swift and effective in the most testing of circumstances. Halothane shares the same characteristics, but is rather more pungent. Enflurane is not dissimilar, although inhalation induction is more prolonged. Isoflurane is more irritant to airways and is associated with a higher incidence of coughing and breath holding. Desflurane is the most inferior agent in this regard, its other benefits being offset by its effective capacity to provoke laryngospasm, excessive secretions and apnoea.
- **Metabolism:** Inhaled agents are eliminated through the lungs, but metabolism still occurs, principally by cytochrome P450 oxidation in the liver. None of the agents has active metabolites, but clearly the greater the proportion that undergoes hepatic metabolism the greater is the excretory load.
  - *Xenon*: Xenon is an inert gas which undergoes no biotransformation.
  - *N_2O*: This undergoes minimal metabolism (0.004%) mainly by gut micro-organisms.
  - *Desflurane*: This is resistant to metabolism (0.02%) and serum fluoride levels do not rise even after prolonged administration.
  - *Isoflurane*: Metabolism is around 0.2%, which can lead to a small rise in fluoride concentrations.

- *Enflurane*: Metabolism is higher at around 3% and serum fluoride levels may reach 25 $\mu mol l^{-1}$, which may be of theoretical importance in patients with pre-existing renal impairment. (Fluoride is nephrotoxic at levels of 50 $\mu mol l^{-1}$and above.)
- *Sevoflurane*: This undergoes 3–5% metabolism and produces more fluoride ions than enflurane. Serum fluoride concentrations may reach 15–25 $\mu mol l^{-1}$ after 1 MAC hour of administration. In theory it should be used with caution in patients with renal dysfunction, but this is not regarded universally as a contraindication for its use.
- *Halothane*: This is the most extensively metabolised of the inhalational agents, with 20–40% being degraded by both reductive and oxidative pathways. A trifluoracetylated compound produced by oxidation can bind to liver proteins, triggering in susceptible patients an immune reaction, which may precipitate hepatic necrosis. This is a separate problem from the transient post-operative rise in liver enzymes, which may be seen in as many as 20% of patients.

- **Stability:** This refers to the molecular stability of the compound when exposed to the normal range of environmental conditions, and to the specific circumstances of its use in an anaesthetic breathing system. Ideally, therefore, it should be stable to light and to temperature, it should undergo no spontaneous degradation and require no preservatives, it should be non-flammable and non-corrosive and be safe in the presence of soda lime and alkali. Most of the agents perform well against these criteria: some specific exceptions include the following.
  - N_2O: The gas supports combustion.
  - *Desflurane*: This agent has a low boiling point that is close to room temperature (23.5°C).
  - *Sevoflurane*: This reacts with strong monovalent hydroxide bases, such as those which are used in soda lime and barium lime CO_2 absorbers, to produce a number of substances including compound A. (The reaction with barium lime is about five times more rapid than with soda lime.) Of the degradation products (compounds A, B, D, E and G) only A, which is a vinyl ether, has been shown to have any toxicity, but the dose-dependent renal damage noted in rats has never been seen in humans despite many millions of administrations.
  - *Halothane*: Halothane may degrade when exposed to light and so is presented in amber bottles in thymol 0.01% as a preservative. Accumulated thymol can affect vaporiser function.

Spinal adjuncts to local anaesthetics

Commentary

This is a question about the drugs that can be added to epidural or intrathecal solutions of local anaesthetics as a means of prolonging or enhancing their action. This is becoming routine practice both in obstetric and in peri-operative analgesic techniques. You may not have direct experience of non-opiate adjuncts, and so this part of the discussion is likely to be purely theoretical. If, however, you have worked with an anaesthetist who is an enthusiast for the use of subarachnoid ketamine or neostigmine, then feel free to say so, because most examiners will be interested to learn of your experiences. When it comes to discussing intrathecal drugs you may be aware that there is some confusion over the use of the terms 'opiate' and 'opioid'. The word 'opiate' traditionally denoted drugs such as morphine that were derived from the opium poppy, *Papaver somniferum*, while 'opioid' was used to mean 'opiate-like'. According to this definition, however, codeine phosphate is classified as an opiate, whereas diamorphine (which is diacetylated morphine) is not. It is more logical to use 'opiate' as the noun, and 'opioid' as the adjective, and this is the convention that appears in the account below. There can also be confusion about the term 'spinal' in the context of drug administration. Texts refer to 'spinal opiates' because that describes not their route of administration, but their site of action.

The viva

You will be asked about drugs that have been used to enhance the actions of local anaesthetics either in epidural or in subarachnoid solutions.

- **Spinal opiates:** The successful use of epidural morphine was first reported in 1979, since which time several different opiates have been administered via the epidural and intrathecal routes. In the UK these include diamorphine, morphine, fentanyl, pethidine and methadone. Both onset and duration of action are related to the lipid solubility of the drug. Morphine has low lipid solubility, whereas that of fentanyl is high, and this is reflected in durations of action of 18 and 2–4 h respectively. The lipophilic drugs cross rapidly into the cord, while hydrophilic agents remain partly within the cerebrospinal fluid (CSF), in which they may be carried rostrally to act on higher centres. This is the mechanism by which delayed respiratory depression and sedation may be caused. It is thus more common with morphine than with other drugs, and is better monitored by sedation scoring rather than respiratory rate. Pulse oximetry may be misleading, because a high-inspired oxygen concentration may mask ventilatory failure. Other complications of intrathecal opiates include nausea, vomiting, urinary retention and pruritus. Naloxone as a specific μ-antagonist will reverse some of these symptoms, but it may also reverse the analgesia. A logical alternative treatment, which is particularly useful for pruritus, is intravenous nalbuphine. This drug antagonises μ-receptor-mediated effects while maintaining analgesia via κ-receptor agonism.
- **Opioid receptors:** Opioid receptors were identified in the dorsal horn of the grey matter of the spinal cord in the mid-1970s, with early work confirming that epidural morphine was associated with prolonged analgesia. The site of action appears to be the specific opioid receptors that are located in the dorsal horn of the spinal cord. They are most densely concentrated in the substantia gelatinosa, which comprises lamina II and part of lamina III of the laminae of Rexed. At least 75% of the receptors are pre-synaptic, and they mediate inhibition of the release of nociceptive transmitters such as substance P following stimulation of the primary afferents.
- **Vasoconstrictors:** These have long been used to prolong the duration of anaesthesia provided by both intrathecal and epidural local anaesthetics, although the practice is much less common in the UK than in the USA. There is

evidence from controlled trials which suggests that the practice is safe, in that it does not lead to spinal cord ischaemia and neurological damage. There is also evidence that the addition of vasoconstrictors does not have a consistent action: the addition of adrenaline (epinephrine) prolongs the action of intrathecal amethocaine but has little effect when added to bupivacaine or lignocaine. The reasons for this disparity are unknown. Vasoconstrictors that have been used include adrenaline, phenylephrine and felypressin (octapressin).

- **α_2-agonists**: It was discovered over 50 years ago that intrathecal adrenaline had a significant analgesic effect, which has been shown since to be due to its α_2-agonist actions at pre- and post-synaptic receptors in the spinal cord. Pre-synaptic activation inhibits noradrenaline release from the nerve terminal, and thereby influences descending pathways, but this alone is insufficient to explain all the analgesic effects. Clonidine doubles the duration of action of intrathecal bupivacaine, prolonging both sensory and motor block. Its complications include hypotension, dry mouth and sedation. The dose–response curve for hypotension is complex because larger doses (as high as 450 μg), are associated with the smallest effects on BP. Dexmedetomidine is both more potent and more α_2-selective.
- **NMDA receptor antagonists:** There are NMDA receptors in the dorsal horn of the spinal cord. Ketamine is effective by both extradural and intrathecal routes, and has been shown (in a preservative-free formulation) to quadruple the duration of effective analgesia in children when added in a dose of 0.5 mg kg^{-1} to sacral extradural (caudal) bupivacaine.

Direction the viva may take

You may not have time to discuss more than the commonly used adjuncts. If you have done well then the viva may move onto other agents that have been used. The underlying receptor theory is both complex and incompletely understood, and so you will do well simply to provide a broad overview.

- **Anticholinesterases:** Part of the effect of α_2-agonists is mediated via the release of ACh from the dorsal horn, which indicates that cholinergic receptors are involved in endogenous modulation of pain sensations. The logic of this hypothesis means that the injection of an intrathecal anticholinesterase should have analgesic effects. So it has proved with neostigmine. The technique did not pass into clinical practice because doses sufficient to permit the use of neostigmine as the sole anaesthetic agent were accompanied by severe nausea and vomiting. Sub-analgesic doses do exert an opiate-sparing effect with minimal nausea, and it may be that cholinomimetic drugs will be developed to exploit this mechanism further.
- **GABA agonists:** Intrathecal midazolam produces analgesia which is antagonised by flumazenil, and it is assumed that it enhances the action of GABA on $GABA_A$ receptors. The effects of a single dose can be prolonged, which raises the suspicion that it may be neurotoxic. Intrathecal baclofen, which is another GABA agonist, is licensed in the USA for the treatment of spasticity, but it also can produce effective analgesia without any evidence of toxicity.
- **NSAIDs:** Spinal NSAIDs may inhibit pre-synaptic adenyl cyclase in the dorsal horn and decrease neurotransmitter release. (This is an oversimplification of a process that may also involve post-synaptic, NMDA stimulated gene expression.) Clinical experience is limited to sporadic case reports.
- **Monamine uptake inhibitors:** Amitriptyline has long been used in chronic pain states. It also enhances noradrenergic and serotonergic inhibition at spinal level after intrathecal administration.

Inotropes

Commentary

Anaesthetists need to know how to support a failing myocardium. The use of inotropes in critical care is routine, and the viva will probably be divided between a discussion of basic pharmacology and clinical aspects. Examiners will be aware that intensive care units have different preferred inotropes, and so you may well be given the opportunity to discuss the one with which you have had the most experience. You may also be asked to talk about a second-line inotrope. You will add credibility to your account if you can make it evident that these are drugs with whose clinical use you are very familiar.

The viva

Whether or not the examiner tries to introduce the subject by setting it in a clinical context, the basic starting question remains the same. What is an inotrope?

- The accurate definition of an inotrope is a substance that affects the force of muscular contraction, either positively or negatively. By common usage, however, the term 'inotrope' describes one of a range of drugs which increase myocardial contractility.
- Most inotropes act via a final common pathway to increase the availability of calcium within the myocyte. The activation of adenylyl cyclase leads to an increase in the production of cAMP from ATP, which in turn activates protein kinase A. This enzyme phosphorylates sites on the α_1-subunits of calcium channels, leading to an increase in open-state probability, a rise in calcium flux and an increase in myocardial contractile force.
- The steps which lead to the activation of adenylyl cyclase are considerably more complex than this final pathway, there being at least 13 G-protein-linked myocardial cell membrane receptors. You will either be doing very well in the viva (or be very unlucky), should the examiner decide to dwell on these in any detail. β-adrenoceptors, and 5-HT receptors, as well as histamine, prostaglandin and vasoactive intestinal peptide receptors interact with $G_{s(stimulatory)}$ proteins to activate adenylyl cyclase. Adenosine, ACh and somatostatin interact with $G_{i(inhibitory)}$ proteins to inhibit adenylyl cyclase activation, and α_1-adrenoceptors and endothelin receptors interact with G_q-proteins to activate phospholipase C and thence protein kinases.
- Calcium is responsible finally for the increase in contractility, and almost all the inotropes in common use have actions that are cAMP dependent. These include dobutamine, adrenaline (epinephrine), dopexamine, noradrenaline (norepinephrine), dopamine, isoprenaline, enoximone, milrinone, ephedrine and glucagon. A much smaller group exert their effects independently of cAMP. The most important are the cardiac glycosides digoxin and ouabain (which is no longer available in the UK).

Direction the viva may take

You may then be asked about the inotrope(s) with which you are most familiar.

- **Dobutamine:** This is a synthetic catecholamine derivative of isoprenaline which is predominantly a β_1-adrenoceptor agonist. It also has dose-dependent effects at β_2- and α_1-receptors. It increases contractility, has minimal effects on HR and has little direct effect on vascular tone. It does not act at renal dopamine receptors, but may increase urine output by improving circulatory performance. The quoted dose range is 2.5–10.0 $\mu g\,kg^{-1}\,min^{-1}$, titrated against response, but much higher rates may be needed in the critically ill.
- **Adrenaline (epinephrine):** Adrenaline is an exogenous and endogenous catecholamine, which is both an α_1- and β-agonist. It causes an α_1-mediated

increase in the force and rate of myocardial contraction, coupled with an increase in stroke volume secondary to enhanced venous return. In low doses β_1-mediated vasodilatation is prominent, but the BP rises because of the increase in CO. As the dose increases so both α- and β-effects are seen, while at high doses α_1-vasoconstriction predominates. In the context of critical care adrenaline is given by intravenous infusion at a rate of 0.05–0.20 $\mu g\,kg^{-1}\,min^{-1}$.

- **Noradrenaline (norepinephrine):** Noradrenaline is another exogenous and endogenous catecholamine. It is a powerful α_1-agonist with weaker β-effects, which are most pronounced at low doses (less than 0.05 $\mu g\,kg^{-1}\,min^{-1}$). It is used more as a vasopressor than as an inotrope.
- **Dopexamine:** Dopexamine is a dopamine analogue which also acts both at dopaminergic and β_2-adrenergic receptors. It has no effect at α-receptors. It is an inodilator, in that it increases myocardial contractility while decreasing SVR. It also dilates the splanchnic circulation, which is the main property that finds it favour among intensivists. The dose range is 0.5–6.0 $\mu g\,kg^{-1}\,min^{-1}$.
- **Dopamine:** Dopamine is an endogenous precursor of noradrenaline, which acts on dopaminergic DA_1 and DA_2 receptors as well as at adrenoceptors. Its effects are dose dependent: at low doses (up to 5.0 $\mu g\,kg^{-1}\,min^{-1}$) it stimulates mainly dopamine receptors, and it was claimed that because this caused renal vasodilatation it conferred a renal-protective effect. At infusion rates of between around 5 and 10 $\mu g\,kg^{-1}\,min^{-1}$ it causes a β_1-mediated increases in myocardial contractility and CO. As the dose rises further α_1-vasoconstriction becomes more predominant, although it may still provoke undesirable tachycardia. Few now believe that dopamine is uniquely useful because of its renal dopaminergic effects and it has ceased to be a first-line inotrope.
- **Isoprenaline:** Isoprenaline is a synthetic catecholamine with very potent β-adrenergic effects (both β_1 and β_2), but with no α-adrenergic activity. Given in a dose of 0.02–0.2$\mu g\,kg^{-1}\,min^{-1}$ it leads both to an increase in myocardial contractility and HR. It is now difficult to obtain in the UK.

Further direction the viva could take

You will probably then be asked to compare the inotrope(s) that you have been discussing with a second-line drug, or one which has a different mechanism of action.

- **Enoximone and milrinone:** These also act via an increase in cAMP, which is mediated by inhibiting the action of phosphodiesterase III (PDE-III). This enzyme is responsible for the intracellular degradation of cAMP. Both drugs increase contractility while causing peripheral vasodilatation. The dose of enoximone is 5–20 $\mu g\,kg^{-1}\,min^{-1}$ after a loading dose of 90 $\mu g\,kg^{-1}$, that of milrinone is 0.375–0.750 $\mu g\,kg^{-1}\,min^{-1}$ after a loading dose of 50 $\mu g\,kg^{-1}$. As the effects of PDE-III inhibitors are not mediated via adrenoceptors these drugs can be useful if myocardial β-adrenoceptor downregulation has occurred and the receptors have become desensitised. This process may be associated with long-standing heart failure and prolonged exposure to circulating catecholamines, but it can also occur acutely, within minutes.
- **Digoxin:** This is one of the cardiac glycosides (another being ouabain from the African tree, *Ouabaio akokanthera*), which also acts ultimately via an increase in calcium in the sarcoplasmic reticulum. Unlike other inotropes, however, it inhibits Na^+/K^+ ATPase by binding to an extracellular α-subunit. The resulting increase in sodium concentration reduces the inwardly directed gradient across the cell membrane. One of the mechanisms by which free intracellular calcium levels are kept low is the Na^+/Ca^{2+} exchange transporter. One molecule of calcium is extruded from the cell in exchange for three molecules of sodium. More calcium, therefore, is available for release from the sarcoplasmic reticulum with each action potential.

- **Glucagon:** Glucagon exerts its postive-intropic effect via an increase in the synthesis of cAMP. It is rarely used for this specific purpose.
- **Ephedrine:** Ephedrine is a sympathomimetic which has both direct and indirect α- and β-effects, but which is used primarily as a vasopressor. It inhibits the breakdown of noradrenaline (norepinephrine) by monoamine oxidase, and this mixture of actions mean that its main influence on BP is via an increase in CO. Its α_1-effects mediate peripheral vasoconstriction, while the β_1-effects increase the force and rate of myocardial contraction.

Bioavailability

Commentary

Bioavailability is a simple concept whose value is disputed by some authorities. It is a subject, however, that can fit readily into the time frame of the viva. Make sure that you are able to define it, and that you can draw the curves of concentration plotted against time, of a drug that is given intravenously and one that is given by some other route. The questioning is likely to revert thereafter to a general discussion of the factors that may affect drug absorption.

The viva

You will be asked to define the term 'bioavailability' and to describe how it could be measured.

- Bioavailability is that fraction of the dose of an administered drug that gains access to the systemic circulation, and is therefore available to act at its receptor sites. It is assumed that the bioavailability of an intravenous dose is 100% (or 1.0). Alternatively bioavailability can be defined simply as the ratio of the effective dose to the administered dose. It has been used most commonly as a measure following oral administration, but it applies equally to drugs given by other routes (of which there are many). These include rectal, vaginal, nasal, ocular, pulmonary, sublingual, extradural, intrathecal and transdermal routes.
- Critics who doubt the usefulness of the term cite the cumbersome American Food and Drug Administration (FDA) definition of bioavailability as: *The rate and extent to which the therapeutic moiety is absorbed and becomes available to the site of drug action. Rate* and *extent* are separate entities and the expression being *available to the site of action* is imprecise. Most such definitions are of limited use because they relate bioavailability only to the total proportion of drug that reaches the systemic circulation while ignoring the rate. Clearly if absorption is complete by 30 min then the clinical effect is likely to be more marked than if that process takes 6 h. The bioavailability of a particular oral drug is affected both by its formulation and by the physiological characteristics of its recipient (as discussed below), and so strictly speaking it cannot accurately be quantified, except in a particular individual on a given occasion.
- It is nonetheless, important to be aware of the concept, particularly in relation to drugs such as digoxin which have a narrow therapeutic index. Different formulations of digoxin, which contain the same mass of drug, can give rise to plasma levels that vary over sevenfold.

Direction the viva may take

You may be asked how you would measure bioavailabilty.

- **Measurement:** Bioavailoability is measured by first giving a drug intravenously and then plotting the plasma concentration against time. When the drug has been completely removed from the system, the same agent is administered by a different route and a second elimination curve is plotted. Both curves are continued until they reach the *x*-axis and the plasma concentration is zero. Bioavailability is given by the ratio of the areas under the curves, $AUC_{non\text{-}iv}$: AUC_{iv}.
- **Analysis of low bioavailability:** If bioavailability is low, then urinary or plasma metabolites may indicate broadly the reasons why. High concentrations of metabolites suggest that a drug has undergone extensive first-pass metabolism in the liver. Low concentrations suggest either that there is poor gastrointestinal absorption or that significant biotransformation has taken place in the gut.

Further direction the viva could take

You may be asked about the factors that can influence bioavailability.

- **Physicochemical characteristics:** Bioavailability is affected by the physicochemical characteristics of a drug and its formulation. Salts which are highly soluble have a much greater dissolution rate than drugs that are presented as strong acids or bases. Drugs of low lipid solubility, of which acidic and basic salts are an example, are in general absorbed poorly from the gut. Acidic drugs are absorbed better from the stomach, however, because low gastric pH reduces the proportion of drug that is ionised. In the more alkaline environment of the small gut it is basic drugs whose ionisation is reduced and which are therefore absorbed more effectively. There may also be significant interactions within the gut: the absorption of tetracyclines, for example, is prevented if they bind to dietary calcium. Particle size is important, in that smaller particles have a greater surface area to mass ratio and therefore dissolve more rapidly. Formulation in a crystalline form also aids dissolution, as does crystal hydration, anhydrous salts of drugs being more water soluble. Excipients also affect the rate of absorption, with water repellents such as magnesium stearate decreasing the rate of dissolution. These properties are utilised in slow-release and enteric-coated drugs.
- **Physiological factors:** Orally (and rectally) administered drugs are absorbed into the portal circulation where they undergo first-pass metabolism by hepatic enzymes. Extensive first-pass metabolism clearly reduces bioavailability. Absorption of oral drugs is related to intestinal motility and integrity, as well as the extent to which they are subject to the action of enzymes in the gut wall. GTN is an example of a drug that undergoes hydrolysis by enzymes residing in the intestinal epithelium.
- Most of the above is relevant for drugs that are given orally. There is probably less extra chemistry and science to discuss in respect of other routes of administration, and there is unlikely to be sufficient time to deal with them in any detail. A logical approach using first principles should be sufficient. Skin, for example, is an effective physical barrier, but lipid-soluble drugs in adequate concentration can be delivered via patches. (Fentanyl, hyoscine, nicotine, and sex hormones are examples of drugs that can be given in this way.) Mucous membranes, in contrast, offer less impediment to absorption, because the physical barrier is thinner.

Drugs affecting mood

Commentary

These drugs are of interest both because they are prescribed very commonly, but more importantly because some of them also have specific implications for anaesthesia. You are unlikely to be asked about all the classes of drugs, and the viva may concentrate on one group with only supplementary reference to the others. Even if you are hazy on their precise details of action (these being drugs which anaesthetists almost never prescribe) at least make sure that you are aware of their clinical significance in the context of anaesthesia and surgery.

The viva

You will be asked to discuss one or more of the groups of drugs that are used to treat affective disorders, particularly those which may interact with anaesthetic agents.

- **Lithium**
  - *Therapeutic uses*: Lithium (Li^+) is an inorganic ion, which is used prophylactically to control the mood swings of bipolar manic depression. In the acute situation it may help to control mania, but not depression. The drug has a very narrow therapeutic index: it is effective at plasma levels of 0.5–1.0 mmol l^{-1}, produces side effects at 1.5 mmol l^{-1} and above, and may be fatal at a plasma concentration of 3.0–5.0 l^{-1}.
  - *Mechanism of action*: As an inorganic ion it can mimic the role of sodium in excitable tissue by entering cells via fast voltage-gated channels that generate action potentials. Unlike sodium, however, it is not pumped out of the excitable cell by Na^+/K^+-ATPase and so accumulates within the cytoplasm, partially replacing intracellular potassium. Its therapeutic effect is thought to be mediated by its interference with two second-messenger systems: cAMP and inositol triphosphate. It may increase 5-HT synthesis in the CNS. Its actions are enhanced by diuretics, which reduce clearance, and by dehydration.
  - *Adverse effects and implications for anaesthesia*: Side effects include polydipsia and polyuria secondary to antidiuretic hormone (ADH) inhibition, diarrhoea and vomiting, hypothyroidism, lassitude and renal impairment. Acute toxicity causes cardiac dysrhythmias, ataxia, confusion, convulsions and in extreme cases, coma and death. Plasma levels must be measured before anaesthesia. The drug enhances the effects of all muscle relaxants (both depolarising and non-depolarising) and potentiates anaesthetic agents. The drug has a long plasma $t_{1/2}$ and so it can be withheld for the 2 days preceding surgery. Maintenance of hydration remains important, as is sodium balance. Low serum sodium increases lithium toxicity, and electrolytes should be restored to normal levels before surgery. NSAIDs may reduce Li^+ clearance and increase plasma levels.
- **Monoamine oxidase inhibitors (MAOIs)**
  - *Therapeutic uses*: Potentially dangerous interactions led to a fall in the number of patients receiving MAOIs for refractory depressive illness. Recently, however, newer agents have been synthesised and this class of drugs has enjoyed resurgence. Monoamine oxidase is a non-specific group of enzymes, which is subdivided into two main classes.
  - *MAO-A*: This is mainly intraneuronal and degrades dopamine, noradrenaline (norepinephrine) and 5-HT (serotonin). Inhibition of the enzyme increases levels of amine neurotransmitters, some of which are associated with mood and affect.
  - *MAO-B*: This is predominantly extracellular and degrades other amines such as tyramine. MAOs have only a minor role in terminating the actions

either of noradrenaline at sympathetic nerve terminals (re-uptake is the more important mechanism) or of exogenous direct acting sympathomimetics.
  - *Drugs*: These fall into one of three groups: non-selective and irreversible MAOIs, selective and reversible MAO-A inhibitors and selective MAO-B inhibitors.
  - *Non-selective and irreversible MAOIs*: Drugs such as phenelzine, tranylcypromine, iproniazid, isocarboxazid and pargyline, potentiate effects of amines (especially tyramine) in foods. Patients are given strict dietary restrictions because the hazard of hypertensive crises is real. Such drugs will potentiate the action of any indirectly acting sympathomimetics, although the use of directly acting sympathomimetics is less dangerous. The drugs may also interact with opiates, particularly with piperazine derivatives such as pethidine and fentanyl. Co-administration may result in hyperpyrexia, excitation, muscle rigidity and coma. The precise mechanism for this reaction is unclear.
  - *Selective and reversible MAO-A inhibitors*: Drugs such as moclobemide cause less potentiation of amines and so fewer dietary restrictions are necessary. Vasopressors which have an indirect action, such as ephedrine and metaraminol, should nonetheless be avoided.
  - *Selective MAO-B inhibitors*: The main example is selegiline, whose primary use is in the treatment of Parkinson's disease. MAO-B predominates in dopamine-rich areas of the CNS.
  - *Implications for anaesthesia*: Patients ideally should discontinue these drugs (apart from selegiline, whose sudden withdrawal may exacerbate symptoms) at least 2 weeks before anaesthesia, because the range of interactions is wide and the response is unpredictable. There is an obvious danger, however, in discontinuing treatment in severely depressed patients, and so expert opinion should be sought. If emergency surgery cannot be deferred the anaesthetic management must take into account any likely interactions. This mandates caution with use of extradural or subarachnoid anaesthesia because of the possible need for vasopressors, and care with the use of opiates. Pethidine should not be used, but morphine is considered to be safe.
- **TCAs, tetracyclics and SSRIs**
  - *Therapeutic uses*: The drugs are antidepressants. Typical examples of the group are amitriptyline and imipramine (TCAs), mianserin, which is a tetracyclic compound and fluoxetine ('Prozac') and paroxetine ('Seroxat'), which are SSRIs.
  - *Mechanism of action*: TCAs are tertiary amines and are related chemically to phenothiazines. They block the re-uptake of amines, primarily norepinephrine and 5-HT, by inhibiting competitively the binding site of a transport protein. They have minimal influence on dopaminergic synapses, but do affect muscarinic ACh and histamine receptors. Tetracyclics have a similar mode of action, but a better adverse effect profile. SSRIs are relatively selective for 5-HT uptake, have fewer anticholinergic side effects than TCAs and are safer in overdose.
  - *Implications for anaesthesia*: The effects of sympathomimetic drugs may be exaggerated, and anticholinergic drugs may precipitate confusion (by causing the central anticholinergic syndrome).
- **Benzodiazepines**
  - *Therapeutic uses*: These anxiolytics and hypnotics, of which there are over 20 available for clinical use, are prescribed commonly, although probably less than hitherto. They are also used regularly in anaesthetic practice.

— *Mechanism of action*: They facilitate the opening of GABA-activated chloride channels and enhance fast inhibitory synaptic transmission within the CNS. They bind to a separate receptor, which effects an allosteric change that increases the affinity of GABA for the $GABA_A$ receptor.
— *Implications for anaesthesia*: Benzodiazepines cause sedation, and when given in combination with other CNS depressants, may be associated with profound respiratory depression.

Drugs affecting coagulation

Commentary

Drugs which influence coagulation are prescribed commonly, and so patients who are receiving anticoagulants are of particular interest to anaesthetists who may be considering regional anaesthesia. You may well be asked to give a view about this problem, but the main part of the viva will concentrate on the basic science aspects of the pharmacology of anticoagulation. The examiners are not likely to ask you to write down the whole coagulation cascade, but you will need to sound knowledgeable about those parts of it which are affected by the drugs that you are discussing.

The viva

You will be asked how drugs may affect coagulation.

- **Haemostatic mechanisms:** An understanding of the actions of anticoagulant drugs requires an appreciation of the normal mechanisms of haemostasis. The process of coagulation ends with a haemostatic plug that forms following platelet activation, and which subsequently is reinforced by fibrin. This final step involves the conversion of soluble fibrinogen to insoluble strands of fibrin, in a reaction catalysed by thrombin. Thrombin is one of several important serine proteases that are present in the coagulation cascade, and is formed from prothrombin (factor II) in the presence of activated factor X. Both coagulation pathways activate factor X which as Xa (the suffix 'a' denotes 'active') converts prothrombin to thrombin.
- **Coagulation pathways:** There are two pathways: the 'intrinsic', or contact, pathway all of whose components are present within blood, and the 'extrinisic', or in vivo pathway, in which some components are found outside blood. The intrinsic system is triggered by contact with exposed collagen in endothelium, while the extrinsic system is activated by the release of tissue thromboplastin. The protein coagulation factors are present in blood as inactive precursors, which are then activated by proteolysis, particularly of serine moieties. The cascade is amplified, with each step producing greater quantities of activated clotting factors than the one preceding it. The process in health is held in check by antithrombin III (ATIII), which neutralises all the serine proteases involved in the cascade.
- **Vitamin K:** Clotting factors II, VII, IX and X are glycoproteins which contain glutamic acid. The interaction of these factors with calcium, and with negatively charged phospholipid, requires the presence of a carboxyl moiety on their glutamate residues. Reduced vitamin K (named from the German word 'koagulation') acts as an essential co-factor in this hepatic γ-carboxylation reaction. During this reaction vitamin K is oxidised from the reduced active hydroquinone form to the inactive 2,3-epoxide. In the presence of vitamin K reductase this process is then reversed.
- **Warfarin:** Warfarin is a competitive inhibitor of vitamin K reductase, and so prevents the regeneration of the reduced active form and the addition of the essential carboxyl moiety to the four coagulation factors. It was first isolated from natural coumarins by American researchers after whom the compound was named (**W**isconsin **A**lumni **R**esearch **F**oundation). Its effect takes some days to develop because of the different rates at which the carboxylated coagulation factors degrade. The elimination $t_{1/2}$ of factor VII is only 6 h, whereas that of factor II is 60 h (the $t_{1/2}$ of factors IX and X are 24 and 40 h, respectively). The effect of warfarin on the prothrombin time (or International Normalised Ratio, INR) starts at 12–16 h and lasts for 4–5 days. It is metabolised by the hepatic mixed function oxidase P450 system, and there are a number of drugs, which if administered simultaneously can interfere with its metabolism. Its effects are potentiated by agents that inhibit hepatic drug metabolism, such as cimetidine, metronidazole and amiodarone. Its effects are attenuated by dietary vitamin K

and by drugs such as barbiturates and carbamazepine which are inducers of hepatic cytochrome P450. Some drugs, such as NSAIDs, displace warfarin from binding sites and increase plasma concentrations, but this is of only modest clinical significance.

- **Heparins:** Heparin is not a single homogenous substance. Heparins are a family of sulphated glycosaminoglycans (extracted first from liver, hence the name) whose actions are assayed biologically against an agreed international standard. They are therefore prescribed in units of activity and not of mass. Heparin fragments, or low-molecular-weight heparins (LMWHs) increasingly are being used in place of unfractionated preparations. Heparin inhibits coagulation by potentiating the action of ATIII. ATIII inactivates thrombin and other serine proteases by binding to the active serine site, and so inhibits factors II, IX, X, XI and XII. Heparin binds specifically to ATIII. To inhibit thrombin, heparin needs to bind both to the protease enzyme as well as to ATIII, whereas to inhibit factor Xa it needs to bind only to ATIII. The larger molecules of unfractionated heparin bind both to the enzyme and to the inhibitor, but the smaller LMWHs increase the action of ATIII only on factor Xa. (The *in vitro* effect of unfractionated heparin is measured by the activated partial thromboplastin time (APTT), which is not prolonged by LMWHs.)
- **Antiplatelet drugs:** Drugs which have an antiplatelet action include the NSAIDs, of which aspirin (acetyl salicylic acid) is a typical example. Aspirin inactivates the enzyme cyclo-oxygenase (COX) by irreversible binding to COX-1 by acetylating a serine residue on the active site. This leads to a reduction in the synthesis in platelets, of thromboxane (TXA_2), which is a substance that promotes platelet aggregation. It also reduces the synthesis in vascular endothelium, of prostaglandin PGI_2 (also known as epoprostenol or prostacyclin), which is the substance that inhibits platelet aggregation. The persistent inhibition of platelet aggregation results from the fact that vascular endothelium is able to synthesise new PGI_2 whereas platelets are unable to produce new TXA_2.

Direction the viva may take

You may be asked to outline your approach to a patient who is taking anticoagulants and who requires surgery.

- The approach depends both on the reasons why the patient may be anticoagulated and on the type of surgery that they face.
  - *Patients*: A patient who has a metal prosthetic cardiac valve requires an INR greater than 3.0, to prevent potential catastrophic sequelae should thrombus be allowed to form. A patient who is receiving warfarin because of atrial fibrillation will have an INR of around 2.5, and is at lower risk of serious morbidity should this fall.
  - *Surgery*: A patient who requires neurosurgery should have normal coagulation, with an INR of 1.0, in the immediate peri-operative period. At the other extreme there are surgeons who will undertake emergency procedures such as hemi-arthroplasty, in patients whose INR is over 3.0. They do so because clinical experience suggests that, contrary to expectation, blood loss under these circumstances is not excessive. Many surgeons would be prepared to perform routine surgery, such as day case arthroscopy, on patients who have INRs of 2.0.
  - *Management*: This will need to be adapted according to the specific clinical situation, but in general warfarin is stopped 48 h pre-operatively. If the INR remains unacceptably high for the planned surgery then the patient can be given vitamin K, and/or fresh-frozen plasma can be made available to cover the operation. After minor surgery the warfarin can be resumed on

the first post-operative day. After major surgery anticoagulation should be maintained by heparin infusion (typically at a rate of 1000–2000 units h^{-1}). If necessary the actions of heparin can be reversed by protamine (1 mg for every 100 units of heparin) whose positive charge neutralises the negatively charged heparin.

Further direction the viva could take

You will probably be asked about your views on central neuraxial blockade in patients who are receiving anticoagulants.

- You can take a firm line, which is that anticoagulation of any type is an absolute contraindication to extradural or subarachnoid block. The reality of clinical practice, however, is that the hard line may not always be in the patient's best interest, and that some form of risk–benefit analysis will be needed.
- Most anaesthetists would agree that full anticoagulation either with warfarin or heparin is an absolute contraindication to central neuraxial block.
- If a patient is receiving a typical twice-daily dose of 5000 units of subcutaneous unfractionated heparin, 3 h should elapse before a block is established or an epidural catheter is removed. If a patient is receiving an LMWHs, these intervals extend to 12 h.
- Some anaesthetists are nervous about siting an epidural catheter in vascular patients who may receive large doses of heparin intra-operatively. There is no prospective evidence which attests to the safety of this practice, but observational studies in large numbers of patients (3000) have not found any increased incidence of epidural haematoma formation.
- There is little agreement in the UK about the potential dangers of patients who are taking aspirin or other NSAIDs.
- Best practice in all these cases is to ensure regular post-operative testing of sensory and motor function and of deep tendon reflexes.

β-adrenoceptor blockers

Commentary

β-adrenoceptor blockers may form the subject matter for a whole viva, or they may be part of a more general discussion of hypertensive drugs and anaesthesia. Their use in hospital is of increasing interest, such that some vascular surgeons have themselves started to prescribe peri-operative atenolol. This has implications for anaesthetic management. There are a large number of β-blockers and you will not be expected to know about subtle pharmacological differences between them. You will, however, need to know enough about the receptors on which they act to be able to address the question from first principles.

The viva

You will be asked about the clinical uses of β-blockers, and how they exert their effects.

- **β-adrenoceptors:** The actions of β-blockers are predictable from what is known about adrenoceptors. The important effects (from an anaesthetic perspective) that they mediate include increases in HR (β_1), myocardial contractility (β_1), conduction velocity ($\beta_2 > \beta_1$), and cardiac glycogenolysis ($\beta_1 > \beta_2$). β_2-receptors mainly are responsible for relaxation of bronchial and vascular smooth muscle.

Cardiovascular uses

- **Angina pectoris:** The drugs are myocardial depressants which reduce cardiac work by blocking the effects of sympathetic stimulation. They decrease left ventricular wall tension, HR and resting contractility and thereby reduce myocardial oxygen consumption. β-blockers do not lead to coronary vasodilatation. Patients with myocardial ischaemia in general may benefit from long-term therapy, and survival following myocardial infarction is increased.
- **Dysrhythmias:** β-blockers lead to a decrease in automaticity, an increase in the duration of the cardiac action potential and an increase in the effective refractory period at the AV node. They are useful in treating cardiac dysrhythmias that are dependent on sympathetic activity, particularly supraventricular tachycardias. It is not advisable to use them to manage abnormalities of rhythm that have been induced by acute myocardial infarction. β-blockers may worsen these dysrhythmias and precipitate heart failure. (They are Vaughan–Williams Class II antidysrhythmics.)
- **Hypertension:** The antihypertensive actions of β-blockers are not fully explained: peripheral resistance may remain unchanged, although CO usually drops. There is no consistent relationship between treatment and alterations in renin levels. They may also inhibit 5-HT both centrally and peripherally.
- **Peri-operative ischaemia:** Evidence supports the use of β-adrenoceptor blockers. They appear to reduce the risk of silent peri-operative myocardial ischaemia, which is important, because the prognosis for patients who do suffer myocardial infarction in this period is poor. Administration of atenolol to patients at risk of ischaemic cardiac events has been shown to halve the incidence of silent post-operative myocardial ischaemia, halve mortality and cardiac complications for up to 2 years, and reduce the incidence of peri-operative infarction. (If you wish to be contentious you could argue that the use of peri-operative β-blockade does somewhat run counter to the technique of pre-optimisation, which also has its advocates.)
- **Hypertrophic cardiomyopathy:** Propranolol reduces the encroachment of the hypertrophic septum into the left ventricular outflow tract under the influence of sympathetic activity.
- **Pressor responses:** β-adrenoceptor blockers, particularly the ultra-short-acting esmolol, can be used to attenuate the pressor response to laryngoscopy.

- **Thyroid disease:** β-blockers are used to reduce the manifestations of a raised metabolic rate in thyrotoxic patients requiring curative thyroid surgery.

Direction the viva may take

You may be asked about adverse effects.

- Propranolol was the first of many β-blockers to be synthesised. The clinical differences between them are probably less significant than is claimed. Some of the drugs are relatively cardioselective, but none is cardiospecific. This means that they will antagonise β_1-receptors at non-cardiac sites, and in higher doses will also affect β_2-receptors. All have the potential, therefore, to provoke bronchoconstriction in asthmatics, and may worsen pulmonary function in patients with other forms of obstructive airway disease. These patients will then not be able to respond to β_2-sympathomimetic treatment.
- Most of the other adverse effects are also related to their primary pharmacological actions. They may precipitate peripheral vascular ischaemia due to unopposed α_1-vasoconstriction, and may mask the symptoms of hypoglycaemia. They may in addition contribute to hypoglycaemia by interfering with β_2-mediated glycogenolysis, carbohydrate and fat metabolism. Reduced exercise tolerance, dyspnoea and fatigue are other generic side effects. Drugs with membrane-stabilising actions (MSA) such as propranolol and metoprolol are more likely to induce significant bradycardia, or worsen pre-existing conduction abnormalities. Sotalol, which is a class III antidysrhythmic drug unlike other β-blockers, delays the slow outward potassium flux and extends the effective refractory period of the cardiac action potential. This prolongation of the Q–T interval is associated rarely with *torsade de pointes*. In patients in whom cardiac decompensation is being prevented by sympathetic drive, β-blockers may precipitate cardiac failure, unless a drug is used which possesses intrinsic sympathomimetic activity (ISA) such as oxprenolol or pindolol. Fat-soluble drugs, particularly propranolol, are much more likely to penetrate the CNS and cause symptoms such as nightmares and sleep disturbance. This is less of a problem with the water-soluble compounds (such as atenolol and nadolol).

Further direction the viva could take

You may be asked about particular implications for anaesthesia and about specific anaesthetic uses for β-blockers.

- The main problem is that a β-blocked patient is one in whom sympathetic reflexes are blunted. This means that compensatory responses to actual or effective hypovolaemia (such as may accompany central neuraxial blockade) can be inadequate.
- Anaesthetists use the drugs for the urgent control of hypertension, including the pressor response to laryngoscopy. Esmolol is a cardioselective drug whose very short duration of action (the elimination $t_{1/2}$ is 10 min or less) is terminated by non-specific plasma esterases. Labetalol can be used to provide control over a longer period. It has combined α- and β-adrenoceptor-blocking actions (in a ratio that is quoted variously as 1 : 5 and 1 : 7), but of differing durations of effect. The α-block lasts for 30 min, whereas the β-block persists for 90 min. Some anaesthetists are sufficiently persuaded by the evidence relating to peri-operative myocardial ischaemia that they prescribe oral atenolol routinely for patients potentially at risk.

Neuromuscular-blocking drugs

Commentary

Questions on neuromuscular blockers can be unpredictable. A single agent may form the basis of a viva, or you may be asked about one or more of the drugs during discussion of another subject, such as the neuromuscular junction. What follows below is not intended to provide a comprehensive monograph on each of the drugs. It aims simply to identify those particular aspects on which an examiner might concentrate, such as aspects of pharmacodynamics or pharmacokinetics that are of specific interest.

The viva

Topics may include depolarising relaxants and their problems, the newer non-depolarising agents, and the means whereby their action is terminated.

- **Classification:** Depolarising relaxants (of which suxamethonium is the only available example) act as agonists at the ACh receptor, and having induced the conformational change that allows the ionophore to open, remain bound to the receptor for some minutes. Non-depolarising relaxants, in contrast, are competitive inhibitors of ACh at the post-junctional nicotinic receptors. They bind to one or both of the α-units to prevent ACh access, but induce no conformational change in the receptor. The α-subunits are separated by a distance of 1.4 nm, but it is not necessary for quaternary nitrogen radicals to have the same spatial separation in order for the drugs to exert their effect.
- **Depolarising muscle relaxants:** See *Suxamethonium*, page 216.
- **Non-depolarising relaxants:** All are quaternary amines, whose potency is increased if the molecule contains two quaternary ammonium radicals. There are two main groups: the benzylisoquinoliniums (drugs ending in *-urium*), and the aminosteroids (drugs ending in *-uronium*). The aminosteroids in general show greater cardiovascular stability and less histamine release.
- **Established agents:** (The duration of action that is quoted below is the time following an intubating dose at which there is 25% recovery and pharmacological reversal can be used.)
  - *Atracurium*: This is a bisquaternary amine, a benzylisoquinolinium mixture of 16 potential isomers. It has a medium duration of action which is reversible pharmacologically at 25 min. It may cause histamine release.
  - *Cisatracurium*: This is one of the isomers of atracurium, which has a slightly longer duration of action (45 min), and has greater cardiovascular stability because it is less likely to provoke histamine release.
  - *Mivacurium*: This is a benzylisoquinolinium diester, of short duration of action which can be reversed at around 15 min. Its capacity to cause histamine release is similar to that of atracurium.
  - *Pancuronium*: This is a bisquaternary aminosteroid whose vagolytic and sympathomimetic actions made its use traditionally popular in haemodynamically compromised patients. It is long acting (75 min), and its metabolism is primarily renal, with 60% being excreted unchanged.
  - *Vecuronium*: This is the monoquaternary homologue of pancuronium, which was developed in an attempt to create a 'clean' version of the older drug. It has minimal cardiovascular effects, and a short duration of action (30–35 min).
  - *Rocuronium*: This is another monoquaternary aminosteroid which is very similar to vecuronium when used in equipotent doses. It provokes minimal histamine release and is cardiostable apart from modest vagolytic effects after large doses. When given in high doses (0.9 mg kg^{-1}) it provides good conditions for tracheal intubation within 60–75 s (hence its name: '*r*apid *o*nset ve*curonium*') and lasts for around 45 min. Lower doses ($2 \times ED_{95}$, as is typical for muscle relaxants) last for around 35 min.

- **Newer agents:** (There is minimal experience of their use in the UK and detailed knowledge cannot reasonably be expected of you.)
  - — *Rapacuronium*: This is an aminosteroid with a rapid onset (60–75 s) and short duration of action (12–15 min). It is metabolised by hepatic deacetylation, but has an acetyl metabolite with active properties. Bronchoconstriction due to its histamine and leucotriene-releasing properties has been reported.
  - — *Doxacurium*: This is a bisquaternary benzylisoquinolinium with a long, but sometimes unpredictable duration of action (80–85 min). It is cardiostable. Renal elimination accounts for 30% and plasma cholinesterase 6% of its elimination. Some of the remainder is excreted unchanged in bile, while the rest is eliminated after hepatic metabolism.
  - — *Pipecuronium*: This is a bisquaternary aminosteroid analogue of pancuronium, which is also very long acting (90–95 min). More than 65% is excreted renally, with obvious implications for its use in patients with renal impairment.
- **Metabolism and elimination:** Most of the drugs are eliminated by more than one mechanism.
  - — *Suxamethonium*: This predominantly undergoes ester hydrolysis (by plasma cholinesterase); a small amount is hydrolysed by non-specific plasma esterases, and 10% is excreted unchanged through the kidney.
  - — *Mivacurium*: This is also metabolised by plasma cholinesterase at a slightly slower rate (88%) than suxamethonium. Abnormal cholinesterases will therefore increase its effective action more than suxamethonium. In E_uE_a heterozygotes it will last for 2 h, and in an E_aE_a homozygote its action will be prolonged for 8 h or more.
  - — *Atracurium*: About 10% is excreted renally, about 40–45% is hydrolysed by hepatic esters and a further 45% undergoes Hofmann degradation at body temperature and pH (this reaction was identified first in industrial processes). The cleavage occurs at the linkage between the carbon chain and the quaternary nitrogen. Ester hydrolysis takes place at the site of the double carbon bond. Hofmann degradation produces laudanosine, a potentially epileptogenic metabolite, which has not been shown to be a problem in humans.
  - — *Cisatracurium*: Metabolism is similar to atracurium, except a greater proportion (around 60–70%) undergoes Hofmann elimination.
  - — *Pancuronium*: 60% is excreted renally, unchanged. The remainder is deacetylated in the liver (with the formation of some 3-desacetyl active metabolites) and rendered water soluble by glucuronidation.
  - — *Vecuronium*: About 30% is excreted renally, while the remainder undergoes hepatic deacetylation. Like pancuronium it produces an active 3-desacetyl metabolite.
  - — *Rocuronium*: Its elimination is mainly hepatic, and it does not form an active 3-desacetyl metabolite.

Direction the viva may take

You may be asked about the site of action of neuromuscular blockers and how you can assess their effects.

- **ACh receptor, assessment of neuromuscular blockade:** See *The neuromuscular junction*, page 133.

Suxamethonium

Commentary

Suxamethonium, arguably, is the only drug used in anaesthesia for which there is as yet no real alternative, although some might make the case for high-dose rocuronium as a substitute. It is a very familiar drug and so you will not be invited simply to give an account of its actions. Instead you might be asked to justify its role in modern anaesthesia, which inevitably will involve a discussion of the significant potential problems associated with its use.

The viva

- **Classification:** Depolarising muscle relaxants (of which suxamethonium is the only currently available example) act as agonists at the ACh receptor, but unlike ACh once having induced the conformational change that allows the ionophore to open, they remain bound to the receptor for some minutes. (Non-depolarising relaxants, in contrast, are competitive inhibitors of ACh at the post-junctional nicotinic receptors. They bind to one or both of the α-units to prevent ACh access, but induce no conformational change in the receptor.)
- **Structure:** In common with all muscle relaxants suxamethonium is a quaternary amine, which is the dicholine ester of succinic acid. This compound is almost identical to two molecules of ACh. It is bisquaternary and each of its ammonium radicals, $N^+(CH_3)_3$, bind to the α-units of the ACh receptor.
- **Indications:** It is an ultra-short-acting agent whose prime use, as every anaesthetist will know, is to allow rapid tracheal intubation in patients who are at risk of pulmonary aspiration of gastric contents. It can be used intermittently (with the problems of bradycardia with subsequent doses) and also by infusion. The maximum quoted total dose is $10\,mg\,kg^{-1}$. Larger doses risk inducing phase II block.
- **Problems – myalgia:** This should not be underestimated because it can be very severe. Its mechanism is unclear: although suxamethonium causes fasciculations and an increase in muscle creatine phosphokinase (CPK) neither of these is directly related to post-administration pain. Myoglobin can also be detected in urine. Early ambulation, female gender, middle age, and it is said, lack of muscular fitness, are all associated with a higher incidence, as is rapid injection and repeated smaller doses. Techniques used to attenuate the problem include pre-treatment with a non-depolarising relaxant, dantrolene, lignocaine and phenytoin.
- **Problems – hyperkalaemia:** Serum potassium may rise about $0.5\,mmol\,l^{-1}$ in the normal patient but this increase can be dangerously high in patients in whom muscle cells are damaged or whose muscles are denervated. Damaged muscle leaks potassium, while denervated muscle demonstrates an increase in extrajunctional ACh receptors. Conditions in which suxamethonium should be avoided, therefore, include renal failure, burns, spinal cord damage, polyneuropathies and crush injury. Dangerous rises can also occur in the critically ill, and the drug must be used with caution in intensive care patients.
- **Prolonged action due to decreased enzyme activity:** Suxamethonium undergoes ester hydrolysis in a reaction that is catalysed by plasma cholinesterase. Qualitative and quantitative changes in this enzyme have a substantial effect on the drug's duration of action. Enzyme activity is reduced by decreased enzyme synthesis due to liver disease, starvation, carcinomatosis, pregnancy, renal disease and myxoedema (hypothyroidism). Such reduction may increase by several times its normal duration of action of 3–5 min. Prolongation may result also from competition by other drugs that are metabolised by esterases, such as diamorphine, ester-linked local anaesthetics, esmolol, and MAOIs. Anticholinesterases inhibit both plasma cholinesterase as well as acetyl cholinesterase.

- **Prolonged action due to abnormal enzyme:** Qualitative differences result from inherited deficiencies of plasma cholinesterase. Its synthesis is controlled by autosomal-recessive genes, of which 14 different mutations have so far been identified. The normal gene is characterised as E_u, and the commonest atypical gene as E_a (others include the fluoride gene E_f and the silent gene E_s). The action of suxamethonium in a heterozygote E_uE_a will be prolonged by around 30 min, whereas in a homozygote E_aE_a this will extend to several hours, and still longer in the case of E_aE_s and E_sE_s variations. Testing using inhibition by dibucaine and fluoride has been superseded by direct assay of cholinesterase activity. The condition is not life threatening, but it is important to remember to maintain anaesthesia in any patient who is being ventilated until the suxamethonium wears off.
- **MH and anaphylaxis:** It is a trigger for MH, and although allergic reactions are rare, anaphylaxis is more commonly seen with suxamethonium than with any other muscle relaxant. (There were two such fatal cases reported in the Confidential Enquiry into Maternal Mortality of 1991–1993.)
- **Metabolism and elimination:** The primary metabolic route is ester hydrolysis in the presence of plasma cholinesterase. A small amount is hydrolysed by non-specific plasma esterases, and 10% is excreted unchanged through the kidney.

Direction the viva may take

You may be asked about its site of action and how you can assess its effects.

- **ACh receptor:** See *The neuromuscular junction*, page 133.
- **Assessment of neuromuscular block:** See also *The neuromuscular junction*, page 133. Using a nerve stimulator a single twich will elicit a diminished or absent response. If a train-of-four stimulus is applied there will be no decrement in the height of successive twitches. Tetanic stimulation may evoke a small sustained response but without any post-tetanic facilitation.

Antihypertensive drugs and anaesthesia

Commentary

Hypertension is common and is treated by a wide range of drugs, often in combination. Most antihypertensive therapy has implications for anaesthesia. There is no unequivocal guidance as to whether patients should discontinue taking some of these agents, such as angiotensin-converting enzyme (ACE) inhibitors, prior to surgery, so be prepared to demonstrate to the examiners that you are prepared to make your own judgements, based on an understanding of how the various drugs work.

The viva

You will be asked to discuss the implications for anaesthetic management of a patient who is receiving treatment for hypertension. The examiner may concentrate on only one or two classes of drugs, depending on how the question is structured.

- **β-adrenoceptor blockers:** See *β-adrenoceptor blockers*, page 212.
- **Diuretics:** The commonest diuretics in use are the thiazides, such as bendrofluazide, chlorthalidone and indapamide, which act on the distal tubule, and loop diuretics, typically frusemide, which act on the loop of Henle. These drugs decrease the active reabsorption of sodium and chloride, by binding to the chloride site of the electroneutral Na^+/Cl^- co-transport system and thereby inhibiting its action.
  - *Anaesthetic implications*: Potassium loss can be significant, particularly in the elderly. Electrolytes should be checked prior to anaesthesia, and consideration should be given to withholding the drugs on the day of surgery.
- **Calcium channel antagonists:** Therapeutically important calcium antagonists act on L-type calcium channels, and are of three main classes: phenylalkylamines (verapamil), dihydropyridines (nifedipine and amlodipine) and benzothiazepines (diltiazem). All three groups bind to the α_1-subunit of the calcium channel, and inhibit the slow inward calcium current in cardiac and smooth muscle cells. Verapamil has primarily cardiac effects, and acts as a negative inotrope and chronotrope. Nifedipine and related drugs are more selective for vascular smooth muscle and so are used usually to treat hypertension. They are primarily arterial and arteriolar dilators and have minimal influence on the venous system. The effects of diltiazem are intermediate, but along with verapamil it is a class IV antidysrhthymic. Both slow conduction though the SA and AV nodes where propogation of the action potential is dependent on slow inward calcium flux. Verapamil terminates supraventricular tachycardias by causing partial AV block. Nifedipine may cause reflex tachycardia. Calcium channel blockers are all negative inotropes, but because they offload the myocardium by vasodilatation, CO is usually maintained.
  - *Anaesthetic implications*: There may be some synergistic action with volatile anaesthetic agents, which also affect slow calcium channels in the myocardium and elsewhere. Nifedipine and verapamil may also potentiate the actions of non-depolarising muscle relaxants.
- **ACE inhibitors:** These drugs affect the renin–angiotensin system. Renin is a proteolytic enzyme secreted by the juxtaglomerular apparatus, which acts on angiotensinogen (a plasma globulin synthesised in the liver) to form angiotensin I. This inactive substance is converted to the potent vasoconstrictor angiotensin II by ACE. (Angiotensin II is then broken down further to angiotensin III and IV.) ACE is a membrane-bound enzyme on surface of endothelial cells, and is particularly abundant in lung with its huge area of vascular endothelium. The local formation of angiotensin II can occur in numerous different vascular beds. ACE inactivates bradykinin and several other peptides. Bradykinin is an

inflammatory mediator and vasoactive peptide, which causes vasodilatation and increased vascular permeability. It may also cause bronchial and other smooth muscle constriction. Angiotensin acts on receptors to mediate vasoconstriction (its pressor activity is 40 times as powerful as that of noradrenaline), as well as noradrenaline release from sympathetic nerve terminals, sodium reabsorption from proximal tubule, and aldosterone secretion from the adrenal cortex. ACE inhibitors include captopril, enalapril and lisinopril. These drugs mediate a significant fall in BP in hypertensive subjects, and reduce cardiac load by affecting both capacitance and resistance vessels. They have no influence on cardiac contractility, although they do act preferentially on angiotensin-sensitive vascular beds in the myocardium, brain and kidney. Cough is a common side effect of their use, which is due probably to bradykinin accumulation.

  - *Anaesthetic implications*: There are concerns that profound and refractory hypotension can complicate the concomitant administration of a general or regional anaesthetic. If major surgery is planned which involves large potential fluid shifts or fluid loss it is prudent to withhold ACE inhibitors on the day of surgery and halve the dose on the day before.

- **Angiotensin antagonists:** Pure antagonists of the angiotensin I (ATI) receptor (examples include losartan and valsartan) should in theory have a similar spectrum of benefit as ACE inhibitors. They have a better side effect profile, and do not cause persistent cough, although they are less effective in the treatment of heart failure.
  - *Anaesthetic implications*: These are broadly similar to those that apply to ACE inhibitors, with the risk of intra-operative hypotension and renal impairment. Consideration should also be given to discontinuing these drugs the day before major surgery.

Cyclo-oxygenase enzymes

Commentary

This question is actually about NSAIDs, but because this is a basic science viva, it will reach that point only after a brief discussion of the COX enzyme system. The use of NSAIDs in anaesthetic practice is widespread, side effects are common and there is current interest in selective COX-2 inhibitors. It will help, therefore, if you can show broad familiarity with the (simplified) information that is summarised below.

The viva

You will be asked about the COX enzyme system. The actions of the prostaglandins that are synthesised are too diverse for you to cover in any detail, except insofar as they are affected by NSAIDs.

- **COX enzymes:** It is now recognised that these exist in at least two isoforms: a 'constitutive' COX-1 enzyme that is present in all tissues, and an 'inducible' COX-2 enzyme which is produced in high concentrations within cells at inflammatory sites. (A COX-3 isoform has also been identified, and which is thought to mediate pyrexia, but fuller details have not yet been elucidated.)
- **Mechanism of action:** COXs catalyse the production of prostanoids, which comprise a family of lipid mediators which have numerous diverse biological roles. The preferential substrate for COX enzymes is arachidonic acid. This is a 20-carbon unsaturated chain which is cleaved from the phospholipid of membranes by phospholipase A_2 (PLA_2). (This exists in at least 10 isoforms. Glucocorticoids both inhibit PLA_2 as well as decreasing the induction of COX.) The initial step in prostanoid biosynthesis is the conversion of arachidonic acid to prostaglandin PGG_2 and thence to PGH_2, which is the precursor to all the compounds in the series, including PGE_2, PGD_2, $PGF_{2\alpha}$, PGI_2 (prostacyclin) and thromboxane (TXA_2). COX enzymes are involved in two different biosynthetic reactions: in addition to catalysing the production of prostaglandin PGG_2, a secondary peroxidase reaction then converts PGG_2 to PGH_2.

Direction the viva may take

You will be asked about the drugs which affect COXs.

- **NSAIDs:** These include non-selective drugs in common use, such as diclofenac, ketoprofen, ibuprofen, aspirin and paracetamol, as well as the newer selective COX-2 inhibitors (the '-coxib' class), parecoxib, celecoxib and rofecoxib. The beneficial effects of NSAIDs are mediated largely through COX-2 inhibition, whereas the adverse effects are related to COX-1 inhibition.
- **Antipyretic action:** NSAIDs inhibit prostaglandin production in the hypothalamus. Interleukin-1 release during an inflammatory response stimulates the hypothalamic production of prostaglandin PGEs, which effectively 'reset' the hypothalamic thermostat upwards. PGD_2 in the brain is also involved in temperature homoeostasis. COX-2 is induced centrally by pyrogens, with an increase in PGE_2 production.
- **Analgesia:** NSAIDs decrease production of the prostaglandins PGE_2 and PGI_2 that sensitise nociceptors to inflammatory mediators such as serotonin and bradykinin. They probably also exert central effects at spinal cord level: COX-2 mediating hyperalgaesia secondary to increased neuronal excitability.
- **Anti-inflammatory effects:** The inflammatory response is complex, involving a large number of mediators (see *Systemic inflammatory response syndrome*, page 328). NSAIDs influence mainly those components in which the products of COX-2 reactions are important. These include vasodilatation, oedema formation and pain. Some NSAIDs (such as sulindac) also act as oxygen free-radical scavengers, which may reduce tissue damage and inflammation.

- **Antithrombotic effects:** NSAIDs reduce platelet aggregation by inhibiting thromboxane TXA_2 synthesis. This is unaffected by COX-2 inhibitors, which have no antithrombotic effect.
- **Antineoplastic effects:** The regular use of aspirin (and by extension any of the NSAIDs) almost halves the risk of colonic cancer. Their potentially protective role relates to the suppression of COX-2, whose expression is markedly increased in adenocarcinomas as well as in other tumours of the oesophagus and pancreas.
- **Mechanism of action:** NSAIDs affect only the main cyclo-oxygenation step and do not influence the peroxidase conversion stage of prostanoid synthesis. Non-selective drugs act mainly by competitive inhibition of the arachidonic-acid-binding site. This is reversible, except in the case of aspirin, which acetylates hydroxyl groups on serine residues in a reaction that is irreversible. The -coxib class are non-competitive, time-dependent COX-2 inhibitors, whereas the -oxicam class (meloxicam and tenoxicam) are competitive.

Further direction the viva could take

You are likely to be asked about adverse effects, and about the potential benefits of COX-2 inhibitors.

- **Adverse effects:** These relate mainly to the inhibition of the COX-1 'housekeeping' enzyme.
  - — *GIT effects*: Gastrointestinal complications are common, with gastric damage present in around 20% of chronic users. Prostaglandins decrease gastric acid secretion, increase mucus production and improve the microcirculatory blood flow.
  - — *Renal effects*: Two prostaglandins are important in renal function. PGE_2 has a role in water reabsorption and also mediates compensatory vasodilatation to offset the action of noradrenaline or angiotensin II. PGI_2 also maintains renal dilatation and blood flow, but does so only under circumstances of physiological stress, such as hypovolaemia. Concurrent administration of NSAIDs, therefore, can cause acute renal impairment. The situation is made more complex by the fact that COX-2 is constitutively expressed in the kidney. This explains why trials of high-dose COX-2-selective inhibitors have shown an association with hypertension and fluid retention. (The chronic use of NSAIDs may also lead to irreversible analgesic nephropathy.)
  - — *Respiratory effects*: An attack can be triggered in about 10% of asthmatic subjects. This may be due partly to the inhibition of PGE_2-mediated bronchodilatation.
  - — *Cardiovascular effects*: Endothelial COX-1 releases PGI_2 to mediate vasodilatation and inhibition of platelet aggregation. COX-2 can also be expressed in vascular smooth muscle with the release of PGI_2 and PGE_2. COX enzymes may therefore have a cardioprotective function. This may explain the findings of the large *VI*OXX *G*astrointestinal *O*utcomes *R*esearch study (VIGOR trial), which showed an unexplained increase in the incidence of myocardial infarction in the COX-2 (rofecoxib) group in comparison with the non-selective (naproxen) group.
  - — *COX-2 inhibitors*: These drugs have a safer side effect profile in respect of the gastrointestinal system, which is the commonest site of adverse effects. They should still be used with caution in patients with renal impairment and there is also some concern about cardiovascular effects.

Target-controlled infusion

Commentary

Target-controlled infusion (TCI) for sedation or for TIVA is becoming a common technique, but only a proportion of this viva will dwell on the reasons for its clinical popularity. The main direction of the questioning will relate to the pharmacokinetics of these systems. You will not be asked about pharmacokinetic mathematical modelling, but you need to be able to define some of the main terms and describe the basic concepts with sufficient confidence to persuade the examiners that you do understand the principles which underlie their effective use.

The viva

You will be asked to describe the pharmacokinetic principles that are relevant for a TCI system, almost certainly using propofol as the example.

- **Introduction:** A TCI system incorporates a computer-controlled infusion pump (with safety features to prevent the risk of overdose), which is programmed with a pharmacokinetic model specific to the drug that is being infused. A microprocessor computes continuously the infusion rate that is required to maintain a predicted blood concentration of the agent, and an adequate concentration of drug at the effector site throughout the duration of the procedure. Examples of such drugs include propofol, alfentanil and remifentanil. The uptake kinetics of intravenous agents mean that the infusion rate needs to be changed exponentially to maintain a steady plasma concentration as peripheral compartments fill up and metabolism and elimination begin. When a lower blood concentration is selected the pump stops infusing and resumes at a slower rate.
- **Propofol:** Propofol is a highly lipophilic hypnotic that distributes rapidly from blood to the effector site. It then undergoes further rapid redistribution to muscle and fat before being metabolised mainly in the liver, undergoing conjugation to glucuronide and sulphate prior to renal excretion.
- **Pharmacokinetic model:** The decay in blood concentrations following a bolus dose or a continuous infusion of propofol is best identified by a three-compartment model which describes its distribution, redistribution and clearance. (Such a model is used in the 'Diprifusor', which is pre-programmed with pharmacokinetic data.) At the starting target concentration a bolus dose fills the central compartment and this is then followed by an intial high infusion rate, which compensates for rapid distribution. Thereafter the infusion rate slows to maintain the steady state. The microprocessor then employs continuous calculations of the concentrations in the different compartments by employing pharmacokinetic information about the elimination and distribution of the drug. (Arguably there should be an additional compartment to represent the effector site, the brain.) The maintenance infusion rate has to compensate for clearance and for redistribution to the peripheral compartments which is governed by different rate constants: K_{10}, which is the elimination rate constant from the central compartment; and K_{12}, K_{21}, K_{13}, and K_{31}, which are the rate constants governing movement of drug between the peripheral compartments (1, 2 and 3). In the early phase of drug administration, distribution to other compartments is much the most important of the factors which decrease drug effects. With propofol the initial distribution $t_{1/2}\,\alpha$, is short (2–3 min) while intermediate distribution, β_1, takes 30–60 min. The terminal phase decline, β_2, is less steep and takes 3–8 h. The immediate volume of distribution is 228 ml kg^{-1}, but the steady-state volume of distribution in healthy young adults is around 800 l.
- **Volume of distribution (V_d)**: The concept of the apparent V_d assumes that a drug is distributed evenly throughout a single compartment. (If, for example, 100 mg of a drug given intravenously yields a plasma concentration of 1 mg l^{-1}, then the V_d is $100/1 = 100$ l. V_d equals the dose/initial concentration.) Were a

drug to remain entirely within the circulation its V_d would approximate the plasma volume ($0.05 l kg^{-1}$). Were it to distribute through the extracellular compartment its V_d would be about 14 l ($0.2 l kg^{-1}$). If it distributes throughout all fluid compartments its V_d approximates to total body water ($0.6 l kg^{-1}$). If, however, it is sequestrated by ion-trapping, cellular uptake or specific tissue binding then its V_d will be much larger. The volumes of distribution of drugs used in TCI are useful in explaining their clinical behaviour, being 800 l for propofol and 30 l for both alfentanil and remifentanil. V_d is however affected by such factors as pregnancy, age and volaemic status.

- **Context-sensitive $t_{1/2}$ (half-time):** This is the time taken for the plasma concentration to halve after an infusion designed to maintain constant blood levels is stopped. This is different not only for dissimilar drugs but also for the same drug depending on the duration of infusion. The context-sensitive $t_{1/2}$ for remifentanil is about 4.5 min after 2 h of infusion, and 9.0 min after 8 h. Fentanyl, in contrast, has a context-sensitive $t_{1/2}$ after 2 h of infusion of 48 min, which extends after 8 h to 282 min. The figures for alfentanil are 50 and 64 min, and for propofol 16 and 41 min. This makes it clear why remifentanil is such a suitable drug for administration in this way.
- **Clearance:** One of several definitions of clearance is the rate of drug elimination per unit time per unit concentration. An alternative, and rather neat model-independent method of determining clearance is to divide the dose of drug by the area under its concentration–time curve. The whole-body clearance of propofol is 2500 ml min^{-1}.

Direction the viva may take

You may be asked about some clinical aspects of TCI and TIVA.

- **Target concentration:** This clearly will vary according to the procedure. For 'conscious sedation' an effect site concentration of 1.0 $\mu g\,ml^{-1}$ might prove sufficient, whereas surgical anaesthesia might require upwards of 8.0 or 10.0 $\mu g\,ml^{-1}$. In practice the range is from around 2.0 to 8.0 $\mu g\,ml^{-1}$. This reflects the considerable pharmacokinetic and pharmacodynamic inter-patient variability. Influences include age, body weight, genetic factors, concurrent disease and administration of other drugs. The addition of alfentanil, for example, reduces the distribution and clearance of propofol.
- **Repeated infusion:** If a patient has to return to theatre soon after TCI has been discontinued, the microprocessor will no longer be storing the pharmacokinetic information. When the TCI is restarted, therefore, the system will deliver another bolus and rapid initial infusion as if there were no residual propofol in the body. The shorter the interval between cessation and resumption, the greater the risk of overdose. Anaesthesia should not, however, be administered by numbers, and any drug should always be titrated against response.

5

Physics, clinical measurement, equipment and statistics

Peripheral nerve location using a stimulator

Commentary

The majority of anaesthetists who undertake regional nerve blockade regularly use peripheral nerve stimulators. Success in their use does to an extent depend on an understanding of how they function, but they are not especially complex devices, and so the viva may focus equally on clinical and practical aspects of their use.

The viva

This may start with a question about your own experience of nerve stimulators.

If your familiarity with these devices is limited then do not pretend otherwise: it is usually very obvious to examiners when candidates lay claim to experience that they do not have.

- Nerve stimulators complement, but do not obviate the need for accurate anatomical knowledge.
- The rationale for their use is twofold.
  - *Efficacy*: Their use has been reported to double the success rate of some blocks.
  - *Safety*: Their use removes the need to elicit paraesthesia. Paraesthesia occurs only when the nerve is touched by the advancing needle, and some chronic pain specialists believe that paraesthesia is associated almost invariably with later dysaesthesia.

Direction the viva may take

The questioning may then proceed to a discussion of the characteristics that are necessary for a nerve stimulator to be effective and safe.

- It should maintain a constant current despite the changes in resistance that the needle will encounter as it penetrates tissues of different densities. This is probably the most important characteristic. These resistances in the external circuit can vary from around 1 to 20 kΩ (kOhm), so were the device to deliver a constant voltage the current could vary 20-fold.
- It should have a linear output which can easily be varied.

- It should have a clear digital display across the current range from 0.1 to 5.0 mA (milliamps).
- It should have a short pulse width of 50–100 μs, which provides better discrimination of the distance between the needle and the nerve. The shorter the pulse width the greater the change in stimulation strength as the needle advances.
- It should incorporate an indicator that shows the integrity of the electrical circuit.
- It should be battery operated (for patient safety).
- Other features include a battery level indicator, low-resistance clips, robust design.

Further direction the viva could take

You may then be asked about the practical considerations of using a stimulator.

- **Electrodes:** The negative electrode should be attached to the stimulator needle rather than the positive. In this situation the current flow towards the needle produces an area of depolarisation which readily triggers an action potential. If the polarity is reversed the current produces a zone of hyperpolarisation immediately around the needle tip, with an area of depolarisation encircling it. The nerve can still be stimulated, but it will need more current to do so.
- **Thresholds:** Techniques thereafter do vary: some anaesthetists start with a relatively high current of up to 2.0 mA, others stay below 1.0 mA. As the needle approaches the likely site of injection the current should be reduced to about 0.5 mA. If you are eliciting a vigorous twitch at much less than that current, at 0.2–0.3 mA, then you will be very close to, or even in the nerve.
- **Injection:** A small amount of local anaesthetic will abolish the twitch by physical displacement. The same phenomenon has been demonstrated experimentally using saline and air. If the twitch does not disappear on injection it means that the needle may be intraneural and should be withdrawn slightly.

You may also be asked about the characteristics of stimulator needles.

- **Insulated or non-insulated:** Most needles are insulated (with Teflon coating) apart from the uncovered tip through which the current passes. You should be aware that non-insulated needles can also be used effectively because the current density remains greater at the tip of the needle than down the shaft. False positives are more common, however, because there can be some nerve stimulation at the level of the shaft.
- **Long bevel, short bevel or side ported:** Long bevelled needles are sharp and penetrate tissues readily. This makes them easier to use but the design may also increase the risk of direct nerve injury. There is some evidence that short bevelled needles are safer in this regard. These are, however, quite blunt. It is necessary to make a small incision or nick in the skin to facilitate penetration, and it can sometimes be difficult to appreciate the tissue planes through which the needle is passing. The same considerations apply to the pencil point atraumatic needles with a proximal side hole. In theory these needles are least likely to traumatise neural tissue. There is at least one theoretical disadvantage with their use, in that it is possible to elicit an effective twitch but then have an ineffective block, because the side hole has remained proximal to the fascial compartment which the needle tip has penetrated.
- **Sizes:** There are numerous sizes, depending on the manufacturer, but common lengths include 30, 50, 90, 100 and 150 mm. Most are 22G.

Depth of anaesthesia

Commentary

The discovery of anaesthesia transformed the human condition, and unplanned awareness returns a patient to the nightmare that was surgery before anaesthesia and analgesia. Significant advances in the pharmacology and technology of anaesthesia have still not brought us much closer to a reliable means of monitoring the depth of anaesthesia; although because awareness is such a serious complication, considerable research effort has been dedicated to the search for methods of detection. Most methods remain research tools, but you should have some idea about which of them may in due course find their way into clinical practice.

The viva

You will be asked about methods of determining depth of anaesthesia.

There is a long list of techniques that have been described, and so a systematic approach may help you to recall them. It does not matter how you do this, but in the description below, the methods are ranked broadly according to their usefulness and practicality. Clinical signs, therefore, are discussed first, not because they are the most reliable, but because every anaesthetist will use them. There is more detail in many of these sections than you could be expected reasonably to know, but without some of this detail it might look otherwise as though you were simply reciting a list.

- **Clinical signs:** In the spontaneously breathing patient who is not paralysed, awareness may be manifest by purposeful movement. Movement is a reliable indicator of light anaesthesia although a patient may have no recall.
- **Sympathetic overactivity:** The main clinical signs are tachycardia, hypertension, diaphoresis and lachrymation. Attempts have been made to quantify these objectively by using the PRST scoring system (blood *p*ressure, heart *r*ate, *s*weating, *t*ear formation), but without any real evidence of its benefit. In the absence of other causes, sympathetic signs may be reliable if present, but the main problem is that their absence does not exclude awareness.

Effective methods

- **Evoked potentials (EPs):** Visual, somatosensory and auditory EPs have been investigated as indicators of the depth of anaesthesia. The few microvolts that are generated by each potential have to be separated from the overall electrical noise that is produced by the brain as a whole. Auditory EPs appear to be the most effective, because they are the last to disappear and so are the best indicator of anaesthetic depth. The patient's auditory system is stimulated by clicks at around 10 Hz. The electroencephalogram (EEG) is recorded immediately after each stimulus and is amplified, before the auditory EPs are extracted by taking the average of a large number of responses. It is obvious that this technique is complex and technically demanding.
- **Compressed spectral array (CSA):** This is a method of simplifying the EEG in which the signals are subjected to Fourier analysis. Fourier transformation is the mathematical technique whereby complex waveforms are analysed into their simpler sine wave components. In CSA, this analysis calculates the total power contained within the different frequencies of cerebral activity. In an anaesthetised patient, power shifts to the lower frequencies.
- **Spectral edge:** This is the frequency above which there is only 5% of the total EEG power. A decrease in the spectral edge frequency accompanies increasing concentrations of anaesthetic agents. The relationship between the two does not, however, appear to be linear, and in the transition between light and deeper anaesthesia there is a poor correlation between spectral edge frequency and drug concentration.

- **Median frequency:** This is another number determined from CSA, and is the frequency above and below which lie 50% of the total power of the EEG. It may correlate better with drug concentrations, but the spectral array shows a pattern that is not consistent between different anaesthetic agents.
- **Bispectral analysis and bispectral index:** This is another modification of the EEG, in which there is analysis of the phase and power relationships between the numerous frequencies. The term 'bispectral' describes the phase and power relationships between any two frequencies in the EEG. The bispectral index is a number generated from these phased and power frequencies that are the components of the EEG, and in essence compares frequency harmonics in the frontal EEG. The scale is from 1 to 100. A patient who is awake has a bispectral index of less than 50. This device has a rapid response time and it is accurate. The technology is complex and it is not widely available.
- **Respiratory sinus arrhythmia and R–R interval variation:** This method does have promise, although it is only useful in the presence of an intact autonomic nervous system and healthy myocardial conducting system. Its value is greatly restricted in patients, for example, who are being treated with β-adrenoceptor blockers, who have autonomic neuropathy or dysfunction (common in the elderly), sepsis, or who have cardiac conduction abnormalities. It provides a measure of brainstem function, which decreases with increasing depth of anaesthesia.

Methods of limited value

- **Isolated forearm technique:** This is not strictly a monitor of the depth of anaesthesia, but it is included as a method of detecting awareness that is simple and ingenious. It was described originally by Tunstall, who was interested in preventing awareness during obstetric general anaesthesia. An arterial tourniquet isolates the arm from drugs which enter the systemic circulation, and prior to the procedure the anaesthetist agrees with the patient the hand signals that they will use to convey awareness. The method is effective, but its practical use is limited both by the considerable degree of cooperation that is necessary, and by the fact that after about 20 min of tourniquet inflation, ischaemic paralysis supervenes which prevents any further arm movement.
- **EEG:** The formal EEG is a highly complex monitor, which produces too much data to be of any practical use in theatre. It also processes a lot of information from the cerebral cortex, which arguably may not be the area most appropriate for examining depth of anaesthesia.
- **Cerebral function monitor (CFM):** This is a processed and simplified EEG which displays only part of the frequency range. It has been used in neurointensive care units as an indirect monitor of cerebral oxygenation. It appears to be of limited value in measuring depth of anaesthesia.
- **Cerebral function analysing monitor (CFAM):** This is a refinement of the CFM, which separates out the main frequencies of cerebral activity. It is technically easier to use, but it may get a disproportionate amount of information from the temporal lobe and also has a slow response time.
- **Oesophageal contractility:** The amplitude and frequency of contractions of lower oesophageal smooth muscle reduce with increasing depth of anaesthesia. The technique is of limited value because of the high rate of false positive and false negative results.
- **Frontalis (scalp) electromyogram (EMG):** This technique measures the amplitude of the EMG, which decreases with increasing depth of anaesthesia. It is of very restricted benefit because it cannot be used in the paralysed patient.

Direction the viva may take

You may be asked about awareness under general anaesthesia: what are the commonest causes, which patients are particularly at risk, and what are the sequelae.

- **Causes:** Its causes lie in equipment and its use, in pharmacology and its application and, very rarely, in the physiology of patients.
- **Equipment and apparatus:** Awareness may result from a failure of the apparatus to deliver adequate concentrations of anaesthetic agent. The anaesthetic machine must deliver an accurate fresh gas flow (FGF) via an appropriate breathing system, using a vaporiser. Alternatively if total intravenous anaesthesia (TIVA) is being used an accurate syringe driver is required, together with a reliable system of infusion tubing. Awareness may result if there are failures in any part of these systems. These would include leaks, faulty or empty vaporisers, a misconnected or disconnected breathing system, inaccurate pumps and occluded infusion tubing.
- **Use of equipment and apparatus:** Awareness may result from a failure of the anaesthetist to use the equipment properly. Circle systems can present a particular difficulty.
- **Monitoring:** Failure to monitor the concentrations of inspired and expired volatile agent monitors may result in inadequate anaesthetic agent being delivered. TIVA is more difficult to monitor in this respect.
- **Pharmacology:** Awareness, by definition, results from inadequate anaesthesia. The dose of induction agent may have been inadequate, as may be the alveolar concentration (it is important to remember that the minimum alveolar concentration (MAC) value that is quoted is only the MAC^{50}) or the computed blood concentration in target-controlled infusion (TCI).
  Awareness is not prevented by hyperventilation, by the use of nitrous oxide (N_2O) and oxygen alone, or by the use of opiates. Muscle relaxants drugs are not anaesthetics and anaesthesia must not be discontinued until their effects have been reversed.
  Very rarely a patient may be 'resistant' to anaesthetic agents. Alcohol and other drugs of abuse are convenient scapegoats but the evidence is unconvincing. Similarly high anxiety is frequently cited as the reason why some patients may need larger than normal induction doses. In any of these situations the anaesthetist should be alert to the clinical signs indicative of inadequate anaesthesia.
  On occasion a patient may be so moribund (or so inadequately resuscitated) that adequate anaesthesia may be incompatible with maintaining cardiac function.
- **Anatomy:** During a difficult intubation the effects of the induction agent may wear off before those of the muscle relaxant.
- **Sequelae:** It is very unusual to cause physical morbidity as a result of cardiovascular stresses provoked by being aware, although it is a theoretical possibility. Much more common are manifestations of a post-traumatic stress syndrome, whose typical features may include nightmares, insomnia, panic attacks and agoraphobia.

Humidification (of inspired gases)

Commentary

This is a standard topic. Artificial humidification of dry inspired gases is important in the context both of anaesthesia and intensive care, and so you will be expected to know about the different methods that commonly are used.

The viva

Questions are likely to start with the physical principles.

- **Humidity:** This is expressed in one of two ways:
  - *Absolute humidity*: This is defined by the mass of water vapour that is present in a given volume of air. The SI unit is $g\,m^{-3}$. Absolute humidity is temperature dependent: at 20°C it is $17\,g\,m^{-3}$, whereas at 37°C it is $44\,g\,m^{-3}$.
  - *Relative humidity*: This is the ratio of the mass of water in a given volume of air to the mass of water in the same volume, were it to be fully saturated. It is usually expressed as a percentage.

Direction the viva may take

You may then be asked about methods of measuring humidity. In common with most other anaesthetists on the planet you will probably never have done this, and so you should not have to take this part of the subject very far.

- **Hair hygrometer:** The hair, which is linked to a spring and pointer, elongates as humidity increases. It is accurate between relative humidities of about 30% and 90%.
- **Wet and dry bulb hygrometer:** This is a cumbersome technique. The temperature difference between two thermometers relates to evaporation of water round the wet bulb which in turn relates to ambient humidity. The figure is calculated from tables.
- **Regnault's hygrometer:** This is a more accurate technique in which air is blown through ether within a silver tube. The temperature at which condensation appears on the outer surface is the dew point, the temperature at which ambient air is fully saturated. The ratio of the saturated vapour pressure (SVP) at the dew point to the SVP at ambient temperature gives the relative humidity. The result is determined from tables.
- **Transducers:** As a substance absorbs atmospheric water there is a change either in capacitance or in electrical resistance.
- **Mass spectrometer:** This is very accurate and has a rapid (breath-by-breath) response time. The equipment is expensive.

Further direction the viva could take

You will be asked about the clinical importance of humidification, and about methods of humidifying dry gases.

- The consequences of failure to humidify gases include drying and keratinisation of parts of the tracheobronchial tree, reduction of ciliary activity and impairment of the mucociliary escalator. In addition there may be inflammatory change in the ciliated pulmonary epithelium, drying and crusting of secretions, mucus plugging, atelectasis, superimposed chest infection and impaired gas exchange. Finally heat loss may occur via latent heat of vaporisation as dry anaesthetic gas is humidified in the respiratory tract.
- Particular patients at risk include those undergoing prolonged anaesthesia and those with pre-existing respiratory disease in whom the impairment of important pulmonary defence functions will be more significant. Those at the extremes of age are at risk (neonates, infants and the elderly) as are all intensive care patients.

- It is also of some importance to maintain the relative humidity of the operating theatre environment at an appropriate level. High humidity is uncomfortable, and low humidity increases the risk of static sparks.

Methods of humidification

- **Heat and moisture exchange (HME) filter:** This is a widely used method, which is passive, and which cannot, therefore, attain 100% efficiency, but which may reach 70%. The HME contains a hygroscopic material within a sealed unit. As the warm expired gas cools so the water vapour condenses on the element, which is warmed both by the specific heat of the exhaled gas and the latent heat of the water. Inhaled, dry and cool gas is thus warmed during inspiration, during which process the element cools down prior to the next exhalation. Problems include moderate inefficiency with prolonged use, increased dead space and infection risk.
- **Water bath (cold):** This system is passive, in that dry gases bubble through water at room temperature. It is inefficient (~30%) and becomes even more so as the loss of latent heat of vaporisation cools the water further.
- **Water bath (warm):** This system is active, in that dry gases bubble through water which is heated, usually to 60°C (to inhibit microbial contamination). These can achieve efficiencies of greater than 90%. They are more complex and there is a risk of thermal injury to patient (which is minimised by thermostats).
- **Cascade humidifier:** This is a variation on the warm water bath. Gas is allowed to bubble through a perforated plate; this process maximises the surface area which is exposed to water.
- **Nebulisers:** These can also be used as active humidifiers. A high-pressure gas stream is directed on to an anvil and entrains water which then breaks into droplets. There are also ultrasonic devices, in which water is nebulised by a plate that vibrates at ultrasonic frequencies. These are not in common use as humidifiers, because they can deliver gas with greater than 100% relative humidity and may therefore overload pulmonary tree with fluid.
- **Droplet size:** Droplets of 1 micron (μm) will be deposited in the alveoli, which is optimal. Smaller droplets may simply pass in and out with the respiratory cycle. Larger droplets (5 μm) risk being deposited in the trachea, which may help loosen secretions, but will not humidify the distal airways (nor deliver a drug dose effectively). Larger droplets still, of 20 μm and above, will not get further than the upper airway and may condense out in the equipment tubing itself.

Pulse oximetry

Commentary

Pulse oximetry has been widely available in the UK only since the late 1980s, but rapidly it became established as arguably the single most important form of monitoring in anaesthetic practice. You might even be asked to discuss that proposition in the viva. Most anaesthetists, in any event, believe that continuous measurement of oxygen saturation during anaesthesia is essential. You will be expected, therefore, to have a broad understanding of how the technique works, with particular reference to its limitations and potential sources of error.

The viva

You will be asked about the physical principles of the oximeter.

- Oxygenated haemoglobin (HbO_2) and deoxygenated haemoglobin (Hb) have differential absorption spectra.
- At a wavelength of 660 nanometers (nm) (red light), HbO_2 absorbs less than Hb, hence its red colour.
- At a wavelength of 940 nm (infrared light) this is reversed and Hb absorbs more than HbO_2. At 800 nm – the isobestic point – the absorption coefficients are identical.
- The pulse oximeter uses two light emitting diodes which emit pulses of red (660) and infrared (980) light every 5–10 μs from one side of the probe. The light is transmitted through the tissue to be sensed by a photocell on the other side.
- The output is submitted to electronic processing, during which the absorption of the blood at the two different wavelengths is converted to a ratio, which is compared to an algorithm produced from experimental data.
- Oximetry aims to measure the saturation in arterial blood, and so the instrument detects the points of maximum and minimum absorption (during cardiac systole and diastole). It measures the pulsatile component and subtracts the non-arterial constant component before displaying a pulse waveform and the percentage oxygen saturation. Hence, strictly defined, it is measuring the Sp (*p*lethysmographic) O_2 rather than the Sa (*a*rterial) O_2.

Direction the viva may take

You may be asked about potential sources of error, limitations of the technique and problems in interpreting the results.

- Pulse oximetry is calibrated against volunteers and so calibration against dangerously hypoxic values is impossible. The instruments are less accurate at SpO_2 values below 70%. You can use this fact to reassure colleagues who are less composed than you in the face of a patient's saturation that otherwise seems alarmingly low.
- Interference for ambient light. This can occur if light is bright and direct, but the pulsed nature of the emissions is intended to allow detection of and compensation for any ambient light.
- Loss of the pulsatile component. This occurs in conditions of hypoperfusion, hypothermia and peripheral vasoconstriction; when there is a narrow pulse pressure, dysrhythmias which distort the points of maximum and minimum absorption or venous congestion. These are all common reasons for a poor signal.
- Movement artefact or electrical interference (neither are major problems).
- Infrared absorption by other substances: such as nail varnish or nicotine staining.
- More significant errors are associated with absorption by abnormal Hb and other substances:
  - *Carboxyhaemoglobinaemia* (COHb): This is seen in heavy smokers or in carbon monoxide poisoning. COHb has a similar absorption coefficient to HbO_2 and will give an abnormally high SpO_2 reading of about 96%.

- — *Jaundice*: Bilirubin has a similar absorption coefficient to deoxygenated Hb and will give abnormally low saturation readings.
- — *Methaemoglobinaemia* (MetHb): MetHb has identical absorption at both wavelengths and gives a saturation reading of around 84%.
- — Dyes such as methylene blue or disulphine blue give falsely low readings.

Problems in interpretation

- Pulse oximetry does not detect respiratory failure. A high F_IO_2 may mask ventilatory failure by ensuring high SpO_2% readings despite a rising carbon dioxide (CO_2).
- In very anaemic patients SpO_2% readings may show high saturations although oxygen delivery to the tissues may be impaired.

Further direction the viva could take

If you have done well on the above, the examiner may have time to explore, for example, the proposition that pulse oximetry is the single most important monitoring device. There are no correct examination answers to this, but it can make briefly for an interesting discussion. If you do have a view then argue your case. Points to consider might include the fact that, in contrast to end-tidal CO_2 measurement, pulse oximetry gives information some of which can be obtained by clinical observation. The examiner might ask what single, theoretical monitoring device would you use, were you to be allowed only one. An answer might be a device that measured reliably the state of cerebral oxygenation. If you do find yourself in such an interchange then you should be able to relax. The examiner will be satisfied that you know the facts, but just wishes to discover whether you have thought further about the subject and are prepared to advance an independent argument.

Measurement of CO_2

Commentary

The capnograph is an essential monitor, one which is used in all but the briefest of anaesthetics. There is not a huge amount to ask about the principles of the commonest technique that is employed in CO_2 measurement (infrared absorption), and unless you are unfortunate enough to encounter an examiner who has a passion for Raman scattering, the viva will move on to clinical implications. Ensure, therefore, that you are able to draw and interpret the range of capnograph traces that you may commonly encounter.

The viva

You will be asked about methods of measuring CO_2.

- **Infrared absorption:** This is the main method of measuring CO_2 in theatre.
- Its principle is that a molecule will absorb infrared radiation (wavelength 1–40 μm) as long as it contains at least two different atoms. This applies to CO_2, as well as to N_2O and to all other inhalational agents.
- The system comprises an infrared source, a filter to ensure that only radiation of the desired wavelength is transmitted, a crystal window (glass absorbs infrared), a sample chamber and a photodetector.
- The fraction of radiation absorbed is compared with a reference gas (so regular calibration against zero and known CO_2 concentrations is essential) before the value is displayed.
- The infrared wavelength absorbed varies with the gas, thereby allowing its identification. For CO_2, this absorption is maximal at 4.28 μm. There is some overlap between CO_2 and N_2O for which modern instruments can compensate; collision broadening would otherwise falsely elevate the CO_2 readings.

Direction the viva may take

You will be asked what other methods can be used.

- **Colorimetric:** Carbonic acid forms from CO_2 and water, and will change a pH sensitive colour indicator. This principle is used in portable devices intended to confirm correct tracheal tube placement in emergency situations in which formal capnography is not available.
- **Mass spectrometry:** This technique is extremely accurate, has a very rapid response time and allows the simultaneous measurement of different compounds. The instruments, however, are very large and expensive and are not used for routine gas monitoring in the UK. The gas sample is introduced into an ionisation chamber in which some of its component molecules pass through an electron beam and become charged. The ionised particles are then accelerated out of the chamber into a strong magnetic field, which deflects the particles according to their mass.
- **Raman effect:** The interaction of electromagnetic radiation with a molecule may result in a partial, as opposed to a complete transfer of energy. Intermolecular bonds absorb the energy and some is then re-emitted at different wavelengths. There is usually a decrease in wavelength, which is characteristic of the individual molecule.

Further direction the viva could take

You may be asked what information you can get from a capnograph trace.

- **Cardiovascular information:** CO_2 production can occur only if the patient has a cardiac output. A falling CO_2 may indicate a decreasing cardiac output, a sudden fall may be a sign of pulmonary embolus, and a flat trace will be seen if there is complete circulatory arrest.

- **Respiratory information:** There are many possible variations of a capnograph trace, some of which may be quite subtle, such as the waveform you may see with intermittent malfunction of an expiratory valve. You will be asked about the traces which convey more commonly important information:
  - — *No CO_2 trace*: This may indicate oesophageal intubation, tracheal tube displacement or disconnection of the breathing system.
  - — *Low or falling end-tidal CO_2*: This may be due to over-ventilation if intermittent positive pressure ventilation (IPPV) is being used, or due to hyperventilation in a patient breathing spontaneously.
  - — *Normal end-tidal CO_2*: This usually reassures the anaesthetist that ventilation is adequate.
  - — *High or rising end-tidal CO_2*: This may be due to inadequate ventilation, to respiratory depression, to rebreathing or to exhaustion of the soda lime. It may rarely be a sign of a hypermetabolic state, of which the most extreme example is malignant hyperpyrexia, in which there is a massive increase in CO_2 production.
  - — *Abnormal capnography waveforms*: A slow upstroke and slowly rising plateau indicates chronic or acute airway obstruction. The obstruction can be anywhere in the system: either in the upper or lower airway, or in the in the breathing circuit. A trace which shows inspiratory dips in the waveform may be a sign of partial recovery from neuromuscular blockade. A raised baseline indicates rebreathing.

Supply of medical gases

Commentary

This conceptually is not a difficult question; it requires of you no judgement and little science. It requires simply facts, and facts at that which are actually of modest clinical relevance, albeit of some general interest. The question is not a good discriminator, so you might as well learn the basic information, repeat it to the examiner, and hope that the next subject about which you are asked is rather more enticing.

The viva

You will be asked how medical gases, namely oxygen, N_2O and medical air are supplied to a typical hospital.

- **Gas cylinders:**
  - The cylinders on an anaesthetic machine are usually size 'E', which contain 680 l of oxygen and 1800 l of N_2O. They have to withstand very high pressures (they are tested to 250 bar) and are made of molybdenum, chromium steel, manganese and high carbon manganese steel. (Cylinders for domiciliary oxygen can be made of lightweight aluminium alloy.)
  - Their features include colour coding (which is not international: oxygen cylinders in the UK are black with white shoulders, whereas in the USA they are green), a pin-index system to ensure attachment only to the correct yoke, and information about the contents of the cylinder. The coloured plastic collar indicates the date of the last cylinder test (the interval is between 5 and 10 years).
- **Cylinder contents:**
  - Oxygen is stored as a gas at a pressure of 13,700 kPa (137 bar).
  - N_2O is in a mixed liquid and vapour phase whose pressure is 4400 kPa.
  - Entonox is a 50 : 50 gas mixture of oxygen and N_2O at a pressure of 13,700 kPa.
- **Central gas supply:**
  - Piped gas (oxygen, N_2O, entonox and medical air) is supplied through high-quality copper pipelines. The outlets have a non-interchangeable coupling in the form of a Schrader-type valve. The hoses from the gas outlet to the anaesthetic machine are colour coded. Gas is supplied at a pressure of 4 bar, apart from the medical gas that is used to drive surgical instruments which is supplied at 7 bar.
  - The gases may come from a manifold of large cylinders. They may be arranged in banks of cylinders, each of which should contain enough gas to supply a hospital for at least 2 days.
  - Oxygen is usually supplied from a liquid oxygen source. Liquid oxygen is stored below its critical temperature at around −160°C and at a pressure of 7 bar, which is the vapour pressure of oxygen at that temperature. The low temperature is maintained both by a vacuum insulated shell, and by the fact that as the oxygen evaporates its temperature will fall. The contents of the storage device can be determined either by weight, or by pressure gauges, which measure the pressure difference between the top and bottom of the liquid oxygen.
- **Oxygen concentrators:**
  - Concentrators provide an alternative method of providing oxygen, although their low flow rates (4 l min^{-1}) and pressures (70 kPa) mean that they are more commonly used to provide domiciliary supplies for individual patients.
  - They comprise zeolite-containing columns. Zeolites are hydrated aluminium silicates which are ion-exchangers and molecular sieves. The flow of air into the cylinders is directed so that nitrogen and water vapour

are absorbed from one cylinder, while absorbed gas from the other is extracted by a vacuum pump. Every 30 s a solenoid valve switches the flow to ensure a constant flow of 95% oxygen to the reservoir. The remaining 5% is argon, which appears to have no adverse effects.

- **Medical air:** This can be supplied from a central compressor or from cylinders. It has to be dry, free from particulate matter, including the mineral oils used to lubricate the compressor, and free from bacteria. The air, therefore, is desiccated and filtered.

Direction the viva may take

You may be asked some miscellaneous definitions before questions about safety, safe storage and supply failure.

- **Filling ratio:** This is the mass of gas used to fill a cylinder divided by the mass of water needed to completely fill the cylinder. It applies to gases that are stored in the liquid phase, and for N_2O it is 0.75. If the cylinder is to be used in hotter climates this is reduced to 0.67. An overfilled cylinder that is exposed to high ambient temperatures will generate dangerously high pressures.
- **Safe storage:** This is largely common sense. Cylinders should be kept in a secure and dry environment, free from extremes of temperature. Full and empty cylinders ideally should be kept in separate areas to avoid the risk of substitution. Large cylinders are usually stored upright; smaller ones may be laid horizontally.
- **Entonox:** This is a 50 : 50 mixture of N_2O and oxygen, at a pressure of 13,700 kPa. Cylinders should be stored flat to prevent delivery of 100% N_2O when the cylinder is first used.
- **N_2O:** You may be asked what happens when a N_2O cylinder empties. In theory the pressure, which is the vapour pressure, should remain constant until the liquid phase is exhausted, after which the pressure would fall to zero as the cylinder emptied. In practice, because the temperature of the liquid N_2O falls as it vaporises, the cylinder pressure also drops. The pressure returns to 4400 kPa only if the gas flow ceases and the cylinder is allowed to return to room temperature.
- **Gas supply or oxygen failure:** Failure of the liquid oxygen source triggers supply from a reserve manifold of large oxygen cylinders, which are also remote from the site of delivery to the patient. There should also be reserve cylinders available in theatre. Should there be a complete failure of oxygen delivery the anaesthetic machine should discontinue the flow of N_2O, and entrain air.

The anaesthetic machine

Commentary

This topic may be asked in various ways. The viva may deal with overall safety features, or it may concentrate on prevention of barotrauma or hypoxia. A structured approach should allow you to answer the question adequately; from whichever direction it is approached. It is a core subject, but not one which is difficult. The safety features of the anaesthetic machine are numerous and you will have little time to do more than list them.

The viva

- The modern anaesthetic machine delivers accurate mixtures of anaesthetic gases and inhalational agents at variable, controlled flow rates and at low pressure. It accomplishes this via a number of features that are best described by tracing the gas flow through the system from the cylinder or pipeline to the fresh gas outlet.
- **Gas pipelines:** These are colour coded for the UK, but there is no international consistency. A Schrader coupling system ensures that the pipeline connections are non-interchangeable. Reducing valves reduce the pressures to 4 bar. The pipeline hose connection to the rear of the anaesthetic machine is permanent. The threads are gas specific (NIST – non-interchangeable screw thread) and a one-way valve ensures unidirectional flow.
- **Gas cylinders:** Again these are colour coded for the UK, but there is no international standard. They are made from molybdenum steel. They are robust and undergo rigorous regular hydraulic testing (as does the cylinder outlet valve). A pin-index system, which is unique to each gas, prevents connection to the wrong yoke, and side guards on each yoke ensure that the cylinders are vertical. A Bourdon pressure gauge indicates cylinder pressure. A pressure regulator/reducing valve reduces pressure to 4 bar, and a relief valve is located downstream in case of regulator failure.
- **Flow restrictors:** These are placed upstream of the flowmeter block and protect the low-pressure part of the system from damaging surges in gas pressure from the piped supply. They may sometimes be used downstream of the vaporiser back bar to minimise back pressure associated with IPPV.
- **Flow control valves:** These govern the transition from the high pressure to the low-pressure system, and reduce the pressure from 4 bar to just above atmospheric as gas enters the flowmeter block.
- **Oxygen failure devices:** Systems vary. In one design, for example, a pressure sensitive valve closes when oxygen pressure falls below 3 bar. The gas mixture is then vented, activating an audible warning tone. The same valve opens an air-entrainment valve so that the patient cannot be exposed to a hypoxic mixture resulting from failure of oxygen delivery. An interlock system between the oxygen and N_2O control valves prevents the administration of a hypoxic mixture. The machine cannot deliver a N_2O concentration greater than 75%.
- **Emergency oxygen flush:** Oxygen is supplied direct from the high-pressure circuit upstream of the vaporiser block and provides 35–75 l min^{-1} (if the oxygen flowmeter needle valve is opened fully it delivers about 40 l min^{-1}). Both methods may cause barotrauma in vulnerable patients.
- **Flowmeters:** These are constant pressure variable orifice flowmeters ('Rotameter' is a trade name), which are calibrated for a specific gas. The tubes have an antistatic coating to prevent sticking, and there are vanes etched into the bobbin to ensure rotation. In the UK the oxygen knob is always on the left, is larger, is hexagonal in profile and is more prominent than the others. This is said to be because Boyle, who designed one of the original anaesthetic machines, was left handed. This position does, however, put the patient at risk of breathing a hypoxic mixture if there is damage to a downstream flowmeter tube. CO_2 has

disappeared from most machines: where it is still delivered it is usually governed to prevent a flow of greater than 500 ml min^{-1}.

- **Vaporisers and back bar:** The commonest type of vaporiser are temperature compensated variable bypass devices which allow accurate and safe delivery of the dialled concentrations. A locking mechanism on the back bar prevents more than one vaporiser being used at the same time. A non-return valve on the back bar prevents retrograde flow due to the pumping effect of IPPV. A pressure relief valve on the downstream end of the back bar protects against increases in the pressure within the circuit.
- **Common gas outlet:** This receives gases from the back bar and from the emergency oxygen flush. It has a swivel outlet with a standard 15 mm female connection.

Direction the viva may take

The features listed above will take most of the viva to describe, and if you can add some extra detail in one or two key areas, there will be little opportunity for the examiners to take it much further.

If the viva concentrates on protection from barotrauma, then the key features from the list above include:

- Pressure reducing valves; both pipeline and cylinders.
- Flow restrictors.
- Flow control valves.
- Pressure relief valves downstream of the vaporiser back bar.

If the viva concentrates on protection from hypoxia, then the key features from the list above include:

- Gas pipelines colour coding and NIST connections.
- Gas cylinders colour coding, pin indexing.
- Oxygen failure devices.
- Interlock system.
- Emergency oxygen flush.

Scavenging

Commentary

This topic is rather dry, but it is hard to argue with the importance of minimising pollution within the theatre environment, a process which may involve individuals with clipboards and sampling devices spending many serious hours determining time weighted averages for anaesthetic gases. Scavenging is something that you will have to know about, even though the direct clinical implications are only modest.

The viva

After an introductory question about the need for scavenging, you will probably be asked to describe the systems in use.

- **Purpose of scavenging:** The safe removal of waste theatre gases is a health and safety issue, and since 1989, with the government introduction of 'Control of Substances Hazardous to Health' (COSHH), has been a legal requirement.
- **Staff health issues:** Some studies have identified increased risks of spontaneous abortion in females exposed to trace concentrations of anaesthetic gases, and also that male anaesthetists were more likely to father daughters than sons. There was in addition the suggestion of an increase in haematological malignancies. The association is not strong, because other studies have not replicated these data. Sufficiently large numbers of anaesthetics, moreover, are administered annually in the developed world, to suggest that were there to be an emphatic problem of this kind then its provenance would be a lot more obvious.
- **Scavenging system:** The basic arrangement comprises collection, transfer, receiving and disposal systems.
  - — *Collection system*: This is usually a shroud that is connected to the adjustable pressure limiting (APL) or expiratory valves of the ventilator via a 30 mm connector (which prevents confusion with components of the breathing system).
  - — *Transfer system*: This comprises tubing to remove the gases.
  - — *Receiving system*: This is a reservoir system, which is protected against excessive pressures by valves. The positive pressure relief valve is set at 1000 Pa (1 kPa); the negative pressure relief valve is set at −50 Pa (−0.05 kPa).
  - — *Disposal system*: This simply vents the exhaust to atmosphere and makes the pollution someone else's problem.
- There are two main types of system: **passive** and **active:**
  - — *Passive systems*: The components of the system are as described above, and the gases are exhausted to atmosphere either by the patient's spontaneous respiratory efforts or by the mechanical ventilator.

    The 'Cardiff Aldasorber' is another passive device and comprises a canister-containing charcoal particles which absorb halogenated volatile anaesthetic agents. Absorption does not render the agents inert: if the canister is disposed of by incineration, the inhalational agents are released to atmosphere. This device does not absorb N_2O.
  - — *Active systems*: The basic components of the system are again as described above, but the vacuum created by a fan or a pump in the disposal system draws the anaesthetic gases through the system. It is important that the negative pressures so generated cannot be transmitted to the patient.

Direction the viva may take

You may then be asked how else you might minimise theatre pollution.

- Theatre air changes (at least 15 times per hour).
- Substitution of TIVA and regional anaesthesia for inhalational anaesthesia.
- Use of low and ultra low flow breathing systems.

Further direction the viva could take

You may finally be asked about the maximum permitted exposures, which are expressed as an 8-h time weighted average. Again the practical relevance of knowing these numbers is elusive, and it also seems suspicious both that there is such a big variation in levels between the UK and the USA, and that in the UK the permitted maxima are all multiples of 10. The science underlying these data may not, therefore, be robust.

- **Permitted maxima:**
  - — N_2O: 100 parts per million (ppm) (25 ppm in the USA)
  - — *Isoflurane*: 50 ppm
  - — *Enflurane*: 50 ppm
  - — *Halothane*: 10 ppm
  - — *Sevoflurane and desflurane*: There are no maximum limits yet prescribed, but COSHH states that their similarity to enflurane suggests that 50 ppm would be appropriate.
  - — All halogenated volatile agents are 2 ppm in the USA.

Soda lime

Commentary

This question appears in the Final FRCA, although it is a topic that you may already have encountered in the Primary. The potential clinical problems with the use of soda lime are almost entirely theoretical, but there will be insufficient time for a discussion of low flow anaesthesia, which logically is where the viva should lead. The subject is conceptually not difficult and so this is one of those questions about which you will just have to know some of the facts.

The viva

You will be asked about the composition of soda lime and its mode of action.

- Soda lime is used to absorb CO_2. The discovery is not recent: it has been known for over two centuries that CO_2 is absorbed by strong alkali ('caustic soda').
- Its main use is to allow the rebreathing of exhaled gases within breathing systems. This is most commonly the circle system, although it was also used in the original Waters circuit. To-and-fro breathing was allowed by the insertion into the system of a small soda lime canister.
- Its chemical constituents are: calcium hydroxide (CaOH) 80%; sodium hydroxide (NaOH) 4%; potassium hydroxide (KOH) 1% (this accelerates the reaction); and water (H_2O) 15%.
- Also added are silicates in trace amounts which harden the granules which otherwise would disintegrate into powder. An indicator dye is also present which changes the colour of the soda lime as it is progressively exhausted. This is either phenolphthalein (the colour changes from red to white) or, less commonly, ethyl violet (the colour changes from white to purple). As these colour changes are in opposite directions it is clearly important to know which dye is being used.
- Soda lime is formed either into granules whose size is 4–8 mesh (mesh describes the number of openings per inch in a uniform metal strainer), or into spheres. The more uniform the shape the greater the likelihood of uniform flow through the canister. The size of the granules or spheres is a compromise between providing the largest surface area for absorption without providing excessive resistance to flow.
- Under ideal conditions 1 kg can absorb 250 l of CO_2.
- In the presence of water and with NaOH and KOH as activators, the chemical reaction can be summarised as follows:

  $CO_2 + Ca(OH_2) \rightarrow CaCO_3 + H_2O$

- Partially exhausted soda lime may regenerate on standing with the migration of unused hydroxide ions from the core to outer areas. Its absorptive capacity in this state is minimal.

Direction the viva may take

You may be asked what other compounds can be used to absorb CO_2.

- **Barium lime (baralyme):** This comprises calcium hydroxide (CaOH) 80% and barium hydroxide (BaOH) 20%. Water is incorporated into the structure of BaOH. The chemical reaction is similar to that of soda lime, although it is less efficient.
- **Amsorb:** This compound (developed in Belfast) contains CaOH, calcium chloride and two setting agents. Its absorption capacity is comparable to other agents but its use is associated neither with carbon monoxide nor compound A formation.

Further direction the viva could take

You may be asked about potentially dangerous reactions between CO_2 absorbents and anaesthetic agents.

- **Carbon monoxide:** Modern anaesthetic machines continue to deliver an FGF of 200 ml min^{-1} of oxygen even when the flowmeters are turned off. If the machine goes unused for some time then this constant flow may dry out a canister of soda or barium lime. Under these circumstances the reaction of the absorbent with the CHF_2 group of isoflurane, enflurane or desflurane can produce high levels of carbon monoxide.
- **Compound A:** Sevoflurane reacts with strong monovalent hydroxide bases, such as those which are used in soda lime and barium lime CO_2 absorbers, to produce a number of substances including compound A. (The reaction with barium lime is about five times more rapid than with soda lime.) Of the degradation products (compounds A, B, D, E and G) only A, which is a vinyl ether, has been shown to have any toxicity, but the dose-dependent renal damage noted in rats has never been seen in humans. Amsorb appears to be safer in this regard.
- **Trilene (trichloroethylene):** Of historical interest, and included just in case you should be asked, is the reaction between trilene and soda lime. This produced dichloroacetylene, which is a potent neurotoxin, and which affected particularly the trigeminal and facial nerves.

Flowmeters

Commentary

There are few anaesthetics given which do not involve the use of at least one flowmeter. It is important, therefore, to be aware of how they function as well as of potential sources of inaccuracy. This is a predictable and straightforward question, but it is fairly thin, and so you will be expected to know the basic physics.

The viva

You will be asked about the physical principles which underlie the function of flowmeters.

- A flowmeter is a variable orifice, fixed pressure difference device, which gives a continuous indication of the rate of gas flow. ('Rotameter' is a trade name which continual use has given generic status.)

Physical principles

- A bobbin floats within a vertical conical glass tube, supported by the gas flow, which is controlled by a needle valve.
- At low flows the orifice around the bobbin is an annular tube, and the gas flow is laminar. Flow rate through a tube is related to the viscosity of the gas and the fourth power of the radius.
- At higher flows and further up the tube the area of the orifice is larger in relation to the bobbin and the flow is turbulent. Flow rate through an orifice is related to the density of the gas and the square of the radius.
- These factors mean, therefore, that flowmeters have to be calibrated for the specific gases that they are measuring. They are not interchangeable for different gases. They are accurate to $\pm 2.5\%$.
- The pressure across the bobbin at any flow rate remains constant, because the force to which it gives rise is balanced exactly by the force of gravity acting on the bobbin.

Other features of flowmeters

- The bobbin is designed with small slots or fins in its upper part so that it will rotate centrally within the gas stream. This is to prevent its sticking to the side of the tube because of dirt or static electricity.
- To prevent the accumulation of static charge, tubes have either a conductive coating or have a conductive strip at the back.
- The flowmeter blocks are designed to ensure that the bobbin remains visible at the top of the tubes, even when the gas flow is at its maximum.

Direction the viva may take

You may be asked about potential sources of inaccuracy.

- Accumulation of dirt or static electricity not overcome by the design features above.
- A flowmeter block may not be vertical: the bobbin must not impinge on the sides of the tube.
- Back pressure on the gas flow may still be a problem on some anaesthetic machines.
- Cracked seals or tubes may provide a source of error. Oxygen is the last gas to be added to the mixture that is delivered to the back bar.

Further direction the viva could take

At some stage the viva may divert into the subject of laminar and turbulent flow. This is covered in more detail in *Laminar and turbulent flow*, page 245.

Laminar and turbulent flow

Commentary

Precise physical principles underlie the concepts of laminar and turbulent flow, and the viva is likely to concentrate more on these than on their practical implications. Factors which influence flow are important in relation to intravenous fluid therapy and to the administration of inhaled gases, but their relevance is obvious, and the potential for discussion is relatively limited. Examiners tend to view this as a straightforward and predictable question. They do not expect candidates to have much difficulty with it, and so you should know the topic well.

The viva

You will be asked about the difference between laminar and turbulent flow.

- **Flow:** Flow is the amount of a fluid (gas or liquid) passing a point in unit time.
- **Laminar flow:**
  - This describes the situation in which a molecule of the given substance maintains a constant spatial relationship to all the others that are flowing in the same layer, or lamina, down the tube. The flow is greatest in the centre of the tube, being approximately twice the mean flow, whereas at the walls of the tube the flow reduces almost to zero.
  - A number of factors influence flow: these include the pressure differential between the ends of the tube ($P_1 - P_2$), the diameter of the tube (d), the length of the tube (l) and the viscosity of the fluid (η).
  - These factors have been combined (together with a proportionality constant $\pi/128$) to derive the Poiseuille–Hagen equation.
  - Poiseuille–Hagen. Flow rate = $(P_1 - P_2) \times d^4 \times \pi/128 \times l \times \eta$.
  - This equation applies strictly only to an ideal or Newtonian fluid, which is defined as any fluid that demonstrates a linear relation between the applied shear stress and the rate of deformation. A flowing liquid can be visualised as a series of parallel laminae. If the flow is to double, therefore, it must overcome a resistive force that is twice as great. Water is a Newtonian fluid, but blood is not.
  - Fluids resist flow because of the phenomenon of viscosity. Viscosity describes the frictional forces which act between the layers of the fluid as it moves down the tube. Its units are pascal seconds.
- **Turbulent flow:** This describes fluid flow in which the orderly arrangement of the molecules is lost and the fluid swirls and eddies, thereby increasing the resistance.
- **The transition from laminar to turbulent flow:**
  - This is given by the Reynolds number, which is an index derived from a combination of linear velocity (v), the density of the fluid (ρ), the diameter of the tube (d) and the viscosity of the fluid (η). Reynolds number = $v\rho d/\eta$.
  - When the Reynolds number exceeds 2000 turbulent flow supervenes. (This information has been obtained empirically from *in vitro* experiments.)
  - Critical flow and critical velocity refer to the situation in which the Reynolds number is 2000, and the flow is liable to become turbulent.
  - A local increase in velocity, such as occurs in the angles or constrictions of a breathing system, is likely to change gas flow from laminar to turbulent, with a resultant increase in resistance and the work of breathing.

Direction the viva may take

You are likely to be asked about the clinical implications of this science.

- **Gas flow:** Turbulent flow increases resistance and so it is important to minimise angles and constrictions in breathing systems. Increased velocity may increase

turbulence, which may be of significance, for example, in an asthmatic who is hyperventilating. In an infant with bronchiolitis, a small decrease in the calibre of the airways due to inflammation and oedema, may critically impair the capacity of the exhausted baby to maintain effective ventilation. These are some of many possible examples.

- **Fluid flow:** The Poiseuille–Hagen equation is well known to anaesthetists because it has obvious clinical relevance. The flow of fluid via an intravenous infusion will double if the driving pressure is doubled, or if the length of the cannula is halved. Fluid resuscitation through long central venous catheters, therefore, may not be effective. Flow, however, in theory will increase by 16 times if the internal diameter of the cannula is doubled. In practice the increase may not be as impressive: a typical 14-G cannula of 2.20 mm (external) diameter has a flow rate of 315 ml min^{-1}, in contrast to an 18-G cannula with a diameter of 1.30 mm through which distilled water flows at 100 ml min^{-1}. The difference remains significant enough, however, to mandate the use of wide bore cannulae for rapid restoration of circulating volume.

Temperature and its measurement

Commentary

The maintenance and control of body temperature are of evident importance in clinical anaesthetic practice. It is rather more difficult to see how an intimate knowledge of thermistors and thermocouples is especially helpful. It clearly excites somebody, however, because this topic reappears in the examination, and it is sufficiently circumscribed to allow it to fit into the time available.

The viva

You will be asked about methods of measuring temperature.

- Heat is an energy form related to the activity, or kinetic energy in the molecules of the particular substance.
- Temperature is a way of quantifying the thermal state of a substance.
- Units of measurement. The SI unit is the Kelvin (K), which equals Celsius (°C) plus 273.15. As 1°C is the same as 1 K, the unit is used universally in medicine.
- There are three main types of device for measuring temperature: electrical, non-electrical and infrared.
- **Electrical:**
  - *Thermistor*: A small bead of a semiconductor material, usually a metal oxide, is incorporated into a Wheatstone bridge circuit. The resistance of the bead decreases exponentially as the temperature rises. These beads are both robust and very small, and are used in the tips of pulmonary artery flotation catheters for thermodilution measurements.
  - *Thermocouple*: If two dissimilar metals are joined, a small potential difference develops which is proportional to the temperature of the junction. (This is known as the Seebeck effect.) Another junction between the metals is necessary to complete an electrical circuit, although another temperature-dependent voltage will develop at this junction. The metals that are used are commonly copper and a copper/nickel alloy. When the thermocouple is used as a thermometer, one of the junctions forms the temperature probe, while the other is kept at a constant temperature and acts as a reference. Thermocouples are stable and accurate to ± 0.1°C.
  - *Resistance thermometer*: These are based on the principle that electrical resistance in metals shows a linear increase with temperature. These systems are not used clinically.
- **Non-electrical:**
  - *Mercury and alcohol thermometers*: Volume increases with temperature. Like all thermometers these are calibrated against fixed points, such as the triple point (at which water, water vapour and ice are in equilibrium) and boiling points of water.
  - *Dial thermometers*: These may use a coil comprising two metals with differential coefficients of expansion. As the temperature changes the coil tightens and relaxes, and an attached lever moves across a calibrated dial.
- **Infrared**
  - *Tympanic membrane thermometers*: The living body emits infrared radiation, whose intensity and wavelength varies with temperature. This property is utilised in tympanic membrane thermometers. These use pyroelectric sensors, which comprise an electrically polarised substance whose polarisation alters with temperature. This change can be used to generate an electrical output, which is proportional to the temperature. Their response time is very rapid compared with other types of clinical thermometer. The tympanic membrane is the favoured site for temperature measurement in anaesthesia because it offers the most accurate indication of cerebral temperature.

Direction the viva may take

You will be unlucky if the entire viva is spent on the technicalities of different types of thermometer. You may be asked about mechanisms by which patients lose heat and about the clinical effects of mild hypothermia. This is covered in more detail elsewhere. (See *Heat loss*, page 249.)

Mechanisms of heat loss

- **Radiation (50%):** The body is an efficient radiator, transferring heat from a hot to cooler objects.
- **Convection (30%):** Air in the layer close to the body is warmed by conduction, rises as its temperature increases and is carried away by convection currents.
- **Evaporation (20–25%):** Moisture on the body's surface evaporates, loses latent heat of vaporisation and the body cools.
- **Conduction (3–5%):** This occurs only if the patient is lying unprotected on an efficient heat conductor.
- **Respiration (10%):** Heat loss is via evaporation and the requirement to heat inspired air.
- **Anaesthesia:** This affects central thermoregulation and causes vasodilatation.

Clinical effects of hypothermia

- **Cardiorespiratory effects:** Oxygen consumption increases and cardiac output decreases. Dysrhythmias are more likely. The oxygen–Hb dissociation curve shifts to the left and reduces oxygen delivery. Blood viscosity increases.
- **Metabolic effects and effects on drugs:** Metabolic rate decreases by 6–7% for each 1°C fall in core temperature. Enzymatic reactions and intermediary metabolism are slower at core temperatures below 34°C. Drugs actions are prolonged; especially those of muscle relaxants. Patients may develop a metabolic acidosis.
- **Surgical outcome:** Hypothermia compromises immune function and increases post-operative infection rates. Wound healing is adversely affected and hospital stay may be prolonged.

Heat loss

Commentary

This topic incorporates some basic science and it is also of clinical importance, given recent evidence that prevention of peri-operative heat loss may reduce infection rates and decrease hospital stay.

The viva

You will be asked about mechanisms by which patients lose heat during anaesthesia.

Mechanisms of heat loss

- **Radiation:** This is the most important mechanism and may account for 50% or more of heat loss. The body is a highly efficient radiator, transferring heat from a hot to cooler objects. The process is accelerated during anaesthesia if the patient is surrounded by cool objects and prevented from receiving radiant heat from the environment. Further heat loss will also occur if the body is forced to heat cold infused fluids up to 37°C.
- **Convection:** This accounts for up to 30% of heat loss. Air in the layer close to the body is warmed by conduction, rises as its temperature increases and is carried away by convection currents. The process is accelerated during anaesthesia if a large surface area is exposed to convection currents (particularly in laminar flow theatres).
- **Evaporation:** This accounts for some 20–25% of heat loss. As moisture on the body's surface evaporates it loses latent heat of vaporisation and the body cools. This is a highly developed mechanism for heat loss in health, but undesirable during surgery. It is accelerated during anaesthesia if there is a large moist surface area open to atmosphere (especially in major intra-abdominal surgery, intrathoracic surgery, reconstructive plastic surgery and major orthopaedic surgery).
- **Conduction:** This is not a significant cause of heat loss during normal circumstances, accounting for only 3–5% of the total. Heat loss by this mechanism increases during anaesthesia only if the patient is lying unprotected on an efficient heat conductor such as metal table.
- **Respiration:** Heat loss occurs due to evaporation and the heating of inspired air. This amounts to around 10% of the total but it can be minimised during anaesthesia by the use of heat and moisture exchangers.
- **Influence of anaesthesia:** Vasodilatation increases heat loss, and anaesthetic agents can also affect hypothalamic central thermoregulation.

Direction the viva may take

You are likely to be asked about the clinical consequences of hypothermia.

- Profound hypothermia with core temperatures of 28–30°C will not occur during anaesthesia unless it has been deliberately induced, but it is common to see patients whose temperatures have dropped by several °C.
- **Cardiorespiratory effects:** Oxygen consumption increases during mild hypothermia (34°C), although oxygen consumption may increase by 500% during shivering as a patient rewarms. Cardiac output is decreased and hypothermia increases the incidence of dysrhythmias. The oxygen–Hb dissociation curve shifts to the left, increasing oxygen affinity and reducing oxygen delivery. Blood viscosity increases and with it the risk of intravascular sludging.
- **Metabolic effects and effects on drugs:** Metabolic rate decreases by around 6–7% for each 1°C fall in core temperature. Enzymatic reactions are slowed and all the reactions of intermediate metabolism are affected at core temperatures

lower than 34°C. The actions of most drugs, therefore, are prolonged. This applies especially to neuromuscular blocking agents. Hypothermia leads to a progressive acidosis. Renal function and hepatic function are depressed, but patients may have a diuresis due to the failure of active reabsorption of sodium and water. Hyperglycaemia may result as glucose utilisation falls.

- **Central nervous system effects:** There is a progressive deterioration in mental function to the point at which the EEG will record no cerebral activity.
- **Surgical outcome:** There is recent convincing evidence that hypothermia compromises immune function and increases post-operative infection rates. Wound healing is adversely affected and hospital stay may be prolonged.
- **Prevention:** Minimise heat losses due to the mechanisms above, by the use, for example, of insulated operating table warmers, heat and moisture exchangers in the breathing system, warm air blankets, warmed infused fluids and protection of the head.

Further direction the viva could take

You may be asked about the management of severe hypothermia.

- The examiner is less interested in the generic approach (investigation of any underlying cause after attention to airway, breathing and circulation) than in specific details of rewarming.
- Techniques include the use of external heat sources (forced warm air blankets, radiant heaters) and internal warming. This can be via the use of warm intravenous, intragastric, and intra-peritoneal fluids, as well as by bladder irrigation via a urinary catheter. The most efficient, but most invasive method of rewarming is to put the patient on cardiac bypass. Other extracorporeal systems such as haemofiltration units may lack the very rapid flow rates that are necessary. Rapid rewarming is better for rapid onset hypothermia (such as sudden immersion), whereas slower rewarming at about 1°C hourly is more appropriate for hypothermia of gradual onset.

Pressure

Commentary

Pressures and their measurement are so much part of anaesthesia that it is not surprising to find them appearing as an examination topic. The first part of the viva will concentrate on definitions and methods of measurement, while the second part is likely to cover some disparate clinical implications, the emphasis of which will vary with the examiner's interests. As always, when a part of the viva becomes less structured, that particular area of questioning may benefit you little even if your answers are sound, but may damage you disproportionately if your answers suggest frailties of clinical judgement.

The viva

You will be asked to define pressure. It is an important concept in anaesthesia and so you should ensure at the outset that you can articulate the basic definitions with assurance.

- **Definitions:** Pressure is defined as force per unit area, force being that which changes or tends to change the state of rest or motion of an object. The units of force are newtons (N), 1 N being that force which will accelerate a (frictionless) mass of 1 kg at 1 ms^{-2} (in a vacuum). The SI unit of pressure is the pascal (Pa), 1 Pa being a force of 1 N acting over an area of 1 m^2. Gravity gives any mass an acceleration of 9.81 ms^{-2}, so the force acting on 1 kg is 9.81 N. One newton is therefore equivalent to 102 g weight. This is a small pressure, hence the use of the kilopascal (kPa) as the main unit of physiological pressure. Higher pressures are still quoted in bar (1 bar = 100 kPa = 1 atmosphere (atm)).
- **Absolute pressure and gauge pressure:** An empty gas cylinder has a gauge pressure of zero, but the ambient pressure inside the cylinder is 1 atm. Absolute pressure, therefore, is given by the gauge pressure plus atmospheric pressure.
- **Examples of methods of measuring pressure:**
  - — *Liquid manometry*: The pressure in the column is equal to the product of the height of the column, the density of the liquid, and the force of gravity. The width and shape of the column have no effect on the pressure reading. Surface tension provides a potential source of error in columns less than 10 mm in diameter, but in the clinical context, in which trends are commonly more important than absolute numbers, this is not significant. (In a water manometer of 6 mm diameter, surface tension will elevate the meniscus by 4.5 mm.)
  - — *Aneroid gauges*: Examples include the Bourdon gauge for high pressures, which comprises a flattened coiled tube, which unwinds as pressures increase.
  - — *Diaphragm gauges*: These are used for many physiological pressures. Pressure changes cause movement in a flexible diaphragm, and these are either read directly or transduced. Electromechanical devices are probably the commonest, employing wire strain gauges whose resistance changes in response to pressure. The sensing diaphragm can also be incorporated as one plate of a capacitor, the other being fixed. The charge that is carried varies with the separation of the plates.

Direction the viva may take

You may be asked about the situations in which pressures may be important in anaesthetic practice. This will be a very long list, so expect to be interrupted, either to explain the physics in more detail, or to outline the clinical significance.

- **Physiological pressures:**
  - — *Non-invasive blood pressure*: Automatic machines utilise the oscillometric principle. The movement of the arterial wall is transmitted to the cuff and

the pressure changes are sensed by a transducer. Above systolic pressure and below diastolic pressure the oscillations are minimal. As the cuff deflates automatically to systolic pressure oscillations begin, and increase in amplitude until mean blood pressure is reached, after which the amplitude decreases until diastolic pressure point is reached. The fluctuations are analysed by a microprocessor prior to being displayed digitally.

- — *Invasive blood pressure*: See *Intra-arterial blood pressure measurement*, page 263.
- — *Central venous pressure*: See *Central venous pressure and cannulation*, page 141.
- — *Intravascular pressures – Laplace's law*: In a tube, such as the aorta, the transmural pressure gradient is given by the wall tension divided by the radius ($P = T/r$). For a sphere the relationship is $P = 2T/r$. This pressure relationship explains why an expanding aortic aneurysm is increasingly likely to rupture as the aorta dilates, and why a reservoir bag on a breathing circuit does not cause barotrauma to normal lungs if it is allowed to distend by tightening the valve.
- — *The Venturi principle*: Flowing gas contains potential energy (from its pressure) and kinetic energy (associated with its flow). At a constriction the flow, and hence the kinetic energy of the gas, increases. The total amount of energy must remain constant and so the potential energy, and hence the pressure decreases, allowing the entrainment of gas or fluid.
- — *Intracranial pressure*: See *(Raised) intracranial pressure*, page 124.
- — *Intrapleural pressures*: See *Pneumothorax*, page 79.
- — *Intraocular pressure*: The normal value is 10–22 mmHg and its prime determinants are choroidal blood flow and volume (influenced by $PaCO_2$, venous drainage and hypoxia), the formation and drainage of aqueous humour, and external pressure on the globe by contraction of extraocular muscles and of the orbicularis oculi muscle (or by orbital local anaesthetic or retrobulbar haemorrhage). Coughing, straining or vomiting will transiently increase the pressure by 40 mmHg or more.

- **Non-physiological pressures:**
  - — *Pipeline and cylinder pressures*: See *Supply of medical gases*, page 236.
  - — *Syringe pressures*: The relationship between force and pressure explains why a small syringe can generate far higher pressures than a larger one. The pressure developed equals force/area. The smaller the area represented by the plunger in the syringe then the greater the pressure generated for a given applied force: hence a 2 ml syringe is much more effective than a 10 ml syringe if used to flush a blocked intravenous catheter.

Jugular venous bulb oxygen saturation

Commentary

Jugular venous bulb oxygen saturation ($SjVO_2$) provides a measure of global cerebral oxygenation and finds uses in neurosurgery, in neurotrauma and in cerebral monitoring during cardiac surgery. This is an area of specialist practice which you may well not have encountered. If you are able to base your answer on first principles it is likely that the examiners will make some allowances for lack of sub-specialty knowledge.

The viva

The topic may be introduced via a question about the clinical value of this investigation, before you are asked how it can be measured.

- $SjVO_2$ is an indirect indicator of cerebral oxygen utilisation.
- $SjVO_2$ is usually measured via an intravascular catheter which is threaded retrogradely up the internal jugular vein as far as the superior jugular bulb. (The jugular bulb is a dilatation at the origin of the vein, and lies just below the posterior part of the floor of the tympanic cavity.) The normal value is 55–75%.
- A fibre-optic catheter uses reflectance oximetry (as in pulmonary arterial catheter monitoring of mixed venous saturation) to provide continuous $SjVO_2$ monitoring. As with pulse oximetry, the apparatus uses the light absorption spectra of HbO_2 and Hb.
- Catheter placement can be facilitated by locating the vessel using ultrasound, and is verified by lateral skull X-ray, which should confirm the tip lying at the level of, and medial to, the mastoid process.
- Alternatively a sample may be taken directly from the jugular bulb and the oxygen saturation measured by co-oximetry.

Direction the viva may take

You are likely to be asked to discuss in more detail the clinical value of $SjVO_2$ measurements.

- $SjVO_2$ is an indirect indicator of cerebral oxygen utilisation: when oxygen demand exceeds supply, then oxygen extraction increases and $SjVO_2$ falls (desaturated at $<50\%$). Conversely when supply exceeds demand the $SjVO_2$ rises (luxuriant at $>75\%$). Bulb oxygen saturation can be used as a specific measure of global cerebral oxygenation but it cannot provide information about smaller focal areas of ischaemia.
- The difference in oxygen content between arterial and jugular venous blood ($AjvDO_2$) is given by cerebral metabolic rate for oxygen/cerebral blood flow ($CMRO_2/CBF$). The normal value is 4–8 ml oxygen/100 ml of blood.
- If $AjvDO_2$ is <4 supply is luxuriant: if >8 it suggests ischaemia.
- **Factors decreasing $SjVO_2$:** An increased oxygen demand, or a decrease in supply (leading to a fall in $SjVO_2$ and rise in $AjvDO_2$) results from raised intracranial pressure (ICP), severe systemic hypotension, hypocapnia (less than 3.75 kPa), arterial hypoxia, seizure activity and cerebral vasospasm. It will also fall if the patient is pyrexial and in response to increased metabolic demand. A decrease in $SjVO_2$ always indicates potential cerebral dysfunction.
- **Factors increasing $SjVO_2$:** A decreased oxygen demand or increase in supply (leading to a rise in $SjVO_2$ and fall in $AjvDO_2$) results from: decreased metabolic demand (such as occurs with hypothermia or sedation), brain death (in which there is minimal demand), an increased blood supply, hypercapnia and arterial hyperoxia. An increase in $SjVO_2$ may therefore also presage cerebral damage.

Surgical diathermy

Commentary

Diathermy is used widely and is in essence a surgical instrument. The anaesthetist, however, unfair though it seems, will in practice be blamed should a patient suffer a burn due to malpositioning of the plate. Diathermy may also interfere with monitors and can disrupt pacemaker function, and so it is a topic on which some basic knowledge is expected.

The viva

You will be asked about the physical principles.

- Diathermy is used widely in surgical practice, both for coagulation and for cutting, and relies on the heat generated as an electric current passes through a resistance that is concentrated in the probe itself.
- Heat generation is proportional to the power that is developed: typically 50–400 W. Heat is proportional to I^2 (current)/A (area).
- A high-frequency sine waveform is used for cutting: typically 0.5 MHz.
- A damped waveform is used for coagulation: typically 1.0–1.5 MHz.
- High frequency is necessary because muscle is very sensitive to direct current (DC) and to alternating current (AC) at low frequencies. Mains frequency is low at 50 Hz, which is a frequency that is particularly efficient at precipitating ventricular fibrillation (VF). Very high-frequency current has minimal tissue penetration and passes across the myocardium without ill effect.
- Burning and heating effects can occur at all frequencies.
- There are two types of diathermy:
  - *Unipolar*: There are two connections to the patient: the neutral (or indifferent) patient plate, and the active coagulation or cutting electrode. Current passes through both, but the current density at the active electrode is very high and generates high temperatures. At the patient plate the current density is dispersed over a wide area and heating does not occur. The patient plate and hence the patient, is kept at earth potential, which reduces the risks of capacitor linkage (in which diathermy current may flow in the absence of direct contact). Modern diathermy machines incorporate isolating capacitors to minimise the problem. An alternative is to use an earth-free or floating circuit.
  - *Bipolar*: In this instance the current is localised to the instrument: it passes only from one blade of the forceps to the other. Bipolar diathermy uses low power, and this limits its efficacy in the coagulation of all but small vessels. The circuit is not earthed.

Direction the viva may take

The questioning is likely to move on to the potential problems of diathermy and the practicalities of preventing them.

- There is a risk of thermal injury at site of the indifferent electrode (the diathermy plate) which must be in close and even contact with a large area of skin, ideally an area that is well perfused and so which will dissipate heat. Adhesive and conductive gels are useful. If the area of contact is small the current density increases to the point at which a burn is probable.
- Thermal injury at a metal contact site may occur if the plate is detached or malpositioned. The diathermy current may flow to earth through any point at which the patient is touching metal (such as the operating table, lithotomy poles or electrocardiogram (ECG) electrodes) and cause a burn.
- The plate should not be placed over an area where there is a metal prosthesis in place (usually the hip). Metal has a low resistance in comparison with tissue and

so the current will flow preferentially through the prosthesis, generating a potentially dangerous current density.

- The instrument may be activated when it is not in contact with the tissue to be cut or coagulated.
- The circuit may be completed via a route that does not include the indifferent electrode: this may also result in a burn.
- Alcoholic skin preparation solutions have ignited after diathermy activation.
- Diathermy may interfere with cardiac pacemaker function. The indifferent electrode should be sited as far distant as possible from the pacemaker and bipolar diathermy should be used wherever possible. If the use of unipolar diathermy is unavoidable, it should be used in short bursts. Cutting diathermy causes more of a problem than coagulation.
- Diathermy may interfere with monitoring devices. This problem can be minimised by the use of electrical filters.
- Diathermy may lead to ischaemia and infarction of structures supplied by fine end-arteries. Classic examples include the penis (hence unipolar diathermy must be avoided in circumcision) and the testis, which has a vulnerable vascular pedicle.

Magnetic resonance imaging

Commentary

Magnetic resonance (MR) scanning has been a huge advance in imaging, and the technique deservedly is popular. It is also true, however, that in practice very few anaesthetists have any wide experience of anaesthetising patients in this environment. The physics which underlies it is also formidable. Why then does the topic continue to reappear in this part of the exam? It may be because the underlying science is elegant, and because the consequences of ignorance are potentially so disastrous.

The viva

The questions will start with the imaging technique itself.

- MR scanning complements computerised tomography (CT) in providing high-quality images of soft tissue.
- MR imaging (MRI) is based on the principle that when a cell nucleus with an unpaired proton is exposed to an electromagnetic field, it becomes aligned along the axis of that field. A charged and spinning nucleus generates a magnetic field and acts itself like a small magnet. The aligned nuclei can then be displaced by brief exposure to another magnetic field, generated at right angles to the first. This provokes the phenomenon of nuclear precession, in which the nuclei rotate around an axis different from that around which they are spinning. When the electromagnetic field is removed, the nucleus resumes its original position, and as it relaxes to this position it emits low radiofrequency (RF) radiation. This signal, which is very small, is converted by sophisticated computer technology into an image. The rate at which the nucleus relaxes to its original position varies with the nature of the tissue. (This explanation is simplistic, but this is the FRCA, not the FRCR, and it would be hard to explain why any more detailed exposition is necessary for the practice of anaesthesia.)
- MR reports usually refer to T_1 and T_2 views. 'T' is a relaxation time constant: T_1 being the image generated a few milliseconds after the electromagnetic field is removed, while T_2 is an image generated somewhat later. Nuclei in hydrogen take longer to decay to their original position. In practice this means, for example, that in a T_1 view, fluid will be dark (as minimal signal is generated), whereas in the T_2 view, fluid will be white.
- MRI requires the generation of very strong magnetic fields: typically between 0.2 and 2.0 tesla (T).
- The tesla is the unit of magnetic flux density. Should you be asked; 1 T is equal to 1 weber m^{-2}, a weber being the SI unit of magnetic flux. It is equal to the magnetic flux that in linking a circuit of one turn produces in it an electromotive force of 1 V as it is uniformly reduced to zero within 1 s. The Earth's magnetic field is approximately 1 G. Ten thousand gauss equal 1 T. It will be a very odd examiner who really wants to know the answer to these questions, but you may as well be prepared.

Direction the viva may take

The questioning may then go on to the anaesthetic implications.

- **Practical problems:** There are practical difficulties in relation to the physical environment. The patient is enclosed within a narrow tube to which access is limited. The scanner is noisy and some patients may be very claustrophobic. Scanning may be prolonged. The process takes much longer than spiral CT scanning.
- **Magnetic field:** All ferromagnetic items within the 50 G line will be subject to movement and will also interfere with the generated image. Items typically affected include hypodermic needles, watches, pagers, stethoscopes, anaesthetic

gas cylinders and ECG electrodes. If these items are close to the field they will become projectile objects.

- **Anaesthesia delivery:** Anaesthetic machines which contain ferrous metals (there are non-magnetic machines and cylinders available) must remain outside the 50 G line. The machine requires very long anaesthetic tubing and long leads.
- **Anaesthetic monitoring:** The field may induce current within electric cabling. The consequent heating may lead to thermal injury. Long sampling leads for gas analysis extends delay. Standard ECG electrodes cannot be used. An oesophageal stethoscope may be useful. Pulse oximetry probes are non-ferrous but a distal site should be used and cable should be insulated. Non-invasive blood pressure cuffs must have plastic connections as well as long leads to the machines, which must be outside the 50 G line. Gas analysis, airways pressure and respiratory indices are usually displayed at the anaesthetic machine and so again the main problem is delayed sampling time due to long tubing.
- **Pacemakers:** Cardiac pacemakers require special consideration, as they will malfunction in fields over 5 G.
- **Infusion pumps:** These may fail if the field strength exceeds 100 G.
- **Implants and foreign bodies:** Most patient implants (metal prostheses, etc.) are non-ferrous, although some surgical clips and wires may be magnetic. Metal foreign bodies are likely to be ferrous. Non-ferrous items may heat.
- **Generic problems:** There are the generic problems of anaesthetising patients in remote, unfamiliar and isolated areas. Patients commonly are children.

Further direction the viva could take

- This may lead to a supplemental question about how you might set up an anaesthetic service for MR scanning. You will not have much time on this (unless you know nothing about the above), and a few generic platitudes about the undesirability of a remote location, of the need for training, the use of protocols, and the importance of safety issues, should be enough to see you through.

The fuel cell

Commentary

It is hard to know why this question continues to appear, given that fuel cell oxygen analysers are no longer widely in use. The subject may broaden to include other methods of measuring oxygen concentrations. A few examiners may be excited by the topic, most will be rather less enthusiastic and so do not worry if the viva seems a bit flat at this stage. It is likely to be due to the line of questioning that the examiners are constrained to follow rather than the fact that they are depressed by your answers.

The viva

You will be asked about the mode of action of a galvanic fuel cell.

- A reliable method of analysing oxygen in the common gas outlet of the anaesthetic machine is fundamental to patient safety.
- The fuel cell is similar in principle to a polarographic (Clark) oxygen electrode. It comprises a lead anode and a gold mesh cathode, bathed in an electrolyte solution. At the anode, lead reacts with hydroxyl ions to produce electrons. At the cathode, oxygen reacts with the electrons and water, and generates hydroxyl ions.
- The current flow is proportional to the partial pressure of oxygen. The response time is around 30 s.
- The fuel cell produces its own voltage and needs no other electrical source. Protecting it from oxygen (air) during the periods when it is not in use will prolong its life. Its function is not affected by water vapour.
- Fuel cells are bulky, heavy and are not robust. They may also be affected by the accumulation of nitrogen that occurs if N_2O is passed though the cell.

Direction the viva may take

You may be asked what other methods you know of measuring oxygen.

- **The Clark electrode:** This comprises a silver/silver chloride anode and platinum cathode bathed in an electrolyte solution. A small potential is applied across the electrodes and the current measured. The electrode works in an analogous way to the fuel cell, in that current flow is proportional to the oxygen tension at the cathode. The Clark electrode measures oxygen in a blood sample from which it is separated by a plastic membrane.
- **Paramagnetic analyser:** Oxygen is paramagnetic, with unpaired electrons in the outer shell, which means that it is drawn into a magnetic field. (Most other gases are diamagnetic.) The traditional paramagnetic analyser comprises a chamber containing a nitrogen-filled glass dumbbell, which is suspended on a wire and allowed to rotate within a non-uniform magnetic field. When oxygen enters the chamber it is attracted by the magnetic field and displaces the dumbbell. The degree of rotation is proportional to the amount of oxygen present. Modern analysers comprise two chambers separated by a pressure transducer. One is a reference chamber containing 20.93% oxygen (air); the other contains the sample to be measured. Both chambers are then subjected to a changing magnetic field, which increases the activity of the oxygen molecules. This agitation changes the pressure in each chamber: the oxygen partial pressure difference is proportional to the pressure difference across the transducer. These analysers are very accurate and have a rapid response time, which allows breath-by-breath measurement.

- **Mass spectrometry:** This technique is highly accurate, has a very rapid response time and allows the simultaneous measurement of different compounds including oxygen. The instruments are large and costly and are not used for routine gas monitoring in the UK. The gas sample is introduced into an ionisation chamber in which some of its component molecules pass through an electron beam and become charged. The ionised particles are then accelerated out of the chamber and into a strong magnetic field, which deflects the particles according to their mass.

Lasers

Commentary

The subject of lasers reappears in the examination, presumably because of purported safety issues. In practice, and with one exception, these concerns are modest: staff and patients clearly must be protected from potential harm, but the precautions required to achieve that aim are not complex. The exception is in ENT surgery where there is risk of instant conflagration if a laser beam hits an unprotected endotracheal tube. This aspect of the subject will not, however, extend to 8 min of questioning, and hence the perhaps unfortunate requirement for you to familiarise yourself with aspects of the basic science.

The viva

You will be asked to define 'laser' and to describe how these instruments work.

- 'LASER' is an acronym: *L*ight *A*mplification by *S*timulated *E*mission of *R*adiation.
- A laser produces a non-divergent intense beam of light, which is of a single wavelength (is monochromatic).
- It is produced by directing an energy source such as an intense flash of light or a high-voltage discharge into a lasing medium. Atoms within the medium absorb the photons of absorbed energy, which drive their electrons to a higher-energy level. As the excited atom falls back to its stable state it emits a photon of energy. If this is reflected back to encounter another excited atom, then another photon will be emitted which is parallel to and in phase with, the first. Multiple reflection by mirrors back into the lasing medium is used to generate a chain reaction which then produces an intense parallel beam of light.
- For medical uses this laser output is directed to tissues by means of fibre-optic cables.
- The wavelength of the light is dependent on the lasing medium that is used. The lasing medium may be a gas, such as CO_2, argon or helium, a solid such as neodymium: yttrium–aluminium garnet (Nd: YAG) or a liquid.
- CO_2 lasers produce infrared light (10,600 nm) whose energy is absorbed by water, which is vaporised. These lasers penetrate tissue no further than 200 μm and so are used for cutting (with simultaneous coagulation). Argon laser light (480 nm) is absorbed maximally by red tissues and so is used, for example, to treat diabetic retinopathy. Nd: YAG lasers (1064 nm) produce energy in the near infrared spectrum and penetrate tissues deeply.

Direction the viva may take

You will be asked about the practical safety implications for the use of lasers in theatre.

- The main danger is to the eyesight of theatre personnel. The non-divergent beam of laser light, even when reflected, may be focused on the fovea and cause irreversible blindness. Other parts of the retina may also absorb the energy as may the lens and the aqueous and vitreous humours. This does not apply to CO_2 lasers, which will not penetrate further than the cornea.
- Staff should be issued with goggles which protect specifically against the wavelength that is being generated, and surgical instruments ideally should have a matt finish, to minimise the likelihood of reflection.
- There is a specific hazard associated with laser surgery to the upper airway. A normal polyvinyl chloride tracheal tube will ignite within a few seconds should it be exposed directly to a laser beam. Stainless steel foil has been used to protect tubes, but there are now specially designed tracheal tubes available for use with laser surgery on the upper airway. Although these have a flexible metal bodies (either stainless steel or aluminium), they still have cuffs and pilot balloons which should be filled with saline as a precaution. Surgical swabs or packs can also ignite, and so these must be kept moistened with saline.

The gas laws

Commentary

This is the kind of question that you thought you had left behind when you passed the Primary FRCA examination, but it does reappear in the Final. It will not be asked of you in any greater detail, and the examiner basically is expecting you to list each gas law and indicate their relevance to anaesthetic practice. If you enunciate each of them slowly and carefully, perhaps writing them down as you go, and even volunteering a little biographical information, then there will be little or no time for the examiner to ask you in detail about anything else.

The viva

You will be asked to describe the gas laws.

- **Boyle's law:**
  - This is the first perfect gas law. It states that at a constant temperature, the volume of a given (fixed) mass of gas varies inversely with the absolute pressure. It can be expressed the other way round, namely that at a constant temperature, the pressure of a given mass of gas is inversely proportional to the volume. Pressure (P) $\times$ volume (V), therefore is a constant.
  - This law was described in 1662 by Robert Boyle (1627–1691), born in Ireland as the youngest of 14 children, but who lived and studied in England and who was one of the founders of the scientific method.
- **Charles's law:**
  - This is the second perfect gas law. It states that at a constant pressure, the volume of a given mass of gas varies directly with the absolute temperature. The relationship is linear which means that at absolute zero that fixed mass of gas would have no volume.
  - This law was described in 1787 by Jacques Charles (1746–1823), a French physicist who constructed the first gas balloon and who later made an ascent to an altitude of over 10,000 ft.
- **Universal gas law:**
  - Boyle's law and Charles's law can be combined to give the universal gas law in which $P \times V = T \times nR$, where R is the universal gas constant ($8.1\,\mathrm{J\,s\,K^{-1}\,mol^{-1}}$) and n is the number of moles of a gas.
- **Gay-Lussac's law:**
  - From the equation $PV = nRT$ it is evident that for a fixed mass of gas at constant volume the pressure varies directly with temperature.
  - The enunciation of this relationship is attributed to another physicist and balloonist, Joseph Gay-Lussac (1778–1850).
  - In some texts this is described as *The third perfect gas law.*
- **Dalton's law of partial pressures:**
  - This states that the pressure that is exerted by each gas in a mixture of gases is the same as it would exert if it alone occupied the container.
  - This law was described in 1801 by John Dalton (1766–1844) who was an English chemist from Manchester. He also did early work on colour blindness which for a while became known as 'Daltonism'.
- **Henry's law:**
  - This states that the amount of gas that is dissolved in a liquid at a given temperature is proportional to the partial pressure in the gas in equilibrium with the solution.
  - This law was described in 1801 by William Henry (1774–1836) who was an English chemist and physician. He also identified as methane the gas known as 'firedamp' that was responsible for the death of miners.

- **Avogadro's law:**
  - This states that equal volumes of gases at the same temperature and pressure contain the same number of molecules. This also means that 1 g molecular weight of any gas occupies the same volume (22.4 l at standard temperature and pressure (STP), which is 273.15 K (0°C) and 101.325 kPa).
  - The law was described in 1811 by Amadeus Avogadro (1776–1856) an Italian professor of mathematical physics who lived and worked in Turin. This theory went unremarked for over 50 years, partly due to the scepticism and opposition of scientists such as Dalton.
- **The combined gas laws:** The gas laws can be combined so that $P_1 \times V_1/T_1 = P_2 \times V_2/T_2$.

Direction the viva may take

It would be more logical were you to be asked to give examples of the anaesthetic relevance of the gas laws as you describe them. In practice, however, this discussion tends to be deferred until the second part of the viva. The reason for this is probably that if a candidate spends a lot of time struggling to identify the clinical application of the first one or two gas laws, then they may not have a chance to give the examiner the rest of the list that is expected.

Some practical applications include the following.

- **Boyle's law:** (At constant T, PV is a constant; so $P_1 \times V_1 = P_2 \times V_2$.)
  - This can be used to calculate the volume of gas remaining in a cylinder. A size E oxygen cylinder has an internal volume of 10 l, and so contains 10 l (V_1) at 13,800 kPa (P_1). (Remember that this is absolute pressure, so 100 kPa of atmospheric pressure must be included.) At atmospheric pressure (P_2) there will therefore be 1380 l of oxygen (V_2) available from the cylinder.
- **Dalton's law of partial pressures:** (The pressure exerted by each gas in a mixture is the same as if it were alone.)
  - This is relevant for the partial pressure of gases in any mixture, whether it be in a cylinder, or within the alveoli.
- **Henry's law:** (The amount of gas that is dissolved in a liquid at a given temperature is proportional to the partial pressure in the gas in equilibrium with the solution.)
  - This has relevance for hyperbaric therapy. At atmospheric pressure and breathing air, the oxygen solubility coefficient (0.003 ml dl^{-1} $mmHg^{-1}$) means that dissolved oxygen content is about 0.26 ml dl^{-1}. In a patient who is breathing 100% oxygen this increases to 1.7 ml dl^{-1} and at 3 atm in a hyperbaric chamber it reaches 5.6 ml dl^{-1}. At this level of pressure, therefore, dissolved oxygen can make a significant contribution to delivery. If nitrogen is present in the gas mixture then it will pass into the tissues, only to come out of solution in the form of bubbles if the pressure is decreased too abruptly. This is the cause of decompression sickness.
- **Avogadro's law:** (Equal volumes of gases at the same temperature and pressure contain the same number of molecules.)
  - This can be used, for example, to calibrate a vaporiser. The molecular weight of sevoflurane is 200, 1 mol is 200 g and will occupy 22.4 l at STP. Imagine, therefore, a vaporiser containing 40 ml of sevoflurane, which is 0.2 mol occupying 4.48 l at STP. If this is vaporised fully into oxygen of volume 224 l then the resulting concentration will be 4.48/224 or 2%.

Intra-arterial blood pressure measurement

Commentary

Invasive arterial blood pressure monitoring is a routine part of modern anaesthetic and intensive care practice and so the viva will not dwell long on clinical aspects such as indications and complications. The bulk of the oral will concentrate on the physics that underlies the behaviour of a measurement system. You will not, however, be asked to discuss Fourier analysis of complex waveforms: time constraints will not allow it and it would take the questioning too far away from applied clinical science. Make sure, nonetheless, that you can draw the waveforms for a system that is underdamped, overdamped and optimally damped, because this does have relevance for clinical practice.

The viva

You will be invited to describe the components of a system for direct blood pressure measurement, before being asked to explain how the arterial waveform is generated.

- The basic system for invasive blood pressure measurement comprises a parallel-walled intra-arterial cannula, a column of saline which is in continuity with blood, and a transducer. (A device that converts the mechanical energy into an electrical signal that is processed and displayed on a monitor.) The column of saline is pressurised to 300 mmHg and incorporates a manual flushing device.
- The fluid-filled catheter is in direct contact with the diaphragm of the transducer. Movement of this diaphragm is associated with alteration in the length of a strain gauge, which in some transducers is in the form of a wire resistor in a Wheatstone bridge circuit. (This contains four resistances, one of which is a strain gauge, another of which is variable. The variable resistance can be altered so that when $R_1/R_2 = R_3/R_4$ there is no current flow.) Most transducers include four strain gauges, comprising the four resistances of the bridge. The resistances of two gauges at opposite sides of the bridge are designed to increase as the pressure increases, while the resistances of the other two decrease. This gives rise to a larger potential change with a deflection in the galvanometer that is amplified and displayed as a pressure.
- This whole system oscillates at the frequency of the arterial pulse, which is the fundamental frequency (the first harmonic). The arterial pressure waveform, however, comprises a series of sine waves of different frequencies and amplitude. In order for the system to reproduce the amplitude and phase difference of each harmonic, so as to produce an accurate waveform, it requires a frequency response that is around 10 times the fundamental frequency (the heart rate). If the heart rate is 150 beats per minute the frequency response would need to be $(150 \times 10)/60 = 25$ Hz. The more rapid the rate of pressure change, the greater the number of harmonics. In practice this means that the system requires a flat frequency response between 0.5 and 30 Hz.
- In order to reproduce the arterial waveform accurately any recording system must also reproduce the amplitude and phase difference of each harmonic in the waveform. The system, therefore, needs a high resonant (or natural) frequency, which can then be optimally damped.
- This natural frequency is the frequency at which any system will resonate, and at which amplification of the signal will occur. If this frequency lies within the range of frequencies that comprise the pressure waveform then that signal may be distorted by the superimposed sine wave that will be generated.
- The resonant frequency of the pressure-measuring system can be manipulated by altering the characteristics of its components. It is directly proportional to the diameter of the catheter, and is inversely proportional to the square root of the compliance or elasticity of the system, to the square root of the length of tubing, and to the square root of the density of the fluid within the system. This has

clinical relevance, because stiffening the diaphragm of the transducer, shortening the length of the intra-arterial cannula or increasing its diameter, will lift the resonant frequency out of the frequency response range.

- If there is no damping the system oscillates at its natural frequency. If the system is overdamped the recorded signal falls slowly to the baseline. This can occur when there ceases to be free communication between the column of blood and the diaphragm of the transducer. A large air bubble, for example, will absorb pressure due to its compressibility, while clot or debris will restrict the pressure transmission even more effectively. The whole waveform trace is flattened as a result. If the damping is adjusted so that the output signal falls more rapidly to the baseline, but without any overshoot, then the system is described as being critically damped. In this situation the amplitude is registered accurately but the speed of response is too slow. The best compromise between speed and accuracy is when the system is optimally damped, which is at 0.64 of critical. An underdamped waveform will increase systolic and decrease diastolic pressures, while an overdamped signal will decrease both. The mean arterial pressure in both instances will largely be unchanged.

Direction the viva may take

You may be asked about the indications for direct intra-arterial blood pressure monitoring and about the extra information that such monitoring may provide.

- **Indications:** These are not difficult to define. Intra-arterial monitoring gives beat-to-beat information, which is particularly useful in patients with actual or potential cardiovascular instability. Many anaesthetists would also regard its use as mandatory whenever intravenous vasoactive drugs are used to manipulate the blood pressure. It is used routinely in the critically ill, both to measure pressures and to allow arterial blood gas analysis.
- **Information:** This is not confined purely to numbers. The slope of the systolic upstroke gives some indication of the contractile state of the myocardium, and the maximum rate of rise of left ventricular pressure, dP/dt max, can be calculated. The position of the dicrotic notch on the downstroke of the waveform reflects systemic vascular resistance. In the presence of peripheral vasoconstriction the dicrotic notch is high: if there is vasodilatation then it moves lower down the curve. Pressure changes during IPPV can also be significant: a systolic pressure variation between the maximum and minimum recorded during the respiratory cycle of more than 10 mmHg suggests at least a 10% reduction in circulating volume.

Further direction the viva could take

You may be asked about complications of the technique.

- **Complications:** Vascular damage distal to the cannula may follow because of direct occlusion, of later occlusion due to thrombosis, or as a result of inadvertent intra-arterial injection. Disconnection is a potential hazard: fatal exsanguination can occur should it go unrecognised. Long-term cannulation, as is common in intensive care patients, may also be complicated by infection.

Defibrillation

Commentary

This is primarily a question about the physics of electrical defibrillation. There has been recent interest in different waveforms, and this may extend the science questioning, but not so far that you will not be asked about the clinical implications. Resuscitation is a core anaesthetic skill and so you must ensure that your knowledge of the treatment algorithms is sound. Otherwise what may seem like a throwaway query about the management of cardiac arrest could fail you, no matter how authoritatively you may have dealt with capacitance.

The viva

The examiner may take an easy way into the subject by asking you to describe what happens when a heart is fibrillating.

- **AF and VF:** In health the sinus impulse is conducted evenly and concentrically to all parts of the atria and thence to the ventricles. When atrial fibrillation (AF) supervenes, the excitation and recovery of different parts of the atria becomes uncoordinated, with various areas at different stages of excitation and recovery. It is similar with VF. The changing amplitude of the ECG reflects electrical activity, but depolarisation is chaotic and unable therefore to generate any cardiac output.
- **Effects:** In AF there is loss of the atrial contribution to ventricular filling, which is usually around 20%. In addition the risk of thrombus formation is substantially increased. A fibrillating ventricle produces no cardiac ouput.
- **Causes:** These are numerous and the examiner will not want you to do more than suggest the most significant. Common causes of AF include ischaemic heart disease and acute critical illness, particularly sepsis. (Other cited causes such as mitral stenosis and thyrotoxicosis are very rare.) VF is caused by myocardial disease, both ischaemic and myopathic, by hypoxia, by profound hypothermia, by electrolyte imbalance, by some drugs and by electrocution.

Direction the viva may take

You will then be asked about the electrical (not the pharmacological) management of fibrillation.

- **AF:** Refractory AF is treated by the application of a DC shock, which is synchronised to the peak deflection of the 'R' wave of ventricular depolarisation on the ECG. The risk of inducing VF is very high during repolarisation (as shown by the 'T' wave on the ECG). This is why the 'R-on-T' rhythm is particularly dangerous.
- **VF:** This can be treated either by mechanical defibrillation or electrical defibrillation. The application of mechanical energy in the form of a praecordial thump (also known as 'thumpversion' in the USA) may convert VF to a viable rhythm only if it is applied early. In electrical defibrillation a defibrillator delivers a charge across the chest which causes simultaneous depolarisation of myocardial cells. If the procedure is successful, there is a short refractory period after which there is resumption of normal pacemaker activity with myocardial contraction and a stable rhythm.
- **Capacitance:** The electrical energy is delivered in the form of DC which is produced by the discharge of a capacitor. (A capacitor consists of two plates that are separated by an insulator and which will store electrons after the application of a potential difference. Capacitance is the ability to hold electric charge. Its units are coulomb, C. One coulomb is the amount of electric charge which passes a point when a current of one ampere flows for 1 s.)
- **Impedance:** The efficiency of the applied shock is greater if transthoracic impedance is minimised by the use of conductive gels, firm paddle pressure, and

if necessary, defibrillation from front-to-back rather than from sternum to apex. (Impedance is the sum of all forces impeding electron flow in an AC circuit.)

- **Waveforms:** When conventional defibrillators are used, the energy is released as a single current pulse, typically 35 A for 3 ms, which causes a synchronous contraction of the myocardium. The pulse is monophasic, travelling in the positive direction only. A monophasic pulse can have two waveforms (exponential current decay and a damped sine wave) which are of similar efficacy. In a defibrillator that uses a biphasic waveform, the current is reversed halfway through the discharge to move both in a positive and a negative direction. (There are also two biphasic waveforms: truncated exponential decay and rectilinear.) Biphasic shocks are both more effective than monophasic, while causing less myocardial injury. Despite these benefits their use is not yet widespread except in implantable defibrillators whose longevity is enhanced if the energy that they need to generate can be minimised.

Measurement of organ blood flow

Commentary

There are several methods that have been used to determine blood flow to a particular organ. Many are not practical for use in the clinical setting, but you will be expected to comment on them briefly before dealing with those that can be used clinically. These include variations on the use of the Fick principle and Doppler ultrasonography.

The viva

You will be asked to describe methods of estimating blood flow.

- **Direct cannulation and measurement:** This is possible, but impractical in any clinical context.
- **Electromagnetic flowmeters:** If a conductor (such as blood) flows at right angles to a magnetic field, then an electromotive force is induced which is perpendicular to the magnetic field and to the direction of fluid flow. The induced voltage is proportional to the strength of the field and to the velocity of blood flow. A determination of the diameter of the vessel allows calculation of flow.
- **Doppler ultrasonography:** The Doppler effect describes the change in the frequency of sound (including ultrasound) if either the emitter or the receiver is moving. If a noise source, for example, a siren, moves towards a listener, the wavelength of the sound decreases, its frequency increases, and so its pitch rises. This principle is utilised in Doppler ultrasonography, in which ultrasound is directed at a diagonal from one crystal and is sensed by a second crystal as it reflects off red blood cells. The frequency of these reflected waves increases by an amount that is proportional to the velocity of flow towards the receiving crystal. It is difficult to calibrate a Doppler ultrasound probe to provide accurate quantitative measurements, because determinations of vessel calibre may be inaccurate, and the shape of the flow profile may not be uniform. The technique, nonetheless, can provide some assessment of the adequacy of flow, particularly after vascular surgery to the carotid arteries or to vessels of the lower limb. It can also be used to give a non-invasive determination of cardiac output by measuring velocity in the arch of the aorta and relating it to aortic diameter. Transcranial Doppler ultrasonography can be used to give a measure of flow through large cerebral arteries.
- **The Fick principle:** This is the basis of several methods which are used to measure both cardiac output and regional blood flow. It underlies thermal and chemical indicator dilution tests, renal clearance estimations and measurement of cerebral blood flow. It has been described as an application of the Law of Conservation of Matter, in that the uptake or excretion of a substance by an organ or tissue must be equal to the difference between the amount entering the organ (arterial flow $\times$ concentration) and the amount leaving the organ (venous flow $\times$ venous concentration). Rearrangement of this relationship gives the familiar formula, namely that: blood flow to an organ = rate of uptake or rate of excretion of a substance/arteriovenous concentration. If oxygen is used as the substance, for example, then cardiac output is given by: oxygen consumption ($\mathrm{ml\,min^{-1}}$)/A–V DO_2 ($\mathrm{ml\,l^{-1}}$). (The Fick principle applies only to situations in which the arterial supply presents the only source of the substance that is taken up.)
- **Indicator dilution methods:** The commonest method in clinical use is the thermodilution technique for measuring cardiac output. Injection and sampling are both carried out via a catheter in the right side of the heart. Cold fluid (such as glucose 5% at 0°) is injected into the right atrium, and the temperature change is detected by a thermistor at the distal end of the flotation catheter in the pulmonary artery. The recorded temperatures generate a concentration against time dilution curve analogous to that which would be seen had a chemical

indicator been used. The equation that is used is: flow (cardiac output) = 'heat dose' × 60/average concentration (AUC) × time (s). The injectate-blood temperature difference multiplied by the density, specific heat and volume of the injectate gives the numerator (the heat dose). The area under the curve (AUC) multiplied by the density and specific heat of blood gives the denominator. The potential complexity of these calculations means that the cardiac output determinations are computer generated.

- ***Para*-amino hippuric acid (PAH) clearance:** The clearance of PAH is used to determine renal blood flow, also using the Fick principle. PAH is not utilised or excreted by any other organ apart from the kidney, and so the peripheral venous PAH concentration will equal the arterial. Renal PAH uptake is given by the product of the urinary PAH concentration and urinary volume. The final simplified equation is the same as that for PAH clearance: renal blood flow = [U] × V/[P]. This actually measures plasma flow, because blood is not filtered at the glomerulus and the volume from which PAH is removed is plasma. Blood flow can thereafter be calculated if the haematocrit is known.
- **The Kety–Schmidt method:** This is an adaptation of the Fick principle which is used to make a global determination of cerebral blood flow. See *Cerebral blood flow*, page 127.
- **PET and SPECT scanning:** Positron emission tomography (PET) is a research technique, which monitors the uptake by different areas of the brain of 2-deoxyglucose labelled with a positron emitter. Scintillography and SPECT scanning use radioactive xenon to trace regional blood flow, with or without enhancement by CT or MRI.

Direction the viva may take

The core of this viva lies in the discussion of the methods described above. Examiners might then ask about blood flow to specific areas such as the brain or the kidney, or about clinical aspects of cardiac output measurement. While they may seem of obvious importance, the fact that these topics are discretionary means, unfortunately, that you will not accrue much credit, no matter how astute your answers.

Evoked potentials

Commentary

EPs are one means of monitoring the depth of anaesthesia, and they are also used to assess spinal cord function during surgery. The first usage remains confined mainly to research centres and the second to specialist centres, yet the topic is of some general anaesthetic interest. The underlying neurophysiology and the signal processing are too complex to explore in a short viva, and a broad knowledge of the principles will suffice.

The viva

You will be asked what you understand by the term 'evoked potential'.

- An EP, also known as an evoked response (ER) or event-related potential (ERP), is an aspect of EEG monitoring. The signal in the EEG is produced when an individual receives a visual, auditory or somatosensory stimulus, and the EPs are detected by an electrode which is positioned over the primary receiving area for that sensory modality.
- The potentials are only a few microvolts in amplitude and so are swamped by the noise of the global EEG. Each can measure from as low as 0.1 μV up to around 2 μV, compared with the EEG background amplitude of 10–300 μV. These low potentials are extracted from the EEG by a process of computer averaging. The patient is subjected to a large number of repeated stimuli, and the EEG is recorded during a fixed period after each one. It is then amplified before the EPs are extracted by taking the average of this large number of responses.
- The processed signals comprise a series of peaks and troughs, which represent the response time or 'latency'. This has been mapped most thoroughly in respect of auditory ERs, which produce a series of waves as the stimulus produces activity as it passes from the cochlea to the cortex. The early signal, from 0 to 10 ms is the 'brainstem response', signals between 10 and 100 ms are middle latency and contain the early cortical response. Signals beyond around 100 to 1000 ms represent the late cortical response, which arises from the frontal cortex and association areas.
- These ERs have six separate peaks, which are believed to relate to their anatomical origin. These are the cochlear nerve (I), the cochlear nucleus (II), the superior olivary complex (III), the inferior colliculus (IV and V) and the primary auditory cortex (VI). These EPs are not affected significantly by intravenous anaesthesia, which limits their value in monitoring anaesthetic depth during TIVA.
- Visual EPs, produced in response to a pulsed flash of light, elicit mainly a cortical response. They are more variable than auditory EPs and so give more qualitative than quantitative information.
- Somatosensory potentials. See below.

Direction the viva may take

You may be asked about the clinical applications of relevance to anaesthesia.

- **Anaesthetic depth:** EP have been investigated as indicators of the depth of anaesthesia. Visual and somatosensory EPs show less promise than auditory ERs. See *Depth of anaesthesia*, page 227.
- **Spinal surgery:** EPs are used to monitor spinal cord function, which can be compromised by distraction during scoliosis surgery. Historically patients were subjected to the intra-operative wake up test, during which anaesthesia was lightened (with appropriate analgesia) to the point at which the subject could respond to a request to move both arms and legs. This technique actually worked better than it may sound to those who have never seen it done, but it is

nonetheless crude in comparison to somatosensory EPs. The potentials are of very low amplitude, and the signal is averaged. The latency and amplitude are measured, as above, usually by electrodes which monitor the cerebral cortex. This technique is based on the assumption that if sensory pathways are intact then motor pathways will not have been damaged. This is not always true, but evoked motor potentials are depressed by general anaesthetic agents. An alternative is to test cord function by means of epidural motor EPs which are relatively unaffected by anaesthetic agents. Somatosensory potentials are also depressed by high-concentration volatile agents and by high-dose opiates (such as fentanyl in doses greater than $50\,\mu g\,kg^{-1}$), but the normal clinical use of these drugs does not compromise the technique. Hypoxaemia and hypoperfusion of the cord are confounding factors which may influence the response. They decrease the amplitude of the response but do not have any effect on its waveform.

Further direction the viva could take

You may be asked briefly about other clinical uses for EPs.

- They are used to aid the diagnosis of a number of neurological conditions. These include multiple sclerosis and other demyelinating diseases; tumours in the posterior fossa, in which auditory EPs are useful, and global head injury.

Ultrasound

Commentary

Ultrasound has diverse uses in anaesthesia and intensive care medicine, but it is the advent of transoesophageal echocardiography (TOE) that has prompted most recent interest. You are unlikely to become involved in mathematical discussions about the Doppler equation, but as with all these physics-based questions, you will have to have some idea of the underlying principles.

The viva

You will be asked about the basic principles of ultrasound.

- **Principles of ultrasound:** Sound waves which exceed the threshold of human hearing (around 20,000 Hz) are described as ultrasonic. Medical imaging equipment uses much higher frequencies in the range of 3–8 MHz. These waves are generated by applying a high-frequency alternating voltage to the two sides of a piezo-electric crystal transducer (which deforms when a voltage is applied to it). This changes the thickness of the crystal, which then emits ultrasonic radiation of the same frequency as the applied potential difference. The crystal also transduces the reflected waves back into an electrical signal from which a computer-generated cross-sectional image can be displayed. The signals are unable to penetrate very far into bone or gas-filled structures, including the lung, and so ultrasound studies of these structures are not possible. Reflected signals are strongest from the interface between tissues of different density.
- **Frequency effects:** The higher the frequency the better the resolution of the image, but this is at the expense of tissue penetration. Lower frequencies will produce images from deeper structures but their definition is less good.
- **Attenuation of ultrasound:** This can be expressed as the 'half-power distance', which is the depth at which the sound is halved. This depth is 3800 mm for water and less than 1 mm for air and lung. Sound is attenuated by bone (2–7 mm) and also by muscle (6–10 mm).
- **Velocity:** Ultrasound moves through tissue at 1540 m s^{-1}. This rapid transmission and reception of pulses of sound allows the generation of dynamic images.
- **2-D images:** These are generated by probes which comprise an array of parallel piezo-electric elements that are activated in sequence, rather than simultaneously. This wavefront can in practice scan a 90° sector of tissue, with the reflected echoes processed into a two-dimensional picture.
- **Doppler effect and colour Doppler:** The Doppler effect (see *Measurement of organ blood flow*, page 267), describes the change in the frequency of sound and ultrasound if either the emitter or the receiver is moving. Colour flow Doppler is able to display blood flow in real time, using three basic colours. Blood flow towards the transducer is red, while that away from the transducer is blue. It is obviously important not to assume that these colours indicate arterial and venous blood. The colour green can be added when blood flow velocity exceeds a preset limit. In areas of turbulent flow, such as may occur across a diseased cardiac valve, all three colours may be displayed.

Direction the viva may take

You are likely to be asked about the clinical uses of ultrasound in intensive care and anaesthesia, and particularly the use of TOE.

- **General ultrasound:** Ultrasound scans of the abdomen and thorax will identify fluid collections, which can then be drained under ultrasound guidance. Ultrasonic devices can also aid central vascular access, particularly using the internal jugular route. Cranial scanning is routine in neonatal intensive care, where it can reveal intraventricular haemorrhage and midline shift.

- **Praecordial Doppler:** The interface between air and blood generates a strong reflected signal, and Doppler provides a method of detecting air embolism sensitive enough to produce ultrasound images from bubbles as small as 2 μm in diameter.
- **Echocardiography:** Transthoracic cardiac echocardiography is becoming a more routine pre-operative investigation, providing useful information about valvular and ventricular function.
- **Ultrasonic devices:** The principles of ultrasound can be used in gas flowmeters, in cleaning devices and in humidifiers.
- **TOE:** Modern TOE probes allow 180° views of the heart, and the absence of large tissue masses between the probe and the myocardium allows for well-defined ultrasound images. It has specialist cardiac uses such as the assessment of valvular heart disease, the diagnosis of bacterial endocarditis, the identification of atrial thrombus and the investigation of congenital heart disease. It can identify aortic atherosclerosis, aortic dissection and disease and can assess para-cardiac masses. For the general anesthetist and intensivist, its main value lies in the determination of left ventricular preload and function (both peri-operatively and in intensive care), the diagnosis of acute left ventricular dysfunction and myocardial ischaemia, and in the detection of air embolism.
- **Contraindications:** These are obvious: an oesophageal probe should not be used inpatients with oesophageal stricture or tumour, and with great caution in patients with oesophageal varices. Cervical spine instability is a relative contraindication (the neck may need to be moved to introduce the probe), as is gastric bleeding.
- **Complications:** These are mainly mechanical, and relate to the passage and presence of a firm probe within the thin-walled oesophagus. The procedure is done blind and so perforation into the mediastinum is a potential risk. This can also happen if the tip of the probe is left for any length of time in a position of extreme anteflexion or retroflexion. Probes should be checked for electrical safety. The reported complication rate is very low: in one (early) series of 10,419 awake patients there were only two cases of bleeding.

Electrical safety

Commentary

Patients are, in general, well protected from electrical danger, and so for most anaesthetists this topic will remain only theoretical. Electricity does appear as a subject but its main application, apart from biological potentials, relates to safety. This by itself barely constitutes a full question, unless it is extended by a discussion of the grades of equipment protection (which can happen), and so the viva may start with an outline of basic concepts which seem a bit disparate and haphazard. Basic knowledge and an understanding of how potential dangers can arise will be sufficient to allow you to pass.

The viva

You will be asked about the electrical risks to patients and how they are minimised, but as a prelude to this discussion you may be asked to define some basic electrical terms.

- **Electricity:** This is the flow of electrons, which is driven by potential difference (the voltage) through a conductor past a given point per unit time. This current is measured in amperes.
- **Resistance:** This is the resistance along a conductor to the flow of current. It is not frequency dependent. Resistance is measured in ohms.
- **Ohm's law:** This states that the electrical potential (V) = current (I) × resistance (R).
- **Impedance:** The impedance is the sum of all the forces impeding electron flow in an AC circuit. Unlike resistance it is dependent upon frequency and includes resistors, capacitors and inductors. (Insulators are high-impedance devices; conductors are low-impedance devices.) Impedance through capacitors and inductors is related to the frequency at which AC reverses direction. Impedance is also measured in ohms (volt/ampere).

Direction the viva may take

You will be asked how this relates to patient safety.

- **Effects of electricity:** These can be summarised as follows: at 1 mA a subject will feel tingling, and at 5 mA definite pain. At 15 mA there will be tonic contraction of muscles, which at 50 mA will involve all the muscles of respiration. At 100 mA VF will supervene.
- **Electrocution:** This can happen when a patient becomes part of an electrical circuit. The main problem is the fibrillatory potential of the current, which if applied externally, need reach only 50–100 mA. Such current disrupts the normal function of cells, causing muscle contraction, respiratory paralysis and VF. The current frequency is also important, with 50 Hz (the frequency of AC in the UK) being optimally lethal. AC at 50 Hz can generate high voltages economically and can readily be transformed, but it will interfere with ion flux across all cell membranes and force ions in both directions. (The ion pump can cope better with DC voltages.) Higher frequencies are much less dangerous and above 100 Hz have no fibrillatory potential. In electrocution there is additional thermal injury, caused as the electrical energy dissipates through tissues. The severity of the electrical burn is directly proportional to the current density and its duration of application.
- **Lethal current:** The relationships described above explain how dangerous currents can be generated. Ohm's law determines the magnitude of the current that flows, $I = V/R$. An individual standing on an antistatic floor may have an impedance of 20 kΩ or more, and so should he touch a live enclosure the current flow will be 240/20,000 or 12 mA. Wet hands or fluid on the floor may reduce the

impedance to 2 kΩ, and so the current, 240/2000, becomes potentially lethal at 120 mA. This is not enough to blow the fuse and so the circuit remains live.

- **Equipment identification:** Equipment designed for medical use is generally of high specification with an identifier to show the grade of protection that it offers.
  - *Class I equipment*: (This carries no specific symbol.) It offers basic protection only. Any conducting part that is accessible to the user, such as the casing, must be connected to earth, and must be insulated from the main supply. (Such equipment has fuses on the live and neutral supply in the equipment, as well as on the live wire in the main's plug.)
  - *Class II equipment*: (This has the symbol of a square within a square.) This equipment has reinforced, or double insulation, that protects all the parts that are accessible. It does not require an earth.
  - *Class III equipment*: (This is symbolised by a small black figure, which is enclosed within the symbol for capacitor plates if it provides defibrillator protection.) This equipment uses safety extra low voltage (SELV) which does not exceed 24 V AC. There is no risk of gross electrocution, but microshock is still possible.
  - *Type B equipment*: (This has the symbol of a small black figure enclosed within a square, in turn enclosed within the symbol for capacitor plates if it is defibrillator protected.) Such equipment has low leakage currents: 0.5 mA for Class IB, and 0.1 mA for Class IIB.
  - *Type BF equipment*: (This is symbolised by a heart within a square, in turn enclosed by capacitor symbol if it is defibrillator protected.) Type BF is the same as Type B, except that the piece of equipment that is applied to the patient is isolated from all its other parts.
  - *Type CF equipment*: This is class I or II equipment but which is considered safe for direct connection to the heart. Leakage currents are extremely low, being 0.05 mA per electrode for Class ICF equipment and 0.01 mA per electrode for Class IICF.

Further direction the viva could take

You may be asked about microshock.

- **Microshock:** Gross electrocution by externally applied energy requires currents of around 100 mA, but very much lower currents, in the region of 50–100 μA, can induce VF if they are applied directly to the ventricle. This rare phenomenon is known as microshock. It can occur only with a combination of factors that arise in specialised situations, in which the patient accidentally becomes part of an electrical circuit. Microshock requires an electrical contact applied directly over a small area of the myocardium and which can be earthed through the patient. Faulty equipment, even with very low leakage currents, but which are connected to intracardiac devices such as pacing wires or catheters, is capable of delivering this microcurrent directly to the ventricle and inducing fibrillation. A member of staff holding a pacing wire in one hand while touching the leakage source with the other may inadvertently complete the circuit and electrocute the patient. The risk is lessened in this instance by wearing gloves, and in general by the use of earth-free mains supply.

Parametric and non-parametric data

Commentary

Statistics questions usually start quite simply, and frequently end up simply, for the reasons outlined in the introduction. It may feel as though you are just being asked to give a series of definitions, but the examiners will be using your answers to discern whether or not you do understand the basic differences between types of data. You might at some stage be given a straightforward theoretical trial to discuss, but you will not be expected to perform any statistical calculations. The viva may divert to include meta-analysis, the design of clinical trials, or evidence-based medicine.

The viva

You will be asked to describe the difference between parametric and non-parametric data, and during the course of that description, to explain the terms that you are using.

- **Parametric data:** These are quantitative data that have a normal (Gaussian) distribution. In such a distribution the mean (average of all the results), the median (the value above and below which contains equal numbers of results) and the mode (the most frequently occurring value) are all the same. The variation around the mean is given by the variance, σ^2, the square root of which is the standard deviation (SD), σ.
- **Non-parametric data:** These do not have a normal distribution and the typical bell-shaped curve is replaced by one, for example, which may be skewed in either direction or may be bimodal (with two peaks). The data can sometimes be transformed mathematically so that they assume a normal distribution and can be analysed by parametric tests. This may be desirable because parametric statistical tests are more powerful than non-parametric.
- **SD:** This provides a convenient way of describing the spread around the mean, with 68% of a population falling within ± 1 SD, 96% within ± 2 SD, and 99% within ± 3 SD of the mean. The information can be expressed the other way round, namely that 95% of the values will be included within 1.96 SD of the mean.
- **Standard error of the mean (SEM):** This is used to determine whether the mean of the sample reflects the mean of the population. It is calculated by dividing the SD by the square root of the degrees of freedom minus 1. ($\text{SEM} = \text{SD}/\sqrt{n-1}$) In effect it is the SD of the mean, thus 68% of sample means lie within ± 1 SE of the true population mean, 96% within ± 2 SE, and 99.7% within ± 3 SE.
- **Confidence limits:** This concept is linked to the SEM. A sample mean will lie beyond 1.96 SE only 5% of the time, and so we can be 95% confident that the sample mean does reflect the population mean. They have the advantage that they are expressed in the same units as the measurements, rather than as a probability value.
- **Parametric tests:** These include Student's *t*-test and analysis of variance (ANOVA). ANOVA and not the *t*-test should be used if there are more than two groups. The data are considered paired if they derive from the same patient. For example, blood pressure measurements before and after laryngoscopy would be analysed using a paired *t*-test. If different but very well-matched patients are entered into separate limbs of a trial then paired statistical tests may also be used.
- **Non-parametric tests:** These are applied to quantitative data which do not have a normal distribution. These include the Wilcoxon signed rank test for paired data and the Mann–Whitney *U*-test for unpaired data. If there are more than two groups then the corresponding tests are the Friedman (paired) and Kruskal–Wallis (unpaired).
- **Qualitative data:** Qualitative data (for example, ASA grades, pain scores and operation type) are usually analysed using the Chi-squared test.

Direction the viva may take

You may be asked what statistical tests you might use in a particular trial, for example in a comparison of two anti-hypertensive agents.

- These are quantitative, not qualitative data, and are likely to be normally distributed. (There are formal tests for normality, but if the mean and median are the same and the range of measurements spans around 5 SD then the data are probably parametric.)
- The data may be unpaired, if two groups of patients are being studied, but will be paired if the anti-hypertensive drugs are being given sequentially to the same individuals.
- An appropriate test, therefore, would be Student's *t*-test (paired or unpaired as above), or ANOVA (also paired or unpaired).
- A *P* value of less than 0.05 may be the level at which the null hypothesis is disproved (that is confirming that there is a difference between the treatments), but this means nevertheless that there is up to a 5% probability that this observed difference could have arisen entirely by chance. This is the Type I or alpha error (false positive).

Further direction the viva could take

The discussion may widen to include the potential errors in data interpretation from clinical trials, meta-analysis and evidence-based medicine.

- **Trial data:** See *Clinical trials: errors in interpretation of data*, page 277.
- **Meta-analysis:** This is a technique that aggregates the data from a number of individual randomised controlled clinical trials (RCTs) with the aim of confirming or refuting an effect that the smaller studies have been unable to do. It combines trials, which individually may have been too small to demonstrate a significant difference.
- **Advantages:** Meta-analysis can produce a conclusion (synthesis) from a number of trials which may even have had contradictory findings. The power and significance of the overview can be increased by this synthesis of the individual results, and may allow a definite conclusion to be drawn even when individual studies have contradictory findings. The technique requires inclusion of all relevant RCTs which are scored according to their methodology.
- **Problems:** Meta-analyses are the tools of statisticians and epidemiologists and are not without drawbacks. They are subject to 'publication bias' since negative studies are much less likely to be published than positive ones. They may also be affected by double counting, which may occur when the same data are incorporated into more than one trial report. Their credibility is also tested severely if the populations in the RCTs are different. The Cochrane Injuries Group Albumin Reviewers concluded in 1998 that albumin increased mortality in critically ill patients. The patient populations were very disparate and even included neonates, and subsequent subgroup analysis suggested that in some of the groups albumin actually improved survival. Even if the populations are similar the trial designs may be very different, with matched subgroups being too small to permit formal meta-analysis.
- **Evidence-based medicine:** See *Evidence-based medicine*, page 330.

Clinical trials: errors in interpretation of data

Commentary

This is not a question about flaws in the design of clinical trials, but about potential problems with statistical analysis. Many of the terms and definitions are similar, and do need precise enunciation so as to avoid confusion of both candidate and examiner. This is one of the areas in which a slow careful delivery is interpreted as clarity of thought and so you may find the viva drawing to a close before you know it.

The viva

You will be asked initially about the basic types of error. You could start by explaining the null hypothesis, because it is integral to a discussion of Type I and II errors, and you will almost certainly be asked about it at some stage of the viva.

- **Null hypothesis:** This is the assumption made at the start of any investigation, that there is no difference between the populations, treatments, samples, etc. that are being compared. Tests of statistical significance aim to disprove the null hypothesis at a given level of probability. This is usually 0.05 (which means that there is a 5% likelihood of the difference occurring purely due to chance).
- **Types of error – Type I or α error:** In this case the null hypothesis is wrongly rejected, and a difference is found when there is none. This is a false positive. The likelihood of a Type I error is reduced by requiring a higher-probability value (making *P* smaller), by increasing the sample size, or both. By convention a 5% probability of making a Type I error is accepted, and the confidence level is given by $(1 - \alpha)$.
- **Types of error – Type II or β error:** In this instance the null hypothesis is wrongly proved, and so no difference is found when one does in fact exist. This is a false negative. Type II errors are easier to avoid than Type I, and their commonest cause is a sample size that is too small. They may also occur if there is a wide variation in the study population or if differences that may be clinically significant are quantitatively quite small. Type II errors are linked with the power of the study. More leniency is allowed in respect of Type II errors, such that a 10% or 20% probability of an error is accepted. A study is adequately powered, therefore, if β is equal to or less than 0.2.
- **Power:** The 'power' of a study is measure of its likelihood of detecting a difference between groups if a difference really does exist. It is also defined by $(1 - \beta)$ where β is the probability of a Type II error. The power of a trial is the probability of avoiding a Type II error, and so it is clear that underpowered studies may reject treatments that in fact may be effective. The determination of the numbers needed is also a reflection of the minimal clinically important difference, which is set by the investigator. It is probably not important, for example, to detect a 5% reduction in systolic blood pressure, but it may be very important to identify a 5% reduction in mortality. Were a study to miss such a fall in mortality then it might lead to the abandonment of a therapy that might save 50 lives for every 1000 patients treated.

Direction the viva may take

By way of an extension to the preceding discussion you may be asked about ways of quantifying the value of a clinical test.

- **Sensitivity:** This is a measure of how good is a clinical test at excluding false positives, and is defined by the proportion of positives that are correctly identified by the test. It is determined by the proportion of patients who test positive, in relation to the numbers who actually are positive.
- **Positive predictive value:** This is an alternative means of determining whether an abnormal result predicts a genuine abnormality. It is defined by the numbers

of patients who both test positive and who are genuinely positive, as a proportion of the total of correct positive tests.

- **Specificity:** This is a measure of how good is a clinical test at excluding false negatives, and is defined by the proportion of negatives that are correctly identified by the test. It is determined by the proportion of patients who test negative, in relation to the numbers who actually are negative.
- **Negative predictive value:** This is an alternative means of determining whether a normal result precludes a genuine abnormality. It is defined by the numbers of patients who both test negative and who are genuinely negative, as a proportion of the total of correct negative tests.
- **Statistical and clinical significance:** It is erroneous to equate statistical with clinical significance. Statistics are essentially measures of probability: clinical judgement must thereafter inform their use.

Further direction the viva could take

This viva also may divert to a more wide-ranging discussion to see whether you have a broad familiarity with clinical trials, and so may include study design, evidence-based medicine and meta-analysis.

- **Clinical trials:** See *Clinical trials: errors in interpretation of data*, page 277.
- **Evidence-based medicine:** See *Evidence-based medicine*, page 330.
- **Meta-analysis:** See *Parametric and non-parametric data*, page 275.

Osmosis

Commentary

This is a fairly circumscribed topic which fits readily into the time frame of this viva. Although its main interest lies in clinical disorders which disrupt plasma osmolality, you will probably spend more time on the basic definitions and concepts, none of which are that complicated.

The viva

You will be asked to define osmosis before the questioning moves on to related aspects.

- **Definition:** Osmosis describes the process of the net movement of water molecules due to diffusion between areas of different concentration.
- **Osmotic pressure:** An effective concentration gradient of water can be produced between two compartments separated by a semi-permeable membrane (permeable to water but not to solute). The movement of water into such a compartment will increase the pressure and/or volume of the compartment. This movement can be opposed by increasing the pressure in the compartment: and the pressure needed to prevent osmosis is defined as the osmotic pressure exerted by the solution. (If one compartment contains 22.4 l and 1 mol of solute at 0°C it will exert an osmotic pressure of 1 atm, or 101.325 kPa.)
- **Calculation of osmotic pressure:** The van't Hoff equation is based on the recognition that dilute solutions behave in a similar way to gases, hence: osmotic pressure = n [(number of particles) × (concentration/molecular weight)] × R (universal gas constant) × T (absolute temerature).
- **Measurement of osmotic pressure:** This is measured by an osmometer, which utilises one or more of the colligative properties of a solution. (These depend on the osmolarity and are depression of freezing point, elevation of boiling point, reduction in vapour pressure and exertion of osmotic pressure.) Osmometers can utilise the fact either that 1 mol of a solute which is added to 1 kg of water will depress the freezing point by 1.86°C, or that the molar concentration of a solute causes a directly proportional reduction in the vapour pressure of the solvent (Raoult's law). (Such devices have the advantage of requiring smaller samples than the freezing point osmometer.) The measurement of change of 1 mosmol requires apparatus capable of recording a temperature change of 0.002°C.
- **Osmolarity and osmolality:** Osmolarity is the number of osmoles (or mosmoles) of solute per litre of solution, Osm l^{-1}, and is influenced by temperature. Osmolality is the number of osmoles per kilogram of solution, Osm kg^{-1}, and because it is temperature independent removes a source of potential inaccuracy.
- **Estimation of osmolality:** The plasma osmolality can be estimated from a simple formula which sums the major solutes: (2 × Na^+) + (glucose) + (urea). The plasma osmolality is kept constant in health at around 290 mosmol kg^{-1} H_2O. More than 99% of the osmolality of plasma is due to electrolytes, with the contribution of plasma proteins (the oncotic pressure) being less than 1%. (1 mosmol is equivalent to 17 mmHg or 2.26 kPa.)
- **Oncotic pressure:** The oncotic pressure is the contribution made to total osmolality by colloids. (Hence the alternative term 'colloid osmotic pressure', COP.) The plasma oncotic pressure, at 25–28 mmHg, is only about 0.5% that of total plasma osmotic pressure, but it is significant because it is the major factor in the retention of fluid within capillaries. Albumin is responsible for about 75% of the total COP.
- **Measurement of oncotic pressure:** The COP can be measured by an oncometer, which comprises a semi-permeable membrane which separates the plasma sample from a saline reference solution. The change to the oncotic pressure can readily be transduced and measured.

- **Tonicity:** In contrast to osmolality, which measures all the particles in a solution, tonicity refers only to those particles which exert an osmotic force. Urea and glucose are freely permeable and so are not included. (The exception is in diabetes mellitus when glucose does not pass into cells and so becomes osmotically active. Urea can exert a local osmotic effect because it does not cross the blood–brain barrier and so a high urea may cause intracranial dehydration and a reduction in ICP.)

Direction the viva may take

You may be asked about conditions that result in derangements of osmolality.

- **Anti-diuretic hormone (ADH):** This increases conservation of water and sodium in the distal renal tubules via a mechanism mediated by cyclic adenosine monophosphate (cAMP). Osmoreceptors in the supraoptic nuclei of the hypothalamus have a mean threshold of $289 \pm 2.3\,\text{mosm}\,\text{kg}^{-1}$. Above this plasma level ADH release is stimulated. (The kidneys should be able to produce a urine osmolality of at least $1000\,\text{mosmol}\,\text{kg}^{-1}$.)
- **Syndrome of inappropriate ADH secretion (SIADH):** This is defined by the non-osmotic release of ADH with consequent water retention and hypotonicity. Its causes are numerous, but include intracranial tumours and pulmonary malignancy and infection. Treatment is via water restriction and in chronic cases with the use of demeclocycline (a tetracycline) which blocks ADH action in the kidney.
- **Glycine intoxication (transurethral resection syndrome):** This may follow excessive absorption of irrigating fluid during transurethral procedures (usually prostatectomy). Treatment is with administration of normal saline and judicious diuretic. Rapid restoration of normal sodium (for example, by the use of hypertonic saline) is associated with central pontine myelinosis.
- **Diabetes insipidus:** This also has many causes and can be neurogenic (with deficiency of ADH synthesis or impaired release) or nephrogenic (with renal resistance to the action of ADH). It is characterised by massive diuresis and hypovolaemia. Neurogenic diabetes insipidus (DI) is treated with desmopressin (an ADH analogue) in a dose tailored to allow a mild diuresis to avoid the complication of water intoxication. Chlorpropamide potentiates the effects of endogenous ADH and also sensitises distal tubules.
- **Water intoxication:** This follows excessive intake of water, usually self-inflicted (29% of the finishers in a recent Hawaiian Ironman Triathlon were reported to be hyponatraemic), but is also associated with iatrogenic infusion of large volumes of glucose solution. The decrease in plasma osmolality inhibits ADH secretion, but it can still cause potentially fatal electrolyte disturbance.

Gases and vapours

Commentary

This is another area that could be seen more properly as being the province of the Primary examination, but anything related to gases, vapours and pressures will be seen, inevitably, as appropriate subjects for discussion. Vivas on these subjects tend to be a bit haphazard, and you may be asked for a number of definitions before moving on to one or more disparate topics, among which may be partial pressure, SVP, vaporisers, water vapour and humidification.

The viva

You may be asked first what is the difference between a gas and a vapour.

- **Gas:** A gas is a substance above its critical temperature.
- **Vapour:** A vapour is a substance below its critical temperature.
- **Critical temperature:** This is defined as the temperature above which a gas cannot be liquefied; no matter how great is the pressure that is applied.
- **Critical pressure:** This is defined as the vapour pressure of the substance at its critical temperature. It is the pressure needed to liquefy the gas at its critical temperature.
- **SVP:** A saturated vapour is one that is in equilibrium with its own liquid, so the number of molecules entering the liquid phase equals those entering the vapour phase. If the temperature rises, more molecules enter the vapour phase and the vapour pressure rises. The SVP is the maximum partial pressure that can be achieved at a given temperature. The relationship of SVP and temperature is non-linear.
- **Boiling point:** When the SVP is the same as the ambient pressure the liquid boils and the vapour concentration at the surface of the liquid is 100%. Hence the boiling point is the temperature at which the vapour pressure of a liquid equals the ambient temperature above it. The boiling point will therefore decrease as the ambient pressure falls, for example, during ascent to altitude.
- **Latent heat:** When any substance changes from a liquid to a vapour or from a solid to a liquid, heat must be supplied despite the fact that this change of state takes place at a constant temperature. This is the latent heat of vaporisation (if the change is from a liquid to a vapour) or the latent heat of fusion (if the change is from a solid to a liquid). In any particular homogenous fluid the molecules do not possess identical kinetic energy. Those with a higher velocity escape the surface of the liquid and are vaporised, thus the mean kinetic energy of the remainder diminishes and the liquid cools. The latent heat of vaporisation is defined as the additional heat that is required to convert a given mass of liquid into vapour at the same temperature. Conversely, heat is generated as vapour condenses back to a liquid.
- **Pseudocritical temperature:** In a mixture of gases there is a specific critical temperature, the pseudocritical temperature, at which the gas mixture may separate into its different constituents. The only stored gas mixture in common use in anaesthesia is Entonox (50% O_2: 50% N_2O). The critical temperature of N_2O is 36.5°C, but the interaction with oxygen lowers this to −5.5°C (its pseudocritical temperature). Thus below −6°C, liquefaction of nitrous takes place. This is potentially dangerous, because although at this point the N_2O has about 20% oxygen dissolved in it, as the oxygen rich supernatant is drawn off the oxygen in the liquid comes out of solution, leading eventually to the delivery of a hypoxic mixture.

Direction the viva may take

You may be asked about the relevance of these concepts for clinical practice.

- **N_2O cylinders:** The critical temperature of N_2O is 36.5°C, and so under normal circumstances in temperate climates it is stored in a liquid phase with its vapour above it. In the UK the filling ratio (the mass of gas in the cylinder divided by the mass of water that would completely fill the cylinder) is 0.75, to allow for expansion and to limit increases in pressure. As the liquid expands it compresses its vapour, some of which then condenses back to a liquid and restricts the pressure rise. In hotter climates the filling ratio is 0.67. If a N_2O cylinder is used continuously it will cool as it vaporises and the SVP and gauge pressure will drop. If the gas is turned off then both will be restored to normal as the cylinder rewarms. The belief that the gauge pressure will remain unchanged until the moment just before the cylinder empties is a misconception.
- **Oxygen supplies:** Liquid oxygen must be kept at a temperature lower than its critical temperature of −118°C. See *Supply of medical gases*, page 236.
- **Vaporisation of volatile anaesthetic agents:** See *Vaporisers*, page 283.
- **Water vapour and humidification:** See *Humidification (of inspired gases)*, page 230.

Vaporisers

Commentary

Vaporisers, volatile agents and circle systems are of obvious clinical relevance, but this being the science viva it is the basic principles which will dominate the questions. The oral should follow a relatively predictable course, including the 'trick' question about the use of vaporisers at altitude.

The viva

You may be asked about the physical principles of vaporisation and the problems that these cause for vaporiser design.

- **SVP:** Vaporisers have to overcome the fact that the SVP of volatile agents at 20°C is many times greater than that required to produce anaesthesia. (The SVP of sevoflurane is 22.7 kPa and so its maximum achievable concentration is 22.4% (22.7/101.325). For desflurane, with an SVP of 89.2, the figure is 88%.) Vaporisers have to be designed to allow the addition of a controlled amount of volatile anaesthetic agent to the FGF, having changed the liquid to a vapour. This is done by streaming the FGF.
- **Splitting ratio:** As the FGF enters the vaporiser it is split into two streams: approximately 20% passes into the vaporisation chamber while the rest enters a bypass chamber. The gas leaving the vaporising chamber should be fully saturated with vapour. This is achieved by increasing the available surface area by the use of wicks or a series of baffles.
- **Latent heat of vaporisation:** As a liquid vaporises so its temperature falls, and compensation for this change is essential. If there is no such compensation then the SVP of the agent and its delivered concentration will also fall. Vaporisers are made of material with high thermal conductivity, which supplies energy for the heat of vaporisation by allowing heat to flow from the vaporiser into the anaesthetic in its liquid phase. The splitting ratio must also be altered as the temperature changes, hence the design of the bi-metallic strip, which allows more gas into the vaporising chamber as the temperature drops.
- **Calibration:** Vaporisers are calibrated for individual agents, and should one inadvertently be filled with a different volatile anaesthetic then it will deliver either excessive or inadequate vapour concentrations depending on the respective vapour pressures. If a volatile with a high SVP (such as desflurane, 89.2 kPa) is used in a sevoflurane vaporiser (SVP 22.7 kPa) then vapour output will be high. If the situation is reversed then vapour output will be low. Even if the SVP differences are small the effect is still significant: isoflurane (SVP 32.5 kPa) in a halothane vaporiser (SVP 32.1 kPa) will deliver a concentration that is 25–50% higher than is dialled up.
- **Potential problems**
  - *Flow rate dependence*: Modern vaporisers function independently of flow rates between 0.5 and 15 l min^{-1}. Outside these limits they will deliver less than the dialled concentration.
  - *Overfilling*: Volatile agent may get directly into the bypass chamber if the vaporiser is overfilled, leading to the delivery of dangerously high concentrations.
  - *'Pumping' effect*: If a ventilator produces cyclical changes in the pressure in the back bar, then this may force gas back into the vaporising chamber and saturated gas in the vaporising chamber back into the bypass channel. The forward flow as the ventilator cycles then increases the concentration of delivered vapour. This occurred with minute–volume divider ventilators which are now in less common use.
  - *'Pressurising' effect*: This occurs if the overall pressure in the vaporiser is raised (as happens in large vaporiser chambers at high flows). When the

gas reaches the common outlet it expands to atmospheric pressure with a lowering of the effective concentration.
— *Monitoring*: Monitoring volatile agent concentrations minimises these theoretical risks.

Direction the viva may take

You may be asked a number of miscellaneous, but largely predictable questions, which may include the use of vaporisers at altitude or under hyperbaric conditions, the characteristics of the desflurane vaporiser and the use of vaporisers inside and outside circle systems.

- **Effects at altitude:** Imagine that the atmospheric pressure halves to 380 mmHg. A vaporiser calibrated to deliver 1% at sea level will therefore deliver 2% (760/380). One per cent at sea level represents a partial pressure of 7.6 mm (0.1 × 760), which is the same as 2% at altitude (0.2 × 380). Although the output of vapour in volumes percent increases, the partial pressure remains unchanged. As it is the partial pressure of the agent that is responsible for anaesthesia the vaporiser can therefore be used as normal either at altitude or under hyperbaric conditions.
- **Desflurane:** The physical properties of desflurane require a more complex vaporiser that is designed like none other in current use. The boiling point of desflurane, at 23.5°C, is close to room temperature. Small changes in operating theatre temperature, therefore, could cause large changes in the SVP of desflurane with an increase in vapour output. In order to control this accurately the vaporiser is heated to 39°C. This produces a gas under pressure (200 kPa) which is then injected into the FGF. This vaporiser design obviates the need for any temperature compensation devices.
- **Position in the circuit:**
  — *VOC (vaporiser outside circle)*: Plenum vaporisers (in which positive upstream pressure drives the gas) have high internal resistance, are unsuitable for use within circle breathing systems, and deliver volatile agent from the back bar of the anaesthetic machine. At low flows, large changes in the dialled concentration are reflected only very slowly within the circle system. A change in FGF rather than vapour concentration may be necessary to effect a more rapid change in the depth of anaesthesia.
  — *VIC (vaporiser inside circle)*: Drawover vaporisers (in which a subatmospheric pressure generated distal to the vaporiser either mechanically, or by the patient's spontaneous respiration, draws the gas through the system) have minimal resistance to flow and can be used within a circle. At low flows the vapour concentration rises, because rather than being diluted it is being added to each inspiration. If the minute volume is large then the risk of delivering very high concentrations of volatile agent is increased.

Further direction the viva could take

If there is time you may be asked about some of the characteristics of the volatile agents. There is unlikely to be time to explore these in any depth, but you should try to demonstrate in your answers that you are confident clinically and practically in their use.

Anaesthetic breathing systems

Commentary

This is a standard topic, which will inevitably involve a discussion of the Mapleson classification. You will probably be invited to draw the different arrangements, and a useful way of dealing with this request is to give a running commentary as you draw the components. This means that you will not find yourself sitting at the table drawing in silence while the examiners watch, and will allow you to demonstrate that you understand how these breathing systems behave. Analysis of the behaviour of these systems can be complex, and so you are more likely to be asked about those (such as the Magill attachment) that can be explained within the time available.

The viva

The viva will start with the Mapleson classification. There are more logical ways of analysing breathing systems, but it has become hallowed by tradition and familiarity and shows little sign of being superseded. (Mapleson was Professor of Medical Physics in Cardiff and published in 1953 his analysis of the behaviour of the various combinations of the valve, tubing, reservoir bag and fresh gas flow (FGF) that were used in breathing systems.) Strictly speaking these should be described breathing *systems* rather than *circuits*, but common usage makes the term permissible, although technically incorrect.

- **Classification:** The systems were classified as A to F, and they all potentially allow rebreathing. They are 'semi-closed' ('semi-open' in the USA) and supply more gas than the patient needs, with the excess being vented to atmosphere. If rebreathing of CO_2 does occur, a healthy patient who is breathing spontaneously will respond by increasing alveolar ventilation, which will rise, by up to 20 times if necessary, in order to keep the P_aCO_2 normal. These systems are defined, therefore, in terms of the FGF that is needed to maintain an unchanged P_aCO_2 in the face of unchanged ventilation.
- **Mapleson A:** This is most commonly used in the form of the Magill attachment and comprises a reservoir bag into which the FGF is directed, a length of corrugated tubing (which is resistant to kinking) and at the patient end, an APL valve.
  - *Spontaneous respiration*: The system is very efficient: at the end of inspiration the valve is closed and the reservoir bag is emptying. During expiration the FGF is filling the reservoir bag, while expired air (dead space gas and then alveolar gas) is passing into the tube. Hence the pressure in both the reservoir bag and the breathing system increase to the point at which the valve opens and vents expired air. The FGF continues to flow down the tube. At an FGF equal to the alveolar ventilation, it is alveolar gas and not dead space gas that is expelled preferentially. This analysis is based on the assumption that there is no longitudinal mixing of dead space and alveolar gases, and Mapleson recommended that the FGF should equal the minute ventilation. (Subsequent investigation suggested that 70% of minute ventilation would be adequate.)
  - *Controlled ventilation*: If controlled ventilation is used the circuit loses all its economy: fresh gas is vented during inspiration, while during expiration the valve tends to close, and all expired air passes back into the system which selectively retains expired air. The FGF should be at least twice the minute ventilation.
  - *Co-axial versions*: Co-axial versions, of which the commonest is the Lack system, function in the same way. Early narrow co-axial systems effectively reduced the capacity of the outer expiratory limb to store gas, and hence expired gas could reach the reservoir bag. Increasing the dimensions solved this problem, but at the cost of increasing the bulk of the system.

- **Mapleson B and C:** The Mapleson C comprises an APL valve at the patient end with the FGF entering just proximally. A short length of tubing connects this to the reservoir bag, which in the classic 'Waters' circuit, includes a CO_2 absorbing canister. The Mapleson B includes a length of corrugated tubing between the FGF and the reservoir bag. The Mapleson C circuit is used in resuscitation and in areas such as theatre recovery. Both systems allow mixing of expired air with the FGF, which must approximate three times minute ventilation to flush the system and prevent rebreathing. A Mapleson B circuit, nevertheless, is still more efficient than the Mapleson A during controlled ventilation.
- **Mapleson D, E and F:** These systems all function as T-pieces, being inefficient for spontaneous respiration but not for controlled ventilation. Analysis of their behaviour is much more complex than that of the Mapleson A system, although as a simplification they require up to three times the minute ventilation to prevent rebreathing during spontaneous respiration (150–200 ml kg^{-1}) but only 70 ml kg^{-1} to achieve normocapnia during IPPV. Analysis is complicated by, among other factors, the influence of the respiratory pattern. The respiratory cycle is a sinusoidal waveform, and in order to prevent rebreathing, the FGF must equal or exceed the peak inspiratory flow rate (PIFR). At end expiration alveolar gas has moved into the expiratory limb where it mixes with the FGF, and in order to prevent rebreathing the FGF should approach three times the minute ventilation. If however, there is an expiratory pause, some alveolar gas will be expelled by the FGF and the flow rate, theoretically, can be decreased.
  - *Mapleson D*: The Bain circuit is the co-axial version of the Mapleson D circuit.
  - *Mapleson E*: This is the original Ayre's T-piece. It can allow both rebreathing of CO_2 containing gas as well as entrainment of ambient air.
  - *Malpeson F*: This differs from the E only in that it has a reservoir bag, added by Jackson–Rees (who was a paediatric anaesthetist) to allow controlled ventilation. The system has no valves and so there is minimal expiratory resistance, hence its traditional use in paediatric anaesthesia.
- **Humphrey ADE system:** The Humphrey block is located at the common gas outlet and exists in both parallel and co-axial versions (of equal efficiency). It comprises an APL valve, a pressure relief valve, a reservoir bag, a ventilator port and a lever for selection of spontaneous ventilation (in the A mode) or controlled ventilation (in D/E mode).
- **Circle system:** Discussion of the circle system is a topic of its own, but in summary it comprises a circuit with unidirectional valves in the inspiratory and expiratory limbs, an APL valve and a reservoir bag. Central to its function is a CO_2 absorber. The circle is efficient in terms of conservation of gases, heat and moisture, and is less polluting. Its volume means that high FGFs are required in the initial phase, after which, at low flow rates rapid changes in anaesthetic depth cannot be achieved. Gas monitoring is mandatory.
- **Monitoring:** It is worth commenting that although it is important to understand the functional behaviour of these breathing systems, the modern ability to measure the concentrations of gases and volatile agents has removed many of the potential hazards posed by imprecision of the analyses and by inter-patient variability.

6

Miscellaneous science and medicine

Mechanisms of action of general anaesthetics

Commentary

This has been the focus of fundamental research which this viva will not have time to explore in any depth. The subject matter is complex; there is no single unifying theory which underpins general anaesthesia and much remains unexplained. It is probable, therefore, that as long as you can give a summary that sounds reasonably plausible then you will pass. It is hard to fail a question to which nobody yet really knows the answer.

The viva

You will be asked what theories you know that have been advanced to explain the action of general anaesthetics.

- Compounds that cause reversible insensibility range from xenon, which is chemically unreactive and whose structure could not be simpler, to barbiturates and phenols, whose structures are both complex and dissimilar. The search for a unifying theory of action is thus made much more difficult, and no specific structure–activity relationship can readily be identified.
- **Meyer–Overton hypothesis:** Meyer and Overton (working separately) were the first to relate the potency of anaesthetic agents to their lipid solubility. They argued further that the onset of narcosis was evident as soon as the particular substance had attained a certain molar concentration in the lipids of the cell, and that the lipid layers of the cell membrane represented the main site of action. Much early research, therefore, was based on the hypothesis that disruption of the lipid bilayer affected the function of membrane proteins and mediated thereby an interruption of neuronal traffic. As a unifying theory, however, it was undermined by the observations that temperature increases disrupt lipid membranes without inducing a state of general anaesthesia, and that there are many compounds with high lipid solubility which exert no anaesthetic effect. There remains, nonetheless, a clear relationship between anaesthetic potency and lipid solubility, which any theory of action must accommodate.

- **Clathrate theory:** This theory suggested that anaesthetic agents form hydrates (clathrates) and from these microcrystals which aggregate in cell membranes to affect their function. The problem with this hypothesis is that at body temperatures very high pressure is needed for clathrate formation.
- **Pressure reversal:** It was discovered that the state of anaesthesia in tadpoles and in mice anaesthetised with halothane could be reversed by subjecting them to pressure, a process which was assumed to restore the normal configuration of the cell membrane. The pressures required to reanimate these creatures, however, were in excess of 50 atmospheres, which suggests that the volume expansion theory is not tenable.
- **Voltage-gated ion channels:** General anaesthetic agents appear to exert minimal effect at voltage-gated ion channels.
- **Neurotransmitter-activated ion channels:** Ligand-gated membrane ion channels have been the focus of most recent investigation, and of these receptors the most promising appear to be the γ-hydroxybutyrate (γ amino butyric acid A, $GABA_A$) receptor, as well as glycine and glutamate receptors. As membrane-bound proteins, $GABA_A$ and glycine receptors contain integral anion-conducting channels, and are among a group which includes $5\text{-}HT_3$ and nicotinic cholinergic receptors, in whom function is altered by the allosteric effects of a number of disparate compounds.
- **$GABA_A$:** $GABA_A$ is the major inhibitory neurotransmitter receptor system which makes it a prime candidate for a major site of action of general anaesthetics. Experimental work confirms that $GABA_A$ receptor enhancement follows administration of various compounds including volatile anaesthetics and intravenous (i.v.) induction agents. Almost all general anaesthetic agents, with the exceptions of xenon and ketamine, appear to influence the $GABA_A$ receptor at therapeutically relevant concentrations.
- **Glycine receptors:** The glycine receptor is the spinal cord and brain stem analogue of the $GABA_A$ receptor of the brain. This too contains an integral chloride channel and is affected by many general anaesthetic agents.
- **$5\text{-}HT_3$ and nicotinic acetylcholine receptors:** General anaesthesia also affects cationic currents through these receptors, but further than this the function of these central receptors is not understood.
- **Glutamate receptors:** These consist of the *N*-methyl-D-aspartate (NMDA) and non-NMDA receptor classes, which comprise the primary excitatory neurotransmitter system in the brain. Inhibition of their function is therefore consistent with a theory of general anaesthesia. Ketamine acts specifically at the NMDA receptor. The non-NMDA glutamate receptors are divided into various sub-classes (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid, AMPA, and kainate) which are both strongly affected by ethyl alcohol, but not by volatile anaesthetics.
- **Conclusion:** There is still no unifying theory of anaesthetic action. Anaesthesia does consist of a spectrum of altered physiological states which include insensibility, amnesia and the loss of reflex responses, but it remains impossible to ascribe the diverse clinical signs of general anaesthesia to specific changes in any of the sites that have been discussed above.

Direction the viva may take

Once you have explored some of the concepts outlined above there is nowhere much for the questioning to go, and so the viva may well move on to the next topic. If you find yourself discussing individual anaesthetic agents then it is likely that either you, or the examiner, or possibly both, have exhausted all mutual knowledge of the subject.

Jaundice

Commentary

This subject sounds as though it should be very relevant to anaesthesia, although in routine practice it is rare to encounter deeply jaundiced patients. This viva may proceed quite quickly to medical and anaesthetic aspects, because the outline science of the topic may not take long to cover. Hepatic disease is a large subject, but you will be expected to recall the important implications for anaesthesia, among which are the hepatorenal syndrome and coagulation problems. If you do forget to mention these it may raise questions about the safety of your practice, which will increase your chances of failing the oral.

The viva

You will be asked to define jaundice and to discuss its aetiology.

- Jaundice (icterus) is the yellowing of skin, sclera and mucous membranes which occurs as a result of the accumulation of bilirubin (either free or conjugated) in the blood. The normal bilirubin concentration is less than 17 $\mu mol l^{-1}$ and jaundice is not usually detectable clinically until it reaches around 35 $\mu mol l^{-1}$. (Some authorities say 50 $\mu mol l^{-1}$.)
- Bilirubin is formed from the breakdown of haemoglobin in the reticulendothelial system. The polypeptides of the haemoglobin molecule (the 'globin') are separated from the haem moiety, which in turn is catabolised to biliverdin. Haem is an iron-containing porphyrin derivative. Biliverdin is converted to bilirubin prior to excretion in bile.
- Fat-soluble unconjugated bilirubin binds to albumin in the circulation and is transported to the liver, where it dissociates prior to conjugation (with glucuronic acid). As the water-soluble bilirubin diglucuronide it is excreted via the bile canaliculi. A small amount does gain access to the circulation to be excreted in urine.

Causes of jaundice

- There are four potential causes of hyperbilirubinaemia. This may be due to excess production, to defective uptake into hepatocytes, to deficient intracellular binding or conjugation and to problems with secretion of bilirubin into the biliary system.
- **Increased bilirubin production:** The major cause is haemolytic anaemia. Free bilirubin concentrations rise, but rarely exceed 50 $\mu mol l^{-1}$ because the liver has substantial reserve capacity to handle the excess.
- **Decreased hepatic bilirubin uptake:** Diminished intake of bilirubin into hepatocytes occurs in Gilbert's disease, which causes unconjugated non-haemolytic hyperbilirubinaemia. It can also occur during the resolving phase of viral hepatitis. Free bilirubin concentration does not usually exceed 50 $\mu mol l^{-1}$.
- **Defective bilirubin binding or conjugation:** This is characteristic particularly of premature neonates whose enzyme systems may be immature. It also occurs in rare (and usually fatal) diseases such as Crigler–Najjar syndrome. Free bilirubin concentrations rise.
- **Diminished secretion into the biliary system:** There are both extrahepatic and intrahepatic causes of a rise in conjugated bilirubin concentrations. Biliary outflow may commonly be obstructed by gallstones, and more rarely by biliary and pancreatic carcinoma. Intrahepatic cholestasis is associated with a large number of conditions. It occurs in infective and alcoholic hepatitis, in severe cirrhosis of the liver, and as a result of primary biliary cirrhosis and sclerosing cholangitis. Cholestasis can occur in pregnancy (it is usually mild and is of unknown cause) and as a consequence of treatment with drugs. Drugs so

implicated include oral contraceptives, anabolic steroids, some neuroleptic agents including chlorpromazine and haloperidol, and sulphonamides.
- More than one of the mechanisms above may be responsible for the clinical picture: hepatocellular damage, for instance, can contribute to an elevated bilirubin by all four.

Direction the viva may take

You may be asked about the peri-operative implications of jaundice.

- **Aetiology:** The cause is important because of accompanying morbidity; cirrhosis may, for example, be associated with alcoholic cardiomyopathy.
- **Coagulopathy:** The liver synthesises many of the protein clotting factors, and jaundice may be associated with derangements of coagulation.
- **Myocardium:** Bile salts can depress the myocardial conduction system leading to significant bradycardia.
- **Renal system:** Anaesthesia in the presence of liver dysfunction can be followed by the hepatorenal syndrome in which acute renal failure (ARF) may supervene in the immediate post-operative period. The cause remains unknown, although it is presumed to be due to a hepatic endotoxin that the damaged liver can no longer contain. Management recommendations include the use of generous fluid therapy with the use of mannitol to enhance urine output. The risk is particularly great if bilirubin concentrations exceed 180 $\mu mol\,l^{-1}$.
- **Infective hepatitis:** Anaesthesia in the acute phase is invariably deleterious to hepatic function. Theatre staff must also be protected against the risks of contamination.
- **Drug elimination:** The reserve even of the damaged liver is very great, but anaesthetists should be aware of the possibility that the normal mechanisms by which drugs are excreted may be impaired. Cytochrome P450 enzymes are converted to the inactive cytochrome P420.
- **Post-operative jaundice:** Causes *de novo* include haemolysis following blood transfusion, and adverse drug reactions. All volatile anaesthetics are metabolised in the liver, and halothane hepatitis is a well-recognised entity. The use of halothane is now negligible in the UK, but hepatitis of unknown aetiology has been reported rarely following the use of enfurane, isoflurane and sevoflurane.

Latex allergy

Commentary

Latex allergy was recognised first in the late 1970s, since which time the use of latex in the surgical environment has become ubiquitous. In the last decade it has been identified as a cause of anaphylaxis, and it has been suggested that because of prolonged exposure to latex-containing products as many as 10% of health care workers may be sensitive. It is an important cause of unexplained intra-operative collapse, and so you will be expected to have an understanding of the problem and its management.

The viva

You will be asked to describe latex allergy.

- Latex is natural rubber produced from the milky sap of the *Hevea brasiliensis* rubber plant. It comprises not only proteins, but also lipid and carbohydrate molecules. It is the soluble proteins that are responsible for the severe allergic responses.
- The reactions to latex products include simple irritant contact dermatitis, and allergic contact dermatitis which is a Type IV T-cell-mediated hypersensitivity reaction to the chemicals used in manufacture. The potentially fatal response to latex exposure is a Type I IgE-mediated hypersensitivity reaction. Sensitised individuals produce IgE antibodies to latex proteins which on re-exposure may lead to an anaphylactic reaction with massive histamine release from mast cells and basophils. See *Immunology (and drug reactions)*, page 325.

Direction the viva may take

You may be asked how you would identify patients particularly at risk, and about their peri-operative management.

- The patient may have a history of atopy and multiple allergy. There is cross-reactivity with a number of foods; among them are kiwi fruit, avocado, papaya and chestnuts. Patients may also describe allergy to poinsettia plants. Occasionally patients have a confirmed diagnosis of latex allergy by radioallergosorbent testing (RAST). There may be a history of sensitivity to rubber products, and also at risk are individuals who are repeatedly exposed to latex products. Health care workers, patients undergoing repeated urinary catheterisation, and patients who have undergone multiple surgical operations are included in this group.
- **Peri-operative management:** All latex-containing products must be identified and avoided. Latex is ubiquitous and is found in trolley mattresses, pillows, TED stockings (those for the lower leg are latex free), surgical gloves, elastic bandages, urinary catheters and surgical drains. Anaesthetic equipment which may contain latex includes the rubber bungs in some drug vials, which should therefore be removed before they are made into solution, some giving sets, blood pressure cuffs, face masks, nasopharyngeal airways, breathing systems and electrode pads. Recognition of this problem, however, has meant that latex-free equipment is now more widely available.

Further direction the viva could take

You may be asked how you would recognise and treat an anaphylactic reaction. This may seem like a throwaway question at the end of the viva, but because it will be fundamental to a patient's well-being, your management of this emergency must be accurate and safe.

- **Diagnosis:** In an established anaphylactic reaction the patient will be hypotensive, with angio-oedema or an urticarial rash, and have severe bronchoconstriction. Hypotension is more common as a main feature than

bronchoconstriction, but the latter may be much more refractory to treatment. Only one system may be involved, and few patients will manifest the full range of clinical features. The onset of an anaphylactic reaction can sometimes be heralded by more subtle signs such as sneezing or coughing, and by the slower development of cutaneous signs. (Reactions to latex usually occur at least 30 min into surgery.)

- **Management:** After discontinuing administration of or contact with the trigger substance, management can follow the airway, breathing and circulation algorithm. The patient should be given 100% oxygen and positioned supine with the legs and pelvis elevated to enhance venous return. The mainstay of treatment is adrenaline (epinephrine), which can be given initially in a dose of 0.5 mg (0.5 ml of 1 : 1000) by intramuscular injection into the lateral thigh. Anaesthetists are likely to prefer i.v. administration; typically 50–100 μg over a minute and repeated according to response. Severe cases may need adrenaline by infusion at a rate of 100 $\mu g\,min^{-1}$. Secondary treatment can include corticosteroids, antihistamines and bronchodilators, although these are of much less importance than adrenaline, which is the drug most likely to save the patient's life.

Brain stem death testing

Commentary

Testing for brain stem death is long established, but still excites some debate. The residual controversy may trouble greatly the relatives of a patient who may be brain dead, and so it is of crucial importance that you understand the neurological basis of the tests sufficiently well to be able to answer any question that they might wish to ask.

The viva

You will be asked to describe the criteria for brain stem death testing.

- **Definition:** Brain death describes the situation in which a patient has undergone the irreversible loss of any capacity for consciousness, together with the irreversible loss of the ability to breathe.
- **Preconditions:** Before testing can be considered, there are preconditions that must be satisfied, the most important of which is that there must be a definite diagnosis of the cause of the brain damage. The patient should also be in an apnoeic coma, with a Glasgow Coma Score of 3: with no eye opening, no verbal response and no localisation of pain.
- **Children:** The clinical criteria theoretically are the same in children, although there are concerns about their applicability which make this a very difficult area. In neonates, for example, central nervous system (CNS) immaturity raises doubts about the validity of brain stem death tests, and there is much anecdotal evidence of children who have recovered substantial neurological function despite severe insult and prolonged coma.
- **Exclusions:** The patient's temperature must be at least 35°C. There should be no residual depressant drugs in the system, which in practice may mean substantial delay until clearance can be assured. Neuromuscular blockade should be excluded (where appropriate) by using a peripheral nerve stimulator. There must be no endocrine or metabolic disturbance that may contribute to continued coma, and there should be no possibility that impaired circulatory function is compromising cerebral perfusion. A high partial pressure of arterial carbon dioxide (P_aCO_2) can obtund cerebral function, and so P_aCO_2 must be kept normal (for that patient).
- **The tests:** These are carried out by two doctors, both of whom have been registered for more than 5 years, and one of whom must be a consultant. Two sets of tests are performed, although there is no set interval between them. In practice they are usually done a few hours apart. There has never been a reported case of a patient who initially satisfied the criteria for brain stem death, and who subsequently failed to do so. The tests aim to confirm the absence of brain stem reflexes, and examine those cranial nerves which are amenable to testing.
- **The cranial nerve reflexes:**
  - *I*: The first nerve (olfactory) cannot be tested.
  - *II*: The second nerve (optic) together with the parasympathetic constrictor outflow is tested by pupillary responses to light (direct and consensual). Pupillary size is not important.
  - *III, IV, VI*: The third, fourth and sixth nerves (oculomotor, trochlear and abducens) are not tested.
  - *V, VII*: The fifth (trigeminal) and seventh (facial) nerves are tested first by the corneal reflex, and then by the response to painful stimuli applied to the face (supra- or infraorbital pressure), to the limbs (nail bed pressure) and to the trunk (sternal stimulation). It is because of the rare possibility of tetraplegia that a stimulus should be applied above the neck.
  - *VIII*: The eighth nerve (auditory/vestibular) is examined by caloric testing. It is important to establish that both drums are visible and intract, after

which 30 ml of ice cold water is instilled via a syringe. Nystagmus is absent if the patient is brain dead. The assessment of doll's eye movements, to test whether the eyes move with the head (which is abnormal) instead of maintaining central gaze, are not part of the brain stem death tests as performed in the UK.
  - *IX, X*: The ninth (glossopharyngeal) and tenth (vagus) nerves are tested by stimulating the pharynx, larynx and trachea. The patient should neither gag nor cough.
  - *XI, XII*: The eleventh (accessory) and twelfth (hypoglossal) nerves are not tested.
- **Apnoea testing:** After ventilation with 100% oxygen for 10 min the patient is disconnected from the ventilator. Oxygen saturation is maintained thereafter by apnoeic oxygenation via a tracheal catheter. In the apnoeic patient arterial CO_2 rises at a rate of about 0.40–0.80 kPa min^{-1}, depending on the metabolic rate, and so it may take some time to reach the arterial blood gas level of 6.6 kPa required by the testing criteria.

Direction the viva may take

You may be asked about potential pitfalls.

- With the preconditions satisfied and the tests performed with scrupulous care, there should be none. There are, however, some conditions of which those carrying out the tests should be aware.
- There are a number of lesions of the brain stem which may closely mimic, if not replicate, irreversible brain death. These include severe Guillain–Barré syndrome, Bickerstaff's brain stem encephalitis and ventral pontine infarction associated with the locked-in syndrome. Brain stem encephalitis is characterised by acute progressive cranial nerve dysfunction associated with ataxia, coma and apnoea. There is no structural abnormality of the brain, but the picture is one of brain stem death. It is reversible. Bilateral ventral pontine lesions may involve both corticospinal and corticobulbar tracts, leading to tetraplegia. Patients are unable to speak or produce facial movements. They can usually blink and make vertical eye movements, and because the tegmentum of the pons is spared they remain sensate, fully conscious and aware. It is the stuff of nightmares and recovery from the locked-in syndrome is unknown.

Further direction the viva could take

You may be asked about any further confirmatory tests that can be undertaken.

- Auditory, visual and somatosensory evoked potentials can be used, as can the electroencephalogram (EEG) and cerebral angiography. None of these is required in the UK.

Haemofiltration

Commentary

Haemofiltration (HF) is a common intensive therapy intervention. Many patients require a period of renal support and you are expected to be familiar with its principles. Remember again that if your examiners do not work in intensive care units then your experience and knowledge may be much more recent than theirs.

The viva

You will be asked about the principles of HF.

Principles of HF

- The filters used in HF are sometimes referred to colloquially as 'kidneys', which reflects their role as literal renal substitutes.
- In the normal kidney the glomerulus filters water, ions, negatively charged particles of molecular weight of less than 15,000 and neutral substances of molecular weight up to about 40,000. Renal corpuscular channels have negatively charged pores, which oppose the passage of negatively charged plasma proteins such as albumin.
- Normal glomerular filtration rate (GFR) is $125\,ml\,min^{-1}$ ($7.5 l h^{-1}$).
- Tubular reabsorption reduces the filtrate of $180 l\,day^{-1}$ to about $1 l\,day^{-1}$, and salvages many of the filtered ions and other particles (diffusion and mediated transport). Tubular secretion is the means whereby larger molecules and protein-bound substances (such as drugs and toxins) are eliminated.
- In the HF system, arterial pressure which may be pump assisted, delivers a flow of up to $100–200\,ml\,min^{-1}$ to the semi-permeable membrane in the filter. Water and low molecular weight substances (up to 20,000) cross the membrane (which is acting as the 'glomerulus').
- Urea and creatinine will be removed, as will electrolytes and some drugs and toxins. Plasma proteins and all formed blood components remain within the circulation.
- Tubular reabsorption is mimicked by the direct infusion of balanced electrolyte solution, with concentrations adjusted as necessary. The volume infused will depend on the clinical situation. If the patient is not volume overloaded, then infusion will be at the same rate as the filtration rate, plus a component for maintenance fluid. If fluid removal is indicated, then negative balance is easily achieved by decreasing the infusion rate.
- HF is an efficient means of treating fluid overload, but in comparison with the kidney itself, it is very inefficient at removing solute. Very high volumes of ultrafiltrate (upwards of $15 l\,day^{-1}$) are required to remove urea, creatinine and other products of metabolism.
- Haemodiafiltration is much more efficient at removing solute. A dialysis solution is passed across the filter in a counter-current fashion so that solute can be removed both by convection (as in HF alone) and by diffusion.

Direction the viva may take

You may be asked about indications for HF (which are straightforward) and complications.

Indications

- **Indications:** These include ARF accompanied by a metabolic acidosis, hyperkalaemia or uraemia. Isolated uraemia is a problem usually only when it is high enough to cause clinical symptoms such as vomiting, diarrhoea, pruritus or mental disturbance. HF is also used to manage volume overload and to clear some drugs and poisons from the circulation. In theory HF can be used in the

management of severe hypothermia, but in practice the flow rates are too small to make it an effective treatment.

Complications

- **Fluid mismanagement:** Very large volumes are both filtered and infused and the scope for error is high.
- **Coagulation problems:** Blood clots in extracorporeal circulations and produces diffuse thrombi on the artificial surfaces unless the system is anti-coagulated, usually with heparins or prostacyclin. Undercoagulation leads to problems with the circuit and not the patient (the 'kidney' fails), whereas an iatrogenic coagulopathy is potentially much more hazardous.
- **Air embolus:** This is always a potential danger with the use of relatively complex extracorporeal circuits.
- **Heat loss.**
- **Disconnection:** HF requires wide-bore dedicated arterial and venous lines.
- **Filter failure.**

Blood groups

Commentary

The importance of the topic of blood transfusion to anaesthetists is self-evident, and so examiners may well assume that your knowledge of the clinical aspects is secure. The viva, therefore, may concentrate initially on the science of the ABO blood group typing system, but because after the relatively straightforward concepts of the major types the subject becomes too complex to explore in a short viva, the questioning is likely to revert to the clinical implications.

The viva

You will be asked to describe the major blood groups.

- The red cell membrane contains various blood group antigens or agglutinogens. These are complex oligosaccharides which vary in their terminal sugar molecule (*N*-acetylgalactosamine in Group A and galactose in Group B).
- The most important of many variants are the A and the B antigens. These are inherited as Mendelian dominants which allows separation of individuals into one of four main types: Group A which have the A antigen, B which have the B antigen, AB which carry both antigens and Group O which carry neither. Red blood cells of all types also carry an H antigen which also differ in their terminal sugar residues.
- Antibodies against these red cell agglutinogens are known as red cell agglutinins, and these are formed early in life. Individuals do not necessarily require exposure to blood: antigens that are related to A and B are found in gut bacteria and even in some foods, and so neonates develop early antibody responses. Type A individuals develop anti-B antibodies, Type B develop anti-A antibodies, Type AB develop neither, while Type O develop both. Type O blood therefore, will agglutinate (clump) blood of all other types, while Group AB will agglutinate none. Thus AB is the universal recipient and O the universal donor. Around 45% of individuals in the UK have the blood group O, 40% group A, 10% group B and 5% group AB.
- **Other agglutinogens:** There are a large number of systems of which the rhesus is the most significant. (Others among many include the Lutheran, the Kidd and the Kell systems.) The rhesus factor comprises C, D and E antigens of which D is the most important, being by far the most antigenic. Eighty-five percent of the caucasian population and 99% of the non-Caucasian population are D-rhesus positive. In contrast to ABO antigens individuals do require exposure to the D antigen in blood in order to develop antibodies; this happens either by transfusion, or by exposure of the maternal circulation to small amounts of fetal D-positive blood. This is significant for subsequent pregnancies should a mother be rhesus-negative but carrying a rhesus-positive fetus. Maternal antibodies will cross the placenta to cause haemolytic disease of the newborn. Hence the importance of administering rhesus immune globulin in the postpartum period to prevent the mother forming active antibodies.

Direction the viva may take

You may be asked about transfusion reactions and other complications of transfusion.

- **Acute haemolytic reactions:** These are rare and occur usually as a result of human error. They are most commonly due to ABO incompatibility. The donor cells are destroyed by antibodies in the recipient plasma, with haemolysis, leading in severe reactions to intravascular fibrin deposition, disseminated intravascular coagulation (DIC) and renal failure. After stopping the transfusion, management is mainly supportive.

- **Other complications:** These are numerous and you are unlikely to be asked to spend very long on any of them. They include delayed reactions as above, non-specific reactions to infused pyrogens, transmission of infectious disease (hepatitis, human immunodeficiency virus (HIV), cytomegalovirus, Creutzfeld–Jacob disease and malaria), circulatory overload, acute hypothermia, hyperkalaemia, citrate intoxication associated with a later metabolic alkalosis, immunosuppression (which was used deliberately in early renal transplantation to reduce rejection rates, but which is now associated with increased metastasis rates following surgery for colonic cancer) and acute lung injury (ALI) leading to acute respiratory distress syndrome (ARDS).

Further direction the viva could take

You may be asked how you can reduce the requirement for banked (stored) blood.

There are a number of techniques which can minimise exposure to allogenic blood with its attendant risks (adverse reactions, infection and immunomodulation).

- **Autologous donation:** Patients donate 450 ml (1 unit) of blood up to twice a week, but more commonly weekly, up to 72 h before surgery. Iron supplementation is routine. The production of endogenous erythropoietin is enhanced during twice weekly donation, but is more modest if donation is less frequent. The procedure is useful for patients undergoing surgery with anticipated major blood loss. Units stored should be matched against likely usage, but wastage is high (around 50%).
- **Acute normovolaemic haemodilution:** Whole blood is removed from the patient and replaced with crystalloid and/or colloid solutions prior to the anticipated blood loss. Blood is then reinfused as appropriate, but in the reverse order of collection, because the first unit collected has the highest haematocrit and concentrations of platelets and clotting factors. The technique is conceptually attractive but mathematical modelling can demonstrate that the actual volumes of saved blood are relatively small (amounting to the equivalent of one unit of packed cells). For example, it has been calculated that a patient from whom three units totalling 1350 ml are withdrawn prior to a blood loss of 2600 ml will require only about 215 ml less allogenic blood than otherwise would be the case.
- **Peri-operative autologous blood recovery:** Intra-operative cell-saver devices can be very efficient, saving the equivalent of up to 10 units hourly should massive transfusion be necessary. Its cost effectiveness is disputed, and some prospective trials in major vascular patients have demonstrated that it does not reduce the requirement to give allogenic blood. It can, however, provide blood rapidly, which may be one of its major benefits. Post-operative reinfusion of blood collected from drains is used after orthopaedic surgery, but the blood so collected has a low haematocrit of around 0.20, is partly haemolysed and may be rich in cytokines. Its benefits are debated.

Cytochrome P450

Commentary

This is the kind of question that risks giving the College and its examinations a bad name. It is not as though cytochrome P450 is a single well-defined entity: on the contrary it comprises numerous key forms, with yet further genetic variations. Nor is it a topic of searing anaesthetic relevance: certainly it is of academic interest, but ignorance of most of its functions is actually no impediment to the delivery of safe and sophisticated anaesthesia. But as a subject that is perceived both as intellectual and topical it is no surprise to find it appearing in the Final FRCA. If the question is asked of you just reproduce confidently some of what appears below, and you will almost certainly know more than your examiners. If, however, you should happen to be discussing this with an examiner whose special interest this happens to be, then do not worry. His or her specialist knowledge will inhibit their line of questioning because they will sense their loss of objectivity regarding this particular subject.

The viva

There is no obvious starting point for this question, and so the viva is likely to start with an invitation to talk about cytochrome P450.

- **Description:** Cytochrome, or more accurately, cytochromes P450, comprise a superfamily of enzymes which are concerned with the metabolism of a wide range of both endogenous and exogenous compounds. They contain a pigment (hence cyto*chrome*) and are characterised by maximal absorption, in the presence of carbon monoxide, at 450 nm. This cytochrome–carbon monoxide compound is pink, which explains the 'P' in the nomenclature.
- **Biochemistry:** They are haem–thiolate proteins, and they act as mixed function mono-oxygenases, which mediate Phase 1 oxidative metabolism of numerous compounds.
- **Numbers:** There are at least 74 isoforms, each of which derives from a different gene. This manifests as a wide variation in the susceptibility of different individuals to particular drugs and toxins.
- **Sites:** These ubiquitous microsomal enzymes are sited on the smooth endoplasmic reticulum of cells, but are found in highest concentrations in the liver and small bowel. Individual hepatocytes may contain several forms of the enzyme.
- **Nomenclature:** The enzymes are divided into main families according to similarities in their amino acid sequences (possessing 40% or more structural homology) and are named CYP1, CYP2 and so on. It is families CYP1, CYP2 and CYP3 which appear to be responsible for most drug biotransformation. These groups are then further classified into subfamilies (possessing 55% or more homology), which are described using capital letters following the family designation. Individual enzymes of the subgroup are designated using arabic numerals, for example CYP3A4 (CYP3 (family), A (subfamily), 4 (individual enzyme)).
- **Important subtypes:** The most abundant cytochrome enzymes are members of the CYP3A subfamily, which comprise 70% of the cytochrome enzymes in the gastro-intestinal system, and 30% of those in the liver. The enzyme that metabolises the greatest proportion of drugs in the liver is cytochrome CYP3A4. This enzyme and CYP3A3 are the major isoforms of the small gut, while the variant that is found in the stomach is CYP3A5. (This is absent in 70% of Caucasians but its functions are replicated in such cases by CYP3A4.)

Direction the viva may take

You may be asked about factors which influence the function of the cytochrome enzymes, particularly in respect of drug metabolism, because this is the area of potential relevance to anaesthetic practice.

- **Induction of enzymes:** As plasma concentrations of drugs increase, so enzyme synthesis may increase to match it, and numerous substances induce cytochrome P450. These include barbiturates, anticonvulsants, alcohol, glucocorticoids and some antibiotics. Tobacco is also a potent inducer of cytochrome P450, and this is of anaesthetic interest because smoking appears to confer a protective effect against post-operative nausea and vomiting (PONV). This may be due to the more rapid metabolism and elimination of volatile agents which are associated with PONV, although the hypothesis remains speculative.
- **Inhibition of enzyme action:** Competitive inhibition occurs when two (or more) drugs are metabolised by the same enzyme. The process can be complex, with reversible and irreversible binding to the haem-binding site, either by drugs or by their metabolites. Such interactions may have serious consequences. An example is the cardiac arrhythmias associated with the antihistamine terfenadine. The drug can lead to a prolonged Q–T interval with the development of *torsade de pointes* (a malignant form of ventricular tachycardia characterised by a changing QRS-axis). Inhibition of CYP3A4 by substances as diverse as the antiobiotic erythromycin or by the bioflavinoids in grapefruit juice may precipitate arrhythmias by inhibiting terfenadine metabolism. Terfenadine itself is a prodrug which is cardiotoxic, whereas its active metabolite is not. Drugs such as metronidazole and amiodarone inhibit CYP2C9, which is the enzyme involved in the metabolism of warfarin. Both can produce significant prolongations of prothrombin time. The analogous effects of cimetidine, which is a non-specific inhibitor of cytochrome P450, are relatively weak in comparison.

Pulmonary artery catheterisation

Commentary

Pulmonary artery (PA) flotation catheters remain widely used in intensive therapy. This is despite a large American study that suggested that not only was the annual cost of 2 billion dollars in the USA alone not justified, but that their use was associated with increased mortality. The papers and accompanying editorials polarised opinion and provoked much discussion, and in the UK the issue remains to be resolved pending the result of the PAC-Man multicentre study. In the meantime, PA catheters are still inserted by clinicians who continue to believe that they provide haemodynamic information of clinical value. The examiners will expect you to understand why, although because the question is predictable and because it usually follows a predictable course, they tend to be somewhat bored with it. You should therefore be able to cover the basic points without much difficulty.

The viva

You will be asked what a PA catheter can measure and what is the clinical relevance of the information.

- **Direct measurements:** PA catheters can measure directly a number of variables. These include PA systolic, diastolic and mean pressures; and pulmonary artery occlusion (or wedge) pressure (PAOP), which usually is a reliable enough indication of left atrial pressure (LAP) and left ventricular end-diastolic pressure (LVEDP). PA catheters also measure cardiac output (CO) (stroke volume $\times$ heart rate), temperature, mixed venous blood oxygen saturation and related indices.
- **Derived values:** A large number of derived variables can be determined, but there are a smaller number that are of immediate clinical use. These include cardiac index (CI), which is derived from CO/body surface area, and systemic vascular resistance (SVR) which is given by [MAP $-$ CVP/CO] $\times$ 80 (MAP: mean arterial pressure; CVP: central venous pressure). Pulmonary vascular resistance (PVR) is similarly obtained from [MPAP $-$ PAOP/CO] $\times$ 80 (MPAP: mean pulmonary artery pressure). Mixed venous oxygen content can also be derived, as may oxygen delivery and oxygen consumption. Oxygen delivery is obtained by the product of arterial oxygen content and CO. Oxygen consumption is obtained by the product of the CI and the difference between arterial oxygen content and mixed venous oxygen content.

Clinical situations in which these values are useful

- **Pulmonary oedema:** Cardiogenic pulmonary oedema is characterised by a high PAOP indicative of left ventricular dysfunction. Non-cardiogenic pulmonary oedema, which is associated typically, but not exclusively with ALI and ARDS, will occur in the presence of a low or normal PAOP.
- **Systemic inflammatory response syndrome (SIRS) including sepsis:** Sepsis leads initially to circulatory collapse with peripheral vasodilatation and fluid losses through deranged capillary membranes. The PA catheter may confirm that there is an increased CI with a hyperdynamic circulation, a fall in SVR and a decrease in PAOP suggestive of effective hypovolaemia. The hyperdynamic circulation delivers adequate oxygen to tissues, but it is utilised poorly. Oxygen consumption is low, and the mixed venous oxygen content is high, indicative of decreased extraction. Later in the process peripheral circulatory failure may supervene, with a rise in SVR and a decrease in oxygen delivery.
- **Haemorrhage and hypovolaemia:** In this condition the depleted intravascular volume decreases CI, left ventricular end-diastolic volume and pressure (LVEDV and LVEDP, respectively). The PAOP will fall, the SVR will rise as a compensatory mechanism and oxygen delivery will be low.

- **Neurogenic shock following spinal injury:** The picture resembles that of hypovolaemia, with vasodilatation with decreased SVR, decreased ventricular filling and PAOP, and reduced CI.
- The PA catheter, therefore, can give information that provides both an aid to diagnosis as well as a guide to rational management. Typical examples might include the use of vasoactive infusions in the treatment of sepsis, inotropes and vasodilators in cardiogenic shock, and volume replacement in hypovolaemia.

Direction the viva may take

You may be asked about complications.

- **Generic:** Many of the complications are associated with central venous catheterisation, including pneumothorax and haemothorax, intrapleural placement, air embolism, cardiac arrhythmias, arterial puncture or inadvertent cannulation, and infection.
- **Specific:** Complications specific to PA catheters include damage to the myocardium or right-sided cardiac valves, PA rupture and pulmonary infarction. Catheters may knot, and if they are positioned inaccurately may give information that is misinterpreted.

Further direction the viva could take

Some final miscellaneous questions might include the following:

- The measurement of CO. (See *Measurement of organ blood flow*, page 267.)
- **Pitfalls in interpretation:** In mitral stenosis PAOP may exceed LVEDP. The same is true in mitral regurgitation, although in addition giant 'v'-waves may interfere with the displayed waveform. In pre-existing pulmonary hypertension from any cause, PAOP may also exceed LVEDP. The use of positive end-expiratory pressure ventilation can also increase PAOP above LVEDP, as will any other factors which increase intra-thoracic pressure. For this reason the PAOP should be measured at end-expiration when the intra-thoracic pressure influences (positive end-respiratory pressure, PEEP excepted) are minimal. When there is aortic incompetence or a stiff left ventricle that has low compliance the LVEDP may exceed PAOP.
- The PAC-Man (effectiveness of PA catheterisation in patient management in intensive care) study is a multicentre prospective study which has been under way since 2000 and is due to be completed within 4½ years. Patients are randomised to one of two limbs: to PA catheterisation or not, and the end-point is mortality.

Mitral stenosis

Commentary

Valvular disease is of keen clinical interest because of the risk that anaesthesia and surgery will cause peri-operative decompensation. Mitral stenosis is a popular examination topic because it allows discussion of physiology and pharmacology applied to a fixed cardiac output state.

The viva

You will be asked about the aetiology and pathophysiology of the condition.

- Mitral stenosis is almost always due to untreated rheumatic fever, usually following streptococcal infection. It is increasingly rare.

Pathophysiology

- The valvular narrowing is slowly progressive. The determination of the pressure gradient across the valve (left atrium : left ventricle) is less reliable than estimations of valvular area, which is the key factor which determines flow. The cross-sectional area of a normal mitral valve area is 4–6 cm^2 and stenosis may be graded as severe (<1 cm^2), moderate (1.1–1.5 cm^2) and mild (1.6–2.5 cm^2). Between 2.5 and 4.0 cm^2 the narrowing is not clinically significant.
- As narrowing becomes more severe there is atrial dilatation and hypertrophy. With this deterioration the contribution of atrial contraction to left ventricular filling becomes progressively more important, increasing from 15% up to 40%. The development of a compensatory bradycardia allows sufficient time for diastolic flow across the stenosis. These factors explain why the onset of atrial fibrillation with the loss of this crucial contribution to left ventricular filling may be so calamitous. In time the increased left atrial pressure (LAP) is reflected in pulmonary hypertension and right ventricular overload.
- As pulmonary venous pressure increases patients will begin to experience symptoms such as dyspnoea on exertion, orthopnoea and paroxysmal nocturnal dyspnoea. Impaired exercise tolerance is a good guide to disease severity. Patients may deteriorate suddenly if there is an increased demand for CO, for example due to pregnancy, or if atrial fibrillation supervenes. Pulmonary sequelae of mitral stenosis may encompass reduced lung compliance and a rise in airway resistance both of which increase the work of breathing. Gas exchange worsens with a widening of the alveolar–arterial oxygen difference ($A-a\ DO_2$).

Direction the viva may take

You will probably be asked about the anaesthetic implications of this disease.

- Mitral stenosis is a progressive condition that leads to a relatively fixed output state. The anaesthetic techniques that are used must minimise interference with various compensatory mechanisms, because attempts to manipulate the CO by the use of fluids or vasoactive drugs may prove fruitless.
- **Maintenance of heart rate:** A bradycardia may allow an increased stroke volume but the CO may drop unacceptably as a result. Tachycardia may diminish stroke volume to the point that CO is even more impaired.
- **Maintenance of cardiac rhythm:** Any sudden onset of atrial fibrillation must be treated aggressively, with direct current (DC) cardioversion if necessary, otherwise pulmonary oedema may supervene. If atrial fibrillation is already present the ventricular response rate must be controlled.
- **Maintenance of circulating volume:** Normovolaemia is important. If LAP drops because of reduced venous return then CO will fall as flow across the stenotic valve decreases. Patients equally may be very sensitive to any increase in venous return, because in cases of severe stenosis CO cannot change, and pulmonary oedema may supervene.

- **Maintenance of myocardial contractility:** As with all valvular lesions effective cardiac contractility is an important component of the compensatory mechanisms, and undue depression must be avoided.
- **Maintenance of SVR:** This is necessary to ensure adequate coronary perfusion during diastole.
- **PVR:** It is important to avoid hypercapnia, hypoxia, acidosis, and in severe cases, the use of nitrous oxide, all of which will increase PVR.
- **Infective bacterial endocarditis (IBE):** This potentially affects any abnormal valve and antibiotic prophylaxis should be given. Guidelines change and it is unlikely that you will be asked to discuss this in great detail, but you should have some idea of the current regimens. Typically amoxycillin is given prior to surgery (either 3 g orally 4 h before, or 1 g i.v. at induction of anaesthesia), followed by i.v. or oral amoxycillin post-operatively. Patients who are allergic to penicillin can be given various drugs including vancomycin, gentamicin and teicoplanin. The simplest regimen to remember is probably clindamycin, 300 mg by slow i.v. infusion at induction, followed by 150 mg i.v. or orally at 6 h post-operatively.
- **Anti-coagulation:** Patients may also be on oral anti-coagulants, which may need to be changed to parenteral heparin during the peri-operative period, depending on the surgery that is undertaken.

Further direction the viva could take

You could be asked to compare mitral with tricuspid stenosis.

- Isolated tricuspid stenosis is very rare, and the condition usually exists in combination with mitral stenosis. The problems are analogous: there is a diastolic pressure gradient across the valve between right atrium and right ventricle, and the compensatory mechanisms are similar. An increase in right atrial pressure (RAP) maintains flow across the stenotic valve, and this leads to right atrial dilatation and hypertrophy. (Clinical signs include a raised jugular venous pressure, hepatomegaly and peripheral oedema.) Right ventricular contractility is usually well maintained. As with mitral stenosis a slow heart rate allows perfusion across the valve during diastole, and the onset of atrial fibrillation may precipitate right heart failure.

Mitral incompetence

Commentary

As with other diseases of cardiac valves, mitral regurgitation is of clinical interest because of the risks of peri-operative decompensation. It is more common than mitral stenosis, and it too is a condition that lends itself to discussion of how anaesthesia may interfere with the mechanisms of cardiac compensation.

The viva

The viva is likely to follow a similar pattern as the question on mitral stenosis, in that you will be asked about the aetiology and pathophysiology of the condition.

- Mitral incompetence may also be rheumatic in origin in around 50% of cases. Other causes include disruption of the chordae tendinae and papillary muscle-supporting structures, which may occur following myocardial infarction and dilatation of the valve ring itself.

Pathophysiology

- During systolic left ventricular contraction there is regurgitant flow back into the left atrium, in addition to forward flow through the aorta. This can be quantified by measuring the regurgitant fraction: up to 0.3 is classified as mild, whereas a fraction of 0.6 or greater is severe.
- This regurgitant flow leads to volume overload of left atrium and left ventricle. Although LVEDV may increase fourfold, the function of the ventricle is usually well preserved because the larger volume of blood can be unloaded both through the aorta and the mitral valve, and so systolic ventricular wall tension is not high. In time, however, this process does lead to an irreversible decline in contractile function.
- The left atrium dilates, and atrial fibrillation may supervene, but this does not cause the critical decompensation in cardiac function that may be seen in mitral stenosis. Mitral incompetence does not in general impose large costs in terms of myocardial oxygen demand (whose prime determinants are ventricular wall tension, contractility and heart rate). This allows some compensation by a relatively rapid heart rate, which reduces the time for further ventricular overload. The prolonged filling time associated with a bradycardia increases ventricular volume, may cause further functional dilatation of the annulus and with it a rise in the regurgitant fraction.
- The left ventricle also dilates, with an increase in LVEDV and LVEDP. Forward flow of blood into the systemic circulation depends on the relative impedances of the two parallel paths, and so is enhanced by low peripheral vascular resistance.

Direction the viva may take

You will be asked first about anaesthetic considerations

- **Heart rate:** A relative tachycardia is preferable to a bradycardia by reducing left ventricular overload. Bradycardia may allow increased ventricular filling and further dilatation of the valve ring.
- **Circulating volume:** Patients may be sensitive to large rises in preload, because this will distend further the left atrium and predispose to pulmonary oedema.
- **Maintenance of myocardial contractility:** Effective cardiac contractility is an important component of the compensatory mechanisms, and so undue myocardial depression should be avoided.
- **SVR:** The forward flow of blood is dependent on low peripheral resistance. Vasoconstrictors, therefore, should be used with great caution.

- **IBE:** Mitral incompetence is more likely to be associated with IBE than any other of the valvular lesions, and antiobiotic prophylaxis is essential. See *Mitral stenosis*, page 303.

Further direction the viva could take

It is just possible that you could be asked to compare mitral with tricuspid incompetence, and so a brief account is included here.

- Rheumatic fever is still an important cause, although a more modern aetiology is bacterial endocarditis associated with i.v. drug abuse.
- As with mitral incompetence, tricuspid regurgitation leads to atrial and ventricular volume overload. The systemic venous system, however, is compliant, and so RAP does not increase to the same extent as does LAP. Compensation is via adequate ventricular filling, which remains effective as long as the right ventricle functions well. Decompensation with loss of forward flow through the pulmonary circulation will become manifest with the progressive loss of right ventricular compliance.

You may be asked some miscellaneous points.

- **Mitral valve prolapse:** This may be associated with papillary muscle rupture, but it may also be relatively benign. In many case patients remain symptom free.
- **PA catheter trace:** Mitral regurgitation may cause large 'v'-waves in the waveform, which are ascribed to the regurgitant flow.
- **Clinical signs:** Patients may be in atrial fibrillation, but often remain symptom free until heart failure supervenes.

Aortic stenosis

Commentary

Aortic stenosis may be caused by rheumatic heart disease, but it also may occur as a consequence of degeneration and calcification in a congenitally abnormal valve. As with other cardiac valvular conditions, anaesthetic interest centres on the need to avoid peri-operative decompensation. Like mitral stenosis, it is a popular examination topic because it allows discussion of physiology and pharmacology applied to a fixed cardiac output state.

The viva

You will be asked about the aetiology and pathophysiology of the condition.

- Rheumatic heart disease, degeneration and calcification of the valve, either as a result of ageing, or in a congenitally abnormal (usually bicuspid) valve. Very rare causes include methysergide-induced valvular fibrosis.

Pathophysiology

- Determination of the pressure gradient across the valve (left ventricle : ascending aorta) is less reliable than estimations of valvular area, which is the key factor which determines flow. The cross-sectional area of a normal aortic valve is 2.5–3.5 cm^2. An area less than 1.0 cm^2 is an indication for immediate surgical valve replacement. At areas of less than 0.7 cm^2 any demand for increased CO, such as occurs during advancing pregnancy or during exercise, is likely to be associated with angina pectoris, syncope and sudden death. Clinical signs of the disease include narrowed pulse pressure (a value of less than 30 mmHg suggests severe disease), and a coarse systolic murmur in the aortic area. Systolic blood pressure (SBP) may be lower than expected because of the reduced CO (blood pressure = CO × SVR). The gradient may be misleadingly low in a patient whose failing left ventricle is unable to generate high systolic intraventricular pressures.
- As narrowing progresses there is increased pressure loading on the left ventricle, which undergoes concentric hypertrophy. The hypertrophic left ventricle is less compliant, thus myocardial oxygen demand increases while supply falls. Systole through the stenosed valve is prolonged and so diastolic time during the cardiac cycle is proportionately reduced. The high intraventricular pressures almost completely abolish systolic coronary flow. Diastolic sub-endocardial perfusion also decreases unless perfusion pressures remain high.
- The decrease in ventricular compliance, and the loss of ventricular filling by passive elastic recoil means that the atrial contribution to filling becomes more important. It may in some cases be responsible for up to 50% of LVEDV. Atrial contraction makes a significant contribution to left ventricular filling, which must be maintained, because atrial fibrillation may lead to decompensation.

Direction the viva may take

You will probably be asked about the anaesthetic implications of this disease.

- Aortic stenosis leads to a fixed output state, which is maintained by compensatory mechanisms that may be disrupted by anaesthesia. Decompensated mitral stenosis manifests as heart failure: decompensated aortic stenosis may be fatal. It is particularly important to maintain coronary perfusion during diastole.
- **Maintenance of myocardial contractility:** Effective contraction is important for maintenance of CO in aortic stenosis (as in all valvular lesions), and undue myocardial depression must be avoided. Increasing myocardial drive, however, will increase myocardial work and oxygen demand, and may precipitate sub-endocardial ischaemia.

- **Maintenance of SVR and diastolic blood pressure (DBP):** If SVR falls, then coronary diastolic perfusion may fail with disastrous consequences. Vasodilatation must be avoided and preload maintained to allow flow across the stenotic valve. This has obvious implications for the use of the many anaesthetic agents which decrease SVR, including local anaesthetics used in subarachnoid and extradural block. Cardiopulmonary resuscitation in the presence of aortic stenosis and left ventricular hypertrophy is rarely successful.
- **Maintenance of heart rate and rhythm:** Bradycardia will decrease CO, but tachycardia is even more detrimental because it limits the time for diastolic coronary perfusion. Dysrhythmias, including atrial fibrillation, require urgent treatment, but myocardial depressants such as β-adrenoceptor blockers are better avoided.
- **IBE:** Prophylaxis is mandatory. See *Mitral stenosis*, page 303.
- Patients with aortic stenosis can be very difficult to manage. Severe cases presenting for non-emergency surgery should be referred to a specialist centre for consideration of aortic valve replacement. Otherwise anaesthesia should include invasive monitoring of intra-arterial and CVP, and it may be necessary to run a continuous infusion of vasopressor such as noradrenaline to ensure that SVR is maintained.

Further direction the viva could take

You will be doing well if you have exhausted the discussion above, and so you could be asked about pulmonary stenosis.

- The condition is analogous to aortic stenosis. The symptoms of fatigue, syncope, dyspnoea on exertion and angina pectoris due to right ventricular ischaemia, are similar, as are the compensatory mechanisms. An initial dilatation of the right ventricle is followed by concentric hypertrophy. A slow heart rate allows increased ejection time. The rise in right ventricular end-diastolic volume and pressure (RVEDV and RVEDP, respectively) leads to a decrease in ventricular compliance. In cases of severe stenosis patients may be cyanosed with a low fixed CO. The foramen ovale may open due to pressure reversal with right to left inter-atrial shunting.

Aortic incompetence

Commentary

As with the other valvular lesions, aortic incompetence is a popular examination topic because it allows a discussion from first principles of applied pathophysiology in which you will be expected to demonstrate knowledge of cardiovascular compensatory mechanisms.

The viva

You will be asked about the aetiology and pathophysiology of the condition.

- Aortic incompetence has numerous causes, most of them rare. There are infectious causes (bacterial endocarditis, syphilis, rheumatic fever), congenital abnormalities (biscuspid valve), degenerative and connective tissue disorders (Marfan's syndrome, Ehlers–Danlos) and inflammatory conditions (rheumatoid arthritis, systemic lupus erythematosus).

Pathophysiology

- The condition usually is chronic, although acute aortic regurgitation can occur with dissection, or following destruction of the valve by bacterial endocarditis.
- The regurgitation during diastole of part of the left ventricular stroke volume results in a decrease in forward blood flow through the aorta. This results in continuous volume overload of the left ventricle, which initially dilates to accommodate this extra volume. On the ascending part of the Frank–Starling pressure–volume curve the increase in myofibril length improves the efficiency of contraction. With increasing dilatation the heart moves onto the descending part of the curve, at which point acute cardiac failure may supervene.
- Compensatory mechanisms act to reduce the volume of regurgitant blood. As with mitral incompetence a regurgitant fraction of 0.6 or greater denotes severe disease. There is an increase in left ventricular size with eccentric hypertrophy. There is also an increase in ventricular compliance, which allows an increase in volume at the same pressure. This means that end-diastolic pressure is reduced, and with it ventricular wall tension, which is a crucial determinant of myocardial oxygen demand. The left ventricular ejection fraction is maintained, since the stroke volume and LVEDV increase together.
- A rapid heart rate is advantageous, because it reduces the time for diastolic filling. LVEDV is decreased and so there is less ventricular overdistension.
- Lower SVR offloads the myocardium and ensures forward flow.

Direction the viva may take

You will probably be asked about the anaesthetic implications of this condition.

- **Preload:** Normovolaemia should be maintained to ensure that the dilated ventricle remains well filled.
- **SVR:** SVR should be kept low so as not to increase the impedance to outflow with an increase in the regurgitant fraction.
- **Heart rate:** Bradycardia will increase the time for ventricular overdistension. A relative tachycardia will reduce the regurgitant fraction.
- **Myocardial contractility:** Effective contraction is important for maintenance of CO in aortic incompetence (as in all valvular lesions), and undue myocardial depression must be avoided.
- **IBE:** Prophylaxis is mandatory. See *Mitral stenosis*, page 303.

Further direction the viva could take

You may be asked how this differs from pulmonary incompetence.

- Pulmonary incompetence may follow balloon valvuloplasty, or less commonly following bacterial endocarditis in drug abusers.
- The right ventricle usually continues to function well by compensatory mechanisms which include an increase in compliance, a rise in heart rate and a decrease in PVR.
- The compliant right ventricle has a steep volume–pressure curve and it is able to function effectively in the face of increased chamber volumes. Forward flow into the pulmonary circulation depends on a low PVR and low left-sided filling pressures. The ejection fraction, however, is not as well maintained in pulmonary incompetence as it is in aortic regurgitation.

Electroconvulsive therapy

Commentary

There is probably no shorter anaesthetic than that which is given for electroconvulsive therapy (ECT). However, this benefit is offset by the fact that the procedure is often undertaken in isolated sites and in patients who may have relevant co-morbidity. The physiological effects may be transient, but they can be extreme, and are effects of which you should be aware. The ECT list is also one of those to which your rota organiser will gratefully allocate you as soon as you obtain the FRCA. You will probably feel happier if you do know something about it.

The viva

After an introductory question about the nature of ECT and its indications (which are restricted) you may be asked briefly to describe the characteristics of the stimulation that is used.

- ECT, in which an electrical shock is used to induce a grand mal convulsion, is an empirical, and somewhat controversial treatment. Its use now is confined mainly to patients with refractory psychiatric disorders, particularly psychotic depression but also catatonia, mania and schizophrenia.
- A shock of about 850 mA is delivered across the cerebral hemispheres by a stimulator that delivers a pulsatile square wave discharge. Pulses of 1.25 ms at 26 Hz are delivered for up to 5 s.

Direction the viva may take

The much more relevant and interesting aspects for anaesthetists are the physiological changes that accompany ECT, and the viva is more likely to concentrate on these. If you are struggling to retrieve this information, then just try to remember instead the effects of a grand mal fit.

- **Grand mal convulsion:** A short latent phase is followed by a tonic phase of general contracture of skeletal muscle which lasts around 15 s. This is succeeded by a clonic phase which lasts 30–60 s. The central electrical seizure (as demonstrated by EEG) outlasts the peripheral myoclonus.
- **Autonomic effects – parasympathetic:** The discharge is short lived, but is associated with typical parasympathetic effects. At their worst these include bradycardia and vagal inhibition leading to asystole.
- **Autonomic effects – sympathetic:** As the clonic phase of the seizure begins there is a mass sympathetic response which peaks at around 2 min. Plasma adrenaline and noradrenaline levels at 1 min exceed baseline by 15 and 3 times, respectively. Predictable effects include tachydysrhythmias and hypertension, with increased tissue and in particular myocardial and cerebral oxygen consumption.
- **Cerebral effects:** The cortical discharge is accompanied by a large increase in cerebral blood flow, which may increase over fivefold, and cerebral oxygen consumption (cerebral metabolic rate of oxygen, $CMRO_2$) which may increase by 4 times. Intracranial pressure rises accordingly.
- **Musculoskeletal effects:** The grand mal convulsion is accompanied by violent contractions of all skeletal muscle, which have been associated with vertebral fractures and other skeletal damage. The Bolam principle, which has underpinned the law relating to medical negligence since 1957, followed from a case in which a patient suffered a dislocated hip during an unmodified convulsion associated with ECT.

Further direction the viva could take

You may be asked about complications of the procedure and finally about the anaesthetic implications.

- There are predictable complications associated with the convulsion, which include cardiac dysrhythmias and hypertension. The risk of skeletal and tissue damage, for example to the tongue, is minimised by 'modifying' the convulsion with a small dose of suxamethonium. This attenuates the force of the muscle contraction on the skeletal system.
- ECT should not be used in patients who have suffered a recent cerebrovascular or myocardial event (within 3 months), who have a CNS mass lesion or have raised intracranial pressure. It probably should be avoided in patients with osteoporotic bone disease because of the risk of fractures, and should be used with caution in patients with glaucoma and severe ischaemic heart disease. A hiatus hernia does not contraindicate ECT but does mandate intubation following a rapid sequence induction.
- Anaesthetic implications relate to the physiological effects outlined above, together with the problems of anaesthetising often elderly patients in remote locations.

Postpartum haemorrhage

Commentary

Deaths due to obstetric haemorrhage continue to feature in successive reports of the triennial Confidential Enquiry into Maternal Deaths in the UK. The absolute numbers are small, yet the preventable death of any young mother has an importance that is belied by the simple epidemiological statistics. This is a more clinically orientated question than many that appear in the clinical science viva, but it does aim to test that your knowledge of factors that predispose to postpartum haemorrhage (PPH) will allow you to manage it aggressively when it occurs.

The viva

You will be asked about the causes of PPH and its predisposing factors.

- **Incidence:** This depends on the definition of PPH. By convention PPH is defined as a blood loss of 500 ml within 24 h of birth, but about 20% of women will lose that much and so this exaggerates the number who are at risk of significant haemodynamic disturbance. In the UK this has been estimated around 1400 cases a year.
- PPH can have uterine or extra-uterine causes.
- **Uterine causes:** The most important immediate cause is uterine atony. The placenta receives almost 20% of the CO at term, or around 600–700 ml min^{-1}, which explains why haemorrhage may be so catastrophic. In the UK, uterine atony accounts for around one-third of all deaths associated with maternal haemorrhage. Other causes include uterine disruption or inversion, complications of operative or instrumental delivery and retained products of conception. Retained placenta itself, although not invariably associated with bleeding, complicates around 2% of all deliveries. Abnormal placentation (placenta accreta, increta and percreta) occurs in 1 in 3000 deliveries.
- **Non-uterine causes:** The main causes are genital tract trauma and disorders of coagulation.
- **Risk factors**
  - Uterine atony has a strong association with augmentation of labour. It may also follow uterine overdistension by multiple births, by polyhydramnios and by delivery of babies weighing greater than 4 kg. It is associated with protracted labour, with the use of tocolytic drugs and also with maternal hypotension. The relative ischaemia that may accompany uterine hypoperfusion or hypoxia will impair the ability of the uterus to contract effectively. There appears to be no link to multiparity.
  - *Abnormal placentation*: A mother with an anterior placenta praevia overlying a previous Caesarean section scar has at least a one in four chance of placenta accreta.
  - *Genital tract trauma*: This very vascular area may be damaged during delivery of a large baby, during delivery complicated by shoulder dystocia, or during a forceps delivery or vacuum extraction. Bleeding from the genital tract may be masked by normal post-delivery vaginal loss.
  - *Coagulopathy*: This may be associated with abruption of the placenta (in 10% of cases), amniotic fluid embolism (40% of cases), intra-uterine death, pregnancy-induced hypertension (particularly Haemolysis, Elevated Liver enzymes and Low Platelet, HELLP syndrome) and Gram-negative septicaemia.

Direction the viva may take

The viva is likely to concentrate on the drugs that are used to treat uterine atony, as this is the most common cause.

- Drugs used to contract the uterus. See *Drugs which stimulate the uterus*, page 185.

Pre-eclampsia

Commentary

Pre-eclampsia complicates about 7% of all pregnancies in the UK, and is part of a spectrum of disease which includes HELLP syndrome, peripartum cardiomyopathy and possibly acute fatty liver of pregnancy. It is the second most common cause of maternal death after thromboembolic disease. Patients with pre-eclampsia are more likely to require anaesthetic expertise than mothers with uncomplicated pregnancies, and so you need to be aware of its important potential problems. If you have worked on a labour ward then you will have seen this condition, and your experience is likely to be more recent than many of the examiners, only a proportion of whom are obstetric anaesthetists. The viva, however, will concentrate much more on the basic science than on the practicalities of managing these sick mothers.

The viva

You will be asked about the condition and its aetiology.

- The cause of pre-eclampsia remains unknown, but a simplification of the pathophysiology is summarised below. It is an ischaemic condition that can affect every organ system.
- The normal vasodilatation of vessels in the placental bed, which normally occurs after the first trimester, does not take place: the vessels instead become constricted and may develop atherosclerosis. Simultaneously there may be evidence of endothelial abnormality and increased vascular reactivity.
- This primary endothelial damage leads to increased production of the vasoconstrictor thromboxane A_2 and decreased production of vasodilatory prostacyclin, which manifests predictably as an increase in SVR. There may also be an increase in platelet turnover, together with abnormal cytokine release that can precipitate intravascular coagulation.
- This process can result in multi-organ failure, with fibrinoid ischaemic necrosis not only in the placenta but also in cerebral, renal and hepatic vessels. Microvascular thrombin is deposited throughout all vascular beds. This in turn can initiate primary DIC.
- HELLP syndrome (described in 1982) is a variant of the parent disorder, which is characterised by **H**aemolysis, **E**levated **L**iver enzymes and **L**ow **P**latelets. There is hepatic ischaemia with periportal haemorrhage, which can proceed to frank necrosis. Micro-angiopathic haemolytic anaemia is accompanied by thrombocytopaenia. Other parts of the coagulation process may be unaffected. Liver dysfunction is characterised by elevated transaminases (aspartate aminotranferase (AST), alanine aminotranferase (ALT) and γ-GT) and renal impairment is manifest by elevated urea and creatinine, and in severe cases, haemoglobinuria secondary to haemolysis. These complications may require critical care: although delivery initiates reversal of the disease, platelets may continue to fall for up to 72 h.
- The aetiology of pre-eclampsia remains elusive. Uteroplacental inadequacy is one factor. This stimulates production of endogenous vasoconstrictors as a means of ensuring uteroplacental perfusion. The resulting hypertension is mediated via circulating vasoactive humoral compounds that have been identified in blood, placenta and amniotic fluid. The vascular damage may be mediated via circulating immune complexes. The fetus is antigenic and it is believed that these immune complexes are the result of an inadequate maternal antibody response to what in effect is a foreign allograft.

Direction the viva may take

You may be asked about the clinical aspects of the condition.

- **Clinical features of severe pre-eclampsia:** Severe pre-eclampsia is characterised by hypertension (SBP greater than 160 mmHg, DBP greater than 110 mmHg and MAP greater than 125 mmHg) and proteinuria of more than 5 g in 24 h. Patients may show renal impairment with oliguria (defined as voiding less than 500 ml in 24 h), and they may complain of headache and visual disturbances. Distension of the liver capsule may cause epigastric and hypochondrial pain. Impaired gas exchange will accompany pulmonary oedema, and clotting may be deranged, particularly by thrombocytopaenia. Hyper-reflexia and clonus may presage the grand mal convulsions associated with eclampsia. Intra-uterine growth retardation of the fetus is common.

Further direction the viva could take

You may be asked to discuss anaesthetic techniques for Caesarean section, particularly regional versus general anaesthesia.

- The choice of anaesthetic technique for Caesarean section in mothers with pre-eclampsia has been controversial. The potential airway and haemodynamic problems associated with general anaesthesia are well recognised, but the choice between spinal and epidural anaesthesia is contentious. Traditional teaching has it that well-controlled incremental epidural anaesthesia should be used so as to avoid the precipitous falls in blood pressure, which it is claimed, will accompany spinal anaesthesia. There is no evidence to support this: indeed there are at least four recent studies which dispute the presumption that severe hypotension accompanies spinal anaesthesia in mothers with pre-eclampsia. There is even a well-designed study now almost 50 years old and unethical by current standards, which examined the effect of high spinal block on pregnant, pregnant hypertensive and non-pregnant controls. Profound hypotension affected only those mothers without hypertension. This is not surprising given that humoral rather than neurogenic factors mediate hypertension in pre-eclampsia.
- **Fluids and vasopressors:** These patients have the typical intravascular depletion of a vasoconstricted hypertensive circulation. An infusion of up to 10 ml kg^{-1} is accepted practice. Hypertensive mothers are said to be much more sensitive to the effects of catecholamines, and so although there are little data, it is prudent to decrease the dose of prophylactic vasopressors such as ephedrine.
- **Other anaesthetic implications:** Coagulopathy may preclude neuraxial blockade, treatment may include anti-hypertensive agents which may influence response to epidural and subarachnoid block. Treatment may also include $MgSO_4$, which can potentiate neuromuscular-blocking drugs. There may be renal dysfunction and these mothers can easily be fluid overloaded to the point at which they develop pulmonary oedema secondary to leaky pulmonary capillaries. Laryngoscopy, tracheal intubation and extubation can provoke pressor response with extreme surges in SBP which may exceed 250 mmHg. Pre-eclampsia is associated with laryngeal and upper airway oedema.

The complex regional pain syndrome

Commentary

Complex regional pain syndrome (CRPS) Types I and II are important examples of neuropathic pain, which may affect a wide range of age groups. The condition is seen almost exclusively in the chronic pain management clinics and you may well have little direct experience of its main features and management. Neuropathic pain, however, complicates many disease states, is severe and difficult to treat, and remains incompletely understood. For this reason it continues to appear as a popular examination topic.

The viva

You will be asked to define the condition.

- **CRPS Type I and II** are the names given to what formerly were known, respectively, as reflex sympathetic dystrophy and causalgia. In some, but not every case, sympathetically maintained pain may be a prominent feature.
- **CRPS Type I** (formerly known as reflex sympathetic dystrophy, or Sudek's atrophy) is associated with injury to tissue: bones, joints and connective tissue, but not necessarily to nerves. The insult may be relatively trivial, and is most commonly precipitated by an orthopaedic injury to a distal extremity such as the lower leg or wrist.
- **CRPS Type II** (formerly known as causalgia) by contrast, is characterised by significant nerve injury without transection. It is more commonly associated with proximal nerves in the upper leg and upper limb. Most frequently affected are the sciatic, tibial, median and ulnar nerves.
- The pathophysiology of the disorders remains unclear. There is a chronic peripheral inflammatory process in addition to alterations of central afferent processing, such as 'wind-up', but the pain may also be maintained by efferent noradrenergic sympathetic activity as well as by circulating catecholamines. There is usually no communication between sympathetic efferent and afferent fibres, but following injury it is apparent that modulation of nociceptive impulses can occur not only at the site of injury, but also in distal undamaged fibres and the dorsal root ganglion itself.
- Both CRPS I and II are examples of neuropathic pain, which are distinguished only by the nature of the injury and the fact that in Type I there is more diffuse pain whereas in Type II there may be more discrete localisation to the distribution of a single nerve.

Direction the viva may take

You may be asked to describe the typical clinical features.

- Symptoms include burning and constant pain, allodynia (which is pain provoked by an innocuous stimulus), hyperpathia (which is an abnormally intense painful response to repetitive stimuli) and hyperalgesia (which is an exaggerated pain response to a noxious stimulus).
- The pain is accompanied by signs of failure of autonomic regulation in the region affected. These include swelling and local oedema, temperature changes due to vasomotor instability, associated skin colour changes and abnormal sudomotor activity.
- There may be associated weakness and trophic changes with loss of the normal healthy appearance of skin, which becomes thin and translucent, hair and nails. There is also focal atrophy of underlying tissue including muscle, and this in turn may precipitate focal osteoporosis.

Further direction the viva could take

You are likely to be asked about treatments.

- **Sympathetic block (diagnostic):** If this is effective it will both diagnose the presence of sympathetically mediated pain and initiate its treatment, although the evidence for benefit is disputed. Procedures include stellate ganglion block, lumbar sympathectomy, plexus blocks or more commonly, guanethidine blocks. Treatment regimens vary.
- **Sympathetic block (therapeutic):** A series of blocks may confer benefit which increases in duration after each one or may confer only temporary relief which finally disappears. Some patients may be considered for a permanent neurolytic procedure.
- It has been recommended that all treatment be directed towards functional restoration, so any window during which analgesia is satisfactory should be used for rehabilitation and sensory desensitisation.
- **Dorsal column stimulation:** Spinal cord stimulation has been used both in CRPS Types I and II. Low-frequency pulsed stimulation appears to be a successful method of attenuating the pain associated with CRPS Type II. Results otherwise have been equivocal, partly because the frequency and duration of stimuli have varied significantly between studies.
- If a patient shows little or no response to sympathetic blockade there are various (largely empirical) treatments that can be tried, the diversity of which suggests that none is universally successful.
    - Amitriptyline (a tricyclic antidepressant) may be helpful, as may the anticonvulsant gabapentin. The membrane-stabilising action of drugs such as phenytoin may benefit patients in whom nerve damage is present. There are no randomised-controlled clinical trials to support these treatments.
    - Simple analgesics, codeine, co-drugs and non-steroidal anti-inflammatory drugs (NSAIDs) may give some patients relief. Again there are no robust data to support their prescription.
    - Opiates are said to be effective in the early stages of the condition, and glucocorticoids may be useful in the acute inflammatory stages of the disease process.
    - There are reports that the NMDA receptor antagonist ketamine, given by low-dose subcutaneous injection, can be beneficial. Side effects associated with racemic ketamine have limited its use, but development of the S-enantiomer may allow it to be evaluated more widely.
    - Topical capsaicin, which depletes peptide neurotransmitters from primary afferents, may help some patients.

Diabetic ketoacidosis

Commentary

This is less a question about the management of this medical emergency than its pathophysiology. In order to discuss the formation of ketones you do need to know some of the pathways of intermediary metabolism. Make sure, at least, that you can explain the final steps which lead to the characteristic metabolic acidosis. The viva will, nonetheless, finish with a discussion of the medical management. In practice anaesthetists become involved only infrequently with cases of diabetic ketoacidosis because although they require intensive management they rarely require intensive care. Examiners, however, will tend to assume, almost unconsciously, that because diabetes is so common you will therefore be familiar with all its uncommon complications.

The viva

You will be asked to define diabetic ketoacidosis (DKA) and to explain its pathogenesis.

- **Definition:** DKA is a serious complication of diabetes mellitus. It can occur both in Type I insulin-dependent, and Type II non-insulin-dependent disease, although it is more common in the former. It is characterised by the biochemical triad of hyperglycaemia, metabolic acidosis and ketonaemia, and is a manifestation of an extreme disorder of carbohydrate metabolism.
- It follows a decrease in the effective levels of circulating insulin, which is accompanied by an increase in the plasma concentrations of counter-regulatory stress hormones, including glucagon, catecholamines, cortisol and growth hormone.
- **Gluconeogenesis:** In the presence of insulinopaenia, hyperglycaemia occurs as a result of gluconeogenesis, accelerated glycogenolysis and impaired glucose utilisation by peripheral tissues. Gluconeogenesis is enhanced by a large number of gluconeogenetic precursors, which include amino acids from proteolysis. Increased glycogenolysis in muscle also produces lactate (CH_3—CHOH—COOH), which is converted in the presence of lactate dehydrogenase to pyruvate (CH_3—C=O—COOH), whose concentration rises as a consequence of all these effects. Glycerol from increased lipolysis, mainly in adipose tissue, makes a small contribution, but there is otherwise no pathway of conversion of lipid to glucose. There is also an increase in the activity of a range of gluconeogenetic enzymes. (These are numerous, but as an example, catecholamines increase the activity of glycogen phosphorylase.) Of these various mechanisms which lead to hyperglycaemia, it is hepatic and renal gluconeogenesis which quantitatively are the most important.
- **Lipid and ketone metabolism:** Pyruvate is at the gateway of the citric acid cycle (Krebs cycle, tricarboxylic acid cycle) of aerobic metabolism. Two molecules of pyruvate become incorporated into each molecule of acetyl-coenzyme A (acetyl-CoA), and so the concentration of acetyl-CoA increases. At the same time insulin inhibits hormone-sensitive lipase, while counter-regulatory hormones, particularly adrenaline (epinephrine), activate it. There follows at least a doubling of the plasma concentrations of free fatty acids (FFAs), whose metabolic utilisation also takes place via acetyl-CoA. When the pathways are saturated, excess acetyl-CoA condenses to form acetoacetyl-CoA. This is then converted in the liver (via a deacylase) to free acetoacetate, which in turn is a precursor of β-hydroxybutyrate, acetoacetate and acetone. These three compounds are known as ketone bodies. β-hydroxybutyrate and acetoacetate are the anions of the strong acids aceto-acetic acid and β-hydroxybutyric acid (β-hydroxybutyrate is the more important of the two, being 3 times as abundant). The acids fully dissociate at body pH and are buffered. When the buffering capacity is exceeded, metabolic acidosis supervenes. (In health ketones are a useful energy substrate, being utilised by brain, heart and muscle.)

Direction the viva may take

You may be asked to describe the clinical features and to outline your management.

- **Presentation:** A typical patient will present with the symptoms and signs of diabetes mellitus, namely polyuria, polydipsia, pronounced dehydration and weight loss. In addition their mental state may be obtunded, and they may hyperventilate due to the metabolic acidosis (Kussmaul breathing). Their breath is characteristically ketotic, due to the exhalation of volatile acetone. Abdominal pain, diarrhoea, and nausea and vomiting may also be evident, most commonly in children. Dehydration of muscle, gastric stasis and paralytic ileus have all been advanced as possible causes for this, although the case is unconvincing.

Management

- **Precipitants:** There is always a precipitating cause of DKA. Disparate factors can be involved, some of which are amenable to treatment. Its onset can be provoked by infection, by inadequate insulin treatment, by alcohol abuse, trauma, myocardial infarction and by the use of certain drugs, among them β-receptor blockers, corticosteroids and thiazide diuretics.
- **Assessment:** Initial assessment can follow broadly the airway, breathing, circulation algorithm, with particular emphasis on the patient's mental state, and their volaemic status. Dehydration is usually severe. There are various methods of determining the fluid deficit. An orthostatic rise in heart rate without a change in blood pressure indicates an approximate 10% decrease in extracellular volume or a deficit of about 2 l. An orthostatic fall in mean blood pressure of 10–12 mmHg indicates a 15–20% deficit (3–4 l), while supine hypotension suggests dehydration greater than 20% (4 l or more).
- **Investigations:** Those specific to DKA should encompass arterial blood gases, plasma glucose, electrolytes, ketones and osmolality. Other investigations may include urinalysis, a full blood count and differential, blood and urine cultures, chest X-ray and electrocardiography (ECG). The blood lactate is usually normal.
- **Treatment aims:** The goals are to restore normovolaemia and adequate tissue perfusion, to reduce plasma glucose and osmolality towards normal, to clear ketones at a steady rate, and to correct the deranged acid–base and electrolyte status.
- **Management – fluids and insulin:** Management of DKA need not be complex and it need not be hurried: it may take 12–16 h to get the condition well under control, and the metabolic acidosis may persist for some days. Initial resuscitation should be with NaCl 0.9% (unless the corrected Na^+ is greater than 150 mmol l^{-1}), given at a rate of 1.0–1.5 l in the 1st hour. This can be reduced to 300–500 ml h^{-1}, thereafter, titrated against response. Some authorities advocate giving bolus i.v. insulin (0.15 unit kg^{-1}) followed by an infusion at a rate of 0.1 unit $kg^{-1}h^{-1}$, while others recommend omitting the bolus dose. A rate of 0.1 unit $kg^{-1}h^{-1}$ is adequate to obtain high physiological levels of insulin, and there is no evidence that an initial bolus dose has any influence on outcome.
- **Phosphate:** Phosphate, like potassium, shifts from the intracellular to the extracellular compartment, while the osmotic diuresis contributes to urinary losses. During treatment of DKA the phosphate re-enters cells to unmask the total body depletion. There are theoretical problems associated with hypophosphataemia which include muscle weakness, haemolytic anaemia, cardiac depression and depleted 2,3-diphosphoglycerate (2,3-DPG), but there is no evidence that supplemental phosphate improves outcome in these cases. The mean phosphate deficit is around 1 mmol kg^{-1}.
- **Bicarbonate:** The administration of HCO_3^- remains contentious. Bicarbonate does not cross the blood–brain barrier and so will worsen intracellular cerebral

acidosis. It can also reduce extracellular potassium and may provoke cardiac dysrhythmias. If the patient's pH is greater than 6.8 there is no evidence of any outcome benefit.

- **Complications:** Cerebral oedema can supervene if glucose concentration drops too fast. It may also follow excessive fluid therapy as well as the administration of bicarbonate.

Further direction the viva could take

You may be asked as a final point (and this will probably be an indication that you have answered the question well), whether DKA can develop in the presence of normal blood glucose concentrations.

- There is an entity described as 'euglycaemic ketoacidosis'. By 'euglycaemic', however, is meant a blood glucose of less than 16.7 $mmol l^{-1}$, and so in some patients the sugar will still be relatively high. The key factor in its pathogenesis appears to be the patient's recent oral intake. If the patient is well fed then liver glycogen stores are high and ketogenesis is suppressed. If the patient has been unable to eat, for example because of intractable vomiting, then glycogen stores are depleted and the liver is primed for ketogenesis.

Pain pathways

Commentary

The neuraxial processing of nociceptive afferent input is formidably complex, and many details both of anatomical pathways and of neurotransmitter systems have yet to be elucidated. You will not be able to take complete refuge behind that complexity, because it is obvious that pain management is a central part of anaesthetic practice. You will be expected to provide at least a simplified account of how a pain stimulus travels from the periphery to the centre, and how it may be modulated within the neuraxis. As the information does remain incomplete, however, you may be able to satisfy the examiners with a relatively limited account. You would be able to suggest, for example, that a drug might exert its effects by activating descending inhibitory noradrenergic pathways. There is little danger of your being asked to develop this much further, because you might find yourself otherwise discussing some of the 20 or more neurotransmitters that are believed to act at the dorsal horn. Examiners will not have the time, and perhaps not the inclination to do so.

The viva

You will be asked to describe the route from painful stimulus to conscious perception.

- The primary afferent nociceptors comprise free, unmyelinated nerve endings that are responsive to mechanical, thermal and chemical stimuli. Following tissue trauma the release of chemical mediators initiates nociception while activating an inflammatory response.
- Stimulation of these nociceptive afferents leads to propagation of impulses along the peripheral nerve fibres to the spinal cord by two parallel pathways. The first is via myelinated A-δ fibres, of diameter 2–5 μm, and rapidly conducting at between 12 and 30 $m\,s^{-1}$. This type of pain is fast, localised and sharp, and provokes reflex withdrawal responses. The second route to the spinal cord is via non-myelinated C-fibres, of smaller diameter (0.4–1.2 μm) and which conduct impulses more slowly at between 0.5 and 2.0 $m\,s^{-1}$. C-fibres mediate pain sensations that are diffuse and dull.
- The primary afferents terminate in the dorsal horn of the spinal cord. The cell bodies lie in the dorsal root ganglia. A-δ-fibres synapse in the laminae of Rexed I and V, while the C-fibres synapse in the substantia gelatinosa. (This comprises lamina II and a part of lamina III.) They relay with various classes of second-order neurones in the cord, some of which are 'nociceptive specific', which respond selectively to noxious stimuli and are located in the superficial laminae, others of which are 'wide dynamic range', are non-specific and are located in the deeper laminae.
- Most of the secondary afferents decussate to ascend in the lateral spinothalamic tract, although some do pass up the posterolateral part of the cord. These fibres pass through the medulla, mid-brain and pons giving off projection neurones as they do so, before terminating in the ventral posterior and medial nuclei of the thalamus.
- From the thalamus there is a specific sensory relay to areas of the contralateral cortex: to somatic sensory area I (SSI) in the post-central gyrus, to somatic sensory area II (SSII) in the wall of the Sylvian fissure separating the frontal from the temporal lobes, and in the cingulate gyrus, which is thought to mediate the affective component of pain. The separation between sensory-discriminative and affective areas of the cortex is likely to be an oversimplification.
- **Modulation:** One of the major complexities of pain pathways is the modulation of afferent impulses which occurs at numerous levels, including the dorsal horn where there is a complex interaction between afferent input fibres, local intrinsic spinal neurones and descending central efferents. Afferent impulses arriving at the dorsal horn themselves initiate inhibitory mechanisms which limit the effect

of subsequent impulses. As pain fibres travel rostrally they also send collateral projections to the higher centres such as the periaqueductal grey (PAG) matter and the locus ceruleus of the mid-brain. Descending fibres from the PAG project to the nucleus raphe magnus in the medulla, and to the reticular formation to activate descending inhibitory neurones. These travel in the dorsolateral funiculus to terminate on interneurones in the dorsal horn. These fibres from the PAG are thought to be the main source of inhibitory control. Descending inhibitory projection also derives from the locus ceruleus. The inhibitory activity mediated from the PAG is also stimulated by endorphins released from the pituitary and which act directly at that site.

- **'Gate' control:** This represents one aspect of modulation. Synaptic transmission between primary and secondary nociceptive afferents can be 'gated' by interneurones. These neurones in the substantia gelatinosa can exert pre-synaptic inhibition on primary afferents, and post-synaptic inhibition on secondary neurones, thereby decreasing the pain response to a nociceptive stimulus. The inhibitory internuncials can be activated by afferents which subserve different sensory modalities, such as pressure (A-β-fibres). This phenomenon underlies the use of counter-irritation, dorsal column stimulation, transcutaneous electrical nerve simulation (TENS) and mechanical stimulation ('rubbing it better'). Descending central efferents from the PAG and locus ceruleus can also activate these inhibitory interneurones.
- **Transmitters:** These are numerous. Excitatory amino acids such as glutamate and aspartate have a major role in nociceptive transmission at the dorsal horn, where there are NMDA, non-NMDA, kainite, glutamate, AMPA, neurokinin, adenosine, 5-HT, GABA, α-adrenergic receptors and μ-, κ- and δ-opioid receptors. The primary afferents release various peptides, among them substance P, neurokinin A and calcitonin gene-related peptide (CGRP). There are different neurotransmitters in the various descending inhibitory pathways, which include neuropeptides (encephalins and endorphins) in the PAG, metencephalin and 5-HT in the nucleus raphe magnus pathway and noradrenaline in the locus ceruleus descending pathway.

Direction the viva may take

In the light of the foregoing you may be asked to outline where in the neuraxis analgesic agents or techniques may work.

- The usual target for analgesics is via ligand–receptor blockade, and the large number of receptor types means that you will only be able to give one or two examples. Opioid receptors, for instance are expressed in the cell body of the dorsal root ganglion and transported both centrally to the dorsal horn, and peripherally. There are also receptors at higher centres, such as the PAG, and so opiates exert their actions at numerous sites in the CNS. Ketamine acts on the open calcium channel of the NMDA receptor, amitryptyline modifies descending noradrenergic pathways, clonidine acts at pre- and post-synaptic α_2-receptors, while NSAIDs have predominantly a peripheral action which attenuates the hyperalgaesia associated with the inflammatory response. You could impress the examiner with a final flourish by explaining that the future lies in analgesics that will regulate gene expression and exert selective modification.

Spinal cord injury

Commentary

This question occurs more commonly in the examination than in most anaesthetists' clinical practice. Approximately two individuals are paralysed each day in the UK after traumatic spinal cord injuries. Anaesthetists may be involved in their immediate care, but the more difficult, and from the examiners' point of view, more interesting aspects of spinal cord injury, only occur once they have been transferred to specialist centres. Your own knowledge, as well as that of your examiner, is likely to be largely theoretical, and the emphasis of the viva will be on the applied anatomy and pathophysiology of the condition.

The viva

You will be asked about the immediate management of spinal cord injury.

- The clinical signs depend on the level of injury. Over 50% of spinal injuries occur in the cervical region, because in comparison with the thoracic and lumbar spines it is mobile and unprotected. In adults the fulcrum of the cervical spine is at C_5/C_6, which is the most common site of cord damage. (In children the fulcrum is higher.) The remaining injuries are divided equally between the thoracic, thoracolumbar and lumbosacral regions. Injuries involving the cervical cord are associated with tetraplegia, those at T_1 and below result in paraplegia.
- High thoracic or cervical cord injury is associated with 'neurogenic shock' which denotes the hypotension and bradycardia consequent upon the loss of sympathetic efferent pathways. This haemodynamic instability can persist. A second phenomenon is that of 'spinal shock' which may last from 3 days to 6 weeks, during which all spinal cord reflexes are profoundly depressed or abolished.
- The early management of cord injury includes immobilisation and a standard approach to airway, breathing and circulation. Tracheal intubation may be necessary if there is any suggestion of respiratory compromise, and patients with lesions at C_3, C_4 or C_5 are likely to have lost some or all diaphragmatic function. A lower cervical injury spares the diaphragm but breathing is still affected. The expansion of the rib cage via the intercostals and accessory muscles of respiration is responsible for 60% of normal tidal volume. Lung capacities are reduced such that vital capacity is only 25% of normal. Ventilation may be impaired leading to sputum retention and chest infection, which is the most common cause of mortality in the first 3 months after injury. In the spontaneously breathing tetraplegic patient it is the supine position that is associated with the greater diaphragmatic excursion. The circulation may not respond to fluid infusion, and both vasopressors and atropine may be necessary. Neurogenic pulmonary oedema occurs in more than 40% of cases in some series, and overzealous fluid therapy will compound the problem.
- **Drugs**
  - *Corticosteroids*: Evidence from the North American Spinal Cord Injury Study suggests that high-dose methylprednisolone 30 mg kg^{-1} may be of early benefit if given soon after injury. Whether or not outcomes are improved remains disputed.
  - *Suxamethonium*: Within about 48–72 h after the acute injury, there is proliferation of acetylcholine receptors in extra-junctional areas of the denervated muscle. Administration of suxamethonium results in a large efflux of potassium into the circulation. This dangerous hyperkalaemic response is proportional to the amount of muscle that is involved and may persist for as long as 9 months.

Direction the viva may take

You may be asked about the later problems that may occur after spinal injury, and in particular how they might complicate anaesthesia.

- When spinal reflexes start to return they are hyper-reflexic. The normal supraspinal descending inhibition of the thoracolumbar autonomic outflow is lost and so there occurs a mass reflex sympathetic discharge in response to stimulation below the level of the spinal lesion. There are changes in denervated muscle as well as the development of collateral neurones in the various reflex pathways. With time the threshold appears to drop, together with the spread of stimulation across reflex centres. This explains why the mass response may be provoked by relatively minor stimuli.
- Both cutaneous and visceral stimuli (particularly associated with bladder distension, other genitourinary stimulus and bowel disturbance) can provoke this reflex response. It is confined to the area below the level of transection, where the autonomic nervous system is not subject to any inhibitory influences: proximally there is compensatory parasympathetic over-activity. It is rare in lesions below T_{10}.
- The clinical features of this response include muscle contraction and increased spasticity below the lesion. There may be vasoconstriction and severe hypertension that can be accompanied by tachycardia or a compensatory bradycardia. Other cardiac dysrhythmias may occur. Above the level of the lesion there may be diaphoresis and flushing. The more distant the dermatome that is stimulated from the lesion the more emphatic is the sympathetic response. Autonomic hyper-reflexia is more pronounced the higher the lesion in the cord, and the more limited the capacity for parasympathetic compensation.
- Patients may require surgery following cord injury, and autonomic hyper-reflexia will complicate anaesthetic management. Reflex discharges can be prevented reliably by neuraxial block, although if an epidural is used it is important to ensure that the sacral segments are anaesthetised. Dense subarachnoid anaesthesia will prevent hyper-reflexia completely. Deep anaesthesia or the use of vasoactive drugs to treat developing hypertension are less successful.

Immunology (and drug reactions)

Commentary

This is a topic that potentially is huge, but which includes an aspect of particular interest to anaesthetists, namely severe adverse drug reactions. This is where the viva may well end up, but not before you have been asked to give an overview of the immune system. Detailed discussion of T-lymphocyte function or of cytokines would itself consume the entire viva, and so questioning on these subjects necessarily will be superficial. The basic science emphasis, however, means that you must at least demonstrate familiarity with the major components of immunity.

The viva

You will be asked to describe the basic components of the immune system.

Innate or non-specific immunity

- The body has a number of non-specific defences against infection. These include the skin, the antimicrobial secretions of sweat, sebaceous and lacrimal glands, and the mucus of the gastro-intestinal tract and the upper airway to which organisms may adhere. The acidic environment of the stomach is hostile, and the lower gastro-intestinal tract (GIT) is populated with commensals which prevent the overgrowth of less benign species.
- Non-specific immune defences do not recognise the substance that is being attacked, and are activated immediately in response to potential threats, for example from infectious agents. These defences include the activation of the alternative complement pathway (see below), phagocytosis by neutrophils, macrophages and mast cells, and the inflammatory response itself.
- **Leucocytes:** These comprise neutrophils (60–70% of the total), which are responsible for phagocytosis and inflammatory mediator release; basophils (1%), which are the circulatory equivalent of tissue mast cells; monocytes (2–6%), which function in the blood like macrophages; eosinophils (1–4%), which destroy helminths and other parasites, and which may mediate hypersensitivity reactions; and lymphocytes (20–30%). Most lymphocytes mediate specific immune defences, but natural killer (NK) lymphocytes bind non-specifically to tumour cells and to cells that are infected by virus.
- **Macrophages:** These cells that are derived from monocytes are ubiquitous. They destroy foreign particles by phagocytosis, mediate extracellular destruction via the secretion of toxic chemicals, and also secrete cytokines. Cytokines are a complex set of protein messengers that regulate immune responses, and include the interleukins (ILs), tumour necrosis factor (TNF), colony-stimulating factors and interferons.

Acquired or specific immunity

- **Lymphocytes:** Specific immunity involves recognition of cell or substance to be attacked, and lymphocytes are the mainstay of the specific immune system. B-lymphocytes differentiate into plasma cells which synthesise and secrete antibody. T-lymphocytes comprise helper cells (T-helper, Th) and killer cells (cytotoxic, Tc). NK cells are non-specific. Th cells produce a large number of cytokines in a process that links the innate and specific components of the immune system.
- **Antibodies:** These immunoglobulins (Ig) are proteins which bind specifically with antigens, which contain two identical light and two identical heavy chains, and which are characterised as IgA, IgD, IgE, IgG and IgM. IgG is the most abundant, and is the only Ig which crosses the placenta.

Direction the viva may take

You may be asked about adverse reactions to drugs. Not all of the described hypersensitivity reactions are necessarily involved in drug reactions, but a summary is included for completeness. This is because whenever Type I reactions are mentioned the examiners will want to see if you are familiar with the rest of the classification.

- **Hapten formation:** Most drugs are low molecular weight and are not inherently immunogenic: they can, however, act as haptens by interacting with proteins to form stable antigenic conjugates.
- **Hypersensitivity reactions:** Hypersensitivity reactions are abnormal reactions involving different immune mechanisms, often with the formation of antibodies. They occur on second or subsequent exposure to the antigen concerned. Four types have been described.
- **Type I (immediate):** This is the classic anaphylactic, immediate hypersensitivity reaction, which is mediated by IgE. IgE is synthesised by B-cells on first exposure to the antigen and binds to mast cells. On repeated introduction, the antigenic drug–protein complex degranulates mast cells with the release of a number of preformed vasoactive substances. These include histamine, heparin, serotonin, leucotrienes and platelet-activating factor. (Mast cells are numerous in skin, the bronchial mucosa, in the gut and in capillaries.)
- **Type II (cytotoxic):** In this reaction circulating IgE and IgM antibodies react in the presence of complement to mediate reactions which cause cell lysis. Such reactions can lead to haemolysis (caused for example, by sulphonamides), thrombocytopaenia (heparin, thiazide diuretics) and agranulocytosis (carbimazole, NSAIDs, chloramphenicol).
- **Type III (immune complex):** The reaction of antibody and antigen produces a circulating immune complex (precipitin), which deposits in small vessels, in the glomeruli and in the connective tissue of joints. These precipitins also activate complement via the classical pathway. Type III reactions underlie many autoimmune diseases including rheumatoid arthritis and systemic lupus erythematosis (SLE).
- **Type IV (delayed):** This is the delayed hypersensitivity reaction, which is cell-mediated without complement activation and without the formation of antibodies. The reaction results from the combination of antigen with T-cell (killer) lymphocytes and macrophages attacking the foreign material. This mechanism underlies the development of contact dermatitis. Granuloma formation in diseases such as tuberculosis and sarcoidosis is a result of a large antigen burden or the failure of macrophages to destroy the antigen. This 'granulomatous hypersensitivity' is also a Type IV response.
- **Complement:** Complement is an enzyme system comprising of twenty or more serum glycoproteins which, in combination with antibody, are activated in a cascade that results in cell body lysis. In summary the complement system coats (opsonises) bacteria and immune complexes, activates phagocytes and destroys target cells. The final pathway is the amalgamation of complement proteins C5–C9 into a complex that disrupts the phospholipids of cell membranes to allow osmotic cytolysis. The classical complement pathway is a specific immune response that is initiated by the reaction of antibody with complement protein C1 and its subcomponents. The alternative pathway is a non-specific response that can be activated in the absence of antibody, but in the presence, for example, of anaesthetic agents, drugs or bacterial toxins.
- **Anaphylactoid reactions:** These clinically may resemble anaphylactic reactions, but they involve the direct release of vasoactive substances (histamine, serotonin) from mast cells or from circulating basophils, rather than release mediated via an antigen–antibody response.

Further direction the viva could take

You may be asked how you would investigate a suspected drug reaction. If you (or the examiner) have run out of things to say about immunity, then you may be asked to describe your management of a severe reaction.

- **Investigation of a reaction:** Non-specific markers include urinary methylhistamine, which increases in the first 2–3 h following a reaction, and mast cell tryptase. This enzyme is responsible for activating part of the complement cascade (it cleaves C3 to form C3a and C3b) and serum concentrations are elevated for about 3 h after a reaction. A clotted blood sample should therefore be taken as soon as possible after emergency resuscitation and 1 h later. Patients can further be investigated by skin testing (at 6 weeks or longer after the event) and by assays of drug-specific antibodies using RAST tests.
- **Management of an anaphylactic or anaphylactoid reaction:** See *Latex allergy*, page 291.

Systemic inflammatory response syndrome (SIRS)

Commentary

Critical care is replete with acronyms; SCARFF, ALI, ARDS, multiple organ dysfunction syndrome (MODS) and now SIRS. Research papers dealing with this subject will include as keywords 'sepsis', 'septic shock' and 'sepsis syndrome' which serve to confirm that the terminology is confusing. If the examiner is not an intensivist he or she may share some of that confusion, which the summary account below should allow you to dispel. The inflammatory response involves far more detail than you will have time to cover, and superficial knowledge of some of the mediators should be adequate, as along as you are able to discuss treatment from first principles.

The viva

You will be asked about the diagnostic criteria and pathophysiology of SIRS.

- **Diagnosis:** SIRS is defined by the presence of two or more of the following:
  - *Temperature*: More than 38°C or less than 36°C.
  - *Heart rate*: More than 90 beats min^{-1}.
  - *Respiratory rate*: More than 20 breaths min^{-1} (or a $P_{a}CO_2$ less than 4.3 kPa).
  - *White cell count*: More than $12 \times 10^3 mm^3$ or less than $4 \times 10^3 mm^3$ (or with more than 10% of immature forms).
- **Definition:** SIRS comprises features of the inflammatory response in the absence of an identifiable pathogen, end-organ damage or the need for circulatory support. It is therefore distinct from sepsis and its variants. Once a pathogen has been isolated then the working diagnosis in a patient shifts from SIRS to sepsis, severe sepsis or septic shock. Once end-organ damage supervenes the diagnosis becomes that of early MODS.
- **The inflammatory response:** SIRS is a pro-inflammatory state, which is part of an exaggerated or uncontrolled host response to a pathological insult. The response is systemic rather than localised. The inflammatory response is complex, comprising a sequence of reactions which involve not only the secretion of key signalling molecules such as the cytokines (protein immunoregulators that include IL-1, 5, 6, 8, 11 and 15, TNF, colony-stimulating factors, interferons and platelet-activating factor), but also the activation of complement. Other inflammatory mediators such as kinins and histamine lead to vasodilatation and increased capillary permeability, while leucotrienes stimulate inward granulocyte migration. Which of these, if any, is the trigger for SIRS is not known. In addition there is an increase in acute phase proteins, such as haptoglobin, fibrinogen and C-reactive protein (CRP). CRP activates monocytes, increases cytokine production and can activate the complement cascade. Other aspects of immune function, such as cell-mediated and humoral immunity may also be mobilised.
- **Causes:** Patients with SIRS appear to have tissue hypoperfusion or infection or both, but the final common pathway to the inflammatory response can be triggered by numerous insults. These include trauma, major surgery and challenges to the immune system by various antigens, including the transfusion of blood and blood products. The hypoperfusion is responsible for the lactic acidosis that is a typical feature of the condition. See *Compensatory responses to blood loss*, page 85.
- **Clinical features:** Consistent with the diagnostic criteria above, patients typically exhibit a tachycardia, disturbed temperature regulation, tachypnoea, a narrowed pulse pressure secondary to the reduced effective circulating volume, and oliguria. These clinical signs are relatively non-specific.

Direction the viva may take

You may be asked about the principles of management (which is mainly supportive).

- **Airway and breathing:** Airway protection and ventilatory support should be used as appropriate.
- **Circulation:** Fluid resuscitation and cardiac performance should be optimised to ensure adequate oxygen delivery to tissues (see *Oxygen delivery*, page 99). Fluid therapy may need to be aggressive in order to overcome maldistribution and hypoperfusion. Large volumes of NaCl 0.9% may induce a hyperchloraemic metabolic acidosis in addition to the lactic acidaemia. Albumin is not the 'killer fluid' identified by some meta-analyses, but on the contrary is a useful volume expander that has been shown in other meta-analyses to improve survival.
- **Drugs:** There are no drugs specific for the management of SIRS as distinct from sepsis or septicaemic shock. In respect of the latter there has been interest in the role of nitric oxide (NO), in which excess production of NO may be associated with the early vasodilatation and myocardial depression that is typical of the condition. Experimental use of NO synthetase inhibitors (such as arginine derivatives) has not fulfilled its theoretical promise. The same applies to the use of monoclonal antibodies such as monoclonal anti-TNF. Activated protein-C, however, does decrease the mortality associated with severe sepsis, and despite its high cost (£5000) is likely to find a place in its management.

Evidence-based medicine

Commentary

This is a rather nebulous topic, which paradoxically generates much fervent opinion and precious little evidence, and it may seem an unlikely subject for a viva. It has, nonetheless, made at least one appearance in a short answer paper, and the question of evidence-based medicine (EBM) will always arise should you be asked about clinical trials and meta-analyses. There is a politically correct approach, which is what the examiners initially will be expecting to hear, but many of them will be rather relieved if you do outline the potential pitfalls of a subject that in some quarters has become almost evangelically fashionable.

The viva

You will be asked to describe what you understand by the term EBM.

- **EBM:** It has been defined as the *conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients*. In practice this should mean the integration of the individual clinician's expertise, born of experience and aptitude, with the best available external evidence from systematic review.
- **The process:** It has been described as a four-stage process, which involves (1) generating a relevant, significant and focused clinical question, (2) a search of the literature for the best evidence, (3) an evaluation of that evidence and (4) if the validity and importance of the evidence is established, the application of that evidence.
- **Levels of evidence:** These have been defined as:
  - *I*: Evidence from at least one review of multiple randomised-controlled trials (RCTs).
  - *II*: Evidence from at least one well-designed RCT.
  - *III*: Evidence from well-designed trials without randomisation or matched controls.
  - *IV*: Evidence from well-designed non-experimental studies from more than one group.
  - *V*: Opinions based on clinical evidence, on descriptive studies or on the reports of expert committees.
- **Recommendations:** These are linked to levels of evidence.
  - *A*: Consistent level I studies.
  - *B*: Consistent level II or III studies, or extrapolation from level I studies.
  - *C*: Level IV studies or extrapolations from level II or III studies.
  - *D*: Level V evidence or inconsistent or inconclusive studies of any level.
- The proponents of EBM suggest that good doctors have to use both their clinical skills and the best available external evidence: on their own neither is enough. Without the modifying influence of such skills, clinical practice may succumb to the 'tyranny of evidence', which may in fact not be appropriate for a particular patient, and which should inform rather than replace individual clinical expertise.
- RCTs and meta-analyses are the most appropriate sources of external evidence about therapeutic interventions. Non-experimental approaches to questions about therapy are habitually subject to false-positive conclusions about efficacy. It is very obvious, however, that not every aspect of clinical practice can be subject to an impeccably conducted prospective RCT.
- EBM, however, is not solely restricted to randomised-controlled clinical trials and meta-analyses. Questions about the accuracy and validity of a diagnostic test, for example, require not an RCT but the identification of a large cohort of subjects who may have the condition that the test is designed to reveal.

Direction the viva may take

The more assured your account of the precepts of EBM, the more likely it is that you may be asked to offer a more robust critique.

- Some commentators have identified what has been described as the 'basic error' of EBM, namely that epidemiological population data do not actually provide the information necessary to treat individual patients. This reflects one of the enduring complexities of clinical medicine: the way that biological variability hinders attempts to extrapolate to the individual patient the results of basic and clinical research.
- Meta-analysis is not the ultimate repository of valid information which dictates patient management. The potential limitations of the technique, which is used more by statisticians and epidemiologists than clinicians, were highlighted by the controversial meta-analysis published in 1998, which concluded that albumin administration was associated with increased mortality in the critically ill. Subsequent larger analyses which controlled for subgroup effects showed that resuscitation with albumin actually improved survival.
- Critics have pointed out that there is a difference between 'medicine based on evidence' and 'EBM'. EBM (the capitals elevate its status) relies mainly on RCTs, meta-analyses and mega-trials, is subject to the basic error, and potentially is flawed. It has been described rather acidly as 'a conceit' and as a dogmatic and authoritarian movement which insists, rather than assists. As another perspicacious commentator has written, EBM guidelines used to be known as textbooks.

Further direction the viva could take

In the course of the discussion of levels of evidence you may be asked in more detail about the design of clinical trials, and about meta-analysis.

- **Clinical trials:** See *Design of a clinical trial for a new analgesic drug*, page 194.
- **Meta-analysis:** See *Parametric and non-parametric data*, page 275.

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