

1. Define the term gene (2)

1. Gene is a sequence of bases on DNA that codes for a specific polypeptide chain.

2. What is the role of oxygen in aerobic respiration? (3)

2. Oxygen acts as a final electron acceptor in the electron transport chain. It removes electrons and combines it with hydrogen ions to form water. This helps to regenerate NAD, which is needed for the Krebs cycle and link reaction to occur.

3. How does a mutation affect the structure of a protein like IGF-1? (4)

3. A mutation is change in the sequence of bases within a gene. This will cause the sequence of bases on mRNA to be different and the sequence of amino acids in the polypeptide chain will also change. A change in the primary structure will change the tertiary structure as different bonds will form between the R groups.

4. Explain how erythropoietin has an affect on cells (3) (p1 paragraph 6)

4. Epo is a hormone. It will bind to specific receptors on the target cells and stimulate the release of adenylyl cyclase, which will convert ATP into Camp (second messenger). The cAMP will activate transcription factors and switch the gene for RBC production on.

5. Using the epo receptor as an example, explain the type of control that the body uses to maintain the oxygen levels in the blood. (4) (page 1, paragraph 6)

5. The oxygen levels in the blood are maintained by negative feedback mechanism. If oxygen levels are low, the epo production by the kidneys increases and more RBCs are produced by the bone marrow. This will raise the oxygen levels in the blood. When oxygen levels are too high, epo production decreases and the bone marrow produces less RBCs. So oxygen levels in the blood will start to decrease.

6. How would you produce recombinant bacteria containing the epo gene? (5)

6. Cut the epo gene from normal human DNA, by using restriction endonucleases. Cut a bacterial plasmid with the same restriction enzymes, so that their sticky ends are complementary. Then paste the two DNA fragments by DNA ligase, which will form phosphor diester bonds between the cut ends of the DNA fragments. Insert the recombinant DNA (plasmid) into the bacterial cells by heat shock. In this process the bacteria is incubated with calcium ions at 0 degrees Celsius. The temperature is then rapidly raised to 40 degrees Celsius. Some of the bacteria absorb the plasmids. These cells are called as transformed cells.

7. Describe the structure of viruses. (2)

7. Viruses are particles which contain either DNA or RNA, never both. The nuclear material is surrounded by a protein coat, called as the capsid. The capsid is made up of proteins called capsomeres. Some viruses may have a phospholipid envelope around the capsid, while others are naked.

8. How are viruses 'recognised and destroyed by the immune system'? (7) (p2, paragraph 4)

8. Antigen recognition – viral proteins are recognized as non-self molecules by the B – lymphocyte and T killer cells. These viral proteins are called as antigens, as they will stimulate antibody production.

Antigen presentation: the B lymphocytes will present antigens on their surface. These B cells will be stimulated by active T Helper cells to start replication or cloning.

Specific T killer cells will also be presented with viral antigens, on the surface of infected cells.

Proliferation or rapid cloning: The activated B cells will undergo rapid mitosis to form many B effector cells and B memory cells. The B effector cells will differentiate into plasma cells and produce antibodies to destroy the virus.

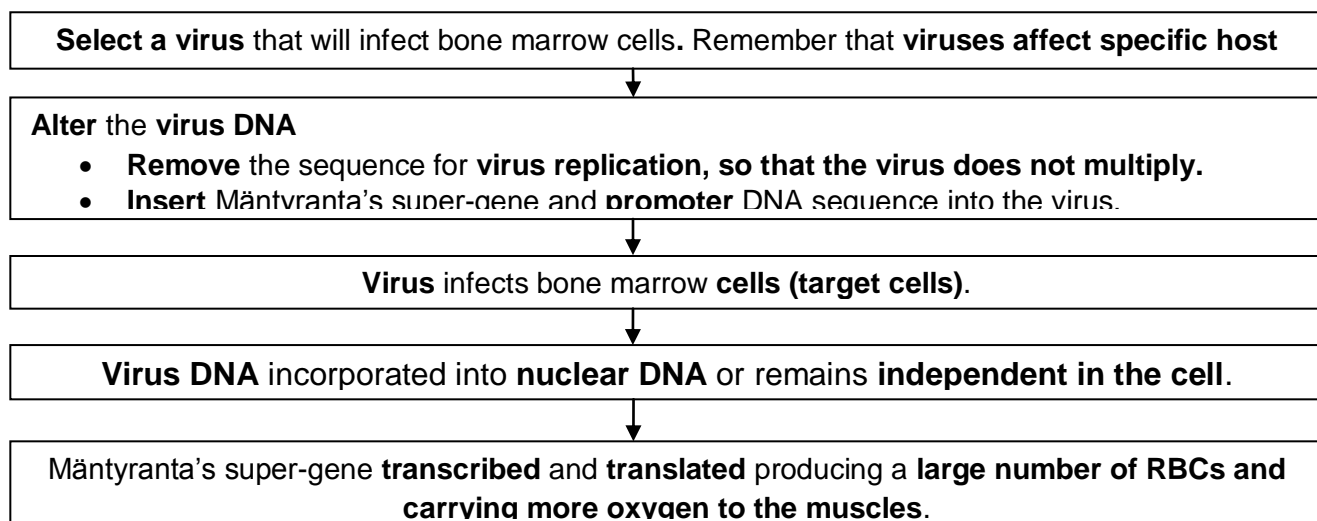
The T killer cells will also multiply by mitosis and destroy infected cells by producing chemicals like perforins. The viruses are then released from the host cells and destroyed by the antibodies.

9. Describe the process by which cells 'pump out the protein'? (2) (p3, paragraph 5)

9. 'Pump out the protein' – the process of transcription and translation, which uses information on DNA to produce the polypeptide chain. It may also mean that the epo is released from the cell by exocytosis.

10. Explain how viruses can be used in gene therapy. (3)

10. Refer to flowchart below.



11. Explain what would be involved in clinical trials (p4, paragraph 1) (6 marks) 11.

Clinical trials will follow preclinical trials, which test the therapy on animals. The clinical trial involves three phases. Refer to table below.

Stage	Purpose of stage
Pre-clinical testing	<ol style="list-style-type: none">1. Proposed drug is tested in a lab with cultured cells to see the general effects of the drug2. Proposed drug is given to animals to see the effects on a whole animal. Any side effects away from target cells are noted.
Clinical Trials Phase 1	<ol style="list-style-type: none">1. A small group of healthy volunteers are given different doses of the drug. They are told what the drug does2. The distribution, absorbance rate, metabolism & excretion profile of the drug are assessed.3. The effects of the different doses are assessed to try and determine the optimum dose4. An independent organisation (UK Medicines Control Agency) assesses whether it is appropriate to move to Phase 2
Clinical Trials Phase 2	<ol style="list-style-type: none">1. A small group of people with the disease are given the drug.2. Studies are very similar to Phase 13. The optimum dose is worked out
Clinical Trials Phase 3	<ol style="list-style-type: none">1. A large group of people with the disease are given optimum doses of the drug2. The patients are either given the drug or a placebo in a double-blind test3. The results are analysed4. If the drug has had a significant positive effect in the treatment of the disease it is put forward to licensing authority

12. Explain how high blood pressure leads to a heart attack. (4) (p4, paragraph 1)

12. Refer to comment SVR45

High Blood pressure → endothelial damage in arteries → monocytes and T cells are activated and move into the smooth muscle layer of the artery's wall → they are transformed into **foam cells**, which are cells that collect fatty materials, mainly cholesterol → cell debris, cholesterol crystals, and calcium forms a patchy deposit called an **atheroma** or **atherosclerotic plaque**. The artery wall **hardens**, so it is **less elastic** than it should be. This is **atherosclerosis**.

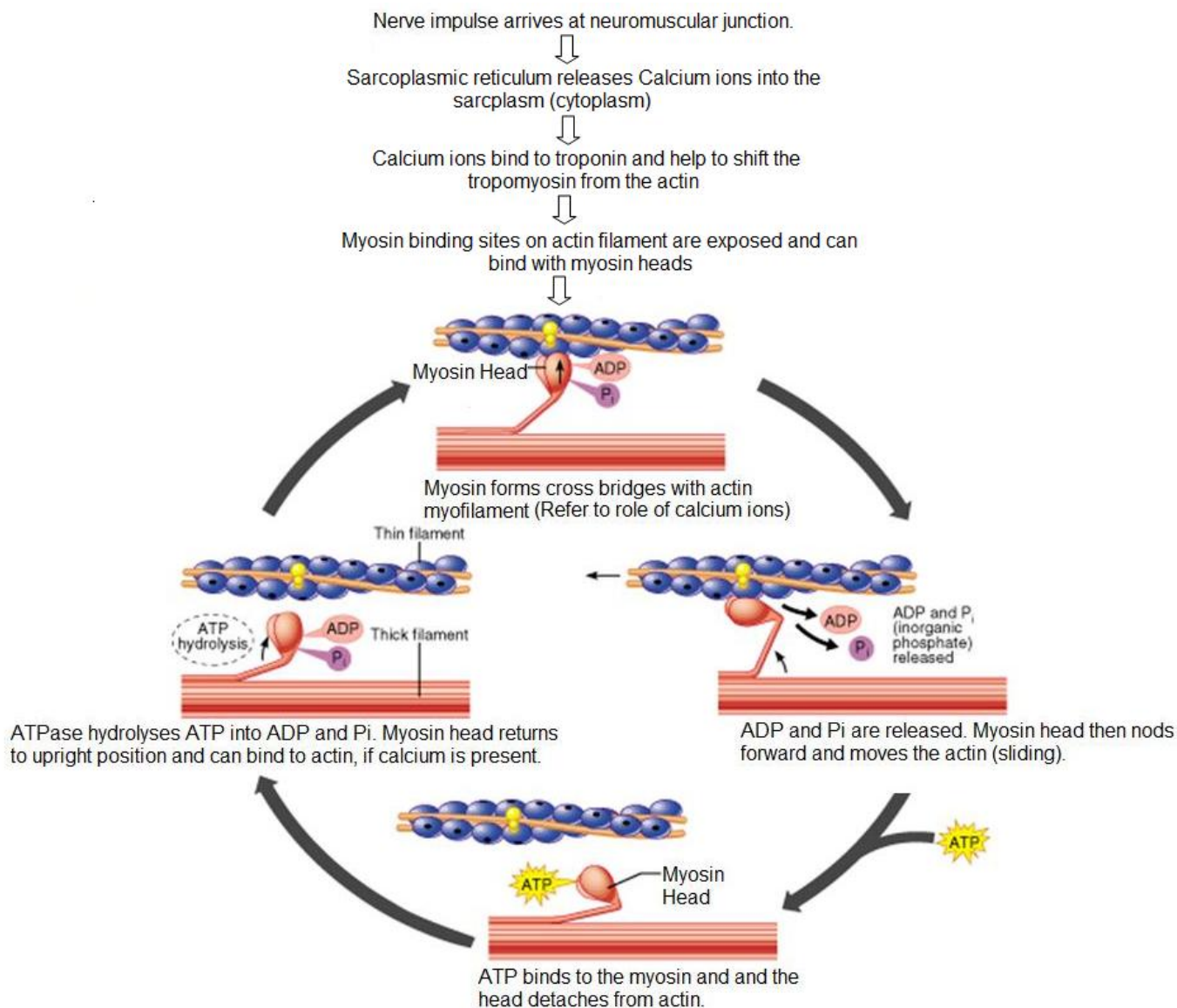
13. Describe the structure of a muscle fibre. (2)

13. Refer to comment SVR100

Actin and myosin (myofilaments) → sarcomere → myofibril → muscle fibre (muscle cell) → muscle tissue

14. What proteins are found in muscle fibres and what is their structure? (4)

14. Actin and myosin. Myosin is thicker and has many myosin heads. Actin is thinner and has myosin head binding sites. The actin can slide over the myosin.



15. IGF-1 exists in 5 forms whose parts are spliced together in different ways. How is this possible? (3) (page 4 paragraph 3).

15. One gene for IGF produces one primary mRNA. Differential splicing causes many types of secondary mRNA transcripts. Refer to notes on one gene several proteins.

One gene – several proteins. post transcriptional mRNA splicing

In the early days of experimental molecular biology, the 'central dogma' or basic belief was. 'Each gene codes for a single protein.' Estimates of the number of genes in an organism's genome were based on the estimated number of different proteins in the organism. This gave a very imprecise figure for the size of a genome, and was usually too large. One reason for the overestimation is that a gene contains both coding

regions known as exons and non-coding regions called introns. The whole gene is transcribed to form preRNA, and then the introns are removed. The exons are joined together before the modified mRNA is translated. This is known as splicing. Some genes can produce several proteins, depending on how the exons are spliced together. Not all the exons may appear in the final mRNA. Some exons appear to be optional.

Example

DNA template strand / antisense

ATC	AGG	GAT	ATA	CGT	GGC	CCG	GCT	TTT	AGC	TTC	GCG	GGA	TTG
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Primary mRNA transcript

Exon 1		Intron1		Exon 2		Intron2		Exon 3			Intron 3			Exon4
UAG	UCC	CUA	UAU	GCA	CCG	GGC		CGA	AAA	UCG	AAG	CGC	CCU	AAC

Secondary transcript one – Introns removed and all exons present

Amino acids	Exon 1		Exon 2		Exon 3			Exon 4	
	UAG	UCC	GCA	CCG	CGA	AAA	UCG	AAC	
	Methionine	Serine	Alanine	Proline	Arginine	Lysine	Serine	Asparagine	

Secondary transcript two – Introns removed along with exon 3 (optional exon)

Amino acids	Exon 1		Exon 2		Exon 4
	UAG	UCC	GCA	CCG	AAC
	Methionine	Serine	Alanine	Proline	Asparagine

Note: Exons and introns are usually made up of longer stretches of nucleotides.

Post – transcriptional modification of mRNA by differential splicing makes it possible to have a fewer number of genes than proteins, because one gene can code for many proteins.

Thus, we can see that the same gene has given rise to two different polypeptide chains due to differential exclusion of exons from the primary mRNA transcript. This is referred to as post transcriptional modification.

16. How could IGF-1 be 'turned on'? (2) (page 4, paragraph 3)

16. The gene is switched on due to environmental signals like exercise.

17. Discuss the ethics of athletes using performing enhancing drugs. (4)

Doping may be unethical because	Doping may be considered ethical because
Athletes have a right of access to fair competition (doping is unfair to those who do not do it). Doping might be good (from the point of view of success in competition) for the few athletes that do it, but is bad for the many that do not.	Athletes have the right to achieve the best performance they can. Doping gives people a chance to be as good as their potential allows. It removes "unfair" genetic advantages.
Athletes have the right to be protected from harmful drugs. Sports governing bodies have a duty to ensure that athletes do not take drugs. It is unethical for athletes to play against the rules.	Athletes have a duty to sponsors to achieve their best performances. Economic benefits are too lucrative to ignore.

Many athletes who take drugs are not really doing so intentionally or willingly. They are usually under pressure from coaches to do so. Many athletes may not have given their informed consent.	It should be up to the individual athlete to decide for themselves whether they will take drugs to improve their performance or not. Especially if the drug is not banned and is not harmful.
Many spectators are disappointed to find that a successful athlete has taken drugs. Athletes know that there are rules against taking certain drugs. An honest and sincere athlete follows the rules.	Individuals have different 'codes of ethics'. If you believe the anti-doping rules are pointless or misguided, then there is no point in following the rules.
Many drugs have harmful side-effects. These drugs are often taken by athletes without medical supervision, which could lead to irreversible harm.	

18. How will your body 'build up antibodies' against the virus? (page 5 paragraph 6) (3)

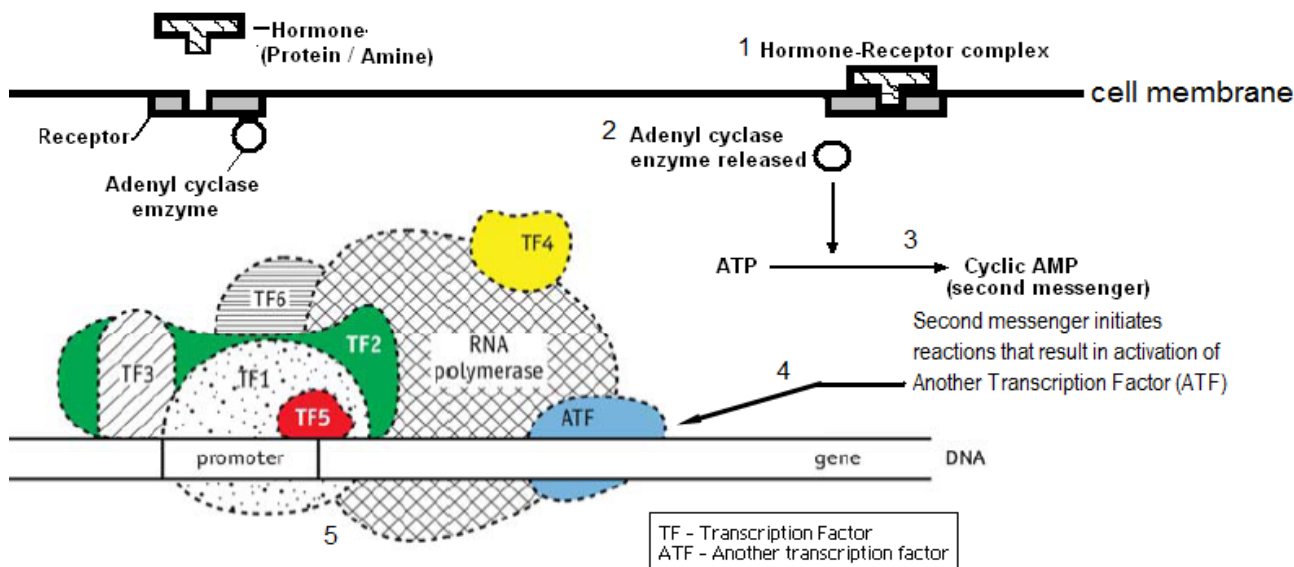
18. Refer to answer for question 8.

19. Why would using a alternate virus overcome the problem? (2) (p5, paragraph 6)

19. New antigen will require the formation of new antibodies and memory cells. Refer to comment SVR59.

20. Compare and contrast the methods of action on cells of steroid hormones and protein hormones. (3)

A peptide hormone



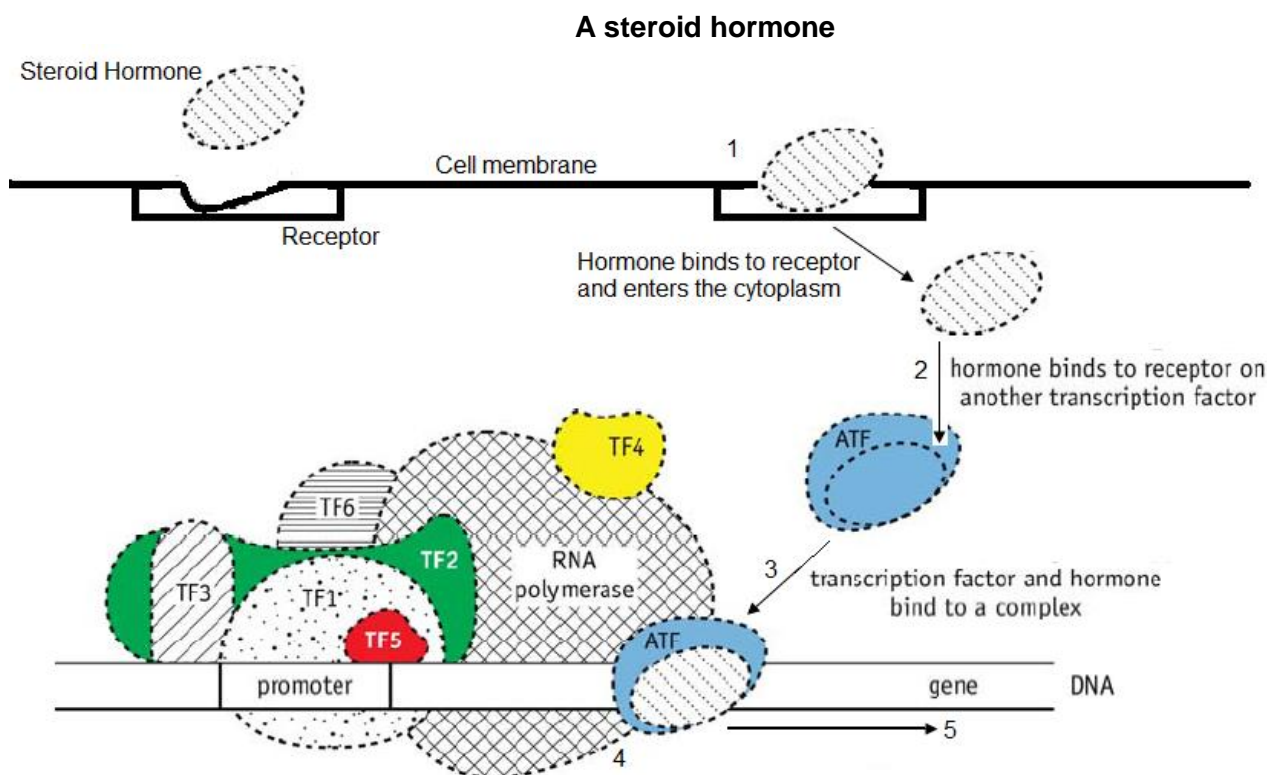
1. Hormone binds to specific receptor on the cell membrane.

2. Adenyl cyclase enzyme is released from the receptor and diffuses into the cytoplasm.

3. Adenyl cyclase converts ATP into cyclic AMP (Second messenger)

4. The second messenger initiates a series of reactions in the cell and activates Another Transcription Factor (ATF), which is usually an enzyme.

5. The new transcription factor (ATF) now binds to the existing Transcription factors (TF1 to TF6, in this case) and completes the Transcription Initiation Complex. This activates RNA polymerase to become active and begin the process of transcription of the gene. The gene is now 'SWITCHED ON'.



1. Steroid hormone binds to specific receptor on target cell and enters the cytoplasm, as the membrane is permeable to steroid hormones, like testosterone or oestrogen.

2. The steroid hormone will bind to a transcription factor in the cytoplasm.

3. The transcription factor and the hormone bind to other transcription factors (TF1 to TF6, in this case) and complete the formation of the Transcription Initiation Complex.

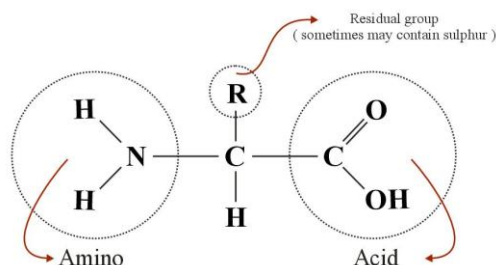
4. The formation of the Transcription Initiation Complex ensures that the gene is 'SWITCHED ON'.

5. Transcription of the gene begins and mRNA is formed.

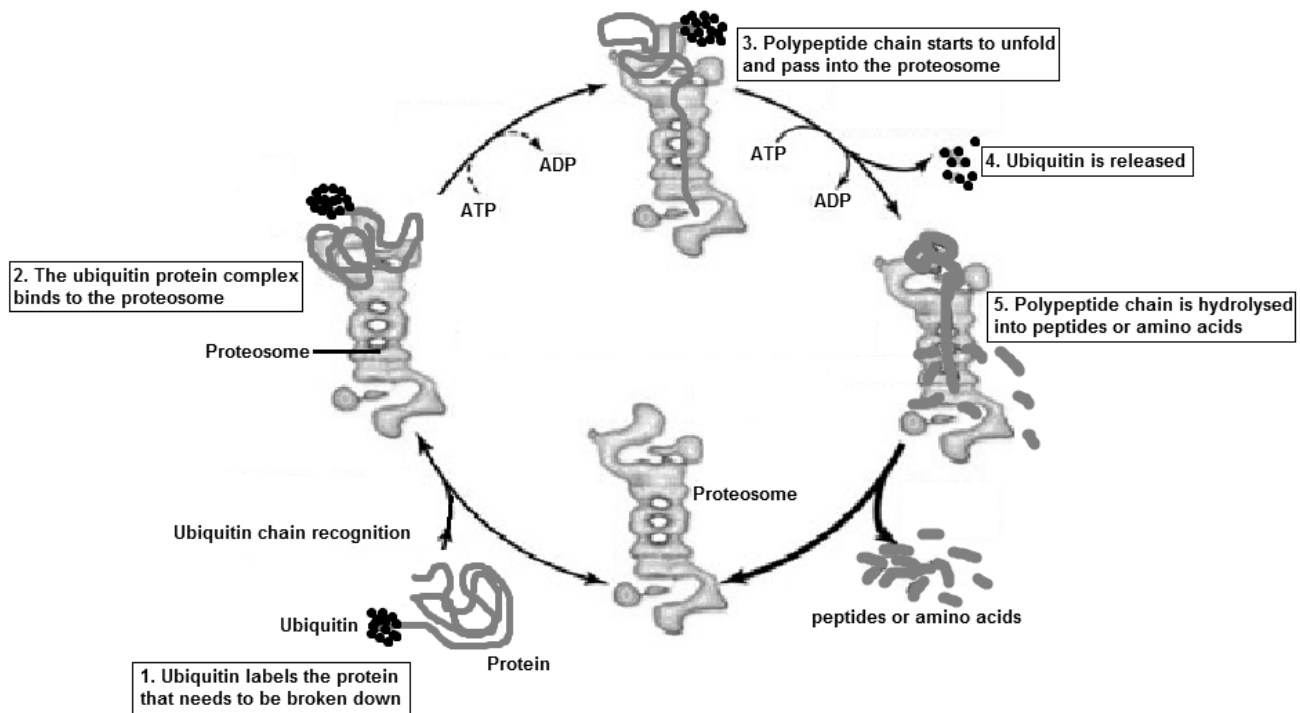
21. What reaction is involved in the breakdown of proteins into their component amino acids. (1)

21. Hydrolysis

22. Describe the structure of an amino acid. (2)



23. Describe the method of action of the enzymes 'ubiquitin ligase' (3) (p7, paragraph 7)



24. Compare cardiac and striated muscle. (2) (p8, paragraph 1)

24. Irrelevant to syllabus

25. Describe the 'rhythm' of the heart. (3) (p8, paragraph 1)

25. The rhythm of the heart refers to the cardiac cycle. It consists of Atrial systole, followed by ventricular systole and subsequent complete diastole.

26. How is the rhythm of the heart controlled? (4)

26. SAN (Sino-atrial node) generates the impulse for heartbeat. The impulse spreads into atrial walls, causing atrial systole. The impulse is then taken up by the AVN (atrio-ventricular node) and passed down to the apex of the heart, through the bundle of His. The impulse then spreads into the ventricular walls, causing ventricular systole. The lack of conducting tissue between the SAN and AVN causes a time delay, which ensures that ventricles start to contract after atria have finished contraction.

27. Why does potassium need to travel through channels? (2) (p8, paragraph 1)

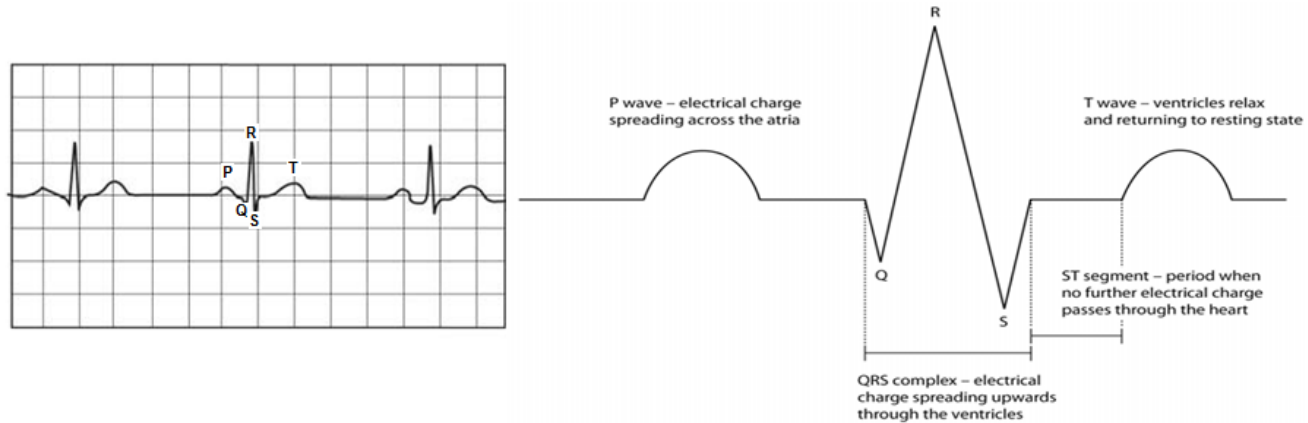
27. The phospholipid bilayer of the cell membrane has non-polar fatty acid tails, which act as a barrier to polar molecules and ions (like potassium).

28. Describe what happens in the process of repolarisation. (2) (p8, paragraph 1)

28. A relaxed muscle fibre is said to be polarised. When ions like potassium, calcium and sodium change place, the muscle cell reverses its potential and contracts. For the muscle to contract again, it must again get polarised. This process is called as depolarizing.

29. Draw and ECG of a normal patient and one with long QT syndrome. (2) (p8, paragraph 1)

Normal ECG



Explanation

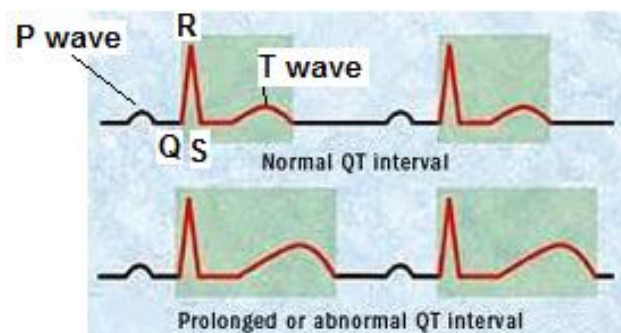
The P wave is the result of a wave of electrical charge spreading across the atria. When it reaches the atrioventricular node at the base of the right atrium there is a slight delay shown by the time between the end of the P wave and the start of the QRS complex; this allows the atria to finish contracting before the ventricle contracts. The P wave is not as elevated as the QRS complex as the atria have thinner wall compared to the ventricles.

The QRS complex is due to electrical charge spreading upwards through the ventricles.

The ST segment is the short period of time when no further electrical impulse can be passed through the heart muscle.

The T wave is the period when the ventricles are relaxing and return to their resting state.

Prolonged QT syndrome



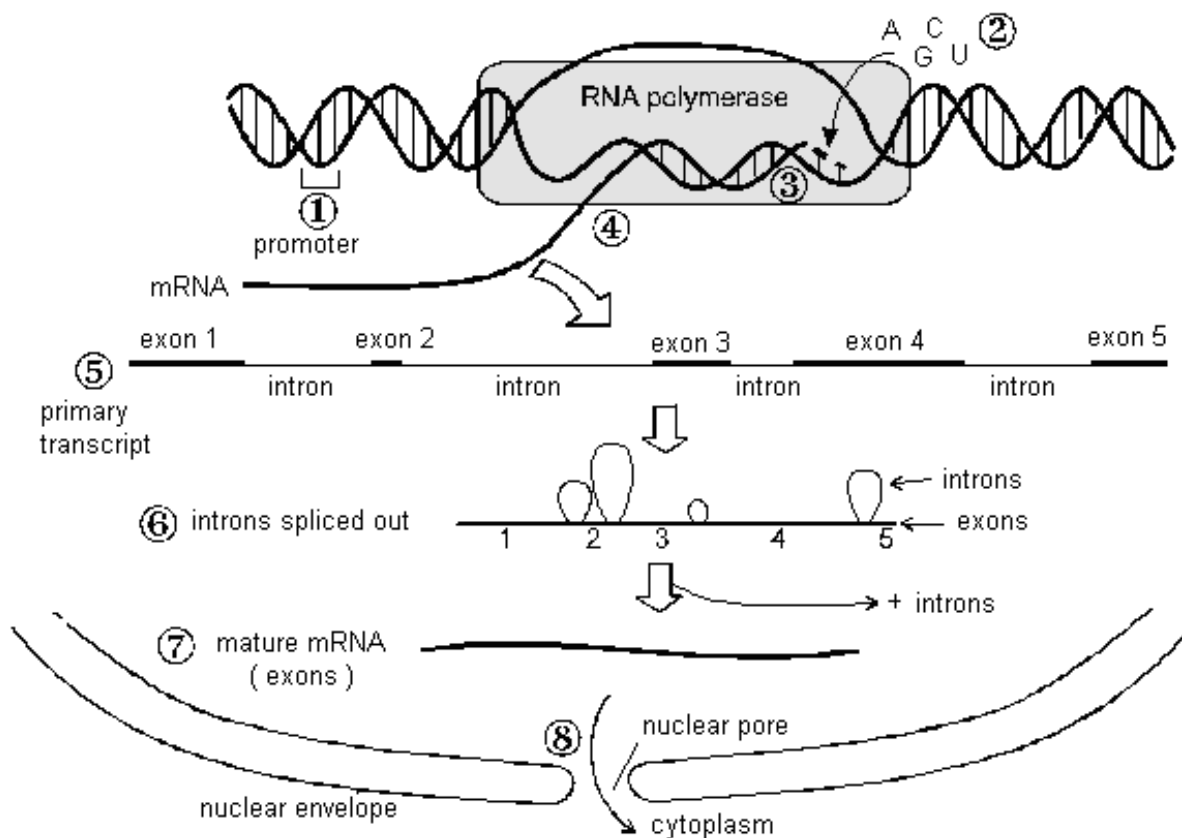
30. How could RNA interference occur? (1) (p8, paragraph 5)

An antisense mRNA is produced, which is complementary to the normal mRNA. So, the two mRNA bind to each other and become double stranded mRNA. So, translation cannot occur and the gene cannot be expressed.

31. Describe the process of transcription. (3)

Transcription: This is the making of mRNA from DNA.

1. The enzyme RNA polymerase attaches at a specific region of DNA (promoter) and begins to unwind the DNA by breaking the hydrogen bonds between the base pairs.
2. Free ribonucleotides in the nucleus pair up with complementary bases on the exposed coding strand or **antisense strand** of DNA. A pairs with U; G pairs with C; T pairs with A.
3. The free nucleotides are linked to each other by the formation of phosphodiester bonds, formed by condensation reactions. It is catalysed by RNA polymerase.
4. The newly formed strand of mRNA then peels away from the coding strand and the DNA rewinds. The process continues until a stop codon is reached.
5. A primary transcript of mRNA is formed.
6. Before leaving the nucleus, some parts of mRNA are cut off. These parts remain in the nucleus and are called introns. The remaining nucleotides rejoin and are called exons. The exons (mature mRNA) leave the nucleus. Poly adenine tail and guanine cap are attached to the mRNA before it diffuses out of the nucleus through the nuclear pores. A length of DNA (a gene) is copied onto a single stranded mRNA molecule.



32. What are the roles of transcription factors? (2) (p8, paragraph 6)

32. Transcription factors are proteins which are produced by regulatory genes. Usually, a group of transcription factors is needed to switch a gene on. If any transcription factor is missing or inactive, the gene remains switched off. So the main role of transcription factors is to switch specific gene on or off.

33. Suggest a way in which IGF-1 could suppress FOXO (1) (p8, paragraph 7)

33. IGF-1 may alter the tertiary structure of FOXO, so that it remains inactive.

34. Why do muscle cells need more 'energy supplying mitochondria'? (5) (p9, paragraph 5)

34. Mitochondria produce lots of ATP by aerobic respiration. The ATP is needed by muscles to detach the myosin heads from actin, so that the contraction cycle can be repeated.

35. What are the side effects of prolonged steroid use? (3) (p9, paragraph 4)

35. Irrelevant to syllabus

36. Using information in the article, discuss the advantages and disadvantages of further research into muscle building. (4)

Advantages.

- Can help patients who suffer from muscular dystrophy or muscle atrophy.
- Can help to prevent wasting in astronauts.
- Could discover new genes involved in muscle building.

Disadvantages.

- Could be misused by athletes to improve performance.
- Clinical trials could cause irreversible damage to some volunteers.

37. Using your own knowledge and information from the article, discuss the advantages and disadvantages of using animals for medical research. (4)

Arguments For	Arguments Against
<p>Clinical Trials Stage 1 involves animals. Without animals we would not be able to discover new drugs</p> <p>Animal testing is better than nothing and does, in some cases, avert potential loss of human life. Animals with advanced nervous systems are more likely to suffer than more primitive animals. Ability to experience pain, and self-awareness should be considered when making a choice of animals for research. Eg. The use of Daphnia is acceptable in UK.</p> <p>Utilitarian argument. Animal testing is for the greater good. Animals will also benefit as the same drugs are used to treat animals.</p> <p>Machines like the MRI were untested using animals.</p> <p>Animal testing has advanced our understanding of human physiology</p>	<p>Why not use computer simulations in Clinical trials instead?</p> <p>Animals have rights too. Animals have no informed consent. Testing on animals when the potential side-effects are unknown is immoral. The species of animal may or may not affect people's perception of an animal's rights.</p> <p>Animals can't tell you when they are suffering</p> <p>Animals are often poorly cared for in labs</p> <p>Animal physiology is different to human physiology. Animal testing is, therefore, unhelpful</p>

Some more **PRACTICE** Questions

1. Why does the continued use of EPO have the potential for heightened risk of high blood pressure and atherosclerosis?

Continued use of epo will increase the number of red blood cells. The blood becomes more viscous and does not flow easily through the blood vessels. So, the heart will have to exert a greater pressure to pump blood into the vessels. This high blood pressure will cause endothelial damage in the arteries. T cells and monocytes migrate to the smooth muscle layer and differentiate into foam cells. The foam cells rapidly absorb cholesterol(LDL), calcium Ions and cell debris to form atheroma or atherosclerotic plaque.

2. Why does increasing EPO levels allow an athlete to improve their performance?

More epo will produce more RBCs and increase the oxygen carrying capacity of the blood. The muscles receive an abundant supply of oxygen and respire aerobically, producing lots of ATP. Anaerobic respiration does not occur and lactic acid will not accumulate. So, muscles will not get tired.

3. What is gene therapy and how could it be used by "drug cheats" in the future to enhance their oxygen carrying capacity?

Gene therapy is a technique of treating a genetic disorder by introducing a normal gene sequence into the patient's cells. The cells will then produce the normal protein and the symptoms of the disorder will be reduced. This technique can be misused by athletes to cheat in sports. For example, Gene therapy for anaemia could be used to increase RBC count, hence stamina of athletes. This could be done by introducing genes to increase epo production, which leads to more RBC production in the body.

4. Why is the use of AVV as a vector for the EPO gene more successful than using adenoviruses?

AVV is non-pathogenic as it is small and can enter host cells without generating an immune response. Adenoviruses are larger and can trigger antibody production.

5. Why would there be a problem with repeated dosing of gene therapy using the same adenovirus? What are the risks associated with using adenoviruses as vectors?

Familiar Antigens on the adenovirus will quickly be recognized by T helper memory cells and B memory cells. This will trigger a rapid immune response and destroy the virus even before it can deliver the gene into the host cell.

6. What is the normal role of IGF-1 in muscle tissue? Why is it important that the effects of IGF-1 are localised in the muscles it is applied to?

IGF-1 is a gene which plays a role in repair of muscle tissue. It prevents atrophy of muscle cells. The localized effect prevents the formation of harmful side effects, like enlargement of the heart or increased blood glucose levels. Genes like MGF (IGF-1), that prevent muscle wasting can be introduced to maintain big strong muscles and increase strength.

7. a) What is muscle atrophy and what circumstances may cause it to develop?

Muscle atrophy is the wasting or decrease in size of muscles, due to lack of use, metabolic disease or fasting.

b) How is the proteasome involved in the process?

Refer to question 23 above.

c) Why is there no atrophy in normal active muscle?

Because activity in muscles, causes wear and tear, which triggers the genes needed for repair and muscle building occurs or atrophy is averted.

d) How can muscle wasting occur and still leave the same number of muscle cells in place?

Less myofibrils per muscle fibre(cell).

8. Why would a "long QT" caused by a mutation in the *erg1* gene potentially lead to sudden death?

Long QT leads to arrhythmia and consequent tiring and cramping of cardiac muscle, leading to cardiac failure.

9. The drug astemizole showed great promise in preventing muscle atrophy yet it was withdrawn in 1999. Why was it withdrawn?

Because it was found to have a harmful side effect on cardiac muscle, leading to long QT syndrome.

10. "Foxo" is a Transcription Factor that controls gene switching. What effect would suppressing "Foxo" have on atrophy in muscle cells.

Atrogenes are genes which cause atrophy in muscles. Foxo is a transcription factor, which switches atrogenes on. Therefore, suppressing Foxo will slow down atrophy in muscles.

11. Explain why both IGF-1 and insulin are banned in sports.

Because they promote muscle growth and that would be unfair for other athletes who do not indulge in doping. (refer to comment SVR 124 on page 8)

12. What is the role of 'transcription factors'?

Transcription factors are proteins which are needed to switch genes on. Every gene will require a specific combination of transcription factors to switch the gene on. If anyone of the transcription factor is missing, the gene will remain switched off.

13. Why is NASA interested in research into stopping muscle atrophy?

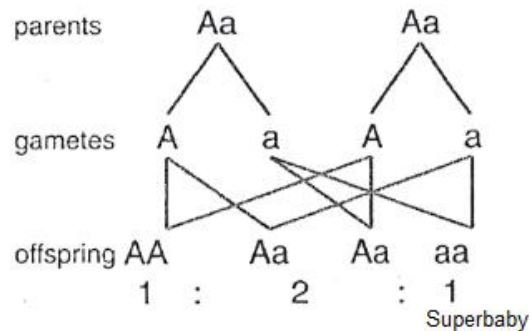
Muscle atrophy means the wasting of muscles, mainly due to disuse (lack of use). Astronauts in space live in microgravity and their muscles are barely used. This leads to loss of muscle tissue. So NASA would be interested in research which stops muscular atrophy.

14. How has myostatin inhibition led to the growth of a "superbaby" in Germany?

The form of the myostatin gene which produces myostatin is the DOMINANT allele(A).

The form of the myostatin gene which DOES NOT produce myostatin is the RECESSIVE allele(a).

The superbaby must have been homozygous recessive(aa) for the myostatin gene. The inheritance is shown below.



Myostatin inhibits the formation of new muscles by preventing satellite cells (stem cells) from differentiating into new muscle cells. If myostatin is inhibited (or absent – as in the superbaby) then satellite cells will differentiate into new muscle cells and increase the volumes of muscles. This lead to the growth of super baby who was homozygous recessive for the myostatin gene.

Note: Atrophy is wasting of muscles, without death of muscle cells, where as dystrophy is wasting of muscles due to death of muscle cells.

All the best for your exams

