



ADVANCED SUBSIDIARY GCE
HUMAN BIOLOGY
Case Studies

2858/01

INSERT

Monday 1 June 2009
Afternoon

Duration: 45 minutes



INSTRUCTIONS TO CANDIDATES

- Questions 1 and 2 are based on the articles that follow on pages 3 to 5 of this insert.

INFORMATION FOR CANDIDATES

- This document consists of **8** pages. Any blank pages are indicated.

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Case Study 1

Thalassaemia – not knowing when to stop!

The name 'thalassaemia' is derived from the Greek word '*thalassa*' meaning 'sea'. It is not really one disease, but rather a group of diseases that are collectively called haemoglobinopathies. Thalassaemia is found among populations who live around the Eastern Mediterranean and its name is derived from this sea.

As the name suggests, haemoglobinopathies are diseases that occur due to problems with haemoglobin. These can take a variety of forms. One of the most well known haemoglobinopathies is sickle cell anaemia. The amino acid glutamate is the sixth amino acid in the beta chain of haemoglobin. In cases of sickle cell anaemia, due to a gene mutation, this glutamate in the haemoglobin is replaced by the amino acid valine. The haemoglobin molecule becomes insoluble at low oxygen concentrations. This can result in 'sickling' and haemolysis of the red blood cells. Different mutations in other parts of either the alpha or beta chains can result in the haemoglobin having a higher affinity for oxygen.

Not all mutations result in a change to the properties of haemoglobin. The amino acid lysine is the 59th amino acid in the beta chain. This can be replaced by glutamate, asparagine or threonine without any change occurring to the physiological properties of haemoglobin.

In thalassaemia, the problem is not with the structure of the alpha or beta chains but whether the two chains are actually present. The most common thalassaemias are due to a failure to produce either enough of the alpha chain (alpha thalassaemia) or the beta chain (beta thalassaemia). This can severely disrupt oxygen transport. For example, in thalassaemia β^0 , no beta chains are produced at all. An individual with this form of thalassaemia will produce haemoglobin F (two alpha chains and two gamma chains). The gamma chain is produced by the foetus, but production stops in early infancy. It is the gamma chain that gives foetal haemoglobin a much higher affinity for oxygen than adult haemoglobin. Once the production of the gamma chain stops, the alpha haemoglobin chains form unstable tetramers that destroy the red blood cells as they are forming in the bone marrow. This is almost always fatal.

In other types of thalassaemia, both alpha and beta chains are made but there may be changes to one or other of the chains. This is the case in one form of thalassaemia known as Constant Spring (CS). This form of thalassaemia is named after a village in Jamaica, which was the home of the first family in which this disease was described. In CS haemoglobin, the beta chain is normal but the alpha chain is longer than normal, with an additional 31 amino acids.

How might this have happened? The most simple explanation seems to be that there is a point mutation in the stop codon of the alpha haemoglobin, which changes it to a sense codon. This means that extra amino acids are added to the chain as the mRNA is translated. However, there is an added complication. The mRNA for this extended alpha haemoglobin seems to be less stable than the mRNA that codes for the normal alpha form. As a result, there are more beta chains made than alpha chains. These beta chains form tetramers with each other, and the resultant haemoglobin – known as haemoglobin H – has a much higher affinity for oxygen, resulting in the problems described previously.

As with all the haemoglobinopathies, there is no cure. The disease can be managed by red blood cell transfusions and by the use of drugs.

Reference:

S.J. Higgins, A.J. Turner and E.J. Wood, *Biochemistry for the Medical Sciences: An Integrated Case Approach*. Longman Scientific and Technical, 1994, ISBN 0 582 10129 8

Case Study 2

The other Philadelphia story

Each year, an NHS trust, in conjunction with their local medical school and Primary Care Trust (PCT), runs a 'Research Day'. Consultants and other members of research teams are invited to present their research to the general public and to students from local schools. Rima, a sixth form student, has been intrigued by a talk given by the consultant haematologist Trish. Over lunch, she asks Trish about her job and about the research she is involved with.

Rima: *I hope you don't mind me asking but what exactly does a haematologist do?*

Trish: Well, it depends on what you mean by a haematologist. Some haematologists are Med Lab Scientists. They are involved in the day-to-day running of a range of labs. They might be in the blood transfusion labs looking at cross matching or they might be in the path lab.

Rima: *Path lab? You mean pathogens?*

Trish: No, pathology. They might be looking at blood counts or clotting times, or maybe they'll be looking at ante-natal haemoglobinopathies... when there is a problem with red blood cells.

Rima: *Oh, you mean like sickle cell anaemia!*

Trish: Right! Well done. But *my* main role is a clinical one. I'm involved in research but I also treat patients with a range of blood disorders. I hope you picked up on this in my talk.

Rima: I remember some of your slides... things like haemophilia and leukaemia and bone marrow transplants... but what I didn't understand was the Philadelphia chromosome.

Trish: Aha – you mean the CML story!

Rima: *CML?*

Trish: Chronic myeloid leukaemia. It's an interesting story. It starts in a bone marrow stem cell. For some reason two chromosomes swap over pieces. Chromosome 9 becomes a bit longer – it loses a small piece of DNA and it picks up a big piece from chromosome 22. Chromosome 22 becomes a bit shorter – it lost a big piece of DNA and it picked up the small piece from chromosome 9. But the piece of chromosome 9 that chromosome 22 picks up contains a proto-oncogene called c-ABL, and c-ABL fuses with part of another gene called BCR. The altered chromosome 22 is what we call the Philadelphia chromosome!

Rima: *I saw your slide – when does that happen?*

Trish: We're never sure. The disease can be there for years with only a slight increase in the leukaemic cells and then suddenly you get a 'blast crisis'... the leukaemic cells which should be dividing and differentiating into macrophages and granulocytes go mad and divide by themselves without differentiating!

Rima: *Why?*

Trish: Well, fusing the two bits of DNA in the Philadelphia chromosome leads to a protein – a fusion protein if you like – and this one happens to be an enzyme which is continually active. With this enzyme working the whole time, the cells just keep on dividing!

- Rima: *Right – but this is what I don't understand. You had a drug which inhibited this enzyme, right?*
- Trish: Right! So?
- Rima: *Well, you said you knew it had worked – it gets rid of the leukaemia, right?*
- Trish: That's right... 98% of the patients in one trial had normal-looking blood, and around 84% of these patients show no sign of the Philadelphia chromosome...
- Rima: *That's what I don't get – how did the drug get rid of the Philadelphia chromosome?*
- Trish: Ah, I see what's confusing you. You have to remember we are talking about cells with a 'life span' – cell cycle? (*Rima nods*) Without the enzyme working, the leukaemic cells can't divide but of course the other cells can. They have other similar enzymes which carry on functioning. Most of the cells with the Philadelphia chromosome die off and aren't replaced – that's all.
- Rima: *I get it! So they are cured of leukaemia!*
- Trish: Well, they do have to keep taking the drug for the rest of their lives. I think 'cure' is probably a bit too strong a word but the drug certainly improves survival.
- Rima: *Thanks for explaining – I really enjoyed your talk. It's good when you can see bits of biology making sense.*
- Trish: And it's good to meet interested A level students – I hope you enjoy the rest of the day.

Reference:

P. Roberts, Riviera Research Day Conference, November 2006

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