Oxford Cambridge and RSA

Friday 16 June 2023 – Morning

A Level Biology B (Advancing Biology)

H422/02 Scientific literacy in biology

Advance Notice Article

Time allowed: 2 hours 15 minutes

9897489470

INSTRUCTIONS
- Do **not** send this Advance Notice Article for marking. Keep it in the centre or recycle it.

INFORMATION
- This is a clean copy of the Advance Notice Article you have already seen.
- This document has **4** pages.

Development of therapeutic antibodies for the treatment of disease

The specific immune response involves the production of antibodies against pathogenic antigens. Clonal selection results in a population of B cells that produce these antibodies. Many different clones of B cells are produced in a normal immune response, and each clone is specific to different antigens. This is known as a polyclonal response, and the antibodies produced are known as polyclonal antibodies.

Monoclonal antibodies (mAbs), on the other hand, are produced by cloning one original B cell. The hybridoma technique for producing monoclonal antibodies was developed by George Kohler and Cesar Milstein, working at the MRC Laboratory of Molecular Biology in Cambridge. By fusing a single B cell with a myeloma (cancer) cell, the hybrid cell gains the ability to divide rapidly, allowing large numbers of identical antibody-producing cells to be grown in culture. Originally, mAbs were produced from mouse cells. These mouse mAbs have been used for many years in basic research and in diagnostic tests such as pregnancy test kits.

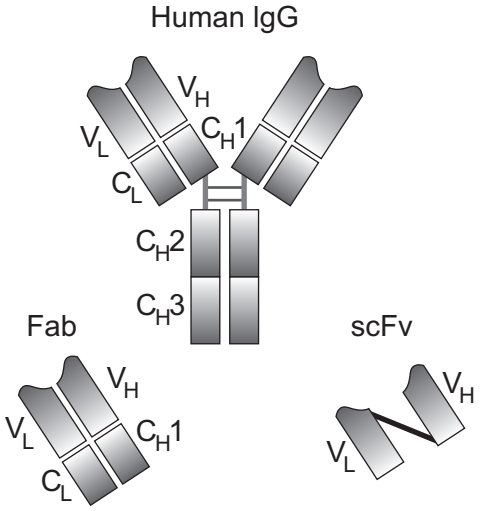
More recently, however, mAbs have been used in clinical applications to treat, rather than simply diagnose, disease. These are known as therapeutic mAbs. In 2018, six of the top ten best-selling drugs worldwide were mAbs. Hundreds of therapeutic mAbs have been studied in clinical trials, and 79 of these had been approved for use as medicines by the end of 2019. Almost half of the approved therapeutic mAbs are for the treatment of cancer.

Problems exist with the use of therapeutic mAbs from mouse cells: they cause a rapid human anti-mouse antibody (HAMA) response. This leads to removal of the mouse mAbs from the blood and can also lead to allergic reactions. To avoid these problems with mouse mAbs, Greg Winter, also working at the MRC Laboratory of Molecular Biology, developed a technique known as CDR grafting to humanise the mAbs. This method uses genetic engineering to graft the antigen-binding portion (variable region, or CDR) of a mouse antibody onto the constant region of a human antibody. In this way, mAbs can be produced that contain much less mouse protein and, therefore, pose less risk of a HAMA response. An example of a widely used humanised mAb is the drug Herceptin, which is used in the treatment of breast cancer.

A subsequent development, known as phage display, created a library of human immunoglobulin G (IgG) genes inserted into a type of virus known as a bacteriophage (phage for short). The variable regions of heavy (V_H) and light (V_L) antibody (IgG) chains are encoded by different genes. The constant region of these antibodies is encoded by a small number of genes. Therefore, it was possible to combine different variable region genes with constant region genes to produce millions of different antibody fragments. Fab fragments consist of the whole of the light chain, the variable region of the heavy chain (V_H) and the first part of the constant region of the heavy chain (C_{H1}). scFv fragments are even smaller and consist of only the variable light chain (V_L) and the variable heavy chain (V_H). Fragments expressed in a phage display can be screened for the required specificity.

Fig. 1 shows the structure of Fab and scFv fragments in comparison to a human IgG molecule.

Fig. 1



The phage display method removed the need for immunisation of mice and the production of hybridomas. It also enabled the production of fully human antibodies. The first approved therapeutic mAb produced using phage display was adalimumab, which is approved to treat inflammatory diseases, such as rheumatoid and psoriatic arthritis, Crohn's disease, and psoriasis. Adalimumab is now the world's best-selling pharmaceutical drug.

Development of new mAbs by these recent methods can take many months, even years. A quicker method is being developed that involves the use of flow cytometry to isolate single B cells that produce a required antibody. The speed of this technique is proving useful as a way of obtaining neutralising antibodies with the potential to treat viral or bacterial infections (e.g. HIV, zika virus, and anthrax, caused by *Bacillus anthracis*). However, therapeutic mAbs produced using flow cytometry are yet to be approved to treat these infections in patients.

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Oxford Cambridge and RSA

Friday 16 June 2023 – Morning

A Level Biology B (Advancing Biology)

H422/02 Scientific literacy in biology

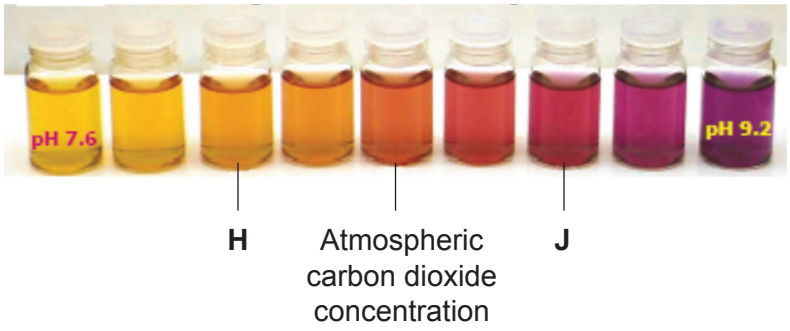
Insert

Time allowed: 2 hours 15 minutes

INSTRUCTIONS
- Do **not** send this Insert for marking. Keep it in the centre or recycle it.

INFORMATION
- This Insert contains **Fig. 6.2**.
- This document has **2** pages.

Fig. 6.2



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Friday 16 June 2023 – Morning

A Level Biology B (Advancing Biology)

H422/02 Scientific literacy in biology

Time allowed: 2 hours 15 minutes

You must have:
- a clean copy of the Advance Notice Article (inside this document)
- the Insert (inside this document)

You can use:
- a scientific or graphical calculator
- a ruler (cm/mm)

Please write clearly in black ink. **Do not write in the barcodes.**

Centre number | | | | | | Candidate number | | | | |

First name(s) _____

Last name _____

INSTRUCTIONS
- Use black ink. You can use an HB pencil, but only for graphs and diagrams.
- Write your answer to each question in the space provided. If you need extra space use the lined pages at the end of this booklet. The question numbers must be clearly shown.
- Answer **all** the questions.
- Where appropriate, your answer should be supported with working. Marks might be given for using a correct method, even if your answer is wrong.

INFORMATION
- The total mark for this paper is **100**.
- The marks for each question are shown in brackets **[ ]**.
- Quality of extended response will be assessed in questions marked with an asterisk (*).
- This document has **28** pages.

ADVICE
- Read each question carefully before you start your answer.

1 This question is based on the Advance Notice Article **'Development of therapeutic antibodies for the treatment of disease'**.

(a) (i) State what is meant by the term **antigen**.

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..... **[1]**

(ii) Scientists can combine antibody fragments using phage display to produce many different antibodies, each specific to a different antigen.

Using the abbreviations from **Fig. 1** in the Advance Notice Article, explain how combining antibody fragments allows scientists to produce many different antibodies, each specific to a different antigen.

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(iii) The B cell receptor is an IgG molecule with the same structure as the human IgG shown in **Fig. 1** in the Advance Notice Article.

Use an abbreviation from **Fig. 1** to identify the part of the B cell receptor that will be attached to the cell surface membrane of a B cell.

..... **[1]**

(b) (i) Explain why mouse monoclonal antibodies (mAbs) have been largely replaced as therapeutic antibodies by humanised or fully human mAbs.

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..... **[2]**

(ii) Explain why the Fab and scFv antibody fragments shown in **Fig. 1** are effective as neutralizing or agglutinating antibodies but are less effective as opsonins or in activation of complement.

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(c) (i) Describe how therapeutic mAbs can be used in cancer treatment.

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(ii) The cost of treating a patient with advanced cancer using therapeutic mAbs can be extremely high. In some cases, the treatment can increase survival time by just a few months.

Pharmaceutical companies justify the high cost of treatment based on the high costs of developing and testing therapeutic mAbs.

Discuss whether the use of therapeutic mAbs to treat cancer justifies the high costs.

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(d)* Describe the role of T and B lymphocytes in the development of long-term immunity.

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Additional answer space if required.

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2 Aerobic fitness and muscle mass decrease as humans age. Both of these changes have an adverse effect on our general health.

(a) VO_2 max is a measure of aerobic fitness.

(i) State the definition of VO_2 max.

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(ii) Describe how VO_2 max is measured.

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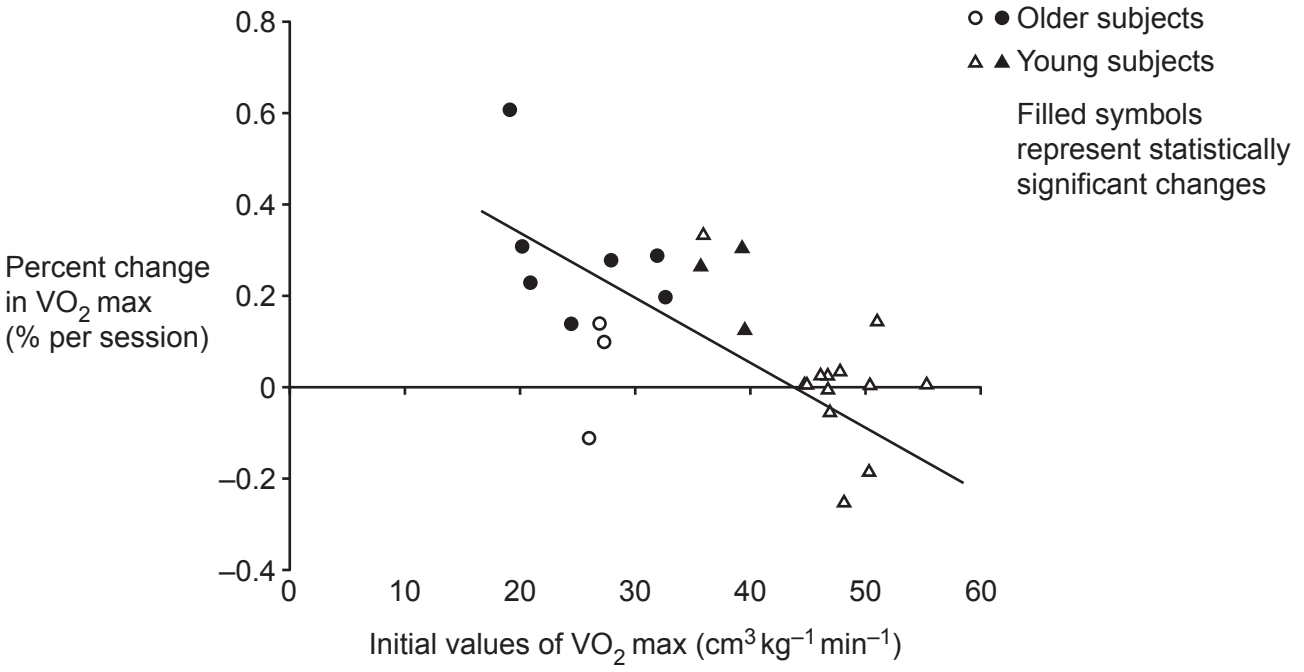
(b) In older people (over 60 years) resistance training (lifting or pulling against a resistance) is a way of increasing muscle mass and improving bone strength. These changes reduce the risks associated with osteoporosis, falls and bone fractures.

Aerobic training might not be advisable in some older people and can also inhibit the development of muscle mass through resistance training.

A group of scientists reviewed published studies of the effect of resistance training on aerobic fitness in both young people and older people. They calculated the percentage increase in VO_2 max after a course of resistance training.

Because the different studies used training courses of different lengths, they expressed their results as 'percentage change in VO_2 max per session'. Their results are shown in **Fig. 2.1**. Each symbol in **Fig. 2.1** represents the result of one study.

Fig. 2.1



The scientists concluded that resistance training increases aerobic fitness in subjects of all ages who had a low starting level of aerobic fitness.

(i) Evaluate this conclusion.

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(ii) Suggest why an increase in muscle mass might lead to an increase in VO_2 max.

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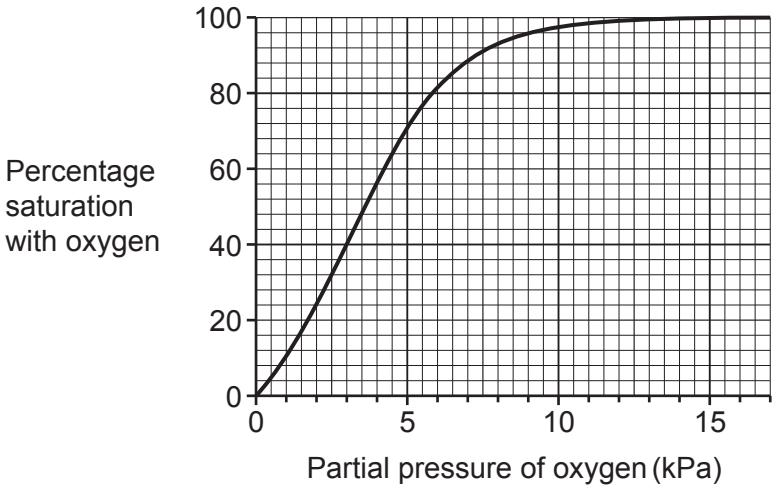
..... **[1]**

(c) High intensity interval training (HIIT) can increase VO_2 max to a greater extent than traditional, long aerobic exercise.

Fig. 2.2 shows the oxygen dissociation curve of an adult male at rest.

Fig. 2.2



(i) Sketch the curve you would expect when the same person is undergoing a period of HIIT.

Answer on Fig. 2.2. **[1]**

(ii) Explain how the curve you have sketched on **Fig. 2.2** helps improve this person's performance.

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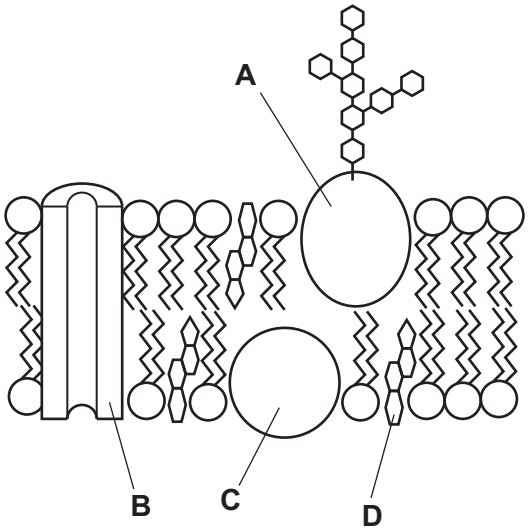
3 TLRs are receptors found on macrophages and are involved in the non-specific immune response.

Gram-negative bacteria have lipopolysaccharide (LPS) in their cell walls.

When Gram-negative bacteria infect a host, such as a human, they release LPS which binds to TLRs on macrophages. This causes the macrophages to release cytokines.

(a) **Fig. 3.1** shows a section of the plasma membrane of a macrophage.

Fig. 3.1



(i) State the letter on **Fig. 3.1** that identifies the component of the membrane that binds to LPS.

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(ii) Explain why the membrane is described as a fluid mosaic.

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(iii) Describe **two** effects of cytokine release by macrophages.

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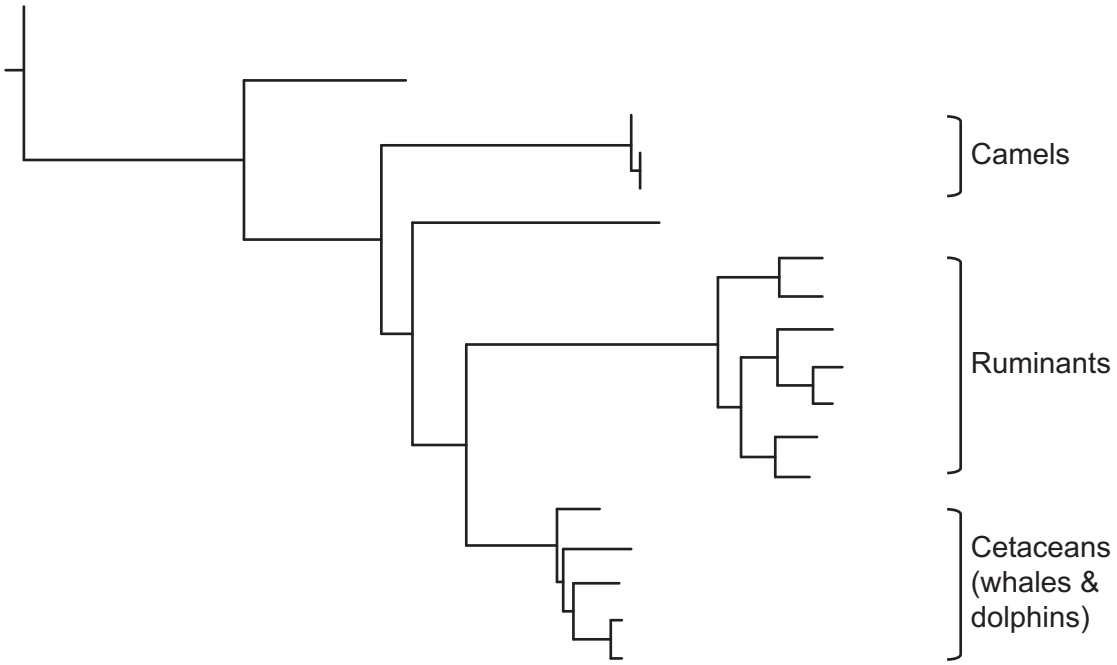
(b) TLRs have been used to study the evolutionary relationships between ungulates, a group of mammals. Many species of ungulate have hooves.

Fig. 3.2 shows the evolutionary relationships in ungulates.

Fig. 3.2



(i) State the name given to the study of evolutionary relationships.

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(ii) Explain how the relationships shown in **Fig. 3.2**, based on TLRs, could have been worked out.

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(iii) Camels and ruminants are herbivores and both groups have an even number of toes. This led a student to conclude that camels and ruminants are the most closely related groups of ungulates.

Discuss whether the results support the student's conclusion.

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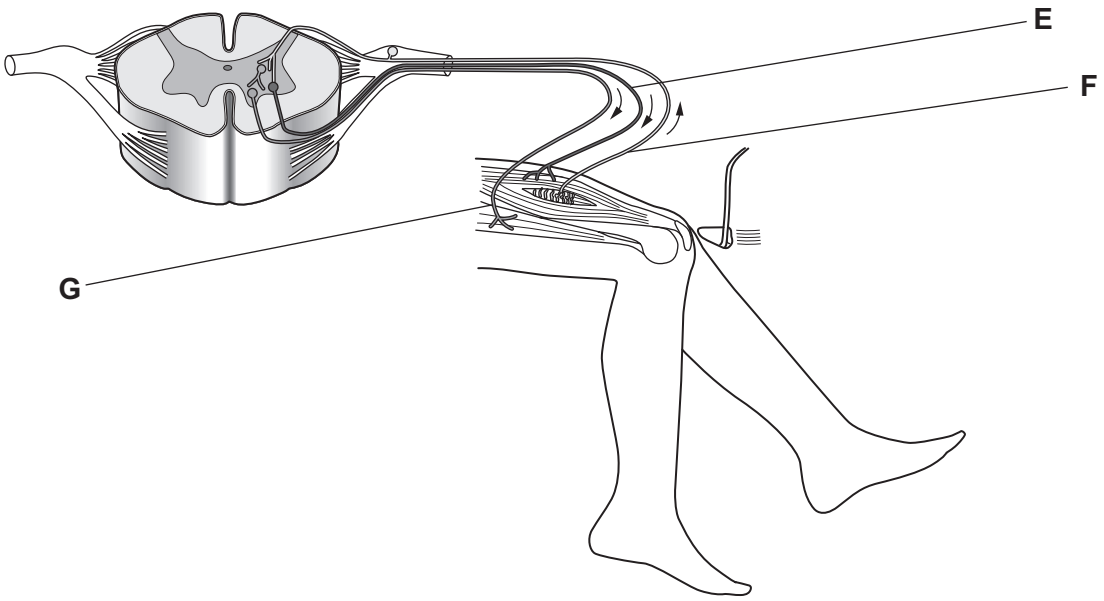
4 The knee jerk reflex is used to identify disorders of nervous conduction. The kneecap is struck with a rubber hammer and the lower leg responds by flexing in a kicking action.

(a) The neurones involved in the knee jerk reflex are shown in the diagram.



(i) Identify structures **E** and **F** on the diagram.

E .....

F .....

[2]

(ii) The neurone labelled **G** inhibits muscle contraction.

Suggest the advantage of this inhibition.

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..... **[1]**

(iii) Explain why reflexes give animals a survival advantage.

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..... **[2]**

(b) Physiotherapists use the knee jerk reflex to identify possible nerve damage in patients.

Based on the physiotherapist's assessment of the speed of response, the knee jerk reflex responses are categorised as:

- Level 0: No evidence of contraction
- Level 1: Decreased, but still present (hyporeflexia)
- Level 2: Normal
- Level 3: Super-normal (hyperreflexia)
- Level 4: Clonus (repetitive shortening of the muscle after a single stimulation).

(i) Explain the limitations of this method for collecting data.

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(ii) Suggest improvements to this method for collecting data for analysis.

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(c) An investigation into reaction times was performed in a school laboratory.

The subjects sat in front of a laptop computer with a touchscreen. A blue square was shown on the screen. The subject was told to tap the screen as soon as the square changed colour to green. The computer measured the subject's reaction time as the time between the change of colour and the screen being tapped.

The study tested three groups, with 10 participants in each group:
- group 1 were all 16 – 18 year old male students
- group 2 were all 16 – 18 year old female students
- group 3 was a mixture of male and female staff members.

The results are shown in **Table 4.1**.

Table 4.1

	Reaction time (ms)		
	Group 1	**Group 2**	**Group 3**
	150	170	150
	158	225	275
	174	220	280
	186	205	350
	196	210	220
	205	195	195
	202	185	205
	188	206	320
	195	222	160
	179	199	153
Mean	183.3	203.7	230.8
Standard deviation	18.2640	17.2694	77.1303

A *t*-test was carried out to compare the reaction times of male and female students.

(i) State the null hypothesis that should be used.

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..... **[1]**

(ii) Use the data in **Table 4.1** to calculate a value for *t*.

Use the formula: $t = \dfrac{|\overline{x}_A - \overline{x}_B|}{\sqrt{\dfrac{s_A^2}{n_A} + \dfrac{s_B^2}{n_B}}}$

t = ... **[3]**

(iii) **Table 4.2** shows the critical values for *t*.

Table 4.2

Degrees of freedom	p values			
	0.10	**0.05**	**0.01**	**0.001**
1	6.31	12.71	63.66	636.60
2	2.92	4.30	9.92	31.60
4	2.13	2.78	4.60	8.61
6	1.94	2.45	3.71	5.96
8	1.86	2.31	3.36	5.04
10	1.81	2.23	3.17	4.59
16	1.75	2.12	2.92	4.02
18	1.73	2.10	2.88	3.92
20	1.72	2.09	2.85	3.85

Use your value for *t* and **Table 4.2** to explain the conclusions the researchers would have reached when comparing the reaction times of males and females.

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(iv) State the conclusion that can be drawn about group 3 compared with groups 1 and 2, based on the standard deviations shown in **Table 4.1**.

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(v) Suggest an explanation for the difference between group 3 and the other two groups.

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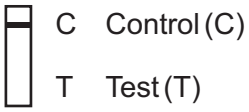
5 Ovulation lateral flow test kits are used by women who are trying to become pregnant.

The kits work on the same principle as pregnancy test kits. They show the presence of LH in urine, which coincides with ovulation.

The base of the test strip contains monoclonal antibodies specific to LH.

The test strip is dipped into a urine sample, and the results are read after a few minutes.

(a) The diagram shows the possible results of ovulation lateral flow tests.



C Control (C)

T Test (T)

Negative result

Positive results

Results not valid

(i) The control and test lines also have monoclonal antibodies attached.

State what would bind to the antibodies on each line.

Control line .....

Test line .....

[2]

(ii) Explain why no lines means that the result is **not** valid.

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..... **[1]**

(b) Describe **one** cause of infertility in males and **one** in females.

Males .....

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Females .....

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[2]

(c)* Discuss the different treatments for infertility.

You should include the ethical issues **and** draw conclusions based on risks and benefits associated with the different treatments in your answer.

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Additional answer space if required.

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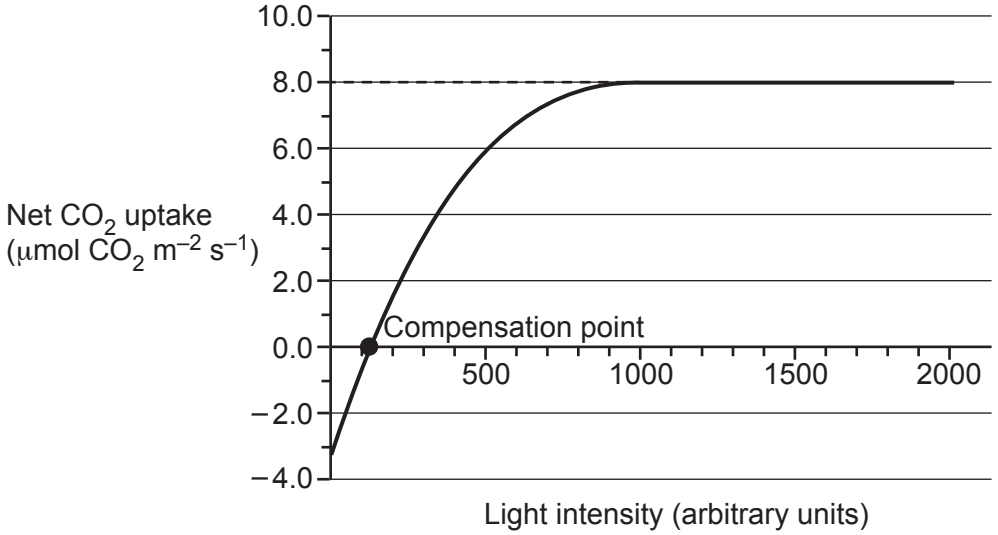
6 **(a)** **Fig. 6.1** shows the relationship between light intensity and the net rate of photosynthesis, measured as net CO_2 uptake, in a plant growing at atmospheric CO_2 concentration (0.04%).

Fig. 6.1



(i) Explain the significance of the compensation point shown on **Fig. 6.1**.

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(ii) Use the data in **Fig. 6.1** to explain why crops growing in greenhouses during the winter months are often grown under artificial lights.

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(b) A student used hydrogen carbonate indicator solutions to investigate the compensation point in leaf samples from two different species of crop plant.

Leaf extracts were prepared and placed in glass bottles containing hydrogen carbonate indicator solution. The bottles were exposed to light for a fixed period of time, and the colours were compared with a set of standards, shown in **Fig. 6.2** on the Insert.

(i) Explain **two** steps that the student should take to ensure an accurate comparison of compensation points.

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[4]

(ii) The colour of the hydrogen carbonate indicator after each plant extract was exposed to light is indicated by the labels **H** and **J** in **Fig. 6.2** on the Insert.

On the basis of this result, the student concluded that crop plant **J** would be more suitable for growing in the winter months than crop plant **H**.

Evaluate the student's conclusions.

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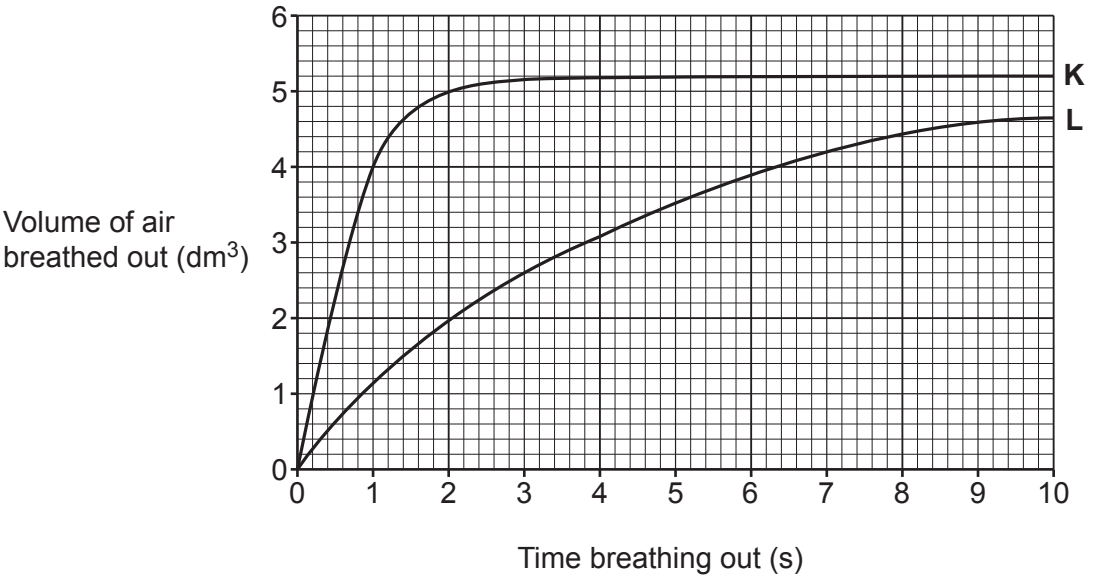
7 **(a)** The graph shows data recorded during forced expiration (breathing out) in two subjects, **K** and **L**. One subject is a patient with chronic obstructive pulmonary disease (COPD) and the other is a normal control.



The table shows the effects of COPD on the vital capacity and forced expiratory volume in one second (FEV_1).

Measurement	Normal range	COPD
Vital capacity	3 – 5.5 dm^3	May be reduced
FEV_1	Calculation based on height and age	Reduced
Ratio of FEV_1 to vital capacity	Approximately 0.7 – 0.8	<0.7

(i) A student said that it was not possible to estimate vital capacity for subject **L** on the basis of the graph.

Evaluate the student's conclusion.

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(ii) With the aid of a calculation, show that it is possible to identify which of the two curves, **K** and **L**, is the normal control and which is the patient with COPD.

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(iii) FEV_1 is calculated using the formula:

(4.3 × height) – (0.029 × age) – 2.49

where height is in m and age is in years.

Use this formula to estimate the age in years of a healthy subject with FEV_1 = 4.4 and height = 1.76 m.

Age = ... years **[2]**

(b) Asthma is another obstructive respiratory disease in which breathing out can be difficult. A severe asthma attack can lead to respiratory arrest, where the person stops breathing.

The first aid treatment for respiratory arrest is to administer expired air resuscitation (EAR).

(i) Explain the reasons for the following aspects of EAR.

1. Gloves and a mask should be worn.

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2. The patient's head should be held back.

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3. Watch to see if the chest rises whilst blowing into the mouth.

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4. If there is no pulse after two breaths, you must perform cardiopulmonary resuscitation (CPR).

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[4]

(ii) Suggest how EAR would differ if you were performing it on a small child.

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(c) Lung surfactant is a mixture of phospholipids and proteins that helps the alveoli stretch and expand during breathing in and prevents them collapsing when breathing out.

The following sentences compare the synthesis and secretion of lung surfactant proteins with other types of protein secreted by cells.

Complete the sentences using the most appropriate words or terms.

All secreted proteins are produced on ..... attached to the rough endoplasmic reticulum (RER). The assembled protein in the RER is then pinched off in ..... vesicles and moved to the ..... where it is processed and packaged into ..... vesicles.

In alveolar epithelial cells these are known as lamellar bodies. These move to the cell surface membrane and the surfactant is released by ..... .

Movement of these organelles requires motor proteins to move them along the ..... .

[4]

END OF QUESTION PAPER

ADDITIONAL ANSWER SPACE

If additional space is required, you should use the following lined page(s). The question number(s) must be clearly shown in the margin(s).