1. Alzheimer's is a neurological disorder. A potential new drug treatment for Alzheimer's has entered clinical trials. The drug has passed the phase 2 trial in which it was tested on 50 patients.

A brief summary of the plan for phase 3 of the trial is as follows:

- The new drug is compared to the best treatment currently available.
- 70 patients receive the new drug in total, 35 from hospital A and 35 from hospital B.
- A placebo is not used.
- Blind trials are used.

(i) Discuss aspects of the planned phase 3 clinical trial and explain how each aspect is likely to affect the validity of the results.

---[3]

(ii) State **two** possible causes of Alzheimer's.

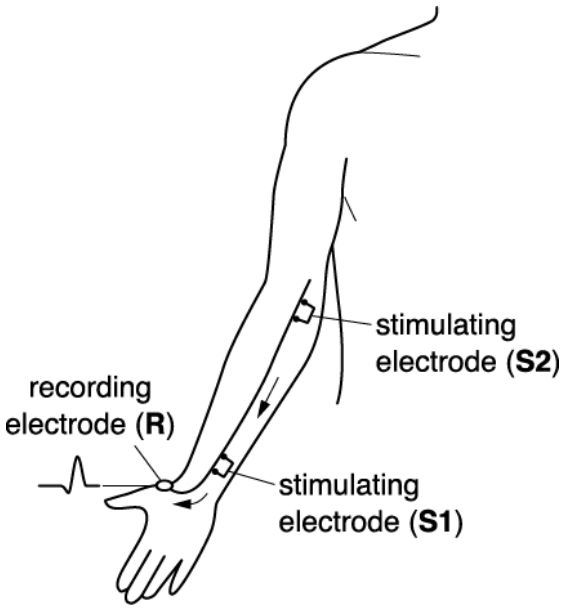
1

2

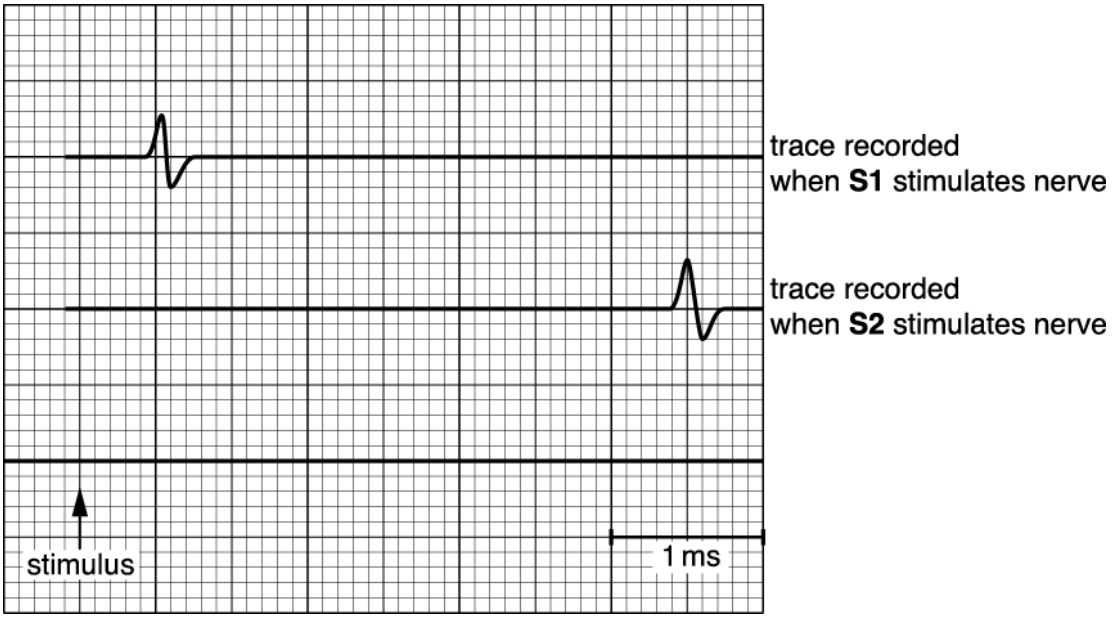
---[2]

2(a). A nerve conduction velocity (**NCV**) test can be carried out to measure the speed of conduction of a nerve impulse.

An NCV test on a nerve in the arm is shown in the following figure.



- Two stimulating electrodes (**S1** and **S2**) are attached to the skin above the nerve.
- The distance (**D**) between the stimulating electrodes is measured.
- The first electrode (**S1**) stimulates the nerve and the resulting electrical response is recorded by the recording electrode (**R**).
- The second electrode (**S2**) stimulates the nerve and the electrical response is also recorded by **R**.
- An NCV trace is obtained, such as that shown in the following graph.



(i) The nerve conduction velocity (NCV) is calculated using the formula:

$$NCV = \frac{D}{T_{S2} - T_{S1}}$$

Where:
D is the distance between the stimulating electrodes
T_{S1} is the time taken between the stimulus given at **S1** and the wave recorded at **R**
T_{S2} is the time taken between the stimulus given at **S2** and the wave recorded at **R**.

Calculate the nerve conduction velocity, assuming **D** is 20 cm.

Show your working. Give your answer to the **nearest whole number**.

Answer _____ mm ms^{-1} **[2]**

(ii) Suggest how a stimulus initiates an action potential in a motor neurone **and** explain how the action potential is transmitted.

In your answer, you should refer to both the initiation and the transmission of the action potential.

[7]

(iii) NCV tests carried out on newborn babies give values that are only half of those found in adults.

Suggest a reason for this observation.

[1]

(b). The conduction velocity in neurones is thought to decrease as a person ages.

In a study of the effect of ageing on **sensory** neurones, NCV tests were carried out on 1000 people. The test was repeated five years later on 500 people from the original group. Two different nerves were tested on both arms for each subject.

The following controls were in place during the study:

- the temperature of the skin surface was kept at 32°C
- subjects diagnosed with diabetes mellitus were excluded from the study.

(i) Explain why it was important to keep skin temperature constant **and** suggest why a temperature of 37°C was **not** selected.

[2]

(ii) Suggest a reason why subjects with diabetes mellitus were excluded from this study.

[1]

(iii) The results from the NCV study are given in the table.

Nerve tested	Mean velocity change after 5 years (ms^{-1})	Probability (P–value)	Confidence limits (ms^{-1})
Nerve 1	–1.1	$p < 0.0001$	–1.49, – 0.62
Nerve 2	– 0.7	$p = 0.002$	–1.15, –0.27

What **two** conclusions about conduction velocity in neurones can be drawn from **all** the information shown in the table?

[2]

3. Three drugs used in the treatment of patients diagnosed with mild or moderate symptoms of Alzheimer's disease underwent clinical trials.

- Patients were tested using an Alzheimer's disease assessment scale (ADAS), which assessed cognitive performance.
- Patients were tested at intervals of 6 weeks.

The results are shown in Fig. 4.1.

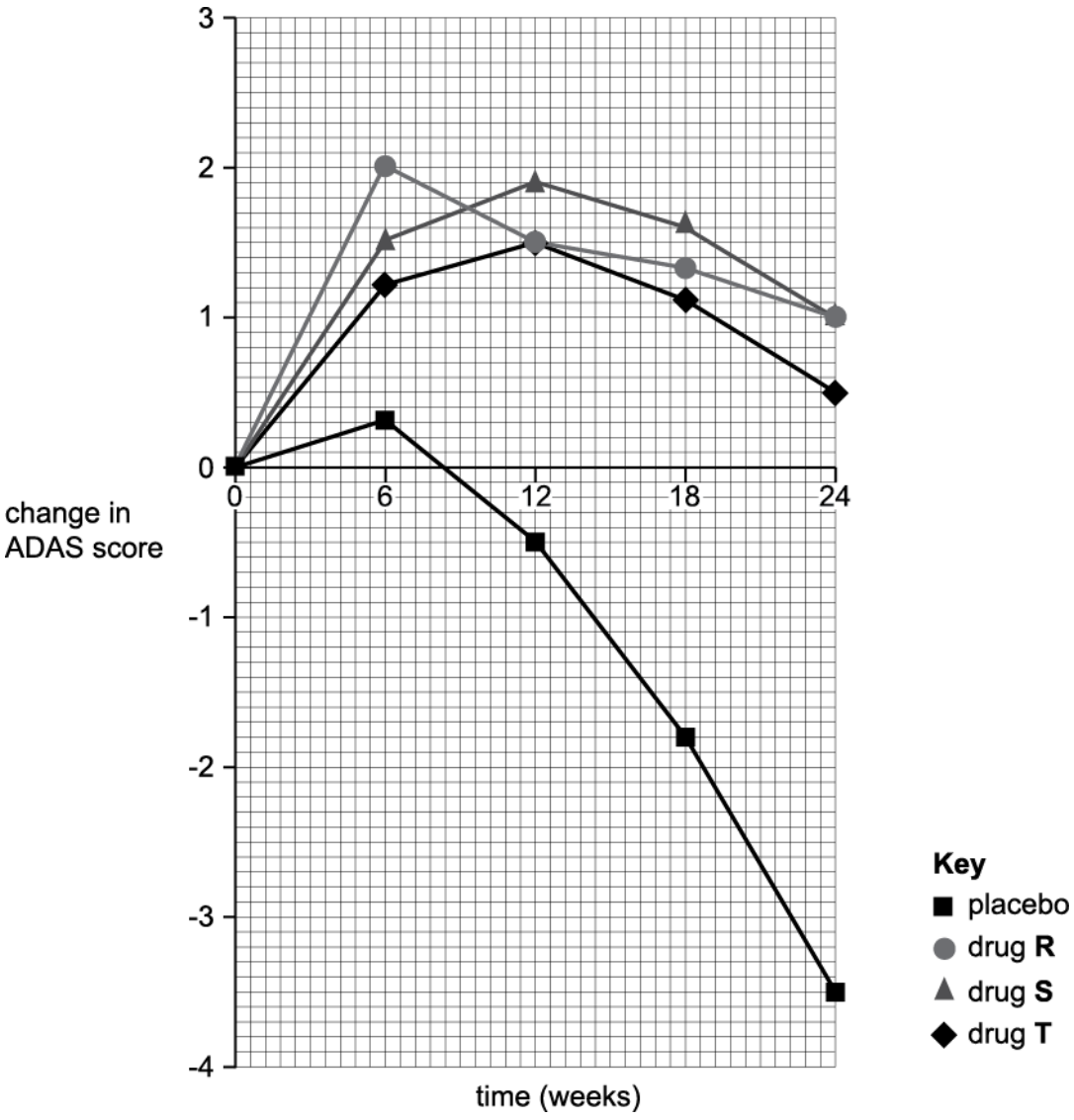


Fig. 4.1

(i) Calculate the percentage decrease in ADAS score between 12 and 24 weeks for those patients who did not receive a drug treatment.

Show your working.

Answer _____ % **[2]**

(ii) Using the data in Fig. 4.1, evaluate the effectiveness of the three drugs in the treatment of the symptoms of Alzheimer's over the trial period.

_____

_____

_____

_____

_____ **[2]**

(iii) All three of the tested drugs act as inhibitors of the enzyme acetylcholinesterase.

- Drug **R** acts as an irreversible inhibitor of acetylcholinesterase.
- Drugs **S** and **T** act as competitive inhibitors.

Fig. 4.2 shows the effect of increasing acetylcholine concentration on the rate of reaction of acetylcholinesterase in the presence of drug **S**.

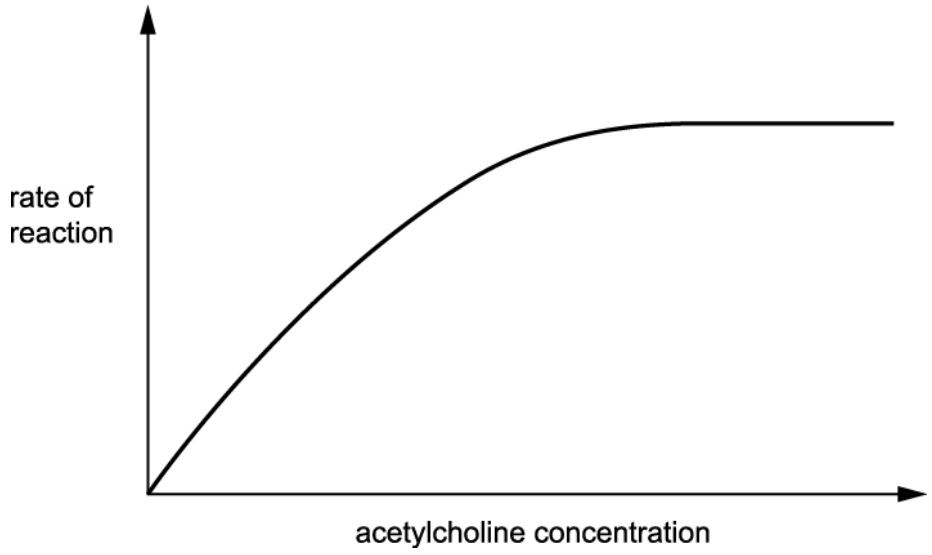


Fig. 4.2

Drug **R** was then used instead of drug **S**. Describe how the curve obtained from drug **R** would be different to the curve shown in Fig. 4.2.

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[1]

END OF QUESTION PAPER

Question			Answer/Indicative content	Marks	Guidance
1		i	**Any 3 from:** *idea that* 70 people is too low for a phase 3 trial (therefore reducing validity) / phase 3 trial should involve, hundreds / thousands, of people *idea that* (sample size of 70 people is) unlikely to differentiate new drug's performance from current drug (therefore reducing validity) blind trials (improve validity by), reducing / removing, bias (of patients) double blind trials (would be), improvement / AW, by removing bias of scientists *idea that* placebo cannot be used because it would be unethical in a phase 3 trial	3	
		ii	**Any 2 from:** genetics head injuries age smoking	2	
			Total	**5**	
2	a	i	57 / 58 mms^{-1};;	2	**Correct answer = 2 marks** If answer is incorrect, look for **200 / 3.5 OR 20/3.5 = 1 mark** **6 = 1 mark** (they have calculated (5.7) correctly but not converted cm to mm) **CREDIT 1** mark for an error carried forward for 200 ÷ x (any number) if answer is correct and a whole number

Question			Answer/Indicative content	Marks	Guidance
		ii	1. (voltage gated) sodium (ion) channels open; 2. sodium ions / diffuse in / rush in; 3. (membrane becomes) depolarised / AW; 4. *idea of* local circuits, ahead (and behind) the active zone; 5. (circuit due to) sideways movement of sodium ions; 6. Ref to (circuit / sodium ion movement) depolarisation / AW, of next region / node; 7. Ref to hyperpolarisation of, previous region / previous node; 8. ref to saltatory conduction / described; 9. ion movement (only) at nodes of Ranvier / myelin sheath insulates between nodes;	6 max	1. DO NOT CREDIT in context of acetylcholine CREDIT Na^+ enters down a concentration gradient ACCEPT influx of sodium ions 3. CREDIT a description e.g. + 40mv IGNORE 'neurone' or 'cell' in this context 4. ACCEPT alternative wording e.g. local currents 7. CREDIT ref to refractory period in previous region
		ii	QWC;	1	AWARD any **two** mark points from **4, 5, 6 or 7**

Question			Answer/Indicative content	Marks	Guidance
		iii	*idea that* myelin sheath is not present at birth OR myelin sheath takes time to develop; AVP;	1	DO NOT CREDIT reference to nervous system not being fully developed IGNORE reference to shorter axons / neurones e.g. ref to neurones having a smaller diameter Examiner's Comments Calculations such as that in (i) have not been asked before and it was pleasing to see how many candidates grasped the principle. The commonest answer was '6' where candidates had not converted their measurements to mm but had followed the rubric and given a whole number for their answer and this gained a mark. Part (ii) was not answered well with many candidates who referred to transmission between neurones rather than the transmission of an impulse within a neurone. The synapse is clearly taught well in Centres and candidates were anxious to display their knowledge but answers written in terms of synaptic transmission did not allow candidates to access the full mark range. The use of the word 'stimulus' in the question prompted some candidates to answer in terms of the reflex arc. Even answers which scored full marks struggled to explain how action potentials are propagated and, although many candidates wrote that the refractory period ensures a single direction of travel, few went on to explain how or why that is the case. A common mistake was candidates referring to sodium ions diffusing into the axon membrane. While lack of myelination was the most common correct answer to (iii), it was pleasing to see answers referring to small axon diameters. However, many candidates simply referred to babies being smaller or axons being shorter despite having calculated an NCV at the beginning of the question.

Question			Answer/Indicative content	Marks	Guidance
	b	i	*Idea that* higher temperatures would give faster, conduction / impulses / diffusion **OR** lower temperatures would give slower, conduction / impulses / diffusion of ions; (not 37°C) *idea that* peripheral/skin temperature will be lower than 37°C **OR** 37°C is the, core body temperature / AW **OR** AVP;	2	**IGNORE** reference to controlling a variable as this is given in the question **IGNORE** reference to high temperatures denaturing proteins (in this context) e.g. 37°C could cause sweating (which could interfere with the readings)
		ii	*idea that* diabetes / high blood glucose leads to damaged neurones /nerves; AVP;	1	**CREDIT** *idea of* damage to receptors e.g. reduced sensitivity **CREDIT** idea of damage to Schwann cells or myelin sheath or reduction in myelination e.g. medication taken could interfere with the results **OR** low blood sugar / hypoglycaemia slows impulses

Question			Answer/Indicative content	Marks	Guidance
		iii	*idea that* Conduction velocity slows, (significantly) / AW (over 5 years); *idea that* (means) not all neurones change at the same rate OR (confidence limits) changes within the same nerve varies within populations;	2	CREDIT answers in either order ACCEPT reference to age slowing transmission in neurones (without further qualification). DO NOT CREDIT references to either nerve being faster or slower (since the data is about change in velocity) ACCEPT nerve 1 changes more than nerve 2 Examiner's Comments In (i), although many candidates could explain that 37°C was core body temperature and that the skin would be cooler, too many wrote in very general terms about why it needed to be controlled. The fact that a variable has been controlled is because it would otherwise invalidate the investigation - but that statement applies to any variable. The question referred specifically to temperature and correct answers referred to higher temperatures speeding up the nerve impulse or the diffusion of ions across the axon membrane. Part (ii) proved to be a challenge and, although many candidates were able to refer to neurone damage, several candidates referred to high blood sugar resulting in the production of too much ATP. This misconception has appeared before. Part (iii) again proved a challenging question with too many candidates focussing on the statistics rather than the question which asked for conclusions about nerve conduction velocity. Good candidates spotted that velocity declined in both neurones but not all neurones declined to the same extent, while weaker candidates answered in terms of one nerve being faster than the other.
			Total	15	

Question			Answer/Indicative content	Marks	Guidance
3		i	600 ✓✓	2	For incorrect reading(s) from the graph but a correct calculation allow **1 max**
		ii	*idea that* (over trial period), cognitive function improved / was higher than baseline for all three drugs tested OR *idea that* no significant difference between the three drugs OR *idea that* improvement not sustained / dropping back to baseline ✓ figures given in support ✓	2	
		iii	(the curve would) plateau / AW, below the curve in Fig. 4.2 ✓	1	
			Total	5	