Please check the examination details below before entering your candidate information

Candidate surname	Other names
StemUp Model Solution	

Centre Number | Candidate Number

Pearson Edexcel Level 3 GCE

Wednesday 18 June 2025

Morning (Time: 2 hours)

Paper reference **9BN0/03**

Biology A (Salters Nuffield)

Advanced

PAPER 3: General and Practical Applications in Biology

You must have:
Ruler, HB pencil, scientific calculator and a copy of the scientific article adapted from New Scientist (enclosed)

Total Marks

Instructions

- Use **black** ink or ball-point pen.
- **Fill in the boxes** at the top of this page with your name, centre number and candidate number.
- Answer **all** questions.
- **Show all your working out** in calculations and **include units** where appropriate.
- Answer the questions in the spaces provided – *there may be more space than you need.*

Information

- The total mark for this paper is 100.
- The marks for **each** question are shown in brackets – *use this as a guide as to how much time to spend on each question.*
- You may use a scientific calculator.
- In questions marked with an **asterisk (*)**, marks will be awarded for your ability to structure your answer logically, showing how the points that you make are related or follow on from each other where appropriate.

Advice

- Read each question carefully before you start to answer it.
- Try to answer every question.
- Check your answers if you have time at the end.

Turn over

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P 7 8 6 5 9 A 0 1 3 2

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Answer ALL questions.

Write your answers in the spaces provided.

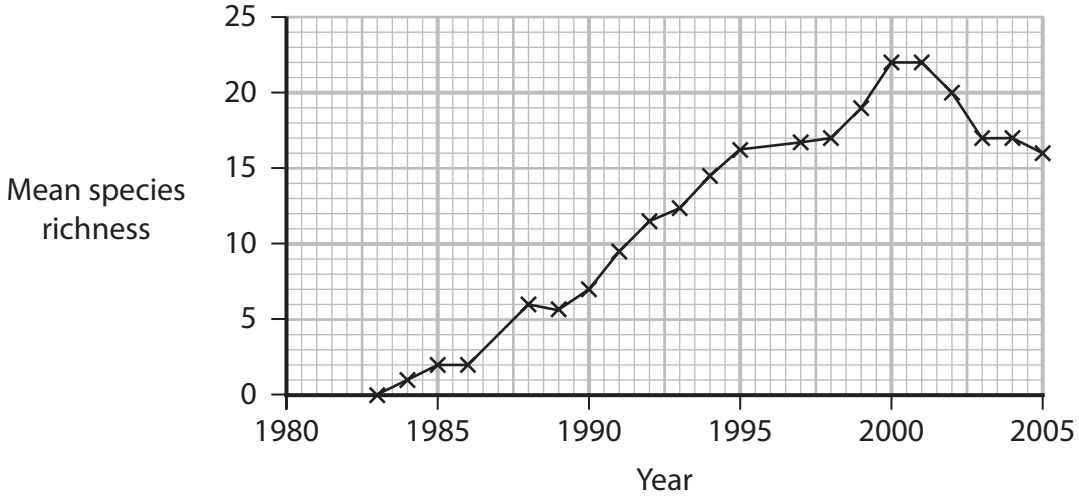
1 In 1980, a volcano erupted in Washington State, USA.

Ash from the volcano covered surrounding vegetation, killing all the plants.

Succession has been investigated on one of the sides of the volcano.

(a) In one study, species richness on the side of the volcano was measured.

The graph shows the change in mean species richness from 1983 to 2005.



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

(2)

Succession is the change in the species (community) of plants and animals in an area, taking place over time, leading to a climax community.

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(ii) Calculate the rate of increase in the mean number of species from 1986 to 1995.

Give your answer to two significant figures and include units.

(2)

from graph: 1986 = 2 species, 1995 = 16 species

16 − 2 = 14 species 1995 − 1986 = 9 years

rate = 14 ÷ 9 = 1.555...

Answer 1.6 species $year^{-1}$

(iii) Following the eruption, one of the first plant species to be observed was *Lupinus lepidus*.

Give the term used to describe the first species to appear at a location.

(1)

Pioneer species (colonising species).

(b) Species of *Lupinus* have organs called root nodules that contain bacteria.

Sugars and nutrients are exchanged between the plant and the bacteria in the root nodules.

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

(1)

A group of different tissues that work together to carry out a specific function.

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(ii) Bacteria in root nodules are able to fix nitrogen gas (N_2) into ammonium compounds that the plant can use.

Name two organic molecules, containing nitrogen, needed to synthesise proteins.

(2)

Amino acids.

Nucleic acids, e.g. DNA and mRNA (nucleotides).

(Total for Question 1 = 8 marks)

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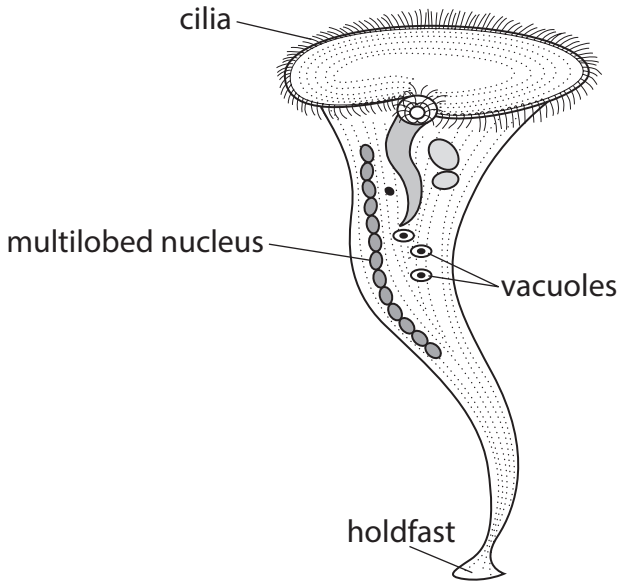
2 *Stentor coeruleus* is a unicellular organism.

The drawing shows the structure of a *Stentor coeruleus*.



(a) This *Stentor* has a height of 1 mm and a diameter of 0.4 mm at the top.

(i) Calculate the volume of this cone-shaped *Stentor*.

Use the equation for the volume of a cone:

$$V = \pi r^2 \frac{h}{3}$$

Give your answer to three decimal places.

(2)

$r = 0.4 \div 2 = 0.2$ mm, $h = 1$ mm

$V = \pi \times (0.2)^2 \times 1 \div 3 = 0.04189$

0.042 mm^3

(ii) Give the domain to which *Stentor coeruleus* belongs.

(1)

Eukaryota (eukaryotes).

(b) *Stentors* are found in fresh water attached to pebbles.

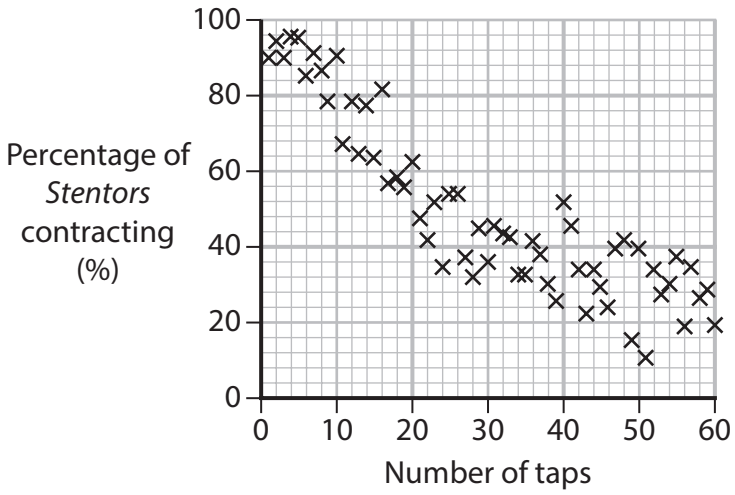
The response of *Stentors* to a stimulus was investigated.

A sample of 150 *Stentors* was allowed to attach to the bottom of a Petri dish filled with stream water. The *Stentors* were then given two hours to acclimatise.

The Petri dish was then tapped with a ruler once every minute.

After each tap, the percentage of *Stentors* that contracted was recorded.

The results are shown in the graph.



(i) The frequency of tapping the Petri dish was controlled.

Give **one other** variable of the tapping stimulus that should be controlled.

(1)

The strength (force) of each tap.

(ii) Show that the mean number of *Stentors* contracting between 50 and 60 taps is approximately 45.

(2)

Between 50 and 60 taps the percentages contracting read from the graph range from about 11% to 38%, so the mean percentage contracting is about 30%.

30% of 150 Stentors = 0.3 × 150 = 45 Stentors.

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(iii) Give **two** conclusions that can be drawn from the results of this investigation.

(2)

1 As the number of taps increases, the percentage of Stentors contracting decreases (negative correlation).

2 The Stentors were becoming habituated to the tapping, although not all Stentors were habituated by 60 taps.

(iv) Explain the results of this investigation.

(2)

The Stentors become habituated to the repeated tapping stimulus, so with increased number of taps they become less responsive and ignore it.

This means less energy is wasted on an unnecessary response to a non-threatening stimulus.

(Total for Question 2 = 10 marks)

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3 Fibrinogen is involved in blood clotting.

A variety of conditions affect the blood clotting process. These include atherosclerosis and dysfibrinogenemia.

(a) Describe the role of fibrinogen in blood clotting.

(3)

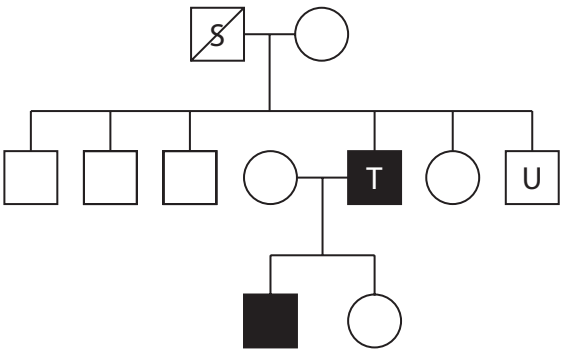
Fibrinogen is a soluble plasma protein which is converted to insoluble fibrin by the enzyme thrombin.

Fibrin forms a mesh of fibres that traps platelets and red blood cells, forming a clot.

(b) Some individuals have a clotting disorder caused by abnormal forms of fibrinogen.

This condition is called dysfibrinogenemia.

The family tree shows the inheritance of dysfibrinogenemia in one family.



Key

- Unaffected male
- Affected male
- Dead male (unknown phenotype)
- Unaffected female

In this family, the mutation responsible for dysfibrinogenemia is in the fibrinogen gene located on chromosome 4.

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(i) Individual T was heterozygous for this mutation.

State whether this mutation is dominant or recessive.

(1)

Dominant.

(ii) Scientists suggested this was a new mutation in this family originating in the genome of individual T.

Explain why the scientists suggested this.

(2)

T did not inherit the mutation from his mother, because she is unaffected (homozygous recessive), and S is unlikely to have had it.

None of T's siblings are affected (only T out of the six offspring had the condition); if the mutation was present in S then more of T's generation would be likely to be affected.

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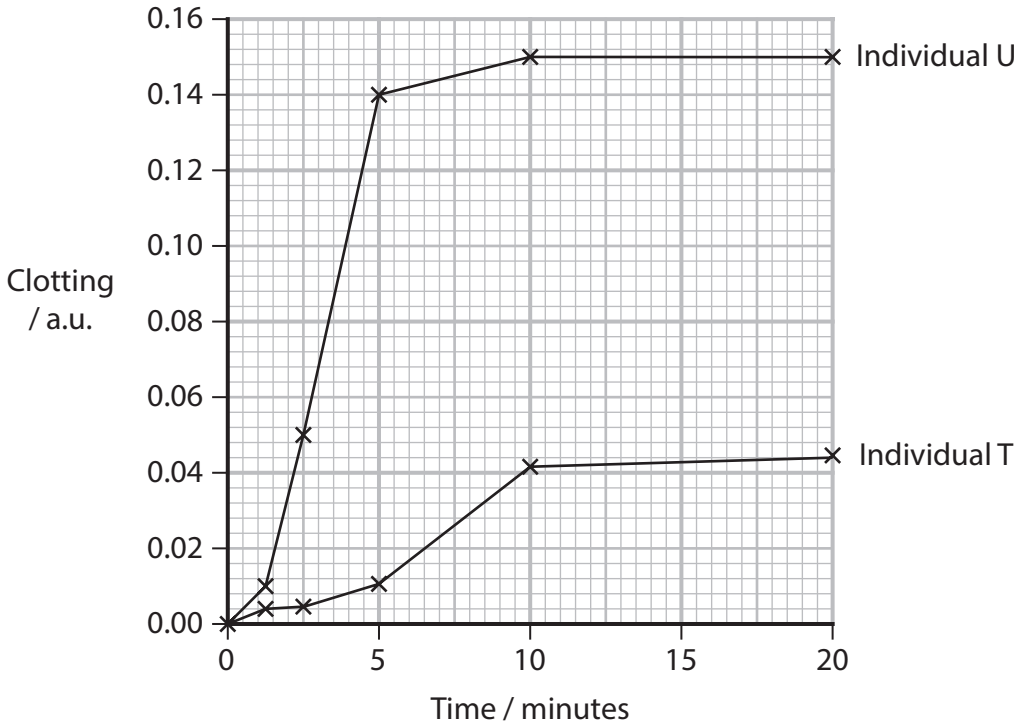
(iii) Blood samples were taken from individuals T and U.

The ability of these blood samples to clot was investigated.

The results are shown in the graph.



Give **two** conclusions that can be drawn from these results.

(2)

1 *Blood from individual T clots less than U (forms fewer clots), so dysfibrinogenemia reduces the ability of blood to clot.*

2 *Blood from individual T clots more slowly than U, so blood takes longer to clot in those with the condition.*

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(c) Atherosclerosis can increase the risk of blood clots forming.

Explain how blood clotting in atherosclerosis can result in the death of heart muscle.

(3)

A blood clot forming at an atheroma can narrow or block the lumen of a coronary artery.

This reduces (or stops) the blood flow to the heart muscle, reducing the supply of oxygen (ischaemia).

So the cardiac muscle cells cannot carry out aerobic respiration, cannot make enough ATP and die.

(Total for Question 3 = 11 marks)

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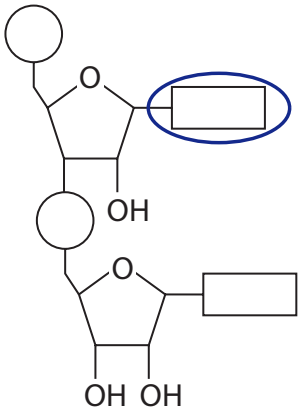
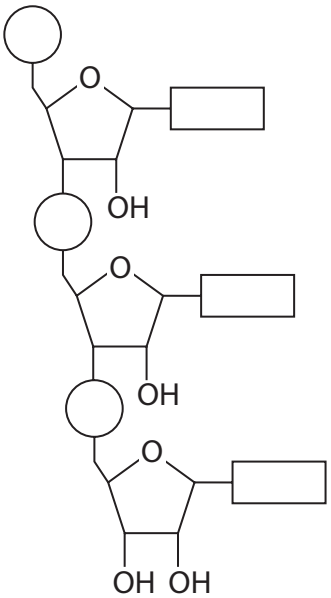
4 The primary structure of a polypeptide, synthesised on a ribosome, is determined by the genetic code.

(a) The diagrams show an RNA dinucleotide formed from two RNA nucleotides and an RNA trinucleotide formed from three RNA nucleotides.



RNA dinucleotide



RNA trinucleotide

(i) Draw a circle around **one** base in the dinucleotide.

(1)

(ii) State **one** difference between a nucleotide used to form RNA and a nucleotide used to form DNA.

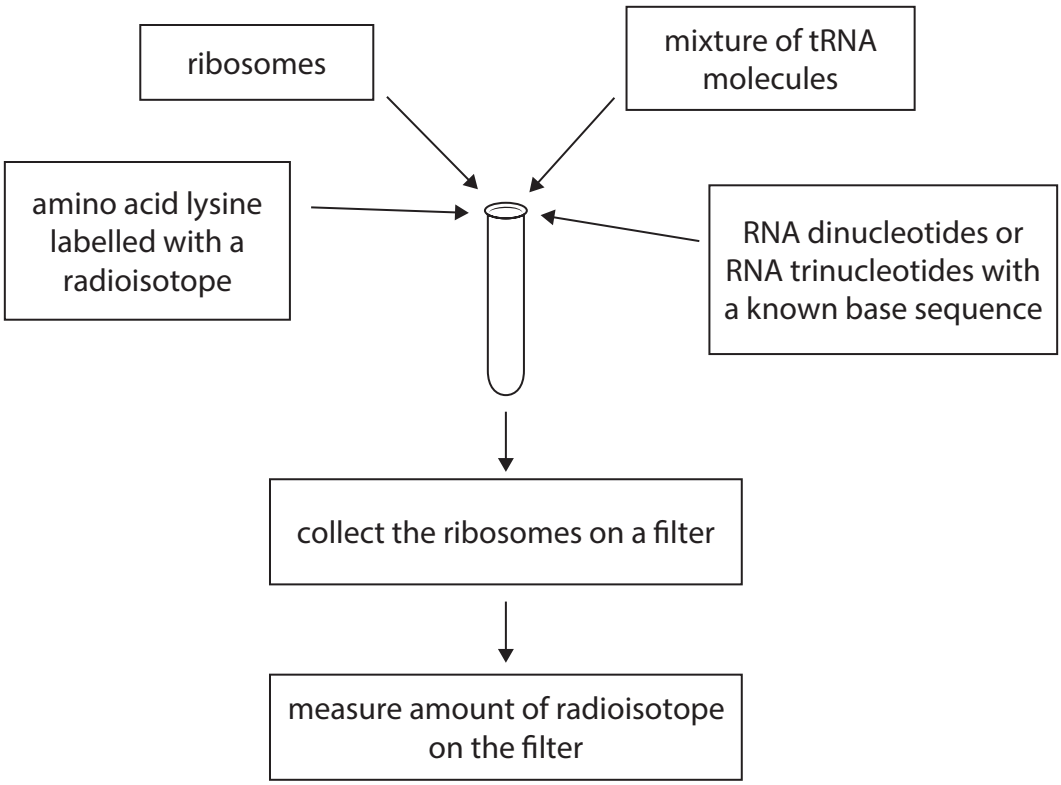
(1)

The RNA nucleotide contains ribose sugar whereas the DNA nucleotide contains deoxyribose.

(b) An experiment to determine the genetic code used amino acids labelled with a radioisotope, RNA dinucleotides and trinucleotides, ribosomes and a mixture of tRNA molecules.

The small mRNA molecules used were dinucleotides and trinucleotides with a known base sequence.

The diagram shows the method used to determine the genetic code of the amino acid lysine.



(i) Describe the roles of the ribosomes, RNA dinucleotides and trinucleotides and the tRNA used in this experiment.

(3)

The ribosomes bind (attach) to the RNA dinucleotides or trinucleotides, which act as mRNA.

The RNA dinucleotides and trinucleotides provide the codons with a known base sequence.

Each tRNA binds (brings) a specific amino acid, i.e. radioactive lysine, and the tRNA anticodon binds to the complementary RNA codon by hydrogen bonds, holding the lysine-tRNA on the ribosome.

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(ii) Some of the results for the amino acid lysine are shown in the table.

RNA dinucleotide or trinucleotide used		Presence of tRNA with radioactive lysine on the filter
Trinucleotide	AAA	Yes
	AAG	Yes
	GAA	No
Dinucleotide	AA	No
	AG	No
	GA	No
	GG	No

Explain **two** conclusions about the genetic code that can be drawn from the results of this experiment.

(4)

1 *The genetic code is a triplet code: three bases are needed to code for an amino acid, because only trinucleotides bind lysine-tRNA to the ribosomes, and none of the dinucleotides do.*

2 *The genetic code for lysine is degenerate, because both AAA and AAG bind lysine-tRNA to the ribosomes, so more than one codon codes for the same amino acid.*

(Total for Question 4 = 9 marks)

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5 Doxycycline (DOX) is a bacteriostatic antibiotic.

(a) State what is meant by the term **bacteriostatic antibiotic**.

(1)

A substance that inhibits the division (increase in number) of bacteria, without killing them.

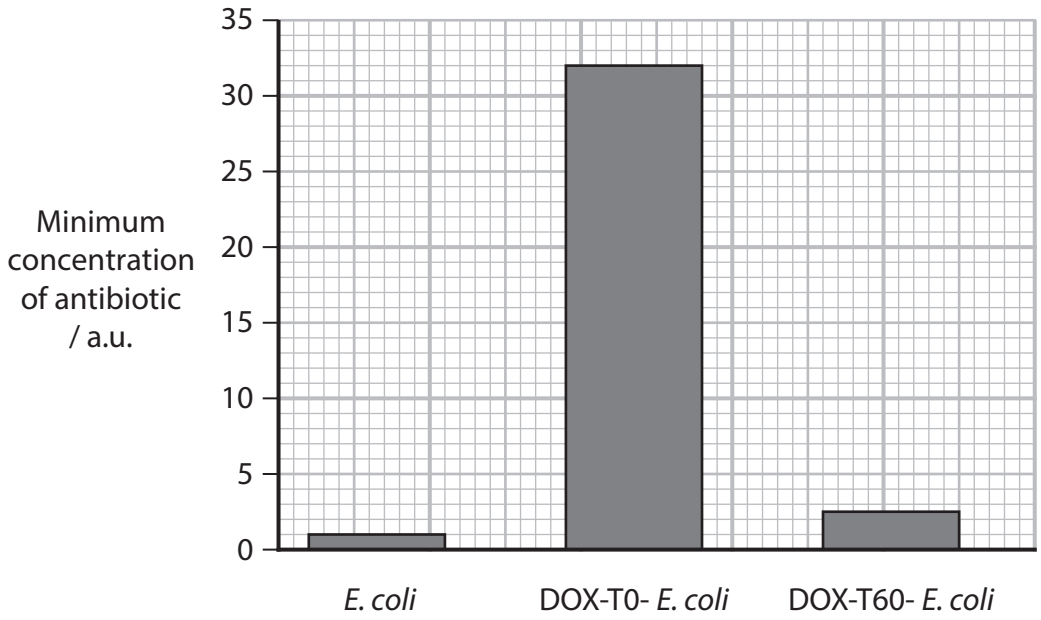
(b) Antibiotic resistance to DOX was investigated.

A culture of *E. coli* was treated with DOX and a resistant strain of *E. coli* called DOX-T0- *E. coli* was produced.

The DOX-T0- *E. coli* were then placed in antibiotic free conditions.

After 60 cycles of cell division, they became a different strain called DOX-T60- *E. coli*.

The graph shows the minimum concentration of DOX required to have a bacteriostatic effect on the bacteria.



(i) Explain the effect of 60 cycles of cell division on DOX resistant *E. coli* (DOX-T0- *E. coli*).

(2)

The antibiotic resistance decreased: the minimum concentration needed fell, so the allele for resistance became less frequent.

With no antibiotic present there is no selection pressure, so the DOX resistant bacteria no longer had an advantage.

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(ii) Devise a procedure to determine the minimum concentration of DOX required to have a bacteriostatic effect on the bacteria.

(4)

Spread E. coli onto agar plates to make a bacterial lawn, using aseptic technique.

Soak filter paper discs in a range of concentrations of DOX, e.g. 0, 5, 10, 15, 20, 25, 30, 35 a.u., and place one disc on each plate (or in wells cut in the agar).

Incubate the plates at a set temperature, e.g. 25 °C, for a set time, e.g. 48 hours.

The minimum concentration is the lowest concentration of DOX on a paper disc that produces a clear zone of inhibition around it.

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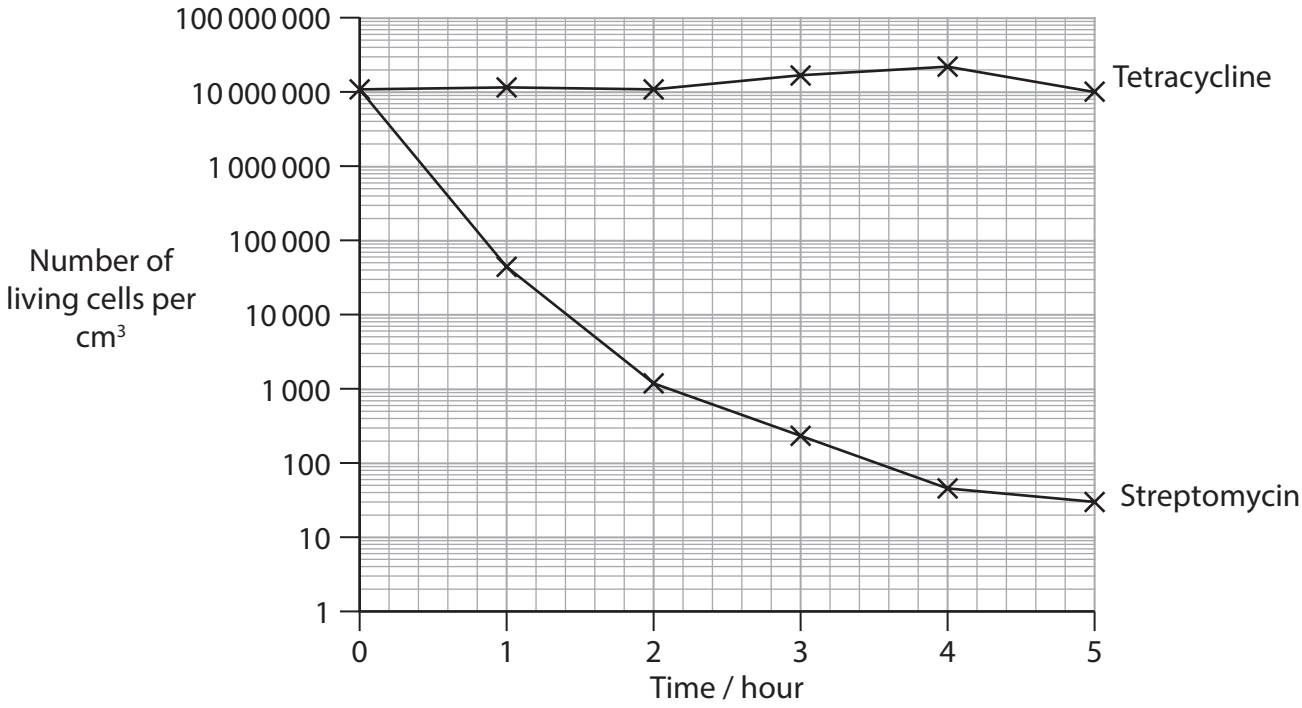
(c) In a different investigation the effects of two antibiotics, tetracycline and streptomycin, were compared on cultures of *E. coli*.

Each antibiotic was added to a culture containing 10 000 000 living *E. coli* bacteria at time 0.

Samples were removed from the cultures every hour and the number of living bacteria was determined.

The results are shown in the graph.



(i) Calculate the ratio of living bacteria in the tetracycline culture compared with the streptomycin culture at five hours.

(2)

tetracycline at 5 hours = 10 000 000 per cm³

streptomycin at 5 hours = 30 per cm³

10 000 000 ÷ 30 = 333 333

Answer *333 000* : 1

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(ii) Deduce the effects of these two antibiotics on *E. coli*.

(2)

Tetracycline has little effect on the number of living cells, it stops the E. coli increasing in number, so tetracycline is bacteriostatic.

Streptomycin decreases the number of living cells, so it kills the E. coli and is bactericidal.

(Total for Question 5 = 11 marks)

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6 The photograph shows a coastal tailed frog that is endemic to Western North America.

(Source: © Nature Picture Library/Alamy Stock Photo)

(a) Coastal tailed frogs live in streams. Coastal tailed frogs feed at night along the edges of streams. They eat invertebrates such as insects, spiders and snails.

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

(1)

Only found in one geographical location (only in Western North America).

(ii) Describe what is meant by the **niche** of the coastal tailed frog.

(2)

The niche is the role of the coastal tailed frog in its ecosystem.

For example, it feeds at night on invertebrates such as insects, spiders and snails along the edges of streams.

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(b) The presence of coastal tailed frogs in streams is used as an indicator of the health of an ecosystem.

In the past, scientists observed frogs and recorded their locations.

Scientists can now use eDNA to study the locations of these frogs. This method detects frog DNA collected from the water and amplified by PCR.

In one investigation, the two methods were compared.

Observational studies and eDNA methods were used to determine if coastal tailed frogs were present or absent in 45 streams.

The results were:

- Observational studies found these frogs in 9 of the 45 streams.
- Frog eDNA was also detected in those 9 streams.
- Frog DNA was also found in 21 streams in which these frogs were not observed.

(i) Calculate the percentage probability of coastal tailed frog eDNA being detected in a stream in which the frogs were not observed.

Give your answer as a whole number.

(2)

streams with no frogs observed = 45 − 9 = 36

eDNA in 21 of these: 21 ÷ 36 × 100 = 58.3

58 %

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(ii) Comment on the advantages and disadvantages of using eDNA methods to identify streams with frogs that are active at night.

(3)

Advantages: eDNA is less disruptive to the ecosystem and to the frogs, as no trapping or handling is needed and the stream is not trampled.

It can be carried out during the day, so the frogs do not need to be seen; at night frogs may be missed as they are hard to observe.

Disadvantages: it does not indicate whether the frog is still present, as DNA can travel in the stream or come from dead frogs, and it gives no idea of how many frogs are present.

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(c) The Rocky Mountain tailed frog is closely related to the coastal tailed frog.

Devise an eDNA method that could be used to identify which of these species of frog is present in streams.

(4)

Collect DNA samples from both species of frog to identify differences in their genomes.

Collect water samples from the streams and extract the DNA from them.

Amplify the DNA using PCR, with primers specific to the DNA of each species.

Cut the DNA into fragments using restriction enzymes.

Separate the DNA fragments by gel electrophoresis: put samples into wells in agarose gel, pass a current through the gel and use a dye to make the bands visible.

Identify the species by comparing the pattern of banding (position of bands) with that of each species, looking for bands unique to each species.

(Total for Question 6 = 12 marks)

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***7** The word 'complementary' is often used when describing the shapes of biological molecules that interact with each other.

Discuss the importance of complementary shapes in **three** types of biological molecule found in living organisms.

(9)

Complementary shapes allow molecules to bind specifically, which is important in enzymes, nucleic acids and receptors (hormones, neurotransmitters and antibodies).

Enzymes: the active site of an enzyme has a specific tertiary structure with R groups that allow only a substrate with a complementary shape to bind, forming an enzyme-substrate complex. For example, amylase only hydrolyses starch and not cellulose. Binding puts strain on bonds and lowers the activation energy, so reactions take place at a useful rate at body temperature. Consequently enzymes are essential for metabolic processes such as respiration, photosynthesis and protein synthesis to occur and be regulated. If the active site changes shape (denaturation), specificity is lost.

Nucleotides: complementary base pairing means adenine pairs with thymine (or uracil in RNA) and cytosine with guanine, held by hydrogen bonds. This holds the two strands together, contributing to a stable double helix, and allows the genetic code to be transferred: during semi-conservative replication DNA is copied to new DNA, so cell division and growth can occur; in transcription DNA is copied to mRNA; in translation tRNA anticodons bind to complementary mRNA codons, so amino acids are joined in a specific sequence to give a specific primary structure and so a specific protein. Transcription factors also bind to specific base sequences to switch genes on or off, regulating gene expression.

Receptors: neurotransmitters such as acetylcholine bind to complementary receptors on the postsynaptic membrane, opening ion channels so sodium ions enter, causing depolarisation and an action potential. Hormones such as insulin, or IAA in plants, bind to complementary receptors, so only target cells with complementary receptors respond,

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triggering a specific cellular response. In the immune system, antibodies have variable regions complementary to specific antigens, and T cell receptors bind to complementary antigens presented by antigen presenting cells.

Overall, complementary shapes allow coordinated and controlled responses to stimuli and a specific immune response, so pathogens are more likely to be destroyed, and memory cells give long-term immunity.

(Total for Question 7 = 9 marks)

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8 The scientific article you have studied is adapted from New Scientist.

Use the information from the scientific article and your own knowledge to answer the following questions.

(a) Explain why 'the distribution of hibernating species on the tree of mammals' suggests that the common ancestor of all mammals was a hibernator (paragraph 3).

(2)

Many different mammals in different groups hibernate, e.g. dormice, hedgehogs, bats, ground squirrels and black bears.

So the genes (alleles) associated with hibernation were probably passed down from a common ancestor, present before the different groups evolved.

(b) Explain how a reduction in physiological activity can result in a reduction in body temperature (paragraph 6).

(3)

A reduction in physiological activity means fewer metabolic reactions (lower metabolic rate), e.g. reduced muscle activity.

This reduces the requirement for ATP, therefore less respiration takes place.

Respiration releases heat, therefore less heat is generated, so body temperature falls.

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(c) Hibernating mammals, such as the black bear, can maintain a lower core temperature. 'The black bear (*Ursus americanus*), for example, lowers its core temperature by about 6 °C' (paragraph 8).

Describe the processes that would maintain the core body temperature of the black bear at a temperature 6 °C lower than normal.

(5)

Body temperature is maintained by negative feedback (thermoregulation, homeostasis).

The hypothalamus sets a new, lower set point, about 6 °C lower than normal.

Thermoreceptors in the skin and in the hypothalamus detect the temperature, and the hypothalamus (thermoregulatory centre) receives impulses from the thermoreceptors and detects changes away from the set point.

Impulses are sent from the heat gain or heat loss centre in the hypothalamus to effectors.

If temperature falls below the set point, vasoconstriction of skin arterioles and shivering increase heat gain; if it rises above it, vasodilation and sweating increase heat loss.

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(d) Tissue samples were collected from different mammals during hibernation. These were analysed to identify which genes were controlling hibernation (paragraphs 10 and 11).

Explain how scientists could use tissue samples to find out which genes were activated.

(3)

Compare tissue samples from hibernating and non-hibernating animals (or from different stages of hibernation).

Extract the mRNA (or proteins) present, as genes that are active are being transcribed.

Use reverse transcriptase to produce cDNA copies of the active genes from the mRNA, then analyse the base sequence of the mRNA (cDNA) to identify which genes were activated.

(e) Explain why there will be changes in blood pressure when a mammal comes out of hibernation (paragraph 13).

(2)

Blood pressure increases to increase blood flow and delivery of oxygen to cells, such as muscles and brain.

This is needed for respiration to generate ATP for muscle contraction and movement.

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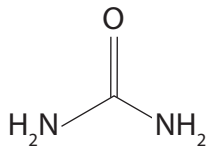
(f) Urea is a waste product that is usually excreted in the urine of mammals.

The diagram shows a molecule of urea.



During hibernation 'the thirteen-lined ground squirrel recycles its urea' (paragraph 13).

Deduce why it is important for a hibernating mammal to recycle urea.

(2)

The mammal does not eat during hibernation, so the amine group from urea can be recycled.

It is used to synthesise amino acids and nucleotides, needed to synthesise proteins and DNA.

(g) Explain why the bones and muscles of astronauts on long missions will waste away (Box "To blearily go" paragraph B).

(2)

In microgravity the muscles do not work as hard, as less force is needed to move the limbs, so there are fewer contractions.

The bones are no longer weight-bearing (under less stress), and cosmic radiation and a lack of nutrients in the diet lead to bone loss and muscle atrophy.

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(h) Explain why reducing body temperature from 37.5 °C to 32 °C would reduce metabolic activity (Box "To blearily go", paragraph C).

(3)

Lowering body temperature means molecules have less kinetic energy.

This results in fewer enzyme-substrate collisions, so fewer enzyme-substrate complexes form and enzyme activity is reduced.

Metabolic activities such as respiration depend on enzymes, so lower enzyme activity reduces metabolic activity.

(i) Describe the role of a neurotransmitter (paragraph 15).

(2)

A neurotransmitter is released from the presynaptic membrane into a synapse, diffuses across and binds to receptors on the postsynaptic membrane.

This transmits nerve impulses from one neurone to another, stimulating or inhibiting formation of an action potential.

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(j) Explain how adenosine affects neural activity in the hippocampus (paragraph 15).

(3)

Adenosine acts as an inhibitory neurotransmitter, reducing neural activity in the hippocampus.

It binds to receptors in synapses in the hippocampus, inhibiting the release of neurotransmitters and depolarisation of neurones.

This causes hyperpolarisation of the postsynaptic neurone (chloride ions move in, potassium ions move out), so threshold is not reached and fewer action potentials are generated.

(k) Explain how boosting the uptake of adenosine in the brains of the rats could lower the core body temperature of rats without triggering shivering (paragraph 16).

(3)

Adenosine binds to receptors in the hypothalamus (thermoregulatory centre).

This reduces neural activity in the hypothalamus, so the thermoregulatory centre is not activated by the fall in temperature.

So fewer impulses are sent to the skeletal muscles, resulting in less contraction of skeletal muscle, so no shivering occurs.

(Total for Question 8 = 30 marks)

TOTAL FOR PAPER = 100 MARKS

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Pearson Edexcel Level 3 GCE

Wednesday 18 June 2025

Morning (Time: 2 hours)

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Biology A (Salters Nuffield)

Advanced

PAPER 3: General and Practical Applications in Biology

Scientific article for use with Question 8

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Scientific article for use with Question 8

THE BIG SLEEP

Were human ancestors able to hibernate and what could that mean for our health, asks Alex Wilkins.

1. IF YOU could rewind the evolutionary clock millions of years, you might discover that your ancestors had a remarkable trait. It wouldn't be obvious at first. But in certain conditions – if food were scarce or there were a cold snap – it is possible that their eyes would grow heavy and their bodies begin to slow until, eventually, they switched off entirely. They would be hibernating.

2. In this low-energy state, today's hibernators can fend off a remarkable array of threats, from the inside and out. Extreme cold and famine are the obvious ones, but hibernation also has the power to combat conditions that plague modern humans, including Alzheimer's disease, stroke and heart attack. It could even hold the key to longevity and colonising space. No wonder some researchers are keen to reinstate what might have been our long-lost superpower.

3. The idea that ancient humans could hibernate may seem farfetched, but mounting evidence suggests that many non-hibernating mammals retain an ability to enter reduced-energy states, including through dormant brain-signalling pathways that slow metabolism. "The distribution of hibernating species on the tree of mammals makes the likely conclusion that the common ancestor of all mammals was a hibernator," says Sandy Martin at the University of Colorado. "It's possible we all have the genetic hardware."

4. It remains to be seen whether any underlying circuitry can be fired up enough to bestow us with some of hibernation's protective properties. But the potential spoils are too great not to try.

5. Hibernation is often associated with small mammals, such as dormice, hedgehogs and bats, but it is also common among reptiles, amphibians and even insects. It resists easy definition, though. In German, Turkish and many other languages, hibernation translates literally to "winter sleep" – and it does bear a passing resemblance to this. But comparing hibernation to sleep is like comparing apples to oranges, according to Vladyslav Vyazovskiy at the University of Oxford, who studies both. "There are criteria for defining sleep and they are purely brain-centric, but hibernation is defined based on metabolism," he says. "This means that, technically, you can be awake and hibernating or asleep and hibernating."

6. In essence, hibernation centres on a state called torpor, in which an animal decreases its physiological activity, marked by a reduction in body temperature and metabolism. The length and extremity of these changes varies hugely. The drop in body temperature can be severe and last for weeks or brief and entail a decrease of only a few degrees. The accompanying metabolic reduction can be near total or only 10 to 20 per cent. What's more, some hibernators regularly come in and out of torpor into states of arousal, while others stay metabolically suppressed.

7. "Among hibernating mammals, there's a continuum of hibernation," says Matthew Regan at the University of Montreal, Canada. At one end, there is the thirteen-lined ground squirrel (*Ictidomys tridecemlineatus*), one of the most studied hibernators, which lowers its body temperature in successive cycles of torpor and arousal until it is barely above the temperature of its environment. It can stay in this state without food or water for more than six months, suspending many bodily functions and recycling key nutrients through specially adapted processes.

8. At the other end of the continuum are large species such as bears. The black bear (*Ursus americanus*), for example, lowers its core temperature by no more than about 6 °C and reduces its metabolic requirements by a quarter – a significant saving for such a modest temperature decrease. "Bears highlight other means of metabolic suppression that are independent of core temperature. And those mechanisms are really very poorly understood," says Kelly Drew at the University of Alaska in Fairbanks.

9. Most experts believe that if we are ever to enter a state of synthetic torpor, it will be similar to that of a less-extreme hibernator. "It's not feasible to think that humans could get down to the levels of the small hibernators, but you can get an awful lot of value from the shallow metabolic depression of a bear," says Hannah Carey at the University of Wisconsin. In particular, it could be extremely useful for long-distance space travel (see "To blearily go").

10. To begin with, we need to understand the weird processes that happen within the bodies of hibernators. Progress here has been rapid in recent years, not least when it comes to identifying the genes involved. Martin is a pioneer. For decades, she has collected and frozen tissue samples taken from a wide range of mammals over the course of their hibernation. "The idea is that the tissue bank is carefully timed, so that you get good information about levels of gene products, which change across a torpor bout, or change very rapidly during the rewarming period, and change seasonally," she says.

11. Martin's grand vision was to analyse these timed tissue samples to identify the genes that throw the switches controlling hibernation in mammals. Once located, these genes could be studied and possibly modified to mimic the beneficial properties that hibernation bestows. When Martin started her tissue bank, a dearth of technology and resources made this extremely challenging. It was difficult to look at more than one gene at a time or find which genes were being expressed across the whole organism. But now things are different. "The tools are finally catching up to the ability to actually use [the samples] in a way that will be productive," she says. Progress has been particularly strong in an area of research called comparative genomics, which compares the complete genomes of different species to identify important genes.

The Arctic ground squirrel can lower its body temperature to –2.9 °C during torpor

(Source: © Nature Picture Library/Alamy Stock Photo)

12. Martin retired from active research this year, but she has passed on her treasure trove to one of her ex-students, Katharine Grabek, who co-founded a California-based comparative genomics start-up called Fauna Bio. Grabek and her team are using findings from the tissue bank, along with a raft of other information, such as transcriptomes – descriptions of the different ways genes make proteins – and human gene data, to identify targets for drugs that can replicate hibernation's benefits.

Genomic insights

13. For instance, the thirteen-lined ground squirrel recycles its urea to preserve nutrients, cleans out harmful brain plaques commonly associated with Alzheimer's in humans, mitigates the insulin sensitivity that comes with huge weight gain before winter and appears to experience no ill consequences from severe spikes and troughs in blood pressure as it comes out of hibernation. By comparing its genome with those from more than 50 other hibernating and non-hibernating mammals, Grabek and her team have already identified molecules that appear to protect against high blood pressure, coronary heart disease and heart infections.

14. As they expand their sample collections and analysis, they hope to identify molecules associated with other conditions that affect human health, and eventually use these findings to design therapeutic drugs.

To blearily go

A As the study of hibernation progresses, it has come to the attention of space agencies looking to protect astronauts on long missions. "We have a real interest in understanding this better because it will solve some of our issues, in a very elegant way that otherwise would require developing new propulsion systems to shorten trip durations," says Leopold Summerer at the European Space Agency (ESA), who leads a team that looks at innovative space travel solutions, like hibernation.

B If ESA, NASA or SpaceX is to put people on Mars, then astronauts will have to spend months on a tiny spaceship with minimal food, in microgravity where their bones and muscles will waste away, being bombarded by cosmic radiation in the absence of Earth's magnetic field. Helpfully, these resemble many of the conditions hibernators appear able to survive: bears and squirrels can preserve bone structure while in torpor, the state accompanying hibernation in which metabolic rate is reduced. Squirrels have also shown resistance to high levels of radiation while hibernating. And Summerer's team is now testing how the cells of hibernators perform in microgravity to see whether torpor might be a viable spaceflight strategy.

C NASA is also funding research in this area and consulting hibernation scientists. One company it is collaborating with is Spaceworks. Its chief executive, John Bradford, says the firm's aim is to lower body temperature from 37.5 °C to around 32 °C, which would cut metabolic activity by about 50 per cent. A flight to Mars would take four to six months, he says. "We don't think you could put people in this state for the entire duration. We were envisioning the crew would cycle through these two-week stints of kind of extended sleep periods, and they'd be active for a couple of days, and then go back into stasis again."

15. Other potential payoffs for medicine are coming from research that aims to understand the changes happening within the brains of hibernators. Much of the focus has been on a neurotransmitter called adenosine, which, among other things, is linked with sleep: when adenosine binds to receptors in the brain's hippocampus, neural activity slows and you feel sleepy. In 2011, when Drew and her colleagues gave Arctic ground squirrels (*Urocitellus parryii*) drugs that either activate or suppress these adenosine pathways, the squirrels spontaneously entered and exited states of torpor. But there was a catch: this only worked in winter when the squirrels were already primed for hibernating. Why that might be remains a mystery. Still, it left Drew and her team wondering what effect adenosine might have in mammals that don't hibernate.

16. To find out, they have since done similar experiments with rats. These didn't result in the full metabolic effects seen in squirrels, but the team discovered that boosting the uptake of adenosine in the rats' brains lowered their core body temperatures. Furthermore, with the adenosine drug, there were none of the adverse effects usually associated with hypothermia, such as shivering and metabolic stress. "That's really exciting because the adenosine mechanism is remarkably effective," says Drew. Her enthusiasm is linked to the fact that, in humans, induced hypothermia is used to treat cardiac arrest – and has the potential to treat strokes too – but the drugs currently given to suppress shivering don't work at very low temperatures.

17. Another researcher focusing on adenosine is Domenico Tupone at Oregon Health and Science University. He believes it is the key to the metabolic anomaly at hibernation's heart, which he calls "thermoregulatory inversion". In mammals, the normal physiological response to plunging temperatures is for the body to turn to brown fat, which is packed with mitochondria that make energy and generate heat. But during hibernation, the opposite happens: cooling inhibits heat production and warming boosts it. Tupone and his team found that they could induce thermoregulatory inversion in rats by giving them drugs that activate adenosine pathways. "Rats are similar to humans in terms of the internal circuitry of the brain," says Tupone. "What we suspect is that this circuit is also present in humans, but we have lost the ability to trigger it."

18. Other researchers have homed in on a small part of the brainstem called the raphe pallidus, which helps control automatic bodily processes. Matteo Cerri at the University of Bologna, Italy, and his colleagues found that inhibiting the neural activity of this region in rats and pigs can lead to a state of hypothermia that resembles torpor in hibernators. The researchers have also shown that the raphe pallidus receives signals from the hypothalamus, another key brain region for controlling hibernation. "All this computation about our

Black bears suppress their metabolism without a big drop in temperature

(Source: © Stan Tekiela Author/Naturalist/Wildlife Photographer/Getty Images)

metabolic and energetic state comes down from the hypothalamus, which is a higher region of the brain, and goes into an older region of the brain, the brainstem," says Cerri. "There, it hits this raphe pallidus region, which will then organise the body's response."

19. Cerri, Tupone and Drew hope that, as we learn more about the neuroscience of hibernation, we can go beyond turning down heat production to controlling metabolism in other ways. The ultimate prize would be a novel approach to boosting longevity. Decades of research on caloric restriction and fasting have revealed a strong link between metabolism and lifespan. In particular, we know that when nutrients are scarce, a network of metabolic pathways switches from stimulating cell growth to suppressing it, boosting repair and feeding off cellular detritus that would normally cause the cellular damage that results in ageing. Hibernators live longer than non-hibernators of the same size, and new research in both bats and marmots shows that, during hibernation, their bodies age more slowly. This suggests that a better understanding of torpor could provide new insights for anti-ageing researchers.

20. In the future, drugs might be created that could influence the neural activity involved in hibernation. It might even be possible to do this using the environmental factors that natural hibernators rely on, like the time of year or fasting, says Cerri. There is a long way to go to fully map out and target the brain circuits involved, but it is already becoming clear that we needn't be hibernators to reap the rewards. "These processes may have evolved to optimise metabolic plasticity for an animal's health during periods of torpor," says Regan. "But those processes don't necessarily need torpor to be elicited, or to have some benefit."

21. While hibernations mysteries still abound, our efforts to better understand it are finally beginning to gather momentum – and we are now waking up to the potential benefits. "People have been studying hibernation for at least a century," says Carey, "But new technologies are making things a lot easier to get at scientifically. This field is too important to not try to get as far as we can."

(Source: Alex Wilkins, New Scientist, 15 October 2022)

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