Please check the examination details below before entering your candidate information

Candidate surname	Other names

Pearson Edexcel
International
Advanced Level

Centre Number | | | | | |

Candidate Number | | | | |

Thursday 31 October 2019

Morning (Time: 1 hour 45 minutes) | Paper Reference **WBI05/01**

Biology

Advanced

Unit 5: Energy, Exercise and Coordination

You must have:
A copy of the scientific article (enclosed), calculator, HB pencil, ruler.

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.
- Answer the questions in the spaces provided
  – *there may be more space than you need.*

Information

- The total mark for this paper is 90.
- The marks for **each** question are shown in brackets
  – *use this as a guide as to how much time to spend on each question.*
- Questions labelled with an **asterisk** (*) are ones where the quality of your written communication will be assessed
  – *you should take particular care with your spelling, punctuation and grammar, as well as the clarity of expression, on these questions.*
- Candidates may use a calculator.

Advice

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

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P 5 8 4 5 0 A 0 1 2 8

Pearson

Answer ALL questions.

Some questions must be answered with a cross in a box ☒. If you change your mind about an answer, put a line through the box ☒ and then mark your new answer with a cross ☒.

1 Plants are able to detect and respond to light.

In an investigation, the effect of different periods of daylight on the flowering of four types of plant was investigated.

The table below shows some of the results from this investigation.

Number of hours of daylight	Percentage of plants flowering (%)			
	carnation	pea	rose	tomato
6	0	99	24	79
10	0	80	26	78
14	95	8	28	80
18	98	0	26	81
22	99	0	25	80

(a) Put a cross ☒ in the box to complete the conclusions made using these results.

(i) The plant that requires a shorter period of daylight than period of darkness to stimulate flowering is the

(1)

☒ **A** carnation

☒ **B** pea

☒ **C** rose

☒ **D** tomato

(ii) The photoreceptor in plants is

(1)

☒ **A** acetylcholine

☒ **B** IAA

☒ **C** phytochrome

☒ **D** rhodopsin

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(b) Suggest **two** factors that need to be controlled to ensure that this investigation is valid.

(2)

.....

.....

(Total for Question 1 = 4 marks)

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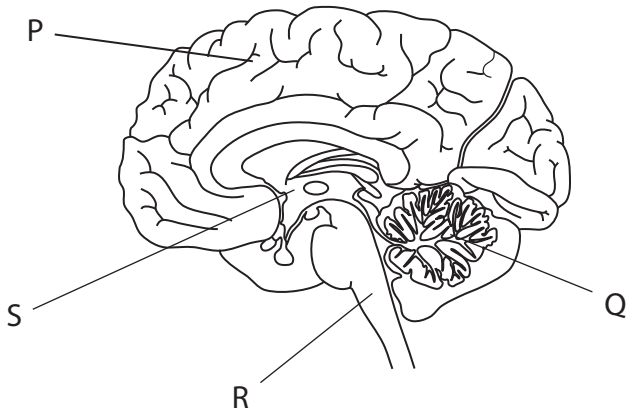
2 Exercise requires the effective coordination of different systems.

The photograph below shows a squash player about to hit the ball.

Source: https://en.wikipedia.org/wiki/File:
Nicol_David.jpg#/media/File:Nicol_David.jpg

The diagram below shows a section through the human brain with four regions labelled.



(a) Using the information provided and your own understanding, put a cross ☒ in the box to complete each of the following statements.

(i) The part of the brain deciding where to hit the squash ball to is labelled

(1)

☒ **A** P

☒ **B** Q

☒ **C** R

☒ **D** S

(ii) The part of the brain maintaining balance and coordinating movement of the arm is the

(1)

☒ **A** cerebellum

☒ **B** retina

☒ **C** hypothalamus

☒ **D** medulla oblongata

(iii) The part of the brain regulating the temperature of the squash player is labelled

(1)

☒ **A** P

☒ **B** Q

☒ **C** R

☒ **D** S

(iv) Regulation of temperature in the squash player is an example of

(1)

☒ **A** dendrochronology

☒ **B** habituation

☒ **C** homeostasis

☒ **D** respiration

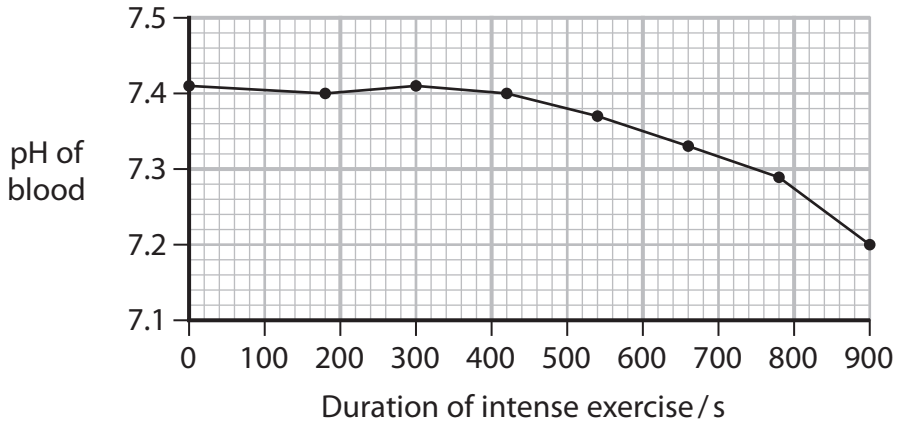
(b) An important part of playing squash is deciding where to hit the ball to in the squash court.

Explain how functional magnetic resonance imaging (fMRI) can be used to identify the parts of the brain involved in making decisions about where to hit the ball.

(3)

(c) Players can undergo periods of intense exercise during a game of squash.

The graph below shows the effect of intense exercise on the pH of blood.



(i) Describe the effect of the duration of intense exercise on the pH of blood.

(2)

(ii) Explain the effect of the duration of intense exercise on the pH of blood.

(3)

(Total for Question 2 = 12 marks)

3 Mitochondria are organelles specialised for the production of ATP.

(a) One part of the process involved in ATP production is the electron transport chain.

(i) State the location of the electron transport chain in mitochondria.

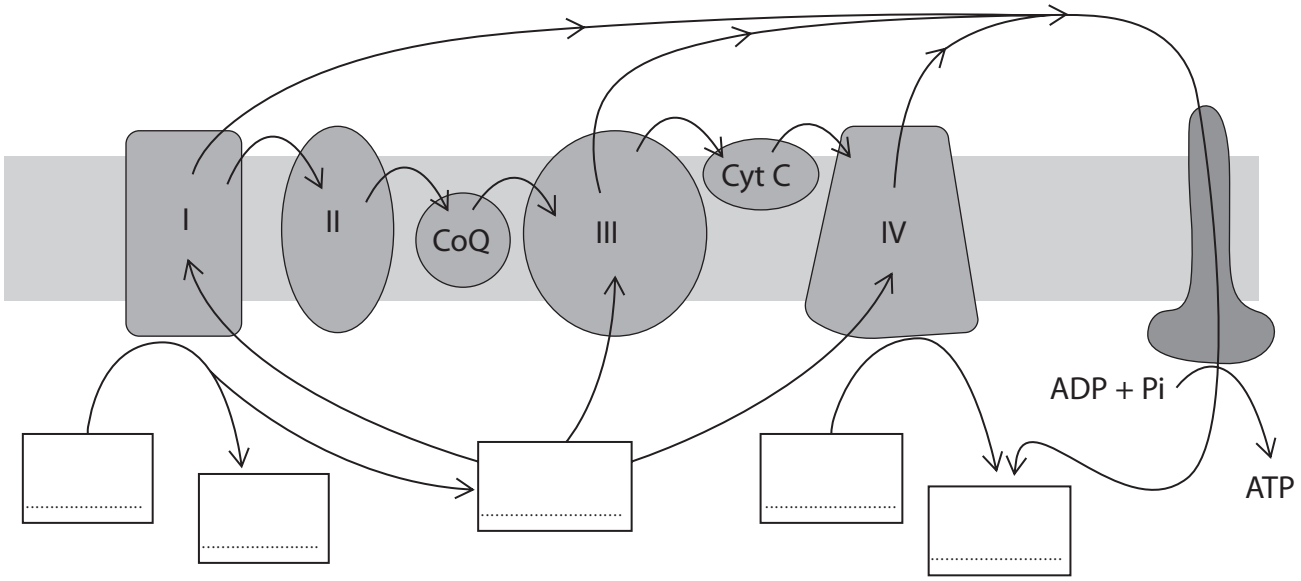
(1)

.....

(ii) The diagram below shows the arrangement of six electron carriers in the electron transport chain.

Complete the diagram by filling in each of the boxes appropriately.

(3)



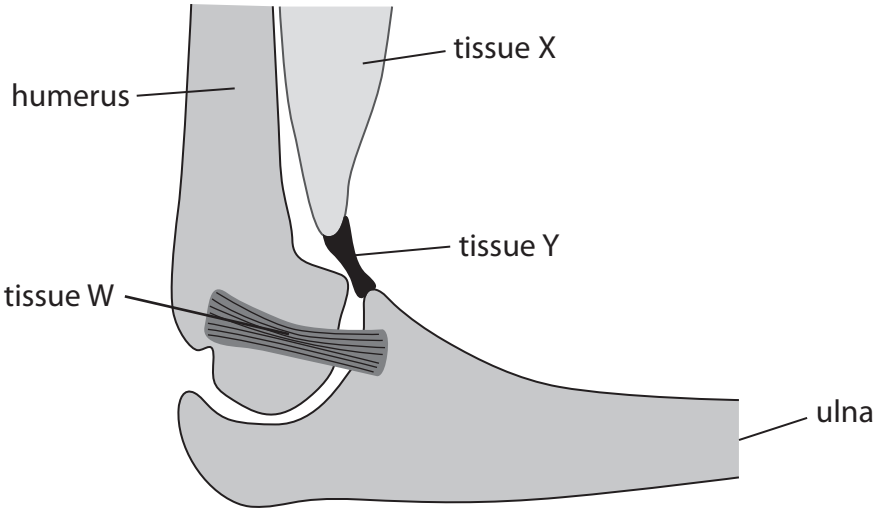
(b) Explain how ATP is formed by the process of oxidative phosphorylation in the mitochondria.

(5)

(Total for Question 3 = 9 marks)

4 Movement at a joint requires the interaction of different tissues.

(a) The diagram below shows a joint in the elbow, together with some of the tissues involved in the movement of this joint.



Explain how the properties of tissues W, X and Y relate to their role in the movement of this joint.

(6)

(b) The anterior cruciate ligament (ACL) is found in the knee joint. Injury to this ligament is common among young, active individuals.

A tear is a common type of ACL injury.

Osteoarthritis is a condition characterised by changes to cartilage on joint surfaces and damaged bone marrow.

In one study, scientists looked at the risk of developing osteoarthritis 24 months after ACL tears.

The table below shows some of the results from this study.

ACL injury	Percentage of individuals showing changes 24 months after the initial assessment (%)		
	reduced cartilage surface area	reduced cartilage thickness	bone marrow damage
no tear (control)	35	9	9
small tear	40	12	4
large tear	75	36	17

(i) The study included 600 individuals with no ACL tear.

Calculate the number of people with no ACL tear, who had no reduction in cartilage thickness 24 months after their initial assessment.

(2)

Answer .....

DO NOT WRITE IN THIS AREA

DO NOT WRITE IN THIS AREA

DO NOT WRITE IN THIS AREA

(ii) Comment on the effect of ACL tears on the development of osteoarthritis.

(2)

(iii) Suggest **one** reason why this study may underestimate the risk of developing osteoarthritis following an ACL tear.

(1)

(Total for Question 4 = 11 marks)

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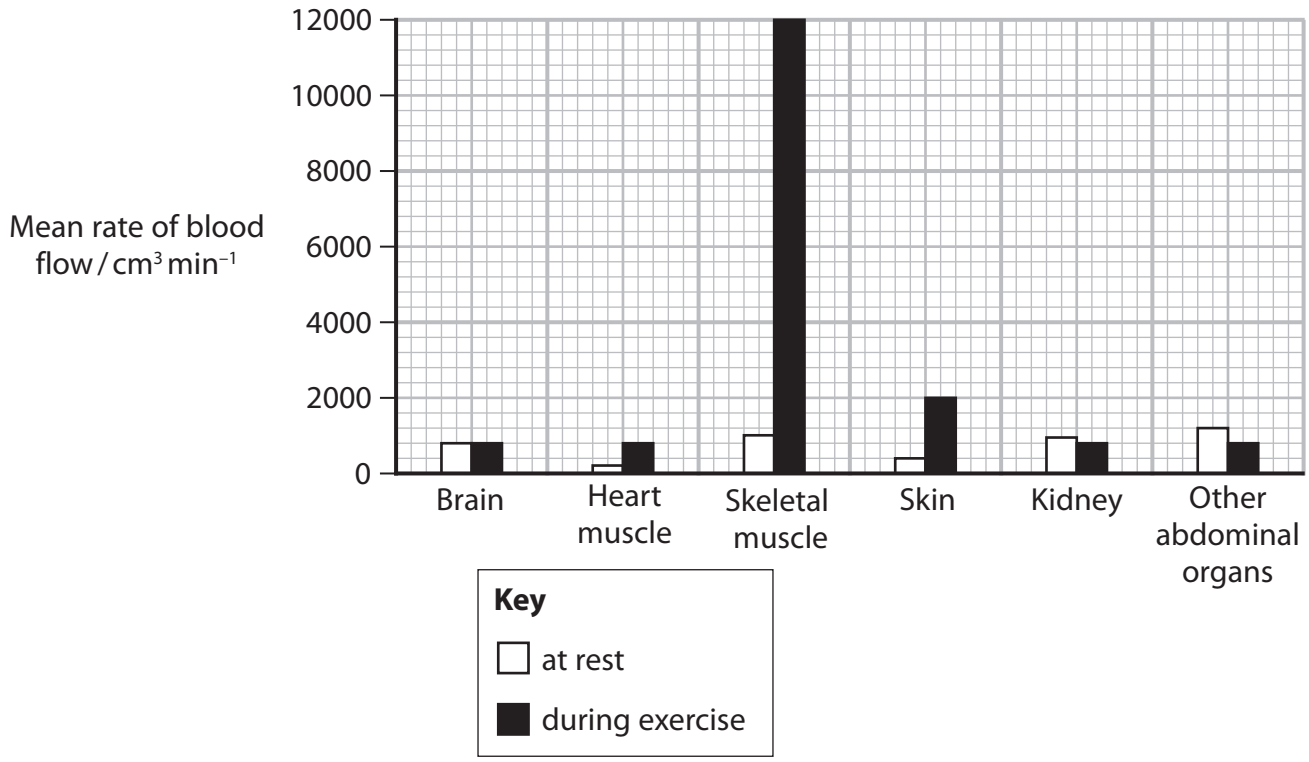
5 During exercise, changes take place in the cardiac output and blood circulation.

In an investigation, the change in blood flow to different parts of the body caused by exercise was measured.

All the volunteers used in the study were healthy males of the same age.

The graph below shows the results of this investigation.



(a) (i) During exercise, the blood flow to the other abdominal organs changes.

Calculate the percentage change in blood flow to the other abdominal organs in response to exercise.

(2)

Answer..... %

(ii) Suggest **two** other factors that should be controlled in this investigation.

(2)

.....

.....

DO NOT WRITE IN THIS AREA

DO NOT WRITE IN THIS AREA

DO NOT WRITE IN THIS AREA

(b) Explain the changes in blood flow caused by exercise.

(5)

DO NOT WRITE IN THIS AREA

DO NOT WRITE IN THIS AREA

DO NOT WRITE IN THIS AREA

*(c) Describe how the coordinated contraction of heart muscle is brought about.

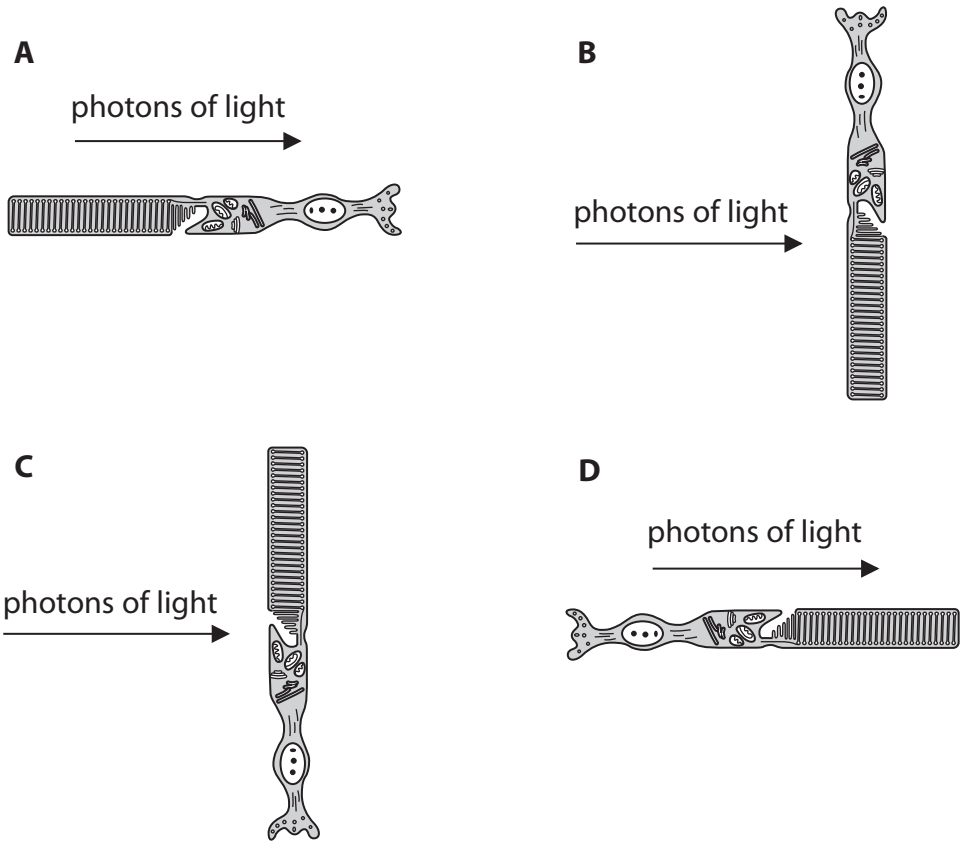
(6)

(Total for Question 5 = 15 marks)

6 The eye is a sensory organ that detects light.

(a) Rod cells are sensory cells located in the retina of the eye.

The diagram shows different possible orientations of rod cells to photons of light hitting the retina.



(i) Put a cross ☒ in the box that shows the correct orientation of rod cells to photons of light hitting the retina.

(1)

☒ **A**

☒ **B**

☒ **C**

☒ **D**

(ii) Put a cross ☒ in the box that describes what happens to rhodopsin when photons of light enter rod cells.

(1)

☒ **A** rhodopsin is bleached producing opsin and cis-retinal

☒ **B** rhodopsin is bleached producing opsin and trans-retinal

☒ **C** rhodopsin is formed from opsin and cis-retinal

☒ **D** rhodopsin is formed from opsin and trans-retinal

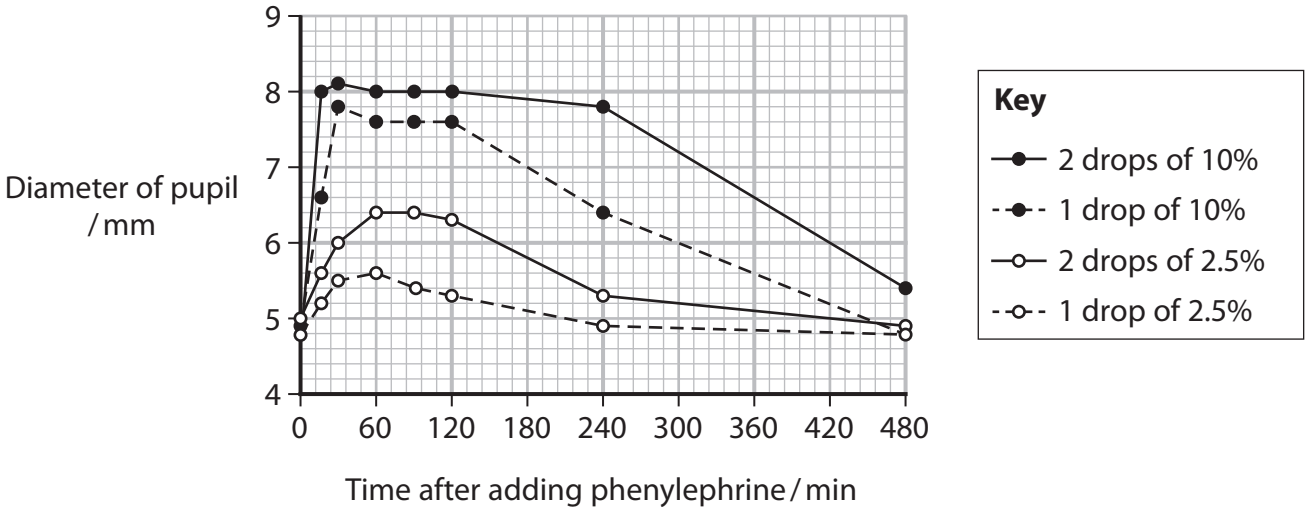
(iii) Put a cross ☒ in the box next to the row that correctly describes the changes in the cell membrane when photons of light enter a rod cell.

(1)

	membrane permeability to sodium ions	activity of the sodium ion pump
☒ **A**	decreases	no change
☒ **B**	decreases	increases
☒ **C**	increases	no change
☒ **D**	increases	increases

(b) During eye surgery, drops of phenylephrine may be placed on the surface of the eye.

The graph below shows the effects of different doses of phenylephrine on the diameter of the pupil.



(i) Using the information in the graph, describe the effect of phenylephrine on the pupil of the eye.

(3)

(ii) Phenylephrine acts directly on membrane proteins of some muscle fibres.

Suggest how phenylephrine causes the diameter of the pupil to change.

(3)

(Total for Question 6 = 9 marks)

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7 The scientific article you have studied has been adapted from *First in Fly: Drosophila Research and Biological Discovery*.

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

(a) Describe how the climbing assay could be used to determine if *Drosophila* can be habituated to tapping on the vial (paragraphs 1 and 2).

(3)

(b) Explain how iPSCs (induced pluripotent stem cells) can be used to study possible treatments for Parkinson's disease (paragraph 4).

(2)

(c) Explain why proteins with similar amino acid sequences could carry out similar functions in the cell (paragraphs 5 and 6).

(2)

(d) Suggest how alpha-synuclein could cause neurotoxicity leading to the symptoms of Parkinson's disease (paragraph 7).

(3)

(e) Describe how lipids are broken down in the 'newly formed bag of trash' (paragraph 8).

(2)

(f) Suggest why some proteins such as the alpha-synuclein molecule aggregate together (paragraphs 8 and 9).

(2)

*(g) Some neurones are stimulated by the neurotransmitter serotonin.

Diazepam reduces anxiety by making these neurones less responsive to serotonin.

Explain how a drug, such as diazepam, could have this effect (paragraph 14).

(5)

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(h) Explain how the expression of a gene could be changed during the development of a disease (paragraph 15).

(2)

(i) Explain why 'Given no other evidence, a best guess is that a recessive mutation is likely to be one that inactivates gene function, and a dominant mutation is likely to result in activation or gain of a function by the gene' (paragraph 22).

(3)

(j) Suggest how 'nondisjunction of chromosome 21' could result in an individual with three copies of some genes (paragraph 23).

(3)

(k) Suggest how *Drosophila*, together with information from human genome sequencing, could be used in the development of new drugs (paragraph 25).

(3)

(Total for Question 7 = 30 marks)

TOTAL FOR PAPER = 90 MARKS

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Pearson Edexcel International Advanced Level

Thursday 31 October 2019

Morning (Time: 1 hour 45 minutes) | Paper Reference **WBI05/01**

Biology

Advanced

Unit 5: Energy, Exercise and Coordination

Scientific article for use with Question 7

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Pearson

Scientific article for use with Question 7

Adapted from: Chapter 8: Coordination, in, *First in Fly: Drosophila Research and Biological Discovery*, Stephanie Elizabeth Mohr, Harvard University Press, 2018.

Coordination

1. Take a clear glass vial of normal adult fruit flies, tap it gently on the table, and the flies will exhibit a stereotyped response: they will remain at the bottom, stunned, for a few milliseconds, then right themselves and quickly begin walking upward along the sides of the vial, toward the stoppered top. The formal name of this test is the "negative geotaxis assay," but in the day-to-day course of research, fly biologists refer to it as the "climbing assay."

2. Just as we slow down and get a little clumsier in old age, so, too, wildtype flies start to perform poorly on the climbing assay as they get older. For certain mutations, the effects of aging on performance in the assay are more pronounced, such as a failure of older flies to climb even halfway up the vial, poor performance beginning at a younger age, or both. As with any good scientific assay, the climbing assay can be "controlled"—with a set of age-matched, wildtype, and untreated flies tested alongside experimental genotypes or drug-treated flies, providing an essential comparison point. One of the things that is both utilitarian and satisfying about the climbing assay is that it allows a complex behaviour involving coordination of several systems—the brain, the peripheral nerves, and the muscles—to be reduced to a single numerical value. Results of the climbing assay are often presented as the percentage of flies that reached some height within some fixed number of seconds after the tap.

3. This assay exemplifies one of the most powerful applications of *Drosophila* for biomedical research: the study of neurological function in an intact living system and over the full course of its lifetime. Combined with studies at the leading edge of technology—from sophisticated microscopy techniques to multifactorial molecular genetic manipulations—assays like the climbing assay are helping to uncover first insights into neurological function, and, perhaps even more importantly, dysfunction.

The Shaking Palsy

4. Many of the genes implicated in Parkinson's disease have orthologs* in flies, opening the door to application of the genetic approach. Various engineered strains of *Drosophila* serve as "disease models," with specific genotypes of flies exhibiting "symptoms" or phenotypes that recapitulate features of the disease at the level of cellular, physiological, and whole-animal outcomes. Indeed, the climbing assay is one of the tools that is being used by *Drosophila* researchers to study Parkinson's disease. *Drosophila* models of Parkinson's disease offer a number of advantages as compared with other approaches to the study of human diseases, such as the use of human iPSCs**.

*orthologs – genes in different species that evolved from a common ancestral gene

**iPSCs – Induced pluripotent stem cells

A Cellular Garbage Strike

5. In I998, T. Kitada, N. Shimizu, and colleagues reported the cloning of a human gene that they called "parkin" (and was given the official human gene name PARK2) that is associated with a rare inherited form of Parkinson's disease. There is a stretch of about 70 amino acids at the beginning of the PARK2 protein that has similarity to short proteins called Ubiquitin proteins. There is also a region with similarity to another type of protein, RING-finger proteins. A molecular process involving Ubiquitin had previously been identified in humans and other organisms, including plants. The process is a tag-and-grab system, wherein damaged proteins or other biomolecules are recognized; one or more copies of the small Ubiquitin protein are "ligated" or attached to these damaged proteins; and this Ubiquitin-tagged "cargo" is then shuttled into the proteasome, a large multi-protein complex that functions as a garbage disposal, breaking proteins up into smaller, recyclable parts (amino acids).

6. The similarity between PARK2 and Ubiquitin suggested that PARK2 might similarly be involved in the Ubiquitin-mediated recycling system. The fact that specific cellular structures called Lewy bodies, which are associated with Parkinson's disease but not with normal cells, appear to contain Ubiquitin and proteasome components further supported the connection between this system and Parkinson's disease. However, the observation that the PARK2 sequence diverged in some ways from the protein to which it was being compared, including the presence of an additional region with a different predicted biochemical function, led researchers to speculate that PARK2 and Ubiquitin might have related but not identical roles.

7. Some researchers turned to *Drosophila* for answers. In 2000, M. Feany and W. Bender reported that introduction of the human gene encoding alpha-synuclein (SNCA) into *Drosophila* resulted in a fly model of Parkinson's disease that "recapitulates the essential features of the human disorder," including age-related loss of neurons and locomotor dysfunction. Versions of the human gene associated with a dominant inherited form of Parkinson's disease resulted in more severe Parkinson's disease-related effects than did introduction of the wildtype human gene, for which there is no apparent related gene in the *Drosophila* genome. Other reports followed, including from N. Bonini and colleagues, who observed neurotoxicity induced by alpha-synuclein, again consistent with what is observed for Parkinson's disease in humans. Unlike the case for SNCA, there is a gene in *Drosophila* that encodes a protein related to PARK2, making genetic tests in the fly even more straightforward to perform and interpret.

8. Insights gained from these studies continued to point researchers in the direction of the cell's ability to clean up a mess, which include not only the ability to recycle individual proteins but also the ability to identify organelles that have undergone damage, and recycle them for parts. Mitochondria are the cell's power plants, making energy in the form of adenosine triphosphate (ATP). They exist in cells wrapped in a double-layer of membranes, and have the ability to fuse together or split apart, to stretch thin, and to make more of themselves when needed. One of the insights *Drosophila* research has provided to the Parkinson's disease field was to uncover the idea that both the parkin gene product and the *Drosophila* ortholog of another Parkinson's-associated gene, PINK1, are required for a process called "mitophagy," the detection, clean up, and recycling of parts from damaged mitochondria. Research performed in the fly also helped to provide insights into the detailed cellular mechanisms of toxicity by alpha-synuclein, pinpointing where the aggregated proteins clog up the cellular system. Similarly, for Huntington's disease, research in the fly suggests a role in autophagy, another clean-up crew process that involves many of the same genes and events as mitophagy. In mitophagy or autophagy, the damaged organelles or other cellular debris are first enclosed in a membrane. This newly formed bag of trash then fuses with an organelle called the lysosome in which the proteins, lipids, and other molecules that make up the enclosed material are broken down into component parts that can either be expelled from the cells or reused to form new large biomolecules.

9. With a growing understanding of the cellular pathology of Parkinson's and other neurodegenerative diseases, researchers are using the fly to ask about earlier events. What are the initiating problems that start cells down a path to neurodegeneration? What are the risk factors? What might the early diagnostic signs be? A number of theories exist regarding the specific catalysing disruption of the system that messes things up, including accumulation of metal ions such as zinc and responses to infection, which might subsequently lead to increases in levels of proteins such as alpha-synuclein (in Parkinson's disease), amyloid beta (in Alzheimer's disease), or Tau (in tauopathies). For biologists and physician-scientists, at least, there remain unsatisfying ambiguity and uncertainty. We dig deeper. We look for the underlying causes of protein aggregation. We ask if aggregation is a protective response of the cells, contributes to pathology, or both.

Ways to Model Neurological (or Other) Diseases

10. *Drosophila* research has furthered our understanding of the molecular mechanisms of neurodegenerative diseases. Can this approach to discovery be applied to other neurological diseases? The answer is yes. Among the things that can differ is the appropriate way in which to model aspects of the disease. As for Parkinson's disease, many fly models of disease are based on genetic manipulation. This can involve introduction of a human gene into flies, as was true for the alpha-synuclein fly models of Parkinson's disease, as well as for the first fly models of neurodegenerative diseases, models of Huntington's disease and spinocerebellar ataxia 3. Alternatively, the best approach might be to disrupt the endogenous fly ortholog (when there is one) or introduce specific changes into the fly gene that parallel those found in affected patients.

11. Below are examples of *Drosophila* models of neurological diseases, or aspects thereof, based on injury, intervention, or observation of relevant normal behaviours. The section that follows explores how, once established, *Drosophila* models of disease can be used in biomedical studies, including for diagnosis and therapeutic discovery.

Mechanical Model of Spinal Cord Injury

12. Axons are projections that extend from the main cell body of a nerve cell, allowing nerve impulses to travel relatively long distances at rapid speed, and facilitating the kind of reactions that keep a fly out of danger from a predator or keep our legs churning in a running race. A particularly long nerve axon extends along the top of the fly wing, where it helps control flight. When this axon is cut, severing the extension from the main body of the nerve cell, the axon degenerates, following a stereotyped sequence of cellular events. Researchers can sever the wing axon from the main cell body in different genotypes of flies and look for mutations that result in preservation, rather than degeneration, following injury to the axon. Identifying such genes might help us understand how to preserve human axons that are disconnected from their cell bodies as a result of axon-damaging diseases or spinal cord injury.

Intervention Model of Depression

13. One aspect of depression modelled in mammals such as the mouse is the phenomenon of "learned helplessness," a failure to escape or avoid a negative stimulus following stress. A learned helplessness assay typically compares mice in each of three groups: animals not subjected to a stress; animals subjected to a stress but maintaining some level of control or ability to escape the stress; and animals subjected to a stress over which they have no control and no means of escape. Within a normal population, animals in the third group will later exhibit signs of "depression" such as decreased movement, passive response to a stress, and failure to try to escape a stress under conditions in which animals from the other two treatment groups would do so. A similar approach has been applied in *Drosophila*. For fly studies, researchers apply a heat stress to a fly only when

it stops walking (control group), or apply the heat stress the same number of times but at random with regard to what the fly is doing when the stress is applied (learned helplessness group).

Behaviour Model of Anxiety

14. Flies will naturally spend more time near the walls of a chamber than in the middle, a behaviour that presumably reduces the risk of predation in the wild. Under normal conditions, wildtype flies will rarely cross the open, middle area of the test arena. Increasing stress, such as through treatment with heat, increases the degree of wall following (the flies cross the middle even less frequently). By contrast, treating the flies with the anti-anxiety drug diazepam reduces the effect (flies cross the middle more often). F. Mohammad, A. Claridge-Chang, and colleagues have shown that orthologs of genes known to be involved in anxiety in mammals are relevant to wall following in flies, suggesting that flies can be used for further studies relevant to anxiety and anxiety-related disorders.

Putting Models to Work

15. Biomarkers can help physicians diagnose a disease and track disease progression. *Drosophila* can be used in large-scale proteomics, transcriptomics, or metabolomics studies that help determine whether detection of a given molecule correlates with the disease. Efforts to find early signs of cellular dysfunction in genetic fly models of neurodegeneration—assigning a "unique profile of neurodegenerative pathology" to diseases such as Parkinson's and Alzheimer's—are among the fly studies that might end up helping identify human biomarkers that assist physicians in diagnosis of neurodegenerative diseases earlier in adulthood or with increased accuracy. The biomarkers themselves might be genes whose expression changes upon development of the disease; proteins (or their enzymatic activities) detectable at higher or lower levels in patients with the disease; or metabolites that accumulate or are depleted in the disease state but not in unaffected individuals.

16. In addition to implicating new genes, models of disease also allow for deep investigation of cellular and subcellular mechanisms relevant to the disease. For a simple being, the fly is surprisingly complex. Implication of mitophagy in Parkinson's disease provides an example of how studies in the fly can reveal molecular and cellular mechanisms of disease. Another example comes from a study reported in 2014 by M. Maheshwari, N. R. Jana, and colleagues that focused on Huntington's disease. The study, initiated in mice and continued in flies, implicated down-regulation of a gene called HSFI, which encodes a transcription factor, in Huntington's disease. Making a connection to HSFI led researchers to consider a drug called dexamethasone, already in clinical use as an anti-inflammatory, as a possible treatment.

17. Independent of genetic studies, researchers can ask whether treating the disease model flies with drugs, small molecule inhibitors or agonists, natural products, or chemical derivatives related to traditional medicines can ameliorate symptoms. With flies, we can do these studies in whole animals, assessing large numbers of individuals, and using assays that span the full natural lifespan of the organism, adding to confidence in the outcomes.

18. An example of the use of *Drosophila* models of disease to identify drug treatments comes from studies of Fragile X syndrome, which is characterized by altered intellectual ability and a number of behavioural disorders, including sleep irregularities and hyperactivity. The syndrome is associated with disruption of a specific human gene, FMRI. Disruption of the fly ortholog FmrI results in changes to neuronal cells that can be quantified and studied, as well as measurable disruptions to fly behaviours, including changes to performance on memory assays and changes in sleep patterns. In common with mouse models of the disease, Fragile X disease model flies also exhibit changes in activity of a specific protein, GluR, that can be targeted with drugs.

19. The 2005 *Drosophila* study by S. M. McBride, T. A. Jongens, and colleagues also provided the first evidence that treatment with lithium, which is already approved for clinical treatment of other conditions and affects GluR-relevant cellular activities, might have a beneficial effect in Fragile X syndrome patients. In 2008, E. Berry-Kravis, W. T. Greenough, and colleagues stated that the results of a small study of human patients were "consistent with results in mouse and fly models," reporting that the treatment is "well-tolerated and provides functional benefits".

Establishing Cause

20. Fly models of disease typically start with an established link between a disease and disruption of a specific gene or genes, or perturbation. But for some diseases, we are far behind in our knowledge.

21. Below are three examples of how *Drosophila* studies helped reshape our thinking regarding mutations known to be causative for a disease, or helped identify the most promising candidates—or the sole causative gene—from a field of many. For one of the cases presented, information gained in *Drosophila* studies led to the identification of a new rare inherited disorder, Harel-Yoon syndrome, the first to be named (in part) for a *Drosophila* researcher. Although these examples are drawn from the neurological field, the approach is by no means limited to that area. Similar approaches are being applied to other types of diseases.

Rethink the Nature of a Genetic Cause

22. The various forms of Charcot-Marie-Tooth disease comprise a common inherited neuropathy associated with disruption of one of several known genes. One thing important to our understanding of an inherited disease is to learn whether a given mutation associated with the disease inactivates or reduces function of the gene, or by contrast, increases or changes its function. Given no other evidence, a best guess is that a recessive mutation is likely to be one that inactivates gene function, and a dominant mutation is likely to result in activation or the gain of a function by the gene. But these assumptions do not always hold true. Charcot-Marie-Tooth type 2B (CMT2B) is an example of a disease with a dominant pattern of inheritance, with one altered copy of the human gene RAB7A (commonly referred to as Rab7) sufficient to result in disease. Based on the pattern of inheritance, protein structure analysis, and other studies, CMT2B-associated mutations in RAB7A were thought to be gain-of-function mutations, such that a route to therapy might include identification of drugs that reduce RAB7A protein activity. In 2013, however, S. Cherry, R. P. Hiesinger, and colleagues reported experimental results obtained in *Drosophila* that suggested a need to rethink the gain-of-function hypothesis for CMT2B-associated mutations in RAB7A. In experimental analyses the researchers obtained data suggesting that CMT2B-associated mutations in RAB7/1 are associated with partial loss of function, rather than a gain of function.

Identify Multi-Gene-Effects

23. Among the most challenging genetic disorders to approach and understand are those that involve changes in more than one gene. Examples include disorders or syndromes associated with chromosome nondisjunction or duplication events that result in the presence of extra copies of an entire chromosomal region in the genome of affected individuals. The best known of these is Down syndrome, which results from nondisjunction of chromosome 21, such that affected individuals have three copies of genes on that chromosome instead of two. We commonly associate Down syndrome with intellectual disability, but it is associated with additional medical challenges as well. An example is a congenital heart defect present in some but not all Down syndrome cases. By 2009, studies in mice, together with detailed human genetic mapping, had limited the chromosomal region implicated in the heart defect to one end of chromosome 21. However, although three likely candidate genes could be identified, there remained uncertainty regarding which specific genes were at fault and the precise relationships among them.

24. A 2011 study by T. R. Grossman, A. Gamliel, and colleagues cleared the fog. They first tested the effects of overexpressing the mammalian or fly version of any of five candidate genes in the region. Three genes scored as positive in at least two assays related to *Drosophila* heart disease. To better mimic what happens in Down syndrome patients—wherein more than one gene is present in an extra copy—the researchers then created flies in which any combination of two of these three genes is expressed at increased levels. They found that increased expression in the fly heart of two genes, COL6A2 and DSCAM, together resulted in a strong effect on fly heart function. They went on to do a similar test in the mouse heart and made similar findings. Although the animal models do not exhibit all the defects observed in the hearts of Down syndrome patients with congenital heart disease, the findings suggest an avenue worthy of pursuit.

Solve a Mystery

25. The NIH-funded Undiagnosed Diseases Network (UDN) is designed to address the problem that "Every year hundreds of men, women and children face hardships and uncertainty when their healthcare providers are unable to discover the cause for their symptoms". Next-generation sequencing provides an opportunity for medical genetics experts and others to identify candidate genes that underlie individual cases. In some cases, genome sequence data point clinicians in the direction of previously identified diseases. In others, the data suggest that the disease might be one previously uncharacterized or undefined at the level of genetic cause. The UDN has purposefully turned to *Drosophila* and other model organism studies in order to help identify genetic causes of previously undiagnosed diseases in an efficient and effective manner.

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