Aerobic Respiration

Question Paper 1

Level	International A Level
Subject	Biology
Exam Board	Edexcel
Topic	Respiration, Muscle and Internal Environment
Sub-Topic	Aerobic Respiration
Booklet	Question paper 1

Time Allowed: **71 minutes**

Score: **/59**

Percentage: **/100**

Grade Boundaries:

A*	A	B	C	D	E	U
>85%	77.5%	70%	62.5%	57.5%	45%	<45%

1 Aerobic respiration and anaerobic respiration produce ATP in cells.

(a) It is thought that 38 ATP molecules are produced from one molecule of glucose in aerobic respiration.

Place a cross in the box ☒ next to the description of where most of these ATP molecules are produced.

(1)

☒ **A** glycolysis in the cytoplasm

☒ **B** glycolysis in the mitochondria

☒ **C** oxidative phosphorylation in the cytoplasm

☒ **D** oxidative phosphorylation in the mitochondria

(b) During anaerobic respiration lactate is produced.

The table below shows the lactate concentration in the blood of a person who is an athlete and in a person who is not an athlete (non-athlete), at increasing levels of exercise.

Level of exercise / arbitrary units	**Blood lactate concentration / mmol dm^{-3}**	
	Athlete	**Non-athlete**
0	1.0	1.5
60	1.1	2.2
120	1.4	3.7
180	3.2	6.2
240	6.4	10.0

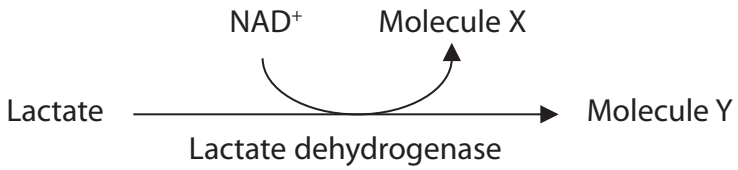
(i) Explain the change in blood lactate concentration with an increasing level of exercise in the non-athlete.

(3)

(ii) Suggest an explanation for the difference between the blood lactate concentration of the athlete and the non-athlete.

(2)

(c) The diagram below shows the fate of lactate after exercise.



(i) Name molecule X.

(1)

.....

(ii) Describe what happens to molecule Y.

(2)

.....

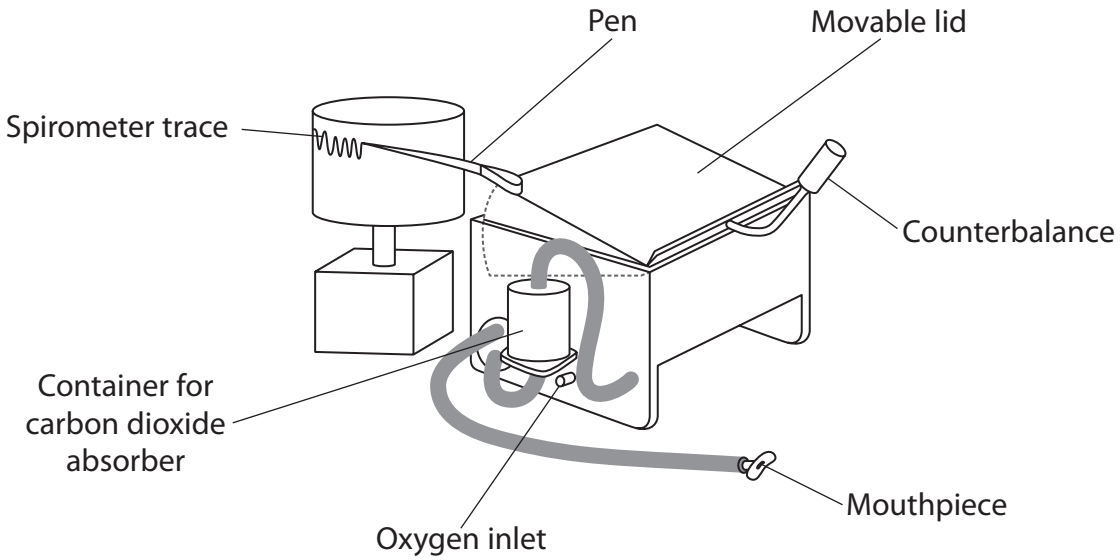
.....

.....

.....

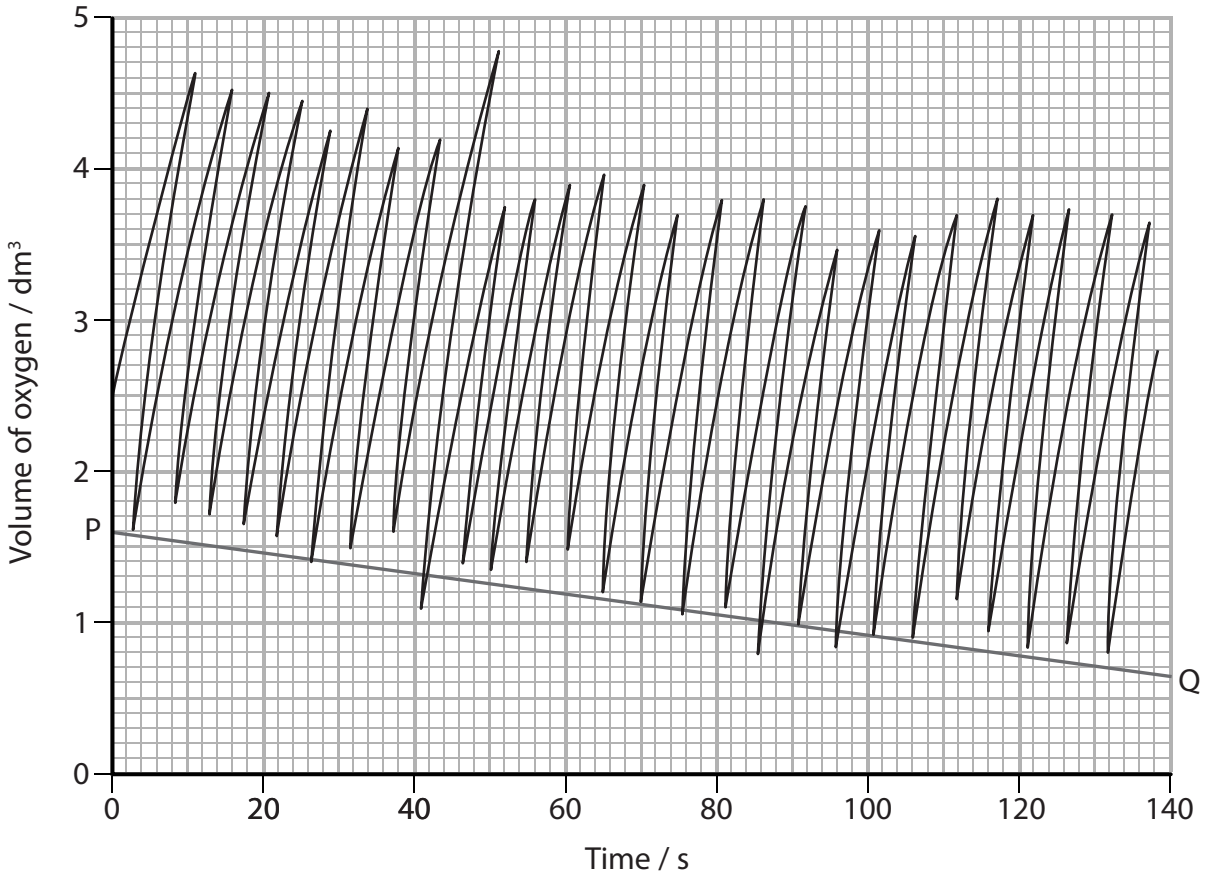
(Total for Question 1 = 9 marks)

2 The diagram below shows a spirometer that can be used to measure lung volumes. A spirometer can also be used to measure the volume of oxygen a person uses.



(a) A student used a spirometer to measure the volume of oxygen he used at rest and during exercise.

The spirometer trace below shows the results he obtained during exercise.



(i) The line P to Q slopes downwards because oxygen is being used.

Use the line, labelled P to Q on the trace, to calculate the volume of oxygen used during one minute of exercise.

(1)

Volume of oxygen used = ...

(ii) The student had a body mass of 70 kg.
Calculate the rate of oxygen used by this student in $dm^3\ kg^{-1}\ h^{-1}$.

Show your working.

(2)

Rate of oxygen used = ... $dm^3\ kg^{-1}\ h^{-1}$

(iii) Suggest **two** differences between this spirometer trace and the one the student obtained at rest.

(2)

.....

.....

.....

.....

.....

.....

(b) (i) The air the student exhaled passed through the carbon dioxide absorber in the spirometer.

Name a carbon dioxide absorber.

(1)

.....

(ii) Explain why the spirometer trace would be different if the carbon dioxide had not been absorbed.

(2)

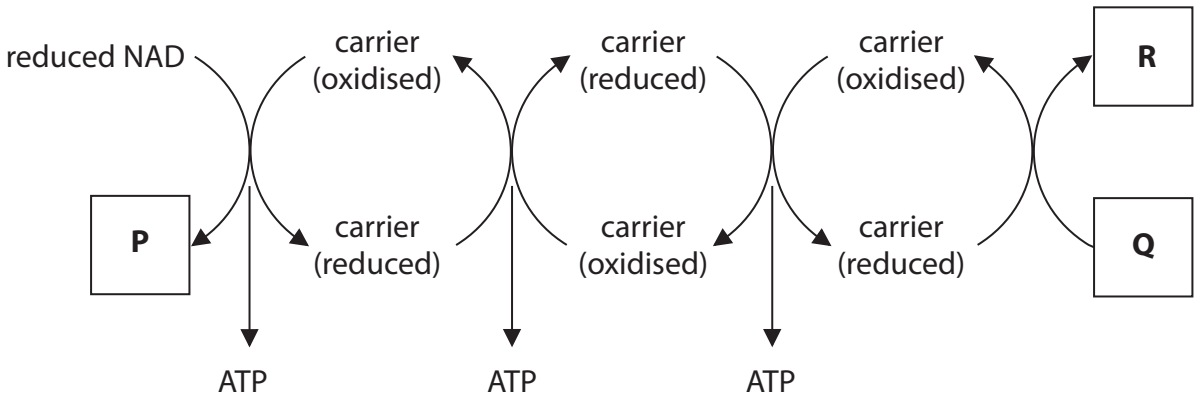
(c) Explain how carbon dioxide is involved in the control of breathing rate during exercise.

(4)

(Total for Question 2 = 12 marks)

3 The electron transport chain is involved in the synthesis of ATP.

(a) The diagram below shows part of the electron transport chain.



(i) Name the molecules P, Q and R.

(3)

P .....

Q .....

R .....

(ii) Place a cross ☒ in the box next to the description of where the electron transport chain occurs.

(1)

☒ **A** cytoplasm surrounding mitochondria

☒ **B** inner mitochondrial membrane

☒ **C** mitochondrial matrix

☒ **D** outer mitochondrial membrane

(b) In 2013, poachers killed over 80 elephants in Zimbabwe by poisoning their drinking water with cyanide. Cyanide inhibits cytochrome oxidase, the last carrier in the electron transport chain.

Suggest how inhibiting cytochrome oxidase would kill an elephant.

(4)

(Total for Question 3 = 8 marks)

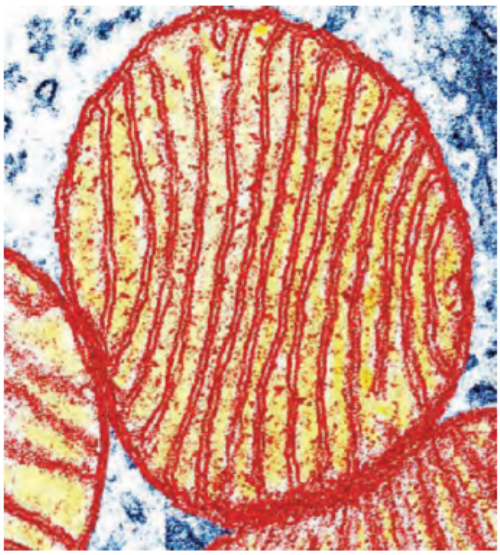
Scientific article for use with Question 4

Mitochondria, Metabolism and Inheritance

Powerhouse of disease

1. Some of Gerald Shulman's patients at Yale University School of Medicine are young and slim. There's little wrong with them, and probably won't be for a decade or two. Yet tests raise an ominous spectre. All are the children of parents with type 2 diabetes, and, already, in their twenties, they are becoming resistant to insulin, the hormone that should be keeping their blood sugar levels under control.

2. The problem seems to lie in their muscles, whose cells lack tiny lozenge-shaped structures called mitochondria. These normally function as powerhouses inside cells, burning up fuel with oxygen. Long regarded as the cell's menial coal-shovellers, mitochondria are emerging as key players in health and disease. The 'organelles' are unusual in having their own DNA, although many of the genes that once resided in the mitochondria have, over evolutionary time, decamped to the cell's nucleus. Shulman is one of a number of scientists who think that tracking down the hundreds of 'missing' genes that have shifted to the nucleus is going to change the way we think about common diseases such as diabetes and Parkinson's.



Genes in the nucleus that encode proteins for the mitochondria (above) could underpin diseases.

3. Mitochondria store the energy released from food in the form of a molecule called ATP, which is used to power virtually all forms of work in the body, from muscle contraction to protein synthesis. Your body's mitochondria generate an impressive total of some 65 kg of ATP every day. The double-membraned organelles perform this feat thanks to a process called chemiosmosis, which pumps protons across one of their membranes. ATP is generated when the current of electrically charged protons, produced by this pump, passes through tiny protein motors embedded in the same membrane.

Ancient union

4. As well as looking like them and using chemiosmosis in the same way as bacteria, mitochondria contain a bacteria-like genome. Indeed, mitochondria were once free-living bacteria; they were engulfed by larger cells two billion years ago in a unique merger that gave rise to all complex, or eukaryotic, cells. The size of the genome housed within the mitochondrion varies between species. All mammals, for example, have retained just 37 genes, whereas yeasts have retained between 40 and 50, and some plants as many as 100.

5. But mitochondrial genomes did not start out so small – they probably once contained at least a few thousand genes, inherited from the free-living ancestor of mitochondria. Exactly what happened to most of these genes is a moot point, but the evolution of a stable symbiotic relationship within eukaryotic cells led to hundreds, perhaps even thousands, being simply transferred to the cell's main genome in its nucleus. These transfers meant that mitochondria became dependent on the host cell for virtually all their functions. Today, some 99% of human mitochondrial proteins are encoded in the nucleus; all the proteins and other molecules required to build mitochondria are synthesized in the main body of the cell, then imported into the organelle. Only a fraction of these genes has been identified; the rest lie hidden in the vast code of the nucleus's genome.

6. This enigmatic 99% is now the focus of intense scrutiny. There are good reasons to believe that genes affecting the mitochondria could play a central role in human health and disease. Most of the genes that have remained in the mitochondrion have been linked to a series of devastating diseases, indicating the importance of fully functional mitochondria to human health.

7. Genes residing in the mitochondria pose a particular problem, however – in part because they are unusually prone to damage. Unlike nuclear genes, which are wrapped in protective proteins and stored safely away in the nucleus, mitochondrial genes are vulnerable to attack from highly reactive molecules called free radicals; these are generated during energy production. In mammals, the mutation rate of mitochondrial genes is 10 to 20 times higher than that of the nuclear genes.

8. The idea that mutations in mitochondrial DNA could cause metabolic diseases, or even ageing, has gained credence since Fred Sanger's group at the University of Cambridge, UK, sequenced the human mitochondrial genome in 1981. According to David Thorburn, at the Murdoch Children's Research Institute in Melbourne, Australia, in the decades since, pathogenic mutations have been discovered in more than 30 of the 37 human mitochondrial genes. Their effects are a long list of rare disorders, best diagnosed and treated by specialists, who refer to themselves as mitochondriacs.

9. The most common childhood condition is Leigh syndrome. This affects about 1 in 40,000 children and tends to develop within the first year of life, often after a viral infection. In most cases, degeneration of the central nervous system leads to loss of muscular coordination and death within a few years, although some children survive into their teens. Lethal infantile mitochondrial disease is much rarer but even more deadly. Children born after an uneventful pregnancy tend to have seizures soon after birth, make few or no spontaneous movements, and die of respiratory failure within weeks. Other conditions have relatively mild symptoms. A common feature of all these diseases is that they tend to worsen with age. Indeed, it is the cumulative effects of free-radical attacks, and the corresponding build up of mitochondrial mutations that may underpin aging.

Faulty engine

10. Mitochondria, along with their tiny genomes, are normally inherited only from the mother – they are present in huge numbers in the egg, whereas the handful in sperm is marked up for destruction in the fertilized egg. This gives at least some mitochondrial diseases a maternal-inheritance pattern. Even so, trying to spot mitochondrial diseases by looking to the mother can be grossly misleading, and has downplayed the importance of these organelles in disease. More than 80% of diseases known to be linked to faulty mitochondria don't follow a maternal-inheritance pattern at all.

11. Why not? At least partly because some mitochondrial diseases may be caused by mutations in the nuclear genes encoding mitochondrial proteins. So far, mutations in more than 30 nuclear genes have been shown to give rise to mitochondrial disease. Thorburn, however, estimates that as much as a tenth of the population may be carrying genetic disorders that could affect mitochondrial function. This is based on estimates of the number of mitochondrial genes in the nuclear genome and the incidence of recessive genetic disorders. He echoes a favourite catchphrase of mitochondriacs: "Mitochondrial deficiency can theoretically give rise to any symptom, in any organ or tissue, at any age, and with any mode of inheritance."

12. The actual contribution of nuclear genes to mitochondrial diseases is highly uncertain for a simple reason – we are surprisingly ignorant of what the nuclear genes actually are, and how they interact with mitochondrial genes. In mammalian mitochondria, the best guess is that the nuclear genome encodes 1,500 distinct mitochondrial proteins. So far, barely half have been formally identified, and of these, the function of a sizeable proportion remains unknown.

13. Nonetheless, the evidence that mitochondrial proteins are responsible for a lot more mischief than once thought is growing. A series of inherited conditions not thought of as 'mitochondrial' have turned out to be caused by mutations in genes encoding mitochondrial proteins. For instance, Friedreich's ataxia (a progressive loss of coordination of voluntary movements) is caused by mutations in a gene encoding a small mitochondrial protein called frataxin. Hereditary spastic paraplegia (a progressive weakness and stiffness of the legs) can be caused by mutations in a mitochondrial enzyme, paraplegin.

14. Other, more complex degenerative conditions, such as Parkinson's disease, progressive blindness diseases and other nervous-system conditions also involve mutations in mitochondrial proteins. Even cancer can be caused by mutations in nuclear genes encoding mitochondrial proteins. Examples are now cropping up almost every year, and together they are beginning to focus attention on the central role of mitochondria in disease.

15. These examples have all unexpectedly turned out to be 'mitochondrial', after years of tracking down candidate genes for the diseases. But new tools are letting scientists turn the old approach on its head. Rather than starting with an inherited condition and trying to track down the genes responsible, researchers are starting off with the mitochondria themselves, and attempting to hunt down the proteins needed to build them. Tracking down this array of proteins, or the mitochondrial 'proteome' is no easy task; researchers rely on a combination of methods to build an accurate picture, including mass spectrometry to identify proteins and molecular-biology techniques to measure RNA, the molecule used by cells as a template from which to build proteins.

16. All the techniques based on this bottom-up approach have strengths and weaknesses, but by taking the best information from each, scientists are gradually piecing the mitochondrial proteome together. Once the normal proteins have been identified, any oddities in patients can be pinpointed. The abnormal protein can be mapped on to the candidate genes for disease, and any causal mutations involved identified.

17. In 2003, Vamsi Mootha, a computational biologist at the Broad Institute in Cambridge, Massachusetts, and his colleagues published a list of several hundred new mammalian mitochondrial proteins, raising the known mammalian total to around 600. Crucially, however, Mootha's group also examined tissue variations. In mice, they found that around half the mitochondrial proteins identified were present in four different tissues – brain, heart, liver and kidney. But the other half tended to be tissue-specific, with some degree of overlap (around 50%) between different tissues.

Building a powerhouse

18. Mitochondria are well known to carry out specific tasks in different tissues; for example, they make haem, part of the oxygen-carrying protein haemoglobin, in bone marrow cells. But the finding that hundreds of mitochondrial proteins varied in amounts from tissue to tissue came as a shock. If corroborated, this variation suggests that the control of mitochondrial gene activity is very sophisticated. And this has a corresponding impact on our susceptibility to disease; the more complicated the control system, the more likely it is to fail.

19. Mootha's group reported the first two tissue-specific mitochondrial proteins, known as Errα and Gabpa/b, in 2004. Both control gene activity, which in turn affects how much mitochondria replicate themselves in particular tissues. If the expression of Errα and Gabpa/b is high, then mitochondria replicate at a high rate, and become densely packed in the tissue. If their expression is lower, the number of mitochondria and their ability to burn fuel falls. Critically, Errα and Gabpa/b influence mitochondrial function and density in particular tissues, notably the heart and muscle, and play a lesser role in tissues such as the liver. Mootha notes that this tissue specificity makes them valuable drug targets, because it restricts the potential for side effects in other tissues.

20. The next question for Mootha and his team was what happens if the activity of Errα and Gabpa/b falls? They predicted that a fall in the number and capabilities of mitochondria in particular tissues would result – a finding that Mootha and others had previously reported in the muscles of patients with diabetes. Sure enough, Mootha's lab found that the activity of these proteins was lower in the muscles of patients with type 2 diabetes. But could such a change be a root cause of diabetes, or was this merely a consequence of some other metabolic problem, such as obesity?

21. Type 2 diabetes has two cardinal features. The first is that cells become resistant to the effects of insulin, the hormone made by the pancreas that normally prompts them to take up and burn glucose. The second is high levels of glucose in the blood, or hyperglycaemia. Insulin resistance is typically one of the earliest signs of diabetes, often preceding hyperglycaemia by decades.

22. Faulty mitochondria have already been linked to the second phase of the disease – namely the emergence of hyperglycaemia. Defective mitochondria in the pancreas fail to burn sufficient glucose, so the levels of ATP in pancreatic cells are abnormally low. But these cells rely on ATP levels to help them estimate the amount of glucose in the blood. As a result, the cells do not sense glucose properly, do not release appropriate amounts of insulin and the blood glucose level creeps up.

23. But what about insulin resistance? Shulman thinks that faulty muscle mitochondria could underlie insulin resistance in muscle tissue and was intrigued by Mootha's findings. "We've been working with volunteers who have a high genetic risk but a low 'lifestyle' risk of diabetes. We hope to eliminate confounding factors such as obesity, or indeed the early stages of diabetes itself, and focus on the earliest underlying genetic influences."

Complex pathways

24. Shulman's group has found three striking oddities in the muscle cells of the young volunteers: they are often very insulin resistant, taking up about 60% less glucose in response to insulin compared with the muscle cells of unaffected people; they have a low mitochondrial density, about 40% lower than normal; and they have a large accumulation of fat molecules, or lipids, around 60% above normal.

25. The key, says Shulman, is the high level of lipids. Lipids can cause insulin resistance by jamming the cellular machinery that helps receive the hormone's signal. But what causes their levels to rise in the cell? There are two main possibilities: a faster rate of lipid breakdown and delivery to muscles from fat tissues; or a defect in the muscle mitochondria themselves. If faulty mitochondria don't burn fats as fast as they should, then that could lead to a build-up of lipids inside the muscle cells. That would suggest the primary genetic cause of type 2 diabetes lies in the mitochondria. Faulty mitochondria also contribute to obesity, by not burning fats properly, and obesity in itself exacerbates diabetes.

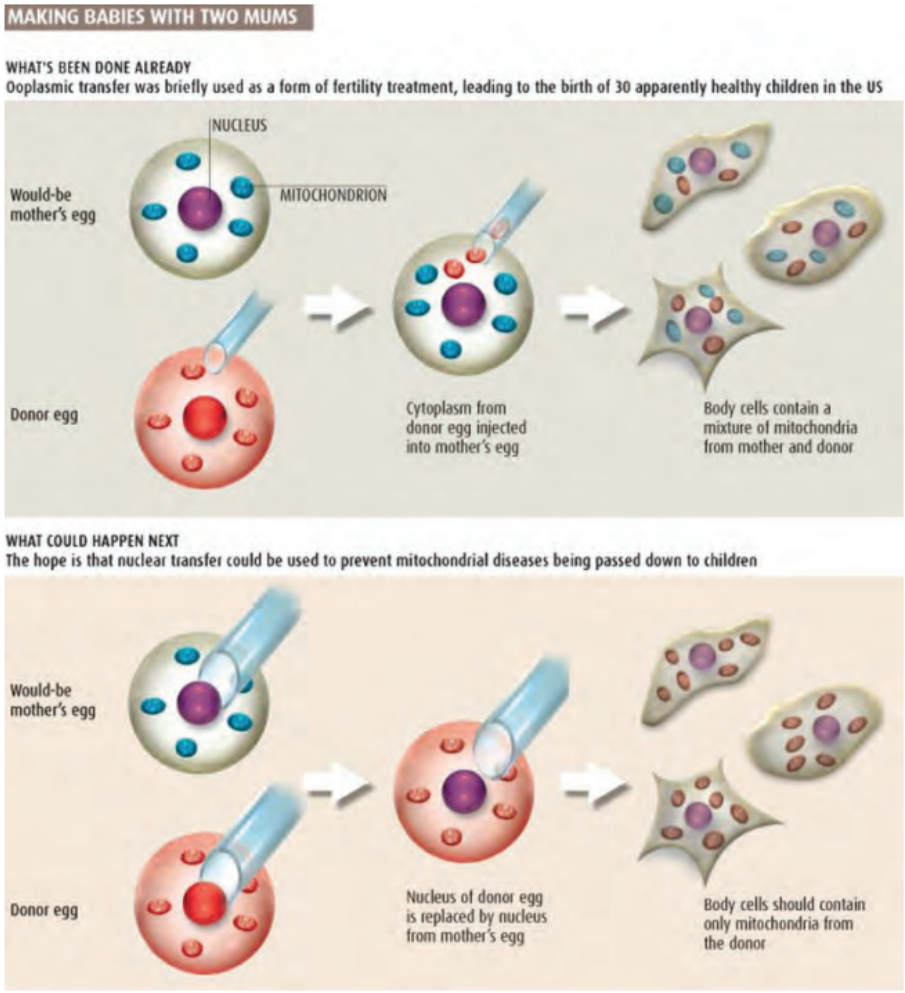
26. Shulman's group could find no evidence that abnormal fat breakdown and delivery from fat tissues was responsible, and so turned to look at possible faults in mitochondria.

27. Following up on Mootha's findings, the team looked as whether a mutation in the genes controlling the tissue-specific mitochondrial proteins Errα and Gabpa/b could underpin the low density of mitochondria in the volunteers. The result was a surprise. They could find no such mutations, implying that the reduction in gene expression measured by Mootha was not the primary cause of diabetes. The primary fault must lie in another, as yet unknown pathway governing mitochondrial proliferation and activity.

28. So faulty mitochondria may well be the cause of diabetes, but we still don't know what makes them faulty. Yet with hundreds of unknown mitochondrial proteins still to uncover, Shulman and Mootha have a long list of possible suspects to work through. Whether they will get results in time to help Shulman's young volunteers is an open question, but the answers seem set to revolutionize our understanding of disease.

Genetically modified humans: Here and more coming soon

29. Children with three parents might sound like monstrous chimeras, but they are among us already. In the late 1990s, an American team created the first genetically engineered humans by adding part of the egg of one woman to the egg of another, to treat infertility. When the US Food and Drug Administration got wind of the technique it was promptly banned, though related methods have been used in other countries.



30. Now a research team in the UK is experimenting with creating three-parent embryos. This time, the goal is to prevent children inheriting a rare group of serious diseases caused by faulty mitochondria, the powerhouses in our cells. Mitochondrial diseases affect at least 1 in 8000 people, probably more, and there are no treatments.

31. Mitochondria are always inherited from the mother, so for women in whom they are faulty replacing the mitochondria in their eggs with healthy ones from a donor would help ensure their children are healthy. What makes the idea controversial is that mitochondria contain DNA of their own, meaning babies created this way will have genes from a "second mother".

32. Supporters of this approach point out that mitochondria contain a mere 37 of the 20,000 or so human genes. Changing them is akin to changing a battery, they argue. Yet it is becoming increasingly clear that the influence of mitochondrial genes extends far further: different variants can affect our energy, athleticism, health, ageing, fertility, perhaps even our intelligence, all of which help make us who we are as individuals.

33. The prospect of trying to prevent mitochondrial diseases by creating babies with two mothers raises a host of issues. On the one hand, if the FDA felt that three-parent embryos were unsafe, what's changed? On the other hand, if this approach really is safe, wouldn't it make sense to equip our children to live longer, healthier and more active lives by giving them the best possible mitochondria? The answers to these questions offer insights into some of the most intriguing aspects of sex, health, disease and longevity – and even into the origin of species.

Mixed up

34. Male mitochondria are an evolutionary dead-end. While there are 100 or so in the tail of every sperm, powering its motility, they are destroyed when the winning sperm gets inside the egg, which is stocked with 100,000 or more mitochondria of its own. As a result, mitochondrial DNA almost always passes from egg to egg, mother to daughter.

35. This is the deepest distinction between the sexes. Forget the Y chromosome, which is a genetic johnny-come-lately, restricted to mammals: reptiles, insects and plants all have different systems of sex determination. Even many simple algae and fungi have two sexes, but the only thing their sexes have in common with ours is the passage of mitochondria down the "maternal" line.

36. How this came about is still hotly debated. The leading hypothesis, proposed in 1992, is that if mitochondria from the father and mother had to compete with each other for survival, "selfish mitochondria" would evolve to the detriment of the entire organism: the mitochondria that are best at proliferating are not necessarily best at providing a cell with the right amount of energy. Whatever the reason, all the mitochondria in our cells are normally identical.

37. In the 1990s, however, the fertility technique pioneered by Jacques Cohen at the Institute for Reproductive Medicine and Science of St Barnabas in Livingston, New Jersey, resulted in children with cells containing a mixture of mitochondria from different individuals – something that almost never happens naturally. The technique, known as ooplasmic transfer, involves transferring tiny extracts of healthy donor eggs into the eggs of infertile women, with the vague aim of "pepping them up" a little. It boiled down to injecting a bit of good egg into a bad egg, and hoping for the best. Surprisingly, it seemed to help, although no controlled trials were done to show this for sure.

Unanticipated consequences

38. The group suspected it was transferring mitochondria, but didn't anticipate the consequences. Despite injecting less than 5 per cent of the egg-cell volume, when blood cells were taken from two of the 30 babies born this way, about a third of the mitochondria were found to come from the donor egg.

39. While there is no evidence that these children will suffer from diseases as a result of their cells having a mixture of mitochondria from two different women, there is no guarantee that they won't, either. This is why most researchers think the FDA was right to ban ooplasmic transfer, at least until a lot more basic research has been done to fully investigate the technique. However, Jonathan Van Blerkom, a developmental biologist at the University of Colorado in Boulder, who sat on that FDA committee, sees the work now taking place in the UK in a different light. The approach holds enormous promise he says, and it would be "criminal" to ban it.

40. The research is led by Patrick Chinnery and Douglas Turnbull of Newcastle University in the UK, who see people with some of the most dreadful congenital diseases known. Leigh syndrome, for instance, occasionally affects adults but usually strikes children under 2 years old. Sufferers have difficulty moving, swallowing and breathing. The symptoms come and go but inevitably worsen, leading to mental impairment, seizures and death within months or years. Leber's hereditary optic neuropathy causes blindness, usually in young men. Another syndrome, called MELAS, can involve everything from diabetes and mild deafness to digestive problems, seizures and stroke-like episodes.

41. "In mice it is possible to prevent the transmission of often disabling and sometimes fatal disease," Turnbull says. "The only focus of our laboratory is to try and determine if this is a valid treatment for our patients." Chinnery and Turnbull are experimenting with a method originally proposed in the 1980s by the guru of mitochondriacs, Doug Wallace, who is now at the University of California, Irvine. The trick, he suggested, is not to transplant any mitochondria, just the nucleus – the repository of the main genome in cells.

Peculiar inheritance

42. Soon after an egg is fertilised, the nucleus is taken from an embryo with faulty mitochondria and injected into a donor egg cell whose nucleus has been removed. The outcome is an embryo with nuclear genes from the prospective parents, and mitochondrial DNA from the second mother. In principle, all the mutant mitochondria should be left behind; in practice, however, a few mutant mitochondria may stick to the transplanted nucleus. Even though their numbers start off small, as the embryo grows the proportion of mutant mitochondria could be ramped up in some cells, as happened after ooplasmic transfers.

43. Typically the proportion of mutant mitochondria per cell has to exceed a certain threshold before problems begin. This means people with the same mitochondrial mutation can have quite different symptoms, or none at all, depending on the fraction of mutant mitochondria in cells in different parts of the body. Chinnery and Turnbull are now investigating whether the transfer of a handful of mutant mitochondria along with the nucleus could result in some cells having a dangerously high proportion of mutant mitochondria. The early results suggest not, but they are in the middle of more systematic studies, and don't want to speak too soon.

44. Even if children conceived in this way are healthy and stay that way, Van Blerkom points out that a disease might reappear generations later. The problem is the random segregation of mitochondria into developing egg cells, which are then amplified in numbers from as few as 10 to the 100,000 in a mature egg cell. If even a handful of faulty mitochondria get into the germline, they could be amplified to a level high enough to cause a recurrence of disease in descendants of the female line.

Dangerous mutations

45. This might seem to be a serious argument against three-parent embryos until you consider the alternative. At the moment, women who discover that their mitochondria bear dangerous mutations face a terrible dilemma when it comes to having children. The peculiar nature of mitochondrial diseases means that even when all a woman's mitochondria are mutant, a child could be anything from perfectly healthy to suffering from a far more severe form of the disease than the mother. In some cases doctors can give more precise odds, but often they can't.

46. Prenatal testing, or IVF with preimplantation genetic diagnosis (PGD), are not much help either. Such screening methods can detect some common mitochondrial mutations but cannot reliably reveal what percentage of mitochondria in cells bear these mutations. Neither method can help women whose mitochondria are all mutant. The bottom line is that the creation of two mother embryos could provide would-be parents with by far the best chance of having healthy children – and healthy grandchildren and great-grandchildren.

47. So let's suppose that all the outstanding issues are solved in the next few years, and that the creation of two-mother babies to prevent mitochondrial diseases becomes routine in the next few decades. Will this be the first step on a slippery slope towards creating designer babies?

Designer babies

48. The idea is not beyond the pale, as we are learning that the role of mitochondrial DNA goes deeper than anyone thought. Perhaps the biggest surprise over the past decade is that mitochondria are responsible not merely for energy production in cells, but also for orchestrating programmed cell death. The state of mitochondria is the decisive factor determining whether cells live or die, with obvious implications for health and disease, from cancer to degenerative diseases such as Alzheimer's.

49. The most striking example comes from Japan. Here, there is a common variant in mitochondrial DNA, a change in a single DNA "letter". A decade ago Masashi Tanaka, now at the Tokyo Metropolitan Institute of Gerontology, and his colleagues reported that this tiny change almost halved the risk of being hospitalised for any age-related disease at all, while doubling the chance of living to 100. Most Japanese centenarians have the variant, but unfortunately for the rest of us it's very rare outside Japan.

50. Since the late 1990s, other variants in mitochondrial DNA have turned out to be implicated in all kinds of traits. Several are linked with longevity, albeit less robustly than the Japanese type. Another common variation is associated with diabetes, while others increase the risk of neuro-degenerative conditions such as Parkinson's disease. Male fertility depends partly on sperm motility, which is also influenced by mitochondrial variants. Even IQ, Tanaka has found, is linked to mitochondrial variations, at least in Japan, though the differences are small.

51. So could we boost intelligence and lifespan, and prevent many diseases by creating "designer" three-parent embryos? The answer is probably not, at least in the foreseeable future. There are two main reasons. The first, Tanaka notes, is that old biological chestnut, trade-off: nothing comes without a cost. In Japan, the mitochondrial group with the highest IQ is most likely to get heart disease, for example.

Tradeoffs

52. Wallace, meanwhile, thinks that our mitochondria evolve to match our climate by regulating internal heat generation. Mitochondria may produce less heat in the tropics, but at the cost of leaking more free radicals, which predisposes individuals to diseases like diabetes. Conversely, people adapted to northern climates generate more heat internally and are less likely to get diabetes, but at the cost of more male infertility. So you choose a trait and pay the penalty. Would you opt for a mitochondrial variant that boosted your child's athleticism, for example, if you knew it would lead to poor health later in life?

53. Then there is an even more fundamental problem. Of the 1500 or so mitochondrial proteins, just 13 are encoded by mitochondrial genes and produced locally. The rest are encoded in nuclear DNA, made elsewhere in the cell and exported to mitochondria. These two sets of proteins, encoded by different genomes, have to work together intimately, yet mitochondrial DNA mutates around 20 times as fast as nuclear DNA. If such mutations mean the two genomes don't function well together, then an individual is more likely to suffer from a range of diseases. At worst, the embryo could die.

54. Ronald Burton, a marine biologist at the Scripps Institution of Oceanography in San Diego, California, has even suggested that such incompatibilities might be behind the origin of species, or at least some of them. He works with tiny marine copepods, shrimp-like crustaceans that live along the Pacific coast close to Scripps. Their populations don't interbreed much, and so steadily accumulate differences in their mitochondrial DNA. When Burton and his colleagues experimented with interbreeding between local populations, they discovered that mitochondrial incompatibilities undermined the health of offspring. The animals lacked energy, developed slowly, were less fertile and were also more likely to die early. It is only a matter of time before these incompatibilities reach a level that rules out successful interbreeding altogether – the very definition of a species. What's more, because mitochondrial genes evolve so quickly, they might even play the dominant role in natural speciation.

55. Wallace and others have found that these evolutionary patterns apply not only to crustaceans, but also to mammals – and notably to primates. Our genes show all the cardinal signs of selection for compatibility with mitochondria, and mitochondrial incompatibilities might play a huge role in human health and happiness.

Inhumane

56. For example, around 40 per cent of all pregnancies end in early miscarriage for unknown reasons. Many could be caused by mitochondrial incompatibilities. Not only that, but Tanaka suspects the high incidence of diabetes among Californian Hispanics is related to incompatibilities between mitochondrial and nuclear genes due to the mixing of long-separated populations. If he's right, there could be many other examples.

57. The issue of compatibility means there is an inherent danger in any attempts to boost health, longevity, fertility, athleticism or IQ by transplanting mitochondria: putting the wrong mitochondria and nucleus together could harm children rather than improving them. Leaving aside the ethics, the risks appear to outweigh the benefits.

58. For those who risk passing on mutant mitochondria, however, the odds are very different. The Newcastle team plans to minimise incompatibilities by picking donors with a broadly similar mitochondrial genome, or haplotype. The risk cannot be completely eliminated but it is far lower than that of inheriting a mitochondrial disease. "It's inhumane not to treat such conditions if we can," says Van Blerkom. "There's no other reason to go into medicine at all."

Acknowledgements

Powerhouse of disease – Nick Lane, Nature Vol 440 30 March 2006 p600–602

Genetically modified humans: Here and more coming soon – Nick Lane, New Scientist Issue 26594 June 2008 p38–41

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4 The scientific article you have studied is adapted from articles in Nature and New Scientist. Use the information from the article and your own knowledge to answer the following questions.

*(a) Describe how the Krebs cycle is involved in 'burning up fuel' (paragraph 2).

(6)

(b) The unique merger 'gave rise to all complex, or eukaryotic, cells' (paragraph 4). The presence of a nucleus is characteristic of eukaryotic cells.

Describe the structure of a nucleus.

(3)

(c) Explain what is meant by the term **mutation** 'of mitochondrial genes' (paragraph 7).

(2)

(d) In 2011 there were 723,913 children born in England and Wales.

Using information from paragraph 9, calculate the number of children born with Leigh syndrome in England and Wales in 2011. Show your working.

(2)

Answer .....

(e) Using information from paragraph 22, explain how cells in the pancreas would detect an increase in blood glucose concentration.

(3)

(f) 'No controlled trials were done to show this for sure' (paragraph 37).
Suggest what the control should have been.

(2)

(g) In MELAS syndrome (paragraph 40), a mutation can occur in a gene that codes for an enzyme involved in oxidative phosphorylation.

This causes lactate (lactic acid) to accumulate in the body.

Suggest how this mutation in MELAS syndrome causes lactate to accumulate in the body.

(5)

(h) Preimplantation genetic diagnosis cannot 'help women whose mitochondria are all mutant' (paragraph 46).

(i) Give a reason why people may wish to use preimplantation genetic diagnosis.

(1)

(ii) Give an ethical reason why people may **not** wish to use preimplantation genetic diagnosis.

(1)

(i) Using information from paragraph 52 and your own knowledge, suggest which climate-related mitochondrial variant may boost athleticism. Give reasons for your answer.

(3)

(j) Using paragraphs 53 and 54, suggest why mitochondrial genes may 'play the dominant role in natural speciation' of copepods.

(2)

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(Total for Question 4 = 30 marks)