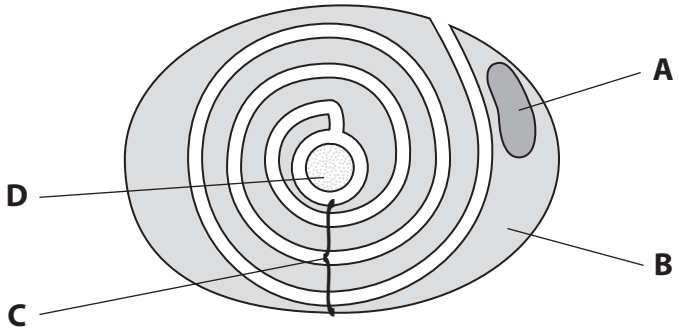
Answer ALL questions.

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 The diagram below shows a section through a motor neurone.



(a) Identify structures A, B, C and D by placing a cross ☒ in the correct box in the table below.

(4)

Structure	A	B	C	D
Axon	☒	☒	☒	☒
Cytoplasm of Schwann cell	☒	☒	☒	☒
Myelin sheath	☒	☒	☒	☒
Nucleus of Schwann cell	☒	☒	☒	☒

(b) Describe the role of the structure labelled **C** in the conduction of nerve impulses.

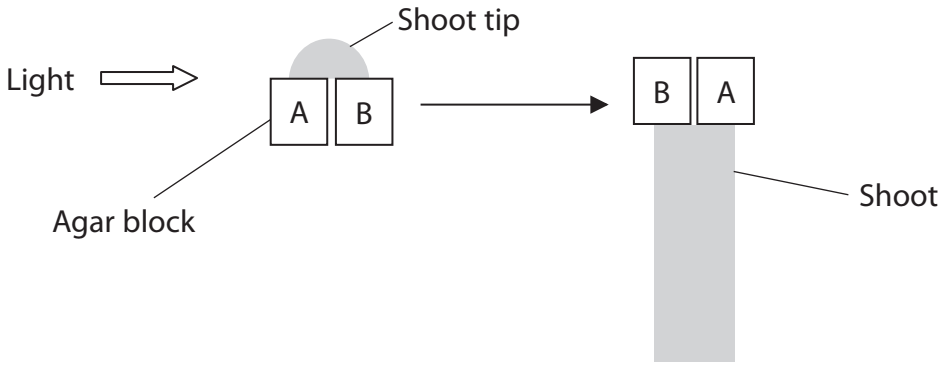
(4)

(c) Explain how the structure of the axon cell membrane is related to the conduction of nerve impulses.

(3)

(Total for Question 1 = 11 marks)

2 The tip of a plant shoot was placed on two agar blocks and light was shone from one side. The tip was removed and the agar blocks were then placed on a shoot without a tip, as shown in the diagram below.



(a) In the space below, draw a diagram to show the shoot as it would appear several hours later.

(1)

*(b) Describe the mechanism that causes the change you have drawn.

(4)

(c) Compare this response of a shoot to light with hormonal coordination in animals.

(4)

(Total for Question 2 = 9 marks)

3 When exercise begins, both ventilation rate and heart rate increase. This supplies more oxygen to muscles.

(a) (i) Describe how breathing rate and tidal volume can be determined from a spirometer trace.

(3)

(ii) Explain how you would use breathing rate and tidal volume to calculate ventilation rate.

(1)

(b) An investigation was carried out to study the changes in oxygen uptake by the blood in the lungs after the first ten seconds of exercise.

Men with artificial pacemakers agreed to exercise with their heart rate controlled at 50 beats per minute. The ventilation rate and the oxygen uptake at rest were measured. These were also measured, after the first ten seconds of exercise and the differences recorded.

This was repeated with the heart rate controlled at 100 beats per minute.

The results are shown in the table below.

Heart rate / beats per minute	**Increase in ventilation rate / $dm^3\ min^{-1}$**	**Increase in oxygen uptake by the blood / $cm^3\ min^{-1}$**
50	4.3	87
100	3.9	190

(i) State **one** factor, other than heart rate, that could have affected the rate at which blood passed through the heart.

(1)

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(ii) Using the information in the table, describe the effect of an increase in heart rate on both the ventilation rate and oxygen uptake by the blood, after the first ten seconds of exercise.

(3)

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(iii) Explain how an increased heart rate results in increased uptake of oxygen by the blood in the lungs.

(3)

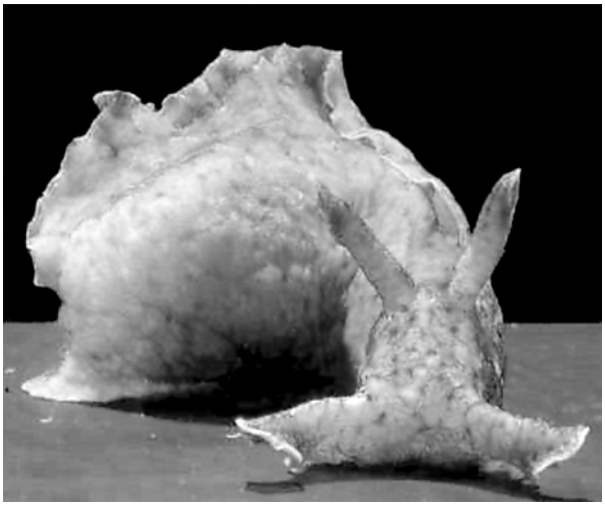
(iv) What conclusions could be drawn from the results of this investigation?

(2)

(Total for Question 3 = 13 marks)

4 In some organisms, the nervous response to a stimulus can reduce as a result of repetition. This is known as habituation.

Sea slugs are marine animals which have gills for the uptake of oxygen from seawater.

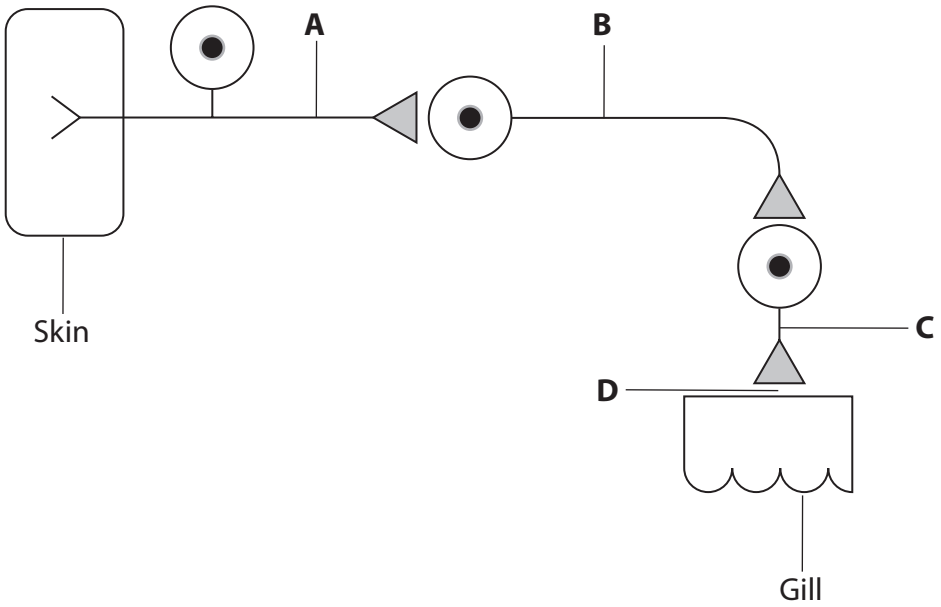


Sea slug

Magnification × 1

A sea slug withdraws its gill when its skin is touched. After some time, the gill is exposed again. With repeated touches, the time taken for it to expose the gill decreases. When the skin is touched frequently, the gill is not withdrawn.

The diagram below shows some of the neurones (nerve cells) involved in this response.



(a) Place a cross ☒ in the correct box in the table below to identify where structures **A**, **B**, **C** and **D**, listed in the table, are shown on the diagram.

(3)

Structure	A	B	C	D
Motor neurone	☒	☒	☒	☒
Sensory neurone	☒	☒	☒	☒
Synapse	☒	☒	☒	☒

(b) (i) Suggest how a repeated stimulus could result in less response from the gill.

(3)

(ii) Suggest how this habituation may be of benefit to a sea slug.

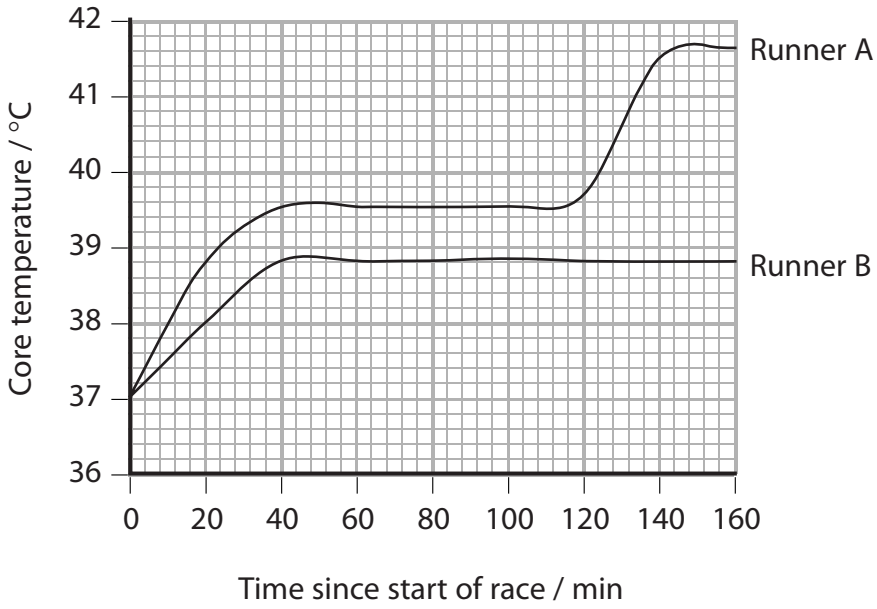
(2)

(Total for Question 4 = 8 marks)

Question 5: N/A

6 Marathon runners can have difficulty with thermoregulation over the course of a 26 mile race, particularly on a hot day. Two marathon runners, A and B, had their core temperatures recorded during a race.

The graph below shows the core temperatures recorded during the race.



(a) Suggest an explanation for the change in core temperatures of both runners in the first 30 minutes of the race.

(2)

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(b) Suggest an explanation for the constant core temperatures of both runners between 60 and 100 minutes of this race.

(5)

(c) During this race, runner A lost 3.02 kg of water and runner B lost 2.43 kg of water.

Using the information in the question and your own knowledge, suggest reasons for the change in core temperature of runner A after 120 minutes.

(2)

(Total for Question 6 = 9 marks)

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

(a) Suggest how erythropoietin (epo) production might be shut down when oxygen levels in the blood are normal (page 2, paragraph 6).

(3)

*(b) Describe how adenoviruses in the blood 'are recognised and destroyed by the immune system' (page 3, paragraph 4).

(5)

(c) 'A single injection elevated hematocrits for over a year in the mice and for 12 weeks in the monkeys.' (page 3, paragraph 5)

Suggest why the injection of genes into body cells does not have a permanent effect.

(2)

(d) 'Sludge blood' (page 4, paragraph 1) can lead to high blood pressure and atherosclerosis.

Explain the connection between high blood pressure and atherosclerosis.

(3)

(e) Name the 'small vessels' (page 4, paragraph 1) that have the greatest effect in producing high blood pressure.

(1)

(f) Suggest **one** way in which one gene could result in the production of several different proteins.

(1)

(g) Use information in the article to describe **three** ways in which athletes might artificially enhance their performance.

(3)

(h) Explain why the governing bodies of sports ban the artificial enhancement of performance.

(2)

(i) A proteasome is 'a barrel-shaped multi-protein complex that chops proteins down into their component amino acids for reuse'.

Explain how muscle protein can be chopped into amino acids inside a cell.

(2)

(j) Explain what is meant by repolarisation of a cardiac muscle cell or a nerve cell.

(2)

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(k) Suggest why large numbers of mitochondria are found in muscle cells.

(2)

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(l) 'Schuelke discovered that the boy had a mutation in both copies of the gene coding for the muscle growth inhibitor myostatin.' (page 10, paragraph 1)

Suggest how this boy could have inherited this condition. Use a genetic diagram to illustrate your answer.

(4)

(Total for Question 7 = 30 marks)

8 Rhododendrons are shrubby plants that are widely distributed throughout the northern hemisphere.
The flowering periods and habitats of two species of rhododendron, found on Yakushima Island in Japan, are shown in the table below.

Species	Flowering period	Main flowering period	Habitat
Rhododendron eriocarpum	April to July	May	Rocky areas in lowland regions
Rhododendron indicum	May to July	June	High mountainous regions

Where these populations overlap, hybrid plants are found that have arisen as a result of cross-fertilisation between these two species. These hybrid plants are capable of flowering and producing viable seeds.

(a) Suggest why some scientists might prefer to classify *Rhododendron eriocarpum* and *Rhododendron indicum* as varieties within the same species rather than as two separate species.

(3)

(b) (i) Explain what is meant by the term **genetic diversity** in a species.

(2)

(ii) Explain why there is likely to be a greater genetic diversity in the hybrid plants than in either of the two separate species.

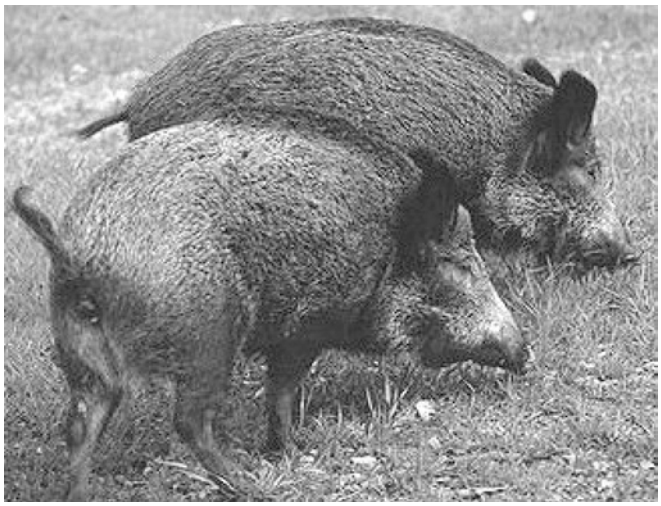
(2)

*(c) Explain how the two different species of Rhododendron on Yakushima Island may have evolved from a single population of an ancestral species.

(6)

(Total for Question 8 = 13 marks)

9 Sardinia is an island in the Mediterranean Sea. Many of the plants and animals on islands, such as Sardinia, show distinct physical and behavioural features that are different from those found in closely-related mainland populations.
The Sardinian ν



Magnification ×0.1

(a) Explain what is meant by each of the following terms.

(i) Gene pool

(1)

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(ii) Allele frequency

(1)

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(b) The population of wild boar in mainland Italy and the population in Sardinia both belong to the species, *Sus scrofa*. The mainland population is placed in the sub-species, *Sus scrofa scrofa*, whilst the Sardinian population is placed in the sub-species, *Sus scrofa meridionalis*.

(i) Suggest why scientists classify the mainland and Sardinian wild boar as two sub-species rather than as two separate species.

(2)

*(ii) Suggest how the two sub-species, *Sus scrofa meridionalis* and *Sus scrofa scrofa*, have developed from a single ancestral population.

(5)

(iii) Explain how the results of DNA profiling of tissue samples from the two sub-species could be used to provide evidence that they share common ancestry.

(3)

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(Total for Question 9 = 12 marks)

Scientific article

Muscles, genes and gym in a bottle

A TENSE HUSH falls on the Olympic stadium as the sprinters crouch on the starting blocks for the men's 100-metres final. With the 2012 Olympic games in full swing, athletes have shattered records as never before, usually by an ample margin. Television ratings are soaring, and as the finalists prepare to compete for the title of world's fastest man, the crowd expects the winner to obliterate this record, too.

Though the Olympic flame still burns in the stadium, these athletes are nothing like their heroic predecessors. Athletes of old honed their bodies with toil and sweat, but at the 2012 games most of the champions have altered their genes to help them excel at their sport. Weightlifters' arms and sprinters' thighs bulge as never before, and long-distance runners have unparalleled stamina – all the result of a few crucial genetic upgrades. Officials are well aware that such "gene doping" is going on, but as the practice is virtually undetectable, they are powerless to stop it.

This may sound like the ultimate sporting nightmare, but the technology to make it come true could well arrive even before 2012. Scientists around the world are working to perfect gene therapies to treat genetic diseases. Soon, unscrupulous athletes may be able to use them to re-engineer their bodies for better performance.

Need more endurance? Add a gene to bolster delivery of oxygen to labouring tissues. Want bigger muscles? Inject them with a gene that will make them grow. Both techniques are under development, and if they work in humans as they do in lab animals, they will change the face of nearly every sport. But at what cost? Knowing how to boost performance is one thing; knowing how to do it safely is quite another. If athletes do turn to gene therapy, these genetically enhanced champions risk paying for their success with heart disease, strokes and early death.

Genes matter when it comes to sport. At the 1964 Winter Olympics in Innsbruck, for example, Finnish sportsman Eero Mäntyranta won two gold medals in cross-country skiing. Though his training programme wasn't radically different from those of his teammates and rivals, Mäntyranta had a distinct advantage: he was born with a genetic mutation that loaded his blood with 25 to 50 per cent more red blood cells than the average man's. Since these cells shuttle oxygen from the lungs to the body tissues, Mäntyranta's muscles got more of the oxygen they needed for aerobic exercise, so he could ski faster for longer.

Mäntyranta got his extra red blood cells because of a mutation in the gene that produces the receptor for the hormone erythropoietin (epo). The kidneys normally churn out epo when oxygen levels in the body's tissues drop, as they do at high altitude, where the air is thin. Epo commands the body to manufacture new red cells, which raises the blood's capacity to carry oxygen. Once oxygen regains its normal level in the blood, the epo receptor should shut down epo production. But Mäntyranta's mutation turned off this crucial feedback, so his body kept making more red cells.

Mäntyranta's mutation is exceedingly rare. But anyone can boost their red cells simply by adding more epo to their bloodstream. In 1989, the biotech company Amgen began marketing Epogen, an injectable form of epo produced by recombinant bacteria, as a treatment for severe anaemia – a serious problem in patients with AIDS or kidney failure.

Athletes were quick to exploit the drug, even though such doping is banned in most sports. At the 1998 Tour de France, for example, French officials caught an employee of the Festina cycling team with a carload of performance-enhancing drugs, including epo. The scandal exposed a dirty secret: "Doping is part of the business of cycling," Swiss rider Alex Zulle told reporters after he confessed to taking epo and other banned drugs.

Secret weapon

Cycling isn't the only sport sullied by allegations of epo use. At the Australian Open tennis championships a year ago, the player Jim Courier told reporters that he suspects epo use is rampant in the game. "I can't play 35 weeks a year and God knows how many matches and keep going. I just can't do it and I don't think anybody else can, either. But they are." Courier says epo makes such superhuman performance possible. Athletes in cross-country skiing, football and track and field athletics are also rumoured to use the drug. "The fact is, we only reward winners, and drugs work," says Charles Yesalis, an epidemiologist at Pennsylvania State University who has interviewed more than a thousand athletes who have admitted to taking banned drugs. With epo rumoured to make athletes run up to 20 per cent faster, the drug's allure is hard for many to resist, he says.

The problem may grow even more widespread if athletes can insert a gene that makes their bodies produce extra doses of the hormone. Instead of injecting themselves with epo several times a week, athletes could use this "gene therapy" to acquire the equivalent of Mäntyranta's super-gene with a single shot. The technology may be just around the corner, as several academic groups and a handful of biotech companies hammer out ways to use epo gene therapy to treat anaemia.

The gene-therapy techniques under development use viruses to carry the epo gene into cells. Researchers remove the genes that make a disease-causing virus harmful and insert the epo gene in their place. "The virus acts as a taxicab," says Philip Whitcome, chairman of the biotech company Avigen in Alameda, California. "You need to get these instructions inside the cells to the machinery that can follow the instructions and make the protein."

Adenoviruses, like the ones that cause the common cold, are a favourite delivery system for gene therapy because they are relatively large and can carry big genes in their payload. However, they are easily recognised and destroyed by the immune system. "There's a race going on to see if the immune system will destroy the taxi before it delivers its passenger to the inside of the cell," says Whitcome. So to evade the body's defences, Avigen has patented the use of adeno-associated viruses (AAVs) for delivering epo. Smaller than an adenovirus, an AAV can't carry as much cargo but is less vulnerable to attack from the immune system, says Whitcome.

Both viral types have shown exceptional results in early tests of epo gene therapy. In 1997, a group led by Jeffrey Leiden, then at the University of Chicago, used an adenovirus to deliver the epo gene to mice and monkeys. After the scientists injected the virus into the animals' muscles, it infiltrated their cells, inserting the epo gene and spurring the cells to pump out the protein. This boosted mouse hematocrits (the proportion of the blood volume made up of red blood cells) from 49 per cent to 81 per cent, while the monkeys' hematocrits rose from 40 per cent to 70 per cent or more. A single injection elevated hematocrits for over a year in the mice and for 12 weeks in the monkeys.

Researchers at the biotech company Chiron in Emeryville, California, reported similar results in a 1998 trial that used AAVs to deliver the epo gene to two. After 10 weeks, their hematocrits had risen from 38 per cent and 40 per cent to 62 and 75 per cent, respectively, and stayed at those levels for the entire 28 weeks of the study.

Promising though these results appear, gene therapy may not be risk-free. Last autumn, an 18-year-old patient died after receiving gene therapy for a rare liver ailment, delivered via an adenovirus. It is still uncertain what went wrong, but scientists are anxiously re-examining the safety of gene therapy in the light of this incident.

Unless safety turns out to be an insuperable problem, we could see clinical trials of epo gene therapy within the next few years. And if the trials prove successful, athletes would inevitably be tempted to hike up their hematocrit – and thus their endurance – with a single injection. But elevating the red blood cell count is a risky business, as the blood thickens when it is packed with so many red cells. "The heart has to pump sludge blood through small vessels, and that puts you at high risk for high blood pressure and stroke," says Leiden. In one family with a mutation similar to Mäntyranta's, for example, the father died of a stroke in his 50s, and a son suffered a heart attack at age 40, notes Josef Prchal, an epo researcher at the University of Alabama in Birmingham.

Even successful gene therapy could still lead to problems, mainly because there's no way to turn the gene off once it has been inserted. "Some of the monkeys in our experiment made too much epo, and we had to bleed them to thin their blood and keep them alive," says Leiden. Healthy athletes who indulged in epo gene therapy might likewise require frequent bleedings to keep their hematocrit low enough to prevent strokes – and they'd still have a heightened risk of high blood pressure and atherosclerosis, says Prchal.

If epo gene therapy can give athletes added endurance and stamina, a different sort of gene therapy can give them the muscles to match, says Geoffrey Goldspink, a biologist at Royal Free and University College Medical School in London. Scientists believe that hard exercise, the kind that leaves you sore the next day, builds muscle by inducing microscopic damage to the muscle fibres. These "micro tears" are repaired by beefing up the fibres with extra proteins so they will be adapted to the exercise the next time. A protein called insulin-like growth factor 1 (IGF-1), which is turned on by mechanical signals such as stretch or exercise overload, seems to play a role in this repair process. IGF-1 exists in at least five different forms, whose parts are spliced together in different ways. All the forms are produced by a single gene.

Pumping genes

Goldspink's group is working on gene therapy that uses a form of IGF-1 called mechano growth factor (MGF) to treat muscle-wasting diseases such as muscular dystrophy. Since MGF is made in muscle tissue and doesn't seem to circulate in the blood, Goldspink expects its effects to be localised to muscle. His group has tested MGF gene therapy in mice, with impressive results. The researchers gave mice a single injection of the MGF gene, and two weeks later the injected muscles had grown by 20 per cent. "We seem to have found the magic potion that makes muscles grow," says Goldspink.

Across the Atlantic, researchers are having similar success with another form of IGF-1 which is made in the liver as well as in muscle. When it circulates in the blood, IGF-1 raises blood sugar levels. But when it is in muscle tissue, "IGF-1 seems to be mainly involved in repairing and building muscles," says Lee Sweeney, a physiologist at the University of Pennsylvania.

Sweeney and his colleagues used an adenovirus to deliver the IGF-1 gene into the leg muscles of mice. Their results made headlines and caught the attention of bodybuilders everywhere. After three months, the mouse leg muscles injected with the IGF-1 gene had grown by 15 per cent, even though the animals had not taken any special exercise. Sweeney is convinced that similar IGF-1 gene therapy could allow people to custom-build their physiques.

"What happened in our mice is that they are essentially expressing IGF-1 as if they had just been exercising hard. They are enormous, and they have no body fat," says Nadia Rosenthal, a geneticist at Massachusetts General Hospital in Boston who also worked on the study. Though the mouse muscles don't need the extra IGF-1, they do much better with it, she says. Sweeney believes IGF-1 could even account for the difference between weaklings and muscle men. "It may be that some people naturally make more IGF-1. That might explain why some people can build muscle more easily than others," he suggests.

IGF-1 gene therapy promises to be relatively safe because the protein produced by the newly added gene seems to stay in the muscle that receives the injection. "We didn't find any IGF-1 circulating in the animals' bloodstream, and so that suggests that it was in fact being made and used locally in the muscle," says Rosenthal. That's important, because it means that IGF-1 injected in, say, a tennis player's biceps won't lead to an enlarged heart, nor will it alter blood sugar levels.

The ability to target IGF-1 therapy at specific muscles could be especially enticing to athletes. "A 20 per cent increase in muscle mass is probably pretty easy with IGF-1 alone. If we start adding in other growth factors it could be as high as 50 per cent," predicts Sweeney. "This could give you the ability to grow new muscle on demand. Because its effects are local, you could just inject the IGF-1 gene directly into the muscle you want to enlarge. You could potentially re-engineer your body."

Sweeney speculates that IGF-1 therapy might be available as soon as two years from now. Rosenthal, however, warns that several problems stand in the way. "Mice are not humans. We have already determined that a completely different protocol would be necessary for larger animals because it's harder to access the inside of a large muscle," she says.

Even if IGF-1 therapy does work, there's no guarantee that it will last over the long haul. "It might wear off more quickly in athletes because they damage the muscle more often than sedentary people. When you damage the muscle through exercise you run the risk of losing the genes that you've put in there," Sweeney says. "These issues are a big unknown because no one really knows to what extent people turn over their muscle cells. Every cell that's in your heart when you're born is there when you die, but we're not sure if that's true of other muscles."

If an athlete's gene therapy does stop working, there's no guarantee that a second dose will have the same effect as the first one. "There's a problem with repeated dosing: your body will build antibodies against the virus that inserts the gene into your cells, so if you give another injection with the same virus, your body's immune system may very well wipe out the virus before it can deliver its genes," says Sweeney. But athletes and their doctors aren't likely to be put off so easily. They might, for example, be able to get around this problem by turning to alternative viruses for delivering their illicit genes.

Catching cheaters

So does this mean that the authorities will finally lose their long battle against drugs in sport? Don Catlin, a biochemist who studies gene therapy abuse at the Olympic drug testing lab at the University of California in Los Angeles, has little doubt that athletes and their doctors will resort to gene doping. "I don't like what they do – it's dirty – but I have to admit I'm impressed with the sophistication of doctors on the `other side'," he says.

Detecting abuse won't be easy. The big problem is that proteins made by engineered genes look identical to the ones the body makes naturally. About the only way scientists might detect illicit gene therapy would be to find traces of the virus that delivered the gene. "If you were looking for MGF or IGF-1, you could take a biopsy from the muscle and look for viral DNA. But you would have to know exactly where it was put in. You're essentially looking for a pinprick in the body," says Goldspink. The same method could detect epo therapy, but again you'd have to know where the gene was injected, says Leiden.

No one seriously expects athletes to line up for muscle biopsies before they go out to compete at the Olympics, so clearly a less invasive strategy must be found. One approach would be to look for abnormally high levels of a gene's product. "You could get the athlete to remain inactive for, say, 12 hours, and then test for MGF," says Goldspink. "If the levels were still high you would have a good indication that you've got a gene that's been switched on all the time instead of being induced by natural activity." But he admits: "Athletes are probably the people least likely to stay inactive for 12 hours, and even that may not be long enough."

This approach might be more useful for detecting epo gene doping, however. People with plenty of red blood cells should have little or no epo circulating in their blood, so if testers found epo in those circumstances, says Leiden, "you'd have a pretty good indication that something was going on." But even there, testing could not separate illegal gene dopers from athletes who carry natural – and presumably legal – mutations such as Mäntyranta's.

If history is any guide, scientists will have a tough time staying ahead of the cheats. That, at least, is nothing new. "There's a lot of money at stake, and drug tests are easy to circumvent," say Yesalis, who thinks many of the records set in the past 30 years have been drug-aided.
"Users have kicked butt on the drug testers for 40 years. What makes anyone think that's going to change?"

So you joined a gym, stuck to your training schedule and, even if you say so yourself, you look good and feel great. In just a few months, you have gone from weedy geek to muscular athlete, with biceps bigger than Madonna's. But there is a catch, of course. To stay looking this good you'll have to keep lifting those weights.

Before you slump on the couch in despair, help could be at hand. Researchers studying how muscles build up and break down believe they are close to creating a drug to stop the body dismantling muscle when we stop using it. Their aim is to tackle weakness in the sick and elderly, and to help make long space flights feasible for humans. However, such a drug should also make staying in shape that bit easier – a boon for couch potatoes and, of course, would-be sports cheats.

Having our muscles beef up when we use them and wither away when we don't, is the body's way of making the best possible use of resources. Do some muscle-challenging exercise and your muscle cells expand to take the strain. Rest up and the muscle proteins will start breaking down almost as soon as you stop moving. Idle muscle is an unnecessary metabolic expense.

For most of us, muscle growth and breakdown exist in a subtle balance, and unless our diet or exercise regime changes dramatically we hardly notice it. But if injury to the bones, muscles or their nerve supply puts part of the body out of action, or the body becomes starved of food, the balance shifts and muscle breakdown outweighs synthesis.

For people confined to bed for long periods of time, or for astronauts in microgravity, muscle wasting is a serious problem. Wasting, or atrophy, is a symptom not only of disuse and injury, but of many diseases, including kidney failure, cancer and AIDS. Once enough muscle has been lost, a vicious cycle sets in as exercise becomes increasingly difficult, which in turn leads to disuse and further atrophy.

Despite more than three decades of research into alternatives, the only way to stop such patients losing muscle is a long course of physiotherapy involving weight-bearing exercise, but this is of little use to the weakest and sickest – and in most cases starts only after wasting has already set in.

The use of anabolic steroids is being explored for some conditions. But these compounds have a huge range of effects on the body besides promoting muscle growth, some of them undesirable, and only appear to work well in conjunction with exercise. A specific treatment to prevent wasting until patients are well enough to get back on their feet, or until astronauts have arrived at their destination, would be ideal.

Active atrophy

Alfred Goldberg, a cell biologist at Harvard University, began studying muscle atrophy in the late 1960s. At the time, virtually nothing was known about what prompts muscles to grow and shrink, but a series of discoveries in the 1980s and 90s changed all that.

What he and others discovered was that, rather than being a passive side effect of disuse or disease, muscle wasting is an active process controlled by a complex genetic pathway. So, if someone found out how it was turned on, it ought to be possible to turn it off.

"Back then we didn't know the pathway for muscle breakdown," says Goldberg "but about five years ago our work showed that no matter what the trigger – disuse, metabolic disease or fasting – the same biochemical programme is responsible."

The process involves the ubiquitin-proteasome pathway (UPP), the disposal machinery used to break down unwanted proteins in the cell. Once the system has been activated, ubiquitin "destroy me" labels are added to muscle proteins. Tagged proteins are then fed into the proteasome, a barrel-shaped multi-protein complex that chops proteins down into their component amino acids for reuse. This breaks down the muscle filaments within cells, but does not change the number of muscle cells. Instead they become thinner and weaker. Further studies showed that at least 90 genes are involved in atrophy; Goldberg calls them "atrogenes".

Although it is still unknown which of these genes trigger atrophy, it soon became clear that two of them are essential to the process. *Atrogin1* and *muRF1* were first described in 2001 and are the only two atrogenes active only during muscle atrophy. They code for ubiquitin ligases, the enzymes that attach the "destroy me" labels to proteins. The genes are barely active in normal muscle but expression levels shoot up in sick animals. Knock out either and muscle wasting all but stops.

At around the same time this was discovered, another group led by David Glass at US pharmaceutical company Regeneron found the same two genes (and confusingly named the atrogin1 gene *MAFbx*). When Glass knocked out each of the two atrogenes in rats, he found they suffered less atrophy after both disuse and disease.

Since then more atrogenes have been found every year. In May this year, a group from Purdue University in West Lafayette, Indiana, reported that they too had found a switch for muscle atrophy. What's more, an existing drug could turn the switch off.

Gym in a bottle

The Purdue team, led by Amber Pond and Kevin Hannon, found that in mice when muscle atrophy sets in there is increased activity of the gene *erg1*. This codes for a potassium channel protein found in both skeletal and cardiac muscle tissue. In heart muscle, the channel consists of two variants of the protein, erg1a and erg1b, which help the heart keep its rhythm by letting the muscle repolarise after each beat. A mutation in the *erg1* gene causes "long QT" syndrome, in which the heart muscle cannot repolarise fast enough, and which can lead to sudden death.

The Purdue team showed that the erg1a variant stimulates atrophy in skeletal muscle. In muscles that were wasting due to disuse or cancer, they found high levels of expression of erg1a. And when they increased the number of erg1a potassium channels on the surface of muscle cells in mice by adding an extra gene coding for this protein, atrophy set in. Adding a gene for the erg1b version of the protein did not trigger atrophy.

Importantly, the team knew that an existing drug, an antihistamine called astemizole, blocks erg1a channels. When they gave it to mice, it almost completely prevented atrophy in muscles not being used. Animals going about their normal activities even built more muscle.

The team thinks the erg1a protein stimulates the ubiquitin-proteasome pathway, although it is not yet clear exactly how. However, there is a problem. Astemizole not only blocks erg1 channels in skeletal muscle, it also blocks them in the heart, potentially causing long QT syndrome. Because of the risk, astemizole was withdrawn in 1999. If this approach is going to succeed, the researchers will have to find a way to target erg1a in skeletal muscle without blocking erg1 channels in the heart, which consist of both erg1a and erg1b sub-units.

Pond believes this should be possible, because erg1a and erg1b differ slightly at one end of the protein chain. "We want to find out what the difference is. Can we target that?" Besides conventional drugs, the team is also investigating the possibility of blocking erg1a expression using a gene-silencing technique known as RNA interference.

Meanwhile Goldberg and the Regeneron team, still working independently, have taken a different approach, focusing on the proteins called transcription factors that turn other genes on or off. In 2004, Goldberg's team identified one called Foxo that controls the activity of many atrogenes. Disabling Foxo blocks atrophy, and all the evidence so far suggests it could be a good target for future therapies.

For now, there's still a lot to learn. For instance, insulin and the related hormone insulin-like growth factor 1 (IGF-1), long known to be involved in muscle synthesis, also seem to prevent muscle breakdown by suppressing Foxo and turning off the *atrogin1* gene. Boosting levels of IGF1, particularly some recently discovered variants of the protein, greatly increases the strength of mice, even if they don't exercise. This is why both IGF-1 and insulin are banned in sports. But beyond that, very little is clear. "You don't see active Foxo in normal muscle because insulin and IGF-1 suppress it," says Goldberg, "but exactly how inactivity or disease activates Foxo we're still trying to find out."

Pond thinks that Foxo could be involved in erg1a-mediated atrophy. The erg1a protein is known to bind to transcription factors like Foxo, so increased erg1a activity might trigger atrophy through interaction with Foxo. "That's what we're pursuing now," she says. Meanwhile, several companies are looking for drugs that block the atrogin1 protein, and Goldberg's team is looking into whether proteasome inhibitors such as Velcade, used to treat cancer, might slow muscle breakdown.

Pharmaceutical company Wyeth of Madison, New Jersey, has taken seemingly the opposite approach. The company recently began trials in people with muscular dystrophy of an antibody therapy designed to stimulate muscle growth, rather than prevent atrophy (see "Pump up the volume"). While coaxing the body to produce more muscle tissue is different to attempting to turn off wasting, the end result could be the same, and the two pathways are likely to turn out to be linked.

There are still many gaps to be filled in, but those in the field agree that the question is no longer if we can develop anti-wasting treatments, but when. As researchers close in on this target, excitement is mounting about exactly what such treatments could achieve. Patients due to be confined to bed for more than a few days could be given the drug as soon as they begin bed rest to prevent muscle loss that would otherwise slow their recovery. Weaning patients off respirators would become easier as doctors could prevent wasting of the diaphragm. Disease need no longer lead to weakness, and broken bones would not mean long and painful physiotherapy sessions to rebuild muscle strength. And since loss of muscle mass is a major reason why we grow frail with age, an anti-wasting drug could keep older people on their feet and living independently for longer.

The prospect of preventing atrophy is also of great interest to NASA, particularly in view of its much talked-about mission to Mars. By the time astronauts reach the Red Planet, they can expect to lose up to 25 per cent of their muscle mass and be too weak to walk, let alone put on a space suit and carry out repairs. That is why Goldberg's work is funded by the National Space Biomedical Research Institute in Houston, Texas, set up by NASA.

While there are valid medical and space applications for anti-wasting drugs, as a safer alternative to steroids they will inevitably be hugely tempting for athletes too, not to mention the lazy as well. Although Goldberg is keen to point out that helping cheats and couch potatoes is not the focus of his work, he admits that it will undoubtedly happen sooner or later.

Of course, muscle size is not everything. Endurance training produces all sorts of other physiological changes, including better blood supply to muscles and more energy-supplying mitochondria in muscle cells. Drugs that maintain muscle size will help keep people strong, but will not keep them fit or provide any of the innumerable other benefits of exercise, from stronger bones to smarter brains.

On the other hand, simply maintaining more muscle will help use up a few extra calories. And being able to stay strong even if you skip gym for a few weeks might encourage people to exercise more rather than less, by making it less painful to get started again.

In the meantime, as we await the arrival of the "gym in a bottle", you will be pleased to hear that there are two tried and tested ways to lower Foxo levels and prevent muscle atrophy. One is to increase your IGF-1 and the other is to stimulate insulin production. Sounds complicated? Not at all. All you've got to do is eat regularly and do a bit of exercise. For the moment at least, there's still no substitute for pumping iron.

Pump up the volume

Six years ago a baby born in Germany surprised everyone. At birth he had double the muscle mass of a normal baby and virtually no fat. By the age of five he could hold a 3-kilogram weight in each hand with his arms stretched out to the side.

His doctor was impressed enough to call in Markus Schuelke, a paediatrician at Charité University Medical Centre in Berlin. Schuelke discovered that the boy had a mutation in both copies of the gene coding for the muscle growth inhibitor myostatin. The boy's mother, a former professional sprinter, turned out to have a mutation in one copy of the gene and reported a history of unusual strength in her extended family. The boy, however, is the first individual known to lack any myostatin at all.

Blocking myostatin in mice makes them twice as muscular as usual, but no one knew whether a similar approach would work in humans. The discovery of the boy opened up that possibility, and made it easier to get approval for a major clinical trial to see if blocking myostatin with an antibody therapy developed by pharmaceutical firm Wyeth will prevent further muscle loss in people with muscular dystrophy.

Muscular dystrophy causes a different kind of muscle wasting from that seen in disuse or disease – the muscle cells do not just shrink, they die. Myostatin is thought to keep muscle stem cells, called satellite cells in check, and in its absence the satellite cells give rise to new muscle cells. Blocking myostatin will not solve the underlying causes of muscular dystrophy, but by boosting muscle growth it might help compensate for the lost tissue. However, it is possible that the treatment might exhaust the supply of satellite cells, in which case it would provide only a temporary reprieve.

The antibody trial is now under way at centres around the world and the first results are expected by the end of the year. It is hoped that myostatin blockers could also help treat other kinds of muscle wasting and the elderly. Meanwhile, everyone is waiting to see whether the first documented superbaby will grow into a superman.