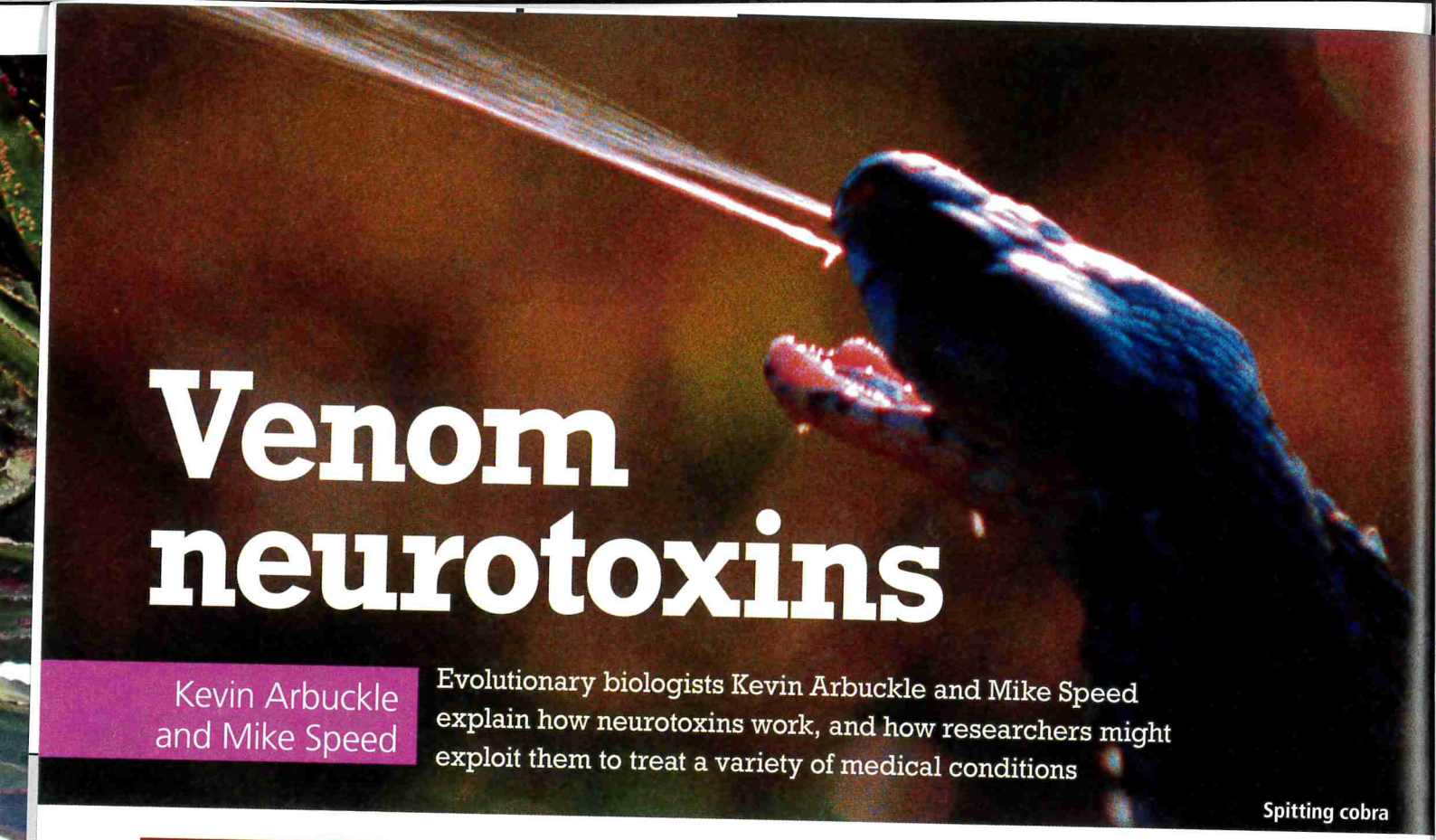


Venom neurotoxins

Kevin Arbuckle and Mike Speed

Evolutionary biologists Kevin Arbuckle and Mike Speed explain how neurotoxins work, and how researchers might exploit them to treat a variety of medical conditions

Spitting cobra

Exam links

AQA Nervous coordination; Skeletal muscles
Edexcel A Muscle contraction; Nerve impulse; Synapse
Edexcel B Nervous transmission
OCR A Neural communication; Muscle contraction
OCR B Muscle contraction; The nervous system
WJEC Eduqas The nervous system; Human musculoskeletal anatomy

An incredible diversity of animals inject **venom** into other animals, usually to help them incapacitate prey or repel predators. Venoms have many different effects on their victims including paralysis, prevention of breathing, and pain. These are all functions of a group of molecules called neurotoxins, which interfere with the function of nerves. Despite causing harm, venom neurotoxins can lead to new medical drugs.

Why have venoms evolved in so many animals?

Animal venoms are versatile tools that help catch prey, defend against predators, or (in the case of mammal venoms) fight off competitors of their own species. Because many good ways to incapacitate prey are also effective in making predators think twice, venoms are often good at both roles simultaneously. For instance, snake venoms primarily subdue and sometimes kill prey — an important helping hand when the snake lacks its own hands to help — but the devastating consequences of venomous snakebites demonstrate their dual role as a defensive aid. Venom has evolved at least once in most major branches of the animal kingdom, including mammals. The abundance of venoms across the tree of life shows their importance in many biological and ecological settings.

Neurotoxins break the nervous system

Many venomous animals have neurotoxins that disrupt signalling across the neuromuscular junction. Each of the key components of the neuromuscular junction (see Box 1) provides a target for animal venoms to attack. These different mechanisms typically cause one of two types of effect. First, they can cause the neurone to generate an abnormally high number and frequency of nerve impulses (action potentials), which causes the muscle to contract far more than usual. This leads to spasms, cramps or paralysis from unrelenting contraction. Second, they can stop the transmission of action potentials across the junction and the victim becomes paralysed, simply because the muscle never gets stimulated to contract. Paralysis contributes to the impressive killing power of neurotoxins — you rely on a muscular diaphragm to breathe, so when that gets paralysed and stops working, so do you.

The sodium channel

One way that neurotoxins can ruin your day is by blocking the Na^+ channels on the neurone. In doing this, the toxins stop the action potential from passing down the neurone and essentially cut it off at the source. With no action potential, there is no muscle contraction.

Alternatively, some neurotoxins in animal venoms boost the action of Na^+ channels, for instance by holding the channels open to let more

Terms explained

Ion channels Pore-shaped proteins that control the movement of ions across the cell surface membrane.

Venom A mixture of harmful chemicals (toxins) produced by an organism and transferred into a victim through a wound (e.g. a bite from a snake fang).

Box 1 Neurones tell muscles when to contract

To understand how neurotoxins from animal venoms interfere with the normal function of neurones, we first have to understand how neurones work. Venom neurotoxins usually work in a region called the neuromuscular junction (see Figure 1.1). The neuromuscular junction is a type of synapse that enables transmission of action potentials across the gap (cleft) between nerve cells and muscle cells. Once they reach the muscle cell, these action potentials trigger muscle contraction.

Action potentials involve the movement of sodium (Na^+), potassium (K^+) and calcium (Ca^{2+}) ions across the cell surface membrane. These ions move through **ion channels** in the cell surface membrane, which regulates the flow of particular ions. The main function of Na^+ and K^+ ion channels is the generation of action potentials. When an action potential reaches the synapse, it causes Ca^{2+} ions to enter the neurone. These ions trigger release of the neurotransmitter acetylcholine into the synaptic cleft.

Acetylcholine binds to receptors on the surface of the muscle cell, leading to generation of new action potentials that in turn lead to muscle contraction. The acetylcholine is then broken down by the enzyme acetylcholinesterase, which is present in the synaptic cleft. Transmission is terminated and the muscle relaxes.

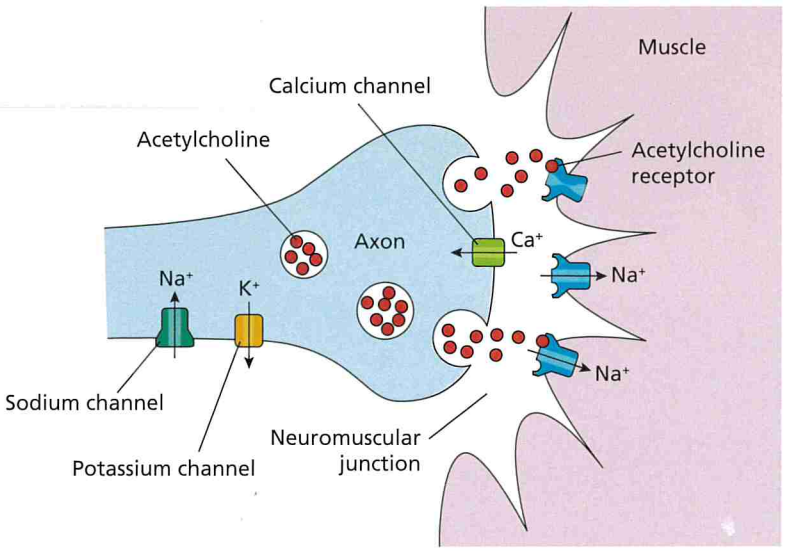


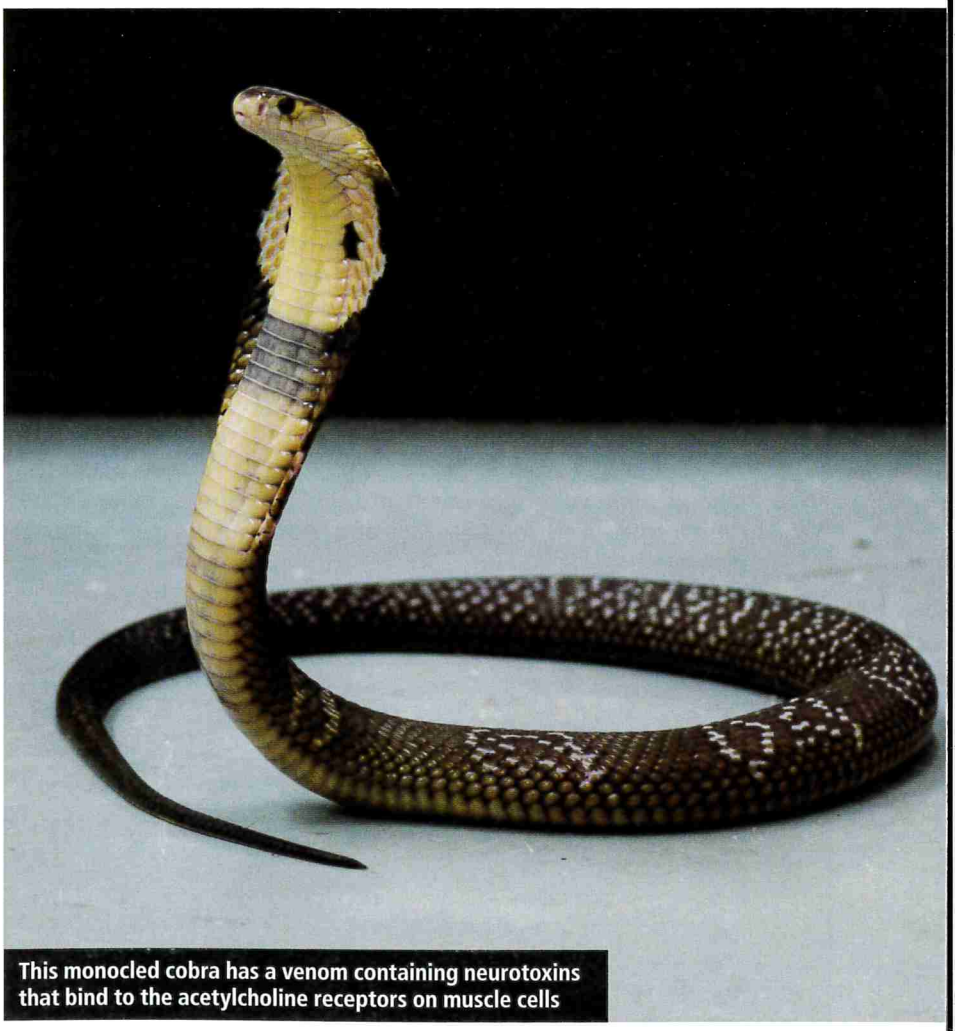
Figure 1.1 The structure of a neuromuscular junction. The neurone uses ion (Na^+, K^+ and Ca^{2+}) channels to control the release of acetylcholine into the gap (synapse) between the neurone and the muscle. The surface of the muscle contains receptors that bind the acetylcholine molecules and trigger contraction

sodium ions through than normal. The same effect can happen for two subtly different reasons. Either the Na^+ channels can be opened more easily (by Na^+ channel activator toxins) or they can open normally but then be jammed open so they cannot close again (via Na^+ channel prolonger toxins). Almost all of these types of neurotoxins are found in the venoms of invertebrates, including spiders, scorpions and cone snails. However, it was recently discovered that one unusual toxin (called calliotoxin) from the venom of the blue coral snake also acts as a Na^+ channel prolonger, a toxin type only previously known from invertebrates.

More rarely, venom neurotoxins that attack Na^+ channels do their damage on the muscle side of the neuromuscular junction. This does the same job in the end, but here the muscle is receiving the impulse to contract, it just lacks the mechanism to let it do so.

Potassium and calcium channels

Other venom neurotoxins interfere with different ion channels (e.g. K^+ and Ca^{2+} channels). Venoms from the honeybee to the notorious black mamba snake block K^+ channels, which stops the neurone from returning to its resting potential. This leads to continuous contraction of the muscle. In contrast, animals including other insects, spiders, snails, lizards and snakes have venom neurotoxins that block Ca^{2+} channels, preventing the release of acetylcholine and so preventing transmission across the junction. This again leads to paralysis.



This monocled cobra has a venom containing neurotoxins that bind to the acetylcholine receptors on muscle cells

Examples of venomous animals. From left to right in each row: (row 1) flat rock scorpion, Komodo dragon, beadlet anemone, adder, cuttlefish, stony coral; (row 2) wasp, squid, nursery web spider, leaf-cutter ant, huntsman spider, tick, assassin bug

Neurotransmitters

Some of the most dangerous venomous snakes, including a group called elapids, which includes cobras and sea snakes, exert their lethal breath-stopping effects after acetylcholine has been released by the neurone. This neurotransmitter has to be picked up by receptors on the muscle on the other side of the synapse, but venom toxins from these snakes block the acetylcholine receptors.

A broad picture is emerging here. If something is important to the physiological function of an animal, venomous animals have probably found at least one way to break it. This is because the evolution of venom toxins is underscored by the fundamental principle that animals regulate their bodies precisely and so, by interfering with that regulation in precise ways, you can do a lot of damage.

Antivenom: a lifesaving treatment with a distribution problem

What happens when a person falls foul of a venomous animal? Although symptomatic care, such as strong painkillers, can help, there is only one specific kind of treatment for venomous bites: antivenom. Different antivenoms are produced against venoms from different animals, but the basic procedure to make them has remained more or less the same for over 100 years.

Because most venom toxins are proteins or peptides, they can cause an immune response in the victim. So, to obtain an antivenom, a large animal, usually a horse, is injected with the relevant venom, starting with a tiny dose and increasing the dose over time as immunity develops. Blood is then taken from the horse and the antibodies that provide the immunity are extracted from the blood. These antibodies form the basis of antivenoms. When these are given to an envenomated person, the antibodies bind to the venom toxins and hence prevent them from harming the victim.

Recently, biologists have started to recognise that animal neurotoxins show strong convergent evolution (the independent evolution of similar phenotypes, in this case similar toxin molecules, in different species). This means that developing antivenom against a few common and convergent toxins might provide an economical, broader coverage, more effective antivenom.

These future antivenom developments are likely to be an important part of treatment, as fixing the current supply problems of distributing antivenom to the people who need it and making it affordable are both crucial. Most dangerous snakebites happen in rural tropical and subtropical areas to poor people who cannot afford good medical treatment, for instance in farming communities in South Asia and Africa.

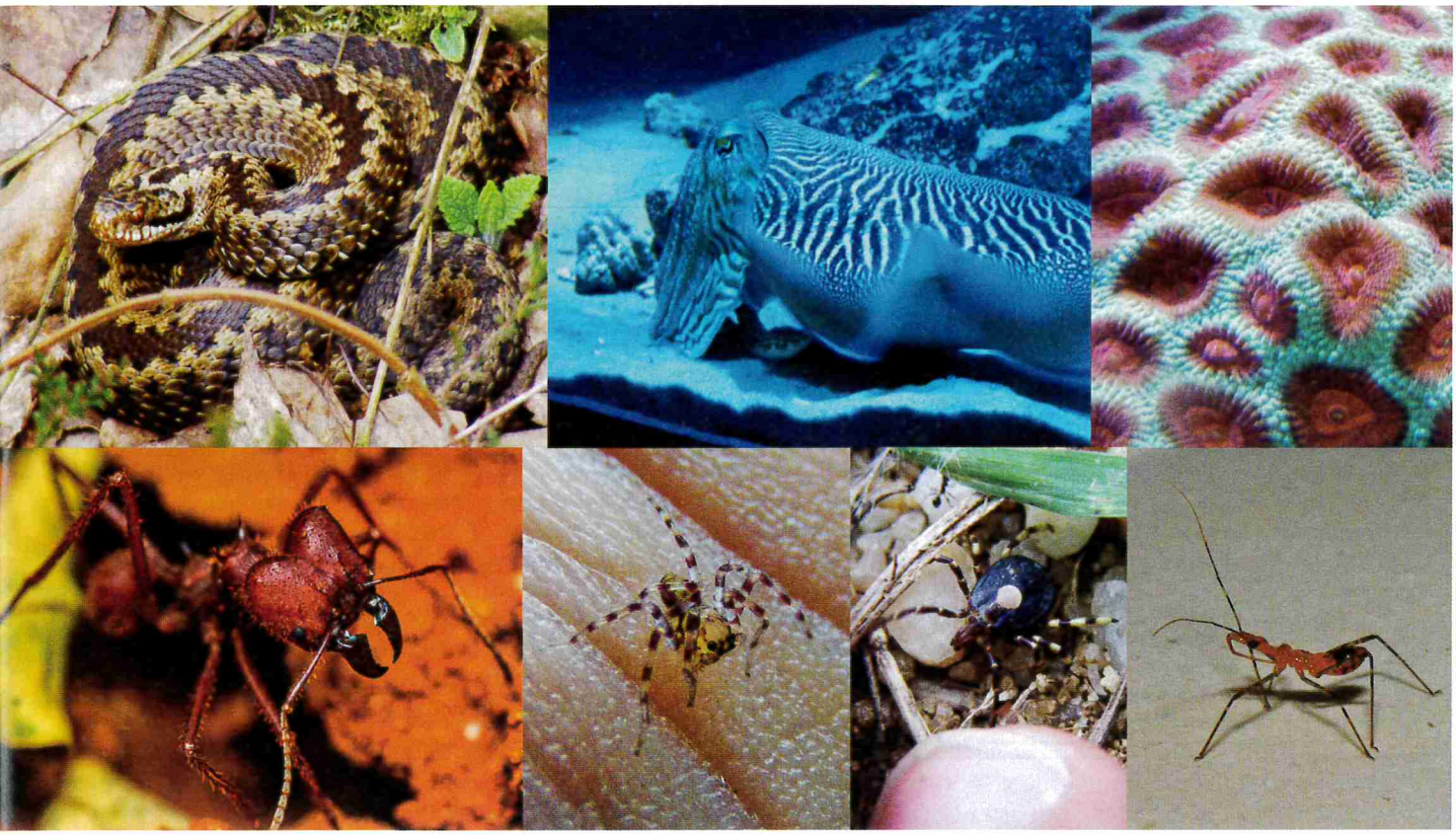
Further reading

Wilcox, C. (2016) *Venomous: How Earth's Deadliest Creatures Mastered Biochemistry*, Scientific American.

Jenner, R. and Undheim, E. (2017) *Venom: the Secrets of Nature's Deadliest Weapon*, Natural History Museum.

Bancroft, D., Venoms and the nervous system, Big Picture: **https://tinyurl.com/yb472fqe**

Brodie, E. D. III (2009) 'Toxins and venoms', *Current Biology*, Vol. 19, No. 20, R931–R935: **https://tinyurl.com/qotxq2b**



So to deal with this 'disease of poverty', advances that focus on the availability of antivenom are of major importance.

Harnessing the power of venom for medicine

Venom is not the only thing that interferes with the physiological regulation of our bodies. The majority of medical conditions can be considered to do the same — illness and disease can generally be considered as the effects of something that prevents aspects of normal physiological regulation. Think about ischaemic strokes, which are caused by blood clots forming and lodging in the brain, or diabetes in which the concentration of glucose in the blood easily becomes dangerously high. Both blood clotting and glucose concentrations are usually regulated tightly by the body's physiological systems, and serious problems arise when these fail.

Most of our physiological values are regulated around one point (or within a narrow range) and values that are too high or too low are harmful to biological functioning. A familiar example is body temperature. We regulate our body temperature within about 1°C (around 36.5–37.5°C) and medical problems arise when we get just 2°C above or below this value (just 5°C in either direction is likely to be fatal).

Modern medicine is largely based around drugs that either up-regulate or down-regulate physiological systems depending on what has gone wrong. If your blood is clotting too fast, you need an anticoagulant drug to reduce clotting, but a different drug might increase clotting and kill you. But if your blood is not clotting properly, you might need the second drug and the first might cause you to bleed to death.

Medical drugs are designed to do essentially the same thing as venom toxins, but with different results. Both might cause a rise in blood pressure, but a medical drug can be used to correct an abnormally low blood pressure (restoring physiological balance) while a venom toxin causes an abnormally high blood pressure (disrupting physiological balance and helping to catch prey). However, unlike the much more recent efforts of human pharmacists,

The venom of this Malaysian blue coral snake contains neurotoxins that force Na^+ channels in neurones to remain open. This causes the neurone to keep sending impulses that cause the muscle to contract, which leads to paralysis. This mechanism is common in invertebrate neurotoxins but rare in vertebrates and might be unique to this snake

the toxins of venomous animals have been evolving under natural selection for many millions of years. So neurotoxins found in venomous animals today are often much more effective and more specific than our drugs.

The study of venom neurotoxins may lead to future treatments for a range of medical problems related to the nervous system, including pain, epilepsy and cerebral palsy. In fact, a snake venom neurotoxin called α-cobratoxin, which binds to acetylcholine receptors, has been patented for use to treat pain and multiple sclerosis. All the more reason to value venomous animals.

Exam-style questions

1 'One way that neurotoxins can ruin your day is by blocking the Na^+ channels on the neurone.' Outline the effect that blocking its Na^+ channels has on the activity of a neurone. [2 marks]

2 Many venom toxins from snakes block the acetylcholine receptors on muscle cells. How would this prevent muscle contraction? [3 marks]

3 An antibody from a horse can be used as an antivenom.

(a) Name this type of immunity. [1 mark]

(b) Explain why the conferred immunity is short-lived. [4 marks]

BiologicalSciencesReview*Extras*

Go online for the answers at **www.hoddereducation.co.uk/bioreviewextras**

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Key points

- Many animal species produce injectable chemical weapons called venom to catch prey or deter predators.
- Venoms are mixtures of harmful molecules called toxins, many of which (neurotoxins) attack the nervous system.
- Neurotoxins interfere with nerve transmission.
- Antivenom treatment for bite victims is based on antibodies extracted from large animals that have been injected with venom.
- Because venom toxins affect physiology in specific ways, they have great potential to be used as medical drugs.

Genetic code or genome?

Second position

First position (5′ end)	U	C	A	G	Third position (3′ end)
U	UUU Phe UUC UUA Leu UUG	UCU UCC UCA UCG Ser	UAU Tyr UAC UAA stop UAG stop	UGU Cys UGC UGA stop UGG Trp	U C A G
C	CUU CUC CUA CUG Leu	CCU CCC CCA CCG Pro	CAU His CAC CAA Gln CAG	CGU CGC CGA CGG Arg	U C A G
A	AUU AUC AUA Ile AUG Met	ACU ACC ACA ACG Thr	AAU Asn AAC AAA Lys AAG	AGU Ser AGC AGA Arg AGG	U C A G
G	GUU GUC GUA GUG Val	GCU GCC GCA GCG Ala	GAU Asp GAC GAA Glu GAG	GGU GGC GGA GGG Gly	U C A G

Figure 1 The genetic code, represented as the amino acid encoded by each mRNA codon. The 5′ end of a polynucleotide is the end with a free phosphate group

In exams, students often write about 'the genetic code of an organism'. When they do this, they are using the term 'genetic code' incorrectly.

Usually when students write about an organism's 'genetic code', they are referring to all the genetic information in a cell of that organism. The correct term for this is the **genome**. In a prokaryotic cell, the genome consists of the nucleotide base sequence of its single circular DNA molecule (referred to as a 'nucleoid' in some biology specifications) and of any plasmids in its cytoplasm. In a eukaryotic cell, the genome consists of the DNA base sequences of its chromosomes, its mitochondria and, if present, its chloroplasts.

The **genetic code** is the relationship between the base sequence of three nucleotides and the amino acid that it encodes. This relationship is **universal**, meaning it is the same in every living organism (although there are some exceptions).

Figure 1 shows the genetic code using mRNA **codons**. Note that some amino acids are encoded by more than one codon, i.e. the genetic code is **degenerate**, and some codons are 'reading instructions'. Also, note that no examination board expects you to remember the information in Figure 1 but could expect you to use it if given as stimulus material in a question.

In your exams, ensure you use the terms genetic code and genome correctly.

Martin Rowland