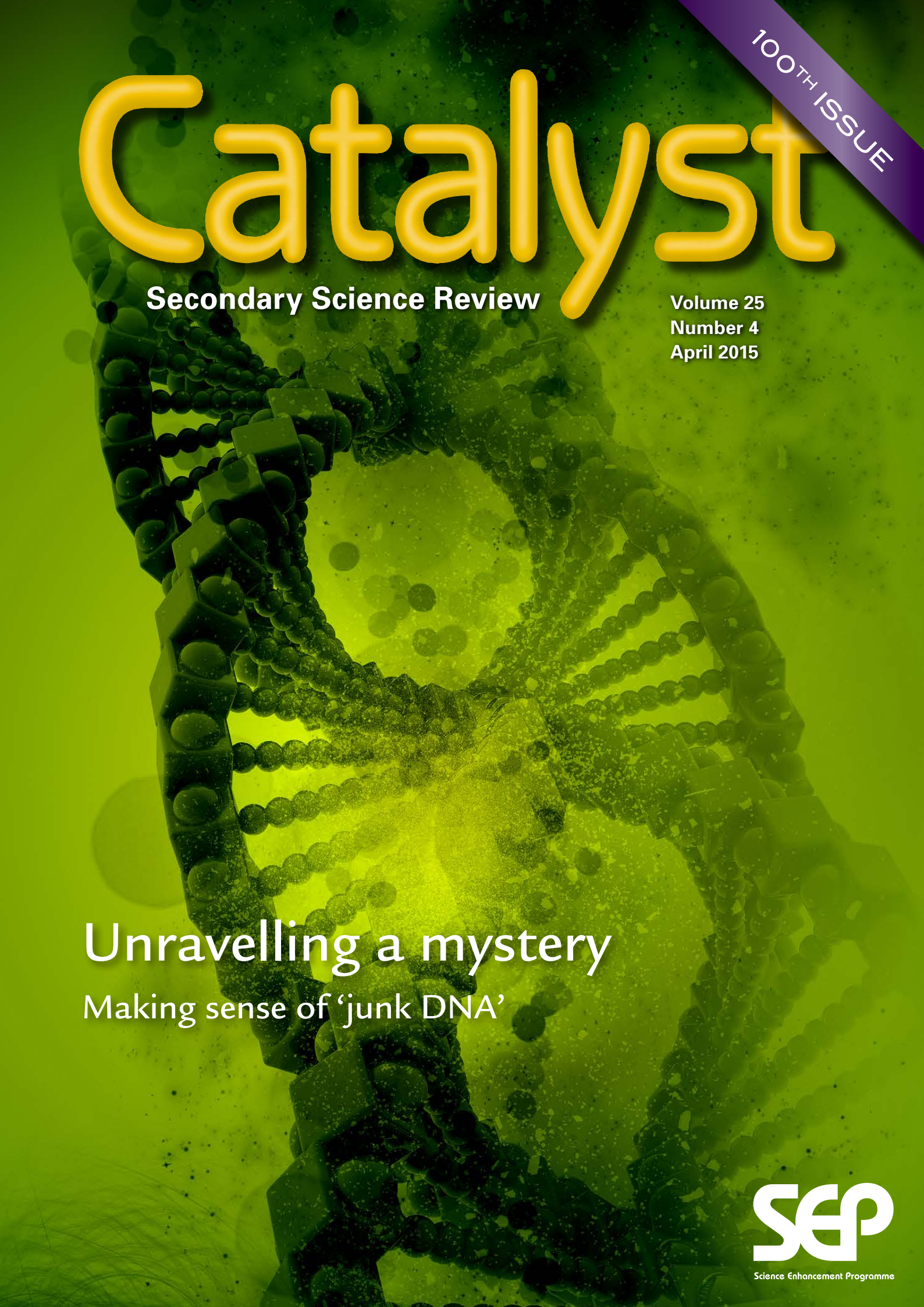

Catalyst

100TH ISSUE

Secondary Science Review

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Unravelling a mystery

Making sense of 'junk DNA'

SEP
Science Enhancement Programme

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The cover image represents a double-stranded molecule of DNA. See David Martindill's article on pages 6-8 to learn how the mysteries of Junk DNA are currently being unravelled. (Bigstock: sscreations)

Contents

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Working with and without animals

This issue of Catalyst includes two articles in which scientists describe work which involves animals.

On pages 1-3, Clara Mancini describes how she and her colleagues at the UK's Open University are working to develop systems which allow animals such as assistance dogs to interact more directly with computer-based technologies.

On pages 4-5, Laura Waters of Huddersfield University describes how her work on testing of household chemicals can reduce the numbers of tests that are done on laboratory animals.

When scientists work with animals, they are obliged to think about the ethical issues involved. Animals are not the same as humans and cannot give their consent, so any work with animals has to be undertaken with consideration for their welfare. Methods of reducing animal experimentation are always sought in preference to using more animals, however worthwhile the outcomes may be.

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Animal-computer interaction

Designing technology for and with animals

Clara Mancini

We live in a society where computing technology has become ubiquitous and interacting with computers no longer means using keyboard and mouse. Embedded in the fabric of our cities, workplaces, homes, vehicles, clothes and even bodies, 'smart' technologies now allow us to relate to the world around us, one another and even ourselves in unprecedented ways. These achievements have been driven by what interaction designers (those who research and design interactive technologies) call user-centred design.

Early uses of Animal Interactive Technology

However, we are not the only species to interact with technology. Being directly or indirectly involved in every aspect of human life, other animals have interacted with technology for a long time. For example, in the 1960s, bears were already wearing tracking devices in conservation studies; while mice and pigeons were operating switches and buttons in behavioural experiments. In the 1980s, great apes started using early touch-screen computers to learn human language in comparative cognition research, followed in the 1990s by dolphins who were given underwater keyboards for similar communication tasks. Meantime, thanks to advances in agricultural engineering, cows were being introduced to early robotic milking systems enabling them to milk themselves.

Sue Savage-Rumbaugh with the bonobo Kanzi, communicating by indicating icons on a lexigraph

In the early 2000s, interaction designers began to reflect on the interaction between animals and technology; they started asking questions about these technological interactions. Seeking answers to such questions is what we do at the Open University's Animal-Computer Interaction (ACI) Lab.

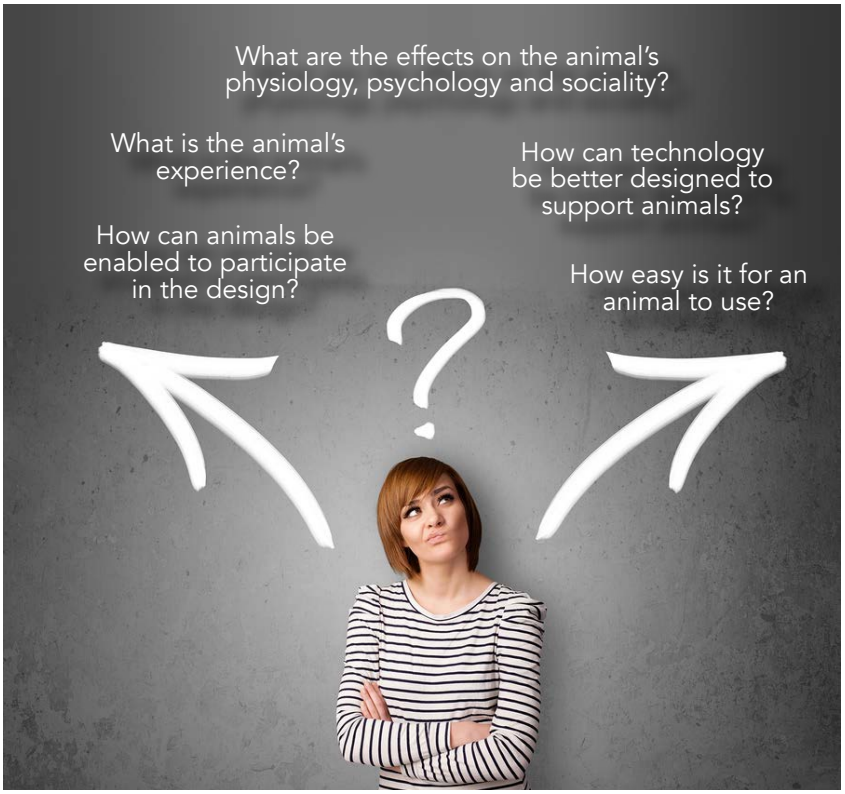
Key words

computer

interactive technology

communication

design



Developing technologies to better suit animals

To see how these questions can be addressed in practice, let us consider the case of working dogs. Dogs are incredibly adaptable and can be trained to do almost anything, including using some of the interactive technologies we have in our homes (e.g. washing machines, telephones, light switches). However, the interfaces of these technologies are designed for humans, not dogs.

Problems with human buttons and switches	Solutions
too small and fiddly for a dog's finger-less paws	large (up to 20 × 20 cm), so they are easy to target; activated by a soft touch, so dogs can use either their paw or nose to activate them
typically positioned too high for dogs	either wired or wireless, so they can easily be positioned where they are most accessible for a particular dog
often use colours such as red and green, which dogs cannot see	they are either blue or yellow, colours which dogs can see well
and they come in many different shapes but similar sizes, which dogs don't easily distinguish between.	they have the same square shape but come in different sizes, which is how dogs prefer to categorise objects.

All this makes it difficult for dogs not only to physically interact with our domestic interfaces, but even to understand how different controls might map onto different functions.

Dog friendly buttons

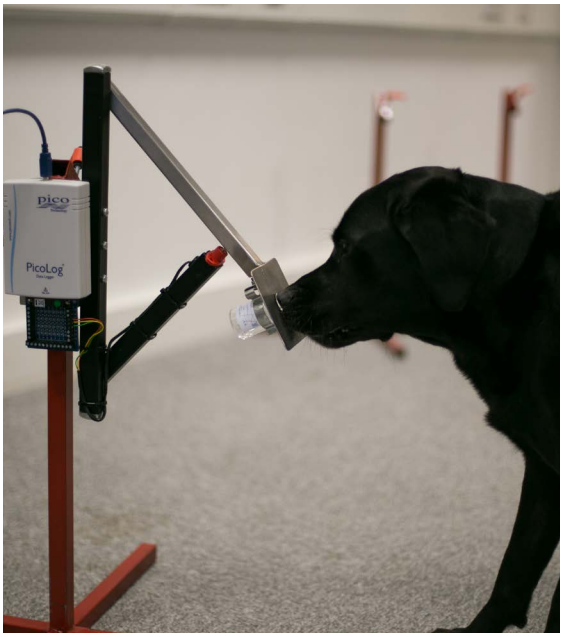
We have been working with the charity Dogs for the Disabled to re-think the way in which our domestic controls are designed, and have developed a suite of dog-friendly buttons for the home or office. The Open University has decided to install them in one of its buildings to make life easier for the assistance dogs who frequent our campus, and for their humans.

Case study: Cancer detection by dogs

In collaboration with the charity Medical Detection Dogs we are developing technology that can help cancer detection dogs. The charity trains dogs to sniff the smell of cancer cells in biological samples such as urine, sweat or breath, and to signal back to their trainer whether they find cancer cells in a sample they are sniffing. The trainers need to be sure to interpret correctly what the dog has found, so they teach the dogs to communicate with them using conventional signals, for example sitting down in front of samples that contain cancer cells.

This signalling system has two limitations. Firstly, it allows the dogs to say, "Yes, there is something here," or "No, there is nothing here," but not to express nuances in between. Secondly, even though that helps the trainers, using conventional signals is not natural for the dogs, so sometimes they don't perform the signals as expected, leaving the trainers in doubt as to what they might be saying.

To address these limitations, we have developed an 'electronic rig' which holds the sample sniffed by the dogs and uses a pressure sensor to measure the interaction of the dog's nose with the sample.



The pressure-sensing electronic rig used in cancer detection

We are finding that the pressure the dogs exert on the plates behind which the sample is secured varies depending on its content, so we can use the pressure recorded to interpret the dogs' reaction to a sample and whether they think that the sample is positive, negative, or somewhere in between. This allows the dogs to communicate with their trainer – so to speak – In their own terms, in a way that is both more subtle and spontaneous.

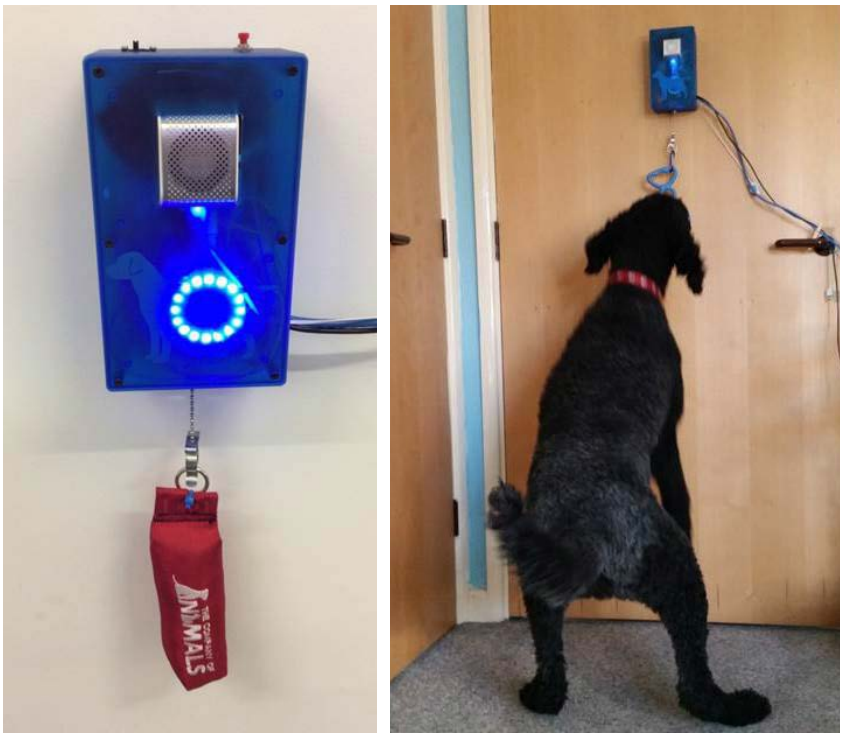
Asking the animals

To ensure that our technology can really support animals, we cannot just design *for* them, we also have to design *with* them. But how can we enable animals to participate in the design process? At our ACI Lab we have tried a combination of methods.

Firstly, it is very important to try to understand as much as possible about an animal's physiology, psychology and sociality; we do this by taking advice from animal scientists (e.g. colleagues at the University of Lincoln) and by talking with those who work with the animals (e.g. their trainers), and by closely observing the animals during their normal activities; this gives us an idea of what they generally like or dislike. Secondly, we seek feedback from the animals on specific designs through 'rapid prototyping': we prototype variations of a design in rapid succession and offer them to the animals under various conditions so they can show us their preferences.

Developing an alarm for medical alert dogs

Charlotte Robinson, a PhD student at the ACI Lab, is developing an alarm to enable medical alert dogs to call for help when their human becomes temporarily incapacitated due to a medical condition such as diabetes. When, during a training session, the human pretended to pass out, the dog refused to leave her side to trigger the alarm that was mounted on a wall far away; he would only trigger the alarm if, to do so, he didn't need to lose sight of his human, which suggested that perhaps the alarm needed to be located on the person rather than on a wall.



The canine alarm (left), and how it is activated by a dog

Animals will let us know what they want, but to be able to do so they need to be free to make choices, and even to choose whether or not to engage with a prototype or with us. In other words, user-centred design is not just about giving animals more control over their environment by designing technology for them; it is just as much about giving them control over the design process by adopting research methods that enable them to express their preferences and autonomy, even when they choose not to engage. I think this is the difference between research done 'on' animals and research done 'with' animals, which is what ACI is all about.

Dr Clara Mancini leads the Animal Computer Interaction (ACI) Lab at the Open University in Milton Keynes, UK.

Laura Waters

Using chemistry to reduce animal testing

Key words
cosmetics
testing
industry
analysis

Fifty years ago it was considered quite acceptable to use animals in scientific studies for new medicines, new cosmetics and general scientific research. However, times have changed and many people now feel that this is ethically unacceptable and so have turned to science for solutions.

Two years ago it became illegal to conduct any animal testing for cosmetics across the whole of the EU (although it is still a legal requirement for new medicines from the pharmaceutical industry). So, if they are not allowed to use animals to check our products are safe, how can they do it? This is where recent scientific developments have played a role, by designing alternative methods to decide if a new chemical is safe enough to be used in items such as make-up, deodorants and household cleaning products.

A laboratory rat: testing cosmetics on animals is now no longer acceptable and chemists are helping to find alternatives.

Devising new products

There are several ways a company can manage to create a new product and be sure it is safe without using animals. The simplest of these is sticking to ingredients that have been around for a long time where we know they are alright to use. In these cases the company must somehow 'redesign' the formulation to make it seem new and exciting even if the ingredients are all the same.

However, if a company wants to be really unique they need to add new ingredients, perhaps to help the product last longer, such as with a hair dye, or have a novel effect, such as a new anti-wrinkle cream. In these cases the company must still prove the chemicals are safe without actually testing them on animals. In a bid to create suitable alternatives, scientists have been working hard to develop an array of alternative methods using biology, chemistry and, more recently, computers, which provide data that they can analyse to decide if a chemical is safe or not.

Chemists have created a reaction database to help predict how other chemicals will react.

Chemistry has played a major role in this explosion of ideas and methods, both directly by helping scientists understand how new ingredients react with chemicals in the body and, indirectly, by creating a 'reaction database' that computer simulations can use to analyse new reactions. Now it is possible to watch chemicals react using modern techniques such as spectroscopy, chromatography and calorimetry. Scientists can then understand how things react and, more importantly, why they react. Once they know this information then they can design chemicals that are unreactive in the body which makes them safe to use.

Make-up has to be safe to use and can no longer be tested on animals

Through the skin

In some cases it is more important to know if the new chemicals even get into our systems in the first place so if you use make-up on your skin you need to be sure it doesn't sink through your skin layers and end up in your blood stream. This is known as transdermal permeation and for household products must be avoided at all costs. Obviously in some products permeation is necessary, such as pharmaceutical products including pain relief creams and nicotine patches, but for everyday items including shower gels and shampoos permeation is undesirable.

Chemicals from shampoo and other cosmetics should not be absorbed into the body.

Scientists traditionally applied these products to animal skin and took blood samples to see if the compound had made its way into their system but in recent years it has become acceptable to apply a new chemical to a skin mimic and see how much gets through and how fast.

Computer tests

When a chemist discovers a new compound then they will firstly spend time working out its structure, figuring out which elements it is made of and how they are bonded within the compound. Then if they slightly change the structure they can re-evaluate the compound and see if it reacts differently. This is known as a structure-activity relationship and is the basis for most computer simulation programs. Breaking up a large molecule into its smaller parts and then identifying which parts of the molecule produce which effects allows scientists to predict the behaviour of any molecule you can imagine making.

The replacement of animal testing is a slow process for industry, and although some alternatives have already been introduced for cosmetics there is still a long way to go in the pharmaceutical industry. Chemistry will certainly play a major role in the future of developing alternative methods as understanding the reactions that occur is essential for understanding their safety.

Dr Laura Waters is a lecturer and Principal Enterprise Fellow at the University of Huddersfield.

You can read more about Laura Waters life as a research scientist in the article on pages 20-21 of this issue of Catalyst.

David Martindill

Anything but junk

Delving deep into the dark matter of the human genome

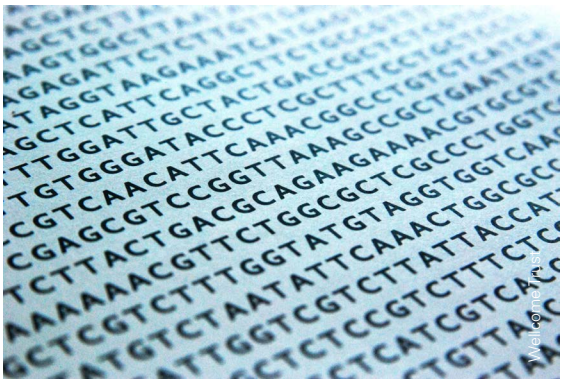
Key words
gene
genome
DNA
medicine

Most biology students know who discovered the structure of DNA. But few can recall Fred Sanger's contributions to genetics – and what about those of Francis Collins and John Sulston?

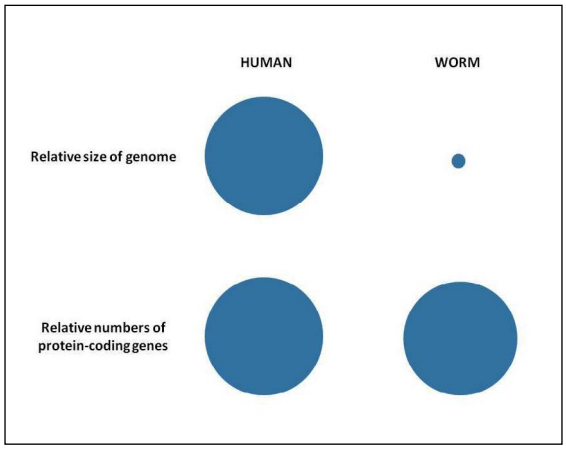
It is now more than a decade since the Human Genome Project concluded. Employing the technique of DNA sequencing developed by Sanger, an international consortium of scientists, including Collins and Sulston, determined the entire sequence of our genome, a code of 3.3 billion letters.

DNA sequencing machines at the Wellcome Trust Sanger Institute

This is much larger than that of many other species, for example the nematode worm, *C. elegans*, which has a genome around 3% the size of ours.



A tiny section of the human genome sequence. A staggering 3.3 billion letters long, it would take over 90 years, day and night, to read the complete sequence at a rate of one letter per second!



A comparison of genome size and gene number in humans and the nematode worm, C. elegans

The alphabet of molecular biology

DNA has a simplified alphabet of four letters, A, T, C and G. These are known as 'bases' and are read by the cell in groups of three. Each triplet encodes a specific amino acid, of which there are twenty different types, which the cell then joins together to form a protein. The function of a protein, encoded by a specific stretch of DNA called a gene, is entirely dependent on the sequence of its amino acids. Proteins control events during foetal development, and processes from respiration to reproduction in the adult.

Francis Crick claimed that, for cells to make proteins, the DNA code is first copied into a related molecule called RNA. This is like a 'photocopy' of a page (the gene) from an encyclopaedia (the genome), in a library (the nucleus). Structures in the cytoplasm called ribosomes convert this RNA copy into protein. RNA, claimed Crick, is a 'middle-man', a short-lived intermediate, between DNA and protein.

Given our complexity, scientists expected the human genome to contain a huge number of genes. It was therefore a shock when it was discovered that humans have just 20 000, roughly the same number as *C. elegans*. Until recently, there was no explanation for why so much of our genome, more than 98%, is non-coding. Scientists dismissed this as 'junk DNA'. This is mainly found in the dark regions of chromosomes, called heterochromatin, once they have been stained with dyes.

A human chromosome stained with a chemical called Giemsa (left) and a diagrammatic representation of the same chromosome (right). Junk DNA is predominantly found in the darker regions, called heterochromatin.

What we knew

Perhaps these figures should not have been as surprising. Even before our entire DNA sequence was revealed, sections of the genome were known not to encode proteins.

Lengths of junk DNA at the end of chromosomes (called telomeres) shorten as a cell divides, and this has been linked with the lifespan of a cell. Conditions characteristic of old age, including some lung diseases, are more common in people with undersized telomeres, while smoking, obesity and stress have all been found to accelerate their shortening. Beyond the telomeres, there appear to be regions of DNA within genes that do not encode amino acids, called introns, and sections of non-coding DNA surrounding genes that are copied by the cell into RNA.

For decades it has been known that mutations in these regions are responsible for a range of genetic disorders. These include Fragile X syndrome, myotonic dystrophy and some cases of the condition made prominent by the 'ice bucket challenge,' amyotrophic lateral sclerosis (ALS). On a more sinister note, remnants of viruses have been detected in the human genome, which slotted into our DNA during our evolutionary past. These 'genomic fossils' present potential dangers, not least an increased risk of cancer, if they decide to 'copy and paste' themselves from one place to another.

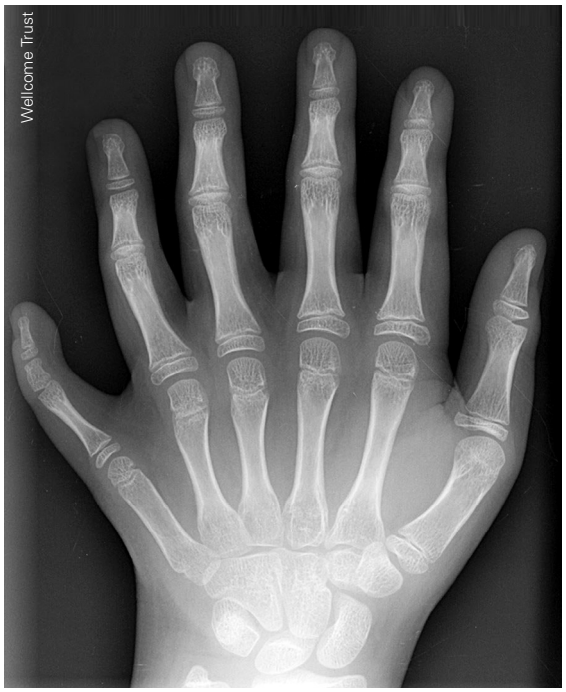
Fine tuning

Switching genes 'on' and 'off' should not be considered an issue of black versus white. The regulation of gene expression can occur in a whole host of shades of grey, and junk DNA is vital in this process.

Junk DNA contains all sorts of 'switches' to tell the cell where, when and for how long genes should be turned on to produce proteins. Some, called imprinting control elements, dictate which gene copy is turned on – the one from your mother or the one from your father. Others, called promoters, enable cells to regulate the extent of gene expression. They do this by acting as 'docking points' for proteins

called transcription factors. These in turn bind the cellular machinery that creates the RNA copy of the gene for protein synthesis.

However, due to mistakes in cell division, chromosomes can become cut and pasted with each other, sometimes leading to a promoter being placed near a gene it shouldn't be, with disastrous results. The best known example of this occurs in patients with a cancer called Burkitt's lymphoma, in which a very active promoter is placed next to a gene that controls cell division. Other junk DNA regions called enhancers also adjust gene expression and are very important in the control of correct development of the foetus. This is because gradients of chemicals called morphogens need to be established to ensure that the right structures develop in the right places. If enhancers are mutated, deformities can result.



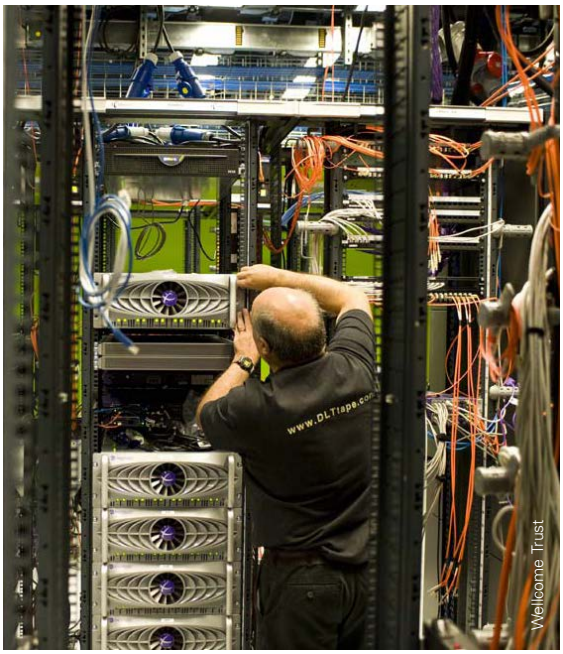
Mutation of one of the enhancers of the Sonic Hedgehog gene interferes with the gradient of this morphogen, resulting in deformities of the limbs. Look closely!

In DNA's shadow

The human genome does not just encode proteins as Crick thought. RNA molecules can have a role in their own right.

Some functional RNA molecules have been known for a long time. For example, ribosomes are made predominantly of RNA. However, the roles of others are only just emerging. Some are thought to be involved in maintaining populations of stem cells in the embryo, possibly by promoting the expression of some genes over others. Deciphering how RNA is involved in these pathways may enable us to increase the potency of cells, namely their ability to specialise into different types.

This has huge potential in the field of medicine which treats degenerative disorders such as diabetes and Parkinson's disease. Interestingly, many of these RNA molecules are often found exclusively in humans, and a high proportion of these are found in the brain. In experiments using rats, problems with production of these molecules during development have been shown to influence intellectual ability, impair muscle coordination and induce alcohol and drug dependency. Some pharmaceutical companies are already developing drugs that work by mimicking their function, with Alzheimer's disease being one such target.



The Wellcome Sanger Centre has 4 petabytes of computer storage to manage the vast amounts of data generated by genome sequencing.

A fruitful future

There are still many scientists who claim that we are paying too much attention to junk DNA. They say it might be like our appendix: important in our ancestors, but without much function in us. Indeed, there can be few explanations for a type of junk DNA called short tandem repeats (STRs), which consist of two- or three-base sequences (e.g. CT or CTG) repeated over and over again. However, our understanding of such sequences can still bring benefits. DNA fingerprinting relies on STRs, as the numbers of repeats differs between people. The coming decades promise opportunities for researchers to unlock further secrets in this sequence – we just have to look closely and use our imagination.

David Martindill teaches biology and has a research background in genetics.

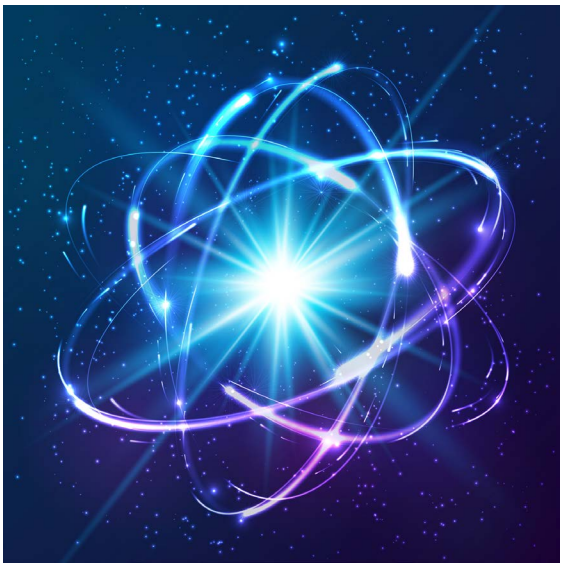
Look here!

You can read more about this fascinating subject in Nessa Carey's new book, *Junk DNA: A Journey Through the Dark Matter of the Genome.*

David Sang

Models of the atom

Today we are very familiar with the picture of the atom as a particle with a tiny nucleus at its centre and a cloud of electrons orbiting around the nucleus. But where did this model come from? What were scientists trying to explain using their models of the atom? To find out, we have to go back to the early years of the twentieth century.



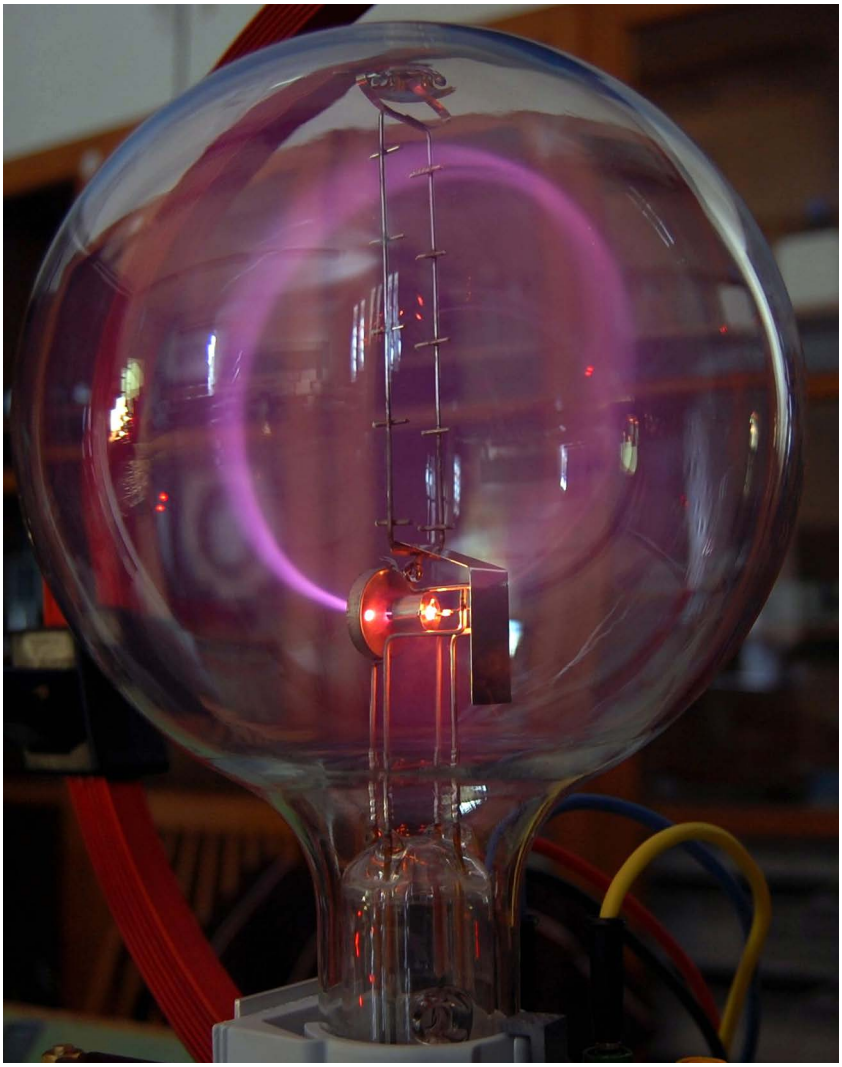
A model of the atom. But does the nucleus glow like this? No. And are electrons blue? No.

Discovering radioactivity and the electron

By the 1890s, most physicists were convinced that matter was made up of atoms. The idea of vast numbers of tiny, moving particles could explain many things, including the behaviour of gases and the differences between the chemical elements.

Then, in 1896, Henri Becquerel discovered radioactivity. He was investigating uranium salts, many of which glow in the dark. To his surprise, he found that all the uranium-containing substances that he tested produced invisible radiation that could blacken photographic paper. What's more, the radiation was constant – there was nothing he could do to speed up or slow down the process.

The next year, J J Thomson discovered the electron. He was studying 'cathode rays', glowing beams which streamed out of the negatively-charged cathode in a vacuum tube. These beams could be deflected by a magnetic field. And, because the beam didn't split up into many thinner beams, Thomson deduced that it was made up of particles of only one type, with negative charge, and all travelling at the same speed.



In this photo, an electron beam is bent along a circular path by a magnetic field. The beam is produced at the bottom in an 'electron gun' and follows a clockwise path inside the evacuated tube. A small amount of gas has been left in the tube; this glows to show up the path of the beam.

The importance of these two discoveries was that they suggested that atoms were not indestructible. Atoms are tiny but they are made of still smaller particles.

Positive and negative

Electrons are negatively charged. However, atoms are neutral, so it seemed that there must also be positively-charged particles in an atom. So the question was, how are the positive and negative particles arranged in an atom?

Several scientists came up with suggestions, which we now describe as **models** of the atom. The next two pages show five different models. Then, on page 12, we consider why the nuclear model was successful.

Key words

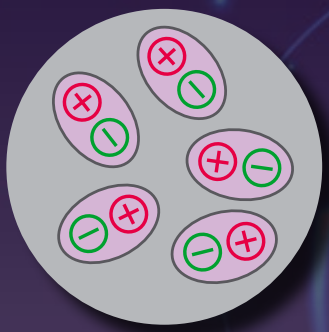
model

atomic structure

electron

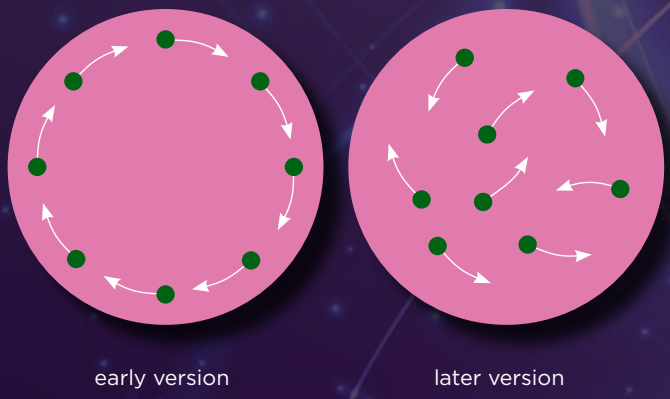
nucleus

ATOMIC MOD



THE DYNAMID MODEL (1903)

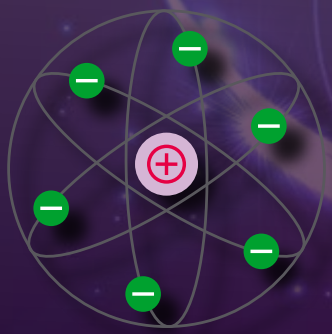
Who? Philipp Lenard (Hungarian-German)
Structure: 'Dynamids' each made of an electron bound to a positive charge. Atoms of different elements would be formed of different numbers of dynamids stuck together – one for hydrogen, four for helium, 12 for carbon.
Explains: Different elements have different atomic masses.
Problem: How do the dynamids stick together to form an atom?



early version later version

THE PLUM PUDDING M

Who? J J Thomson (British)
Structure: Electrons equally spaced a
charge. Later version: the electrons ar
like the dried fruit in a Christmas pudd
Explains: Atoms are neutral because p
Problem: Alpha scattering (see p12) sh
charge were concentrated in a small fra



THE NUCLEAR MODEL (1911)

Who? Ernest Rutherford (New Zealand) but originally suggested by Jean Perrin (France)
Structure: All of the positive charge of the atom and most of its mass are concentrated at the centre with the electrons orbiting around it.
Explains: Alpha particle scattering results (see p12).
Problem: What holds the nucleus together?
And why don't electrons spiral into the nucleus?

DELS

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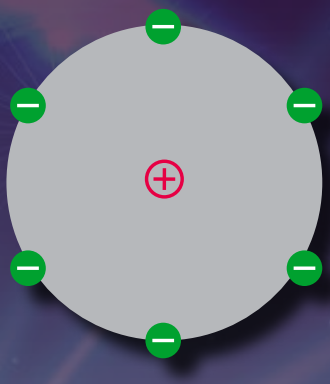
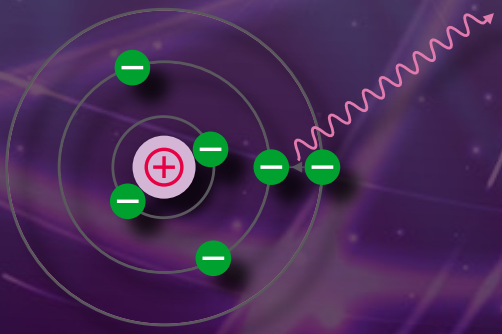


THE SATURNIAN MODEL (1904)

Who? Hantaro Nagaoka (Japanese)
Structure: Electrons form rings around a central positively-charged 'planet' like Saturn. The attraction between opposite charges keeps the electrons in their orbits.
Explains: Different elements have rings with different energies, so they have different colours in their spectra.
Problem: Not enough supporting evidence at the time.

MODEL (1904)

around a ring, orbiting inside a sphere of positive
e scattered about inside the positive charge, rather
ing.
positive and negative charges are balanced.
nowed that most of the mass and all of the positive
action of the atom.



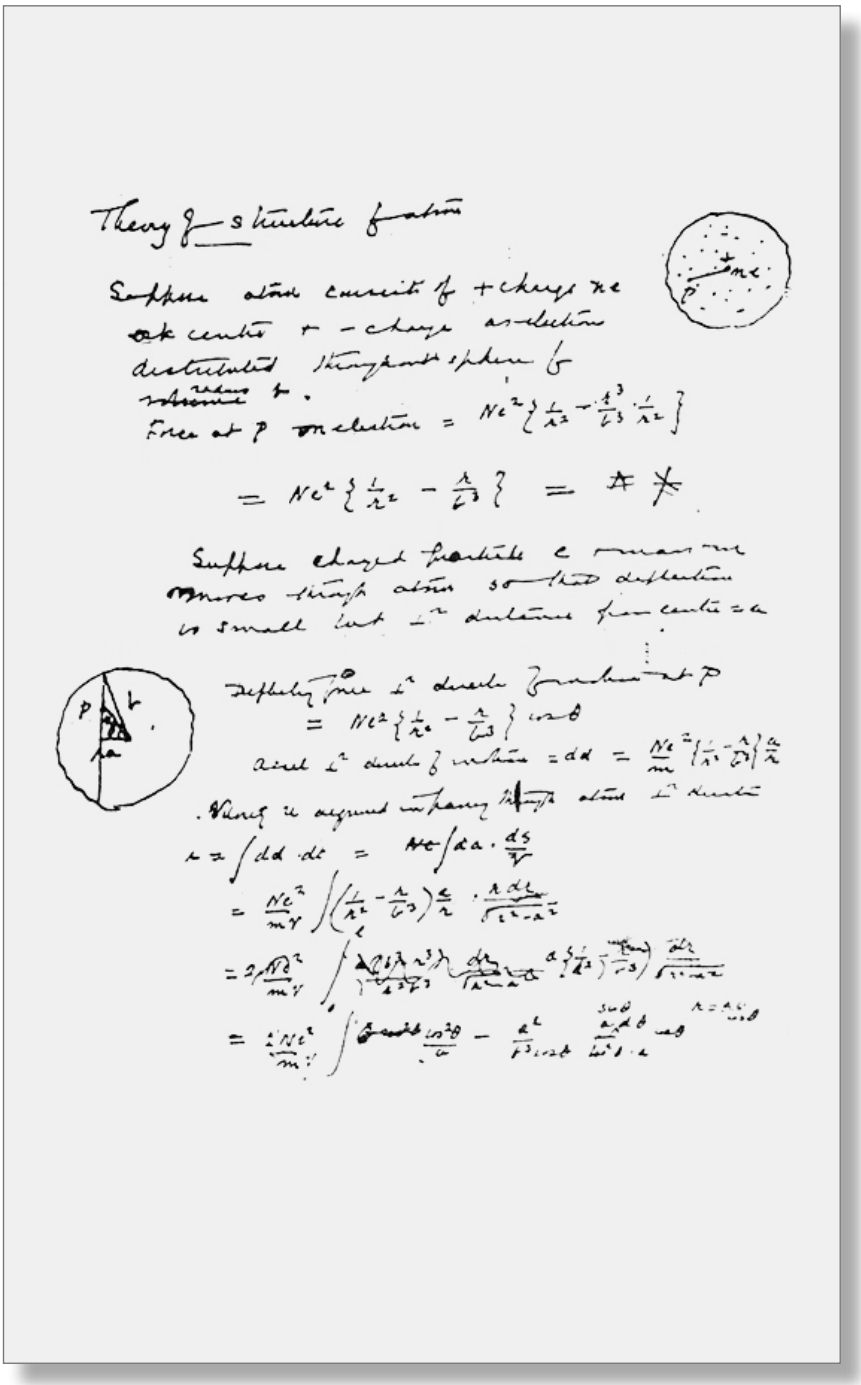
THE BOHR MODEL (1913)

Who? Niels Bohr (Denmark)
Structure: Electrons only in orbits with fixed energies around the central nucleus. They can jump from one orbit to another, emitting or absorbing energy.
Explains: The wavelengths of light emitted by hydrogen atoms.
Problem: Breaks several laws of classical Physics, paving the way for Quantum Physics to be developed.

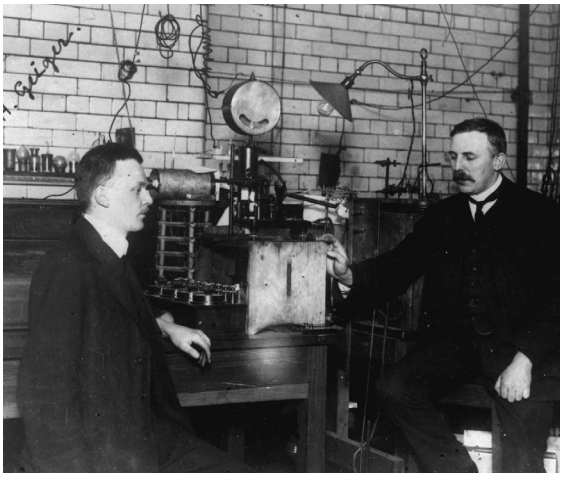
What makes a good scientific model?

Models are used in science to help to explain observations and to develop theories. A good model can explain experimental evidence and lead the way to a theory.

You can see that each of the atomic models shown on pages 10-11 (and there were several others) had some good features. They might be able to explain why atoms are stable, why the atoms of one element differ from another, why different elements emit different colours of light, why some atoms decay and so on. But, in the end, a good model must explain everything we know or it will have to be modified or discarded.



Rutherford's notes, in which he used the laws of static electricity to work out how a charged particle would move through an atom.



Ernest Rutherford (right) with his colleague Hans Geiger in their lab in 1912.

Ernest Rutherford's most famous experiment involved directing alpha radiation (positively-charged particles) at a thin gold foil. Some of the alpha particles were scattered back towards their source; he guessed that gold atoms had a tiny charged nucleus which reflected them.

The nuclear model was rapidly developed by Rutherford and others. A striking feature of Rutherford's thinking is that he realized that it was hard to explain why the nucleus, made only of positive charge, didn't fly apart. Gradually it came to be understood that the nucleus is made up of two types of particle, protons and neutrons, and a new force, the strong nuclear force, was discovered which holds these particles together.

The nuclear model had another problem: when charged particles such as electrons travel round in circular paths, they usually radiate energy, slow down and spiral in towards the centre of their orbit. Niels Bohr developed the idea that this simply doesn't happen in atoms, because they have to be in one or other of a fixed set of orbits around the nucleus. They cannot be somewhere in between, so spiraling is out of the question.

Both Rutherford and Bohr showed that sometimes bold thinking is necessary. They were prepared to discard long-held ideas and move ahead, acknowledging that there were problems still to be solved but optimistic that they could adapt their models and the ideas they represented to give a deeper understanding of the nature of matter at the level of atoms.

David Sang is Physics editor of Catalyst.

Some other scientific models you may know

The lock-and-key model of enzyme action

The kinetic model of a gas

The heliocentric model of the Solar System

The wave model of light

Hafeeza Ayuoob
Vytautas Kontrimas
Mark Dallas

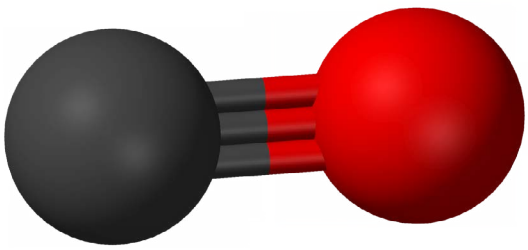
Toxic gases! Therapeutic? What?!

Carbon monoxide is a toxic gas – could it really be used as a treatment for disease?

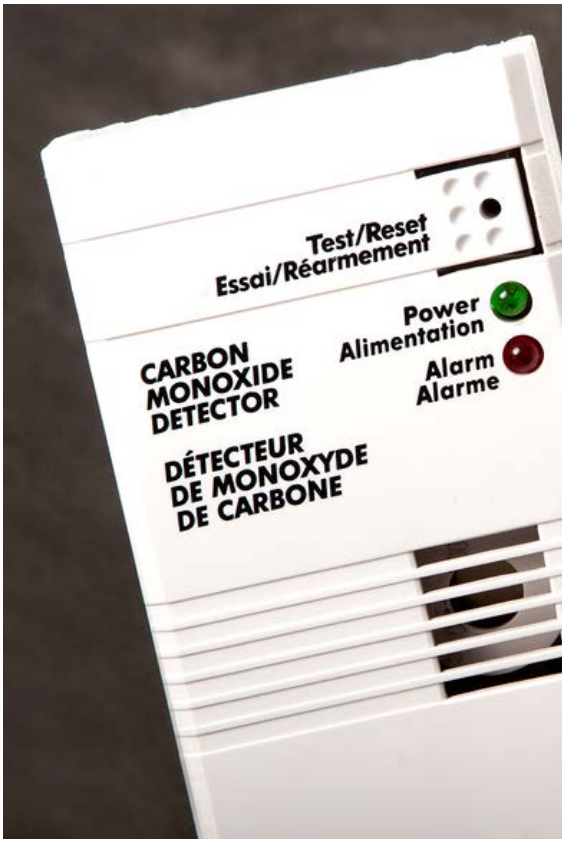
Key words
carbon monoxide
Alzheimer's disease
heart arrhythmia

Carbon monoxide (CO) is best known as a toxic gas but may one day be used as a therapy for difficult to treat diseases, as three scientists from the University of Reading explain.

Carbon monoxide is an odourless gas produced during the incomplete combustion of carbon, for example in faulty heating and gas appliances. Although carbon monoxide is rightly regarded as a highly toxic gas, it has been known since the 1890s that organisms generate CO within their bodies. CO can interfere with oxygen transport in the blood as it binds to the haemoglobin in red blood cells. However its main toxicity is believed to be due to its disrupting the function of the mitochondria.



Carbon monoxide molecules contain one carbon and one oxygen atom bonded together. It is more reactive than carbon dioxide.



Many homes have a carbon monoxide detector as the gas can kill.

What is now becoming apparent through exciting scientific research is that this gas could be a potential therapeutic treatment for many neurological (brain and nerve) diseases. As a result, scientists have been looking at the effects of low levels of CO in the body with the hope that CO could be a therapeutic remedy for complex and difficult to treat diseases such as Alzheimer's disease (AD).

CO in the body

Most research into how CO can help the body is focussed on enzymes called heme oxygenases. These enzymes are essential in the body and break down heme, which is part of the haemoglobin molecule which carries oxygen round the body. The heme is broken down to produce the chemical bilirubin, Fe^{2+} ions and CO. Ridding the body of heme is essential and organisms that lack the gene to produce heme oxygenase have a severely shortened life span.

In many age-related neurodegenerative diseases such as Alzheimer's, patients have an increased amount of heme oxygenase in the brain cells. An increased amount is also found when not enough blood reaches the brain, for example during a stroke. Research seems to suggest that the heme oxygenase enzymes protect the brain in event of a stroke, but it is not clear which of the products of breaking down heme provide that protection. The evidence is starting to point towards it being CO.

As you can imagine, finding out which of the products of the breakdown of heme provide protection to the brain is not an easy task, but it has been helped recently by the development of molecules which release carbon monoxide. These are called CO Releasing Molecules (CORMs) and can be given to patients, releasing CO at the required site in the body. At Reading University we are using these to investigate the role of carbon monoxide in the cardiovascular and nervous systems.

What we have uncovered is a tale of two systems and that what is good for the head is not good for the heart.

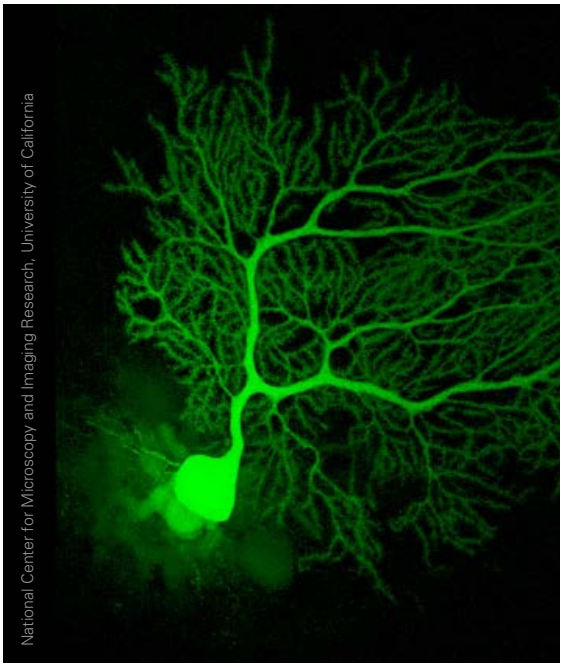
Tackling Alzheimer's

Alzheimer's disease (AD) affects some 820 000 individuals in the UK with no treatments currently available to prevent this disease. Our studies have revealed a surprising protective effective of carbon monoxide against the nerve cell death caused by AD.

The author Terry Pratchett died of Alzheimer's disease in March 2015. He donated a million dollars to research into the disease.

Previous research has shown that there are toxic proteins involved in the development of AD, one of which is called amyloid beta (Aβ) which causes nerve cell death. Our innovative experiments tested to see if CO could prevent it causing cell death. To our surprise, application of CO does prevent the cell death previously observed in the presence of Aβ. We tested our experiments in a range of experimental models and the result was consistent: CO prevented Aβ-induced cell death. While these are laboratory experiments it suggests that, in the case of Alzheimer's, CO could provide a novel therapeutic option.

This research is in support of previous work highlighting that CO protects nerve cells. Further research has shown that it is the brain's support cells (glia) which produce the CO which protects the nearby neurons.

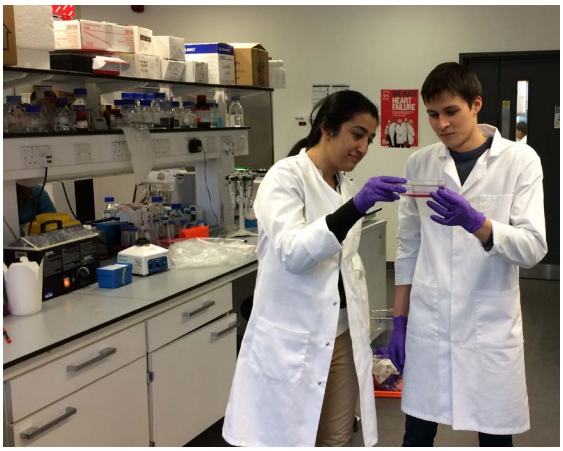


A neuron or brain cell, shown up using a fluorescent dye. Each one connects with many others forming a network in the brain.

CO and heart muscle

It has been known for some time that exposure to carbon monoxide from environmental pollution can lead to heart problems such as arrhythmia, which is irregular beating of the heart. This can occur through exposure to low concentrations of CO which are not enough to kill (30-200 ppm) and are therefore not often associated with CO poisoning. Until recently there was no scientific explanation for these effects.

We carried out studies both *in vitro* (in the lab or literally 'in glass') and *in vivo* (in living cells) to determine the effects of CO on heart muscle cells. Exposure to CO disrupted the normally regular heart rhythm.



Hafeeza Ayuoob (left) and Vytautas Kontrimas (right), two summer students looking at the effects of carbon monoxide on cultured brain cells.

Proteins known as ion channels are found on individual heart muscle cells and are essential for the coordinated beating of the heart.

Malfunctioning ion channels are the cause of many cardiac diseases. Through a series of experiments we showed that CO interacted with a sodium ion channel to change its function and produce arrthymias (irregular heartbeats). Further work showed that another gas, nitric oxide, was also involved in this damaging effect to the heart rhythm.

This is bad news for using CO to help the brain – it would not be wise to protect the brain but damage the heart while doing so. However, we have also found a drug which could alleviate the effects of CO on the heart. Ranolazine, a drug already prescribed for angina, prevented the irregular heart rhythms that were induced by CO. Therefore this could be used as a therapy for patients presenting with low level carbon monoxide exposure and cardiac complaints.

Next steps

While this research area is progressing at a rapid pace, more work is required. The next steps will be to conduct further experiments to test the functional effects of exposure to these gases and find the detailed mechanisms of how they have their effects. It is also necessary to examine the effects of these gases on the diverse cell types within the body.

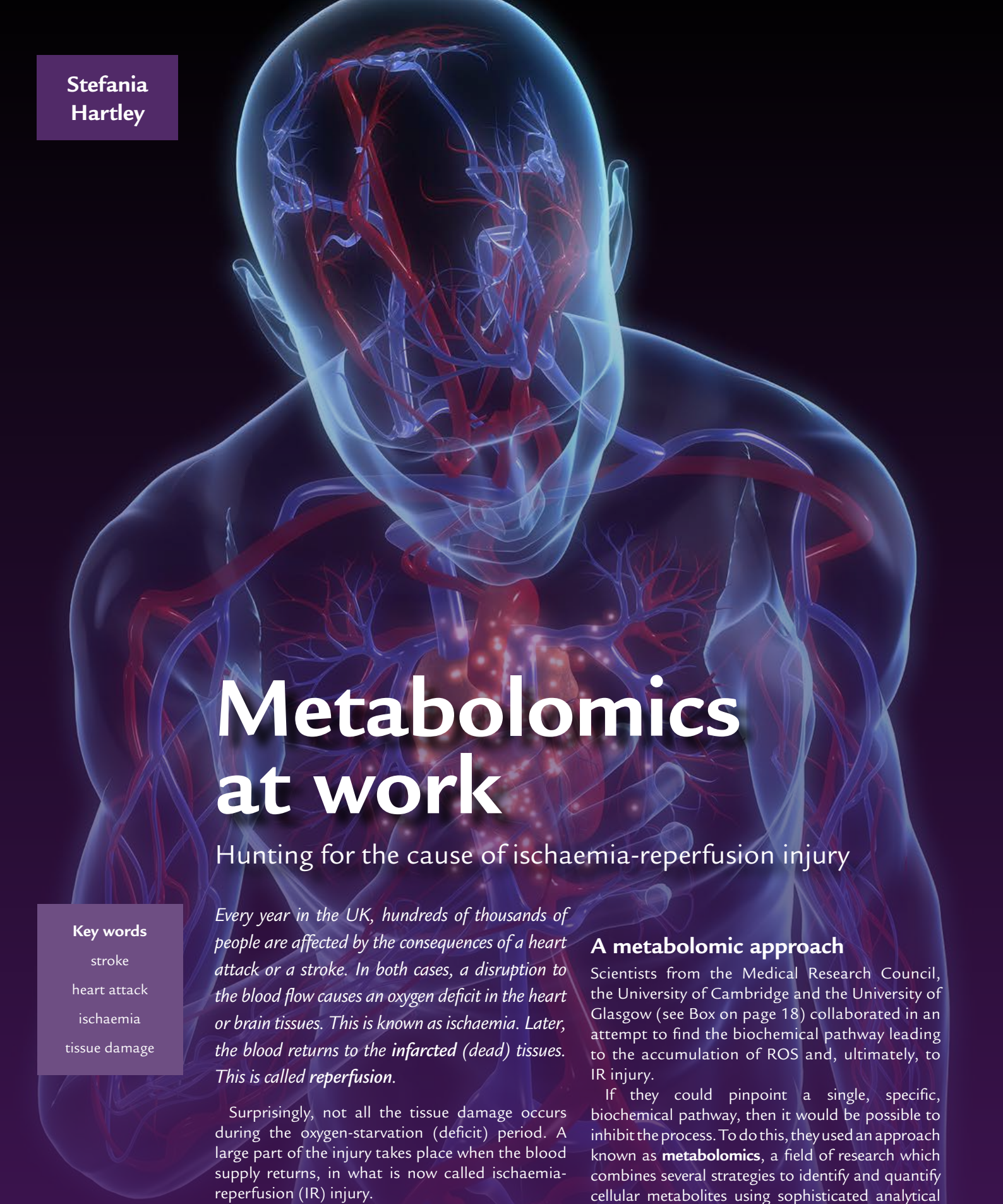
It is interesting that an already approved drug prevented the effects of CO and it could be trialled in patients presenting with cardiovascular complications where it is thought that CO might be causing the problems. Firefighters, for example, have high exposure to CO over the course of their career and this might cause heart problems.

As we said above, although a lot more research is still required in order for a potential therapy to be produced, we can still speculate about how the gases could provide a promising future to patients with neurodegenerative diseases such as Alzheimer's. For a start, carbon-monoxide releasing molecules (CORMs) are widely used in current research projects and pharmaceutical companies are working on the next generation of compounds. There are fewer molecules that can be used to release H_2S in the body to observe its effects but research groups at the University of Exeter are tackling this problem.

Most recently, a medical device capable of delivering controlled amounts of CO has been investigated in controlled medical trials. This device is aimed at respiratory disorders such as asthma; however it would be logical to speculate that similar devices could be adapted as therapeutic options to slow down neurodegenerative diseases such as Alzheimer's disease in the future. We are therefore closer to using toxic gases for the treatment of complex diseases, which re-enforces Paracelsus's adage that 'the dose makes the poison'.

Dr Mark Dallas is a neuroscience lecturer at the University of Reading, UK; Hafeeza and Vytautas are third year Pharmacy students who spent the summer in Dr Dallas's lab.

Stefania Hartley



Metabolomics at work

Hunting for the cause of ischaemia-reperfusion injury

Key words
stroke
heart attack
ischaemia
tissue damage

Every year in the UK, hundreds of thousands of people are affected by the consequences of a heart attack or a stroke. In both cases, a disruption to the blood flow causes an oxygen deficit in the heart or brain tissues. This is known as ischaemia. Later, the blood returns to the ***infarcted*** *(dead) tissues. This is called* ***reperfusion****.*

Surprisingly, not all the tissue damage occurs during the oxygen-starvation (deficit) period. A large part of the injury takes place when the blood supply returns, in what is now called ischaemia-reperfusion (IR) injury.

Reactive oxygen species (ROS) have long been recognised as the culprits for IR injury. These chemicals contain positively-charged oxygen ions which can cause damage in several different ways, such as by damaging DNA and by deactivating specific enzymes. The question, though, is why are ROS so abundant in reperfused tissues?

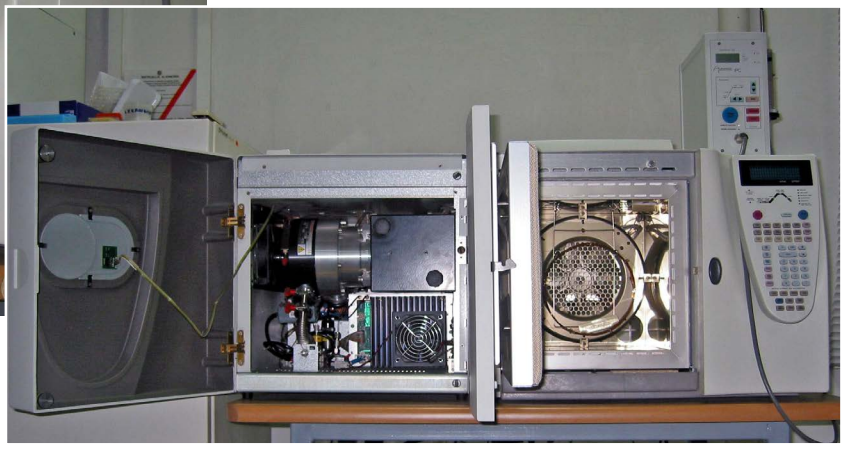
metabolite an intermediate in a sequence of chemical reactions in living cells

A metabolomic approach

Scientists from the Medical Research Council, the University of Cambridge and the University of Glasgow (see Box on page 18) collaborated in an attempt to find the biochemical pathway leading to the accumulation of ROS and, ultimately, to IR injury.

If they could pinpoint a single, specific, biochemical pathway, then it would be possible to inhibit the process. To do this, they used an approach known as **metabolomics**, a field of research which combines several strategies to identify and quantify cellular metabolites using sophisticated analytical technologies.

The teams used Liquid Chromatography and Mass Spectrometry to measure and compare levels of different metabolites in ischaemic and reperfused mouse kidneys, livers, hearts and brains, together with ones in which the concentration of oxygen was normal.

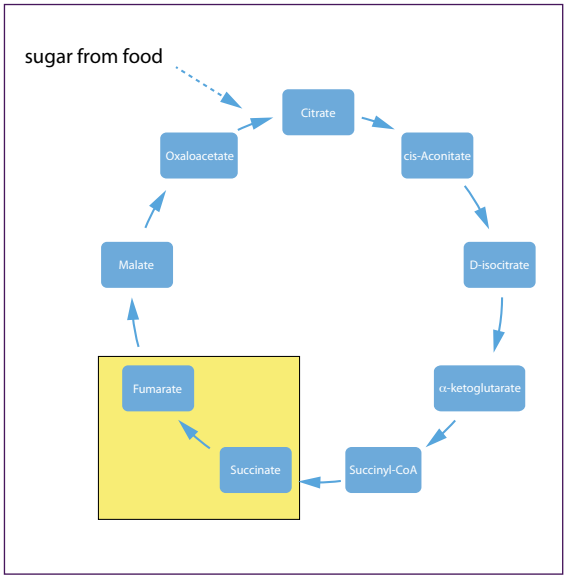


A liquid chromatography mass spectrometer (LCMS). The sample to be analysed is inserted at top right. The different substances in it are separated in the chromatography column in the oven on the right. They then pass into the mass spectrometer on the left which identifies each compound by determining its molecular mass.

The likely culprit

Only three substances were found to increase in abundance in tissues after ischaemia. One of these was succinate, which was the most interesting, because it is a mitochondrial metabolite. Succinate levels increased three- to nineteen-fold across all tissues tested, and so could be used as a chemical signature of ischaemia.

Further metabolomics tests showed that succinate accumulated in areas that were subsequently affected by IR injury and that concentrations were proportional to the duration of ischaemia. This provides confirmation of the involvement of succinate in IR injury. But where did the succinate come from?



The Citric Acid Cycle (CAC) showing the placing of succinate and fumarate

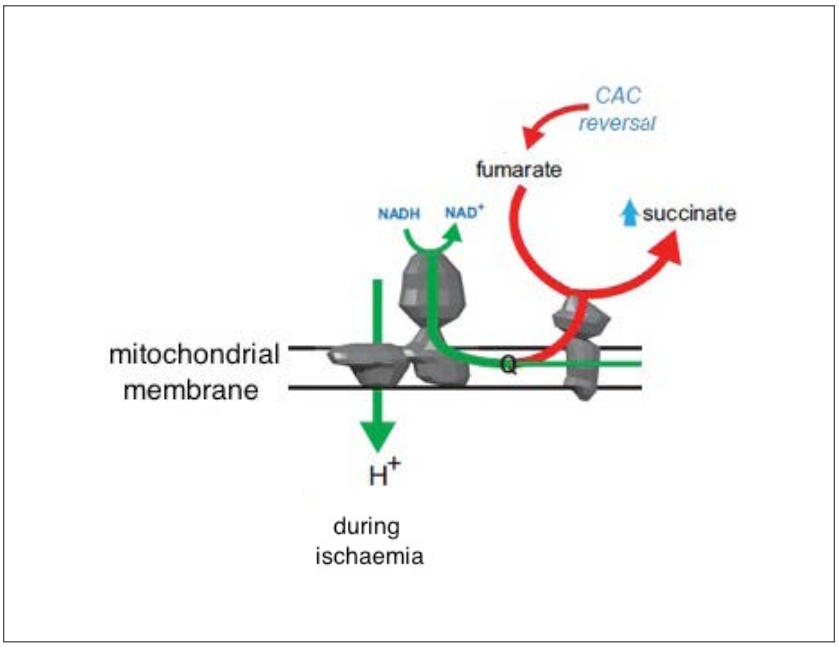
If succinate were part of the mechanism that led to IR injury, finding succinate's origin would be a step towards preventing IR injury. Succinate is an intermediary in the Citric Acid Cycle (CAC) which takes place inside mitochondria and is essential for the release of energy from food. The possibility was that, in anaerobic conditions, succinate dehydrogenase, which during the Citric Acid Cycle turns succinate into fumarate, might work in reverse. The team tested the hypothesis by inhibiting succinate dehydrogenase in mice. As expected, they found a decrease in the accumulation of succinate, as well as an improvement in the mice's scores in post-stroke neurological tests.

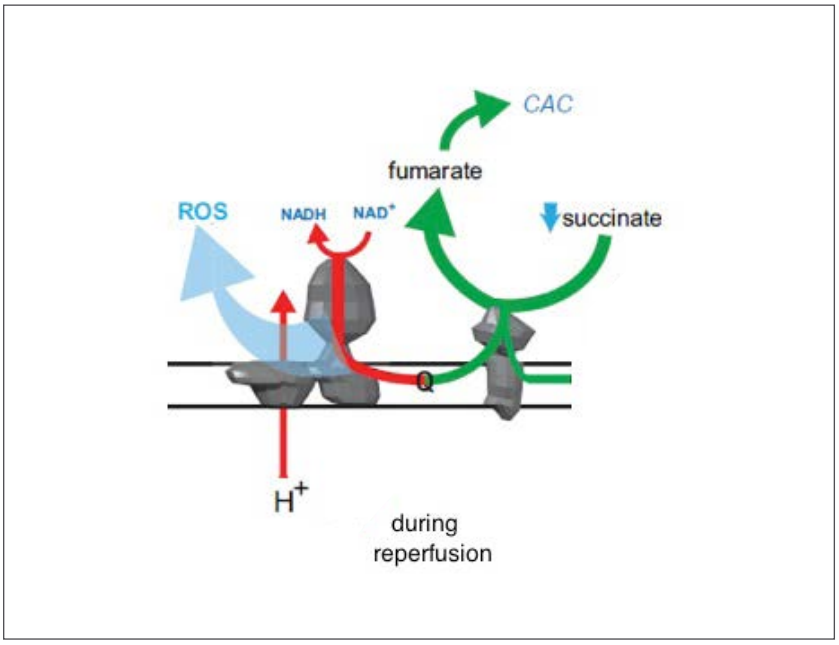
From succinate to ROS

Once it was established that the extra succinate – produced by the enzyme succinate dehydrogenase working in reverse – was somehow responsible for IR injury, the team needed to make the final connection between succinate and ROS.

The answer was to be found in the last stages of mitochondrial respiration, where a series of electron transporters bring about the production of ATP by the ATP synthase.

Computer simulations showed that, straight after reperfusion, succinate dehydrogenase turned succinate into fumarate at a speed such that the electron transporters couldn't keep up, generating an excess of protons inside the mitochondria. These attach themselves to oxygen atoms, resulting in the oxygen ions which are what make ROS so reactive.





During ischaemia the CAC (citric acid cycle) goes into reverse, generating a build up of succinate. During reperfusion the build up of succinate is removed but this leads to a build up of protons (H^+) on the wrong side of the mitochondrial membrane, thus causing the production of excess ROS and leading to all the IR damage.

Further experiments involved increasing the levels of succinate and testing for ROS with fluorescent probes. The results further confirmed the relationship between succinate levels and ROS production at reperfusion. The pieces of the puzzle had finally come together.

The good news is that inhibiting succinate production by succinate dehydrogenase is quite straightforward and cheap. The identification of a single pathway leading to IR injury has opened the way for a new therapeutic approach to dealing with IR injury.

Stefania Hartley is a science teacher living in Singapore.

Interview with Dr Richard Hartley

Dr Richard Hartley, Professor of Chemical Biology and Organic Synthesis at the University of Glasgow, is one of the co-authors of the research paper.

Which aspect of the research was contributed by your lab?

A molecular probe from my lab, MitoB, helped answer one big question in this research: dimethyl malonate prevents IR injury, but does it really do this by reducing mitochondrial ROS? To answer this, the teams needed a way of measuring mitochondrial ROS produced in vivo, and only MitoB can do this.

What are the consequences of the discovery of succinate as a key player in the onset of IR injury?

Before this work, it was believed that IR injury was a general consequence of oxygen returning to the heart or brain when the blood flow was restored. This would make it very difficult to prevent. Now we know that there is a single biochemical pathway causing the damage and that it can be stopped! At last we can see how to give people the best chance of good health after a stroke or heart attack. The race is now on to find compounds that are even better than dimethyl malonate.

Is the image of the lone scientist making new discoveries a thing of the past?

There is a place for research in a single field, but this work on IR injury needed experts in everything from chemistry to medicine. It could not have been achieved in any other way and it's a testament to Dr Murphy and Prof. Krieg that they gathered and co-ordinated such a team. I think this is a pattern for future success: big discoveries will come from scientists working together.

Try This

Conker Tree Science

Take part in real science this summer

Have you noticed our horse-chestnut trees recently? They are the trees which produce conkers each autumn, and in the spring they look fantastic with fresh green leaves smothered with white flowers. But by mid-summer the leaves may begin to look blotchy and quickly turn brown. The cause is a tiny moth with caterpillars that live inside the leaves and mine their way through – and you can undertake research to help us discover more about it through Conker Tree Science.

The leaf-mining moth is fascinating because it has spread so rapidly across most of the England and Wales over the past 13 years. It has been seen once in Scotland and it got to Ireland only two years ago. Where will it spread to this year? And how bad will the damage get in different parts of England and Wales? The only way we can do this science is with the help of people from across the country and across the summer! You can visit the website at **www.conkertreescience.org.uk** to take part and discover more. From mid-June we will launch a revamped smartphone app to make recording even easier.

The Cameraria *moth which damages the conker trees*

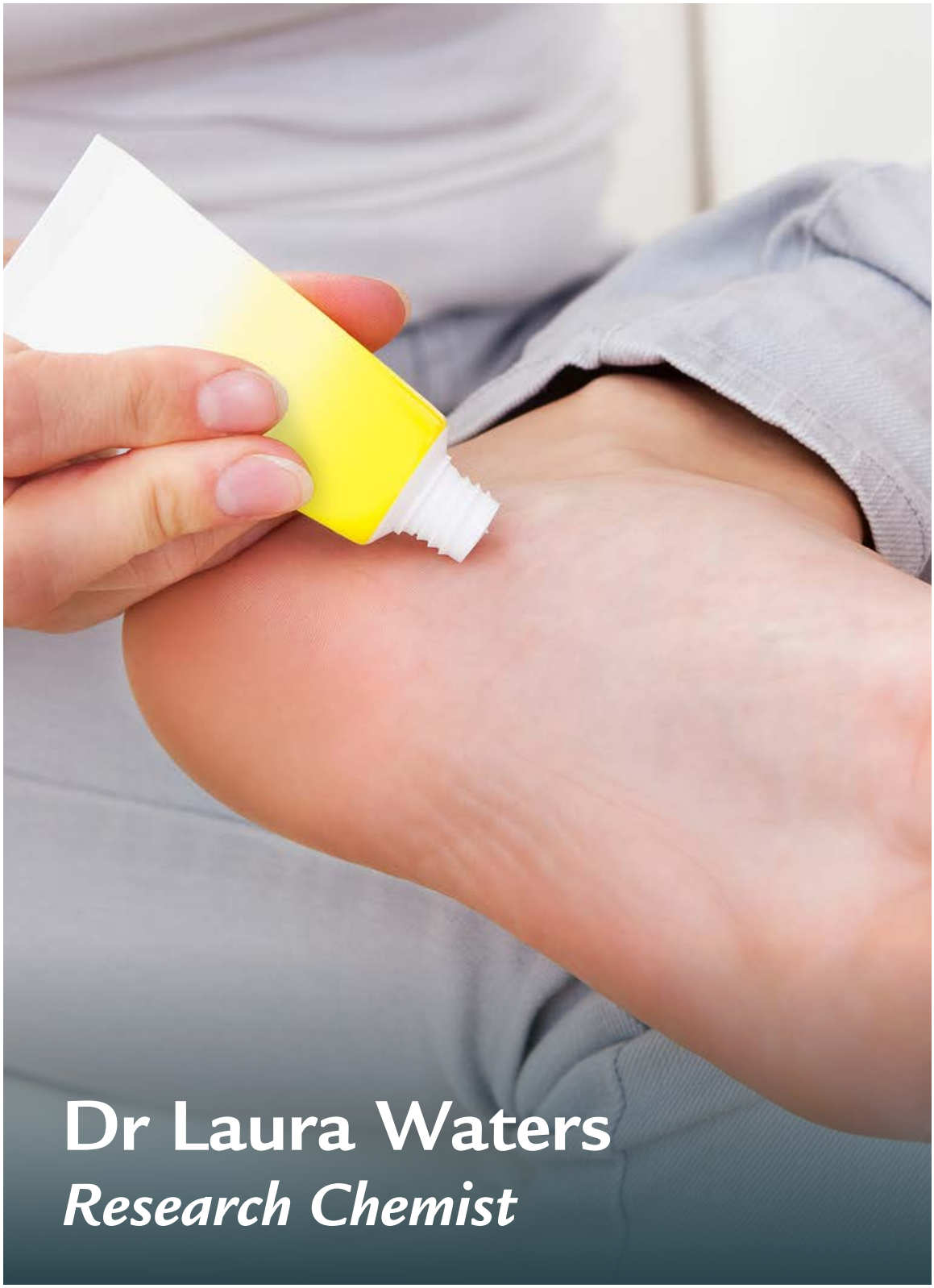
Conker leaves showing moth damage

Fruits (conkers) and leaves of the horse-chestnut, one of our most recognizable trees.

In the past few years we have run different 'missions'. The instructions are still on the website (under Take part > Missions) and are ideal school projects. Let us know if you take part in the pest controllers mission in the first week of July. You can rear your own tiny moths and see if you can find the tiny pest-controlling wasps that eat the caterpillars from the inside out!

Just to prove that this is real research, you can read about the contributions of thousands of people to this citizen science project in the past and the resulting discoveries in the freely-available scientific paper by Pocock and Evans (2014) at *http://bit.ly/1ICm7Ev*.

Michael Pocock is an ecologist at the Centre for Ecology and Hydrology.



Dr Laura Waters
Research Chemist

Laura has used chemistry to find out how much medicine will get from a cream into the body.

When I was sixteen I knew I loved learning about chemistry and understanding why reactions happened, even after burning my skin with some strong acid during an experiment at school one day! After completing my A-Levels, I studied Pharmaceutical Chemistry at university so I could understand how to make new medicines, thinking that my career was to be in industry helping develop new products. Then, whilst sitting in a lecture one day I thought that perhaps it would be fun to stay at university forever, teach others how to design medicines and also do my own research on topics I could choose.

Laura preparing to explain her work to the TV cameras

A PhD is a higher degree which is usually completed after a first degree; to be awarded a PhD you need to write a thesis which is usually around 100 000 words about research you have carried out.

To be a lecturer I needed a PhD so I headed off to London for three years and worked hard to complete my thesis on a combination of environmental and pharmaceutical chemistry. Being young and brave I applied for a lectureship at the University of Huddersfield and managed to persuade them I could be their newest recruit. So began my career as a lecturer and researcher but the main question was: What should I research?

Making a difference

The most important part for me was to feel that my research was relevant and makes a real difference in the world so now I focus on two things – firstly to make medicines that work better for patients suffering from all sorts of diseases and secondly to replace animal testing with other experiments that don't need animals to get the same answers.

Redesigning medicines is interesting as you can take a compound that does not work and turn it into a fantastic product that people can take to cure a disease or relieve unpleasant symptoms, and it can all be done using chemistry.

Replacing animal testing is just as complicated as redesigning medicines as the pharmaceutical industry insists all new products are tested on animals before they can be given to human volunteers in clinical trials. However, I'd argue that testing medicines on animals doesn't help predict what will happen when you give the same chemical to a human as they react very differently and perhaps we can obtain more relevant data by not using animals but using other options instead.

Work in progress

At the moment I have several research projects in progress. They tend to take several years to complete and require very specialised equipment. One project that I have worked on over the last few years has been to see if we can predict how much medicine will get through your skin, from something like a cream or gel, but using chemicals and computers rather than animal skin. In the end I wrote a paper that was published in a journal to show that we can predict how much will get through human skin and into your body using chemical methods only. Other on-going projects include trying to predict how much compound will be absorbed in your intestine when you swallow a tablet and again, not using animals but chemical methods.

Another aspect of my work is to communicate science to a wider audience and engage with the general public to help people understand science and appreciate why we all need to take an interest in the science around us. There are lots of ways that scientists engage with a wider audience, such as the work of STEM ambassadors, public lectures, science cafés and media work. I try to do as many of these events as I can as I enjoy inspiring others and hoping they share my passion for science. Several times I have been asked to be an expert scientist for radio programmes and more recently on television, including BBC1, BBC3 and Channel 4. The topics that I am asked to comment on range from the chemicals you would find in coffee through to ways to measure how good a moisturiser is.

Laura working in her lab at the University of Huddersfield

Coffee chemistry: in media appearances, Laura has commented on the chemicals in coffee.

Chemistry career

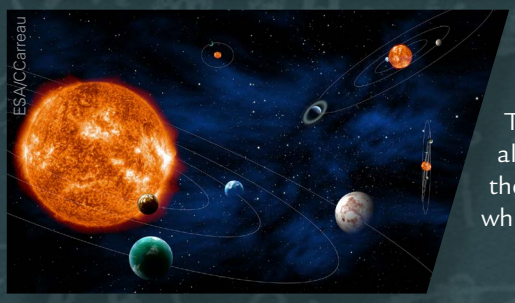
I honestly believe that being a chemist is a fantastic career, particularly as a university lecturer as there is so much variety in my work. One moment I may be teaching students how to design a new type of tablet, the next I'm working on research to understand how a cancer drug works, and then I'm filming for television.

Dr Laura Waters is a lecturer and Principal Enterprise Fellow at the University of Huddersfield.

Look here!
See Laura speak about her work on her Youtube channel: *http://tinyurl.com/lgvn2be*

TWENTY-FIVE YEARS

This is the 100th issue of CATALYST *— we have been around for 25 years. Here are some of the most significant discoveries that we have reported on in that time.*



An artist's impression of multiple planetary systems orbiting stars

1995

The first exoplanet was discovered. Now astronomers have identified almost 2000 planets orbiting stars other than the Sun. It is estimated that there are over 10 billion Earth-like planets in the Milky Way galaxy alone which might harbour life.

1997

The first mammal to be cloned was Dolly the sheep, the result of work at the Roslin Institute near Edinburgh. Today, geneticists are trying to produce improved strains of farm animals and poultry as well as to recreate extinct species such as the mammoth.

The announcement that a sheep had been cloned for the first time aroused great media interest.

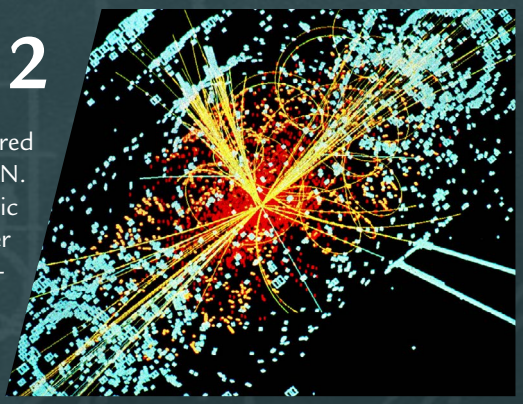
The results of the Human Genome Proaject were published in the scientific journal Nature in February 2001.

2001

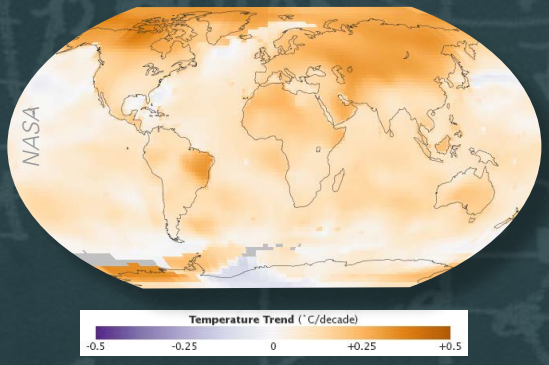
The human genome was sequenced for the first time, a mammoth effort involving scientists from over 20 institutes. DNA sequencing is now much faster and cheaper. The UK's 100 000 Genomes Project will sequence 100 000 whole genomes from NHS patients by 2017.

2012

The Higgs boson was discovered using data gathered by experimenters at the Large Hadron Collider, CERN. This confirmed the current theory of sub-atomic particles and the forces between them. The collider has now been overhauled, allowing for higher-energy collisions to be studied.



A simulated collision in the CMS detector of the Large Hadron Collider. Data from 6 quadrillion collisions were analysed.



This map shows the rate of increase of the Earth's surface temperature between 1950 and 2014.

2014

The fifth report of the Intergovernmental Panel on Climate Change (IPCC) studied all the available evidence and confirmed that carbon dioxide released when fossil fuels are burned is the major cause of global warming. They called for more urgent action on the part of governments around the world.

You can read over 350 articles from previous issues of CATALYST on our website: http://www.catalyststudent.org.uk