Bang!

The Modern Medicine Issue

Oxford Science Magazine
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Trinity Term 2013

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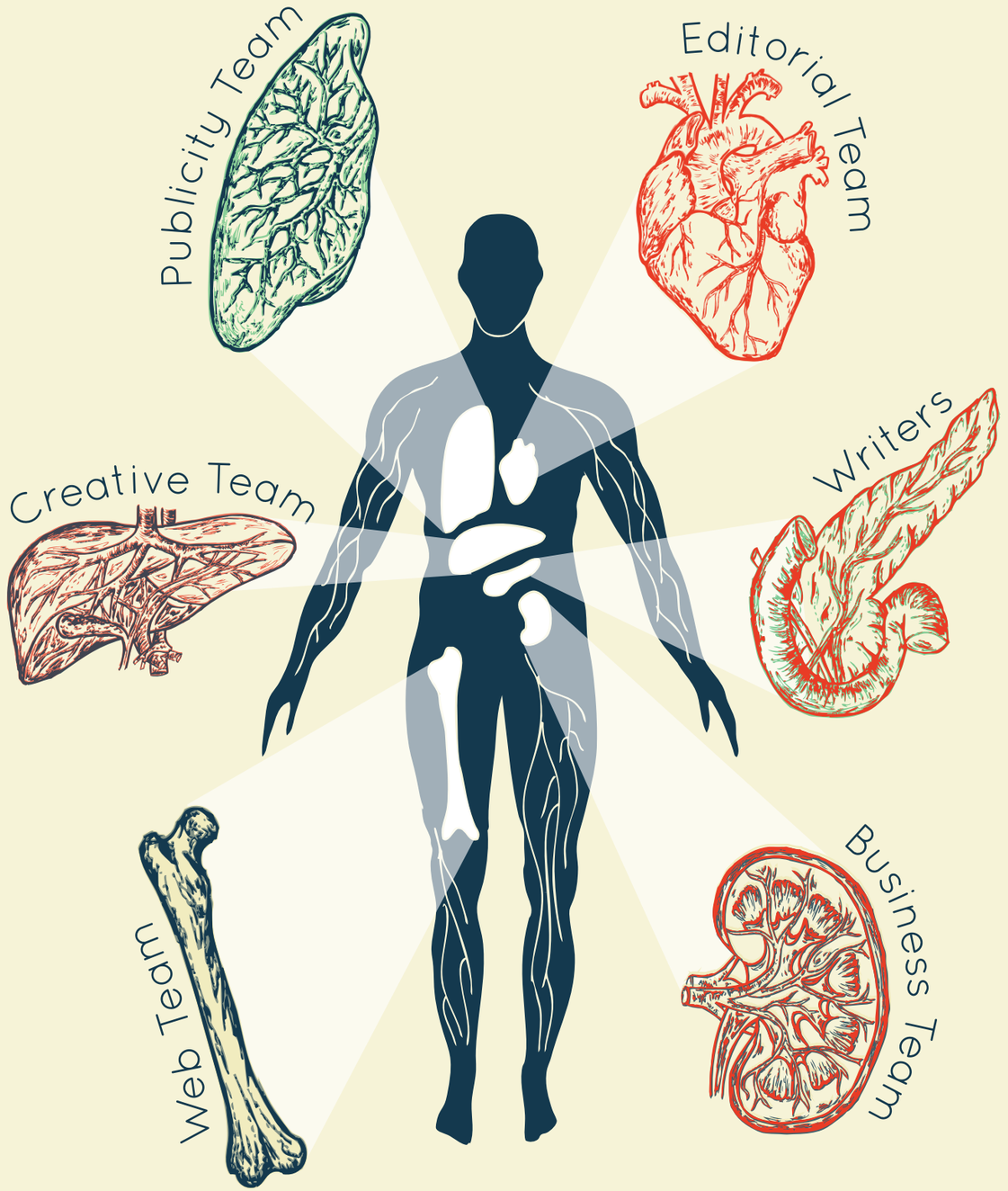

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Editorial

A little while ago I visited the Wellcome Collection in London. The collection itself consists of medical curiosities from throughout history, amassed by the Victorian entrepreneur and traveller Sir Henry Solomon Wellcome. Glass cabinets display everything from ancient offerings to the gods of health, through to devices which must have seemed cutting-edge to Wellcome, such as some rather clunky early 20th century prosthetics.

As you leave the collection, you step into an adjacent room containing a small exhibition on modern-day medicine. It has been less than 80 years since the death of Wellcome, yet the contrast between the two rooms could not be greater. Here you can marvel at a bookcase containing the entire sequence of the human genome, or view high-resolution images of the brain. I couldn't help but ask myself what Wellcome himself would have made of all this. Just eight short decades ago, we did not even know how genetic information was encoded, and the idea that we could look at the inside of a living human's brain must have seemed fanciful in the extreme.

It is this sense of the incredible and the ultramodern that pervades the current issue of *Bang!* magazine. You will read of the successful transplantation of artificial organs and the use of contact lenses which regenerate damaged corneas. You will learn about drugs which regulate how our genes are expressed, and research that harnesses modern means of communication in the hope of finding a cure for cancer. These advances in medical science sound like something out of science fiction, yet, in the past few years, they have become a reality.

Modern medicine is also about finding novel approaches to treating illness where the existing methods are not adequate. This is not always easy. I had the pleasure of interviewing Professor David Nutt, who is conducting research into the use of illegal drugs for treating mental disorders. He has encountered many obstacles along the way, but his message is clear: we desperately need new psychiatric drugs, and this is a way forward. Sometimes medicine has to turn to more unusual sources for solutions.

Perhaps the next 80 years will see developments in medicine that are as mind-boggling as those of the past eighty, and maybe by then our artificial organs and miRNA-regulating pills will exist only in glass cabinets in museums. But for now, I hope that you take away from this issue of *Bang!* magazine some sense of wonder at just how far medicine has come.

Matthew Warren
Editor

News

Sea change

New research has implied that rising sea levels due to climate change will not be as dramatic as feared. A team of scientists called Ice2sea comprehensively assessed the existing data, analysing rises in sea level and global temperature changes, with reassuring results.

The researchers modelled changes in sea level by assuming that carbon dioxide emissions will continue to rise rapidly until the century's end. They created sophisticated models to quantify some previously unexplored factors, particularly the effect of the ocean itself on ice sheets' melting. They concluded that melting ice sheets will add 3.5–36.8cm to sea levels by 2100. The results will be a relief to the Intergovernmental Panel on Climate Change (IPCC), who were deemed hopelessly optimistic when they suggested that the maximal change in sea levels would be 59cm.

The IPCC will publish Ice2sea's research, allaying previous fears that sea levels could rise by as much as two metres, which would be catastrophic for populations across the world. With the consequences of climate change set to impact the entire globe, any indication that changes may be controllable will surely be met with hope by governments worldwide, as they seek to limit the future damage.

Probing the causes of congenital heart disease

Congenital heart defects are relatively common in our population: thousands of babies are born each year with such problems. These are often reparable, but in some instances have severe and lasting consequences for the child's quality of life. Published in *Nature* this month, the world's first large-scale genetic analysis of families pinpointed a major cause of congenital heart malformations.

Over 600 families participated in the study, including 362 families with two healthy parents who had a child affected by heart problems. The members of these families had their genomes sequenced and compared, before overall comparison with 264 'control' families, who had neither a history of heart disease nor children with congenital defects. The children who had congenital heart malfunctions were found to have modifications in their DNA that were not present in the healthy parents; these spontaneously arising *de novo* mutations are thought to account for 10% of heart defects in newborns.

The mutations were present in several hundred different genes, but crucially were clustered in a regulatory pathway involved in activation of critical developmental mechanisms. These genetic alterations change developmental gene expression, pathologically remodelling the heart's structure.

Using modern sequencing techniques, results like this allow scientists to home in on the molecular 'keys' of disease, with the potential to unlock ever-more sophisticated treatments as our understanding continues to grow.

Speeding up drug development

Currently our drug development process is somewhat prolonged, to say the least. On average a drug takes ten years and over a billion pounds to reach the market, an uncomfortable fact against the backdrop of other advances in medicine worldwide. Work being done in Oxford is aiming to speed this up, with obvious benefits both for patients and the pharmaceutical industry.

The University's Professor Adrian Harris is behind a pioneering new type of trial, undertaken with the support of Cancer Research UK. Essentially the development process is accelerated by shortening the time between the usual phase I initial tests (testing the drug in isolation) and subsequent 'arms' of the trial (combining the drug with existing cancer treatments). The drug under scrutiny in this new approach is called AZD0424, and researchers have been granted a new degree of flexibility in their tests: there will be three concurrent prongs during the process.

Each of these approaches pairs AZD0424 with an established cancer drug already in use clinically. As Harris explains, "...the drug may be effective on its own, [but] we expect substantial synergy in combinations". The real hope in this testing technique therefore lies in the refinement of the various combinations of old and new cancer drugs, which should yield higher therapeutic benefit. Such tweaks to the current system could revolutionise drug development and therefore quality of patient treatment.

Sophie McManus is a 2nd year Biomedical Sciences student at Magdalen College.

Art by Camille Fenton.

Bang! Explains: The Badger Cull

A beloved and iconic species, the European badger (*Meles meles*), has divided opinion amongst scientists and policy makers since the first *Mycobacterium bovis*-infected badger was discovered in England in 1971. The incidence of Bovine tuberculosis (bTB), an economically costly disease, has been rising for over a decade in Britain, resulting in the slaughter of 37,753 cattle in 2012. For decades scientists have been researching the contribution of badgers to the spread of bTB to decide whether culling really is the most effective control available to us. Thus far, science has not provided us with conclusive answers. Are badgers the loveable "Wind in the Willows" characters we want them to be, or is a widespread cull justified?

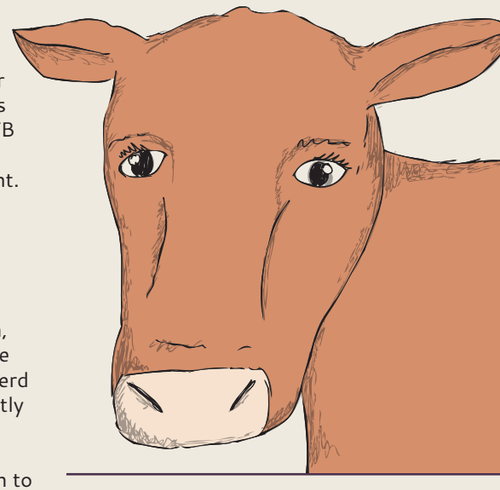
In 1997, the government commissioned an independent review which recommended implementation of the Randomised Badger Culling Trial (RBCT) to test and quantify the impact of badgers on the spread of bovine tuberculosis. Nine years and £50 million later, it was found that proactively culling badgers resulted in a 23.2% reduction in the incidence of cattle bTB within the trial area. However, the mapping of badger home ranges has shown that badgers flee to surrounding, unculled areas, the 'perturbation effect', causing a 24.5% increase in cattle bTB immediately outside of the culled area. The estimated net impacts of culling were initially detrimental, becoming beneficial after the fourth and later culls. There were also no long-term benefits associated with the cull, as beneficial effects were undetectable just three years after the trial.

In 2011 it was concluded that culling 70% of badgers over a larger area could cause a reduction of cattle bTB incidence of up to 16%, but not everyone is convinced that this figure justifies a cull. In spite of some major opposition, pilot culls will begin in west Gloucestershire and west Somerset in the summer of 2013, where around 5,000 badgers will be killed by free-shooting over the next four years. However, uncertain badger population densities undermine the feasibility of accurately meeting the 70% target. The significant differences between the timescales and methodologies of this culling programme and the RBCT introduce much uncertainty into its outcome.

Although we cannot deny that badgers carry and transmit bTB, cows themselves are also to blame. When a herd experiences a case of bTB, despite subsequently undergoing tight controls and intensive testing, the disease often recurs within 12 months. Not only is this reflective of the imperfect sensitivity of the testing programme, but also of the many missed routine tests and delays in removing infected cattle from farms. A model of the number of cattle movements in a region has been shown to predict 84.5% of bTB incidence, supporting the case for stricter controls on cattle movement. Pathogen genome sequencing combined with modelling has also shown that subsequent outbreaks on a farm tend to involve the same pathogen lineage ('spoligotype') previously detected in that location, which suggests that some cases are consistent with extensive within-herd transmission occurring independently of badgers.

Badger vaccination has been shown to reduce the likelihood of developing a positive test result by 76%, but it has been argued that applying the vaccine over large areas would be difficult and expensive due to the lifestyle of badgers. We do not have this problem with cattle as they are easily tagged and monitored, making vaccination relatively simple. However, vaccination is currently banned by EU law as all vaccinated cattle would fail the current bTB test and thus couldn't be traded, although a new 'DIVA' (Differentiation of Infected from Vaccinated Animals) test is now awaiting approval, which would solve this issue.

With over 200,000 people having signed a government e-petition against the cull, the policy is under heavy attack. Unfortunately it is badgers that will be bearing the brunt of the many flaws of this programme; although they are not innocent, they are also not the evil menace that is being portrayed. The government has managed to flout both public opinion and scientific evidence; a risky move, and a potentially disastrous distraction from TB control across England.



Sarah Earle is a 3rd year Biological Sciences student at Hertford College.

Art by Natasha Lewis.

Size isn't Everything

How the 'hobbit' got its height

In 2003, a team working on the small Indonesian island of Flores discovered the fossil remains of a 3'6" tall member of the *Homo* genus. *Homo floresiensis,* predictably dubbed the 'hobbit', has puzzled anthropologists with its unusual combination of human and ape-like traits and remarkably small body size. Since the discovery of the 'hobbit', there has been much debate over how long ago this population diverged from other members of the *Homo* genus, and how it ought to be classified.

Some authors suggest that the Flores fossils represent an isolated group of *Homo sapiens* who suffered from some pathological condition, such as severe thyroid problems. However, others have pointed out the fossils' striking dissimilarities from all other members of the human species, and propose instead that the bones come from an older species of *Homo* for whom small body size was an evolved adaptation to local conditions. If small body size was the result of adaptation rather than pathology, what advantages might it have afforded? To help answer this question we can look for clues both within and between living species.

There is a surprising amount of variation in stature between populations of modern humans. Although some of this variation can be explained by environmental and nutritional differences, much of it is genetically determined. While no modern populations are as short as *floresiensis*, a number of human populations across the tropics have an average adult stature of less than 5' for men and 4'6" for women. Many hypotheses have been advanced to account for this variation. For example, it has been suggested that short stature may afford thermoregulatory advantages or allow greater ease of movement through dense forest. Alternatively, a short height may have been encouraged through sexual selection. Although compelling, such hypotheses either lack empirical support or have failed to account for the diversity of environments in which short stature is found.

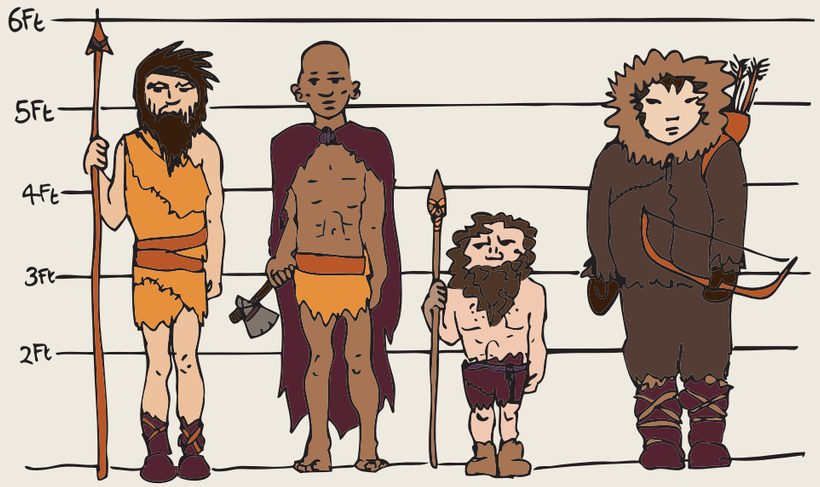
An alternative account of small body size in humans has been proposed by Andrea Migliano and colleagues. They found that short populations experience an early cessation of growth, rather than slower growth in general, and that many other so-called 'life history' events (such as menarche, puberty, and menopause) also occur earlier. Critically, the researchers found that these populations also experience high mortality rates. They suggest that early development is a response to these high death rates: in risky and unpredictable environments where a long adult lifespan is not guaranteed, those who 'cash-in' on early reproduction at the expense of growth are rewarded. Thus, they propose that small body size is not advantageous in itself, but is a by-product of a 'live-fast, die-young' reproductive strategy. The relationship between body size and reproductive strategies is also clear across species. Organisms with a large body size tend to live a long time and have fewer offspring, in whom they invest much time and energy. Elephants are simply too big and energetically expensive to breed like rabbits.

So why is *floresiensis* so vertically challenged? Given our understanding of body size variation between and within species, it seems likely that its short stature is a by-product of life in the fast lane, rather than a direct adaption to a specific stressor such as a hot climate or dense forest. Although we cannot establish what the mortality rates were for the extinct *floresiensis* population, modern indigenous people living in the region have some of the highest mortality rates in the world. They also rank among the shortest.

The evolution of small bodied creatures provides an example of how important compromise and trade-offs are in shaping the organisms we see around us, both alive and, in the case of *floresiensis*, extinct. In other words, natural selection is not always a perfecting process. Being the 'fittest' is often about making the best of a bad job.

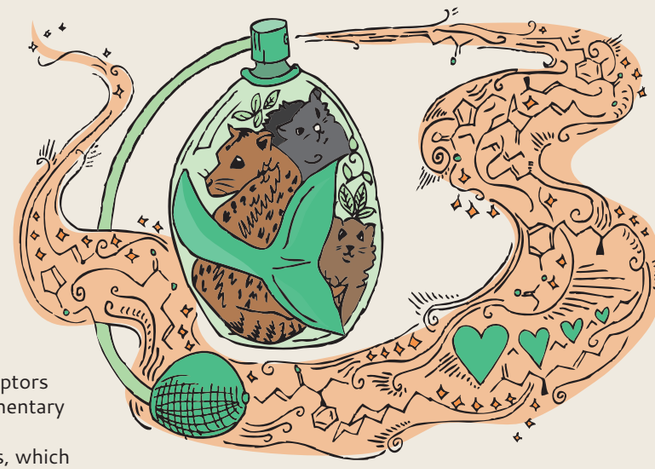
Mark Dyble studied at St Catherine's College. He is currently studying for a PhD at UCL on the evolutionary ecology of hunter-gatherers.

Art by Hannah Buckley .



Talking Scents

The science of perfumery



Whether a science or an art form, perfumery is a hugely successful sector of the beauty industry, with annual sales at around £640 million in the UK alone. As consumers, we are faced with scantily clad celebrities and taglines no one seems to truly understand, all in the name of fragrance advertising. But behind the glitz and glamour, the perfume industry has a few surprises up its sleeves. From the bizarre ingredients of the past to new artificial equivalents, the science of olfaction has had a huge impact on fragrance production.

But where do the scents used in perfumes come from?

The African civet marks its territory with a potent, long lasting scent, highly valued as a perfume ingredient, most famously in Chanel No. 5. Unfortunately for the civet, it used to be extracted by scraping the secretion from the creature's anal glands, often whilst it was still alive. Since the animal is now an endangered species, synthetic and natural equivalents have been developed. One such substitute, hyraceum, is made from the fossilised faeces of another African mammal, the Cape hyrax.

Ambergris comes from the intestinal secretions of a sperm whale, which have hardened whilst drifting at sea. Initially having a pungent, unpleasant odour, the substance develops a sweet earthy scent once it has aged sufficiently. Despite its bizarre origin, ambergris can be found in Dior Poison, Vera Wang Princess and Gucci Guilty.

With advances in modern chemistry, many of these weird and wonderful ingredients have been replaced with synthetic counterparts since natural derivatives can be expensive or difficult to obtain. However, to recreate a certain scent, chemists still have to trawl through hundreds of molecules before finding the right one. By developing a general theory relating the structure of a molecule to the way we perceive its odour, we can accelerate the process of finding the highest quality fragrances.

Shape theory is based on the concept that chemicals and receptors consist of complementary and highly specific geometrical shapes, which bind together to form a complex. In 1991, the Nobel Prize was awarded to olfactory researchers Linda Buck and Richard Axel, who identified protein receptors, working as olfactory sensors, in the noses of mice. This gave valuable insight into the mechanism of smell; since all known types of this protein receptor were understood to work using the complementary shape mechanism, it was assumed smell receptors identify different smells in the same way.

Despite a multitude of studies, shape theory is yet to demonstrate any significant success in predicting how a molecule smells. An alternative is vibrational theory, which suggests that rather than the shape of molecules being important, it is their characteristic spins, stretches, twists and waggles that affects how we perceive their fragrance. The olfactory receptor contains an electron acceptor site and an electron donor site. These sites have different energy states so an electron cannot move between them. If the olfactory molecule reaching the receptor vibrates at the correct frequency, then this allows an electron to tunnel through to the acceptor site, overcoming the difference in energy state. This initiates a neural response and the molecule is recognised as a certain smell.

When a hydrogen atom in a molecule is replaced with heavier deuterium, the molecule vibrates more slowly whilst its shape remains the same. Vibrational theory predicts that organisms can differentiate between the two molecules. A 2011 study supported this assertion, showing that flies avoided deuterated versions of compounds normally known to attract them. However, vibrational theory does have its limitations, in particular when it comes to optical isomers, compounds that are mirror images of one another. Since the bonds contained within two isomers are identical, vibrational theory predicts that the molecules should smell the same, yet one isomer of the molecule carvone smells clearly of caraway whilst the other smells of spearmint.

The scientific community remains divided on which theory is more accurate, and for now, the elusive nature of scent remains a conundrum. Despite this, the field of olfactory exploration looks to be on the brink of serious expansion. With new advances, we can anticipate faster, cheaper perfume production. Perhaps we can look forward to even more radical fragrances on our shelves and inevitably, even more scandalous adverts to showcase them.

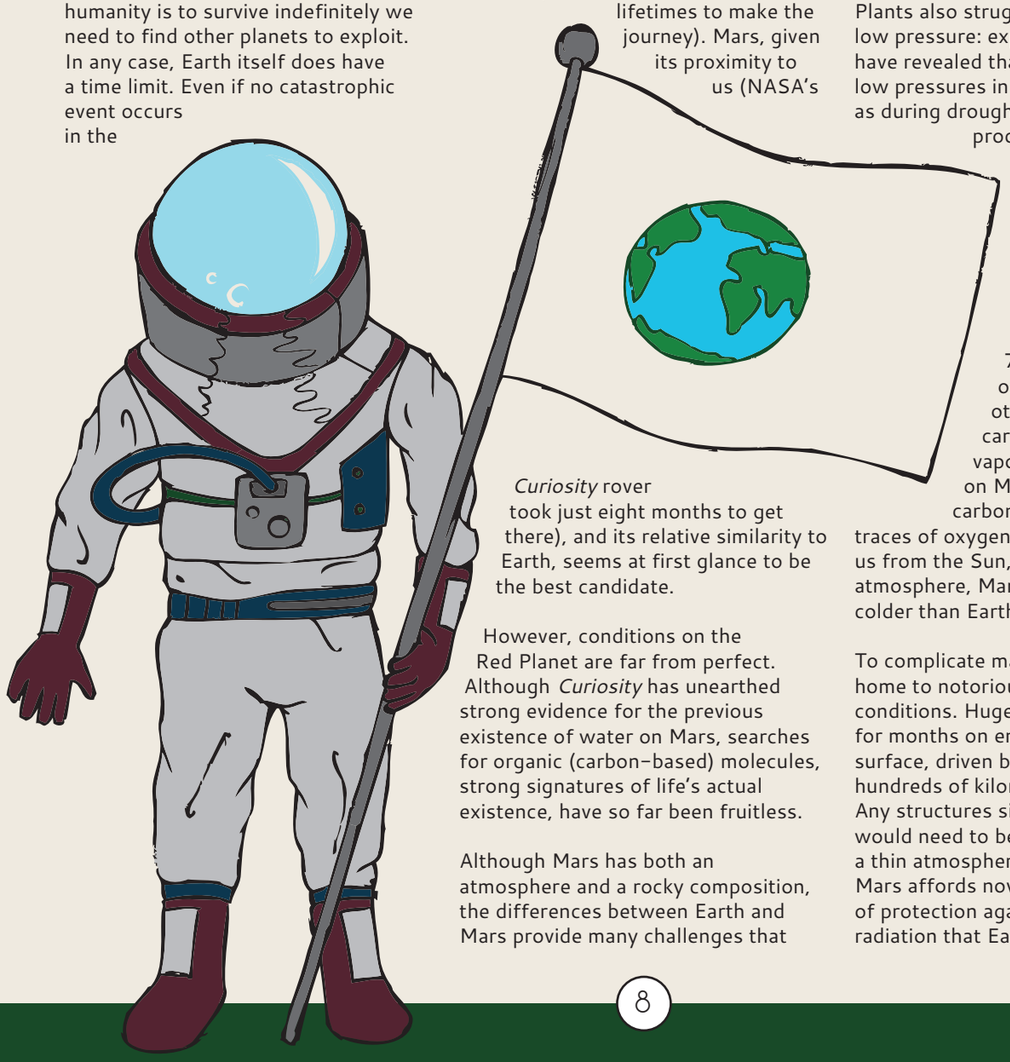
Eleanor Thurtle is a 1st year Chemistry student at Pembroke College.

Art by Hannah Buckley .

The Only Way is Mars

How we could colonise Mars with the help of reality TV

Many reputable scientists and prominent figures, especially over the last century, have spoken about the necessity of extraterrestrial colonisation. Some consider establishing a settlement on another planet vital to ensure the ongoing survival of the human race. Stephen Hawking cites the immediate threats of natural disasters and warfare as reasons to expand our territories into the Universe, and science fiction writer Larry Niven once remarked: "The dinosaurs became extinct because they didn't have a space programme." For others, the natural resources offered by Earth are simply too limited, so if humanity is to survive indefinitely we need to find other planets to exploit. In any case, Earth itself does have a time limit. Even if no catastrophic event occurs in the meantime, the eventual expansion of the Sun in approximately seven billion years will make Earth far too hot for life to survive.



> "What if we could physically adapt the conditions on Mars to suit us? Incredibly, this is not as far-fetched as it might sound, and is called terraforming"

The sheer size of the Universe immediately makes our search for a new home rather difficult; even our nearest neighbouring star, Proxima Centauri, is over four light years away (currently, it would take thousands of lifetimes to make the journey). Mars, given its proximity to us (NASA's *Curiosity* rover took just eight months to get there), and its relative similarity to Earth, seems at first glance to be the best candidate.

However, conditions on the Red Planet are far from perfect. Although *Curiosity* has unearthed strong evidence for the previous existence of water on Mars, searches for organic (carbon-based) molecules, strong signatures of life's actual existence, have so far been fruitless.

Although Mars has both an atmosphere and a rocky composition, the differences between Earth and Mars provide many challenges that must be overcome before we can move in. For example, the average atmospheric pressure on the surface of Mars is only 6.1 millibars, compared to over 1,000 millibars on Earth. At such low pressure, water can easily boil or freeze upon small fluctuations in temperature, which makes life precarious for anything that depends on (or consists largely of) liquid water. Plants also struggle to survive at low pressure: experiments by NASA have revealed that plants respond to low pressures in the same manner as during droughts, by desperately processing large quantities of water very inefficiently. Then there is the atmospheric composition. While Earth's air is fairly oxygen-rich, containing 78% nitrogen, 21% oxygen, and traces of other gases, including carbon dioxide and water vapour, the atmosphere on Mars consists of 95% carbon dioxide, with only traces of oxygen. Being further than us from the Sun, and with a thinner atmosphere, Mars is also significantly colder than Earth.

To complicate matters further, Mars is home to notoriously extreme weather conditions. Huge dust storms lasting for months on end race across the surface, driven by winds blowing at hundreds of kilometres per hour. Any structures sitting on the surface would need to be strong. Having such a thin atmosphere also means that Mars affords nowhere near the level of protection against hazardous solar radiation that Earth so kindly provides, so extra steps to protect residents would be required.

Rather than designing structures to cope with the adverse conditions on the fourth rock from the Sun, what if we could physically adapt the conditions on Mars to suit us? Incredibly, this is not as far-fetched as it might sound, and is called 'terraforming'. Terraforming Mars might not actually be too difficult, because changing one of the physical characteristics of the planet is likely to influence many others.

Many billions of years ago, the conditions on Earth were very similar to those currently on Mars. We have natural processes to thank for making our own planet inhabitable, and the aim now is to replicate and accelerate such processes on Mars.

Several plans for how we might go about terraforming our planetary neighbour have been discussed. One idea involves using giant mirrors to reflect radiation back onto the Martian surface, which would release the frozen carbon dioxide at the south pole, creating a thicker atmosphere. The same result could also be achieved by adding greenhouse gases to the atmosphere manually, by importing them from other planets or releasing them from chemical reactions in factories on the Martian surface. Thickening the atmosphere would not only increase the surface pressure, but also increase temperatures while simultaneously providing more shielding from solar radiation. Overall, Mars would become better able to support water, and far more comfortable for life.

> "Believe it or not, the entire enterprise of colonising Mars looks set to become the subject of a reality TV show"

Believe it or not, the entire enterprise of colonising Mars looks set to become the subject of a reality TV show. The bold *Mars One* project, which somewhat ambitiously aims to establish a human colony on Mars by 2023, claims to have "developed a precise, realistic plan based entirely upon existing technologies", that is "both economically and logistically feasible". Turning the venture into a reality TV show is crucial; raising the initial $6 billion required just to get the first four astronauts onto Mars will largely be achieved by generating unprecedented international media interest and publicity.

The plan is to televise the entire process, from the training and selection of the contestant astronauts, right through to living on Mars. Although it might sound bonkers, the project has the backing of both the Nobel Prize winning physicist Prof Dr Gerard 't Hooft, and Paul Römer, one of the original creators of "Big Brother".

In order to prove that the permanent settling of humans on Mars is possible (as well as slashing the initial $100 billion estimated cost), the mission is only intended to be one-way. No return flight is planned for the brave astronauts. Any reader desiring interplanetary fame and a permanent extra-terrestrial new home is in luck: applications for *Mars One* contestants are now open. Personally, though, I'll be waiting to see how life on Mars takes off before joining them.

MARS ONE MISSION

2013: selection process begins

2014: preparations for the 2016 supply mission are made

2016: supply mission, carrying supplies and spare parts, will launch in January and arrive in October approximately where the settlement will be constructed

2018: a rover, similar to *Curiosity*, will be sent to find the ideal spot to establish the settlement

2021: all the necessary equipment to construct the settlement for the first four astronauts will be sent to Mars

2022: first four humans are sent to Mars

2023: arrival on Mars, followed by five cargo missions. The new residents of Mars build accommodation in anticipation of the next team

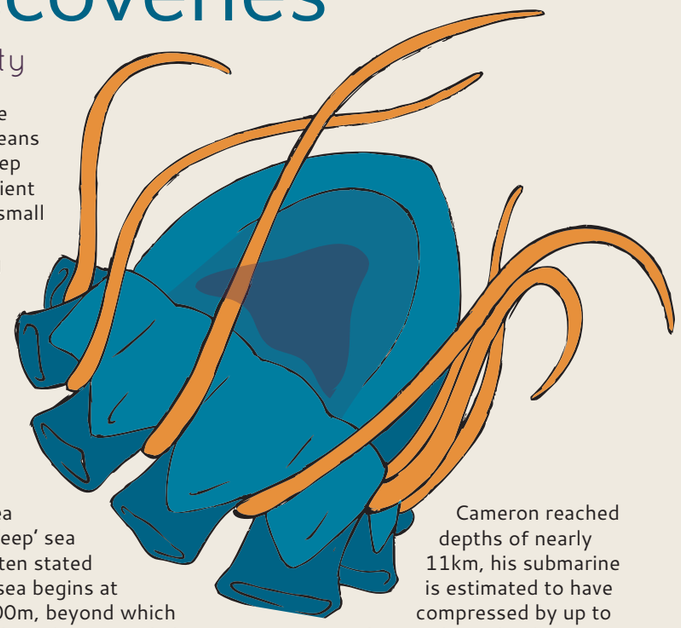
2025: the second team of four astronauts arrives

Jeremy Libre is a 3rd year Physics student at Oriel College.

Art by Joy Aston.

Deep-Sea Discoveries

An underwater world of opportunity



Recently my childhood dreams were shattered when I discovered that NASA excludes anyone over 193cm from becoming an astronaut. As a 198cm giant I am never going to get the opportunity to go into space! I have therefore had to reconcile myself with the fact that if I really want to find alien life I am going to have to follow in the footsteps of James Cameron and explore the weird and wonderful realms of the deep-sea.

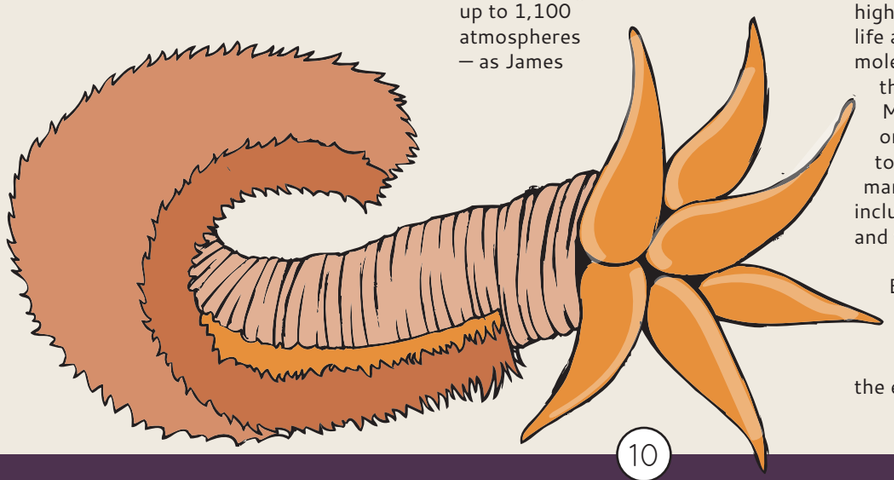
Over the last few decades, deep-sea exploration has benefitted from something of a renaissance, whilst funding for space exploration has been steadily decreasing. In both cases we watch with bated breath as our intrepid explorers disappear into the realms of the unknown. We wait to discover what hidden treasures have been unearthed and how we might be able to manipulate these riches for our own gains. Space travel has given us mobile phone technology, satellite imaging, Teflon and even the possibility of colonising another planet. So what does the deep-sea have to offer us in order to justify this reversal of fortunes?

> "The deep-sea is probably the most extreme environment on Earth and indisputably the largest"

The deep-sea is probably the most extreme environment on Earth and indisputably the largest. The oceans represent a steep ecological gradient with relatively small differences in depth requiring organisms to develop completely different combinations of adaptations, thus making it difficult to define where the 'shallow' sea ends and the 'deep' sea begins. It is often stated that the deep-sea begins at a depth of 1,000m, beyond which there is a complete absence of light.

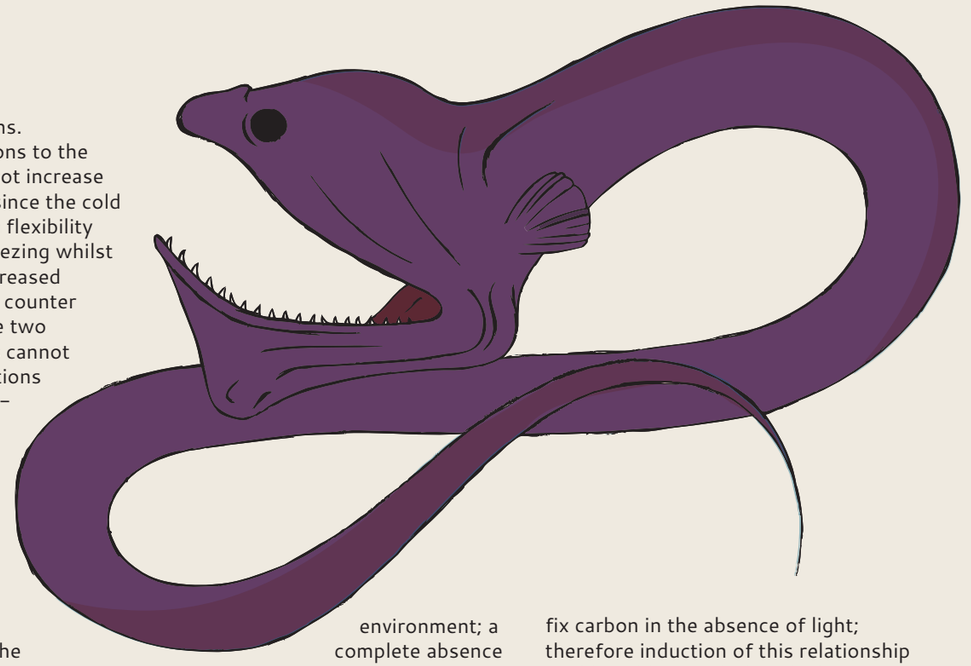
However, for the purposes of our story we need to skip a few kilometres and descend to the Abyssal Plain and beyond.

The Abyssal Plain is a single ecosystem that lies beneath the oceans at a depth of 4-6km, covering roughly 30% of the Earth's crust. Beyond the Abyssal Plain we descend into the Hadal Zone, characterised by extremely high pressures of up to 1,100 atmospheres – as James Cameron reached depths of nearly 11km, his submarine is estimated to have compressed by up to three inches. The deep-sea is also notably inhospitable as a result of the near freezing water temperature which mirrors that of the poles – the cold water of the Arctic and Southern oceans is denser than the warmer waters of the world's other oceans and therefore sinks to the bottom. This fact, coupled with a complete absence of light, means that the average water temperature at the bottom of the ocean is around 2˚C.



Whilst it might appear as though these conditions make the deep-sea completely uninhabitable, it is in fact an environment that is teeming with life. Organisms have had to become highly specialised in order to cope with life at depth and it is these, largely molecular, specialisations that make the deep-sea worth exploring. Many adaptations of deep-sea organisms have the potential to provide solutions to some of mankind's most critical concerns, including potential cures for cancer and ways of increasing food security.

Both high pressures and low temperatures alter the way that proteins fold, thus affecting the shape of enzymes and reducing the efficiency of physiological processes within organisms. Unfortunately, modifications to the proteins themselves will not increase the efficiency of folding, since the cold requires increased protein flexibility to resist the effects of freezing whilst high pressure requires increased protein rigidity in order to counter compressive forces. These two antagonistic requirements cannot be reconciled by modifications to the protein itself. Deep-sea organisms have therefore developed a high concentration of molecules known as 'molecular chaperones' which bind to proteins as they are produced and cause them to fold optimally. Molecular chaperones that counter the effect of high pressure and of low temperature can be found within the same organism thus reconciling the two opposing requirements of flexibility and rigidity. These molecules have the potential to form the basis of effective anti-cancer drugs by 'detoxifying' mutations that produce misfolded proteins that can lead to the proliferation of cancerous cells.



Deep-sea hydrothermal vents are some of the least explored habitats on Earth, but with a little bit of creative thinking, scientists may be able to find ways to exploit the biomolecular processes that organisms in these environments rely upon, in order to increase food security. Hydrothermal vents occur as a result of cracks in the ocean floor, causing hot, molten rock to mix with the near-freezing water of the deep. The mixing of these fluids results in a violent chemical reaction which culminates in the release of large amounts of hydrogen sulphide. As well as having to adapt to high pressure and low temperature, vent organisms must also be able to obtain energy in an extremely nutrient-poor environment; a complete absence of light at these depths means that carbon cannot be incorporated into organisms by photosynthesis. Bacteria living on these vents are the only known organisms able to fix carbon without light, and most other vent organisms have a symbiotic relationship with these bacteria in order to meet their metabolic demands.

> "Many adaptations of deep-sea organisms have the potential to provide solutions to some of mankind's most critical concerns"

Issues of food security are among the most pressing that will face mankind in the near future. Plant scientists are currently working on ways to induce symbiotic relationships between the world's major crops and nitrogen-fixing bacteria in order to create a new chloroplast-like organelle, called a nitrogenosome. This would allow food production in nutrient-poor soils. If the same principles used for the production of the nitrogenosome could be applied to the induction of a symbiotic relationship between our crop plants and sulphurous vent bacteria, then we might have the potential to be able to drastically increase yields. Unlike photosynthetic bacteria, vent bacteria are able to fix carbon in the absence of light; therefore induction of this relationship could enable round-the-clock crop growth. There are issues surrounding the toxicity of sulphur but the vents themselves could also provide a solution to this problem, as most vent organisms produce molecules called hypotaurines that have detoxifying properties.

It is important not to understate issues surrounding food security, as it is a complex problem that requires integration of many academic disciplines. However, this example should highlight the fact that the deep-sea has the potential to provide solutions to some of the world's most pressing issues. We have explored only one per cent of the ocean's floor and already have the potential to find a cure for cancer and feed the world – imagine what there may yet be to discover in the other ninety-nine!

I didn't want to be an astronaut anyway!

Max Bodmer is a 2nd year Biological Sciences student at St Peter's College.

Art by Joy Aston.

Making Dyslexic Mice

Decoding the genetics of dyslexia

Not everyone looking at these words will be capable of reading this text with ease and fluency. Dyslexia is one of the most common neurodevelopmental disorders, affecting 5–10% of school-age children. Around a hundred years ago, researchers had already identified that 'word-blindness' could be inherited within families, indicating that genes play an important role in its development.

Having emerged around 5,000 years ago, written language is a very recent innovation thought to have developed through cultural evolution rather than being directly targeted by natural selection. In fact, the brain seems not to be specialised for reading, as our reading capacity appears to 'piggyback' on other existing brain systems, such as those involved in vision and language. So it is not surprising that some individuals are not equipped with the 'best' genetic material and neural circuitry for the complex task of reading.

The human genome currently has nine 'dyslexia susceptibility loci', stretches of DNA containing genes which, when mutated, increase an individual's likelihood of developing dyslexia. But how can mutations in these susceptibility genes lead to a dyslexic brain? Most of these genes appear to be involved in the development of the brain by helping neurons to migrate through the cortex so they reach their appropriate final position and form the right connections. If this hypothesis is correct, dyslexia may be the result of subtle problems in this 'neuronal migration' process, leading to abnormal brain connectivity.

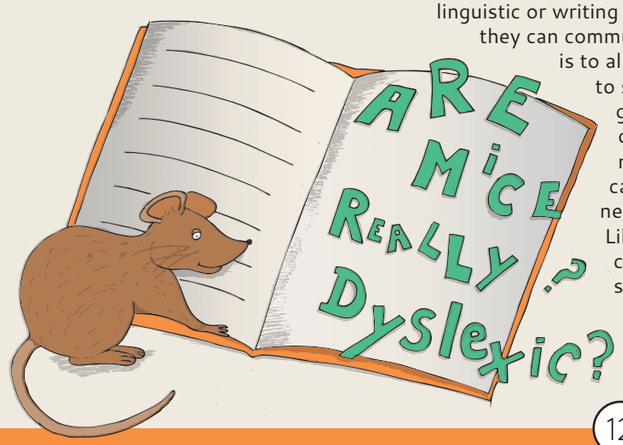
In order to test this, researchers have used a genetic engineering technique to switch off genes in mice: a gene 'knockout'. Given the obvious limitations with human experimentation, work with mice provides a powerful and cost-effective way for studying gene function in living mammals. Mice carrying modified versions of two of the strongest candidate genes for dyslexia susceptibility, the rodent equivalents to human *KIAA0319* and *DCDC2*, have been created at Oxford and in the United States. Research is currently under way to understand how the malfunction of these genes may lead to the neurobiological underpinnings of dyslexia.

> "The brain seems not to be specialised for reading, as our reading capacity appears to 'piggyback' on other existing brain systems"

Without fail, mention of this in any pub discussion invariably leads to the question: "How do you know the mice are dyslexic?" The gene knockout method does not aim to simulate dyslexia in an animal; an impossible task, as mice are yet to develop a linguistic or writing system (though they can communicate). The goal is to allow researchers to study what the genes in question do and how their malfunction can affect the nervous system. Like in any other complex disorder, such as autism or schizophrenia, a mutation in one gene is not enough for the development of dyslexia. Development of dyslexia depends on the interaction of multiple mutated genes and also non-genetic factors such as hormone levels, in contrast to Mendelian disorders such as cystic fibrosis where one mutation is sufficient. Studying each component separately is critical to putting all the pieces of the puzzle together.

Work on the neurobiology of dyslexia is in its early stages, but initial data suggest that switching off *Kiaa0319* or *Dcdc2* in the mouse brain does not cause problems with neuronal migration. However, this does not validate the sceptical position questioning the use of animal models for understanding uniquely human traits or disorders, as there have been many success stories. Animal models have revealed how the gene *FOXP2*, which can cause language impairment in humans by affecting speech motor control, may affect the development of neurons in motor circuits that are important for song learning in birds, and for motor learning and possibly ultrasonic vocalisation in mice. Still, no one says these animals 'have language'.

It is a matter of time and effort until we understand how dyslexia-susceptibility genes affect behaviour and brain development, and further research could give a critical insight into understanding the dyslexic brain. Or, perhaps, the sceptics are right: the mice aren't dyslexic after all.

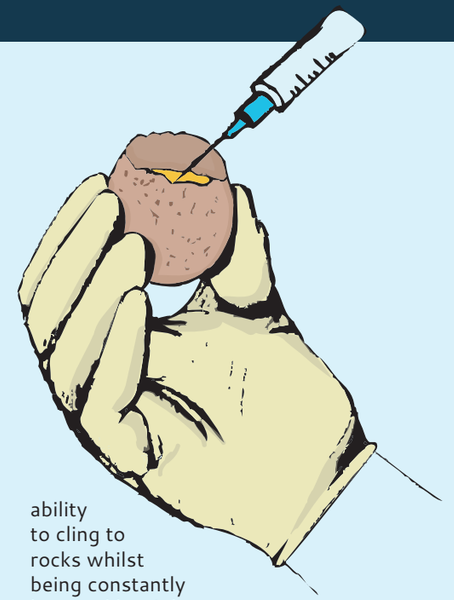


Luiz Guidi works at the Wellcome Trust Centre for Human Genetics. He is starting a DPhil in October.

Art by April Hills.

Animal Hospital

The many uses of animals in medicine



Throughout history, animals have been widely used in medicine, and humans continue to find novel and sometimes bizarre ways to use creatures big and small for treatments, vaccines, and even cures.

Why are animals so useful? They can perform complex molecular skills that an intricately designed machine would struggle to do, offer a versatile array of natural compounds, and the staggering number of species on the planet means they have a potentially huge number of diverse medical applications. Animals have been used in the past, present and will continue to advance medicine in the future.

THE PAST

Leeches were first prescribed for blood-letting by the ancient Egyptians around 3,500 years ago, and have had a role in medicine ever since. The popular medical leech *Hirudo medicinalis* boasts the ability to ingest five to 15 millilitres of blood at each feeding – almost ten times its own weight! Whilst not a one-stop-shop for all ailments as 19th century doctors thought, leeches are highly effective at draining blood from swollen areas, and their saliva contains a cocktail of proteins that reduce swelling, numb pain and promote blood flow.

Maggots were employed by the ancient Mayans and Aborigines to clean infected wounds. Whilst regarded with disgust by many, these remarkable critters secrete an enzyme which breaks down dead tissue but leaves live tissue unharmed. By feasting on the fluids oozing from decaying flesh, they also kill bacteria and stimulate cell regeneration. Although maggots went out of fashion due to the development of antibiotics in the early 20th century, the recent rise of antibiotic-resistant bacteria has boosted maggot therapy today; maggots were approved as a medical device by the U.S. Food and Drug Administration in 2004, and are commonly used as a highly effective and relatively inexpensive treatment for diabetic foot ulcers, gangrene and burns.

THE PRESENT

The term 'pharming' describes the process in which animals (or plants) can be genetically modified to produce pharmaceutical products. Goats are popular as scientists can reprogramme their genes so their milk contains huge quantities of recombinant protein (protein containing DNA from more than one species). For example, the anticoagulant ATryn is used to treat the rare disease antithrombin deficiency, which increases the risk of blot clots. ATryn is produced by inserting a human antithrombin-producing gene into a goat's genome, so the genetically engineered animal produces antithrombin in their milk.

Chicken eggs represent a cheap and versatile kitchen ingredient for many, and are also routinely used to prepare influenza vaccines. Scientists crack the shell of fertilised eggs to inject virus, infecting the embryo and allowing the virus to multiply rapidly. As the same virus infecting the embryo also infects humans, the virus can be removed, purified, deactivated with various chemicals, and used to produce vaccines guarding us against flu.

> "Chicken eggs represent a cheap and versatile kitchen ingredient for many, and are also routinely used to prepare influenza vaccines"

THE FUTURE

The chemical dopa is responsible for the strength of the sticky glue secreted by *Mytilus edulis*, giving the common mussel its extraordinary ability to cling to rocks whilst being constantly battered by violent waves. Dopa can be added to various manmade polymers to create a powerful, water-resistant glue, and in the future it may enable doctors to patch over holes in foetal membranes which can trigger miscarriages.

The shortage of organ donors is a pressing issue. Could xenotransplantation – the transfer of cells, tissues, and even whole organs between different species – be the solution? Pigs are commonly used for transplant research as they possess similarly sized organs to humans, and unlike primates, they pose less risk of carrying viruses that affect humans. In the future, pigs could be genetically modified so their organs are not rejected by the immune response when transplanted into humans.

As scientific research progresses further and further into the animal kingdom, the debate concerning the ethical issues linked to using animals in medicine will also continue. However, there may be a multitude of animal solutions to medical problems discovered in the not too distant future.

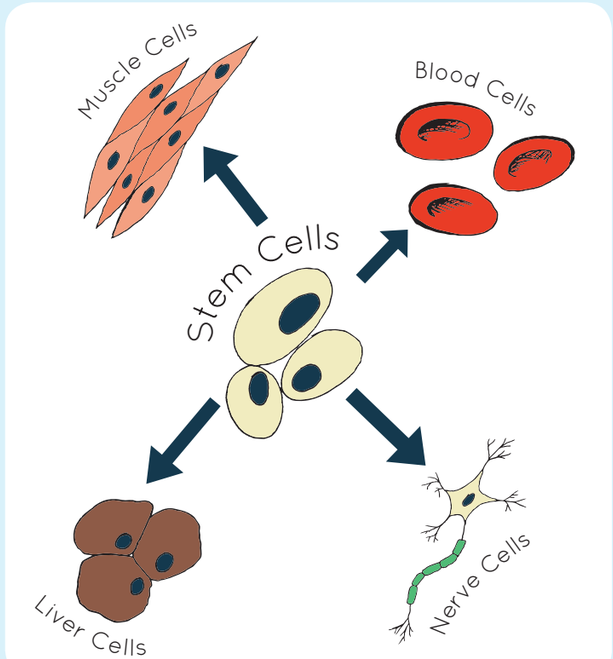
Jessica Wong is a 4th year Biochemistry student at Somerville College.

Art by Camille Fenton.

Transplanting Stem Cells

Revolutionising regenerative medicine with stem cells

When someone sustains organ or tissue damage from disease or injury, it is sometimes not possible for them to heal on their own, and they may require an organ transplant or tissue graft. The NHS estimates that three people die every day due to a lack of organ donors. A serious issue with transplants is the extremely high chance of rejection, particularly where transplanted tissue has come from another individual or even another species. This is because of the action of the body's immune system, which detects foreign antigens and creates antibodies to combat and destroy them. In normal circumstances this keeps the body healthy, but it is the biggest barrier to successful grafts and transplants. Organs and grafts can be attacked by the immune system just hours after surgery. Therefore most people who receive a donor organ will spend the rest of their life on immunosuppressant drugs, which are expensive and dangerous because they cause immunodeficiency: a state of weakened health where the body is vulnerable to infection and disease.



For this reason, doctors try to find donors with similar immune system characteristics to the patient. To assess compatibility between individuals, a test called panel reactive antibody is performed, which looks at the major histocompatibility complexes (MHCs) on immune cells. This gives an indication of how likely an individual is to react to foreign antigens via existing antibodies. But finding donors that are both willing and a close match at the right time is extremely difficult, and patients often have to settle for mismatched or cross-species transplants.

> "Most people who receive a donor organ will spend the rest of their life on immunosuppressant drugs"

How then do we overcome the enormous problem of transplant rejection in patients? The answer may lie in stem cells.

Stem cells are undifferentiated cells found in all organisms, which can divide and specialise into many cell types. There are two types of true stem cell: embryonic and adult. Embryonic stem cells are taken from the inner cell mass of a blastocyst, the name given to the ball of cells that forms about five to eight days after fertilization. They are pluripotent as they give rise to all the cell types that make up the later structures of the organism. Adult stem cells are found in various places in the body, and act as a repair system for cell replenishment. They are multipotent, meaning they have less differentiation potential than embryonic stem cells, but still have the capacity to develop into different cell types. The differentiation potential of adult stem cells also depends on where they are found in the body.

Isolating embryonic stem cells for medical use poses an ethical question. Because the embryo is destroyed in the process and the point at which life begins in the gestation process is a grey area, many people believe this is equivalent to destroying a life. However, the use of adult stem cells provides a less controversial alternative. Adult stem cells can be isolated from bone marrow, adipose tissue, blood, dental pulp and even umbilical cords. Furthermore, in 2006 Shinya Yamanaka created induced pluripotent stem cells (IPS cells), by taking skin cells and introducing genes that cause embryonic pluripotency.

Stem cells have the potential to develop into a variety of different cells, including immune cells. A study on eight experimental kidney transplants in which the donor was 'mismatched' to the patient showed that when the donor gave a donation of blood stem cells alongside the kidney transplant, the patient's immune attack was greatly reduced. Five out of the eight patients were able to have their immunosuppressant drug dose reduced within a year and there was no evidence of the donor's immune cells mounting an attack on the patient's healthy tissue.

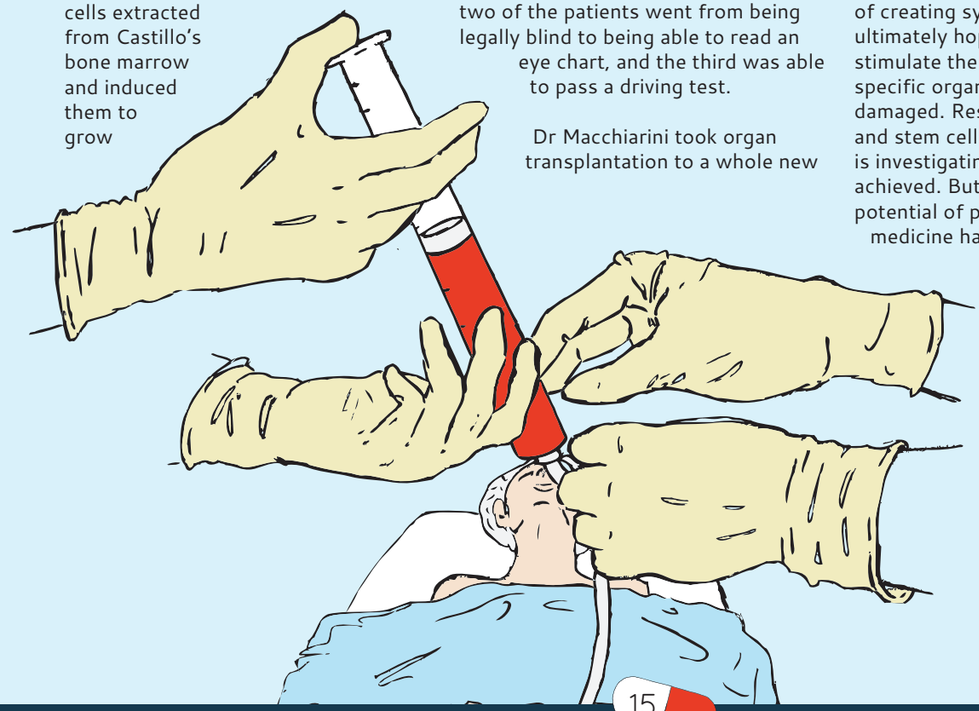
> "Beyene's stem cells were spooned over the rotating structure, like a rotisserie chicken, bringing the organ to life"

But the potential doesn't stop there. The world of regenerative medicine has been rocked by the promise of stem cells. In 2008, Claudia Castillo, who was suffering from tuberculosis, underwent a pioneering tracheal transplant at the University of Barcelona, led by Dr Paolo Macchiarini. Scientists from Bristol used stem cells extracted from Castillo's bone marrow and induced them to grow into cartilage cells. A segment of windpipe from a deceased donor was decellularised with strong chemicals and enzymes, leaving a protein scaffold free of donor cells. The segment was then seeded with Castillo's own stem cells and grown for four days in a rotating bioreactor. The operation was a huge success: the transplant grafted perfectly with no signs of rejection and the need for risky immunosuppressant drugs was eliminated.

In 2009, scientists at the University of New South Wales developed contact lenses that could regenerate damaged corneas in blind patients. Patients had limbal stem cells taken from within the eye, which were then allowed to grow on special contact lenses. The patients wore their personalised stem cell lenses for ten days, allowing the stem cells to move off the lens and onto the cornea. The results were remarkable: two of the patients went from being legally blind to being able to read an eye chart, and the third was able to pass a driving test.

Dr Macchiarini took organ transplantation to a whole new level in 2011. Andemariam Beyene, a 36-year-old from Eritrea, had a cancerous tumour the size of a golf ball in his trachea. With no donor windpipes available, he only had a few weeks to live at best. But Dr Macchiarini wanted to try something different. Just like Castillo's transplant in Barcelona, he wanted to use the patient's own stem cells to create the organ. But this time the scaffold was not taken from a deceased donor. Instead, tissue engineers at University College London created a nanocomposite polymer scaffold, tailor-made to the patient's chest. The porous synthetic scaffold was incubated with growth factors in a special bioreactor and Beyene's stem cells were spooned over the rotating structure, like a rotisserie chicken, bringing the organ to life. The windpipe now looked like a functional organ, pink and fleshy and ready to be transplanted. The surgery was successful, as were several further transplants by Dr Macchiarini using the same technology.

Dr Macchiarini wants to bypass the expensive and complex procedure of creating synthetic organs and ultimately hopes for drugs which will stimulate the body to regenerate the specific organ or tissue that has been damaged. Research into cell-signalling and stem cell differentiation pathways is investigating how this might be achieved. But now that the startling potential of personalised regenerative medicine has been unlocked by stem cell treatments, the future looks very bright indeed.



Madeleine Hurry is a 2nd year Biological Sciences student at St Peter's College.

Art by Ellen Foley-Williams and Iona Richards.

Laughing it Off

The healing power of laughter

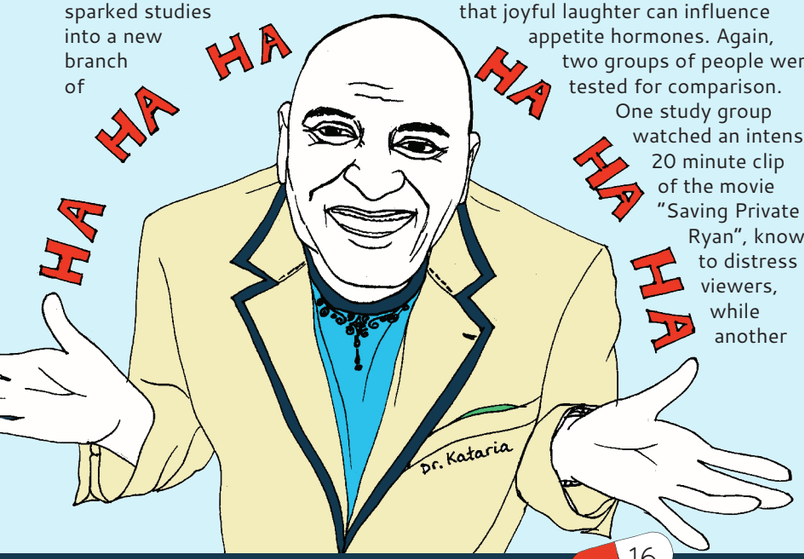
Laughter is as natural as breathing. When babies are born, their first instincts are either to laugh or to cry. Without language, laughter arises as a universal medium that allows babies to interact with the world. As babies grow up, they quickly learn to communicate in more complex and subtle ways. Laughter starts to function more as a reaction to an external source than as an expression of an internal mind and so its frequency is diminished. Over the last few decades however, scientific evidence has suggested that adopting new techniques to induce frequent laughter could give rise to a physically and mentally healthier generation. It seems that laughter could really be the best medicine.

In a famous 1964 case, Norman Cousins, an American journalist who was suffering from spinal arthritis, discontinued his medications after experiencing adverse effects. Instead, he prescribed himself a regimen of laughter, consuming high doses of Vitamin C and amusing himself with funny films. Amazingly, his experiment worked: Cousins' disease went into remission and he documented his experience in the book "Anatomy of an Illness". Cousins' suggestion that the brain and body are interconnected sparked studies into a new branch of medicine called 'integrative care,' or 'lifestyle medicine'.

Between 2006 and 2009, Dr Lee Berk and colleagues in California confirmed laughter's effects on human health. They asked high-risk diabetic patients with high blood pressure and elevated levels of fat in their blood to watch self-selected humorous videos for half an hour every day, while maintaining standard drug therapies. These patients had higher 'good' cholesterol, lower blood pressure, lower inflammatory signals, and lower detrimental stress hormones compared to a control group that did not watch funny videos. The team concluded that laughter can lower the risk of cardiovascular disease and heart attacks.

While laughter itself can enhance immune activity by reducing inflammation and stress, even the mere anticipation of laughter promotes positive psychological mood states. The deep diaphragmatic breathing that accompanies laughter also stimulates the parasympathetic nervous system, which causes the body to settle into 'rest and digest' mode, providing significant respiratory benefits.

In 2010, the same team also proved that joyful laughter can influence appetite hormones. Again, two groups of people were tested for comparison. One study group watched an intense 20 minute clip of the movie "Saving Private Ryan", known to distress viewers, while another group watched a self-selected 20 minute humorous video clip. The distressed group showed no statistically significant change in appetite hormone levels, while the laughter group experienced increased levels of appetite hormones. The researchers therefore suggest laughter as a treatment option for handicapped, depressed, or elderly patients who suffer from loss of appetite. Through laughter, the patients can regain their appetites and consequently their mental and physical well-being.



Many modern researchers have shown that the physical act of laughing can be beneficial to human health, but how can anyone laugh if they are unhappy or do not find things humorous? The answer is 'laughter yoga', a technique devised in 1995 in Mumbai by Dr Madan Kataria, who was investigating the medicinal benefits of laughter on the body and mind. Dr Kataria discovered that the body cannot distinguish between pretend and genuine laughter, and by guiding participants through a series of deep breathing exercises and laughter games, he created an atmosphere filled with pretend laughter that soon turned into real and contagious laughter. From humble beginnings with a small group of people performing laughter exercises in a park, laughter yoga has spread globally through Laughter Yoga Clubs from India to the United States, where the army plans to use laughter yoga to help returning soldiers overcome post-traumatic stress disorder. Today Laughter Yoga International describes itself as a "Global Movement for Health, Joy & World Peace."

Have you laughed today?

Thao Do is in her 3rd year of a DPhil in Biomedical Sciences at Green Templeton College.

Art by Thao Do.

A Game of Genomes

Curing cancer? There's an app for that

Liberating ourselves from cancer is a goal that has long been pursued by individuals, their families, and medical professionals, but soon a piece of software could allow the public to join in the effort more than ever before. In the past, an encouraging amount of funding and community support has been generated from public participation events, but now an app could enable those among us who are a little lazier to do our bit to help.

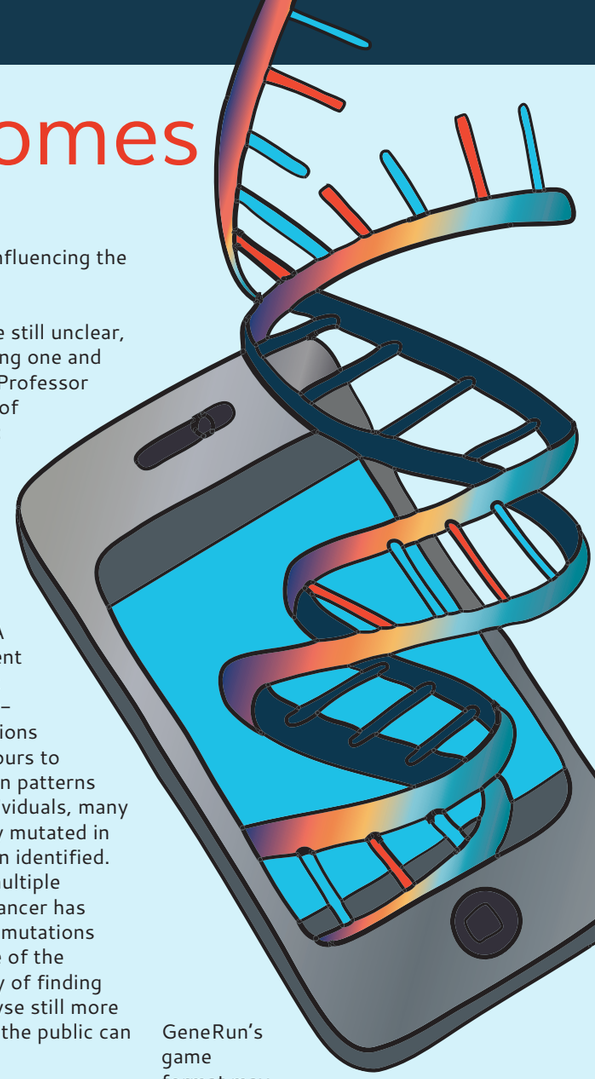
It seems that the Internet and the worldwide smartphone revolution may play a part in combating the disease by allowing researchers to crowdsource scientific information. Crowdsourcing is a technique that involves combining the efforts of a large number of people to complete a task. In this case, Internet giants such as Facebook and Google have teamed up to produce an app: GeneRun. In theory, it will allow members of the public to analyse long strings of genetic data by eye in a fun, everyday format to look for common mutations that could potentially contribute to diseases like breast cancer.

The GeneRun game is based on microarrays, short DNA sections bound to a glass microscope slide that are used to measure gene expression. Visual inspection of microarrays allows identification of which genes are switched on and off, revealing those that could potentially contribute to a tumour. The problem is that precisely when these genes are switched on and off is a factor still unidentifiable by a computer, and which therefore requires a human eye. Few specifics have been released, but the game will allow scientists to cut down the hours they spend trawling through data (leaving that to the public), to focus instead on analysis and investigation of the genetic patterns influencing the disease.

> "The game will allow scientists to cut down the hours they spend trawling through data, leaving that to the public"

Whilst the particulars are still unclear, the idea seems a promising one and has been well received. Professor Caldas of the University of Cambridge told the BBC: "Future cancer patients will receive treatment targeted to the genetic fingerprint of their tumour and we hope this exciting project will bring forward the day this becomes a reality." A need for tailored treatment comes from the fact that a large number of cancer-promoting genetic mutations are required for the tumours to form. Whilst the mutation patterns often differ between individuals, many genes that are frequently mutated in cancerous cells have been identified. Sequencing DNA from multiple patients with the same cancer has allowed identification of mutations that are a regular feature of the disease, but the best way of finding these patterns is to analyse still more samples, which is where the public can help.

Perhaps the format of GeneRun will help people who are not sure how to make a useful contribution to cancer research. Having it as an app enables usage on the go, borrowing the recipe for success that has helped mobile game developers sell millions of copies of their software. However, for such a significant way of utilising the technology everyone has in their pockets, there's been a startling lack of media attention in the run up to GeneRun's launch. One can only hope this will change once the software is actually released.



GeneRun's game format may be the ingredient needed to boost the download count beyond that of the slightly less successful medical resource apps that are already available. Essentially what the app needs is people and their support. So instead of downloading the new version of Angry Birds or Temple Run, download GeneRun and see how you can help. The app is set for release this summer, so keep a look out – doing your good deed for the day has never been so easy!

Ellen Foley-Williams is a 1st year Biological Sciences student at Wadham College.

Art by Joy Aston.

Small and Mighty

How microRNA can solve big problems

Consider for a moment the scale of the perpetual task faced by every organism – controlling gene expression. To pick only the right genes, to be expressed at the right time, in the right place, in the right quantities is no mean feat. Failure at any part of this task could result in disease or death. MicroRNAs (miRNAs) are essential to this process. As their name suggests, miRNAs are tiny, even in relation to the microscopic cellular environment. Typically just 22 nucleotide bases long, they influence genes over 1,000 times longer than themselves. Proving that size isn't everything, they may be key to revolutionising the way in which diseases are diagnosed and treated.

RNA molecules come in a variety of shapes and sizes and can carry out diverse roles in the cell. Similar to DNA, RNA consists of nucleotides, so can carry genetic information as a special code. Unlike DNA however, miRNAs are non-coding, and instead dynamically regulate our complex genome. They control which genes are expressed by targeting specific coding messenger RNAs to be destroyed, or by inhibiting the translation of these into protein. The central dogma of biology dictates that the manufacture of proteins requires the transmission of a code contained within DNA molecules from the cell nucleus to the main body of the cell, via messenger RNA molecules. The messenger RNA acts as the middle-man, carrying the precious code to the ribosome, the machinery responsible for translating the code, allowing the resulting protein to be synthesised. Challenging this dogma, miRNAs are a spanner in the works, interfering with the flow of genetic information, and effectively silencing genes by shooting their messenger RNA.

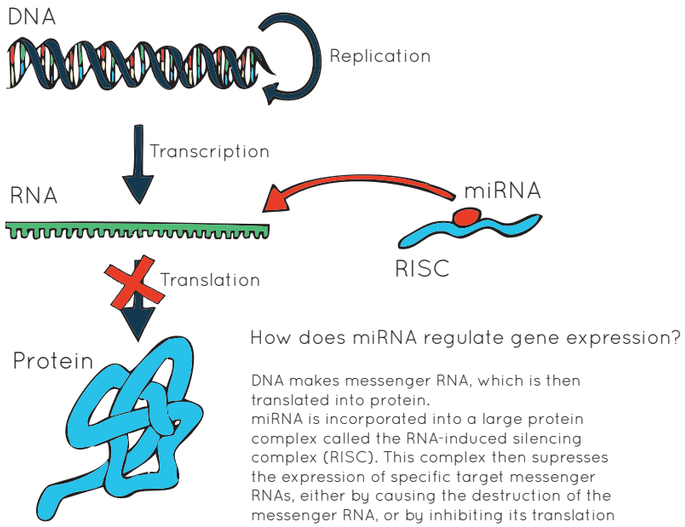
The first miRNA was discovered 20 years ago in the microscopic worm, *Caenorhabditis elegans*. Since then there has been an explosion of structural and functional knowledge, with miRNAs found in most organisms, from flowers to flies to fish. In the human genome, many regions originally thought to be 'junk DNA', actually encode functional and often indispensable miRNA molecules. To date, over 1,500 human miRNA genes have been identified, estimated to collectively govern a staggering 30% of our genes.

> "To date, over 1,500 human miRNA genes have been identified, estimated to collectively govern a staggering 30% of our genes"

Each miRNA efficiently coordinates numerous cellular pathways, by negatively regulating the expression of up to hundreds of genes. This empowers miRNAs to perform a plethora of roles in cell differentiation, proliferation, development, metabolism, and programmed cell death. But with great power comes great responsibility: such is the magnitude of miRNA's role in cellular function, that aberrant miRNA expression or behaviour can contribute to a myriad of illnesses, such as diabetes, cancer, and neurological and cardiovascular disease.

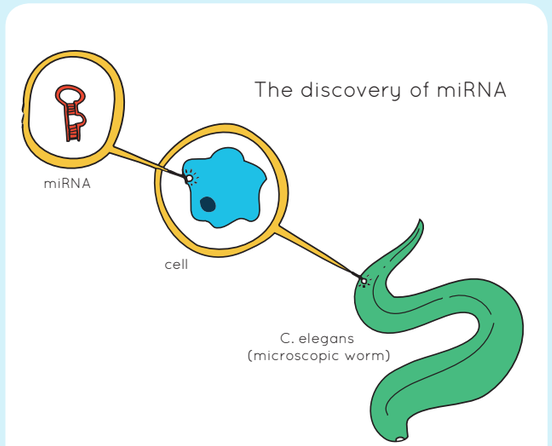
So how can our expanding knowledge of miRNAs help to treat these diseases? As diagnostic tools they can provide a wealth of information, and drugs can be designed to shackle harmful miRNAs or to mimic the effects of beneficial miRNAs.

Given that the expression of certain miRNAs increases or decreases in many diseases, they can act as biomarkers, giving a measurable indicator of a disease state. Studying the differences between the miRNA profiles of healthy and affected tissues allows disease biomarkers to be identified, providing valuable knowledge which can be harnessed to predict the course of a disease in patients. miRNAs are linked intrinsically with cancer: they are erroneously expressed in all studied cancers, and often target the messenger RNA of cancer-preventing tumour suppressor genes or cancer-causing oncogenes. A great challenge encountered when treating metastatic cancer (which spreads from where it originated to another site in the body), is determining precisely where the tumour started. Wide-ranging studies of several known tumour types have generated miRNA profiles which have been used successfully in diagnostic tests to classify cancers of unknown origin, allowing more effective treatment.



How does miRNA regulate gene expression?

DNA makes messenger RNA, which is then translated into protein.
miRNA is incorporated into a large protein complex called the RNA-induced silencing complex (RISC). This complex then supresses the expression of specific target messenger RNAs, either by causing the destruction of the messenger RNA, or by inhibiting its translation into protein.



miRNA's striking ability to simultaneously target multiple cellular pathways has fuelled interest in the development of drugs which mimic miRNAs. One advantage of using miRNA mimics over non-biological molecules is that they are natural, so less likely to cause adverse effects. A highly promising drug, MRX34, has been designed to imitate miR-34, a tumour-suppressing miRNA. Intravenous administration of MRX34 can inhibit the growth of pre-existing liver, lung and prostate cancer. Patrolling the cellular environment, MRX34 can eliminate over 20 oncogenes, putting a block on their damaging expression. Clinical trials with liver cancer patients are due to commence this year, and the results will be eagerly awaited by many.

Therapeutic applications are not limited to cancer. A beneficial miRNA termed miR-22 was identified by its diminished expression in sufferers of Huntington's and Alzheimer's disease. Studies revealed that miR-22 alleviated neurodegeneration in an experimental model of Huntington's disease, and impressively, miR-22 improved neuronal health in a model of brain ageing. The protective role of miR-22 in the brain has sparked interest in the feasibility of manipulating this miRNA in the body. Innovative treatments could stimulate our cells to produce more miR-22, thus preventing the onset of such incapacitating diseases.

> "Miravirsen operates like a police force, arresting miR-22, a miRNA found in the liver and required for illegal replication of the hepatitis C virus"

miRNAs also offer an attractive target for new drugs, as faulty miRNAs can play devastating roles in disease. Globally, the hepatitis C virus places 170 million chronic carriers at a high risk of developing liver cirrhosis or cancer. Soon, Miravirsen, the first miRNA-targeted drug to enter human clinical trials, could offer highly effective treatment. Miravirsen operates like a police force, arresting miR-22, a miRNA found in the liver and required for illegal replication of the hepatitis C virus, thus protecting the cell from the danger posed by the virus. Also in development is a drug targeting miR-208, a miRNA linked to cardiovascular disease. Remarkably, man-made miR-208 inhibitors can suppress cardiac damage in a model of heart failure, while simultaneously enhancing cardiac function.

For microRNA-based treatments, many challenges remain on the long journey from bench to bedside. There is the issue of miRNA delivery to the target cells, and the unravelling of the complex genetic networks which they orchestrate. But the future looks promising; these micro-managers of gene expression may be about to deliver massive advances in modern medicine.

Jessica Wong is a 4th year Biochemistry student from Somerville College.

Art by Aparna Ghosh and Iona Richards.

Bang! talks to...

Professor David Nutt

Professor David Nutt is Edmond J Safra Chair in Neuropsychophamacology at Imperial College London. He was famously sacked as chairman of the government's Advisory Council for the Misuse of Drugs in 2009, after publishing a paper comparing the harms of ecstasy use with those of horse-riding. More recently, he has received attention for his research into the therapeutic effects of illegal drugs. Bang! *met Professor Nutt at Imperial to discuss his current research.*

You are about to start studying the antidepressant effects of psilocybin, the psychoactive component of magic mushrooms. What is the background to this study?

People don't necessarily appreciate that many of the drugs that are illegal now were originally being used therapeutically. Psilocybin had been used as a treatment for OCD for quite some years, and MDMA was particularly liked by psychotherapists in the United States, who used it for couples' psychotherapy, helping people break down barriers of hostility.

> "The drugs laws are essentially an arbitrary set of constraints that politicians and the government use to parade their toughness on drugs"

The psilocybin experiment came about partly from research conducted by Phil Cowen's group in Oxford, showing alterations in the serotonin $5\text{-}HT_{2A}$ receptors in patients with depression. Psilocybin works on these receptors, which are most densely localised in areas which receive and integrate sensory information, like the association cortices and anterior and posterior cingulate cortex. I'd been interested in serotonin all my life, so I thought using psilocybin would be an interesting way of probing those receptors and getting some insights into consciousness in the psychedelic state.

So we did a brain imaging study with healthy volunteers, predicting that there would be an increase in neural activity, and therefore blood flow, in these areas after taking psilocybin. This seemed quite tenable given that people see coloured lights and geometric hallucinations when they take the drug. And what we found was exactly the opposite – a *decrease* in blood flow, particularly in the cingulate cortex, and the magnitude of that decrease correlated with the magnitude of the psychedelic experience.

We noticed that some of our volunteers said they had a greater sense of well-being after having had the experience. It occurred to us that the alteration of activity in the anterior cingulate might have led to the sense of well-being, because lots of antidepressant treatments switch off overactivity in this region. So we wrote a grant to try to use psilocybin in depression, and the Medical Research Council funded it. There's still the challenge of getting ethical approval, but I'm sure that this will be sorted because depression is a major problem and people need new treatments.

You've mentioned past and present therapeutic uses of psilocybin. Yet the drug, like MDMA, cannabis and LSD, is classified as a Schedule 1 drug, which means it has no known medical use.

It goes back to the 1961 and 1971 UN conventions. They essentially wanted to put all drugs into Schedule 1, but were forced to have other schedules for drugs that were definite medicines, like morphine. Even then, countries like Tanzania never licenced opiates for pain control because it was easier for them to comply with the UN regulations by banning all opiates than set up regulations internally. You can't believe the way in which opiates have been denied to so many millions of people.

Schedule 1 is a historical artefact, and it is so deceitful because cannabis was put into Schedule 1, even though cannabis was part of medicine in Britain for 300 years! They put drugs they didn't like into Schedule 1 and said they had no medical use. So they put psilocybin in there as well.

Is that creating problems for conducting research into these drugs?

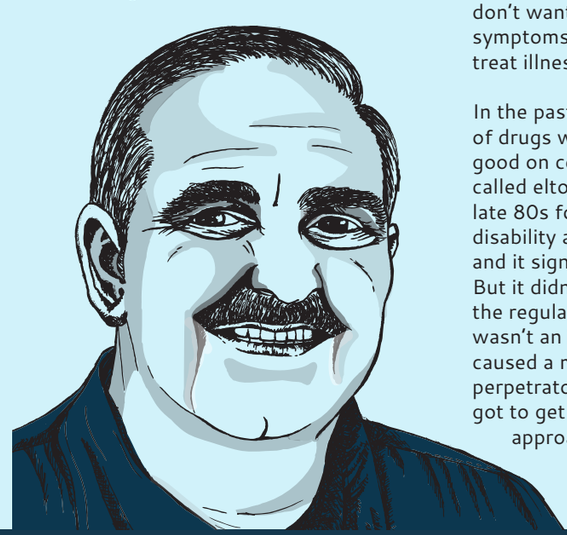
Absolutely. About five years ago the Home Office decided it was going to start having special regulations for Schedule 1 drugs, so now you have to go through the process of getting a licence, the drugs have to be held in a special lockable fridge bolted to the floor, and you've got to have police checks to make sure you are not misusing the stuff. So it's virtually impossible, and there are only three hospitals and a few individual investigators in the country that have a Schedule 1 drugs licence.

But these are absurd laws. Non-psychedelic variations on LSDs like 2-bromo LSD are Schedule 1 even though they are not psychoactive. This limits their potential use in conditions such as cluster headaches and the only way you can contest that is in law, which takes time and money. The drugs laws are essentially an arbitrary set of constraints that politicians and the government use to parade their toughness on drugs. It's creating big problems, and I am campaigning at present to try and do something about that.

New designer drugs are often produced to be chemically similar to illegal drugs, but different enough to get around legislation. Are these a candidate for research when it might be hard to study the illegal equivalents?

That's a very interesting question. Of course you *could* use these drugs to get around the law for therapeutic purposes. But there's a very good chance that the government would change the law and make them illegal, so it's a high-risk strategy. There's no logic to what they do at present, so why should they be any more logical for a new drug?

It's a route that in the long-term would be worth exploring, because if psilocybin works for depression, we might be able to enhance its efficacy by producing safer or more effective analogues. But the laws currently mean that traditional companies won't work in this field, because there's too much chance of everything being screwed over by a drug being made Schedule 1, and the extra cost and the burden of investigating Schedule 1 drugs means that it becomes commercially unsustainable. Pharmaceutical research for psychiatric disorders is dying and this is one way of trying to bring it back. But the law is working against us at present.



Where do you see the future of pharmaceutical research?

We've got to sort out the regulatory problems to start with. The current approach to drug regulation and licensing makes it very difficult for companies to target subtypes of psychiatric disorders. We know that not every person with schizophrenia or depression is the same. So I think subtyping disorders is a critical way forward, but we've got to get the regulators to accept that and support that.

Another approach is being developed by Tom Insel at the USA National Institute of Mental Health. It's called the Research Dimension Criteria, and instead of looking at illnesses as syndromes, it's looking at the dimensions of behaviour that cluster together, and trying to dissect those in terms of their neurochemistry and neurobiology. Again, that opens up opportunities for drug discovery, but we need the regulators to say they are ready to facilitate progress. Traditionally they've been pretty difficult to move because funders don't want to fund the treatment of symptoms or behaviours. They want to treat illness, which is too simplistic.

In the past we've had examples of drugs which were actually very good on certain dimensions. A drug called eltoprazine was trialled in the late 80s for people with learning disability and aggressive outbursts, and it significantly reduced aggression. But it didn't get a licence because the regulators said that aggression wasn't an illness, even though it caused a massive problem both to the perpetrators and the targets. So we've got to get a much more sophisticated approach to what we are doing.

Do you think that requires a focus on basic neuroscience research?

Well, human neuroscience research. I'm not sure that the mouse brain is inevitably the right way forward, particularly for higher level functions like depression and cognition. I'm very happy for people to do mouse research – it's very powerful technology – but we haven't invested enough in human brain research. For instance there are a number of neurotransmitters still to be discovered, and building models of the brain without actually knowing exactly what 30% of these building blocks are is a little bit premature. I think some neuroscientists have overstated the amount of understanding we have of the human brain – we've done fantastic things, but we certainly don't completely understand it yet.

You've written articles for several newspapers and magazines, and last year published a book, "Drugs: Without the Hot Air". Is science communication something that you were always interested in?

I've always been interested in telling the truth. When I was a lecturer at Oxford I started working on anxiety and panic disorders, and I realised that there was a lot of disinformation about anxiety. People didn't know what it was, didn't know that there was a biology to it – and worse, they didn't care. So my first exposure to the media was in a series of hour-long phone-ins to Radio Oxford talking about anxiety. I remember that I was nervous as hell when I first started and now I couldn't feel more relaxed about it! I'm passionate about science and I think everyone in the public should be, but if we don't get our passion out there, why will the public be passionate about what we're doing?

Interview by Matthew Warren.

Art by Thao Do.

The Unselfish Gene

The existence of green-beards in nature

The origin of altruism is one of the most interesting issues in evolutionary biology. How did nature, 'red in tooth and claw', come to favour altruistic behaviours which benefit others at a cost to the individual?

When the great 20th century biologist W.D. Hamilton tried to explain altruism, he posited a hypothetical gene, which both causes some distinctive trait in its carriers and directs them to behave more favourably towards others displaying that same trait. Such a gene would spread through the population despite being disadvantageous to the individuals carrying it, as they would be treated more favourably. The term 'green-beard' originated in Richard Dawkins' "The Selfish Gene", in which he posited a gene that coded for distinctive thick green beards and kind behaviour towards other green-bearded people.

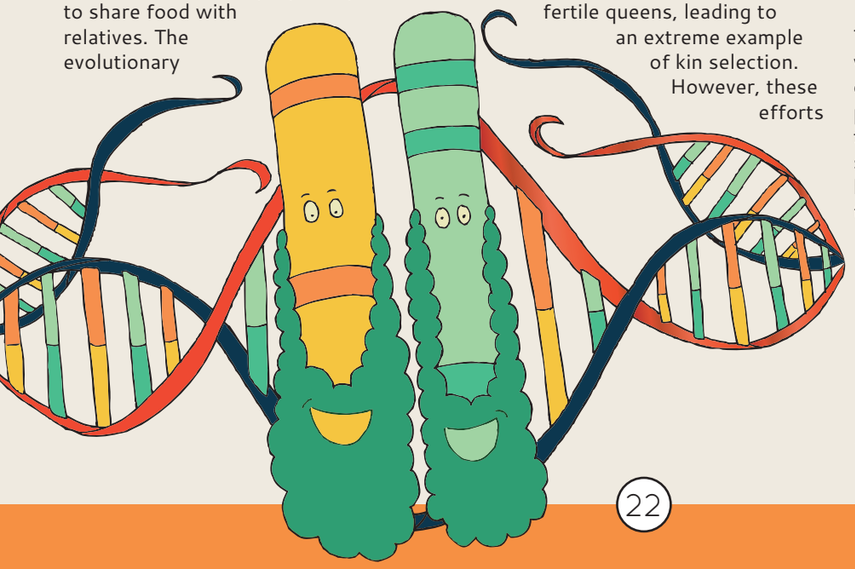
Both Hamilton and Dawkins were careful to stress that the occurrence of altruistic behaviour does not depend on the existence of any such gene. Rather, the hypothetical gene illustrates the more general case of 'inclusive fitness': genes with a fitness cost for their carriers can still be favoured by natural selection if they lead to a large enough benefit for other carriers, like a propensity to share food with relatives. The evolutionary biologist J.B.S. Haldane summed this up with his facetious remark that, while he would not lay down his life to save his brother, he would "to save two brothers or eight cousins" (since our siblings share half of our genes and cousins one eighth). When inclusive fitness is applied to close relatives this is known as 'kin selection'.

When Hamilton was writing, even proponents of inclusive fitness agreed that the odds were pretty low that a single gene would code for an altruistic characteristic and recognition of that characteristic in others, as well as for favourable behaviour towards them. However, in the last 20 years green-beard behaviour has been reported in a small number of species, including slime mould and yeast. Historically, the green-beard effect has been discussed in terms of promoting altruism towards fellow carriers, but the same principles can also apply to a more violent possibility: the identification and elimination of non-carriers.

Eusocial insects, such as bees, wasps or ants, with a sterile worker class, have long been of interest to evolutionary biologists. Being completely incapable of passing on their own genes, the workers devote themselves to the care of the fertile queens, leading to an extreme example of kin selection. However, these efforts do not always benefit the queens when their genetic interests fail to align with those of the workers. In 1998, a study of red imported fire ants by Laurent Keller and Kenneth Ross was printed in *Nature*. At a particular genetic locus, these ants exhibited two different alleles, B and b, so all ants in the colony were either homozygote BB or heterozygote Bb specimens (the bb combination proved fatal).

Despite both combinations being observed among the workers, none of the colony's multiple queens was found to be homozygous; they all had the Bb genotype. Keller and Ross tried introducing queens into the colony, and found that Bb queens were accepted readily, while over 90% of BB queens were attacked by workers within a fortnight. Analysis of the attacking workers showed that they were mostly Bb heterozygotes, and the trigger for their aggression seems to be a chemical secreted by the BB queens. Even fellow workers found themselves under attack if they were rubbed against the queens and contaminated with this substance. The clear conclusion was that the b allele was causing its carriers to attack the non-carrying queens, whose execution would free up more resources for Bb queens and so increase the chance of passing the b allele on to future generations.

This kind of aggression is consistent with the rationale of the green-beard effect; even though the above example pertains to spite rather than altruism, the principles and mechanisms are still the same. Nevertheless, there can be few greater thrills for a theorist than discovering one of their thought experiments being acted out in nature.



Paul Taylor is studying for a DPhil in Systems Biology at New College.

Art by April Hills.

Not-So-Dark Matter

Shedding light on this mysterious substance

In May 2011, we waved goodbye to the Space Shuttle *Endeavour*. Two months later *Atlantis* hit headlines across the world as it completed its last mission, thus closing the final curtain on NASA's 30-year Space Shuttle programme. But amidst the poignancy of these stories, we seemed uninterested in what the space shuttles themselves actually carried. Two years on, however, *Endeavour*'s final payload, the Alpha Magnetic Spectrometer (AMS), is considered to be "on the threshold of a major discovery".

The AMS is a $1.5 billion particle detector mounted on the International Space Station. The research group in charge, led by Nobel Prize-winning physicist Professor Samuel Ting, aims to use the data they collect to resolve arguably the two biggest mysteries in modern cosmology: what makes up the Universe's invisible mass, and what happened to the primordial antimatter? At the annual conference of the American Association for the Advancement of Science earlier this year, Professor Ting claimed the first results would "give humans a better idea about the nature of dark matter", the enigmatic material which makes up 83% of the mass in the Universe.

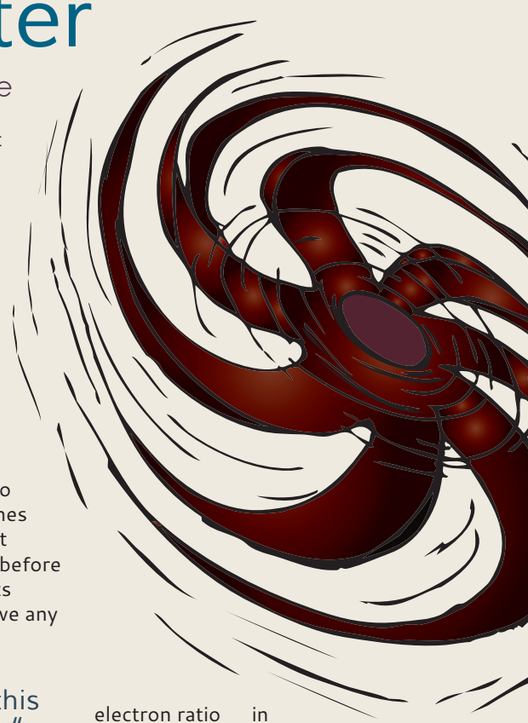
Dark matter is defined as any material which does not interact electromagnetically. Atoms are mostly empty space; everyday objects only appear solid because the electrostatic repulsion from their atoms is strong enough to stop the atoms in our bodies moving through them. Since dark matter doesn't interact electromagnetically, it doesn't experience solidity, and as a result up to 50 trillion solar neutrinos (the one form of dark matter we actually know something about) can pass through our bodies every second, almost completely without hindrance.

Electromagnetic interactions are also the only way we can detect subatomic particles, and this makes dark matter impossible to detect directly. We therefore have to wait for it to decay into electromagnetically active particles before we can detect it. Unfortunately, once this happens, the particles are no longer dark matter, and it becomes impossible to tell whether or not they were dark matter particles before they decayed. The way physicists usually deal with this is to remove any electromagnetically active particles from the detectors, so if anything is detected, it must have been dark matter before it decayed. In order to do this, vast chasms containing highly sensitive detectors are built deep underground to ensure that as many electromagnetically active particles as possible are absorbed by the Earth before they can reach the detectors and contaminate the results.

> "Electromagnetic interactions are also the only way we can detect subatomic particles, and this makes dark matter impossible to detect directly"

So how is a comparatively small detector flying through space 300km above the Earth hoping to shed any light on this perplexing subject? Aside from neutrinos, dark matter particles are grouped together within a family known as Weakly Interacting Massive Particles (WIMPs). They weigh in at anywhere from 30 to 300 times the mass of the proton, and theory predicts that they should decay in a similar way to normal matter, exploding upon collision into a shower of positrons, antimatter particles which have the same mass as the electron but the opposite charge. A sharp peak in the positron to electron ratio in high-energy collisions is the tell-tale sign of dark matter annihilation that the AMS is looking for. While the AMS is yet to produce data at the predicted high energies, recent results have shown unprecedented accuracy at energy levels high enough for the team to observe many new phenomena which they claim are "tantalisingly close" to those predicted by WIMP theory.

Does this mean we are finally about to lift the veil on dark matter? It will be a few years until conclusive evidence is presented – if it is found at all – but within the cosmological community all eyes are focussed on the AMS to bring us into what some academics are already calling "the decade of the WIMP."



Andrew Smith is 1st year Physics student at Somerville College.

Art by Ruby Byrne.

It's Elementary, Dear

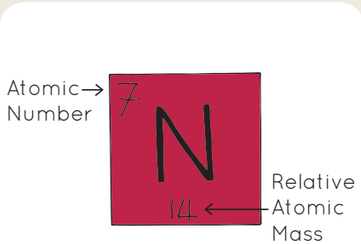
The periodic table's power of prediction

The periodic table is a pictorial structure, containing all known chemical elements. The early pioneers of the periodic table had no idea about atomic structure, which was only revealed in 1909 by Ernest Rutherford. So to categorise an element, they defined it as a substance which cannot be broken down further by any chemical reaction. This definition is still correct, but the most remarkable thing about the periodic table is that simply by considering the element's chemical properties, it displays the quantum mechanical structure of the atom which only began to be discovered towards the beginning of the 20th century.

In the late 1800s, Russian chemist Dmitri Mendeleev significantly advanced the development of the periodic table by writing down the elements and their atomic weights on cards and playing around with them. He noted that chemical and physical properties repeated themselves every eighth element, which gives the table eight columns (a pattern originally discovered by English chemist John Newlands in 1865), and as was convention at the time, Mendeleev began ordering the elements by increasing weight. Under this convention, tellurium would occur after iodine because it is heavier. However, Mendeleev noticed that iodine had similar chemical properties to the other halogens (fluorine, chlorine and bromine), while the recently discovered tellurium was chemically similar to sulphur. Ignoring convention, he swapped the elements, regarding chemical similarity within the group more important than ordering by increasing atomic weight.

> "Simply by considering the element's chemical properties, the table displays the quantum mechanical structure of the atom"

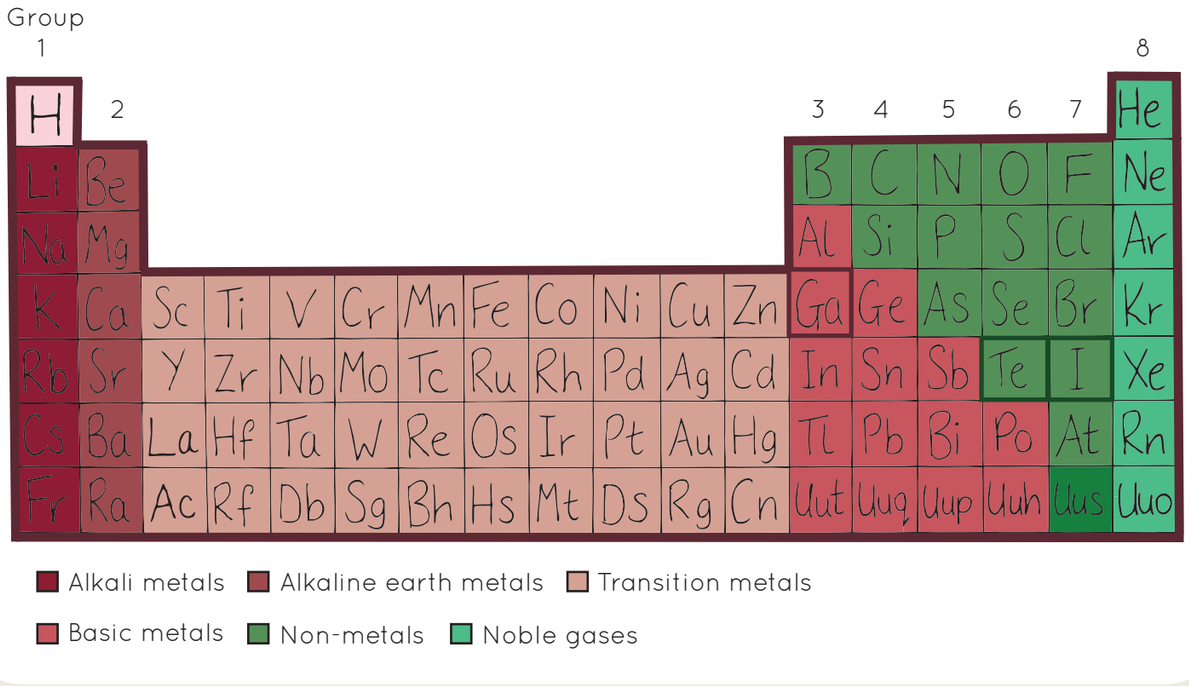
This pursuit of groups of chemically similar elements meant that there were places in the table where there was no element with the appropriate atomic weight and chemical properties of the group. So he left the gaps and, using data from the other elements to derive trends, predicted the density, melting point, boiling point and even colour of the missing elements. A French chemist, Boisbaudran, discovered an element with an atomic weight of about 70 (named Gallium after 'Gaul'), but the value he obtained for its density differed from Mendeleev's prediction. Such were Mendeleev's convictions that the pattern should not be broken by the anomalous density that he instructed Boisbaudran to re-measure it. Re-measure he did, and the revised result agreed with Mendeleev. The pattern remained intact.



Once this ordering was established, the elements were numbered sequentially so we could talk about the 'nth' element. Initially, this was just a way to label the elements, and was not thought to have any physical significance. But then the British physicist, Henry Moseley, discovered what is now known as Moseley's law. This work was done in the context of Bohr's theory of the atom's structure in which electrons orbit a central nucleus in discrete 'shells'. Electrons have to be in one shell or another, not in between.

One of the key properties of an element is its 'characteristic X-ray frequency', the frequency of light emitted from an atom when an electron jumps from the second closest shell to the nucleus to the closest shell. Moseley's law states that the square root of the characteristic X-ray frequency of an element is proportional to the element's integer, the 'atomic number'. The original graph expounding the proportionality is displayed outside the Martin Wood Lecture Theatre in the physics department at the University of Oxford. Thus, each element is identified by this unique atomic number, which finally gave this previously arbitrary integer a physical significance and generated a precise way of ordering the elements. And, since each element had a unique number, any more missing elements could be identified by using Moseley's law.

The periodic table we are familiar with was published in 1923 by Horace Deming. Well before quantum mechanics as we know it today was established, the periodic table was able to tell us so much about the discrete structure of electron shells that has since been revealed from a quantum mechanical treatment of atoms. Elements with similar chemical properties are grouped into columns (called 'groups'), numbered one to eight in the table. As we jump from column to column we move to a group of elements with different chemical properties and if we jump along eight columns, we end up in the same group we started at but in the row below (the periodicity of eight Newlands noticed). We now understand that moving from column to column adds an electron to the outermost shell but when that number reaches its maximum we move to a new row and the electron goes in a new shell.



Alternative tables have been suggested. One worth drawing attention to is Charles Janet's left-step table, which takes the first two columns of the standard table, putting hydrogen and helium on top, and appends them to the right hand side. This highlights an important quantum mechanical rule. We can see that the first and second rows have two elements while the third and fourth have eight, the fifth and sixth have 16 and the seventh and eighth have 32. This is a prediction from quantum mechanics staring us in the face: it tells us that the first two shells can hold two electrons, the third and fourth can hold eight and so on. This highlights the power the table has, as a picture, to tell us inner details about the structure of the atom. However, the standard table wins out because it preserves the chemical and physical similarities between elements in a group. Additionally, the groups are numbered according to the number of elements in the outer shell (one to eight), which is very useful to know.

> "Moseley's law states that the square root of the characteristic X-ray frequency of an element is proportional to the element's integer, the 'atomic number'"

Given that its predictive power is so great, it is tempting to elevate the periodic table to the status of "Scientific Theory", joining the greats of gravity, the Big Bang theory, and the theory of evolution. In hindsight, we can see how the table was able to depict the quantum mechanical structure of the atom, far before quantum mechanics itself yielded the electron shells and the rules governing how many electrons are allowed in each. It is historically very curious that the learning aid came before what needed to be learnt.

James Wills is a 2nd year Physics and Philosophy student at Brasenose College.

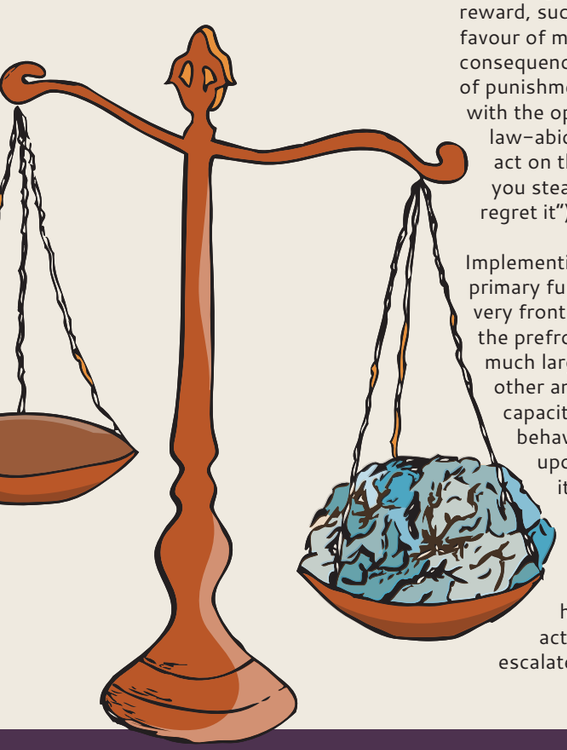
Art by Iona Richards.

The Emergence of Neurolaw

Bringing brain scans into the courtroom

First she murdered her sister by force-feeding her mind-altering drugs. Then she burnt her sister's body. Finally, she attempted to murder her mother. This is the 2009 case of 28-year-old Italian Stefania Albertani, who was handed a 30-year prison sentence in the midst of conflicting psychiatric reports regarding her mental condition. However, two years later a judge reduced this sentence to 20 years, after a brain scan indicated that the part of Stefania's brain important for behavioural inhibition – the medial prefrontal cortex – was abnormally small. This case cast attention on a potential future in the courtroom: the use of neuroscientists to determine the extent to which a criminal is responsible for his or her actions.

> "Neurolaw provides one way in which we might use a continuum to measure how capable an individual is of inhibiting illegal actions"



Mental illness is sometimes used to excuse criminals. Take, for example, the 1988 case of Lee Robin who killed his wife and daughter but was found not guilty after he was deemed too insane to understand the morality of his actions. Yet this poses a problem, since psychological symptoms actually lie on a continuum of severity. Doctors use a standardised set of behavioural criteria to determine whether a person has a mental disorder or not. However, in court it may be wiser to inform the jury of the defendant's degree of control rather than assign categorical labels of sanity or insanity.

'Neurolaw' provides one way in which we might use a continuum to measure how capable an individual is of inhibiting illegal actions. Such inhibition typically involves sacrificing an immediate and tangible reward, such as gaining money, in favour of more abstract long-term consequences, such as morality or fear of punishment. So, when presented with the opportunity to commit crime, law-abiding citizens choose how to act on the basis of a learnt rule ("if you steal from this shop you will regret it") rather than an urge.

Implementing such rules is the primary function of an area at the very front of our brains known as the prefrontal cortex. It is a region much larger in humans relative to other animals, which gives us the capacity to inhibit animalistic behaviours which are frowned upon by society. For example, it enables us to restrain the evolutionary urge to approach an attractive member of the opposite sex in a context in which he or she is unfamiliar, an action which could otherwise escalate into a sexual assault. Therefore, our prefrontal cortex helps us obey the law.

Thus far, research has mainly demonstrated the role of the prefrontal cortex in simple laboratory situations, in which participants learn to follow rules that vary depending on the context presented. Future research is needed to test whether this role generalises to more complex behaviours in everyday contexts. If this is found to be the case, then a person with abnormal functioning of prefrontal cortex may, for example, be more likely to commit a sexual assault, given their compromised ability to restrict physical contact to appropriate contexts. A brain scan could reveal such abnormal functioning by measuring the volume of a criminal's prefrontal cortex or its responsivity to a laboratory inhibition task, and comparing this to the average volume or activity in the general population. Unlike the all-or-nothing sanity defence, this could provide a continuous indicator of a defendant's neural control resources.

There are, however, limitations to the use of neuroimaging in court. Brain scans taken after a crime has been committed may not be reflective of neurology at the time of the crime. In fact, neural or mental abnormalities could be an effect rather than cause of criminal behaviour; for example, stress is known to halt the creation of new cells in the hippocampus (an area important for memory). A less controversial role for neuroimaging may lie in monitoring the success with which we can train a criminal's neural capacity to control undesirable behaviour through rehabilitation.

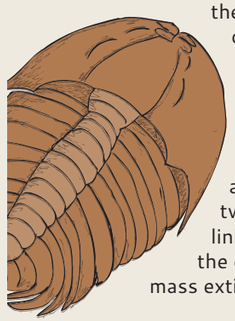
Robert Blakey is a 2nd year Experimental Psychology student at St Catherine's College.

Art by Haneesh Sidhu.

The End of an Era

Explaining the biggest mass extinction of all time

It is well known that the dinosaurs were lost in a mass extinction 65 million years ago. However, a more dramatic event happened around 251 million years ago at the end of the Permian period. With at least 83% of all genera and 90% of all marine species becoming extinct as a result, it is the biggest mass extinction of all time. Around the same time, the largest-known continental flood basalt was formed as the result of enormous volcanic eruptions of basalt lava. It is widely accepted that these two events are causally linked, but how could the eruptions cause a mass extinction?



The Late Permian eruptions produced the Siberian Traps, a large region of solidified basalt. Basalt is an igneous rock that is generally not erupted explosively but emerges more slowly than other lava types. Around 2 million km^3 of basalt lava was released which covered 1.6 million km^2 of land. Unlike explosive volcanic eruptions involving a brief release of gases into the atmosphere, the release of gas from flood basalt eruptions is much more prolonged. Carbon dioxide (CO_2), sulphur dioxide (SO_2) and halogens are released, which are capable of having a big impact on the global climate and environment.

An increase in halogens in the atmosphere would have caused a decrease in the ozone levels. Because the ozone layer absorbs UV rays, a depletion of ozone would increase the amount of UVB light reaching the surface of the Earth. This type of radiation damages DNA, causing mutations in organisms. It is thought that the disappearance of the conifer forests that covered Europe during the Late Permian was owing to mutations in their spores, causing sterility.

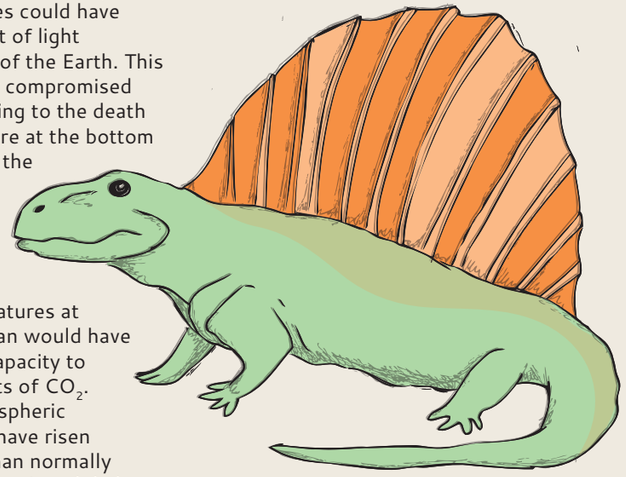
The SO_2 released from the eruptions would have been converted to fine particles of sulphates in the stratosphere. These would have only been present for less than one hundred years after being released and so could only have had a relatively short-term effect. The CO_2 released would have longer-term effects than the sulphates, as CO_2 has a longer average lifespan (around 30,000 years).

> "With at least 83% of all genera and 90% of all marine species becoming extinct as a result, it is the biggest mass extinction of all time"

Large levels of sulphates would have reflected and absorbed sunlight, causing a cooling effect. Organisms alive at the time would have been adapted to the previous high temperatures and so probably would have been unable to cope with life in the new climate. A particularly high level of sulphates could have restricted the amount of light reaching the surface of the Earth. This would have seriously compromised photosynthesis, leading to the death of plants. As plants are at the bottom of most ecosystems, the repercussions would have been felt across Earth's life forms.

High oceanic temperatures at the end of the Permian would have limited the oceans' capacity to capture large amounts of CO_2. As a result, the atmospheric levels of CO_2 would have risen much more rapidly than normally might be expected, causing global temperatures to increase. Warming oceans would have decreased levels of oceanic circulation, which is the large-scale movement of water in the oceans. This, together with the low Late Permian atmospheric oxygen levels, could have led to ocean anoxia (absence of dissolved oxygen). Many marine fossil sections from this period through to the Triassic period (251-200 million years ago) show evidence of oxygen levels that are reduced or completely absent. In the present day, the oceans are oxygenated to all depths. Absence of oxygen means that organisms that use oxygen for respiration are unable to live there, and is therefore thought to have been the cause of the huge loss of marine life in the Late Permian.

It is clear, then, that the eruptions in the Late Permian had wide-ranging effects on the climate and the environment at the time. This led to the enormous fall in biodiversity at the end of the Permian period, with severe consequences for life on land and in the oceans.



Catherine Joyce is a 1st year Biological Sciences student at Pembroke College.

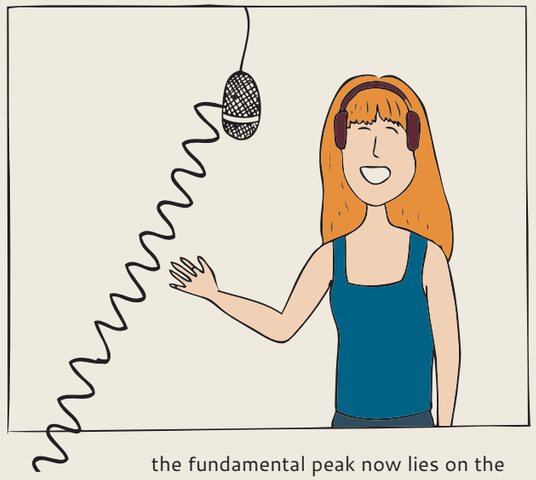
Art by Natasha Lewis.

Pitch Perfect

The maths behind your favourite songs

Most of us have heard of Auto-Tune by now. If you haven't, you will almost certainly have heard it used if you listen to any sort of popular music. Auto-Tune is a piece of audio processing software designed to correct the pitch of an input, most commonly a voice, to be in tune with the rest of a composition. This technology has proved so effective that it is used nearly ubiquitously in the music industry to 'tidy up' an artist's vocals and has even allowed people to produce music just from speech (see the YouTube channel "Auto-Tune the News"). Its use has also been widely criticised since it is seen to allow less talented singers to continue to succeed in the music industry.

In order to understand how Auto-Tune works we must first understand what the Fourier transform does and how it is useful. The Fourier transform can be thought of as a set of filters which tell us what the 'ingredients' of an input are and how much of each is needed in order to recreate the input. By giving us this information, it allows us to change the amounts of specific ingredients in our signal. For example, if we imagine our signal as a meal and we think that it is too salty, then an analogous 'Culinary Fourier Transform' would give us a list of the ingredients for our original meal, from which we could reduce the amount of salt. We could then use the 'Inverse Culinary Fourier Transform' (more commonly known as cooking) to recreate our improved meal. The ingredients of a sound wave are simple sine waves of different frequencies and the 'amounts' are their amplitudes and phases.



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Auto-Tuning is essentially a two-step process which uses and manipulates the 'recipe' of a signal calculated by the Fourier transform. The first step is called pitch detection and the aim is to find out what the pitch of a given signal is. A musical note, be it sung or played, is produced by creating a standing wave in some medium such as a guitar string or a resonating cavity. The standing wave will have zero amplitude at the boundaries of the medium. This means that the lowest possible, or 'fundamental', frequency wave is one that completes half of a full oscillation in this space, and the higher possible frequencies ('harmonics') will be multiples of this fundamental frequency. Pitch detection works by identifying this pattern of peaks in the spectrum of a signal and uses the fundamental frequency as the pitch.

Since we know the frequencies of every musical note, all we need now is a process to make the fundamental frequency of the input the same as the frequency of a desired musical note. This second step is known as pitch-shifting. This step is special since it changes the pitch of the signal without changing its length, as would happen if the playback rate was merely slowed down or sped up. Put simply, this process involves translating the shape of the spectrum up or down so the fundamental peak now lies on the desired frequency and the harmonics lie on its multiples.

This is, in essence, how Auto-Tune works. Of course, it is a little more complex than this since a singer's voice will change pitch over time. A more subtle problem arises because we are only analysing a signal of finite length. This means that the Fourier transform only gives us information about certain frequencies. Both of these problems are solved by using a 'phase vocoder', although the specifics of how this works are a little too complicated to go into in this article.

Auto-Tune, like photo editing software and other products common in today's digital world, relies on the Fourier transform in order to perform processes that would otherwise be much more computationally expensive or even impossible. This is not bad going for a piece of mathematics developed in the 18th and 19th centuries to aid the calculation of heat propagation, and demonstrates just how unpredictable the applications of scientific research can be.

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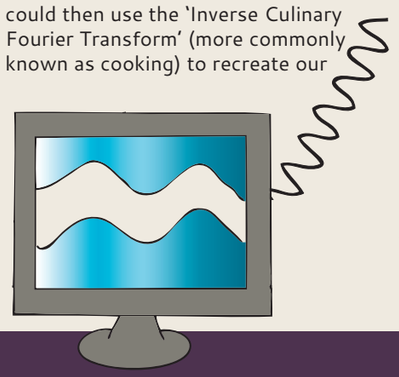
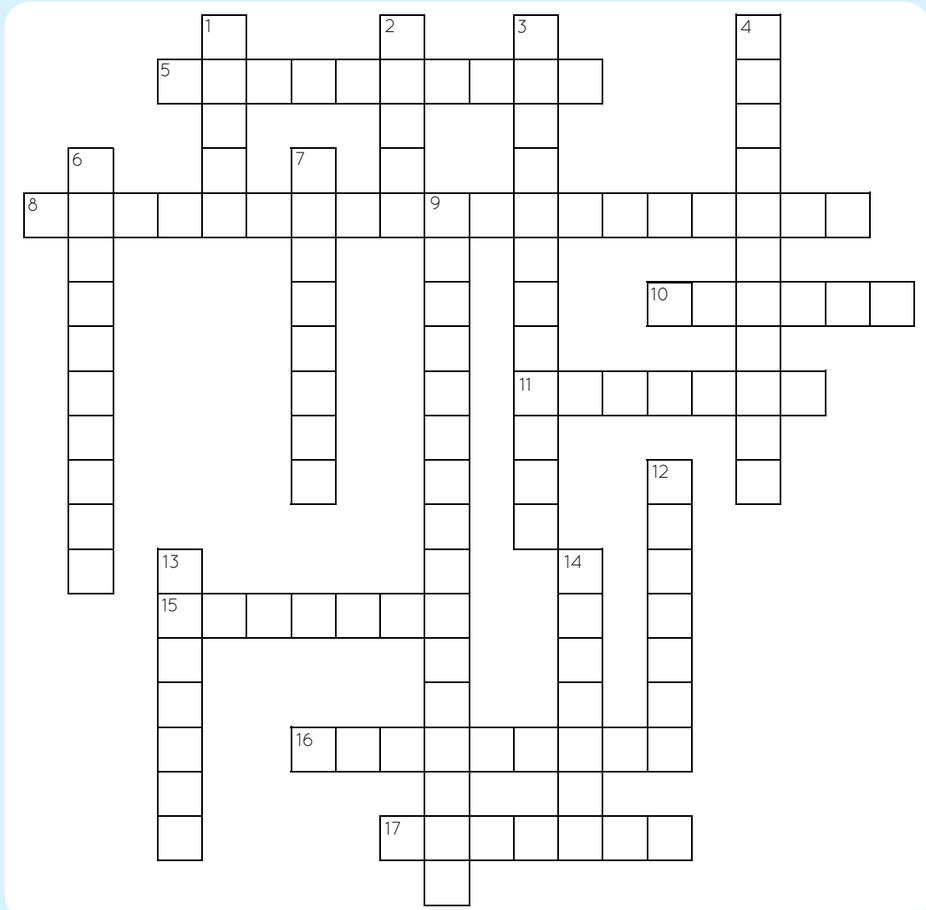
Art by April Hills.



Bang! Crossword

Find the answers throughout the magazine



Across

5. The first miRNA-targeting drug (10)
8. Transfer of tissue or organs between species (19)
10. Island on which the fossils of *Homo floresiensis* were found (6)
11. ____'s law gave meaning to the atomic number (7)
15. ____ Plain, ecosystem 4-6km under the sea (7)
16. Process by which neurons reach their appropriate position in the cortex (9)
17. New app that will allow the public to help in cancer research (7)

Down

1. Animal whose anal gland produces a perfume ingredient (5)
2. Dark matter particles being studied at the International Space Station (5)
3. Process of changing a planet's atmosphere and ecology (12)
4. Stem cell that can differentiate into all cells (11)
6. Scientific name for the badger (5,5)
7. Biologist who first proposed a 'gene for' atruism (8)
9. Brain area which inhibits impulsive behaviour (10,6)
12. Period in which the biggest mass extinction of all time occured (7)
13. Doctor who invented laughter yoga (7)
14. Mathematical transform used in Auto-Tuning (7)

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