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Drug development

Inside the pharmaceutical industry

Science Enhancement Programme

Catalyst

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Contents

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The front cover shows a scientist working with a library of chemical substances which have the potential to be used as medical drugs (see the article on pages 13-15). In the background is a robotic arm used to automate this work. (Hank Morgan / Science Photo Library)

Chemistry meets biology

This issue of Catalyst includes two linked articles on the pharmaceutical industry – the industry which designs and manufactures medical drugs. This industry is one of the most scientifically advanced, spending £4 billion a year on research and development.

- On page 13, Alan Steven describes the role of process chemists. These are the people who take the idea of a new drug from the laboratory bench and turn it into a safe and successful product which can be manufactured in bulk.
- On page 16, five young scientists and technologists working in the industry describe their different roles.

While we can think of drugs as chemical compounds, they are required to work in the complex biology of the human (or animal) patient for which they are designed. So pharmacology is an intricate mix of chemistry and biology; it is an industry where each individual has his or her own expertise combined with an understanding of the roles of everyone else in the development team.

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The Catalyst archive

Many articles from this issue of Catalyst, and from earlier issues, are available in pdf format from the SEP website (www.sep.org.uk/catalyst).

Amoret Whitaker
Martin Hall

Forensic Entomology: Using insects to solve crime

Most people avoid contact with insects and are repulsed by the sight of maggots. In this article, Amoret Whitaker and Martin Hall of the Natural History Museum in London look at the positive way in which insects can be used as evidence in criminal investigations.

Key words
forensic entomology
insects
decomposition
succession

Working in the Entomology Department at the Natural History Museum is not just about identifying and sorting our 28 million preserved insect specimens. We regularly receive telephone calls from Crime Scene Managers when a body has been found in suspicious circumstances, asking if we can collect the live insects and work out how long the body has been dead.

Forensic entomology is the study of insects and other **arthropods** in a legal context. It covers many different areas, such as pests in stored food products and insect infestations in human habitations. However, the most high-profile use of forensic entomology is in estimating the time since death, or post-mortem interval (PMI), in cases of unexplained or sudden death.

Succession of insects

When a person or animal dies, the body starts to decompose immediately and gives off odours. The chemical composition of these odours changes over time, as does the physical state of the body, which goes from fresh to active decomposition, through to dry and finally skeletal. At different stages during the decomposition process, different types of insect are attracted to the body to feed and lay eggs or larvae on it, so their offspring can also feed. The type of insects follow a predictable pattern, with blowflies (Figure 1) coming in at the earliest stage, followed by many other groups of arthropod such as carrion beetles, ants, mites and moths.

Figure 1 *The blue-bottle blowfly,* Calliphora vicina, *feeding on a dead animal, with larvae.*

Arthropod:
Any animal which has an exoskeleton, a segmented body and jointed limbs, such as crabs, spiders, insects and woodlice.

Blowfly life cycle

Because the blowflies (blue- and green-bottles) are the first insects to be attracted to a body, within hours or sometimes minutes of death, they are the most useful insects for estimating PMI. The adult flies will come to feed on the body and the females will **oviposit**, laying batches of 50-100 eggs in a single egg mass. These eggs hatch out into tiny larvae, called 1st instars, which as they feed and grow, will moult and go through two more stages, called the 2nd and 3rd instars. At the end of the 3rd instar stage, the larvae finish feeding and usually move away from the body to pupate, at which stage they are called post-feeding larvae. Once a suitable place has been found to pupate, the outer skin of the larva constricts and hardens, becoming the pupal case, or puparium. Inside the case the larva metamorphoses into an adult fly, which eventually breaks out of the pupal case, completing the life cycle (Figure 2).

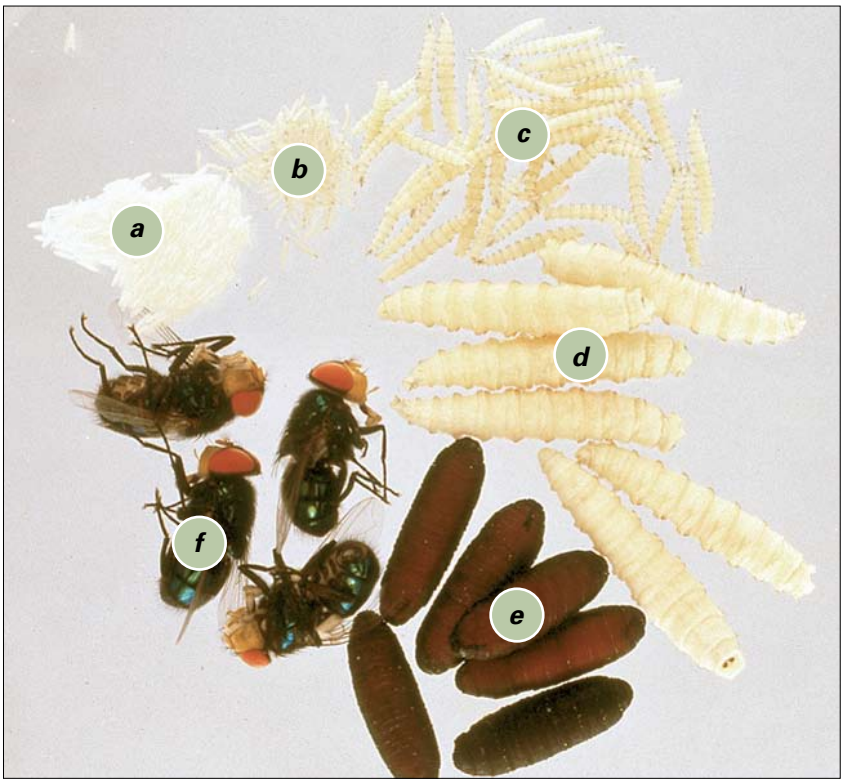


Figure 2. *Stages of blowfly development:* ***a*** *eggs,* ***b*** *1st instar larvae,* ***c*** *2nd instar larvae,* ***d*** *3rd instar larvae,* ***e*** *puparia containing pupae,* ***f*** *adults.*

Effect of temperature

The rate of development of insects is almost entirely dependent upon the temperature at which they develop, i.e. the warmer it is the faster they will develop, and the colder it is the slower they will develop. Therefore in a typical UK summer, when the temperatures are averaging 15°C, blowflies will develop from egg through the larval and pupal stages to adult flies in approximately 15 days. In a typical UK winter, when the temperatures are well below 10°C, dropping to below 0°C at night, it may take many weeks for blowflies to develop.

Estimation of post-mortem interval

It follows that, if blowflies are found associated with a body, you can estimate the post-mortem interval if you can find out: a) what the species of blowfly is, b) what stage the blowflies are at, and c) under what temperatures they developed. It is important to know the exact species of blowfly as different species, even closely related ones, may develop at different rates. The stage may be fairly easy to recognise, e.g. eggs, instar stage, post-feeding or pupal, but the length of the larvae can also be measured to gain greater accuracy, and pupae can be dissected or X-rayed to gauge the stage of development (Figure 3). Finally, the temperature at which they developed can be estimated by obtaining the weather data from the nearest meteorological station to where the body was found.

A more accurate estimation can be made by placing an electronic datalogger at the place where the body was found for a period of time (typically 7-10 days) and comparing these temperatures with those of the local meteorological station over the same period of time. This is called a regression analysis, and the resulting equation can then be used to estimate what the temperatures at the deposition site would have been in the period before the body was found, i.e. during the time when the blowflies were developing on it.

Figure 3 *Pupa of the bluebottle fly,* Calliphora vicina, *dissected from its puparium.*

Larval (or maggot) masses

When the larvae reach the end of the 2nd instar, and throughout the 3rd instar stage, they congregate together to feed in large masses (Figure 4). Their combined feeding activity generates heat, so the larval mass may be many degrees higher than the ambient (surrounding) temperature (Figure 5). In colder climates, the larval mass temperature can be up to 20°C or more above the ambient temperature, resulting in a faster rate of development of the insects. However, there is an upper temperature threshold of about 42°C, above which the larvae will die. If the blowflies found on the body have reached, or gone beyond, the late 2nd instar stage of development, then larval mass temperatures must be taken into consideration, or the PMI is likely to be overestimated. before the body was found, i.e. during the time when the blowflies were developing on it.

Figure 4 *Larval mass, feeding on a body.*

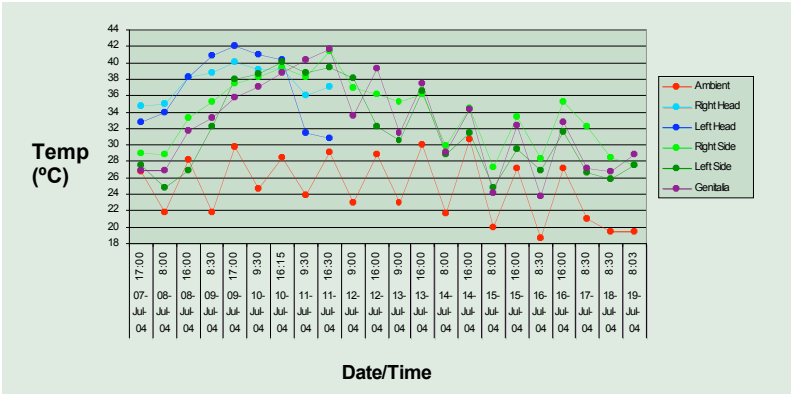


Figure 5 *Larval mass surface temperatures recorded on a human cadaver used during research study. Compare the blue, green and brown lines (larval masses) with the red line (ambient temperature). The difference between ambient and larval mass temperatures is greatest at 8:30am on 09-Jul-04.*

Other factors to be considered

When we estimate PMI, we are actually estimating the time when flies oviposit on the body and, therefore, the minimum PMI. In other words, we estimate the minimum amount of time since the person has died, because the blowflies would not have been present prior to death, and as we don't know exactly when the eggs were laid, we cannot give an actual PMI.

There are many other circumstances within which the body is deposited, which will also affect the speed of oviposition and the speed of development of the insects. For instance, if a body is buried, submerged, wrapped or enclosed in some way, it may be either totally or partially inaccessible to adult flies which may delay or inhibit their ability to oviposit. If a body is found with no insects on it, where they would normally be expected, this can give some indication of the manner in which the body was deposited, for instance whether it was buried immediately or kept in an enclosed fly-free space. Bodies found indoors may decompose at a different rate from those outside, depending on factors such as whether the windows were open and if the heating was turned on.

Forensic entomologist at the crime scene

Sometimes a crime scene manager or pathologist will collect the insect evidence themselves, which is fine, as long as they have been adequately trained to do so. Ideally, though, the forensic entomologist will attend the crime scene themselves, prior to removal of the body to the morgue. Firstly, this enables the entomologist to get a full picture of the scene, firsthand. Secondly, insect evidence may not always be conspicuous and can easily be overlooked by the untrained eye, e.g. fly eggs may be hidden from view and difficult to identify, or if the larvae have already left the body to pupate, the oldest insects may not even be on the body itself, but in the surrounding environment. In addition, if only eggs or pupae are present, they may not be recognised as being insects because they do not move. Thirdly, if the insect evidence is not preserved and/or labelled correctly (Figure 6), it may not be possible to use it in the analysis.

Figure 6 *Insect evidence in sealed forensic evidence bags.*

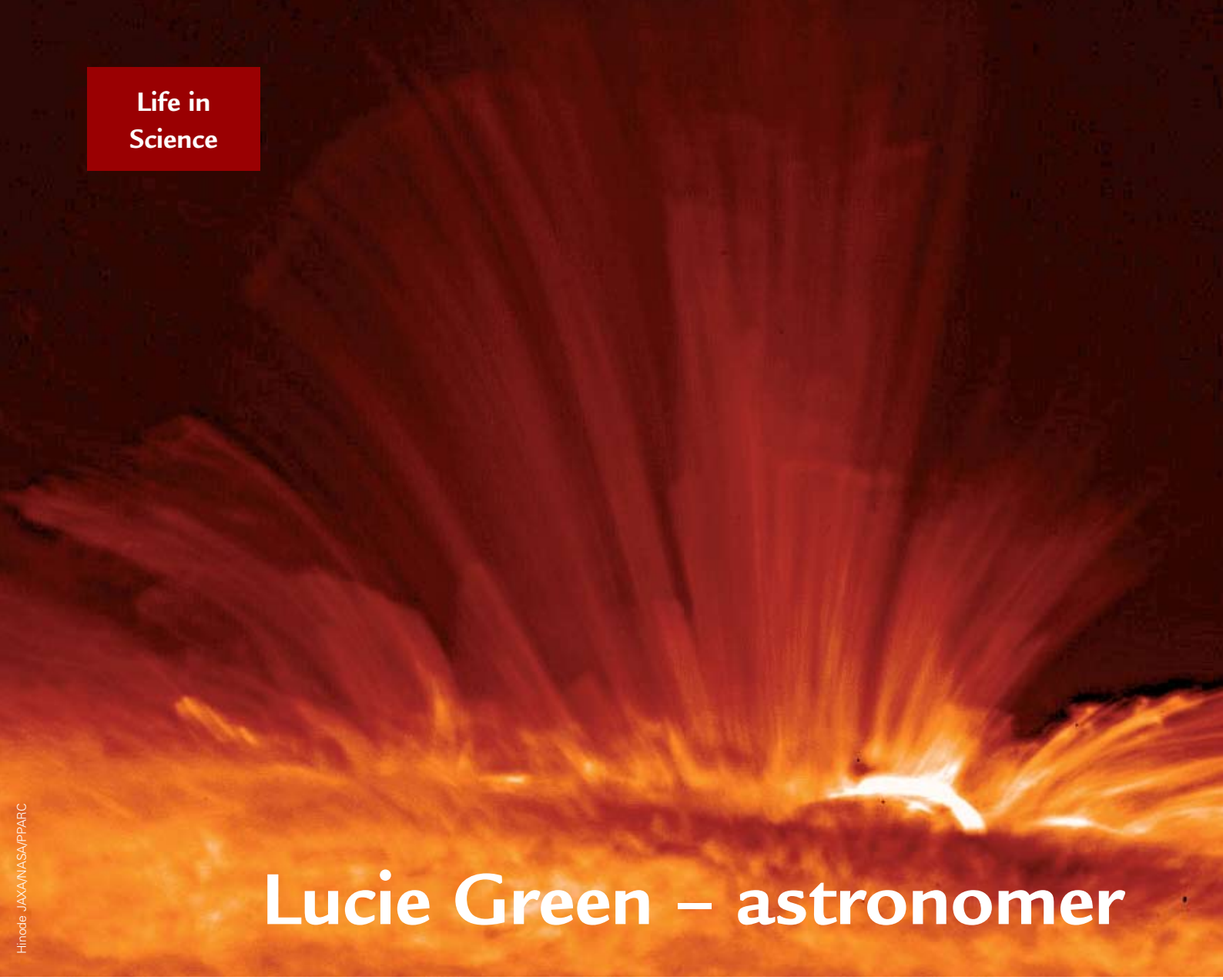
Forensic entomology as evidence

Any estimation of PMI can never be exact (unless the death has actually been witnessed!), so a forensic entomologist should not be tempted into giving an exact PMI, but more realistically a likely range of dates/times will be suggested, which is typically wider, the more decomposed a body is. If the time of death becomes an important factor in the investigation, or if no other evidence can be found to support it, the forensic entomologist may be required to attend court, to explain their findings and to answer any questions. More often, though, the estimation of time of death given by the forensic entomologist will enable the investigating team to focus their enquiries within the suggested timeframe, thus maximising financial and personnel resources.

Amoret Whitaker *and* ***Martin Hall*** *are Forensic Entomologists, based at the Natural History Museum in London.*

Look here!

These two sites explain more about forensic entomology:
www.forensic-entomology.com
www.research.missouri.edu/entomology/
To watch a talk by Martin Hall, go to:
www.nhm.ac.uk/nature-online/life/insects-spiders/webcast-forensicentomology/forensic-entomology.html

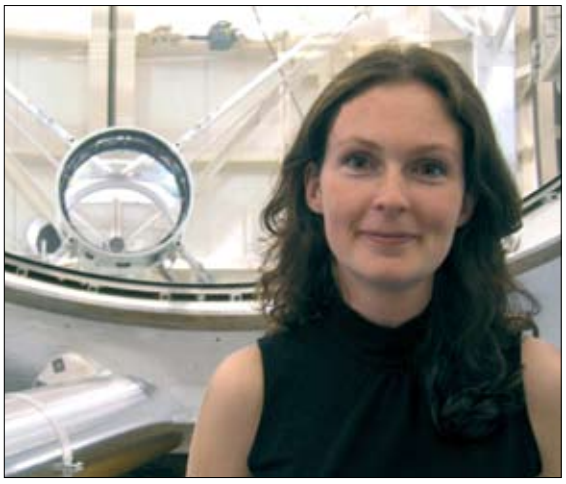


Hinode JAXA/NASA/PPARC

Lucie Green – astronomer

An image of the Sun's surface, made by the Hinode spacecraft. The Sun's magnetic field is revealed rising out of a sunspot (an area with a strong magnetic field).

You may have seen Lucie Green on television – she has appeared on The Sky at Night with Patrick Moore. Here she describes her work as an astronomer and the opportunities it has given her to explain science to a wider audience.



Lucie in front of a telescope in Arizona.

Lucie left school with 9 GCSEs, 4 A-levels and one AS-level.

Throughout school I had a love for physics. I found it fascinating to learn about how the world around us worked and how laws are formulated to describe what we see. Later, when I developed a passion for art, I couldn't decide which path I should follow after A-levels. A one year course in art seemed like to good way to test the water so I began an art foundation degree.

After a year I decided that art wasn't a career path I wanted to proceed down, and I was left with my other love, physics. There are a whole range of physics courses at university now and I saw one that really caught my imagination; physics with astrophysics. I went to study at Sussex University where the course gave me a great grounding in maths and physics and also taught me what we have learnt about the workings of the Universe.

During one of my summer holidays I spent some time doing work with funding from the Nuffield Foundation. Part of the project involved an observing trip at the Crimean Astrophysical Observatory in the Ukraine. That was somewhere I never thought I would go! This trip was a turning point for me and even though I didn't realise it at the time, everything I do now has come from it.

I went there to observe binary systems; two stars in orbit around each other. But the observatory also had telescopes that are used to observe our nearest star, the Sun. I still remember my first views of the Sun using their telescopes when I saw the Sun in a completely new way. Instead of an overwhelming bright yellow disc I saw structure and detail. Giant structures known as prominences seemed to be leaping off the Sun's edge and our local star seemed a hive of activity.

Research life

I then went on to do a PhD at the Mullard Space Science Laboratory (MSSL), part of University College London. I studied the immense eruptions that blast away from the Sun when prominences do manage to break away from the solar surface. local star seemed a hive of activity.

I still work at MSSL researching these eruptions. At the moment we have some exciting new data coming from two recently launched space missions. One is a Japanese spacecraft called Hinode. The UK has a telescope on board so we are heavily involved and are making a great contribution to the science being carried out. Hinode is allowing us to study the changes which lead to prominences erupting; in particular we are able to monitor their relation to the Sun's giant magnetic field which changes over time.

An artist's impression of the Hinode spacecraft; Lucie receives results from this spacecraft and tries to interpret them.

What amazes me about astrophysics is that even though our knowledge has come a long way, we still know so little about the Universe. I find that idea that we are only able to see 5% of what the Universe is made of completely mind-boggling. I have always thought that searching out and discovering new things is fundamental to humanity. Not only do new discoveries in science have a very obvious impact on us, often leading to a better quality of life, but we also have a drive to understand our place in the Universe.

Talking science

I'm interested in doing science but also in telling people what is being found out in my area of astrophysics. For the last 8 years I have been involved in many projects which talk to schools and the general public about astrophysics. I have given talks, done regular radio slots, appeared on The Sky at Night and also co-presented two other astronomy programmes.

Lucie has appeared on The Sky at Night alongside its presenter Patrick Moore.

I am now funded by the Royal Society under their Dorothy Hodgkin scheme. (Dorothy Hodgkin was a British scientist who won the Nobel Prize for Chemistry in 1964.) The scheme allows me to do research for part of my time and for the other part I am involved in activities that communicate science. At the moment I am working on publicising International Heliophysical Year, a United Nations initiative which celebrates solar system research and exploration. The Sun plays a central role as, through its emissions, it affects all the objects in the Solar System.

Look here!

Read Lucie's article in an earlier issue of Catalyst in which she introduced the International Heliophysical Year: **http://www.sep.org.uk/catalyst/download_article.asp?article_code=34**

For a while, Lucie worked on the Faulkes Telescope Project, a scheme which allows school students to use a real telescope: **faulkes-telescope.com**

Lucie contributed to the Suntrek project, helping to develop a website which explains solar physics: **www.suntrek.org**

Averil Macdonald

Fantastic plastic

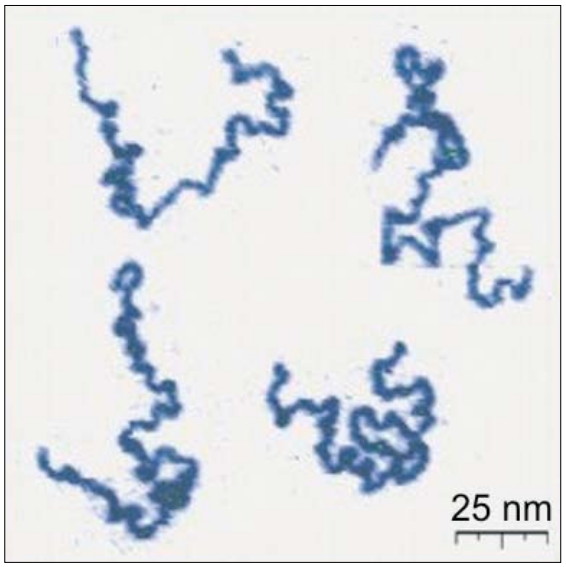
Prototype Organic LED television screens. These screens use polymer LEDs to produce the picture; many millions of smaller OLED screens are already in use in mobile phones.

Think of polymers (or plastic) and probably you come up with plastic bags and toys. Think a bit harder and you get to plastic plates and cups, plastic pens and pencil cases. Now look around you. It's very likely that the majority of objects in your room at made of polymers. In this article, Averil Macdonald of Reading University asks: why are people getting more and more excited about what polymers are going to do in the future?

Key words
polymer
molecular structure
material processing

Molecular chains

Polymers, like many other materials, are made of atoms bonded together into molecules. What makes polymers different is that these molecules are then bonded together into long chains.



An unusual sight - this photograph shows four individual polymer chain molecules. It was made using an atomic force microscope.

The exciting thing about polymers is that we can make polymers behave in so many different ways by organising their long chain molecules in different ways – polymers are the ultimate designer material.

For example, scientists have developed improved house paints consisting of a polymer solution so that now they last longer between repainting and are more waterproof, while in the kitchen your non-stick pans only work because they are coated in a polymer called Teflon.

How polymers are processed can make big differences to their properties. All of these items are made from polystyrene.

Polymer families

Most of the materials we call 'plastic' are made from one of five 'families'.

- PE: polyethylene e.g. carrier bags
- PP: polypropylene e.g. drinks cups, kettles
- PS: polystyrene and expanded polystyrene (EPS) e.g. insulating cups, packaging
- PVC: poly(vinyl chloride) e.g. window frames
- PET: poly(ethylene terephthalate) e.g. transparent water bottles

Polymers from different families: milk bottle (polyethylene), fast-food container (polystyrene), pipe (PVC) and rope (nylon).

Then there are the polymers with trade names like Nylon™, Polythene™ and Kevlar™ (bullet-proof vests are made from Kevlar™ – designed to be the strongest material on Earth!).

Choosing the right polymer

When a company chooses the right polymer for its product it will take account of all of its different properties such as

- the melting temperature – we can't have a cup that melts when warm water is poured into it
- do we need it to be a good thermal insulator – this is important for food containers so we often use expanded polystyrene
- do we need it to be a good electrical insulator - some plastics can conduct electricity! PVC is often used as an insulator in household cables but isn't good enough for high voltages up to 500 000 V where we have to use cross-linked polyethylene
- how easy it is to mould into shapes – if it is a hard, inflexible plastic then you can't use it for something that has to be flexible so you would add lots of 'plasticiser' such as phthalates to PVC
- does it have to be transparent – PET is used for bottles as it is easy to make transparent
- does it have to be easy to add colours to – if you want an attractive product you have to be able to colour it – PVC is good for colouring
- does it matter if it becomes brittle when is it left outside or in the cold – crates made of polypropylene may become brittle after a while if left in the cold because this material becomes very hard below -5°C
- should it be degradeable – some plastic bags are degradeable because a special ingredient is added to the mix so that the long chains begin to fall apart after a while and the bag will simply turn to dust
- and, of course, the cost of the polymer.

Future polymers

In the future we will be using many more polymers. This worries some people as they know that most polymers are made from oil products and they are concerned that we will run out of oil. In fact we only use 4% of our oil to make polymers and we can always burn the polymer after use in the same way as we burn oil in power stations to generate electricity. This means we have had the use of the polymer and we get the energy out of it at the end of its life.

But scientists are always thinking about the future. A team of scientists are already working on a way to genetically modify the chloroplasts of a cress cell so that when it photosynthesises it doesn't produce starch (starch is the food of the plant and is a natural polymer). Instead the plant produces another polymer called polyhydroxybutyrate or PHB which we can use to make useful things but which also biodegrades naturally at the end of its life.

Carlos Muñoz-Yagüe/Eurelios/SPL

The Biocomposites Centre at the University of Wales, Bangor, is developing plastic materials derived from plants. This researcher is examining a polymer material extracted from plant cell walls.

Barak Brudo/Bigstockphoto

Plastic crates like these, exposed to the elements, gradually degrade.

Polymers will also make a big difference in medicine. We already use plastic lenses in people's eyes if they have developed cataracts – the surgeon simply cuts round the iris, pops out the patient's cloudy lens and puts in a new clear plastic one before sewing the flap back onto the eye.

Surgeons also use replacement plastic heart valves for people with heart disease, and replacement plastic hip or knee joints for people with arthritis or who have damaged their joints playing sport. They are also working on plastic replacement skin for burns victims and plastic replacement veins to be transplanted into people who have suffered thrombosis (a blockage in the vein due to a large blood clot).

In the future we can look forward to the possibility of plastic organs such as livers and kidneys for people who have life-threatening diseases and require a transplant. The big advantage here is that, if scientists can get this to work, patients will be able to have a transplant as soon as they become ill. They won't have to wait for a donor to die. Some people spend years on kidney dialysis before they get a compatible donor and some die waiting!

John Cole/SPL

This model, photographed at the Glasgow Science Centre, shows some of the many applications of polymers in medicine – artificial hips and knees, breast implants, stents to prop open collapsing blood vessels, and even artificial voice boxes (larynges).

Getting hi-tech

Another big area where plastics will make a difference is in hi-tech goods. This year will see the first really flat screen television launched. The screen will be only 3 mm thick – much thinner than present flat screen TVs. Also it will be much more energy efficient than plasma screen TVs. These will be very different from present day televisions. They will be made of Organic Light Emitting Diodes (OLEDs). This means a polymer that conducts electricity but this polymer also acts like a semiconductor so it is possible to make a diode from it which emits light at a particular colour. The television picture is made up of lots of dots of the three primary colours of light – red, green and blue, just like a conventional television. Wait another couple of years and we could well have televisions that are so thin and flexible you can roll them up and carry them under your arm!

Finally plastics will make a big difference to climate change. A polymer called Nafion™ is an important part of hydrogen fuel cells. These cells can generate electricity from hydrogen and oxygen. The Nafion is the barrier or electrolyte between the two gases. The protons from the hydrogen go through the Nafion but the electrons cannot. If a wire is provided linking one side of the Nafion to the other, then the electrons flow through the wire to catch up with their parent protons on the other side. This makes an electric current which can power the car. The hydrogen and oxygen combine to make water which drips slowly out of the exhaust pipe.

If we can get the hydrogen by electrolysing water, using solar power, this means we can have electric cars that run on water! And we can power our houses using water too. We won't need petrol for cars or power stations to generate electricity. We won't need overhead cables either as we will each have our own hydrogen fuel cell in the house generating our heat and power. This means that we won't have the problems of pollution and greenhouse gas production that we get from cars and power stations at the moment – and that has to be good!

Martin Bond/SPL

This London bus is powered by hydrogen. You can see steam emerging from the exhaust (top left); this results from the oxidation of hydrogen in the polymer-based fuel cells.

So when you look at plastic items and think they are boring, remember that plastic is going to make a big difference to your life. There will be millions of jobs working on all these new and exciting developments and products in the future – solving the problem of climate change or improving medical care or simply making more exciting electronic gadgets. Only people with science qualifications need apply!

***Averil Macdonald** is Professor of Science Communication at Reading University*

Flying weightless

David Sang

Astronauts in orbit around the Earth experience weightlessness, and this is something they must be trained for. One way they do this is to travel in a large aircraft flown by experienced pilots who can put the aircraft through a special manoeuvre in which the occupants are weightless for up to 30 seconds.

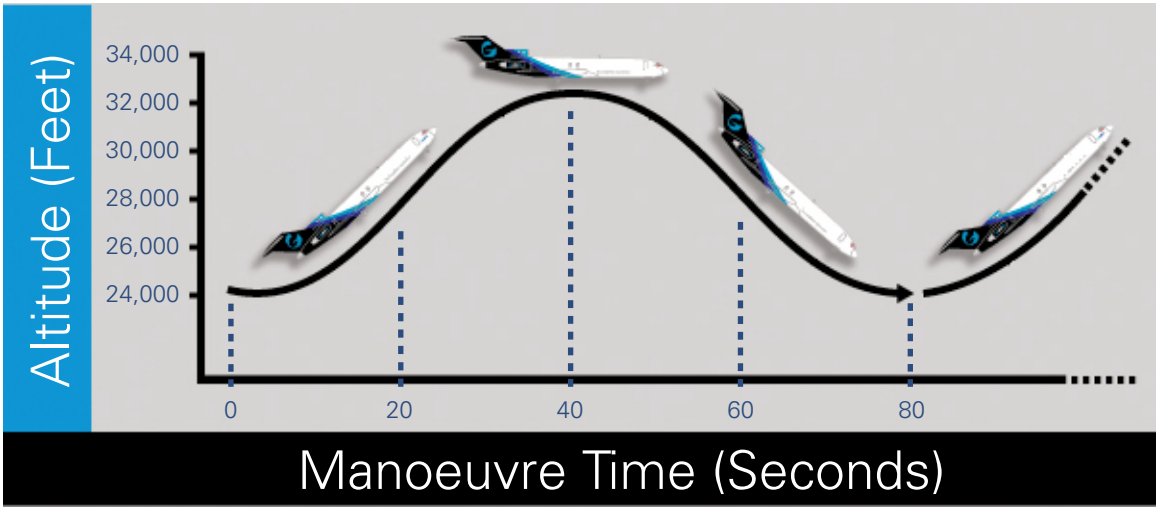
To achieve this, the aircraft flies steeply upwards and then tips over into a downward, parabolic path. It is during this phase that the passengers experience weightlessness. Although the experience lasts only a short time, passengers can perform simple experiments and learn to control their body position.

The pilots can adjust the path of the aircraft to achieve the reduced gravity which astronauts will experience if they ever visit another planet such as Mars (where gravity is roughly one-third of the value on Earth).

Underwater work

An alternative technique used in training is to work underwater where the upthrust of the water cancels out the astronaut's weight. The experience of moving arms and legs is different from that experienced in true weightlessness because of the drag of the water.

Astronauts Soichi Noguchi and Stephen K Robinson in the immersion tank at NASA's Neutral Buoyancy Laboratory in Houston, Texas. They are accompanied by divers to ensure their safety.



The Zero-g aircraft completes several manoeuvres in succession.

A parabola is the curved path followed by a ball or other object when thrown through the air.

What to look for

The photograph on pages 10-11 was taken on 29 April 2007.

- All the interior surfaces of the aircraft are padded to prevent injury to weightless passengers.
- The crew member on the left is setting Hawking spinning freely in mid-air.
- Hawking was diagnosed with amyotrophic lateral sclerosis, a form of motor neurone disease, over 40 years ago. He is almost completely paralysed so extra care was needed to prevent him from coming to any harm.
- Also in the picture is Nicola O'Brien, a nurse practitioner who is Hawking's aide.

Hawking has applied to fly into space in a tourist spacecraft to be launched in 2009.

Flights in the ZeroG aircraft are offered as a tourist attraction at various US airports.

Physicist Stephen Hawking of Cambridge University experiencing weightlessness inside an aircraft as it follows a parabolic path.This manoeuvre is used in astronaut training.

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NASA

Free-fall, weightlessness and acceleration

Why do astronauts experience weightlessness? Are they really free from gravity?

There are two different situations to think about. Firstly, consider an astronaut in the International Space Station orbiting the Earth. The ISS travels 350 km above the Earth's surface. The illustration shows this orbit to scale; the Earth's radius is 6400 km, and the ISS is well within the Earth's gravitational field.

In fact, it is the pull of the Earth's gravity which keeps the ISS in its circular orbit. If the Earth's gravity was switched off, the ISS would fly off in a straight line, at a tangent to its orbit.

In effect, the ISS is endlessly falling towards the surface of the Earth, but the curvature of its orbit is just right for it to follow the curve of the Earth's surface. We say that the spacecraft is in free-fall, and so are the astronauts inside it.

Imagine that you were inside a lift when its cable broke. As the lift accelerated freely downwards, you would be in free-fall. You would be able to take your feet off the floor and twist and turn in midair just like a weightless astronaut – until you reached the bottom of the shaft.

Free from gravity

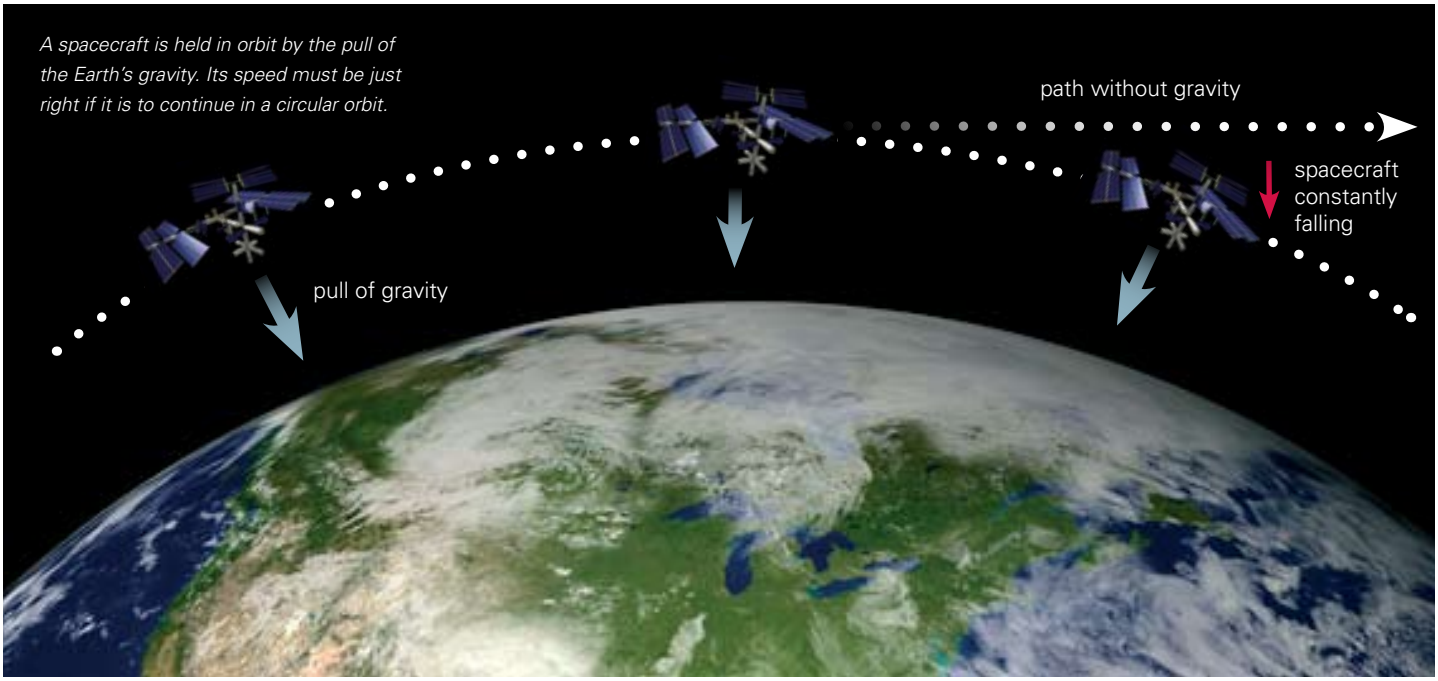
How can an astronaut truly escape from gravity? This can happen on a long space flight such as to the Moon or to another planet. The further the spacecraft is from Earth, the weaker is the pull of the home planet's gravity. Eventually, deep in space, with the rocket motors switched off, the astronauts on board will experience weightlessness because of the absence of gravity.

Now switch on the rocket motors. As they make the spacecraft accelerate forwards, the astronauts feel a force pushing them back in the other direction (just as you are pushed back in your seat as a car accelerates forwards).

Thinking about this, Albert Einstein realised that (unless you could look out of the windows of your spacecraft) you wouldn't know whether you were being pulled by gravity or accelerating because of the force of your rocket motors. That simple idea led him towards his General Theory of Relativity.

David Sang is Physics editor of Catalyst.

Russian cosmonauts Oleg Kononenko (top) and Sergei Volkov experience weightlessness during Expedition 17 of the International Space Station.



A spacecraft is held in orbit by the pull of the Earth's gravity. Its speed must be just right if it is to continue in a circular orbit.

Alan Steven

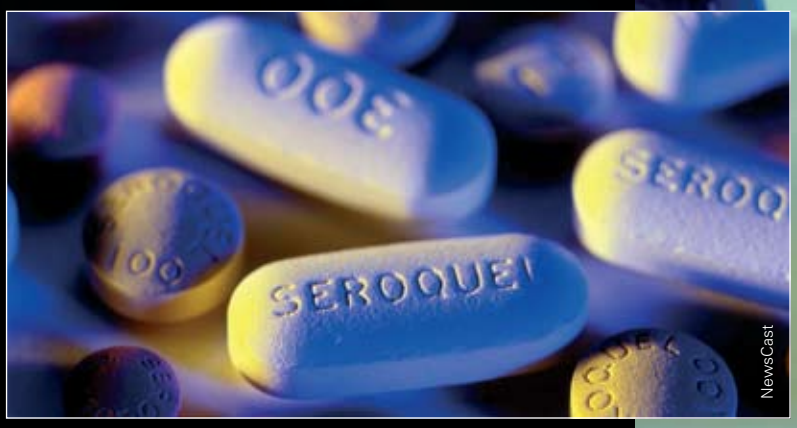
Process Chemistry

Process chemists work within the pharmaceutical industry and are a link in the chain from an initial idea to a new drug making it to the market. It generally takes at least 10 years from an idea by a medicinal chemist to a new treatment for patients – during this time, the process chemist devises the best possible method for producing the drug in large quantities. In this article, Alan Steven describes the role that the process chemist plays.

Drugs are normally compounds with the ability to promote a response from our bodies that reduces the level levels of harmful foreign bodies (such as bacteria, fungi or viruses), or re-establishes the equilibrium of a process that has previously been disturbed or is out of control.

A compound that may eventually become a drug will first be made by a medicinal chemist with some knowledge and understanding of how the compound affects the function of its target in the body, how it is likely to distribute itself in the body, and whether the body may turn it into a more toxic substance. The medicinal chemist will have modified the structure of the compound several times, improving its good characteristics and minimising the bad points such as toxicity.

Only milligram quantities of the compound will have been made thus far, however,at this stage and the assessment of its potential has only just begun. The vast majority of such compounds will ultimately not turn out to be suitable as drugs, and so they are onlycalled drug candidates at this stage.



When a patient takes a tablet, he or she is receiving a dose of a drug – the compound with the desired therapeutic effect. The tablet consists of the drug substance mixed in with other, inert (unreactive) compounds such as cellulose.

A chemist working in AstraZeneca'a research and development labs at Charnwood, Leicestershire.

Key words
drug
synthesis
toxicity

Samples from AstraZeneca's Culture Collection Bank of freeze-dried micro-organisms from around the world.

NewsCast

The process chemist

Toxicology is the study of the adverse (negative) effects of chemicals on living organisms.

It is the process chemist who must supply much larger quantities of the most promising compounds made by the medicinal chemist for the study of short- and long-term **toxicological** effects, the transformation of the actual drug substance into a tablet by pharmaceutical chemists, and, ultimately, its testing with patients in clinical trials. As a compound progresses through this phase, increasing amounts are required for these key studies, which can be delayed if there is a problem in making the compound. Someone is often waiting for more of the drug candidate, so process chemists often have little time to develop an ideal synthesis. The best route which is currently available may be fine-tuned, whilst, in the background, work on a completely new route which allows the drug candidate to be synthesised with even greater efficiency in the future may be carried out.

Synthesis is the making of compounds.

There is usually a lot of scope for improving the **synthesis** of the drug candidate. This is because medicinal chemists are less interested in the efficiency of the synthesis but need to produce large numbers of compounds for biological testing quickly. A medicinal chemist will usually choose his/her reaction conditions so as to achieve a high percentage yield, which is a measure of the efficiency of converting a starting material into a product, whilst a process chemist considers the efficiency of a reaction from a much wider perspective. For example, process chemists try to use cheap, readily available starting materials, environmentally-friendly reagents that can be disposed of cheaply, and reaction temperatures that do not require excessive amounts of energy.

A route that has been improved by the process chemist on the laboratory scale also has to be developed into a series of processes that are suitable for manufacturing the compound on a multi-kilogram scale. When a process chemist is trying to join a series of isolated reactions together into a scalable process the following questions may be asked:

- Must the product be isolated, or can it be reacted on without having to change the solvent from the preceding reaction?
- How are any byproducts from the preceding reaction going to react in the present reaction?

A developed process will use the minimum number of different operations to form the maximum number of bonds in the reaction vessel in the shortest amount of time and for the lowest cost per kilogram of drug candidate.

Bath-tub-scale chemistry

Processes should also be robust, safe, simple and reproducible. Robustness is built into the reactions by identifying all factors (e.g. temperature, stoichiometry, reaction time) that may change the outcome and establishing the values of these factors that can be tolerated before the reaction starts to misbehave or change in some way. A developed process will also be as simple as possible: ideally, its reactions can be performed by an operator in the equivalent of a bath tub with the pure product crystallising out of the reaction and later being collected by filtration. The reactions should also be reproducible – it is more important that we get the product in the same yield and with the same quality, than for the yield to fluctuate between being very high and very low. Our reactions are designed with a view to scaling them up so they can be performed in a 6000 litre vessel (or even bigger). If something goes wrong on that scale, you need an awfully big spatula to scrape the vessel out!

Process chemists are synthesising drug candidates that we all hope will ultimately improve a sick person's health when ingested. We therefore need to be able to prove exactly what a participant in a clinical trial is putting in his/her mouth to ensure the reverse is not the case due to contamination with toxic impurities. This is done by manufacturing the drug using certain good manufacturing practices that are based on good science and ethics. They include questioning where the starting materials for a reaction have come from, proving that your reaction will not be contaminated by any materials left over from the previous reaction run in your reaction vessel and establishing that your product is really what you think it is.

Fine-tuning a reaction

In order to be able to produce as pure a drug substance as possible, and to control its purity, the process chemist needs to understand the chemical reactions used, as well as any side reactions that are taking place to form impurities. Impurities that can not be detected when the reaction is performed on a small scale in the laboratory soon become an issue when a reaction is scaled up, even if they are formed in the same percentage yield as on a small scale. To get this understanding about our reactions, we need to study how fast the reaction is taking place (the kinetics) as well as how the starting material is converted into product in terms of making and breaking bonds (the mechanism). Often this understanding allows us to tune the reaction conditions so that a reaction is steered along just one of many possible paths. Let us say an unknown impurity has appeared in the drug substance during development. The process chemist will have to isolate the impurity, determine its structure using a variety of techniques (often with help from analytical colleagues), propose a mechanism for its formation, and change the reaction conditions accordingly in order to minimise its formation.

The role of the process chemist is truly one of the most rewarding in drug discovery and development. The odds of discovering a marketable drug within one's life as a medicinal chemist are very small. A chemist working in process research and development, by contrast, gets to work on more advanced projects, and so has a real chance of developing a synthesis for a drug that may ultimately save people's lives when it reaches the marketplace.

Alan Stevens is a process chemist working for the pharmaceutical company AstraZeneca.

Process chemists working in AstraZeneca's labs in Boston, USA.

Look here!

http://www.sep.org.uk/catalyst/articles/catalyst_17_1_293.pdf
An article from a previous issue of CATALYST about testing new medicines
www.abpi-careers.org.uk for more information about working in the pharmaceutical industry and the different roles which are available
http://tinyurl.com/2mkx5e
This web page allows you to access a publication from the Wellcome Trust about how drugs are developed.

Careers in the Pharmaceutical Industry

A hundred years ago there were no antibiotics, no paracetamol and no readily available relief from common illnesses like diabetes or asthma. There was no hope of remedies or cures for more serious conditions like cancer. The medicines which doctors can prescribe (and many which you can buy without a prescription) were developed and often discovered by the pharmaceutical industry. In this article, five people who work in the industry explain what they do and why they enjoy it.

Drug Industry

The industry employs more than 70 000 people in the UK in a variety of roles including drug development and scientific research, manufacturing and making the medicines, IT, statistics, testing the drugs and clinical trials, human resources and looking after the staff and sales and marketing.

Economics

- In 2006, the British pharmaceutical industry spent around £11 million each day on pharmaceutical research and development, which is nearly £4 billion each year.
- The value of the UK pharmaceutical exports in 2006 was £13.8 billion (more than £200 000 per employee), making the industry one of the UK's largest exporters.

Sarah Marshall, 25

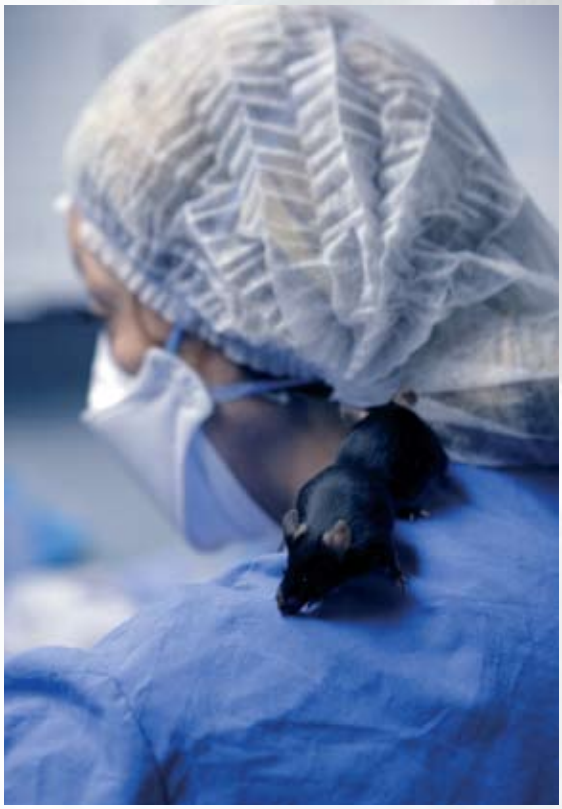
Toxicology Study Director for a Contract Research Organisation

"I came into the company with a degree in Anatomical Sciences and began work as a laboratory scientist. After a year I was promoted to my current role."

Toxicology is the study of the adverse or negative effects of chemicals on living organisms. If a new drug is potentially going to be given to people, we need to be reasonably sure that there are not going to be terrible side effects.

I work as a Toxicology Study Director. I run general toxicology studies in rodent and non-rodent models. We study pharmaceutical, agricultural and industrial compounds to find out what negative effects they may have. I manage all the procedures that contribute to a study, have responsibility for how the study is carried out and its final report. In the report we will interpret clinical data such as body weight, organ weight data, electrocardiographs (ECGs) and other observations of the animals.

In my company we carry out a wide range of pharmaceutical research for our clients. As I am the single point of control for the study, I have to liaise with the clients, design a study which meets their needs and host their visits and inspections. Although I work mainly on my own, there is a lot of teamwork involved in a successful study and it is important to have good communication skills, time management and to be able to multi-task.



An ECG measures the rate and regularity of the heart beats and can be used to detect problems with and damage to the heart

Drug Development

- On average it takes at least 10 years from initially making a new compound to it becoming a prescribable drug
- For every new compound which makes it onto the market, around 10 000 will have been made which do not

Mark Bratt, 32
Process Development Chemist, Pfizer

"I have a degree and a PhD in Chemistry and decided that I wanted to work with products which were actually being manufactured or going to be manufactured as it seemed to be based more in the real world."

I work at a laboratory in a manufacturing facility where the medicines are made. My role is to redevelop existing manufacturing processes with the aim of creasting a more efficient manufacturing route. Most of the compounds we make are not made in one single step; they are multi-step processes. I might try to increase the yield for an individual step; use cheaper or less hazardous reagents or solvents; reduce the number of steps. This might involve either an alternative synthesis or 'cleaning up' an earlier step to reduce the amount of purification requried. If I succeed we might be able to manufacture for example 8 batches in the same reactor volume and time that it would normally take to produce 6. This reduces wastage and also cuts costs.

As part of the job I need to appreciate the issues involved in making the compounds not just in the lab but on a chemical plant scale where the risks are much greater due to the scale we work on. Any changes we propose making need to be discussed with project managers and engineers so communication skills are important as well as practical skills.

A PhD is an advanced degree requiring 3 or 4 years further study which can be taken after a first degree (which is usually a Bachelor's or Master's degree)

Tamsin Jenkins, 28
Formulation Scientist, Pfizer

"I did Science A-levels at school but got very nervous in the exams and did not do as well as I had hoped so did not get onto my first choice of course. However, I went to university to do an HND and did so well on it that after a year I was able to swap to the degree course that I had originally intended to follow. I now have a degree in Pharmaceutical and Cosmetic Science."

I work as a scientist within a formulation group and focus on treatments for allergy and respiratory problems. I spend about half my time in the lab and the other half at my desk. In the lab I formulate dry powder blends and test them. This involves blending the active drug with other materials (called excipients) and then filling the blend into a given format before testing it, to develop a product which can be inhaled. The formulation of the drug is what it is mixed and blended with and is very important as we are trying to target the lungs. They have a very large surface area and can only easily be reached by using an inhaler. The formulation must be able to be placed into the delivery device – but also come out and get to where it is needed in the lung.

The project that I am working on is about to go into clinical trials (where it is tested in people) which is exciting and I am looking forward to learning about the next phase of development.

As part of my degree I did a year long placement in the pharmaceutical industry. I really enjoyed it and decided to make it my career.

The simplest type of chromatography is paper chromatography which can be used to separate colours in inks or food dyes. Other more complex types of chromatography are used in industry to separate and purity compounds, but they work on the same principles

Emma Rees, 25

Drug Safety Officer for Hospira UK

"I have a degree in Pharmacy. I prefer the work-life balance which you have in my job to that which I had in my previous experience being a Pharmacist in the community or in hospital."

Pharmacovigilance is the detection, assessment, understanding and prevention of adverse effects, particularly long term and short term effects of medicines

I work in the pharmacovigilance department of a large pharmaceutical company. My role is to monitor reports which come in with information about an adverse reaction which a patient has had when receiving a drug manufactured by my company. These reports come from sources such as the regulatory authorities, health professionals (doctors, nurses and pharmacists), articles in published scientific literature and during clinical trials.

We write safety update reports where we gather together all the information on adverse events (a bad reaction to the drug) that have been received over a certain time period for one particular drug. We then use this data to analyse if there are any patterns in a particular side effect. Depending on what our data shows we can act in different ways: we may not need to take any action; we can make changes to prescribing information given to doctors and in patient leaflets; or in the worst case we can issue a withdrawal notice for the drug and stop it being used. Fortunately, this hardly ever happens.

As part of my degree course I did an industrial placement and loved it. I work mainly at my desk on my PC, but work as part of a team so it is important to be able to communicate well, be organised, work with others and be willing to learn.

I enjoy my job enormously and it is very satisfying to feel that I am helping to ensure that the medicines which we make are as safe for people to take as possible.

In the UK, the main regulatory authority is the Medicines and Healthcare Regulatory Agency who are part of the Department of Health. They monitor the safety of medicines and medical devices, in addition to the monitoring done by the pharmaceutical companies themselves

Marie Timms, 28

Analytical Chemist, Discovery for Lilly

"I joined the company straight from school where I had completed Science A-levels. I started as a lab technician but have been promoted several times. I have now completed a Masters degree while working at the same time which took me 5 years."

I work as part of the Discovery Chemistry group whose aim is to make and analyse new compounds. My role as an analytical chemist is to analyse and purify these compounds so that they can be passed onto the biological group for initial testing.

I begin work by checking to see which compounds have come in and need to be purified. I may then begin to develop a method so a sample can be purified or I will start purifying a sample. It is hard to plan exactly what I will do during the day as urgent samples can come in which need to be dealt with immediately. I mainly use different types of chromatography in my work, but do sometimes work on other projects using different methods of analysis. I have also been able to go to several scientific conferences including one where I presented some of my own, novel (new), work.

World Leader

The UK has an impressive track record when it comes to discovering new medicines and drugs – nearly 1 in 5 of the top 100 medicines in the world were discovered and developed here. That is higher than for any other country apart from the USA.

Vicky Wong – with thanks to Sarah Jones from the ABPI for her help in preparing this article.

Look here!

For more information about careers in the pharmaceutical industry, see www.abpi-careers.org.uk

In the Mountains – Going up?

Jill Sutcliffe

Holidaying in high places such as the Andes or Himalayas is becoming increasingly popular. Jill Sutcliffe describes the dangers that await the unwary traveller and explains how, if we understand our bodies, we can avoid the worst problems of life at high altitudes.

Key words
respiration
human health
atmospheric pressure

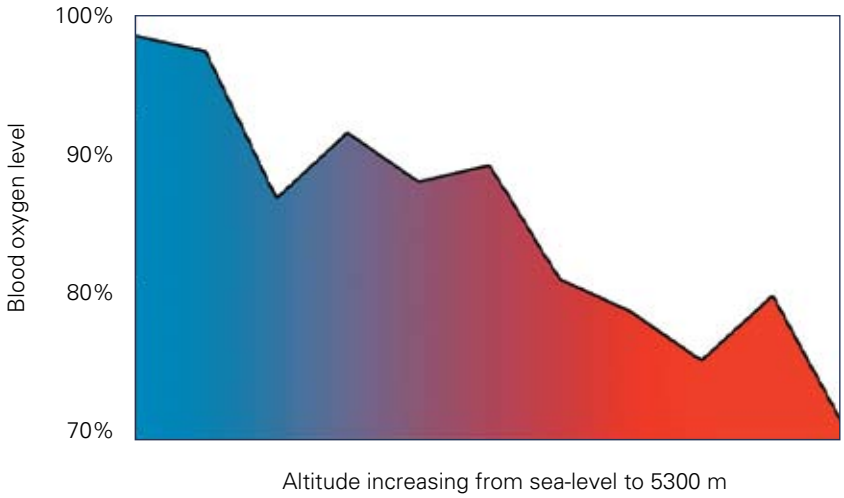
From time to time, mountain rescue groups are called out to take action to find someone and to rescue them when they've found themselves in difficulties. In the UK the highest mountain, Ben Nevis, is about 1500m high; it is exhilarating – with the right kind of preparation and equipment – to visit such areas. You need to take notice of the weather conditions and be prepared to decide *not* to go if the forecast is bad.

However, walking in places which are higher than Ben Nevis can start to have an effect on the body. Everyone knows that when you heat water at height it boils more quickly – the reduced atmospheric pressure lowers the boiling point of water. The body also starts to behave slightly differently as it tries to make up for the reduced oxygen level. So what is the difference about travelling at altitude?

Effects at altitude

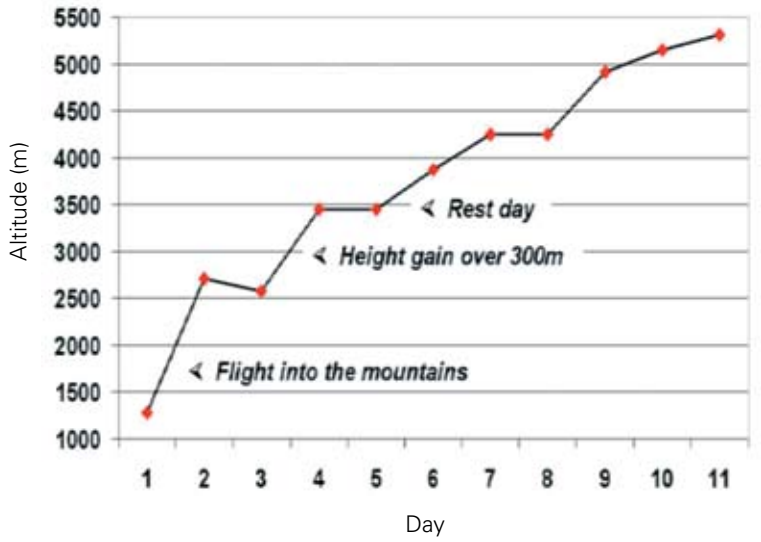
The main difference it that as you go higher the air pressure gets lower (the air gets 'thinner'), and this means that for every breath you take there will be less oxygen in it for your body. Oxygen is needed for respiration, the process which releases the energy to move and for your brain and digestive system to work. So as your body gets less oxygen it has to adapt. Initially you start to breathe faster and deeper and the body starts to make more red cells so that it can carry more oxygen in the blood.

In some unfortunate people, fluid starts to collect in the lungs. They suffer severe breathlessness even when at rest, and they cough up frothy, bloodstained spit. This is 'high altitude pulmonary oedema' and the sufferer may need to be given oxygen quickly and must descend straight away.



Measurements of an individual's blood oxygen saturation during a climb.

At high altitudes, snow can be very cold and dry.



Gaining height: how one walker's altitude increased during a trek in Nepal.

Such changes take time to happen. If you go up slowly you should be OK and stay healthy. However, if you go up too fast you risk suffering from altitude-related illness. At heights above 3000 m the best advice is *not* to go up more than 300 m in any one day. If the route means going up more than 300 m you will need to come down to a level so that you've only changed your altitude by 300 m. One danger arises when people fly in and land at a high altitude and then only have a short time for their holiday and try to rush things. You need to build in some time to acclimatise and for your body to get used to the change.

Most people going up high feel altitude-related symptoms. If the illness is dealt with correctly, it is unlikely to be a major problem but if it is not recognised and understood, that can spell disaster.

Camping during a blizzard: snow is an excellent insulating material so the climbers stay warm in their tents.

Top score:

how footballers do better at high altitude

In South America, several countries have capitals which are high up in the Andes. The highest, La Paz in Bolivia, is at 3700 m above sea-level. What problems does this pose for footballers?

There are two answers to this. Local footballers who live and train at altitude are well-adapted to the low atmospheric pressure. Their circulatory systems have a high concentration of the red blood cells which carry oxygen around the body.

For visiting teams from lower altitudes, it's a different story. They can suffer symptoms of altitude sickness (as described in the main article), and this affects their performance.

Teams from lower altitudes spend several days acclimatising to high altitudes. In May 2007, football's governing body FIFA banned international matches at altitudes greater than 2500 m, citing concerns about players' health and possible distortion of competition.

However, even after acclimatisation, it seems that the footballers from high altitude have an advantage. This finding emerged from a study by Dr Patrick McSharry of the Department of Engineering Science at Oxford University. He looked at the results of 1460 matches between football teams of 10 different countries S America. Some have home grounds close to sea-level; others regularly play high up in the Andes mountain range.

Possible illnesses

It is important to find out before you leave for your trip about what can happen and what to look for. Some very strange things can happen to your body when you go high! Things such as headaches, being out of breath, feeling or being sick, sleeping badly and not feeling hungry. These are symptoms of Acute Mountain Sickness. One of the main impacts is not being able to think straight so it helps if someone else is keeping an eye on you.

The brain is affected by altitude because it needs a good supply of oxygen. With less oxygen available the brain may swell causing pressure. You need to look out for headaches, becoming dizzy and experience mood changes. It is a good idea to keep a log so that you can monitor your own condition. One young traveller wrote:

I set off at the back with a sore head, coughing. My cough and head got worse. A 'drag' feeling began in my mouth. When I met the others I plucked up the courage to ask if my speech was slurred. The shock hit me. I heard myself mumble incoherently. They looked horrified as my words just dribbled out. I couldn't use my left arm, no power, my left hand tingled, the left of my face was paralysed and my head sore. I was done for!!! Expert medical care and a descent to a much lower altitude as quickly and safely as possible saved my life.

Help

A British doctor was the medic employed on an expedition in the mountains in 1991. One of the group developed Acute Mountain Sickness and died. The doctor hadn't known what to do. When he got back to England he talked with others and set up a group – Medical Expeditions – to find out more and, importantly, to train other people about the effects of high altitude. The group runs annual courses, organise expeditions to mountainous areas and undertake research on the participants so that they can learn more about what happens to the body at high altitude. They have just published a short, easy to carry manual, *Travel at High Altitude*. Regular articles about health and travel are published in *Wanderlust* magazine by Dr Jane Wilson-Howarth who is also the author of *Bugs, Bites and Bowels,* a guide to keeping healthy when travelling. The latter deals with more than just altitude and includes a section on the beasts, large and small, to avoid.

Jill Sutcliffe is an environmental scientist and a keen (but careful) traveller. Excerpts with permission from Medex.

Look here!

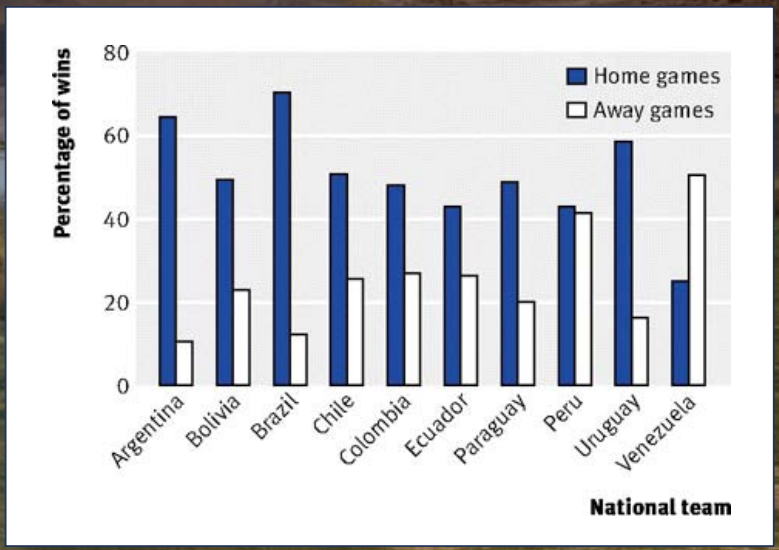
Download a copy of the Medical Expeditions guide Travel at High Altitude from: *www.medex.org.uk*

Dr McSharry's statistical analysis, published in the *British Medical Journal*, showed that teams such as Argentina, Brazil and Uruguay, with low-level home grounds, were much less likely to win when they played teams such as Colombia, Ecuador or Bolivia, all over 2500 m up.

What's more, he was able to show that teams from high up still had an advantage when they played lower down – there is evidence that the players' increased blood supply can help their running performance.

The outcome is that the Bolivian team effectively has a 1.5 goal advantage in matches where they play teams whose base is at sea-level. To put it another way, that's a 0.5 goal advantage for every 1000 m difference in altitude.

Dr McSharry emphasises that adaptation to altitude may be only one of several factors which affect the results. The ball behaves differently at high altitude where the air is thinner – it spins less, and moves faster and further. Or it might be that these teams are simply better-trained and managed. Perhaps you'll think twice before accepting a challenge from some mountain athletes.



Natural born healers

Many drugs which are commonly used today are similar to naturally occurring compounds which have been used for centuries to treat illnesses.

Chemists have identified and purified these substances. By determining their molecular structures they can then synthesise similar compounds which may have improved medicinal effects.

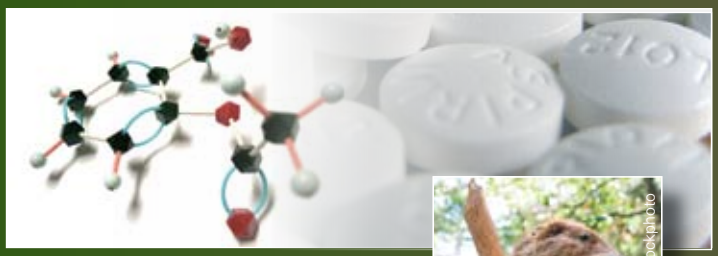
Dale Wagler/Bigstockphoto

Foxgloves

Digitalin is an extract of the foxglove (*Digitalis*) which is used to treat heart conditions. The plant itself is poisonous, but biochemists have isolated the active ingredient and determined how it works.

Beavers and willows

Willow trees (*Salix*) contain salicylic acid, a substance similar to aspirin. Beavers (*Castor*) eat the bark and cambium of willows; the acid accumulates in their anal glands. People discovered that eating these glands could reduce a fever, and so beavers were hunted almost to extinction.



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Mould

Many blue cheeses are made using a mould called *Penicillium*. This is the source of the antibiotic penicillin.

ewa albrecht/Bigstockphoto

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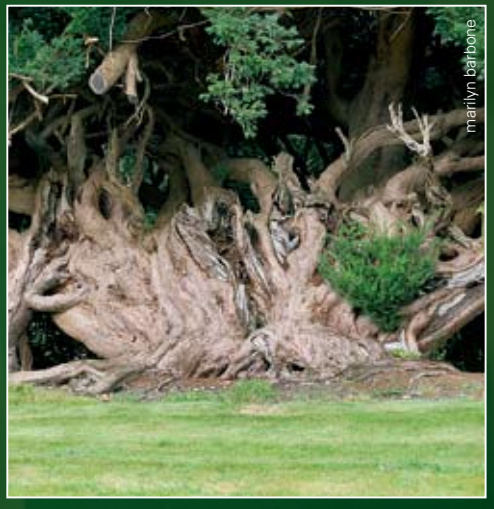
Yew

Leaves of the yew tree (*Taxus*) contain a substance which can be modified to produce an anti-cancer drug, docetaxol. People with yew trees are asked to supply clippings to drug laboratories.



marilyn barbone

Paulus Rusyanto/Bigstockphoto