It might seem odd that a word can cover such opposites. But medicines and poisons are closely related. Both act in the same way – by interfering with biochemical processes in the body. This can kill us or cure us.

Our attitudes to pharmaceuticals also swing between positive and negative. We have much to be thankful for. We now have an unrivalled range of medicines to bring us back to health. Huge amounts of effort and resources are being put into the development of new medicines.

So far, so rosy. But while providing immense benefits, drugs are not the perfect solution. They only work on a proportion of patients, sometimes they harm us, and we’re not very good at taking them as we should.

For some diseases, particularly those affecting only developing countries, there are no drugs available or they are too expensive. Even in the UK, some patients find they cannot obtain drugs.

Meanwhile the NHS drug bill – the greatest cost, after staff – continues to rise. Drugs seem to be the answer to everything from rheumatism, through birth control, to depression. And yet while agonising over pill-popping, we consume vast amounts of untested complementary remedies.

How has this situation come about? What part do pharmaceuticals play in modern life? And where might we go in the future? These are some of the questions tackled in this Big Picture on Drug Development.
We live in a pharmaceutical age. When we are ill, we look to manufactured medicines to make us better. We have access to more treatments than at any time in human history.

Our access to medicines is controlled, mainly by our GP. Most medicines we take are produced by giant multinational corporations.

It is a far cry from the days when we would turn to a local herbalist or old wives’ remedy when confronted by illness. Yet if we take aspirin, the same compound that eased our pain in the Middle Ages banishes our headache in the 21st century.

A sense of humour

Our medicine, like our politics and philosophy, owes its origins to Ancient Greece.

The roots of modern Western medicine lie in Ancient Greece, around the 6th century BCE. Before then, disease and healing were seen in a supernatural context; healing and religion went hand-in-hand. Illness was often seen as divine punishment.

By the time of Hippocrates (left), around 400 BCE, Greek medicine had come to focus on the body and on natural explanations for sickness and health. The Greeks believed that the body was made up of four humours or fluids – blood, phlegm, yellow bile and black bile – and that the balance of these humours was central to health.

Il-health was thought to stem from an imbalance of the humours, so treatments aimed to restore balance. This could mean use of pepper to induce sneezing fits, bleeding people, or subjecting them to enemas or potions to trigger violent vomiting.

Later, Ancient Rome embraced Greek medical thinking. Their best physicians were nearly all Greek, including Galen, the most celebrated Roman medical man. Making the most of nature’s bounty was core to Roman medicine: dock for paralysis of the legs (possibly scurvy), St John’s wort to expel bladder stones, fenugreek as an enema and to treat pneumonia, figs for cough remedies.

The balance of the humours was an enormously influential idea. Only in the past century or so has its popularity waned. Even now, however, echoes appear in popular thinking – detoxification, phlegmatic personalities and so on.
In the late 1800s, Burroughs, Wellcome & Co. introduced machine-made compressed medicines or ‘tabloids’ into Britain. This was the key to Henry Wellcome’s business success. It introduced an era of drug mass-prodution, though the term ‘tabloid’ later came to be associated with ‘compressed news’ and hence popular newspapers.

Paul Erhlich and others proposed the idea of ‘magic bullets’ – chemical compounds that attacked and destroyed only infectious organisms.

Western medicine sees disease as a disruption to our body’s physiology, which treatment aims to correct. But there are other medical traditions – such as traditional Chinese medicine and the Ayurvedic tradition of India. Like the humours, these share the idea of balancing life forces.

Non-Western and Western traditions differ significantly. A crucial distinction is the way they answer the question ‘does it work?': Western medicine argues for evidence from scientific studies; other traditions rely more on the ‘test of time’.

See www.wellcome.ac.uk/bigpicture/drugdev.

The Victorian era saw the beginnings of the pharmaceutical industry.

By the end of the 19th century, medical doctors had become established pillars of society. They would diagnose illness and write prescriptions. The medicines themselves would be prepared by apothecaries – the dispensing chemists of the day. This conventional system coexisted with a flourishing trade in ‘patent medicines’ or quack cures.

The Victorian era saw a series of profound changes. Firstly, the modern scientific disciplines began to emerge, and science began to move into specialist facilities such as laboratories. With the emergence of germ theory, it became clear that microbes were responsible for many of the killer diseases of the day.

Chemists began to purify the active principles from plants to provide a supply of drugs. Morphine was isolated from the opium poppy, atropine from the deadly nightshade, colchicine from the autumn crocus.

Making medicines

But yields were low. Chemists began to explore ways to make useful compounds by chemical synthesis. In the 1850s, 18-year-old prodigy William Henry Perkins tried to synthesise quinine from coal tar. Instead he produced the first synthetic dye, mauvein (mauve). This colour, associated with royalty and privilege, was difficult to obtain by natural means and highly prized. Perkins made a fortune and also helped create a successful synthetic dye industry, which Germany came to dominate.

In a neat twist of fate, the chemicals produced by the dye industry turned out to have medically useful properties, leading to the appearance of many famous pharmaceutical company names, including Hoechst, Bayer, Sandoz and Ciba.

Postwar expansion

In the past 50 years, the pharmaceutical industry has become a huge global enterprise.

After World War II, drug companies led a therapeutic revolution.

Key discoveries of the early 20th century – notably insulin, vitamins and antibiotics – were mass manufactured and available to all.

New compounds were ushered in: cortisone for inflammation, drugs to treat heart conditions, antibiotics to cure syphilis and tuberculosis, and psychiatric drugs to treat, rather than lock up, the mentally ill.

Yet the ‘white heat of technology’ that inspired the 1960s has given way to a more sceptical mood, and pharmaceuticals are no exception. The drugs had side-effects or were addictive. Bacteria developed resistance. Progress in tackling some diseases has been disappointingly slow. Doctors are accused of dispensing medicines with little thought for patients’ greater wellbeing.

At the same time, concerns have grown about the tactics of pharmaceutical companies – their marketing muscle, their political influence, their activities in developing countries and their alleged manipulation of clinical trial data to support their own products.

Pharma is said to be more profitable than any other business. In 2006, global spending on prescription drugs topped US$600 billion (£300bn).

Are such sums excessive? One could argue that drug discovery is a risky and expensive business and, in return, pharmaceutical companies provide life-saving medicines. But some people have voiced concerns over how the industry operates. They accuse drug companies of spending huge sums promoting their products directly to doctors and lobbying politicians.
Developing a new drug is a long process. What are the key stages, and who does what during them? By way of illustration, this fictional case study examines the people and processes involved in drug development.

Professor Felicity Workwell leads a group of researchers at the University of Chortlington. She is studying Huntinzheimer–Parks disease (HPD), a common and painful bone condition affecting people in middle age.

She doesn’t work alone. As well as her team of 20, she has several collaborators:

- **Dr Hamish Bedside-Manor**, a clinical scientist who runs a clinic for HPD at Chortlington General Hospital
- **Professor Randy Beckhammer III**, an HPD expert in the USA
- **Dr Pierre Souris**, a French researcher who studies HPD in mice.

With funding from the Huntinzheimer–Parks Disease Foundation, Professor Workwell’s group is studying the basic science of HPD, in an attempt to identify possible new therapies. After five years, they have made great progress. They have:

- worked out how the disease affects people
- studied disease mechanisms in more detail in the mouse, and identified the main type of cell affected
- found a growth factor that binds to a specific receptor on this cell
- shown that genetically engineered mice lacking this receptor do not display the symptoms of HPD.

These exciting findings, published in the scientific literature, suggest that the receptor could be a target for new therapeutics.

They have also patented their antibody – essential for later commercial development.

Professor Workwell considers next steps. One possibility would be to set up a ‘spin-out’ company, where university researchers leave to work in a commercial environment.

But Professor Workwell enjoys working in the University. Instead, she teams up with a small biotech firm, FlexiBioTher. This firm is run by Dr Graham Gogetter, a former university researcher who left academia to run his own company.

At this point, it is too early for large pharmaceutical companies to be interested. The chances that a useful drug will emerge are, unfortunately, very small. Instead, Professor Workwell and Dr Gogetter apply for ‘seed’ funding to test their agent further.

After exhaustive work, FlexiBioTher has chemically tweaked the original agent and painstakingly analysed its effects on bone cells. It has raised several million pounds from venture capitalists – investors who put money into high-risk projects. It's looking good, but there is still less than a one in ten chance that this agent, now codenamed FBT1000, will make it to market.

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**Beginnings...**

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**Enter pharma**

Professor Workwell and FlexiBioTher have gone as far as they can. The firm is too small to undertake the expensive research and clinical testing that will now be needed.

But FBT1000 looks promising, and there would be a large market for a new therapeutic. So FlexiBioTher enters into a partnership with a large pharmaceutical company, Merphizoglax.

Merphizoglax brings its mighty drug discovery skills to bear, running many tests to find out how FBT1000 behaves in the body, checking in animal studies for signs of toxicity and characterising further its effects on bone cells. The company’s scientists assess how FBT1000 is metabolised, how long it stays in the body and where it goes.

After more chemical refinement, FBT1000 is finally ready to be tested in people.
FBT1000 has passed its toxicity tests, and the data from animal studies suggest that it should tackle the disease in people.

Morphizoglax engages a specialist company to organise phase I clinical trials on its behalf. Before these can start it has to get approval from the Medicines and Healthcare Products Regulatory Agency (MHRA).

The trials involve six healthy volunteers who are given doses much lower than have proved safe in animals. The drug is given by medically qualified staff in a facility linked to Chortlington District Hospital. The volunteers are monitored carefully.

The news is good. The volunteers have suffered no ill-effects. The company can move on to phase II trials – the first time actual patients get the drug.

The phase II trials involve a small group of patients and are designed to check that the drug is safe in people with disease and that it does have beneficial effects.

This is another critical ‘go/no-go’ decision point for Morphizoglax. The company cannot afford late failures. Fortunately, the phase II trial has gone well – FBT1000 gets the green light.

Now it is time for large, phase III trials. Dr Bedside-Manor and Professor Workwell are involved in the trial, which recruits patients from a series of hospitals in the UK, as well as in the USA and France. In all, almost 5000 patients volunteer to take part.

FBT1000 has been tested in a double-blind randomised control trial – neither doctor nor patient knew what was being given, real drug or placebo. When the codes are broken and the data analysed, the news is good: FBT1000 has reduced symptoms and has only minor side-effects.

FBT1000, now named osteomab, could be a blockbuster. But first Morphizoglax has to convince the regulators that it deserves a licence. It collects together all the data it has gathered during its research and clinical trials and submits them to the MHRA.

Looking through the trial data, the MHRA is concerned about possible effects on the liver. It requests more data. Eventually, though, it is satisfied. Osteomab gets its licence.

It has taken more than ten years to go from a research lead to a licensed product. But the path has been relatively smooth. And of 100 similar leads, only a handful will ever make it through to being marketable drugs.

Yet more hurdles

But the story isn’t finished yet. Morphizoglax still has to convince doctors and NHS trusts to make osteomab available to their patients.

Central to this will be the decision of the National Institute for Health and Clinical Excellence (NICE), which will decide whether osteomab offers good value for money (see page 14). Without NICE’s seal of approval, osteomab would be dead in the water.

Morphizoglax also has to raise awareness of osteomab’s existence. It launches an awareness campaign to persuade doctors to prescribe it (it cannot market directly to patients in the UK, though it can in the USA). It may still take years for all patients to get the drug.

Drugs can now be designed on the computer screen.

In the past, drugs were developed on the basis of their ability to tackle symptoms. How they worked – what biochemical process they targeted – was rarely known. Now, rational drug design takes the opposite approach. Researchers start with a target biochemical pathway or molecule and try to find a way to interfere with it.

Central to this approach has been the growth in structural biology – working out the three-dimensional shape of large molecules such as proteins. This was first done for myoglobin (a relative of haemoglobin) in the 1950s. Now the structures of thousands of proteins are known and can be studied on computers.

The structure of a protein, combined with findings from other studies, can reveal how it functions. It is then possible to identify key parts of the protein – such as its active site if it is an enzyme – and to design small chemicals that stop it working (or change how it works).

A good example is the antiflu drug Relenza (zanamivir). This targets the neuraminidase enzyme (above) on the outside of influenza virus particles. Its development started with the structure of neuraminidase, bound by an inhibitor known as DANA. The structure of DANA was refined so that it was a better fit and hence better inhibitor of the enzyme. Zanamivir was approved for use in the USA in 1999.
WHAT DRUGS DO

We are used to seeing pharmaceuticals in their blister packs, or medicines in brown bottles. Less common treatments might call for injections or use of a drip in hospital.

But what’s in those anonymous pills and fluids? And what do they actually do inside our bodies?

Small wonder?

Most drugs are small organic chemicals.

Many drugs are small molecules that latch onto specific structures in or on our cells. Our cells have numerous specialist functions, regulated by instructions from genes. The drug molecules alter these processes, subtly changing cell biochemistry.

Herbs and minerals were used in ancient cultures. During the European Renaissance, apothecaries experimented with plants retrieved from the Americas by explorers, such as the bark of the quina tree. This contains quinine, used to treat malaria.

Even when an active ingredient had been identified, doctors rarely knew how it actually worked. A profound change came when researchers began to use an understanding of the molecular basis of human physiology to develop new drugs – so-called rational drug design.

A true magic bullet?

Monoclonal antibodies are becoming a more common therapeutic tool.

A critical part of drug development is getting a therapeutic agent binding specifically to its target. But, as usual, nature is several steps ahead of us, and has already created highly targeted molecules: antibodies.

Sir James Black was behind two major drug families: beta-blockers to treat coronary heart disease and drugs that blocked histamine receptors, which are used to treat stomach ulcers. He introduced a new way of thinking to drug development. Black’s approach involved understanding how cells use messenger molecules to communicate with each other.

Small is beautiful

Drug companies have preferred to create drugs from small molecules. This should make them easy to synthesise, to modify and to characterise, as well as more likely to reach their targets in the body. They can generally be given in pill form. A small, stable molecule is easier to quality assure, and scaling up to full production is more straightforward.

WHAT HAVE POTATOES, GOATS AND RICE IN COMMON?

They are all being used to produce pharmaceuticals. The use of living organisms to produce drugs – ‘pharming’ – is covered in Big Picture Online.

ONLY ABOUT 5 PER CENT OF A PILL IS ACTUALLY AN ACTIVE PHARMACEUTICAL. What else is in there and how does it affect the development of new drugs? See Big Picture Online to find out.
The pharmaceutical industry is at its happiest with small chemicals – especially stable, easy-to-make ones. It is much less keen on proteins – large structures with an irritating tendency to denature. And they cannot be taken as pills as they are rapidly digested.

On the other hand, the human body uses proteins for most of its important jobs, and they are very versatile. Some proteins have been turned into usable drugs. A classic example is insulin. It was first used back in 1922, in a remarkable demonstration saving the lives of a ward of comatose diabetics. Initially, insulin was obtained from animals such as pigs, but human insulin was later obtained by genetic engineering. This technology has led to large-scale production of therapeutic proteins. One of the first therapeutics produced this way was erythropoietin (EPO), which stimulates blood-cell production and is used to treat anaemia. (Cyclists and athletes can also benefit from extra red blood cells; it is now a banned substance in these sports.)

Etanercept (Enbrel) has been licensed for treatment of rheumatoid arthritis. It is a modified form of the receptor for TNF-\(\alpha\), and binds to TNF-\(\alpha\) in the bloodstream (much like infliximab).

There are hopes that other proteins could make their way into clinical practice. Growth factors, for example, cause particular types of cell or multiply. They are used to boost blood-cell numbers in some cancers. There are also hopes that growth factors could help to repair nerve injury.

What do pharmaceuticals actually do?

Drugs interfere with our biochemistry. Usually, they stop something happening (inhibitors); sometimes they kick a biochemical process into life (activators).

The molecule that a drug acts on is its target. Targets need to be accessible, so they are commonly molecules on the surface of cells, such as receptors for signalling molecules. Binding of the drug prevents it being activated by its ligand.

Drugs may also bind to ion channels – pores in the cell membrane that traffic ions into or out of the cell. Or they may target molecules that transmit signals between cells.

Clean kill?

Ever since Paul Ehrlich proposed the idea of a ‘magic bullet’, drug development has sought ‘clean’ compounds that are highly specific. But there are indications that ‘dirty’ compounds might also be useful.

Part of the rationale comes from studies of antipsychotic drugs such as clozapine for schizophrenia, which binds to at least 17 different receptors. Now it is known which receptors they recognise, they have been refined chemically to try to reduce cross-reaction and side-effects. Unfortunately, cleaner versions don’t work – dirtiness seems to be crucial to their effects.

Some researchers are now talking in terms of a ‘magic shotgun’, with agents taking out several targets simultaneously. For complex diseases, where multiple interacting biochemical pathways may be influencing a disease process, a shotgun might be a better weapon than a rifle.
SAFE AND SOUND

It typically takes more than a decade for a new drug to go from initial research to use in the clinic. During this time, companies have to show that their drug actually does something beneficial and that it is safe.

There are a host of regulatory processes that have been set up to ensure that these criteria are met before a drug is made available. They are designed to protect the public from harmful drugs and modern-day snake-oil salesmen.

But no drug is entirely without side-effects, and medicines can themselves be a source of ill-health. While companies developing conventional medicines spend millions proving that their products work, there is no such regulation of complementary and alternative products (though various moves are being made to enhance quality control). This could help overcome the risk of contamination and batch-to-batch variation.

Safety first

Use of animals in safety testing is a key stage in drug development.

In 1937, US company S E Massengill used diethylene glycol, a sweet-tasting chemical, to prepare a new sulfa drug in syrup form. The sweet preparation had a sour aftertaste – more than 100 people, mostly children, died after taking it.

Although Massengill’s chemists studied the appearance, flavour and smell of their ‘elixir of sulfanilamide’, they did not test its toxicity – and unfortunately diethylene glycol is a poison.

And although the thalidomide case is sometimes used as an argument against animal testing – it was shown to be safe in animals – in fact the reverse is true. Despite being marketed as a remedy for morning sickness, it was never tested on pregnant animals to see if it affected the fetus.

Both these cases led to a tightening-up of drug-testing regulation. Animal testing determines whether the drug is non-toxic, and also whether it is absorbed by the blood, goes to the right part of the body, works effectively and is properly excreted. It can also reveal how it is metabolised – a single chemical may be converted into tens or even hundreds of metabolites in the body. Crucially, animal tests lessen the risk to human volunteers, the next stage in the drug development process.

Although there are alternatives that can substitute for some aspects of safety testing, nothing can yet model the complexity of a living organism.

So does animal testing perfectly predict what happens in people? No. Some drugs went through an animal screening stage yet still turned out to be toxic in humans. This is hardly surprising – rodents are similar to humans but obviously not identical. It is a question of reducing risk. The leap from test-tube to human is still too great.

TRIAL AND ERROR

A disastrous phase I trial (see page 5) in 2006 raised questions about the safety of drug testing.

In March 2006, six healthy volunteers taking part in a phase I drug trial at Northwick Park Hospital, London, were given small doses of a new drug being developed for rheumatoid arthritis. The drug, a monoclonal antibody known as TGN1412, had been through animal testing; the trial had been approved by the Medicines and Healthcare Products Regulatory Agency (MHRA).

Within an hour of receiving the drug, the first volunteer reported a headache and began to complain that he was ‘burning up’. Within 24 hours all were in intensive care. Though none died, all spent at least a month in hospital.

What went wrong? Intensive investigations revealed that the firm responsible for TGN1412, TeGenero, which has since gone bust, followed all appropriate safety regulations and the materials themselves were not contaminated.

The likely explanation is that the drug acted in unexpected ways in the volunteers, triggering a massive immune response. The drug had no such effect in the monkeys it had been tested on previously, even though they have a very similar version of the target molecule.

So, should the trial have been approved? The drug targeted a key component of the immune system. Was it too risky to be trialled in people? Extra safeguards are now being put in place for agents that target the immune system in this way.

The case is a reminder that clinical trials are risky. Mercifully, extreme reactions like this are very rare. It also emphasises why phase I trials are so important.

Although safety is paramount, and lessons will be learned from the TGN1412 incident, it is worth remembering that additional safety measures and scrutiny are not without cost. They may lengthen the time it takes to develop a drug and add to the cost of development. And that may mean fewer drugs, or a longer wait, for those who need them.
Holistic hullabaloo

Where do complementary and alternative medicines fit into modern medical practice?

A popular but controversial approach is homeopathy, founded 250 years ago by a German doctor, Samuel Hahnemann. He conceived the principle that ‘like cures like’. For example, onions, which produce streaming, itchy eyes, might, in minute doses, relieve hay fever.

But critics are scathing. Homeopaths dilute a substance so many times that the final remedy is unlikely to contain a single molecule of active substance. Although some have proposed that water may maintain a ‘memory’ of the active substance, there is no known mechanism by which homeopathy might work.

In addition, put under scientific scrutiny, homeopathy fails to measure up. A recent analysis of well-conducted trials of homeopathy found no evidence that it was better than a dummy medicine (placebo).

The placebo effect should not be rubbished, however. In any clinical trial, typically around 30 per cent of people given a placebo will respond positively. The success rate of many drugs is not much better than that.

But does it work?

A source of dispute is whether CAM remedies work – and how this can be judged. Support for CAM tends to be anecdotal evidence – a patient given a medication improves, therefore the medication works. This is not accepted as valid evidence by the scientific community.

Conventional medicine uses randomised controlled trials as a stern test of effect. CAM practitioners respond that individualised treatment cannot be tested in this way.

Some herbal medicines have passed stringent tests. There is now evidence that St John’s wort is effective for mild depression, and Echinacea can protect against colds.

Dangerous drugs

Despite the years of research and clinical trials, a drug may still turn out to have harmful side-effects.

A 78-year-old man prescribed an antifungal agent after treatment for leukaemia began to hear music in his head. It was so realistic that he wrote to his hospital to complain. He compiled a list of the song titles, which included ‘Do You Hear What I Hear?’ Doctors changed his medication and the music stopped.

In another unusual series of cases, patients using a particular drug for Parkinson’s disease turned into compulsive gamblers. One female patient lost US$100 000.

These cases illustrate extremely rare side-effects, but adverse drug reactions as a whole are surprisingly common. About 250 000 people are admitted to hospital each year in the UK because of adverse reactions – roughly 5 per cent of hospital admissions. They are responsible for around 5000 deaths annually (more than the number of people killed on the roads). In the USA, the number of adverse reactions – and related deaths – nearly tripled between 1998 and 2005. Five of the top six killers were painkillers.

‘Safety’ is not an absolute: it involves a cost-benefit analysis, weighing up the risks with the benefits. These will depend on the drug, the nature of the illness, the availability of alternatives – and individual choice.

TALE OF TWO DRUGS: VIOXX MEETS THALIDOMIDE

1953: Thalidomide is synthesised by German company Chemie Grünenthal.

1955: Despite lacking supporting evidence, the company distributes thalidomide to German doctors as an epilepsy treatment. Patients report a deep soothing sleep.

1957: Grünenthal launches it as an over-the-counter drug mainly for morning sickness.

1961: Australian researcher William McBride publishes a BMJ paper linking hundreds of cases of malformations (see above) to thalidomide use.

In all, 8000–12 000 babies were affected, only about 5000 surviving beyond childhood. After thalidomide, the regulation of drug testing was tightened considerably and systems introduced to report adverse reactions.

1998 and 2005. Five of the top six killers were painkillers.

Safety is much improved, but not infallible, as the case of Vioxx illustrates.

Vioxx

Vioxx and related drugs were supposed to be good painkillers with fewer side-effects than existing drugs. It was launched in 1999, but almost immediately some researchers questioned whether it was really safe. In 2004, with global sales exceeding US$2.5bn (£1.2bn) a year, Merck withdrew the drug after a cancer trial revealed a doubling of risk of heart and stroke.

What happened? Vioxx is estimated to have caused 88 000–139 000 heart attacks, 30–40 per cent of them fatal. Some critics accused the FDA, the USA’s drug-licensing body, of not doing enough to protect patients. Merck was accused of massaging data (which it denies). It recently agreed a settlement of nearly US$5bn (£2.5bn) for Vioxx lawsuits – without admitting liability.

Yet both drugs may rise again. Thalidomide is used to treat leprosy and cancer. Vioxx could be made available in the USA (with warnings), as it works well for some patients: but Merck has not relaunched it.

SHOULD A DYING GIRL GET ACCESS TO AN EXPERIMENTAL DRUG?
See Big Picture Online.

www.wellcome.ac.uk/bigpicture/drugdev
DRUGS AND PEOPLE

We talk about ‘drugs for high blood pressure’ rather than ‘drugs for Mrs Smith’. What is given to Mrs Smith is also given to Mr Smith and Mrs Jones.

But this one-size-fits-all model is beginning to undergo a radical change. People are different and what works for Mrs Smith may not work for Mrs Jones. As the genetic and molecular understanding of disease mechanisms and drug responses become clearer, so medicine is getting closer to tailored therapeutics.

But what do we really think about drug taking? Some people might want to restrict their pharmaceutical intake but others are keen to take them even though they are in good health.

Gender trap

Will we ever have ‘his ‘n’ hers’ medicines?

Until recently, men and women were assumed to be identical, pharmacologically speaking. If a drug worked on men it should be fine for women. Male and female physiologies differ markedly, and this can affect both the effectiveness and side-effects of medications.

Among known medical sex differences are:

- different responses to certain painkillers (kappa-opioids, such as pentazocine, work better in women)
- women suffer more severe reactions to some anti-HIV drugs
- some lung cancer treatments seem to work better in women (though others work less well)
- the drug alosetron is licensed for severe inflammatory bowel disease only in women.

Overall, we simply don’t know enough about sex differences. Partly this is because in the 1970s women were explicitly ruled out of drug trials, for fear that medications might harm an unborn child early in pregnancy. That situation is changing and in most cases women are now enrolled. But the data are not always analysed by sex, to see whether sex differences exist.

One problem is that, to break down a study group like this, greater numbers of participants are needed – increasing the cost and complexity of the trial.

ETHNIC DIFFERENCES

The prospect of different drugs for different ethnic groups brings medicine into complex ethical areas.

Some diseases are known to affect certain human populations particularly severely. Sickle-cell disease, for example, is more common in African/Caribbean groups; people of South Asian origin are particularly prone to type 2 diabetes.

While such observations are relatively uncontroversial, the idea that medicines could be targeted at particular ethnic groups is an ethical hot potato.

The difficulty is both scientific and social. For a condition such as sickle-cell disease, the cause of the high incidence is clear – it arises from a mutation in a haemoglobin gene, which has survived because it provides protection against malaria. But for more complicated conditions, the situation is less clear. Do biological or social factors underpin a high incidence of disease? Is heart disease in, say, someone from Denmark the same as that in someone from Bangladesh?

We currently do not know enough about disease mechanisms to answer such questions confidently. And the concern is that by proposing that genetic factors predispose certain groups to a disease, it may reinforce the idea of genetically distinguishable ‘races’ – something that touches upon a long and disturbing history of discrimination.

On the other hand, if factors specifically affecting one ethnic group could be identified, treatment for that group might be improved.

Of central importance is the notion of ‘race’. Crucially, race is a social not scientific label: it is one way in which society groups people, but it has no underlying scientific principles. Some argue that it is useful – races may reflect some genetic substructure, including variation that affects health. Others argue that it is too crude a way to group people, and given the history of the area should be avoided.

BLACK AND WHITE

BiDil is licensed in the USA specifically for congestive heart failure in African-Americans, who have a high incidence of this condition and do not respond well to other treatments. Its link to race has been further complicated by its economic backdrop. The drug was initially rejected by the US licensing authorities. Following reanalysis of clinical trial data, it was then ‘reinvented’ as a medicine for African-Americans, which provided new patent protection.

Research is now underway to pinpoint the genes that correlate with responsiveness to BiDil. A genetic basis for selective prescribing would be scientifically and socially more desirable. At one point it seemed likely that black US celebrities would endorse BiDil, inspiring a spoof ad from The Beast magazine (right).
Tailoring medicines

What are the prospects for personalised medicine?

One of the main justifications for human genetic research is the prospect of medicines tailored to an individual’s unique make-up — pharmacogenetics.

The idea is that a patient would be diagnosed with, say, heart disease and a doctor would do a quick test to find out which drug would work best on them or which they should not take because of its side-effects. It’s an appealing vision, but how realistic is it?

Pharmacogenetics may well be the future but it is likely to be some time arriving.

There are some applications:

- Trastuzumab (Herceptin) is prescribed only for breast cancer patients with HER2 mutations.
- Imatinib is given to chronic myeloid leukaemia patients with a specific chromosome abnormality.
- The anti-HIV drug abacavir causes a rash in 5 per cent of patients with a particular gene variant. Patients can be screened before medication is given.

Among the most significant factors in pharmacogenetics are the cytochrome P450 (CYP) enzymes mainly found in the liver, which metabolise drugs.

The blood thinner warfarin, originally used as a rat poison, is metabolised by liver enzymes. It can prevent blood clotting, but the correct dose for a patient will depend on which liver enzyme genes they have.

Many different forms of CYP enzyme exist, and each form may have many variants. The way an enzyme metabolises a drug may therefore differ significantly. Duplication of CYP2D6 has been linked to poor response to antidepressants; other variations underlie limited response to painkillers such as codeine. One potential use is to screen people for CYP2C9 variations, which predict how well people respond to warfarin, a drug used to prevent blood clotting but which can also cause excessive bleeding.

Unfortunately, although the promise is great, the translation of pharmacogenetics into clinical practice is likely to be slow. The identification of a variant linked to a particular drug response is only the beginning. Many factors are likely to influence the body’s response to a drug, and clinical trials will be needed to confirm that patients actually benefit from targeted treatment — something that so far has rarely been done. And even then the practicalities of changing healthcare delivery will have to be tackled.

Attitudes to drugs

We can’t seem to make up our mind about drugs.

In 1979 author M N G Dukes described “the love–hate relationship which exists between the public and its drugs – substances which are hailed one moment as the solution to every problem and castigated the next as the cause of every ill”.

We are consuming more medicines than ever before. We take for granted that they will cure our headaches, see off infections, lower our blood pressure. We give enthusiastically to medical research charities and see health-related research as a positive thing.

But we are terrible at taking medicines as instructed; around a half of people being treated for chronic diseases do not stick to their prescriptions. We worry that we are overmedicating, giving young children a ‘chemical cosh’ (as Ritalin has been described) at the first sign of hyperactivity. Our final years are spent consuming a colourful cocktail of daily medications.

We have concerns about what drugs might do to us, and don’t take them unless we absolutely have to. And yet we are happy to turn to ‘natural remedies’ that have been studied far less intensively, rarely have any track record of success, and may contain a whole host of bioactive chemicals. Paradoxically, the word ‘clinical’ has come to mean something cold, logical and uncaring. How has it come to this?

The shift in attitude could be inflamed by a growing unease about conventional medicine. Pharmaceuticals-based medicine is based on treating disease, not patients, in a highly mechanistic way. A quick consultation and here’s a prescription. Next.

In contrast, complementary therapies can seem caring and focused on the patient not just the disease. Remedies may seem more ‘natural’ and kinder, a relatively safe way to improve one’s health (whatever the reality).
Sarah uses homeopathic medicines.

What conditions do you take homeopathic remedies for?

S I took them for eczema. They reduced my symptoms dramatically and gave far better results than anything else I tried – including conventional steroid creams, organic creams made by other complementary healthcare practitioners, and Chinese medicine.

Would you take them for all your health problems?

S No. Some conditions are life-threatening, like septicemia.

What encouraged you to try them out?

S Partly because I felt that it might address the causes, not just the symptoms. My eczema started 12 years ago, during work stress. It disappeared completely whilst I was pregnant with each of my two children. Then it got much worse after they were born.

After talking to me, the homeopath prescribed tablets that were linked to cravings I had during pregnancy. First of all she gave me a course of Sepia. Then she treated the eczema, with lycopodium.

There is no doubt that since the first five-day dose there was a dramatic improvement in my hands – greater than I had ever seen.

What effect do they have on you?

S My skin is much less dry and feels more resilient, and I feel well and fortified in general, more than I usually do, despite having had a cold recently.

How do you think they work?

S I don’t know because I’m not a homeopath. I do know they offered me a real solution. I think precise diagnosis of the cause is probably key; a qualified homeopath can listen and give you exactly what you need for your individual case. I also think they give you stronger tablets than the ones you can buy at the chemists.

What do you say to people who question whether they work?

S You can question anything. Homeopathy is easy to undermine because of its nature. It’s worked for me, that’s all I can say.

Do you think they should be provided on the NHS?

S Yes. But people expect too much of the NHS anyway. Homeopathy might be another burden.

If the Government paid for it, great. But patients would have to be cooperative, have the right expectations and attitudes, and do what they are told. You can’t drink tea or coffee whilst you are having homeopathy, for example, and you can’t use menthol toothpaste.

Roger is a volunteer who has taken part in drug trials.

How did you hear about the drug trials?

R There was a small advert in a local newspaper, and someone pointed it out to me.

What made you want to volunteer?

R The arrival of my two daughters, around 15 years ago. My wife had stopped working, and I can’t deny the money was a big issue. You get between £500 and £3000 per trial. Another benefit is the thorough medical checks you get before and during the trials.

How was the trial run?

R If you’re an inpatient, you go in the night before, and sign all the documentation with witnesses. The next day, you get your dose of the drug at timed intervals, and they start taking your blood samples, also at regular intervals. You can see the results if you want. Some people don’t like needles, but you have to have a canula. That’s as invasive as it gets.

There are often restrictions on what you can eat and drink, but they don’t tend to be harsh. They might say no grapefruit and no poppy seeds, for example.

How concerned were you about possible side-effects?

R People have been nervous since Northwick Park. But I’ve never had any lingering effects.

My attitude is that I’m more likely to get killed on the bike on the way over there, than during the trials. It’s in the company’s interests to look after me, and they are loath to release anyone with any effect, however small. You’re very well monitored – both for your individual benefit, and for their statistics. I may have been affected long-term and not realised it. But I’m confident that I won’t be, and I feel well very looked after.
Daniel’s wife Susan speaks for Daniel, who was denied the drug Lucentis, in this interview.

What drug did you want access to?
S Daniel’s got wet age-related macular degeneration (AMD) in one eye, which is caused by blood vessels leaking behind the retina. It’s the biggest cause of blindness in the UK and the USA.

We wanted access to Lucentis, made by Genentech, which shrinks the blood vessels behind the eye. It’s licensed in Europe, the USA, Scotland, but not England.

Who decided that you could not have it?
S Our local Primary Care Trust (PCT).

What reasons were given?
S They said it’s not available. Then they said they would only fund it if it spreads to the second eye. You have to go blind in one eye first.

What did you do?
S We fought the PCT for three to four months. We paid for one injection of Lucentis privately. It cost £1560. But one injection didn’t give any improvement: you could need 20 to 24 injections, which would be too expensive for us.

Do you know of other people who did gain access?
S Yes. Some PCTs do give Lucentis. It’s a postcode lottery.

Should all drugs should be available to patients?
S Yes, definitely. Whatever you need, breast cancer drugs or eye injections, if you’ve got the disease, they should give it to you.

What if they only provide small benefits?
S Yes, because you don’t know until you’ve tried how it will work, especially for something as important as eyes or cancer. You deserve a chance.

How could the NHS keep on top of costs?
S If Daniel had had the injections quickly, there would be fewer costs in the long run. If he goes completely blind, there’ll be his benefits claims, hospital visits, and my attendance allowance. It’s a false economy, thinking of the here and now, rather than tomorrow.

How can we decide between different deserving causes?
S You can’t pick some people to be treated and leave the others. It shouldn’t be like that.

If they’ve got the drug, they should give it to you. We’ve worked all our lives, paid taxes and national insurance all our lives.

We need to divert more funds to the NHS. Something else has to go.

How good a job is NICE doing?
S It’s not. It’s a bureaucracy, with people sitting in little offices, giving patients no help or advice. They should ask the Government for more money.
The pharmaceutical industry is enormously profitable. Is that a good or bad thing? The industry employs people, contributes to the economy and national wealth, and invests in the next generation of medicines. But does it have too much power and influence? Is it too interested in its own ends?

Drugs for all

Have the days of drugs being available free to all finally gone?

A key founding principle of the National Health Service was that it was free at the point of use. Anyone, anywhere, would get the healthcare they needed regardless of their ability to pay. If they were ill, people knew they would get the treatment they needed.

Now things are changing. The annual NHS drugs bill has risen to nearly £10 billion (2004/05), a 40 per cent increase in real terms since 1999/2000. The era when everyone could get every available treatment is over.

Politicians have been reluctant to use the ‘R-word’: rationing. The affordability question has been passed onto the National Institute for Health and Clinical Excellence (NICE), set up in 1999. Its role is to determine whether treatments are effective and offer good value for money. Without NICE approval, care providers in the NHS usually do not make treatments available.

To make its decisions, NICE calls together expert review groups and commissions assessments of health technologies or products. NICE is, in effect, acting on behalf of taxpayers. As well as medical input, it also seeks the opinions of healthcare professionals, patients and carers, and the general public, during consultations and through permanent bodies (a Citizens Council and a Partners Council).

It has been criticised by pharmaceutical companies and patient groups, for refusing to sanction certain drugs, such as beta-interferon for multiple sclerosis, trastuzumab (Herceptin) and four drugs for Alzheimer’s disease (except in moderate and severe disease).

NICE faces a difficult task. It can be seen to be denying individual patients potentially beneficial medicines. But if healthcare costs are to be kept in check, some body will have to make hard choices about what the NHS will provide. NICE has become the route by which, in effect, rationing has been brought into the health service.

GLOBAL MARKET FOR DRUGS

Developing countries are doubly disadvantaged in drug development:
• companies are reluctant to develop drugs for diseases affecting only developing countries
• when drugs do exist they are often too expensive.

Progress is being made, though, in a variety of ways:
• public–private partnerships for drug development
• negotiated price reductions (e.g. for HIV medications)
• innovative economic solutions, such as government commitments to buy products in bulk
• not-for-profit drug development companies
• drug development in academia (e.g. at the University of Dundee).

Find out more at www.wellcome.ac.uk/bigpicture/drugdev.
Drug costs

How much does it cost to develop a new medicine?

Several figures are banded about, but the generally accepted figure is produced by a US body, the Tufts Center for the Study of Drug Development, which uses data supplied by the pharmaceutical industry. In 2001 it put the cost of developing an entirely new drug at US$800 million. A more recent study from another US group suggested a range from US$500m to US$2bn, depending on the drug.

A biotech product, such as a protein or monoclonal antibody, is more expensive to produce (US$1.2bn) and takes longer to bring to market; however, fewer fail during development (success rates are around 30 per cent compared with 20 per cent for traditional pharmaceuticals).

About 40 per cent of the cost reflects expenditure on clinical failures. Around half the cost of drug development is classed as ‘opportunity cost’ or ‘time value of money’ – reflecting the long time periods and intensive efforts needed to develop a new drug.

The figures refer to entirely new drugs – which are relatively rare (20–30 are launched each year). Many drugs are refinements of pre-existing agents, and hence cheaper to produce.

The market decides

Pharmaceutical development is based on free-market economics. This significantly shapes the nature of the industry.

For some, the idea that money can be made out of ill-health is distasteful. But we live in a free-market economy, and the economic rules that apply to, say, food production, also hold for healthcare. By some tokens, it is a highly successful model: we have drugs we can rely on for many conditions, and research is actively being carried out to develop new therapies.

But the way that the market operates has some unfortunate consequences.

For a start, there is a strong focus on the diseases of the rich industrialised world. There is little incentive to develop medicines for diseases affecting developing countries, as companies would find it hard to recoup development costs.

Even in rich countries, the emphasis tends to be on the treatment of chronic diseases – where people have to take medication for long periods. From a financial point of view, a drug such as an antibiotic or a vaccine, which generally needs to be used just once, is a less attractive option. Nevertheless, vaccine development in industry is growing.

Another common feature is that of ‘me-too’ drugs – minor variations on existing products. Companies fight each other for a slice of a profitable cake. Development costs will be substantially lower, but benefits to patients may not be great.

As patents are crucial to the industry, compounds not protected in this way – even if effective – are not attractive for investment. Why put millions of pounds into developing a drug that your competitor can make as soon as it is approved?

TOP 5 BLOCKBUSTERS

The modern pharmaceutical industry pins most of its hopes on ‘blockbusters’ – drugs for common diseases generating millions (even billions) of pounds in profits. Technically, a blockbuster is a drug that generates more than US$1bn sales a year. Around 100 blockbusters exist.

The upshot is that firms concentrate heavily on a small number of products. Extremely large sums are spent marketing the drugs (typically more than 30 per cent of revenue and at least twice what is spent on R&D; the industry’s total annual marketing costs have been estimated at US$60bn).

The days of the blockbuster may be numbered, however. The trend for more targeted medicines is leading to a fragmented marketplace.

Annual sales

Drugs

1 Lipitor (atorvastatin) for high cholesterol
2 Nexium (esomeprazole) for heartburn
3 Seretide/Advair (fluticasone/salmeterol) for asthma
4 Plavix (clopidogrel) for heart disease
5 Norvasc (amlodipine) for hypertension

FACT

It is estimated that the global healthcare marketplace will be worth US$1.3 trillion by 2020.

THE FUTURE IS NOW

Drugs are supposed to be for when we are ill – but they can also make us ‘better than well’.

A drug to boost brain power? It sounds far-fetched but it already exists. Drugs intended for medical use may have applications outside the clinic, raising challenging ethical questions:

Modafinil (Provigil), a treatment for sleep disorders, can boost mental powers, by increasing alertness and the ability to concentrate on a task.

Methylphenidate (Ritalin), used to treat attention deficit hyperactivity disorder (ADHD), improves concentration.

Donepezil (Aricept), a drug for Alzheimer’s disease, may improve normal memory.

None of these drugs is licensed for use in normal people. They have side-effects and the impact of their long-term use is unknown.

There is growing evidence that such drugs are being used by healthy people, including students preparing for exams. Is this cheating or much the same as getting a kick from caffeine in coffee or Red Bull?

For more on this, and how a drug called propanolol may help us lose unwanted memories, see www.wellcome.ac.uk/bigpicture/drugdev.
• Modern medicine is based mainly on a biochemical model of disease.
• Drugs interfere with biochemical processes.
• Drugs were originally selected for their ability to treat symptoms, with little understanding of how they worked.
• Drug development is increasingly based on known disease mechanisms – rational drug design.
• Most drugs are small chemicals, though protein therapeutics are becoming more common.
• Drug development is a lengthy and expensive process – many drugs never make it to market.
• Drug development aims to maximise safety and efficacy.
• Clinical trials will not pick up rare side-effects, so the use of new drugs is monitored.
• A drug will rarely, if ever, work for everybody.
• All drugs have side-effects; these have to be weighed against the benefits a drug provides.
• Adverse drug reactions are a common cause of hospital admission and a leading cause of death.
• There is a trend towards personalised medicines, including drugs matched to patients’ genetic background (pharmacogenetics).

Although some pharmacogenetics-based approaches are used in medicine, their introduction is likely to be slow and gradual.

• The pharmaceutical industry is strong in the UK, contributing to employment and national wealth.
• Critics of the industry argue it has too much influence, promoting drug-based approaches and being too focused on economic rather than medical priorities.
• New medicines have to be approved by the MHRA, the Medicines and Healthcare Products Regulatory Agency.
• To be used in the health service, medicines usually also need to be recommended by NICE, the National Institute for Health and Clinical Excellence, which assesses value for money.
• People are often reluctant to take medicines and commonly do not take them as prescribed.

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T +44 (0)20 7611 8651
E publishing@wellcome.ac.uk

Or write to:
Big Picture series
The Wellcome Trust
FREEPOST
SGE 7446
Slough SL3 0BP

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