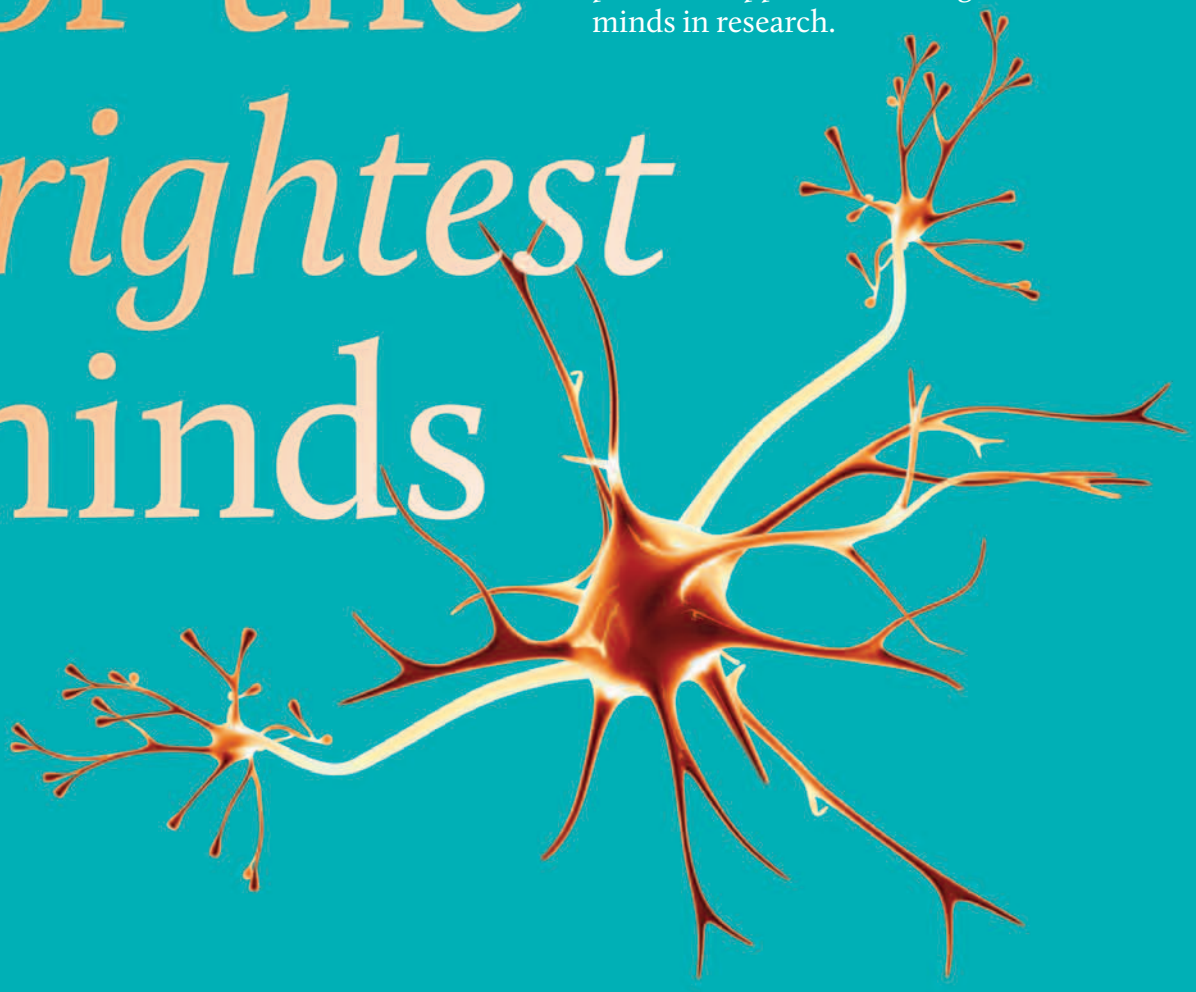
# Support for the *brightest* minds

Highlights of the Wellcome Trust's work in 2011, our 75th anniversary year, in which we redoubled our personal support for the brightest minds in research.



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*As at December 2011*

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*As at December 2011*

## Wellcome Trust

We are a global charitable foundation dedicated to achieving extraordinary improvements in human and animal health by supporting the brightest minds in biomedical research and the medical humanities.

Our ten-year Strategic Plan for 2010–20 provides the framework for how we intend to evolve our support to be even more effective in achieving this aim.

**Our funding focuses on:**
1. Supporting outstanding researchers
2. Accelerating the application of research
3. Exploring medicine in historical and cultural contexts.

**Our five major challenges are:**
1. Maximising the health benefits of genetics and genomics
2. Understanding the brain
3. Combating infectious disease
4. Investigating development, ageing and chronic disease
5. Connecting environment, nutrition and health.

# Contents

# An overview of some of our activities in 2010/11, from research successes and public engagement campaigns to the grants we have awarded and the performance of our investments.

### 75th anniversary
The Wellcome Trust turned 75 in 2011, and we celebrated with events looking at past achievements and future ambitions.

### Investigator Awards
World-class researchers won flexible personal support in the first round of Wellcome Trust Investigator Awards.

### *eLife* journal
The Wellcome Trust, the Howard Hughes Medical Institute and the Max Planck Society announced plans for a new open access life sciences journal, *eLife*.

### MRI for newborn intensive care
An MRI scanner small enough to be used in neonatal intensive care units is being developed with Wellcome Trust support.

### 1000 genomes – and more
After successful pilot results from the 1000 Genomes Project, the new phase is even more ambitious.

### Malaria study leads to revised treatment guidelines
The largest ever clinical trial of patients hospitalised with severe malaria has led the World Health Organization to change its recommendations.

### Health Innovation Challenge Fund
This Wellcome Trust–Department of Health collaboration has funded exciting new projects on genetics, acutely ill patients and chronic illness.

### Twenty years of the Children of the 90s
A landmark longitudinal study of thousands of children and their families has moved into its third decade.

### Dirt season
Wellcome Collection ran an exhibition and events series exploring humanity's relationship with dirt in all its forms.

### Healthy debates
Two Strategic Awards are supporting five-year programmes encouraging people to debate issues in health and biomedicine.

## Funding and achievements

**1062**
Total grants awarded

**33**
Countries receiving funding

**466 043**
Wellcome Collection visits

**161**
Fellowships awarded (or renewed)

**£122m**
Venture capital finance secured by grantholders for commercialisation of R&D

**4402**
Scientific research papers associated with the Wellcome Trust
(Published in calendar year 2010, indexed on PubMed and in Thomson Reuters databases)

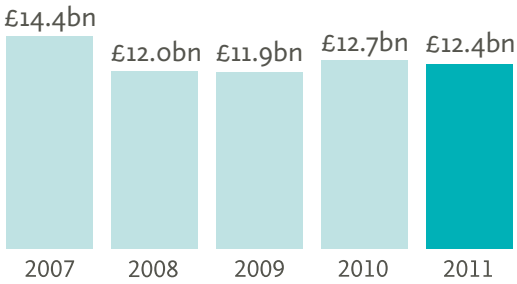
For more content related to the stories featured in the *Annual Review*, see **www.wellcome.ac.uk/annualreview**.

## Key financials at a glance

### Net asset value

£12.4bn

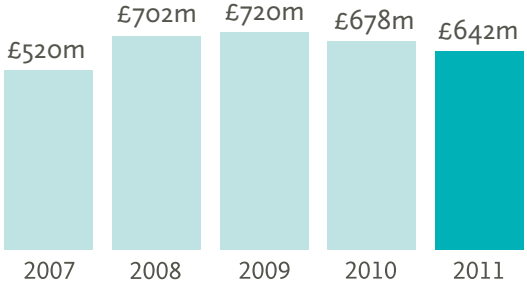
As at 30 September.




### Charitable funding committed in year

£642m

For the year ended 30 September.




For more details, see our *Annual Report and Financial Statements* at **www.wellcome.ac.uk/annualreport**.

**Financial summary**
Our ability to support research and other charitable activities depends on the success of our investment portfolio. We invest globally across a very broad range of assets and strategies. In 2010/11, in the face of continuing global instability, we were pleased that our investment portfolio recorded a total return of 2%.

We have returned a total of 19% (annualised 6%) over three years and 24% (annualised 4%) over five years to September 2011. Since the inception of our investment portfolio in 1985, it has provided a total return averaging almost 14% a year.

Our annual grant-making budget is set by reference to a three-year weighted average of our portfolio's value in order to smooth the effects of short-term volatility. Over the next five years we aim to commit in excess of £3 billion for charitable activities, but this will depend on our investment performance.

# This year, we extended new forms of support to the brightest and best researchers, and many of our funded projects made advances that will improve health.

## Supporting researchers

Over the Wellcome Trust's 75-year history, the tools of science have changed almost beyond recognition. What has not changed is the need for imaginative, talented people who can develop and apply these tools. The Trust supports outstanding researchers and helps them to make new discoveries, develop better treatments and improve the health of people and animals throughout the world.

We celebrated the 75th anniversary of the Wellcome Trust in 2011. This was an opportunity to reflect on the considerable successes in science, medicine and the medical humanities achieved by the thousands of extraordinarily talented researchers funded by the Wellcome Trust over many years.

Of course, what really matters is that our work continues to lead to improvements in medicine and health. This year's *Annual Review* presents a selection of stories of discoveries and inventions that have arisen from work we have funded recently, as well as some new initiatives to enhance the support that we offer to individual researchers and the scientific community as a whole.

In his will, Sir Henry Wellcome set out the purpose of the Wellcome Trust and how it should develop his legacy. He specified areas of research he thought particularly promising, including chemistry, bacteriology and pharmacy; the passage of time has shown that his choices were absolutely correct. Today, we might point to additional tools and areas of science such as genomics, stem cells and neuroscience. Sir Henry could hardly have imagined how biomedical science would progress and change in 75 years.

What has not changed is the need for imaginative people to develop and apply these new tools and technologies. As a research funder, we are always looking for the best ways to support researchers and to foster a culture in which the brightest minds can flourish. This is why we introduced Wellcome Trust Investigator Awards as a new model of funding to give scientists in universities and other research institutions the opportunity to be more creative and pursue more speculative lines of enquiry.

This year, we funded the first cadre of Wellcome Trust Investigators: 20 Senior Investigators and seven New Investigators were appointed, each working on important research relating to the challenges in our Strategic Plan. The work supported includes basic research on topics such as epigenetic reprogramming and stem cell biology, and at the clinical end of the research spectrum, stroke prevention and how to reduce obesity by encouraging physical activity.

## Working together

While it will always be important to support individual researchers, science works best through teamwork and collaboration. The best science requires the best partnerships and collaborations.

One such partnership is the 1000 Genomes Project, which reported results from its pilot phase this year. A major international collaboration, it has proved so successful that its goal has been extended from sequencing 1000 genomes to 2500. The result will be an even more detailed understanding of human genetic variation.

The 'Children of the 90s' longitudinal study is also being extended – with joint funding from the Wellcome Trust, the Medical Research Council and the University of Bristol. This pioneering research, following over 14 000 women and their children since 1991, has produced a wealth of data on the factors that determine health and wellbeing throughout life. The new phase will include other members of the families, including the next generation of children, giving more insights into how the interplay of genes and lifestyle affects our health.

Partnerships between research funders are equally important for translating scientific discoveries effectively into new treatments for patients. The Health Innovation Challenge Fund is a joint initiative from the Wellcome Trust and the Department of Health that aims to improve the uptake of technological advances in the NHS and to help to integrate the clinical, research and technology communities. This year, the initiative funded six research projects on how to improve emergency care and three on the theme of monitoring chronic illness in the home.

## Solid foundations

Talented scientists need world-class research infrastructure to underpin their work. Funding laboratories was a mainstay of the Wellcome Trust's early years and we still provide support for buildings and facilities, not least the Francis Crick Institute, due to open in 2015. However, it is as important to address some of the less tangible elements of scientific infrastructure.

Central to the scientific process are academic peer-reviewed journals, which allow scientists to share their research. The internet has the potential to transform how scientific publishing operates, and to make the very best science truly accessible to all. In partnership with the Max Planck Society and the Howard Hughes Medical Institute, we have announced plans to launch a new top-tier, open access journal, which we hope will set a benchmark for modern scientific publishing.

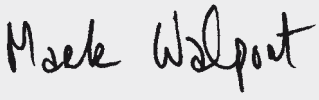
More broadly, the Wellcome Trust has always been committed to helping everyone appreciate and debate biomedical science, its context and its implications. We fund research in the medical humanities to explore the history of medicine and address important ethical questions raised by some of today's science. We also support projects that engage the public with science, most notably the hugely popular Wellcome Collection, which explores connections between medicine, art and life. This year's *Dirt* and *High Society* exhibitions were the most successful to date. They developed a trend of reaching out beyond the Wellcome Collection building to engage audiences with public events across the UK.

## Looking to the future

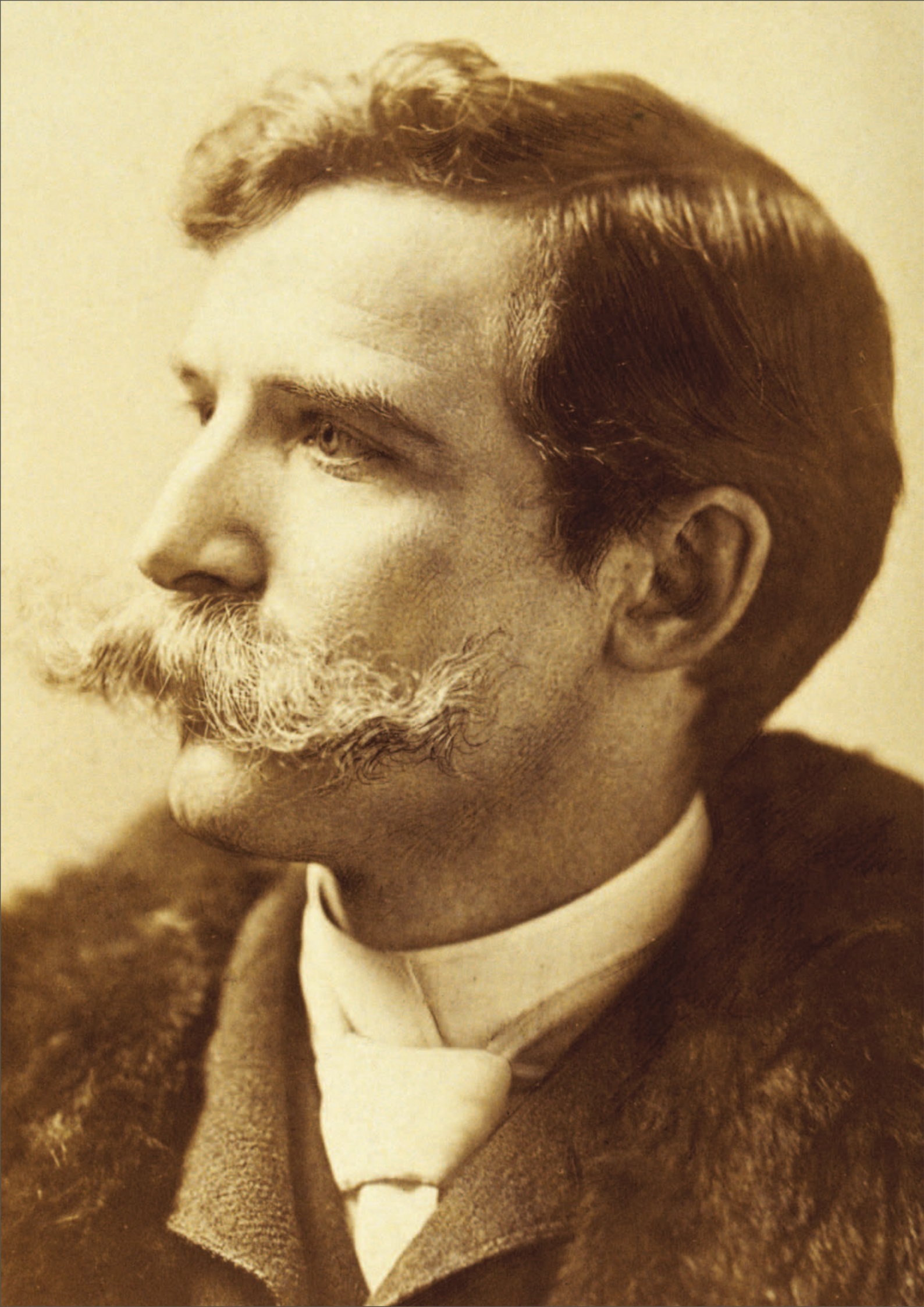
It is not surprising that there is such a public appetite for science – one of the most dynamic, challenging and enthralling of all human endeavours. It is always opening up new opportunities to learn about ourselves, our bodies and the world around us. At the Wellcome Trust, our responsibility is to ensure that biomedical research is strongly supported and that the fruits of research are used to improve health.

To pick just one example from this year, the largest ever clinical trial among children in hospital with severe malaria has shown definitively that artesunate is a better treatment than quinine, which has been used since Sir Henry's day. The World Health Organization has consequently revised its guidelines to recommend artesunate as the first-line treatment for managing severe malaria in African children.

This could save tens of thousands of young lives every year. It is exactly the kind of legacy that Sir Henry wanted to achieve through the Wellcome Trust. We will continue to fund excellent researchers who will use all the tools at their disposal to make new discoveries, develop better treatments and improve health for people across the world.



**Sir Mark Walport**
*Director of the Wellcome Trust*
*December 2011*



# In 2011, the Wellcome Trust celebrated 75 extraordinary years of achievement while looking forward to even greater successes to come.

The Wellcome Trust was established after Sir Henry Wellcome's death in 1936, to advance medical research and related historical studies. In his will, Sir Henry wrote of "the enormous possibility of development in chemistry, bacteriology, pharmacy and allied sciences" and "vast fields opened for productive enterprise for centuries to come".

He was right and, thanks to 75 years of "productive enterprise", much of today's science would be unrecognisable to him. If he marvelled at X-ray images that offered a glimpse inside our living bodies, for example, how would he have reacted to seeing a modern brain scan? Or, given that he died before it was known that genes were made of DNA, what would he have made of our ability to read a person's entire genetic code?

But some things have not changed. For all the remarkable technology at our disposal, science still depends on the scientists who are driven to answer fundamental questions about the world. From Henry Foy, the Trust's first scientific employee, to today's Wellcome Trust Investigators, fellows and other grantholders, we have always supported talented people to make important medical and scientific discoveries.

In our history, we have funded work across all aspects of medical research. We have contributed to advances in understanding how our bodies work, to new drugs and vaccines for life-threatening diseases, and to historic research efforts such as the Human Genome Project. We have supported thousands of researchers in science, the history of medicine and the ethics of biomedical research, and hundreds of artists and performers involved in creative projects to engage the public with science.

In celebrating our 75th anniversary, we very much wanted to look beyond our own achievements, though. We produced the Wellcome Trust 75th Anniversary Summer Series, a programme of innovative events across the UK that explored and explained the world of science through the fields of art, music, film and theatre. Researchers from the biggest initiatives we support in the UK received funds to engage their local communities with the stories of their specific research fields, and the challenges that the next 75 years will bring.

Sir Henry Wellcome was an extraordinary individual whose vision for medical research created a lasting legacy in the Wellcome Trust. We constantly look for the best ways to fund research, as science evolves and changes. What will never change is our commitment to support world-class researchers whose work will drive extraordinary advances in health now and in the future.

> "The Trust has every appearance of being a big undertaking, perhaps bigger in the next generation than it can be in this."
>
> ***British Medical Journal*, January 1937**

Henry Wellcome, 1890. *Wellcome Library*

# Investigator Awards: The Wellcome Trust's five research challenges address complex, globally important questions that can be solved only over the long term and by harnessing the ingenuity, knowledge and vision of outstanding scientists.

This year, we moved towards more expansive, longer-term funding and a hands-off approach that will give world-class researchers the freedom they need to drive advances in their field.

Our new funding scheme – Wellcome Trust Investigator Awards – enables scientists to tackle major research problems relating to our challenges, free from the cycle of focusing on securing grants. These awards replace our project and programme grant schemes and extend our successful fellowships funding model to scientists with an excellent track record who are in established, salaried academic posts.

In June 2011, 27 outstanding researchers received the inaugural Wellcome Trust Investigator Awards in biomedical science. The duration and resources associated with each Award are tailored to meet the needs of the researchers and their specific investigations, large or small. Awards were made at two levels – to seven New Investigators and 20 Senior Investigators – according to how experienced each is.

Most of them are based in the UK (including institutions in London, Liverpool, Edinburgh and Manchester) and one is in Brazil. Each received between £1 million and £3m for up to seven years to support ambitious projects that could transform our understanding of the mechanisms of health and disease.

Their research projects include: exploring how malaria-infected red blood cells adhere to blood vessel walls; investigating interactions between the immune system and intestinal bacteria; developing ways to prompt stem cells to stimulate bone and heart tissue regeneration within the body; and finding effective ways to get people more physically active.

The potential benefits of this model of funding are not restricted to science. The pace of progress of biomedical research makes it ever more vital that we examine its social, political and historical contexts and implications. We need to understand its enormous potential to reach far into aspects of our lives beyond health and medicine.

We have therefore extended our Investigator Awards to world-class scholars asking the most important questions at the interface of science, medicine and the humanities. The scheme covers two categories – Medical History and Humanities, and Ethics and Society – with the Awards offering support of up to £200 000 per year for up to seven years to scholars in established academic posts. Like the Awards in biomedicine, they will be made at two levels: New or Senior Investigator.

Investigator Awards build on our strategic goal of supporting the brightest researchers with the best ideas. The funding will allow each Investigator to pursue a compelling long-term vision for his or her research.

Professor Sara Rankin of Imperial College London, one of the first cadre of Wellcome Trust Senior Investigators. *Wellcome Images*

## New research facilities in Hanoi

His Royal Highness The Duke of York opened new Clinical and Research Laboratories at the National Hospital of Tropical Diseases in Hanoi, Vietnam, in October 2010. The Laboratories provide a state-of-the-art environment for research to improve the prevention, diagnosis and treatment of major infectious diseases.

Jointly supported by the Wellcome Trust, the Li Ka Shing Foundation and the South East Asia Infectious Disease Clinical Research Network, this is a further extension of the Wellcome Trust Major Overseas Programme in Vietnam, which was established in 1991.

## Engaging fellows

In July 2011, Dr Richard Barnett and Dr Kevin Fong were awarded the first ever Wellcome Trust Engagement Fellowships. They will each receive two years of funding to promote and develop public engagement across the Trust's portfolio of work.

Dr Barnett is a medical historian, author and poet. He received the 2006 Promis Prize for poetry and writes for numerous popular magazines and academic journals. In 2008, he wrote *Medical London: City of diseases, city of cures* with Mike Jay.

Dr Fong holds degrees in medicine, astrophysics and engineering. He has presented medical documentaries on BBC 2 and Channel 4 and, in July 2011, a programme for the BBC about the last space shuttle mission.

## Francis Crick Institute

Formerly known as the UK Centre for Medical Research and Innovation, the Francis Crick Institute has a new name that honours one of the UK's greatest scientists. Francis Crick was awarded the 1962 Nobel Prize for Physiology or Medicine for his part in discovering the structure of DNA.

Sir Paul Nurse, Director and Chief Executive of the Francis Crick Institute, said Crick embodied the qualities he wants to cultivate in the Institute: collaboration, creativity and tenacity.

In December 2010, Camden Council approved plans for the Institute, which is being funded by the Wellcome Trust, the Medical Research Council, Cancer Research UK and University College London, and the ground was broken in July 2011. Construction is due to be completed in 2015.

> “Francis Crick was a superb British scientist. He embodied the qualities of collaboration, creativity and tenacity we would like to instil within the culture of the institute to be named for him.”
>
> **Sir Paul Nurse**

From left:

A child being examined at the National Hospital of Tropical Diseases in Hanoi. *Mads Monsen*

Drs Richard Barnett and Kevin Fong. *Wellcome Images*

Architectural image of how the Francis Crick Institute will look. © *Justin Piperger Photography/Wadsworth3d*

Global information artwork. *Vasiliy Yakobchuk/ iStockphoto*

> It is my strong feeling that there is a need for a scientific journal at the very high end that is run by active practising scientists embedded in an academic environment, individuals who experience both the frustrations and satisfactions of research."
>
> **Professor Randy Schekman**

## New research journal

Ensuring that the best research papers reach as many scientists as possible, efficiently and effectively, requires leadership from the best currently active scientists, a rapid and decisive peer-review process and publication in an online open-access journal. In 2011, in partnership with the Howard Hughes Medical Institute and the Max Planck Society, the Wellcome Trust announced the launch of a new top-tier, open access journal called *eLife*.

Crucially, the new journal will be run by an editorial team of highly regarded active scientists – people who deal with the practicalities of research on a daily basis. That experience will enable them to make swift, unbiased and scientifically based editorial decisions: to identify the best papers, judge the quality of the submitted work and the reviewers' responses, and exercise leadership in steering papers through peer review.

The Editor-in-Chief will be Professor Randy Schekman, an outstanding cell biologist who has edited the *Proceedings of the National Academy of Sciences* since 2006 with great distinction. Among other major awards, Professor Schekman shared the 2002 Albert Lasker Basic Medical Research Award with James Rothman. He will continue as a Howard Hughes Investigator at the University of California, Berkeley, devoting half of his time to the new journal.

Professor Schekman has been recruiting a team of two deputies (Professor Fiona Watt, Deputy Director of the Wellcome Trust Centre for Stem Cell Research in Cambridge, and Professor Detlef Weigel, Director of the Max Planck Institute for Developmental Biology in Tübingen, Germany), 15 to 20 senior editors (devoting 20 per cent of their time to the journal) and a larger board of reviewing editors. The editorial team will be independent of the three funders, having sole responsibility for publishing the best research. The Managing Executive Editor of *eLife* will be Dr Mark Patterson, formerly director of publishing at the Public Library of Science.

Quality and innovation are the watchwords of the new journal: editorial decisions will be clearly communicated swiftly and fairly, the published content will be of the highest standard, and the research will be presented in ways that take advantage of digital media. The journal's editorial policy will be to avoid asking authors to make extensive modifications or perform unnecessary additional experiments before an article can be published. Articles will be accepted or rejected as rapidly as possible, generally with only one round of revisions.

As a result, we hope that researchers will have confidence in robust editorial decisions taken by their active scientific peers, and that *eLife* will attract outstanding papers from all over the world.

The entire content will be freely available for all to read and reproduce without restrictions. *eLife* will use the Creative Commons Attribution licence and explore new technologies so that new research can be widely shared and used. We hope this will be a major new vehicle for the rapid publication and sharing of the world's best research in the life and biomedical sciences.

# A five-year partnership, the Health Innovation Challenge Fund, is supporting a range of projects to develop innovations in healthcare that can rapidly lead to improved patient treatment.

The Health Innovation Challenge Fund (HICF) is a £100 million, five-year funding partnership between the Wellcome Trust and the Department of Health that launched in 2009. Its aim is to stimulate the development of new healthcare products, technologies and interventions so that they can be used to treat patients in the NHS and beyond. The funding supports the development of innovations to the point of being 'patient-ready' within five years of the start of the award.

HICF awards are being made through a series of themes, each focusing on unmet needs in healthcare relevant to the NHS. The first theme, 'Advancing Genetic Discoveries into Clinical Practice', seeks to capitalise on the wealth of information created by human genome analysis so that it can be translated into practical healthcare applications. The 15 awards made in this theme so far include projects to improve treatment in young-onset diabetes, gene therapy for blindness and a test to diagnose and direct therapy in blood cancers such as leukaemia.

The second theme, 'Time-critical Intervention: Solutions for effective management of deteriorating, acutely ill and injured patients', aims to give healthcare professionals greater diagnostic and treatment capacity when dealing with emergency situations such as trauma. Such innovations could improve patient outcomes and reduce costs. The six projects awarded funding in October 2010 included work on: detecting in real time the onset of secondary brain injury in intensive care; immediate point-of-care molecular diagnostics for lung inflammation or infection in critical care; and tissue-oxygen monitoring to detect impending shock states in critically ill patients.

Three awards were made in March 2011 under the third theme, 'Monitoring of Chronic Illness in the Home and Remote Settings', which was launched in June 2010 with a budget of up to £10m. The World Health Organization has projected chronic conditions to become the leading cause of disability by 2020 – and, if not successfully managed, the most expensive problem for healthcare systems. The successful projects included long-term home monitoring of patients with heart failure to improve care and reduce hospitalisation, and using video games to monitor arm and hand rehabilitation after stroke.

Calls have been made under the next two themes – 'Smart Surgery: Innovative technologies or interventions to reduce, replace or refine invasive surgical procedures' and 'Infection Response Systems: Development and application of technology for prevention, diagnosis, intervention and control of infection' – and awards will be made in 2011/12.

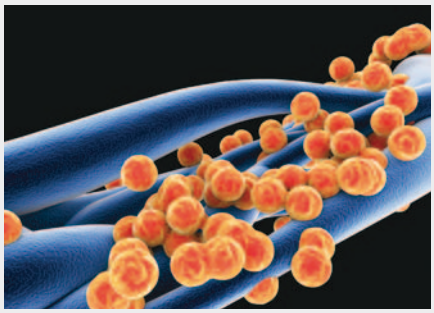
The Health Innovation Challenge Fund will support projects to make surgery 'smarter'. *Wellcome Images*

## Global health trials

To improve the flow of new healthcare solutions to low- and middle-income countries, the Wellcome Trust, the Medical Research Council and the Department for International Development are running a Joint Global Health Trials scheme. The initiative is investing £36 million to fund late-stage trials of health interventions in these countries. Awards are being made through three calls for proposals in successive years. Ten awards were made under the first call this year, including support for trials of a rapid antenatal diagnostic test for malaria, and trials of a tuberculosis vaccine in children whose mothers are infected with HIV.

## Artificial aortic valve

An elegant new design of prosthetic heart valve is being developed by researchers at University College London with support from the Wellcome Trust. The replacement valve is folded into a small tube that is passed through a catheter to the heart so that it can be fitted without the need for open-heart surgery. While not the first to use this delivery method, the new design allows the valve to be unfolded and finely manipulated until it is anchored in the best position. This makes it safer for patients and, together with the increased durability of the new design, means valve replacement could become an option for many people who would currently be judged to be too ill or weak to benefit.



## Membrane-targeted antibiotic

The Wellcome Trust Seeding Drug Discovery programme facilitates early-stage small-molecule drug discovery. An award to researchers at the University of Queensland is helping them to develop a new antibiotic that should be able to target a number of drug-resistant bacterial infections more effectively than current antibiotics.

Their plan is to enhance an existing antibiotic, giving it the ability to target certain bacterial cell membranes rather than human cells. This should increase the drug's potency and, it is hoped, reduce the likelihood of adverse reactions.

From left:

The Joint Global Health Trials scheme is funding work to improve healthcare in low-to-middle-income countries. *Gates Foundation/Flickr*

Digital artwork showing heart valves. *Oliver Burston/Wellcome Images*

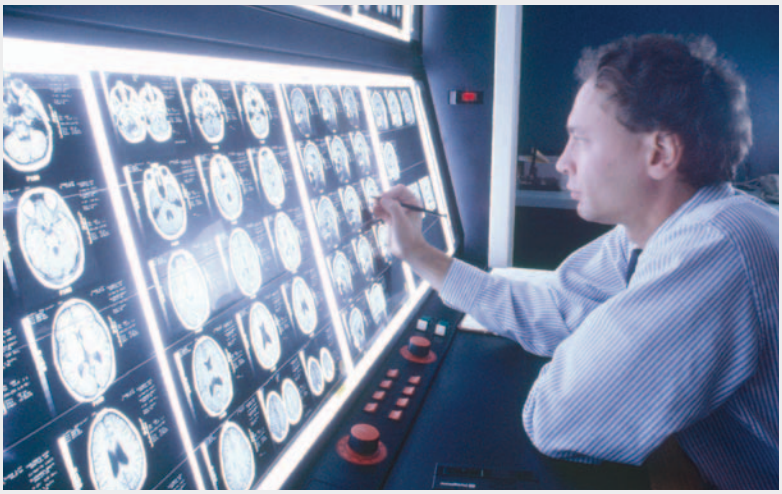
Methicillin-resistant *Staphylococcus aureus* bacteria. *Pasieka/SPL*

Studying children's MRI scans. *Doug Plummer/SPL*

“

As we continue to push the boundaries of discovery using specialty MRI in novel ways, we’re always mindful of the significant impact…on the diagnosis and treatment of even the smallest patients.”

**Paritosh Dhawale, GE Healthcare**



### MRI for newborn intensive care

Considering the potential risks, most births today are relatively harmless for mother and child. However, five in every 1000 babies born in the UK suffer brain injury during birth. Of those, one in five dies and the other four are at high risk of developing lifelong problems with speech, movement, and intellectual and social functioning.

The damage could be mitigated – perhaps even prevented – by swift and accurate diagnosis of potentially deadly or crippling brain injuries directly after birth. With a precise image of what is happening in the brain, doctors might be able to intervene and stop or limit the damage.

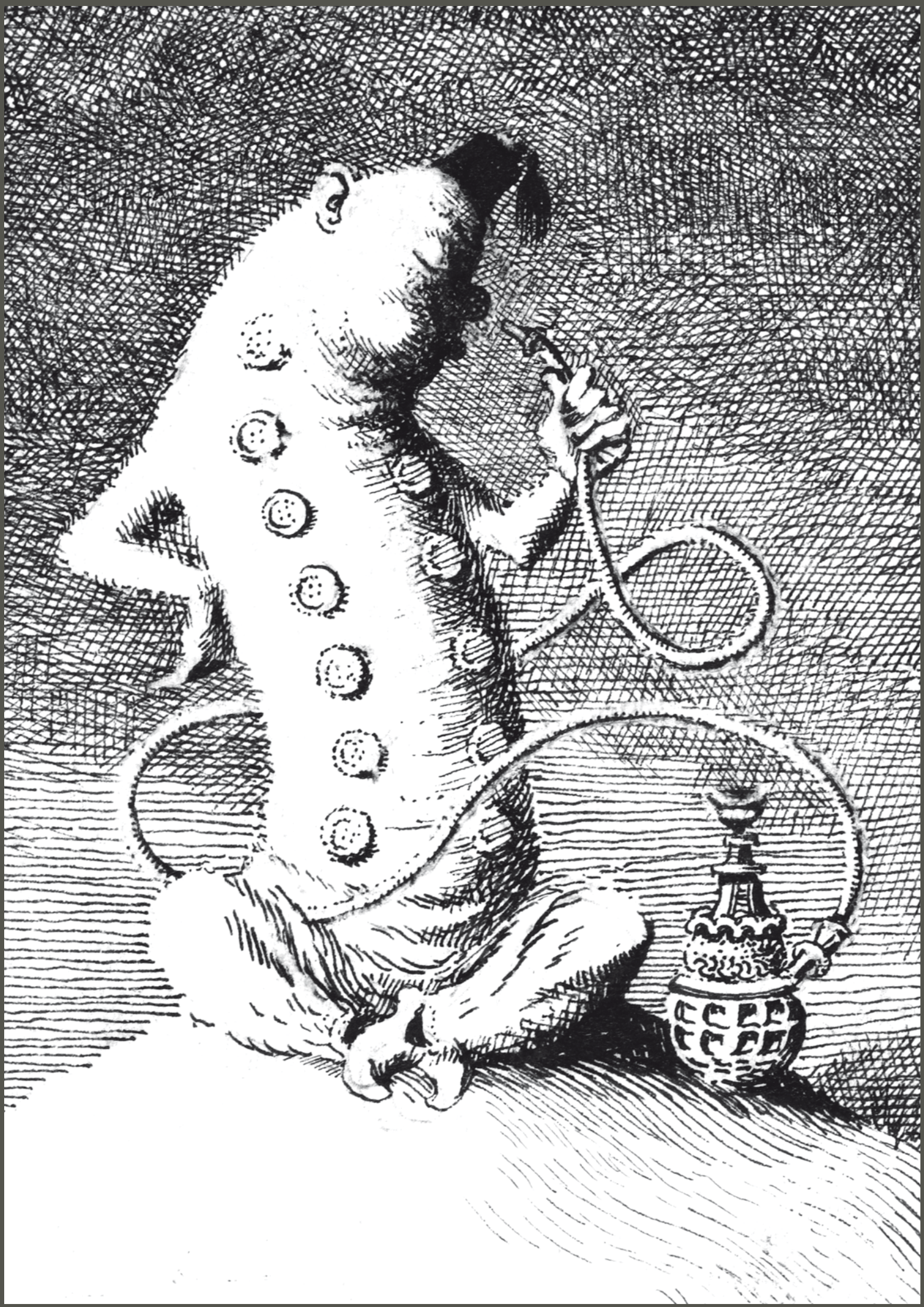
Magnetic resonance imaging (MRI) would be the ideal tool to use because of its capacity to show with high sensitivity what is happening in the brain. However, MRI scanners are large, heavy machines that create a powerful magnetic field from which staff and other patients need to be protected. For this reason they tend to be located some distance from neonatal intensive care units and other wards. They also generate noise that might subject vulnerable newborns to dangerous levels of stress.

Transporting a vulnerable newborn outside the protective environment of intensive care is possible but can be extremely risky, so MRI is less likely to be used unless other options have proved inadequate – by which point a health problem may be dangerously advanced.

Most neonatal intensive care units use ultrasound scanners to try to get a picture of the infant’s brain. Although less sensitive than MRI, these small, silent machines are currently better suited to neonatal units. The ideal solution would be a dedicated MRI machine that could be used within the unit – lighter, quieter and with a much smaller magnetic field than conventional scanners.

In April 2011, the Wellcome Trust awarded GE Healthcare a Strategic Translation Award worth almost £2.5 million to co-fund the development of MRI equipment for newborns. The award will initially allow engineers at GE Healthcare to build one small prototype system that can be installed in a neonatal unit. This prototype system will then be evaluated in a number of neonatal units.

The work is likely to lead to a better understanding of the technology required to care for infants in a neonatal intensive care environment – and possibly to a change in the clinical management of newborns at risk of brain injury.



# Wellcome Collection, the Wellcome Trust's public venue exploring medicine, life and art, goes from strength to strength.

When Wellcome Collection opened in 2007, we anticipated 100 000 visits a year. However, by the time it celebrated its fourth birthday in July 2011, 1.5 million people had come through its doors. More than 466 000 visitors came in the last year alone, a 14 per cent increase on the previous year, which was a much bigger rise than for many other attractions in London.

Such sustained growth in Wellcome Collection's popularity means we are now planning to expand our facilities, services and programmes to accommodate this level of public interest and reach new audiences over the next few years.

Our two major exhibitions this year – *High Society* and *Dirt* (see page 38) – were our most successful to date.

*High Society* – our winter exhibition, which ran from November 2010 to February 2011 – explored the role of mind-altering drugs in history and culture, and challenged the perception that drugs are a disease of modern life. It attracted wide-ranging and extremely positive press coverage, with a five-star review in *Time Out* and a critics' choice in the *Guardian, Sunday Times*, *Times* and *Independent*.

Events accompanying the exhibition included discussions on the experience of drug taking, the definition of 'drugs' across different cultures and stories of famous and infamous drug users of the past. These proved extremely popular, as did our online game *High Tea*, which explored the history of opium smuggling in the run-up to the Opium Wars. It attracted 3.4m plays from people all over the world and engaged a broad audience with a controversial part of history, sparking debate and analysis on a range of gaming websites.

Continuing 2009's successful collaboration with the BBC, we ran a second series of 'Exchanges at the Frontier' in the autumn of 2010 – with a third starting in late 2011.

Philosopher A C Grayling met some of the biggest names in world science in the Wellcome Collection auditorium to discuss their work. Topics included the battle against malaria, the quest for eternal youth and the purpose of string theory. Each event was recorded and broadcast on the BBC World Service, reaching an audience of 40 000 listeners around the world.

Illustration by Mervyn Peake from *Alice's Adventures in Wonderland*, used to accompany the *High Society* exhibition. *Reproduced by kind permission of the Mervyn Peake estate*


> “The fast pace of scientific advances is having an increasing impact on human health. This project gives us a chance to bring together scientists, young people, artists and teachers to explore these vital issues.”
>
> **Nigel Townsend, Y Touring Theatre Company**

## Science centre stage

We want people to consider, question and debate the key issues in science and society. Through public engagement grants, the Wellcome Trust supports projects that encourage people of all ages and from all walks of life to be informed, inspired and involved. This year, two initiatives with a history of support from the Trust received Strategic Awards to extend their work in engaging young people with issues around biomedical research.

In 2010/11, the Institute of Ideas Debating Matters competition for 16-to-18-year-olds entered its seventh year in the UK and its third year in India. Originally supported by a Wellcome Trust Society Award, Debating Matters entails rigorous discussion of contemporary issues, many with a biomedical dimension such as organ donation, genetic screening, clinical trials, ageing and human enhancement.

The final of the UK’s Debating Matters competition took place over three days at the Royal Society of Medicine in London in July 2011. The team from St Francis Xavier’s, a comprehensive school and sixth-form college in Liverpool, were crowned champions.

Over the past seven years, Debating Matters has involved more than 12 000 students in thought-provoking debates, and a wide variety of schools in both India and the UK have been inspired to host events that follow the Debating Matters format. Its popularity means the competitions are oversubscribed, so in March 2011 the Institute of Ideas was awarded £875 000 to double the capacity of the competition in both countries.

The award will also enable the Institute of Ideas to further develop its annual Battle of Ideas event – a two-day festival of high-level public debate for people of all ages that takes place at the Royal College of Art in London every October.

Theatre company Y Touring has also received a Wellcome Trust Strategic Award – almost £1 million funding to support their work over the next five years. Their goal is to use drama to inspire school students aged 14–16 to reflect on complex ethical questions arising from scientific research and human health.

The award will allow Y Touring to develop and produce one new Theatre of Debate project a year for five years. These use theatre and digital media to stimulate debate about an aspect of biomedical research and its effects on individuals and society. The dramas will tour schools around the UK, be streamed to cinemas throughout the country and be performed at the Royal Albert Hall during National Science and Engineering Week.

The first year’s project, *Dayglo*, by playwright Abi Bown, will explore ethical questions in pharmacogenetics – the science of tailoring medicines to best fit an individual patient’s genetic make-up – and tour in 2012.

From left:

A Debating Matters event. *Wellcome Images*

Rebecca Skloot.

Roger Kneebone’s inflatable operating theatre. *Matthew Harrison*

Work at the Wellcome Foundation laboratories in Beckenham, 1959. *Wellcome Images*

### Winning stories

At an awards ceremony in November 2010, the story of a poor tobacco farmer from the American South won the 2010 Wellcome Trust Book Prize, which celebrates medicine in literature. *The Immortal Life of Henrietta Lacks* by Rebecca Skloot reveals how cancer cells taken from Henrietta without her consent became one of the most important tools in medicine. Her cells have been vital in understanding cancer and viruses, helped to lead to advances such as *in vitro* fertilisation and cloning, and have been cultured, bought and sold in their billions.

Another award winner was *Love at First Sight*, a short film made with the support of a Wellcome Trust People Award. The film was developed with the Bradford Dementia Group at the University of Bradford and stars John Hurt as Arthur, a 70-year-old man with dementia living in a nursing home who poignantly falls in love with a fellow resident, played by Phyllida Law. It has picked up numerous prizes since its premiere in November 2010, including awards from the Royal Television Society and the British Independent Film Festival.

### Simulating surgery

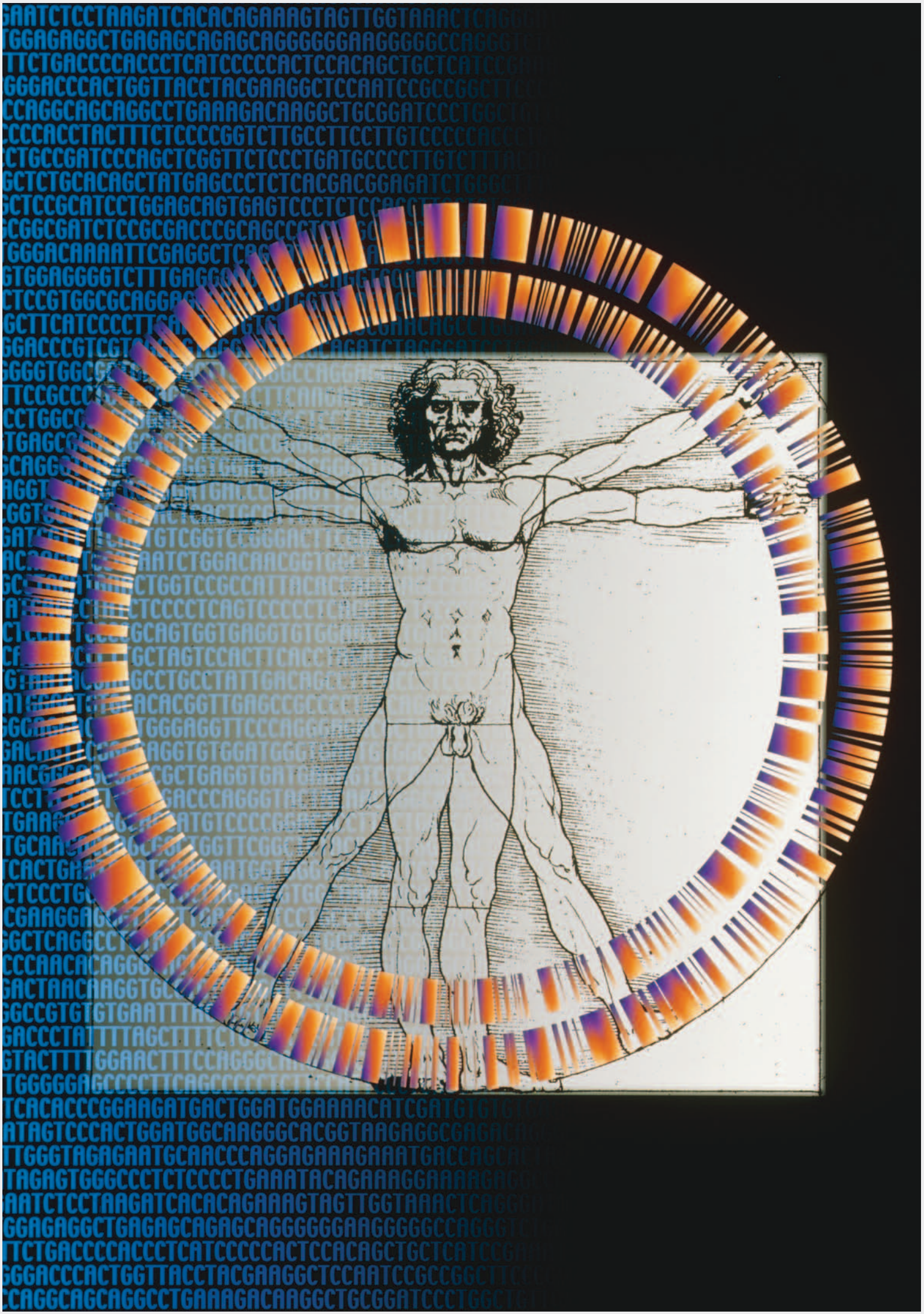
Your heart in their hands, or their hands in your heart? Professor Roger Kneebone is taking an inflatable operating theatre around the UK to perform a simulation of coronary angioplasty – an operation to unblock the blood vessels around the heart. Using the latest simulation technology, the artistic eye of a theatre director and Professor Kneebone's extensive experience as a teacher of surgery, this performance will show the perspectives both of the team performing the operation and then of the patient. This project opens the operating theatre to all, allowing an unprecedented appreciation of modern surgery.

### Before 'translational medicine'

The process of generating medical products from basic scientific knowledge is often referred to as 'translational medicine'. The phrase is relatively new but the activities it encompasses are not: everything from fundamental research through preclinical development to clinical trials and evaluation.

At the Wellcome Unit for the History of Medicine in Manchester, Professor Michael Worboys and his team are studying the changing relationships between the research laboratory and the medical clinic since 1950, focusing in particular on mental health. By exploring the history of these relationships, they hope to identify lessons relevant to the development of goals and policies in translational medicine today.

> "This is an engaging account of the life of Henrietta Lacks, who died in Baltimore nearly 60 years ago, and the immortal life of her cancer cells, which continue to replicate in research laboratories around the world to this day."
>
> **Clive Anderson, chair of judges, Wellcome Trust Book Prize**



# After early successes, the 1000 Genomes Project is expanding to give us an even more thorough map of human genetic variation.

In October 2010, results from the pilot phase of the 1000 Genomes Project were published in *Nature*. The project – an international public–private consortium of scientists that includes researchers at the Wellcome Trust Sanger Institute, the Beijing Genomics Institute and centres across the USA – was funded by foundations such as the Wellcome Trust and by national governments.

The original aim of the project was to sequence the genomes of at least 1000 people from different ethnic backgrounds and identify genetic differences with a frequency of at least 1 per cent. Following the success of the pilot phase, this has now been extended to 2500 genomes.

The pilot phase, launched in 2008, brought together researchers at academic centres and at technology companies that produce sequencing equipment. They analysed the whole genomes of 179 people and the protein-coding genes of 697 people from populations with European, west African and east Asian ancestry. The work has not just provided DNA sequences: it has also led to many innovations both in the technology of DNA sequencing and in the processing, analysis and interpretation of genetic data.

The consortium is using the data to create a comprehensive, free, publicly available map of human genetic variation. The map is unmatched by current resources, both in capturing and integrating data on all types of variation and in studying samples from numerous human populations. It is estimated to contain approximately 95 per cent of the genetic variation of any person on Earth – over 15 million variants, more than half of which had never been identified previously.

The project is already having an impact on research for both rare and common diseases as the map is helping researchers to identify all the candidate genes in a region of the genome associated with a disease. Numerous studies using next-generation sequencing to find mutations in rare diseases and cancer have used data from the 1000 Genomes Project to filter out variants that might otherwise obscure their results.

The data have also provided information on genetic variation within populations. For the first time ever, researchers can observe the precise rate of mutations in humans: every child has around 60 new mutations not present in either parent's genome.

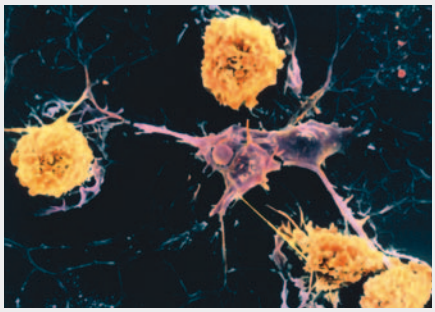
Following the completion of the pilot phase, the 1000 Genomes Project has expanded beyond its original aim and will sequence 2500 genomes from 27 populations worldwide over the next two years. It will identify more than 99 per cent of human variants to form an encyclopedia, a free public resource that will underpin future genetics research.

Artwork combining genome sequence data and Leonardo da Vinci's 'Vitruvian Man'. *Pasieka/SPL*

### Should I Test My Genes?

Award-winning director Adam Wishart received a Broadcast Development Award in 2009 and *Should I Test My Genes? The price of life* was shown on BBC 2 in July 2011. It followed him as he decided whether to have his genes tested following the death of his mother from cancer. As well as charting his own story, he looked at other aspects of genetic testing, including pre-implantation genetic diagnosis.

Wellcome Trust Broadcast Development Awards support the development of outstanding early-stage ideas for television, radio or new media projects. They enable broadcast professionals to fully research biomedical issues in order to generate programme proposals that will engage an audience with scientific content in an innovative, accessible and entertaining way.



### Multiple multiple sclerosis genes

An international team of scientists has identified 29 new genetic variants linked to multiple sclerosis, more than doubling the total number found to date. Many of the implicated genes are active in the immune system, shedding light on the immunological pathways that underlie the development of the disease.

The research, led by investigators at the Universities of Cambridge and Oxford, was funded by the Wellcome Trust and was the largest multiple sclerosis genetics study ever undertaken. It involved almost 250 researchers from the International Multiple Sclerosis Genetics Consortium and the Wellcome Trust Case Control Consortium.

Multiple sclerosis causes damage to nerve fibres in the brain and spinal cord. It is one of the most common neurological conditions among young adults, affecting around 2.5 million people worldwide.

### Out of Africa

Researchers at the Wellcome Trust Sanger Institute have provided new insights into our history by analysing whole genomes from four different parts of the world. Their results, published in *Nature* in July 2011, confirmed that there was a dramatic decrease in the human population starting around 60 000 years ago, about the time that human migration out of Africa was starting. But unlike previous studies, the analysis suggested that African and non-African populations continued to interbreed for thousands of years.

Dr Heng Li and Dr Richard Durbin sequenced the whole genomes of individuals from China, Korea, Europe and west Africa. Because the human genome is so large, combining information from tens of thousands of sites within an individual's genome can build up a history of ancestral contributions to that person's DNA. Comparing the X chromosomes from men in different populations revealed more about how their ancestral populations had separated.

“

Our findings highlight the value of large genetic studies... This would simply not have been possible without a large international network of collaborators and the participation of many thousands of patients.”

**Professor Peter Donnelly, University of Oxford, joint leader of the Wellcome Trust Case Control Consortium**

“

Over 6000 babies are born each year with serious developmental disorders…These families can directly benefit from the rapid growth in our understanding of the human genome.”

**Dr Nigel Carter, Wellcome Trust Sanger Institute**

## Deciphering developmental disorders

Thousands of children in the UK experience problems in their physical or psychological development because of rare genetic abnormalities. Doctors currently diagnose such disorders only by recognising the pattern of symptoms and the appearance of the child, supplemented in some cases by the use of microscopes to identify major rearrangements of the genetic material in the child’s chromosomes, called copy number variations.

Modern molecular testing methods can identify previously undetectable changes in chromosomes, which would allow for more accurate diagnoses. However, the clinical use of these methods has been hampered by limited availability, inconsistent application and the lack of basic knowledge to link genetic changes directly to symptoms. As such, it has been extremely difficult to make accurate clinical diagnoses in all but a small number of children.

DECIPHER (Database of Chromosomal Imbalance and Phenotype in Humans using Ensembl Resources) was set up in 2004 by Dr Nigel Carter of the Wellcome Trust Sanger Institute and Dr Helen Firth, a clinical genetics consultant at Addenbrooke’s Hospital in Cambridge, to enable clinicians to share information about copy number variation in patients.

Clinical geneticists anywhere in the world can register to use DECIPHER; with consent from patients and their families, they can record clinical symptoms and the type of DNA change detected. More than 100 centres worldwide have registered to date. For clinicians, identifying a case similar to their patient’s own is an important check that a rearrangement is actually causing the symptoms – everyone’s genome has some copy number variation, most of it harmless.

Sharing information can also help clinicians to define new syndromes. A small deletion on chromosome 17, for example, was identified in three cases – two from Cambridge and one from Brazil. A similar cluster of cases, this time two from Vancouver, Canada, and one from Cambridge, revealed a new syndrome linked to loss of part of chromosome 14.

As well as revealing which areas of the genome are vulnerable to damaging copy number variation, the database also highlights candidate genes – those within the deletion or duplication that might be causing the clinical abnormalities.

As our understanding of the genome increases, it will also be possible to identify other genomic regions that, while not causing a given syndrome directly, affect how a child develops.

In March 2011, Dr Carter’s team received £10 million from the Health Innovation Challenge Fund (see page 13) to improve the diagnosis of developmental disorders. They will build on the DECIPHER database to create a more detailed resource and cheaper, more efficient diagnostic microarray tools for genetic testing.

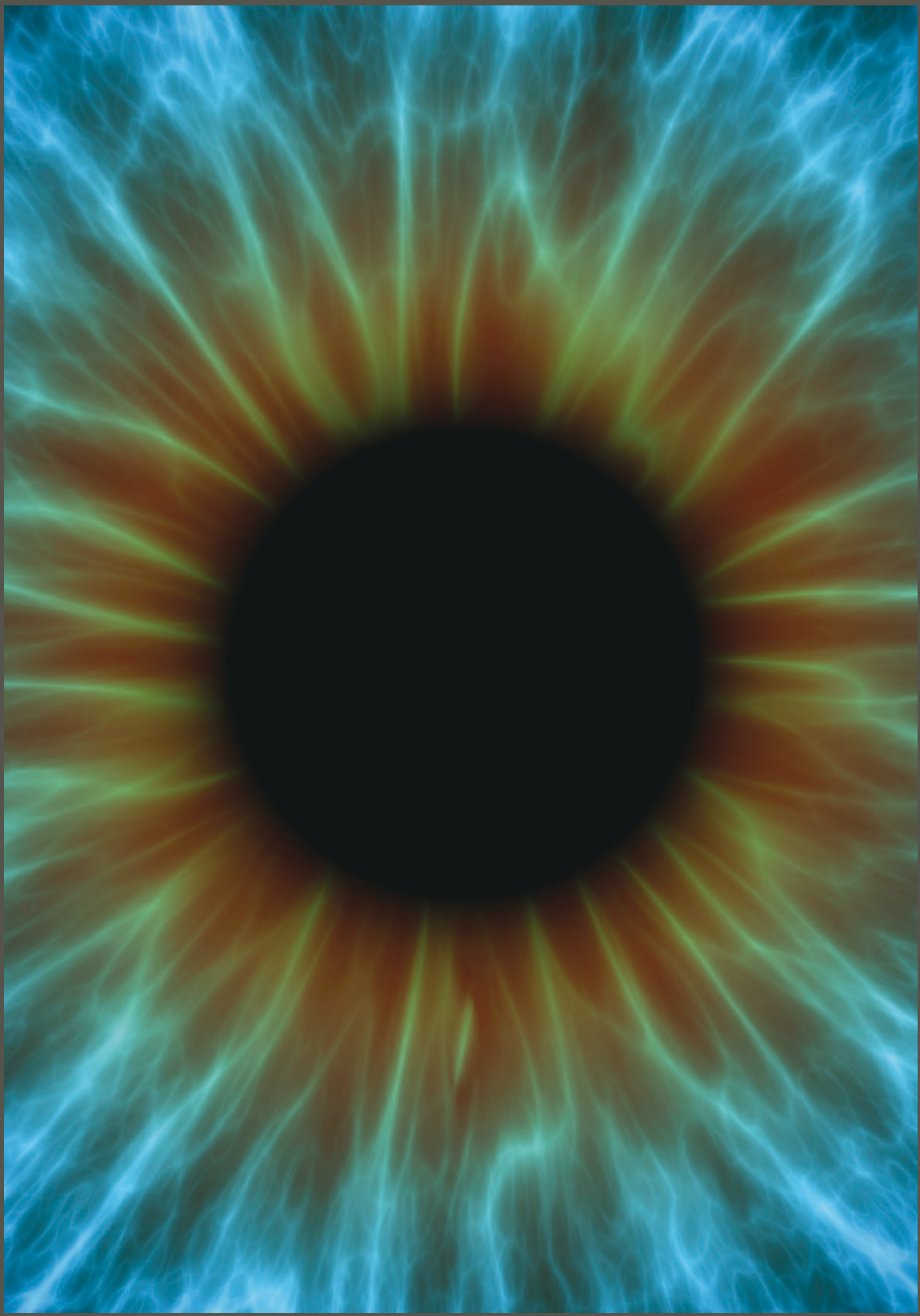
From left:

Adam Wishart’s film looked at the pros and cons of having a genetic test for a disease. *Tek Image/SPL*

Microglial cells (yellow) ingesting branched oligodendrocyte cells (purple), as happens in MS. *Dr John Zajicek/SPL*

Human populations across the world appear to have interbred for long after the exodus from Africa. *James Lee/iStockphoto*

Dr Nigel Carter. *Wellcome Images*



# A new drug has been shown to help people with inherited blindness recover some of their vision.

The most common form of inherited irreversible blindness is Leber's hereditary optic neuropathy (LHON), affecting 2000 people in the UK. The disease strikes early in adulthood; people who can see normally until the onset of the condition generally lose the sight in one eye first and then, within three to six months, in the other eye.

LHON causes a decline in levels of the antioxidant coenzyme Q10 in the mitochondria of eye cells. Mitochondria are the cell's 'batteries' that power its function, and it is notoriously difficult to treat mitochondrial disorders. In July 2011, however, Wellcome Trust-funded researchers published the results from a trial of a drug for LHON, which suggested they had identified the first effective treatment for a mitochondrial disease.

The team, led by Professor Patrick Chinnery, a Wellcome Trust Senior Research Fellow in Clinical Science at Newcastle University, conducted a multi-centre double-blind randomised controlled trial in 85 patients with LHON caused by mitochondrial DNA mutations.

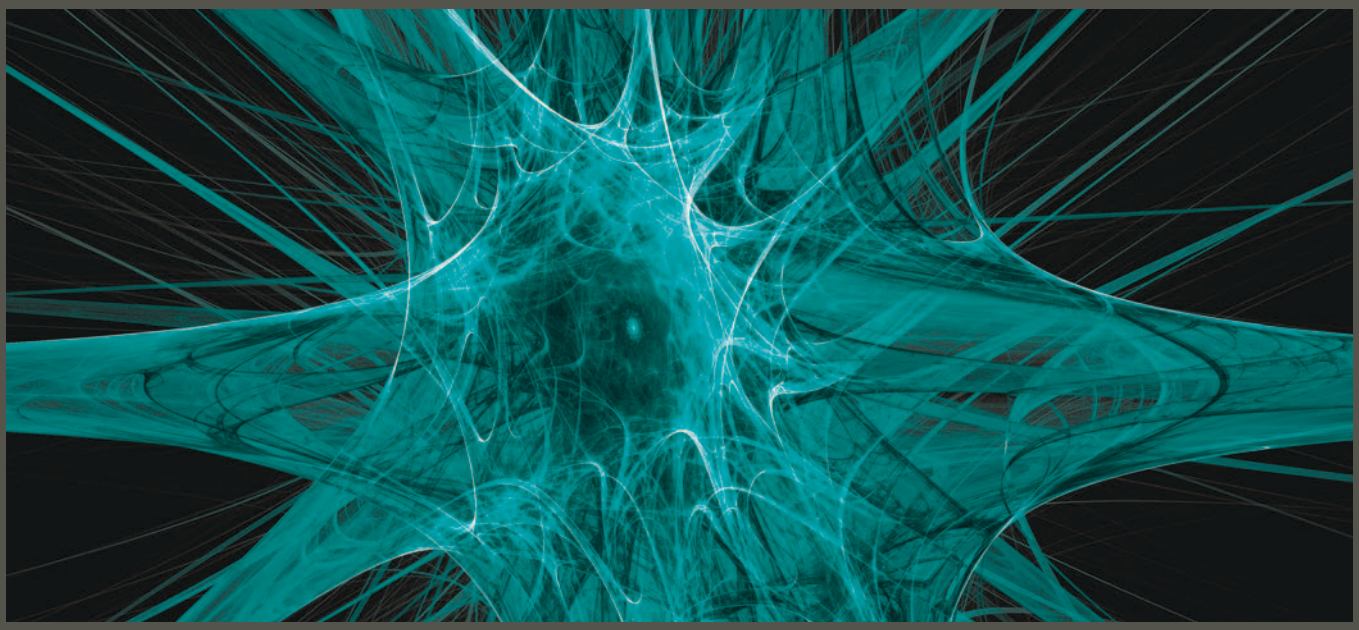
Participants recruited from hospitals in Newcastle, Munich and Montreal were given either a drug called idebenone or a placebo for 24 weeks. Idebenone is a synthetic analogue of coenzyme Q10 and, although it had not been evaluated in a clinical trial, anecdotal reports had suggested that it improved vision in people with LHON.

Published in the journal *Brain*, the findings indicated that idebenone was safe and well tolerated, and that after six months, some patients who had received it had improved vision and perception of colour. The greatest improvement was seen in those at an earlier stage of the condition.

In nine out of 36 severely affected patients, who could not see an eye chart on the wall at the start of the trial, treatment with idebenone resulted in a marked improvement: their vision improved to the extent that they were able to read at least one row of letters on the chart. None of the 26 patients given the placebo improved to that extent.

Restoring some vision to people legally certified as blind can mean a vast improvement in their quality of life, enabling them to move around more easily, use a computerised viewer to read, get dressed and even see family photos again. Moreover, patients report that they still have improved vision, even though they are no longer taking the drug. The team now aims to verify this and study the effect further. They believe there may be a case for offering idebenone from the moment that LHON is diagnosed – preferably before any symptoms develop.

Artwork of the iris and pupil. *Pasieka/SPL*



## Untangling the complexity of the brain

While the broad functions of many regions of the brain are well documented, we do not yet understand how individual nerve cells – neurons – interact with each other. Knowing which cells are connected, and how information flows through circuits in the brain, will be essential to a full explanation of how our brains work and what goes wrong in conditions as diverse as schizophrenia and stroke.

With around 100 billion neurons, each one connected to thousands of others, the brain has an estimated 150 trillion connections, or synapses. Mapping these connections is a daunting task but research published in *Nature* in April 2011 described a way to map the function of individual neurons and their synaptic connections in unprecedented detail.

Lead author Dr Tom Mrsic-Flogel, a Wellcome Trust Research Career Development Fellow at University College London, developed the technique and used it to study the visual cortex – the part of the brain that processes information from the eye. Within the visual cortex, different nerve cells have different functions. For example, some cells specialise in detecting edges in images; of these, some will be activated by the detection of horizontal edges, others by vertical edges. In this way, the brain constructs our perceptual images of whole objects and scenes.

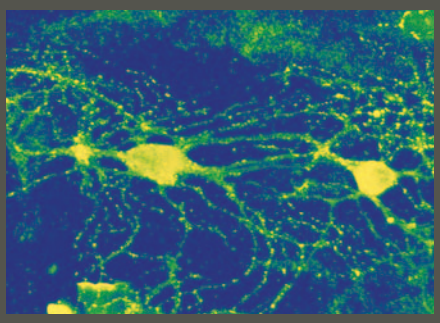
Dr Mrsic-Flogel and colleagues used high-resolution imaging to look into the visual cortex of the mouse brain, which contains thousands of neurons and millions of synapses. First, they identified those neurons that responded to a particular stimulus – detecting a horizontal edge, for example.

Then they applied small electrical currents to a subset of these cells to see which others responded, indicating a synaptic connection between them. Repeating this process many times, the team was able to trace the function and connectivity of hundreds of cells.

They found that neurons with similar functions, such as responding to horizontal lines, tended to connect to each other more than to those with other functions. This showed that the neural connections were ordered at a local level.

Using this technique, Dr Mrsic-Flogel is hoping to generate a 'wiring' diagram of the visual cortex. This will help us to understand the full repertoire of computations carried out by the neurons in this brain region and reveal more about their connections with related parts of the brain that underpin hearing, touch and movement.

Applied to the other parts of the brain, this technique could eventually produce the data needed to develop a computer model to explain how our neural networks generate thoughts, sensations and movements.



### 2401 Objects

A play about Henry Molaison, whose experimental surgery for epilepsy in 1953 left him unable to form new memories, won a Fringe First Award at the 2011 Edinburgh Festival and was shortlisted for the Carol Tambor Best of Edinburgh Award 2011. Part-funded by a Wellcome Trust Arts Award, *2401 Objects* was created by theatre company Analogue in collaboration with leading neuroscientists. It was well received in the press, earning five stars in the *Edinburgh Fringe Review*, four stars in the *Telegraph* and *Times*, and 'Pick of the Festival' in the *Sunday Express*.

### Sunburn reveals possible new targets for pain relief

In July 2011, the London Pain Consortium, funded by a Wellcome Trust Strategic Award, showed for the first time the role of a molecule called CXCL5 in mediating pain. Their findings revealed that CXCL5 was significantly overexpressed in the skin of volunteers exposed to UVB radiation. Examination of the biology of CXCL5 in rats confirmed that it significantly reduced the sensitivity to pain caused by UVB radiation. The team's novel approach reverses the traditional method of studying diseases in animal models first, and then trying to translate the findings in the clinic.

### Brain cells protect themselves from stroke damage

Scientists at the University of Bristol have identified how a nerve cell in the brain protects itself from damage during stroke. They looked at CA3 cells from the hippocampus region of the brain, which is involved in memory and navigation, and found that these cells had adenosine A3 receptors on their surface.

The findings, published in August 2011 in the *Journal of Neuroscience*, showed that CA3 cells' adenosine receptors were activated by the adenosine released during a stroke. The activated receptors removed glutamate receptors, making the cells more resistant to glutamate, high levels of which cause brain damage in stroke. This natural protection mechanism in CA3 cells may be useful in developing strategies to protect other types of nerve cell.

"He was a very gracious man, very patient, always willing to try these tasks I would give him. And yet every time I walked in the room, it was like we'd never met."

**Dr Brenda Milner, who carried out many studies of Henry Molaison's memory**

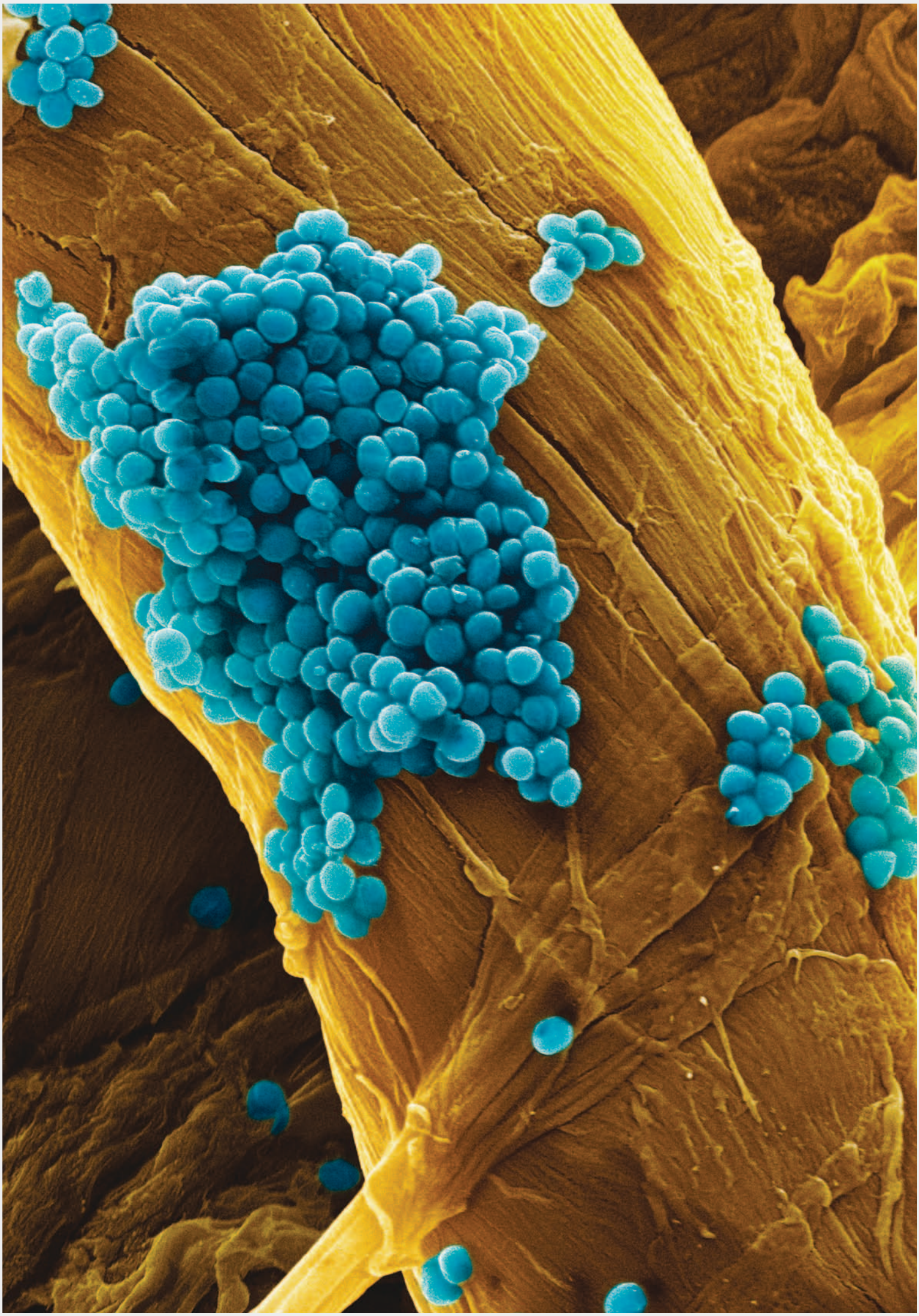
From left:

Abstract artwork of nerve cells. *Laguna Design/SPL*

A scene from Analogue's *2401 Objects*. *Andreas Etter*

The CXCL5 molecule reduces sensitivity to the pain of sunburn. *Shane White/iStockphoto*

Hippocampal neurons with glutamate receptors showing. *Dr A Irving, University of Dundee/Wellcome Images*



# Race against resistance: as fast as we develop new antibiotics and vaccines, bacteria develop resistance to them.

Understanding the precise genetic events that enable the evolution of drug resistance in bacteria could help us design more powerful – and permanent – ways of controlling infection.

In a paper published in the journal *Science* in January 2011, Wellcome Trust-funded researchers described in detail the adaptive changes that allow a drug-resistant form of *Streptococcus pneumoniae*, called PMEN1, to continue to thrive.

The team at the Wellcome Trust Sanger Institute and Imperial College London used next-generation DNA-sequencing technology to analyse 240 samples of PMEN1 collected over 24 years. They compared the DNA sequences, looking for differences over that time.

The findings revealed for the first time the patterns of genomic adaptation that have allowed the PMEN1 strain to fight its evolutionary war against our vaccines and antibiotics in recent decades. They showed that *S. pneumoniae* evolves and reinvents itself with remarkable speed: the degree of diversity between bacteria within the PMEN1 strain itself was surprising.

The critical first step in unlocking the evolutionary history of the PMEN1 lineage was separating two kinds of DNA change. Vertical changes occur when bacterial cells divide to create offspring, while horizontal changes are when pieces of DNA are swapped between two bacteria.

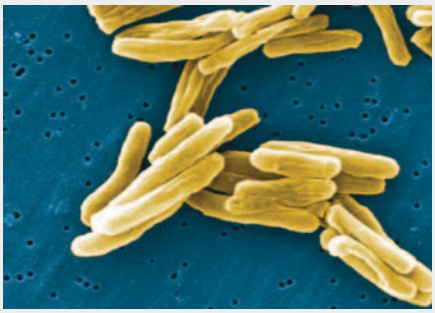
Mapping the vertical changes – DNA mutations passed down through direct ancestry – enabled the researchers to construct an evolutionary tree. They saw that the drug-resistant PMEN1 lineage originated around 1970 – about the time that the widespread use of antibiotics was introduced to fight pneumococcal disease.

They could then see that the horizontal transfer of DNA between bacteria had affected three-quarters of the *S. pneumoniae* genome. Hotspots particularly prone to horizontal transmission often coded genes for antigens – molecules that trigger an immune response in humans – suggesting that *S. pneumoniae* evades vaccines and antibiotics by changing the antigens that are being targeted.

The authors also identified differences in the patterns of adaptation in response to antibiotics and vaccines. With antibiotics, different strains often adapted in the same way to become resistant. In the case of vaccines, however, there was a decline in the prevalence of bacteria susceptible to the vaccine, which opened the door for others that could evade the vaccine to fill the niche and become dominant.

Further focused sequencing programmes may prove crucial to the future fight against this and other bacterial pathogens that use similar mechanisms to outsmart our control measures.

*Streptococcus pneumoniae* bacteria.
*Steve Gschmeissner/SPL*



### WHO endorses tuberculosis tests

In December 2010, the World Health Organization (WHO) backed the use of a test called GeneXpert to diagnose tuberculosis and identify resistance to rifampicin, one of a combination of drugs widely used to treat the disease. The decision was based on preliminary results of a study that was later published in the *Lancet*. The Wellcome Trust funded the research and is also supporting an extension of the project, including follow-up studies.

This came a month after the WHO had endorsed a separate test for tuberculosis called microscopic observation drug susceptibility (MODS), for use in resource-poor settings. This is a rapid, low-cost test that can be used to diagnose tuberculosis and multidrug resistance. MODS was developed by a team based at the London School of Hygiene and Tropical Medicine and Imperial College London with support from the Trust.

### Smallpox timeline wins BAFTA

A free school resource on the history of smallpox won the BAFTA for Secondary Learning in November 2010. Smallpox Through Time was made for Timelines.tv, a website that provides free broadcast-quality films about history for teachers and students.

Starting with the death of the pharaoh Rameses V in ancient Egypt – the first recorded victim of smallpox – the resource consists of 13 short online video clips. They trace the history of the disease through the ages: from the story of Pocahontas and the devastating consequences of smallpox among the indigenous people of America, to Edward Jenner's discovery of a vaccine for the disease and its eventual eradication.

Smallpox Through Time was funded by a Medical History and Humanities public engagement grant from the Wellcome Trust, which also provided the film makers with access to archival resources and expert academic advice.

### New antibiotic recommended for typhoid

A large clinical trial in Nepal comparing treatments for enteric fever, which includes typhoid, has supported the use of the antibiotic gatifloxacin. The results of the trial, which was funded by the Wellcome Trust and the Li Ka Shing Foundation, were published in May 2011 in *Lancet Infectious Diseases*.

Enteric fever kills 200 000 people a year, primarily in South Asia, and the bacteria that cause it have been developing resistance to the standard treatments. Gatifloxacin, one of a new generation of typhoid drugs, was released in 1999 but withdrawn after a 2006 study suggested it caused dysglycaemia (irregular blood sugar metabolism) in older obese people in North America.

In Nepal, where obesity is less common, the study found that gatifloxacin was as effective as the standard treatment and had less severe side-effects. It had other advantages in that treatment with gatifloxacin is shorter and cheaper, and it worked against drug-resistant typhoid. The researchers have submitted their evidence to the World Health Organization for consideration.

> “Through human ingenuity, human cooperation… we learned to prevent the spread of this terrible disease…wiping the virus off the face of the Earth. Without exaggeration, it's one of the great epic stories of human history.”
>
> **Andrew Chater, presenter of the Smallpox Through Time videos**

“

Intravenous artesunate should be used in preference to quinine for the treatment of severe *P. falciparum* malaria in children. *Strong recommendation, high quality evidence*”

**WHO revised *Guidelines for the treatment of malaria*, April 2011**

## Malaria study leads to revised treatment guidelines

Malaria kills around 1 million African children every year. For the last 100 years, injected quinine has been the best available treatment. The drug binds to the DNA of the parasite that causes malaria, preventing it from reproducing and giving the person's body an opportunity to fight the infection and get well.

Although quinine is reliably effective, it is difficult to give by injection and can cause serious and life-threatening bleeding problems and kidney injury.

Five years ago, the Wellcome Trust part-funded what was then the largest ever trial in patients hospitalised with severe malaria. It showed that a new drug, artesunate – derived from a Chinese herb and also given by injection – lowered the death rate more than quinine.

That trial was conducted in Asia and most of the patients studied were adults. In recent years it has become increasingly clear that drugs that work in some settings and populations may not be as effective in others due to variables such as co-infections, drug resistance and even genetics. Uncertainty therefore remained as to whether artesunate injections should replace quinine as a treatment for severe malaria in African children.

In November 2010, the results of a trial funded entirely by the Trust to examine the effects of artesunate in African children with severe malaria were published online in the *Lancet*.

The study, known as AQUAMAT (African quinine versus artesunate malaria trial), was the largest ever clinical trial among patients hospitalised with severe malaria. Researchers across Africa worked in collaboration with the scientists in Thailand and the UK who had conducted the original study in Asia, and the international consortium was led by Professor Nick White of the Wellcome Trust–Mahidol University–Oxford Tropical Medicine Research Programme in Bangkok.

Findings showed that treatment with artesunate reduced the fatality rate of severe malaria to 8.5 per cent, compared with 10.9 per cent with quinine (which in a population of 1 million amounts to 24 000 lives saved). The results were very similar in all the study sites. Artesunate was also easy to administer, well tolerated and proved very safe.

In April 2011, the World Health Organization announced that, in light of the rigorous evidence supplied by the trial, it was revising its treatment guidelines to recommend artesunate as the first-line treatment in the management of severe malaria in African children. If implemented, this could save hundreds of thousands of young lives.

From left:

*Mycobacterium tuberculosis. AJ Cann/Flickr*

Edward Jenner treating smallpox patients. By James Gillray, 1802. *Wellcome Library*

Children in Nepal. *Eric Montfort/Flickr*

Sweet wormwood (*Artemisia annua*), source of the key ingredient of artesunate. *Rowan McOnegal/Wellcome Images*

# Trials in India are showing promising results for combined 'polypills' to treat risk factors for heart disease and stroke.

High blood pressure and high cholesterol are both risk factors for the progression of cardiovascular disease. At present these symptoms are treated individually with separate agents, such as diuretics, ACE inhibitors and statins – drugs that are prescribed to millions of people worldwide.

Many experts believe that combining these treatments into a single pill will make it more manageable for people – as well as being considerably cheaper – than taking four or five different pills.

However, there are concerns that a 'one-size-fits-all' pill could give some patients too little of the medication they need – or some medicine that they don't need at all – and expose them to needless potential side-effects.

The Wellcome Trust has funded two international multi-centre trials to assess whether combined pills are safe, effective and practical. Each trial used a different formulation of combined pill – each made by a different Indian pharmaceutical company.

The first was a pilot study, intended to inform the design of a subsequent larger trial, of a one-a-day polypill manufactured by Dr Reddy's Ltd, Hyderabad. The researchers looked at the effects of the polypill on blood pressure and cholesterol levels in 378 people at high risk of cardiovascular disease. The results, published in May 2011 in *PLoS ONE*, showed that taking the polypill for 12 weeks reduced the levels of both risk factors compared with taking a placebo.

In June 2009, the Trust had agreed to support a much larger international trial of another combined pill: Polycap™, developed by Cadila Pharmaceuticals Ltd, Ahmedabad. The award was made through the Trust's R&D for Affordable Healthcare in India initiative, which aims to develop innovative, affordable healthcare products on a large scale.

Polycap™ had earlier been tested in 2053 people throughout India – again over 12 weeks – and its effect on the various risk factors compared with those of the individual components of the pill given separately. The results, reported in 2009 by the *Lancet*, showed that the combined pill was almost as effective as the individual pills, with no increase in side-effects.

The new Wellcome Trust-funded phase III controlled trial will now evaluate whether Polycap™ reduces the number of deaths among people at high risk of cardiovascular disease. It will involve at least 5000 individuals, over five years, in centres in India, China and several other countries.

Combined pills are being tested for their effectiveness against heart disease. *ImageZoo Illustration/Veer*

## 20 years of the Children of the 90s

The 'Children of the 90s' project (formally known as the Avon Longitudinal Study of Parents and Children, ALSPAC) recruited more than 14 000 pregnant women in Bristol in 1991 and 1992. Part-funded by the Wellcome Trust, this pioneering longitudinal study has been charting the health of the women and their children ever since.

Every one or two years, the enrolled women bring their children to the project's home at the University of Bristol, where they are given thorough health examinations. Biological samples are taken and mothers, fathers and children answer detailed questionnaires and take part in interviews about their lifestyle, health and behaviours.

The result is an extraordinary range of in-depth, detailed information. Researchers can use this rich and comprehensive resource to investigate the interplay of genes and lifestyle, and how this helps determine health and wellbeing throughout a lifetime.

The children of the study are now entering adulthood. New data collected from them will provide valuable evidence into how behaviours such as smoking or exercising – from before birth through infancy, childhood and adolescence – affect our health later in life.

Likewise, new data from their parents will help researchers to identify the causes of common health problems that occur with increasing age, such as raised blood pressure, heart disease, depression and osteoporosis.

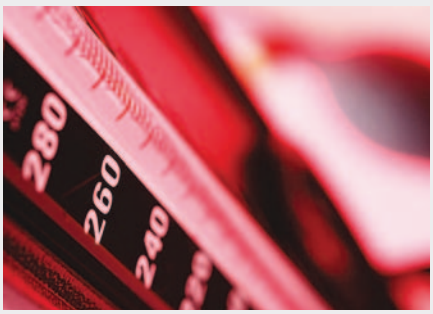
Among the key findings of the project to date are the discoveries that 15 minutes of moderate exercise per day can reduce childhood obesity, that fathers can suffer from postnatal depression and that taking paracetamol in pregnancy can increase the risk of childhood asthma. Studies using ALSPAC data have also shown that many common genes have a small but definite influence on obesity, height and many other aspects of growth and development.

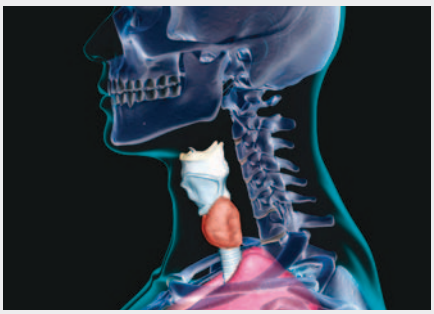
As it celebrated its 20th anniversary in April 2011, the Children of the 90s received an additional £6 million from the Wellcome Trust, the Medical Research Council and the University of Bristol. This will enable the project to move into its next phase – a study of the children of the Children of the 90s. The researchers also intend to broaden its scope and involve other interested family members, including grandchildren and other children of the study mothers.

The data they collect in this second phase will shed light on how our health depends in part on what happened in the early lives of our parents and grandparents. This knowledge is likely to make important contributions to policy and public health, and improve the health of current and future generations – the ultimate goal of the project.

"Whilst some of the data collected seems a bit random – such as taking cross-sectional scans of my leg, or asking if I can hear voices that no one else can – this was always the intention: to collect everything. This is what makes the study such an exceptional resource."

**Emma James, a 'Child of the 90s' and a 2011 Wellcome Trust Summer Intern**



## Looking for the causes of ageing

New research has thrown doubt on the role of proteins called sirtuins in the mechanism by which some organisms' lifespans have been extended in the lab. The claimed target of some anti-ageing creams, sirtuins have been linked to ageing and longevity in yeast, nematode worms and fruit flies. When these organisms' genes were manipulated to overproduce sirtuin proteins, they lived longer – up to 50 per cent longer in the case of nematodes.

A paper published in *Nature* in September 2011 described experiments led by Dr David Gems at the Wellcome Trust-funded Institute of Healthy Ageing, University College London. This showed – surprisingly – that sirtuin genes were not the cause of the longer lifespans seen previously. Dr Gems suggests scientific efforts should be redirected towards other genes that seem to play more of a role in ageing.

## Blood pressure genes

Two studies published in *Nature* and *Nature Genetics* in September 2011 have identified several gene regions associated with blood pressure and other measurements that can predict cardiovascular disease. The findings identify potential targets for new therapies to prevent heart disease and stroke.

Both studies were from the International Consortium for Blood Pressure Genome-Wide Association Studies and were funded by the Wellcome Trust, the Medical Research Council, the British Heart Foundation and the National Institute for Health Research. The research involved hundreds of scientists from 24 countries around the world.

More than one billion people have high blood pressure; even small changes in blood pressure can increase risk of heart disease and stroke, the biggest cause of death worldwide.

## Larynx transplant

Professor Martin Birchall at the Royal National Throat, Nose and Ear Hospital in London has developed pioneering techniques that are transforming transplants of the larynx.

In October 2010, he joined an international team of surgeons at the University of California, Davis to restore the voice of a woman whose larynx had been damaged during surgery. She had not spoken for 11 years and could not breathe, eat or drink unaided. The 18-hour operation was first time that the larynx, trachea and thyroid had been transplanted together. After two months of rehabilitation, during which the nerves regenerated, the patient learned to speak again and she can now breathe, eat, drink and talk unaided.

The surgical techniques Professor Birchall used in the operation were developed over more than ten years of research funded principally by the Wellcome Trust.

From left:

The Children of the 90s study is now looking at several generations of families. *Orange Line Media/Veer*

Ageing affects our bodies. *Yurok Alexsandrovich/Veer*

A sphygmomanometer gauge for checking blood pressure. *Wellcome Images*

Illustration showing the larynx. *Medical RF.com/SPL*

# An international project has shed light on social and cultural factors in obesity and their importance in planning strategies against it.

The Pacific region has the highest rates of obesity in the world and the problem is increasing among its young people. Attempts to control it have had limited success, in part because of a lack of understanding of how diverse environmental factors – at home, in school and in the wider community – interact to influence eating and exercise behaviour.

A series of linked studies in Fiji, Tonga, New Zealand and Australia – the Pacific OPIC (Obesity Prevention In Communities) project – aimed to better define and address these challenges. The five-year study was funded jointly by the Wellcome Trust, the National Health and Medical Research Council in Australia and the Health Research Council in New Zealand.

OPIC researchers collected information about weight, diet and exercise, social experiences, gender, ethnicity and quality of life from 17 150 high-school students aged 12–18 across the four countries.

The findings revealed that around one-quarter of students were overweight and more than 10 per cent were obese. Large variations in obesity levels across the four countries indicated the contribution of environmental differences. The numbers of overweight or obese students were much higher in New Zealand and Tonga than in Australia and Fiji.

Investigators explored the social and cultural factors that promote obesity and incorporated their findings into community-based interventions, which they then evaluated for impact and cost-effectiveness. Interventions included: increasing opportunities for structured physical activity in and after school; improving the healthiness of foods sold in school canteens; encouraging families to replace sugary snacks and soft drinks with fresh fruit and vegetables; and increasing the price of unhealthy foods, while reducing their availability and promotion of them in the media.

As before, results varied across the four countries. The interventions produced a significant reduction in overweight and obesity in Australia, while in Fiji they had little impact. This highlights the importance of research and thorough evaluation to ensure that efforts to reduce obesity, and other health problems, are targeted and effective. The project concluded in 2010 and the researchers presented 40 specific, evidence-based policies to the four governments as priorities for improving their young people's health.

The OPIC study has also helped to increase capacity for obesity prevention research in the region. The investigators identified and supported several promising young researchers in the study countries to further their careers in research. This is particularly important in the case of Fiji and Tonga, where there is an extreme shortage of trained researchers.

More opportunities for structured physical activity are recommended. *Tony Tremblay/iStockphoto*

> *Dirt*…takes us on a fascinating tour through the grimy sublime to illustrate the ways in which we use filth to construct our worlds, social systems and hierarchies."
>
> **Christopher Turner, the *Guardian***

## Dirt season

*Dirt: The filthy reality of everyday life* ran from March to August 2011 and attracted more than 130 000 visitors – the greatest number drawn to a single exhibition at Wellcome Collection to date. The exhibition and accompanying season of events encouraged visitors to explore our ambivalent relationship with dirt: microbes are essential to life and health, yet are capable of causing devastating disease.

The exhibition featured an eclectic range of 200 artefacts from six sites around the globe, spanning four centuries (including a look into the future). They encapsulated the multifarious nature of dirt and its changing meanings in different cultures and contexts, including its defeat by Joseph Lister's pioneering antiseptic techniques, its metaphorical role in the Nazi 'purification' of race, and its economic significance for the sewage scavengers of New Delhi today.

A central feature of the exhibition was 'Laid to Rest', a sculpture of 500 bricks commissioned from artist Serena Korda, who collected dust from people and institutions around London and baked it into the bricks.

*Dirt* gripped the imagination of public and press alike. Double-page features were dedicated to it in the *Times* ("utterly fascinating"), *Guardian* ("poignant"), *Telegraph* ("gripping"), *Independent* and *International Herald Tribune*. It was discussed on the BBC's *Review Show* ("joyous" and "extraordinary") and all major radio stations, and well over half a million websites linked to the exhibition online.

Dirt events reached new audiences for the Wellcome Trust. For example, the Decontamination Chamber at Glastonbury entertained festival-goers in their 20s and 30s. It was created in collaboration with Guerilla Science and the Shangri-La installation – a dystopic city laid out in Glastonbury's Shangri-La field. A fictional 'virus' – in the form of UV reflective paint – contaminated people who wandered through the city. Symptoms were detailed on billboards and public health announcements over loudspeakers urged sufferers to visit the Decontamination Chamber – a giant white cube in the same field – immediately.

On arrival they were physically 'decontaminated' by two microbiologists in biohazard suits and offered private sessions with bona fide psychiatrists to cleanse themselves morally. Around 800 visitors went through the process – and many more of the 150 000 people who went to Glastonbury will have seen the billboards and engaged with the story.

A collaboration with the Eden Project delighted under-14s by exploring the biology and smell of our bodily waste – and where it goes once flushed down the toilet. And two Dirty Weekends in Glasgow in September – collaborations with the Hunterian Museum and Art Gallery and Glasgow Science Centre – allowed older audiences to explore Glasgow's middens and industrial history, discover the city's other secret history of bodysnatching by medical students and their tutors, or become temporary crime scene investigators.

From left:

Funeral procession taking Serena Korda's 'Laid to Rest' sculpture for burial. *Wellcome Images*

Sandwich. © *Steve Buchanan/the food passionates/Corbis*

Children in Kenya. *Amanda Kline/stock.xchng*

Weighing scales. *Nicholas Belton/iStockphoto*


### Big Picture: Food and Diet

The summer 2011 issue of *Big Picture* focused on food and diet, looking at what drives us to eat, what happens to food once we've eaten it and what impact dietary choices have on the health and wellbeing of people across the world.

*Big Picture* is the Wellcome Trust's free, post-16 educational resource for teachers and learners exploring issues around biology and medicine. Published twice a year, it is supported by online content, all tailored to complement the science curricula used in the UK. Previous topics featured in *Big Picture* include obesity and climate change.

Issues and resources are available through the Guardian Teacher Network, TES Teaching Resources and the Wellcome Trust website.

### Health dynamics in Africa

A Wellcome Trust-funded programme at the African Population and Health Research Center in Kenya has been looking into the links between poverty, migration and health in the slums of Nairobi. The programme aims to assess the factors affecting people's wellbeing throughout their lives, with an emphasis on children, adolescents and elderly people.

Findings from the research informed the Kenyan government's decision to pilot a scheme to fund safe childbirth, family planning services and gender-based violence recovery services. The programme has also informed current rethinking of strategies to improve urban health in low-income countries more broadly.

### *FTO* gene linked to obesity

Research published in November 2010 provided the first direct evidence that overactivity of the *FTO* gene leads to overeating and obesity in mice. Funded by the Wellcome Trust and the Medical Research Council, the study is a crucial step towards understanding the role of the *FTO* gene in obesity, which raises the risk of heart disease, type 2 diabetes and cancer.

A genome-wide association study in 2007 had found a genetic variant within *FTO* that was associated with an increased likelihood of obesity, but more work was needed to confirm the gene's precise role in the condition. Knowing that *FTO* is directly linked to obesity raises the possibility of developing drugs to reduce the activity of the gene in obese people.

> "Whenever I hear, see or read something, I get a specific taste…We were read the Lord's Prayer every morning [at school]: it had a taste of very thin crispy bacon. I can taste it now."
>
> **James Wannerton, President of the UK Synaesthesia Association, *Big Picture: Food and Diet***

# We are indebted to the researchers and experts who give up their time to sit on our advisory committees or review our grant applications.

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