Celebr a d of discove

Highlights of the Wellcome Trust's work in 2010 – a year that saw us celebrating a decade of discovery since the draft sequence of the human genome was unveiled.

wellcome trust

Vision

To achieve extraordinary improvements in human and animal health.

Mission

To support the brightest minds in biomedical research and the medical humanities.

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As at January 2011

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This year, we celebrated the tenth anniversary of the first draft of the human genome and, with the publication of our new Strategic Plan, looked forward to the decade ahead.

In 2000, Tony Blair and Bill Clinton announced the completion of the draft sequence of the human genome. This was a milestone in biology and medicine. The Human Genome Project brought together thousands of scientists from six countries to master the technical challenge of lining up 3 billion bases of DNA into the genome sequence. We took the lead in ensuring that all of these data were freely available on the internet. This approach has enabled scientists worldwide to use the reference sequence in their studies of almost every aspect of human biology.

A decade later, we have seen remarkable progress in deciphering and understanding the content of the genome. We are learning how our genome compares with those of other species, how genes are expressed and regulated, and about the functions of the RNA and proteins that it encodes. Equally important are collaborations between geneticists and clinicians that are discovering how inherited and acquired differences in DNA sequence influence human variation in health and disease. Leading the way in this latter field of research are genome-wide association studies – notably the Wellcome Trust Case Control Consortium – that are uncovering the myriad genetic variants that influence our susceptibility to many common diseases. Such research would not be possible without the remarkable technological innovations that have enabled a phenomenal increase in our ability to sequence DNA. The first genome took ten years to produce and cost approximately £700 million; today, the Wellcome Trust Sanger Institute can sequence the equivalent of two genomes each day at a fraction of the cost. There is every expectation that the price of sequencing will continue to reduce dramatically as technology advances.

Despite this progress, there is still much to discover. We still do not know the full extent of the variation in the human genome, some of which is common and found in many millions of individuals, and some of which is rare and found in only a tiny fraction of the world's population. And we are only a small part of the way towards an understanding of the links between genes and health. Hence, this year, we launched major projects to study the genomes of 10 000 people in the UK (UK10K) and thousands of people in Africa (the Human Heredity and Health in Africa Project, or H3 Africa). The UK10K project aims to apply whole genome sequencing to find many uncommon or rare genetic variants that are important in human disease. H3 Africa, a partnership with the US National Institutes of Health to fund scientists working in Africa, will help us to understand how genes and the environment interact in the development of diseases such as cancer, heart disease and malaria.

We take a long-term view to funding research, allowing the researchers that we support to tackle difficult and ambitious questions. This is evident in our new Strategic Plan for 2010–20: *Extraordinary Opportunities*, which was launched in February 2010. The Plan set outs our three areas of focus for the next decade: supporting outstanding researchers, accelerating the application of research, and exploring medicine in historical and cultural contexts. It also poses five research challenges: maximising the health benefits of genetics and genomics; understanding the brain; combating infectious diseases; investigating development, ageing and chronic disease; and connecting environment, nutrition and health. Each challenge has many research questions and brings together the many different activities of the Trust – including research in biology and medicine, the translation of research into healthcare products, public engagement, the history of medicine and the ethics of research.

How can we ensure that we make progress as effectively as possible in these challenges? The key is to fund the best researchers, so we have launched a new scheme – Wellcome Trust Investigator Awards – that extends the ethos of our highly successful fellowship schemes to researchers who are in established posts.

We also want to make sure that researchers have the best facilities and equipment. The flagship new project for UK science is the UK Centre for Medical Research and

Innovation (UKCMRI) in London, which is expected to open in 2015. The Centre's goal is to make discoveries about mechanisms of disease and to develop these into new ways to diagnose, prevent and treat major diseases.

The UKCMRI is a partnership between the Medical Research Council (MRC), Cancer Research UK, University College London and the Wellcome Trust, and partnerships are key to many of our major initiatives. The Neurodegenerative Diseases Initiative, for example, is a collaboration with the MRC, through which we are funding three new research programmes on Alzheimer's disease, Parkinson's disease and motor neurone disease. The £10m Insect Pollinators Initiative is a partnership with four other funding agencies that has funded nine projects to investigate the causes of the fall in numbers of bees, wasps and other insect pollinators, and what can be done to reverse this trend. The £45m R&D for Affordable Healthcare initiative is our second major partnership with the Government of India's Department of Biotechnology and will fund the development of innovative and affordable new devices, diagnostics, medicines and vaccines. And, finally, the new £37m Bioscience Campus in Stevenage, Hertfordshire, will foster early-stage biotech companies and is a partnership with GlaxoSmithKline, the UK Government, the Technology Strategy Board and the East of England Development Agency.

These are just a few examples of the wide range of initiatives launched during 2009/10, a year that has also seen many fascinating discoveries enabled by support from the Wellcome Trust. One key breakthrough was the decoding by the Sanger Institute of the complete genomes of a lung cancer and a melanoma. These showed extraordinary complexity, with both having thousands of mutations. The pattern of these mutations differed between the two cancers, reflecting their different environmental stimuli to mutation: ultraviolet from sunlight for the melanoma and cigarette smoke for the lung cancer. It is crucial to identify cancer-causing mutations, as these can define potential targets for drug therapy. In the case of melanoma, for example, a drug based on the discovery of mutations in a growth factor called BRAF – a discovery made by Professor Mike Stratton and his team – is showing positive effects in early clinical studies.

Other discoveries that you can read about in this *Annual Review* include the analysis of nerve signals from the spinal cord system that prevent tremors, and the identification of regions of the brain involved in literacy – a fascinating study involving former guerrillas in Colombia who, as adults, were learning how to read for the first time.

It has been a busy year for our many public engagement activities, which bring science to life for general audiences in exciting and innovative ways. Foremost has been an exploration of scientific and social perspectives of identity through the Identity Project, a nine-month season of exhibitions, events and experiments that encouraged debate and discussion across the country. The season included the *Identity* exhibition and the production by Mike Gordon and Billy Bragg of *Pressure Drop* at Wellcome Collection, and it culminated with the reopening of the Science Museum's *Who Am I?* gallery in its Wellcome Wing. Fittingly, this was in June 2010, on the week we celebrated the tenth anniversary of the completion of the draft sequence of the human genome.

Finally, I would like to congratulate Andrea Gillies, the winner of the first Wellcome Trust Book Prize. *Keeper* is a poignant account of the demands of looking after a relative with Alzheimer's disease. This book reinforces why it is so important that the Wellcome Trust and our partners continue to fund vigorous, innovative research that will bring important improvements to the health of this and future generations.

Sir Mark Walport
Director of the Wellcome Trust

Supporting outstanding researchers

Wellcome Investigator Awards bring the ethos of our fellowship schemes to a wider community of researchers.

In 1966, the Wellcome Trust embarked on a major change in its funding strategy. Over the previous 20 years, it had spent almost two-thirds of its income providing new equipment and buildings for the UK's under-resourced scientists. But when funds for such essentials became available from the government, it changed tack. Individual researchers became the new focus, and fellowships became its hallmark funding schemes.

Today, the Wellcome Trust has a portfolio of fellowship schemes that provide researchers with the resources and flexibility to pursue their vision – at every stage of their careers. The schemes help young researchers to be trained and mentored in the best environments, enable more experienced researchers to develop their own independent research programmes, and fund internationally recognised researchers to undertake world-class research.

This year saw the launch of the new Wellcome Trust Investigator Awards, a transition in our funding that is just as important as that of 1966. Currently, fellowships are not open to researchers who hold established positions and want to remain with their employing institution. Now, through Investigator Awards, we will be bringing the fellowships ethos to a wider community of researchers who are salaried by their university or research institute. We are offering two categories for researchers at different stages of their careers: New Investigator Awards and Senior Investigator Awards. New Investigator Awards are targeted specifically at exceptional researchers who have just taken up their first academic post.

These new awards replace our old project and programme grant schemes, which required applicants to describe in detail what they intended to achieve and did not readily embrace the unexpected twists and turns that research often takes.

> “Simply put, the best way to administer a creative research environment is to find people of great talent and reasonable ambition – whatever their specific disciplines – and leave them to their own devices.”
>
> **Joshua Lederberg, *The Scientist*, 1991**

Furthermore, as many of our project grants lasted for only three years, the scheme required researchers to submit multiple, successive applications. By contrast, the Investigator Awards emphasise flexibility and individually tailored support. This means we will fund grants that can deliver our resources more strategically and effectively, in a way that will bring a greater impact from our funding.

Over time, we believe that backing talented researchers who can demonstrate clear scientific vision, creativity and leadership will be the best strategy to generate breakthrough improvements in health.

Investigator Awards opened for applications in October 2010.

www.wellcome.ac.uk/investigatorawards

Wellcome Trust Investigator Awards focus on the the vision of the researcher and the scale of ambition of the research programme.

Building science

Major new initiatives are providing state-of the-art facilities that are essential for researchers to carry out their work.

If scientists are to work at their best, we need to look at the facilities that surround and support them. In today's world of high-tech science, equipment and environment are becoming ever more important. Laboratories need to be well designed and the buildings that house them must encourage collaboration and the sharing of ideas.

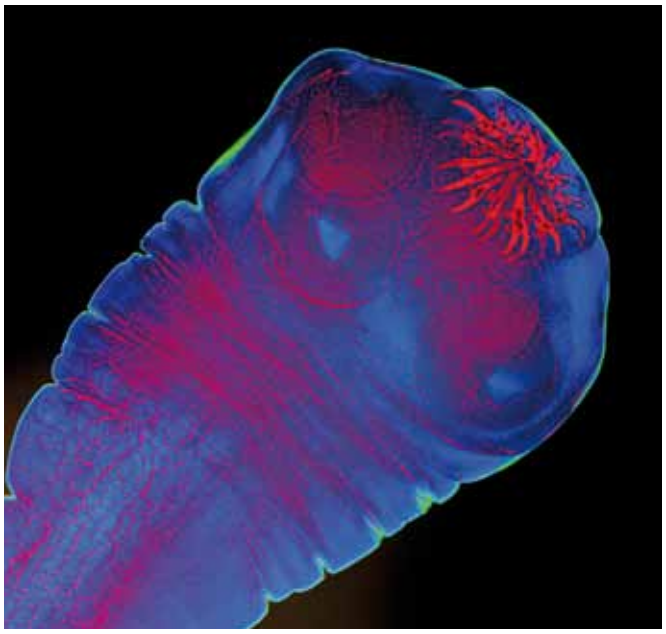
The sheer scale of some projects means that partnerships are the way forward. This is the case for a new flagship research institute, the UK Centre for Medical Research and Innovation at St Pancras and Somers Town in London. The Centre is a £600 million partnership between the Wellcome Trust, Cancer Research UK, the Medical Research Council and University College London.

With space for more than 1500 staff, including 1250 scientists, the Centre has four goals: research excellence; training and developing future scientific leaders; supporting the nation's biomedical research endeavour; and fostering innovation and translation. It will bring together researchers from a range of disciplines to investigate human health and to translate discoveries into new treatments for disease. Work on the Centre is due to begin in early 2011, and it is scheduled to open in 2015.

In another partnership, we are working with the Wolfson Foundation on large-scale university infrastructure projects through the Wellcome–Wolfson Capital Awards in Biomedical Science. In 2010, we announced £32m of investment in UK research infrastructure, including the construction of new buildings and refurbishment. Seven projects at universities across the UK, including three in Scotland, are receiving between £3m and £5m each.

Further afield, our Major Overseas Programme in Thailand celebrated its 30th anniversary in December 2009. It opened in 1979 as a collaboration between scientists from the University of Oxford and Mahidol University in Bangkok, and is recognised internationally for its excellence in tropical disease research. Several vital discoveries have been made as part of the programme, such as the development of artemisinin combination therapy, the frontline treatment for certain types of malaria. Celebrations to mark the anniversary included the opening of new laboratories with a traditional Buddhist ceremony in Bangkok, a cultural retreat to Khao Yai National Park and a commemorative book. Core support, as well as support for the Major Overseas Programme in Vietnam, has been renewed until 2015.

Images: Computer-generated images of how the UK Centre for Medical Research and Innovation will look.



A first for international fellowships

Peruvian Hector Garcia is our first Wellcome Trust Senior Fellow in Public Health and Tropical Medicine.

Our suite of fellowships in Public Health and Tropical Medicine launched in 2006. Open to basic scientists, social scientists, public health researchers and clinical researchers from low- and middle-income countries, these awards cover all levels of career support from Master's training to senior fellowships.

In Peru, Professor Hector H Garcia from the Universidad Peruana Cayetano Heredia, Lima, has become the first Wellcome Trust Senior Fellow in Public Health and Tropical Medicine. Professor Garcia is working on the brain disease neurocysticercosis – the major cause of acquired epilepsy in low-income countries, which occurs when the larvae of the pork tapeworm *Taenia solium* enter the brain. Professor Garcia will be investigating how it contributes to the burden of seizures in Peru, where the disease is endemic, and the characteristics and role of the brain scars that can form when the parasites die.

Tackling neurodegeneration

Three major awards are boosting research into Alzheimer's disease, Parkinson's disease, and motor neurone disease and frontotemporal dementia.

Alzheimer's disease and other dementias cost the world economy 1 per cent of global GDP (over £380 billion) in 2010, according to a report in September. And with the number of people with dementia estimated to double by 2030 and more than triple by 2050, the need for research into the mechanisms of this disease (and other neurodegenerative diseases that will increase as populations age) is becoming ever more pressing.

Funding for three major research programmes into neurodegenerative diseases was announced this year by the Neurodegenerative Disease Initiative, a £17 million partnership between the Wellcome Trust and the Medical Research Council. Professor Peter St George-Hyslop at the University of Cambridge is leading the research into Alzheimer's disease and related neurodegenerative disorders. Professors Nicholas Wood, John Hardy and Anthony Schapira of University College London are heading the research on Parkinson's disease. Finally, Professor Christopher Shaw of King's College London is directing the research into motor neurone disease and frontotemporal dementia.

Each programme brings together leading academic research teams from around the UK along with international groups and pharmaceutical companies. The teams aim to understand the causes of these diseases, to improve early diagnosis and to develop more effective therapies.

In brief

- *Funding in Ireland*

New funding arrangements with the Republic of Ireland were unveiled in September 2010. We have formed, with Science Foundation Ireland and the Health Research Board Ireland, the SFI–HRB–Wellcome Trust Biomedical Research Partnership. This will fund Investigator Awards, fellowships and Strategic Awards in the Republic of Ireland.

- *UK PubMed Central*

Four European research-funding organisations – the Health Research Board Ireland, Science Foundation Ireland, Telethon Italy and the Austrian Science Fund – have agreed to participate in UK PubMed Central and will mandate that all biomedical research outputs that arise from their funding are made freely available from the repository.

- *Synthetic biology*

Six teams of UK students received our inaugural stipends to support their entry to iGEM – the International Genetically Engineered Machine competition. iGEM, the leading undergraduate synthetic biology competition, gives the students a kit of biological parts that they can use to design and build biological systems that operate in living cells.

The pork tapeworm *Taenia solium*. Its larvae can cause neurocysticercosis when they enter the brain.

Accelerating the application of research

Working with the Indian Government's Department of Biotechnology, we have launched a £45 million partnership to support the development of innovative healthcare products at an affordable cost.

"India offers a vibrant and growing biotechnology sector, with a wealth of scientific talent and a skilled workforce to support scientific innovation. It can make a huge contribution to solving its own healthcare needs and to global health efforts." These were the words of Wellcome Trust Director Sir Mark Walport in the summer of 2010, while accompanying the UK Prime Minister on a visit to India. Sir Mark was speaking at the launch of a new multimillion-pound initiative investing in Indian science – our second partnership with the Indian government.

In 2008, we set up the £80 million Wellcome Trust–DBT India Alliance with the Government of India Department of Biotechnology. The Alliance is strengthening Indian biomedical sciences through a series of fellowship programmes, supporting the most promising researchers at different career stages.

Now, a new £45m scheme – R&D for Affordable Healthcare in India – is a second partnership between the Wellcome Trust and the Department of Biotechnology. We are each contributing £22.5m to a five-year fund that is focusing on affordable healthcare products such as new devices, diagnostics, medicines and vaccines. The fund will support research and development projects to produce safe and effective healthcare products that can be produced on a large scale at reasonable costs. That way, they can benefit both India and other low- and middle-income countries.

Developing such products needs technological and business skills of a high order, so the initiative aims to bring together researchers in the public and private sectors, largely working in India. It is open to for-profit and not-for-profit institutions, governmental or non-governmental organisations and international bodies operating within India.

The initiative follows our successful pilot of the concept, which has several awards in the pipeline in areas such as cardiovascular disease, tuberculosis and ophthalmology. One such project involves a collaboration between the LV Prasad Eye Institute in Hyderabad and the University of Sheffield. They are working to develop new ways to restore sight when the cornea has been damaged by a chemical injury or burns.

> "India offers a vibrant and growing biotechnology sector, with a wealth of scientific talent and a skilled workforce to support scientific innovation."
>
> **Sir Mark Walport**

Their technique uses new biocompatible materials for a stem-cell-based therapy, which they use to treat the limbus – the border of the cornea and the sclera (the white of the eye). The Eye Institute, which offers eye care to millions of people across the state of Andhra Pradesh through its secondary eye care centres in towns and primary care centres in large villages, has already treated 700 people with the new therapy.

The University of Sheffield and the LV Prasad Eye Institute in Hyderabad are developing new ways to restore sight.

A new hub for biotechnology

The £37 million Bioscience Campus in Stevenage aims to be a world-leading hub for early-stage biotechology companies.

Like many industries, biotechnology and drug development have struggled during the recession. Yet there are still many excellent ideas that could be turned into new healthcare products. With the right facilities, backing and environment, early-stage biotechnology companies could drive the development of such products forward. And if such companies could be brought together, sharing ideas and experience, the sector as a whole would be given a major boost.

Such 'open innovation' is the idea behind California's renowned Silicon Valley, and what worked for the IT sector could soon be doing the same for biotechnology at a new £37m Bioscience Campus. Located in Stevenage, Hertfordshire, the Campus is a partnership between the UK Government, GlaxoSmithKline, the Technology Strategy Board, the East of England Development Agency (EEDA) and the Wellcome Trust. The science park will be a hub for early-stage biotech companies, located beside GlaxoSmithKline's research and development facilities in Stevenage. Companies will also benefit from the proximity to academic centres of excellence in the South East, including the developing UK Centre for Medical Research and Innovation at St Pancras (see page 6).

The Campus will offer each company state-of-the-art facilities and access to specialist skills, equipment, mentorship and expertise to help stimulate innovation in healthcare R&D. It will provide small biotech and life sciences companies and start-ups with access to resources traditionally associated with multinational pharmaceutical companies. This range of opportunities for scientific and commercial networking would be impossible for a small- or medium-sized enterprise to develop alone.

Facilities include a 4750-square-metre bio-incubator building of office space and laboratories with an extra 4100 square metres of space for small companies to grow into. Initially home to around 25 companies, the plan is to increase capacity at the park fivefold over the next ten years. With buildings and an infrastructure for companies of up to 100 employees each, it is expected that the development of the Campus could create up to 1500 new jobs, most of which will be high-skilled and will be in addition to GSK's 2000 on-site employees.

Construction of the Campus began at the end of 2010.

Artist's impressions of parts of the Bioscience Campus, Stevenage.

The monoclonal mouse

A genetically engineered mouse that can produce monoclonal antibodies could soon lead to treatments for many different diseases.

The mouse is called Kymouse™. In its engineered chromosomes, Kymouse™ will have the entire diversity of the B lymphocyte component of the human immune system. This means that it can be used to generate new, well-tolerated monoclonal antibodies against disease targets. It has been developed by the former Director of the Wellcome Trust Sanger Institute and world leader in genome engineering using embryonic stem cells, Professor Allan Bradley.

Our Investment division is providing £20 million of financing to Kymab, a spin-out company from the Wellcome Trust Sanger Institute that will be commercialising the mouse.

Restoring your nerve

There are currently no therapies available for spinal cord injury and limited relief for those suffering from neuropathic pain, but two awards from the Wellcome Trust's Seeding Drug Discovery initiative aim to change that.

At the Wolfson Centre for Age-Related Diseases at King's College London, Dr Jonathan Corcoran is working on an oral therapy that could help nerve cells in the spinal cord grow back. The therapy is based on retinoids, small molecules that can stimulate nerves to grow back by inducing a specific pattern of protein expression in the cells. Dr Corcoran's previous research has shown that this can lead to recovery of function in mouse and rat models of spinal cord injury.

Meanwhile, Professor David Wynick of the University of Bristol is developing a new pain relief drug based on galanin, a small protein made by nerve cells. Galanin is produced in much greater quantities when these cells are damaged. Over ten years of research, Professor Wynick and his colleague Dr Fiona Holmes have shown that the protein reduces neuropathic pain in several animal models of disease, including diabetes.

Finding the fakes

A new detector is being developed for counterfeit and substandard drugs – an already significant and fast-growing threat to public health worldwide.

In low-income countries, 10 to 30 per cent of drugs are thought to be counterfeit, and the proportion of substandard drugs may be higher still. How can the fakes be identified? A technique called quadrupole resonance (QR) spectroscopy may be the answer, and we have given Dr Kaspar Althoefer and colleagues at King's College London and Lund University in Sweden a Technology Transfer award to develop the system. Their goal is to produce an inexpensive and robust instrument that can be used in low-income countries.

QR spectroscopy uses harmless radio waves to look at the chemical structure of solid materials. This can readily distinguish counterfeit or substandard versions of a drug from samples with the correct profile. Furthermore, the radio waves are non-destructive – so there is no need for the drugs to be removed from their packaging before they are analysed.

Exploring medicine in historical and cultural contexts

With two major exhibitions in London and a joint exhibition in Tokyo, Wellcome Collection has continued to bring science to life in new and exciting ways.

Wellcome Collection has a reputation for challenging the norm – presenting exhibitions and events that challenge us to look at the human experience in new and unexpected ways. This year was no exception: the theme running through its two major exhibitions – *Identity* and *Skin* – and the associated programme of events was the human body. Throughout history, people have tried to uncover our body’s mechanisms and find ways to treat them when something goes wrong. And through art, we have sought to express the body’s mysteries.

What makes one person distinct from another? How does science inform human identity? These were the major themes in the *Identity* exhibition, which opened in November 2009 and launched the Identity Project – a nine-month nationwide season of activity (see page 20).

Skin, a multidisciplinary exhibition at Wellcome Collection from June to September 2010, invited visitors to re-evaluate the meaning skin has had for us throughout history. As our most visible organ, our skin is part of our public identity. It is also a barrier between our private and public selves, and between our inner body and the outside world. More than that, it is a means of communication between the two: it responds to the world, and other people, by shivering, sweating and blushing.

With *Time Out* naming it Critic’s Choice and the *Guardian* and the *Telegraph* calling it “fascinating” and “a revelation”, *Skin* included early medical drawings and textbooks that revealed how anatomists in the 16th and 17th centuries viewed skin as an obstruction to be cut away to get to the ‘interesting’ bits of our body: the internal organs underneath. By the 20th century, the study of skin had become a science in its own right, fuelling a hugely lucrative industry dedicated to preserving and protecting it through surgery, injections and moisturisers. Contemporary artworks in the exhibition explored our modern fascination with skin: the need to preserve it in the name of beauty or to celebrate it as a living document of our lives. Scars, wrinkles, tattoos and texture all tell a story about how we have lived and expressed ourselves, where we come from and what matters to us. Skin is an organ of touch, and to explore its sensory nature visitors experimented with skin-flap models used in plastic surgery, examined biological jewellery, tried on latex skin-suits and designed tattoos.

During the year, Wellcome Collection’s popular events programme launched two new series. Exchanges at the Frontier, a partnership with BBC World Service, hosted notable scientists, who discussed the social impacts of their discoveries and the frontiers of scientific knowledge with A C Grayling, Professor of Philosophy at Birkbeck College, University of London. Eureka Live, a partnership with *The Times*, invited attendees to join a panel of experts in discussing the latest science news stories.

Although it is based in London, Wellcome Collection also travels abroad. This year it showcased 180 historical objects and contemporary artworks for a new international audience in Japan. *Medicine and Art: Imagining a future for life and love* ran from November 2009 to February 2010 at the Mori Art Museum in Tokyo. The exhibition was an enquiry into the eternal questions about the meaning of life and death – with the human body as a meeting place for medicine and art. It explored the ongoing scientific investigation of the human body, the devices and mechanisms developed to fight threats to it, and the impact modern science might have on how people see themselves and the meaning of their lives in the future. Objects on loan included anatomical drawings by Michelangelo, Charles Darwin’s walking stick and illustrations by Francis Crick of the double-helix structure of DNA, along with contemporary artworks from Walter Schels, Marc Quinn, Francis Bacon and Damien Hirst.

Wellcome Collection’s *Skin* exhibition featured ‘Mr Green’ by Araminta de Clermont, 2008. This portrait is from a body of work documenting the cultural phenomenon of the ‘chappies’ from the South African Numbers Gangs, following their release from prison.

Inspirational science education

Science education not only helps provide young people with skills and knowledge they can use in their life and work, but also inspires the next generation of scientists.

Young people tend to learn most of what they know about science at school, while those who go on to a research career usually have their interest sparked at school. So it is essential to make sure they all get the best – and most enthusiastic – teaching possible.

Since the launch of the UK network of ten Science Learning Centres in 2003, science teachers have had the chance to update their skills and get practical experience of contemporary science, then transmit that knowledge and excitement to their students. There was a further boost in 2008 with the launch of Project ENTHUSE, a £27 million partnership between the Wellcome Trust, the UK Government and industry. This provides bursaries to science teachers and school technicians from state schools across the country so they can attend high-quality residential professional development courses at the National Science Learning Centre in York.

A year later, in October 2009, a report published by the National Science Learning Centre showed that Project ENTHUSE is already having a knock-on effect in motivating students. More than 90 per cent of teachers who attended the courses said the experience had a significant positive impact on themselves or on their pupils. The courses made teachers feel like valued professionals, and the experience, skills and knowledge they gained fired their interest and passion for their subject.

Directly interacting with scientists themselves and asking them about their work can have an electrifying effect on school students' enthusiasm for science, as we saw from an *X Factor*-style event in June 2010. Around 100 scientists and 5000 students across the country took part in *I'm a Scientist, Get Me out of Here!* Like its jungle equivalent, the event pitted scientists against each other to prove themselves to students, win their votes, and avoid eviction from the competition.

For two weeks, students read about the scientists' work, asked them questions and chatted with them live on a dedicated website. The scientists had to explain their work and prove its value. Students then voted for the one they wanted to win the £500 prize. Dealing with real scientists who took them seriously, in a real situation involving real prize money, showed students that their opinions – and vote – can count. As well as empowering them, it gave students a reason to engage with abstract ideas and see science for the living, dynamic, human process it really is.

Can children of an even earlier age – at primary school – be captivated by the excitement of science? The Primary Science Quality Mark was launched to develop and celebrate excellent science teaching for that age group. Primary schools who sign up for the scheme can aim for bronze, silver and gold awards for the quality of their science teaching. This encourages them to invest time and effort in expanding, enlivening and enriching their science teaching. After successes in two regional pilot schemes, the Primary Science Quality Mark received further funding from the Wellcome Trust to roll out the project on a national basis.

Teachers at the National Science Learning Centre in York.

Digitising the Wellcome Library

The Wellcome Library, one of the world's great cultural treasures, has started digitising its unique and irreplaceable collections of books, manuscripts, archives, films and pictures and putting them online.

The three-year Wellcome Film project has digitised over 100 hours of film and video that record medical progress during the 20th century. Now, the Library has begun the immense task of digitising major parts of its vast and ever-growing collection of books, manuscripts and archival collections, starting with those on the theme of 'Modern Genetics and its Foundations'.

The two-year pilot project, which was launched in August 2010, aims to digitise up to half-a-million manuscripts and images relating to genetics and its history. These will include nearly 300 boxes of scientific papers from the Francis Crick archive, spanning his DNA and neurobiology research. They include draft articles and books, lectures, research notes, and his extensive correspondence with scientific colleagues and the general public.

First Wellcome Trust Book Prize winner

A disturbing, frank and moving account of the day-to-day reality of caring for someone with Alzheimer's disease won the inaugural Wellcome Trust Book Prize in November 2009.

Andrea Gillies's book, *Keeper: Living with Nancy – A journey into Alzheimer's*, describes her experiences in caring for her mother-in-law with Alzheimer's and the knock-on effect that it had on her. She felt as if her own mental powers were dimming in parallel and later discovered that this is a common experience called 'caregiver's dementia'.

She resorted to journal writing as an outlet for feelings she didn't want to lay on her family and began researching and making notes about dementia as a way of coping. This blend of science with personal accounts of her experience in the book is one of the reasons that the judges awarded her the Prize. Comedian Jo Brand, chair of the judging panel, called the book "the perfect fusion of narrative with enough memorable science not to choke you". *Keeper* subsequently won the won 2010 Orwell Prize, Britain's most prestigious prize for political writing.

Public attitudes to medical research

"Science is interesting and important." That was the overwhelming opinion of 1600 adults and school students who took part in the Wellcome Trust Monitor.

The Monitor, a survey of public attitudes to medical research, found that over 90 per cent of respondents thought research should be supported and encouraged. Conducted by the National Centre for Social Research in April 2010, the survey also indicated that efforts by the Wellcome Trust, government and industry to make science interesting, challenging and fun for school students may be paying off. Eighty-one per cent of young people found science lessons interesting (compared with 69 per cent of adults who had found science lessons interesting at school), and 44 per cent said they were interested in pursuing a career in science – with medicine, forensic science and engineering the most popular choices.

In brief

- *Child surgeons*

More than 1200 children found out what it is like to be a surgeon at the ER Surgery Workshop. Held at the Edinburgh International Science Festival and funded through a Wellcome Trust People Award, the workshop allowed children to investigate and 'operate on' a range of diseased or injured manikin 'patients'.

- *Wellcome Image Awards*

The tenth Wellcome Image Awards were presented in October 2009, celebrating the best new images acquired by the Wellcome Images picture library in the previous 18 months. The 19 images included capillary networks and liver cells, summer plankton, and bird of paradise seeds.

www.wellcomeimageawards.org

- *Experiences of the NHS*

'Ordinary People Tell the Story' charts people's experiences of the NHS over its first 60 years. The study, compiled by Linda Lamont and Fran McCabe, and supported by a Trust History of Medicine grant and the Department of Health, highlights how expectations have changed over the decades, people's positive and negative experiences of the health service, and the strong commitment to the founding concept of the NHS.

bit.ly/grKCc4

Maximising the health benefits of genetics and genomics

The human genome sequence has revolutionised studies of cancer. It is allowing us to find the mutations that drive malignancy and to find new ways to diagnose and treat the disease.

"It is now conceivable that our children's children will know the term cancer only as a constellation of stars," said US President Bill Clinton at the announcement of the completed working draft of the human genome sequence in 2000. It's too soon to tell whether that vision will come to pass – but how, ten years on, has the completion of the human genome sequence influenced how we study cancer and what we now understand about its genetic basis?

Mutations make their mark

Cancer is a disease of changes. Tiny (and not so tiny) changes in our DNA occur frequently. Our body's repair mechanisms do what they can to undo these mistakes, but mutations can accumulate. In some cases, the combination of changes becomes enough to tip a cell from normal function into uncontrolled replication: cancerous growth. Finding these changes is therefore at the very heart of cancer research.

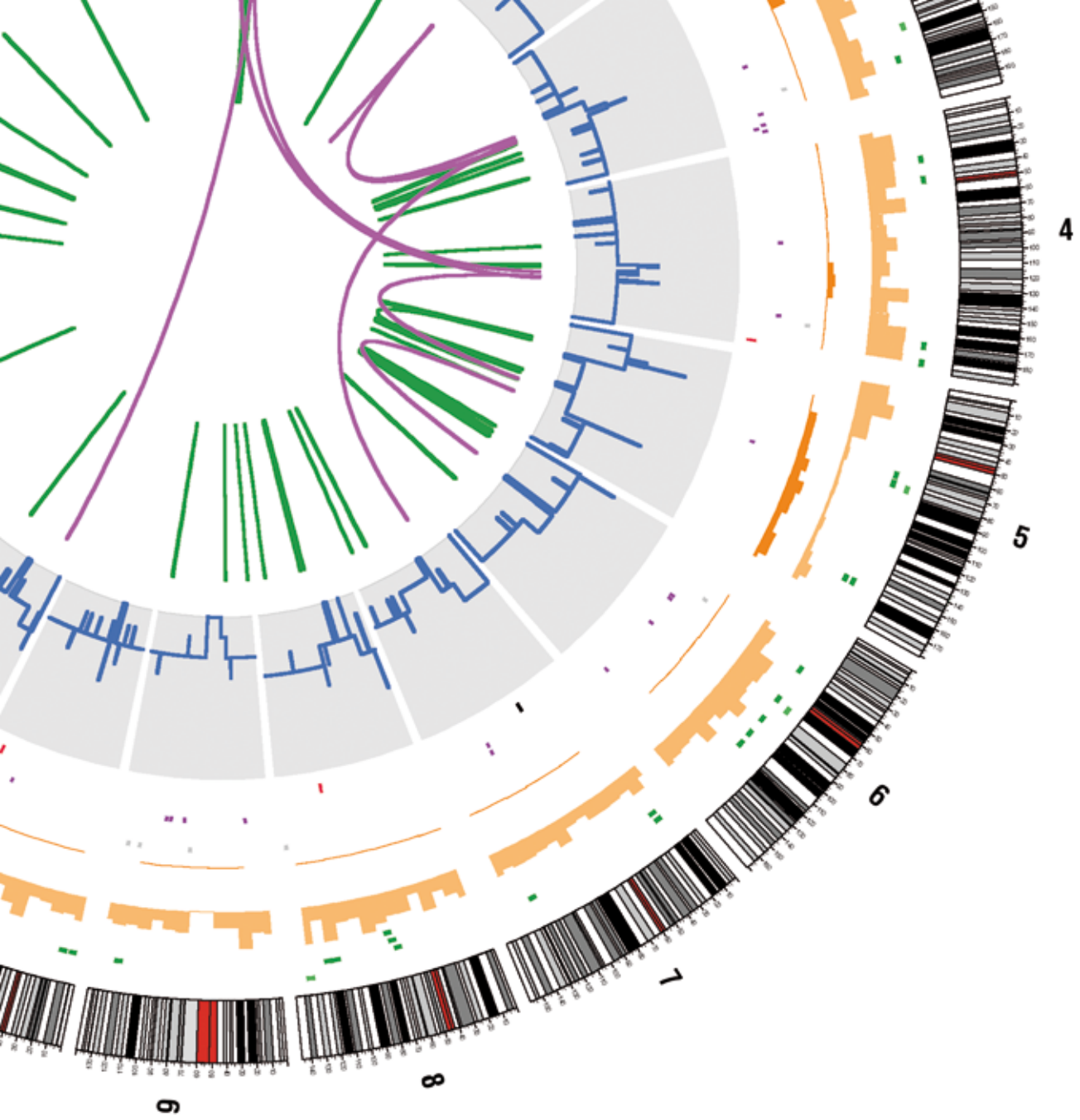
There are two types of mutation involved in cancer. First, cancer occurs through a multi-step process of somatic cells (those that make up the body, excluding egg and sperm) acquiring genetic mutations. Although such somatic mutations may eventually cause cancer, they are not passed on to offspring. These mutations can be found by studying the tumours themselves.

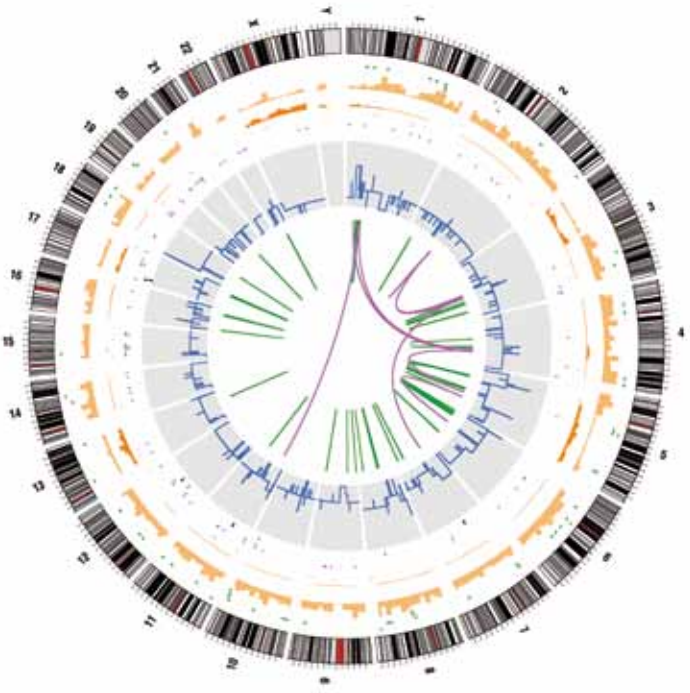
However, whether someone develops cancer is also influenced by genetic changes that are inherited from a parent. These are present in all of an individual's body cells and can increase susceptibility to cancer. Identifying which genetic changes predispose someone to a given cancer should make it easier to see which individuals are at increased risk before disease arises, as well as giving researchers a better understanding of the molecular processes involved in the development of that disease.

One fruitful approach to unpicking the genetic changes behind cancer is to compare the genomes of healthy people with those of people who have the disease: this can highlight relevant genetic differences. For example, new research on testicular cancer (the most common cancer in men aged 15–45) has doubled the number of inherited genetic variants known to be associated with susceptibility to the disease. Dr Clare Turnbull from the Institute of Cancer Research and colleagues, including researchers from the Wellcome Trust Sanger Institute, found links to variants on three different chromosomes. Two of the genes they identified as likely suspects, *TERT* and *ATF7*, keep the ends of chromosomes – the telomeres – the right length. Telomere regulation has been implicated in the development of several cancers, and genetic variants at the *TERT* locus have already been linked to many malignancies, including lung, bladder, cervical, pancreatic, skin and prostate cancers.

Other research carried out at the Institute of Cancer Research and the University of Cambridge used a similar technique to find five new genetic regions linked to breast cancer, which is diagnosed in 1.1 million women globally every year. The variants they found have a modest impact on the risk of developing breast cancer, but identifying more of these so-called 'low-risk' variants, which now total 18, will help researchers develop reliable tests to predict who will go on to get breast cancer.

Such studies are also showing us that any one type of cancer may, in fact, be a collection of different diseases, each with distinct genetic changes. In the case of the most common form of kidney cancer, for example, Cancer Genome Project researchers at the Wellcome Trust Sanger Institute have found two different types. They screened 101 different samples of clear cell renal cell carcinoma, looking for mutations in more than 3500 genes. Mutations in the gene *VHL* are thought to be involved in many cases of this cancer – and the researchers did, indeed, find mutated *VHL* in over half of the samples. But they also found a subset of these cancers that seemed to be driven not by *VHL* but by another gene.





The mutations found in the genome of a small-cell lung cancer genome. The outer ring shows chromosomes. Insertions and deletions are represented by green rectangles, substitution density by orange bars, coding substitutions by coloured squares, copy number changes by blue lines, and rearrangements by green and purple lines.

In breast cancer, the extent to which a genome is 'broken' also seems to relate to different subtypes of the disease. In this case, the Cancer Genome Project team looked at rearrangements in the genome, such as shuffling, deletions and duplications of chunks of DNA sequence. They found that the degree of rearrangement in breast cancers varied markedly – of the 24 different cases examined, one showed just one genomic rearrangement, while some had more than 200. Moreover, the broad groups of rearrangements that they found tied in with different subtypes of breast cancer that have been identified. The results are consistent with the idea that breast cancer is actually several diseases.

Looking genome-wide

What if we could find every genetic change in a cancer cell? How many mutations might there be? That we can now start to answer such questions is testament to the remarkable progress in DNA sequencing technology over the past few years. This has allowed the Cancer Genome Project team at the Wellcome Trust Sanger Institute to produce the first ever genome sequences of two cancers: a lung cancer and a malignant melanoma. By comparing the genome of a healthy cell with the genome of a cancer cell taken from the same patient, the researchers revealed nearly all the genetic changes present in each cancer.

These cancers weren't chosen at random. They are cancers for which the main environmental triggers are known – exposure to sunlight for malignant melanoma and cigarette smoke for lung cancer. The extent of the damage is startling: the small-cell lung cancer genome had almost 23 000 mutations, equating to one per 15 cigarettes for an average smoker. Meanwhile, exposure to sunlight had caused some 30 000 mutations in the melanoma genome.

These cancer genomes will soon be joined by myriad others thanks to the International Cancer Genome Consortium, which was launched in April 2008 with the Wellcome Trust Sanger Institute among the founder members. Groups from across the world will be sequencing the genomes of 50 different tumour types or subtypes. This goal, the equivalent of sequencing 25 000 cancer genomes, would have been unimaginable (and unaffordable) back when the human genome sequence was first released. The capacity of today's sequencing technology is between 100 000 and 1 000 000 times greater than in 2000.

Towards treatment

The ultimate aim of these types of study is to help develop new ways to prevent, diagnose and treat cancer. A prime example of how genome research can lead to therapies relates to a gene called *BRAF*, which is mutated in around 7 per cent of tumours and some 66 per cent of malignant melanomas.

Work on this gene came out of the Cancer Genome Project, established at the Wellcome Trust Sanger Institute in 2000 by Professor Mike Stratton (now the Institute's Director). He describes this as the "first post-genome project" carried out there, although work actually started before the human genome sequence was completed. The Cancer Genome Project's first major success was the finding that *BRAF* was mutated in many malignant melanomas and in a wide range of human cancers. This led researchers to examine the BRAF protein as a target for anticancer therapy.

Professor Richard Marais, an author on the original *BRAF* paper, and colleagues at the Institute of Cancer Research have been working on developing drugs to block the protein. Sorafenib was a promising drug candidate but failed to show significant anti-tumour effects in people with advanced melanoma. Recent work by Professor Marais and colleagues has shown that this is because sorafenib doesn't target the mutant *BRAF* seen in so many melanoma cases, but this work did reconfirm that *BRAF* is a good target for drugs to treat melanoma. The progress made around *BRAF* so far is compelling and shows how information generated as part of the Human Genome Project can help researchers tackle specific mutations seen in particular tumours.

Responding well

An improved understanding of the genetic make-up of cancers will allow doctors to tailor treatments more closely to individual patients, and give them an indication of how each tumour might respond to a particular treatment.

As part of the attempts to link the genetic make-up of cancers to drug response, the Wellcome Trust Sanger Institute has teamed up with the Massachusetts General Hospital Cancer Center. In the Genomics of Drug Sensitivity in Cancer project, funded by a Wellcome Trust Strategic Award, researchers are testing how 1000 cancer cell lines respond to 400 chemicals – known anticancer drugs and drugs in development. The first results – of 350 cell lines and 18 anticancer drugs – were released in July 2010. The data are free to use and should prove useful to researchers and doctors across the world who want to better understand how particular genetic changes relate to drug responses.

Although much has been achieved, there are still many questions to answer: why does a particular cluster of mutations cause cancer in one organ and not another? Now we know that some mutations are common to cancers in different parts of the body, what will this mean for how we classify, diagnose and treat them in the future? It will take time to find the answers, but the decade of discovery since the Human Genome Project is a significant foundation for future work unpicking the molecular changes that can turn cells into killers.

Exploring our identity

The Identity Project explored the gap between identification and identity and between biology and 'self', and examined how we define ourselves by both our uniqueness and the groups we belong to.

A nine-month season of activities, exhibitions, events and experiments, the Identity Project was launched in November 2009 with a major exhibition at Wellcome Collection in London entitled *Identity: Eight rooms, nine lives*. Each room represented someone who had contributed to our understanding of an aspect of identity, such as Francis Galton, whose work led to identification by fingerprinting, and Alec Jeffreys, who invented DNA profiling.

The season continued with a lively programme of events, films, exhibitions and debates around the UK. *Interior Traces*, for example, was a six-part radio drama, video, performance and debate that toured the UK and looked at how brain imaging affects our understanding of identity. It examined the possible lives of two characters had they lived in Britain in 1906, 2009 and 2030 and questioned how society should regulate brain imaging in the future. *Mincemeat* was a drama by Cardboard Citizens, which explored the identity of the Royal Marine involved in World War II's Operation Mincemeat: his body washed up on a Spanish beach in 1943, with fake documents that successfully misled Germany about Allied plans. But who was he?

We also funded a number of films exploring aspects of identity. *Nature's Great Experiment* looked at the work of the Department of Twin Research at King's College London, focusing on how psychological problems develop in childhood.

Meanwhile, Wellcome Collection commissioned its first major theatrical production for the Identity Project. *Pressure Drop* was created by award-winning artistic director Mick Gordon and legendary singer-songwriter Billy Bragg, who wrote and performed new work for the production. Part play, part gig and part installation, *Pressure Drop* presented three generations in a white working-class family caught in contemporary multicultural Britain and dramatised their attempts to define themselves in relation to each other and to the changing social landscape. More than 3700 people attended 20 public performances in April and May 2010 at Wellcome Collection, with eight out of ten of them rating their experience as 'excellent'. High-profile interviews with Billy Bragg appeared in the *Independent on Sunday*, the *London Evening Standard* and Reuters, and on *Channel 4 News*, Radio 4's *Today* programme and numerous other BBC channels. Dominic Cavendish, writing in the *Telegraph*, described the event as "a compelling 360-degree tour of...Bragg's hometown of Barking, Essex".

The Identity Project culminated in June 2010, on the tenth anniversary of the sequencing of the draft human genome, with the reopening of the Science Museum's *Who Am I?* gallery in the Wellcome Wing. The gallery was refurbished in part through a £2.5 million capital award.

Participants at the 'China: Birth and belonging' event – part of the Identity season.

Avoiding faulty mitochondria

A new *in vitro* technique offers a way to prevent devastating genetic diseases being passed on to babies.

One in 6500 children is born with a serious mitochondrial disease such as severe muscular weakness, heart failure, blindness or liver failure. The culprits are genetic mutations in mitochondria, which we inherit exclusively from our mothers. Mitochondria, power sources for the cells they live inside, have their own DNA, independent of the cell's nuclear DNA.

Professor Doug Turnbull and colleagues at Newcastle University are pioneering a new technique to help mothers with these mutations; it involves transferring DNA between two human eggs.

Using donated IVF eggs, the team transferred nuclear genetic material from each egg into another donor egg that had had its nucleus removed but retained all its cytoplasm and mitochondria. A small number developed to the blastocyte stage of 100 cells, allowed by the licence granted by the Human Fertilisation and Embryology Authority.

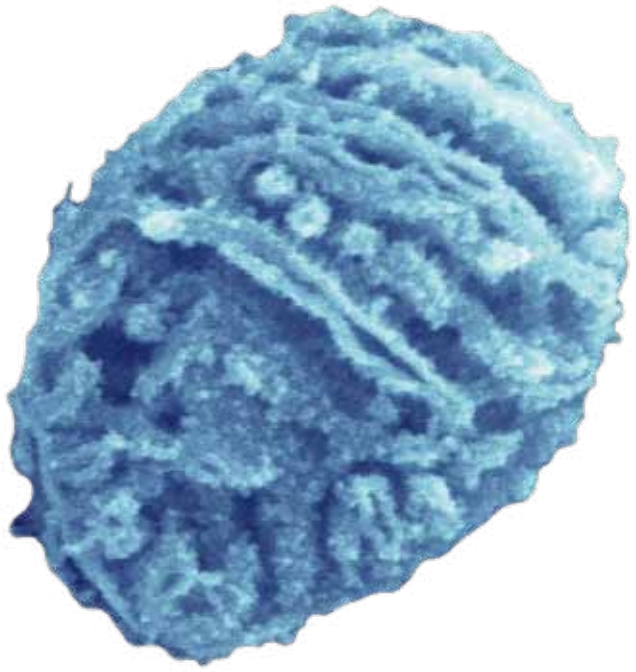
The results give hope that in the future it will be possible for children to be born with all their parents' nuclear genes – and with healthy, fully functioning mitochondria from a female egg donor to power their cells.

Major new genetic studies

Two studies that were launched this year will help us understand the genetic basis of many diseases.

The first study is on a scale that would have been unimaginable to the scientists who, 20 years ago, set out to sequence just one human genome. UK10K, as the project is known, will decode the genomes of 10 000 people over three years. The whole genomes of 4000 people, who have been studied for many years as part of the TwinsUK and ALSPAC (Avon Longitudinal Study of Parents and Children) studies, will be sequenced. Meanwhile, the gene-containing regions of the genomes of 6000 people with extreme obesity, neurodevelopmental disease and other conditions will also be studied.

The second study is a partnership with the US National Institutes of Health. The Human Heredity and Health in Africa Project (H3 Africa) will study thousands of people in Africa to see how genes and the environment interact in the development of infectious and chronic diseases.



An isolated mitochondrion. Transferring genetic material from an egg with faulty mitochondria to one with healthy mitochondria could prevent severe genetic diseases being passed on.

In brief

- *Genome music*

Music from the Genome brought together a new choral work – 'Allele', performed in July 2010 – and research into the genetic determinants of musical ability. Members of the New London Chamber Choir supplied samples of their DNA for Dr Andrew Morley's genetic research, while composer Michael Zev Gordon used the data to generate unique musical material for each singer's part in 'Allele'.

- *Cataloguing genetic history*

Our Research Resources in Medical History grants scheme supports projects to preserve, catalogue and conserve significant medical history and humanities collections in libraries and archives. Dr Kate West has received an award to catalogue and conserve the historical collections at the John Innes Centre in Norwich, which include the collections of two key figures in the early history of genetics: William Bateson and Cyril Dean Darlington.

- *Counting copies*

Copy number variations – large sections of DNA that vary in terms of how many copies of them people have – are unlikely to have a significant impact on our susceptibility to disease, according to two studies. The first study found that the variants are likely to explain only a small proportion of cases when a disease clusters in a family, and the second found that common variants are unlikely to play a major part in conditions such as diabetes, heart disease and bipolar disorder.

Understanding the brain

This year, a series of fascinating studies have been helping to uncover some of the biological bases of our behaviour.

Our behaviour is a fusion of biology and experience. It is influenced by neurotransmitter chemicals in the brain, the brain regions themselves, the people we meet and what we learn. All of these factors influence whether our behaviour is helpful or hostile and unremarkable or unusual.

New studies are providing insights into how the chemical dopamine can determine how impulsive we are and into the role of the amygdala in processing fear. Yet they also show that the mind does not live by chemistry alone.

Meeting people

As infants, one of the early skills we need to develop is joint attention – sharing attention with someone else on the same object. This underpins many types of human activity such as learning language, collaboration and teaching. When do we start to share attention in this way? Much earlier than had been thought, according to Dr Tobias Grossman, a Sir Henry Wellcome Postdoctoral Fellow, and colleagues at Birkbeck, University of London. They found that when five-month-old babies shared attention with an adult, looking together at the same object, they activated their left prefrontal cortex – the same region adults use when sharing attention.

As we grow older, our interactions with other people deepen and become more complex: we start to recognise emotions in others and adjust our behaviour towards them accordingly. Yet this ability does not seem to develop in everyone. Around 5 per cent of school-aged children behave so aggressively we say they have a 'conduct disorder'. Is this simply because they decide to act this way? Or is there a biological basis to such behaviour?

> "In the long history of humankind (and animal kind, too) those who learned to collaborate and improvise most effectively have prevailed."
>
> **Charles Darwin**

Professor Ian Goodyer and colleagues at the University of Cambridge used functional magnetic resonance imaging (fMRI) to record the brain activity of 75 young males – with and without conduct disorder – who were shown images of sad, angry and neutral faces. The findings showed that the males with conduct disorder had less activity in the amygdala, an area of the brain known to be involved in processing emotion. This might make it harder for them to read others' emotions and realise when people are distressed or angry.

It is not just men who behave badly, but so far little research has been done on antisocial behaviour in girls – even through the problem is increasing in the UK. Researchers led by Dr Graeme Fairchild, again at Cambridge, have found that girls with violent, volatile behaviour have difficulties recognising anger, disgust, sadness and fear. These results suggest that both girls and boys with antisocial behaviour may have brains that are 'wired' differently to others' brains, and that this, rather than immature choices, is what drives their aggression.

Fear and reward
Emotion affects how we interact with other people, but it can also influence our financial decisions. One example of this is our bias towards loss aversion – we avoid choosing options that may lead to losses, even when they may also lead to equal or much larger gains. In high-stakes gameshows such as *Who Wants to Be a Millionaire?*, contestants baulk at gambling with their winnings, even when they could double their prize.

But what if we have no fear? Dr Benedetto De Martino, a Sir Henry Wellcome Postdoctoral Fellow, and colleagues at the California Institute of Technology had the opportunity to ask this question in their studies of two people with damage to the amygdala that prevents them from feeling or recognising fear. They found that these individuals were far more willing than healthy controls to gamble in the face of potential losses – and sometimes that turned out to be the best choice. But we do need to have a certain amount of fear to stay safe, and the amygdala helps us to do that.

For some people, fear is to be actively enjoyed, and it seems this is particularly the case for teenage boys. Researchers led by Dr Stephanie Burnett at University College London asked 86 males aged nine to 35 years to choose between risky and safe options in a computer gambling game. After each game, they recorded how satisfied or dissatisfied each player was with the outcome. They found that teenagers chose the riskiest options and reported the strongest relief or regret after learning the result. This happened despite the fact that teenage boys had a greater ability to weigh up the pros and cons and foresee the consequences of their actions than younger children.

The intensity of the thrill generated by lucky escapes peaks at 14 years old then starts to lessen again. This may be because in adolescence our brains are still developing – particularly the dopamine system. Dopamine is essentially a pleasure chemical; it is released by rewarding experiences such as eating, drinking alcohol, taking drugs, gambling and sex. It motivates us to do what we need to do to survive, which sometimes means exploring new possibilities.

Consequently, the extra buzz we get from taking risks when we are teenagers might be our developing reward system pushing us to expand our limits while we are still young and healthy enough to do so.

A life with dopamine
As we pass beyond our teenage years, our choices, in general, get safer. But dopamine affects us throughout our lives. Even imagining an enjoyable activity can produce a rush of pleasure and a dopamine spike, as researchers led by Dr Tali Sharot at the Wellcome Trust Centre for Neuroimaging at UCL have shown. They asked volunteers to imagine themselves in 80 holiday destinations and rate them. They then gave half of the group L-DOPA (a drug that boosts dopamine levels in the brain) and gave the other half a placebo, before asking them to imagine and rate the same holidays again. The people on L-DOPA rated the same destinations more highly – and the effect was so strong it lasted until the next day. The findings show how crucial dopamine is in how we estimate the pleasure of future events and, hence, how it influences our choices and actions.

Indeed, dopamine is known to have a wide range of functions in different parts of our brain. We need it to move and think, as well as to feel motivated and interested. Too little causes tremors and movement problems, as in Parkinson's disease. A dopamine deficiency also makes it hard for people with ADHD to lock their focus onto a task or conversation.

Dopamine, shown here as crystals, has many roles in the brain but is particularly important for motivation and pleasure.

> “Increasing dopamine in volunteers’ brains made them more intolerant of the time delay involved in waiting for the larger reward and diminished its perceived value.”

Too much dopamine, by contrast, leads to overstimulation and impulsivity. Indeed, impulsivity (including gambling and hypersexuality) is a side-effect of L-DOPA, which is given to people with Parkinson’s disease: the optimum dose to improve their motor function may sometimes be an overdose in terms of their behaviour.

Researchers led by Professor Ray Dolan at the Wellcome Trust Centre for Neuroimaging found that raised dopamine levels make us more impulsive by making us more sensitive to delay when we are imagining a future reward. The study showed that volunteers given L-DOPA were more likely to behave impulsively than controls and opt for a ‘smaller, sooner’ reward rather than a ‘larger, later’ reward. Increasing dopamine in their brains made them more intolerant of the time delay involved in waiting for the larger reward and diminished its perceived value. Moreover, fMRI scanning showed that the people whose choices were most influenced by the drug had increased activity in the amygdala when contemplating a sooner rather than a later reward.

Beyond chemicals

Are neurochemical approaches the only way to modulate our behaviour? Not according to two other new studies. Researchers from the University of Nottingham led by Professor Chris Hollis showed that behavioural therapy, such as rewarding positive behaviour and giving penalties for negative behaviour, had the same effect as dopamine-increasing drugs such as Ritalin in helping children with ADHD modify their behaviour.

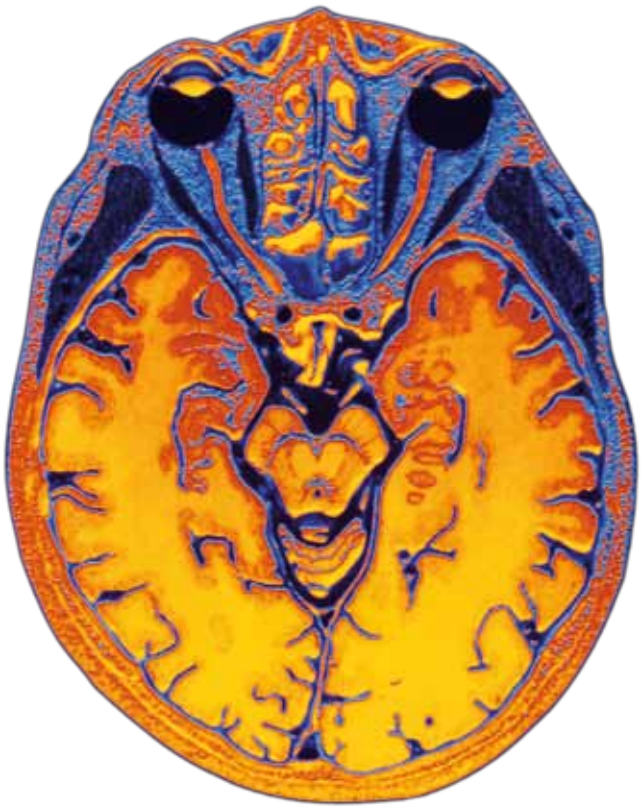
Their findings showed that both Ritalin and incentives improved attention and reduced impulsivity in the children. Furthermore, electroencephalogram recording showed that their brain activity also normalised in similar ways, although the neural effects of the behavioural approaches were smaller.

Using a different approach, Professor Elaine Fox and colleagues at the University of Essex hope to find out whether computer training could help make people less vulnerable to stress. The first steps have been to identify what makes some people more prone to stress than others – and to develop a way of accurately predicting that vulnerability so that it can be addressed.

Professor Fox asked 100 students to fill out a questionnaire to assess their levels of anxiety and depression, before measuring the level of cortisol (a physiological marker for stress) in their saliva. She then measured their attention to positive and negative images (of smiling babies and puppies or snarling dogs and guns) on a computer. Four months later she tested the students’ cortisol levels in response to a laboratory-based stressor (delivering a five-minute speech) and again after a further four months in response to a real-life stressor (examinations). The findings showed that those students whose attention had been drawn to the negative computer images had greater cortisol levels in response to stress at later dates. Measures of these biases were much better at predicting vulnerability to stress than the questionnaire.

The next step is to investigate whether computer-based efforts to retrain people’s brains so they are drawn towards positive situations might make them more resilient to traumatic life events. If this is the case, we might turn out to have more power over our brains than we think.

Professor Ray Dolan.



Learning to read

A unique study of former revolutionary armed forces in Colombia has helped scientists to redefine our understanding of the key regions of the brain involved in literacy.

Until a few decades ago, scientists believed that our brains were static and unable to regenerate once we passed our teens. Indeed, most of our 100 billion neurons are generated in the womb, and our IQ does not change much past the age of seven.

Today, we know that the adult human brain can indeed generate new neurons and form new pathways, giving hope to those of us who want to keep learning after our teens. These changes are being unveiled by brain-imaging techniques – such as magnetic resonance imaging (MRI) – that help researchers peer more closely at our grey matter, where the processing is done, and the white matter that connects up the processing areas.

Even so, it can be difficult to separate out which brain changes are related to a skill as complex as reading: most of us learn to read in childhood, at a time when we are learning many other things very quickly. So for Professor Cathy Price, a Wellcome Trust Senior Research Fellow at University College London, and colleagues from the UK, Spain and Colombia, the opportunity to study a group of adults who were learning to read was rather unusual.

The adults were former guerrillas in Colombia. After decades spent fighting, members of the guerrilla forces – a sizeable population of illiterate adults with no formal education – have begun reintegrating into mainstream society. Some had the opportunity to learn to read for the first time in their early 20s, so the research team were able to compare the MRI scans of one group who had completed a literacy programme in their native tongue (Spanish) and the scans of another group before they started the same programme. The scans showed that in adults who had learned to read, the density of grey matter was higher in several areas of the left hemisphere of the brain. As might be expected, they were the areas that are responsible for recognising the shapes of letters and translating the letters into speech sounds and their meanings. Reading also increased the strength of the white matter connections between the different processing regions.

The connections to and from an area of the brain known as the angular gyrus were particularly important. For more than 150 years, it has been known that this brain region is important for reading, but it had been thought that it acted like a dictionary that translates visual words into their sounds and meanings. The new research shows that it has a rather different role: it provides predictions of what the brain is expecting to see, like the predictive texting function of a mobile phone.

The findings are likely to prove useful for researchers trying to understand the causes of the reading disorder dyslexia. Studies of people with dyslexia have shown areas of reduced grey and white matter in regions that grow after learning to read. The new study suggests that some of the differences seen in dyslexia may be a consequence of reading difficulties rather than a cause.

Computing cells

New research suggests that single neurons are powerful computing devices in their own right.

The brain, with its billions of neurons, is a computer of exceptional power. One of its key roles is to process sequences of information from the outside world. It had been thought that large numbers of neurons working together were required for such processing, but Professor Michael Häusser and colleagues at University College London have found that single neurons, and even single dendrites (the neuron's 'antennae'), can distinguish between sequences of information that the brain receives.

The researchers used a laser to activate inputs on dendrites in precisely defined patterns and recorded the resulting electrical responses of the neurons. Surprisingly, each sequence produced a different response, even those that were delivered to a single dendrite. This indicates that individual neurons can play an important part in sorting and interpreting the huge input received by the brain.

Above: MRI brain scan.
Right: Brain neurons. Brain waves from parts of the brain controlling movement are counteracted by waves from the spinal cord, preventing tremor.

Healthy tremors

Nerve signals in the spinal cord work to counteract signals from the brain that would otherwise lead to tremors in our movement.

Sometimes, instead of asking what is wrong, it helps to ask what is right – and why. Newcastle University scientists decided that, instead of trying to understand why some people have tremors, they would look at why most people do not. Professor Stuart Baker and colleagues knew that the brain waves from the parts of the brain controlling movement work at ten cycles per second. This means everyone should have a tremor at that frequency. In fact, most of us do, but the tremor is usually so small as to be hardly noticeable.

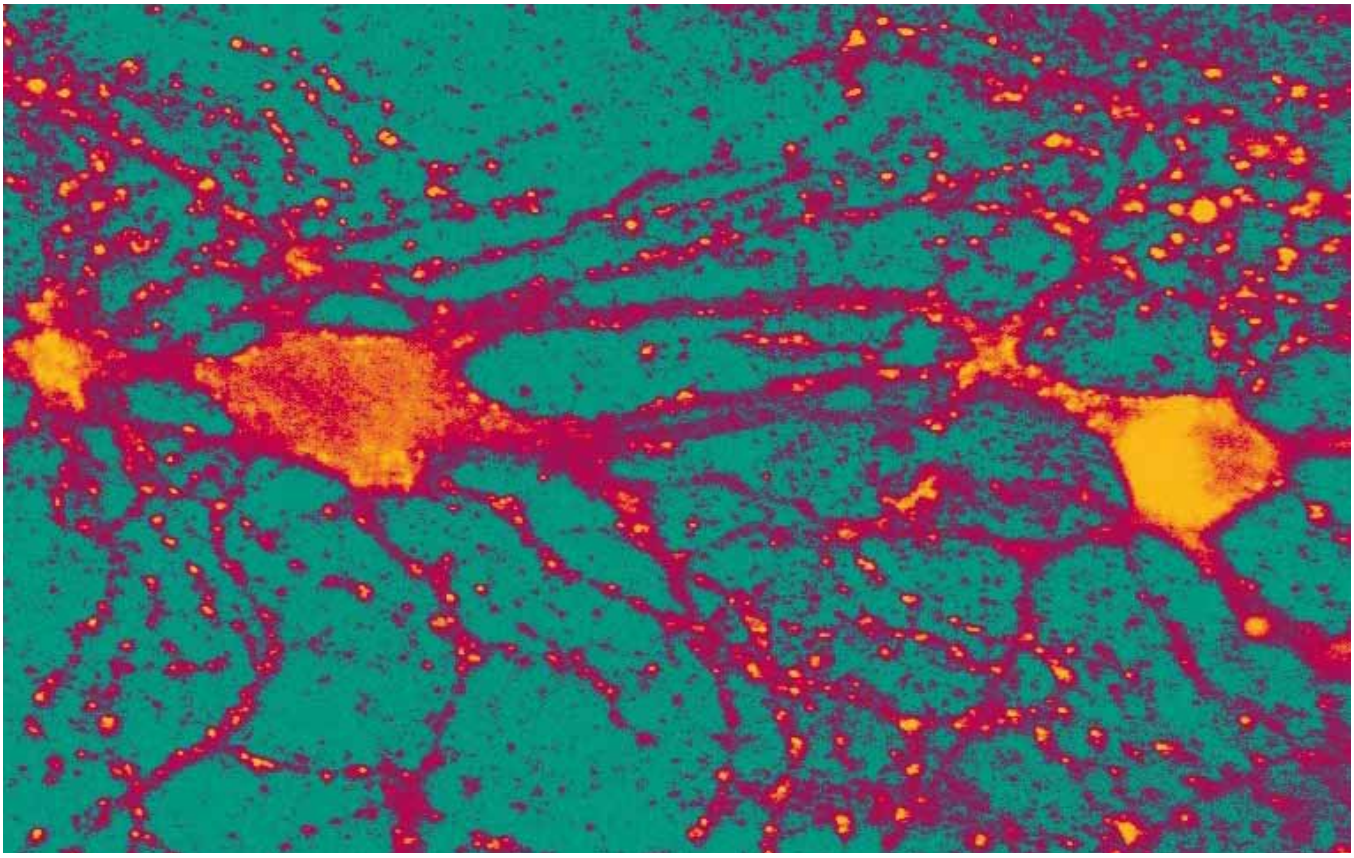
Something was cancelling the tremors out in healthy people. To find out what that was, the researchers taught macaque monkeys to move their index finger in a way that exacerbated their natural minor tremors, and recorded the activity of nerve cells from both the brain and the spinal cord. Both sets of cells showed rhythmic activity at the same frequency as the tremor; however, they appeared to cancel each other out. When the wave in the brain was at its peak, the wave in the spinal cord was at its lowest and vice versa. The net effect was to reduce the size of the tremor. Understanding more about how this spinal controller of tremors works could make it possible to manipulate the system and lead to new treatments for tremors.

Dispelling mental health myths

A website and a series of animations aim to dispel myths and misconceptions about mental illness.

The website **mentalhealthcare.org.uk** provides information for relatives and friends of people with psychosis. It explains mental health terms, medication and other treatments, and it describes how mental health services work. It also has video interviews with health professionals and researchers and sections such as 'Ask the Psychiatrist'. The website is a joint venture between the Institute of Psychiatry at King's College London and South London and Maudsley NHS Foundation Trust, in association with the campaigning mental health charity Rethink.

The *Troubled Minds* animations explore mental health issues affecting young people. The animations examine eating disorders, obsessive–compulsive disorder, self-harm and Asperger's syndrome, and have testimony from people who have experienced these forms of mental distress. Made by Mosaic Films and Teachers TV, the series won a BAFTA in the Best Learning – Secondary Education category at the 2009 British Academy Children's Awards. It also won the category for best programme for 14-to-19-year-olds at the Royal Television Society's Educational Awards, and won the 2009 Mental Health Media Award for Young People's Media.



Combating infectious disease

Why are some pathogens so dangerous? And why are some of us more vulnerable to disease than others? Advances in genetics and genomics are helping to answer these questions.

In 1977, Fred Sanger and his team sequenced the first DNA-based genome, of the the bacteriophage phiX174. This was also the first genome of a pathogen to be decoded and the start of an extremely fruitful area of research. The data obtained from sequencing these genomes are helping us to understand the biology and evolution of pathogens and are speeding the development of new therapies and control measures.

Yet DNA sequencing is not just helping us to understand pathogens. The molecules that make up our immune systems are produced by an array of genes within the human genome. New research is showing how subtle variations within these genes influence how likely we are to succumb to an infecting pathogen.

Uncovering pathogens' genetic secrets

The 'superbug' *Clostridium difficile* is one of the foremost public health problems of recent times. Outbreaks occur in hospitals all over the world when an opportunistic infection takes advantage of the disruption to normal gut bacteria caused by antibiotic treatment. This allows *C. difficile* – which is resistant to most common antibiotics – to overrun the gut, producing toxins and leading to diarrhoea and gut damage. Little is known about how the bacterium evolved, but researchers at the Wellcome Trust Sanger Institute have now shown that the species is millions of years old, despite becoming a significant health problem to humans just three decades ago.

The researchers looked at the genomes of eight different *C. difficile* samples taken from humans and cattle from six countries. They found that it is a highly diverse organism: two strains of *C. difficile* may differ genetically by about 2.4 per cent – greater than the divergence between chimpanzees and humans. Epidemic and disease-causing variants occur on several branches of this diverse tree, so its rapid emergence as a pathogen may be down to changes in the environment, caused by human activity such as the use of antibiotics or healthcare practice. The researchers identified clusters of mutations and whole regions that had been swapped between distantly related *C. difficile* cousins, making it the menace it is today.

DNA sequencing at the Wellcome Trust Sanger Institute has also revealed the genetic secrets of a severe form of *Salmonella*. The multidrug-resistant ST313 strain has swept through human populations in remarkable fashion: in an 18-month period in 2002–03, 95 per cent of *Salmonella typhimurium* isolates identified in Africa were ST313. It is better adapted to infecting humans than the common form of *S. typhimurium*, affecting vulnerable children and adults in many regions of sub-Saharan Africa, and killing up to one in four people infected.

Working with scientists at the Malawi–Liverpool–Wellcome Trust Clinical Research Programme and the KEMRI–Wellcome Trust Research Programme in Kenya, the researchers at the Wellcome Trust Sanger Institute compared samples from people showing severe symptoms with those that caused milder symptoms. This revealed genetic changes that make the new strain more invasive and dangerous. According to Dr Robert Kingsley from the Wellcome Trust Sanger Institute, they give it "a unique armoury", and it appears to be adapting to humans. For example, the strain has lost around one in 50 of the genes found in the 'typical' *S. typhimurium*, a sign that it may be becoming more closely adapted to one host: in this case, humans. The pathogen normally circulates among animals and is introduced to humans through food poisoning. However, ST313 may be passed on predominantly through person-to-person contact. Although worrying, such an insight could help us to predict where new pathogens will emerge and to design new vaccines against them.

That discovery was gained through the Wellcome Trust Sanger Institute's expertise in genome sequencing, and this year also saw their delivery of another important draft genome: *Trypanosoma brucei gambiense*, the parasite strain

responsible for almost all cases of sleeping sickness (African trypanosomiasis). By comparing the sequence with that of the related strain *T. b. brucei* (which infects cattle), the researchers found that sequences of comparable genes were remarkably similar – on average, 98.2 per cent identical. This suggests that *T. b. gambiense*'s ability to infect humans cannot be easily explained by the addition or removal of a few genes. Instead, it is more likely to be due to small changes in the genome, differences in the number of copies of genes, or changes in how the activity of genes is regulated. The genome sequences will aid the search for those small genetic differences, and hopefully better, targeted drug treatments – which are much-needed because current drug treatments can be toxic, difficult to administer and lead to unpleasant side-effects.

Human genes and infectious disease

Why is it that some people's immune systems are more robust than others? One clue has come from scientists at the University of Washington in Seattle and the Wellcome Trust Vietnam Research Programme. They identified a new genetic variant that affects susceptibility to tuberculosis and leprosy. Both are caused by rod-shaped, aerobic bacteria known as mycobacteria. Exposure causes varying outcomes: for example, some people resist infection by *Mycobacterium tuberculosis*, others will carry the bacteria unaware, and some will develop life-threatening symptoms.

Studying zebrafish, the researchers looked at how adaptive immunity – the immune response that 'learns' from invading pathogens – responds to control mycobacterial infection, as well as how the inbuilt 'innate' immune system reacts to a new invader. By watching the early steps of infection, they identified a key locus, *LTA4h*, which increased susceptibility to the bacteria.

The human equivalent is responsible for regulating the production of key chemicals involved in the inflammatory response to infection. By evaluating tuberculosis patients in Vietnam and leprosy patients in Nepal, the researchers confirmed that gene variants of *LTA4h* offer protection against the mycobacterial diseases, opening up a potential new target for drugs against these diseases.

We are slowly learning more about the genetic factors that influence our likelihood of developing diseases such as tuberculosis. Researchers from the Singapore Agency for Science, Technology and Research (A*STAR) and Singapore's National University Health System have collaborated with the Wellcome Trust Centre for Human Genetics in Oxford to identify new genetic variants that increase susceptibility to tuberculosis, malaria and bacteraemia.

By analysing the genes from more than 8000 people in the Gambia, Hong Kong, Kenya, Malawi and Vietnam over five years, they found a striking association between a gene called *CISH* and increased risk of susceptibility to these diseases. *CISH* encodes a protein that dampens down signals between immune system cells. Within the population studied, having just one of a set of five *CISH* gene variants increased susceptibility to disease by 18 per cent, a "substantial" effect for one gene, according to Dr Fredrik Vannberg of the Oxford Centre.

Meanwhile, a study of populations in the Gambia, Malawi, and Ghana has found a separate genetic variant that also increases susceptibility to tuberculosis. By analysing hundreds of thousands of genetic markers across the whole genomes of more than 11 000 people, researchers from the African Tuberculosis Genetics Consortium and the Wellcome Trust Case Control Consortium have

Trypanosoma brucei, the parasite responsible for sleeping sickness in humans and nagana in animals in Africa.

> *Trypanosoma brucei gambiense*'s ability to infect humans cannot be easily explained by the addition or the removal of a few genes."

identified a variant on chromosome 18, located in a region of DNA that does not code for a gene. This suggests that the variant is affecting susceptibility to tuberculosis by influencing the activity of other genes.

Tuberculosis can exist in a latent form, carried by people for years without ever causing any symptoms. Likewise, people can carry the bacteria causing meningococcal meningitis intermittently throughout their lives without any harm. If the disease does develop, however, it can cause critical illness within hours – meningococcal meningitis kills one in ten cases. Why are some people affected and others not?

Genetic studies again offer some clues. Scientists from Imperial College London and the Genome Institute of Singapore studied the genomes of 1500 patients from Austria, the Netherlands, Spain and the UK. Those who developed meningococcal meningitis had distinct markers around the genes for factor H and related proteins. These regulate a part of the body's immune system called the complement system, which recognises and kills invading bacteria.

Normally, this regulation ensures that the complement system does not cause excessive damage to the body's own cells. But previous Wellcome Trust-funded research showed that meningococcal bacteria hijack the body's factor H, using it as a disguise so they can evade the body's defences. It is the "strongest evidence so far that there are genetic factors that lead to people developing meningitis", according to Professor Michael Levin from Imperial College London, who led the study.

Susceptibility to one disease is not always a bad thing – it could protect against another. Researchers from the Cambridge Institute for Medical Research and the KEMRI–Wellcome Trust Research Programme in Kenya found that people with two copies of a particular gene variant are more susceptible to developing systemic lupus erythematosus, which leads to inflammation and tissue damage. But this also protects them against malaria.

The team looked at a variant of the gene *FCGR2B*, previously linked to lupus in Asians and commonly found in those from South-east Asia or sub-Saharan Africa, where malaria is endemic. The gene produces a receptor that acts as a 'brake' on some functions of the immune system. In lupus, this gene does not function normally, resulting in 'brake failure' and a hyperactive immune system.

The researchers compared hundreds of people with lupus in Hong Kong and the UK, then contrasted their genetic profiles to those of people with severe malaria in Kenya. This confirmed a strong association between lupus susceptibility and Asians with two copies of the *FCGR2B* gene variant (we inherit two copies of any gene, one from our mother and one from our father). And Kenyans with two copies of the same gene variant were almost 50 per cent less likely to contract severe malaria.

Tackling malaria

Every year, there are more than 200 million cases of malaria, killing nearly a million people. The culprits are parasites – notably *Plasmodium falciparum* and *P. vivax* – that are passed into the bloodstream via infected mosquitoes.

We fund a wide range of studies into malaria: research into the parasites themselves, into new drugs that can help to treat people with the disease, and into control measures, such as bednets, that can stop mosquitoes passing on the parasites.

One of our major initiatives is the Kenya Medical Research Institute (KEMRI)–Wellcome Trust Research Programme, which has been tackling malaria and other infectious diseases in Kenya since 1989. This year, KEMRI researchers and the Wellcome Trust Sanger Institute showed why the malaria parasite is such a dangerous adversary: it can disguise itself to avoid the human immune system. *P. falciparum* produces molecules called PfEMP1 that make infected red blood cells stick to the walls of blood vessels; this prevents them from being flushed through the spleen and destroyed. But they can also adapt their molecules depending on which antibodies they encounter: as immunity develops, the parasites can switch on a different set of genes to disguise themselves and stop the immune system from clearing the infection.

One approach to preventing the disease could be to use antibiotics to give the immune system more time to mount a defence against the parasite. Researchers from the Kenya Programme have shown that, in mice infected with malaria parasites, two antibiotics cause a defect in the parasites as they enter the liver. This stops the parasite from changing into the disease-causing form that enters the bloodstream. With this extra time, the mice developed immunity sufficient to protect against further infections 40 days later.

If the technique works in human trials, it could help to control or eliminate malaria in high-risk populations.

Another promising treatment for malaria has been developed by an international collaboration of researchers led by the Novartis Institute for Tropical Diseases. The drug, called NITD609, clears malaria infection in mice with a single oral dose and is active against *P. falciparum* and *P. vivax*, including a range of drug-resistant strains. NITD609 works by suppressing the parasite's protein synthesis; it has been approved as a preclinical candidate and is ready for phase I studies in humans.

Other researchers have emphasised that maintaining and building on control strategies is the key to fighting malaria in Africa. Although increased use of insecticide-treated bednets, improved rapid diagnostic tests and the replacement of failing drugs with artemisinin-based combination therapies (ACTs) have helped to reduce malaria transmission and incidence substantially across the continent, researchers from the Kenya Programme warn that positive results are not universal. Studies have shown that ACTs still only reach a small proportion of the African population, and 33 African countries have coverage of less then 40 per cent in the use of treated bednets.

Indeed, older children (between the ages of five and 19 years) are the least well protected by nets, according to another study from the Programme. This is because parents and young children under the age of five are more likely to have access to protection from nets than older children in the same house. An estimated 80 per cent of human-to-mosquito transmission comes from over-fives. The researchers suggest delivering nets through schools as a quick and cost-effective approach to reaching universal coverage.

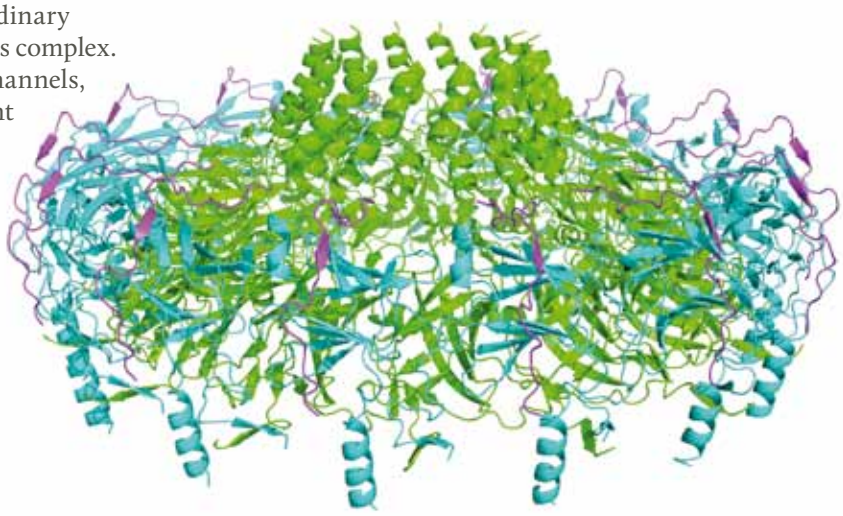
Wellcome Trust-funded researchers in Africa are investigating how to improve the treatment and prevention of malaria.

Getting close to bacteria's machines

Gram-negative bacteria are hardy. An outer membrane protects their cell wall, making them particularly difficult to kill, and their rising resistance to many common antibiotics is narrowing treatment options.

The quinolones, antibiotics used since 1962, attach to the enzyme topoisomerase, which is essential for the bacteria to produce proteins and replicate. Now, however, a new experimental antibiotic may be able to take the place of quinolones. Using X-ray crystallography, a team from GlaxoSmithKline (GSK) has shown that the new antibiotic attaches to the enzyme in a different place to the quinolones, enabling it to stop the same bacteria that are resistant to older treatments. The research is the result of two collaborations between GSK, our Seeding Drug Discovery initiative and the US Defense Threat Reduction Agency.

Meanwhile, Professor Gabriel Waksman and colleagues at Birkbeck and University College London are building a clearer picture of the machinery used by bacteria to spread antibiotic resistance or cause diseases such as whooping cough, peptic stomach ulcers and legionnaires' disease. They are studying type IV secretion systems, tiny machines that behave like pumps. Spanning the double membrane of the bacteria, type IV secretion systems pump toxins out into host cells and antibiotic resistance genes into antibiotic-sensitive bacteria. Using X-ray crystallography, they have shown the extraordinary complexity of the outer membrane part of this complex. Toxins enter the pump through membrane channels, which are made of three proteins, each present in 14 copies. This first glimpse at the inner workings of the machinery provides new clues for the design of antibiotics.



The outer membrane complex of the type IV secretion system.

Protecting against reinfection

***Streptococcus pneumoniae*, as its name suggests, is a primary cause of pneumonia. For people with HIV, however, it poses even greater dangers.**

It is usually a rare occurrence for an *S. pneumoniae* infection to spread to the blood and brain, causing septicaemia and meningitis – so-called invasive pneumococcal disease. But for HIV-infected adults, particularly in sub-Saharan Africa, the risk of developing these serious, often fatal illnesses increases 30- to 100-fold.

Because of this, a recent trial of a new vaccine was particularly welcome: the trial showed that the vaccine could prevent three out of four cases of reinfection in HIV-infected adults in Africa. The vaccine, Prevnar, is a 'conjugate vaccine' as it is bound to a carrier protein to enhance its effects.

Dr Neil French and colleagues at the Malawi–Liverpool–Wellcome Trust Clinical Research Programme tested the vaccine on almost 500 adults, mostly with HIV, who recovered from invasive pneumococcal disease after being admitted to the Queen Elizabeth Central Hospital in Blantyre, Malawi. They found that the vaccine prevented 74 per cent of recurrent cases of invasive pneumococcal disease in patients with underlying HIV infection.

In brief

- *Colonial medicine*

Professor Mark Harrison, Director of the Wellcome Unit for the History of Medicine at the University of Oxford, has published *Medicine in the Age of Commerce and Empire: Britain and its tropical colonies, 1660–1830.* The book examines how colonial doctors pioneered medical knowledge, explored new botanical and chemical remedies, and implanted these developments in their civilian practices in Britain.

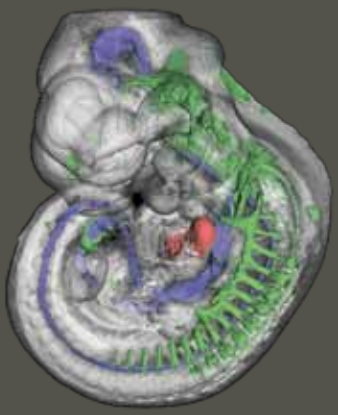
- *Giant trypanosome*

A seven-metre-long trypanosome parasite appeared at the West End Festival Parade in Glasgow and in a comic book. The trypanosome, which resembled a Chinese dragon, was the brainchild of Jamie Hall, a researcher at the Wellcome Trust Centre for Molecular Parasitology at the University of Glasgow, who wanted to showcase the research on African sleeping sickness taking place in the city.

- *Counterfeit medicines report*

The challenges and urgent action needed in the global fight against counterfeit medicines were outlined in a report we published with the American Pharmaceutical Group in November 2009. The report summarises a conference, held the month before at the Trust, which brought together experts from the public health, economic, industry and national regulatory sectors.

Investigating development, ageing and chronic disease



Studies of telomeres at the ends of our chromosomes and caloric restriction are bringing new insights into how our cells age and into healthy ageing.

As we get older, we are more likely to be affected by cardiovascular problems, arthritis, cancer and a range of other diseases. Over time, our cells accumulate damage and our tissues become less efficient. But there are two forms of ageing – chronological ageing, or age in years, and biological ageing, or how quickly (or slowly) our cells deteriorate over time. Growing evidence suggests that the risk of age-associated diseases, such as heart disease and many cancers, is more closely related to biological age than chronological age.

Indeed, the discovery of the first gene variants linked to biological ageing suggests that some people may be genetically predisposed to age at a faster rate or to age faster when they are exposed to environmental factors. The research – by teams at the University of Leicester, King's College London and the University of Groningen in the Netherlands – studied telomeres, structures on the ends of chromosomes that are used as markers for biological ageing because in many cells telomeres shorten as the cells divide and age. The researchers found that people carrying a particular genetic variant had shorter telomeres, appearing biologically older. This suggests that individuals carrying the variant are at greater risk of developing age-related diseases, or that they are genetically programmed to age at a faster rate. Alternatively, genetically susceptible people may age even faster when exposed to conditions that are 'bad' for telomeres, such as smoking or obesity.

Yet there is also mounting evidence that this ageing process is not fixed. Reducing the number of calories that a mouse, worm or fruit fly eats can help it to live longer and improve its health – with a downside of reduced fertility. Research by Professor Linda Partridge at University College London (UCL) and colleagues suggests that getting the correct balance of proteins in the diet may be more important than calorie reduction for healthy ageing, with the added benefit of preserving fertility.

They measured the effects of manipulating the diets of female fruit flies and found that varying the amount of amino acids in the diets affected lifespan and fertility. When this effect was studied further, they found that the level of the amino acid called methionine was vital to maximising both lifespan and fertility, suggesting that it is possible to extend lifespan without the side-effect of lowering reproductive capacity. Methionine is one of the most important amino acids because it is essential to the formation of all proteins. Getting the protein balance right seems to be important for healthy ageing, and the researchers think that further study could make it possible to apply similar principles to human diets.

Professor Dominic Withers and colleagues, at UCL and Imperial College London, have found that altering just one mouse gene mimicked the effects of dietary restriction: the lifespan of the mice was extended by up to a fifth and the number of age-related diseases they suffered was reduced. These mice were unable to produce a protein called S6 kinase 1 (S6K1), which affects another molecule, AMPK, that regulates energy levels in cells. Because drugs that activate AMPK or block S6K1 also seem to extend the lifespan of mice, this biological pathway could be key to understanding the relationship between ageing and chronic disease.

Investigating diabetes

Research is exploring not only genetic links to diabetes but also its screening and diagnosis.

When the US Centers for Disease Control described diabetes as an "epidemic" in 2007, it did so with good reason. The disease affects 220 million people worldwide today; increasing life expectancy, rising obesity levels and decreasing activity levels all mean that, by 2030, more than 350m people are likely to have diabetes.

While obesity and inactivity are often seen as the causes of type 2 diabetes – the most common form of the disease, in which the body's cells become less responsive to the hormone insulin – it is also known to have a genetic component. In June 2010, for example, an international consortium of scientists, led by the Wellcome Trust Centre for Human Genetics at the University of Oxford, identified 12 new genes associated with type 2 diabetes, bringing the total number of genetic regions known to be associated with the disease to 38. Intriguingly, several of the genes seem to be important in controlling the number of insulin-producing pancreatic beta cells that an individual has.

Another genetic clue to type 2 diabetes has come from a less obvious source – a study of genes that affect birth weight. Although lower-weight babies are known to be more at risk of type 2 diabetes in adulthood, research had tended to focus on the womb environment and mothers' nutrition. However, two genetic variants with strong associations to birth weight have now been discovered, one of which is also linked with susceptibility to type 2 diabetes. The research, by Dr Rachel Freathy, a Sir Henry Wellcome Postdoctoral Fellow at the Peninsula Medical School, Exeter, and colleagues in a large international team of researchers, found the two variants in a study of 38 000 Europeans. People who inherit two risk copies of the *ADCY5* variant have a 25 per cent higher risk of diabetes in adulthood than those who inherit two non-risk copies, and they also weigh less at birth.

Screening and diagnosing diabetes in its early stages is crucially important for keeping patients healthy. Left unchecked, it can lead to kidney failure, blindness and an increased risk of heart disease and stroke, but it can be controlled with diet and exercise.

Research we have funded jointly with the British Heart Foundation has now found early signs of type 2 diabetes among UK schoolchildren of South Asian and African-Caribbean origin. It was already known that South Asian adults in the UK are about three times more likely than white Europeans to develop type 2 diabetes, and African-Caribbeans have about double the risk. Professor Peter Whincup at St George's, University of London, and colleagues found that raised levels of blood markers associated with the condition are already present in children as young as ten. This may mean that effective measures for preventing the disease from an early age could be established. Further research needs to be done, however, to find out which particular factors make individuals more susceptible.

> "Man may be the captain of his fate, but he is also the victim of his blood sugar."
>
> **Wilfrid Oakley**, *Transactions of the Medical Society of London*, 1962

If people are given a 'clean bill of health' by the doctor, does this encourage unhealthy behaviour? Not in the case of diabetes screening, according to a study led by researchers from the University of Cambridge and the MRC Epidemiology Unit in Cambridge. They compared groups of patients who were invited for diabetes screening with patients who were not screened and found that those who tested negative for diabetes did not seem to be falsely reassured. The results showed no significant difference between the two groups in terms of people's perceived risk of future diabetes or their intentions to adopt healthy behaviours. There are estimated to be 500 000 people in the UK with undiagnosed diabetes, who would benefit from screening.

In brief

- *Inflammatory bowel disease*

Genetic regions that increase susceptibility to inflammatory bowel disease (IBD) have been identified. An ulcerative colitis study has shown the first conclusive evidence of the part played by genetic defects in the epithelium, the layer of cells that lines the gut, and a study on childhood IBD found multiple regions previously implicated in adult-onset IBD.

- *Fish oils*

A study has revealed why fish oils help to alleviate inflammatory conditions such as rheumatoid arthritis. Our bodies convert docosahexaenoic acid – an omega-3 fatty acid found in fish oils – into resolvin D2. This causes endothelial cells to produce small amounts of nitric oxide, which discourages white blood cells from sticking to the cells, thereby preventing inflammation.

- *Ovarian cancer*

Are GPs under-investigating older patients with symptoms of ovarian cancer? A study of electronic patient records suggests that age plays a part in how quickly diagnosis and referral occur: the older the patient, the later they seem to happen.

Helping to reduce hypertension

In Pakistan, a study has looked at how effective home health workers and general practitioners (GPs) can be at reducing high blood pressure.

High blood pressure is pernicious. It develops gradually, goes unnoticed unless a test is taken and is a leading cause of cardiovascular disease – itself a leading cause of death in both high- and low-income countries.

The two-year study worked with 12 communities of people in Karachi. Three communities received GP training about hypertension; three communities received home health education (HHE) from health workers about hypertension self-management; three communities received both GP and HHE interventions; and three communities received no intervention.

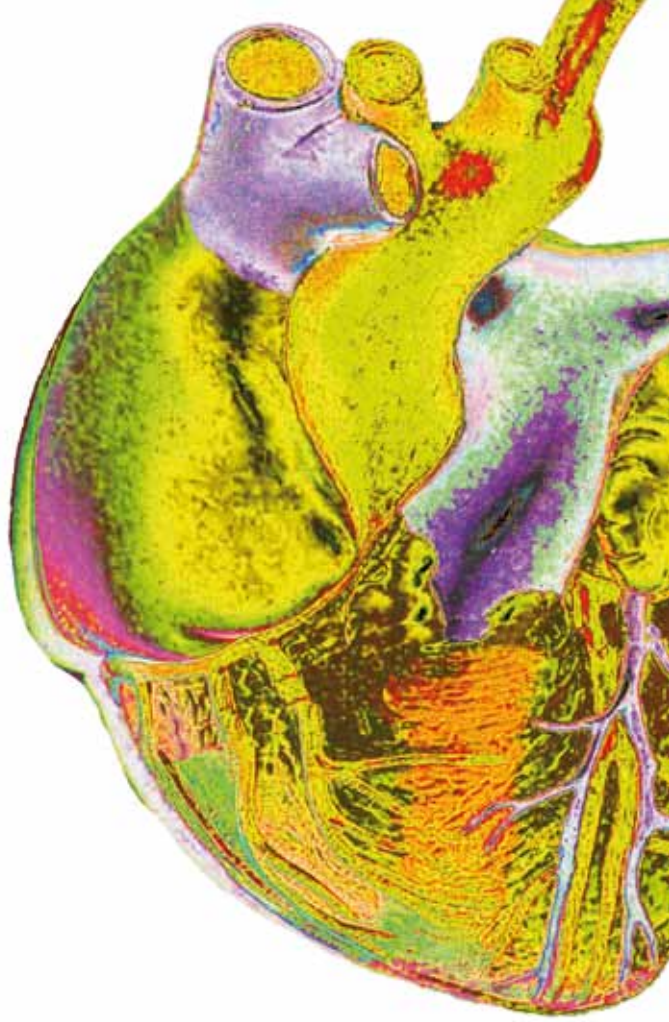
The researchers, from Aga Khan University in Karachi and Imperial College London, found that maximum blood pressure decreased across all treatment groups, but the reduction was highest in the communities that had received both GP and HHE training. This suggests that a combined approach of delivering the message at a household level and reinforcing it with information from the local GP was the most effective strategy for reducing hypertension.

A major milestone for UK Biobank

In July 2010, UK Biobank recruited its 500 000th volunteer.

The UK Biobank project has created a major resource for studies of the impact of lifestyle, the environment and genes on the health of people from the UK. It has gathered biological samples and medical and lifestyle data from people aged 40–69, who are at risk of developing serious diseases – including cancer, heart disease, stroke, diabetes, dementia, depression, arthritis and osteoporosis – over the next few decades.

Recruitment began in Manchester in March 2007, and other recruitment centres were opened in Oxford, Cardiff, Glasgow, Edinburgh, Stoke-on-Trent, Newcastle-upon-Tyne, Leeds and Reading. Each volunteer gave a range of standard body measurements, such as blood pressure and lung function, along with samples of blood, saliva and urine. The researchers also collected information on each participant's lifestyle and medical history. UK Biobank will now follow their health for many years through their medical records, producing a database that researchers can use to better understand why some people develop particular diseases and others do not.



Enhanced image of a human heart.

On the surface

A new imaging technique shows how heart failure affects individual heart muscle cells and why adrenaline may be causing additional damage.

When the heart begins to fail, the body has to respond; without help, the heart will be unable to supply adequate blood flow to meet the body's needs. But the hormones the body produces to stimulate the weakened heart, such as adrenaline, can eventually cause even more damage and deterioration.

Using a technique called nanoscale scanning ion conductance microscopy, Dr Julia Gorelik from the National Heart and Lung Institute at Imperial College London and colleagues have scanned the surface of heart muscle cells from healthy and failing hearts. They found that in failing hearts, the distribution of adrenaline receptors changed: the beta2ARs, receptors that can protect the heart, move next to beta1ARs, which can damage the heart in the long term. This altered distribution may affect beta2ARs' ability to protect cells, leading to more rapid degeneration of the heart.

It is hoped that a better understanding of what happens to these receptors in heart failure could lead to the design of improved beta-blockers, one of the most important categories of drug for slowing the development of heart failure.

Connecting environment, nutrition and health

A major international study has concluded that many measures to reduce greenhouse gas emissions will have positive impacts on health.

The climate change debate has been going on for over 200 years, ever since scientists began arguing about whether the Earth had once experienced an Ice Age. Today, it is clear that climate change is a major problem and that a key factor is the dramatic increase in greenhouse gases emitted since the 18th century, when we first began burning fuel on a massive scale.

The effects of climate change are likely to be erratic. Rather than getting uniformly warmer, different regions will become hotter, colder, wetter or drier, and we will experience more extreme weather events. The results are potentially devastating: many plant and animal species could become extinct and millions of people made homeless.

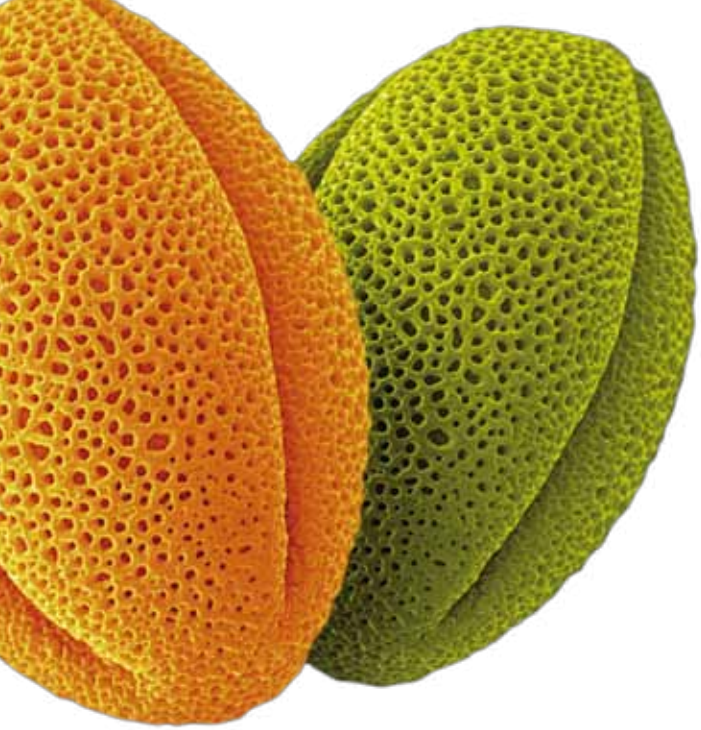
As the United Nations Framework Convention on Climate Change point out, "steps have to be taken – and the sooner the better – to limit damage from consequences of global warming that are now inevitable". Such steps could include expanding our (carbon-dioxide-absorbing) forests, switching to renewable forms of energy such as solar and wind power, and cutting down on livestock and manufacturing. Unfortunately, implementing these strategies on a national level is expensive and could also harm economic growth, so reaching an international agreement is difficult.

One vital issue that tends to get left out of the debate is the health impacts of climate change. This is something of great concern to the Wellcome Trust: connecting environment, nutrition and health is one of the five major challenges set out in our Strategic Plan 2010–20. We felt it was important to provide evidence on the health impacts of climate change – and the health impacts of measures to reduce greenhouse gas emissions – to inform the UN Climate Change Conference in Copenhagen in December 2009.

We coordinated a global consortium of funders and contributed £80 000 to a total award of £405 000 for a team of 50 researchers in nine countries, led by Professor Sir Andrew Haines at the London School of Hygiene and Tropical Medicine. They modelled the health effects of different policies to reduce greenhouse gas emissions in high- and low-income countries in four key sectors: power generation, transport, household energy, and food and agriculture.

The results, published in a series of papers in the *Lancet*, suggest that many measures to reduce greenhouse gases can have important health benefits that would offset their costs. This would help to reduce the considerable economic burden of ill-health along with greenhouse emission and, in effect, kill two birds with one stone. For example, encouraging people to walk and cycle instead of drive would reduce levels of cardiovascular disease, depression, obesity, diabetes and dementia. Cutting the amount of saturated fat from meat and dairy produce that people eat could also have a marked benefit for cardiovascular health. In low-income countries, replacing traditional solid-fuel stoves, which pollute the air around them, with low-emission stoves could reduce respiratory and cardiovascular disease. Changing to renewable methods of electricity generation would likewise reduce respiratory and immune disorders caused by pollution.

These 'co-benefits' of action on climate change had not been widely appreciated by policy makers or given sufficient prominence in international negotiations. A greater awareness of them could better inform the debate about the pros and cons of climate change policies.



Ideas to save pollinators take wing

The Insect Pollinators Initiative has announced £10 million of funding for nine projects investigating the decline of honeybees and other pollinating insects in recent years.

Bees and other insects, including wasps and hoverflies, pollinate plants. By transferring pollen from the male parts of flowers to the female parts, they perform a vital part of the process of fruit and vegetable production. Their widespread role in food production is reflected in pollinators' economic value: in 2009, this was estimated to be over €150 billion (around £130bn) annually across Europe.

But pollinators are under threat. Research published in 2006 indicates that the diversity of wild bees has declined severely since the 1980s. Another major pollinator, honeybees (the vast majority of which are in managed colonies), are prone to a number of diseases. The mite *Varroa destructor*, for example, carries viruses that can quickly destroy entire colonies. The mite, which invaded the UK in 1992, has spread almost completely around the world in the past 30 years.

So, to investigate why bee, wasp and other insect pollinator numbers are falling and what can be done to reverse this trend, the Insect Pollinators Initiative was set up as a partnership between the Wellcome Trust, the Biotechnology and Biological Sciences Research Council, the Department for Environment, Food and Rural Affairs, the Natural Environment Research Council and the Scottish Government, under the auspices of the Living With Environmental Change partnership.

In June 2010, the nine projects that will share the £10m funding were announced. These diverse projects will involve people with a wide range of skills, from beekeepers to mathematical modellers. Their subjects fall into two main groups: bees and their ecology, and bee diseases and health.

Dr Koos Biesmeijer from the University of Leeds will be working with colleagues to explore which insects are pollinating crops in the UK, to try to understand how much additional pollinators would increase crop yield. Also at Leeds, Professor Bill Kunin and colleagues will look at how the abundance of insect-pollinated crops and wild flowers correlates with bee diversity and bee density in rural settings. The state of insect pollinators in towns and cities will be explored by a team led by Professor Jane Memmott.

Bumblebees are the focus of Dr Claire Carvell from the Natural Environment Research Council Centre for Ecology and Hydrology; her group will study five species to understand more about nesting and foraging behaviours and how these are influenced by landscape. Finally, Dr Geraldine Wright of Newcastle University will be investigating a bee's ideal diet and how nutrition influences their learning and memory.

Disease is a major threat to pollinators, and four groups are tackling this issue. Dr Eugene Ryabov from the University of Warwick and colleagues will explore the link between the honeybee, the *V. destructor* mite and the viruses it carries to try to understand the effects of infection on the bees.

Dr Robert Paxton, from Queen's University Belfast and the University of Tübingen, Germany, will be leading research into the effects of and possible treatments for two organisms that cause major diseases in the honeybee: deformed-wing virus (carried by the *V. destructor* mite) and a fungus-like microorganism called *Nosema ceranae*.

Dr Giles Budge from the Food and Environment Research Agency will work with modellers to unlock information within the Agency's years of collected data and understand better how disease spreads between pollinators.

Finally, Dr Chris Connolly, University of Dundee, a neuroscientist more used to studying human brains, will be tackling the bee brain. He and colleagues will explore the effects of different combinations of pesticides on the brains and behaviour of honeybees and bumblebees.

Peony pollen.

Diet and our genes

New research is uncovering how food influences our bodies' systems by interacting with our genes.

One such study has looked at the influence of mothers eating a high-fat diet before and through pregnancy on the risk of congenital heart defects in their children. Professor Shoumo Bhattacharya and colleagues at the Wellcome Trust Centre for Human Genetics in Oxford are studying the *Cited2* gene in mice, a lack of which leads to heart defects (in mice and in humans). If the mothers without *Cited2* were fed a high-fat diet, the chance of a particularly severe heart defect – atrial isomerism, where the left–right asymmetry of the heart is disturbed – more than doubled and the risk of cleft palate increased more than sevenfold. This suggests that congenital heart defects could often be avoided by the right kind of maternal diet.

Another study has shown the importance of getting enough vitamin D. Using new DNA-sequencing technology, researchers at the University of Oxford have created a map of where vitamin D receptors bind along the length of the genome. They found unusual concentrations of these receptors near several genes associated with susceptibility to autoimmune conditions, such as multiple sclerosis, Crohn's disease, systemic lupus erythematosus and rheumatoid arthritis, and to cancers such as chronic lymphocytic leukaemia and colorectal cancer. This indicates that vitamin D deficiency may make us more susceptible to a wide range of diseases.

Lose to gain

The loss of a key segment of DNA can lead to severe childhood obesity.

When Dr Sadaf Farooqi and Dr Matt Hurles found a copy number variation in the human genome that could lead to severe childhood obesity, their discovery had an additional benefit. It was the first time that this kind of genetic variation – a large piece of DNA either duplicated in or deleted from the genome – had been linked to a metabolic condition such as obesity, but the study also helped to remove some of the children being studied from a social services risk register.

The research, led by Dr Farooqi from the University of Cambridge and Dr Hurles from the Wellcome Trust Sanger Institute, looked at copy number variations in the genomes of 300 children with severe obesity. They found that a certain part of chromosome 16, which included the *SH2B1* gene, was missing in some children. People with deletions involving this gene had a strong drive to eat and therefore gained weight.

These findings have wider implications for diagnosing severe childhood obesity, which has on occasion been misattributed to abuse. Some of the children in the study had been formally placed on the social services 'at risk' register on the assumption that their parents were deliberately overfeeding them and causing their severe obesity. They have now been removed from the register.

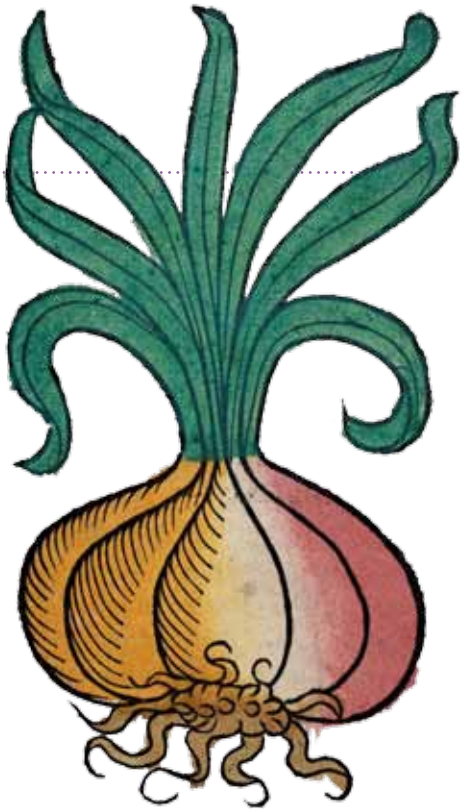
In brief

- *Gastric banding*

The Irish company Crospon Ltd was granted a Strategic Translation Award to improve the outcomes of gastric banding procedures. Crospon will modify its EndoFLIP imaging system, which measures the different components of the gastrointestinal tract. The new device, BaroFLIP, will be used to measure the pouch and passageway in gastric banding, and Crospon hopes that it will remove the need for multiple adjustments.

- *Medieval food*

Historians and scientists from the Universities of Leeds and Bradford served up a lesson in medieval nutrition at Pontefract Castle in July. The event was part of 'You Are What You Ate: Food lessons from the past', a three-year project funded by a Trust Society Award. Visitors to the Castle were invited to taste portions of medieval food cooked on the day and to learn about nutrition and diets then and now.



Woodcut of an onion from *Ortus sanitatis*, 1491.

The scale of our charitable giving is driven by the returns that we earn on our investment portfolio.

Over the past 25 years, we have been able to increase the nominal value of our charitable expenditure from £20 million a year to more than £600m a year because our financial investments over the period have given a return of more than 2700 per cent.

At 30 September 2010, our investments were valued at £13.91 billion. Over the year, we enjoyed a return of 11 per cent, equivalent to £1.45bn, as returns recovered to an all-time high despite the financial crisis.

Our portfolio is diversified into several different types of asset (see 'How we invest our money' on the opposite page) and in many different parts of the world. This global approach has been particularly beneficial, as investment returns have been strong in the faster-growing economies of Africa, Asia, Latin America and the Middle East – where we have invested about 30 per cent of our money. Our £1bn investment in London residential property, centred on Kensington, also continues to deliver strong returns.

In late 2008 and early 2009, we invested directly in the shares of 32 very large global multinational companies, ranging from Apple to Vodafone. As stock markets have recovered, these shares have provided a return of 25 per cent, more than £400m. Overall, about 45 per cent of our portfolio is invested in global stock markets.

About 17 per cent of our portfolio is invested in hedge funds. These funds employ very skilled investors to take advantage of market anomalies to provide a less volatile set of returns. Over the past year, our hedge funds delivered a return of 9 per cent.

Finally, we have about 24 per cent of our portfolio invested in privately owned companies. The largest component consists of venture capital funds that specialise in start-up companies. We are partnered with many of the world's most successful entrepreneurs; through them, we are original investors in successful companies such as Facebook and Twitter. We have also grown our investments in funds that invest in private companies based on sectors, such as energy or financial services, or on regions, such as China or India.

We have over £500m of directly held investments in over 30 private companies; this is the fastest-growing part of the private portfolio. We have invested directly in healthcare companies for over a decade, and in the past three years, we have added investments in secure data centres, private universities, technology, nuclear energy, bioenergy and financial services. More investments will be made over the next year.

We are comfortable with the existing distribution of our portfolio. We strive to continue to improve the quality of our assets and partnerships, to take advantage of the disruptive opportunities created by economic dislocation and to benefit from our genuinely long-term investment horizon.

Meanwhile, we are continuing to develop our internal Investments team. The 30-strong team, investing directly in assets and managing our external managers, is crucial to the continued success of our investments and to our ability to grow the scale of our charitable expenditure.

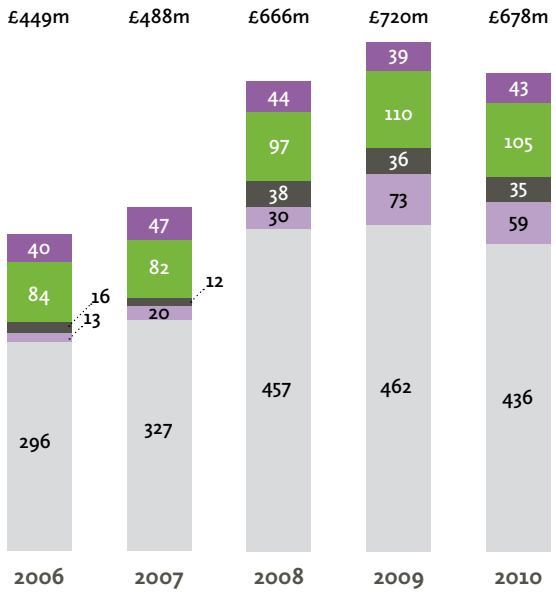
The global economic outlook remains very mixed: in the UK and other parts of Europe, government austerity programmes, which are necessary to reduce public deficits, will keep economic growth subdued for some time to come. As in the USA, strong companies are likely to become stronger, especially as they expand into new markets. However, there are major challenges ahead, especially as levels of unemployment remain high. Faster-growing economies will not be able to avoid these headwinds indefinitely, even as they benefit from a shift of economic power that increases the need for global cooperation.

Danny Truell
Chief Investment Officer

Total charitable expenditure for the year was £678 million (2008/09: £720m). Overall, our total charitable expenditure has increased during the past five years, mainly due to initiatives in 2008 and 2009 arising from the special dividend released in 2007.

Charitable expenditure 2006–10 (£m)

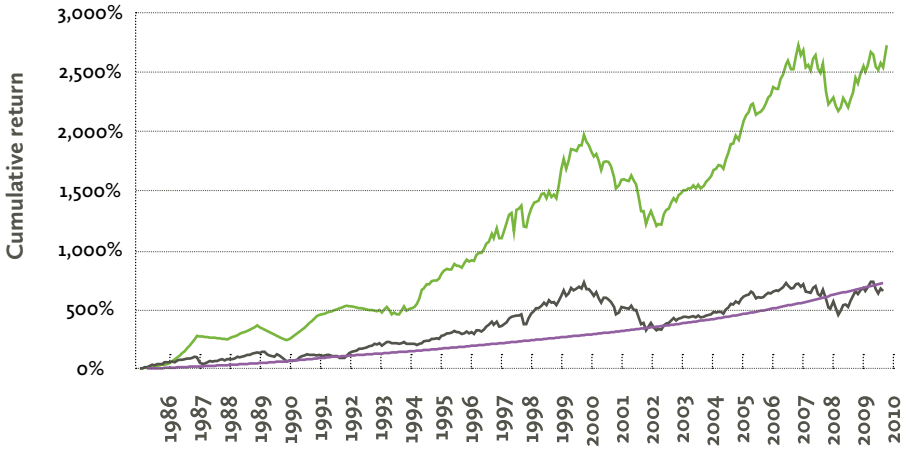
- Support costs
- Wellcome Trust Genome Campus
- Medical Humanities and Engagement
- Technology Transfer
- Science Funding



Total portfolio cumulative net returns since 1986

£ from 1986 to 30 September 2009 (UK CPI)
Blended £/$ from 1 October 2009 (UK/US CPI)

- Wellcome Trust
- MSCI World
- CPI + 6%



How we invest our money

Asset allocation (%) over the past five years.*

	2006	2007	2008	2009	2010
Public equity	62.5	52.0	38.4	37.8	44.5
Private equity	12.1	13.9	19.3	20.6	23.7
Hedge funds	14.8	20.7	23.3	17.8	16.6
Property	8.7	11.9	11.9	10.8	9.4
Cash and bonds	5.8	5.4	9.3	13.0	5.9

*Note that the percentages exclude the impact of currency overlay, which can be positive or negative.

Further detail is provided in the Wellcome Trust's *Annual Report and Financial Statements 2010*, available at www.wellcome.ac.uk/publications.

Our new Strategic Plan focuses on how we will achieve our mission through a range of exciting activities. It also highlights how important it is for us to be an efficient and effective organisation.

The professionals we employ in support and operational functions underpin our work across a broad spectrum of activities. The challenge these departments face is to maximise efficiency while maintaining business practices of the highest standard.

Our major focus during 2010 was the launch of our new Wellcome Trust Investigator Awards. Implementing this new funding scheme, ahead of its formal launch on 1 October 2010, required extensive teamwork across the organisation and with the external research community. Grants Management worked closely with Science Funding and consulted with existing committee members, grantholders and university administrators to ensure the scheme meets our needs as well as the needs› of our external stakeholders.

Risk management
Every organisation manages risks. At the Wellcome Trust, we want to ensure that we do this effectively and, accordingly, have appointed an Enterprise Risk Manager. This helps to ensure that we continue to embed good risk management practices throughout the organisation and for all our projects, and has helped in the development of our corporate risk register. One particular focus has been our grant assurance framework – how we ensure that the monies we award as grants are used effectively. The good controls we already have in place will be enhanced in 2010–11.

Employee development
We actively encourage our 580 staff to develop and learn new skills and to expand their knowledge and expertise. Over the year we improved our performance and development reviews and linked these directly to our performance pay scheme. Secondments have been encouraged, to enhance and share skills and to encourage cross-departmental working; 17 staff secondments took place over the year. In 2011 we will introduce graduate and intern programmes.

We recognise that having greater staff diversity will enhance the organisation and have initiated ways to actively encourage this. One such development has been changing the way we recruit to avoid bias and encourage a broader range of applicants.

Improving efficiency
We have two buildings on Euston Road in London. The costs of running these buildings are always under scrutiny and we actively seek ways to reduce these costs. We have successfully reduced our environmental impact with the introduction of a range of energy-saving measures that have brought down our electricity usage by 11 per cent in 12 months. In addition, through effective collection of recycling material, we have reduced our waste sent to landfill by 73 per cent.

It was agreed this year that we should rent out the empty space in our main building (the eighth floor of 215 Euston Road) on normal commercial terms to suitable tenants. This space has been empty since the building was completed in 2005 and will now bring in a significant revenue stream.

The future
To ensure that we continue to remain effective, next year we will review all of our support services activity and benchmark our performance with other organisations.

Simon Jeffreys
Chief Operating Officer

Staff at work in our headquarters building in London.


wellcometrust
The more you look into it, the more extraordinary it becomes.

Communicating the work of the researchers we fund is an integral and essential part of what we do. Never have there been so many ways to find out about – and engage with – this work.

The Wellcome Trust has many stories to tell. Every week we see exciting new research papers published by scientists we fund, a steady flow of new awards to researchers, announcements of initiatives and a buzz of excitement around the latest exhibition at Wellcome Collection.

Sifting through this flood of news, planning stories for the future and presenting our work to the world is our Communications group – a mix of writers and editors, press officers, graphic designers, web developers and marketing experts. We have a Publishing team, led by Hugh Blackbourn, which produces our publications, websites and marketing materials, and a Communications and Media team, led by Katrina Nevin-Ridley, whose members work with journalists, TV and radio and highlight our activities and initiatives to the relevant communities.

So who are our readers and our audiences? For some publications and materials, this is easy to know. *Wellcome News* goes (largely) to our grantholders, *Big Picture* goes to teachers and press releases go to the media. But a more strategic approach will be at the heart of a new plan for how we communicate. We'll be tailoring our communications to the needs of specific audiences and campaigning to these audiences on key issues. In addition, we'll be presenting our work in a striking new brand.

Our brand is based around the fact that the Wellcome Trust is an extraordinary organisation. We had an extraordinary founder, and thanks to our independence, financial strength and the talented individuals we work with, we set our ambition high to achieve extraordinary things. An important expression of our brand is how we communicate through our written work. We strive to make our writing accessible and engaging and to highlight the human dimension to our work through a storytelling approach. A strong and effective visual design is also key to how we present our brand. We are fortunate to have access to vivid imagery – both contemporary and historical – through the work of the Wellcome Library and its Wellcome Images resource (**images.wellcome.ac.uk**), which is available for others to use.

So what changes will you see? The first major change is to the appearance of our publications, which are being rolled out in the new brand identity. The *Annual Report* and this *Annual Review* have been updated and will be followed by *Wellcome News* – making it more feature-led, with stories about the researchers we fund. Our other brochures and the flyers produced to promote schemes and activities are also being updated in the new look and feel, as are our websites.

Finally, we will continue to evolve our communications to reflect the ways in which society is adapting to use social media. A few years ago, RSS feeds were exciting and new – for the first time you did not have to visit websites to find out the latest news. Now, social media such as blogs, Twitter and Facebook dominate the ways in which we communicate. We too have adapted to be part of the conversation and aim to be ready for whatever comes next.

Clare Matterson
Director of Medical Humanities and Engagement

Front window display of our headquarters building on Euston Road, London.

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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