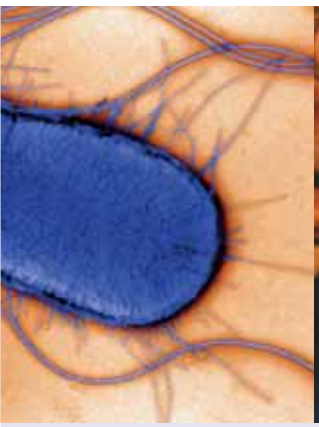
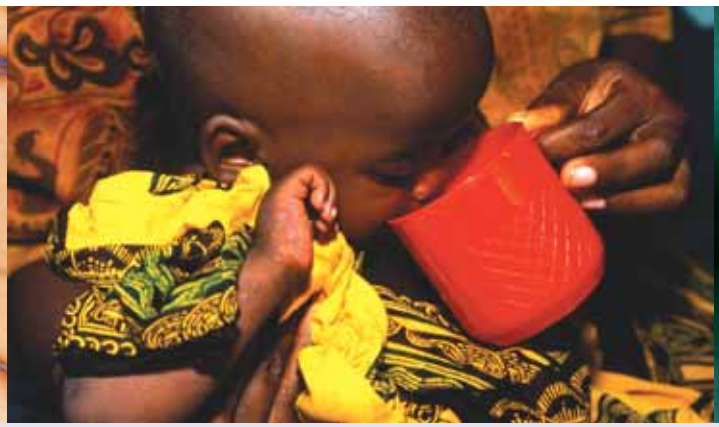
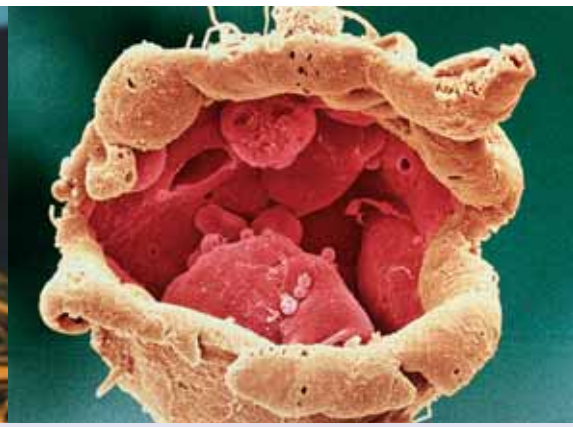
ANNUAL REVIEW

2004

wellcome trust

THE WELLCOME TRUST

An independent, privately owned endowed medical research charity. Our mission is to foster and promote research with the aim of improving human and animal health.

CONTENTS

This Annual Review covers the Wellcome Trust's financial year 1 October 2003 to 30 September 2004.

AIMS AND OBJECTIVES

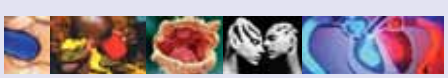
Our four Aims identify the priorities on which we concentrate. Each Aim is underpinned by a series of Objectives which establish the practical measures being taken to achieve the Aims and, ultimately, our mission.

4 Knowledge
Advancing knowledge and understanding in the biomedical sciences and their impact on society – past, present and future.

- Supporting basic, applied and strategically important research in biomedical sciences.
- Researching the societal impact of biomedical science – past, present and future.

14 Resources
Contributing to a long-term and vibrant research environment.

- Human resources: meeting training and career development needs of researchers.
- Physical resources: building suitable conditions for research.



L to R

The bacterium, *Escherichia coli*.

Kenyan child.

Human embryo at the blastocyst stage.

A portrait of twins by David Teplica.

Interactive exhibit at the science centre, Thinktank, in Birmingham.

WORKING WITH OTHERS

It's been a year when working in partnership has delivered real benefits.

Highlights of the year

- The highly accurate and complete 'gold standard' human genome sequence is released.
- Mutations in the *ERBB2* gene are discovered in a subset of lung cancers, opening up the prospect of targeted therapy.

Looking back on a busy year, I am delighted at the progress we have seen – the discoveries our researchers have made, the accelerating application of research, and the changes we have made within the Wellcome Trust itself. And I am also pleased that so much has been achieved in partnership with others. I firmly believe that scientific opportunities will be exploited to best effect, and medical needs met, when people work together to harness their energies to common purpose.

Our Major Overseas Research Programmes in developing countries, for example, have been based on partnerships with local Governments and academic and health infrastructures. By dealing with local issues, they have provided genuine benefits to their host countries. Because of these strong links, their activities have quickly fed into local policy and practice.

This year we report on the continuing success of artemisinin combination therapy for malaria, pioneered by Professor Nick White and colleagues in South-east Asia, as well as a trial of steroid therapy in tuberculous meningitis, which has significantly cut death rates, and has led to changes in government health policy.

Recently, the Wellcome Trust was awarded a Merit Award from the People's Committee of Ho Chi Minh City, which I had the honour of accepting for the Trust during a fascinating visit to see the work of our researchers in Thailand, Vietnam and Laos. Professor White and Dr Jeremy Farrar were also honoured by the Committee. This recognition is an endorsement of our long-standing collaborative approach in the region.

UK science

In the UK we have continued to work constructively with the UK Government, which has consistently recognised the importance of the country's research base. There is an outstanding community of imaginative and productive researchers in the UK. We will continue to support research in the UK whilst its excellent science base is maintained. The additional funds for science provided in the 2004 Spending Review, including more resources as an explicit underpinning of charity-funded research, are signals that the Government is as committed as we are to the future of UK science.

There are other areas in which we are working closely with the Government. A long-standing partnership, to construct the UK's new synchrotron facility, received a further financial boost this year (£120 million in total, with more than £100 million extra from the Government).

Although we are pleased to work in partnership with Government in support of research, our independence also enables us – and, indeed, requires us – to play an important role as a critic of Government when it pursues policies that may have an adverse impact on biomedical research for public good. We have worked very hard during the year to gain acceptance of amendments of proposed legislation that could have serious adverse consequences for important medical research.

Partnership also increases the effectiveness of our voice in this public policy work; we have worked closely with the UK research funding and academic community to produce joint responses to, among other things, the draft Human Tissue Bill and Mental Capacity Bill. A single coherent voice has undoubtedly benefited all parties and led to more considered legislation.

Two of the most important and challenging areas are clinical and international research. The creation of a new partnership, the UK Clinical Research Collaboration (UKCRC), is recognition that clinical research will only thrive if all the key protagonists work together – funders, the health service and the higher education community. We look forward to announcing new initiatives under the UKCRC umbrella in the very near future.

We have also developed a joint commitment to prioritise malaria research, and are discussing with other

- A biochemical defect causing neonatal diabetes is identified, allowing babies to be given medication rather than injections.
- Beneficial effects of rapamycin analogues in models of Huntington's disease suggest a new therapeutic approach.
- Avian flu victims are treated at Wellcome-funded facilities in Vietnam, capturing valuable data on the impact of the virus.
- Analysis of clinical trials data for artemisinin combination therapy confirms its potency as an antimalarial drug.
- A trial with steroids markedly cuts deaths from tuberculous meningitis in Vietnam.
- 'Myskin', an innovative dressing incorporating patients' own cells, is launched in the UK NHS.
- *Pain* exhibition at the Science Museum attracts a record number of visitors.

funders, including the Department for International Development, how we might best work together. Moreover, with the UK assuming presidency of the G8 group of nations on 1 January 2005, and a spotlight on Africa as a major priority, we have a real opportunity to make a difference to a continent that suffers so badly from disease.

In our Public Engagement work, we developed ground-breaking exhibitions with the Science Museum and the British Museum (and in 2005 will be collaborating with the Victoria and Albert Museum on a new exhibition on touch). Our science centre and museum exhibit renewal initiative, Rediscover, was also a partnership venture – with the Millennium Commission and the Wolfson Foundation.

Building work began in the year for the National Science Learning Centre, funded by us as part of a £51 million partnership with the Department for Education and Skills. The Science Learning Centre network will provide a major boost to science teaching in the UK, benefiting the next generation of scientists and, more generally, helping to create a scientifically enquiring population.

This year has seen many exciting research findings published. A small selection of these are summarised in the following pages. It is clear we are living in a golden age of biomedical research, as human genome data and high-throughput technologies offer experimental possibilities undreamed of a generation ago; similarly, new approaches to imaging and the study of the brain give us unprecedented insight into the workings of the brain.

An important challenge is not only to nurture this age of discovery but also to ensure that we capture practical medical benefits afforded by the flow of new knowledge.

Streams

Internally, our year was marked by a move into a new building, the implementation of a new corporate identity, and the introduction of our streams model of funding.

Our new building has been designed to encourage greater interaction between staff – fostering 'internal partnerships' and a greater sense of integration and common purpose. Our building is also open and welcoming, a physical symbol of our desire to engage with our multitude of stakeholder communities. Our new corporate identity similarly reflects a desire to be seen as approachable, as well as distinctive and independently minded.

All these strands will come together in our new strategic plan, which we will develop during 2005 and launch towards the end of the year. The strategic plan, the follow-up to *Planning for the Future: The Wellcome Trust 2000–2005*, will outline our aims for 2005–2010, and identify more specifically how we will achieve these.

Ultimately, it is the unstinting work of our grantholders that enables us to meet our objectives, and we look forward to continuing to work in partnership with them to advance towards our ultimate goal – improving human and animal health.

Mark Walport
Director
January 2005

Mark Walport (right) visiting a ward at Mahosot Hospital, Laos.

Supporting basic, applied and strategically important research in biomedical sciences.
Researching the societal impact of biomedical science – past, present and future.

The human genome sequence is a driving force behind much of today's biomedical research. In particular, research is focusing on the impact of genetic differences between people, many of which affect health. Another key theme is how genetic information is translated into biological function:

- Page 6: Surprises in the 'finished' human genome sequence;
- Page 6: The impact of genetic population structure in the UK;
- Page 7: How an unusual genetic quirk causes a deadly inherited disease.

Neuroscience is a second area of great progress. Fascinating insights are being gained into the brain's control of our behaviour:

- Page 8: A possible cause of inflexible thinking patterns;
- Page 8: What happens in the brain when we think we are being lied to;
- Page 9: The ethically sensitive area of mental capacity and informed consent.

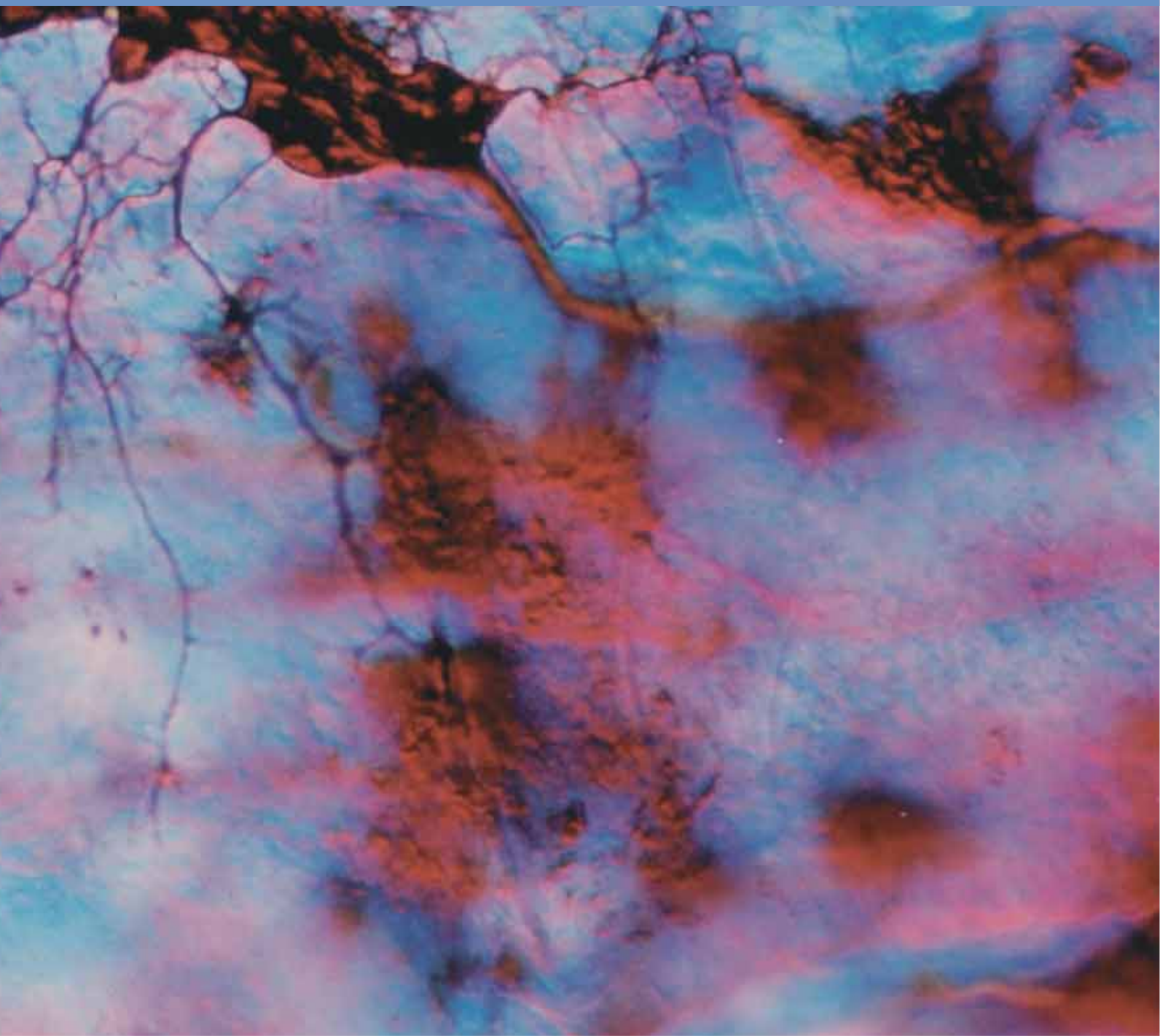
On a different scale, infectious organisms continue to threaten our health. A key issue is to understand how such diseases are spread, and the impact the environment has on their transmission:

- Page 10: Is global warming the cause of the resurgence of malaria in Africa?
- Page 10: A new twist to the spread of the *Leishmania* parasite;
- Page 11: Intercontinental spread of drug-resistant malaria;
- Page 11: How weather systems affect population density modelling.

Finally, we are gaining new insight into type 2 diabetes – which is leading to better treatments for this growing health problem:

- Page 12: How an ion channel mutation leads to diabetes in babies;
- Page 12: Type 2 diabetes caused by a single gene defect;
- Page 13: Possible targeted treatments for different forms of diabetes.

KNOWLEDGE



VANISHING GENES

The ‘gold standard’ genome has been published and is full of surprises.

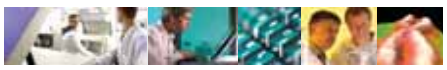
The International Human Genome Sequencing Consortium has published its scientific description of the finished human genome sequence – the ‘gold standard’ genome.

The current genome sequence contains 2.85 billion nucleotides and encompasses around 99 per cent of the euchromatic (or gene-containing) portion of the human genome. All but 341 of the 150 000 gaps present in the 2001 working draft sequence have been filled in, and the sequence is 99.99 per cent accurate – ten times more accurate than the original goal.

The most surprising finding – and one that hit the headlines worldwide – was the tiny number of protein-coding genes in the genome. The new analysis predicts that there are only 20–25 000 protein-coding genes in the genome, far fewer than the 100 000 confidently predicted a decade ago, and even the 30–40 000 estimated in 2001.

A further intriguing finding is the number of pseudogenes – genes that have lost their function and are gradually decaying away. Indeed, recent studies have already identified about 20 000 pseudogenes, and there may even be more ‘dead’ genes in our genome than ‘live’ ones.

The largest single contribution to the human genome sequence was made by the Wellcome Trust Sanger Institute. It is now trying to work out how so few genes can build something as complex as a human being.



L to R

Sequencing at the Wellcome Trust Sanger Institute.

Professor Lon Cardon, who is studying genetic variation in the UK population.

Professor Inderjeet Dokal (left) of Imperial College London.

Faulty chromosome repair is the cause of dyskeratosis congenita.

GENE GEOGRAPHY

DNA variation shows geographical clustering, which can distort the findings from large genetic studies.

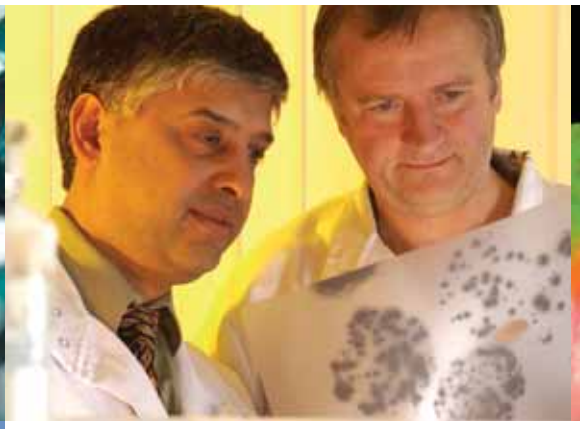
Finding that a particular genetic variant is more common in people with, say, diabetes than in those without is a clue that the gene may be increasing susceptibility to the disease. But is the association real, or are the different genetic make-ups of the people involved in the study – the population structure – clouding the results?

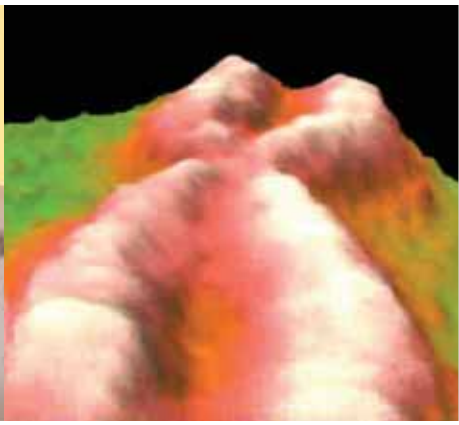
The extent of the problem was highlighted in a study by Professor Peter Donnelly and colleagues in Oxford and Montreal, which examined 15 000 DNA variations across three population groups (European American, African American and Asian) and within the Asian group.[1] Using statistical models, they found that the effects of population structure increase markedly with sample size, leading to false positive results and missed real effects.

This is a real headache for researchers searching for genetic factors that have only small effects on common diseases, who need to examine large numbers of people.

SHORT NOT SWEET

The length of telomeres can predict when a rare inherited disorder will strike.





Life would be much easier if we understood the genetic structure of the UK – and that is the goal of a new £2.3 million Wellcome-funded project being led by Sir Walter Bodmer, with Professor Donnelly and Professor Lon Cardon in Oxford. DNA will be collected from 3500 people, in 30 rural locations, whose parents and grandparents also lived in the same area.

The data and DNA samples will become a national resource for researchers to use to match their disease samples, thus reducing the chances of spurious associations. The resource will be particularly valuable with a number of very large population studies, such as the UK Biobank project, now underway.

1 *Marchini J, Cardon LR, Phillips MS, Donnelly P. The effects of human population structure on large genetic association studies. Nat Genet 2004; 36(5): 512–7*

Dyskeratosis congenita is a devastating disease that leads to premature ageing, bone marrow failure and cancer. Over the past few years, Professor Inderjeet Dokal and colleagues at Imperial College, London, have identified the genetic basis of this rare inherited disorder. Most recently, they have clarified one of its most perplexing features – why symptoms appear earlier in successive generations.[1]

Affecting one person per million, the mutations that cause dyskeratosis congenita disrupt telomeres – the tips of chromosomes. When chromosomes are copied during cell division, telomeres tend to get shorter. To compensate for this, actively dividing cells make an enzyme, telomerase, which repairs telomeres. Without it, cells tend to go through a certain number of divisions and then die.

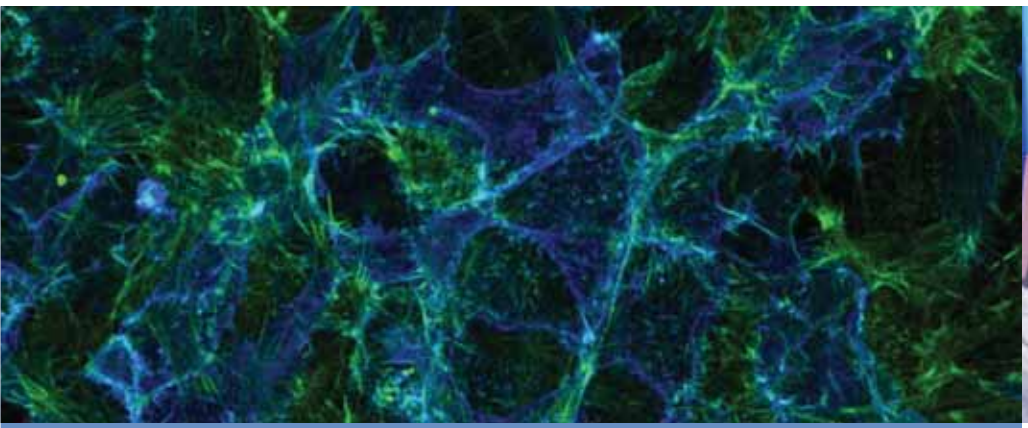
In dyskeratosis congenita, mutant genes (such as that coding for telomerase, *TERC*) mean that chromosome repair is faulty, and telomeres erode at an accelerated rate. Tissues with actively proliferating cells – gut, skin and bone marrow – are the first to be affected. The earliest sign of accelerated wear and tear is usually abnormal skin pigmentation followed, years later, by cancer, premature ageing and bone marrow failure, which often proves fatal.

But why do children's symptoms appear at an earlier age than in their parents? This phenomenon is also seen in some other genetic disorders, where a three-letter fragment of DNA multiplies in successive generations. What Professor Dokal and colleagues discovered was that the length of a patient's telomeres predicted when symptoms would first emerge – the shorter the telomere, the sooner symptoms appeared. As the telomeres get shorter in successive generations, so the disease strikes earlier.

1 *Vulliamy T et al. Disease anticipation is associated with progressive telomere shortening in families with dyskeratosis congenita due to mutations in TERC. Nat Genet 2004; 36(5): 447–9.*

STUCK IN A RUT

Serotonin depletion could explain the inflexible behaviours seen in people with psychiatric disorders.



People with obsessive–compulsive disorder (OCD) or schizophrenia, and those who abuse drugs, typically have something in common: inflexible behaviours. New research points the finger at deficiencies in the neurotransmitter serotonin: as Professor Trevor Robbins, Dr Angela Roberts and colleagues at the University of Cambridge have discovered, depletion of serotonin in the prefrontal cortex leads to very similar abnormalities.[1]

We need cognitive flexibility to cope with daily life. Both learning and 'unlearning' – changing tack in light of further experience – are critical to human experience. If that flexibility breaks down, a whole array of uncontrollable behaviours can emerge: toe tapping, finger drumming, tics, knocking or pacing. In humans, there are other signs that the brain has lost its flexibility: a rigid way of looking at things, a refusal to let go of an idea, or fanatical attitudes.

To explore the possible involvement of serotonin pathways, the Cambridge team depleted serotonin from the orbito-frontal cortex of marmosets. They then tested the animals' ability to solve both a visual learning task and a 'reverse learning' task.

Those marmosets whose serotonin had been depleted were stuck in a learning rut: they had no difficulty in acquiring knowledge, but made more mistakes in 'unlearning', suggesting that their cognitive flexibility had declined. A similar effect has been seen in human volunteers whose serotonin levels were reduced by dietary manipulation.

The finding that low serotonin in the prefrontal cortex inhibits flexible thinking provides insight into human psychiatric disorders. Not only will it help clinicians understand the difficulties experienced by patients with OCD, schizophrenia or drug-induced damage, but it also has significant implications for their treatment.

1 *Clarke H et al. Cognitive inflexibility following prefrontal serotonin depletion. Science 2004; 304: 878–80.*

LIVING BRAINS

Brain imaging is revealing brain activity during social interactions.

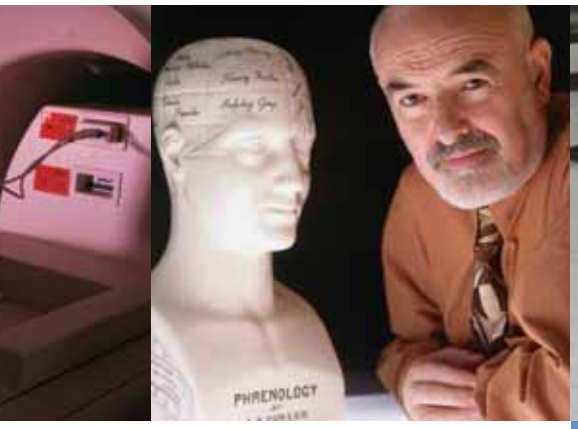
Humans are intensely social creatures. It is vital, then, that our brains can perceive and interpret socially relevant information. A team led by Professor Chris Frith at the Institute of Neurology in London has been locating the neural areas we engage during a range of social interactions.

One valuable skill is our ability to associate people with particular values or characteristics: are they honest, trustworthy and so on. To understand how the brain responds to people's moral standing, volunteers were scanned while they judged faces of people known to be fair or unfair players in the Prisoner's Dilemma game. The faces of fair players lit up specific neural circuits, confirming that there is an area in the brain dedicated to processing information about people's moral status.[1]

It is also useful to know whether a person is trying to deceive us. Working with collaborators in France, Professor Frith studied people who had been watching videos of actors lifting a box. The participants were asked to judge whether the actors were lifting a heavy box or just pretending. Again,

MAKING CHOICES

Patients should consent to medical treatment. But an inability to give reasoned consent may be more common than doctors appreciate.



specific areas of the brain lit up when people thought they were being deceived.[2] These areas are linked to emotional responses, which fits with the fact that we find deception emotionally distressing.

Empathy is a unique human attribute, a 'social glue' that allows us to understand what others feel. To explore the neural basis of empathy, Professor Frith's group compared brain activity in volunteers either receiving a painful stimulus or witnessing their loved ones experience pain.

Painful stimuli triggered both physical and emotional areas of the brain, but witnessing someone else in pain triggered just the emotional response.[3] So we cannot share a loved one's physical pain, but we can share a similar emotional experience.

1 *Singer T et al. Brain responses to the acquired moral status of faces. Neuron 2004; 41(4): 653–62.*

2 *Grezes J, Frith C, Passingham RE. Brain mechanisms for inferring deceit in the actions of others. J Neurosci 2004; 24(24): 5500–5.*

3 *Singer T et al. Empathy for pain involves the affective but not sensory components of pain. Science 2004; 303(5661): 1157–62.*

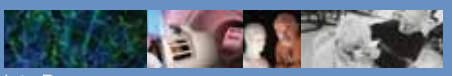
To consent to medical treatment, patients should be making voluntary and informed choices, and have the mental capacity to make a decision. Patients lack mental capacity when they cannot understand the information being given to them, or use it to decide on a course of action, or are unable to communicate their decision. Usually, mental capacity is taken as read unless the patient's difficulties are very obvious. However, recent research suggests that the numbers of mentally incapacitated patients may be being significantly underestimated.

Professor Matthew Hotopf and colleagues at the Institute of Psychiatry, Preston and Yale tested the degree of cognitive impairment of patients admitted to a London hospital. Some 31 per cent of inpatients were considered to lack mental capacity. However, when clinical teams interviewed inpatients, they rated just 8 per cent as lacking mental capacity.[1]

Most patients probably rely on doctors to make the most appropriate decision for them. A need to assess mental capacity in a medically pressing situation could present significant difficulties to the medical profession. On the other hand, there is clearly also a need to protect vulnerable patients, particularly when major – and irreversible – medical decisions are being made.

These kinds of issues are being considered in the UK's draft Mental Capacity Bill. The researchers suggest that, even if legislation is seen as too heavy handed, the issue of patients' mental capacity should be given more attention by doctors.

1 *Raymont V et al. Prevalence of mental incapacity in medical inpatients and associated risk factors: cross-sectional study. Lancet 2004; 364(9443): 1421–7.*



L to R

Neurons in the brain.

Brain imaging can reveal the neural areas used during social interactions.

Professor Chris Frith of the Institute of Neurology, London.

People with Alzheimer's disease may lack the mental capacity to give informed consent.

HEATED DISCUSSION

Global warming does not appear to have driven the rise in malaria across Africa.

A belief that global warming is responsible for the recent resurgence of malaria is misguided, according to an analysis of 80 years of climate data in Africa. The analysis, led by Dr Simon Hay and colleagues at the University of Oxford, found no evidence that climate had changed the suitability for malaria transmission across Africa.[1]

After decades in decline, malaria has made a comeback in many parts of Africa. Malaria mortality in young children almost doubled from the 1980s to the 1990s. The disease now causes around 3000 deaths each day.

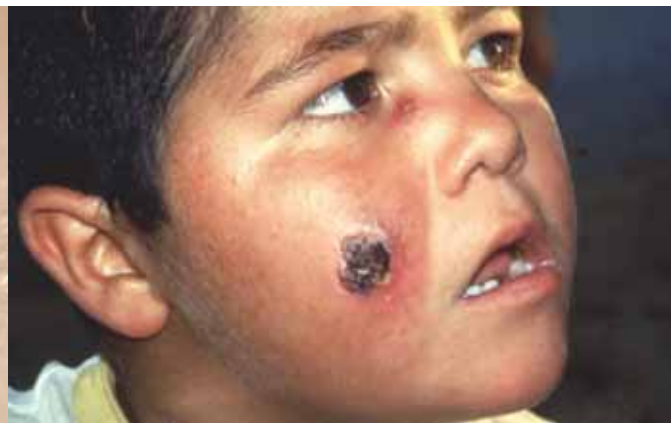
To find out whether this resurgence could be linked to climate, Dr Hay's team used a climate-driven biological model of malaria transmission to show that changing patterns of temperature and rainfall between 1911 and 1995 had not made for a more hospitable climate for mosquitoes and malaria. In a couple of regions, shifts in malaria transmission suitability were linked to changes in rainfall.

Rather than global trends, the researchers emphasise that local factors – migration, health service provision and, particularly, the rise in drug resistance – are likely to have a bigger impact on malaria transmission.

1 *Small J, Goetz SJ, Hay SI. Climatic suitability for malaria transmission in Africa, 1911–1995. Proc Natl Acad Sci USA 2003; 100(26): 15341–5.*

VOMITING SAND FLIES

By creating a sticky 'hairball' in the sand fly gut, the *Leishmania* parasite promotes its transmission – and ensures its survival in its new host.



A bite from an infected sand fly is all it takes to catch the tropical disease leishmaniasis. Yet exactly how the sand fly delivers its lethal cargo has, until recently, remained a mystery. Now Wellcome-funded scientists have discovered a key aspect of transmission: a sticky gel secreted by the parasite and regurgitated by the sand fly.

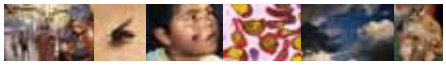
Leishmaniasis is a parasitic disease affecting about 12 million people worldwide, causing disfiguring ulcers and, in severe cases, death. Major epidemics have occurred in India and Bangladesh, and it is a scourge of migrating populations, such as those affected by civil war.

Infection starts when a sand fly bite injects the single-celled parasite *Leishmania*, along with sand fly saliva. However, a team led by Dr Paul Bates at the Liverpool School of Tropical Medicine has discovered that *Leishmania* is not a passive passenger in this process. It produces a gelatinous secretion that forms a thick plug in the sand fly's gut. This 'hairball' stops the fly from feeding properly and, as a result, the insect bites repeatedly, and for longer, increasing the likelihood of transmission.[1]

As well as manipulating the behaviour of its insect vector, the parasite secretion also affects its new human host. It includes a long, sugar-coated, phosphorylated protein (filamentous proteophosphoglycan, fPPG), which is regurgitated by the sand fly and injected into the victim. The fPPG appears to promote parasite survival and exacerbates disease.

The research has important implications. It immediately suggests possible new strategies for tackling transmission, by blocking the action of the gel. But it also highlights how interactions between all the key players – parasite, vector and host – need to be studied to give a clear view of disease transmission.

1 *Rogers ME et al. Transmission of cutaneous leishmaniasis by sand flies is enhanced by regurgitation of fPPG. Nature 2004; 430: 463–7.*



L to R

Climate is unlikely to play a part in the malaria resurgence in Africa.

Sand flies regurgitate a sticky gel secreted by the *Leishmania* parasite which makes infection more likely.

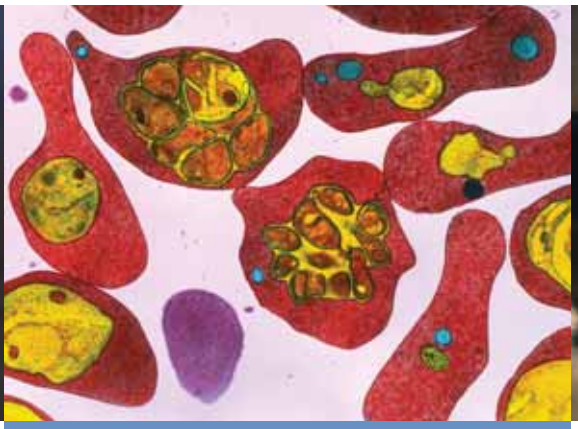
Boy with an ulcer caused by *Leishmania* infection.

Malaria-infected red blood cells.

Soay sheep populations on a remote Scottish island are sensitive to weather conditions.

UNWANTED IMPORT

Scientists have tracked down the origins of Africa's drug-resistant malaria parasites.



Scientists co-funded by the Wellcome Trust and the US National Institutes of Health have uncovered evidence that drug-resistant malaria in Africa was imported from South-east Asia.

The boom in air travel has meant that malaria travels the globe too. Every year 30 000 malaria cases are imported into industrialised countries. The figure for Africa is unknown, but is likely to be substantial.

Today pyrimethamine (coformulated with sulphadoxine) is a mainstay of malaria treatment. But mutations in a gene known as *dhfr* (dihydrofolate reductase) allow the parasite to survive. Parasites have up to four mutations in the *dhfr* gene – the more they have, the hardier they are; with the full complement of four, they are resistant to all drugs targeting this enzyme.

By genotyping the *dhfr* gene and surrounding DNA, Dr Cally Roper, London School of Hygiene and Tropical Medicine, and collaborators have shown that the most resistant parasites in Africa did not arise there, but originated in South-east Asia.[1] The parasite with four mutations has not yet been seen in Africa, but if malaria parasites are travelling from Asia to Africa, then there is every chance it could be imported and become established.

1 *Roper C et al. Intercontinental spread of pyrimethamine-resistant malaria. Science 2004; 305(5687): 1124.*

SHEEP DIP

In a study of periodic sheep decimations, seasonal fluctuations in bad weather may be better at predicting mortality than local climate.

Our lives and those of other species are inextricably entwined – we are all part of a natural system. Climate obviously has an enormous impact on this system, yet the links between climate and population numbers are rarely well understood. With current fears about climate instability, this is becoming a matter of growing concern.

A team of scientists led by Dr Bryan Grenfell at the University of Cambridge has spent 20 years exploring the impact of climatic factors on a natural population – Soay sheep living on a remote Scottish island. This sheep population 'crashes' every three to four years, when 70 per cent of the animals perish during winter. They typically die from starvation, either because they burn up more energy to keep warm or because there is little grass left to graze on.

Dr Grenfell's team has been trying to find out why this population is so unstable. They looked for correlations with a range of possible causes and found that foul weather over a three-month period was the strongest predictor of a population crash. Surprisingly, local weather variables failed to predict these deaths. Instead, variation in a large-scale, seasonal climate index spanning several months – the North Atlantic Oscillation – provided the most reliable forecast.

A harsh spell – heavy rain, strong winds or low temperatures – at any time during a three-month period was associated with high sheep mortality, either immediately or after a few days. This appears to be obscured in the local climate data, but is captured in crude form by the North Atlantic Oscillation.[1]

These counter-intuitive results suggest that, in order to predict population changes in response to ecological stresses such as climate change, large-scale, seasonal climate indices spanning several months – such as the North Atlantic Oscillation – may be preferable to local records. In the longer term, though, the need is to identify more specifically which local factors are ecologically most important.

1 *Hallett TB et al. Why large-scale climate indices seem to predict ecological processes better than local weather. Nature 2004; 430: 71–5.*

Data collection has been funded by the Wellcome Trust, the Natural Environment Research Council and the Biotechnology and Biological Sciences Research Council.

CROSS-CHANNEL THERAPY

Thanks to the discovery of the precise cause of infant diabetes, young children can be given medication rather than insulin injections.

Permanent neonatal diabetes is a severe, but fortunately rare form of diabetes. The causes have been largely unknown, but researchers have now found that many cases are due to a genetic mutation that disrupts control of insulin-releasing beta cells.[1] The research also suggests that sulfonylurea drugs typically used by adults with type 2 diabetes may be a useful treatment.

In neonatal diabetes, a lack of insulin becomes apparent in the first three months after birth. Insulin treatment is required for life.

Insulin is produced by beta cells in the pancreas, which sense changes in the blood's glucose levels, and alter their secretion of insulin accordingly. Crucial to this process is an ion channel – the ATP-sensitive potassium channel (K_{ATP} channel) – that spans the membrane of beta cells.

If glucose levels go up, more ATP is made in the cell; this ATP binds to the channel and closes it, thereby reducing potassium loss and depolarising the beta-cell membrane. This causes an influx of calcium, which triggers the release of insulin.

Professors Andrew Hattersley (Peninsula Medical School, Exeter) and Frances Ashcroft (University of Oxford) and colleagues found mutations in the gene encoding Kir6.2, a key subunit of the potassium channel, in ten out of 29 infants with neonatal diabetes. The mutation stops the channel responding to ATP, so it never closes totally. The beta cell constantly leaks potassium, and it cannot secrete insulin.

Sulfonylurea drugs are known to act on the K_{ATP} channel, and some patients with mutant Kir6.2 did secrete insulin when given such drugs. Follow-up studies have confirmed that children with Kir6.2 mutations no longer need insulin injections when given sulfonylurea drugs.

1 *Gloyn AL et al. Activating mutations in the gene encoding the ATP-sensitive potassium-channel subunit Kir6.2 and permanent neonatal diabetes. N Engl J Med 2004; 350: 1838–49.*

DISSECTING DIABETES

The mechanisms of type 2 (adult-onset) diabetes are beginning to be unravelled.

If the body's tissues become insensitive to the action of insulin, rising blood sugar levels have a variety of damaging effects – leading to the symptoms of type 2 diabetes.

While most cases are thought to involve interactions between many genes and environmental risk factors, diabetes can sometimes be caused by a mutation in a single gene.

Dr Inês Barroso (Wellcome Trust Sanger Institute), Professor Steve O'Rahilly (University of Cambridge) and colleagues found just such a mutation in a gene called *AKT2*. AKT2 protein is a crucial component of the cell's systems for regulating cell growth, survival and metabolism. This study reveals its central role in cellular responses to insulin.[1]

Mutations in *AKT2* are unlikely to explain most cases of diabetes. A more likely scenario is that other subtle variations in or around the *AKT2* gene contribute to the common form of diabetes. The team is now hunting for variants in populations with type 2 diabetes to explore this possibility.

1 *George S et al. A family with severe insulin resistance and diabetes due to a mutation in AKT2. Science 2004; 304: 1325–8.*

TAILORED TREATMENT

Two forms of diabetes respond very differently to drugs – pointing the way to tailored drug treatments based on genetic make-up.

The genetic make-up of patients with type 2 diabetes has been found to affect their sensitivity to drug treatments. The findings could lead to more tailored treatments, and is an early example of a pharmaco-genomic approach to medicine.

Type 2 diabetes is an adult-onset form of diabetes that frequently requires treatment with drugs. The most commonly used drugs are sulphonylureas or metformin, which increase insulin secretion or reduce insulin resistance, respectively. Treatment guidelines assume that all patients respond similarly, even though the underlying causes of the diabetes may be quite different.

Professor Andrew Hattersley, Ewan Pearson and colleagues at the Peninsula Medical School, Exeter, compared the drug responses of people with a specific form of diabetes caused by mutations in the *HNF-1α* gene with those in other patients who had diabetes of unknown cause.

They found that people with *HNF-1α* diabetes responded differently to the two drugs: patients with *HNF-1α* diabetes had around a fivefold greater response to sulphonylureas than to metformin, while patients in the other group responded similarly to the two treatments.[1] The difference arose because the response to sulphonylureas in *HNF-1α* patients was fourfold greater than in the second group, even though the former used a lower drug dose to avoid hypoglycaemia.

As the genetic basis of type 2 diabetes is untangled, it is likely that further different forms of the disease will be identified, each with a particular pattern of responses to diabetes drugs. If so, drugs and the doses used could then be refined according to a patient's genetic background.

1 *Pearson ER et al. Genetic cause of hyperglycaemia and response to treatment in diabetes. Lancet 2003; 362: 1275–81.*

L to R

Laboratory research into diabetes is helping to change treatments.

Inês Barroso (right), who is studying the role of the *AKT2* gene in type 2 diabetes.

Diabetes can cause damage to the retina.

Professor Andrew Hattersley (left) examines a patient's eye.

BALANCING ACTS

With fears of an 'obesity epidemic' growing, it is crucial we learn more about the metabolic processes underlying our energy balance, and how they can trigger disease.

- The 'metabolic syndrome' (a combination of high blood pressure, insulin resistance and impaired lipid metabolism) is usually associated with obesity. An international team including Professors John Mullins and Jonathan Seckl in Edinburgh has shown that high levels of glucocorticoid hormone regeneration in the liver can give rise to the metabolic syndrome in the absence of obesity.[1] This could occur in people of normal weight who have symptoms of metabolic syndrome, such as those with 'fatty liver' disease.

- A mammalian enzyme known as PASK is related to a bacterial oxygen sensor, FixL. A team led by Professor Guy Rutter in Bristol has discovered that PASK is also a sensor: in pancreatic beta cells, it responds to glucose concentrations, regulating key beta-cell genes.[2] PASK thus appears to play a role in the body's response to changing nutrient levels.

- CBS domains are tandemly repeated 60 amino acid domains found in most living organisms. Although mutations in CBS gene sequences cause a range of inherited diseases, the domain's role has been unclear. Professor Grahame Hardie and colleagues at Dundee have now shown that the domains bind adenosyl compounds (such as AMP, ATP or S-adenosyl methionine). In many cases, including AMPK, a key energy sensor in the body, the domains appear to link the protein's activity to the cell's energy status.[3]

1 *Paterson JM et al. Proc Natl Acad Sci USA 2004; 101: 7088–93.*

2 *da Silva Xavier G et al. Proc Natl Acad Sci USA 2004; 101: 8319–24.*

3 *Scott JW et al. J Clin Invest 2004; 113: 274–84.*

RESOURCES

Human resources: meeting training and career development needs of researchers.
Physical resources: building suitable conditions for research.

Wellcome-funded research fellows have produced many exciting research discoveries this year. Articles here summarise two examples, both of which could have major medical implications:

- Page 16: Huntington's disease is currently untreatable but a study in mice has suggested a possible new therapeutic approach;
- Page 17: Small offspring often go through 'catch-up' growth – which could affect their long-term health.

Historians have quite different resource needs from scientists:

- Page 16: One danger is that source materials literally disappear. A special Wellcome scheme is helping to ensure that irreplaceable papers are secured for future generations;
- Page 18: The Guildford Archiving Project is ensuring that internal tobacco industry papers remain accessible on the web, a valuable resource for anyone studying industry tactics and behaviour.

Through the Joint Infrastructure Fund and Science Research Investment Fund, two partnerships with the UK Government, the Wellcome Trust provided £450 million to tackle deficiencies in the UK's academic research infrastructure:

- Page 18: Two internationally significant facilities opened in Oxford this year. They are not just a better working environment but are also changing the way scientists interact and conduct research.

Finally, research itself generates biological resources. Sharing these provides a fillip for research:

- Page 19: Genetic resources are accelerating research on mouse models and making the frog an even more useful tool.

HUNTINGTON'S HOPE

Work on fruit flies and mice has identified a potential therapeutic strategy for Huntington's disease.

A drug normally used to prevent organ rejection could stop a toxic protein accumulating in the brains of people with Huntington's disease. Researchers at the University of Cambridge, led by Wellcome Trust Senior Research Fellow Dr David Rubinsztein, have discovered that the drug rapamycin reduces the effects of the Huntington's disease mutation in cultured cells, fruit flies and mice, raising hopes that it could be used to treat this nervous system disorder in humans.[1]

Huntington's disease is a rare, inherited disease characterised by abnormal body movements and impaired cognition; symptoms typically appear in middle age.

It is caused by a faulty gene that changes the huntingtin protein into a toxic product which accumulates in the brain and interferes with brain cell function. There are genetic tests to detect the faulty Huntington's gene, but there is no cure or effective treatment.

The Cambridge researchers discovered that rapamycin may be able to protect the brain by cranking up 'autophagy' – one of the ways in which the cell can dispose of proteins. In their models, when used before too much toxic protein accumulated, rapamycin funnelled mutant huntingtin into compartments of the cell that digest it.

The researchers found that a rapamycin analogue, CCI-779, slowed down neurodegeneration in a fly model of the disease, while in the mouse, it improved performance on four different behavioural tasks.

CCI-779 has the advantage that it is designed for long-term use. The drug is currently in phase 2 and phase 3 clinical trials for cancer, though more studies would be needed before human trials were begun for Huntington's.

1 *Ravikumar B et al. Inhibition of mTOR induces autophagy and reduces toxicity of polyglutamine expansions in fly and mouse models of Huntington disease. Nat Genet 2004; 36(6): 585–95.*

SHELF PRESERVATION

Material relating to key figures in Edinburgh's distinguished medical history has been preserved.

Those who cannot remember the past, said philosopher George Santayana, are condemned to repeat it. Historical enquiry aims not just to remember the past but to understand it and, perhaps, to ensure that we learn from it rather than repeat it.

The Research Resources in Medical History scheme was set up to ensure that significant collections are preserved and opened up for study, through use of new conservation and preservation technologies and cataloguing. Some £2 million has been awarded so far, to support 58 projects.

In Edinburgh for example, Lothian Health Services Archive has preserved the Royal Infirmary of Edinburgh case notes of two leading mid-20th century medics – Derrick Dunlop, Christison Professor of Therapeutics and Clinical Medicine from 1936 to 1952, and James Learmonth, University Professor of Surgery from 1939 to 1956, who included George VI among his patients.

CATCH-UP GROWTH

Feeding up lightweight babies may be storing up longer-term problems.

The collection includes some 37 000 case notes which provide a fascinating glimpse of day-to-day life on the wards during a crucial period of change in medicine. As such they help illuminate everything from changing medical education to shifts in attitudes towards experimentation on patients. Edinburgh was central to many of these developments.

In an earlier project, the archive restored material from two other key characters in Edinburgh medicine – Edwin Bramwell, widely regarded as the founder of Edinburgh postgraduate medical education, and Norman Dott, the first medic after Joseph Lister to receive the Freedom of the City of Edinburgh.

Without preservation, these collections might have been lost for ever – victim to the ravages of time and rusty paper-clips. Now, historically valuable material has been carefully conserved and secured for future generations.

Parents take pride in seeing their tiny newborns fill out into chubby toddlers. But for very small babies, rapid 'catch-up' growth may not be as healthy as it seems – a study of mice suggests it could actually be shortening their lifespan.[1]

The startling results were obtained by Dr Susan Ozanne, a Research Career Development Fellow,* and Professor Nick Hales at the University of Cambridge. They monitored the longevity of mice whose mothers were fed a poorly nutritious diet during their fetal development or just after birth. They also tested the impact of a 'cafeteria-style' diet after weaning.

The pups that lived longest were those that were well fed in the womb and then suckled by mothers on a relatively low-quality diet. Their lifespans were further enhanced if they were not given a cafeteria-style diet, rich in sugar and fat, after weaning.

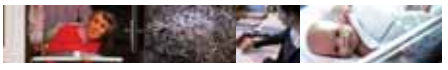
At the other extreme, the pups that lived the shortest lives were those that grew poorly in the womb, but were subsequently suckled by mice on a high-quality diet. Their lifespans were cut further if they ate obesity-inducing food after weaning.

Low birth weight is already known to predispose to late-onset conditions such as high blood pressure and diabetes. These results suggest that the normal reaction to low birth weights – a period of catch-up growth to bring infants up to a normal size – may contribute to these detrimental long-term effects.

The results could have implications for babies born underweight, who are usually fed a rich diet to accelerate growth. In view of the findings, the researchers argue that more attention needs to be paid to the nutrition of human infants in the early years.

1 *Ozanne SE, Hales CN. Lifespan: catch-up growth and obesity in male mice. Nature 2004; 427(6973): 411–2.*

**Dr Ozanne is now a British Heart Foundation Lecturer at the University of Cambridge.*



L to R

Rapamycin analogues could help people with Huntington's disease.

An archivist from the Lothian Health Services Archive.

Paper-clips can cause significant damage to archive collections.

A period of 'catch-up' growth for underweight newborns could damage their long-term health.

OPENING TIME

The Wellcome Trust's recent infrastructure investment is now bearing rich fruit.

Seventeen new buildings funded by two high-profile Wellcome Trust partnerships with the UK Government – the £750 million Joint Infrastructure Fund (JIF) and £1 billion Science Research Investment Fund (SRIF) – were opened or occupied during the year. Two buildings in Oxford illustrate how new facilities are supporting larger-scale and more integrated approaches to biomedical research.

In February 2004, HRH The Queen and HRH The Duke of Edinburgh officially opened the new £60 million Chemistry Research Laboratory at the University of Oxford. With nearly 17 000 square metres of laboratory and office space, it is one of the largest research departments in the world. Facilities include 11 nuclear magnetic resonance machines, 11 mass spectrometers and an X-ray crystallography facility.

In September 2004, Nobel Prizewinner James Watson opened the Henry Wellcome Building of Gene Function. The new £19 million building has been designed to encourage greater interaction between researchers in genetics, human anatomy and physiology and experts in important new fields such as bioinformatics and biostatistics.

This will allow researchers to mount a united effort to discover how genes cause disease – and to focus on ground-breaking treatments for many important diseases.

TOBACCO ARCHIVE

A massive photocopying operation is ensuring a tobacco giant's inner workings will remain in the public domain.

A website containing 1 million pages of formerly secret documents from the world's second-largest tobacco company, British American Tobacco (BAT), went online in October 2004. Researchers and the public will now have free and unfettered access to information relating to BAT's activities, which reveal disturbing evidence of the industry's efforts to thwart anti-smoking initiatives and market cigarettes to vulnerable populations.

The website is a joint project, known as the Guildford Archiving Project, between the London School of Hygiene and Tropical Medicine, the University of California San Francisco and the Mayo Clinic. BAT was forced to make the documents public in 1998 after a legal settlement by a US court against a number of tobacco companies. The settlement ruled that all corporate documents submitted during the 'discovery' process for the case must be made available via two archives, one at Guildford, UK (operated by BAT), and the other at Minnesota, USA (operated by an independent paralegal firm).

Information currently on the new website relates to company practice from the early 1900s to the mid-1990s. Internal correspondence, research and reports offer a unique insight into the strategies used by tobacco companies to promote themselves and their products, including influencing scientific research and public policy, targeting marketing, advertising and promotion activities at young people and women, and the strategic exploitation of cigarette smuggling. The documents reveal how BAT has targeted emerging markets in the developing world, including, for example, its intention to market to "dirt poor little black farmers" and "low income low literacy" people in South Asia and the Middle East.

Crucially, the site will preserve the collection beyond 2009, when BAT is allowed to close the depository.

The Guildford Archiving Project has been funded by the Wellcome Trust, the Flight Attendant Medical Research Institute, Cancer Research UK, Health Canada and the American Heart Association. The BAT document archive website can be accessed at www.bat.library.ucsf.edu

L to R

Aerial view of the new chemistry labs at Oxford.

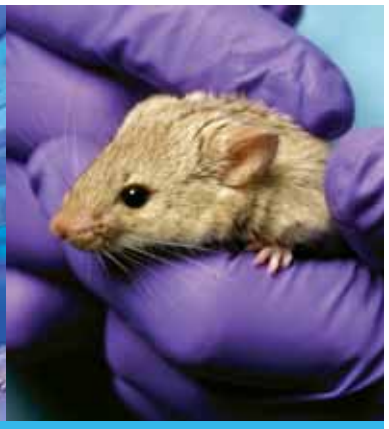
Nuisance smokers, by Henry Heath, 1827.

Allan Bradley of the Wellcome Trust Sanger Institute.

Research on mice is providing valuable insight into important biological processes.

SHARING SUCCESS

Resources created for a laboratory's own research are also being shared to benefit the wider community.



Studies in model organisms are providing many insights into the biological roles of genes. Thanks to genome sequencing projects, gene-based approaches are wildly popular. Now, new techniques are being developed to enable even greater use to be made of genomic reources.

At the Wellcome Trust Sanger Institute, Dr Allan Bradley's team has developed a technique to speed up research on mice. To explore the function of a gene, researchers often study the effects of mutations that disrupt or change the gene. Producing such mutations can be time-consuming, however.

Dr Bradley's team has developed a new high-throughput method to alter genes – MICER (Mutagenic Insertion and Chromosome Engineering Resource). The MICER resource[1] consists of a large collection (library) of DNA fragments, corresponding to parts of mouse genes, which can be used to target and disrupt mouse genes (or even insert specific new sequences). Some 100 000 different MICER vectors are available from the Sanger Institute. Another technical advance from the Bradley lab makes these vectors even more useful. Mammalian cells carry two copies of each gene, and the new method ensures that both copies are disrupted.[2]

Meanwhile, researchers in Cambridge have launched a new genomics resource for the frog *Xenopus tropicalis*. The African clawed frog *Xenopus laevis* has long been a favourite of biologists. Unfortunately, having a duplicated genome, it is not good for genetic studies, and it takes more than a year to reach sexual maturity. Conveniently, *Xenopus tropicalis* is diploid and matures in just four months.

To speed up research into *X. tropicalis* – a field that is still in its infancy – Dr Enrique Amaya, Dr Nancy Papalopulu and Professor Jim Smith at the Wellcome/Cancer Research UK Gurdon Institute in Cambridge, in collaboration with the Sanger Institute, have sifted through more than 200 000 fragments of the *X. tropicalis* genome and identified 7000 genes.[3] Full-length clones are available through the MRC Geneservice, while the Gurdon Institute has also produced a database describing the sequences and associated genomic information.

Such resources should help kick-start a potentially valuable field of research and add to the pantheon of experimental organisms used in research around the globe.

1 *Adams DJ et al. Mutagenic Insertion and Chromosome Engineering Resource (MICER). Nat Genet 2004; 36(8): 867–71.*

2 *Guo G, Wang W, Bradley A. Mismatch repair genes identified using genetic screens in Blm-deficient embryonic stem cells Nature 2004; 429(6994): 891–5.*

3 *Gilchrist M et al. Defining a large set of full length clones from a Xenopus tropicalis EST project. Dev Biol 2004; 271: 498–516. (www.gurdon.cam.ac.uk/informatics/Xenopus.html)*

BEYOND THE HELIX

We now know that humans have only about 23 000 genes. Our biological complexity is thus more to do with how those genes are used – how and where they are turned on and off. Many different mechanisms of gene control are being discovered – and the higher-order arrangement of DNA is turning out to be particularly important.

- In budding yeast, Professor Nick Proudfoot and colleagues at the University of Oxford found that the DNA of active genes was not linear, as typically drawn in textbooks, but was looped, with control proteins shared between the start and end points of the gene. This looping was essential to the activation of the gene.[1]

- RNA interference (RNAi) is an exciting area of study, as these tiny RNAs can silence genes very effectively. Generally, they act by triggering a massive destruction of the RNA intermediate (messenger RNA) read from a gene, but Dr Vera Schramke and Professor Robin Allshire, a Wellcome Principal Research Fellow at the Wellcome Trust Centre for Cell Biology, University of Edinburgh, have discovered that small RNA molecules can somehow drive the formation of 'closed', tightly packed DNA conformation and shut down genes.[2]

- A collaboration led by Dr Nigel Carter at the Wellcome Trust Sanger Institute and Dr Wendy Bickmore at the MRC Human Genetics Unit in Edinburgh has examined DNA conformation across the entire human genome. As expected, active genes lay in regions of open chromatin, and inactive genes in tightly packed chromatin. But there were exceptions: some genes in open chromatin were inactive, while some in compact chromatin were active.[3]

1 *O'Sullivan JM et al. Nat Genet 2004; 36(9): 1014–8.*

2 *Schramke V, Allshire R. Science 2003; 301: 1069–74.*

3 *Gilbert N et al. Cell 2004; 118(5): 555–66.*

Promoting patient-oriented and health services research. Advancing the dissemination and exploitation of the results of Trust-funded research.

'Translation' is all about making a practical difference – generating and using new knowledge to provide health benefits to people. There are many ways in which those benefits may be realised:

- Page 22: Genetic analysis of cancers is revealing new drug targets;
- Page 22: A 'dipstick' diagnostic tool for *Chlamydia* is being taken up and used, and adapted for other infections;
- Page 23: Field tests of malaria diagnostic kits confirm their practical value;
- Page 23: Studies of deadly avian flu are helping us prepare for further outbreaks.

Malaria continues to exact a devastating toll, particularly among young children in Africa. Around 3000 children in Africa die every day. Clinical research is tackling several aspects of the disease:

- Page 24: Artemisinin combination therapy – drug treatment pioneered in South-east Asia – could have a major impact if widely used in Africa;
- Page 24: Unravelling the complex immune response to the malaria parasite;
- Page 25: How the parasite becomes resistant to the antimalarial drug mefloquine;
- Page 25: Why cerebral malaria isn't always what it seems.

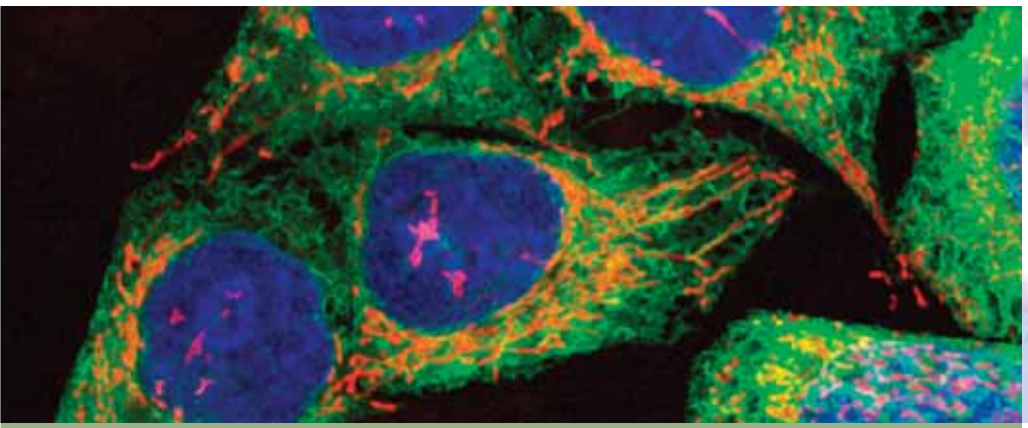
The most direct benefits, of course, come from studies on patients. Wellcome-funded clinical research is continuing to suggest and test new therapies, in the UK and in developing countries:

- Page 26: In Vietnam, steroids have been shown to enhance survival after tuberculous meningitis infection;
- Page 26: In the UK, the Wellcome Trust's Clinical Research Facilities have begun to deliver a stream of important findings and are having a significant local impact;
- Page 27: The 'Myskin' smart dressing was launched during the year for burns patients.

TRANSLATION

GENE TARGETS

The identification of genes responsible for particular forms of cancer is opening up the possibility of targeted cancer therapies.



The Cancer Genome Project at the Wellcome Trust Sanger Institute has, for the first time, identified mutations within the *ERBB2* gene in human lung cancer.[1] The mutations, found in 10 per cent of a specific type of lung cancer called adenocarcinoma, cause the ERBB2 protein to be permanently active. These cancers may be treatable with an existing drug, trastuzumab.

The Cancer Genome Project team is cataloguing the changes within the genomes of cancer cells and identifying the mutant genes responsible for the disease. Lung cancer is a particularly important target, as it is the second most common form of cancer in the UK, after breast cancer.

The *ERBB2* gene (also known as *HER2* or *Neu*) is present in multiple copies in 20 per cent of breast cancers and less often in other cancers. The discovery that *ERBB2* mutations can also cause lung cancer is significant as the drug trastuzumab (marketed as Herceptin) targets ERBB2 and is very effective for the treatment of breast cancers with multiple copies of the *ERBB2* gene. Previous trials of trastuzumab for lung cancer were not successful, but the Cancer Genome Project team proposes that it, or another drug that targets ERBB2, should be retested in cases of lung adenocarcinoma with *ERBB2* mutations.

This finding follows the team's discovery in 2002 that the *BRAF* gene is mutated in 70 per cent of cases of malignant melanoma, a potentially lethal form of skin cancer. The mutations appear to produce a permanently activated BRAF protein. With Wellcome Trust Technology Transfer funding, the team has been searching for molecules that can switch off the mutant protein – and several promising leads have emerged.

1 *Stephens P et al. Lung cancer: intragenic ERBB2 kinase mutations in tumours. Nature 2004; 431: 525–6.*

TESTING TIMES

The dipstick diagnostic test for *Chlamydia* is being widely adopted.

The rapid testing technology created by Dr Helen Lee and colleagues at the University of Cambridge has moved on apace since the team completed the development of its *Chlamydia* 'Firstburst' dipstick a year ago.

This rapid test provoked interest from organisations around the world, including the American Red Cross, a major pharmacy chain, as well as a number of diagnostic companies and non-profit organisations that deal with women's sexual health. The first-void urine collector the group developed received the Best Medical Futures Diagnostic Innovation award.

The *Chlamydia* rapid test was recently adapted to detect trachoma, an eye disease that affects 150 million people worldwide and causes 6 million cases of blindness or visual impairment. Field trials on schoolchildren in Tanzania have produced excellent results.

Now Dr Lee's Diagnostics Development Unit, based at Addenbrooke's Hospital, is developing a triplex rapid test capable of detecting HIV, hepatitis B and hepatitis C viruses in the same sample. The test, supported by a Wellcome Technology Transfer Award, will be used to improve blood safety in developing countries.

FIELD TEST

Handy diagnostic tests for malaria can be used easily in the field, new research suggests.

A trial of two malaria diagnostic kits has shown that error rates are low and that they can be used with minimal training.[1] These kinds of diagnostic tests thus seem highly suitable for use in the field.

Diagnosing malaria quickly can make a huge difference to the treatment of the disease. The standard method of diagnosis, looking at blood smears under the microscope to spot parasites, is time-consuming, expensive and requires extensive training.

With help from the Wellcome Trust's research programme in Thailand, Dr Mayfong Mayxay and colleagues in rural Laos have trialled two tests, ParacheckPf and OptiMAL, which use 'dipsticks' to test blood samples for the presence of proteins from the parasite. After one hour of training, 64 village health volunteers, with no previous laboratory experience, performed two different tests accurately.

The researchers then followed six volunteers over ten months to check the accuracy of the testing and how often retraining was required. Error rates were extremely low compared to microscopy (less than 2 per cent), and minimal training was required.

1 *Mayxay M et al. An assessment of the use of malaria rapid tests by village health volunteers in rural Laos. Trop Med Int Health 2004; 9: 325–9.*

FLU FEARS

South-east Asia needs its own local high-quality clinical centres to tackle the perils of avian flu.

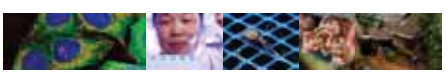
People infected with the deadly avian influenza virus strain H5N1 were treated and studied at Wellcome-supported facilities in Vietnam. Having excellent clinical and laboratory facilities in a country directly affected by avian flu is an enormous benefit with a disease that is so rapidly lethal and of such global public health importance.

During late 2003 and early 2004, the avian influenza virus H5N1 swept through poultry stocks across Asia. Most worryingly, it also spread to some people, causing a severe and often fatal respiratory illness.

There are constant fears that this strain will spread from birds to humans. An even greater worry is that the virus adapts to human hosts, and begins to be transmitted from person to person – in a manner similar to the 'Spanish flu' in 1918. It is vital, therefore, that we learn as much as possible about the virus and its effects on people.

The Hospital for Tropical Diseases and the Clinical Sciences Research Institute supported by the Wellcome Trust in Ho Chi Minh City was chosen by the Vietnamese government as the national centre for admission of all suspected cases and for the clinical and scientific analysis of the virus. The detailed examinations of ten patients infected with the virus (eight of whom died) were published by the *New England Journal of Medicine*,[1] and the speed of publication – only a few weeks after the patients were admitted to hospital – highlights the value of combining clinical and scientific expertise in a single institution.

1 *Hien TT et al. Avian influenza (H5N1) in 10 patients in Vietnam. New Engl J Med 2004; 350: 1179–88.*



L to R

Melanoma cells: 70 per cent of malignant melanoma are caused by *BRAF* mutations

Helen Lee and her team at Cambridge have developed a rapid test to detect chlamydia.

Anopheles gambiae, which transmits the malaria parasite.

Poultry is the main host of the avian flu virus.

There are fears that an avian flu epidemic could begin in South-east Asia.

ACT NOW

An analysis of clinical trials with artemisinin combination therapy has confirmed its enormous value.

Artemisinin combination therapy (ACT) – the use of artemisinin or related compounds along with a second antimalarial drug – has been pioneered by Professor Nick White and colleagues at the Wellcome Trust's South-east Asia Major Overseas Programme. Extensive trials have shown that ACT is safe and effective. The Thai unit has published nearly 10 per cent of all antimalarial drug trials since 1966, enrolling more than 20 per cent of patients.

Derived from the plant *Artemisia annua*, artemisinin and its derivatives are now widely used in South-east Asia. To reduce the risk of resistance, combination treatments are preferred. In 2004, the International Artemisinin Study Group reported a meta-analysis to assess the value of artesunate when added to other drugs. Pooling data from 16 studies and nearly 6000 patients, they found that the addition of artesunate had significant benefits.[1]

Since 2001 the World Health Organisation has increasingly promoted ACT, recommending that any country changing antimalarial treatment policy should switch to ACT. Over 20 countries have switched, and many others have begun to change. The latest study reinforces how valuable the therapy could be in a continent in which malaria is threatening to run away unchecked.

1 *International Artemisinin Study Group. Artesunate combinations for treatment of malaria: meta-analysis. Lancet 2004; 363: 9–17.*

FIGHTING BACK

Models suggest how the malaria parasite evades the human immune system so successfully, and new hope for a malaria vaccine.

The human immune system wages war against the malaria parasite as it tries to eradicate an infection. Having identified parasite proteins, the system ramps up production of antibodies that will help kill the parasite; the parasite's response is to change its proteins. But possibly not too much, a new mathematical model suggests.

The models, produced by a collaboration between researchers in Oxford, Edinburgh and Kenya, examine the parasite's PfEMP1 receptors, proteins that it inserts into the surface of red blood cells while it is reproducing inside. This protein is a prime target for the immune system, but with more than 50 variants the parasite can switch to a new type, allowing it to prolong the infection.

The new model suggests that each variant elicits two types of immune response: a long-lived response directed against that protein alone; and minor, short-lived responses that target parts of the protein shared by more than one protein.[1] The latter responses delay the appearance of variants with similar shared portions. So the switching occurs sequentially, each new variant being the most immunologically distinct from its preceding types. As a result, the overall duration of infection is increased; eventually, long-lasting responses are produced against the entire variant repertoire, and the infection ends.

Meanwhile, in their quest to develop a malaria vaccine, Professor Adrian Hill (University of Oxford) and colleagues have been studying parasite proteins that induce an immune response. One problem facing vaccine researchers is that while proteins have been found that do stimulate an immune response, none so far has led to protection against natural malaria infection.

In studies in The Gambia, the researchers have tested a new candidate that includes part of the parasite's circumsporozoite protein, which it produces in its sporozoite stage – the stage that is injected into the bloodstream by a feeding mosquito.

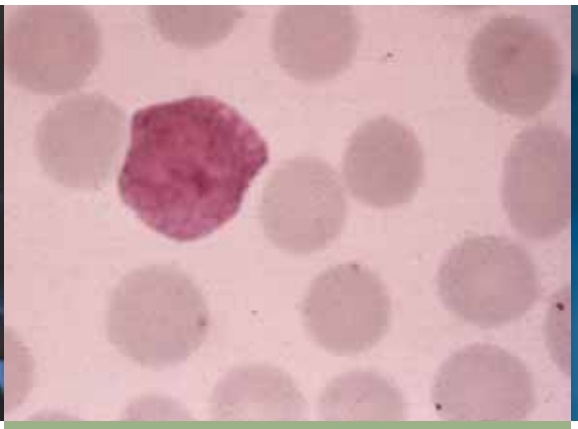
They found that while several portions of the circumsporozoite protein induced an immune response, one fragment in particular was associated with a longer-lasting immune protection against malaria.[2] This, they suggest, makes it a good option to include in new vaccines.

1 *Recker M et al. Transient cross-reactive immune responses can orchestrate antigenic variation in malaria. Nature 2004; 429: 555–8.*

2 *Reece WH et al. A CD4(+) T-cell immune response to a conserved epitope in the circumsporozoite protein correlates with protection from natural Plasmodium falciparum infection and disease. Nature Med 2004; 10(4): 406–10.*

EJECT AND SURVIVE

The genetic basis of mefloquine resistance has been revealed.



Resistance to the antimalarial drug mefloquine, introduced in Thailand in 1984, took just six years to develop. Researchers have now discovered how the parasite became resistant to the drug – by duplication of a key parasite gene.

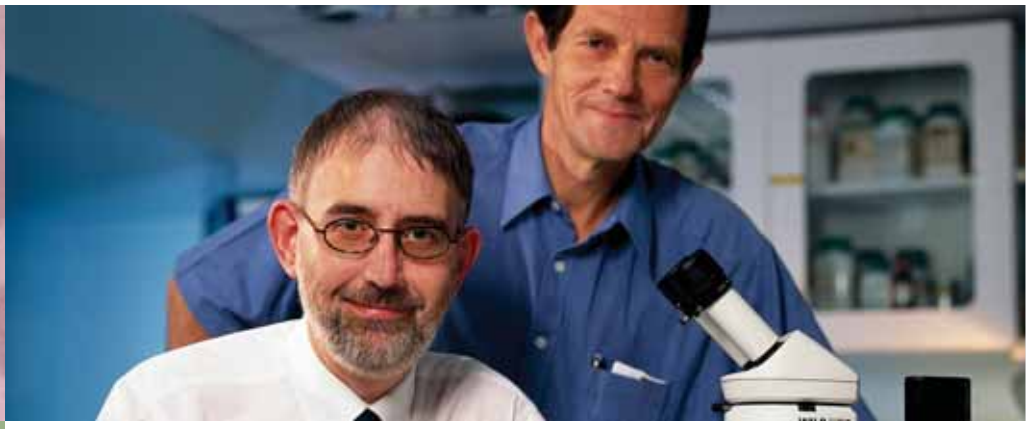
Dr Ric Price (a Wellcome Career Development Fellow in Clinical Tropical Medicine), Professor Sanjeev Krishna (St George's Hospital Medical School, London), Professor Nick White and Dr François Nosten (Wellcome Trust–Mahidol University–Oxford Tropical Medicine Research Programme, Thailand) and colleagues have studied patients in the Karen community living in a malarious hill forest on the northwestern border of Thailand. This harbours the world's most multidrug-resistant *Plasmodium falciparum* parasites.

They found that resistance to mefloquine was associated with extra copies of a *Plasmodium* gene known as *pfmdr1*.[1] The gene codes for a molecular pump that ejects the drug from the parasite cell before it has a chance to do any harm. Presumably, the more copies of the *pfmdr1* gene that a parasite has, the more pump protein the parasite makes – and the more likely it is to survive treatment with mefloquine.

1 *Price RN et al. Mefloquine resistance in Plasmodium falciparum and increased pfmdr1 copy number. Lancet 2004; 364: 438–47.*

ASSESSING MALARIA

Deadly cerebral malaria is difficult to diagnose and is poorly understood. Research in Malawi is providing a clearer picture.



Plasmodium falciparum, the most dangerous malaria parasite, spends part of its life multiplying within red blood cells. Later on, infected cells become 'sticky' and adhere to the walls of blood vessels; when this occurs in the brain, as it does in about 1 per cent of cases, cerebral malaria and coma result. Even with the best treatments, 15–20 per cent of children in such comas will die.

In reality, it is not easy to tell whether a child in a coma has cerebral malaria or some other coma-causing illness. In addition, the effects on the brain are not well defined.

To investigate, Professor Malcolm Molyneux (Malawi–Liverpool–Wellcome Trust Cinical Research Programme) and colleagues in Malawi, the UK and USA conducted autopsies on 31 children who had been diagnosed with cerebral malaria. They found, surprisingly, that although all the patients had parasites in their brains, seven of them (23 per cent) had actually died from other causes.[1]

The only clinical way of distinguishing malarial from non-malarial coma was to examine the eye – almost all of those with malarial coma had damage to the capillaries in the retina.

Another study by Professor Molyneux and colleagues in Malawi and France identified a second feature peculiar to children with severe malaria – much higher levels of tiny particles derived from the lining of blood vessels.[2]

Parasitised red blood cells attach to this lining, usually in deep, inaccessible tissues. These particles may therefore be an indicator that infected cells are collecting in vital organs.

1 *Taylor TE et al. Differentiating the pathologies of cerebral malaria by postmortem parasite counts. Nature Med 2004; 10: 143–5.*

2 *Combes V et al. Circulating endothelial microparticles in Malawian children with severe falciparum malaria complicated with coma. J Am Med Assoc 2004; 291: 2542–4.*

This study was funded by the Wellcome Trust, the French Ministry of Research, the PAL+ Programme, and the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases.

L to R

Artemisia annua, a source of agents used to treat drug-resistant malaria.

Kevin Marsh, head of Wellcome's research programme in Kenya.

Kenyan children, for whom malaria is an everyday scourge.

A malaria-infected red blood cell.

Professors Peter Winstanley (left) and Malcolm Molyneux.

STEROID SUCCESS

Steroids help people survive a tuberculous meningitis infection.

Tuberculosis is usually associated with lung disease. But its cause, *Mycobacterium tuberculosis,* can also invade other parts of the body, such as cerebrospinal fluid. The resulting inflammation (tuberculous meningitis) causes death or severe neurological problems in more than half of those affected. Research in Vietnam, however, has shown that steroid use significantly reduces mortality.

Reasoning that corticosteroids might reduce inflammation, a team led by Guy Thwaites at the Pham Ngoc Thach TB and Lung Hospital, the Hospital for Tropical Diseases and the Oxford University Clinical Research Unit, Ho Chi Minh City, ran a trial of the steroid dexamethasone plus antibiotics in 545 patients in Vietnam.[1]

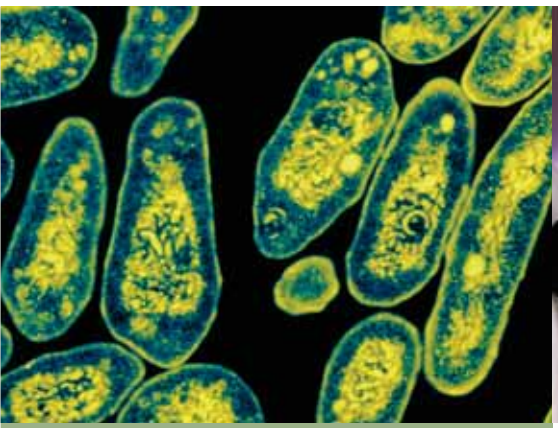
The trial showed that additional treatment with dexamethasone reduced mortality (although it did not reduce the risk of severe disability after nine months). The steroids not only reduce inflammation, but may also reduce the risk of other severe problems, such as potentially fatal clinical hepatitis, which would have forced doctors to change the antibiotic therapy.

The work has led to changes in treatment guidelines for managing tuberculous meningitis.

1 *Thwaites, G et al. Dexamethasone for the treatment of tuberculous meningitis in adolescents and adults. N Engl J Med 2004; 351(17): 1741–51.*

CLINICAL ADVANCES

As well as hosting valuable patient-oriented research, Clinical Research Facilities are having important regional influence.



Wellcome Trust Clinical Research Facilities (CRFs) were set up to provide a specialist hospital environment dedicated to research involving people. A review of progress has revealed that all five CRFs have established effective infrastructure and management systems. High-quality research is being carried out within them. And they are also playing influential roles locally and nationally.

The CRFs – at Birmingham, Cambridge, Edinburgh, Manchester and Southampton – were established as partnerships between the Wellcome Trust, the Department for Health, and the Scottish Executive.

As well as hosting valuable research, the CRFs are having wider influence, becoming recognised regional centres of clinical research excellence. They act as beacons of best practice for governance and ethics, have developed strong collaborative links with local NHS R&D offices, and created local educational programmes targeted at clinical researchers in their areas. The Edinburgh facility now also hosts a regional centre of the National Translational Cancer Research Network.

One notable feature has been the development of a strong network of nurse managers around the CRFs, as well as a growth in nurse-led research.

The CRFs have been used as a model for other similar facilities set up around the country.

Evidence of the success of the venture also comes from the steady stream of research papers coming out of the CRFs. Among the many important studies are the following:

Birmingham: Cannabinoid therapy for multiple sclerosis; antibody therapy for vasculitis; gene therapy for liver cancer.

Cambridge: Genetic causes of obesity; neurochemical impact of drug abuse; immune response to respiratory syncytial virus in children.

Edinburgh: Impact of air pollution on cardiovascular disease; genetic susceptibility to cardiovascular disease in a rural population of Orkney.

Manchester: Using pelvic floor exercises to tackle stress incontinence; molecular genetics of autoimmune disease.

Southampton: Management of hepatitis C virus infection; effects of low birth weight on infant lung function.

One future challenge is to identify ways to capitalise on this initial success to strengthen clinical research in the UK.

LIVING BANDAGES

An innovative product launched this year will provide a new option for burns victims.

Skin grafting is the first-line treatment for burns but sometimes, in severe cases, there is not enough skin to go round. CellTran, a start-up company based in Sheffield and a recipient of Wellcome Technology Transfer funding, has come up with a solution: Myskin, 'living bandages' containing the patient's own skin cells.

The skin cells are usually taken from the thigh, under local anaesthetic, and then transferred to a small polymer disc, coated with a chemically controlled plasma polymer film which promotes the growth of skin cells. After five to seven days, the discs are placed directly onto the wound and the area is wrapped in bandages. The polymer film is engineered to release the cells when exposed to the wound, thus helping new layers of skin to grow.

There is a strong surgical need for this kind of device. CellTran's new technology is faster, simpler and more robust than other methods, which take up to two to three weeks to grow the cells and involve a much more complicated process. Myskin also marks the first time cells have been placed directly onto a patient's wound via a bandage.

Myskin was launched for the treatment of severe burns in April 2004 at the British Burns Association, Manchester. CellTran has partnered with a UK distribution partner, Vernon Carus, a Top 50 NHS supplier, so the product is easily available within the NHS.

CellTran has begun a large clinical trial of Myskin's effects on diabetic ulcers, and preliminary studies have shown that it works well on difficult-to-heal wounds.

CellTran Ltd has been funded by the Wellcome Trust, Sheffield University Enterprises Ltd, and the White Rose Technology Seedcorn Fund.

L to R

Mycobacterium tuberculosis, which can cause tuberculous meningitis.

Body fat scanning equipment at the Cambridge Clinical Research Facility.

The Edinburgh Clinical Research Facility building.

CellTran has developed 'living bandages' to treat severe burns.

OF PIGS AND PEOPLE

The Wellcome Trust–Burroughs Wellcome Fund Infectious Diseases Initiative, launched in 1999, brought together researchers from the UK, North America and the developing world. The initiative aimed to provide large-scale, long-term support for trilateral partnerships, in which the centre of gravity would be in the developing country. Some 13 projects were funded, to the tune of £18 million (US$27 million), based in Asia, Africa and South America.

While many projects are at early stages, they have clearly delivered major benefits to the participants and host institutions, and in some cases have had a direct impact on public health.

- A study in Bangladesh on the causes, prevention and treatment of neonatal infections in the community has raised the profile of neonatal healthcare locally. The research has fed into national policy making, while a training manual in newborn care is being adopted at a national level.

- In Vellore, India, a project on rotaviral gastroenteritis in children has had an unexpected benefit – a substantial decrease in infant mortality in the urban slum in which it was based, as field workers now recognise illness and refer it to the project's local clinic.

- The Peruvian cysticercosis project is studying infection with the intestinal tapeworm *Taenia solium*, which forms cysts in both humans and its intermediate host, the pig. The team is also testing candidate vaccines, with spectacular success: the vaccines provide more than 99 per cent protection. The project team has now been awarded US$15.5 million by the Bill and Melinda Gates Foundation to evaluate a cysticercosis elimination programme in an area of Peru.

Stimulating an informed dialogue to raise awareness and understanding of biomedical science, its achievements, applications and implications.

Public engagement aims to build bridges between scientific and other communities. The language, concepts and accumulated knowledge of science can be daunting, and present obstacles to the wider public sharing in the excitement (and frustrations) of modern science, or joining debate into its possible implications or application.

By the same token, separating science from other aspects of modern life will surely impoverish the discipline – particularly one with such a human dimension as biomedicine.

Bridge building can take many forms:

- Page 30: 'Medicine in Context' exhibitions at London's Science Museum, such as this year's on pain, have provided unique interpretations of fascinating topics;
- Page 30: The Engaging Science Programme has brought new blood into the field, with fresh ideas and enthusiasm;
- Page 31: The award-winning 'Living and Dying' exhibition at the British Museum illustrates how different cultures perceive their health;
- Page 32: Innovative medical training at the Peninsula Medical School shows how the sciences can gain from the arts;
- Page 32: The Eden Project has benefited from a visitor centre grants scheme to rejuvenate its exhibits;
- Page 33: The poignant Foundling Museum is a reminder of the social context in which medicine is delivered.

The experience gained from these and other projects will be invaluable as plans are laid for a new public venture at 183 Euston Road, London, due to open in 2006.

PUBLIC ENGAGEMENT

PLEASURE AND PAIN

Combining art, history and science at a scientific venue – London's Science Museum – has proven a popular mix.

"Beautifully organised... intelligently curated… The exhibition weaves between the witty, the horrific, the challenging and the banal." This was *The Spectator*'s verdict on *Pain: Passion, compassion, sensibility* – a Wellcome Trust exhibition at the Science Museum.

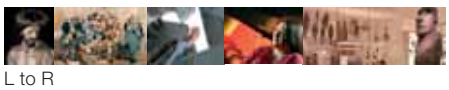
The exhibition – which attracted nearly 100 000 visitors – highlighted how, despite its universality as a human experience, the meaning of pain has changed over time and across different cultures.

Pain has variously been seen as a means of salvation, a route to self-enhancement – or a sign of injury or illness. People's responses to pain vary accordingly: sometimes we suffer it, sometimes we contemplate or study it, and sometimes we try to alleviate it. At other times, willingly or not, we inflict it.

Pain: Passion, compassion, sensibility, curated by Professor Javier Moscoso, explored the ceaselessly shifting cultural place of pain, and how science and other ways of thinking have shaped our beliefs and responses to it.

Reflecting the compelling nature of the exhibition, the CD-ROM catalogue for *Pain* was short-listed for the 2004 AXA Art Exhibition Catalogue Award.

Pain and other Science Museum exhibitions have provided evidence of a wide public enthusiasm for a 'culturally integrated' view of biomedical science. This approach will be picked up further in the redeveloped Wellcome Building, due to open in 2006, which will be a public venue dedicated to the exploration of science and its social and historical contexts.



L to R

'Ecce homo' by Nicholás de Bussy, a centrepiece of the *Pain* exhibition.

Leg amputation in the 18th century, by Thomas Rowlandson.

Playwright Simon Turley and Rebecca Gould at the Theatre Royal Plymouth are involved in a drama project funded by a Society Award.

The *Living and Dying* exhibition in the Wellcome Trust Gallery at the British Museum.

GREAT AND SMALL

Projects of vastly different scales have been funded through the new Engaging Science Programme.

Since its launch in September 2003, the Engaging Science Programme has enabled a diverse range of people and organisations to get involved in public engagement.

The £3 million programme has been geared around flexibility, with small, fast-turnaround People Awards offering the chance for people to turn ideas into action and larger Society Awards available for bigger, longer-term and nationally important ventures. A whole range of applicants has been tempted to apply – including health practitioners, community workers, teachers, postgraduate students, as well as academics and science communicators. And quirky or 'off-beat' projects have been supported as well as the worthy.

The year's smallest award, for example, went to Dr Jonathan Cox, a postdoc at the University of Bath. His People Award of £786 enabled him to bring Sir Alec Jeffreys – the inventor of DNA

LIVING AND DYING

Beautiful objects from all over the globe illustrate how different cultures perceive and protect their health and well-being.

fingerprinting – to an event for members of the local community, schools and the university.

At the other end of the scale, Society Awards support research or significant public activities – and focus on specific areas of public engagement. Young people's education was a theme through 2004, and was the focus of a £415 000 Society Award to the science centre At-Bristol.

A team from the centre will work closely with teachers and a range of experts (including scientists, policy makers and consumer group representatives) to develop a suite of tools that teachers can use to get young people thinking and talking about science and its wider impact. New techniques might include video conferencing, drama and filming, role-play, internet research tasks and ethics committees. The most successful approaches will be disseminated widely within the UK's teaching community.

Living and Dying – the first exhibition in the Wellcome Trust Gallery at the British Museum, London – explored the different ways in which people around the world seek well-being for themselves or their communities, and how they deal with the harsh realities of life.

Different societies have different understandings of the causes and symptoms of sickness, and different ways of averting or confronting sorrow or need. This diversity is reflected in the objects produced by different cultures. *Living and Dying* dramatically illustrated this fascinating diversity with material from all over the world – from the Andes to Zimbabwe.

The centrepiece of the exhibition, however, had its roots closer to home. The specially commissioned art installation, 'Cradle to Grave', produced by the Pharmacopoeia collective (artists Susie Freeman and David Critchley, and GP Liz Lee), resembles a shop counter, running the length of the gallery. Inside, it shows the medicines a typical British man and woman take during their lives, stitched into two 13-metre pieces of fabric mesh. These are surrounded by family photographs with handwritten captions, and various medical objects, such as a mammogram, an X-ray and a hearing aid.

Living and Dying, which opened in November 2003, won a prestigious Museums and Heritage Show 2004 Award for Excellence for best permanent exhibition.

The Wellcome Trust Gallery at the British Museum will house a series of long-term exhibitions examining life's challenges and the ways people from different cultural backgrounds deal with them. Using objects from vastly different times and places as a window onto common human experience, the gallery will offer a distinctively fresh perspective on the outstanding ethnography collections of the British Museum.

The Pharmacopoeia collective was formed thanks to one of the Wellcome Trust's first-ever Sciart awards. www.pharmacopoeia-art.net

MEDICAL INNOVATION

Art is well known to benefit from science. Less well appreciated is that science can gain from art.

Working with artist Helen Storey – on a Sciart project exploring the nature of creativity – was a life-changing episode in Professor John McLachlan's life. He was strongly struck by the humanising influence of art. And being responsible for developing the courses at the new Peninsula Medical School (PMS), he was also able to put theory into practice.

The PMS aims to encourage medical students to see patients as individuals in particular social and cultural contexts. The arts and humanities – including poetry writing, life-drawing, sculpture and photography – are an important part of this programme.

Among its many innovations, the PMS teaches anatomy without using cadavers, relying on imaging and examination of living bodies instead. Medical students first experience patients as living people rather than as devitalised corpses. Similarly, the course is case-based and students encounter patients in normal settings, from hospitals to family planning clinics.

Drama and role play form a key part of students' training, and drama performances are even being taken into local schools to encourage students to consider a career in medicine. The medical school also draws upon historical contexts, collaborating with the historians at the University of Exeter, a group supported by a Wellcome History of Medicine Strategy Award.

PARADISE GAINS

Cornwall's Eden Project aims to combine science, art and drama to create a rich sensory experience for its visitors.

The Eden Project site is dominated by 2.2 hectares of covered 'biomes', themed around tropical and Mediterranean landscapes, alongside a further 15 hectares of outdoor temperate displays. The adjacent Visitor Centre contains exhibits that explore contemporary issues in science, especially relevant to food and health – including its advances, decisions, dilemmas and impacts.

In 2004, the Eden Project received a £734 000 Rediscover award from the Millennium Commission and the Wellcome Trust to redevelop its exhibition space. To engage visitors, the exhibits have the air of a fairground attraction with extensive use of automata and arcade game style exhibits. All, however, illuminate the connections between people and plants, wild places and cultures, across the globe.

But the Rediscover award is only one way in which the Eden Project has attempted to use innovative approaches to tackle scientific issues. In 2002 it hosted an exhibition of the dresses produced by the Sciart partnership of Helen and Kate Storey, which were inspired by early embryonic development.

And it has actively drawn upon drama to engage young people, thanks to a Wellcome Trust Pulse award. Graham Mitchell's *Signs of Life*, which explored people's responses to genetic modification, was developed in collaboration with students on a foundation degree course in performance at Truro College. Accompanied by associated role-play workshops, it toured secondary schools in the south-west, and from July 2004 was performed to school groups and the general public at Eden's Visitor Centre.

The Rediscover initiative was a £33 million joint venture between the Millennium Commission, the Wellcome Trust and the Wolfson Foundation.

L to R

Teaching anatomy without cadavers at the Peninsula Medical School.

'March of the guards to Finchley', one of Hogarth's contributions to the Foundling Hospital.

The biomes of the Eden Project in Cornwall.

FOUNDLING FATHER

A new exhibition provides an insight into the lives of abandoned children in the eighteenth century.

Visitors to London's Foundling Museum, which opened in June 2004, can learn the remarkable story behind the Foundling Hospital, which, like an early-day Live Aid, used artistic creativity to publicise shocking social ills.

In the mid-18th century thousands of unwanted children were left to die on the streets of London. In 1719, after a life spent as a successful ship-builder and sailor in the New World, retired sea captain Thomas Coram tripped over one such baby left in a gutter.

Stunned by the appalling social conditions all around him, he spent the rest of his life establishing a refuge for abandoned children. His efforts were rewarded in 1739, when George II granted a Royal Charter for the establishment of a Foundling Hospital, to provide a home and education for young children.

Coram solicited the help of a talented set of friends. Handel wrote the hospital anthem; Hogarth contributed paintings, and persuaded many of his contemporaries, including Gainsborough and Reynolds, to do likewise. At that time there were no public places for artists to exhibit, so the Foundling Hospital became the first British public art gallery.

In the 1920s the Foundling Hospital was demolished, but its artistic treasures were saved and moved to 40 Brunswick Square. The Foundling Museum houses the internationally important Foundling Hospital Collection, which includes paintings by Hogarth, Gainsborough, Hudson and Roubilliac, and material relating to Handel.

The Wellcome Trust provided funds for an exhibition on the life and welfare of these unfortunate youngsters. The Museum includes many objects reflecting the social and personal history of its children, including hundreds of personal mementos or 'tokens' left by mothers in the hope that they might one day be able to return and identify their child. These tokens, including a hazelnut shell, a label from an ale bottle, and pieces of ribbon, are poignant reminders of past anguish.

The Foundling Museum, at 40 Brunswick Square, London WC1N 1AZ, is open Tuesday – Sunday, 10.00–18.00.

A DRAMATIC YEAR

Drama is highly effective at engaging young people, providing a way in for students who may be put off by 'pure' science. And it provides much inspiration for people whose first interest is in the performing arts.

- Many Pulse performances took place during the year. Among the most notable performances, the Trestle Theatre Company premièred their puppetry work, *The Smallest Person*, at the Edinburgh Fringe festival – "Visually ingenious and delightful", said the *Guardian* – while students from Sir John Colfox School in Bridport collaborated with hospital staff and artists to create an imaginative and occasionally surreal site-specific work, *Visiting Time*, performed at a variety of locations within Dorset County Hospital.

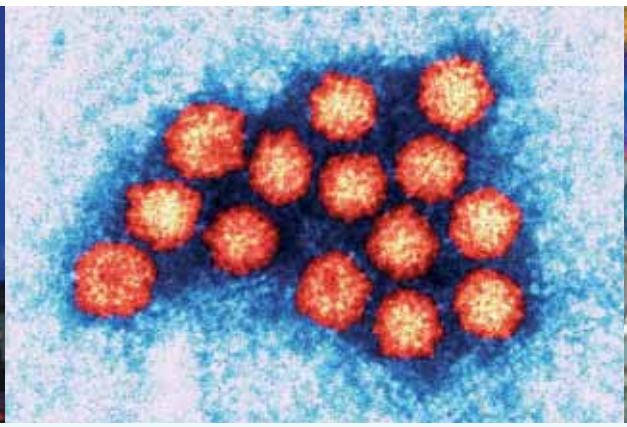
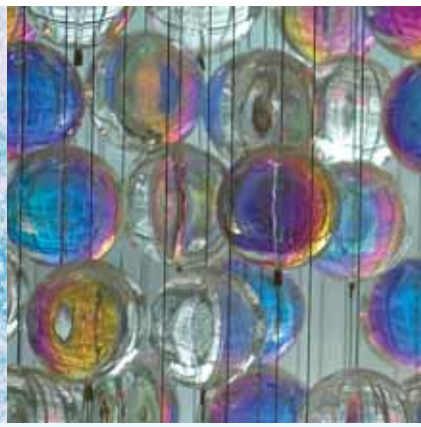
- 'Imagining the Future', held at the Theatre Royal Plymouth in February 2003, brought together playwrights, theatre practitioners and scientists for a week-long workshop. At least two new works emerged from the workshop – Simon Turley's *Seeing Without Light*, about immunity and the impact of HIV, and Peter Morgan's *Special*, which explored the medical and cultural history of eugenics.

- The Theatre Royal Plymouth went on to apply for a £250 000 Society Award to build on the success of these two plays. The theatre will work with professional casts and local community groups to develop the plays and educational projects.

- A reading of Peter Morgan's play took place at the EuroScience Open Forum (Stockholm, August 2004). The play deals with Sweden's policy of compulsory sterilisation of the 'mentally defective' – which only ceased in the 1970s. The reading was followed by a discussion involving the author and artist and commentator Eva Dahlgren, who has written extensively about the Swedish policy.

A YEAR AT THE WELLCOME TRUST

A brief overview of corporate activities in 2003/04.

UK science

We worked closely with the UK Government in the run-up to the launch of its ten-year framework for Science and Innovation. We welcomed the Government's decision to increase framework spending from £3.9 billion in 2004 to £5 billion in 2008.
We have agreed to work jointly with the Government in key areas, such as international health and public health in the UK. We were also pleased to note the Government's acknowledgement of the contribution made by charities to research in UK higher education institutes, and its decision to provide additional funds through the dual support system.

Open access

We have continued to promote the 'open access' model of science publishing, to help ensure that scientific research findings are shared as widely and as rapidly as possible. In April 2004, we published the findings of research carried out by the consultants SQW, *Costs and Business Models in Scientific Research Publishing*, which analysed the economic consequences of different models of academic science publishing. The research suggested that open access publishing was economically viable and offered the potential for significant cost savings.

Human Tissue Bill

During the year, we liaised with legislators and other parties to address issues raised by the draft Human Tissue Bill, which in its original form would have posed serious problems to medical research in the UK. The Human Tissue Bill was a response to cases in which the organs of deceased children were taken and stored without the consent or knowledge of parents or families. While supportive of the aims of the bill, we and others feared that in its original form it could have put major obstacles in the way of potentially life-saving research. The revised bill addressed many of the medical research community's concerns, while still providing important protection to individuals' rights.

Public health research

A working group commissioned by the Wellcome Trust called for a national strategy to foster and enhance research into major public health problems facing the UK population. The study was carried out by an independent working party chaired by Professor Stephen Frankel, Professor of Epidemiology and Public Health at the University of Bristol. The group's report, *Public Health Sciences: Challenges and Opportunities*, addresses a major issue identified in the recent Treasury-led Wanless Report, which recommended that the NHS should focus more on health improvement and disease prevention rather than just treatment of ill-health.

Consultation submissions

During the year, we submitted 27 formal responses to consultations launched by the UK Government and other bodies, including the draft charities bill, the Ten-Year Science and Innovation Investment Framework and the Scientific Publications Inquiry.

Streams

In October 2004, we introduced a funding 'streams' model for our research funding activities. The new streams cover: Immunology and Infectious Disease; Populations and Public Health; Neuroscience and Mental Health;

L to R

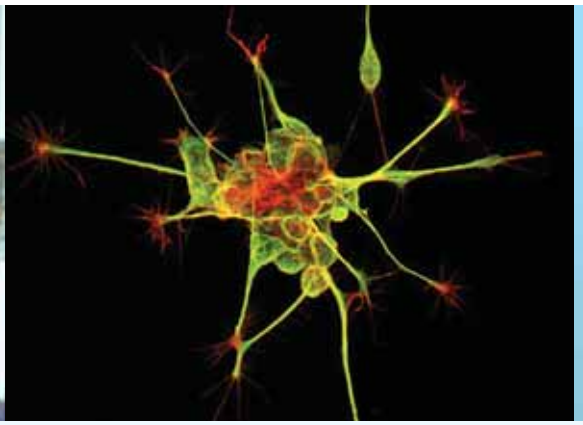
The Gibbs Building – new headquarters of the Wellcome Trust.

Colour-enhanced electron micrograph of the norovirus.

Detail of a spectacular sculpture by the Thomas Heatherwick Studio, in the Gibbs Building.

Dorsal root ganglion nerve cells.

Frances Norton, who joined the Trust as Head of the Wellcome Library in July 2004.


Physiological Sciences; Molecules, Genes and Cells; and Medical Humanities. These streams are complemented by 'cross-cutting' strands of activity such as technology transfer and public engagement. The aim of the reorganisation is to focus more strongly on research priorities and strategy, rather than on the funding process. Funding Committees and Strategy Committees are being set up to assess grants and consider strategy issues in each area.

Flexible funding

In 2004, we made a number of changes to our grants management processes, with the aim of providing greater flexibility for grantholders and reducing administrative burdens for grantholders, universities and the Trust. The changes allow grantholders to move funds between budget headings (except salary costs), and grants now include a 'flexible funding award' to provide for unanticipated direct costs and to provide additional flexibility to researchers.

New Governors

Three new Governors were appointed in 2003/04: Dame Patricia Hodgson, former Chief Executive of the Independent Television Commission; Ronald Plasterk, Professor of Developmental Genetics at the University of Utrecht; and Peter Smith, Professor of Tropical Epidemiology at the London School of Hygiene and Tropical Medicine.

Sir David Steel

Sir David Steel, former Chairman of the Wellcome Trust, died on 9 August 2004. Sir David, previously Chairman of BP, was the Wellcome Trust's Chairman from 1982 to 1989.

New staff

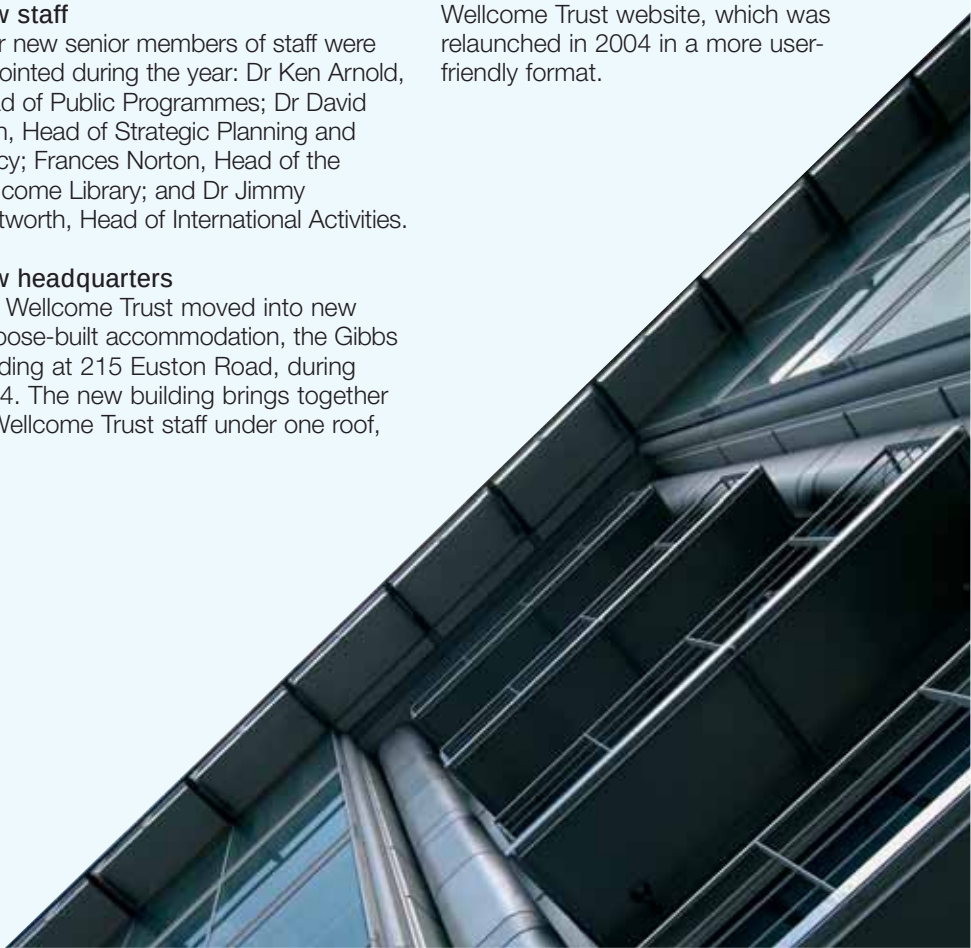
Four new senior members of staff were appointed during the year: Dr Ken Arnold, Head of Public Programmes; Dr David Lynn, Head of Strategic Planning and Policy; Frances Norton, Head of the Wellcome Library; and Dr Jimmy Whitworth, Head of International Activities.

New headquarters

The Wellcome Trust moved into new purpose-built accommodation, the Gibbs Building at 215 Euston Road, during 2004. The new building brings together all Wellcome Trust staff under one roof, except for Wellcome Library personnel, who have moved to 210 Euston Road while the Wellcome Trust's previous headquarters building at 183 Euston Road is refurbished. The refurbished 183 building will be opened as a public venue in 2006.

New corporate identity

A new logo and corporate identity were launched during the year. The new identity, launched to coincide with the occupation of the new headquarters building, is being rolled out gradually. The new identity is also reflected in the Wellcome Trust website, which was relaunched in 2004 in a more user-friendly format.



FINANCIAL SUMMARY

1 October 2003 to 30 September 2004

Grants awarded: **£251 million**

Direct activities: **£86 million**

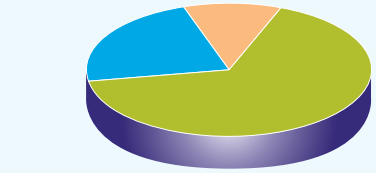
Applications: **2988; 1141 awards**

Total charitable expenditure: **£378 million**

Investment assets: **£10.5 billion**
(as at 30 September 2004)

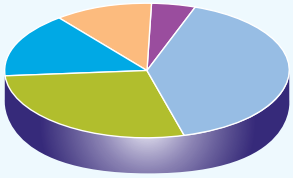
Additional financial information can be found in the Wellcome Trust's Annual Report and Financial Statements 2004.

Charitable resources expended (£ million)



Grants awarded	251
Direct activities	86
Support and administration costs	41
Total charitable expenditure	378

Breakdown of grants awarded (£ million)*



UK funding	101.4†
Careers	70.2
International	38.8
Infrastructure and equipment	28.4‡
Medicine, Society and History	11.9
Total	250.7

In the year to 30 September 2004, the Wellcome Trust's total charitable expenditure was £378 million. This represents a drop on the figure for 2002/03 (£516 million), due primarily to the decline in infrastructure funding through the Joint Infrastructure Fund and Science Research Investment Fund as these initiatives drew to a close.

Of the total charitable expenditure, grants worth £251 million were awarded. Although grants expenditure was down on last year, the number of grant applications received also decreased significantly – from 4312 in 2002/03 to 2988, a drop of 30 per cent. Outstanding grant commitments again shrank slightly this year, but remain in excess of £1 billion.

As in previous years, the bulk of grant support was for investigator-led proposals in biomedical science. Fellowships and other careers funding also continued to be a major area of support (27.5 per cent of grants spend). International expenditure (funding for schemes focused on the needs of developing and restructuring countries) increased as a proportion of total spend (15.5 per cent of grants spend).

Grants for the medical humanities (history of medicine and biomedical ethics) and public engagement with science amounted to £26.1 million. This consists of £11.9 million for response-mode funding (2002/03: £13 million) plus capital awards to the Natural History Museum (£10 million) and for the National Science Learning Centre (£4.2 million).

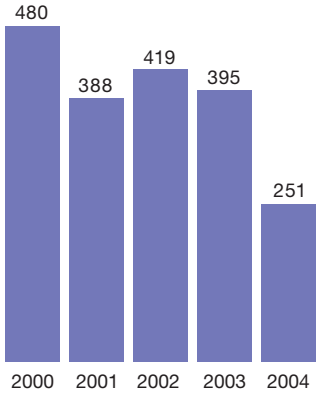
Expenditure on direct activities, those organised by the Wellcome Trust, rose slightly to £86 million. The bulk of these costs were for research at the Wellcome Trust Sanger Institute, which received £64 million in grants in 2003/04. Also included is £11 million committed to the Diamond synchrotron project at the Chilton/Harwell Science Campus. Direct activity costs also include support for the Wellcome Library.

Administration and support costs fell again, from £44 million to £41 million. Wellcome Trust subsidiaries such as the Genome Campus accounted for £6.7 million of this expenditure.

Investments

The Wellcome Trust's investments are managed to preserve (at least) the purchasing power of its long-term asset base and to provide an income stream to support ongoing activities. This year, the Trust's asset base increased from £10.1 billion to £10.5 billion.

Grants awarded (£ million)

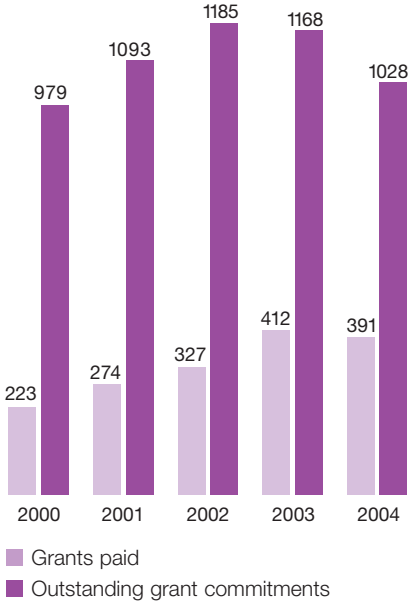


* An additional £76.6 million was awarded to Wellcome Trust subsidiaries, mainly to support activities at the Wellcome Trust Sanger Institute.

† Including £86.9 million awarded through the UK Subject Panels; £12.4 million awarded through the Functional Genomics Development Initiative.

‡ Includes £14.2 million of capital awards in Medicine, Society and History.

Grants paid and outstanding (£ million)



Grants awarded (left) represent the total funds committed to successful applications during the Trust's financial year. Most awards are made to researchers' host institutions, which then claim monies from the Trust.

The light purple in the figure above (grants paid) represents the amounts claimed by host institutions during the year for expenses incurred, while the dark purple (outstanding grant commitments) represents the total sums committed by the Trust to projects which had not been claimed by the end of the financial year. The gap between committed funds and cash paid is due to the long-term nature of many grants, and to the time lag between a grant award and the subsequent claim for funds from an institution.

THE FUNDING YEAR

A summary of major awards and key Wellcome Trust expenditure for 2003/04.

The Wellcome Trust supports research and other activities in four main areas:

- Biomedical Science
- Technology Transfer
- Medical Humanities
- Public Engagement with Science

In **biomedical science**, project and programme support continued to account for the bulk of the Wellcome Trust's support in the UK. Research is primarily funded through response-mode mechanisms, with support provided for investigator-led proposals in almost all areas of biomedical science and for a wide range of basic and applied studies. The following pages describe some of the major projects funded in 2003/04.

Career development support is provided at all levels from PhD (through Four-year PhD Programmes) to professorial-level Principal Research Fellowships. The 12 UK Four-year PhD Programmes all received five-year renewals during the year. Eight new Senior Research Fellowships were awarded (six Basic Biomedical Science and two Clinical Science), and eight fellowships were renewed. Three Principal Research Fellowships were renewed.

Infrastructure investment has returned to levels seen before the surge of spending through the Joint Infrastructure Fund and Science Research Investment Fund. Funding of £11 million was approved for phase 2 of the Diamond synchrotron project.

The Wellcome Trust's **international** funding is primarily focused on regional centres of excellence, particularly in South-east Asia (Thailand and Vietnam), Kenya, Malawi and South Africa. The Malawi programme received a £2.3 million grant, to enable it to continue its research on malaria and other infections.

A £1.86 million grant was awarded to support research on women's health and ageing populations in Lebanon and elsewhere in the Middle East. Four awards totalling £3.8 million were made to countries in Latin and Central America – Brazil (two awards), Costa Rica and the West Indies.

In 2003/04, 12 International Senior Research Fellowships were awarded (seven in India, four in central/eastern Europe, and one in South Africa); ten were renewed (eight in India, one in central/ eastern Europe, and one in South Africa).

Technology Transfer

This year was the first in which awards were made through the Wellcome Trust's new technology transfer schemes. **University Translation Awards** provide support for early-stage development of promising lines of research. The 16 awards made this year covered a range of areas, including therapeutics, vaccines, diagnostics and medical devices.

Strategic Translation Awards are large awards in areas of strategic importance to the Trust. Four awards are currently at advanced stages of consideration.

Medical Humanities

In the **history of medicine,** the year's sole Strategic Award went to the University of Oxford, for a programme of work on the history of tropical disease and medicine. Twentieth-century history continued to provide a major focus, with topics being studied ranging from Unani practice in India to the history of myxomatosis in the UK.

Funding continued for **Biomedical Ethics** studies, in the UK and the developing world. Studies supported are of practical relevance, including the function of clinical ethics committees and an assessment of the impact of research on health policy makers in Kenya.

Public Engagement

Public engagement funding is primarily through the **Engaging Science** programme. **Rediscover** funding – a partnership with the Millennium Commission and the Wolfson Foundation – has enabled public venues such as the Eden Project in Cornwall and ThinkTank in Birmingham to update exhibits.

A £10 million award to the Natural History Museum, for phase 2 of its Darwin Project, was confirmed. A £4.2 million award was made to the White Rose Consortium (an alliance between the universities of Leeds, Sheffield and York), to support construction of the National Science Learning Centre at York.

Direct activities

As well as funding others, the Wellcome Trust organises activities directly, either independently or in partnership with others. The **Wellcome Trust Sanger Institute** accounted for £64 million for its ongoing highly productive research programmes in genome sequencing and analysis.

Partnerships lay at the heart of several public engagement projects, including the Imagine photographic competition run with the BBC, and the *Pain* exhibition at the Science Museum.

Looking forward

In October 2004, the Wellcome Trust introduced a 'streams' model of funding. This is intended to provide a greater focus on the needs and opportunities within particular areas.

Funding Committees and Strategy Committees are being established to assess grant applications and to consider how the Trust might best make an impact in these areas. Future Annual Reviews will report on the progress made by the streams in funding and developing strategy.

The Diamond synchrotron, which received a funding boost in 2004.

IMMUNOLOGY AND INFECTIOUS DISEASE

The Immunology and Infectious Disease stream aims to increase our knowledge and understanding of the infectious organisms that cause disease in humans and animals, and of the immune system that fights these organisms.

During the year, 70 immunology and infectious disease awards were made, including 15 new programme grants or renewals, to a total value of £26.6 million.

Research funded in the immunology and infectious disease area ranged from fundamental and applied research in basic immunology and infectious diseases conducted in the UK through to field, epidemiological and clinical research based in developing countries.

Professor Brian Spratt, Imperial College, had the programme grant associated with his Principal Research Fellowship renewed at a cost of £1.7 million. Professor Spratt, who has been a Principal Research Fellow since 1989, studies the epidemiology and evolution of bacterial populations, and has pioneered the use of multi-locus sequence typing as a scientific and epidemiological tool.

Senior Research Fellowships in Basic Biomedical Science were awarded to Dr Allison Green, University of Cambridge, for studies into inflammation and autoimmune disease, and to Dr Daniel van Aalten, University of Dundee, for his studies on structural biology and inhibitor design in chitin metabolism.

Fifteen programme grants were awarded, including grants to:

- Professor Jose Vazquez-Boland, who moved from the University of Leon in Spain to take up the Chair of Veterinary Molecular Microbiology at the University of Bristol, for his studies of the molecular and cellular pathogenesis of *Listeria* infection. Listeriosis has one of the highest hospitalisation and mortality rates of all food-borne infections. Professor Vazquez-Boland is investigating the actin-based mechanism of cell–cell spread used by the bacterium.

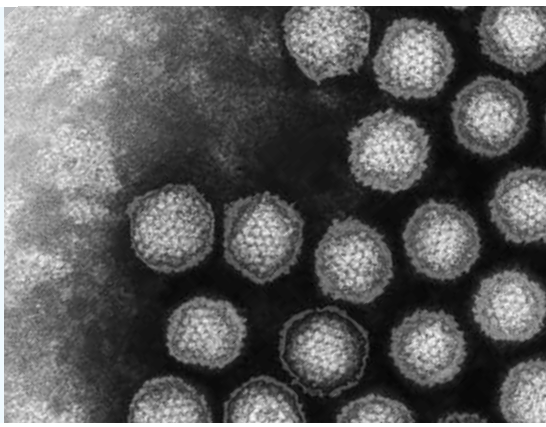
- Dr Gavin Wilkinson, University of Wales College of Medicine, Cardiff, for studies into human cytomegalovirus. This herpesvirus is able to evade the immune system of healthy but infected persons, but in immunocompromised individuals it presents a major clinical problem. Using clinical isolates, Dr Wilkinson will look at how the virus interacts with natural killer cells, the main weapon in fighting viral disease. The team will use whole genome cloning techniques to investigate the role of different viral genes in evading these immune cells.

- Professor David Wraith, University of Bristol, for research on the differentiation and stability of induced regulatory T cells. Professor Wraith's research is aimed at the development of therapies to control autoimmune conditions, such as multiple sclerosis.

Under the **Tropical Medicine Programme**, awards included a Senior Clinical Fellowship in Tropical Medicine to Dr Elizabeth Corbett, London School of Hygiene and Tropical Medicine, for trials of TB case-finding strategies in an urban community in Zimbabwe severely affected by HIV, and a Career Development Fellowship to Dr Cameron Simmons, University of Oxford, for his studies in Vietnam on cellular immune response and disease pathogenesis during dengue infection. Dr Corbett was awarded the 2004 Chalmers medal by the Royal Society of Tropical Medicine and Hygiene for her contributions to tropical medicine.

An interim review was carried out of the **Wellcome Trust/Burroughs Wellcome Fund Infectious Diseases Initiative**. Launched in 1999, the initiative awarded £18 million to support 13 projects, each involving partners in the UK, USA and a developing country, and has played an important role in fostering international partnerships and developing capacity.

While many projects have yet to come to full fruition, it is clear that they have delivered major benefits to the participants and host institutions, and in some cases have had a direct impact on public health. For example, the project based in Bangladesh has raised the profile of neonatal healthcare locally, attracting the interest of the Ministry of Health and other NGOs/charities (see page 27).



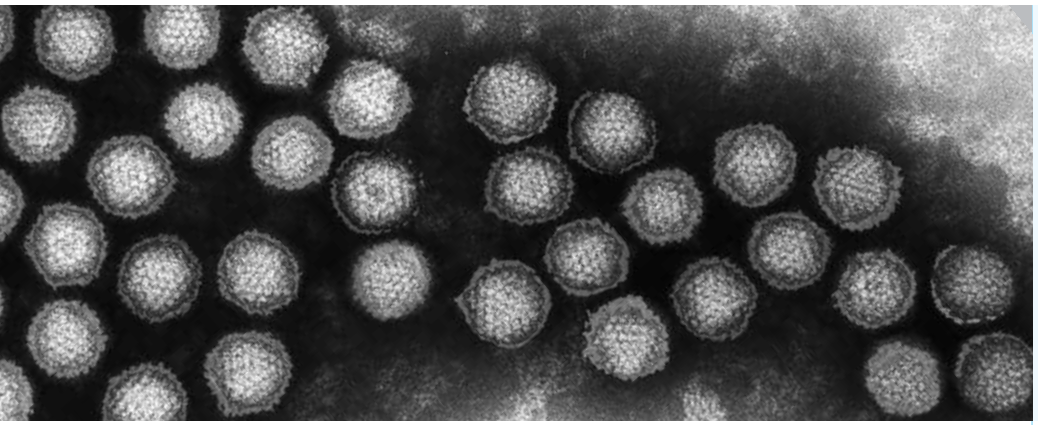
Major Overseas Programmes

Following a favourable review in 2004, an award of £2.3 million was made to the University of Liverpool for the **Malawi–Liverpool–Wellcome Trust Clinical Research Programme**. The programme, which is led by Professor Malcolm Molyneux and is based in the Wellcome Trust Research Laboratories at the University of Malawi College of Medicine, Blantyre, conducts research into malaria, HIV, TB and other bacterial and viral infections, and anaemia. In addition to research costs, the award provides funds to support the training of local researchers associated with the programme (see page 25).

In Kenya building work began on new laboratories in Kilifi for the **Wellcome Trust/Kenya Medical Research Institute Research Programme**, led by Professor Kevin Marsh. The building has been funded by a Wellcome Trust grant of £2.75 million to the Kenya Medical Research Institute. The building should be completed by August 2005.

Research highlights from the Kenya programme include:

- The completion of a survey of epilepsy in over 160 000 people and the identification of all cases of active epilepsy, the largest study of its kind ever conducted in Africa.



- Analysis of data on the spectrum of bacteraemia in children, with data from over 20 000 children admitted to hospital. Of all hospital deaths, 14 per cent were attributable to *Streptococcus pneumoniae* and *Haemophilus influenzae*, for which effective vaccines are available but only partially implemented.

- Dr Sam Kinyanjui and Dr Faith Osier were awarded Research Training Fellowships for Scientists from Developing Countries to conduct research at the KEMRI–Wellcome Trust programme in Kilifi.

In **South-east Asia**, which encompasses research centres in Thailand (led by Professor Nick Day) and Vietnam (Professor Jeremy Farrar), research highlights include:

- Demonstration that variable horizontal gene acquisition by *Burkholderia pseudomallei* is an important feature of its recent genetic evolution.

- Continued translation of the Programme's research results into health policy. Biological, economic and clinical evidence from the research publications of the programme have provided a basis for a change in global antimalarial treatment recommendations to artemisinin combination therapies (ACTs) (see page 24).

- A mathematical–economic model of drug resistance has been used as a basis for the global recommendations on antimalarial drug policy issued in a recent Institute of Medicine report (*Saving Lives, Buying Time*).

- In Vietnam, the Programme has completed the largest-ever study of TB meningitis (see page 26).

- The Vietnam Programme has been at the forefront of the battle against the outbreak of avian flu (see page 23).

- The New Adult Intensive Care Unit at the Hospital for Tropical Diseases opened in 2004, funded jointly by the Vietnamese Government and the Wellcome Trust.

Adenovirus particles.

The Wellcome Trust Centre for Molecular Parasitology

The Wellcome Trust Centre for Molecular Parasitology at the University of Glasgow, led by Professor Dave Barry, carries out research on basic features of parasites, using genetic and molecular technology allied with organismal biology. One aim is that such studies will lead to novel control approaches.

Much of the research at the Centre concerns African trypanosomes, microscopic parasites that cause human sleeping sickness and the wasting disease nagana in domestic animals. The malaria parasite, *Plasmodium*, and a related parasite, *Theileria*, which infects cells of the cattle immune system, are also studied at the Centre.

In 2004, the Centre established a new partnership with INSERM, the national medical research agency of the French Government. INSERM has begun to locate its researchers in universities abroad, and the first of these INSERM Research Units, led by Professor Christian Doerig, has been established at the Centre.

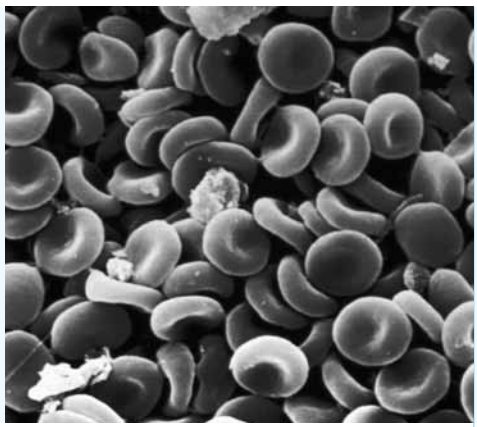
During the year, a programme grant was awarded to Professor Andy Tait at the Centre, based on his application of genetics to the identification of important trypanosome genes. Professor Tait's mapping and annotation of the trypanosome genome has been invaluable to the genome sequencing work on the parasite being carried out at the Wellcome Trust Sanger Institute and elsewhere.

www.gla.ac.uk/centres/wcmp/index.html

MOLECULES, GENES AND CELLS

The Molecules, Genes and Cells stream aims to support high-quality research that will further our understanding of the fundamental molecular, cellular and genetic processes involved in health and disease.

During the year, 75 awards were made, including nine new programme grants or renewals, to a total value of £21.8 million. Two Principal Research Fellowships were renewed: to Professor Angus Lamond (University of Dundee), for his structural and functional analysis of the mammalian cell nucleus, and to Professor Bill Earnshaw (University of Edinburgh) for his studies of non-histone chromosomal proteins in mitosis and apoptosis.



Membrane trafficking and **protein folding** were notable themes in this year's molecular and cell biology funding. Professor Margaret Robinson (University of Cambridge) had the programme grant associated with her Principal Research Fellowship on coated vesicle adaptors renewed. She is characterising the adaptor protein complexes that facilitate the transport of cargo between intracellular organelles. A new line of investigation will focus on how the human immunodeficiency virus (HIV) may exploit adaptor proteins to evade the immune response.

Professor Colin Stirling (University of Manchester) received continued programme grant funding for studies of protein biogenesis in the yeast endoplasmic reticulum. By using both the powerful genetic systems of yeast and biochemical approaches, his group will investigate the partitioning of proteins into the secretory pathway via the endoplasmic reticulum and the role of the translocon complex and associated chaperones.

Professor Neil Bulleid (University of Manchester) was awarded a programme grant to continue his studies on oxidative folding in the mammalian endoplasmic reticulum. His group studies the redox conditions within the endoplasmic reticulum that allow proteins, particularly those containing disulphide bonds, to fold correctly.

Professor Christopher Dobson (University of Cambridge) received continued programme grant funding to study protein folding and misfolding using an array of biophysical techniques and theoretical simulations.

Several important and innovative grants were also funded in the area of **epigenetics and gene silencing**. Jane Mellor (University of Oxford) was awarded a programme grant to elucidate the role of a novel chromatin remodelling ATPase in gene silencing and gene regulation.

Professor Constanze Bonifer (University of Leeds) received continued project grant funding for her studies on the epigenetic mechanisms regulating the expression of the lysozyme gene, while Dr Brian Hendrich (University of Edinburgh) was awarded a grant, complementing his ongoing Wellcome fellowship support, to investigate the epigenetic silencing mechanisms in cell fate decisions. Dr Maria Vogelauer received a Research Career Development Fellowship to study the molecular mechanisms by which histone acetylation regulates the timing of replication origin firing.

Biological chemistry

The partnership with the Royal Society of Chemistry to encourage the area of chemical biology continued during the year. A successful workshop on 'Chemistry at the Biological Interface' was held at the University of Warwick in September 2004. The participants, from universities in and around the Midlands, enthusiastically discussed collaborative projects and it is likely that several new grants will be submitted from ideas first aired at the workshop.

Wellcome Trust Centre for Cell Biology

The Wellcome Trust Centre for Cell Biology at the University of Edinburgh, led by Professor Adrian Bird, seeks to understand the fundamental characteristics of living things at the cellular level, such as growth, movement, self-replication and development.

It has particular strengths in the study of RNA, including its transcription, processing, transport and destruction; the cell division cycle; and gene expression in developing systems, particularly epigenetic processes such as DNA methylation.

During the year Professor Bill Earnshaw's Principal Research Fellowship was renewed (see left), as was Dr Kenneth Sawin's Senior Research Fellowship in Basic Biomedical Science (Regulation of eukaryotic microtubule nucleation and microtubule-mediated cell polarity). A Research Career Development Fellowship was awarded to Dr Maria Vogelauer (see left).

Professor David Tollervey, a Wellcome Principal Research Fellow at the Centre, was elected to the Royal Society, while Professor Jean Beggs was awarded the Royal Society Darwin Trust Research Professorship.

www.wcb.ed.ac.uk/intro.htm

• *RNA-based gene silencing: see page 19*

Wellcome Trust Centre for Human Genetics

The Wellcome Trust Centre for Human Genetics at the University of Oxford, led by Professor Tony Monaco, studies the mechanisms controlling genetic susceptibility to human disease. This includes the localisation and identification of disease genes; functional analysis of gene variants responsible for

susceptibility; and understanding how gene variants contribute to risk of disease in the population and how genetic factors contribute biologically to a disease process.

The Centre, located in the Henry Wellcome Building of Genomic Medicine, houses multidisciplinary research teams in human genetics, functional genomics, bioinformatics, statistical genetics and structural biology. The Centre is focusing on three main disease areas in its genetics research programme: neurogenetics, genetics of inflammation and immunity, and the genetics of cardiovascular disease/metabolic syndrome.

A Senior Research Fellowship in Clinical Science was awarded to Dr Julian Knight (Characterisation of genetic variation regulating gene expression within the MHC class III region). A Senior Research Fellowship in Basic Biomedical Science was renewed: Dr Dominique Gauguier (Functional genomics of type 2 diabetes quantitative trait loci in rat models). A Research Career Development Fellowship was awarded to Dr Richard Wade-Martins (Functional analysis of the tau genomic locus and its role in neurodegeneration).

Dr Kalim Mir, a Wellcome Career Development Fellow, received a Technology Development Grant (Ultra-throughput parallel DNA sequencing using a heuristic single molecule array strategy). Researchers at the Centre also received two clinical training fellowships.

www.well.ox.ac.uk

• *Population genetic structure: see page 6*

Wellcome Trust Centre for Cell-Matrix Research

The Wellcome Trust Centre for Cell-Matrix Research, led by Professor Martin Humphries, is an interdisciplinary research centre embedded within the Faculty of Life Sciences at the University of Manchester. Its long-term aims are to elucidate the structure and function of the extracellular matrix (ECM) and cell–matrix adhesions, define the contribution of cell–matrix interactions to human diseases, and develop approaches for preventing and treating these diseases.

Research within the Centre is organised as four integrated programmes: (1) molecular basis and cellular control of ECM assembly, (2) organisation of signalling at the cell–ECM interface, (3) microenvironmental determination of cell fate, and (4) cell–ECM engineering and tissue regeneration. While each programme is highly focused on extracellular matrices and cell–matrix interactions, the long-term promise of the work overlaps with some of the most important areas of biomedical research – signalling, tissue engineering and medical genetics.

In 2001, the University of Manchester was awarded £15 million from the Joint Infrastructure Fund (JIF) to help set up a new Integrative Centre for Molecular Cell Biology. An additional £35 million from the university was used to create a large research facility for biomedical research sited at a central location in the university's biomedical corridor, adjacent to the Manchester Royal Infirmary and the Wellcome Trust Clinical Research Facility. This building, named in honour of Professor Michael Smith, was occupied in 2004 and now houses the Wellcome Trust Centre for Cell-Matrix Research.

During the year a Senior Research Fellowship in Basic Biomedical Science was awarded to Richard Kammerer (Elucidating the mechanisms of angiopoietin function and amyloid formation by protein engineering and *de novo* design). A Research Career Development Fellowship was awarded to Dr Eleni Tzima (Role of cell–cell junctions and integrins in endothelial cell responses to fluid shear stress). A programme grant was awarded to Professor Neil Bulleid (see left).

www.wtccmr.man.ac.uk

Wellcome Trust/Cancer Research UK Gurdon Institute

The Wellcome Trust/Cancer Research UK Gurdon Institute of Cancer and Developmental Biology at the University of Cambridge, chaired by Professor Jim Smith, focuses on two inter-related aspects of cell biology: how cells acquire and maintain their normal function during development, and how they escape from normal controls and become cancerous.

The Institute adopted its new name during the year, in recognition of the pioneering scientific contributions made by its founding Director, Sir John Gurdon. Sir John was also awarded the Royal Society's Copley Medal, its top honour.

In 2004, the Institute also occupied its new building, constructed with support from the Joint Infrastructure Fund.

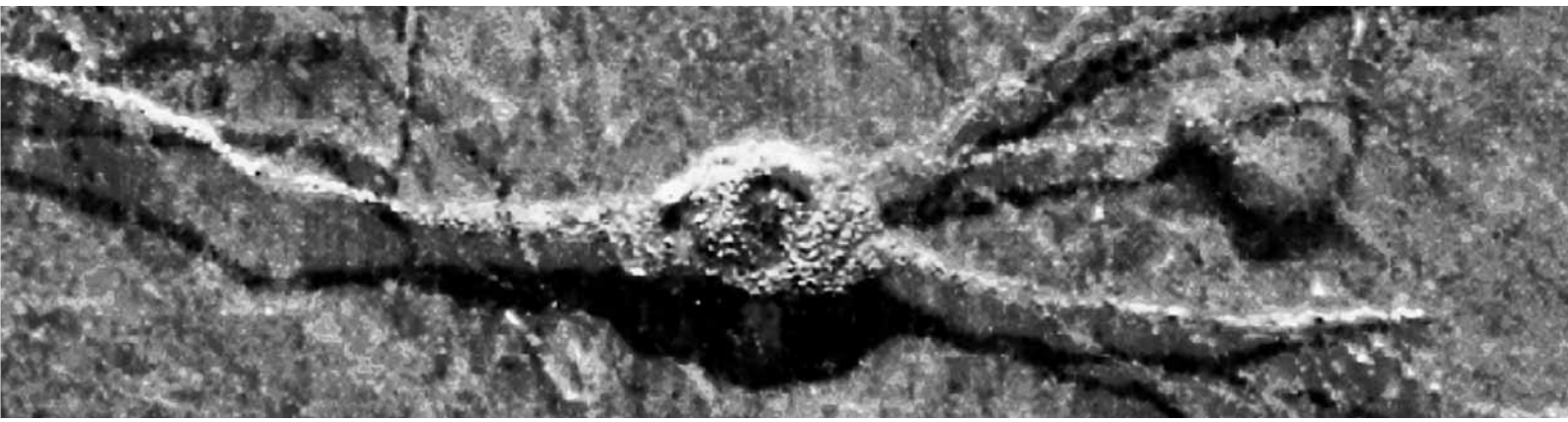
www.gurdon.cam.ac.uk

• *Research resources: see page 19*

Normal red blood cells.

NEUROSCIENCE AND MENTAL HEALTH

The Neuroscience and Mental Health stream aims to support high-quality research into the function of the nervous system in health and disease.



During the year, 62 neuroscience awards were made, including 11 new programme grants or renewals, to a total value of £26.6 million. One Principal Research Fellowship was renewed, to Professor Chris Frith (Institute of Neurology) for his studies of social interactions (see page 8).

Neuroscience awards continued to cover a wide range of both **basic** and **clinical** research topics throughout 2003/04. Two examples of the diversity of funding are awards to Dr Lucia Sivilotti (University College London), for a highly detailed study of the subunits of the nicotinic acetylcholine receptor, and Dr Marianne van den Bree (University of Wales, Cardiff) who is carrying out a longitudinal study in adolescents of the risk factors associated with substance abuse.

Two significant awards were made in the field of **child psychiatry**. The first was to Professor Alan Stein (University of Oxford) for his ongoing work which aims to understand how maternal postnatal psychiatric disorders can affect the development of a child, even after the mother has recovered. His group will be looking at how interactions between mother and child are affected by postnatal depression, following infants in the first years of life to see how they subsequently develop.

In a related study, Professor Ian Goodyer (University of Cambridge) will be looking at how genetic and environmental risk factors in infancy affect the occurrence of psychiatric disorders during the key changes accompanying adolescence. His group will be carrying out a longitudinal study of 13 and 14 year-olds to find associations of selected genes and childhood adversity with depression and associated conditions.

Several awards were for basic research projects aiming to increase our knowledge of **how neurons communicate** with each other – essential for our understanding of the nervous system. Two awards were made to groups at University College London, to Professors David Attwell and Stuart Cull-Candy. Professor Attwell's group will be involved in studies into how neurotransmitters function in ways distinct from conventional fast synaptic transmission between neurons, looking particularly at their communication with glia cells. Professor Cull-Candy's research will examine how changes in receptor subunits define the nature of neurotransmission at glutamate and GABA synapses.

Other research projects are looking at chemicals that are not classical neurotransmitters but have a major role in neuronal transmission. One such award was made to Professor Alan North (University of Manchester), who is studying the role of **ATP**, classically known as a molecule which transfers energy within cells, which interacts with specific receptors on neurons.

Furthering our understanding of how these molecules enable neurons to communicate is important in their further development as targets for drugs for diseases of the nervous system.

A number of projects are aiming to clarify how the very **complex connections** in the nervous system develop. Dr Uwe Drescher (King's College London), for example, is examining how neurons can be directed to their targets, which are often a great distance away, by guidance molecules. Dr Drescher is studying the differential expression of genes at critical times of development which assist in guiding neuronal projections from the retina to the tectum.

Professor Kristjan Jessen (University College London) was awarded a grant to study the development of **Schwann cells** within the nervous system. These very specialised cells form the myelin sheath which insulates nerve axons and are essential for normal nerve function. However, following injury they can revert to an immature state, leading to demyelination of the axon and loss of function. Professor Jessen's group is examining the signals that control Schwann cell differentiation and the process of myelination, and will also look at mechanisms that may allow the Schwann cells to form new myelin sheaths and thus aid nerve repair following injury.

PHYSIOLOGICAL SCIENCES

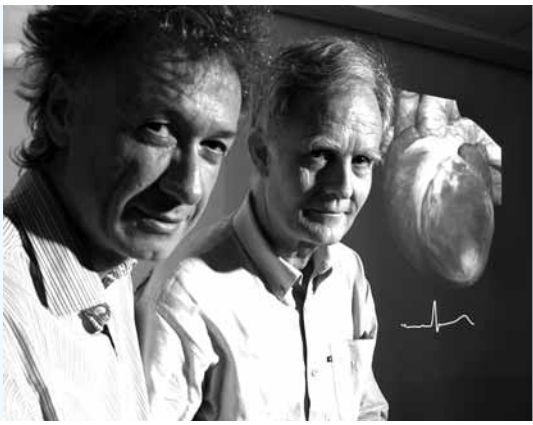
The Physiological Sciences stream aims to support high-quality basic and clinical research relevant to the understanding of biological processes at the cell, organ, system and whole-animal level in health and disease.

During the year, 63 physiological sciences awards were made, including seven new programme grants or renewals, to a total value of £20.2 million.

Physiological science awards covered a broad range of basic and clinical research. Awards were made in areas as diverse as **epidemiology** – for example, to Dr Louise Parker (University of Newcastle), for an analysis of a historical birth cohort to explore the effect of pre- and post-natal exposure to airborne particulate matter on subsequent mortality and health – and **organ transplantation** – such as the award to Professor Peter Friend (University of Oxford), for the development of a novel preservation technique for donor livers involving warm perfusion.

One notable theme during the year centred on **appetite control, nutrition and body size, obesity and their impact on health**, particularly diabetes. Awards included a programme grant to Professor Stephen Bloom (Imperial College London) for his studies aimed at exploiting the discovery that gut hormones physiologically control appetite. This programme will examine how different gut hormones produce their effects and interact in obese and lean volunteers. The research should provide a better understanding of the complex interactions in appetite regulation and provide new strategies to treat and prevent obesity.

Another significant award in a related area was made to Professor Patrik Rorsman (University of Oxford), for his studies into the physiology and pathophysiology of beta-cell exocytosis and insulin secretion. Greater insight into the control of insulin secretion has the potential to inform both our fundamental knowledge of the defects involved in type 2 diabetes and the development of novel therapies to treat this debilitating and widespread condition. This award was of further importance as it aided the recruitment and retention of Professor Rorsman, an internationally renowned scientist previously working outside the UK.



In this same general theme, an award was made to Professor David Dunger and colleagues (University of Cambridge) for a study looking at the effect of genetic variation in the insulin gene on birth weight and perinatal survival in African populations. This study will, for the first time, test the hypothesis that genes relating to size at birth influence fetal and postnatal survival.

A significant amount of **multidisciplinary research** was also funded through the year. This included an award to Professor David Paterson and colleagues at the Universities of Oxford and Auckland (New Zealand) for a **heart 'physiome' project**. The aim of their project is to demonstrate the use of integrative multi-scale modelling – at the levels of atoms, proteins, cells, tissues and organs – to relate detailed genomic information to a model of the structure and function of the human heart. Since biological systems are extremely complex, the team will develop specially designed instrumentation, databases and software to help understand the genetic basis of mechanisms underlying arrhythmia in the heart. These tools will be accessible on the web for other investigators to use in further studies.

Another award for multidisciplinary research was made to Dr David Webb (Aston University) and colleagues at the University of Birmingham. They are developing a 'smart vest' which, when worn next to the skin, will collect clinically useful information related to respiration. Such information should aid clinicians in the diagnosis of respiratory disease.

As well as grant funding, a joint MRC/ Wellcome Trust workshop was organised on integrative physiology. The workshop, held in May 2004, brought together basic and clinical physiologists and explored how an appropriate strategy to further encourage integrative physiology might be developed.

L to R

Neurons in the brain.

Professors David Paterson (left) and Peter Hunter of the Heart Physiome Project.

POPULATIONS AND PUBLIC HEALTH

The Populations and Public Health stream aims to improve our understanding of the determinants of disease and quality of life in populations. It promotes the use of this understanding to improve public health and healthcare delivery.

During the year, 53 awards were made in this area, principally through the Health Consequences of Population Change Programme, to a total value of £12.7 million.

Latin America

An initiative to support **Centres of Excellence in Latin America** culminated in the award of four programmes (totalling £3.8 million) to support multidisciplinary research on the impact on health of demographic and socioeconomic changes in the region. Professor Mauricio Barreto (Univesidade da Bahia, Salvador, Brazil) will study the impact of urbanisation, migration and lifestyle changes on allergic diseases (atopy and asthma). A parallel study in Quito, Ecuador, in collaboration with Dr Philip Cooper (a Wellcome Trust Senior Research Fellow), will compare the prevalence of allergic diseases, and risk factors, in rural and urban populations.

Also in Brazil, Professor Cesar Victora (Federal University of Pelotas) will compare two large birth cohorts to explore how early life factors – such as nutrition, socioeconomic, cultural and healthcare issues – influence adolescent and adult health.

Professor Luis Rosero-Bixby's team (Universidad de Costa Rica) will address the role of social, nutritional and healthcare factors in longevity and active life expectancy in the country, while collaborations with Cuba and Mexico will study how different public health approaches affect ageing in the region.

Finally, Dr Elsie Le Franc (University of the West Indies) will examine the possible causes of family and interpersonal violence, especially among adolescents and young adults. The project will assess a number of possible risk factors, including family structure, social networks, and instabilities resulting from migration.

Major centres

Dr Michael Bennish at the **Africa Centre for Health and Population Studies**, University of KwaZulu-Natal, South Africa has been awarded funding for a feasibility study to examine different approaches to using antiretroviral drugs against HIV infections in resource-poor settings. These drugs are normally used on a long-term basis to suppress disease, with careful monitoring of patients – presenting major challenges where the numbers of people in need are large and resources are scarce.

The Trust-funded building housing the Africa Centre at Somkhele has been widely praised – a tribute to a distinctive building that reflects the Centre's commitment to community-based health research. A series of regional and national awards culminated in the South African Institute of Architects Award of Excellence for 2002, where the building was described as one of the best ever built in South Africa.

Professor Huda Zurayk, Center for Research in Population and Health, American University of Beirut, was awarded a £1.86 million programme grant to continue her studies on reproductive health of women, health of adolescents and the elderly in the Middle East. The award reflects the progress made since it was awarded a 'regional centre of excellence' grant in 2001.

Training

The **Master's-level Research Training Fellowship** scheme was reviewed during the year. The awards consist of a taught course, followed by a research project in the applicant's home country. In all, 67 individuals received Masters' support between 1998 and 2002. Most have thrived professionally and still appear to be working in their home country, attesting to the success of the scheme in strengthening research capacity.

Other notable awards

Two awards under the **Health Consequences of Population Change Programme** address key areas in ageing research – diet and vision. Professor Ricardo Uauy (London School of Hygiene and Tropical Medicine, with the University of Chile) will be evaluating a nutritional supplementation and exercise programme initiated by the Government of Chile.

Professor Astrid Fletcher (London School of Hygiene and Tropical Medicine, with the All India Institute of Medical Sciences) will continue research into age-related eye disease in India, following a successful Trust-funded pilot study. This is a population-based study to map prevalence rates for macular degeneration and cataract, the impact of these conditions on quality of life, and possible risk factors such as diet, smoking and use of cooking fuels.

UK Biobank

The UK Biobank project, a partnership between the Wellcome Trust, the Medical Research Council and the Department of Health, will collect current health, lifestyle and medical history data on 500 000 volunteers aged 40–69. The data will be a powerful tool for researchers exploring the origins of complex diseases. In November 2003, UK Biobank Ltd was established as a charitable company and in January 2004 the Board of Directors, chaired by Sir Alan Langlands, Principal and Vice-Chancellor of the University of Dundee, held its first full meeting. In August 2004, Alastair Campbell, Professor of Ethics in Medicine at the University of Bristol's School of Medicine, was appointed chair of the UK Biobank Ethics and Governance Council.

MEDICAL HUMANITIES

The Medical Humanities stream aims to enhance understanding of the historical and social context of medicine and biomedical science. It supports research programmes in history of medicine and biomedical ethics, and encourages use of research findings, for example to inform public policy making.

In the history of medicine, a Strategic Award was made to Dr Mark Harrison (University of Oxford) for his study 'The history of infectious disease, and medicine in the tropics'. Enhancement Awards were made to Professor Virginia Berridge (London School of Hygiene and Tropical Medicine), Professor Anne Crowther (University of Glasgow) and Dr Nick Hopwood (University of Cambridge).

Two University Awards were made, to Dr Tim McHugh (Oxford Brookes University; Rural medical charity and society in Brittany, 1598–1789) and Dr Rosemary Elliot (University of Glasgow; Smoking and health in Germany from occupation to reunification, 1945–1995). Fellowship and project support covered a wide range of topics, from Unani practice in India to fungal diseases in modern medicine.

Preservation

The **Research Resources in Medical History** scheme was set up to improve access to documentary collections that are important to historians of medicine, by funding preservation, conservation, cataloguing and digitisation projects.

In June 2004, the scheme was extended for a further two years, with funds of £500 000 available each year. In its first four years, the scheme has funded 58 projects to a total value of £2 million.

An evaluation of the scheme carried out in 2004 discovered that institutions that have received funding for cataloguing now urgently require second-stage funding for preservation and conservation. As a result, the new scheme is focusing primarily on preservation and conservation, although proposals for cataloguing projects will still be accepted.

Biomedical ethics

Research is supported on issues relevant to policy and practice in the UK and the conduct of biomedical research in the developing world. A total of 50 awards in biomedical ethics were made in 2003/04, primarily project grants but including six fellowships, nine studentships and 17 symposia. The Wellcome Trust also organised a workshop, 'Investigating ethics and mental disorders'.

Among the research projects funded, Dr Sheila McLean (University of Glasgow) was awarded a project grant to review and evaluate **clinical ethics committees** in the UK. Dr Robin Williams (University of Durham) received project grant funding for follow-up to his previous study on the **UK National DNA database**, this time reviewing forensic databasing in support of criminal investigation in the EU states, and how DNA data are being shared across national borders.

Dr Mike English, a clinician at the KEMRI/Wellcome Trust Major Overseas Programme in Kenya, was awarded project grant support to investigate the **research-to-policy-to-practice pathway** in Kenya. He will explore the environment in which health policy decisions are made, mapping out the linkages and information flow between key stakeholder groups.

The development of novel diagnostics, therapeutics and health services is increasingly predicated on the search for significant biological differences within and between populations. Dr Paul Martin (University of Nottingham) was funded to investigate how the categories of **race/ethnicity** are used in research and what their practical impact might be.

Wellcome Trust Centre for the History of Medicine

Research at the The Wellcome Trust Centre for the History of Medicine at University College London, led by Professor Hal Cook, spans a wide range of topics, eras and countries. The Centre also organises outreach activities and teaching at undergraduate, Master's and PhD levels. The Centre began a new MA course in 2004, recruiting 13 students from a variety of backgrounds.

Professor Janet Browne continued to add to the prizes awarded to her book *Charles Darwin: Volume 2 – The power of place* (Jonathan Cape), including the W H Heinemann prize from The Royal Society of Literature. Her book was also short-listed for the British Academy Book Prize 2003.

Professor Vivian Nutton's *Ancient Medicine* was published by Routledge in 2004, while six *Wellcome Witnesses to Twentieth Century Medicine*, published by the Centre, are now available online.

The Centre has a varied outreach programme. Professor Roger Cooter began a column in the *Lancet* on 'Keywords in the history of medicine', while members of the Centre appeared in the six-part Radio 4 programme *The Other Medicine* presented by Anna Ford. Dr Sanjoy Bhattacharya and Dr Andrew Hull advised and appeared on the recent Channel 4 documentary *The Great Asian Invasion* discussing the role of Asian doctors in the formation of the NHS. Professor Kan-wen Ma contributed to parliamentary consultations on the regulation of complementary and alternative medicine.

www.ucl.ac.uk/histmed

L to R

Boys in Kenya.

Dr Mark Harrison of the University of Oxford.

TECHNOLOGY TRANSFER

Technology Transfer at the Wellcome Trust seeks to maximise the impact of research innovations on health by facilitating the development of early-stage projects to a point at which they can be further developed by the market.

For the Wellcome Trust to achieve its mission, it is important that the basic discoveries made by the scientific community are translated into practical innovations that can be utilised directly or indirectly to improve human and animal health. To be effective in translating scientific advances into health products, scientists need to engage with the business and investment community. Bridging the gap between academic research and commercial R&D is difficult because of the risks inherent to early-stage translation. This is a particular problem in the healthcare sector, where the technical and regulatory hurdles are a significant challenge on the path to market.

Technology Transfer at the Wellcome Trust seeks to mitigate the risks of **early-stage translation** by funding projects that are too early to attract venture capital or to be seen by industry as credible in-licensing opportunities. Up to 2003, it achieved this through the £20 million **Development Fund**. Over a period of five years, this has supported around 40 projects from 14 institutions. Many of these have raised additional investment and two have developed products already (see pages 22 and 27), although it is still too early to appreciate the full impact of the funding provided.

In March 2003 the Wellcome Trust announced two new forms of translation award. **University Translation Awards** provide a response-mode funding stream. As such, they are used to support a diverse array of technologies, not only from biology but also from the physical sciences and mathematics. The common requirements are that the research is aimed at the improvement of health and that the project can be advanced to a point at which it represents an attractive proposition for follow-on support by a third party. Both academic institutions and associated early-stage companies are eligible to apply for these translation awards. Managing projects to a successful outcome is the responsibility of the institution or company management.

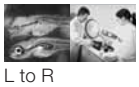
Technology Transfer has just completed the first full year of funding of University Translation Awards. Of 58 applications received from 30 institutions, 25 per cent were awarded. An equivalent number of awards were made to university departments and small businesses. The mean value of these awards was £276 000 (range: £48 000 to £594 000). In keeping with the response-mode nature of the scheme, projects were funded that addressed a wide range of potential applications – including therapeutics, vaccines, diagnostics and medical devices, as well as new platform technologies. One award was made to investigate the effectiveness of policy tools for promoting translation in neglected diseases, such as malaria and African sleeping sickness.

Strategic Translation Awards are a second form of funding designed to support translational research in areas of key importance to the Wellcome Trust. These may be technologies that have a particular role in support of the Trust's mission and address an unmet need in healthcare, and where Technology Transfer can add value by providing project management support or securing follow-on funding.

Four Strategic Translation Award applications have been considered since the scheme was announced. These related to diagnostics, vaccination and a novel genotyping technology. The mean value of the awards was £1.3 million. Further developments in strategically important translational research are likely to be announced in the coming year.

There has been encouraging progress in a number of the projects supported through the Development Fund. **CellTran**, a spin-out company from the University of Sheffield, launched a 'smart bandage' product called '**Myskin**' for the treatment of serious burns (see page 27). Another early-stage company, **Diagnostics for the Real World**, has developed dipstick technology for the diagnosis of *Chlamydia* infection (see page 22).

The year also saw important developments in a drug discovery project, based at the Institute of Cancer Research, on a mutant form of the **B-Raf kinase associated with malignant melanoma.** The project is being taken forward by a partnership that includes the Institute itself, Cancer Research Technology, the Wellcome Trust Sanger Institute, the Wellcome Trust and **Astex Technology**, a biotech company with expertise in drug discovery, especially structure–activity relationship research. With the expanded team, the programme is set to progress through the critical phases of lead selection and lead optimisation over the coming year.



L to R

Zebrafish embryos.

Scientists at the Sanger Institute.

WELLCOME TRUST GENOME CAMPUS

The Wellcome Trust Genome Campus, at Hinxton, near Cambridge, is home to the Wellcome Trust Sanger Institute, the Wellcome Trust Conference Centre and Wellcome Trust Advanced Courses. The Genome Campus is currently being extended to provide additional laboratory and ancillary space.

Wellcome Trust Sanger Institute

The Wellcome Trust Sanger Institute is one of the world's leading scientific establishments, generating and providing data and resources to the global scientific community. Genome sequence and the multitude of variants present in a population are responsible for many of the differences between individuals, from cognition to cancer predisposition in humans to virulence in pathogens. Hence DNA sequence provides an essential platform for much of biomedical research.

The Sanger Institute produced the largest contribution to **finished human genome sequence** (see page 6), and has also developed tools such as the **Ensembl** gene browser which enable hundreds of thousands of researchers to view and utilise genome sequence data from 17 different species via the web, with human and mouse the most popular.

In 2004, papers from the Sanger Institute describing the sequence content of **chromosomes 6, 9 and 10** – a total of nearly 400 million base pairs – were published. The Sanger Institute has now produced some **2.5 billion base pairs** of finished sequence.

The Sanger Institute has increased its faculty strength to 35, as its programmes evolve to place a greater emphasis on gene function through genetic analysis in humans and model organisms.

High-volume sequencing continues to fuel many of these activities: during last year the **zebrafish genome** was a priority, but there was an increasing emphasis on re-sequencing in humans, mice and pathogens to document variation and identify disease-causing alleles.

In the past year the Sanger Institute has identified genes that play a role in **diabetes** and **lung cancer** (see pages 12, 22), while the genome of MRSA (methicillin-resistant *Staphylococcus aureus*) was decoded. The Sanger Institute plays a leading role in identifying variation in the **major histocompatibility complex** – a key part of the immune system which is also involved in autoimmune diseases such as arthritis and type 1 diabetes.

Teams from the Sanger Institute have been funded by the US National Institutes of Health to contribute to the **ENCODE** (Encyclopedia of DNA Elements) project, a consortium that aims to put in place the best technologies to map all functional elements of the genome. In its initial pilot phase, 1 per cent of the human genome is being evaluated.

The Sanger Institute now has established major activities in **mouse genetics** and this year announced the development of SITGR and MICER, two resources for mouse functional genomics. These freely available resources are dramatically accelerating the process of discovering gene function in mice in laboratories across the globe.

Wellcome Trust Conference Centre

The Conference Centre continued to expand its activities, hosting some 200 meetings and more than 7500 delegates. Highlights of the year included five large Wellcome Trust Conferences – Functional Genomics, Days of Molecular Medicine, Genomes 2004, Functional Genomics of Host–Pathogen Interactions, and Genome Informatics.

The latter two events were held jointly with Cold Spring Harbor Laboratory. International collaboration was also a feature of Days of Molecular Medicine (coorganised with the University of California San Diego and *Nature Medicine*) and Genomes 2004 (with The Institute for Genomic Research and Institut Pasteur).

These events have been well attended and well received, and more will be organised for 2004/05 and beyond.

Wellcome Trust Advanced Courses

The Wellcome Trust Advanced Courses programme provides postdoctoral researchers with **hands-on training in emerging research techniques**. The courses, which are attended by researchers from all over the world, are held in dedicated laboratories in the Wellcome Trust Sanger Institute.

During the year four Advanced Courses were held – Genotype to Protein, DNA Microarrays, Functional Genomics and Human Genome Analysis. In addition four bioinformatics **Open Door Workshops** were held, giving participants hands-on experience of working with human and pathogen genome sequences.

The Advanced Courses programme was positively reviewed in 2003, and new courses will be added from 2004/05 onwards in key areas.

South Field Project

The South Field Project, the £95 million development of the Genome Campus, remained on schedule to be completed in 2005.

The 13 000 square metre development will provide additional **research laboratories and data-handling facilities** for the Sanger Institute and improved ancillary facilities for all Genome Campus staff. The laboratories will provide additional space for genomic and molecular biology research, while the data centre will provide a substantial increase in the computing power of the Sanger Institute, making it one of the most advanced in Europe. The **ancillary building** houses a new lecture room, restaurant facilities and sports hall and gymnasium. Completion and handover of the project is scheduled for spring 2005.

PUBLIC ENGAGEMENT

The Wellcome Trust's Public Engagement activities aim to raise awareness and understanding of biomedical science, its social and ethical implications and its historical context.

Grants

A total of 41 Society Awards were awarded under the £3 million Engaging Science grants programme. These large awards of £50 000 or more support public engagement projects in designated areas – in 2003/04, 'broadening access', 'young people's education' and 'Sciart'.

Society Awards under the 'broadening access' theme included an award to Dr Guto Roberts to introduce biomedical science to the National Eisteddfod of Wales, the most important annual cultural festival of Wales, and one to Dr Carolyn Stephens at the London School of Hygiene and Tropical Medicine, to see whether children's participation in epidemiological research can stimulate an interest in medical science.

Ten Research and Development Awards of up to £15 000 were awarded under the Sciart theme, as were four Production Awards of around £100 000: *The Fluent Heart*, an original music and dance work inspired by the cardiovascular system, created by composer Sir John Tavener, heart imaging specialist Dr Philip Kilner and choreographer Wayne McGregor; *Projected Worlds*, an exhibition and events season at Camden Arts Centre exploring how scientific intervention transforms our surroundings; *How To Live*, a live performance by Bobby Baker, inspired by her experience of dialectical behavioural therapy and created with psychologist Professor Richard Hallam; and *Tomorrow Belongs to Me*, a series of filmed interviews with scientific and medical professionals researching inherited genetic disorders, by artist Jacqueline Donachie and geneticist Dr Darren Monckton.

A notable award under the Young People's theme was for a project at the University of Bristol, which will create young people's Research Ethics Committees. School students will consider real grant applications and feed back comments to the actual panels considering the applications.

A total of 31 **People Awards** – a fast-response mechanism to support smaller projects – were also funded under the Engaging Science programme.

In 2003, 27 awards were made through the **Pulse** initiative, which encouraged youth theatre and dance companies to develop new performance arts projects to engage young people with science. The projects embraced a huge spectrum of themes, including the bioscience of light, neuroscience, cloning, eugenics, ageing and vaccination programmes.

This year saw many performances based on projects funded through Pulse. In addition, a two-day conference at the University of Manchester (25–26 June 2004) featured performances and enabled participants to share thoughts about their experiences. The initiative has been so successful that a second competition is planned for 2005.

Grants worth £2.5 million were made by the Wellcome Trust through the £33 million Rediscover initiative. This partnership with the Millennium Commission and the Wolfson Foundation provided funds for science centres and museums to redevelop their exhibits. Recipients of Trust funds included the Centre for Life in Newcastle upon Tyne, W5 at Odyssey, Belfast, Sensation in Dundee and the Eden Project in Cornwall (see page 32).

Public participation

In September 2004 the Wellcome Trust and BBC Science launched the second **Imagine** photographic competition to encourage school groups, young people and adults to explore 'how is science changing us?'

The Wellcome Trust organised a series of **online debates** and public events with **Spiked**, an online publisher and discussion forum (www.spiked-online.com). The opening debate in the series, 'Fearing the Unknown: Are we too risk averse?' questioned whether society was excessively preoccupied with exaggerated risks. The second debate, 'Human Body Parts', focused on issues around the Human Tissue Bill, including consent and the use of human tissue and organs in research. Debates were also organised with the **Institute of Contemporary Arts**. The first debate looked at privacy and questions of how personal biomedical data are used; the second at the pathway from research to the media.

Exhibitions

Pain: Passion, compassion, sensibility ran from 13 February to 20 June 2004 at the Medicine in Context Gallery at the Science Museum (see page 30). To accompany the exhibition, a public event, *The Heartache of St Valentine's Day*, was held at the Dana Centre on 11 February 2004, while a series of films and debates about pain were organised at the Institute of Contemporary Arts (ICA) in London.

An innovative multimedia **CD-ROM** catalogue was produced for the exhibition, featuring a gallery of works from the exhibition, audio and video clips, and specially commissioned essays. The CD-ROM catalogue was shortlisted for the prestigious 2004 AXA Art Exhibition Catalogue Award, run by the Art Newspaper and specialist insurer AXA Art.

Woodland ecology.

The Wellcome Trust Gallery at the **British Museum**, funded by a £5.4 million grant to the British Museum, opened on 3 November 2003 with ***Living and Dying*** (see page 31).

Pharmakon ran from 17 October 2003 to 6 February 2004 at the TwoTen Gallery on Euston Road. The exhibition featured works from the US artist Beverly Fishman.

Wonderful: Visions of the near future, a major collaborative science and art venture exploring the languages and assumptions of art and science and what happens when these research interests fuse, opened at the Arnolfini Gallery in Bristol in February 2004. Supported by the Wellcome Trust and other partners, *Wonderful* comprises a national touring exhibition, new commissions, live work, an education CD-ROM, conference, publication and interpretative film.

Education

Construction work began on the new **National Science Learning Centre** at the University of York, part of the £51 million national network of Science Learning Centres being funded by the Wellcome Trust and the Department for Education and Skills. The national centre, which is due to open in autumn 2005, will be run by the White Rose Consortium. The national network aims to provide enhanced professional development opportunities for science teachers and technicians.

Life Study, a research report describing the views and attitudes of a range of stakeholders and interested parties towards **A-level biology**, was published in October 2003. The research was commissioned by the Wellcome Trust and carried out by the Centre for Education and Industry at the University of Warwick.

Two editions of ***LabNotes: New biology and society*** – a publication providing teachers with up-to-date information on research findings in biomedicine and their wider social implications – were published during the year. ***Ageing*** covered the science and social implications of increased longevity, while ***Dying for change: Infectious disease in the developing world*** examined the reasons underlying the huge impact of infectious disease in resource-poor countries.

Wellcome Library

Significant progress was made on the cataloguing of the **Wellcome Foundation Ltd** archive (which was transferred to the Wellcome Library from GlaxoSmithKline in 2001). The cataloguing project will help illuminate both the early development of the Wellcome pharmaceutical company and the wider history of the pharmaceutical industry in the UK.

Public outreach, particularly with schools and young people, was a feature of the Wellcome Library's year. Fourteen students from South Camden Community School, all refugees, embarked on the Remedies and Recipes project. After visiting the Wellcome Library to examine a range of recipe books they compiled their own books of home cures from both the UK and their home countries.

Two GCSE **Medicine Through Time INSET days** were run by the Wellcome Library in partnership with the Schools History Project (www.tasc.ac.uk/shp) with the aim of improving teachers' knowledge and increasing their confidence in teaching the history of medicine. The first, held in January 2004, examined why Victorian industrial towns were so unhealthy; the second, held in June 2004, explored changes in medicine, surgery and our understanding of the human body over this period.

The Wellcome Library ran a programme of 40-minute **video-conference sessions** for schools. Topics included 'What's the Difference?', looking at medical advances in the 19th and 20th centuries, and 'What Was it Like?', exploring Tudor and Victorian healthcare. During the sessions children could see unique items from the Wellcome Library collections (such as Louis Pasteur's notebooks from his time as a student in Paris) via a video link. They then had the opportunity to ask questions about the material and the subject. This enabled them to get first-hand experience of historically significant objects without needing to make a special trip.

The Wellcome Trust contributed £750 000 to a project promoting **open access to published scientific papers**. Run by the Wellcome Library, the Joint Information Systems Committee and the US National Library of Medicine, the new project will digitise the full text of every issue of a number of important medical journals.

Publications

Talking Heads: Cognitive behavioural therapy comes of age, the latest *Wellcome News Supplement*, was published in June 2004. It featured articles exploring the latest thinking on cognitive behavioural therapy – and how it is being applied to a wide range of disorders, including depression, social phobia, post-traumatic stress disorder, schizophrenia and borderline personality disorder.

An evaluation of ***The Human Genome microsite*** – which provides key information about the human genome – indicated that the site is a valuable and widely used resource; it attracted around 280 000 visitors in the year. A microsite was also developed to accompany the *Pain* exhibition, providing articles on the science, medicine, culture and history of pain.

An Advocacy and Training Interactive Guide was produced in 2004 for the Schistosomiasis Control Initiative (SCI). The CD-ROM was produced in collaboration with the SCI at Imperial College, London, which is funded by the Bill and Melinda Gates Foundation. The CD-ROM delivers programme-oriented advocacy messages and training materials to those responsible for implementing the programme. A French translation of a *Lymphatic Filariasis* CD-ROM was published in August 2004. In the Topics in International Health series of CD-ROMs, a revised edition of *HIV/AIDS* was launched in November 2003.

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Cover: Pyramidal neurons forming a network in the brain. *J Clarke*

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