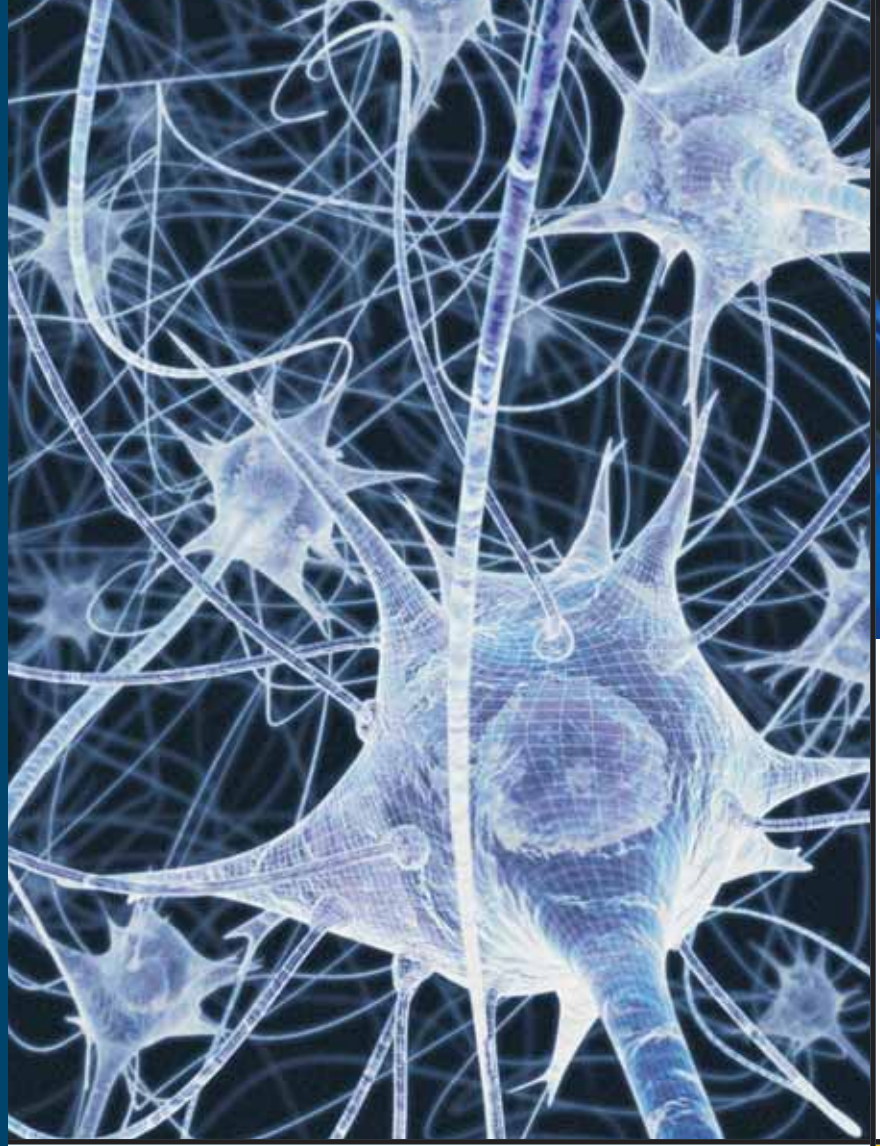


1 October 1999 – 30 September 2000

ANNUAL REVIEW

THE WELLCOME TRUST

The Wellcome Trust

CONTENTS

Highlights of the year

KNOWLEDGE BASE

Genomics
The first draft of the human genome is completed by the Wellcome Trust Sanger Centre and international partners, and the achievement announced to all at the Wellcome Trust on 26 June 2000.

Sequencing of the *Salmonella typhi* (typhoid) and *Yersinia pestis* (plague) genomes is also completed at the Sanger Centre.

Post-genomics
Data released by the SNP Consortium – a £30 million collaboration between the Trust and a number of pharmaceutical and technological companies – are used to create a high-resolution map of genetic markers.

The Trust invests in a new microarray facility at the Sanger Centre, in partnership with the Imperial Cancer Research Fund.

The Trust begins planning a major new initiative in functional genomics, Integrated Thematic Programmes, which aims to bring together research groups from different disciplines to address a single biological question.

International
Seven awards totalling £12 million are made to trilateral research collaborations in the first round of the Wellcome Trust–Burroughs Wellcome Fund Infectious Diseases Initiative. A second competition is launched in 2000.

History of medicine
The Trust publishes a survey appraising the development of history of medicine in the UK over the last 30 years.

The Academic Unit – formerly part of the Wellcome Institute for the History of Medicine – is transferred to University College London (UCL) and becomes the Wellcome Trust Centre for the History of Medicine at UCL.

Professor Hal Cook from the University of Wisconsin at Madison, USA, is recruited as Director of the Centre at UCL in June 2000.

Medicine in society
The Trust's Biomedical Ethics Programme calls for proposals for research into the ethical, legal and social implications of pharmaco-genetics and biological sample collections.

RESOURCES

Infrastructure
The Trust awards £124 million and £71.8 million in the second and third rounds of the Joint Infrastructure Fund, a £750 million partnership between the UK Government and the Wellcome Trust to inject much-needed funds into the UK university research infrastructure.

The Trust pledges £225 million to the £1 billion Science Research Investment Fund, established by the UK Government in 2000.

Careers
Seven new four-year PhD Training Programmes are awarded to universities in December 1999, bringing the number of programmes to 12.

The Wellcome Trust publishes the results of two surveys of past and present Trust-funded PhD students in March 2000.

The Trust publishes the results of an investigation into grant application behaviour to examine why fewer women than men apply for grants.

Centres
The Wellcome Trust and Cancer Research Campaign Institute of Cancer and Developmental Biology in Cambridge and the Wellcome Trust Centre for Cell-Matrix Research at the University of Manchester are reviewed and their core funding is renewed.

International
The Trust's international units in Kenya and South-East Asia receive site visits and are awarded funding for another five years.

The Wellcome Trust Centres for Research in Clinical Tropical Medicine in the UK are also renewed.

History of medicine
The Wellcome Trust's History of Medicine Library celebrates its 50th anniversary in December 1999.

The History of Medicine Library joins with the Information Service and the Medical Photographic and Film and Video Libraries to form the Wellcome Library for the History and Understanding of Medicine.

The Trust adds a Senior Research Fellowship scheme to its History of Medicine Programme and makes two awards.

Company history

Glaxo Wellcome (now GlaxoSmithKline) donates the company records of the pharmaceutical company, the Wellcome Foundation Ltd, to the Trust, bringing all the personal and business archives of Sir Henry Wellcome and his partner, Silas Mainville Burroughs, together under one roof.

Professor Roy Church and Dr Tilli Tansey unearth the account book of Burroughs Wellcome & Co., documenting its financial activity between 1880 and 1940.

TRANSLATION

Dissemination

The Trust awards £8 million to a collaboration between the Sanger Centre and European Bioinformatics Institute (EMBL-EBI – part of the European Molecular Biology Laboratory) to develop Ensembl, an annotated view of the human genome.

The Trust's Tropical Medicine Resource launches four new CD-ROMs in its 'Topics in International Health' series of multimedia teaching materials.

Exploitation

Six awards are made by the Catalyst BioMedica Development Fund, set up to facilitate the exploitation of Trust-funded research.

Clinical research

The Trust holds a workshop to encourage debate on research issues in complementary and alternative medicine, and presents a report on the workshop to the House of Lords Select Committee on Science and Technology.

International

The Trust funds an international meeting in Liverpool to discuss the implementation of Lapdap, a new antimalarial drug developed at its Kenyan unit.

PUBLIC ENGAGEMENT

Surveys and consultations

Science and the Public, a nationwide survey of public attitudes to science sponsored by the Wellcome Trust and the Office of Science and Technology, is published.

The Wellcome Trust and Medical Research Council commission research to discover the public's views on the proposed UK Population Biomedical Collection.

Science Centres

Five of the eight Science Centres, to which the Trust has contributed £45 million, open in London, Manchester, Newcastle, Bristol and Dundee.

The Wellcome Wing of the Science Museum is opened by the Queen on 27 June 2000.

Art and drama

A total of £200 000 is awarded to 11 innovative science–art partnerships in the 2000 sciart competition.

Three Trust-sponsored plays perform at the Edinburgh Fringe Festival: *The Idiot*, *Learning to Love the Grey*, and *Safe Delivery*.

A new Science on Stage and Screen competition – seeking to engage the public's interest in biomedical science or health through the use of drama, film/video and multimedia – is approved.

Schools

The Trust commissions the Institute of Education to investigate how teachers approach the social, legal and ethical implications of science in the classroom.

Seventy-seven PhD students spend four days working alongside teachers and pupils in schools as part of the Researchers in Residence scheme.

Two new issues of the *LabNotes* series – 'Down at the Pharm' and 'Beyond the Genome' – are published.

Director's introduction

The future within

More than ten years ago, I discussed with my colleagues the logistics and philosophy of a huge new undertaking, the Human Genome Project. For the logistics, our feeling then was that the project was entirely feasible and would bring enormous benefits in the future should it succeed. But perhaps more interesting were the philosophical discussions about how the human genome would change our views of science and of what it means to be human. It brings to mind a comment by the French ocean explorer Jacques Cousteau: "What is a scientist after all? It is a curious man looking through a keyhole, the keyhole of nature, trying to know what's going on". Once the human genome is completed, the curious geneticist will have stopped looking through the keyhole and will have stepped through the door to gaze upon human inheritance.

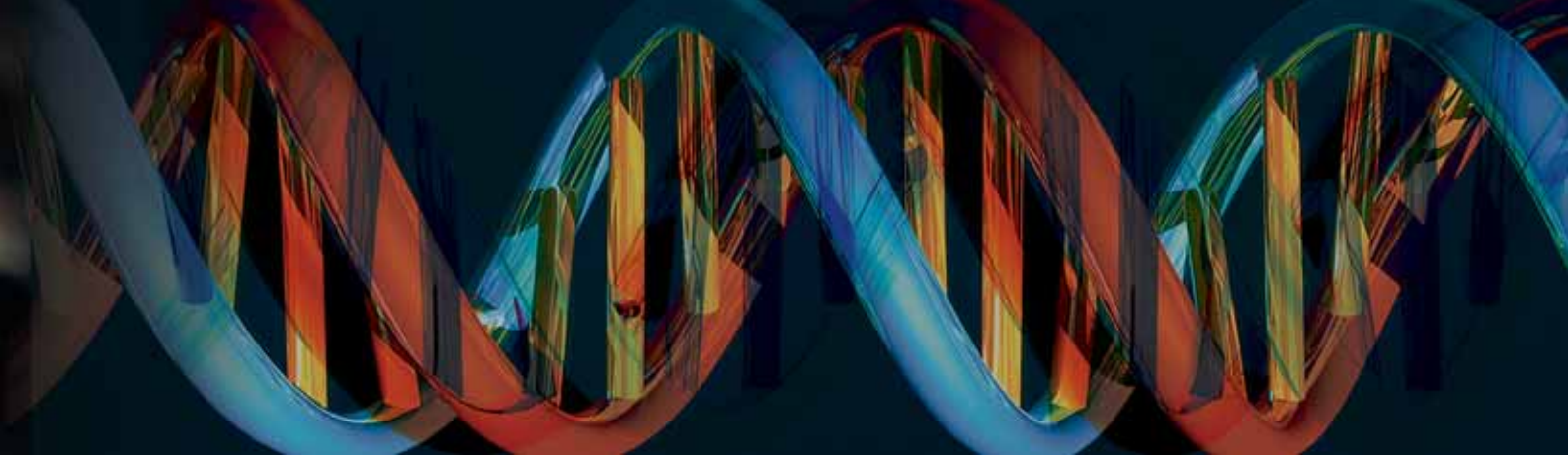
The announcement in June 2000 that the milestone of the first draft of the human genome sequence had been reached was – quite rightly – headline news around the world, and it is a source of enormous pride that the UK is responsible for fully one-third of the human genome sequencing.
The members of the team at the Wellcome Trust Sanger Centre, led by Sir John Sulston, deserve every plaudit they receive as they have demonstrated outstanding commitment and dedication in reaching their targets and maintaining standards of excellence.

Of course, much work remains to be done – not only on finishing the human genome sequence, so that it can be the definitive resource for all researchers, but also on finding ways to use this information to advance health. To realize the full benefits of years of work by the scientists involved in the sequencing programme, it is imperative that all the human genome sequence is immediately and freely available to the biomedical research community, whether in academia or industry, with no restrictions on how it is used. We are fully committed to such principles, as enshrined in the Bermuda agreement of 1996, and the Trust's grant of £8 million to the Ensembl website will help the development of this free-access Internet 'gateway' to the genome.

The UK is fortunate to have so many talented and innovative scientists, and it is essential that we back them with the high-quality resources and facilities they deserve. Through the Joint Infrastructure Fund (JIF) – a partnership between the Trust and the UK Government – we have been working to address the infrastructure problems that had become apparent in the UK universities. We have now completed all the funding rounds of the JIF, and the Trust has committed £300 million to 56 awards that will provide new buildings and equipment for researchers all over the country. The awards of the first year of the Fund are already bearing fruit, with new equipment installed and construction continuing apace. In total, 152 awards have been made to 41 institutions throughout the UK through the JIF scheme.

Yet the scale of the infrastructure problem has been emphasized by the large number of high-quality applications that we have had to turn down because the threshold for success was so high. It was for this reason that we approached the UK Government with a view to establishing a successor to JIF, the Science Research Investment Fund, in which we have committed £225 million to a £1 billion infrastructure fund for UK universities.

That we can make commitments on such a scale is due to the remarkable growth of the Trust over the last ten years under the chairmanship of Sir Roger Gibbs. The business acumen and foresight of Sir Roger led the unprecedented growth of the Trust from a small charity, spending some £65 million on biomedical research in 1990, to the largest biomedical charity in the world, spending some



£640 million in 1999/2000. This growth has enabled us to make a major contribution to biomedical science not only through our support for scientists and their ideas – the essential bedrock of future development – but also by becoming involved in many ambitious international and UK-based projects.

One of these projects, a first for the Trust, was the development of a consortium with pharmaceutical companies, to identify and map single nucleotide polymorphisms (SNPs) – the differences in our genetic code that play a large part in making us what we are as individuals. I mention this project because it shows how much can be achieved by working in partnerships with others. For a modest outlay, many more SNPs were identified than originally planned, and all of these are now in the public domain, accessible freely and by all.

Sir Roger retired as Chairman of the Trust at the end of 1999 and it is fitting that one of the first tasks of our new Chairman, Sir Dominic Cadbury, was to work with the other Governors in approving the new Corporate Plan for the Trust, *Planning for the Future* (see page 6). Any organization that grows rapidly risks losing sight of its priorities; as Sir Dominic quotes in his preface to *Planning for the Future*, "how do you teach the giant to dance?". The Corporate Plan, the product of more than a year's hard work by staff at the Trust, therefore identifies the key areas in which we intend to focus, providing a framework for all our activities, and helping us to make an impact in areas in which we choose to concentrate.

During the next five years, we anticipate committing more than £3 billion in support of our mission. We will also use this time to enhance a number of our areas of interest. While the Trust has always promoted excellence in almost all fields of biomedical science, fundamental basic research has often taken centre stage. We are looking carefully at ways to improve our impact on clinical, patient-oriented research, the translation of basic research findings into health benefits, international research, and public engagement.

Planning for the Future also help us to set the scene for this, our new *Annual Review*. While the Corporate Plan sets out a framework, here we flesh out these guiding principles, illustrating specifically how the Trust is working to fulfil its aims and objectives through its activities of the last year. In the centre section, we examine just a few of the practical outcomes and outputs of Trust-funded research. Of course, with many thousands of projects around the world supported by the Trust, we can only provide a few pointers to the many discoveries, insights and innovations of Trust-funded researchers. But all of the projects and discoveries are underpinned by one desire – that we can really make a difference to healthcare of the future.

Mike Dexter

April 2001

PLANNING FOR THE FUTURE

The Wellcome Trust 2000–2005

The Wellcome Trust's first Corporate Plan was published in October 2000. *Planning for the Future* sets out a philosophical and practical framework of mission, aims and values that will underpin all of the activities of the Trust for the next five years. Here, we present a brief overview of this framework and describe on the following pages how the Trust's activities in the past year are working towards the key aims and objectives of the Trust.

MISSION

THE WELLCOME TRUST'S MISSION IS TO FOSTER AND PROMOTE RESEARCH WITH THE AIM OF IMPROVING HUMAN AND ANIMAL HEALTH.

AIMS

The four aims identify the priorities on which the Trust concentrates. Each aim is underpinned by a series of objectives which establish the practical measures being taken to achieve the aims and, ultimately, the mission of the Trust.

VALUES

In all that it does to achieve its mission, the Wellcome Trust is guided by a set of values, shared by the staff and Governors.

INDEPENDENCE
To retain our independence of decision making

LEADERSHIP
To create and seize opportunities and help shape the agenda

EVIDENCE
To base funding priorities and policy making on the best available evidence

FLEXIBILITY
To support innovation and manage risk so that we can move rapidly into new and emerging areas in imaginative ways

EXCELLENCE
To achieve excellence within our own work and in the work of those we support

1 KNOWLEDGE BASE

Supporting basic, applied and strategically important research in biomedical sciences
The key objective is to improve the understanding of human and animal biology. Through a variety of mechanisms, the Trust provides support for high-quality research in biomedical sciences in the UK and many countries worldwide.

Researching the societal impact of biomedical science – past, present and future
In order to maximize impact on healthcare, the changing role of medicine in society needs to be understood. To this end, the Trust provides support for research into the history of medicine, public engagement with science and biomedical ethics.

2 RESOURCES

Human resources: meeting training and career development needs of researchers
In order to ensure that academic research is an attractive career for the most creative and innovative scientists, the Trust provides a portfolio of personal award schemes – from early to professorial levels and with competitive salaries, for basic and clinical scientists, historians of medicine and other researchers in fields within the Trust's sphere of interest.

Physical resources: building suitable conditions for research
In order to give researchers the right environment and tools for their work, the Trust provides scientists with state-of-the-art technology and high-quality facilities. For historians of medicine, the Trust maintains and augments its important collections that preserve and record the history of medicine.

3 TRANSLATION

Promoting patient-oriented research and health services research
To encourage application of new knowledge in the clinic, the Trust supports clinical research in the UK and overseas and the study of the provision and use of health services to meet healthcare needs.

Advancing the dissemination and exploitation of the results of Trust-funded research
To ensure that best possible use is made of the results of research, the Trust actively encourages the dissemination of research information into the public domain. To help generate practical medical benefits, Catalyst BioMedica Ltd, a business subsidiary of the Trust, supports the translation of fundamental biomedical research into innovative healthcare products.

4 PUBLIC ENGAGEMENT

Stimulating an informed dialogue to raise awareness and understanding of biomedical science, its achievements, applications and implications
To help develop a culture of mutual respect and understanding, the Trust supports a wide variety of projects that engage the public on the wider ethical, legal and social implications of developments in biomedical science.

WELLCOME TRUST ORGANIZATION

The structure of the Trust reflects the type of support provided to researchers. The activities of major funding divisions of the Trust over the last year are detailed on pages 64–79 of the *Annual Review*. This structure is currently being reviewed to ensure that the Trust's organization reflects and supports the Corporate Plan.

Science Programmes
- UK Panels
- Career Schemes and Clinical Initiatives
- Centres and Initiatives
- International Programmes

Medicine, Society and History
- Medicine in Society (Biomedical Ethics and Public Engagement with Science Programmes)
- Consultation and Education
- History of Medicine Programme
- Wellcome Library for the History and Understanding of Medicine
- Tropical Medicine Resource

Directly Managed Major Initiatives
- Wellcome Trust Genome Campus
- SNP Consortium
- Synchrotron
- Advanced Courses Programme

Catalyst BioMedica Ltd

Directorate
- Director's Office
- Communications
- Legal
- Policy Unit

Other divisions
- Investments
- Finance and Information Management
- Personnel and Services

INTEGRITY
To act responsibly and with integrity in our work and interactions with others

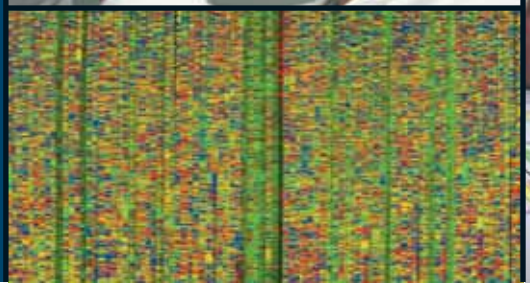
RESPONSIVENESS
To maintain close relationships with our communities and, through this, continue to respond flexibly to their needs

OPENNESS
To be open and transparent in our work

PARTNERSHIP
To work with others where this achieves the greatest benefits to achieve our mission

EMPOWERMENT
To empower and develop our staff to enable them to fulfil their potential and the Trust to fulfil its mission

Knowledge Base



The Wellcome Trust's investment in biomedical research generates new understanding, both of science and of its impact on society. This will provide the essential 'raw material' from which improvements in human and animal health will ultimately be derived.

Genome sequencing

The most significant contribution to the knowledge base last year was celebrated on 26 June 2000, when the Wellcome Trust and international partners in the Human Genome Project announced that the working draft of the human genome sequence had been read. Through its support of the Wellcome Trust Sanger Centre, which sequenced one-third of the human genome, the Trust has contributed more than £200 million to the public-sector endeavour.

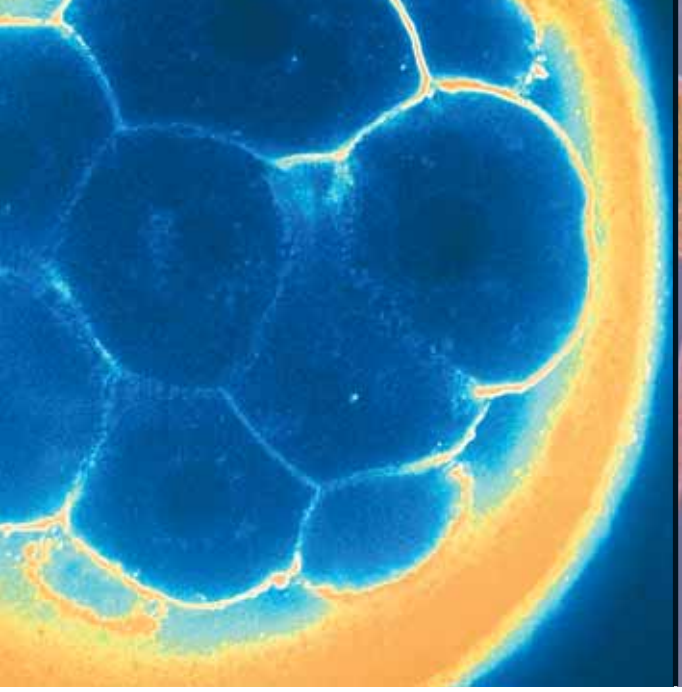
The human genome is the 3 billion base pairs of genetic inheritance carried in every cell of our bodies. Sequencing and mapping of the genome allows us to glimpse what it takes to build a human being and provides clues to our evolution over millions of years of human and pre-human history. The achievement can be seen as the beginning of biology and medicine based on a deeper understanding of the underlying processes of life, and will open up many new possibilities for the diagnosis, treatment and prevention of disease.

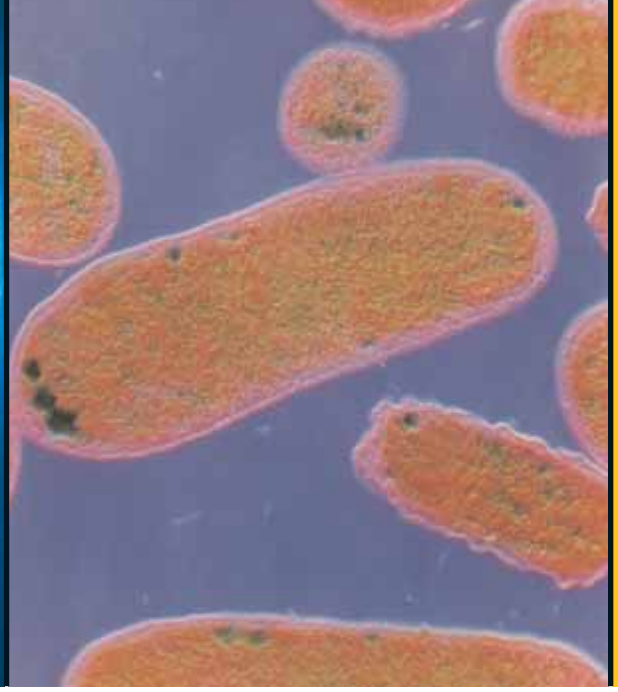
Completion of the first draft means that more than 90 per cent of the human genome is now freely available in Internet databases, providing an immensely valuable resource for researchers in academia and industry. The project is now working to eliminate the gaps and ambiguities in the first draft and to produce a 'gold standard' sequence by 2003.

During 2000, Professor Allan Bradley was recruited to take over from Sir John Sulston as the new Director of the Wellcome Trust Sanger Centre. He will be developing a strategy for the Centre in the post-genomics era. While high-throughput sequencing has been important there is also a need to move on to analysis of gene function.

Models and microbes

As many genes are highly conserved through evolution, the genome sequences of other organisms can offer important clues to the location and function of human genes. In addition, the study of model organisms can help us gain a better understanding of how genes work





Far left to right:

Sir John Sulston.

Read-out from a DNA sequencing experiment.

Dr Julian Parkhill at the Pathogen Sequencing Unit at the Wellcome Trust Sanger Centre.

Section through the nematode worm *Caenorhabditis elegans* – the first multicellular organism to have its genome completely sequenced.

Coloured transmission electron micrograph of *Salmonella typhi*, which causes typhoid fever.

in the complexity of a living system. To this end, in June 2000 the National Institutes of Health (NIH), the Wellcome Trust and three private companies formed the Mouse Sequencing Consortium to speed up the sequencing of the mouse genome and ensure free and rapid data release. The mouse genome will be particularly useful because gene sequences are very similar in mice and humans.

The Pathogen Sequencing Unit of the Sanger Centre is ensuring that the genome sequences of major pathogens are made freely available. In 1999/2000 genome sequences of *Campylobacter jejuni* (food poisoning) and *Neisseria meningitidis* (meningitis) were published, and sequencing of *Salmonella typhi* (typhoid) and *Yersinia pestis* (plague) was completed. Of the parasites, the sequencing of chromosome 1 of *Trypanosoma brucei* (sleeping sickness) was completed, and sequencing began on *Leishmania* (a debilitating ulcerative disease). In June 2000, the Wellcome Trust launched a call for proposals for sequencing the genomes of further pathogens at the Sanger Centre.

The SNP Consortium

A close relation of the Human Genome Project, and one that probably offers the prospect of more immediate medical benefits, is the SNP Consortium, launched by the Wellcome Trust and a number of pharmaceutical and technological companies in 1999. The Wellcome Trust contributed £9 million to the £30 million SNP Consortium, which commissioned four leading academic centres worldwide, including the Wellcome Trust Sanger Centre, to create a high-quality map of genetic markers known as SNPs.

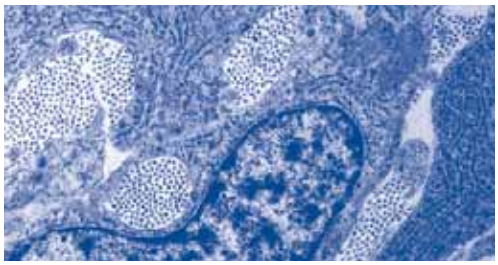
SNPs – single nucleotide polymorphisms, which represent variation at single letters in the genome – occur about once every 1000 base pairs. The 3 million SNPs in our genome account for much of the variation between individuals, and are likely to hold the key to variations in our susceptibility to disease – providing an opportunity for prevention by lifestyle adjustments or medical treatment. SNPs also underlie variation in response to drugs (pharmacogenetics) and could herald an era of 'personalized medicines'. With the torrent of data emerging from the Human Genome Project, many more SNPs have been discovered than originally forecast. SNPs were periodically released freely into the public databases to speed research.

Collagens and cell matrix

The tissues of our body are held together by extracellular matrix (ECM), which provides a network for cell movement, anchorage and support. The most abundant structures in the ECM are collagen fibrils, but it is not fully understood how these fibrils assemble and how they direct tissue organization and function.

In August 2000, Professor Karl Kadler at the Wellcome Trust Centre for Cell-Matrix Research at the University of Manchester was awarded a £1 million programme grant for research into the molecular and structural basis of collagen fibril assembly and function. Professor Kadler and his colleague, Dr Neil Bulleid, are also in receipt of a Development Fund award from Catalyst to support the development of novel engineered collagens for tissue engineering applications.

The programme aims to determine the three-dimensional structure of fibrils, using sophisticated electron microscopy approaches, and to identify some of the mechanisms and molecules involved in their assembly. The work will improve our understanding of normal tissue structure and function, as well as of the pathway of events leading to fibrosis, osteoarthritis and wound healing, where abnormal or new synthesis of collagen occurs.



Emotions on the brain

In February 2000, Professor Jay Belsky, Chair of Psychology at Birkbeck College, was awarded a three-year project grant of £210 000 to test whether the amount of positive or negative emotional stimulation babies receive could affect the development of their brains, making them particularly responsive to either positive or negative stimuli.

Professor Belsky and colleagues are studying the reaction of seven-month-old babies, whose mothers score relatively high or low on a measure of emotional traits, to positive and negative facial expressions. The hypothesis is that an infant whose mother has a relatively 'negative' temperament will respond more to negative facial expressions and vice versa. If this proves to be the case, it would lend credence to the widespread but still empirically unsubstantiated view that early experiences influence the development of parts of the brain involved in processing emotions.

Beyond the genome

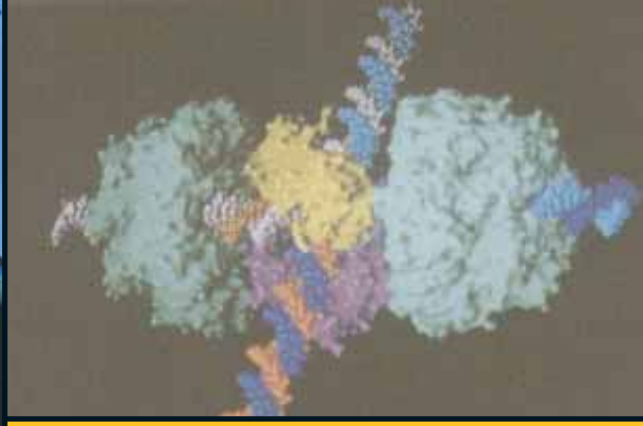
With the human genome sequence readily accessible, researchers have the opportunity to examine gene function on a grand scale – functional genomics. The Wellcome Trust launched its Functional Genomics Development Initiative in 1999 to foster a 'big science' approach towards assigning functions to genes, using high-throughput technologies to study thousands of genes or proteins simultaneously.

A major focus of the initiative is the development of innovative technologies that will make it possible to conduct large-scale experiments. Microarrays, for example (also known as 'DNA chips'), make it possible to monitor the changes in the expression of thousands of genes at once, and the Trust has invested in a new microarray facility at the Sanger Centre, in partnership with the Imperial Cancer Research Fund.

The first phase of the initiative provided support for three schemes: 'biological collections', 'bioinformatics' and 'technology sharing' (page 68). In 1999/2000, the Trust began planning a major new initiative in functional genomics. The aim of its Integrated Thematic Programmes is to bring together research groups from different disciplines to address a single biological question. Collaborations – particularly between biologists and technologists to develop new science-driven technology to interpret the genome – will be an important feature of the scheme.

To gain a fuller picture of the role genes play in the complex functioning of whole organs, systems and bodies – in disease and health – they need to be studied in living organisms. The Wellcome Trust launched its Integrative Animal and Human Physiology Initiative in July 2000 to promote research exploring the relationship between genomic information and physiological mechanisms in humans and animals. As physiology has not received the attention accorded to genomics in recent years, there is a need to develop additional expertise in this area, and training is thus a major focus.

Although some rare diseases are linked to a single gene, most common diseases are multifactorial, with many genes involved. The proposed UK Population Biomedical Collection, a joint project with the Medical Research Council and the Department of Health, aims to investigate the role of genes and environmental factors in predisposing individuals to common diseases such as diabetes and heart disease. The project



Far left to right: Apparatus for recording an infant's response to positive and negative stimuli.

Drs Stephan Beck and Jane Rogers in the sequencing room at the Wellcome Trust Sanger Centre.

The European Bioinformatics Institute at the Wellcome Trust Genome Campus provides researchers worldwide with electronic access to DNA sequences.

A model for the binding of *E. coli* recombination proteins to a DNA Holliday junction.

would involve up to half a million adult volunteers in the UK and would be the largest genetic study ever undertaken in this country.

As well as raising a number of ethical issues (page 26), the proposed collection poses important scientific and logistical questions, such as what cohort and which diseases to study, and how to collect samples and medical information from 500 000 people. These issues are still being considered and a final decision on Trust support will be made in 2001.

Reactive and proactive support

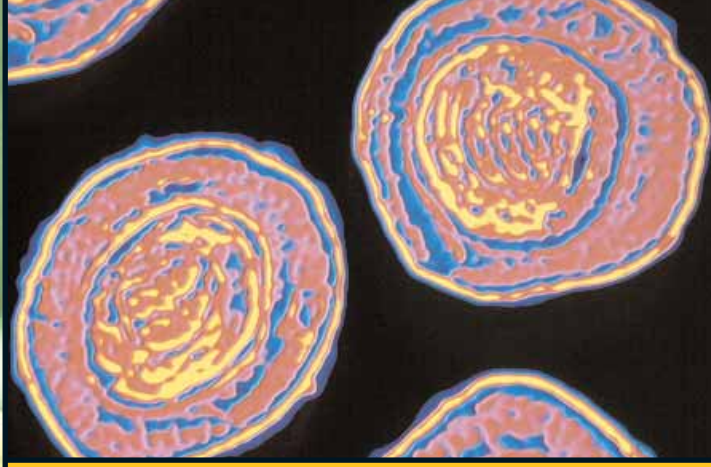
While genes and genomes have been centre stage this year, the Trust has continued to provide significant support for high-quality investigator-led proposals. In 1999/2000 project and programme grants worth more than £150 million were awarded, spanning almost all areas of biomedical science (see page 64).

The Trust's four UK funding Panels form part of the Trust's newly delineated 'baseline funding' stream, which provides ongoing security of support, in a non-directive manner, for outstanding curiosity-driven research. Its 'fixed-term' funding stream provides support for specific, time-limited initiatives – either to take advantage of an emerging area of science, tackle a specific medical issue or build capacity in important or neglected areas.

The third funding stream for 'emerging opportunities' represents resources the Trust has not yet allocated to a particular fixed-term initiative but will commit over the next five years as opportunities are recognized, giving it the flexibility to react swiftly to new challenges and opportunities.

International support

A significant portion of the Trust's annual spend – £72.2 million in 1999/2000 – supports research overseas. Two primary funding mechanisms are travelling research fellowships, which enable scientists from the UK and elsewhere to undertake research projects outside their home countries, and collaborative grants fostering partnerships between laboratories in different countries. The Trust's international units and major programmes in Africa and South-East Asia provide important vehicles for funding research into local health problems. Some UK-based research is also relevant to diseases afflicting the



From left to right: Maternal and child health – a major focus of international research.

Coloured transmission electron micrograph of the whooping cough bacterium.

Professor Jonathan Glover of the Centre of Medical Law and Ethics at King's College London.

Studies on mental health treatments could lead to important implications for healthcare professionals.

A global research collaboration in Mexico

Globally, tuberculosis causes some 1.5 million deaths every year, yet 90 per cent of those infected do not become ill. One hypothesis is that this is due in part to genetic variation between different strains of the *Mycobacterium tuberculosis* bacterium (below).

Funded by a Wellcome Trust–Burroughs Wellcome Fund Infectious Diseases Initiative grant, Mexican scientists led by Dr Ma de Lourdes García-García (Institute Nacional de Salud Publica) and Dr José Sifuentes-Osornio (Institute Nacional De Nutricion) will collaborate with Dr Peter Small (Stanford University, USA) and Professor Douglas Young (Imperial College School of Medicine, London, UK) to study the 'Population pathogenesis of tuberculosis' in Mexico.

The researchers will search for associations between different strains of the bacterium and outbreaks of clinical disease. Identification of the genes that make certain strains of *M. tuberculosis* particularly infectious would be a key step towards better diagnosis, more specific control strategies and improved vaccines in Central America and potentially elsewhere too. Other benefits of this interdisciplinary programme will be substantial training and transfer of expertise among the collaborators, thus increasing the capacity of Mexican science.

developing world. Malaria research, for example, is particularly strong in the UK (page 57), and the genome of the malaria parasite, *Plasmodium falciparum*, is being sequenced at the Wellcome Trust Sanger Centre as part of an international collaboration.

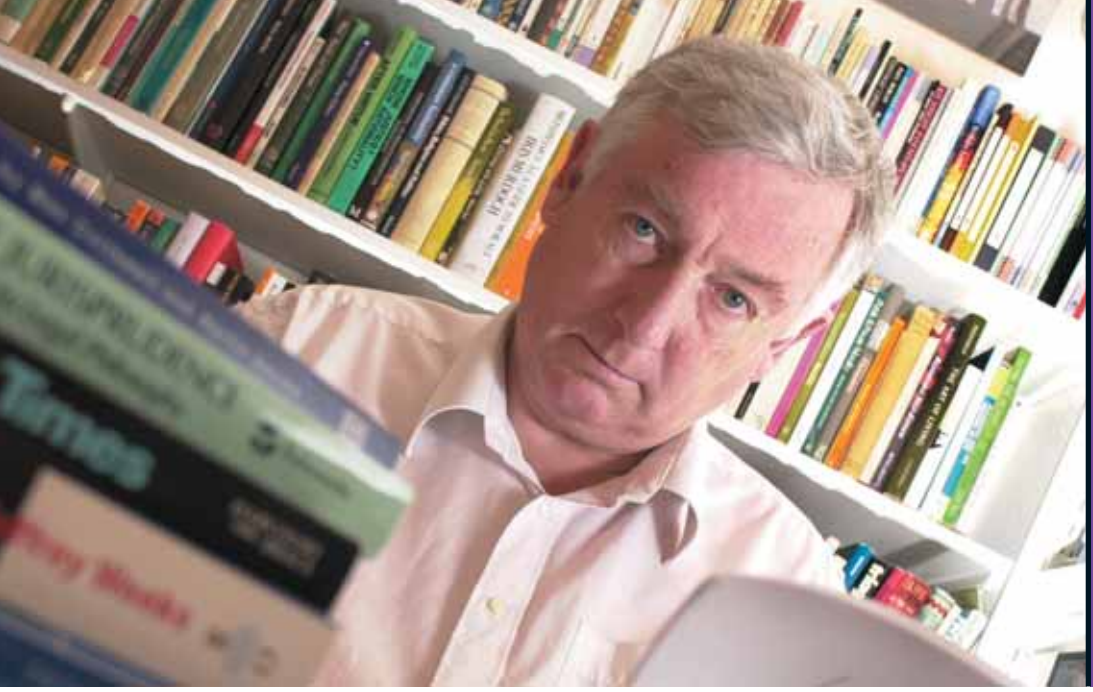
Seven awards totalling £12.6 million were made in the first round of the Wellcome Trust–Burroughs Wellcome Fund Infectious Diseases Initiative late in 1999. The competition aims to foster trilateral research collaborations between developing countries, the UK and North America, with the centre of gravity in the developing world. These awards will support research in countries throughout Africa, and Central and South America, covering diseases such as TB, measles, hepatitis C virus and sexually transmitted diseases. A second competition was launched in 2000.

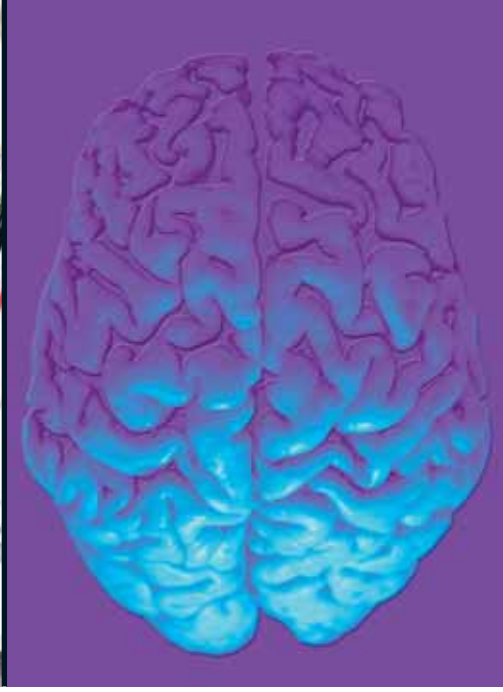
Science and society

The ways in which new findings in biomedicine are assimilated into society are far from straightforward. A greater understanding of these processes will help to ensure that advances in medicine are taken up rapidly, and any unintended negative impacts are anticipated and avoided.

The Wellcome Trust's Biomedical Ethics Programme supports research into the social, ethical and public policy consequences of biomedical advances, particularly in genetics and neuroscience. In 1999/2000, pharmacogenetics and human biological sample collections were identified as high-priority issues where there is likely to be a public policy demand for information, and applications were invited in these areas.

The emphasis of the programme is on empirical research into the experience of researchers, pharmaceutical companies, clinicians, other healthcare professionals, patients and their families. By grounding the research in the real world, the programme aims to contribute to an evidence base that will support well-informed and responsible public policy making – and to help ensure that biomedical science will be able to flourish within prudent and ethical safeguards. In 1999/2000, five project grants, two Research Fellowships, four Research Studentships, two Research Leave Fellowships and seven symposia were awarded.





Historical perspectives

Historical studies enable us to explore the changing role of medicine in society at different times and in different cultures. They can also offer practical input into policy making.

A survey of the development of the history of medicine over the last 30 years confirmed that it has become a flourishing, internationally respected academic discipline in the UK, well integrated into the mainstream university system – and that the Wellcome Trust had played a crucial role in its development. The survey also revealed a strong desire on the part of historians of medicine to communicate to a wider audience, and a belief that the field should communicate with health policy makers and the wider public.

The year ended with the completion of the transfer of the Academic Unit – formerly part of the Wellcome Institute for the History of Medicine – to University College London (UCL), where it became the Wellcome Trust Centre for the History of Medicine at UCL. Professor Hal Cook from the University of Wisconsin at Madison, USA, was recruited as Director of the Centre in June 2000.

Difficult dilemmas

The Biomedical Ethics Programme supports research into the social and ethical impact of biomedical advances. Sharing genetic information in families has emerged as a particularly important theme.

Dr Sheila Simpson at the University of Aberdeen is investigating how and why people at risk of genetic disorders make the decision to inform their children or siblings. The dilemma is heightened by the fact that some inherited diseases, such as Huntington's disease, cannot be prevented or cured. Moreover, people may be disadvantaged emotionally, socially or financially if information is disclosed, and disadvantaged in other ways, perhaps medically, if it is withheld.

Professor Paul Atkinson at the University of Wales in Cardiff is exploring how genetic information is shared or withheld as part of a wider network of social relationships, information exchange and practical family membership. Understanding how and why risk information is shared would be useful for the development of guidelines for genetic counselling.

Resources

The generation of new knowledge depends on the work of talented, committed and well-equipped researchers. The Wellcome Trust aims to give its scientists the professional career support they need and to provide them with state-of-the-art equipment and a research environment conducive to exploration at the frontiers of knowledge.

Career paths

The Wellcome Trust personal support schemes cover a spectrum of careers – from 'tasters' of research for undergraduates to fellowship support at the highest levels of academia – and provide basic scientists, clinicians and veterinary-qualified researchers with a number of career options. Although no promotion is automatic and competition for awards is fierce, 1999/2000 saw a number of Trust-funded fellows successfully apply for more senior awards.

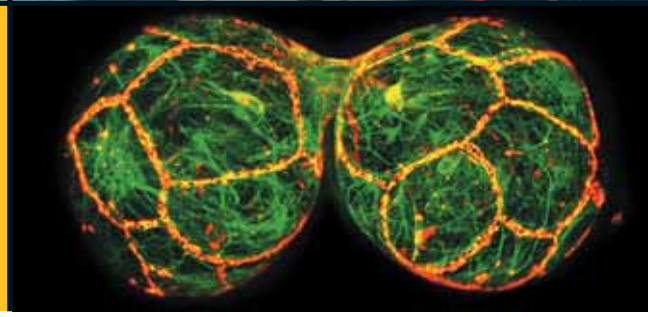
Seven Wellcome Trust Research Career Development Fellows made the transition to Senior Research Fellows in Basic Biomedical Science. The prestigious, highly-competitive Senior Fellowships provide five years' secure support plus the possibility of renewal for a further five years, the chance to develop a larger research team, and the autonomy to follow up interesting discoveries or ideas.

At more junior levels, nine of the 48 International Prize Travelling Research Fellowships awarded this year went to Wellcome Trust Prize or four-year PhD students, while six International Prize Travelling Research Fellows went on to secure Research Career Development Fellowships.

On the clinical side, five Senior Research Fellowships in Clinical Science were awarded to clinician scientists who had held intermediate Wellcome Trust awards (four held Advanced Fellowships and one a Clinician Scientist Fellowship), and five Advanced Fellowships were awarded to more junior Wellcome Trust fellows.

The Trust has a number of dedicated schemes to provide clinical tropical medicine researchers with career-progression opportunities. This year, four Wellcome Trust junior researchers successfully applied for Career Development Fellowships in Clinical Tropical Medicine.

The Wellcome Trust supports outstanding scientists regardless of gender. A 1997 survey by the Trust's Policy Unit revealed that, while women do not appear to be discriminated against in the Trust's peer-review



From left to right: Dr Sara Melville at the University of Cambridge is developing a resource centre for the *Trypanosoma brucei* research community.

Research at the Wellcome Trust Centre for Human Genetics, University of Oxford.

Principal Research Fellow, Professor Dorothy Bishop at the University of Oxford incorporates a computer game in her study of language impairment in children.

In vivo labelling of larval brain lobes of *Drosophila* with two different variants of green fluorescent protein.

Below right: Three-dimensional structure of the Semliki Forest virus fusing with a lipid vesicle.

process, fewer women than men apply for research grants. In partnership with the six Research Councils, the Trust commissioned a follow-up study. The results indicated that several factors, particularly level of seniority, had a significant influence on grant application activities, and that women were under-represented in senior jobs. The deep-rooted nature of some of the factors affecting women's grant application behaviour suggests that a review of funding policies and strategies, as well as higher education institutions' employment practices, would be needed to help address the imbalance.

Training and development

Seven new Four-year PhD Training Programmes were awarded in December 1999, bringing the number of programmes to 12. The awards enabled universities to establish the new programmes, offering students an additional year in which to learn a range of laboratory research skills and gain a taste of life working in different laboratories and with different supervisors before they commit to their three-year research projects.

To evaluate the effectiveness of its PhD schemes in training and attracting young people to an academic career, the Wellcome Trust conducted two surveys of past and present Trust-funded PhD students. The results, published in March 2000, confirm that Trust studentship schemes are training high-quality researchers, and that students are generally content with the PhD training they receive.

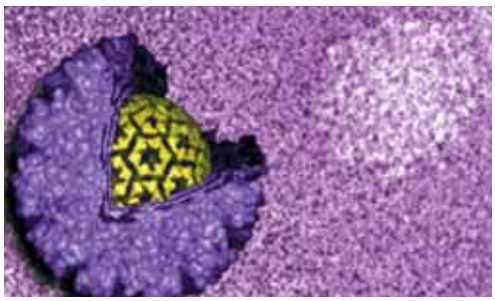
However, there are disquieting signs of disenchantment with research careers. Only half the current students thought they would continue to postdoctoral research work immediately after their PhD and more than one-third of students on four-year PhD programmes were fairly sure that they would not remain in any area of scientific research.

During 2000, three Wellcome Trust Advanced Courses were held at the Wellcome Trust Genome Campus at Hinxton: 'Functional Genomics', 'Genetic Analysis of Multifactorial Diseases' and 'Genetic, Molecular and Informatic Methods for *C. elegans*'. These summer schools, which are free to academic scientists, provide researchers with hands-on training in advanced research techniques. Hinxton was also the location for a summer school in biomedical ethics, 'Genetics and Society Research', which introduced young postgraduate researchers or researchers from

Of PhDs and PRFs

The Wellcome Trust supports outstanding scientists at the start and through to the pinnacle of their careers, as evidenced by the career trajectories of Dr Sarah Blakemore and Dr Stephen Fuller. Dr Blakemore completed her Wellcome Trust four-year PhD in neuroscience at University College London in 2000 and successfully applied for a highly competitive International Prize Travelling Research Fellowship to spend two years in Lyon, France.

In February 2000, Dr Fuller was awarded the most senior of the Trust's awards, a ten-year Principal Research Fellowship, facilitating his move from the European Molecular Biology Laboratory in Germany to the Wellcome Trust Centre for Human Genetics at the University of Oxford. A scientist of international standing at the forefront of structural biology, Dr Fuller pioneered the application of cryo-electron microscopy and image reconstruction to the study of pathogenic organisms (such as the Semliki Forest virus, shown below fusing to a lipid vesicle). He will be using these emerging technologies to study the structures of medically important viral pathogens, including HIV.



From left to right: Senior Research Fellow Dr Ben Luisi at the University of Cambridge is looking at the crystallographic and functional studies of regulatory assemblies.

The Henry Wellcome Building of Genomic Medicine, home to the Wellcome Trust Centre for Human Genetics, Oxford.

Side view of the brain taken from research by Professor Malcolm Young, Joint Infrastructure Fund awardee, at the University of Newcastle.

Researchers at the Wellcome/CRC Institute in Cambridge are studying integrin-linked kinase fused with green fluorescent protein in a developing embryo.

Below right: Keratinocyte stained with antibodies to NF-κβ, a protein that controls gene expression.

Tackling strangles

In June 2000, Dr Josh Slater, a clinical lecturer in equine medicine at the University of Cambridge, was awarded a four-year Research Leave Award for Clinical Academics to study *Streptococcus equi*. *S. equi* infections represent a major disease burden in horses and are of considerable economic importance worldwide. *S. equi* causes a serious upper respiratory tract disease, known as strangles, which can be fatal. All vaccinations to date have proved ineffective at controlling the infection. Dr Slater aims to improve understanding of the molecular basis for bacterial–host cell interactions in *S. equi* in order to improve vaccine design.

The highly competitive Research Leave Awards for Clinical Academics are of similar status to Senior Research Fellowships. Clinical academics who have reached a critical point in their research but are overburdened by routine clinical work or teaching commitments are released from these duties, enabling them to pursue a major research programme.

other disciplines moving into the field to some of the social, ethical, and public policy implications of human genetics.

UK research infrastructure

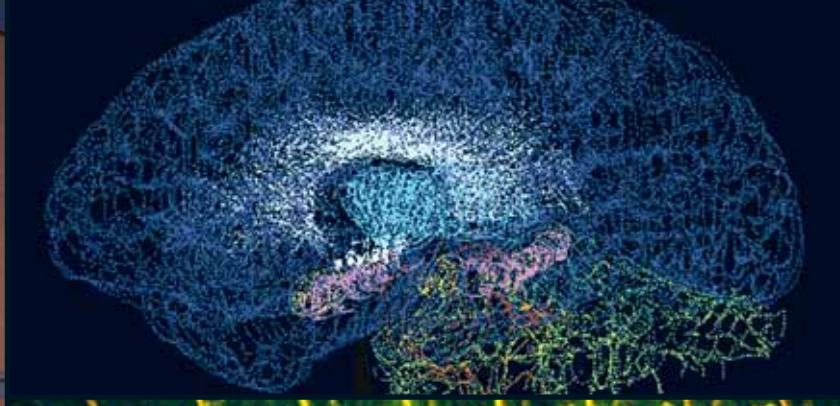
The Wellcome Trust Centres enable groups of outstanding scientists to work in close proximity to each other on related programmes, achieving a synergistic effect that adds considerably to the value of each individual programme.

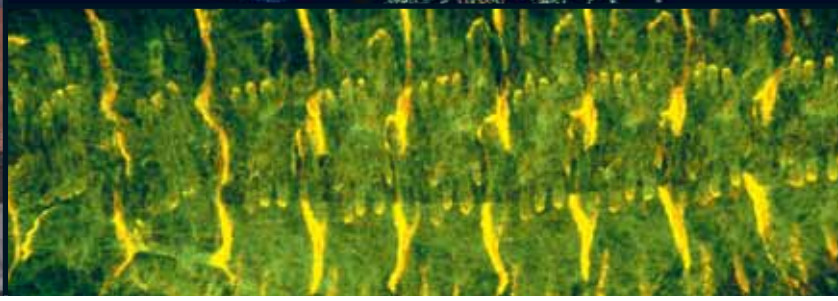
Centres are funded on a five-year cycle subject to a full review by an international committee. The core grant of the Wellcome Trust and Cancer Research Campaign Institute of Cancer and Developmental Biology in Cambridge was renewed in 1999/2000 and a new chairman designate was appointed. Professor Jim Smith from the National Institute for Medical Research at Mill Hill, one of the world's leading researchers in embryonic development, was awarded a £2.6 million programme grant, and he moved to the Institute in September. The Wellcome Trust Centre for Cell-Matrix Research at the University of Manchester was likewise renewed, and Professor Martin Humphries, a molecular cell biologist of international standing and Wellcome Trust Principal Research Fellow, took over as director.

The excellence of the Centres is reflected in the fact that three were successful with applications to the highly competitive Joint Infrastructure Fund (JIF) – a £750 million partnership between the Government and the Wellcome Trust, launched in 1998 to inject much-needed funds into the UK university infrastructure. The JIF award to the Wellcome/CRC Institute will enable it to relocate to custom-built laboratories on a new site. The Wellcome Trust Centre for Cell-Matrix Research received a grant to build a centre for molecular cell biologists, and the Wellcome Trust Centre for Human Genetics in Oxford received a laboratory refurbishment award for post-genomic studies. The Henry Wellcome Building of Genomic Medicine which houses the Centre for Human Genetics was opened in June 2000.

The Trust awarded £124 million and £71.8 million in the second and third second rounds of JIF. Notably, several successful applications will provide new facilities in post-genomics. It is fortuitous that the JIF partnership has provided an opportunity for universities to invest in technology and infrastructure for this exciting new era in biology.

Competition has been extremely fierce and many high-quality JIF proposals have not been funded. The £1 billion Science Research Investment Fund





(SRIF), established by the Government in 2000 – to which the Trust has pledged £225 million – will help ensure that some of these applications will receive funding.

Synchrotron

The Government announced in March 2000 that the new synchrotron radiation facility would be located at the Rutherford Appleton Laboratory in Oxfordshire. The presence on the site of the ISIS neutron source, as well as a neighbouring MRC unit with significant strengths in genetics and radiobiology, provides the opportunity to create an interdisciplinary research centre for the physical, engineering and biological sciences.

The name 'Diamond' was adopted for the new facility, which will be invaluable in post-genomics research, enabling researchers to determine the structure of large complex molecules such as proteins. The Trust has committed £110 million to this partnership with the UK and French governments.

International capacity building

The Trust runs a range of programmes to strengthen the science base overseas. In 1999/2000, ten Senior Research Fellowships were awarded to scientists in Australia, New Zealand, South Africa and India, enabling them to establish their careers in their home countries. A Senior Research Fellowship awarded to Dr Chetan Chitnis at the International Centre for Genetic Engineering and Biotechnology in New Delhi, India, has allowed him to set up a laboratory and train local scientists while continuing his research into the malaria parasite. Seventeen major equipment grants were also awarded to scientists in New Zealand, Australia and South Africa.

Career schemes for both UK and overseas researchers run by the Tropical Medicine Programme are designed to strengthen research capacity in diseases afflicting the tropics (page 70). Additionally, the international tropical medicine units in Kenya and South-East Asia have been funded to develop training programmes for local scientists.

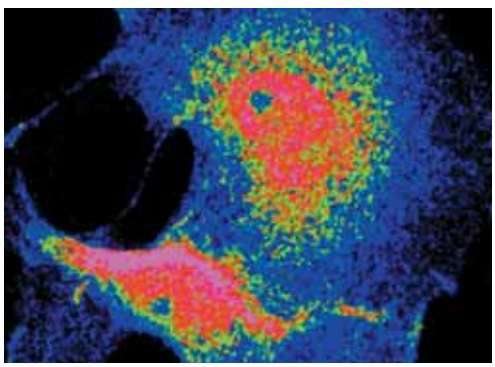
Travelling Research Fellowships, 53 of which were awarded during the year, allow overseas scientists to benefit from training and research opportunities in UK laboratories or regional centres of excellence. In addition, 41 collaborative grants enabled scientists from less developed nations to undertake collaborative research with a UK group.

Zooming in on Strathclyde

Professor Alison Gurney at the Department of Physiology and Pharmacology at the University of Strathclyde received an award to create a Centre for Biophotonics in the first round of the Joint Infrastructure Fund awards. Building work started on 22 May 2000.

Among other projects, bio-engineering researchers will use the facility to look at the function of living cells in artificial medical devices, while cell biologists will be able to follow intra-cellular signalling in intact tissues. The Centre will focus initially on multiphoton microscopy, which provides high-resolution three-dimensional images of living cells. Compared with other techniques, multiphoton imaging has a less detri-mental effect on samples, so longer-term imaging of living tissue is possible, and it can be used to look much deeper within tissues.

Application of the technique to biology and medicine calls for close interaction between developers and users, and the new facility will enable biomedical and optical scientists to work side by side to create a nationally important resource.



A historical find

In November 1999, Professor Roy Church and Dr Tilli Tansey (below) unearthed the account book of Burroughs Wellcome & Co., documenting its financial activity between 1880, when the partnership between Henry Solomon Wellcome and Silas Mainville Burroughs was formed, until 1940. In 2000, Glaxo Wellcome (now GlaxoSmithKline) agreed to donate the company records of the pharmaceutical company, the Wellcome Foundation Ltd – formed in 1924 to incorporate Burroughs Wellcome & Co., and Henry Wellcome's various research laboratories, museums and library under a single organizational umbrella – to the Trust.

These papers and records – now to be housed together at the Wellcome Trust – create a formidable information resource on its founder, Henry Wellcome, his partner Silas Burroughs, and the work of the company the two men founded. As well as providing a comprehensive history of Burroughs Wellcome & Co. these documents will allow important insights into the birth of the UK pharmaceutical industry at the start of the twentieth century.

The latter included a partnership between Dr Vladimir Polshakov at the Centre for Drug Chemistry in Moscow (previously a Wellcome Trust Travelling Research Fellow) and Drs James Feeney and Thomas Frienkel at the National Institute for Medical Research, Mill Hill, London to undertake structural studies into how drugs bind to their targets. There are benefits for both sides: the Moscow team will have access to the high-powered nuclear magnetic resonance technology at Mill Hill, while Dr Polshakov's expertise in the dynamics of drug interaction with target molecules has been a major driving force in research at Mill Hill into antibiotic resistance in bacteria.

Population studies

The international research base in population studies is in its infancy. The Trust's Population Studies Programme, now being reviewed after five years, concentrates on training younger people in research to help build the research base from the bottom upwards. Unusually therefore, the programme supports Master's studies in population studies, ten of which were awarded this year.

In July 2000, a week-long course on 'Ethical Issues in International Health', co-funded by the Wellcome Trust and held in Durban, South Africa, was attended by researchers from various African countries, thus helping to strengthen local capacity in biomedical ethics. Held in conjunction with the Thirteenth International AIDS Conference, the course was chaired by Professor Hoosen Coovadia of the Trust's Africa Centre for Population Studies and Reproductive Health in KwaZulu-Natal, South Africa.

A new building planned for the Africa Centre will house staff under one roof. The land for the new building was granted by the local Zulu Chief who invited staff to a special celebration, or *'Imbizo'*, which symbolizes the giving of the land. Dr Michael Bennish took up his position as the first Director of the Africa Centre on 1 November 1999.

From left to right:
Research at the Africa Centre in KwaZulu-Natal is based on a detailed demographic map of the local population.

The Trust's Kenyan unit has developed training courses to aid shopkeepers selling anti-malarial drugs.

PhD student Sam Kinyanjui extracts deep-frozen malaria parasite samples at the Wellcome Trust Kenyan unit in Kilifi.

Exhibitions held in the Wellcome Library for the History and Understanding of Medicine included one related to medical-anatomical works from pre-modern India.

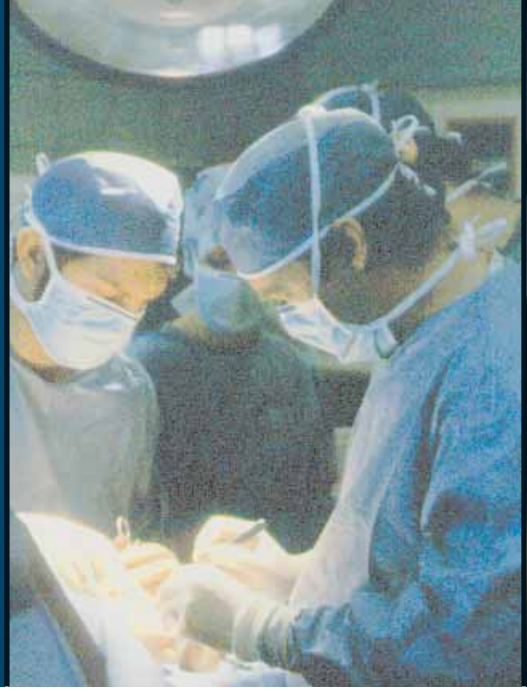
Historical resources

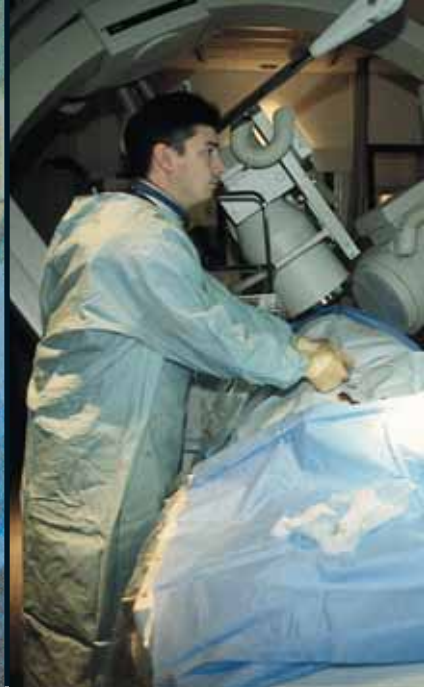
The Wellcome Trust's History of Medicine Library, which celebrated its 50th anniversary in December 1999, continues to develop its world-class collections of historic material to complement its already extensive holdings. New acquisitions this year included a rare pamphlet on reconstructive surgery published in 1825.

In 1999, the History of Medicine Library joined with the Information Service and the Medical Photographic and Film and Video Libraries to form the Wellcome Library for the History and Understanding of Medicine. The Wellcome Library provides an innovative world-leading resource – in various different media – on the past, present and future of medicine.

During the year, funding was approved for a new £1 million joint initiative with the British Library. Through a competitive grants scheme, institutions throughout the UK will be able to apply for funds to improve access to their collections, either through a programme of conservation work, a cataloguing project, or the creation of databases. The scheme will help libraries and archives to preserve and improve access to medically important but fragile archive materials – opening up rich new resources for historians of medicine.

Translation





The Wellcome Trust encourages the dissemination and use of new knowledge to advance medical healthcare. It does so through a number of routes: by actively promoting the progression of basic and applied research from the laboratory to the bedside; by supporting research focused on the patient; by encouraging the dissemination of useful information; and by promoting the development of products and services of medical value.

Clinical research

The UK Cardiovascular Research Initiative was launched in 1996 to meet a future need for cardiovascular researchers who were comfortable with molecular technologies, placing particular emphasis on training and multidisciplinary interactions. Two research programmes were funded, at the Universities of Oxford and Edinburgh, headed by Professor Hugh Watkins and Professor David Webb, respectively. In the two years since they have been running, the programmes have attracted a rich array of world-class talent (the Edinburgh programme now has eight fellows associated with it and the Oxford programme has seven).

In 1999, the Trust committed £20 million to create five UK Clinical Research Facilities (CRFs) in Birmingham, Cambridge, Edinburgh, Manchester and Southampton. As partnerships between university medical schools and NHS Trusts, the CRFs will be hospital-based facilities dedicated to patient-oriented research. They will have their own research-based healthcare support staff and laboratory facilities, and will act as a resource for local clinical researchers. The CRFs also hold potential as 'nurseries' for those who want to train in clinical research. With the appointment of Professor Chris Byrne as Director of the Southampton CRF in 2000, all the CRFs now have Directors. All the new buildings should be completed by autumn 2001.

Although £500 million is spent by consumers every year in the UK on complementary and alternative medicine (CAM) therapies, they are the subject of little research. While CAM research is within the Wellcome Trust's remit, few applications are submitted in this area. In March 2000, the Trust held a workshop to encourage debate on CAM research issues, and presented a report on the workshop to the House of Lords Select Committee on Science and Technology in May. A key point was that the CAM industry, unlike the pharmaceutical industry, is under no obligation to test the safety and effectiveness of its products.

From left to right:

International and UK clinical research is earmarked as a priority in the Trust's five-year plan.

Heart disease, one of the UK's biggest killers, is the focus of a Cardiovascular Research Initiative programme led by Professor David Webb at the University of Edinburgh.

Professor Hugh Watkins (right) head of the Cardiovascular Research Initiative programme at the University of Oxford.

On the western borders of Thailand, clinical trials of combination therapies to combat malaria have proven highly successful.

International clinical research

The Wellcome Trust has two major routes for supporting disease- or patient-oriented research overseas: through the international units, and through the international career awards and collaborative grants schemes.

The tropical medicine units in South-East Asia and Kenya have been evaluating different treatments for malaria and optimizing dosages. Work on the western border of Thailand has shown the potential of using combination therapies to slow the development of drug resistance. Professor Nick White, Director of the South-East Asia Unit, and Dr François Nosten, a Wellcome Trust Senior Fellow, conducted trials of mefloquine plus artesunate and found that the combination halted the progression of mefloquine resistance.

Dr Bill Watkins of the University of Liverpool, who has had a long association with the Trust's Kenyan unit, similarly hopes to begin combination trials of Lapdap with artesunate. Lapdap was developed as an antimalarial treatment by Professor Peter Winstanley and Dr Watkins through a collaboration between the Kenyan unit and the University of Liverpool. Trust-funded studies commenced some 15 years ago and more recently a public–private partnership has enabled development of the drug to be moved forward rapidly.

Sex and contraception

In February 2000 the Trust funded a three-day Frontier Meeting on Sexually Transmitted Disease (STD) Diagnostics, in Durban, South Africa, attended by 50 international STD experts. The meeting reaffirmed the need for new rapid, easy-to-use diagnostic tests that could be used as part of public health screening strategies worldwide. Since this meeting the WHO and the Trust have made a concerted approach to promote research priorities in this neglected area.

The Medicines Control Council of South Africa re-scheduled the status of emergency post-coital contraception in 2000 to give public access to emergency contraceptive pills from chemists without prescription. This move was a direct result of a Wellcome Trust project grant awarded to Dr Jennifer Smit at the University of Durban-Westville, South Africa, for a study on emergency contraceptive choice in Africa.

Lapdap

In the 1990s, in collaboration with the Wellcome Trust's Kenyan Unit (above), Professor Peter Winstanley, Dr Bill Watkins and colleagues devised a new treatment for malaria: Lapdap, a mix of two antimalarial compounds, chlorproguanil and dapsone.

During 1999/2000, Wellcome Trust international units and laboratories participated in clinical trials of Lapdap in sub-Saharan Africa, funded by a partnership between the World Health Organization (WHO), the UK Department for International Development, and SmithKline Beecham (now GlaxoSmithKline). The trials demonstrated that Lapdap is effective in the treatment of uncomplicated malaria, including malaria resistant to other standard first line therapies, and GlaxoSmithKline and the WHO subsequently signed an agreement to develop the project. This public–private partnership will achieve important practical results in terms of malaria control, including a price structure that aims to make the drug affordable for those who need it.

From left to right: An African child with AIDS: HIV/AIDS is a major focus of research at the Wellcome Trust's Africa Centre in South Africa.

The Tropical Medicine Resource launched *Nutrition*, a new multimedia teaching aid for healthcare professionals.

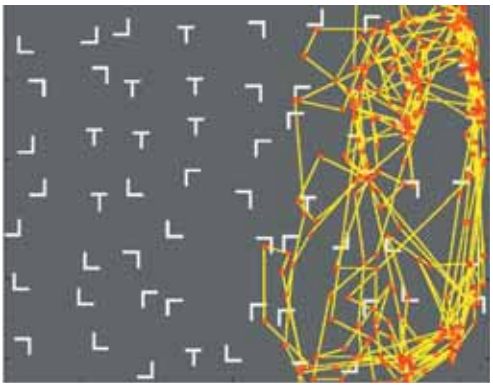
Neonatal intensive care: medical research has dramatically improved the survival of premature babies.

Professor Philippa Garety at Guy's, King's and St Thomas' School of Medicine is co-directing a trial of psychological treatments for psychosis.

Seeing both sides

In July 2000, Dr Masud Husain at Imperial College London was awarded a Senior Research Fellowship in Clinical Science to investigate the disabling disorder of spatial neglect which can follow a major stroke. Typically patients with neglect are unaware of objects or events on the 'blind' side opposite their lesion, bumping into people who approach them from that side and leaving food untouched on one side of their plate. These difficulties cannot be attributed to simple sensory or motor impairments; they are due to the disruption of subtle processes within the brain, the precise nature of which is disputed. The picture below shows eye scan paths of a patient with left visual neglect.

Some of these mechanisms recover and others do not, which could explain why some patients improve rapidly and regain all-round spatial awareness while others do not. Dr Husain aims to establish precisely which parts of the brain are affected in spatial neglect and to use this understanding to improve treatments for stroke patients.



Clinical collaboration

A number of collaborative awards and research fellowships have a clinical emphasis. A Collaborative Research Initiative Grant facilitating a partnership between St Mary's Hospital (Professor Jonathan Weber) and the Ivanovsky Institute in Moscow (Professor Alexei Bobkov) is enabling researchers to study a new subtype of HIV emerging in Russia. As well as supporting the training of young Russian investigators in clinical epidemiology and virology, the award will provide a unique opportunity to monitor viral mutation – valuable information in the quest to develop an anti-HIV vaccine.

In the same field, an Overseas Senior Research Fellowship awarded to Dr Lynn Morris at the National Institute for Virology in Johannesburg will enable her to continue her work studying local strains of HIV. Such work is important as the strains found in South Africa are not the same as in the West.

Good science, good business

Turning discoveries and inventions made in the laboratory into products to improve health is a long, complex and costly process, and requires the specialist set of skills and experience most commonly found in the corporate sector. Catalyst BioMedica Ltd, the business subsidiary of the Wellcome Trust, was set up to facilitate the development and transfer of Trust-funded technologies into this sector. Working closely with researchers and their host institutions, Catalyst assists in protecting intellectual property, developing exploitation strategies, identifying appropriate commercial partners and start-up opportunities, and negotiating agreements.

Catalyst completed its first fully operational financial year on 30 September 2000, comfortably meeting its financial targets. Profits made by Catalyst from licence fees and equity stakes in start-up companies will be transferred back to the Wellcome Trust to support its charitable activities.

Catalyst has negotiated many licensing agreements and facilitated the formation of several start-up companies, including Oxxon Pharmaccines Ltd (see right), De Novo Pharmaceuticals Ltd and Paradigm Therapeutics Ltd.

It is a common problem that drug companies will consider new research to be at too early a stage or too high a risk for them to

take up. Catalyst therefore administers a £20 million Development Fund on behalf of the Trust to help scientists move promising research towards commercial application. Fifteen Development Fund awards of up to £500 000 have been made to date (six during the year), to institutions across the UK. The portfolio of research is spread across a range of diagnostic and therapeutic product opportunities – from compression bandages for wound healing to a novel approach for cognitive dysfunction.

In 1998 the Wellcome Trust contributed £18 million to the £45 million University Challenge Fund – a partnership with the UK Government and the Gatsby Charitable Foundation – to provide local seed venture funds to help universities translate research discoveries into the commercial sector.

Fifteen university-based consortia won awards of some £3–5 million and during 1999/2000 began to use their funds to drive forward promising exploitation projects. The University of Cambridge, for example, made its first investment in June, allocating £78 000 to develop an innovative technique to detect viruses and bacteria.

Dissemination of genome data

The Wellcome Trust is committed to the principles of free data release to avoid duplication of effort and to stimulate research. Data from both the Human Genome Project and SNP Consortium are submitted to the public databases as soon as possible to speed up the global effort to interpret the genome. Although the Trust is in favour of the protection of intellectual property rights, including gene patents, which attract the investment essential to develop new treatments, it does not support the patenting of raw DNA sequence data with no known function.

In July 2000, the Trust announced a major investment of at least £8 million over five years in Ensembl, a software tool developed by the Sanger Centre and the European Molecular Biology Laboratory's European Bioinformatics Institute on the Wellcome Trust Genome Campus.

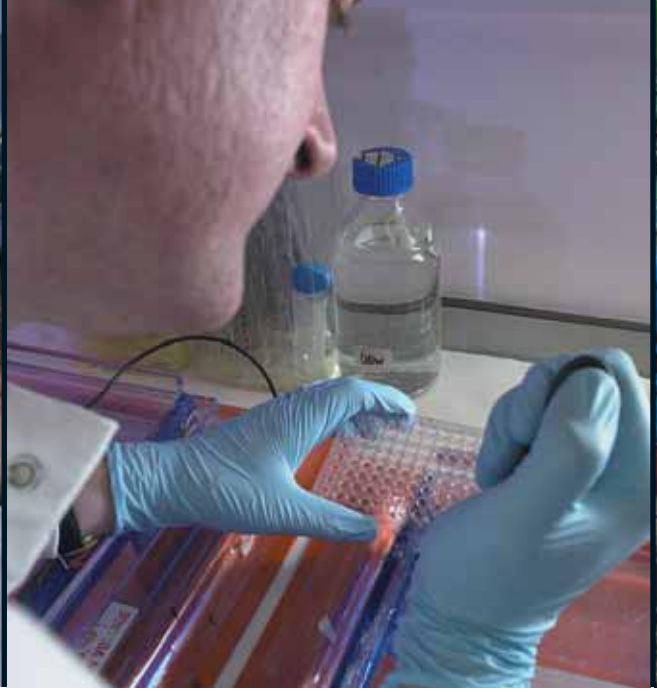
Health information

The Wellcome Trust encourages the dissemination of medically relevant information to make a real impact on health. The effectiveness of adolescent sex education programmes in combating problems

Oxxon Pharmaccines

Oxxon Pharmaccines, a biotechnology start-up company based in Oxfordshire, was set up with the help of Catalyst BioMedica Ltd to exploit Trust- and MRC-funded research at the University of Oxford. Catalyst has an equity stake in the company, which is developing new vaccines for hepatitis, HIV, malaria and melanoma, using a new vaccine delivery system, Prime-Boost™. The system was developed by Wellcome Trust Principal Research Fellow Professor Adrian Hill (below) and colleagues at the Nuffield Department of Clinical Medicine.

Part of this work is being advanced through a Development Fund award to Dr Sam McConkey, a Senior Research Fellow in Adrian Hill's laboratory, who will be testing a therapeutic vaccine for the hepatitis B virus in The Gambia. Data from the trial will help create a healthcare product that could be widely used.


Free unrestricted access for all

All data from the publicly funded Human Genome Project are disseminated immediately to researchers across the globe – free of charge and with no restrictions or conditions placed on users. To enable researchers to gain the most value from sequence data, the Trust awarded an £8 million grant to Ensembl, the Europe-based online genome data service jointly run by the Wellcome Trust Sanger Centre and EMBL-EBI (European Bioinformatics Institute – part of the European Molecular Biology Laboratory) on the Wellcome Trust Genome Campus in Hinxton, Cambridge (see below).

Ensembl provides researchers with automatic annotation and analysis of the human genome sequence – including the location of genes, transcripts, exons, DNA repeats and other features of interest. Ensembl itself is also freely available on the Internet as open-source software, which researchers across the world can improve and develop as they use it.

Latest figures suggest that around 5000 researchers in more than 80 countries are already using the Ensembl site every week to access the public data.

associated with unintended pregnancies and sexually transmitted diseases was addressed by a Trust-funded Frontier Meeting on Adolescent Sex Education in Hampshire in September 2000. The meeting encouraged dialogue between various school-based studies evaluating sex education programmes in the UK, including one developed with Trust funding by Dr John Tripp at the University of Exeter.

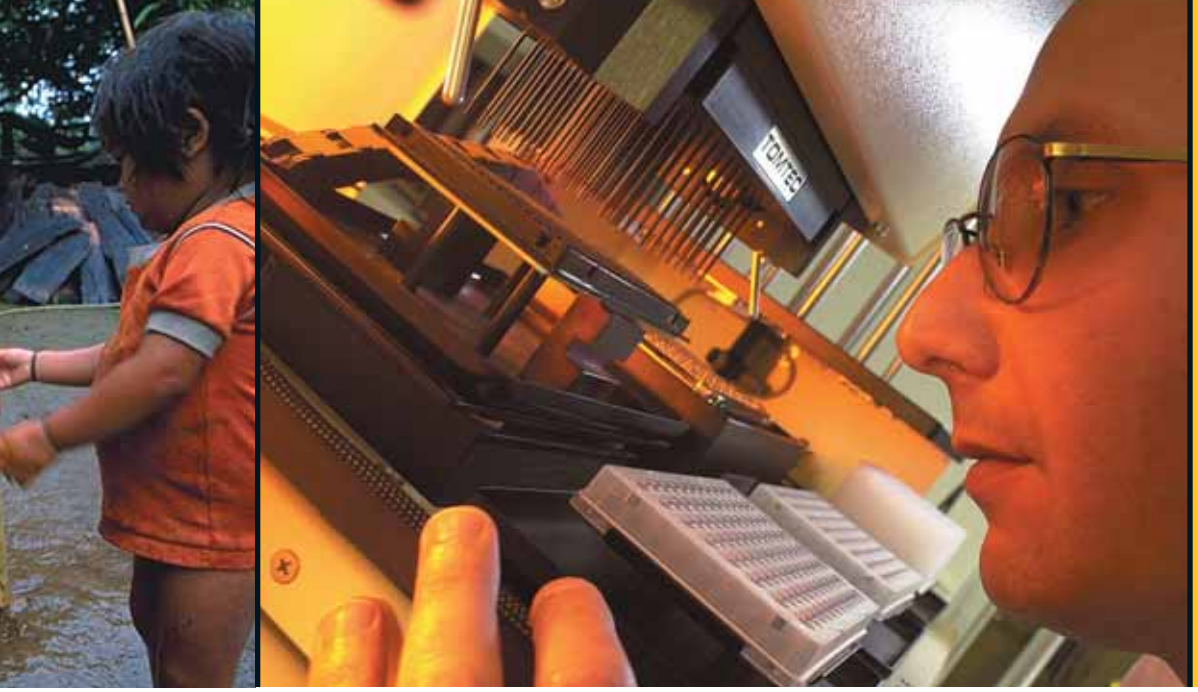
The Wellcome Trust's Tropical Medicine Resource produces the 'Topics in International Health' series of multimedia teaching materials for students and healthcare professionals. This year, four new CD-ROMs were launched: *Nutrition*, *HIV/AIDS*, *Leishmaniasis* and *Kusta* (the local Bahasa Indonesia translation of the *Leprosy* CD-ROM). More than 3300 discs in the series were distributed in 1999/2000, and there are now more than 5000 users worldwide in 90 countries.

Informing policy

Dissemination is a particular feature of the clinical research projects of the International Programmes, which are often linked to specific health priorities. Researchers are encouraged to establish links to international bodies such as the World Health Organization and to local ministries of health and healthcare delivery services in order to influence policy. For example, Senior Research Fellow Professor Bob Snow at the Trust's Kenyan unit, whose fellowship was renewed during the year, works closely with the Kenyan Ministry of Health's Malaria Control Unit so that his research into malaria risk and epidemic potential can be used to develop effective national or local antimalarial strategies.

Dissemination is an equally important facet of the Trust's work on the social impact of biomedical research. Its Biomedical Ethics Programme places a strong emphasis on the need to provide useful information to policy makers, helping them to make informed, evidence-based decisions. Applicants to the programme are asked to indicate how their work could provide information useful to policy making and to contribute to policy papers to bring their research to a wider audience. Project summaries of awards are published on the Wellcome Trust website.

The Trust's Science Policy Seminar Series disseminates ideas and information by bringing together people who may not ordinarily meet to debate important issues in scientific research. 'Cloning and Stem Cells' in November 1999 helped inform the Wellcome Trust's interim position



From left to right:
Researchers at the Wellcome Trust Sanger Centre release genomic data into the public databases where it is freely available to all.

DNA sequence analysis at the Wellcome Trust Sanger Centre.

Understanding the spread of infectious diseases in the community is central to much of the Trust's international clinical research.

Professor Mike Stratton co-established a cancer genome project at the Wellcome Trust Sanger Centre.

statement on stem cells. In March 2000, a seminar on 'Science and Commercialization' encouraged top-level policy makers, scientists and venture capitalists to debate issues raised by the race for intellectual property rights in the wake of genome sequencing and the need for constructive public–private sector collaborations to promote research. The Trust also held a workshop to debate issues surrounding research into complementary and alternative medicines.

Endometriosis in India

Endometriosis – abnormal development of the lining of the womb – is a major healthcare problem, causing debilitating pain to millions of women worldwide. One of the key problems in treating the disease – difficulty of diagnosis – could be addressed if it is shown that the disease has an identifiable genetic component.

In September 2000, Dr Stephen Kennedy at the University of Oxford and Dr Sisinthy Shivaji at the Centre for Cell and Molecular Biology (CCMB) in Hyderabad, India, were awarded a Collaborative Research Initiative Grant to help confirm evidence of genetic linkage produced by earlier research.

The collaborators aim to collect DNA samples from 200 sister-pair families (families with at least two daughters with endometriosis) in Hyderabad, India. Indian scientists will be brought to the Wellcome Trust Centre for Human Genetics in Oxford for training in automated genotyping, then return to the CCMB to perform a genome-wide scan on these samples and test for linkage. Identifying which genes predispose women to endometriosis may clarify which aberrant molecular mechanisms underlie the condition and enable the development of new therapies.

Public Engagement

Advances in biomedical science cannot happen in isolation from the rest of society, and much of the new knowledge being generated has the potential to produce profound changes in the way we live and how we see ourselves. These changes will question our views on issues such as individual rights and collective responsibilities – and emphasize the need for full and informed public debate.

The introduction of new medical practices or therapeutic approaches is rarely straightforward, being connected to a host of factors, ranging from societal structure through ways of thinking to media representation. Given that the ramifications of our better understanding of biology will be felt widely – in medicine, law, insurance and the home – the possible implications of research should be discussed as openly as possible.

The Wellcome Trust is therefore committed to communicating its aims, values and activities to the public and seeks to engage the public by encouraging dialogue and debate. By developing a two-way flow of information with the public, the Trust hopes to create a relationship based on mutual respect and understanding from which all parties will benefit. The public will have a framework on which to base their decisions, and the Wellcome Trust will be able to understand and respond to people's concerns and reactions, and help ensure that such views feed into internal and external policy making.

Public consultation

The design of the proposed UK Population Biomedical Collection project (page 11), for example, has been informed by extensive dialogue with the public. Because of the sensitive ethical and social issues the project raises, the Wellcome Trust and MRC commissioned research into the public's views on various issues. The consultation found that the initial response to the idea of a collection of human biological samples was largely favourable, but when possible implications were highlighted – particularly regarding access to data, feedback of information and informed consent – concerns tended to emerge. However, further information and discussion of these issues generally restored positive views. These findings are being used to help structure the proposed project, particularly in terms of how information would be used and what safeguards should be put in place.

To gain a comprehensive understanding of what British people think about science, the Wellcome Trust and the Office of Science and

Left: Independent research on the public's views to the proposed UK Population Biomedical Collection raised issues over data access and informed consent.

Centre and right: The Wellcome Wing of the Science Museum – home to an Imax cinema and exhibitions on discoveries and innovations.

Technology sponsored a nationwide study of public attitudes to science. Following qualitative research funded by the Trust, more than 1800 people – from across the country and all backgrounds – were asked about their attitudes to science, life and authority, and their leisure interests.

On the whole, public attitudes towards science were very positive, although there was some concern about its regulation. The survey provides useful information about different audiences to help develop science communication plans.

Genetic implications

The Wellcome Trust communicated widely to the media and the public on the draft sequence of the human genome, working closely with journalists to help ensure that reporting was informed and responsible and that extensive newspaper coverage would bring these developments to as wide an audience as possible. The Trust also provided extensive background information on its website in an accessible format (www.wellcome.ac.uk/genome).

Healthcare professionals play an important role in communicating developments in biomedicine and their implications to the public. In February 2000, the Trust and the King's Fund jointly organized a meeting, attended by 30 senior policy makers and opinion leaders from the health sector, to consider ways in which the health service could assimilate and maximize the benefits from new developments in biomedicine. It was recognized that the NHS needs to be proactive in predicting the potential impact, and that it needs to work in partnership with a range of sectors and to engage the public in consultation.

Reaching the people

The Wellcome Trust has organized a number of innovative initiatives to involve the public in science and the issues it raises. It has contributed £45 million (£10 million 'in principle' to the Darwin Centre at the Natural History Museum) to a network of eight interactive science centres across the UK, five of which opened in 1999/2000.

The Wellcome Wing of the Science Museum was opened by the Queen on 27 June 2000. The museum's new gallery houses a rolling exhibition of new discoveries and innovations, on-site research projects and an Imax cinema. Where the rest of the museum

Dancing astronauts

Zero-gravity environments produce changes in the perception and control of body movements, which can lead to severe disorientation and sickness. This can severely limit performance and has important implications for use of the International Space Station and similar ventures.

Dancer Kitsou Dubois (below) embarked on a science–art partnership with the Biodynamics Group at Imperial College London to determine scientifically whether dance training may help astronauts adapt to lengthy weightlessness. In addition to obtaining scientific results regarding the way the body moves and is controlled in altered gravity conditions, the team aim to produce striking film images of dance in weightlessness.

The project, named 'Gravity Zero', is funded by a £36 100 award from the sciart consortium which aims to encourage creative art–science partnerships and innovative cross-disciplinary thinking.

LIFE in Newcastle

LIFE Interactive World (above), a Wellcome Trust-funded Science Centre that opened in Newcastle in May 2000, is a dramatic exploration of DNA and its impact on all our lives. It uses the latest interactive technology to explore some of the principles that underpin life on earth, including a 3-D film showing a baby developing from embryo to birth. Visitors can take a ride on the 'Celebration of Life Motion Simulator Ride', the world's longest rollercoaster (below); play a game of virtual volleyball in outer space; and see what happens inside a human brain when a person falls in love. Two laboratories run educational workshops for school children on genetics, microscopy and forensic biology.

LIFE is part of the International Centre for Life in Newcastle, which also houses research and clinical work in the Genetics Institute, commercial applications in the BioScience Centre, and bioethics research and education at the Policy, Ethics and Life Sciences Research Institute.

concentrates on past achievements, the Wellcome Wing looks at present and future science, with exhibitions exploring topics such as visual patterns in modern science and recent discoveries in genetics, brain science and developmental biology.

The Wellcome Trust's 'Science for Life' exhibition moved to the Manchester Museum at the University of Manchester where it opened on 29 June 2000. It includes a new section on the advances in medicine made in and around Manchester, whilst a new laboratory in the exhibition offers visitors hands-on experience of modern scientific techniques.

LIFE Interactive World in Newcastle, @-Bristol and Sensation in Dundee also opened, and work is progressing on the Glasgow Science Centre, Thinktank in Birmingham, and the Darwin Centre at the Natural History Museum. Discussions are underway to include other science centres across the UK in the network to ensure the best possible use is made of this new national resource.

Drama and art

Theatre can offer a compelling route through which to bring discussion about biomedical science out of the laboratory and into people's everyday lives. Three Trust-sponsored plays were performed at the Edinburgh Fringe in August 2000. Two were winners of the 1998 Science on Stage and Screen awards: *Safe Delivery*, written by Tom McGrath in collaboration with his daughter, Dr Julie Webb – a genetics researcher in the Institute of Child Health – which examines the issues surrounding gene therapy against the backdrop of life in the laboratory; and *The Idiot*, a one-man show about epilepsy (page 29). *Learning To Love The Grey* was specially commissioned for the three-year Creating the Debate for the Millennium Initiative awarded to the Y Touring production company in 1998. Written by Jonathan Hall and performed by Y Touring, the play revolves around the issues raised by stem-cell technology and therapeutic cloning.

Following the success of Wellcome Trust's sciart awards in 1997 and 1998, a consortium comprising the Arts Council of England, the British Council, the Calouste Gulbenkian Foundation, the Scottish Arts Council, the National Endowment for Science, Technology and the Arts (NESTA) and the Wellcome Trust was formed in 1999 to continue and extend the sciart initiative, which supports partnerships between

From left to right: LIFE Interactive World, part of the International Centre for Life in Newcastle.

Images of identical twins by photographer David Teplica were the focus of the 'Take Two' exhibition at the Two10 gallery.

'The New Anatomists' exhibition, held at the Two10 Gallery.

Researchers in Residence – PhD students working alongside teachers and pupils in schools.

Science on Stage and Screen's award winning production of *The Brain* by Forkbeard Fantasy.

artists and scientists. In the 2000 awards, a total of £200 000 was awarded to 11 innovative science–art partnerships.

Four exhibitions were also held at the Wellcome Trust's Two10 Science and Art Gallery in Euston Road during the year, looking at a variety of themes, including identical twins and questions of identity, and the growth of digital representations of reality.

Attracting the young

Young people are an audience the Wellcome Trust is particularly keen to reach, since they are likely to be the first real beneficiaries of developments in science and will lead the scientific agenda in the future. The classroom is a key arena for engaging young people in science, and the Trust takes part in a number of initiatives aimed at making science an attractive option to pupils and encouraging classroom debate on the wider societal impact of biomedical advances.

Seventy-seven PhD students spent four days working alongside teachers and pupils in schools as part of the Researchers-in-Residence scheme, acting as role models to inspire pupils to consider a career in science. More than 600 'Nuffield Science Bursaries' – around 100 of them funded by the Wellcome Trust – were also awarded to young people on A-level science and technology courses. These bursaries aim to encourage students to stay in science by giving them hands-on work experience in a laboratory alongside enthusiastic research scientists.

Supporting teachers

To support teachers wishing to generate classroom discussions on science and its societal impact, the Wellcome Trust published two further issues of its *LabNotes* series – a free resource with up-to-date information on research in biomedicine and its social and ethical implications. 'Down at the Pharm' looked at genetically modified organisms, and 'Beyond the Genome' covered the Human Genome Project.

To inform its education-based activities, the Trust commissioned the Institute of Education to investigate how schools approach controversial issues in science. The findings revealed a widespread conviction that these matters are important. However, many teachers feel that a content-dominated curriculum presents little opportunity for them to incorporate socio-scientific questions into their lessons – an obstacle compounded by the lack of any formal assessment of the subject.

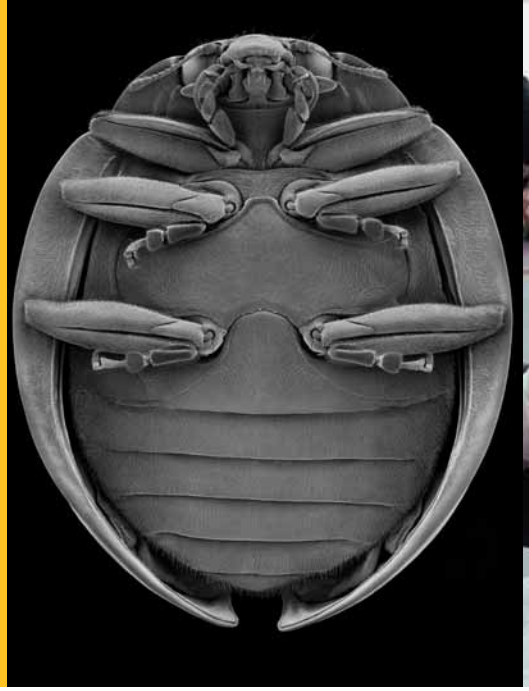
The Idiot

Despite being a common illness, epilepsy still arouses misunderstandings and fears among much of the population. Freelance theatre director and writer Paul Jepson was inspired by the Wellcome Trust's Science on Stage and Screen competition to expand a short one-man show about the condition he had devised with well-known Danish TV actor, Claus Damgaard (above). Successful in his application, he began talking to people with epilepsy and their families and with the national epilepsy charities in order to develop the piece into its present form.

The Idiot is an intensely physical piece of theatre, which blends the insights gained from the real-life stories of these people into the marvellous, frightening world of Dostoyevsky's Prince Myshkin as he struggles in equal measure with epilepsy and with the ignorance and condescension of society. The play premiered in Leeds in April 1999 and was performed again at the Edinburgh Festival Fringe on 2–28 August 2000. It was Critic's Choice in the *Guardian* and *The Times*.

From left to right: Electron microscope image of a ladybird by Giles Revell, part of the 'Noise' exhibition at the Two10 gallery.

Education-based activities produced by the Trust provide teachers with resources to stimulate discussions in the classroom.



First draft grabs headlines

The Wellcome Trust achieved wide media coverage of the first draft of the human genome. Headlines celebrated 'the story of life' *(Guardian)*, 'the miraculous map of mankind' *(Daily Mail)*, and 'one small piece of man…one giant leap for mankind' *(Mirror)*.

There was great optimism about the potential benefits, with *The Sunday Times* contemplating the awesome power of 'genes that will make us live for 200 years', while the *Daily Express*, placing a rather more cautious bet, welcomed a 'science breakthrough that could extend man's lifespan by 25 years'. There was also an attempt to temper elation with realism and keep the role that genes play in context. 'This is the key to life but not the secret to a perfect one', warned the *Sunday Telegraph*, and there is 'more to the human condition than genes alone' agreed the *Independent*.

Another important question was who should actually do the teaching. Science teachers tend to feel insecure when dealing with opinion rather than fact, while their non-science colleagues may feel more secure confronting these issues but often have an inadequate grasp of the technical information. The Institute of Education researchers recommended that the subject should be mediated by science teachers – although cross-curriculum activities are also worth exploring. The survey will be published in 2001.

A separate piece of research funded by the Trust and carried out by Jonathan Osborne and Sue Collins of the Department of Education at King's College London explored pupils' and parents' views of the science curriculum. Again the findings show that the demands of the national curriculum lead to the elimination of time-consuming activities such as classroom discussion and practical work – the very components that generate interest in science in the first place.

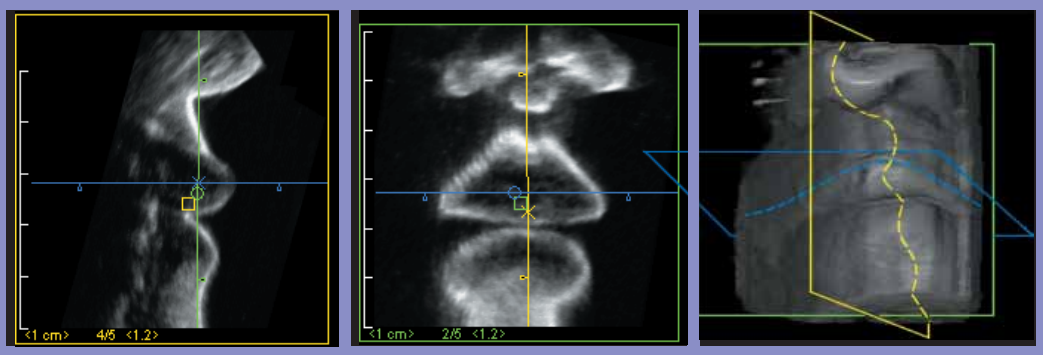
PART 2

RESEARCH REPORTS

MAKING FACES

MEDICAL IMAGING IN FOUR DIMENSIONS

JING DENG



Opposite page: Dr Jing Deng (left) using a prototype device to image lips by ultrasound.

Two-dimensional images, such as from the side **(left)** and front **(centre)**, are combined to form a three-dimensional image **(right)**.

Four-dimensional ultrasound images that capture the structures of lips in motion will assist in reconstructive surgery. Dr Jing Deng and Dr Nina Newton have developed an ultrasound imaging device enabling plastic surgeons to pinpoint exactly which muscles extend and contract whilst patients pout underwater, so that they can provide the full range of lip movement.

CAT, CT and MRI: medical imaging uses a wealth of acronyms and modern technology. Yet the most commonly used method of imaging structures within the human body is also the oldest – ultrasound. The technique is particularly important in obstetrics because, unlike computerized tomography and magnetic resonance imaging, it is non-ionizing (and therefore relatively safe), repeatable and cheap to do. It also has the advantage that the imaging is in real time, so structures – or a baby growing in the womb – can be visualized while they are moving.

To see a fetus in the womb, for example, ultrasound waves (sounds higher than the human ear can hear) are sent out, and when they hit a surface, they echo back and can be detected. The technique has its origins in sonar – indeed, the first ultrasound used on the human body was built around a device borrowed from a shipyard.

At University College London, Dr Jing Deng is developing new techniques in ultrasonography – computer-enhanced graphics of the signals that come back from the ultrasound. While working on a project with Professor Charles Rodeck to visualize the fetal heart in four dimensions, a plastic surgeon – Dr Nina Newton – came to see him. Dr Newton wanted to improve the image quality of the two-dimensional ultrasound used to visualize the orofacial area – the lips and the tissue around the lips – to assist in reconstructive surgery.

Underwater pouting

The simplest way to use ultrasound is to put a probe on the surface of the body and then to visualize structures beneath the skin. Two-dimensional ultrasound has been used to visualize the lips since the late 1980s, but placing the probe on the lips flattens and deforms the curved, delicate structures, and prevents the lips from performing functional movements.

Dr Deng and Dr Newton therefore developed a prototype device that could image the lips more accurately, and allow the lips to move while being imaged. A container bowl was sealed around the lower half of the volunteer's face and filled with water, and the ultrasound probe was then moved back and forth across the face, taking recordings. Each individual recording was in a two-dimensional, single plane – a slice through the tissue. But by taking a series of images across the tissue, Dr Deng could use a computer to produce a three-dimensional reconstruction of the tissue.

To add a fourth dimension, the images were recorded across the structure while the structure was moving – producing a movie of the dynamic target. When modelling the lips

and face, for example, the volunteers pouted, and the ultrasonography images showed how the hook-shaped muscles that straighten the lips extended and contracted as the lips moved in and out.

At higher resolutions, the images show the tiny bundles of muscles that control the lips. Measurements of the lengths and thicknesses of the different muscles lying under the skin of the lips can be very useful to plastic surgeons so that, during reconstructive surgery, they can provide the normal range of movement.

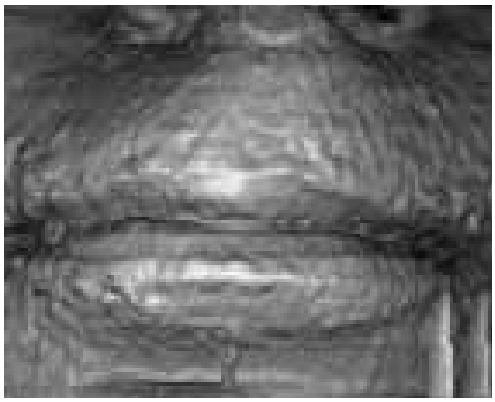
The new device has already been used to help inform reconstructive surgery for patients. For one patient, for example, the ultrasound images showed that subcutaneous connective tissues had overproliferated following surgery to remove a benign tumour. By comparing the abnormal side of the face to the normal side, Dr Deng could show which tissues needed repair.

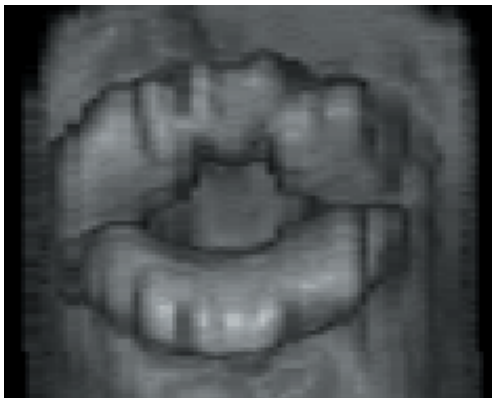
In the past, the movements of the facial muscles have been inferred from cadavers or from anaesthetized patients during surgery – in both cases when the muscles are relaxed. So it is not well known which of the many muscle groups in the face are responsible for which facial movements. Now, the four-dimensional images are providing a wealth of data of how the lips are controlled, and with new techniques such as real-time volumetric imaging (which takes ultrasound images across an area) likely to provide even more detailed pictures in the future once the technology improves, plastic surgeons could use pinpoint surgery at the level of individual muscle bundles.

Dr Jing Deng is at the Department of Medical Physics, University College London. Dr Deng's work is funded by a Wellcome Trust project grant held by Professor Charles Rodeck.

Further reading

J Deng, *et al.* (2000) 'Novel technique for three-dimensional visualization and qualification of deformable, moving soft tissue body parts', *Lancet*, 356:127–131.

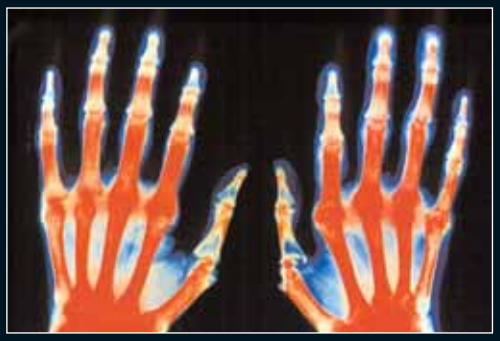




Dr Nina Newton looks at computer graphics of the signals coming back from the ultrasound.

Below: Three-dimensional images of static lips **(left)** and moving lips **(right)**.

Normal hands **(left)** and arthritic hands **(right)**.



TIPPING THE BALANCE

Novel therapies for rheumatoid arthritis ▪ MARCO LONDEI

In a healthy person, the cells, organs and chemicals that comprise the immune system maintain a delicate balance. Tip the scales one way, and immune deficiency results: the body becomes defenceless to attack from microorganisms. Tip them the other way and the immune system begins to attack the body's own tissues as foreign. Such autoimmune diseases, as they are known, include rheumatoid arthritis, diabetes, multiple sclerosis and inflammatory bowel disease.

At Imperial College School of Medicine, London, Professor Marco Londei is studying the process of inflammation that occurs in rheumatoid arthritis. His goal is to develop a therapy that will damp down the inflammatory response that causes the symptoms of rheumatoid arthritis, but without damaging the immune responses that are essential for fighting infections. Together with his colleague Yuti Chernajovsky, Professor of Rheumatology at the Bone and Joint Research Unit at St Bartholomew's and Royal London School of Medicine in London, Professor Londei is investigating several approaches, including gene therapy and use of antibodies that block pro-inflammatory molecules.

One focus of their research is the molecule known as CD40, found on many cells of the immune system. It has to bind to another molecule in order to trigger an inflammatory response. Professor Londei, together with colleagues Claudia Mauri and Lennart Mars at Imperial College School of Medicine, has found that antibodies that block CD40 can treat rheumatoid arthritis in a chronic mouse model of the disease developed by this team.

More recent investigations have shown that in the laboratory, the antibodies that interact with CD40 cause white blood cells to produce higher levels of a chemical called interleukin-10, which is a powerful natural inhibitor of inflammation. The team is therefore pursuing experimental ways of delivering interleukin-10, as well as other natural anti-inflammatory molecules, to joints affected by rheumatoid arthritis.

As T cells migrate naturally to sites of inflammation, one strategy being investigated by Professor Londei – and already used successfully by Professor Chernajovsky's team in other experimental settings – will involve genetically manipulating the T cells so that they manufacture large amounts of the anti-inflammatories. The T cells could then be returned to the body, ready to ferry the anti-inflammatory molecules to where they are needed most.

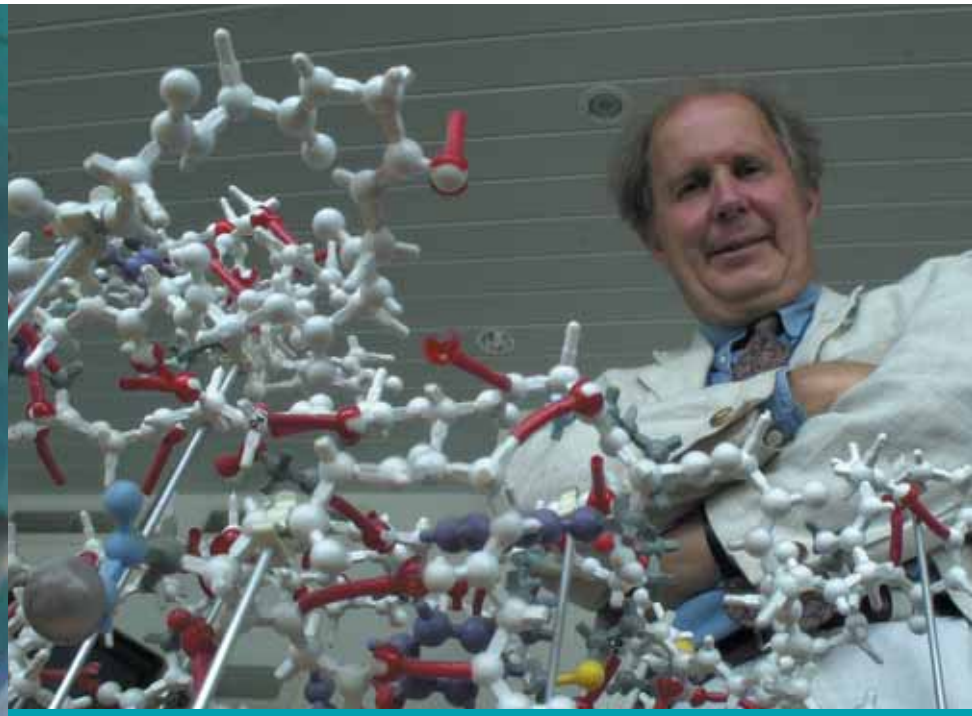
Professor Marco Londei is at the Kennedy Institute of Rheumatology, Imperial College School of Medicine, and holds a Wellcome Trust project grant. Professor Yuti Chernajovsky is at the Bone and Joint Research Unit, St Bartholomew's and Royal London School of Medicine in London.

Further reading

C Mauri, L T Mars and M Londei (2000) 'Therapeutic activity of agonistic monoclonal antibodies against CD40 in a chronic autoimmune inflammatory process', *Nature Medicine*, 6: 673–679.

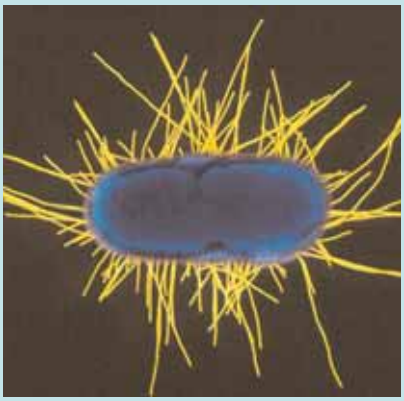
STARFISH AND MOUSETRAPS

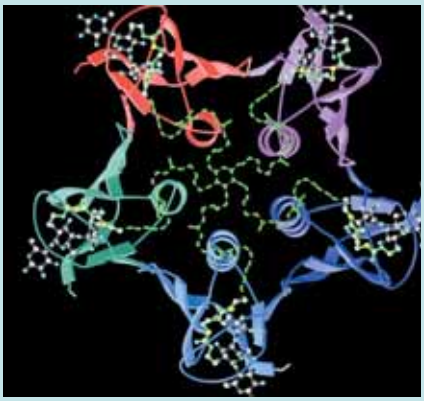
Protein crystallography and clinical medicine

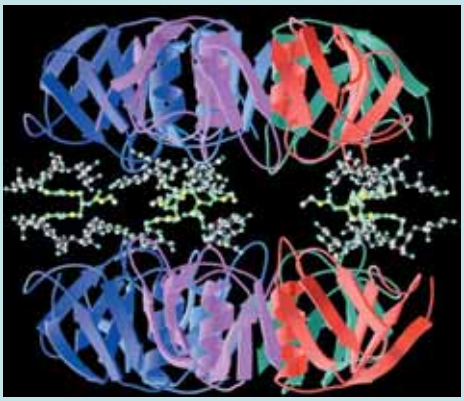


RANDY READ AND ROBIN CARRELL

Determining the three-dimensional structures of proteins can provide crucial insights into a broad range of clinical disorders. Researchers at Cambridge have found a 'starfish'-shaped carbohydrate molecule that binds to toxins produced by the *E. coli* bacterium, and discovered the 'mousetrap' action by which protease inhibitors deactivate over-prolific enzymes, thus preventing diseases such as emphysema, dementia and thrombosis.







Far left: Professor Randy Read.

Left: Professor Robin Carrell.

Above left to right: Toxins secreted by the *E. coli* bacterium cause food poisoning. The structure of the Shiga-like toxin B subunit, five copies of which associate to form a pentamer with five-fold symmetry. The top view (centre picture) shows how the arms of the 'starfish' inhibitor reach out to the five subunits, and the side view (right) shows how the inhibitor glues two toxins together.

From food poisoning to thrombosis, crucial insights into a broad range of clinical disorders are being revealed by research on molecular structures led by Professors Robin Carrell and Randy Read at the Wellcome Trust Centre for Molecular Mechanisms in Disease in Cambridge. The group consists of a crystallographic unit headed by Professor Read, and a structural medicine group headed by Professor Carrell working on different molecular diseases.

Crystallography can be used to determine the three-dimensional structure proteins involved in disease, providing an essential framework for a detailed understanding of the biochemistry of potential drug or vaccine targets.

Food poisoning and Shiga-like toxins

Professor Read has been working for some years on the structure and action of the Shiga-like toxins, which are secreted by strains of the bacterium *Escherichia coli* that cause food poisoning. The symptoms of an infection with these bacteria can vary widely in severity, from relatively mild diarrhoea to haemolytic uraemic syndrome. The latter condition causes kidney damage that can be permanent and require long-term dialysis. Some patients die, with the young and old most at risk.

In most countries, the treatment for *E. coli* food poisoning is supportive therapy, rather than directly attacking the bacteria or the toxins they produce. Antibiotics are not generally used because not all of the toxin is secreted by the bacteria – some remains in the area between the bacterial membrane and the cell wall. When the bacteria are killed with antibiotics, they release a large additional amount of toxin.

The Shiga-like toxins are in the class known as AB toxins (other members of which include cholera toxin, diphtheria toxin, and pertussis toxin responsible for whooping cough). As their name suggests, the AB toxins are proteins with two subunits, A and B, which play different roles in toxin action. When the Shiga toxin is secreted by the bacterium, it comes into contact with a host cell in the intestine, and the B subunit binds to a receptor molecule on the host cell surface. The toxins are then taken up into the target cell, and the A subunit enters the cytoplasm, attacking and blocking the ribosomes responsible for protein synthesis, and leading to the death of the cell. The B subunit, being responsible for the first, extracellular, phase of the toxin's action, is therefore a good target for therapies that do not have to cross the cell wall.

The cell surface receptors to which the toxin binds are glycolipids, which themselves have two components: a fatty 'tail' that sticks into the cell membrane, and a sugar component that sticks outwards and to which the B subunit of the Shiga toxin binds.

Using X-ray crystallography, Professor Read and colleagues found that the B subunit of the Shiga toxin is a pentamer with five-fold symmetry. In fact it is very similar to the structure of cholera toxin, a surprising finding as the amino acid sequences of the two toxins are very different. The similarity with cholera has proved useful, however, as it allows comparisons to be drawn with what is already known about how cholera toxin binds to its receptors.

Using a sugar similar to that of cell-surface receptor molecules, Professor Read and colleagues discovered that each of five parts of the B subunit of the Shiga toxin has three separate binding sites. The resulting 15 bound molecules nearly cover the entire surface of the pentamer. This explains why the Shiga-like toxin is so effective, despite the fact that individual binding actions are relatively weak. Velcro provides a useful analogy – an individual binding is feeble, but a great number across a small area produce a very tight bond.

Professor Read and colleagues established that two of the binding areas (sites 1 and 2) have a greater role in toxicity than binding site 3. The goal in producing a therapeutic agent is to produce a molecule more attractive to the

toxin than the host cell is. In this case, the goal was to produce a molecule that can bind to all ten of the binding areas on sites 1 and 2 of each of the five parts of the B subunit pentamer of the toxin.

The organic chemistry involved in creating these complex carbohydrates is difficult, but Professor Read and his collaborators at the University of Alberta in Canada, Professors David Bundle and Glen Armstrong, eventually came up with a carbohydrate molecule they christened the 'starfish'. It has a glucose centre and five arms, each with a bridged pair of sugars. This molecule binds a million times more tightly to the Shiga toxin than a single sugar, and is the first inhibitor to compete with the cell binding process.

Analysis of the action of the starfish molecule revealed a surprise. Instead of binding at sites 1 and 2 of one toxin, the molecule's trisaccharide arms bind to site 2 only, but on two toxins. The effect is to neutralize two toxins with one starfish molecule – to create a kind of 'starfish hamburger'.

The success of the starfish has shown that multivalent carbohydrate inhibitors can be successfully designed. The next step is to investigate whether other molecules can be used in a similar way. This is done by an initial process of 'computational docking', whereby the structures of a number of molecules are tested in three dimensions to see if they will bind with just one toxin molecule. The same linker technology used to create the starfish can then be applied to create a molecule that binds as tightly as the starfish molecule but may be easier to synthesize. This could form the basis for a therapy for preventing haemolytic uraemic syndrome in patients with *E. coli* producing Shiga-like toxins.

Conformational diseases

Professor Robin Carrell and colleagues have concentrated on the diseases associated with mutations in a family of proteins known as serpins. These proteins are protease inhibitors, selected by evolution to control a multitude of pathways essential to life, not only in the plasma – such as coagulation, fibrinolysis and complement activation – but also the proteolytic pathways that control the biology of the cell.

Research by Professor Carrell and others over the last 15 years has shown the way in which mutations affect this family of proteins as a whole, and result in disease. The story had been incomplete until late last year, when Professor Carrell and Dr Jim Huntingdon reached a goal that had eluded the field for many years. This was the solving of the structure formed when the target proteolytic enzyme is complexed to the protease inhibitor.

The inhibitor mechanism can be compared to a mousetrap. The protease approaches the inhibitor, as the mouse to the trap. The inhibitor is a perfect target for the protease because of its external peptide loop at its reactive centre. The protease cleaves the reactive centre of the inhibitor, which then undergoes a complete change in conformation; the inhibitor flips the protease to its other end, where it is crushed and distorted so that it loses all activity. The effect of this mousetrap mechanism is to give total and complete inhibition. The serpins therefore have absolute control of a number of the proteolytic pathways that are essential to physiological function.

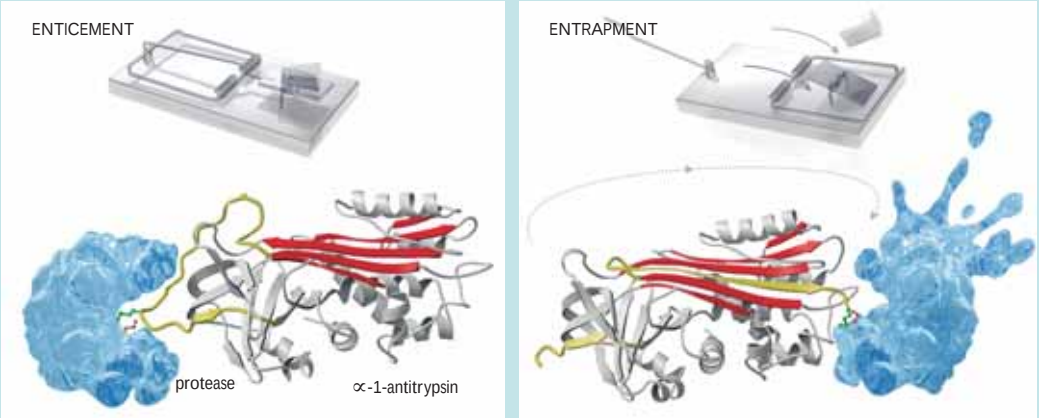
Together with Professor David Lomas, also at the Wellcome Trust Centre for Molecular Mechanisms in Disease, Professor Carrell and colleagues have recognized the common basis of a whole group of disorders they have termed conformational diseases. The solving of the structure of the protease–serpin complex enabled a number of previously puzzling aspects of the relationship between mutations in serpins and these diseases to be clarified.

Thrombotic disorders and heparin co-factor 2

A number of medical clinicians in the group are working on aspects of serpin research directly related to major clinical problems such as thrombosis. Dr Trevor Baglin, a consultant in haematology, is researching the function of a serpin called heparin co-factor 2. This is a natural coagulant, present in high concentrations in the blood.

Coagulation is controlled by the regulation of a number of clotting agents, thrombin being the principal one. Antithrombotic therapy currently involves using the drug heparin to activate the inhibitor antithrombin. However, the exact function of heparin co-factor 2, which is present in concentrations similar to those of antithrombin, is unclear.

Dr Baglin, together with Dr Huntingdon, has crystallized heparin co-factor 2 for the first time, and also its complex with its target protease thrombin. This work will open up leads that will clarify the physiological role of this inhibitor and could lead to significant therapeutic benefits. For example, heparin co-factor 2 is a much more targeted inhibitor than antithrombin, which inhibits most of the clotting factors in the blood in addition to thrombin. The action of heparin on antithrombin means that unwanted bleeding is a serious side-effect of current antithrombotic therapies, as the drug cannot be 'clot specific'. Clarifying the structure and function of heparin co-factor 2, which is much more targeted at thrombin and also more localized at the site of clots, will have significant implications in the prevention of thrombotic disease.



The protease inhibitor attracts and neutralizes its target enzyme in a similar way to a mousetrap. **(Left)** The protease trypsin, shown in blue, takes the bait presented by the exposed reaction loop, in yellow, of the inhibitor antitrypsin. Formation of an ester linkage between the active site serine [red] of the protease and the reactive centre methionine [green] of the inhibitor results in cleavage of the loop. **(Right)** The cleaved loop then springs into the middle strand position of the main ß-sheet of the inhibitor, flinging and smashing the tethered protease at the opposite end of the molecule.

Neurological disorders, neuroserpin and antichymotrypsin

Dr Damian Crowther, a senior trainee neurologist, is picking up work previously done by the group on neuroserpin and alpha-1-antichymotrypsin. The common neurodegenerative disorders, including Alzheimer's, the spongiform encephalopathies and early-onset Parkinson's disease, are all known to be associated with the aberrant intermolecular linkage of specific proteins. Dr Crowther's studies involve particular forms of familial dementia caused by the accumulation of neuroserpin. By studying the structural biochemistry of the polymerized neuroserpin, he hopes to uncover possible ways of modulating the polymerization process.

Dr Crowther and colleagues are developing a model using the fruit fly *Drosophila*. It is now possible to insert into the fruit fly the gene for the abnormal proteins associated with familial Alzheimer's, Parkinson's and spongiform encephalopathies. This will give unique insights into the cellular pathologies associated with molecular abnormalities in each case. The correlation of findings concerning neuroserpin with those involved in similar disorders is likely to clarify the general processes involved in these neurological disorders.

Emphysema and antitrypsin

Dr Ravi Mahadeva, a respiratory physician, is working with Professor Lomas on the serpin-related factors causing inflammatory lung disease such as emphysema. The initial research has been based on alpha-1-antitrypsin, a deficiency of which causes emphysema by allowing the enzyme elastase to remain uninhibited and destroy lung tissue. Deficiencies of antitrypsin are caused by a genetic mutation – the Z mutation. Individuals who are homozygous ZZ genotype, with consequent antitrypsin deficiency, will develop loss of lung function in their fifth decade, and earlier if they smoke.

The Z mutation makes the antitrypsin fold abnormally, and it then tends to be retained where it is synthesized, within the liver. Hence the lung tissue is deprived of its elastase inhibitor. However, polymers of the aggregated and mutated serpin do also appear in lung tissue, where they have an additional damaging effect – they attract neutrophils.

This offers up a new angle on emphysema. Previously the disease has been understood simply as a lack of antiproteinase. But the recruitment of neutrophils by the polymerized antitrypsin explains the dramatic localized inflammatory response in the lungs, a symptom previously noted, but neglected. This finding has immediate relevance to the pathogenesis of emphysema, and also cystic fibrosis, in which there is also an excess of elastase.

There has been a great pay off in the Cambridge group's achievement in identifying the mechanism causing conformational changes in the serpins, and their subsequent intermolecular associations. Because the same essential mechanism is involved in the whole range of conformational diseases, their discoveries have made possible huge leaps in the search for agents that will interfere in the pathological processes in each of these diseases.

Professors Randy Read and Robin Carrell are at the Department of Haematology, the Wellcome Trust Centre for Molecular Mechanisms of Disease, University of Cambridge. Professor Read is a Wellcome Trust Principal Research Fellow and Professor Carrell holds a Wellcome Trust programme grant.

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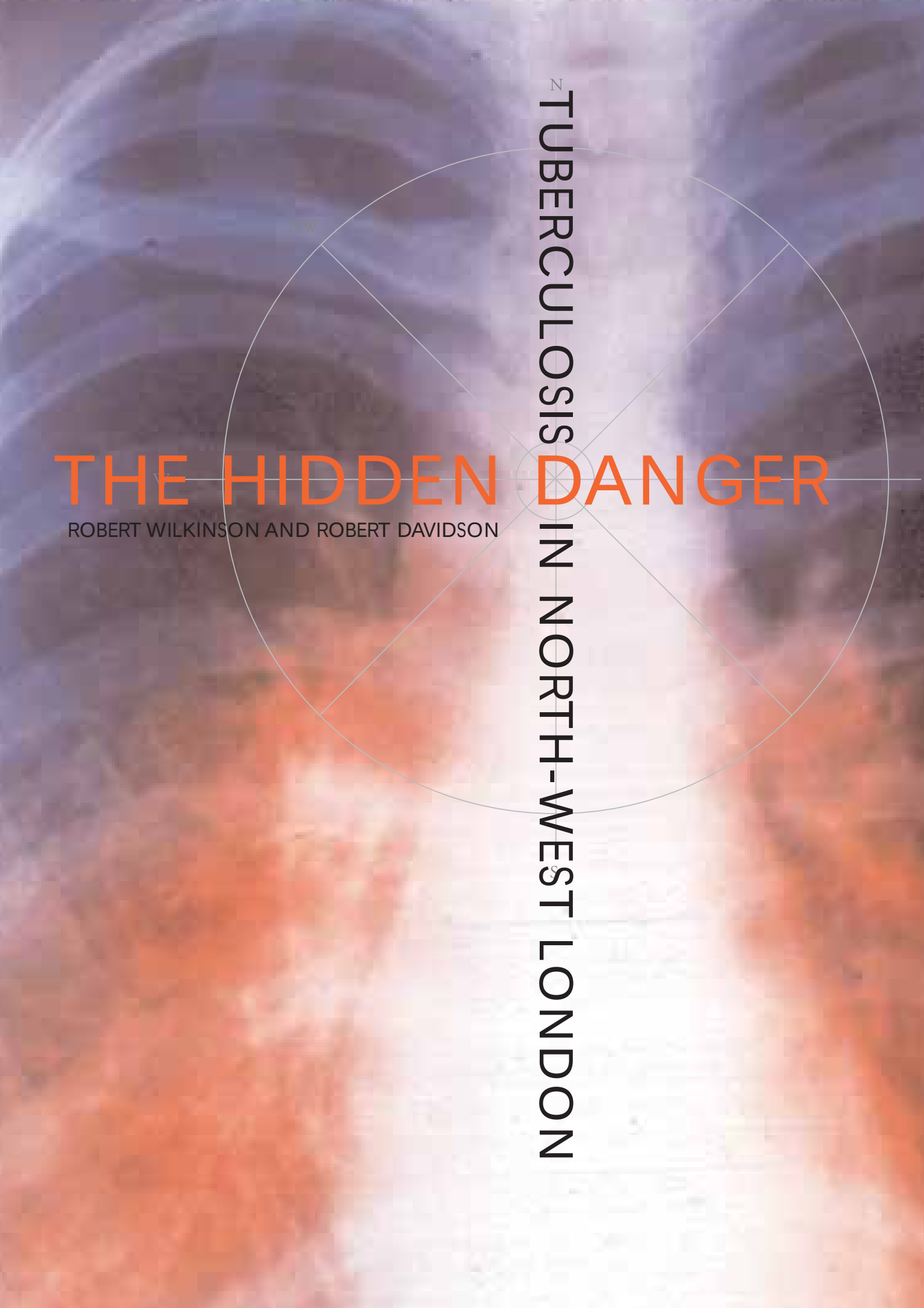
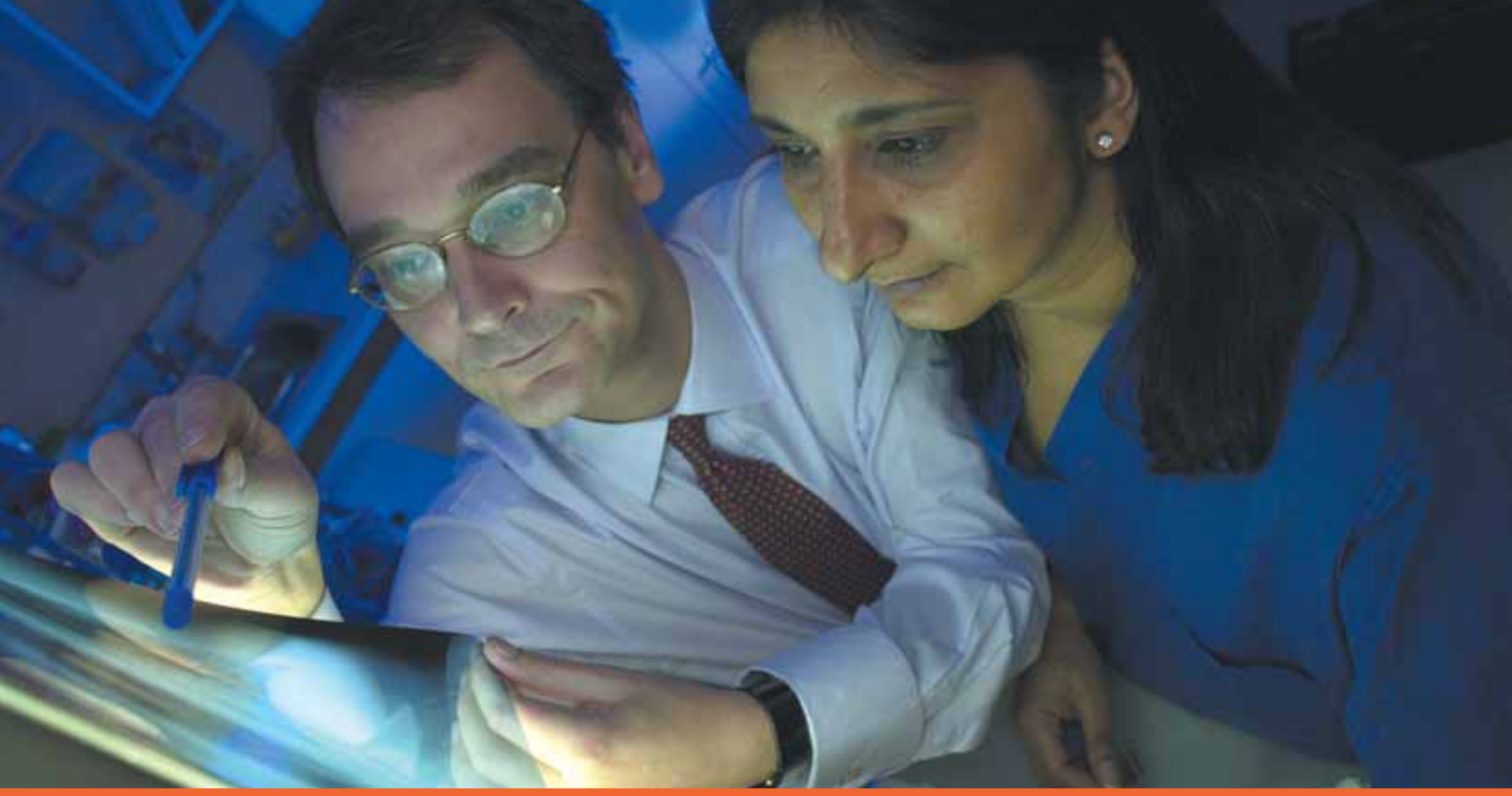

TUBERCULOSIS IN NORTH-WEST LONDON
THE HIDDEN DANGER
ROBERT WILKINSON AND ROBERT DAVIDSON



Dr Robert Wilkinson and Dr Robert Davidson have found that vitamin D deficiency in Harrow's Gujarati community leads to an increased risk of reactivating a tuberculosis infection. Vitamin D supplements could be a simple and cost-effective way of preventing the onset of tuberculosis disease.

Left: Chest X-ray showing an advanced case of TB.

Above: Robert Wilkinson is investigating the factors underlying tuberculosis reactivation.

The 'white death', tuberculosis, continues to haunt communities worldwide. About one-third of the world's population is infected with the tuberculosis bacterium, and even though in the majority of cases the infection is contained by the immune system and only a minority of people go on to develop active disease, tuberculosis remains the most common bacterial cause of death in the world.

It might be expected that people who move to the UK from countries in the developing world where tuberculosis is common would have a lower risk of developing the disease. Quite the reverse appears to be true. For example, the risk of tuberculosis in a person who has migrated from the Indian subcontinent within the last five years is 92 times greater than the risk in resident white Caucasians.

The problem is particularly acute in London, where the hospitals treat nearly 40 per cent of the 5–6000 cases of tuberculosis that occur in the UK every year. The cases are concentrated in only a few boroughs, almost entirely among immigrant populations.

In Harrow, north-west London, for example, many of the tuberculosis patients seen by Dr Robert Wilkinson and Dr Robert Davidson, researchers at the Wellcome Trust Centre for Research in Clinical Tropical Medicine at Northwick Park Hospital, are Gujarati Indians, who make up about a quarter of Harrow's population. The incidence of tuberculosis in this community is alarmingly high: more than 800 cases per 100 000 people occur every year, a rate notably higher than that in Gujarat in India.

Tuberculosis and vitamin D

Following infection by *Mycobacterium tuberculosis*, some people contract active tuberculosis immediately, while in others the bacteria lie dormant or latent in the body and can reactivate to cause active disease many years later. At Northwick Park, Dr Wilkinson and Dr Davidson deal almost entirely with the latter cause of tuberculosis – most of their patients have been infected overseas, and the bacterium has become reactivated while in the UK.

To investigate the factors that underlie this reactivation, Dr Wilkinson and Dr Davidson

looked first at factors that are known to increase risk in other parts of the world. Neither poverty nor overcrowding were risk factors, as the Gujarati Indians of Harrow enjoy a good standard of living, and while stress and HIV infection may have played a role in a small number of cases, they did not account for the significant number of tuberculosis cases.

Dr Wilkinson and Dr Davidson then investigated whether a lack of vitamin D might lead to an increased risk of tuberculosis. Vitamin D plays an active and complex role in many systems of the body, including the immune system – vitamin D receptors are found on the surface of most immune cells – and the skeletal system (rickets is caused by vitamin D deficiency, for example). Active vitamin D is produced in the skin by the action of sunlight's ultraviolet rays on its precursor, which is absorbed from the diet, especially from milk, meat and fish oils. A link between vitamin D and tuberculosis has historical precedent: in the past, patients were treated with cod liver oil, rich in vitamin D, or were sent to convalesce in the sun at high altitude, increasing their exposure to ultraviolet rays.

Most Gujarati Indians are strict vegetarians, and although there is very little vitamin D precursor in the vegetarian diet, what precursor is eaten would be converted rapidly by Gujarat's plentiful sunshine. The UK has many fewer hours of sunlight than Gujarat, however, and Dr Wilkinson and Dr Davidson found that most of the tuberculosis patients they tested had very low levels of vitamin D, and about half had undetectable levels of vitamin D. Furthermore, this latter group had a tenfold increase in risk of developing tuberculosis.

Dr Wilkinson and Dr Davidson also looked to see whether genetic variation in the gene encoding the vitamin D receptor might increase risk of tuberculosis. This gene has been identified previously as a genetic risk factor, one of 11 genes thought to underlie genetic susceptibility to tuberculosis (although, on their own, none of these genes appears to have a major influence on risk). Dr Wilkinson and Dr Davidson did not find any correlation between variation in the vitamin D receptor gene and risk of tuberculosis, but certain genetic variants together with vitamin D deficiency led to a significant increase in risk.

Reversing vitamin D deficiency with supplements could therefore be a simple and cost-effective way of preventing delayed tuberculosis disease. And such supplements could help reduce the risk of tuberculosis not just in the Gujarati Indian community of Harrow, but also in other communities of people who have moved from sunny climes – such as other parts of the Indian subcontinent or Africa – to the clouds and rain of the UK.

Dr Robert Wilkinson holds a Wellcome Trust Training Fellowship in Clinical Tropical Medicine at the Wellcome Trust Centre for Research in Clinical Tropical Medicine, Northwick Park Hospital, London.

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Robert Wilkinson checks a tuberculosis patient in an isolation ward for anaemia.

CAPPING IT ALL

Maintaining telomeres ▪ ED LOUIS

Above: Coloured scanning electron micrograph of a colony of yeast cells.

The telomeres at the ends of our chromosomes have been likened to aglets, the small metal or plastic tubes on the ends of shoelaces that stop the laces from fraying. Telomeres are stretches of highly repetitive DNA that 'cap' the chromosomes. If some of the DNA at the ends of the chromosomes is lost during cell division, as it commonly is, it is the telomeres that get shorter rather than important sequences of DNA containing genes. The telomeres are also thought to help the cell distinguish between the natural ends of the linear chromosomes, which do not need to be repaired, and broken chromosomes, which should be.

At the University of Leicester, Professor Ed Louis is studying yeast to investigate the function of telomeres and how they replicate. The results have helped researchers to understand both what happens in normal cells and what goes wrong in cancer cells.

Cells that are dividing to produce eggs or sperm, or cells such as stem cells which divide to produce more specialized cells needed by the body, produce an enzyme called telomerase which replicates and maintains the telomeres during cell division. The other cells of a healthy adult human do not produce telomerase, and lose parts of their telomeres gradually over time. After a certain number of divisions, the telomeres are eroded too far, and the cells die.

In many kinds of cancers, however, the machinery for making telomerase has been turned back on. In recent years, a huge research effort has been directed at developing drugs that would block telomerase, so preventing cancer cells from dividing too many times.

Yet telomerase is not the only player in the replication of telomeres. Between 15 and 20 per cent of tumours do not have telomerase switched on. Instead, the cells in these tumours use an alternative mechanism to maintain their telomeres. Much of Professor Louis's recent work has focused on elucidating the genes and enzymes involved in this second method, using yeast cells that maintain their telomeres in the absence of telomerase.

He and his colleagues have identified a known enzyme – SGS1 – that is required by yeast cells using the alternative mechanism. This enzyme is found in all organisms, from bacteria to humans, and is thought to be a helicase that unwinds DNA. Mutations in human genes similar to SGS1 cause Werner syndrome, a premature ageing disease, and Bloom syndrome, which predisposes to cancer.

Professor Louis proposes that SGS1 and other members of its family are involved in processing a DNA structure specific to eroding telomeres. As well as improving our understanding of the processes of cell division, he predicts that it may one day be possible to develop a drug that will block the enzyme that allows cells to compensate for the absence of telomerase, which could be used in conjunction with anti-telomerase therapy.

Professor Ed Louis is at the Department of Genetics, University of Leicester, and holds a Wellcome Trust project grant.

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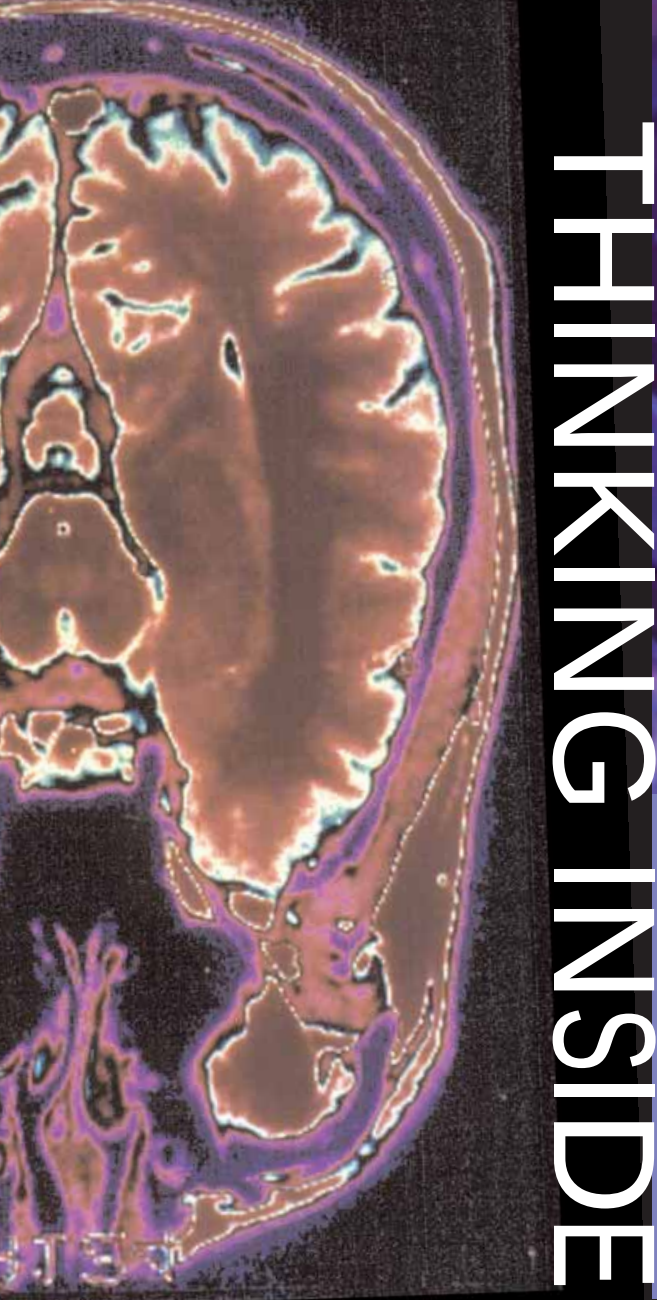


THINKING INSIDE THE BOX

Professor Roger Traub views the neurons in the brain as a society, working together and talking to each other. His computer models of networks of neurons are helping us to understand how the brain works, and what may be the cause of some cases of epilepsy.

Computer modelling of the brain

ROGER TRAUB

In 1997, chess world champion Garry Kasparov played six games against IBM's supercomputer Deep Blue – 'the brain's last stand' as *Newsweek* termed the match. Deep Blue's stunning victory demonstrated its colossal number-crunching power, yet even Deep Blue is a pale imitator of the most complex, sophisticated and least understood computer known – the human brain.

With millions or perhaps billions of neurons talking to each other, the circuitry of the brain is mind-boggling. At the University of Birmingham, Professor Roger Traub is using a supercomputer of his own – affectionately named Rose, a baby sister of Deep Blue – to model the wiring of the brain.

He views the neurons as a society, and models how new properties and a sense of order emerge from a network of neurons talking to each other, as opposed to each neuron doing its own thing.

Building a neuron

The first step in building a network is to make computer models of single neurons. All the different components involved in a neuron firing have to be taken into consideration – the structure and shape of the neuron in the brain, the receptors in the synapses that receive neurotransmitters, and the ion channels that open and close, changing the electrical charge in the neuron (see page 46).

The initial modelling therefore takes information from many different fields of research. A neuron has channels and receptors all over its membrane, so the model has to take into account the different kinds of receptors, the different types of channels (which conduct sodium, calcium or potassium ions), estimates of the numbers of each channel in the cell, and the properties of the channels. Professor Traub distils the information to a simplified, symmetrical structure (as a real neuron has too much complexity even for a supercomputer to handle), writes a computer program of the first unit of the model and then makes sure that the model behaves as a real neuron.

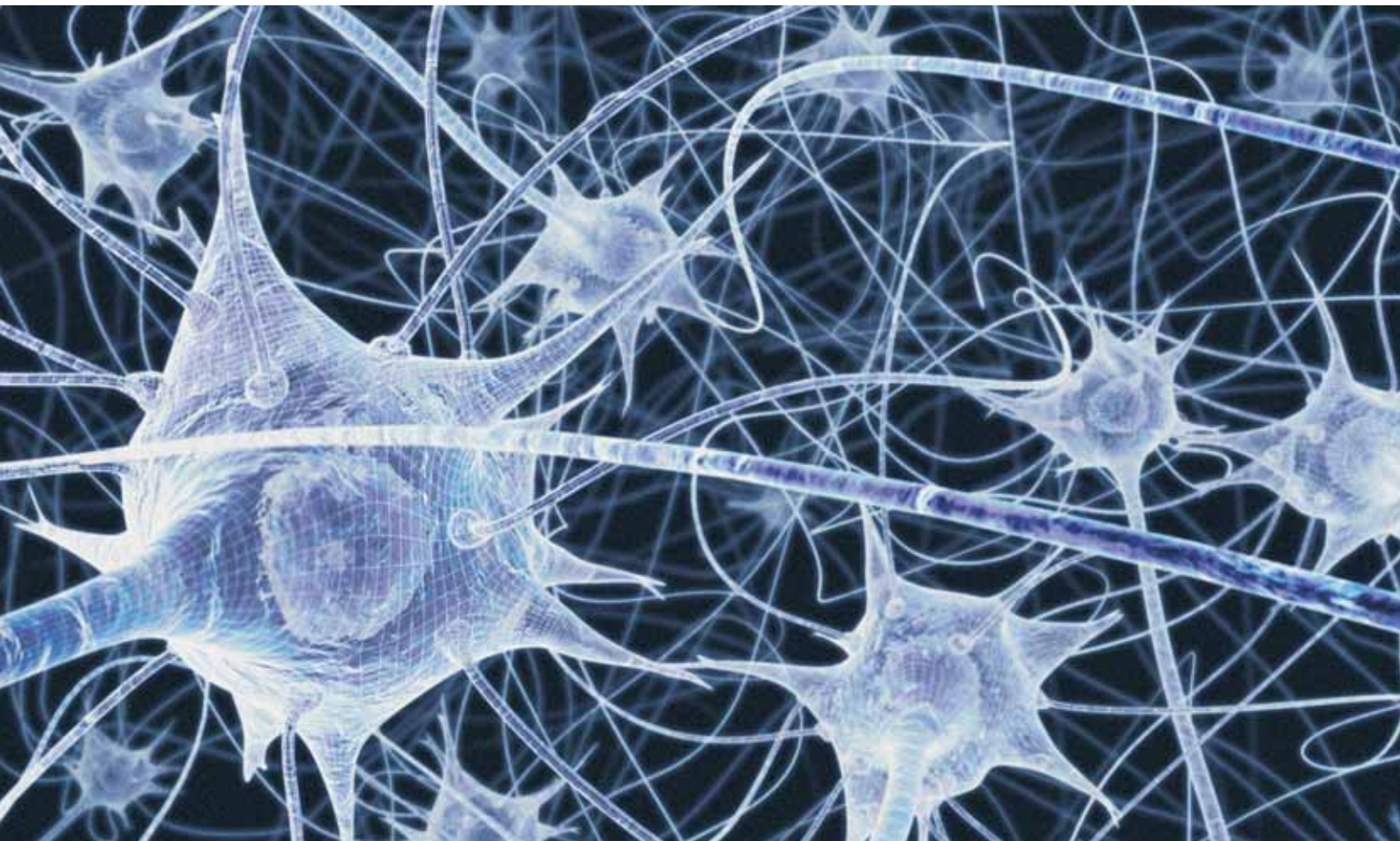
Dancing together

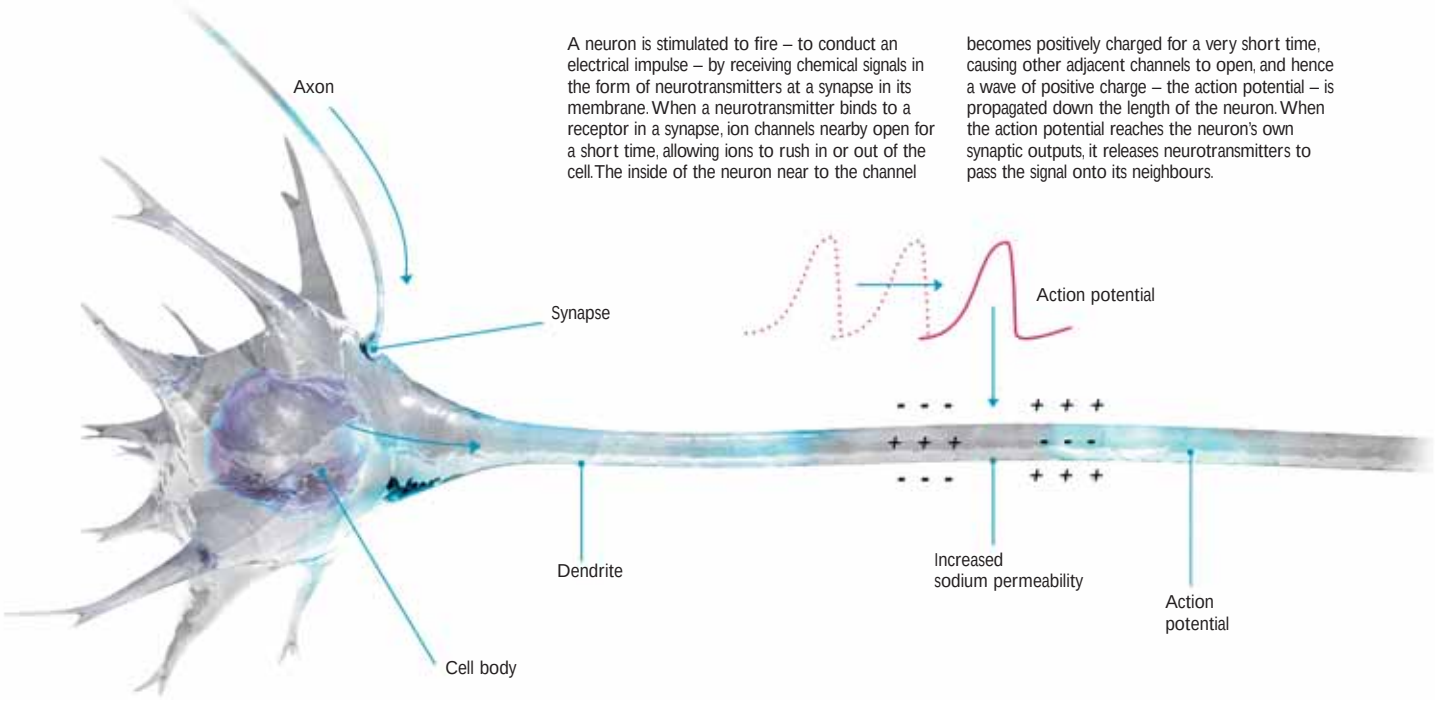
With the models of the neurons in hand, Professor Traub can then take multiple copies and connect them together. Using this technique, he has been building models of the circuitry of the hippocampus that involve hundreds or thousands of neurons. Over more than 20 years, the models have become more refined and 'rich' in detail, allowing precise predictions to be made about how the hippocampus works.

The human brain has two hippocampi, one each side of the head, hidden under the temporal lobes. The hippocampus is critically involved in episodic memory – remembering an event, such as what you had for breakfast

Left: Colour-enhanced human brain. **Above:** Professor Roger Traub with his supercomputer, Rose, in the background.

Below: An artist's impression of the population of neurons in the brain.





A neuron is stimulated to fire – to conduct an electrical impulse – by receiving chemical signals in the form of neurotransmitters at a synapse in its membrane. When a neurotransmitter binds to a receptor in a synapse, ion channels nearby open for a short time, allowing ions to rush in or out of the cell. The inside of the neuron near to the channel becomes positively charged for a very short time, causing other adjacent channels to open, and hence a wave of positive charge – the action potential – is propagated down the length of the neuron. When the action potential reaches the neuron's own synaptic outputs, it releases neurotransmitters to pass the signal onto its neighbours.

(other parts of the brain are involved in repetitious memory, such as learning how to ride a bicycle). And as it has only a million – or a few million – cells in a single layer, the simple anatomy of the hippocampus makes it attractive for computer models and for direct experimentation.

The two key types of cells in the hippocampus are the excitatory pyramidal cells, which respond to sensory input, and the inhibitory interneurons; the latter cells make sure that the chain reaction of neuron firing from the pyramidal cells is kept in check and does not run out of control. The interplay between different types of cells is crucial to the correct function of the brain; indeed, the hippocampus is the part of the brain with the lowest threshold for starting epileptic seizures. From a computer model of the hippocampus, Professor Traub and colleagues suggested such seizures could begin when an imbalance in the hippocampus could cause excessive firing of the pyramidal cells, overloading the system.

Yet the true value of computer modelling of brain networks comes not just in theoretical insights, but in the dialogue between the modellers and the experimentalists. Professor Traub's collaborator, Miles Whittington at the University of Leeds, examines slices from the hippocampus which contain a few thousand cells and can be kept alive for a few hours. Drugs or electrical currents can be applied to the slice, and the responses of the neurons recorded using sensitive electrodes. From his models, Professor Traub can make predictions about how the network will behave. These predictions can then be tested by Dr Whittington, and the results of the experiment fed back into revisions and refinements of the model.

An example of this dialogue can be seen in their work on the 'binding problem'. More than ten years ago, it was discovered that visual input – such as a bar moving across a screen – would cause cells in different parts of the brain to respond at a specific frequency, so-called 40 Hz oscillations (bursts of electrical activity that occur 40 times per second). This would be unremarkable, except the oscillations are synchronized over distance. Seeing the bar causes different cells to respond in different parts of the brain. This phenomenon remained a mystery for many years – how do you get diverse parts of the brain that are devoted to the same task to work together? The mystery was compounded by the speed with which the synchrony is set up – the cells may be far enough apart that the signals take a while to conduct, yet synchronize almost immediately.

Professor Traub's discovery of one possible origin of this synchrony came almost by accident. While working on his model of the hippocampus, with its network of pyramidal cells and interneurons, he introduced a delay of a few milliseconds (quite long by neuron standards) into the conduction delay between neurons. When the interneurons then fired a pair of spikes, the two sides of the brain in the model synchronized almost immediately. Dr Whittington's experimental research confirmed that this doublet firing was indeed the key to the synchrony – the timing of the doublet interval determined whether the two sides would synchronize.

Short circuit

Another mystery of the brain is the very fast oscillations, up to 200 Hz or more, which have been recorded from the brains of some children and adults at the start of epileptic seizures. These 200 Hz oscillations are so fast that it appears as though the cells are talking to another electrically; such communication usually occurs only through gap junctions, channels that allow direct communications between neurons with membranes that are in contact.

Professor Traub investigated these spikelets using a model of two cells connected together by an electrical contact. When the contact was in the dendrites or the cell bodies – the logical place for connections, as this is where the synapses are – the model did not produce any realistic spikelets. But when they were connected in the axon – the main trunk of the neuron – the spikelets occurred. In theory there should not be a connection in the axon, as it would produce cross-talk: imagine you are calling someone on the telephone, the wires short out, and suddenly you are talking to ten people at the same time. Nevertheless, networks of neurons, interconnected by electrical contacts between axons, can generate (in models) very fast oscillations.

Further studies by Dr Whittington suggest that gap junctions can account for fast oscillations. When a hippocampal slice was stimulated with an electric current, the expected 40 Hz oscillation occurred. But when a drug was added that opens up gap junctions, and the slice was stimulated again, a seizure occurred, beginning with fast oscillations. Conversely, adding a different drug that blocks gap junctions allowed the 40 Hz sensory response, but no fast oscillations and no seizure. During the 200 Hz fast oscillations, it appears that the axons of the pyramidal cells begin firing sending signals backwards and forwards and releasing neurotransmitter indiscriminately. Although it is still not clear what the gap junctions on axons may do normally, these findings may well have practical significance for the treatment of some cases of epilepsy, as the drug that blocks gap junctions in these experiments is in clinical use in the UK for the treatment of ulcers.

Scaling up

Professor Traub's latest project is looking at even more complex parts of the brain – the cortex and the thalamus. Most sensory input from the outside world comes into the thalamus and then goes to the cortex. The thalamus acts like a gateway to the cortex, allowing the cortex to be disconnected from the outside world – while we are asleep, for example.

Unlike the relatively simple hippocampus, the huge folded sheet of the cortex has more cell types, six layers of principal cells, and incredibly complex interconnections. So, before this big model can be built, about a year's groundwork is required to build the individual models of the types of cells found in the cortex and thalamus. Then, 10 000 neurons will be connected together – not the first model of such a size designed by Professor Traub, but the first with neurons rich in detail and much more like the real thing.

Even with 10 000 neurons, the new model will represent only a tiny portion of cortex, about 1 mm across and 0.2 mm thick. As computers continue to increase in power, Professor Traub looks forward to the next evolution in brain modelling: connecting together many large models of the cortex at once. Then, he says, we will have a reasonable fraction of the human brain on our computer screens.

Professor Roger Traub held a Wellcome Trust Principal Research Fellowship at the University of Birmingham.

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WHY ART?

BIOMEDICAL SCIENCE AND CONTEMPORARY ART

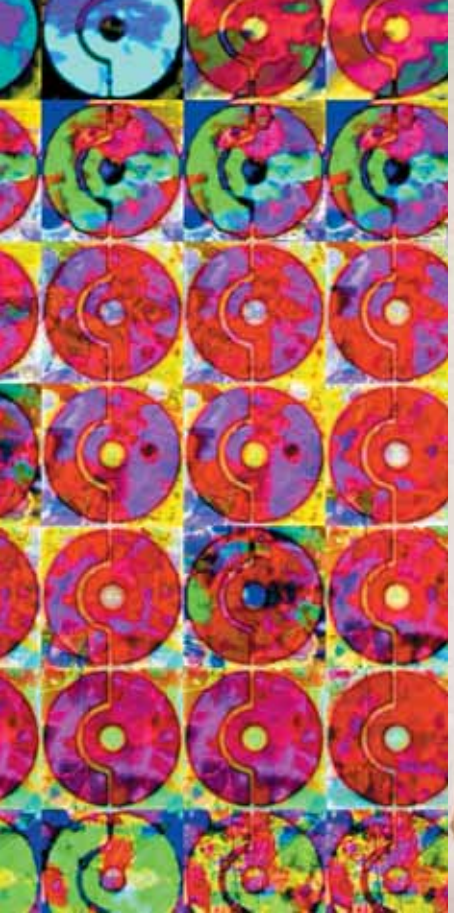
The Wellcome Trust's science and art/drama collaborations enable the Trust to reach new audiences who may not otherwise be drawn to biomedical science.

A rough-hewn set of wooden sculptural reliefs showing simple red designs such as a heart and a cross by contemporary artist Franco B; beguiling footage of jellyfish pulsing delicately into the distance in the work of Irish artist Dorothy Cross; a set of audacious haute couture frocks resembling embryological forms made by fashion designer Helen Storey; and a thoroughly ironic fantasy about the brain by the avant-garde theatre company Forkbeard Fantasy. At first glance, all this seems a far cry from the work more usually associated with the Wellcome Trust – the DNA sequencers unveiling the human genome at the Sanger Centre or the NMR (nuclear magnetic resonance) imaging equipment exploring molecular structures at the Universities of Birmingham and Oxford. And yet these artworks and projects have all recently been shown or supported by the Trust. What on earth could the former have to do with the latter – contemporary art with biomedical science?

A look through some of the treasures stored in the Wellcome Library quickly reveals that there is at least a historical precedent for bringing artworks under the Trust's roof. The same man who articulated its initial scientific goals also collected, to take just a few examples, Rembrandt and Van Gogh etchings and a range of Renaissance master drawings. Henry Wellcome was in fact one of last century's greatest collectors; but he was no art connoisseur. The extraordinary aesthetic treasures that he did collect were all gathered with another purpose in mind, namely to shed light on a very broadly conceived history of health and medicine.

This predilection of its founder, one which during his life grew from a hobby into an all-consuming passion, provides the first clue to the puzzle of just what the Trust is doing with the works of Franco B, Dorothy Cross, Helen Storey and Forkbeard Fantasy. The tradition of collecting in the history of art has then led to an involvement with contemporary art practice. But there is much more to it than a simple patronage of the arts; the motivation in these activities is instead focused on the Trust's commitment to engaging the public in informed dialogue about biomedical science.

The range of arts-related projects undertaken with this goal in mind is in fact fairly diverse. The Exhibitions Department at the Trust is responsible for two programmes of exhibitions, some that link contemporary science and art, and others that add the ingredient of medical history: it initiated and



Left: *The Brain* by Forkbeard Fantasy is a Science on Stage and Screen production.

Above: 'The Search for Terrestrial Intelligence', a sciart project.

Right: 'The Primitive Streak', a sciart project.

runs the sciart award scheme which (in collaboration with five other arts and science funding bodies) gives grants to partnerships between scientists and artists; it coordinates another competition for live theatre, digital and broadcast media (Science on Stage and Screen); it acts as host to two artists-in-residence per year; and finally it is also preparing a major exhibition concerning Sir Henry Wellcome's collections, to be mounted at the British Museum in 2003, which is the 150th anniversary of his birth. Broad and eclectic in their approach, these projects nevertheless do all share the same education and communication goals.

The rationale for these activities combines four strands of thinking. First, there is what one might call the 'famous beer' strategy – the use of the arts to reach audiences who might not otherwise be drawn to biomedical subjects and ideas. Second, the visual and dramatic arts enable us to exploit different formats, different languages if you like, through which to communicate ideas about medicine and its history – ones which audiences engage with in an altogether different way to the lectures, conferences, reports, consultations, articles, science centres and so forth that the Trust also supports and undertakes. Third, these projects have an uncanny ability to provoke reactions, sometimes strongly emotional ones. As a consequence, they frequently attempt to deal with social, ethical and cultural aspects of medicine rather than scientific facts, information and theories. Lastly, working in the arts and with exhibitions often provides a means of promoting unusual and collaborative ways of working with biomedical sciences that cut across traditional academic disciplines and professional domains.

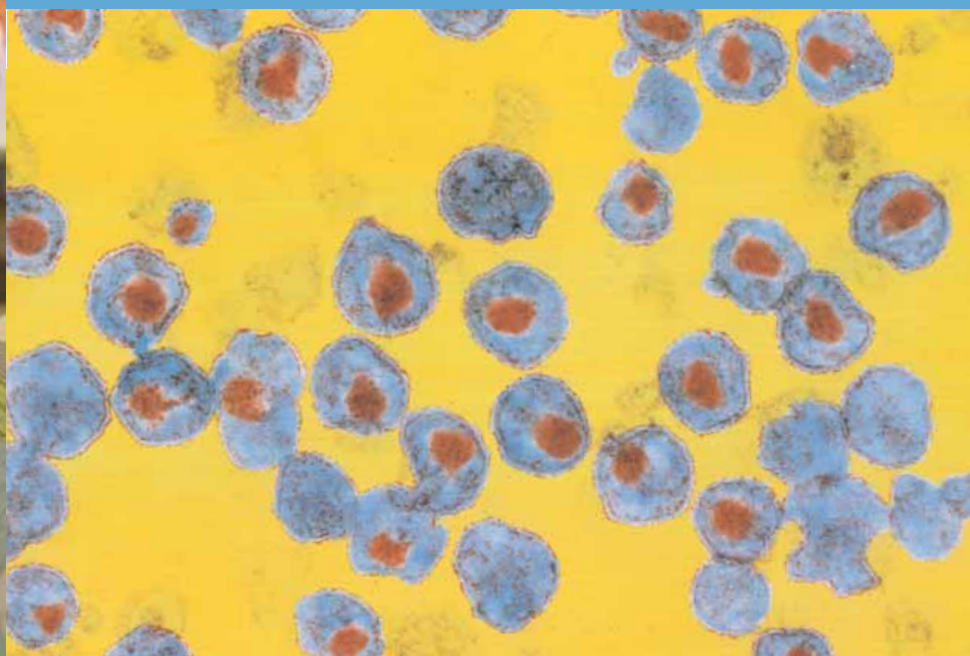
That is the theory at least. You can decide for yourself what you think the effect and impact of mixing arts and sciences is by visiting exhibitions in the Two10 Gallery or, from 2002, a new gallery in the Science Museum, by making contact with the Trust's artist-in-residence, by experiencing one of the plays or programmes funded through the sciart or Science on Stage and Screen competitions, or by clicking on the 'Science/Art' and 'Exhibitions' sections within the Trust's website (www.wellcome.ac.uk).

MATTHEW SMALLMAN-RAYNOR AND ANDREW CLIFF

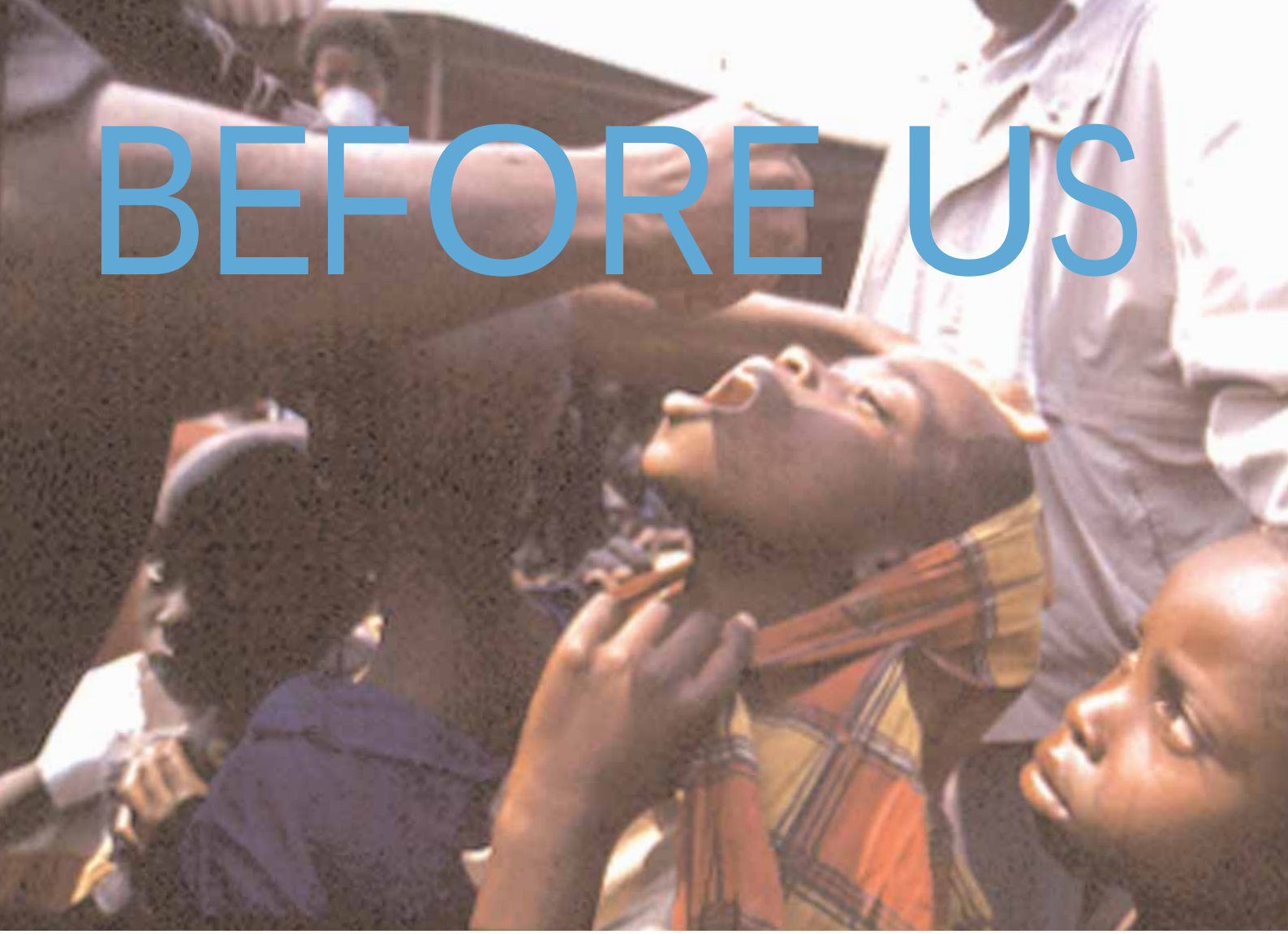
THE PAST IS

Historical geography of epidemics

Professor Andrew Cliff and Dr Matthew Smallman-Raynor are mapping a historical geography of the world's major infectious diseases. By uncovering the processes that have triggered the emergence and spread of such diseases in the past, the researchers hope to provide data on which the forecasting – and possible prevention – of future epidemics can be based.



BEFORE US



Far left: Dr Matthew Smallman-Raynor at the University of Nottingham looking at maps of diseases.

Left: Coloured transmission electron micrograph of HIV type 1.

Above: The polio vaccine was introduced in the 1950s and the disease in now targeted by the WHO for complete global eradication.

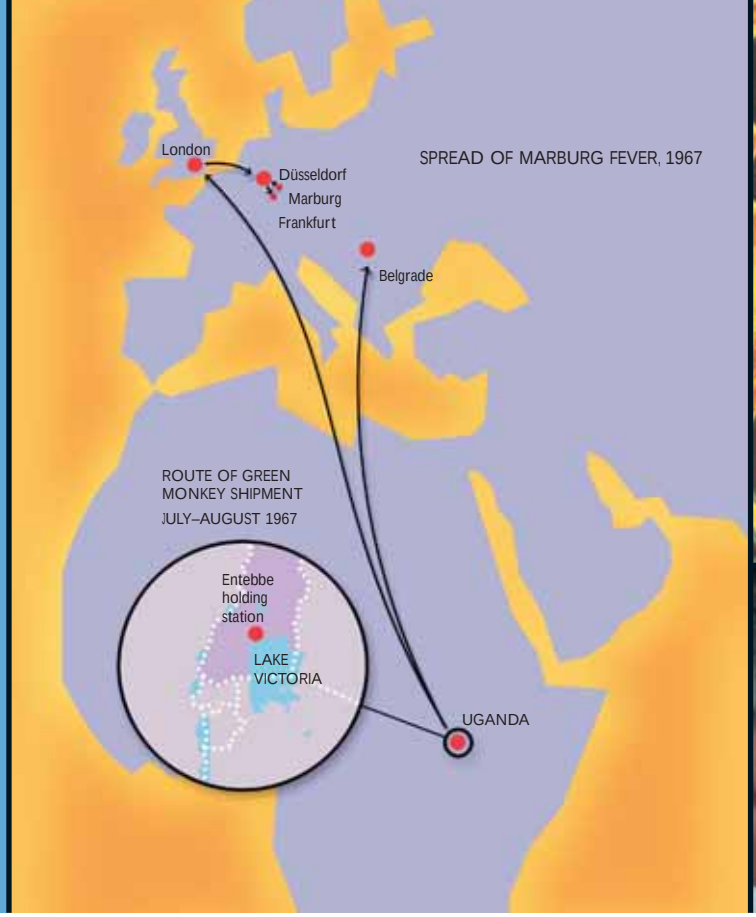
According to Buddhist teaching, 'the past is before us, the future behind us'. All forms of forecasting rely on this principle, though its usefulness has not always been immediately recognized. When the climate change group at the University of East Anglia, Norwich, first started collecting historical climate information 30 years ago, for example, they were regarded by some as a little eccentric. Now, that historical information is of signal importance in predicting future climate change.

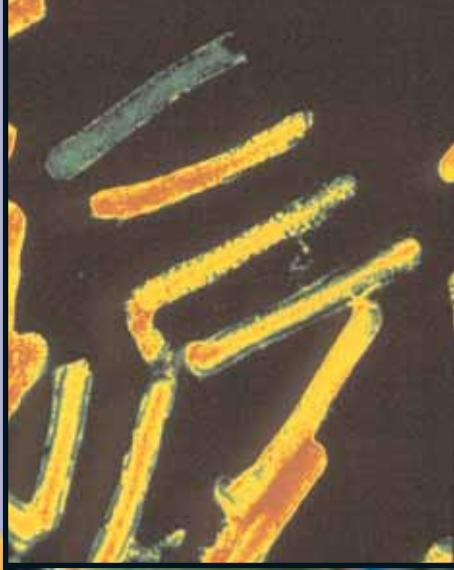
The analogy with weather forecasting is an apposite one for the work of Professor Andrew Cliff and Dr Matthew Smallman-Raynor. In 1991, together with their recently retired colleague Professor Peter Haggett and under the aegis of two five-year Wellcome awards to the Epidemic History Geographical Information System Programme, they began to map and analyse historical time series of disease morbidity and mortality for the world's major infectious diseases, dating back to 1850. Covering 40 or so diseases – including diphtheria, enteric fever, measles and tuberculosis, as well as 'new' diseases such as HIV/AIDS and Marburg, Lassa and Ebola fevers – these long-run data series provide a historical benchmark against which contemporary trends can be analysed and future trends predicted.

At first glance the field of geography and the study of infectious diseases may seem slightly odd bedfellows. But in fact, with the exception of genetic mutation, almost all the factors impinging on the emergence or re-emergence of epidemics can be classified as geographical. They break down broadly into five distinct, but closely interacting, categories: population growth, urbanization, collapse of geographical space, ecological/land-use change, and civil disruption or war.

Understanding population trends is one key to Professor Cliff and Dr Smallman-Raynor's modelling. Ninety-four per cent of the world's population growth over the next 20 years will occur in developing countries, exposing a greater share of the world's population to tropical diseases. At the same time, global warming is increasing the range of the tropical or subtropical conditions some disease agents need to survive. The net result is a far greater range of people who had not previously had contact with infectious diseases suddenly being exposed to them.

Populations are also increasingly urbanized. UN figures show a rise in the number of cities with one million or more inhabitants – from 200 in 1985, to 425 by the beginning of 2001.





Right: Spread of Marburg fever in 1967. Marburg fever is a rare, severe type of haemorrhagic fever caused by Marburg virus, a close relative of Ebola virus. The virus was first recognized in 1967 when outbreaks of haemorrhagic fever occurred in laboratories in Marburg and Frankfurt, Germany, and in Belgrade, Yugoslavia. The first people infected had been exposed to tissues and blood from African green monkeys imported from Uganda for research or to prepare polio vaccine. A total of 37 people became ill and seven people died in the outbreak.

Centre: Coloured transmission electron micrograph of the Marburg virus. Professor Andrew Cliff.

Far right: Global spread of HIV-2.

The disease implications are complex, but previous work by Professor Haggett has shown that high-density 'islands' of population are important in providing reservoirs for infection chains. This is clearly illustrated in contemporary epidemics, for example, in the spread of HIV/AIDS in the USA.

The collapse of geographical space – in terms of time and cost – is another profound influence on epidemic patterns. While world population growth since the middle of the twentieth century has been between 1.5 and 2.5 per cent a year, the annual growth in international movements of passengers across national boundaries is between 7.5 and 10 per cent. Again, HIV/AIDS provides a clear modern example of the impact of travel on a disease pattern. The spread of HIV is thought to have involved travel between central Africa and Haiti, and then from Haiti to the USA, Latin America and Europe.

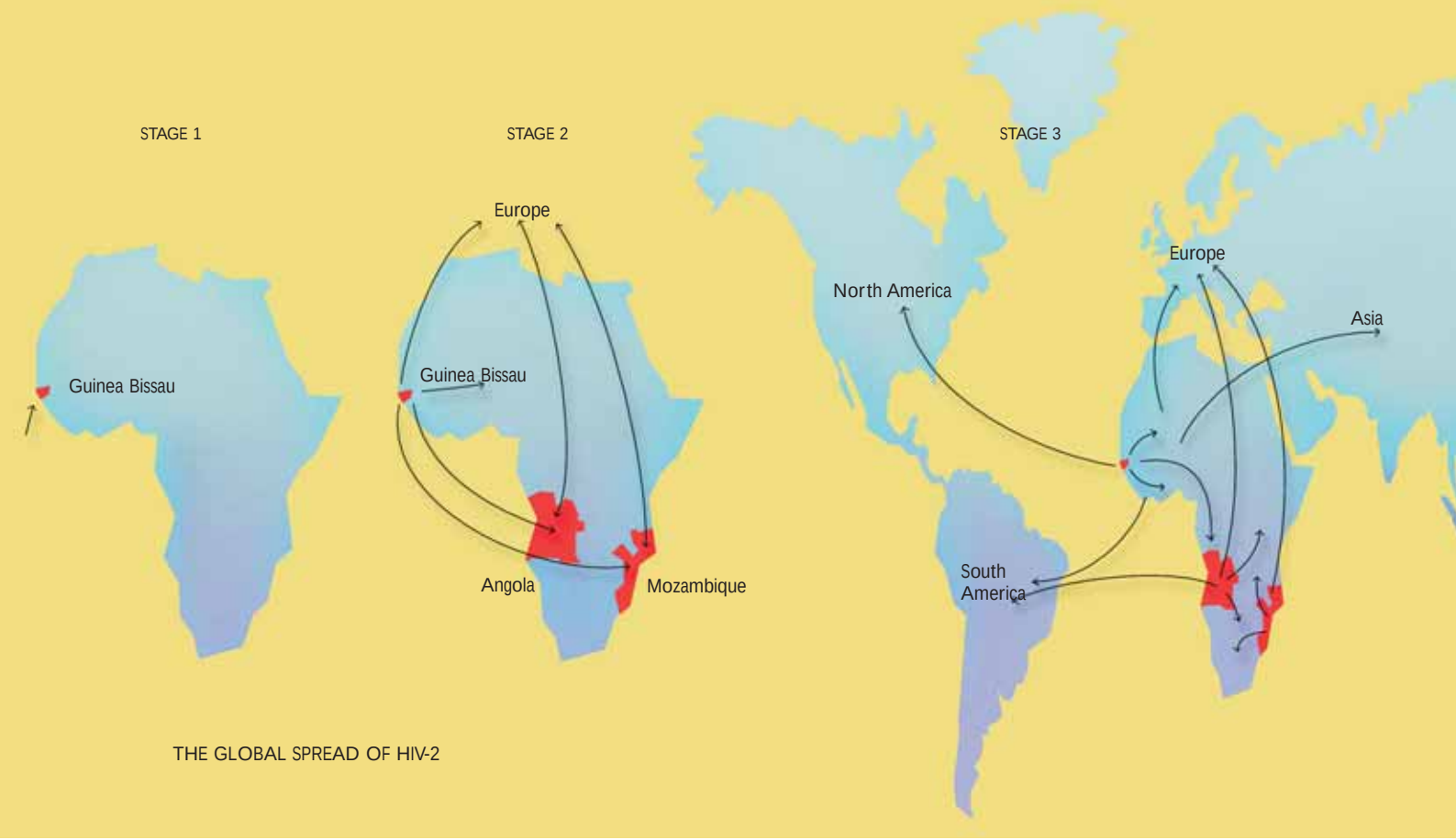
Civil disturbance and war can play a large part in the spread of epidemics. There is inevitably a breakdown in sanitation and hygiene systems, and in medical care, often combined with large movements of refugees. All these factors have made fertile ground for the great killers of history, particularly cholera, dysentery, tuberculosis and typhus. Typhus claimed many lives during the Rwandan conflict of the mid-1990s, and poliomyelitis made a brief reappearance in Europe during the Bosnian war.

Polio is a disease of particular interest to Professor Cliff and Dr Smallman-Raynor, who describe it as one of the great emergent diseases of the twentieth century. There is little evidence of polio until the nineteenth century, when there were isolated outbreaks on the island of St Helena and in Scandinavia. The major epidemics began with the New York epidemic of the early 1900s, and polio became a global killer in the 1930s and 1940s. World War II spans a remarkable period in the polio pandemic, with the Malta epidemic of 1942 a landmark. The disease was probably brought in by troops from North Africa, and went through the Maltese population with great virulence resulting in high mortality rates.

Then, in the 1950s, the polio vaccine was introduced. Because humans are the only reservoir for the infective agent for polio, vaccination had a dramatic impact. The disease is now targeted by the World Health Organization for complete global eradication, and there are currently only around 4000 cases of paralytic polio globally each year.

Polio provides Professor Cliff and Dr Smallman-Raynor with a benchmark for a modern epidemic, its beginning and end more or less contained by the twentieth century. When smallpox was eradicated in 1979, the World Health Organization produced a global history of the disease. Professor Cliff and Dr Smallman-Raynor aim to produce a similar narrative for the historical geography of polio.

There has been much publicity in recent years of seemingly 'new' infections such as Ebola, Lassa and Marburg fevers, Lyme disease and HIV/AIDS. Professor Cliff and Dr Smallman-Raynor point out that these newly emerging infectious diseases are highly unlikely to have



THE GLOBAL SPREAD OF HIV-2

arisen spontaneously in the population. AIDS illustrates the point once more: the first officially recorded AIDS case was in 1979 in the USA, but it is now clear that HIV was around at least as early as the 1950s. They feel the same is probably true of Ebola, Lassa and Marburg fevers – these diseases will have existed in isolated populations before an epidemic forced them into public consciousness.

By studying previous epidemics, Professor Cliff and Dr Smallman-Raynor hope to begin to unravel why an epidemic is suddenly triggered off in a population. It is a highly complex process. Is it the environment and the population providing a seedbed for the disease, or is there some change in the virulence of the infectious agent? Cliff and Smallman-Raynor feel that most often it is environmental and demographic changes that are the trigger. There are, of course, examples of infectious organisms changing – influenza is capable of rapid change, for example which is why flu epidemics can affect the same populations year on year. But, in general, the causative agents are very stable, and so their appearance and disappearance can only be attributed to changes in environment and demography.

Taking a global perspective, Professor Cliff and Dr Smallman-Raynor point out that it is still essentially the same 'top ten' infectious diseases, such as typhus, cholera, malaria and tuberculosis, that account for most of the global burden of disease and death.
The old killers are still the most effective.

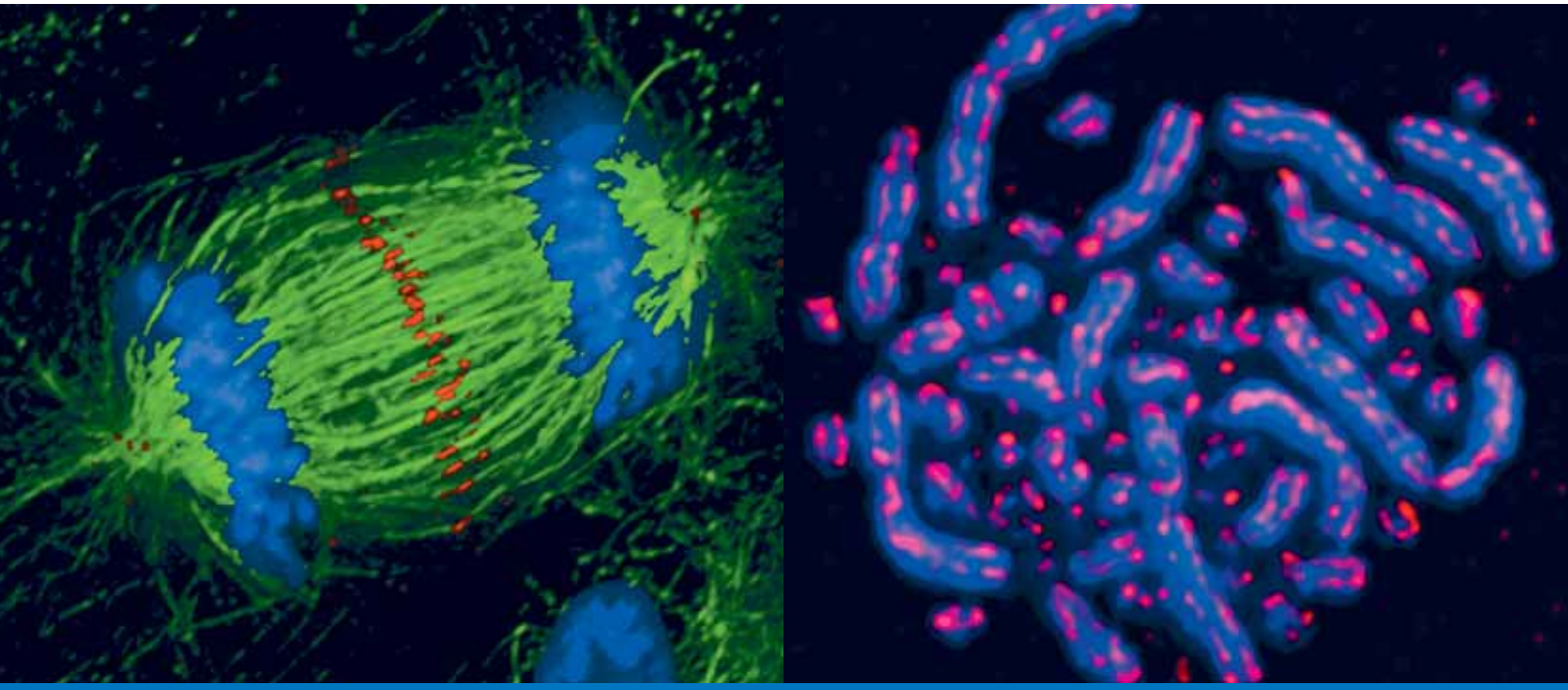
By understanding the processes that have triggered the emergence or re-emergence and spread of these infectious diseases, Professor Cliff and Dr Smallman-Raynor hope to use the past as our protection for the future.

Professor Andrew Cliff is at the Department of Geography, University of Cambridge.
Dr Matthew Smallman-Raynor is at the School of Geography, University of Nottingham. Their work is funded by a Wellcome Trust History of Medicine programme grant.

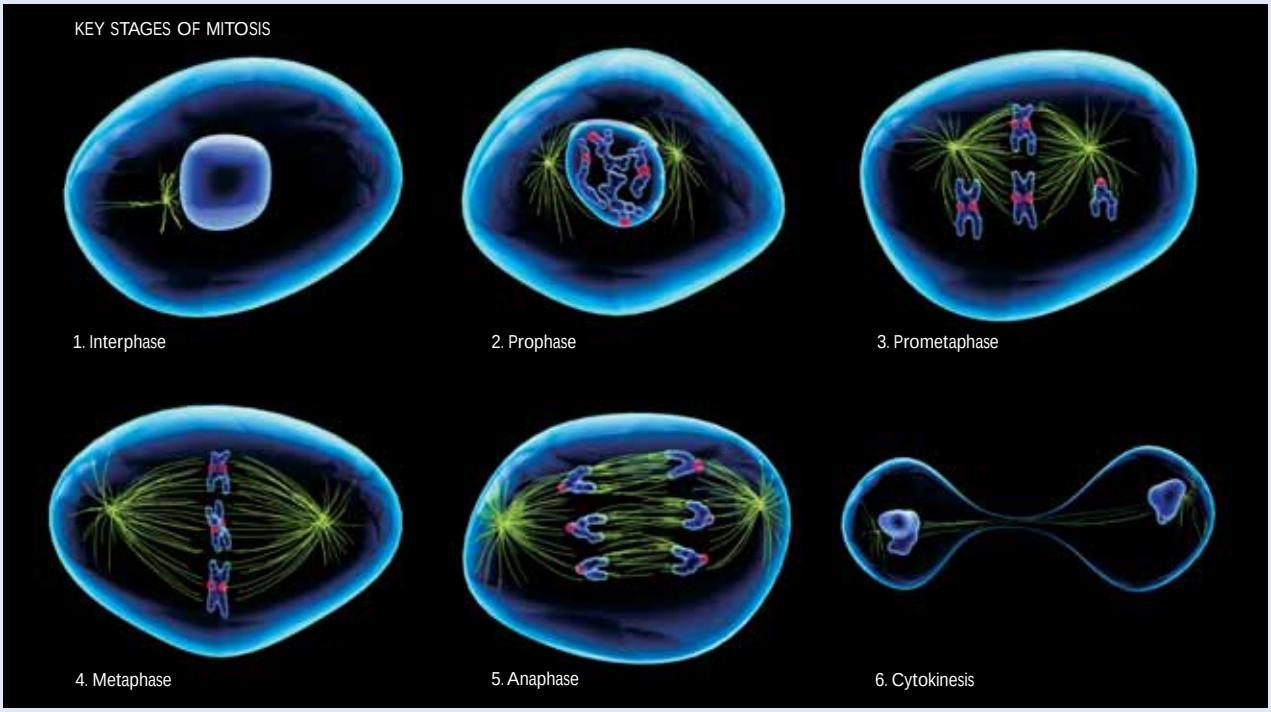
BIRTH OF A CELL

Lighting up mitosis

BILL EARNSHAW



Cell division – mitosis – is one of the most hotly contested fields of biomedical research and the focus of hundreds of research groups worldwide. Professor Bill Earnshaw and colleagues are investigating proteins that play key roles in mitosis, a fundamental, basic area of research that is bringing insights into the normal biology of the cell, and is of direct relevance to the processes of cancer.



Left: Professor Bill Earnshaw is trying to understand how DNA in the chromosomes is moved around so accurately during mitosis.

Above: As a cell divides into two daughter cells, its cytoskeleton, membrane networks and chromosomes undergo profound structural changes. Adapted from a diagram by Charles Earnshaw, aged 7.

Every human cell contains nearly two metres of DNA, packed into a nucleus only one thousandth of a millimetre across. Like a fishing line, there would appear to be ample opportunity for the DNA to get tangled up. Yet the cell copes with DNA strands that are orders of magnitude more complicated than those a fisherman uses: each time a cell divides, the chromosomal DNA must be replicated and condensed, and the chromosomes carefully moved around.

At the University of Edinburgh, Professor Bill Earnshaw's research is underpinned by a desire to understand how the DNA is packaged so carefully in the chromosomes, and moved around so accurately during mitosis. Yet his studies have come to encompass wider aspects of how the cell changes its shape and structure during division – mitosis. As it divides, the cell's cytoskeleton, membrane networks and chromosomes undergo profound structural changes and move around, ready for the cell to cleave into two daughter cells.

The division bell

When a cell is about to go into mitosis, and has replicated the DNA in its nucleus, it checks over the DNA one last time to ensure that replication is complete and that the chromosomes are not damaged. Once it has the go ahead (and enters prophase) the chromosomes start to condense, the cytoskeleton – the cell's internal scaffolding – starts to change its shape, and the centrosome splits in two and moves to opposite sides of the cell (the centrosome is a control centre for the dividing cell, organizing the microtubules that winch the chromosomes apart). Many of these events, and the events that follow in mitosis, are choreographed by the master controlling enzyme – cdc2 – which regulates the behaviour of a host of proteins throughout the entire cell.

In the next phase – prometaphase – the envelope enclosing the nucleus breaks down, the microtubule scaffolding binds to the chromosomes, and the chromosomes start jostling for position and lining up at the centre of a scaffolding of protein filaments called the spindle. Once the chromosomes are fully lined up, the cell is said to be in metaphase. Another signal then prompts the replicated chromosomes to move to opposite poles of the cell (anaphase), and the cell cleaves down the middle into two daughter cells (cytokinesis).

Each chromosome is like an articulated lorry. The centromere is the cab that controls how the rest of the chromosome – with its heavy load of genes – moves around. Indeed, chromosomes are self-drive vehicles: motors attach to the centromere and move the chromosome in the cell. While in the USA, Professor Earnshaw was investigating patients with an autoimmune disease called scleroderma, and identified a family of proteins that reside in the centromere of the chromosome. These proteins are important antigens in the autoimmune process, and one of the proteins is now the basis of a test for the disease.

Further investigation identified another centromere protein, INCENP (inner

centromere protein). During prophase, INCENP can be found all over the chromosomes, but as mitosis continues it starts moving to the centromeres, and is located there by metaphase. Then, strangely, when the chromosomes start separating, INCENP transfers its allegiance and leaves the chromosomes for the centre of the spindle. Later on, some INCENP also moves to the cleavage furrow where the cell will split.

INCENP and aurora

While many of Professor Earnshaw's group work on cells from chickens, it was from the eggs of another organism – the frog *Xenopus* – that INCENP was first isolated. In a pond, the fertilized egg must develop very quickly, so quickly in fact that there is not time, in just a few hours, for the egg to synthesize all the proteins required for the 20 000 or so nuclei. So the egg is provided with stockpiles of soluble proteins, which become divided between the daughter cells during development. These stockpiles have proved invaluable to researchers investigating the cell division cycle, as the proteins can be isolated in soluble form, ready for further analysis. One such protein is INCENP, and Professor Earnshaw and colleagues found that INCENP exists in the stockpile in a complex with a particular class of protein kinase called aurora.

Like many other kinases, aurora plays an essential role in cell division. Kinases often act as master regulators at specific points in the cell cycle, switching on many other proteins at once, but aurora appears to have a number of important tasks to complete at different stages of mitosis. Not only is aurora essential for the activation of the centromeres when it is time for the centromeres to pull the chromosomes around, but it also appears to regulate the cytoskeleton and furrowing mechanism that will cleave and divide the cell. If the function of aurora is disrupted, mitosis goes haywire and the cells do not divide correctly.

Aurora cannot act alone, however. It appears to rely entirely on INCENP to transport or target it to particular parts of the cell at particular times. If the function of the taxi, INCENP, is disrupted completely, its passenger, aurora, does not move and the cells do not begin the process of mitosis. Or, if the production of the INCENP protein is stopped more gradually so that it takes a couple of days for the existing protein to be broken down and to disappear, there are problems later in mitosis – the process fails at prometaphase and the chromosomes do not line up properly. Professor Earnshaw's group have also used certain mutant INCENP proteins to interfere with the function of the natural INCENP, a relatively mild disruption of the system. In this case, mitosis fails in its final stages – the cleavage of the cell.

Enforcing the party line

It used to be thought that cdc2 was by far the most important regulator of mitosis, carrying the weight of organizing mitosis on its shoulders alone. The research by Professor Earnshaw's group shows that cdc2, the Prime Minister of mitosis, has an essential assistant – the Chief Whip aurora – which ensures that everyone down the line does their job. How aurora enforces the party line is still unknown, so Professor Earnshaw and colleagues are now working to find out which proteins are phosphorylated by aurora and how it regulates the centromere and cleavage furrow. They are also investigating a third protein, survivin, found in the complex with INCENP and aurora. Originally thought to be a cell death protein, Professor Earnshaw's team are characterizing the role of survivin in cell division.

Although a fundamental, basic area of research, the processes of mitosis are directly relevant to a clinical understanding of cancer, where cell division is uncontrolled. Indeed, INCENP, aurora and survivin have been found to be overexpressed in a number of cancer types. Whether they play a direct or indirect role in the cause or progression of cancer is unknown at present – Professor Earnshaw speculates that inappropriate levels of the proteins may decrease the accuracy of mitosis, with the knock-on effect of creating imbalances between the genes that control cell division. Yet it is only by understanding their normal role in mitosis that future methods of intervening in their function can be designed.

Professor Bill Earnshaw is a Wellcome Trust Principal Research Fellow at the Institute for Cell and Molecular Biology, University of Edinburgh.

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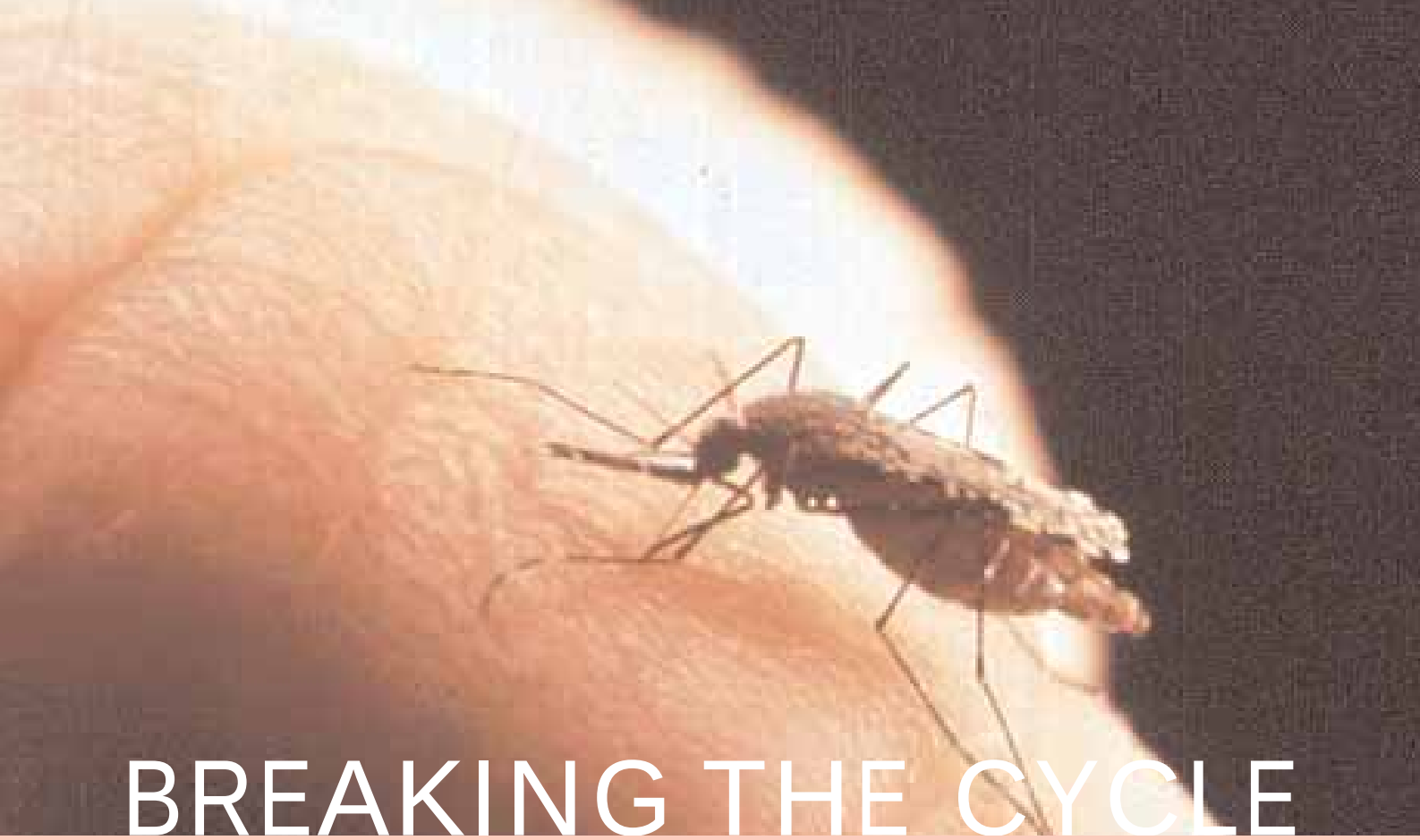
www.icmb.ed.ac.uk/research/earnshaw/index.html



BREAKING THE CYCLE

Progress in malaria research

Testing new antimalarial drugs, designing vaccines and finding ways to control mosquitoes are some of the ways in which Trust-funded researchers aim to tackle the huge problem of malaria. But developing rational intervention strategies requires a clear understanding of how the parasite interacts with its human host. Here we describe recent Trust-funded research which aims to do just that.

The breadth of malaria research funded by the Trust reflects the complex nature of *Plasmodium falciparum*, the parasite that causes most cases of the disease. The parasite's multi-stage life cycle, strategies to avoid the host's immune system and rapid development of drug resistance make it one of the world's biggest killers.

The life cycle of the malaria parasite can be divided into two stages, the first taking place in the mosquito, and the second in the human host. Parasites are taken up by a mosquito feeding on an infected individual. In the mosquito gut, the parasites develop into 'sporozoites' which migrate to the salivary glands, ready for transmission to a new host when the mosquito feeds again.

The sporozoites travel via the bloodstream of the human host to the liver. There, the parasite develops into its 'merozoite' form, bursting out in large numbers from the liver cells and entering the circulation, this time invading red blood cells.

Inside the red blood cells, the parasites grow, divide and develop, then rupture the host cells and invade new red blood cells. This cycle is repeated and results in malaria disease, and the appearance of characteristic symptoms such as fever, anaemia, and in severe cases coma and death. Understanding the events that take place once the parasite enters the red blood cell should lead to the development of novel strategies for the prevention of malaria disease.

THE LIFE CYCLE OF THE MALARIA PARASITE IN THE RED BLOOD CELL

Adapted from
L H Bannister *et al.* (2000) 'A brief illustrated guide to the ultrastructure of *P. falciparum* asexual blood stages', *Parasitology Today*, 16: 427–433.

1 The malaria parasite, in its 'merozoite' form, attaches to and invades the red blood cell.

2 Nutrients taken from the red cell help the parasite to develop from a 'ring' stage into its 'trophozoite' form.

Dr Graham Mitchell is at Guy's King's and St Thomas' School of Medicine, London, and holds a Wellcome Trust project grant. Dr Alister Craig is at the Liverpool School of Tropical Medicine, University of Liverpool, and holds a Wellcome Trust University Award. Professor Chris Newbold is at the University of Oxford and holds a Wellcome Trust programme grant. Dr Sanjeev Krishna is at St George's Hospital Medical School, London, and holds a Senior Research Fellowship in Clinical Sciences. Professor Malcolm Molyneux is at the Liverpool School of Tropical Medicine and Wellcome Trust Research Laboratories in Blantyre, Malawi, and holds a Wellcome Trust Research Leave Award. Dr Jana McBride is at the University of Edinburgh and holds a Wellcome Trust project grant. Dr David Conway is at the London School of Hygiene and Tropical Medicine and previously held a Wellcome Trust project grant. Dr Bart Barrell is the Head of the Pathogen Sequencing Unit at the Wellcome Trust Sanger Centre.

1 Stop the invasion

Preventing the parasite from entering the red blood cell would stop it dead in its tracks and halt development of malaria disease. It is important therefore, to understand the events that take place during the invasion process. Several proteins on the cell surface of the parasite are involved in its attachment to the red blood cell surface. Using electron microscopy Dr Graham Mitchell and colleagues at Guy's, King's and St Thomas' Medical School, London, have carefully characterized the parasite molecules, including merozoite surface protein 1 (MSP-1), which form intimate links with proteins on the red cell surface. They have shown that this interaction is followed by the actions of parasite-encoded proteins collectively known as the acto-Pfmyo-A motor which allow the parasite to enter the red blood cell.

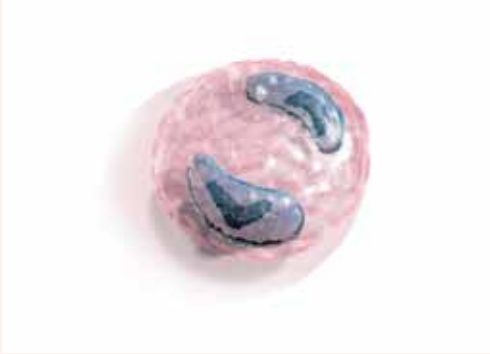
Antibodies directed against MSP-1 can be used to block the interaction between the parasite and the red blood cell surface, preventing invasion. Studies using animal models have shown that the presence of antibodies to MSP-1 can protect against further infection and Dr David Conway (London School of Hygiene and Tropical Medicine) and Dr Jana McBride (University of Edinburgh) have confirmed recently that humans generate antibodies to MSP-1. If they bind to particular forms of MSP-1, these antibodies can provide protection against further infection. MSP-1 is highly variable and the parasite can change the fine detail of this protein during the course of a single infection, a feature that enables it to avoid attack by the host's defence mechanisms.

2 Strike the transporters

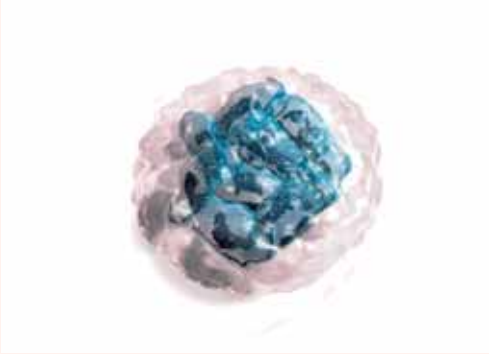
Once inside the red blood cell, the parasite starts to siphon off cellular nutrients and transports them into its own cell. Professor Sanjeev Krishna at St George's Hospital Medical School, London, has been studying these transport mechanisms using a model system and has recently identified a family of transporters, a novel subclass of calcium ATPases found only in *Plasmodium* and its relatives. These enzymes could prove to be useful drug targets. Dr Krishna's work has been spurred on by a multimillion pound project to sequence all 14 chromosomes of the *P. falciparum* genome. In 1996, the Trust, as part of an international consortium of funders, committed £7 million to the sequencing project. To date, sequence data from two chromosomes have been published, and the project has already had a major impact on malaria research.

Draft sequence from the malaria parasite genome is updated and posted on the web every day, and is being used by researchers in many different countries. For example, a research group in Germany has used the draft sequence to identify a pathway – the isoprenoid biosynthetic pathway. Because this pathway is not found in humans it makes it a suitable target for an antimalarial drug. Fortuitously, a drug designed to inhibit the action of the same pathway had been developed already, as an antibacterial agent. The drug is now being tested in clinical trials as an antimalarial agent, and it is hoped it will be the first of many developed as a result of the malaria parasite genome sequencing project.

Malaria Genome Sequencing Consortium
The parasite's 14 chromosomes are being sequenced at three sequencing centres: the Institute for Genome Research, Maryland; Stanford University, California; and the Wellcome Trust Sanger Centre. The Pathogen Sequencing Unit at the Sanger Centre, headed by Dr Bart Burrell, is sequencing nine of the parasite's chromosomes. The sequencing effort is a joint funding venture between the Wellcome Trust, Burroughs–Wellcome Fund, National Institutes of Health and the Department of Defense, USA. Data from the project are posted on the sequencing centres' websites on a daily basis.



3 As development continues, the parasite inserts its own proteins into the surface membrane of the red blood cell.



4 About 48 hours after the cell was first infected the parasite forms a 'schizont'. The cell becomes very sticky and adheres to blood vessel walls. Finally, the red cell ruptures, releasing eight to 12 merozoites into the circulation, which then invade new red blood cells. The periodic fever associated with malaria occurs when a large number of schizonts rupture at one time.

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Wellcome News Q4 1999, p.11

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3 Variations on a gene

While the parasite continues to develop within the red blood cell, it begins to express its own proteins on the surface of the red blood cell. Some of these proteins allow the parasite to stick to blood vessel walls, helping it to avoid expulsion from the host, but at the same time blocking vessels and contributing to the most severe symptom of disease, cerebral malaria. By adding its own proteins to the red cell surface, the parasite exposes itself once again to the host's immune system.

Remaining one step ahead of the host, *P. falciparum* alters the fine detail of the proteins expressed on the red cell surface. It does this by encoding a large number of variations of a single protein on several different chromosomes. The malaria parasite genome sequencing project has revealed the extent of the parasite's armoury of variant proteins and already several such families of genes have been identified, including VAR, CLAG and RIFINs. At Oxford University, Professor Chris Newbold has shown that a single parasite can produce many different variants of a protein, but only one form of the protein appears on the surface of the red blood cell at any one time.

4 A sticky business

In collaboration with Louis Miller in the USA, Professor Newbold and colleagues have shown that the PfEMP-1 (*P. falciparum* erythrocyte membrane protein-1), one of the protein families implicated in malaria pathology, binds to ICAM-1 (intercellular adhesion molecule-1), a protein found on the surface of endothelial cells. They believe that preventing this binding could prevent the potentially lethal cerebral malaria, which occurs when infected red blood cells stick to blood vessel walls in the brain.

Other Trust-funded researchers are also interested in these adhesive events. Dr Alister Craig at the Liverpool School of Tropical Medicine is developing a 'flow adhesion assay', in which endothelial cells expressing molecules such as ICAM-1 are adhered to glass slides and parasitized red blood cells passed over them. Parasite strains were found to differ in their avidity for ICAM-1, and Dr Craig hopes the technique will be used to identify compounds which could inhibit binding of these infected cells to blood vessels, thereby reducing parasite sequestration and possibly the incidence of cerebral malaria.

Using similar techniques, Professor Malcolm Molyneux and colleagues (Wellcome Trust Research Laboratories in Blantyre, Malawi) have identified a novel adhesive receptor present on the placenta of pregnant women, who are particularly susceptible to *P. falciparum* infection. They have shown that the parasitized cells which stick to the placenta bind to hyaluronic acid and chondroitin sulphate-A, but rarely to ICAM-1. The interaction between hyaluronic acid and the parasite can be prevented using polysaccharides – yet another observation that may have implications for the development of therapeutic and preventative interventions.

CROSS-TALKING NETWORKS

STEPHEN HILL

Molecular mechanisms underlying intracellular signalling

Designing more selective drugs is the goal of much pharmaceutical research. Professor Stephen Hill and colleagues at Nottingham are studying the signalling pathways activated by certain drugs, and how these pathways interact with one another. This research could open up important new avenues in drug development, leading to more specific drugs with fewer side-effects.

Many drugs act on receptors on the surface of target cells, activating particular signalling pathways within the cell. It is becoming clear that these pathways interact with one another much more than was previously thought. This realization could have important implications for the design of highly specific drugs, targeted to an organ, tissue or cell, and the minimization of harmful side-effects.

Professor Stephen Hill and his colleagues at the Institute of Cell Signalling at Queen's Medical Centre in Nottingham are trying to address the problem of pharmacological selectivity by unravelling receptor signalling pathways. Through the work of Professor Hill and others, it is becoming increasingly clear that these modulating interactions between different signalling pathways are very important in the regulation of normal physiological functions. It is also clear that understanding how these modulating mechanisms work could open up new areas for pharmacological development.

Signalling chemicals such as neurotransmitters or hormones control physiological functions by producing a wide range of direct effects on target cells. Adenosine, for example, plays a particularly key role in the central nervous, cardiovascular, gastrointestinal, urogenital, respiratory and immune system. In addition to these direct effects, it also acts as a modulator of other signalling pathways.

Choosing your target

The effects of signalling molecules, including adenosine, are mediated and controlled by receptors – proteins on the surface of cells. These cell surface receptors are the mainstay of many traditional pharmacological therapies – including drugs used in the treatment of hypertension and other cardiovascular diseases, and diseases of the central nervous system. Because receptors recognize particular neurotransmitters, the receptor ligands can be selectively tinkered with to produce therapeutic drugs that either mimic the effect of the neurotransmitter (agonists) or prevent its action (antagonists).

However, a problem remains with lack of selectivity in body tissue. Sometimes the receptor that is the target of a particular therapeutic action also happens to be sited elsewhere in the body, and the result is an unavoidable side-effect. An example would be the atropine-like compounds found in some decongestants or motion sickness treatments. The drug achieves its therapeutic effect, but also causes a dry mouth and drowsiness.

The ideal for pharmacological development therefore is to target not only a specific cell surface receptor, but also a specific organ or tissue type. This can be achieved to a certain degree by the mode of delivery – for example, in treatments for asthma it is possible to deliver the drug straight to the lungs, while this is difficult to achieve for other organs.

Cross-talk

To understand the problem of pharmacological selectivity, Professor Hill is unravelling the complexities of the receptor signalling pathways. The start of the research programme was the observation that activation of certain cell surface receptors can amplify signalling from other systems. The adenosine A1-receptor, one of a large family known as G protein coupled receptors (GPCRs), normally produces its effect by reducing the level of an intracellular messenger chemical, cyclic AMP.

Professor Hill and colleagues have discovered that activation of the adenosine A1-receptor not only produces the expected decrease in cyclic AMP, but an unexpected increase in intracellular calcium. Calcium is normally released in response to a different set of receptors, including the H1-receptor that responds to histamine. In effect the adenosine A1-receptor seems to be acting as an amplifier on a different signalling pathway in a kind of 'cross-talk'.

Professor Hill has already shown a similar amplification process involving the compounds for the 5-hydroxytryptamine (5HT or serotonin) receptor family, another set of GPCRs with a similar action to the adenosine receptors. 5HT has been shown to amplify the contractile responses caused by noradrenaline. Noradrenaline is known to act on alpha1 receptors, leading to constriction of the arteries. Others have shown that, in aorta cells, neither a low dose of noradrenaline nor a low dose of 5HT has an effect, but low doses of both at once causes a large contractile response.

In both cases, the activation of the GPCRs does not lead to a direct, solitary effect on a particular signalling pathway, but to the amplification of the response produced by a separate coincident signal within the same cell or tissue.

An example of what these reactions mean to the human body may be seen when adenosine is squirted into the lungs. In normal lungs, nothing will happen. But if adenosine is squirted into the lungs of someone with asthma, their airways will go into spasm. This may well be the result of some form of amplification process.

There may be potential for using this cross-talk to introduce subtle and specific targeting of therapeutic agents, and Professor Hill and colleagues are unravelling the underlying molecular mechanisms to understand more fully possible pharmacological implications.

Left: Professor Stephen Hill is at the Institute of Cell Signalling at the University of Nottingham.

Choosing a G protein

As their name suggests, G-protein coupled receptors work through an intermediary, an intracellular interface protein called a G protein. The receptor's role is to bind to the G protein and allow it to load up with GTP molecules, which then go off and do their work of stimulating a particular reaction in the cell. There is a large family of G proteins, and quite often the receptors are very selective in which G protein they interact with. However, it is clear that if there are a lot of receptors present in a particular cell type, they might couple with the 'wrong' protein, which then allows their action to be felt through other pathways. So in certain conditions a particular receptor will couple to one G protein, and in other conditions it will couple to a different one.

A great deal of Professor Hill's work is done on model cell systems – in particular the Chinese hamster ovary cell, which has few receptors of its own on the cell surface and so can be a *tabula rasa* for receptors taken from human cells. This allows discrete pharmacology, so that one specific receptor can be expressed on the cell, and then another added, so that interactions can be examined in a controlled environment.

Having worked out which molecules are switching on and off in the model systems, Professor Hill and colleagues are now looking at the same process in human cells. New laser imaging techniques and fluorescent reagents will now allow them to look at individual receptors on single human cells, so removing the need to culture the cells.

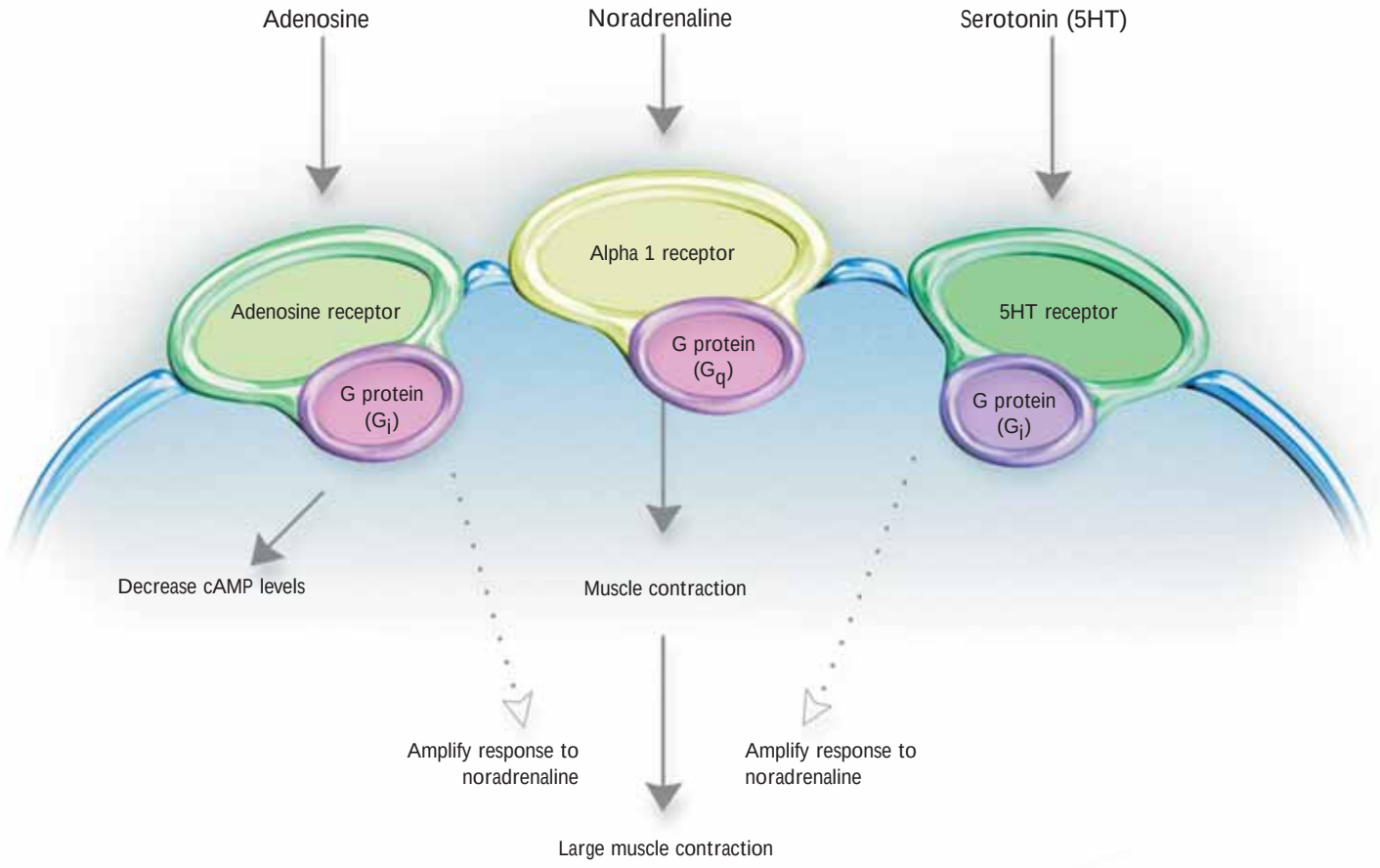
The ultimate aim is to enable pharmacological actions to be selective towards a particular organ, tissue or cell. Most pharmaceuticals mimic the actions at a specific receptor. But it is now clear that those receptors can couple with more intracellular signalling systems than was previously thought. Understanding the molecular switching mechanisms that cause proteins to signal one way or another opens up the possibility of designing drugs that not only target a specific receptor, but make it use one signalling system rather than another. This is a concept that can potentially apply to a number of different receptor systems, and could open up important new avenues in drug development.

Professor Stephen Hill is at the Institute of Cell Signalling, University of Nottingham, and holds a Wellcome Trust Programme Grant.

Further reading

L A Selbie, S S Hill (1998) 'G protein-coupled-receptors cross-talk: the fine-tuning of multiple receptor-signalling pathways', *Trends Pharmacol Sci* 19: 97–93.

CROSS-TALK BETWEEN RECEPTOR-SIGNALLING PATHWAYS



PART 3

A YEAR IN THE TRUST

UK FUNDING

One of the most important ways in which the Trust fosters research is through its continuing support of innovative, investigator-led proposals in all areas of biomedical science. During 1999/2000, more than £153 million was allocated through the four main UK Panels, largely in the form of project and programme grants – including 44 new programme grants, which provide long-term support of up to five years for major research programmes.

The **Infection and Immunity Panel** spent £45.6 million supporting basic and applied research into all kinds of infectious agents, including parasites, bacteria and viruses, and immunology. Research funded ranged from studies of novel anti-inflammatory agents from parasitic nematodes (Dr Murray Selkirk, Imperial College London), the role of B cells in the modulation of resistance to *Salmonella* infections (Dr Pietra Mastroeni, University of Cambridge), and the dynamics of immune responses to HIV infection (Professor Rodney Phillips, University of Oxford, and Professor Jonathan Weber, Imperial College London).

A similarly wide range of research was funded by the **Molecular and Cell Panel**, which spent £48.3 million on all areas of molecular and cell biology – including biochemistry, developmental biology and genetics. Projects funded included X-ray crystallography studies of the 3-D structures of human angiotensin-1 converting enzyme (Dr Ravindra Acharya, University of Bath), an investigation of the cellular interactions controlling tooth development (Professor Paul Sharpe, King's College London), and research into protein-based inheritance in a yeast prion (Professor Michael Tuite, University of Kent).

The **Neurosciences Panel** spent £32.1 million on studies that ranged from molecular and cellular studies of neurons, systems-oriented and cognitive studies, through to clinical research. Work funded included a study of neuronal calcium channels (Dr Annette Dolphin at UCL), research into brain region specialization and visual control of movement (Dr D Armstrong, University of Bristol), and an epidemiological study of autism in the UK (Dr Gillian Baird, King's College London).

The **Physiology and Pharmacology Panel** spent £27.3 million on research ranging from basic cellular and molecular studies to whole organ and animal studies and clinical investigations. Awards included a study to test the accuracy of ECG recordings of the electrical activity of the heart *in vivo* (Dr David Paterson, University of Oxford); a study of calcium channel protein complexes in the brain (Dr David Beech, University of Leeds); and a quantitative investigation of the genetics of cutaneous inflammation (Dr Jonathan Rees, University of Edinburgh).

In addition to project and programme grants, the Trust also runs some specific fixed-term schemes to encourage research in specific important or neglected areas. Some of these are administered through the UK Panels.

The **Bioarchaeology Programme** was established in 1995 to encourage the use of 'cutting edge' biomedical technology in archaeological research. After a review in 1999/2000, which highlighted the significant development of the field and the high quality of research funded through the bioarchaeology schemes, the Bioarchaeology Programme has been extended until 2005. By that time it is hoped the discipline should be established as a robust 'stand-alone' discipline with no further need of ring-fenced support. The funding strategy will shift away from postgraduate training to support at the senior level and from 2001 will be centred on University Awards to attract 'champions' to lead the field and four-year training fellowships to draw experienced researchers from other fields. During the year, the Bioarchaeology Panel awarded a Research Fellowship and six Studentships.

In other specific areas, a Research Career Development Fellowship, two Research Training Fellowships and two Research Training Studentships were awarded through the **Biodiversity Programme**. Three Research Fellowships in **Medical Microbiology** were awarded to help develop expertise in this important area, as bacterial infections continue to pose a threat to the nation's health. In addition, 32 Sir Henry Wellcome Commemorative Awards for Innovative Research (**'Showcase'**) awards were made to encourage high-risk research. These were typically imaginative proposals, including research into the

Left: Professor David Pritchard at the University of Nottingham has a Wellcome Trust Showcase award to investigate the wound-healing properties of maggots.

Above: *Trichinella spiralis*, the trichina worm. Dr Murray Selkirk at Imperial College, London received a programme grant through the Infection and Immunity Panel to study novel anti-inflammatory agents from parasitic nematodes.

	Advisory committee	**Infection and Immunity Panel**	**Molecular and Cell Panel**	**Neurosciences Panel**	**Physiology and Pharmacology Panel**
	Remit	Funds fundamental and applied research relating to infectious diseases and immunology. This ranges from epidemiology, cellular immunology, mechanisms of immunity and the pathology of infections through to genetic and molecular studies relevant to infectious disease.	Considers grant applications that fall into the general area of molecular and cell biology, including biochemistry, molecular immunology, developmental biology and genetics; proposals may involve basic, clinical or veterinary research.	Considers applications investigating the function of the nervous system in health and disease. It considers proposals in both cellular and cognitive neuroscience as well as clinically oriented proposals investigating common neurological, ophthalmological and psychiatric conditions.	Supports physiology and pharmacology in its broadest context, ranging from basic cellular and molecular studies in model systems to whole-organ and animal studies and clinical investigations, including studies of integrative physiology. Epidemiological and mathematical studies are also covered.
Spend	Total spend	£45.6 million	£48.3 million	£32.1 million	£27.3 million
	Long-term*	£15 million	£12 million	£10.9 million	£10.7 million
Applications No. considered	Project/programme grants	277	304	283	303
	All awards and supplements	308	362	333	350
Success rate	Project/programme grants	38.3%	41.8%	40.3%	40.3%
	All awards and supplements	39.3%	43.4%	42.3%	42.9%

*Long-term grants include programme grants, University Awards and high cost flexible funding.

Infection and Immunity figures include Biodiversity.
The above figures include awards made to Wellcome Trust Centres according to scientific subject area.

wound-healing secretions of maggots and an investigation into whether sound stimulation can enhance the growth and development of the human fetus. Applications for several other schemes are handled by the UK Panels. Four **University Awards** were awarded, creating new permanent positions for researchers. University Awards provide five years' funding during which time salary support gradually transfers to the host institution. Six **Research Leave Awards** were awarded to release university staff from their teaching and administrative duties and enable them to undertake a period of full-time research.

CLINICAL AND CAREERS

The Career Development Programmes' personal support schemes cover all stages of a research career in basic and clinical science. In 1999/2000, the Trust spent £85.5 million providing personal support for outstanding scientists at all levels and supporting specific clinical initatives.

Some 250 Vacation Scholarships provided undergraduates with their first taste of hands-on research experience. For those who had already graduated, 61 three-year Wellcome Prize Studentships and 73 Four-year PhD Studentships were awarded.

Last year, the Trust's four-year Research Career Development Fellowship scheme enabled 33 postdoctoral **basic scientists** to establish themselves as independent researchers, whilst at the senior level, 13 prestigious and highly-competitive five-year Senior Research Fellowships were awarded to high-flying researchers in the basic sciences.

Schemes for **medically qualified researchers** also offer support for every stage of a clinical academic research career. A total of 21 medical students received Student Elective Prizes last year, enabling them to gain experience in a biomedical research laboratory during their elective period. In addition, 26 Entry-level Training Fellowships were awarded to young doctors undertaking clinical training to give them the research experience they will need to apply for longer-term funds.

Research Training Fellowships enabled 36 clinically qualified graduates with little or no research experience to gain research training at an early stage in their careers. Six Advanced Fellowships provided career support for researchers at a more intermediate level. One new Clinician Scientist Fellowship, which allows fellows a substantial period of higher clinical training enabling them to become accredited in their chosen clinical specialty, was awarded.

Four Research Leave Awards for Clinical Academics provided funds to release researchers of high promise (at either clinical senior lecturer or consultant level) from some or all of their service commitments, in order to pursue their research on a full-time basis for up to five years. The level of independence and quality of research that must be proved to gain these highly prestigious fellowships is on a par with that required for the Senior Research Fellowships in Clinical Science, five of which were awarded last year.

A Research Career Re-entry Fellowships in Basic Biomedical Science was awarded to a researcher recommencing a scientific research career after a career break. Four Advanced Training Fellowships were also awarded, enabling post-doctoral researchers to spend up to three years obtaining research training in a new discipline or in a new aspect of their own field.

At the very highest echelons of the academic system, nine new **Principal Research Fellowships** were awarded. In 1999/2000 there were 39 Wellcome Trust Principal Research Fellows, all of them international leaders in basic and clinical science.

The Career Development Programmes also run some subject-specific fellowships, last year awarding four Training Fellowships in Clinical Epidemiology and three Training Fellowships in Health Services Research. (International fellowships in these subjects are awarded through the Tropical Medicine Programme, page 70.)

Veterinarians competed successfully at all levels in both the basic and clinical career schemes. Clinical veterinarians were awarded two Entry-level Training Fellowships in clinical research, two Research Training Fellowships and one Research Leave Award for Clinical Academics, whilst in the basic science career schemes, veterinarians gained six Wellcome Trust Prize PhD Studentships and three University Awards.

In March 2000 the Trust provided funds to establish a BSc Honours degree course in veterinary pathology at the Royal Veterinary College in London as an intercalated year for basic veterinarians to attract them into clinical veterinary research, particularly in pathology. The scheme will fund ten students from veterinary schools across the UK each year for five years. In June to October, an additional 12 veterinarian students attended the first Trust-funded veterinarian summer school in Cambridge where they received a combination of research training in first-class laboratories and leadership training.

The Trust's **clinical initiatives**, the Cardiovascular Research Initiative and the five Clinical Research Facilities, are discussed on page 20.

Above: At the University of Edinburgh, Wellcome Trust Principal Research Fellow Professor David Tollervey is leading a proteomics team investigating RNA processing in yeast.

Right: Principal Research Fellow Dr Margaret Robinson at the Wellcome Trust Centre for Molecular Mechanisms in Disease in Cambridge is investigating protein transport in the cell.

Advisory committee	**Basic Science Interest Group**	**Clinical Interest Group**	**Veterinary Medicine Interest Group**
Remit	This group is responsible for several schemes including: the Prize (PhD) Studentships, Four-year PhD Training Programmes, Research Career Development Fellowships and the Senior Research Fellowships in Basic Biomedical Science. A separate sub-committee is responsible for Research Training Fellowships in Mathematical Biology.	The schemes that support the clinical and research training needs of medical and dental graduates are the responsibility of this group. A separate subcommittee advises on Training Fellowships in Clinical Epidemiology and Health Services Research and related project grant support.	The Group advises the Trust on any matters relating to veterinary research in a national context and on the training needs of the profession. It considers applications for intercalated BSc awards to veterinary undergraduates and for other veterinary research training grants. Applications for project and programme grant support for veterinary research are considered by the Trust Panel most relevant to the subject of the proposed research. Applications from veterinary graduates for personal support (fellowships and studentships) are taken through the schemes run by either the Basic Science Interest Group or the Clinical Interest Group, depending on which is most appropriate for the research training and career needs of the individual.
Total spend	£61.2 million	£22.6 million	£0.9 million
Spend on longer-term personal support*	£47.7 million	£11.4 million	£0.6 million
Awards include: Senior fellowships	13 new awards and nine renewals	Nine new awards and two renewals	
Intermediate fellowships	34	7	
Training fellowships and studentships	145	83	20
Major awards	Nine new Principal Research Fellows and three renewals (total cost £25.4 million)		£0.42 million to establish intercalated BSc in Veterinary Pathology at Royal Veterinary College. £0.31 million to establish a leadership programme at University of Cambridge.

*Schemes of five years' duration or longer.

CENTRES AND INDIRECTLY MANAGED MAJOR INITIATIVES

The Trust's Centres and Indirectly Managed Major Initiatives support a number of important enterprises within academic centres across the UK. As well as running a large-scale grant-giving initiative in functional genomics, the programme manages major infrastructure awards and provides core funding for the Wellcome Trust Centres.

Functional Genomics

The Functional Genomics Development Initiative was launched in 1999 – with a budget of £100 million over five years – to support the development of new technologies and resources to enable researchers to exploit genome sequence information. Three committees to assess applications were established: the Functional Genomics Development Advisory Committee was established to award grants, along with the Biological Collections Committee and Bioinformatics Advisory Committee, and an initial call for proposals was launched in three areas in December 1999.

The 'collections' scheme funds the development of collections of biological materials, which will provide a valuable resource for the research community. The 'bioinformatics' scheme supports the development of databases and software tools to help aggregate and exploit the vast amounts of data accumulating from genomic and related research. And the 'technology sharing' scheme enables researchers to visit groups with key expertise and learn new techniques and technologies that they can transfer to their own laboratories.

To inform the initiative, the Trust provided support for two international workshops at Hinxton Hall Conference Centre: 'From Gene to Structure and Function II' in March 2000 and the 'First International Structural Genomics Meeting' in April 2000.

Functional genomics aims to build an understanding of the specific functions of genes. An important aspect of this understanding is how these products and their functions impact on biological processes at the tissue, organ and whole-organism level. The Integrative Animal and Human Physiology Initiative was set up in 2000 – with a budget of £15 million over five years – to support research in this area. Preliminary applications were received in 2000 and awards will be made in 2001.

The Trust also made plans for a fifth functional genomics initiative. The Integrated Thematic Biological Research scheme – with a £30 million budget over five years – aims to foster research collaborations between a number of disciplines in functional genomics that focus on a specific biological question.

Joint Infrastructure Fund

The Trust injected a considerable sum into the UK university infrastructure in two high-profile partnerships with the Government, contributing £300 million to the £750 million Joint Infrastructure Fund (JIF) and pledging a further £225 million to the £1 billion Science Research Investment Fund (SRIF).

During 1999/2000, the Trust spent some £196 million in rounds 2 and 3 of the JIF awards. JIF has supported excellent proposals the length and breadth of the country – from Aberdeen in the north to Sussex in the south, Cardiff in the west and East Anglia in the east. It has also enabled universities to equip themselves in emerging and exciting new areas of science, particularly proteomics and post-genomics.

SRIF was set up in response to the number of very high-quality applications that could not be funded through JIF. The Wellcome Trust contribution to the SRIF totals £225 million and is split into two streams. These comprise £150 million for new buildings and refurbishment which will be used to fund the construction elements of highly ranked, but unfunded JIF bids, and £75 million for project-related equipment to be allocated via the Trust's normal competitive funding mechanisms. It is anticipated that the majority of awards will be made during 2002–3 and 2003–4.

Centres

The UK Wellcome Trust Centres Programme provides essential personnel and equipment infrastructure for all members of a centre of excellence to enable them to maintain an internationally competitive thematic research programme. The aim is to create, in partnership with a university, an intellectually stimulating environment that is well resourced and will attract and encourage the most able scientists from the UK and abroad.

Top left: The second and third rounds of the Joint Infrastructure Fund, a £750 million partnership with the Government to revitalize the UK university infrastructure, were awarded in 1999/2000.

Bottom left: At the University of Edinburgh, Paul Barlow is using nuclear magnetic resonance techniques to study protein folding. Dr Barlow was an applicant on a successful bid to the Joint Infrastructure Fund.

Right: The Wellcome Trust and Cancer Research Campaign Institute of Cancer and Developmental Biology in Cambridge.

The Centres Programme is working to fulfil all four aims of the recently published Corporate Plan. Through their support of basic, applied and strategically important research in the biomedical sciences, the Centres contribute towards increasing the knowledge base. They also provide an excellent environment that optimizes the training and career development needs of researchers. Whenever appropriate, the Wellcome Trust seeks to ensure that the best possible use is made of the results of Trust-funded research at the Centres and that the potential medical benefits of the research are realized. Last, but not least, the Centres provide an excellent forum from which the Wellcome Trust aims to engage with the public through informed dialogue.

A new Centres team was established in October 2000 to manage the Wellcome Trust Centres and a programme of visits initiated to establish a working rapport with the Centre members. The team is also working to establish a website to provide information on the Centres programme for the scientific community.

The Wellcome Trust and Cancer Research Campaign Institute of Cancer and Developmental Biology at the University of Cambridge and the Wellcome Trust Centre for Cell-Matrix Research at the University of Manchester were both reviewed and the core funding renewed during the year. Both Centres, along with the Wellcome Trust Centre for Human Genetics at the University of Oxford and the Wellcome Trust Centre for Molecular Parasitology in Glasgow, were also successful with JIF awards – further evidence of the excellent scientific standards of the Centres.

INTERNATIONAL FUNDING

The Trust spent £72.2 million on international research during 1999/2000. Its three International Programmes aim to address disease problems in defined geographical areas by supporting the careers of overseas scientists, and to form strong links between the UK and overseas science bases. Since the global disease burden is greatest in the countries least able to combat it, another key aim of the Trust's International Programmes is to support research that directly tackles local problems in developing and restructuring countries.

International Biomedical Programme

Science thrives on the exchange of information and experience, and in 1999/2000 the International Biomedical Programme spent a substantial portion of its £22.7 million outlay promoting international partnerships between scientists in developing and restructuring countries and UK groups.

In 1999/2000, ten **International Research Development Awards** enabled young scientists from these nations to build an independent research programme in collaboration with a UK group. In addition, 31 new **Collaborative Research Initiative Grants** enabled established scientists to embark on research projects (page 18) in collaboration with UK groups. Also, 53 **Travelling Research Fellowships** enabled overseas scientists to spend up to three years working in UK laboratories.

The five-year **Overseas Senior Research Fellowship** scheme, initiated in the 1980s, has offered around 50 outstanding researchers the opportunity to establish and maintain a scientific career in Australia, New Zealand and South Africa, with a further ten awards made last year. In 1999, the Trust extended the initiative to India. Five further Indian Senior Fellowships were awarded in 2000.

As independent evidence of the calibre of these scientists, awards were made to four Australian and one Indian Senior Fellow by the Howard Hughes Medical Institute under its Infectious and Parasitic Disease Initiative in July 2000.

Tropical Medicine Programme

During the year, the Tropical Medicine Programme spent £27.8 million supporting research into infectious and noninfectious human diseases and veterinary problems afflicting developing countries.

The Trust's international tropical medicine research units in **South-East Asia** and **Kenya** act as bases for much of the Trust-funded tropical medicine research carried out overseas. The Trust allocated around £20 million, a major part of the year's expenditure, to provide core funding for its research units in South-East Asia and Kenya. Both of these had full site visits during the year, receiving extremely positive reviews and were renewed for a further five years.

Six career awards were made to overseas researchers to help nurture indigenous talent: four Research Development Awards in Tropical Medicine and two Training Fellowships, one in Noncommunicable Diseases and one in Infectious Disease, were recommended.

The Tropical Medicine Programme also offers three fellowship schemes in association with the **UK Centres for Research in Clinical Tropical Medicine**, which were renewed during the year, to provide a career progression structure for UK researchers in this field. In 1999/2000, six researchers at an early stage in their academic career were recommended for Training Fellowships in Clinical Tropical Medicine; five high-flyers with an established research record were recommended for intermediate-level Career Development Fellowships in Clinical Tropical Medicine; and Professor Kevin Marsh from the University of Oxford, Director of the Trust's Kenyan Unit in Kilifi, was awarded a Career Post in Clinical Tropical Medicine – the most senior of the three awards – to study naturally acquired immunity to malaria at Kilifi.

Above: The Wellcome Trust's Kenyan unit is an important vehicle for on-the-ground patient-oriented research.

Right: Professors Airat Ziganshin and Lilia Ziganshina, researchers in Tatarstan, Russia, hold a Wellcome Trust grant to aid their collaboration with Professor Geoffrey Burnstock at University College London.

Far right: Professor Kevin Marsh is Director of the Trust's Kenyan unit.

Advisory committee	**International Interest Group**	**Population Studies Panel**	**Tropical Medicine Interest Group**
Remit	Develops international research strengths, through fellowship exchange and collaboration. Senior fellowship schemes are run in several overseas countries.	Supports research in population studies and reproductive health targeted at areas of most need – developing and restructuring countries.	Promotes research in tropical medicine (infectious and noninfectious diseases) in developing countries and maintains UK research strength in this area.
Total spend	£22.7 million	£9.1 million	£27.8 million
On longer-term support*	£4 million	£6.5 million	£22.7 million
Applications: number considered	558	90	101
Success rate: all new grants	48%†	48.9%	54.5%
Major awards	10 Overseas Senior Fellowships (Total £4.0 million.) 17 Major Equipment Awards		• Seven awards in Wellcome Trust–Burroughs Wellcome Fund Infectious Diseases Initiative (£12.6 million) • Renewal of Kenyan and South-East Asian Units • Core support for five Centres for Research in Clinical Tropical Medicine • Two Senior Fellowships

*Includes overseas research units and grants of over three years' duration

† Of grants peer reviewed

Above: The Vietnam unit has been involved in evaluating treatments for malaria.

Right: Training local scientists – and thereby strengthening research capacity in developing and restructuring countries – is an important feature of all three International Programmes.

As cures are found for infectious diseases, the noncommunicable diseases traditionally associated with the Western world are likely to become a major health problem afflicting developing and restructuring countries. The **Noncommunicable Disease Initiative** was launched in 1998 to address this emerging problem. Several project grants were awarded this year in the areas of mental health, stroke and hypertension in Africa, Latin America and Southern Asia, as well as a major programme grant in India, which seeks to explore the role of maternal nutrition and the development of insulin resistance in offspring.

Under the Tropical Medicine Programme's subject-specific schemes to promote research in **clinical epidemiology** and **health services research**, two Research Training Fellowships were awarded in each area.

In October 1999, in conjunction with the Multilateral Initiative on Malaria, the Trust published a detailed report reviewing research training availability in developing countries, focusing particularly on malaria research. The report, *Strengthening Health Research in the Developing World: Malaria Research Capacity in Africa*, identified existing centres of excellence in Africa and highlighted areas of remaining need.

Population studies

The Population Studies Programme was launched in 1995 to support research into the consequences of population change and poor reproductive health on the developing world community and the environment. The scheme spent £9.1 million in 1999/2000 on strengthening research capacity in this important area. Seventeen research training fellowships – ten at the Master's level and seven at the doctoral level – were awarded, along with 14 project grants and five programme grants.

The Population Studies Programme provides core funding for the **Africa Centre for Population Studies and Reproductive Health** in KwaZulu-Natal, South Africa. Meetings held in association with the Africa Centre include a Trust-funded Frontier Meeting on Sexually Transmitted Disease (STD) Diagnostics, in Durban, South Africa, attended by 50 international STD experts (February 2000), and a week-long course on 'Ethical Issues in International Health', co-funded by the Trust and chaired by Professor Hoosen Coovadia, a Principal Investigator at the Africa Centre (July 2000).

In addition to the Africa Centre, the programme also supports other overseas population studies centres, including a virtual 'meta-centre' at the University of Singapore which electronically links six centres of population research in Asia; and an award to Mahidol University in Thailand to build a new Centre for Studies of Population Change.

DIRECTLY MANAGED MAJOR INITIATIVES

The Trust's Directly Managed Major Initiatives encompass a number of large projects managed directly by the Trust rather than through other academic bodies.

The SNP Consortium

The Wellcome Trust contributed £9 million to the SNP Consortium – a £30 million collaboration between the Trust and 13 pharmaceutical and technological companies – launched in 1999 to create a high-quality map of genetic markers known as SNPs (page 9). DNA sequencing for the Human Genome Project has helped to uncover variation between individuals and provided a major input into the SNP identification programme. The Consortium has vastly exceeded its original target to identify 300 000 SNPs in three years and the Human Genome Project has led to the identification of some 1.42 million SNPs to date.

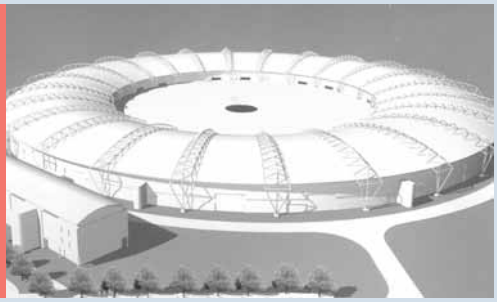
The Structural Genomics Consortium

Determining the three-dimensional structures of proteins provides important clues to their function, and an opportunity for rational drug design. On 4–6 April 2000, the Trust and the US National Institute of General Medical Sciences co-sponsored 'The First International Structural Genomics Meeting' at Hinxton Hall to discuss the large-scale mapping of protein structures. An agreement on the need for free data release was a key output of the meeting.

During the year, the Wellcome Trust also began discussing the possibility of setting up a Structural Genomics Consortium – a partnership with a group of pharmaceutical and other companies, modelled on the SNP Consortium – that would drive high-throughput structure determination and release all structures freely onto the Internet.

UK's new international synchrotron

Synchrotrons play a key role in protein structure determination as a source of high-energy X-rays for X-ray crystallography. The Trust has committed £110 million to the new **synchrotron radiation facility** in partnership with the French and UK Governments. The site – at the Rutherford Appleton Laboratory in Oxfordshire – and basic specification of the instrument were decided on during the year and the name 'Diamond' adopted for the facility.



Right: An artist's impression of the new synchrotron radiation facility.

Wellcome Trust Genome Campus

The Wellcome Trust Genome Campus at Hinxton near Cambridge is home to a number of institutes, all involved with genomics and bioinformatics. The Sanger Centre (now administered through the Centres Programme) was responsible for the sequencing of more than one-third of the first draft of the human genome. The Sanger Centre also sequences the genomes of pathogens important in human and animal health.

The Genome Campus also houses the MRC's Human Genome Mapping Project Resource Centre, which supplies databases, biological resources and computing services for the research community and the European Bioinformatics Institute (EBI), an outstation of the European Molecular Biology Laboratory in Heidelberg, which provides researchers with instant electronic access to an up-to-date and comprehensive collection of DNA sequences and other biological information. The Ensembl database, providing an ordered annotated view of the human genome, is a joint endeavour between the Sanger Centre and EBI.

Hinxton Hall Conference Centre is also situated on the Genome Campus and over the past year a number of major Trust-sponsored meetings have been held there, including post-genomic meetings on structural genomics, microarrays, bioinformatics, and intellectual property rights in genomics. Three Advanced Training Courses in new technologies and a biomedical ethics summer school were also held, as well as numerous pathogen-specific meetings, including sessions on malaria, *Aspergillus fumigatus* and *Neisseria meningitidis*.

The Wellcome Trust continues to explore and develop plans to extend the Genome Campus and in order to achieve this, discussions are on-going with the local authority (South Cambridgeshire District Council).

MEDICINE, SOCIETY AND HISTORY

The Trust's Medicine, Society and History (MSH) division aims to broaden and deepen our understanding of the past, present and future role of medicine in society. Its ultimate goal is to foster an environment in which science is actively pursued and viewed as a positive force in society, with the support of an informed public.

MSH supports academic research into the ethical, legal and social implications of biomedical research with the aim of informing policy makers and supporting evidence-based decision making. In 1999/2000, the **Biomedical Ethics Programme** (page 12) awarded five project grants, two Research Fellowships, four Research Studentships, two Research Leave Fellowships and seven symposia. The **Public Engagement with Science Programme** – which supports researchers trying to understand public perceptions of science – awarded two project grants, one Research Leave Fellowship and three symposia.

The Trust's **History of Medicine** Programme awarded 11 project grants and one programme grant, as well as 14 Research Fellowships, three short-term Fellowships for Clinicians and Scientists, one five-year Unit Fellowship, two University Awards, four doctoral studentships, and one Research Leave Award. The Trust also decided to reinstate open University Awards in the History of Medicine from 2001 onwards, following a review of the field (page 13) in which respondents expressed concern about career opportunities.

MSH is responsible for much of the Trust's work in public engagement, both its directly managed or commissioned activities and its Impact Awards, which support a diverse range of activities aiming to involve the public in science and its wider social and ethical implications. Eight Impact Awards were awarded during the year, including one to Judith Willetts at the British Association for the Advancement of Science to develop a website (named 'Alphagalileo') to assist the world's media to communicate recent developments in European science to the public.

Performances were held of three of the four plays funded by the Trust's Creating the Debate for the New Millennium initiative: *Pig in the Middle*, *The Gift*, and *Learning to Love the Grey*, which premiered at the Edinburgh Fringe in August 2000. Two of the winners in the drama section of the 1998 Science for Stage and Screen awards – *Safe Delivery* and *The Idiot* – also performed at the Edinburgh Fringe. The third play in the section, *The Brain*, performed at more than 30 venues in the UK, including the Natural History Museum in London.

The multimedia and film/video and television award winners all brought their projects – which included a video programme (*Oh No, He's Not Is He?*), a television drama (*Inside Out*), a CD-ROM (*Why Me?*) and two web-based resources (*Kidney Patient Guide and ScienceWeb*) – to fruition. The success of these awards prompted plans for a new competition in 2001, which were approved in June.

The third Wellcome Trust Prize, launched in September 2000, offers a reward of £25 000 to enable a professional life scientist to take a break from his or her normal routine to write an original science book to inform and entertain lay readers. Last year's winner, Chris McManus, started work on his book on the 'handedness' of the natural world, which will be published by Weidenfeld and Nicolson. The first prize for the Millennial Science Essay Competition for PhD students went to Adrian Glover for his description of his work on marine worms. MSH is also responsible for the sciart initiative, science centres and exhibition programmes.

To reach young people in schools, MSH produced two new editions in the *LabNotes* series of updates for teachers on biomedical research findings, and their social and ethical implications for teachers. It also commissioned the Institute of Education to investigate how school science teachers handle classroom debates about issues in biomedical ethics and awarded various grants to encourage the teaching of socio-scientific issues.

Science and Plants for Schools (SAPS), part of the Biotechnology Scotland project, received funding to run a pilot residential summer school at the University of Edinburgh in June 1999, at which 50 teachers learnt about the latest developments in

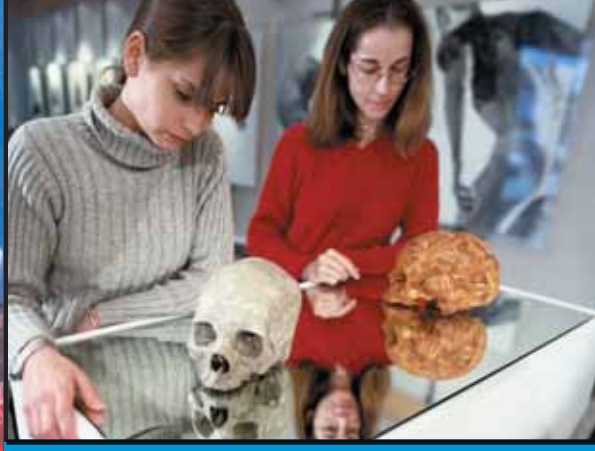
Left: *Learning to Love the Grey*, a Trust-sponsored play looking at the issues raised by stem-cell technology and therapeutic cloning, premiered at the Edinburgh Fringe in August 2000.

Centre: 'Medusae', a winning science-art collaboration in the 2000 sciart awards, tells the story of three people whose lives revolved around jellyfish using underwater filming.

Above: Young people are an audience the Wellcome Trust is particularly keen to reach.

Advisory committee	**Medicine in Society Panel – Public Engagement with Science**	**Medicine in Society Panel – Biomedical Ethics**	**History of Medicine Grants Panel**
Remit	To make recommendations on grant applications in the areas of public engagement wih science. Awards may be for research or activities (Impact Awards).	To make recommendations on grant applications in the field of biomedical ethics.	A broad definition of the history of medicine embraces the study of all factors affecting the medical and health experience of people and animals in all countries at all periods. Areas that the Panel wishes to develop can be found on the Trust's website (www.wellcome.ac.uk) or in the Grants Handbook.
Total spend	Research Awards £0.6 million / Impact Awards £0.8 million	£1.4 million	£17.5 million*
Applications: No. considered	17 / 27	49	139
Award rate:†	41.2% / 37.0%	46.9%	50%

*Includes £12 million for the Wellcome Trust Centre for the History of Medicine at UCL.
†Of applications going to Panel meetings.
Other awards include £0.06 million awarded for sciart and a £0.3 million Millennium Award for Helix, Newcastle.



Left: This oil painting of the last moments of HRH Albert, Prince Consort is part of the Iconographic Collections of the Wellcome Library for the History and Understanding of Medicine.

Above: The Two10 Gallery on Euston Road holds a number of science-art exhibitions to capture public interest in science.

biotechnology and their social and ethical implications. SAPS has now been awarded a grant for a further three summer schools.

As well as its work on 'Topics in International Health' CD-ROMs, the Trust's **Tropical Medicine Resource** is undertaking a collaborative project with researchers at the Wellcome Trust Centre for the History of Medicine at UCL to produce *Medicine in Literature*, a CD-ROM for second-year medical students. The Trust also contributed funds and material to Bamber Gascoigne's 'historynet' project – a web-based history database.

To foster communication and dialogue, the Trust holds large-scale consultations with the public on specific issues, such as the proposed UK Population Biomedical Collection (page 11), gene therapy and pre-implantation diagnosis. To enhance this particular interface between science and society, MSH also funds research into new public consultation methods. Other direct activities during the year include commissioned social research into public attitudes to science (page 27) and workshops on science and industry and on cloning and stem cells jointly organized with the Trust's Policy Unit.

These activities are complemented by the Information Service in the Wellcome Building on Euston Road, which provides an advisory service and resource for the public on topics including science policy, research funding and ethics. In 1999/2000, the Information Service joined with the History of Medicine Library and the Medical Photographic and Film and Video Libraries to form the Wellcome Library for the History and Understanding of Medicine. The History of Medicine Library celebrated its 50th anniversary in December 1999.

CATALYST BIOMEDICA LTD

If findings from academic research are to be translated into new healthcare products – in line with the Wellcome Trust's mission of improving human and animal health – it is vital that they are made available to the commercial sector, which has the skills and resources necessary to develop them further.

Catalyst BioMedica Ltd, the noncharitable business subsidiary of the Wellcome Trust, was set up to help Trust-funded researchers develop and transfer promising technologies into the commercial sector. Catalyst works with scientists and their host institutions on intellectual property protection and helps develop a business strategy for the exploitation of inventions – either through **licensing agreements** to industry or by establishing **start-up companies** to develop the technology.

Catalyst completed its first fully operational trading year on 30 September 2000, comfortably meeting its business targets. Profits made by Catalyst are returned to the Wellcome Trust to further its charitable purpose.

Catalyst has evaluated well over 500 projects to date, negotiated more than 30 licensing agreements, and facilitated the formation of some half dozen start-up companies centred around Trust-funded research findings. These include Oxxon Pharmaccines in Oxford (vaccine technology), DeNovo Pharmaceuticals in Cambridge (computational drug design), Paradigm Therapeutics in Cambridge (functional genomics) and D-Gen in London (CJD diagnostics).

During 1999/2000, Catalyst made six awards from the £20 million Development Fund it administers on behalf of the Trust to help move promising research forward to a stage where it is more likely to be taken up by industry. Catalyst works with researchers to formulate Development Fund proposals, which then undergo commercial review in which issues such as market size, competition, intellectual property position, and delivery of the end product to the patient are assessed. Rigorous scientific and commercial due diligence ensures that, if the therapeutic potential of the science is not well justified or the business case is poor, the proposal will not be selected.

Proposals that pass this review are presented to the Development Fund Board. Since a great deal of preparation has preceded this stage, the award rates tend to be high. Development Fund awards have been made to institutions across the UK, creating a diverse, risk-managed portfolio of product-oriented research projects, encompassing new potential treatments for cancer, psoriasis, obesity and cognitive dysfunction, and novel devices for wound healing and glucose monitoring.

It can be difficult to interest the pharmaceutical industry in products likely to offer little in the way of profits, which adds to the difficulties experienced by developing countries in urgent need of new therapies for diseases primarily affecting such regions. In September 2000, Catalyst began an audit of UK tropical medicine research funded by the Trust to identify technologies that might be translated into innovative products to meet healthcare needs in developing countries.

Catalyst launched its website (www.catalystbiomedica.org.uk) in December 1999. The site offers information and tools for scientists wishing to develop and transfer research and technologies into the commercial sector, including draft confidentiality and material transfer agreements, and advice to researchers on filing for patents, market opportunities and project evaluation. The site has secure areas as well as public areas, enabling Catalyst business analysts to exchange confidential information with Trust-funded institutions.

Right: The Catalyst team helps Trust-funded researchers develop business strategies to exploit new technologies.

FINANCIAL SUMMARY

Investment

The value of the investment assets of the Trust at 30 September 2000 amounted to £15.0 billion. This compares with a figure of £11.7 billion at 30 September 1999. This growth should be seen against a background of expenditure of £641 million, an increase of £174 million from the figure of £467 million for the year to 30 September 1999. Income for the year was £311 million compared to the previous year's figure of £314 million.

The Trust's investment portfolio comprises quoted equities (diversified over a wide number of stocks and spread across many countries), fixed interest securities, private equity funds, absolute return funds and real property holdings. The property portfolio comprises residential, commercial and agricultural property which is run with the assistance of external managers. This diversification is a key factor in managing the inherent risk of investments.

In the calendar year 1999 (the latest date where good comparative data are available), the Trust's portfolio of quoted securities produced a return of 17.9 per cent, and the total return on all investment assets, including property and private equity, was 24.2 per cent. These returns are over 2 per cent above the mean return of all pensions funds, both including and excluding property, covered by the WM Company, one of the most widely used performance measurement houses. Performance figures may also be compared with the increase in the Retail Price Index for the calendar year 1999 of 1.8 per cent, thus showing a growth in the real value of the Trust's investments of more than 22 per cent.

During the year, the Trust made a number of changes to its external management arrangements. These changes were the result of a number of factors including poor performance of some incumbent managers, the exit of incumbent managers from the institutional investment business and improving the existing asset allocation. Seven new managers were appointed, and the appointment of two managers was terminated.

Expenditure

Total Trust expenditure in 1999/2000 was £641 million, of which grants committed amounted to £479.8 million, direct activities £72.5 million, support and administration costs £42.5 million, and investment management costs £46.3 million.

The Trust committed some £459.5 million in support of biomedical science in 1999/2000, compared with £345.4 million in 1998/99. This year included significantly higher value single awards made through the JIF scheme; 29 awards were made for JIF this year for a total of £115.9 million. Grant expenditure for the history of medicine and public engagement with science rose from £8.4 million (1998/99) to £20.3 million (1999/2000). This increase is due to a £12 million award, being the first five-year grant to University College London for the Wellcome Trust Centre for the History of Medicine, formerly the Academic Unit. The Trust awarded 2342 grants in 1999/2000, and now supports 4649 individuals.

Expenditure on direct activities has increased substantially from £46 million to £72.5 million. This was mainly due to the increased expenditure at the Wellcome Trust Genome Campus of £26 million, reflecting the increased activity at the Sanger Centre this year.

While competition for Trust grants remains extremely strong, award rates (by number) increased slightly this year (refused applications for JIF awards led to a decrease in award rates by amount). A total of 81 different UK institutions received Trust funding, and 41 universities and institutes received £1 million or more support from the Trust in 1990/2000 – including those in England, Scotland, Wales, the Republic of Ireland, South Africa, USA and South America – and 12 received more than £10 million.

Additional financial information can be found in the Wellcome Trust's Annual Report and Accounts 2000, available from the Trust's Finance Department.

Figure 1 Investment assets (£ billion)

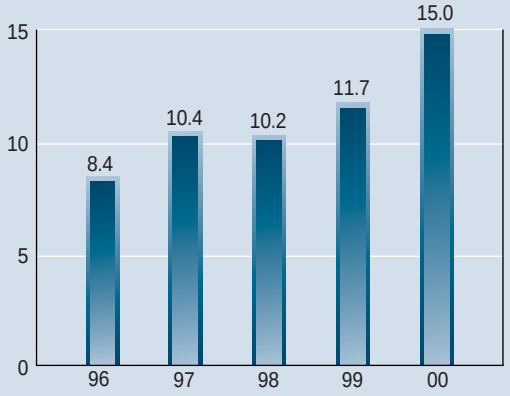


Figure 2 Income (£ million)

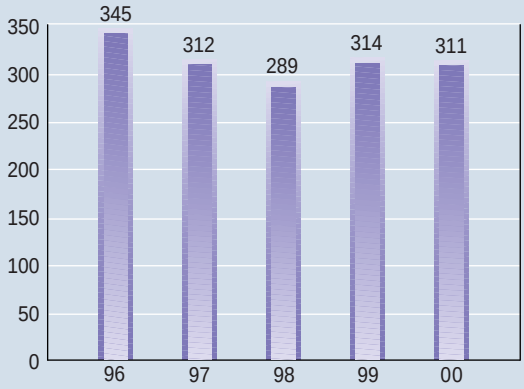


Figure 3 Grants expenditure (£ million)

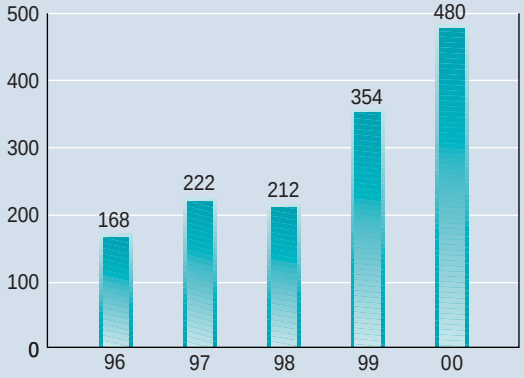
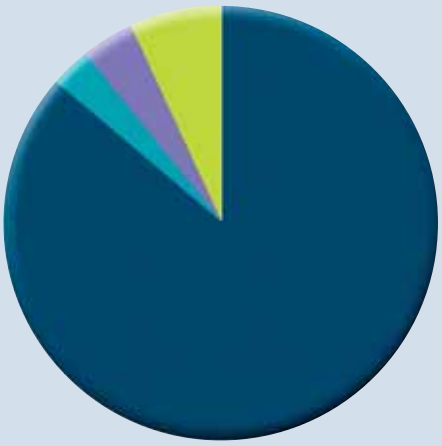


Figure 4 Breakdown of biomedical research funding 1999/2000

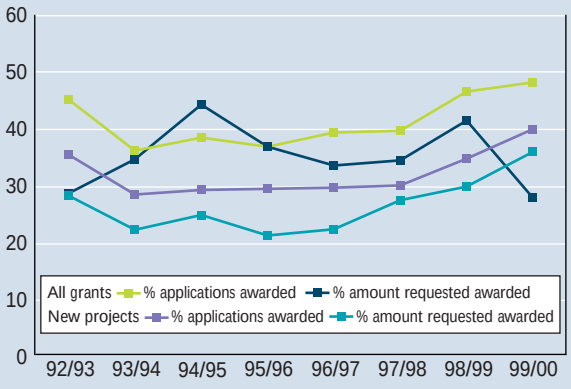
	£ million
JIF	115.9
Careers	85.6
International	59.6
UK expenditure	153.3
Genetics	82.8
Buildings and equipment (excl. JIF)	11.3
Other schemes	6.4

Figure 5 Breakdown of Medicine, Society and History funding 1999/2000



	£ million
History of Medicine	17.5
Public Engagement with Science Research Awards	0.6
Public Engagement with Science Impact Awards	0.8
Biomedical Ethics	1.4

Figure 6 Award rates for new grants* (%)



*excluding Medicine, Society and History Grants

THE BOARD OF GOVERNORS AND EXECUTIVE BOARD

Overall responsibility for the direction of the Wellcome Trust lies with its Board of Governors. The members of the Board are distinguished in the fields of medicine, science and business. The Board of Governors decide on strategic priorities, establish funding policies and allocate budgets. Governors draw on the advice and help of advisory committees of experts in various fields.

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Chairman (from January 2000)

Professor Sir Michael Rutter
Deputy Chairman

Professor Julian Jack
Governor

Professor Roy Anderson
Governor (until May 2000)

Professor Adrian Bird
Governor (from October 2000)

Professor Martin Bobrow
Governor

Sir David Cooksey
Governor (until December 1999)

Professor Christopher Edwards
Governor

Professor Sir John Gurdon
Governor (until October 2000)

Professor Sir David Weatherall
Governor (until December 2000)

Professor Jean Thomas
Governor (from October 2000)

Professor Mark Walport
Governor (from October 2000)

Edward Walker-Arnott
Governor (from October 2000)

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Director of Science Programmes
Dr Robert Howells

Director of Medicine, Society and History
Dr Laurence Smaje
(until December 2000)
Clare Matterson (from January 2001)

Chief Executive of the Wellcome Trust Genome Campus and Head of Directly Managed Major Initiatives
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Chief Investment Officer
Ian Macgregor
(until April 2000)
Gary Steinberg (from May 2000)

Director of Finance
Peter McNelly
(until December 2000)

Director of Finance and Information Management (from January 2001)
Linda Arter

Director of Personnel and Services
Graham Meredith (until October 1999)
John Cooper (from October 1999)

Other senior staff

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Clare Matterson (until December 2001)
Dr Jonathan Grant (from January 2001)

Head of Communications
Trish Evans

Head of Legal Services and Company Secretary
John Stewart

Head of Grants Administration
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Head of Career Schemes and Clinical Initiatives
Dr Howard Scarffe

Head of Centres and Initiatives
Dr Ted Bianco

Head of International Programmes
Dr Richard Lane

ADVISORY COMMITTEES

The Wellcome Trust is committed to the principles of peer review. It is indebted to the many researchers who give up their time to sit on the Trust's advisory committees, and to the many thousands of scientific referees, in the UK and overseas, who provide comments on grant applications. The following pages list the membership of the Trust's advisory committees during 1999/2000.

UK FUNDING PANELS

Bioarchaeology

Dr S Payne
(Chairman) English Heritage, London

Professor Sir Michael Rutter
(from February 2000) Governor, The Wellcome Trust

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George Washington University, USA

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Dr D G Bradley
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Professor M Ashburner
University of Cambridge

Professor B G Spratt
University of Oxford

Professor A Tait
University of Glasgow

Professor H Townson
Liverpool School of Tropical Medicine

Infection and Immunity Panel

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Governor, The Wellcome Trust

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University of Leicester

Professor C R M Bangham
Imperial College School of Medicine at St Mary's, London

Professor J D Barry
University of Glasgow

Professor P C L Beverley
(from January 2000) The Edward Jenner Institute for Vaccine Research, Compton

Dr J P Derrick
(from January 2000) University of Manchester Institute of Science and Technology,

Dr D W Dunne
University of Cambridge

Professor M A J Ferguson
University of Dundee

Professor F Gotch
Imperial College of Science, Technology and Medicine, London

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University of Aberdeen

Dr A A Holder
MRC National Institute for Medical Research, London

Dr J McCauley
BBSRC Institute for Animal Health, Compton

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University of Oxford

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University of Edinburgh

Professor T F Schulz
University of Liverpool

Professor D C Wraith
University of Bristol

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National Public Health Institute, Finland

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Gloucestershire Royal Hospital

Professor J S Kroll
Imperial College of Science, Technology and Medicine, London

Professor T F Schulz
Medizinische Hochschule Hannover, Germany

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Governor, The Wellcome Trust

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University of Southampton

Dr G Banting
University of Bristol

Professor S Busby
University of Birmingham

Professor M Buckingham
Institut Pasteur, Paris, France

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University of Oxford

Professor D R Critchley
University of Leicester

Professor A Hall
University College London

Dr W N Hunter
University of Dundee

Professor P W Ingham
University of Sheffield

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University of Oxford

Dr S Rastan
Ceros Ltd, London

Professor T Strachan
University of Newcastle upon Tyne

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(from November 1999) King's College London

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University of Cambridge

Professor M G Castro
(from November 1999) University of Manchester

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Addenbrooke's Hospital, Cambridge

Professor A Derrington
University of Nottingham

Dr M Gill
Trinity College Dublin, Republic of Ireland

Dr S G N Grant
University of Edinburgh

Dr M C Holley
University of Bristol

Mr P T Khaw
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Professor P N Leigh
Institute of Psychiatry, London

Professor R Lemon
The National Hospital for Neurology and Neurosurgery, London

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Guy's, King's and St Thomas' Schools of Medicine, Dentistry and Biomedical Sciences, London

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University of Leicester

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University of Sheffield

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Royal Free and University College Medical School, London

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University of Manchester

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University of Bath

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University of Nottingham

Professor J J Mullins
University of Edinburgh Medical School

Professor J E Tooke
University of Exeter

Professor D J Webb
University of Edinburgh

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Professor D B Kell
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Ceros Ltd, London

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Professor W G Richards
University of Oxford

Professor S M Roberts
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Dr A M Tolkovsky
University of Cambridge

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Governor, The Wellcome Trust

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Governor, The Wellcome Trust

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University of Southampton

Professor E B Lane
University of Dundee

Professor G Murphy
University of East Anglia

Professor S O'Rahilly
University of Cambridge

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National Institute for Medical Research, London

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Governor, The Wellcome Trust

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National Heart and Lung Institute at St Mary's, London

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University of Edinburgh

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(for assessment of Entry-level fellows)
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Scottish Office Health Department

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Dr J A Schlechte
University of Iowa, USA

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Mr T A Chandler
British Veterinary Association

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University of Cambridge

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Pedigree Master Foods, Melton Mowbray

Professor I McConnell
University of Cambridge

Professor H Miller
University of Edinburgh

Professor W I Morrison
BBSRC Institute for Animal Health, Compton

Professor S Trees
University of Liverpool

Professor A Waterman-Pearson
University of Bristol

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Governor, The Wellcome Trust

Professor J O Thomas
Governor, The Wellcome Trust

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Pfizer Central Research, Kent

Dr P Bork
EMBL, Germany

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The Wellcome Trust Centre For Human Genetics, Oxford

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University of Edinburgh

Professor J Darlington
Imperial College of Science, Technology and Medicine, London

Professor D B Goldstein
University College London

Dr P Grindrod
Numbercraft Ltd, Oxford

Dr P Jeffreys
Rutherford Appleton Laboratory, Didcot

Dr A McLean
University of Oxford

Biological Collections Committee (from March 2000)

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Governor, The Wellcome Trust

Professor P Donnelly
University of Oxford

Professor K Gull
University of Manchester

Dr M Holley
University of Bristol

Professor C Mathew
Guy's, King's and St Thomas' Schools of Medicine, Dentistry and Biomedical Sciences, London

Professor C Peckham
Institute of Child Health, London

Professor J E Tooke
University of Exeter

Functional Genomics Development Panel (from March 2000)

Professor A Bird
Governor, The Wellcome Trust

Professor M Bobrow
Governor, The Wellcome Trust

Dr R Brent
The Molecular Sciences Institute, Berkeley, USA

Professor K E Davies
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ANNUAL REVIEW 1999/2000

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