A quest for the code of life : genome analysis at the The Wellcome Trust Genome Campus / by Liz Fletcher and Roy Porter.

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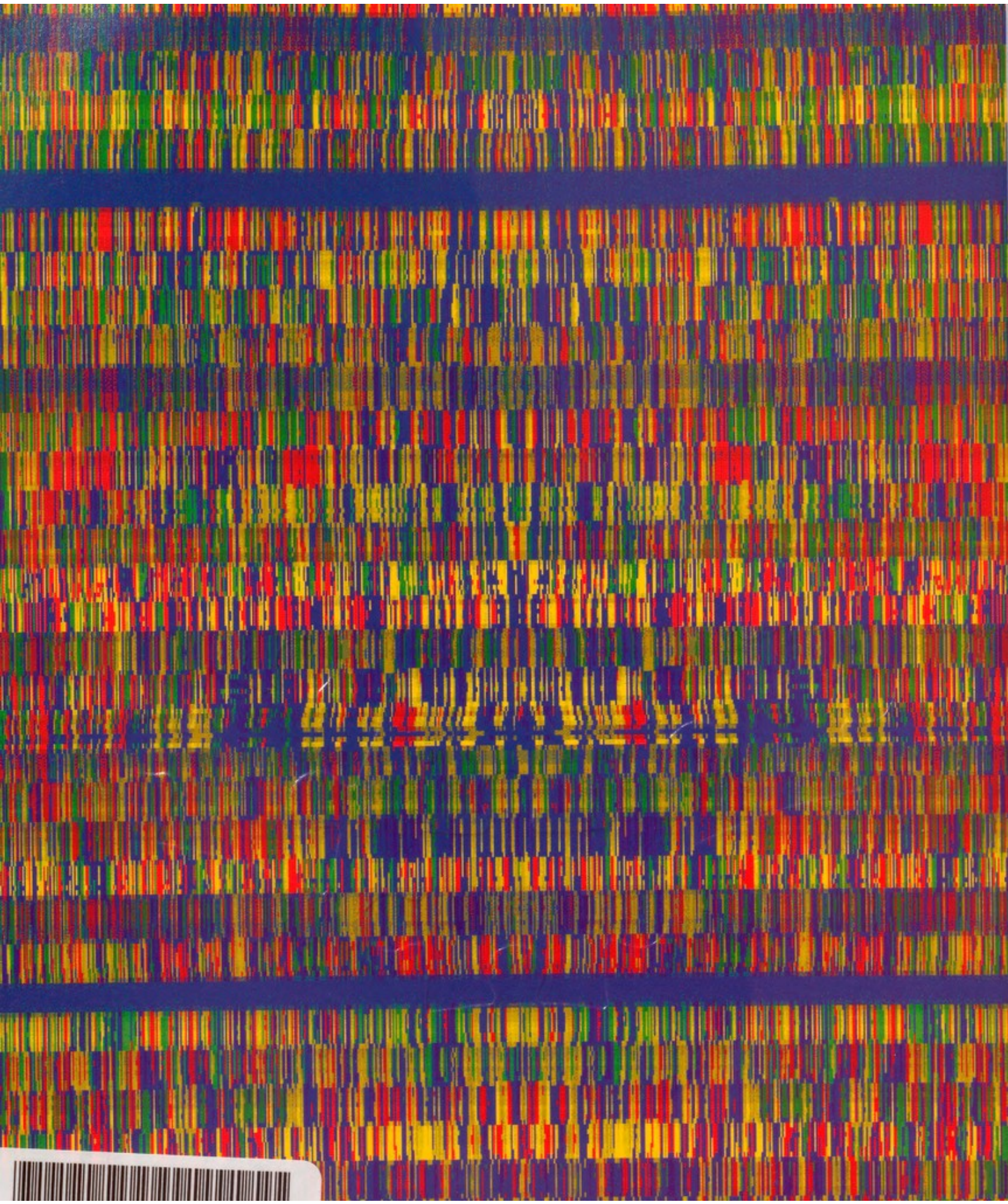

A Quest for the Code of Life

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Genome Analysis at The Wellcome Trust Genome Campus

by Liz Fletcher and Roy Porter

The Wellcome Trust
helping medical science to flourish

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From the Director

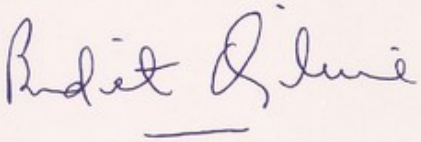
This book has been produced to mark the opening of the Wellcome Trust Genome Campus at Hinxton. It all began when, at the end of January 1992, Sir (then Dr) Dai Rees, Chief Executive of the Medical Research Council, came to see me to tell me that the MRC felt that it was timely to embark on the momentous task of sequencing the human genome. Sir Dai said that the MRC was unable to provide the resources by itself on the scale required and asked if the Trust would be prepared to use some of its recently increased income to get this exciting and, in the eyes of many, risky project under way. I knew that this proposal was based on the MRC's long-term and highly successful investment at its Cambridge Laboratory for Molecular Biology in developing techniques to study the genetics of multicellular organisms using the model system, *Caenorhabditis elegans*, and I also knew through the Trust's own advisers that the field of genetics was ripe for a development of this kind. I was, however, completely unaware that this meeting would lead to the Wellcome Trust Genome Campus at Hinxton which is the largest investment the Trust has ever made.

The project has grown far beyond the scale originally envisaged and because of the continual increase in its income and the enthusiasm of both Governors and staff for the project, the Trust has become the major funder. As originally envisaged, the Sanger Centre under Dr John Sulston is playing a leading role internationally in mapping and sequencing the human genome, whilst completing the sequence of *C. elegans* and yeast (*Saccharomyces cerevisiae*) in international partnerships. Most recently it has also embarked on the sequencing of the genomes of pathogenic organisms.

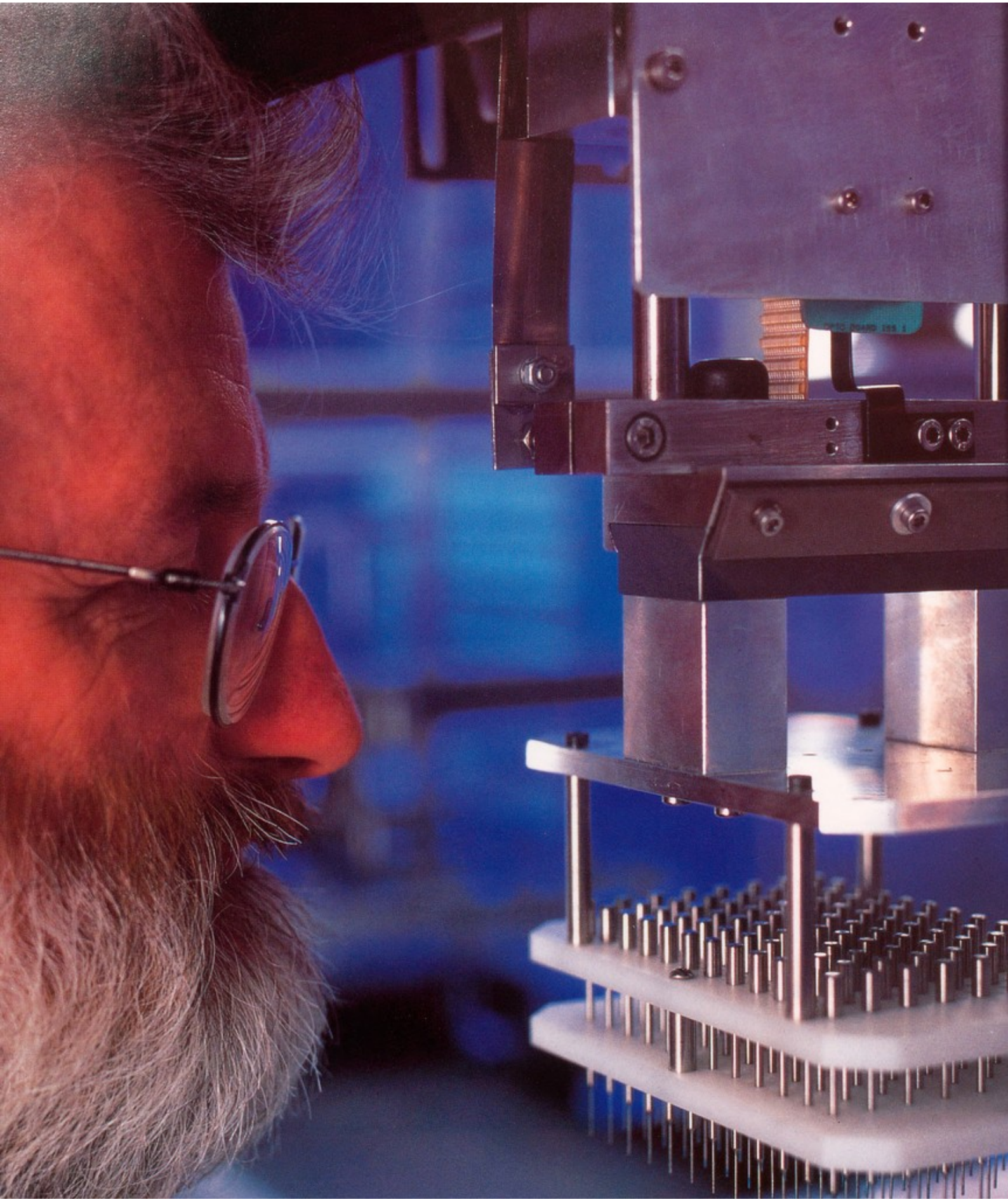
The Wellcome Trust Genome Campus houses the European Bioinformatics Institute, which has been on site since 1993, and, since 1994, the MRC's Human Genome Mapping Project Resource Centre. There is also a splendid Conference Centre built around the original house and its associated outbuildings and garden.

This book tells the story of the creation of this complex and outlines the nature of the scientific activities going on there. It explains why so much is being invested at the Wellcome Trust Genome Campus and elsewhere nationally and internationally in the human genome project and in genetics. In accord with the Wellcome Trust's interests in the history of medicine, there are chapters outlining the history of the Wellcome Trust, of Hinxton itself, and one placing modern genetics into a historical perspective.

It is wonderful to see this large development come to fruition. I congratulate and thank all those involved in getting this large new development up and running so quickly. I wish all those working on the Campus good fortune in their endeavours that are so important for the improvement of the health of all of us.

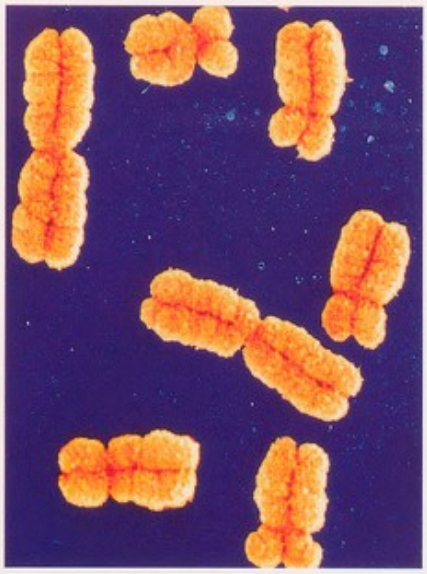


Bridget M Ogilvie, July 1997



Introducing the Wellcome Trust Genome Campus

Medicine is in the midst of a revolution. Modern genetic research is radically changing our understanding of the factors that make us prone to disease, as well as those that determine, at least in part, the individuals we are destined to become. The key to understanding the very basis of life lies at the heart of almost every cell in our body; it is literally in our genes. Cataloguing each of our estimated 100 000 genes – the 'recipe book' for a human – is the ambitious goal of the Human Genome Project. Described by some as biology's equivalent of sending a man to the moon, the Human Genome Project will provide the information that will transform medical care in the twenty-first century.



ABOVE: Human chromosomes contain the code of life. *SPL*

LEFT: The Sanger Centre – research in a rural setting.

OPPOSITE: John Sulston, Director of the Sanger Centre, examines the modern sequencing equipment.

The elegant eighteenth-century Hinxton Hall.

To ensure that the UK is at the forefront of this global enterprise, the Wellcome Trust has invested over £180 million in realizing its vision for a Wellcome Trust Genome Campus at Hinxton in Cambridgeshire, UK. These funds covered the many costs involved in purchasing the site, providing the research and conference facilities, and ongoing support for the research projects. Set in 55 acres of parkland in rural Cambridgeshire, but within a short drive from the world-class research institutions of Cambridge, the Genome Campus now forms the central hub of gene sequencing in Europe – and indeed the world.

The Sanger Centre – a state-of-the-art research facility – is home to over 300 staff who, equipped with the best of modern equipment, are working around the clock to meet their ambitious goal: to sequence more than a sixth of the human genome by the year 2002. Under John Sulston's direction, the Sanger Centre currently provides the largest single contribution to the Human Genome Project, ensuring that the UK remains a world leader in the field. While sequencing is fundamental to the Human Genome Project, equally important is the further interpretation and dissemination of the data produced; to this end, the Wellcome Trust Genome Campus is also home to two units devoted to associated disciplines – the European Molecular Biology Laboratory's European Bioinformatics Institute (EBI) and the Medical Research Council's Human Genome Mapping Project Resource Centre.

The Genome Campus also blends high technology with architectural heritage: the fine country home on the estate – Hinxton Hall – has been painstakingly restored and refitted to offer the best in contemporary conference facilities. The 300-seat auditorium, seminar rooms and residential accommodation will offer the world's leading scientists an elegant rural retreat in which to discuss some of science's most exciting developments.

In the Cambridge tradition

The innovative and pioneering work carried out at the Sanger Centre is very much in keeping with the rich scientific tradition of the ancient University of Cambridge, one of the world's finest academic institutions. Many Nobel Prize-winning advances in genetics have been made in Cambridge, including the elucidation of the structure of deoxyribonucleic acid (DNA – the chemical of which genes are made) by James Watson, Francis Crick and Maurice Wilkins (of King's College, London), and the prototype of modern DNA-sequencing techniques by Fred Sanger. The MRC Laboratory of Molecular Biology (LMB) in Cambridge, once home to Watson, Crick and Sanger, and indeed many other of the greatest minds in biology, has maintained an international reputation as a centre of research excellence.

Watson (left) and Crick (right) discuss the double helix in their Cambridge lab (c.1953). *SPL*

(Continued from page 3)

The LMB has nurtured many other scientific breakthroughs. Its researchers developed methods to determine the structure of proteins, discovered how cells read the genetic code, and devised a means to produce unlimited quantities of antibodies, the molecules on which our immune system is dependent. The city continues to attract the world's best scientists, who come to work in centres such as the LMB, the Wellcome Trust/Cancer Research Campaign Institute for Cancer and Developmental Biology (founded in 1989), and the Wellcome/MRC building that will house the Institute for Cellular and Genetic Medicine currently being built at Addenbrooke's Hospital. The work carried out at the Sanger Centre undoubtedly contributes further to Cambridge's reputation for world-class research.

ABOVE: Alan Coulson and John Sulston spearheaded the worm genome-sequencing programme.

OPPOSITE: The worm *C. elegans* is widely used as a model organism in genetic research. *SPL*

As with many scientific endeavours, the concept for a 'Genome Campus' developed gradually as several trains of thought coalesced into a coherent vision. In the early 1980s, Medical Research Council (MRC) scientist Sydney Brenner and others, including Walter Bodmer, fought to secure money from the government so that the UK could participate in the Human Genome Project. It was essential, they argued, that the UK play a significant part in this ambitious endeavour. This train of events spawned genome-sequencing programmes for the nematode worm *Caenorhabditis elegans* (*C. elegans*) and, in time, that for the human genome. Around this time, scientific staff at the Wellcome Trust also recognized the need for the UK to remain internationally competitive in this area, a field that was undoubtedly set to have far-reaching effects on both basic biology and human medicine.

ABOVE: The Western Pavilion of the Sanger Centre.

LEFT: Taking a break in the cafeteria at the Sanger Centre. *Dennis Gilbert*

OPPOSITE: The MRC's Laboratory of Molecular Biology in Cambridge. *MRC/Laboratory of Molecular Biology*

Another important impetus was the need to ensure that the wider scientific community could continue to enjoy freedom of access to genome sequence information; the concealing of sequence information for private exploitation can lead to unnecessary duplication of effort and may slow down the advance of medical knowledge. The final push for the creation of the new site thus came with the realization that a sequencing site could be combined with a relocation of the world's first sequence database, the European Molecular Biology Laboratory (EMBL) Data Library, and its expansion to form the EBI. Fortuitously, the Wellcome Trust's sale of shares in the pharmaceutical company Wellcome plc in 1992 greatly boosted the Trust's income, making available further funds that could be used to support such a costly venture.

The Human Genome Project

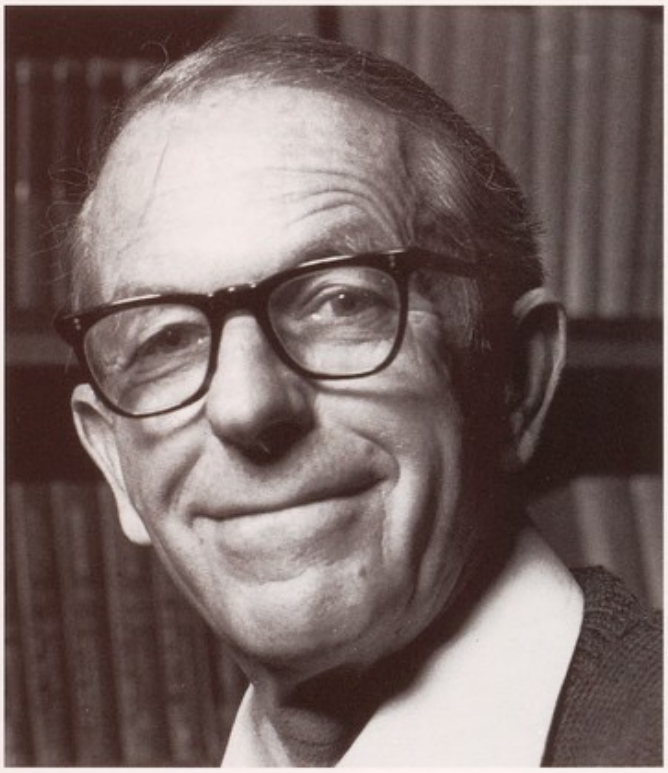
The origins of the Wellcome Trust Genome Campus are intertwined with those of the Human Genome Project. There are between 60 000 and 100 000 genes in the human genome and therefore these genes represent the blueprint for human life. Genes are made up of deoxyribonucleic acid (DNA), the famous double-helix molecule whose structure was determined by Watson and Crick in 1953. DNA is written in 'genetic code', a wonderfully simple language consisting of just four chemical 'letters' – the bases G, A, T and C. The sequence of the human genome is over three billion 'letters' long, so reading them all – the next major goal of the Human Genome Project – demands a significant investment in time, energy and money.

As recently as the late 1980s, the notion of reading each of these billions of letters sounded far-fetched. No one had even sequenced the genome of simple organisms – such as bacteria – which contained just one or two million bases of DNA. At best, a single researcher could generate no more than 20 000 bases of sequence a year; at this rate it would have taken more than 1500 scientists an entire century to sequence the human genome. Moreover, the cost would have been astronomical, at a price of several pounds per base to sequence. Who would be willing to invest in such a costly project? More realistically, who could devise a way to improve the efficiency of the technology to start high-throughput sequencing?

Key figures in the move for large-scale genome sequencing were Cambridge biochemist John Sulston and his colleague Alan Coulson, then both working at the MRC Laboratory of Molecular Biology (LMB). During the 1980s, these two researchers had worked with Bob Waterston from Washington University in St Louis, Missouri, to piece together a detailed map (an ordered set of fragments of the genome) for *C. elegans* – an organism widely used to investigate animal biology. The prospect of moving on from the map to the actual sequence (the 'letters' or bases) of the entire *C. elegans* genome was hugely enticing.

In the late 1980s, available sequencing technology was slow and expensive; even though the worm's genome is considerably smaller than that of the human, the plan to sequence it was met with some scepticism. However, the genome-sequencing movement was beginning to gain momentum; efficiency of the techniques used was increasing and costs were dropping rapidly. Indeed, the MRC was actively supporting attempts to improve sequencing techniques, keen as it was to ensure that the UK kept up with advances in the field. As Sir Dai Rees, Chief Executive of the MRC at that time, recalls, many researchers had focused their energies on developing completely new methods of sequencing; Sulston and Waterston, on the other hand, were more interested in simply maximizing the efficiency of the existing method. This more conservative route turned out to be very effective.

By 1989, Sulston, Coulson and Waterston (encouraged by James Watson) had advanced far enough to go to the US National Institutes of Health (NIH) to request support for a *C. elegans* genome-sequencing programme, and were awarded a grant to start the project late in 1990. At the



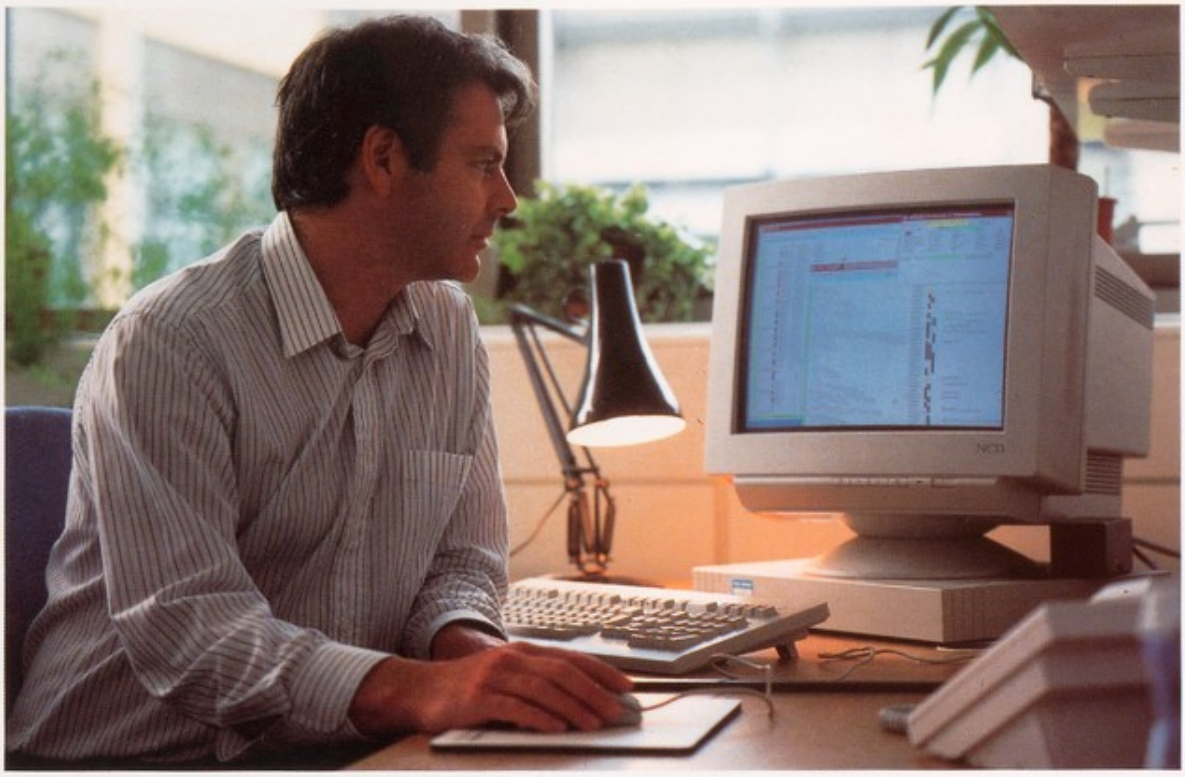
THIS PLAQUE WAS UNVEILED BY
FRED SANGER
ON THE OCCASION OF THE
OFFICIAL OPENING OF
THE SANGER CENTRE
ON THE 4TH OF OCTOBER 1993

TOP: The Sanger Centre was first located in pre-existing laboratories in the Hinxton grounds.

ABOVE: Plaque commemorating the opening of the Sanger Centre.

LEFT: Fred Sanger, pioneer of modern sequencing techniques. *MRC/Laboratory of Molecular Biology*

David Bentley joined the Sanger Centre from Guy's Hospital in London.



same time, the UK's MRC provided additional funds to support five more years of worm genome sequencing in Cambridge.

However, it soon became clear that while high-throughput sequencing was viable, especially with new automated machines from Applied Biosystems Inc., sequencing the entire genome in a reasonable length of time required a significant scaling-up of the project. Lack of space and resources – in both personnel and funds – at the LMB in Cambridge proved to be the primary obstacle. In addition, the speed at which the worm sequencing was progressing suggested that the ultimate prize – the sequence of the human genome – was becoming a realistic rather than futuristic proposition. The situation became more urgent as commercial enterprises in the USA began to stake claims, threatening to monopolize the wealth of information that would be derived from this project.

James Watson, Director of the Cold Spring Harbor Laboratory in New York, USA, picks up the story: "As clearly the world's most successful sequencers, John and Bob's talents soon came to the notice of American venture capitalist Frederick Bourke. He and Leroy Hood (who had moved from the California Institute of Technology to the University of Washington) had considered forming a private company, based in Seattle, to sequence the human genome. Through patenting key genes they hoped to effectively dominate the commercial exploitation of the human genome. When I learnt that Bourke was trying to move Waterston and Sulston to Seattle, I worried that the NIH might lose its most successful genome-sequencing effort, and the UK government might abandon large-scale genome research. The Genome Project would then lose the great intellectual resources nurtured by the MRC at the LMB.

"I knew that John Sulston would prefer to stay in Cambridge but he was dependent on procuring committed funding from a UK source. While the MRC had joined forces with the NIH to fund worm sequencing for three years, it wasn't clear that the MRC could find the much

greater sums of money to join the USA as a major force in the Human Genome Project. Potentially the key UK role would be played by the Wellcome Trust, whose annual income had greatly risen as a result of the sale of a large proportion of its shares in its pharmaceutical company.

"Happily, in 1992, the Wellcome Trust moved swiftly to reassure John that with their help a large new Genome Centre would be set up in or near Cambridge. Its facilities would allow John's group not only to complete sequencing the worm genome, but also to move on to become a major player in the eventual sequencing of the human genome. Out of these aspirations has come the Sanger Centre and the extraordinary opportunity for it to contribute to the advancement of biology and medicine."

The idea for a joint Wellcome Trust/MRC investment in an independent venture to sequence the human genome was, indeed, enthusiastically supported by the Chairman of the Trust, Sir Roger Gibbs, the Governors of the Trust, and the Trust's Director, Dr (now Dame) Bridget Ogilvie. Before the request for funds, the Wellcome Trust had already convened a group of experts who had pointed to the genetic basis of human disease as an area that could benefit from Wellcome Trust investment. Turning the grand scheme into a reality has relied on the Trust's unswerving commitment to develop a world-class facility – a vision championed by Programme Director at the Trust, Michael Morgan, who has seen the project through in its entirety.

First, a board of management for the proposed centre was established, consisting of John Sulston, Bart Barrell, Alan Coulson, Richard Durbin and Jane Rogers, from the MRC in Cambridge, and David Bentley and Murray Cairns, from further afield. Rodger Staden was involved in the initial planning but decided to remain at the LMB. Bart Barrell and Alan Coulson had both worked with Fred Sanger to decipher the genetic material of viruses, and were now engaged in yeast and nematode sequencing, respectively. Richard Durbin brought experience with informatics, which underpins all aspects of genome research, and Jane Rogers her skills as a science

Members of the original board of management, Richard Durbin (left) and Jane Rogers (right).

LEFT: Builders first dug a huge hole to accommodate the underground car park.

LEFT AND ABOVE: The plans for the Genome Campus envisaged a modern research facility that blended in with estate parkland.
Sheppard Robson

RIGHT: The EBI building was completed in record time.
Sheppard Robson

RIGHT: Michael Morgan, Programme Director at the Wellcome Trust, developed the vision for the Genome Campus.

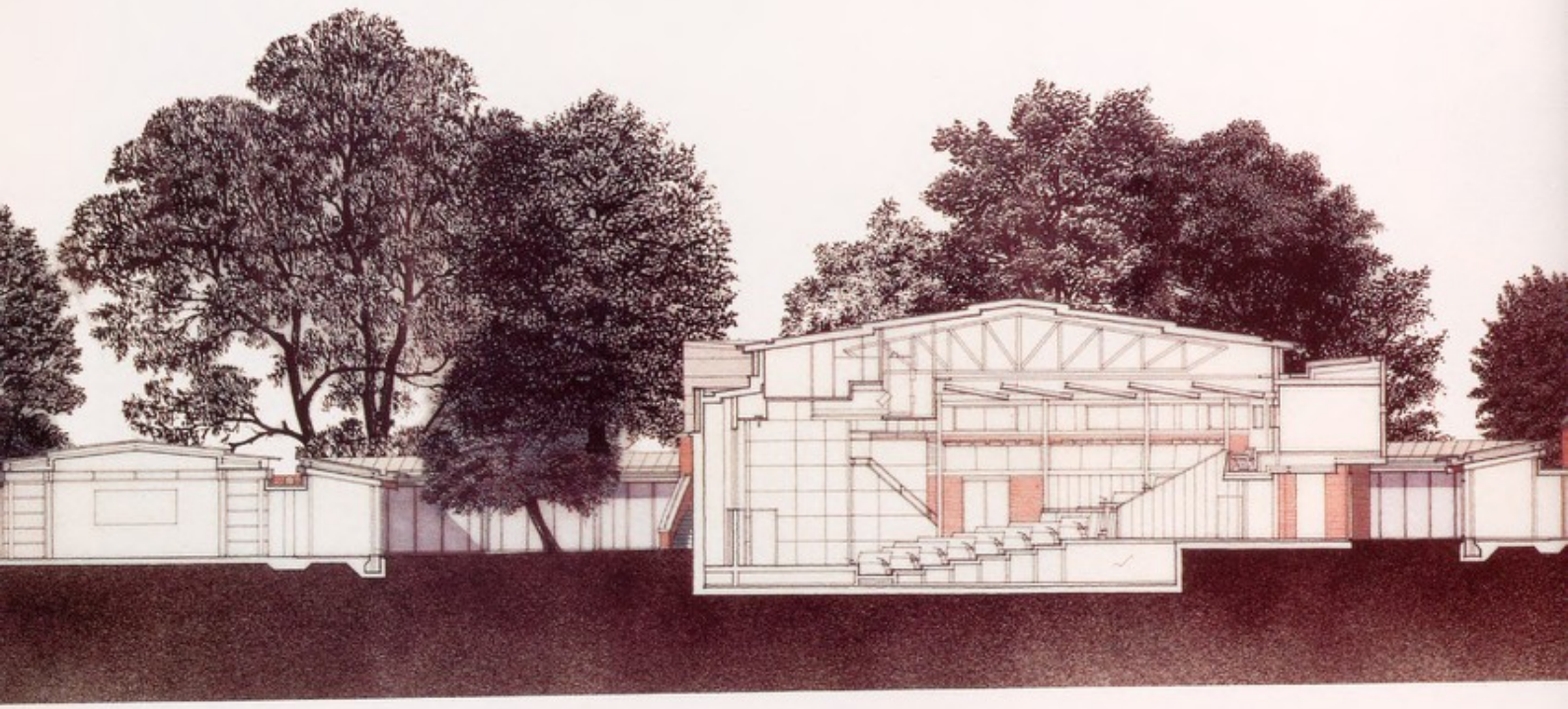
BELOW: The architect's drawing of Hinxton Hall with the planned conversion of the stables and kitchen-garden into a conference centre. *Sheppard Robson*

administrator, required for planning and management of the scientific facilities. David Bentley arrived from Guy's Hospital, London, with expertise in human mapping and genetics. Finally, Murray Cairns, formerly a manager with Bass plc, provided the financial and legal administration for the centre.

The scientists were raring to go and the financial support was available, but where could the genome sequencers get to work? Several sites in and around Cambridge were considered, and eventually a country estate at Hinxton was agreed upon; the estate had previously been owned by Tube Investments plc, the industrial conglomerate which had used the site as its national research centre. Hinxton Hall was an ideal location: it was close to Cambridge, with its local centres of genetic research excellence, and the estate already possessed a suite of research laboratories. The existing laboratories were quickly converted to ones more suited to molecular biology, and by April 1993, 15 staff were already hard at work in their new home. By the end of the year, there were over 80 members of staff on site.

All in a name

The first incarnation of the Sanger Centre was officially opened on 4 October 1993 by Fred Sanger. A Cambridge biochemist originally supported by the MRC, Fred Sanger has had the rare distinction of being awarded two Nobel Prizes



for his scientific research. The choice of name neatly reflected his key scientific contribution to genome sequencing.

Although the old Tube Investment laboratories provided adequate accommodation for the initial stages of the sequencing project, it was clear from the beginning that new facilities would have to be built, and the site for a more permanent home needed to be agreed upon. By coincidence, it was at this time that the MRC and various researchers, primarily Cambridge geneticist Michael Ashburner, saw the opportunity to win the proposed new centre for bioinformatics (the EBI) for the UK. Sulston and Ashburner needed to identify a new home for the centre – and quickly. Hinxton fitted the bill perfectly: the proximity of the Sanger Centre and the University of Cambridge, as well as excellent local electronic communication systems, were all major advantages.

In the face of stiff competition from Sweden and Germany, the UK's bid for the EBI – jointly drawn up by Michael Ashburner, John Sulston and staff of the Wellcome Trust and the MRC – proved to be a winner. Having the EBI on UK soil is a valuable contribution to the UK's scientific community, greatly accelerating researchers' access to its databases and placing the UK at a pivotal point in Europe's gene-sequencing highways. The Wellcome Trust's backing of the initiative reflects its policy of free public access to all sequencing data produced by the laboratories it funds, in the belief that this represents the fastest route to advances in healthcare.

As part of the EBI bid, the Wellcome Trust agreed to construct a new building on the Hinxton site to an extremely tight schedule. Half the cost of the building was provided by the Trust and the rest by the MRC. With the new purpose-built buildings for the Sanger Centre and the EBI, the concept of a 'Genome Campus' – a term coined by Michael Morgan – began to take shape. Right in the middle of the Genome Campus was the old country house, Hinxton Hall. What better solution than to convert it into a scientific conference centre, in peaceful surroundings conducive to academic discourse but right at the heart of Europe's main genome-sequencing centre.

OPPOSITE: Lazy summer days – punting is a favourite pursuit for visitors and residents of Cambridge. *John Beatty, Tony Stone*

LEFT: Cambridge: home to a world-class university and some of the country's oldest colleges, here King's College. *Joe Cornish, Tony Stone*

BELOW LEFT: A detail from the gateway of Trinity College. *Simon Wilkinson, Image Bank*

At the hub of it all

Geographically, Hinxton is a highly suitable location for the conference centre. The Genome Campus is close to the cosmopolitan city of Cambridge, nine miles to the north, and has excellent road and rail access from London. For international visitors, London's main airports are within easy travelling distances, and Stansted Airport is almost on its doorstep.

ABOVE: A view through the foyer to the MRC's Resource Centre.

OPPOSITE: An investment in the future – automated equipment is essential to the genome-sequencing initiative.

An investment for the future

The Trust's growing income also enabled it to award the Sanger Centre £60 million to begin a concerted effort to sequence the human genome. Today, the Sanger Centre, the Genome Sequencing Center at Washington University in St Louis, and other centres in the USA and around the globe, are scaling-up production. With additional Trust funding, a number of groups at the Sanger Centre are investing effort in sequencing the genome of simpler organisms such as brewer's yeast (completed in March 1996) and pathogens that cause tuberculosis and malaria.

Housing a modern research facility, national and international bioinformatics institutes, and a contemporary conference centre, the Wellcome Trust Genome Campus is a substantial investment in genetics not just for the UK but for the entire world. The Trust's decision to create the site was enthusiastically endorsed by the international scientific community, confirmation indeed that the time was ripe to launch a major genome-sequencing operation. The Trust was in the fortunate position of being able to react rapidly, and with the necessary finances, to support the venture.

The MRC's Human Genome Mapping Project Resource Centre moved to Hinxton from Northwick Park in 1994. Thus, the Genome Campus is very much a partnership, incorporating the national funding body, the MRC, and international funders (under the EMBL treaty) whose presence on site forms a significant contribution to the vision of the Genome Campus as a whole.

The Wellcome Trust – Henry Wellcome's legacy

The Wellcome Trust Genome Campus is a bold initiative entirely in keeping with the philosophy of the Wellcome Trust's founder, Sir Henry Wellcome (1853–1936). A successful businessman and noted philanthropist, Henry Wellcome decreed that on his death the share capital of his company – confusingly called the Wellcome Foundation even though it was a commercial operation – should be vested in Trustees. The Trustees were to decide how to spend the income generated by the company, according to the wishes laid out in Wellcome's will. Although a complex document, the core request of Wellcome's will was that his legacy – now known as the Wellcome Trust – should support "scientific research which may conduce to the improvement of the physical conditions of mankind".

OPPOSITE: Founder of the Wellcome Trust – Sir Henry Solomon Wellcome.

LEFT: The young Henry Wellcome (left) and his brother George (right) (c.1877).

The American-born Englishman

Henry Wellcome was born in a pioneer town in the American Midwest in 1853. When his father's health began to fail, the family moved to Garden City, Minnesota, where Henry helped his father in the pharmacy attached to his uncle's medical practice. Although the store would have borne little resemblance to today's pharmacies, it was here that Henry's interest in medical matters was kindled. Initially tempted to train as a doctor, Wellcome soon realized he was a businessman at heart. In a letter to his parents, he wrote, "I have always had a desire for wealth and still have … but I want to live a life devoted to the true God and to mankind". Wellcome thus left for Philadelphia to study pharmacy and his future direction was set.

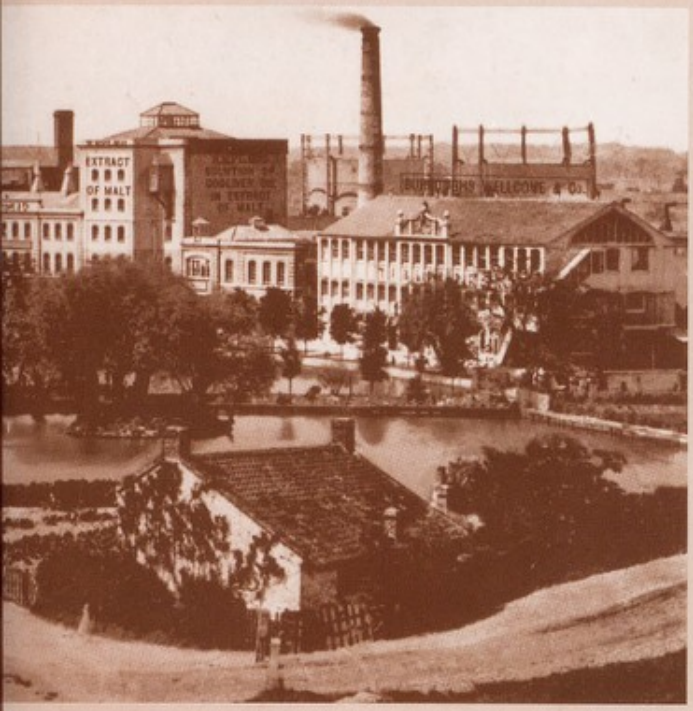
Within five years of graduating, Wellcome had earned a reputation as a talented salesman for a succession of US pharmaceutical companies. He then received an offer of a business partnership with Silas Burroughs, a former student friend, who was then based in London, the centre of the British Empire. Wellcome was a shrewd man, gifted at spotting golden business opportunities, and he realized that the British Empire was the perfect market for the exploitation of novel techniques developed in the New World. In particular, the development of the 'Tabloid' pill (see page 22) represented a major step forward in medical technology. Thus in the spring of 1880, Henry Wellcome set sail for UK shores.

The Tabloid pill

In Wellcome's time, drugs were not sold in the modern pill form but were prepared by pharmacists using a pestle and mortar. Inevitably, the dose of drug administered varied greatly, and so the Americans developed a technique in which a compressed form of the drug, containing a specified amount of the active ingredient, could be produced. The modern concept of a pill was born. Burroughs Wellcome & Co. imported this new concept to the UK and from it made their fortune. A new trade name was needed and Wellcome coined the term 'Tabloid' which was to become one of the most famous brand names in business history.

ABOVE: The Dartford factory, opened in 1898, manufactured the products that made Burroughs Wellcome & Co. a household name. *Glaxo Wellcome Group Archive*

LEFT: Wellcome developed a more portable version of the traditional medicine chest – the tabloid chest. *Science Museum*



LEFT: Burroughs Wellcome & Co. brought the tabloid pill to the UK. *Glaxo Wellcome Group Archive*

BELOW: Women packing products in the Dartford factory (1909).

TOP AND RIGHT: Posters advertising Burroughs Wellcome products. *Glaxo Wellcome Group Archive*

ABOVE: Silas Burroughs – co-founder of Burroughs Wellcome. *Glaxo Wellcome Group Archive*

Burroughs Wellcome & Co. greatly benefited from Wellcome's talent for publicity. Having coined the term 'Tabloid' as a trade name, he fought ruthlessly in the courts to protect its use – Wellcome travelled widely to ensure that the whole world got to hear about Burroughs Wellcome products. Tabloid chests (portable medicine chests equipped with drugs for travellers) were donated to famous personalities like Sir Henry M Stanley (who found Dr David Livingstone), William Gladstone, King George V and President Theodore Roosevelt.

In 1895, tragedy struck when Silas Burroughs died of pleurisy while on a cycling holiday in France. In truth, however, Wellcome's relationship with Burroughs was already under strain and he wasted little time mourning his partner's death. Indeed, Wellcome saw it as an opportunity to shape the company much more in his own image – which he did with remarkable success over the next 40 years.

During his life, Wellcome became a well-respected and leading member of the scientific community in the UK and, in recognition, was made a Fellow of the Royal Society and of the Royal College of Surgeons. The UK remained Wellcome's adopted home; he gained British citizenship in 1910, and was knighted in 1932 for his services to medicine.

Wellcome was quick to see that basic medical research was essential for identifying the medicines of tomorrow, and for securing the health of his business in the long term. Wellcome created several nominally independent research laboratories, such as the Wellcome Physiological Research Laboratories and Chemical Research Laboratories – a highly innovative idea at the time. Wellcome employed the brightest of minds, granted them freedom to choose their research projects, and encouraged the publication of their results. The laboratories made many significant advances in medical treatments at that time.

Staff of the Wellcome Physiological Research Laboratories based at Brockwell Hall, Herne Hill (1904).

Wellcome's desire to support research was not simply good business sense, it also reflected his belief that all basic medical knowledge ultimately benefits mankind. To this day, this belief remains a fundamental tenet of the Wellcome Trust's research funding policy.

Henry Wellcome – the private man

Wellcome was an enigmatic character. In his early days in the UK he was a vivacious socialite, a generous host and bon viveur.

ABOVE: Sir Henry Wellcome and his wife Syrie.

LEFT: Mother and child – Syrie and her son, Mounteney.

However, after a disastrous marriage to Gwendoline Syrie Barnardo, the daughter of Dr Barnardo of London orphanage fame, he gradually withdrew from social life and in later life became a distant, almost austere figure. He wrote, "I shall try to drown my sorrow in my work. Work is a great comforter, and my life work is one that contributes to the welfare of others, as well as myself, and this thought helps to brighten one's life."

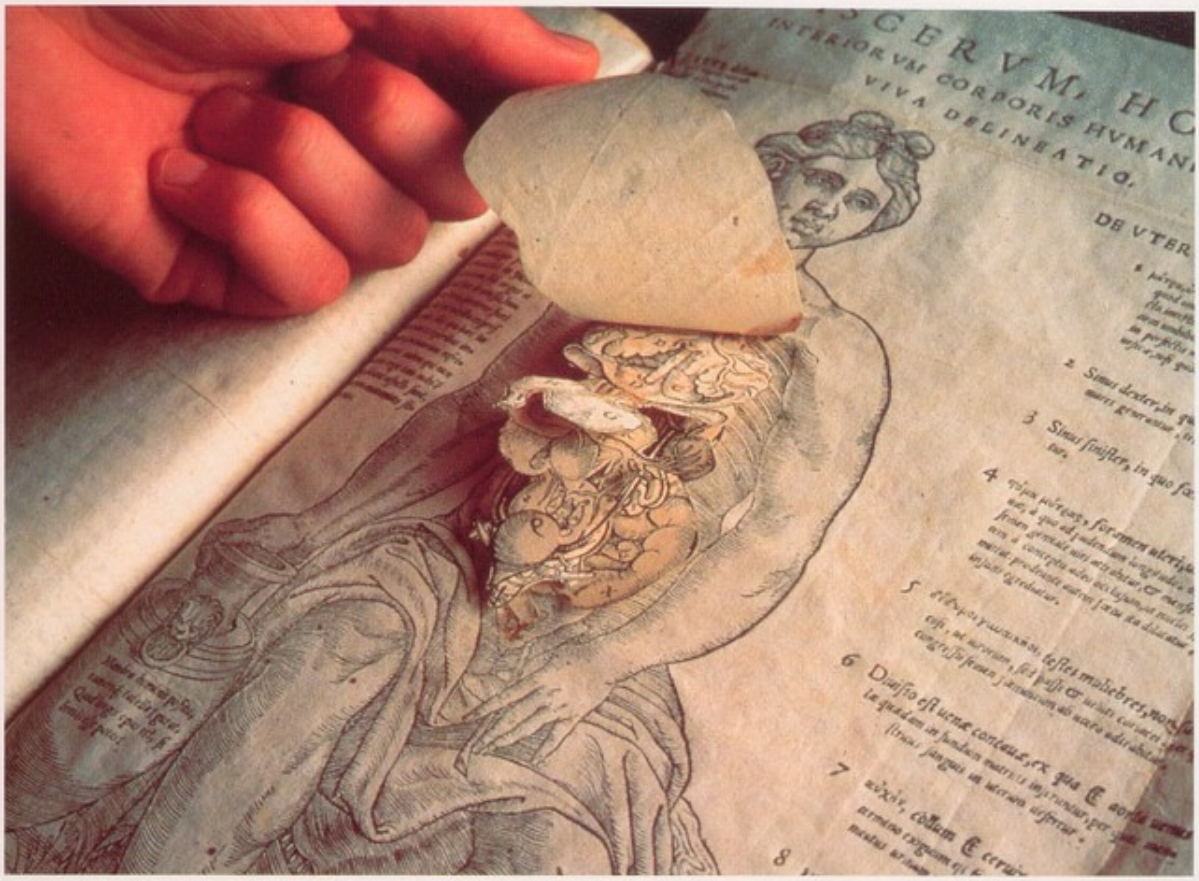
To Wellcome's further regret Mounteney, the only child from his marriage, showed little of Wellcome's talent for business and even less interest in the future of the company. In fact, it seems likely that Mounteney's 'backwardness' was caused by learning difficulties associated with dyslexia – a problem that was poorly understood, and not treatable, at the time. To the end, however, Wellcome remained a loving father to his son and supported him in his chosen profession, farming in Buckinghamshire.

Henry Wellcome – the collector

Wellcome is perhaps less well known as a collector. Throughout his travels as a salesman Wellcome acquired paintings, artefacts, manuscripts and books that together painted a picture of the cultures and history of different nations. In his later years, Wellcome hired dealers to attend auctions all over Europe to acquire additional material for his collections. His ambitious goal was to create a Museum of Mankind, a re-creation of the medical history of man.

By his death, the Wellcome collection of medically and anthropologically related objects had reached a staggering million-and-a-half items, most of them still in their original packing. The collection was subsequently pruned to include only those items relevant to the history of medicine, and the rest was donated to other museums and collections. What remained, still around 112 000 items, is on permanent loan to the Science Museum in London where selected items are on display in the Wellcome Galleries. The books, paintings and other artworks now form the basis of the world-renowned Library of the Wellcome Institute for the History of Medicine.

Life-size re-creations of an operation (left) and a pharmacy (below) at the turn of the century, still on display in the Wellcome Galleries of the Science Museum in London. *Science Museum*



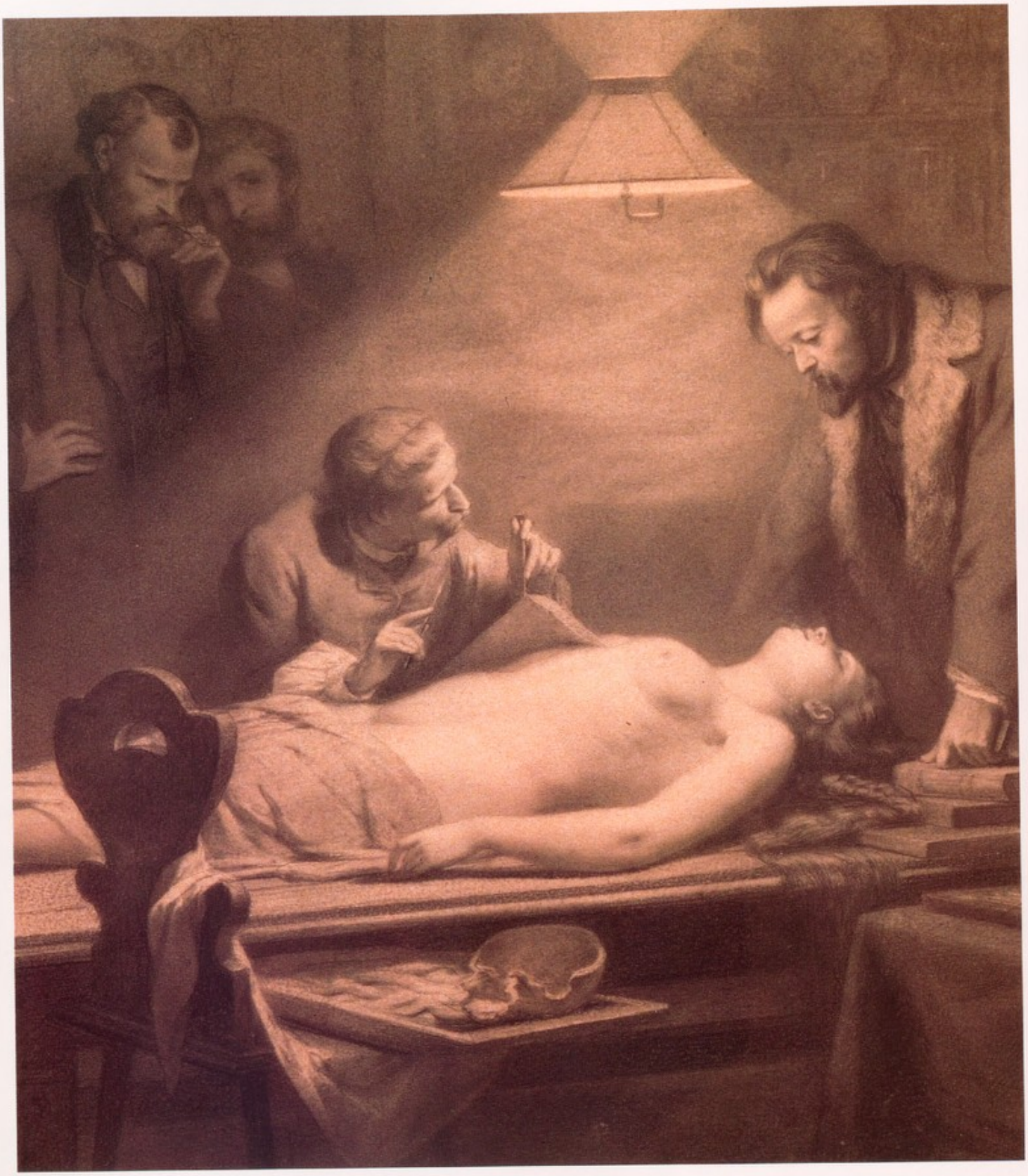
Items from the Wellcome collections.

OPPOSITE: A Persian collage illustrating traditional childbirth practice. *Science Museum*

LEFT: An anatomical illustration from Venice known as 'Adam and Eve sheets' (c.1539).

BELOW LEFT: One of four vignettes showing different cauterization points on the body (twelfth century).

BELOW: A coloured etching by H Heath of pedestrians causing a nuisance by smoking in the street (1829).



Sadly, a Wellcome Museum of Mankind was never realized, but in chasing his dream Wellcome left us with a very tangible record of how humans have wrestled with their health through the centuries. Wellcome felt that museums should be able both to entertain the public, and to educate scholars. Today, the collection fulfils both roles through the public exhibit at the Science Museum, and the book and manuscript collection held by the Wellcome Institute for the History of Medicine in the Wellcome Building. The Institute remains part of the Trust and offers a rich and freely accessible resource for researchers of the history of medicine. As Wellcome believed, there is much to be learnt from the past before starting to build for the future.

ABOVE: An African fetish figure used in native medicine and healing. *Science Museum*

LEFT: A surgeon attempts to rescue a naked woman patient from the embrace of death, I Saliger (c.1894).

OPPOSITE: The dissection of a beautiful young woman, J H Hasselhorst (1864).

OVER PAGE: Tooth-pulling in the sixteenth century would have been a painful ordeal, T Rombouts (1597–1637).

Henry Wellcome – the traveller

In common with many of his contemporaries, Sir Henry Wellcome was an avid traveller to Africa and the tropics, and an expert in tropical medicine. Wellcome's concern for indigenous peoples prompted many charitable acts, and did much to fashion the research activities of his company. During his lifetime, Wellcome set up a medical centre in Khartoum, in the Sudan, and equipped doctors with a floating laboratory to reach inaccessible communities along the Nile. In Uganda he funded a maternity hospital and child welfare centre for a local mission, and for many years he supported the mission of his friend Father William Duncan, helping American Indians in British Columbia.

Today, tropical medicine remains an important focus for Wellcome Trust funding, and the Tropical Medicine Resource, based at the Wellcome Trust headquarters in London, provides educational software for health workers in the developing world. In addition, the Trust supports a number of research groups in Thailand, Vietnam and Africa which carry out research geared primarily to local health needs.

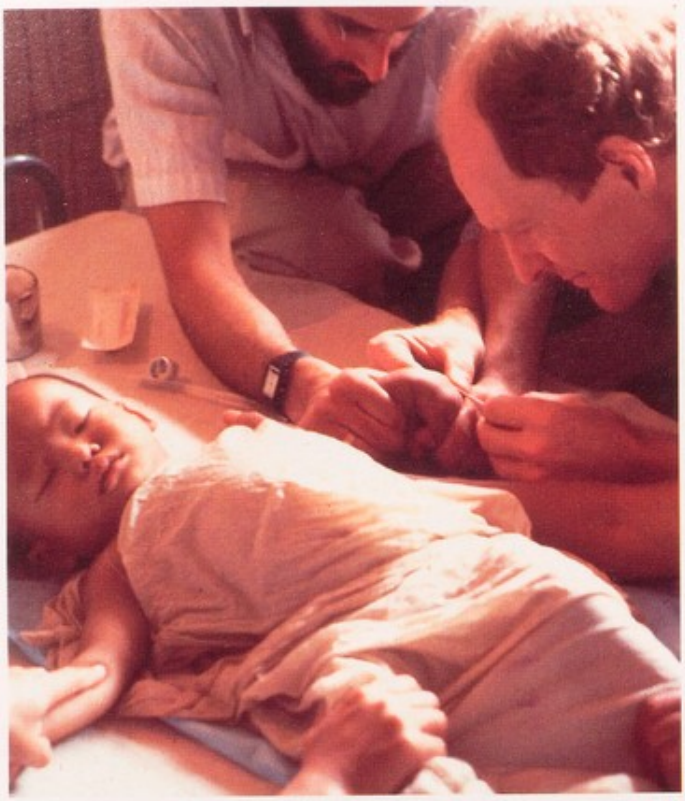
The Wellcome Trust today

When Sir Henry Wellcome died in 1936, the share capital of the Wellcome Foundation was, at his request, placed in the care of five Trustees, and the foundations of the existing Wellcome Trust were laid. Through the 1980s and 1990s, the

OPPOSITE: Sir Henry Wellcome supported many archaeological excavations – here Jebel Moya in the Sudan (1912).

ABOVE: Wellcome's floating laboratory on the Nile (1908).

RIGHT: Wellcome in the Sudan: Wellcome travelled widely and was intrigued by peoples from other lands.



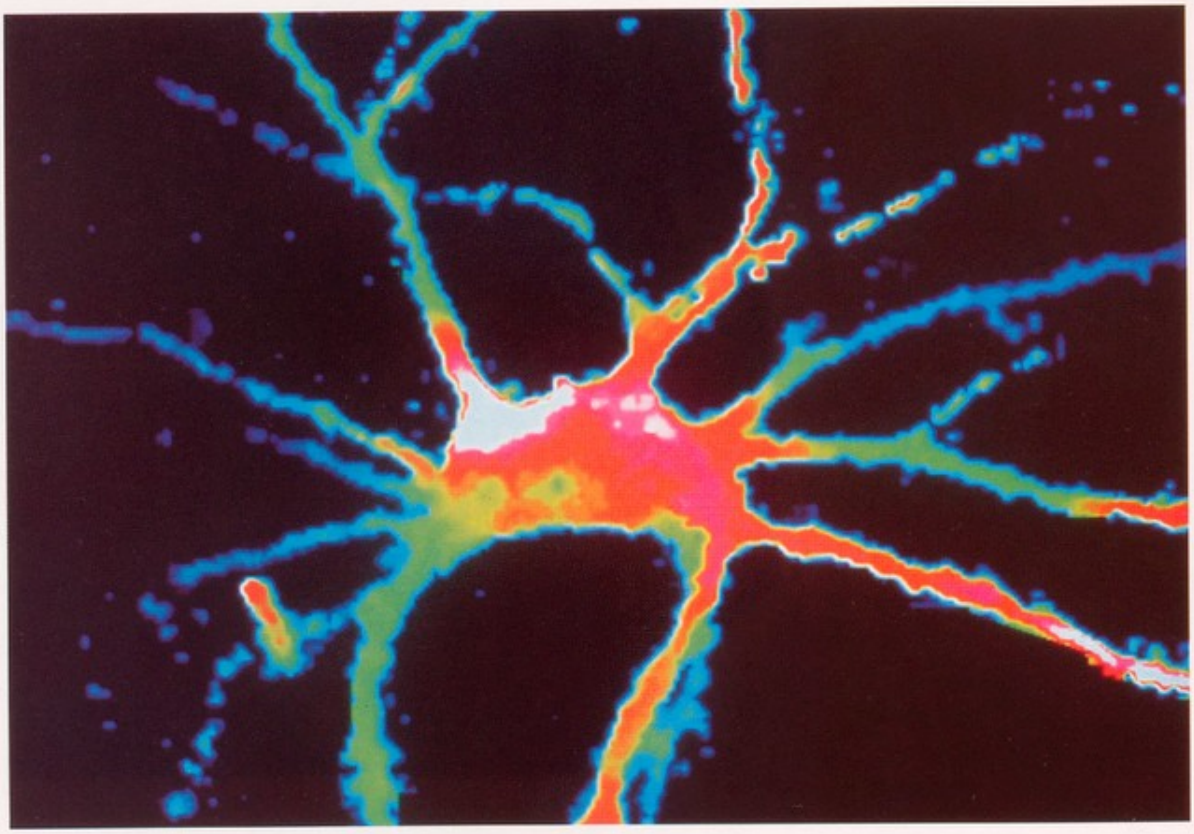
Trust gradually sold its shares in the pharmaceutical company, The Wellcome Foundation Ltd (latterly, Wellcome plc), primarily to diversify its assets, a necessary precaution for a charity that supported the livelihoods of an ever-increasing number of UK scientists. In 1995, the Trust's independence from its business roots was finalized, when what remained of its shares in Wellcome plc were sold to the pharmaceutical giant Glaxo plc (now Glaxo Wellcome plc).

Today, the Trust is the world's largest independent charity. In the financial year 1995/96 alone, the Trust spent around £250 million on medical research, of which about £4 million went towards research into the history of medicine, and £12 million on research overseas. The Trust supports basic and clinical medical science in fields as diverse as infection and immunity, tropical medicine, genetics, neuroscience, molecular and cell biology, and physiology and pharmacology, with application to both veterinary and human medicine. The Trust does not fund cancer research, as many other charitable

ABOVE: Treating a child with malaria: the Trust has had a long-standing interest in tropical medicine. *Wellcome Trust Tropical Medicine Resource*

RIGHT: Rat spinal cord motor neuron: neuroscience is just one area of Trust funding. *Dr David Becker, University College London*

OPPOSITE: The 'Science for Life' exhibition in the Wellcome Building aims to increase appreciation and understanding of the fruits of medical research for visitors of all ages.

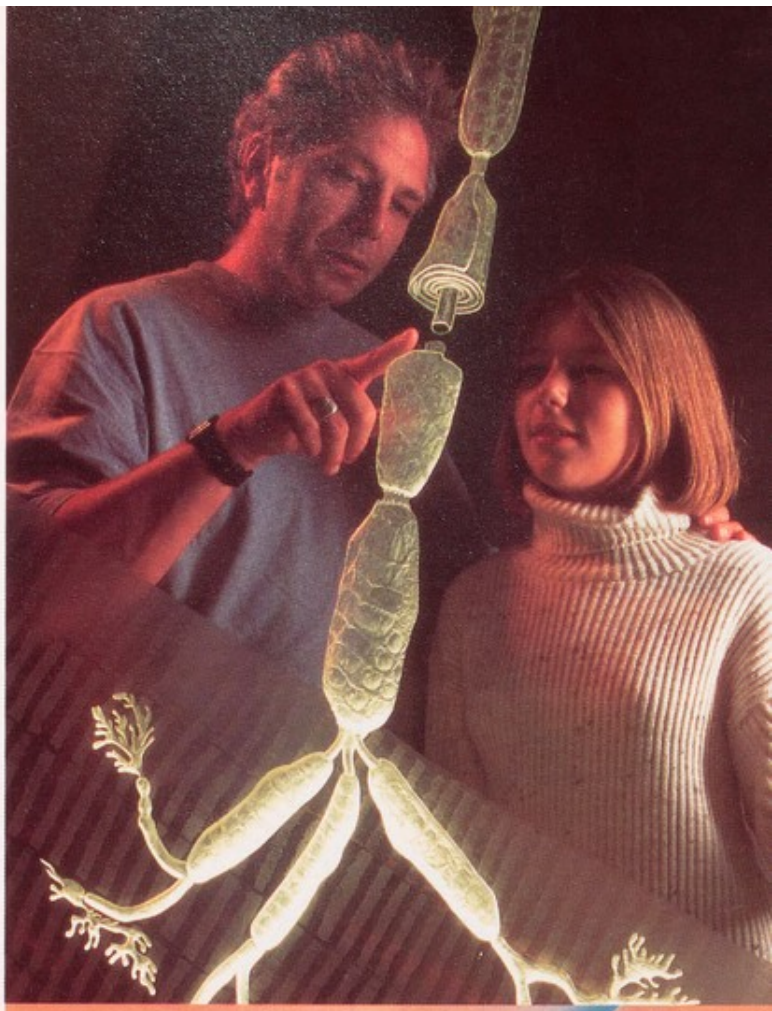


organizations are active in this area. The Trust primarily supports research in UK universities. The Wellcome Trust Genome Campus at Hinxton is thus an unusual venture for the Wellcome Trust.

Communication and collaboration are the life-blood of modern scientific endeavour, and so the Trust encourages scientific exchange between UK scientists and researchers from overseas. The Trust awards travelling grants and supports a variety of collaborative projects between UK scientists and their colleagues abroad. Currently, the Trust's International Programme has focused on funding of researchers in the developing world and countries of the former Communist bloc. The support has a catalytic function, creating regional centres of research excellence around which local expertise can be built – enabling countries to carry out research into their own healthcare problems. Financial support of scientists based in South Africa, New Zealand and Australia, where the research enterprise is blossoming, has also been a more recent focus of Trust-funding initiatives.

Science for the people

The Wellcome Trust also offers a range of support services for scientists and other groups involved in medical research, and seeks to promote the public understanding of biomedical topics. It communicates the products of medical research in



many diverse ways including various publications, as well as plays, art exhibitions, newsletters and interactive exhibits.

The Wellcome Trust not only supports and publicizes the current strength of the UK's research community, but also helps to preserve the country's intellectual heritage. In 1996, the Trust helped English Heritage rescue Charles Darwin's home – Down House in Kent – from decay and an uncertain future; the seclusion of Down House was undoubtedly instrumental in helping Darwin focus on his revolutionary work, *On the Origin of Species*. The Trust has also donated £16.5 million to the Science Museum in London, to help it build a stunning new Wellcome Wing – a bold and imaginative gesture towards the public understanding of science of which Henry Wellcome would no doubt have approved.

In the Wellcome tradition – the Wellcome Trust Genome Campus

In the light of Sir Henry Wellcome's goals and ideals, the Wellcome Trust believes that the creation of the Genome Campus at Hinxton is fundamental to the progress of medical research. It was with the foresight so characteristic of Henry Wellcome's endeavours that the Trust saw the potential of the scientific venture, and responded in a timely fashion to the opportunity. As a result, the UK has secured a vital part in this international and ground-breaking project.

Moreover, the opening of the Genome Campus at Hinxton is in tune with Sir Henry Wellcome's belief in building on the past for the future. The Trust has devoted considerable effort and expense in ensuring that Hinxton

TOP: Where science and art meet – an exhibition in the Two10 Gallery on Euston Road, London. *Steven Hyde*

MIDDLE: Down House in Kent, once home to Charles Darwin. *English Heritage Photo Library*

LEFT: An interior of Down House, which will become the Darwin Museum. *English Heritage Photo Library*

Hall and its estate are restored to their former grandeur, and that the modern conference facilities are a sympathetic marriage of the old with the new. It is hoped too that the people of Hinxton village also feel part of the exciting scientific adventure happening on their doorstep.

An artist's impression of the exciting new Wellcome Wing which will be completed for the new millennium. *Science Museum*

Hinxton – past and present

The Wellcome Trust Genome Campus has put Hinxton firmly on the map of gene sequencing worldwide. Creating an independent research facility was a unique endeavour for the Wellcome Trust, and one that created some special challenges. Alongside the provision of modern research facilities, the contractors also faced the challenging task of restoring a dilapidated eighteenth-century mansion and its outbuildings, while converting it into a modern conference centre. There were additional surprises along the way, including the unexpected appearance of some of Hinxton's more ancient residents.

From fishing for trout to fishing for genes

The Hinxton estate, with its Hall and 55 acres of parkland, lies on the banks of the River Cam, which also flows through the old university city of Cambridge, nine miles to the north. The link is fitting, as the first recorded owner of the estate, in 1506, was the college of Michaelhouse in Cambridge. However, the first building on the site was a modest hunting and fishing lodge, erected in the early eighteenth century by Captain Joseph Richardson of Horseheath. Hinxton was a perfect location for a gentleman's retreat as the estate ponds were well stocked with trout and the fields were alive with partridge.

Tradition meets technology at Hinxton. Once home to wealthy country gentry, the Hinxton estate now houses the high-tech research facilities of the Sanger Centre.

OPPOSITE TOP: The village flower show in Hinxton Hall gardens (1909).
Cambridge Collections

OPPOSITE BOTTOM: The Robinsons at Hinxton (left) and their daugther Rita in her nurse's uniform (*c.*1920).
The Robinson family

LEFT: Hinxton was, and still remains, at the heart of a farming community.
Cambridge Collections

A family home was first built on the site by John Bromwell Jones in 1748, and the central three-storey block of the existing Hall is from this period. An acquaintance of Captain Richardson fondly recollected time spent at Hinxton: "[As] Cpt. Richardson's small box was built by him for a private retreat and for a fishing retirement … his friend always styled it Trout Hall. When he [Bromwell Jones] rebuilt it, he had the figure of a large trout carved in stone and placed over the door." The Trout plaque can still be seen today from the garden. At this time, Hinxton Hall was an integral part of the village, lying at the southernmost end of its high street – the road that ran from Cambridge to Saffron Walden in the south. Opposite the house were some fine stables, a well-tended kitchen-garden and an orchard, all of which survive today, albeit in altered form.

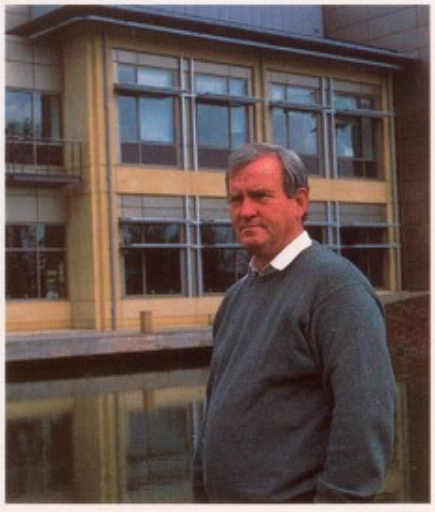
By the 1830s, the estate had been enlarged and enclosed, and Hinxton High Street diverted around the parkland to take the route it follows today. New north and south wings provided two additional parlours, and later a library was added to the front of the north wing. In 1831, the resident family announced the completion of their fashionable new Pompeiian parlour, a room richly decorated with Roman-style frescos and murals. As the Hall passed through the hands of a variety of owners, a north extension was constructed to house a kitchen, offices and extra bedrooms necessary to meet the requirements of the growing estate. The 'Pleasure Grounds' were immaculate and boasted an extensive collection of ornamental shrubs and trees. Flower beds were planted, and gravel paths laid for the owners to stroll by the lakes. By 1860, the Hinxton estate incorporated around 13 acres of parkland and the Hall was a country home its residents – the Green family – could be proud of.

Then and now: Hinxton High Street has changed little in the last century. Today, Hinxton estate 'workers' can still enjoy a pint at the Red Lion Pub! *Cambridge Collections*

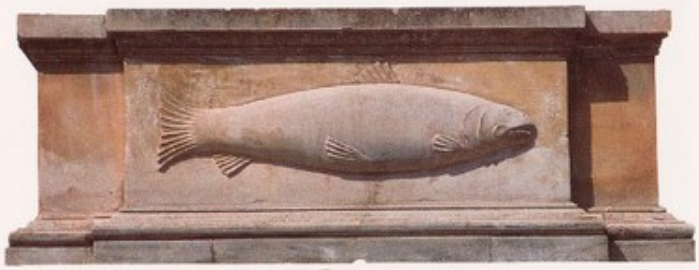
Hinxton's rescue

By the turn of the century the Greens had vacated the estate and in 1920 it passed into the hands of the Robinson family. The Robinsons were survived by their two daughters, Rita and Laura, who had distinguished careers as army nurses in the First World War. The sisters remained in a flat at the top of the Hall when it was used for billeting American soldiers, stationed at the local airbase at Duxford (now part of the Imperial War Museum), during the Second World War. Finally, in 1953, the Hall and grounds were sold to Tube Investments plc, which erected research laboratories in the grounds and converted the Hall into office space. In the late 1980s, the company closed its laboratories and the site was purchased by Capital and Counties plc who had ambitious plans for a business park – a venture that never got off the ground. At this time, John Sulston and Wellcome Trust staff were looking for temporary accommodation for the new sequencing centre; Hinxton was an ideal choice, and so late in 1992, the Wellcome Trust became the new 'landlord' of Hinxton. Since then, the Trust has been fortunate enough to purchase some 1400 acres surrounding the Hall from the Robinson family, thus increasing the Trust's investment in the area.

With impressive efficiency, the metallurgy labs were restyled to those more suited to molecular biology, and its first new occupants moved in during March 1993. By the end of the year, there were over 80 staff on site and space was tight. However, Murray Cairns, Head of Corporate Services at the Sanger Centre and the first man on site, recalls: "The old building, for all its inadequacies (like being boiled in summer and frozen in winter) had the advantages of being a highly flexible structure that could readily accommodate the changing demands of both the science and the increasing staff numbers. It was also a very friendly community; you just couldn't help but bump into everybody."



LEFT: Murray Cairns, Hinxton's new 'landlord', keeping an eye on the estate.



ABOVE: A stone carving of a trout decorates the rear of the Hall.

Where ancient feet once walked

Before a larger and more modern research facility could be built, an archaeological survey had to be conducted to comply with planning regulations. As Murray Cairns recalls, "About a dozen people turned up and started digging holes everywhere. We thought nothing of it. Then all of a sudden they were leaping about in excitement and, before we knew it, a bulldozer had stripped off the topsoil and huge trenches were dug." Building was halted, and four-and-a-half months and £250 000 later, archaeologist Paul Spoerry and a team of 25 workers from the Archaeological Field Unit of Cambridgeshire County Council had uncovered evidence of Hinxton's oldest residents.

The Hinxton estate has always had untapped potential for archaeologists. The fertile valley of the River Cam, with its chalk and gravel deposits, would have made it an attractive habitat for ancient communities. A medieval road from Hinxton to Great Chesterford, a Roman town lying a mile due south, ran through the site and so it was likely that satellite settlements, or at least their remains, might be scattered along its length. Furthermore, as the

LEFT: Archaeologists worked hard to uncover Hinxton's secrets. *Archaeological Field Unit, Cambridgeshire County Council*

OPPOSITE TOP: The lone burial site of an ancient Hinxton resident remains a macabre mystery. *Archaeological Field Unit, Cambridgeshire County Council*

OPPOSITE BOTTOM: A walrus-ivory sword handle was a rare and precious find during the dig. *Archaeological Field Unit, Cambridgeshire County Council*

private park had been protected from deep ploughing (an intensive farming practice adopted after the Second World War), any archaeological remains would have been left intact. It was a rare opportunity, and the archaeologists were not left disappointed.

Ancient feet had, indeed, once trod upon Hinxton's soil. The archaeologists excavated a number of pits, including a deep chalk shaft, which indicated that our ancestors from the Neolithic period (4400–2000 BC) had once worked in the area. The function of the pit is unknown, although early Bronze-age residents, several hundred years later, adopted it as a ritual site and filled it with bits of finely decorated beakers. The prehistoric visitors might have worked in the area, as traces of flint were retrieved from a number of natural ponds; however, there is no indication that they lived on the site.

The real excitement was generated when the archaeologists came across the tell-tale signs of an Anglo-Saxon settlement, right in the middle of the proposed construction site. With the assistance of carbon dating, and knowledge of the structure of more intact Saxon sites elsewhere, the archaeologists were able to trace the changing fortunes of this homestead occupied over 1000 years ago.

From what the archaeological team can make out, Anglo-Saxon residents in the sixth to seventh centuries AD had at least four huts, known in the trade as sunken-featured buildings or *grubenhäuser* ('grubbing houses'), on the site. All that remains of these crude buildings are the shallow pits that formed the floor, and the two holes that held roof supports. In some houses, a suspended floor might have kept the workers off the ground and, inadvertently, created a repository for small fragments of Saxon life: a collection of doughnut-shaped loom weights made of unfired clay, and some exquisitely carved and polished needles and pin beaters (for keeping weaving threads separate), suggest that the Saxons wove fabrics in the huts.

A cache of burnt flax seeds, the largest find in the country, make it likely that linen was made, although wool would also have been woven. Family members, and their servants or serfs, would have lived in timber halls, some of which were up to 12 metres long. All that remains of these buildings are the post holes that outline the walls.

Over the later stages of Saxon occupation of Hinxton (around AD 900–1200), there were several successive rebuildings of the main hall and huts, and a ditch was dug around the settlement to provide security, possibly some drainage, and a means to control livestock. Analysis of seeds suggests that wheat, rye, barley, oats, peas, beans and flax were grown, while bone fragments of cows, sheep, pigs and the odd goose indicate the range of domestic livestock on the settlement. It was a thriving community; new wells and cesspits were dug over the years, drying ovens and cooking pits were built, and a building, possibly a kitchen, was constructed outside the enclosure. Even before excavation had begun, the physical biography of the Saxon community had been identified by a magnetometer survey which can detect the presence of iron oxides left by the residents.

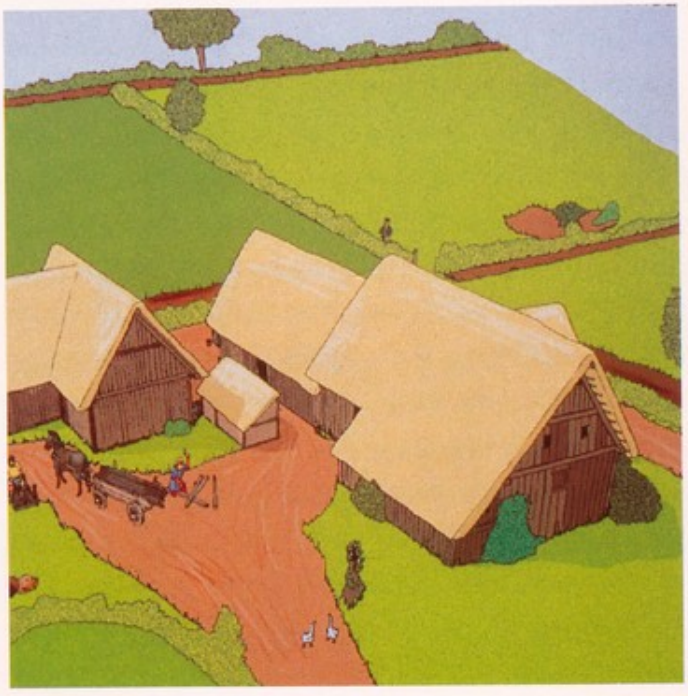
The excavation provided a wealth of interesting artefacts. A bone comb, a section of a musical wind instrument called a drone (a part of a bagpipe-like instrument), and the finely decorated pieces of the boardgame tabula (the forerunner of modern backgammon) provide insight into the personal Saxon world. A particularly precious find was a walrus-ivory sword handle, the first of its kind excavated in this country, which had probably originated in Scandinavia. The dig also unearthed a couple of mysteries. Why was a woman buried alone in a grave outside the enclosure, rather than in the communal burial ground which has still to be located? And who broke the large Ipswich-ware pot and placed it carefully at the bottom of a pit?

Yet, for all the evidence of life, the settlement was abandoned by the thirteenth century. The face of rural England was radically changed by the Norman conquest in

RIGHT TOP: The excavation caught local imagination and provided a rather unconventional location for a radio interview. *Archaeological Field Unit, Cambridgeshire County Council*

RIGHT BOTTOM: Clay loom weights, needles and thread separators suggest the Saxon residents were weavers. *Archaeological Field Unit, Cambridgeshire County Council*

BELOW: A computer-generated 'history' tracing the changing fortunes of the Hinxton settlement. The buildings, made of timber, would have suffered from fire and water damage and so much rebuilding was done. Later, a ditch enclosed the homestead. *Archaeological Field Unit, Cambridgeshire County Council*



1066, and the imposition of feudalism. By then the emergence of Christianity (sixth to seventh centuries AD) had already started focusing rural communities around parish churches; the conquest probably accelerated the creation of the modern 'nucleated' village. However, the modern community of Hinxton still bears the mark of its ancient roots: 'Hinxton' is Anglo-Saxon for 'Hengest's farm'.

It is clear that the project stirred the imagination of locals as well as the archaeologists. Project manager Paul Spoerry was caught delving into our muddy past by local Radio Cambridgeshire personality, Chris South. The site was opened to the public before the foundations of the new Sanger Centre were started, and over 1300 visitors came to have a final look before the site was given back to the scientists, to let them start building the foundations of our genetic future.

The frustrations of renovations

Pride of place in Hinxton Hall itself is the Pompeiian parlour, a room decorated in classic Roman style, a rare find in the UK, and one reason why Hinxton Hall is a Grade II* listed building and protected by legislation. With the discovery of the Pompeiian room frescos, the Wellcome Trust carried out changes to the building as sympathetically as possible in the appropriate style, using authentic materials, and mindful of the original structure of the Hall. They thus sought expert advice and approval from English Heritage and the local authority – South Cambridgeshire District Council.

When Tube Investments took over the estate such restrictions were not in place, and the company had been at liberty to change whatever it wanted. Architects Sheppard Robson and building contractors Bovis were thus faced with a major rescue bid. Fortunately, because of Tube Investments' interest in metals, the original tiled roof had been stripped and replaced with one of corrugated steel that had successfully protected the Hall from the worst of the water damage. However, the builders' first task was to strip the roof and re-tile it, for which they 'gift-wrapped' the scaffolds in waterproof sheeting to shield them from the East Anglian wind and rain. Inside, electric fireplaces and ugly 1970s light fittings were removed, and temporary doors and walls ripped out until only the original shell remained. From here, repair work could begin in earnest.

Extravagance and eccentricities

Restoration of the Hall did not come without its headaches and a number of unforeseen additional costs. Rejuvenating the Pompeiian room alone took art restorer Pauline Plummer and her team of highly skilled craftspeople around 14 months, an endeavour for which the Trust carried an additional £150 000 expense. While cleaning the south wing, the chance removal of a strip of wallpaper revealed a lime green rococo motif, which an expert in paint analysis, summoned from the Victoria and Albert Museum, confirmed was authentic. More preservation work was thus required, and the final product is the lime dining room in the new conference centre – a contrast to the frenzied colours of the Pompeiian room.

Alerted to the possibility that the Hall might disclose yet more decorative features, particular care was taken with the other rooms. The large central room was found to be decorated with imitation wooden panelling and was emblazoned with various coats of arms. This theme extended to the foyer, and some wonderfully detailed wallpaper was uncovered. However, the original decor was thought to be too dark and heavy, and the local authority eventually agreed to having it cleaned, protected, and covered over with a lighter paint, deemed to be more suitable decor for the twenty-first century conference attendee.

The relevance of one of the coats of arms was established when a match was found on a memorial plaque – called a

OPPOSITE: Art restorer Pauline Plummer. *Country Living/Simon Page-Ritchie*

ABOVE: The elegant Green Room in Hinxton Hall.

RIGHT: The Green family coat of arms found in Hinxton parish church (left).

hatchment – in the local parish church. Above the hatchment reads, "In loving memory of Edward Henry Green de Freville, late of Hinxton Hall, Cambridgeshire ... and of Henrietta Elizabeth Green his mother". However, the coat of arms is of the de Freville family, not that of the Greens. Why the name change?

The history books record that Hinxton Hall passed from Edward Green to his son Edward Humphrys Green in 1834, and it was the latter who adopted the surname de Freville. Edward Humphrys was particularly fascinated with his lineage, especially after inheriting the de Freville family home – Shelford Manor – in 1850. The de Freville manor had originally been granted to Sir Richard de Freville, a descendant of Bernard de Freville who was known to have been a companion of William the Conqueror. Edward Humphrys Green was so enamoured with his notorious connections that he requested that his cousin, Edward Henry Green, adopt the de Freville name on his death – this Edward Henry obediently did. However tenuous the link, these aspirations of noble lineage may well have prompted the Green family to decorate their home in this baronial style.

All in the name of fashion

More unexpectedly, inspiration for the interior decoration of the other main function room of the house came from further afield. The reverberations from the eruption of Mount Vesuvius in AD 79 continued to be felt, at least in the art world, centuries later. When the ruins of the city of Pompeii were dug from the ashes in 1738, the art world drew breath at the exquisite murals and frescos that adorned the walls of the city's villas. This classical style became a favoured form of decoration by 1800, and is the style that Pauline Plummer and colleagues have so lovingly re-created in the Pompeiian room at Hinxton Hall.

The Pompeiian room was first recorded when the Hall passed into the hands of Tube Investments in 1953. The

One of Hinxton's treasures – the richly decorated Pompeiian room.

company had covered the walls with a purple flock wallpaper, leaving two small aluminium 'windows' for interested visitors to catch a glimpse of the murals beneath. However, neither the Trust nor Pauline Plummer had guessed the full extent of what remained. As she recalls, "It was a bit of a gamble; we just didn't know what would lie underneath. So, we were astonished to find that a lot of the paintings remained intact." Her photographs of the walls at this stage show just how well preserved many of the paintings had been; with a little cleaning the colours sparkled once again. In some areas it is even possible to see the dark spots of charcoal that were originally applied through a stencil to outline the figures.

However, many of the murals had been severely damaged by damp. At certain places on the wall only the shadows of the original paintings – ghosts of Roman figures – remained. At times art restoration is akin to police detective work; the whole scene had to be pieced together from just a few scraps of evidence. Pauline Plummer scoured art books in a search for clues to the missing sections: a rump of a horse and fragment of a scarf looked similar to that of a Pompeiian engraving; the centaur above the door bore a strong resemblance to that of a painting she remembered hanging in Stowe school.

Pauline Plummer made good use of a large folder of photographs of original Pompeiian art work to generate suitable topics for the more badly damaged areas. The Romans' appreciation of nature is echoed in her own interpretations: a glass bowl filled with fruit, a mischievous fox, a startled hare, and a proud rooster, all alive and vibrant. Gaps

A substantial investment in time and money was needed to repair the damage done to the frescos.
Sheppard Robson (top). Pauline Plummer (bottom)

Restoration in progress: the paintings were first cleaned, any holes replastered, and finally the painting retouched. *Pauline Plummer*

BELOW: Pauline Plummer's original sketch was used as a template for the mural. *Pauline Plummer*

in the lower frieze were filled with some of our own native birds – a goldfinch and a mistle thrush – although the Romans favoured more exotic African animals such as lions, tigers and elephants. For some bizarre reason, at some point in the room's history, all the images of cats in the murals had been blacked out; Pauline Plummer has subsequently freed them from their prison of paint.

The focal point of the room would have been the two figures on the north wall, but these had been covered with red paint perhaps by a previous owner affronted at the nudity. Pauline Plummer guessed that one was Apollo, the sun god. She chose Diana as a suitable partner and sketched her from a statue held in the Louvre in Paris. Along the north

OPPOSITE: The god Apollo stands to one side of the fireplace on the north wall of the Pompeiian room.

LEFT: A selection of Pauline Plummer's original sketches for the murals. *Pauline Plummer*

BELOW LEFT: The vibrant murals fashioned in the original Roman style.

BELOW RIGHT: Pauline Plummer's sketch of one of the panels in the Pompeiian room. *Pauline Plummer*

wall, she added four Roman maids, each representing one of the four seasons, in the style of Roman mythology.

The artist behind this Regency decorative extravaganza is unknown. Pauline Plummer first thought that the Craces – a family of artists well known for their historic re-creations – might have been involved. Their handiwork can be seen in places such as Buckingham Palace and Brighton Pavilion. Ickworth Hall in Suffolk also has a Pompeiian room fashioned by the Crace family. However, experts think that the style at Hinxton is distinctly different and potentially the work of another artist (or artists). Whoever the creator was, the amount of work involved would have been little less for those who were originally commissioned, than it has been for the Trust to have it restored. The house owners were indeed quick to boast of its completion in the local paper. Pauline Plummer muses, "We can only guess why they had it done. Perhaps it was to celebrate a marriage, or the arrival of a new family member." A pair of distinctly English faces painted on one wall

may hold the clue. Although we can continue to puzzle over why the room was so decorated, its restoration offers visitors to the Hall a rare show of Regency extravagance.

Tricks with bricks and mortar

Repairing any old home can be a challenge, let alone one that was built over 200 years ago. Legislation stipulates that identical or closely matched materials should be used for repairs, a requirement that greatly complicated the rebuilding process. Gaps in the garden walls, for instance, could not be filled by modern bricks but needed a combination of five different types; when weathered the mixture of bricks should blend in better with the 'look' of the older sections of wall. Many interior walls needed replastering and the recipe for a traditional horse-hair plaster had to be concocted. It is tricky stuff to make: too little horse hair and the plaster falls away; too much and the walls look hairy. The solution was largely a case of trial and error, although having skilled craftsmen was invaluable.

A feature of Hinxton Hall common in country houses is tuck pointing – the thin white line of putty embedded in the mortar to give the bricks a sharper finish. This was an expensive and time-consuming decorative effect, and the builders compromised by finishing only the north and south wings; the central block is noticeably darker in the absence of this finishing. The tuck pointing, along with the interior decoration, suggest that the family had wanted to create a quality home in this rural location – a reflection of their financial status.

A striking addition to the stables are the two Islamic-styled towers. Far from a thoughtless addition, they were cleverly engineered into the basic structure of the stables, and the original wooden beams can still be seen from inside the new conference centre. Continuing in the tradition of the Hall, the stylish tower carries a weather vane in the shape of a trout.

Refurbishing the old laboratories, and constructing the new, let alone overseeing a unit of high-tech research laboratories, a country house, 55 acres of parkland and two fish ponds, created a number of headaches for site administrators Murray Cairns and Jane Rogers. A plague of rabbits and moles, trees felled by gale-force winds, an overly people-friendly buzzard and a drying lake full of carp "swimming on their sides" were among the unexpected problems the pair have faced during the creation of the Campus.

Marrying the old with the new

In the course of the renovations, the stables have been converted into 'rustic' seminar rooms, and a 300-seat auditorium has been built inside the kitchen-garden. An ancient mulberry tree has been uprooted and relocated to make room for this conference facility. Where fruit once hung on vines, posters can now hang in the cloisters built against the kitchen-garden walls. A new seminar room to the west of the building overlooks the orchard and parkland. The architects have taken great pains not to mimic the old, but to construct distinctly new additions; thus, if necessary, it will be an easy task to remove the modern components to leave the restored, older shell intact.

A stroll through the rooms of Hinxton Hall today is evocative of times when it was an elegant country house, rather than the hub of an international high-tech project. The gardens have been carefully landscaped by Elizabeth Banks Associates to preserve the flavour of their past glory. A lakeside path offers staff and visitors an attractive perspective of the Hall and modern research facilities. The Wellcome Trust hopes too that local residents will make full use of parkland beyond the lakes, and perhaps occasionally challenge the staff of the Sanger Centre to a game of cricket on the new pitch within the estate. Thus, the Hall will continue to be a focus of interest for local people, as it has been for decades.

The auditorium of the new conference centre, cleverly constructed within the original kitchen-garden, and the Islamic towers over the old stables.

Science at the Sanger Centre

The Sanger Centre at Hinxton currently makes the single largest contribution to the international endeavour to sequence the entire human genome. When the Sanger Centre was first opened in October 1993 by its namesake Fred Sanger, he referred to the Human Genome Project as a "venture into our own selves". But what exactly did he mean? And what impact will the project have on each of us and our society?

Genetics at a glance

The genetic code

When a child is conceived, the fertilized egg comes packed with 46 chromosomes – 23 from the mother and 23 from the father. The chromosomes contain the instructions with which a single cell can multiply and diversify to form an adult, and subsequently orchestrate the day-to-day running of its body. Deciphering this human 'recipe book' is the goal of the Human Genome Project.

The instructions inscribed in the chromosomes are written in a chemical language called deoxyribonucleic acid or DNA. In all living organisms, DNA has a simple four-letter alphabet – the genetic code – consisting of the 'letters' G, A, T and C, which are abbreviations for four related chemicals called bases. Long sequences of these bases form 'sentences' that can be read by the cell; a discrete sentence is a gene.

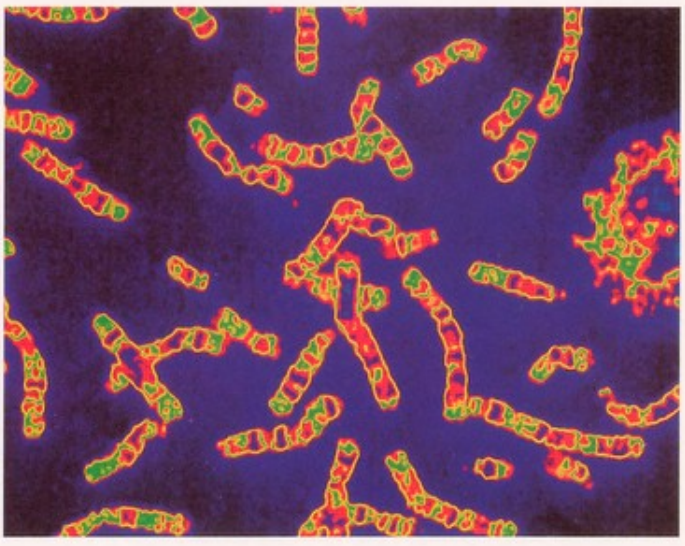
OPPOSITE: Work at the Sanger Centre.

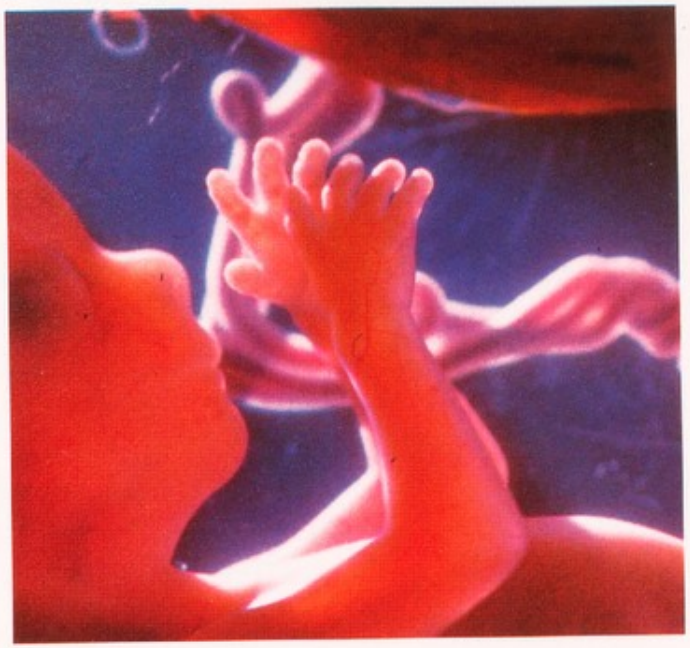
RIGHT: The Human Genome Project will decode the instructions stored in human chromosomes. SPL

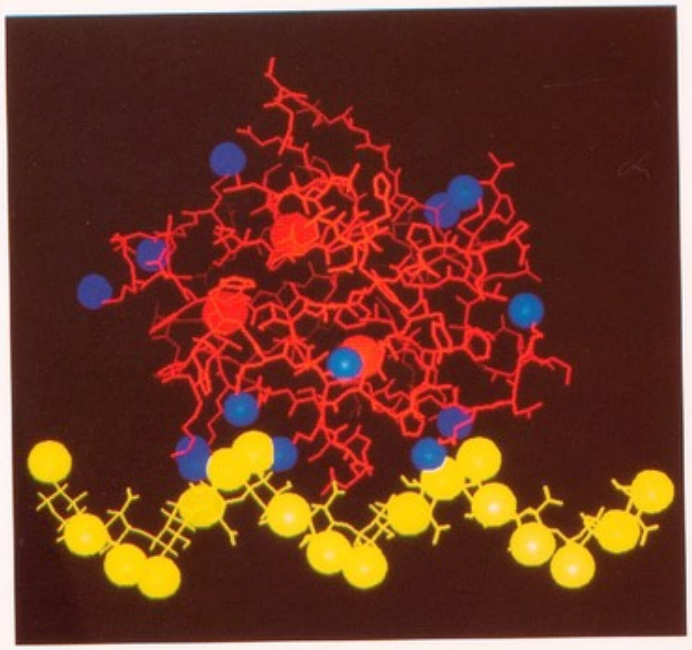
Genes means proteins

Each gene contains the recipe for a unique protein. All proteins are made up of amino acids, and cells have the machinery to join a chain of amino acids together in the right order to create a specific protein.

Proteins are essential for life. The diversity among proteins is a reflection of the amazing repertoire of functions that they perform in the body: some are the basic construction materials of the body found in muscle, tendon, and skin; some, namely enzymes, control the pace at which energy and chemicals are generated; while others, hormones, regulate essential processes like reproduction, growth, and our response to our changing environment. In becoming conversant with the language of our genes we will be privileged with an insight into the very basis of life itself.







Understanding the Human Genome Project

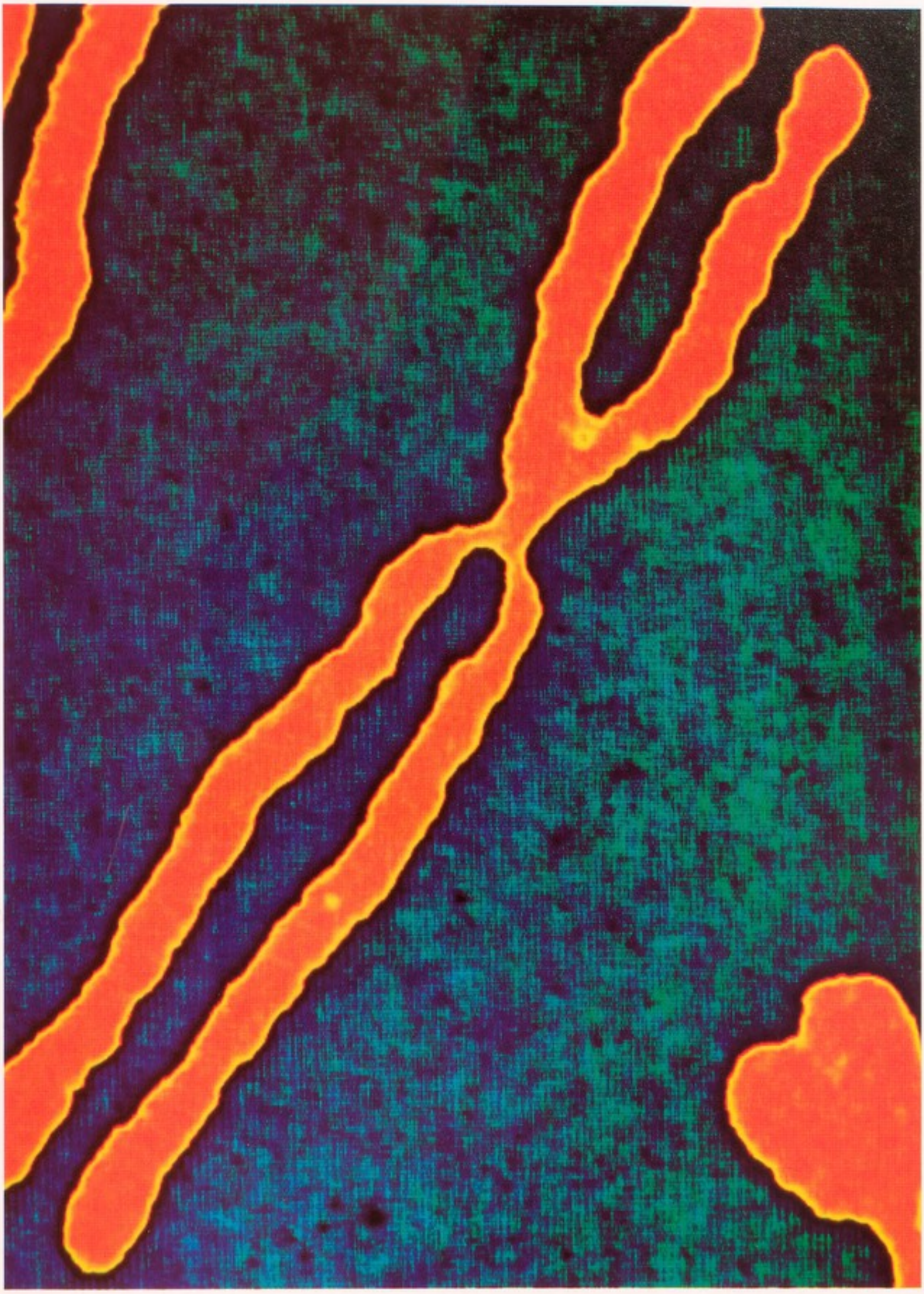
The link between genes and proteins may seem simple, but the challenge arises from the sheer size of the task involved. Unravel the tightly packaged chromosomes of a single human cell, and you will have around six feet of DNA, comprising two copies of the 3000 million bases (a million bases is a megabase, Mb). It is estimated that there are somewhere between 60 000 and 100 000 different genes lurking in this chemical spaghetti – finding them is a goal of the Human Genome Project.

Finding our way around the genome

To negotiate their way around the lengthy human genome, researchers have created a number of 'road' maps. Historically, information about our genes and their role in the body came from studying families suffering from inherited disorders. Geneticists found that abnormalities in a 'disease' gene were common to all affected family members, but they could only determine its position on the chromosome very approximately. However, in attempting to locate such genes, researchers discovered that genes in the regions bordering the 'disease' gene – linked genes – were inherited along with it, and so they could construct linkage maps. Unfortunately, this linkage map was rather bare of useful road signs as so few genes were known. More recently, a more detailed map has been constructed by reading short stretches of DNA and determining their position along the entire length of each chromosome. This physical map forms the skeleton which the sequencing teams at the Sanger Centre, the Genome Sequencing Center in the USA, and others around the globe are fleshing out. By the year 2002, many of those 3000 million bases will have been read and the Sanger Centre will have contributed around 550 million.

Gene spotting

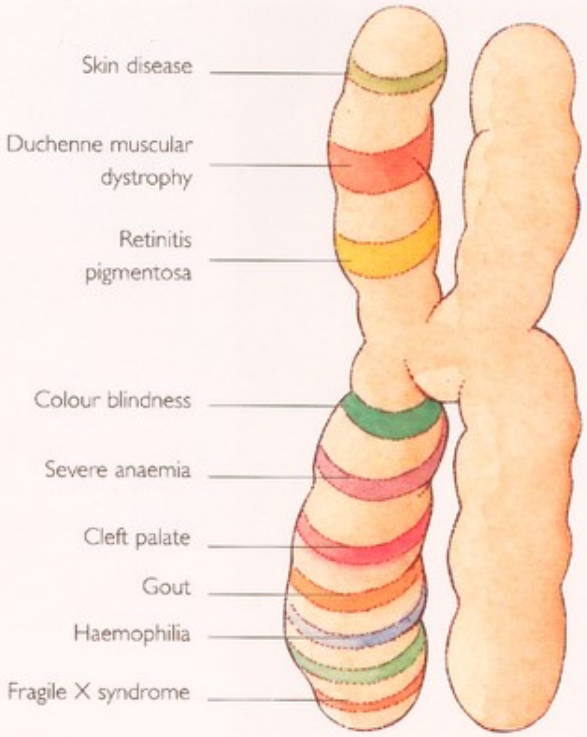
The possession of the sequence for the entire human genome will be a tremendous resource for biology and medicine. However, scientists will still be faced with the arduous task of working out which bits of this sequence represent the thousands of genes. Current estimates suggest that the protein-coding parts of genes occupy only five per cent of the human genome. Much of the genome has no obvious function, but scattered throughout the non-coding regions are the all-important control sequences which serve to regulate

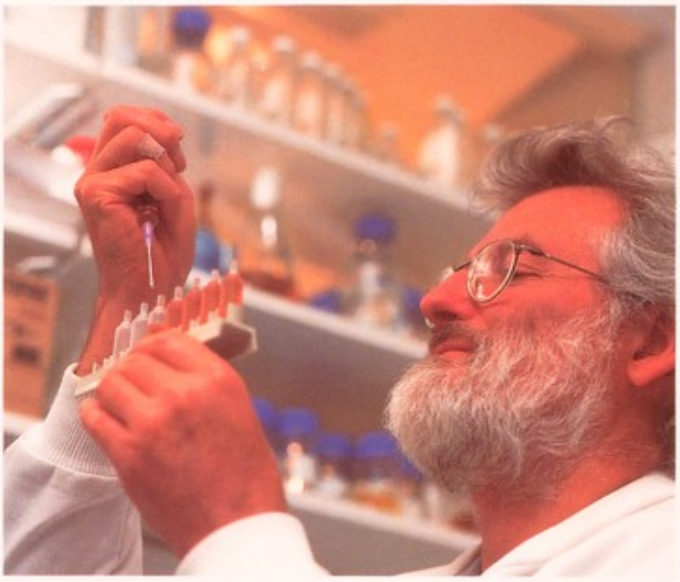


OPPOSITE LEFT: The Human Genome Project will ultimately help to answer one of biology's greatest puzzles – how we develop from a single fertilized egg. *SPL*

OPPOSITE RIGHT: Genes code for proteins, here a growth factor vital for wound healing and tissue repair. *Robert Longuehaye*

LEFT: Human chromosomes exist in pairs. When cells multiply, each chromosome splits at the centre and each half is duplicated. *Alfred Pasieta, SPL*



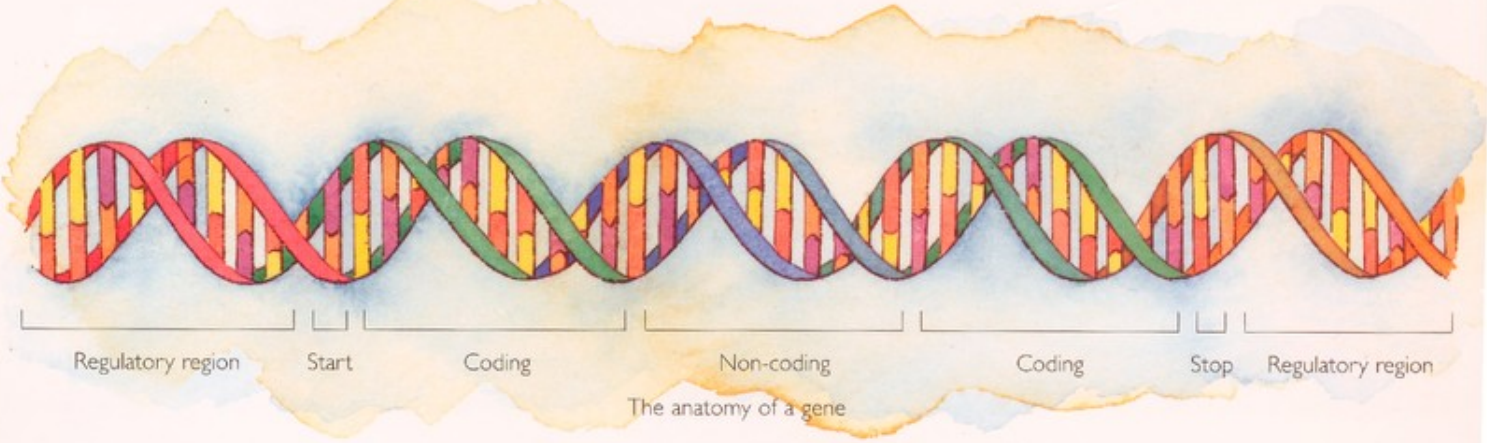


ABOVE: The work of John Sulston and his colleagues will help pinpoint the genetic errors that contribute to many diseases.

ILLUSTRATION: Disorders known to be linked to errors in the X chromosome.

how the gene is 'read'. One of the reasons why it is valuable to sequence the entire genome is that such regulatory sites can be identified. Another advantage is that only by sequencing the entire genome can we identify and understand the entire set of genes. Nevertheless, looking for that all-important gene is like looking for the proverbial needle in a haystack; to date, only 6000 human genes have been identified.

One of the important tasks of researchers at the Sanger Centre is the construction of annotated maps of chromosomes. In the summer of 1997, the team are continuing to put together comprehensive pictures of five human chromosomes (1, 6, 20, 22 and the X chromosome), compiling on the same map all the relevant data available – from basic sequence information, to the position of known genes, their function and any involvement they might have in disease. This task is of great benefit to groups looking for 'disease' genes in a particular region of the chromosome, and has already helped discover a candidate gene for breast cancer, *BRCA2*.

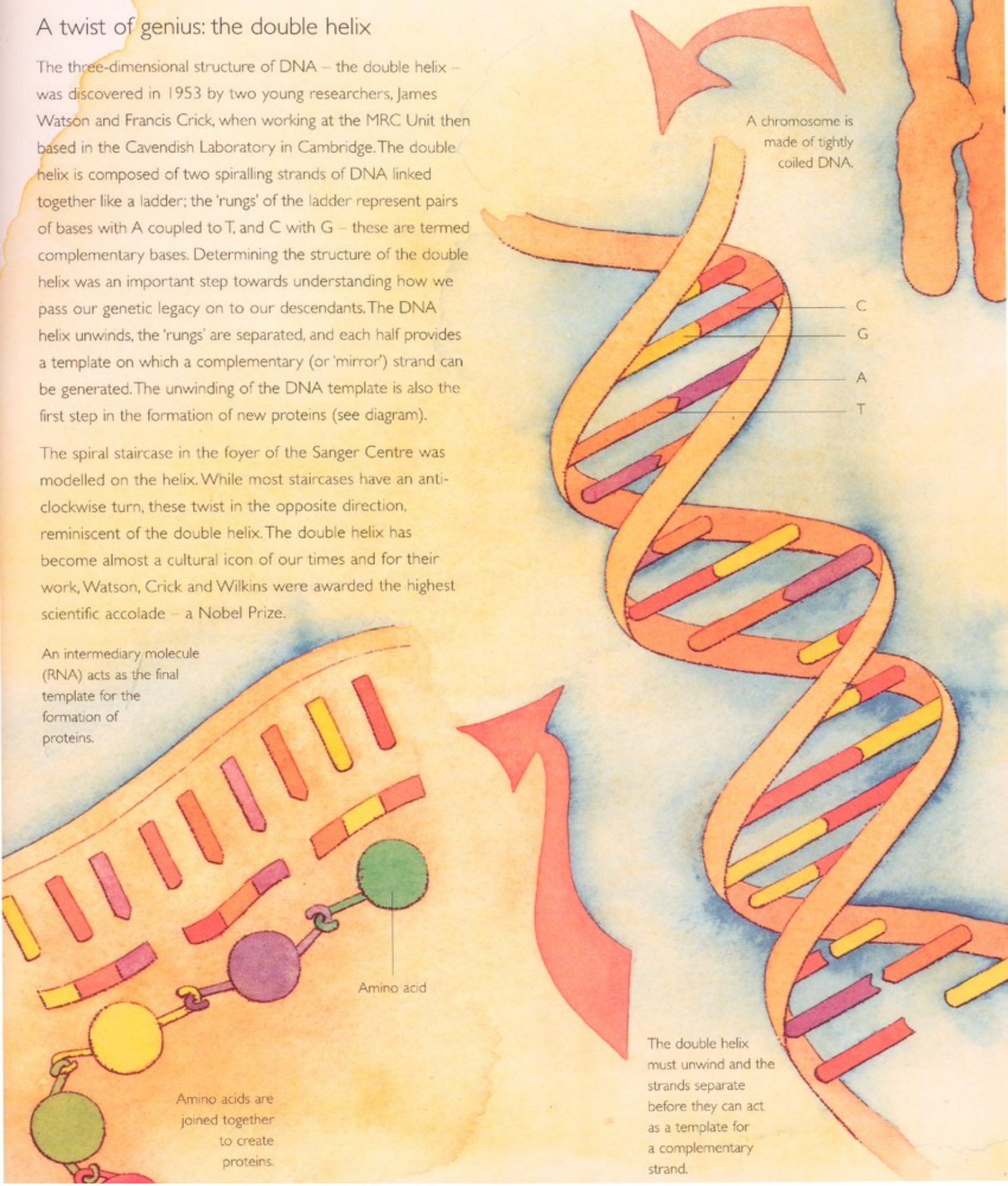


The anatomy of a gene

A twist of genius: the double helix

The three-dimensional structure of DNA – the double helix – was discovered in 1953 by two young researchers, James Watson and Francis Crick, when working at the MRC Unit then based in the Cavendish Laboratory in Cambridge. The double helix is composed of two spiralling strands of DNA linked together like a ladder; the 'rungs' of the ladder represent pairs of bases with A coupled to T, and C with G – these are termed complementary bases. Determining the structure of the double helix was an important step towards understanding how we pass our genetic legacy on to our descendants. The DNA helix unwinds, the 'rungs' are separated, and each half provides a template on which a complementary (or 'mirror') strand can be generated. The unwinding of the DNA template is also the first step in the formation of new proteins (see diagram).

The spiral staircase in the foyer of the Sanger Centre was modelled on the helix. While most staircases have an anti-clockwise turn, these twist in the opposite direction, reminiscent of the double helix. The double helix has become almost a cultural icon of our times and for their work, Watson, Crick and Wilkins were awarded the highest scientific accolade – a Nobel Prize.



So why bother?

What are the justifications for the enormous effort, and cost, involved in the Human Genome Project? Without doubt, having a catalogue of all human genes will help us better understand, and possibly treat, many inherited disorders and possibly a wide range of forms of human ill-health – from cancer to cardiovascular disease. Furthermore, having all genes to hand will help us put together a better picture of the complex actions and interactions that together orchestrate the creation of an adult human.

Genes and disease

Errors in the genetic code – be they spontaneous, or through damage by chemicals or radiation – are translated into faulty proteins no longer capable of carrying out the task they were designed to do. As proteins are fundamental for life, the loss or defect of genes can have profound effects on our health.

At present, we know of over 4000 different conditions that arise from defects in just a single gene. Around 2.5 per cent of the population are affected by this type of inherited condition. Some of these disorders can be effectively managed by drugs or treatments, but many are relentlessly distressing diseases for which there is no cure. Moreover, damage to genes is permanent: genetic errors, and thus disease, can be passed on to future generations.

Whether or not a defective gene affects health depends on the nature of the disorder. In cystic fibrosis, for example, a child must inherit two defective copies (one from each parent) of the 'cystic fibrosis' gene to suffer from this lung and intestinal disorder. If only one copy is defective, its functional partner can still meet the needs of the child's body. Around one in 2500 people suffer from cystic fibrosis, making it the most common genetic disorder in the UK. It remains a debilitating disease: even with the best medical care, patients rarely live beyond 40.

In other disorders, a single defective copy of a gene is sufficient to cause disease. An example of such a condition is Huntington's chorea which manifests as a progressive degeneration of mental and physical abilities in middle age, and proceeds rapidly to an early death. Here the normal copy of the gene cannot compensate for the damage wreaked by its defective partner.

Scientists suspect that many of the big killers in Western society, such as heart disease, diabetes and cancer, have a genetic component, possibly from a combination of errors in a number of genes. Whether or not we develop these diseases, and with what severity, is likely to be influenced by other factors such as our environment and lifestyle. Doctors continually warn us that a high-fat diet, obesity, insufficient exercise, smoking, excessive drinking and stressful lives can lead to a greater risk of heart disease, but part of the risk we run may also be written in our genes. The Human Genome Project is thus vital if we are to understand the complex factors underlying common disorders that account for a large proportion of today's healthcare expenditure.

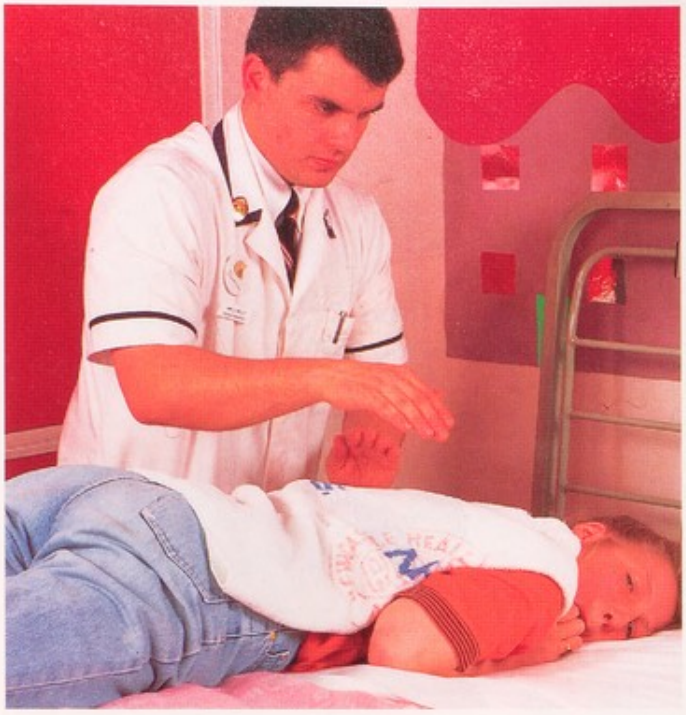
A revolution in healthcare

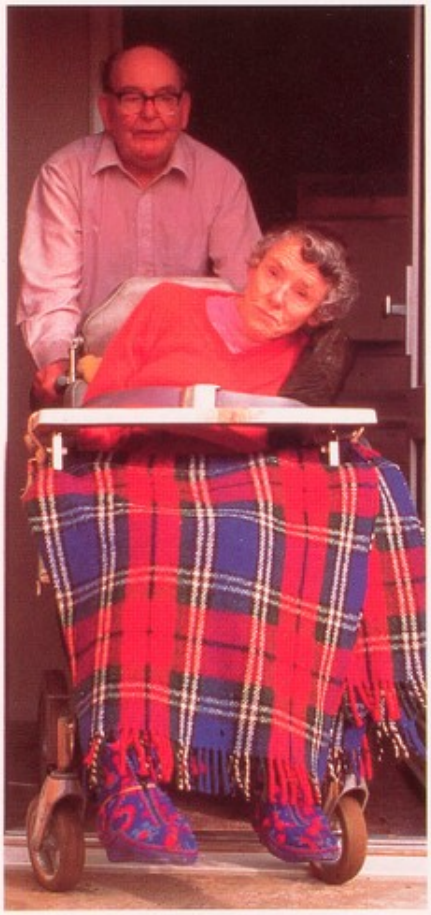
Genes are central to many aspects of our health. Through the efforts of the Human Genome Project, researchers are steadily compiling an inventory of all human genes, their chromosomal location and their potential function in the body. The information gained offers several new opportunities for medical researchers. First, they can start to piece together the sequence of events – from damaged gene, to defective protein and then to disrupted function – that results in ill-health. A detailed understanding of each disease will have the added benefit of uncovering new targets for therapeutic intervention in the future.

Second, the identification of disease genes will greatly improve predictive medicine by offering a means to identify individuals at risk of a disease long before the symptoms appear; preventive measures could then be applied as early as possible. Genetic tests are currently used to check for a variety of inherited disorders such as cystic fibrosis and sickle-cell anaemia. Perhaps in the future, we might be tested at birth for a range of genetic defects that might make us prone to illness in the future – a personalized health forecast.

Of equal importance, researchers are exploring ways in which they can correct errors in the genome of patients with genetic disorders like cystic fibrosis, by compensating for the faulty gene with a flawless copy – the principle behind gene therapy. While researchers have had some success getting genes into cells, it has proved difficult to keep them there, but gene therapy still has great potential for permanently curing many lethal diseases.

Having the genetic code for a protein can be useful in the design of small molecules that have potential use as medicines. For example, many of the drugs used to treat nervous disorders operate by interacting with proteins called receptors embedded in the surface of nerve cells. By identifying the genes for these receptors, it is possible to make the proteins artificially in the laboratory, and then test how they are affected by drugs. Sophisticated computer-





ABOVE: Cystic fibrosis remains the most common genetic disorder in the UK. Physiotherapy helps to clear the large quantities of mucus that build up in the lungs of cystic fibrosis patients. *Simon Fraser, SPL*

LEFT: Huntington's chorea – a devastating disorder that destroys mental and physical ability. *Conor Caffrey, SPL*

OPPOSITE: Duchenne muscular dystrophy is a muscle-wasting disease that results in paralysis.

ILLUSTRATION: The size of the task in hand: the human genome is over 30 times larger than that of *C. elegans* (not drawn to scale).

OPPOSITE TOP: Bart Barrell of the Sanger Centre.

OPPOSITE MIDDLE: The cause of tuberculosis in humans – *Mycobacterium tuberculosis*. *Dr Lounatmaa, SPL*

OPPOSITE BOTTOM: Yeast – the organism used in the baking and brewing industry. *David Scharf, SPL*

modelling programs can also be used to predict the three-dimensional structure of proteins, and so design molecules that 'fit' with the protein; such molecules are more likely to be effective drugs. Together, computer scientists, pharmacologists and molecular biologists can start creating drugs in cyberspace.

Why sequence bugs, parasites and brewer's yeast?

One of the most exciting applications of human genetics is in developmental biology, where the central question is how a single fertilized egg cell can divide and differentiate to form an adult. Cells as diverse as those in the skin, bone, heart and brain develop from the same genetic recipe book; different combinations of genes are switched on, or off, in each cell type. Understanding how this amazing process is orchestrated is one of biology's greatest challenges. However, researchers have to look to simpler organisms – such as the nematode worm and yeast – for clues as to how the human system might work.

Researchers at the Sanger Centre and Washington University have nearly finished sequencing the genome of the worm *C. elegans*. The worm is a particularly useful model for researchers because its 100 Mb genome is a fraction the size of that of the human, but it still has a broad range of specialized tissues. Armed with both a detailed picture of the development of the nematode worm and its genetics, scientists are linking each gene of the worm with the task that it carries out. *C. elegans* is an ancient creature, lying early in the evolutionary tree, and so harbours genes common to many more complex creatures. The worm's genetic 'tool kit' will thus provide an excellent framework in which to understand the biology of all animals, including humans.

Bart Barrell and his team at the Sanger Centre made the largest single contribution in the international initiative to sequence yeast (*Saccharomyces cerevisiae*), vitally important

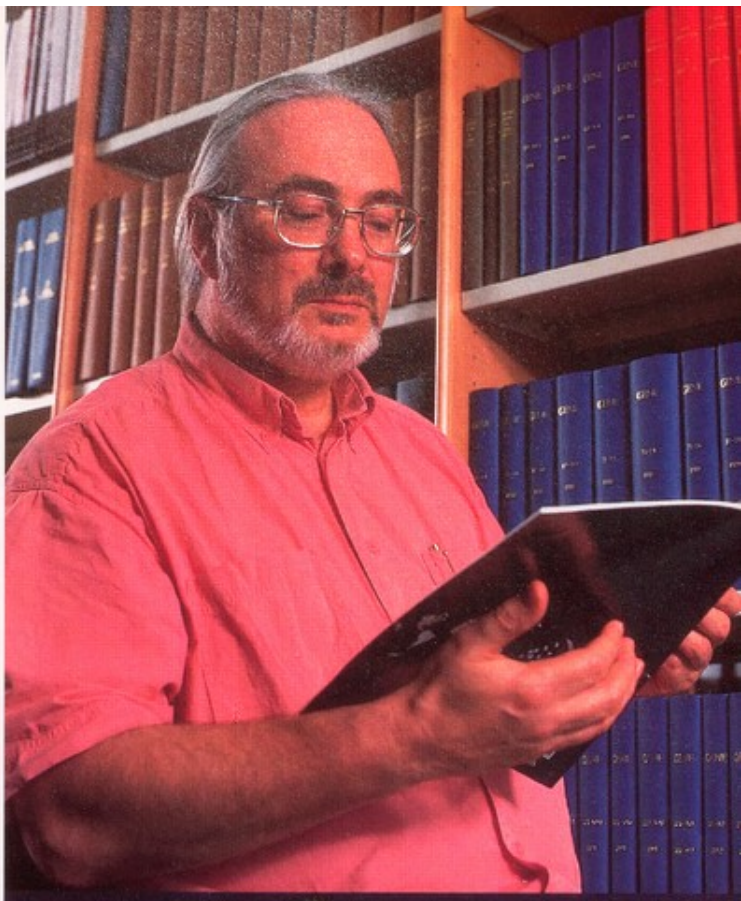
in the food and drink industry. The entire sequence of the yeast genome, around 12 Mb, was completed in April 1996. Like the worm, yeast provides a cheap and user-friendly model for identifying the genes that regulate fundamental cellular activities – like cell division and cell growth – common to all living creatures. Indeed, the venture revealed that over half of the yeast's genes bear some resemblance to those in humans, among them genes for cystic fibrosis, as well as breast and ovarian cancer. The yeast model can thus provide important information for medical researchers working on these diseases.

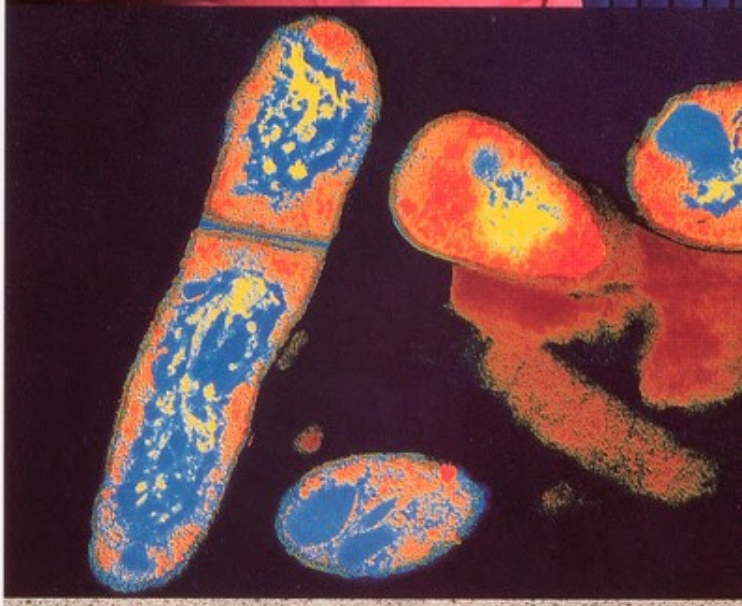
The full potential of the sequencing of model organisms such as *C. elegans* and yeast has yet to be realized. It is clear that genes are highly conserved among all living creatures; related genes carry out related tasks even in quite disparate species. Indeed, some researchers are questioning whether there are any unique human genes.

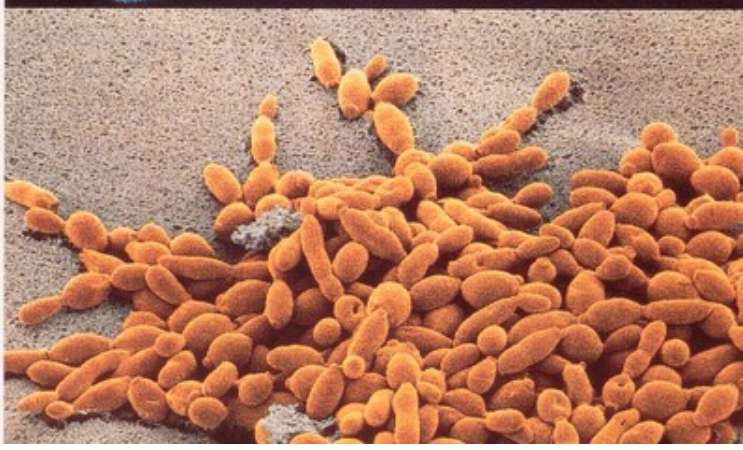
Gene warfare: genes against pathogens

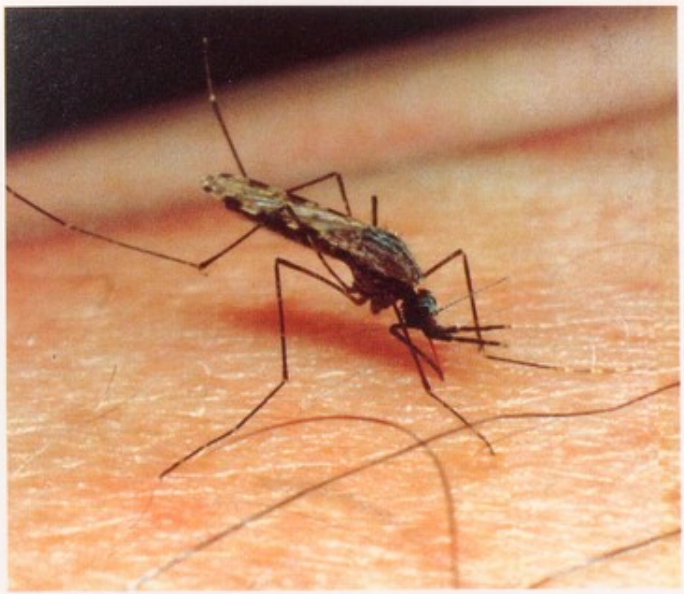
The genomes of disease-causing bacteria (microbes) and parasites that afflict millions of humans and farm animals are also coming under the scrutiny of sequencers. It is hoped that genomic sequencing will identify new weapons against the microbe that causes tuberculosis (TB), and against the malaria parasite.

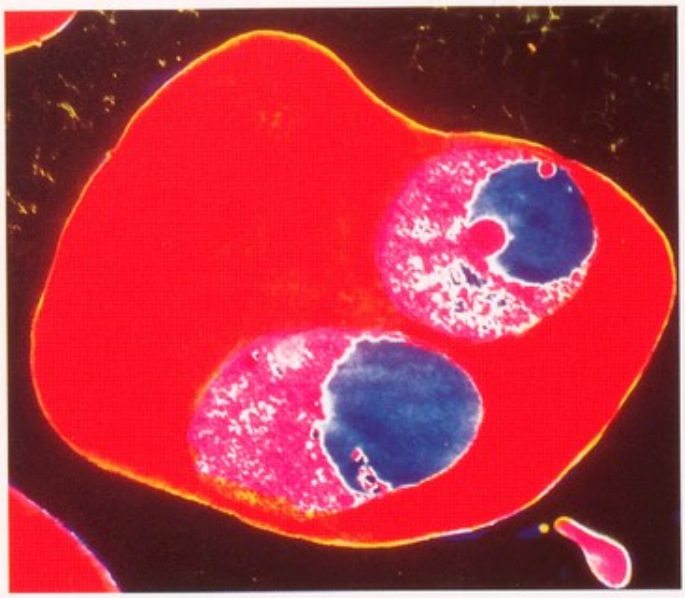
Often thought of as a relic of the Victorian era, TB remains one of the world's leading killer diseases. Even though the protective BCG vaccine has been available for over 30 years, the TB-causing microbe (*Mycobacterium tuberculosis*) still infects around a third of the world's population, and kills over three million people every year. Over the past three decades, the microbe has become resistant both to the previously effective antibiotics and to the vaccine. As a result, the incidence of TB has escalated, especially among individuals with AIDS whose immunity is already low. As a consequence, in 1996 the World Health Organization declared TB a 'global emergency'.









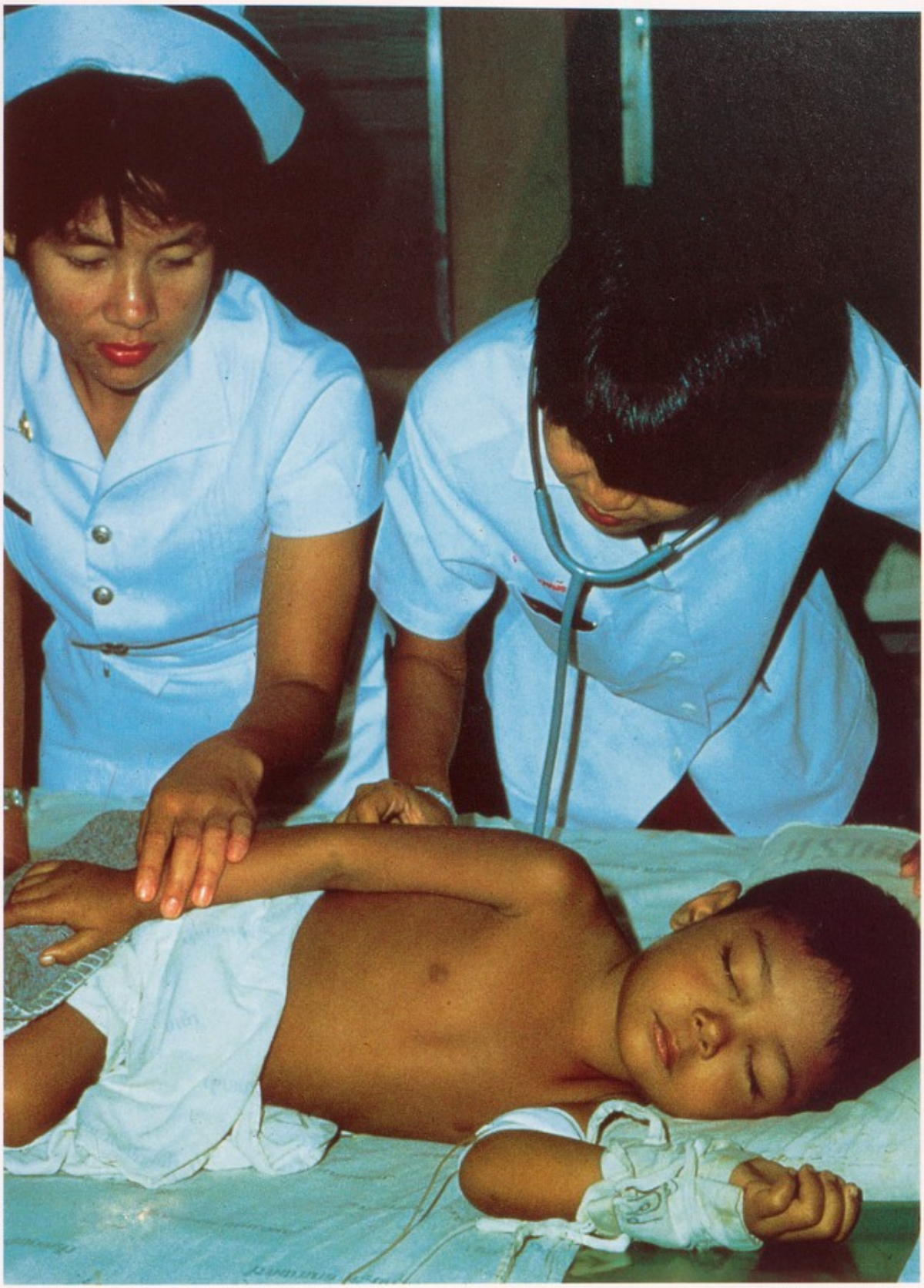


With funding from the Wellcome Trust, Bart Barrell and colleagues at the Sanger Centre are working in collaboration with a research team at the Institut Pasteur in Paris, France, to sequence the entire 4.4 Mb genome of the TB microbe. With this sequence to hand they can then start hunting for the genes that contribute to its infectiousness, such as those that enable it to attach to the host cell wall. As well as offering new approaches for the control of TB, the sequence information will prove valuable for research into related pathogens, including *Mycobacterium bovis*, the cause of cattle TB, a major problem for farmers in the developing world, and *Mycobacterium leprae*, the cause of leprosy in over a million people worldwide.

Researchers at the Sanger Centre are also part of an international collaborative venture to sequence the genome of *Plasmodium falciparum*, the most virulent form of the malaria parasite. There are over 500 million cases of malaria each year, resulting in nearly three million deaths, mainly within native populations of the sub-Saharan Africa, Asia, and Central and South America, although Western travellers are increasingly at risk. No effective vaccine has ever been developed and drug-resistant forms of the parasite are spreading at an alarming rate. New vaccines and treatments targeted at weak points in the parasite's life cycle are desperately needed; identifying the genes that control these critical stages may therefore prove vital. At 30 Mb, the genome is considerably larger than that of the TB microbe, and a joint venture was essential. It is hoped that the genome will be fully sequenced by the year 2000, with the Sanger Centre contributing around a half of the sequence and a number of groups in the USA sequencing the rest.

The Sanger Centre – a gene production line

Just 20 years ago, the idea of sequencing the entire human genome was an unrealistic and expensive dream – big science. The technique for DNA sequencing, developed by Fred Sanger at the LMB in Cambridge, was initially entirely manual and therefore slow and costly. With advances in materials, and automation of specific parts of the procedure, the same basic method can be performed at a much lower cost. In the foyer of the Sanger Centre an electronic display reels off the bases as they emerge from a production line in which people and machines work together harmoniously. The whole process is continually being refined, allowing ever more sequence to be determined for a given cost.



OPPOSITE LEFT:
The mosquito carries the malaria parasite, injecting it into the host when feeding. *A Stich, Wellcome Trust Tropical Medicine Resource*

OPPOSITE RIGHT:
A red blood cell harbouring the malarial parasite. *SPL*

LEFT: Millions suffer each year with malaria. The cerebral form is particularly lethal. *D Worrell, Wellcome Trust Tropical Medicine Resource*

Fred Sanger – the father of sequencing

As a Cambridge biochemist in the 1950s, Fred Sanger was among the most influential men in his field, helping to lay the foundations of protein chemistry. Sanger worked out the protein sequence of the hormone insulin, for which he was awarded his first Nobel Prize.

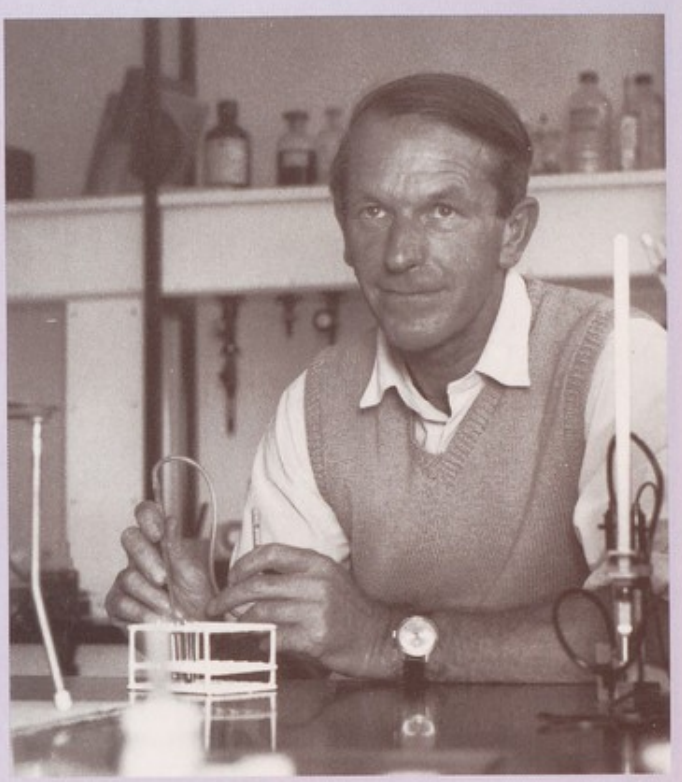
During the 1950s, it became abundantly clear that the information of life is stored as a sequence of bases in DNA, and Sanger worked for years on methods to read the sequence. His final method was to copy the DNA with enzymes, and to block the copying process in a base-specific manner. The resulting DNA strands, radioactively labelled, were separated by length; from these patterns the sequence of the bases along the DNA could be read. With a few alterations, this sequencing technique is still used today, although fluorescent rather than radiolabelled tags are used and the sequence is read by machine. For his pioneering efforts, Fred Sanger was awarded a second Nobel Prize, a rare honour in the world of science.

Fred Sanger retired in 1983, but when he opened the Sanger Centre in 1993 he was delighted to receive a security pass to the building, a pass he still uses today to visit the staff and keep up to date with the progress of his scientific descendants.

Fred Sanger recalls the early years of his work on DNA:

"During the last 50 years, there have been enormous advances in our understanding of living matter. When I started working in the Department of Biochemistry at the University of Cambridge, I thought of DNA as an inert substance. The notion of DNA containing all the information for making a complete organism would have been thought of as science fiction. But that is the way it is.

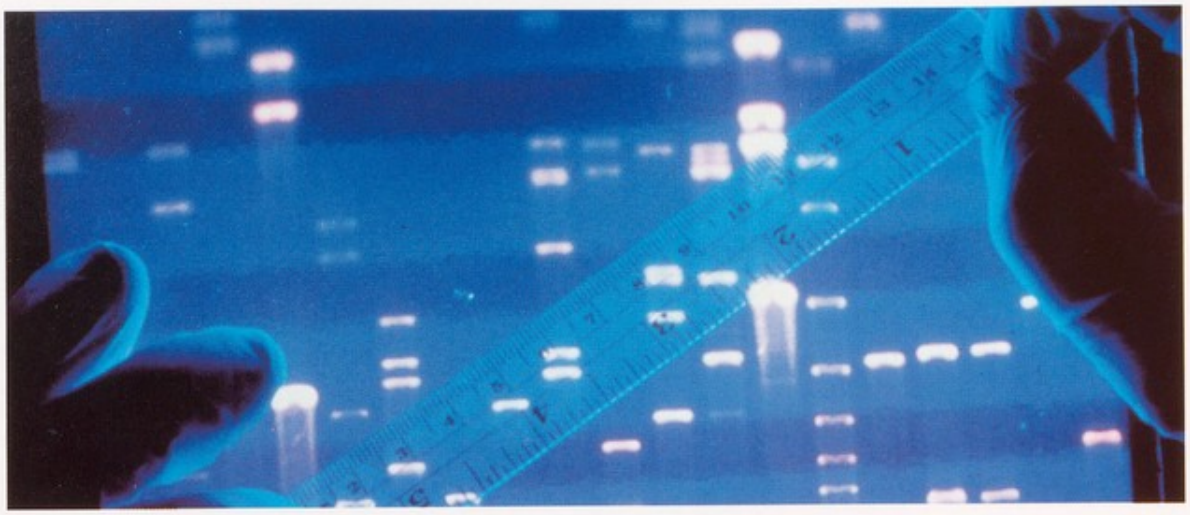
"The DNA is the genome, and we now know how to read the information contained in it: this is what the Genome Campus is about. Due to the size of genomes it is, of course, a very large international project but it seems to me a very exciting and worthwhile one, much more worthwhile than sending a man to the moon, or flying a balloon around the world. It is an exploration into our own selves.



"About 15 years ago, John Sulston and Alan Coulson decided to study the genome of a somewhat lowly organism, a worm. At the time this seemed very ambitious; it was difficult to see what they'd achieve. However, they were well supported by the MRC and the Wellcome Trust and so things moved rapidly. All of us who have worked on DNA are very grateful to the Wellcome Trust for the excellent and stimulating new campus that has been built at Hinxton, where various genomes are being studied. I feel sure that medical science will soon share our gratitude."

TOP: Fred Sanger, Cambridge biochemist, developed the sequencing technique fundamental to the work at Hinxton. *MRC/Laboratory of Molecular Biology*

OPPOSITE: Today, the technique is more streamlined and automated but still requires an expert eye.



LEFT: Reading the code of life.

ILLUSTRATION: Each year many thousands of researchers – from Australia to South America – access the MRC databases.

Making sense of it all – Bioinformatics at Hinxton

As advances in technology speed scientists towards their goal of sequencing the genome of their chosen organisms, powerful new number-crunching computers had to be developed to cope with the data explosion – the new discipline of bioinformatics was born. The European Bioinformatics Institute (EBI) provides an essential channel through which the sequence data generated by the Sanger Centre can flow to the outside world. The MRC Human Genome Mapping Project Resource Centre provides additional support for genetic researchers in the UK. Together the bioinformatics and resource units offer a virtual meeting ground for those working in genetics and molecular biology worldwide.

Information for life

Without bioinformatics it would be almost impossible to make any sense of the rising tide of biological data flooding the Internet. In the summer of 1997, there were over 1 billion bases and 150 000 sequences stored in the world's databases. However, these databases must be more than passive storehouses for sequences, they must also work as tools to increase the value of the data invested. For example, scientists search databases for significant motifs or patterns – the tell-tale indicators of the presence of genes – in the seemingly endless strings of bases. Others may search the databases with the sequence of a novel gene to try to find a match with an existing one – similar sequences may indicate proteins with related functions.

Insight into the three-dimensional structure of a protein is helpful in determining how it might function. The large database of protein structures – Macromolecular Structure Database – is of particular interest to researchers in the drug industry, who find it useful in designing small molecules with therapeutic purposes. Databases are also important in the study of the way in which genes have evolved over time – molecular evolution. Tracing our own genes back in time, by looking for related ones in simpler creatures, may help to reveal human evolution. Parallel investigations of the genome of different races may elucidate their similar or disparate origins, along with racial variations in susceptibility to disease.

While sequencing of the genome of organisms is proceeding at break-neck speed, interpretation and application of this information is largely limited by the interpretive powers of bioinformatics. Bioinformatics is a challenging and expanding field where those practising must be biologists, information specialists and part-time crystal gazers; they need not only an excellent grasp of the biology, but also an ability to foresee the use that the data will be put to, along with the expertise needed to develop databases to achieve this end. Not surprisingly, staff at the EBI come from

backgrounds that vary from physics, mathematics and computer science to biochemistry and molecular biology. It is an ever-evolving field and the demand for people with this training looks set to increase in the future.

The MRC Human Genome Mapping Project Resource Centre

The MRC Human Genome Mapping Project Resource Centre was set up in 1989 by the MRC as a service to the scientific community, with the objective of providing biological samples and sequence information, and to facilitate the transfer of genetic information from academia to industry. Initially housed in the Clinical Research Centre in Harrow, the Resource Centre moved to the Hinxton site in 1994 and, with its state-of-the-art computing facilities, is viewed as an integral part of the concept of the Genome Campus.

Resource Centre databases, which can be easily accessed from any desktop computer connected to the Internet, offer not only access to sequence information, but also over a hundred different analysis programs carefully selected to extract the 'best value' from the data in store. The Resource Centre also offers a vast selection of DNA and cell collections which reduces the duplication of the efforts of researchers working in the field.

As Dr Duncan Campbell, the Director-designate of the Resource Centre, points out, the role of the Resource Centre must evolve to keep up with the changing needs of the scientific community. As the sequencing nears completion, efforts will become focused on systematically identifying all human genes, their function, where and when each gene is turned on in the body, and the various factors that control this process. The existing strengths of the Resource Centre in bioinformatics will continue to be a cornerstone of this programme. Its versatile and powerful databases can be applied to determine the links between human and model organisms, matching genes with similar functions. It will be a powerful and rich source of information for those interested in the role of genes in the human body.

Continental flavours:

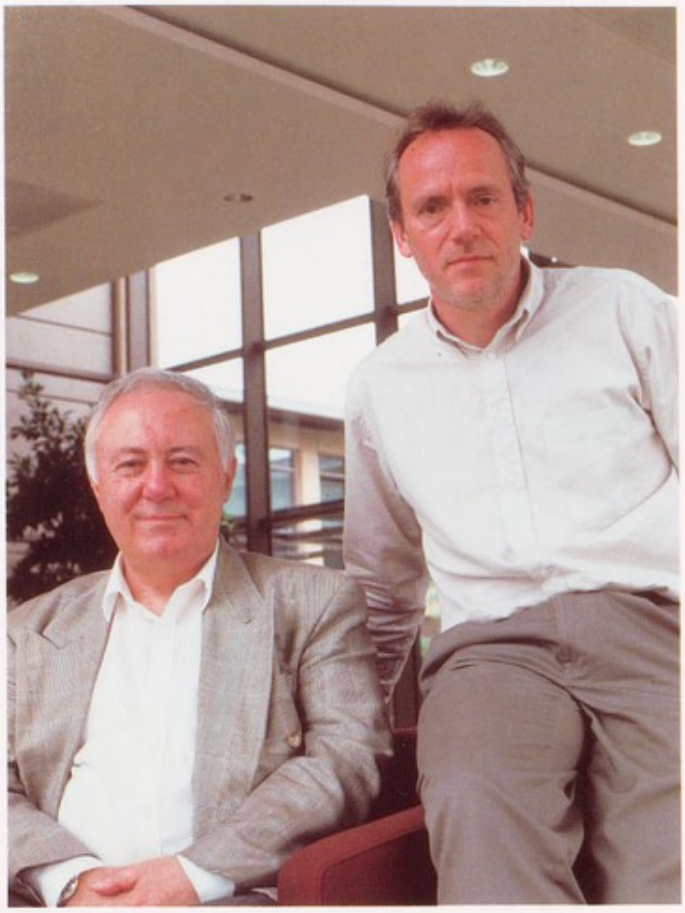
The European Bioinformatics Institute

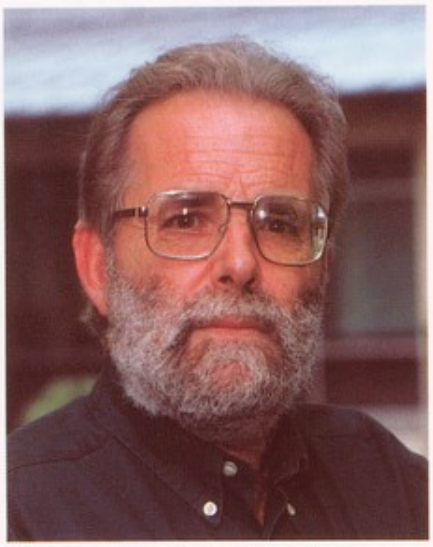
The EBI is an outstation of the European Molecular Biology Laboratory (EMBL), an international research organization funded by a consortium of 15 European countries and Israel. At its headquarters in Heidelberg, Germany, this prestigious Laboratory has been carrying out molecular biology research for the last three decades. It was here, in the early 1980s, that the idea for a central 'honey pot' of DNA sequences was first conceived. Previously, researchers interested in sequence data had to read it directly off the pages of the scientific journals, a rather tedious, time-consuming and often unrewarding activity. Compiling all the published sequences in a single database was the perfect solution.

In the early 1980s, EMBL employed a small group of information specialists (of whom Graham Cameron was one) to set up a DNA data library for European scientists; it was a great success. By the end of the decade, when electronic communications took off and the process became fully automated, the database rapidly increased in size and the demand for access rose in parallel. The available resources were soon stretched to their limit. Cameron saw the answer might lie in a more substantial, autonomous initiative – the European Bioinformatics Institute. In the UK, Michael Ashburner and John Sulston were stalwart supporters of the idea and persuaded the MRC and the Wellcome Trust to place a bid to have this resource in the UK.

Hinxton was seen as an ideal location for the EBI. The proximity of the genome sequencing carried out at the Sanger Centre, and the tradition of excellence in genetics and molecular biology in Cambridge, were major attractions. With enthusiastic government backing, the then science minister William Waldegrave lending his weight to the project, an official bid was submitted in February 1993.

RIGHT: The EBI building on the Wellcome Trust Genome Campus.





FAR LEFT: Paolo Zanella, Head of the EBI (left), with Graham Cameron, Head of Services (right).

LEFT: Michael Ashburner steers the Research Programme, ensuring databases remain up to date.

ILLUSTRATION: Serving a global community: databases around the world are updated on a daily basis.

The location and facilities offered proved to be a winning combination and by May 1994, Graham Cameron and 15 of the original staff had moved to temporary accommodation at Hinxton, provided by the MRC.

Walking down the corridors of the EBI, now housed in new premises on the Wellcome Trust Genome Campus, as many as eight different languages can be heard, testament to the Institute's continental roots. The EBI continues to be supported by the European Union, EMBL and the Wellcome Trust – an indication of the collaborative nature of the project.

EBI serving the world

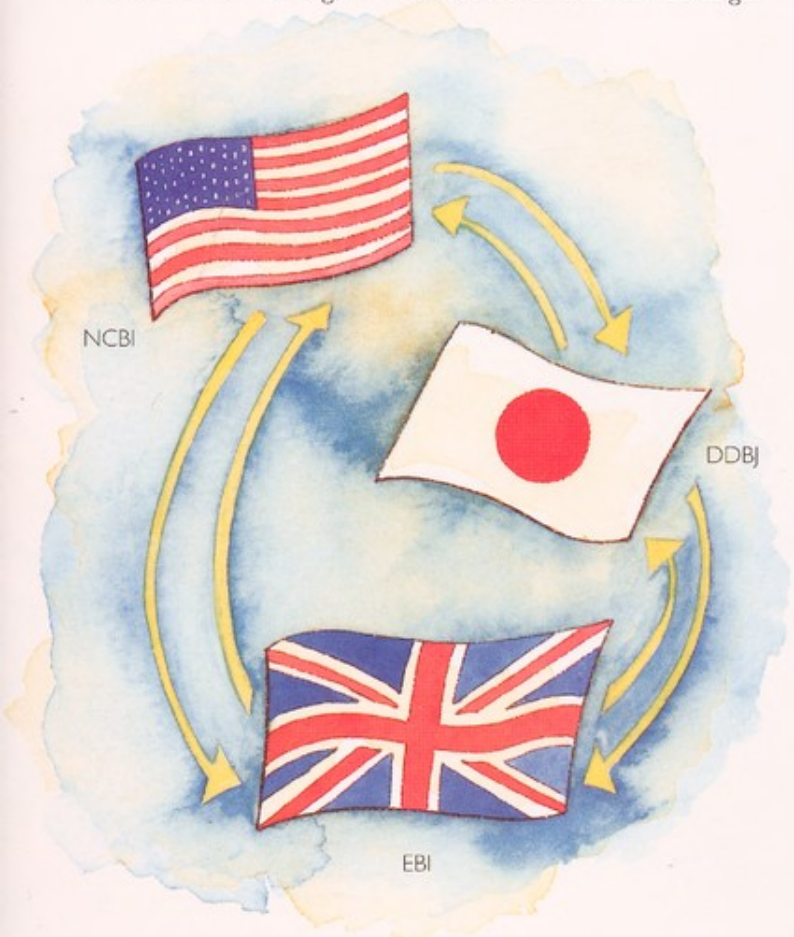
Today, the EBI continues to provide a wide range of services to the European scientific community. Graham Cameron, Head of the Services Programme at the EBI, estimates that over 10 000 enquirers log on to the EBI database every day both to access and to submit data. Currently, around one million bases are downloaded every day – around 700 every minute – from users worldwide, and this figure is predicted to escalate as sequencing becomes more efficient. The database is updated daily with new sequences from its American counterpart, GenBank, based at the National Center for Biotechnology Information (NCBI) at the NIH in Washington DC, USA, and also with the DNA Database of Japan (DDBJ), held at the Center for Information in Biology in the National Institute of Genetics in Mishima, Japan. Together, the three centres form the International Nucleotide Sequence Database which, as of July 1997, contained over 1 billion bases of sequence information. The Sanger Centre currently contributes over ten per cent of the total number of bases submitted to this database each year.

The ceaseless accumulation of data demands that the EBI continually reassess its existing databases and analysis programs to ensure they can keep up with public demand. Michael Ashburner, Professor of Biology at the University of Cambridge, also works part-time at the EBI as Head of Research to manage projects to develop innovative ways to access and interpret the information flooding the EBI.

The development of new means of diagnosis and treatment of genetic disorders necessarily involves the transfer of modern genetic research to the pharmaceutical and biotechnology industries. Professor Paolo Zanella, the Head of the EBI and its Industrial Programme, is keen to emphasize that the Institute is ensuring that "knowledge flows across the board to meet the bioinformatics needs of both academia and industry". As a result, the EBI has tailored many of its services to meet the special needs of industry, and now has a club of more than 20 companies in its programme.

Information for all – Wellcome Trust policy on sequence release

Sequencing various pathogens and bacteria, let alone the entire human genome, is a daunting task and collaboration is essential if the task is to be completed efficiently. Each year the Trust hosts a meeting for the leaders of the world's larger sequencing teams to discuss the progress made and future strategies. The Director of the Sanger Centre, John Sulston, is adamant that "genetic information is public and not private property". He argues that there is no basis for the commercialization of DNA sequences. However, secrecy is essential for filing patents in Europe – the primary incentive for industry to continue to invest in research and development – and many industrialists argue that gene sequences should be patentable. While the patenting debate rages on, John Sulston maintains that academic researchers should be able to have free access to all sequence information. "It is not the sequence itself which is of real value, but what we can do with it." Restricting access will inevitably slow the pace of medical research.



Modern genetics – how far will it go?

Unravelling the human genome offers new means for diagnosing and treating inherited diseases, as well as many common forms of ill-health. Tantalizingly, it also offers us clues about our individual characteristics; our physical attributes (such as hair and eye colour, height and build) as well as the foundations of our personality, sexuality and intellect are, to some degree, predetermined in our genes. While our upbringing and lifestyle also have profound influences on us as individuals, the potential to manipulate these genetic controls raises many complex ethical and moral issues for society. The Human Genome Project provides only knowledge, but as with all knowledge this can be used to the benefit or detriment of mankind.

The technologies capable of profoundly changing the natural world are firmly in place. Scientists such as John Sulston believe that society must learn to use its new powers wisely: "The information is a challenge to the way we think about ourselves and one another, and therefore our social structures. The exciting prospect is that this knowledge and power will force us to become more responsible, and that means everyone – not just scientists and politicians."

Modern genetics in perspective

ROY PORTER

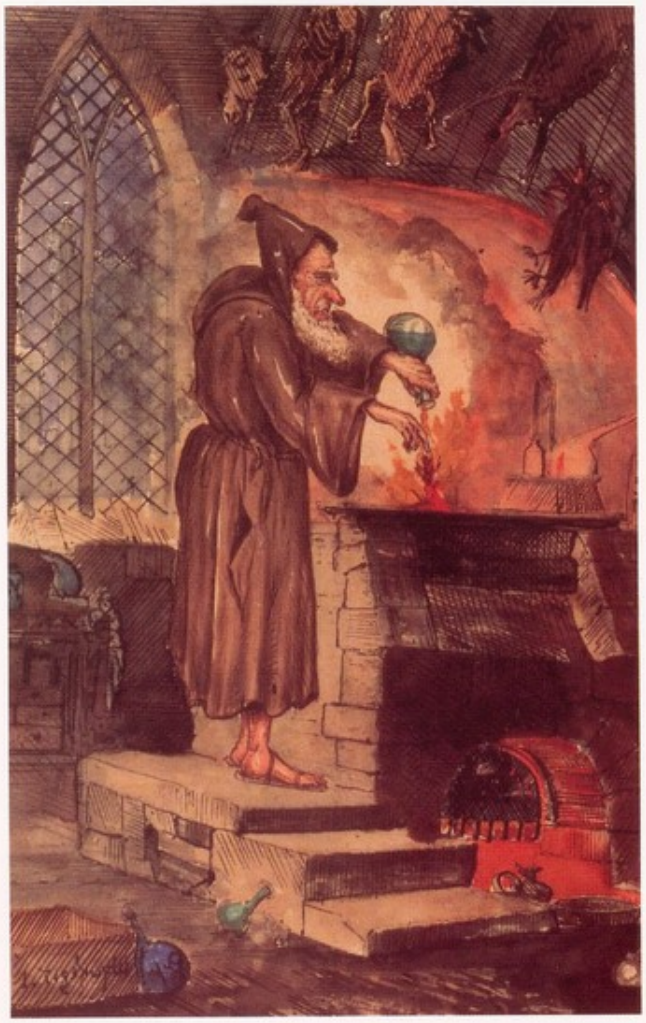
The Human Genome Project, so full of medical promise, is a child of our times – the offspring of dazzling theorizing since World War II about the mechanisms of inheritance, of new scientific disciplines like molecular biology, and of today's international cooperation. But the scientific vision driving the project is ancient, going back to the very roots of the Western biomedical tradition. To understand its full significance, its potential and its pitfalls, we must take a longer historical perspective.

Societies the world over have attributed sickness to evil spirits, sorcery, witchcraft and diabolical or divine intervention, and have appealed to Higher Powers for relief. Such ways of thinking, still common in Africa, South America and the Pacific, remained influential in Christendom until the 'age of reason'. Nevertheless, in Europe from Graeco–Roman Antiquity onwards, supernatural beliefs about sickness and health were challenged by naturalistic medical theories: disease was read as a natural event that emerged from the order of things. The body became interpreted in the Classical tradition of philosophical medicine as part and parcel of a comprehensive order of regular law-governed processes. Here lie the assumptions underpinning medical inquiry as we understand it today.

Greek philosophers sought answers to the basic questions through a quest for the ultimate 'stuff' of nature. Discovering this would be the key not just to the

RIGHT: Evil spirits: demons and blood letting are now largely confined to the pages of historical medical texts (c.1830).

OPPOSITE: Man and modern genetics, Bill Sanderson (1990).

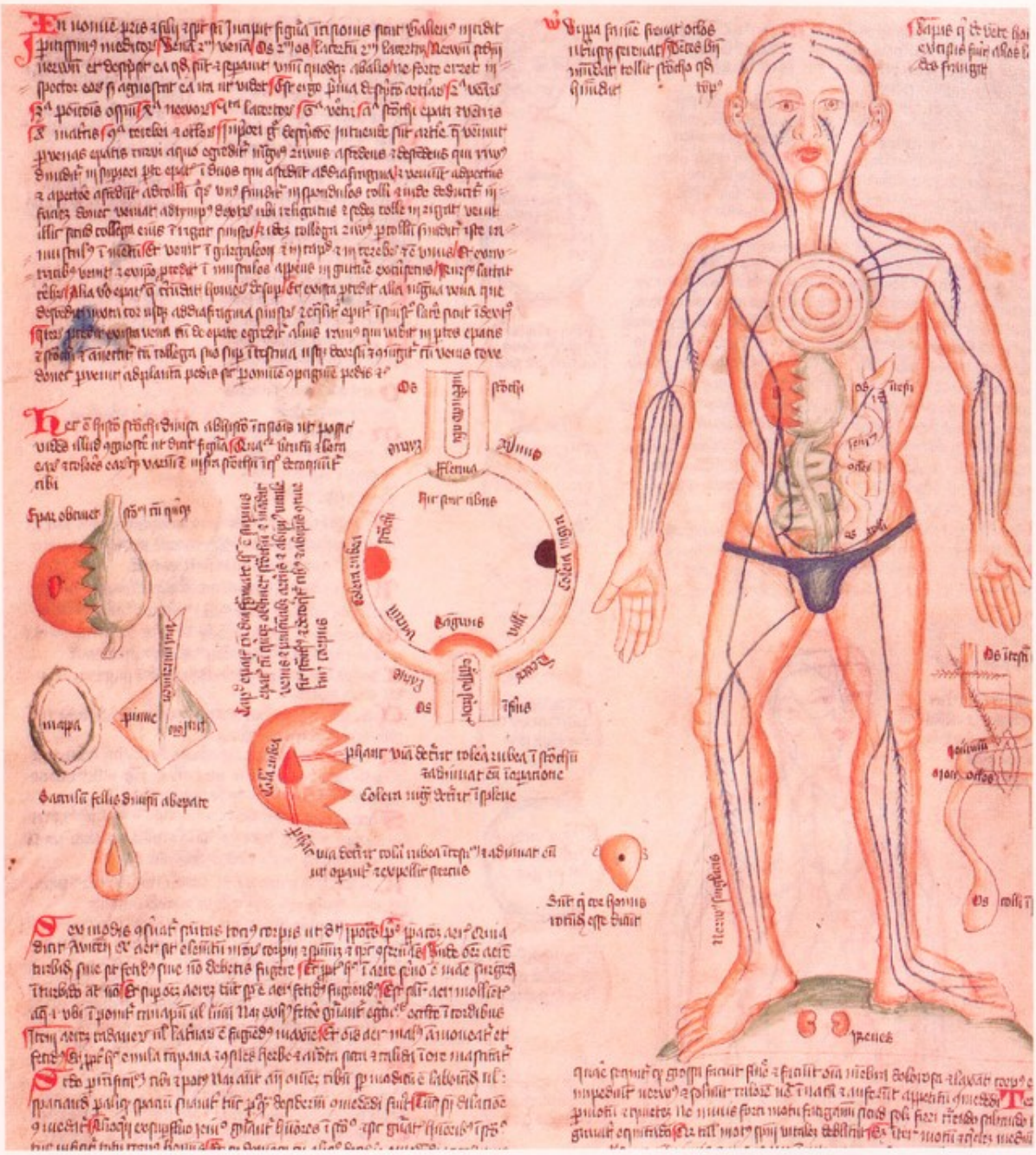


ABOVE LEFT: The magic of medicine: a caricature of the alchemist at work.

ABOVE RIGHT: Appeasing the devils that cause disease. Woodcuts by T Norris (1722).

RIGHT: Hippocrates, the Greek 'Father of Physic.' Line engraving by P Pontius (1638).

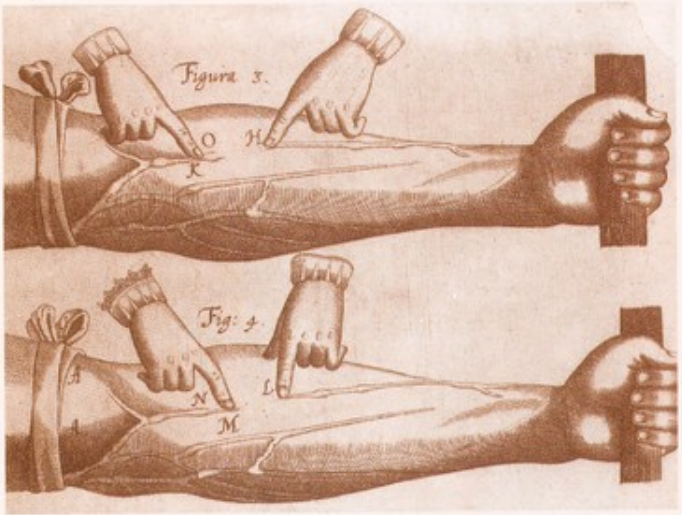
riddle of the universe but to the question of how to lead one's life, including how to attain personal health, something Greek thinkers held dear. The earliest philosophers disputed whether a single element like fire, air, earth or water could be the prime reality. Subtler answers followed: for Pythagoras the key lay in geometry and harmony; for Heraclitus the only true constant was



LEFT: For centuries ill-health was explained by an imbalance in the four humours shown here in the *Apocalypsis S Johannis* (c.1420).

change itself; for Democritus everything was a flux of atoms in a void – an idea destined to have a great future.

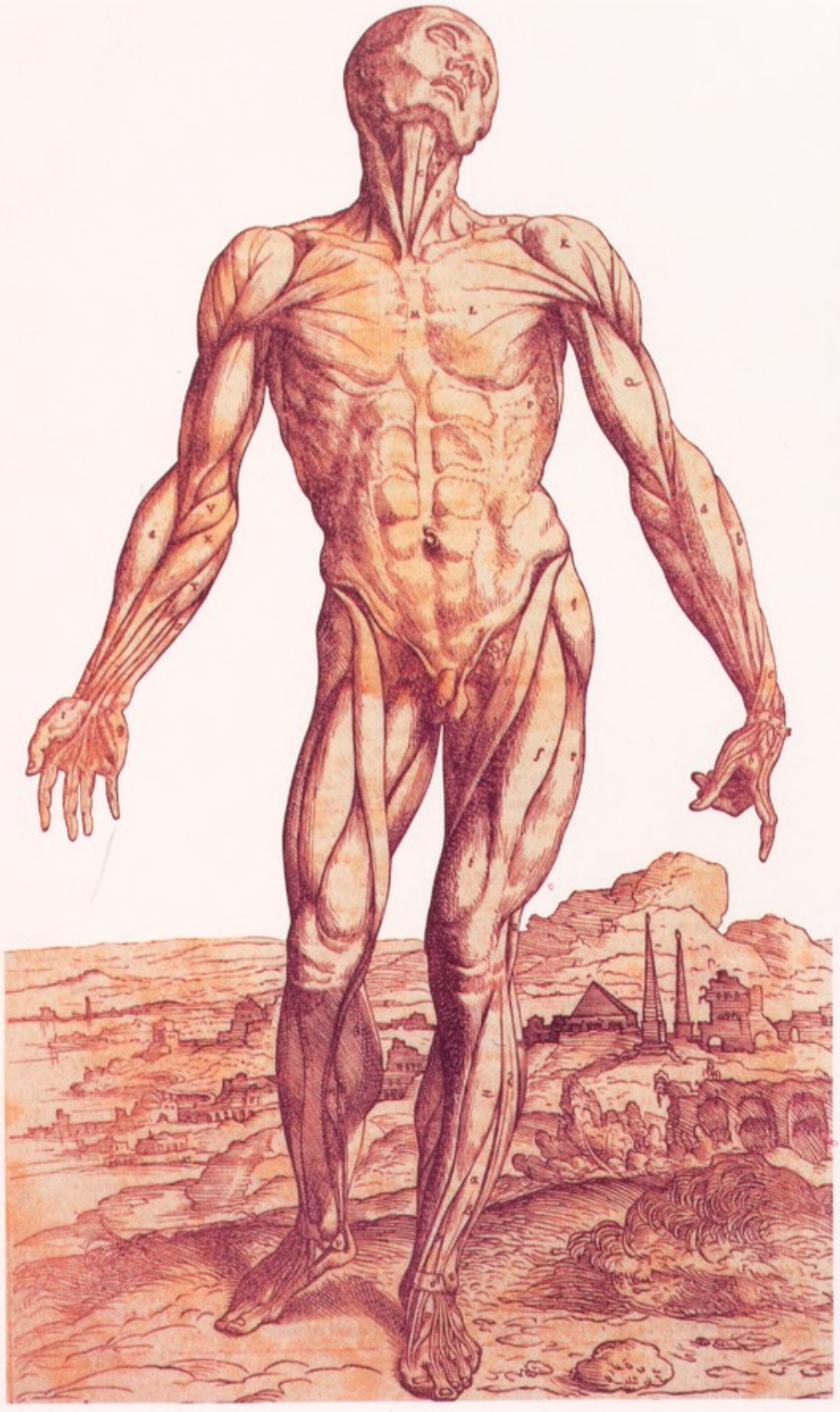
But how were the secrets of the human body and its workings to be unveiled? After all, the Greeks had no stethoscopes, let alone X-rays and scanners. Moreover, the very respect for life which led them to prize health made it taboo for most Greeks to contemplate dissecting human bodies – an act of defilement. Hence the laws of health and disease had to be deduced by imagining the body's inner constitution as a microcosm of the economy of external nature. The four elements of external nature (fire, water, air and earth) found their epitome in the four humours (blood, phlegm, choler and black bile), whose balance determined health, whose upset led to sickness.



The doctrine of the humours or body fluids thus gave medicine its first naturalistic basis. Further speculations about physiology and pathology were elaborated, and for nearly 2000 years medicine spoke the language of the humours, supplemented by what gross anatomy Graeco–Roman physicians like Galen could pick up from dissecting pigs and examining human wounds.

From early Renaissance, the growing practice of human anatomy led, however, to a shift in medical notions as to where biological truth would be found. The landmark was the *De humani corporis fabrica* (1543) by the Paduan professor, Andreas Vesalius, a momentous anatomical atlas that challenged teachings sanctified since Galen. The practice of dissection inexorably created the expectation, over the following centuries, that fresh discoveries were to be made by cutting open the body; the road to a full understanding of disease and its cure lay in systematic research into the fabric of the body.

What such investigations uncovered often contradicted traditional medicine – William Harvey's *De motu cordis* (1628), with its experiments demonstrating the circulation of the blood, affirmed that truth lay not in the books of Galen but in bodies themselves. Thanks to such investigations, the old humoral model dissolved away and new realities appeared posing fresh interpretative problems – the lymphatic system, the lacteals, the ductless glands and the mechanisms of the nervous system. Experiments revealed the functions of the heart, the lungs and the liver. Scientists became convinced that medical progress depended on probing ever more deeply into the flesh itself. How precisely this could best be done was disputed – as, indeed, were the findings – but the principle won general assent. Western medical science thereafter was involved in a hunt to discover the ultimate stuff of the body. Many believe the Human Genome Project will bring that quest to a successful conclusion.



ABOVE AND LEFT: Andreas Vesalius was among the first to explore the body systematically by dissection (c.1543).

OPPOSITE TOP: A woodcut of Galen.

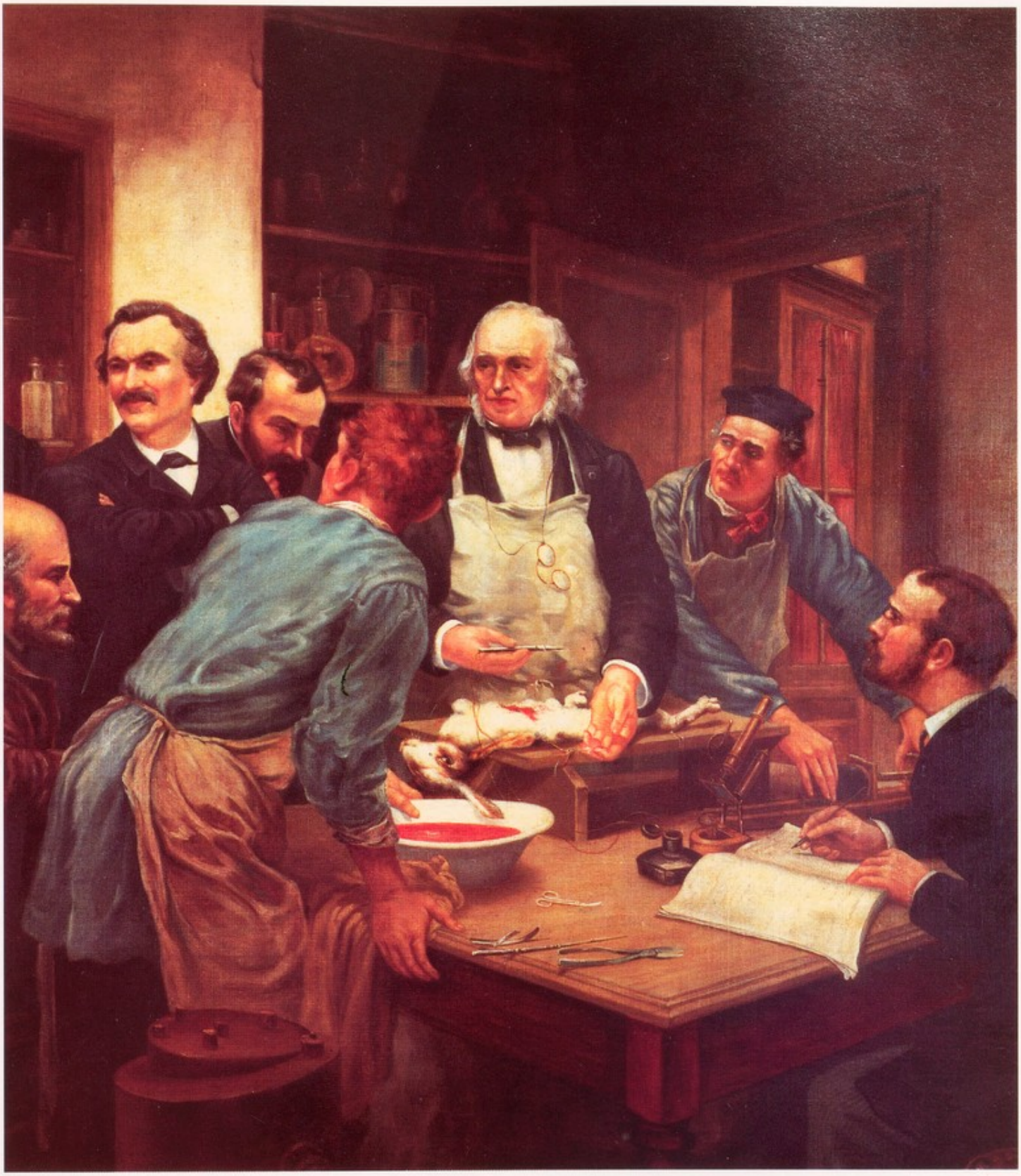
OPPOSITE BELOW: William Harvey's theories on the circulation of the blood.

At the beginning of the nineteenth century French hospital medicine created a new tool for understanding the body: the anatomico-pathological gaze. Instead of symptoms or organs, Bichat's *Treatise on Membranes* (1799) gave tissues pride of place, viewing them as basic building blocks and as prime pathological sites. Bichat told fellow doctors how to proceed: "You may take notes for twenty years from morning to night at the bedside of the sick and all will be to you only a confusion of symptoms," he drily observed; "but start cutting bodies open and this obscurity will soon disappear".

ABOVE: Fit for a king – William Harvey demonstrating the beating of a deer's heart to King Charles I. Engraving by H Lemon (1851) after oil painting by R Hannah (1848).

LEFT: Marie François Bichat.

OPPOSITE: Claude Bernard, one of the fore-fathers of experimental medicine, Leon L'Homite (1889).



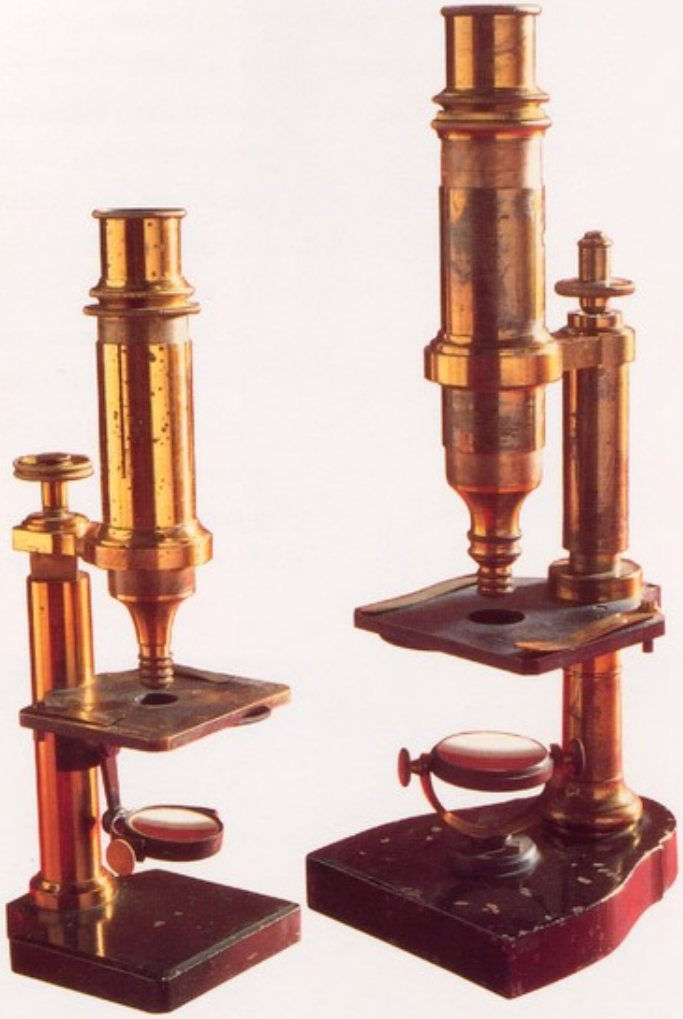
RIGHT: René Laennec treating a patient with TB, T Chartran (1816).

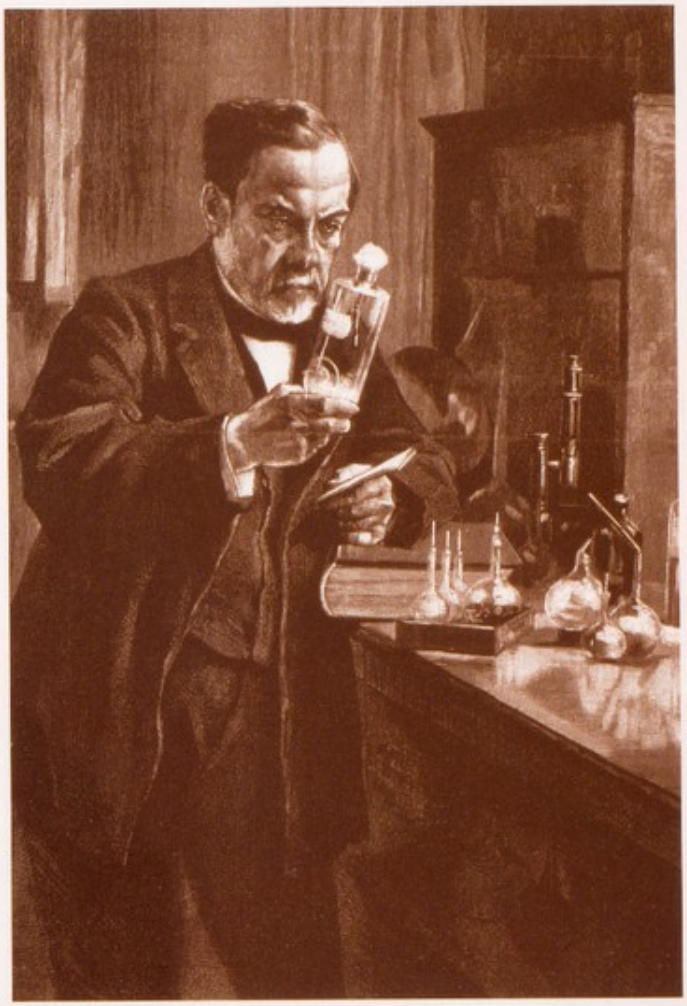
OPPOSITE LEFT: An early form of the stethoscope. *Science Museum*

OPPOSITE RIGHT: Anatomists were not always treated with respect. In this caricature, a young woman tries to warn an aged anatomist that his subject is still alive, T Rowlandson (1811).

Many took up Bichat's challenge to 'look and see'. René Laennec devised the stethoscope in 1816, the chief tool of this new medicine of objective signs until the discovery of X-rays a century ago. At last, the living body was no longer sealed up, a closed book: pathology could now be done on the living as well as the dead. The new French hospital medicine established the lesions of 'clinical material' in hospitals by the thousand before cutting up corpses in the morgue.

A few decades later another Frenchman, Claude Bernard, taught that this new window on the body was not enough. Hospital medicine had two drawbacks: being an observational science, it was essentially passive, like natural history; furthermore, the sickbed involved too many imponderables to permit precise scientific understanding. Scientific progress demanded active experimentation in a strictly controlled laboratory environment. Vesalian anatomy had highlighted organs, Bichat the tissues; nineteenth-century physiology was to discover the cell. With the aid of microscopes, investigators created cytology. Cells also explained diseases like cancer. Diseases, stated Rudolf Virchow in his *Cell Pathology* (1858), came from abnormal changes within cells, and in turn abnormal cells multiplied through division – diseases were thus the result of disturbances in cellular structures. Comparable developments in organic chemistry were meanwhile leading to a better understanding of respiration, nutrition, the digestive system and deficiency diseases, and pointing to new specialities such as endocrinology.





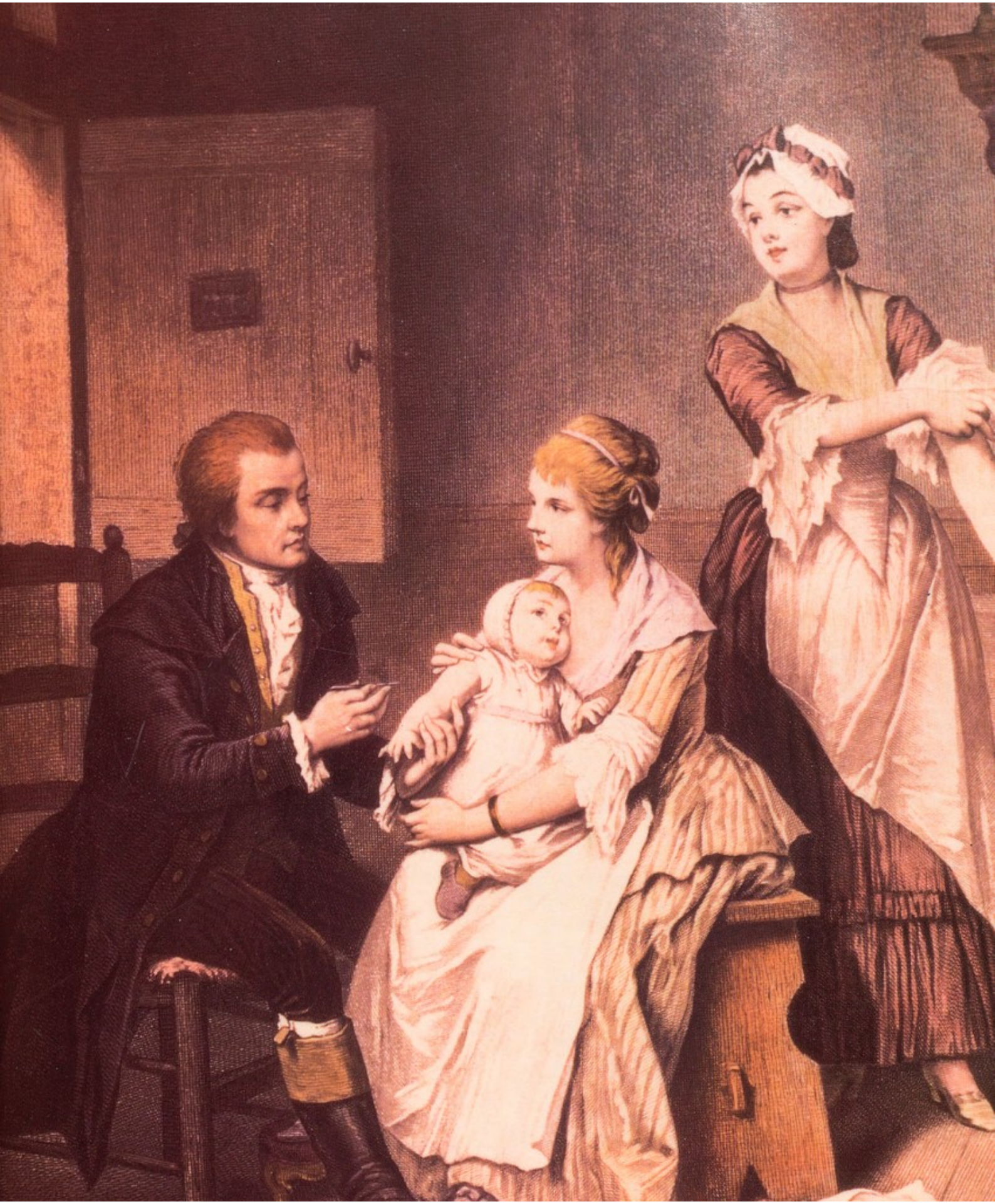
Investigations in search of the essence of organized bodies posed again and again the fundamental question: what is life? The great Louis Pasteur upheld the irreducible difference between the vital and the merely material. This conviction helped give rise to bacteriology – the idea that diseases are caused by living microorganisms, and can be countered by them through live vaccines and antibiotics. A mainly German tradition argued, on the contrary, that it was science's job to reduce the phenomena of life to their basic chemical and physical components. Physiology's task, pronounced Pasteur's contemporary, Karl Ludwig, was that of "determining the functions of the animal body and of deriving them consequentially from its elementary conditions". With such reductionist ends in mind, and with new technological

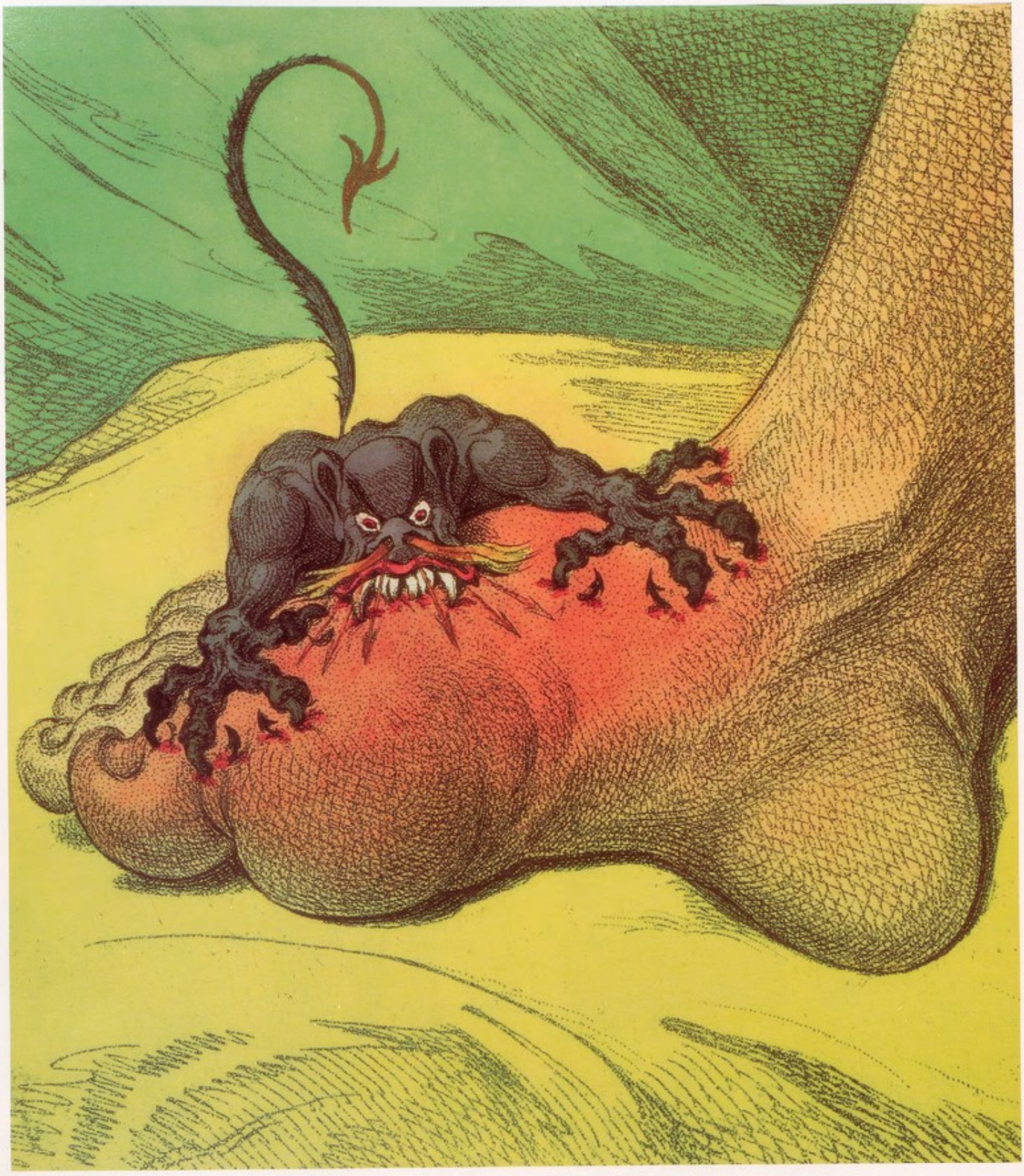
ABOVE LEFT: The microscopes used by Pasteur and Lister. *Science Museum*

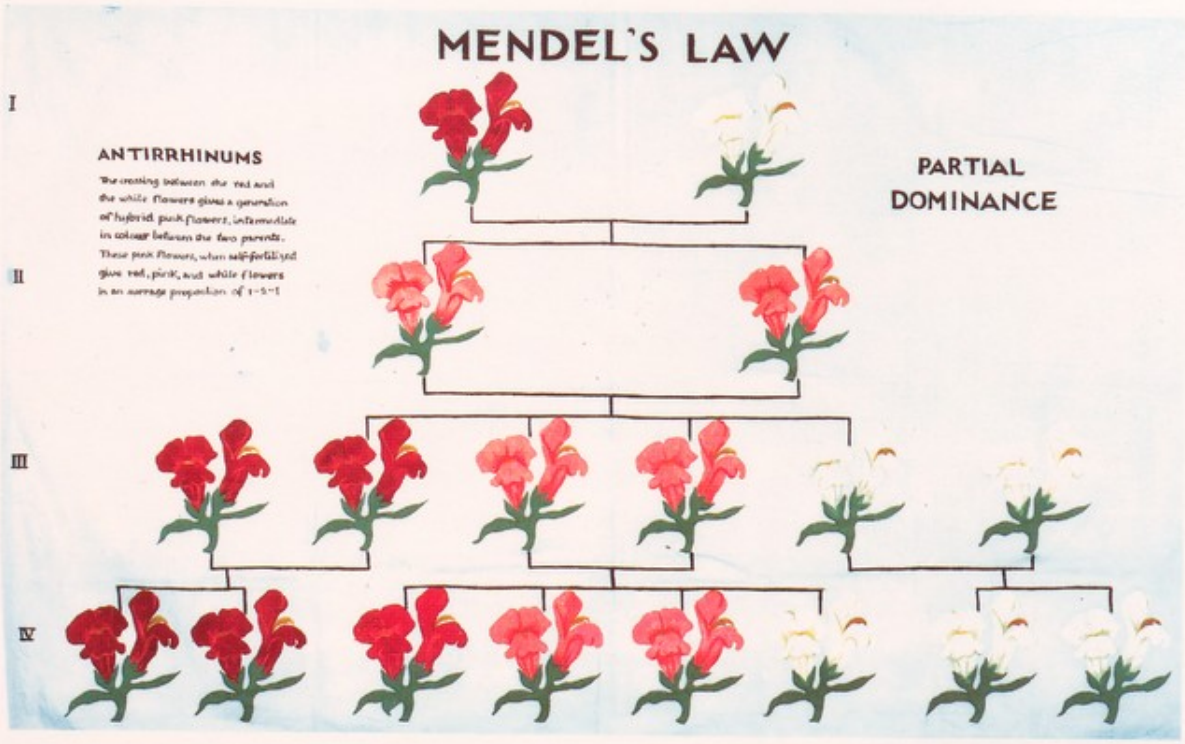
ABOVE RIGHT: Louis Pasteur, the father of bacteriology. Wood engraving by C Baude (1885).

LEFT: Karl Ludwig. Lithograph by R Hoffmann (1856).

OPPOSITE: Edward Jenner vaccinating a child, E Hamman (late nineteenth century).







OPPOSITE: Coloured etching entitled 'The Gout' by James Gillray (1799).

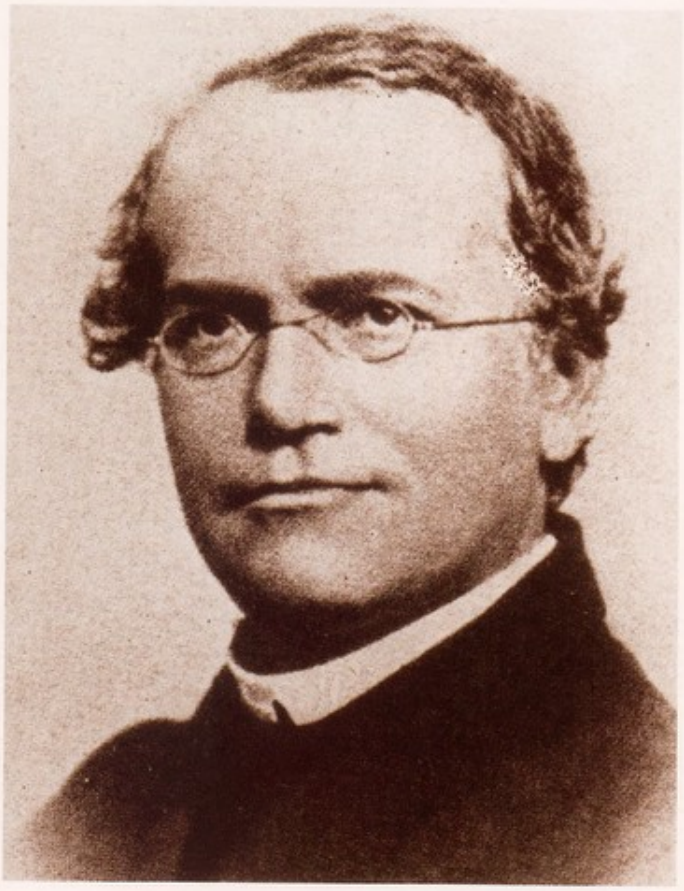
LEFT: An embroidery produced by the Eugenics Society explains Mendel's hybridization experiments.

BELOW: Gregor Mendel who laid the foundations for modern genetics.

aids (ever more powerful microscopes and sophisticated chemical analysis) and the controlled experimentation that laboratories offered, small wonder that the twentieth century gave rise to genetics and molecular biology.

Though genetics is a latecomer amongst the sciences, it draws upon ancient ideas, especially the notion that 'like begets like'. Experience suggested that some diseases ran in families, for instance gout. Such clinical facts might be well known, but what were the mechanisms? What were the laws of reproductive biology?

Modern genetic theory stems from the hybridization experiments conducted by the monk Gregor Mendel with the common garden pea at his Augustinian monastery in Brno in Bohemia. Though he reported his results in 1865, little attention was paid to them at first. By the 1890s, however, numerous investigators were pursuing similar heredity experiments of their own. In Cambridge, William Bateson (1861–1926), an ardent evolutionist, was unable to reconcile his belief in the discontinuous nature of hereditary variation with Charles Darwin's own model of evolution through



continuous variation, spending years in doubt before reading of Mendel's experiments where he found the mechanism for discontinuous variation.

But while the workings of heredity remained obscure and controversial, bedside medicine continued to accumulate evidence of inherited disease. In 1897, Archibald Garrod became fascinated by alkaptonuria, a disorder which turns the urine dark and often leads to severe arthritis. The popular view was that it was due to a bacillus – such ideas were all the rage – but Garrod concluded it arose out of an 'error of metabolism' which was congenital. He noted that in four families in which unaffected parents had produced alkaptonuric offspring, three of the parental pairs were first cousins. From this he deduced that the pathology must be discontinuous, all-or-none, affected or normal. He hypothesized that other disorders like albinism might share the same hereditary origin.

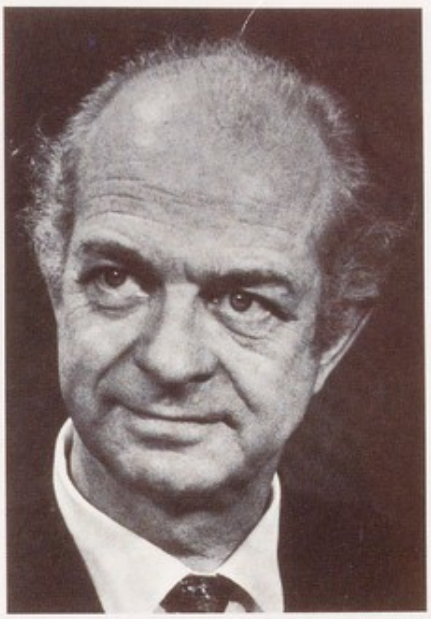
Garrod's incorporation of biochemistry and Mendelian laws into the study of diseases was farsighted, but his theories went largely unnoticed. Further confirmation that many human diseases had a hereditary basis did not come until mid-century. Two disorders paved the way to this acceptance: sickle-cell anaemia and Down's syndrome.

Sickle-cell anaemia was first reported in 1910 by the Chicago physician, J B Herrick, and the first scientific investigation of 'sickling' was reported seven years later by another American, V E Emmel. Reporting the case of a black woman with severe anaemia and leg ulcers, Emmel found some of the red cells from the patient's father (who was not anaemic) underwent sickling in cell culture conditions. Emmel himself did not point to a possible hereditary component – that came in the 1920s from J G Huck, who explored the family pedigrees in sickle-cell cases.

RIGHT: Archibald Edward Garrod (1857–1936).

LEFT: An albino negress. An engraving by Schmitz after de Saeve. Garrod suspected that there could be a hereditary basis to albinism.

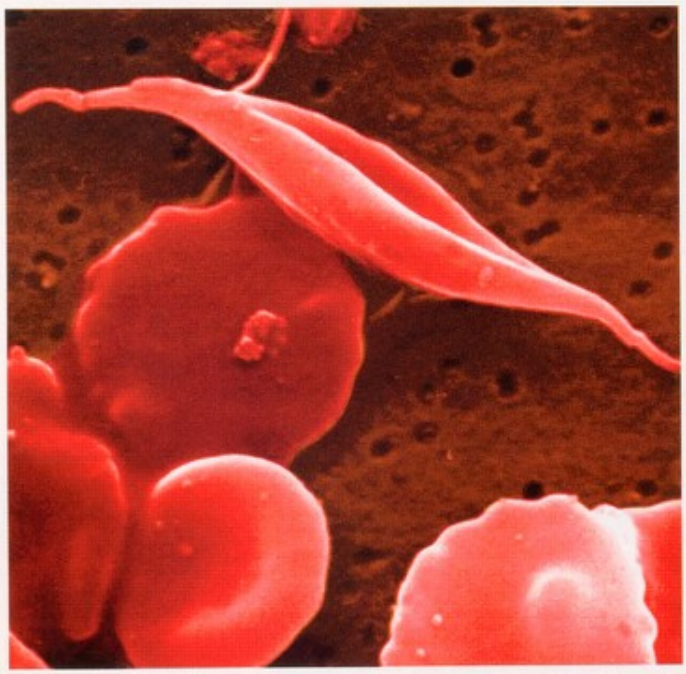
RIGHT: Nobel Prize-winning chemist Linus Pauling identified the underlying defect in sickle-cell anaemia. *Mary Evans Picture Library*



OPPOSITE: A computer-generated model of haemoglobin. The ribbon-like globin molecules (blue) can be seen distinct from the four haem groups (pink). *SPL*

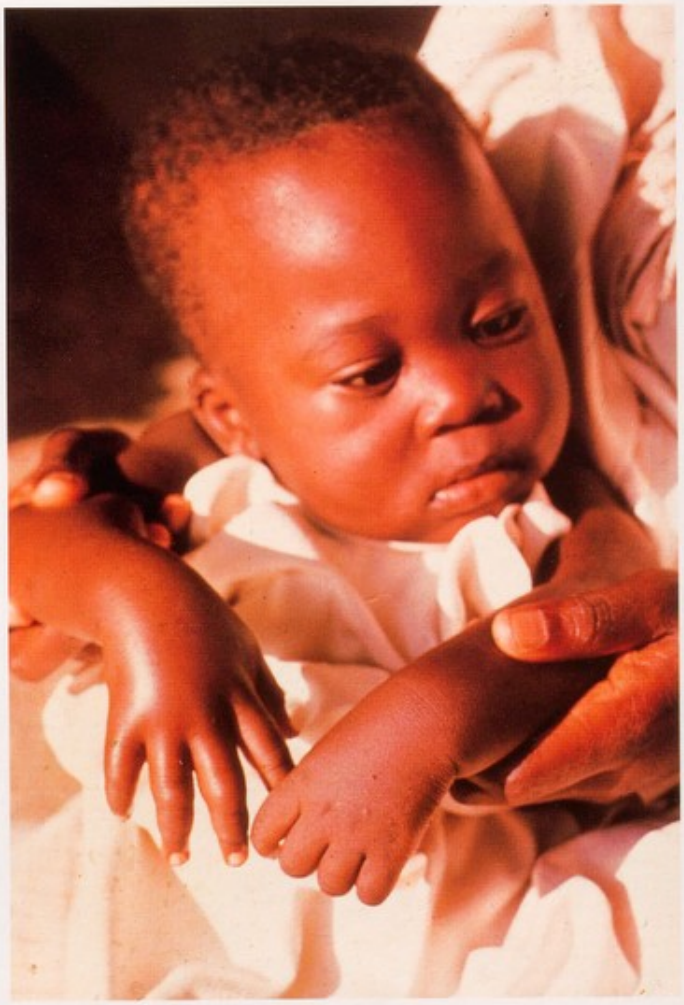
Once sickle-cell anaemia had been accepted as a hereditary disease, the nature of its cellular abnormalities was investigated. The Nobel Prize-winning chemist Linus Pauling showed in 1949 that the haemoglobin molecules in individuals with sickle-cell anaemia were fundamentally different from normal ones. The abnormality would be found, he predicted, in the globin part of the molecule and not in the haem groups; investigations proved him correct.

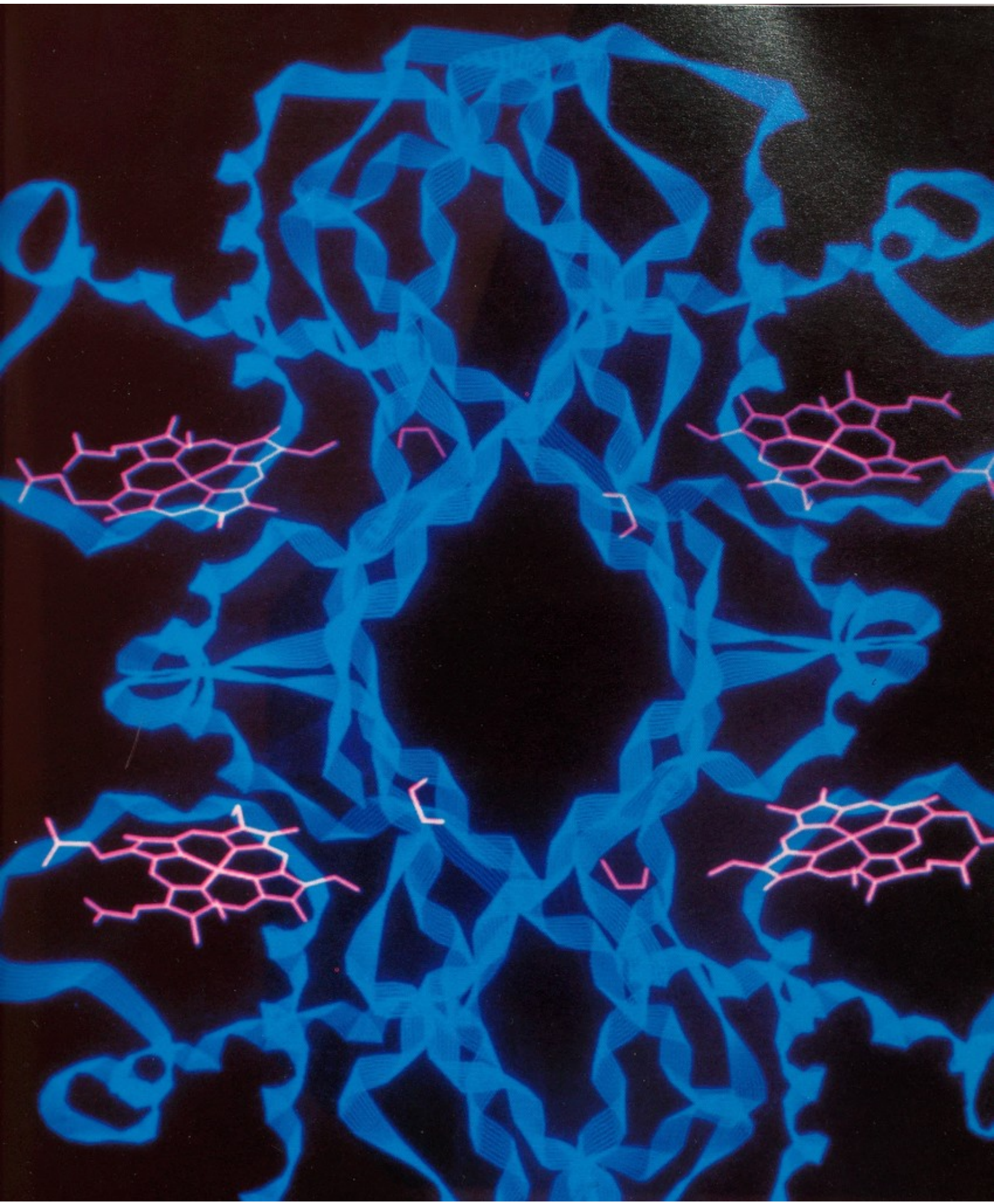
Soon after, an old medical puzzle was finally solved. A condition called 'furfuraceous idiocy' had been described back in 1846 by the French physician, Eduard Séguin. Its traits included unusual facial features, slow and incomplete growth and mental retardation. In 1867 J Langdon Down suggested these abnormalities might be a kind of throwback to the



ABOVE: Sickling of red blood cells. *Professor Revell*

RIGHT: Sickle-cell anaemia is a common blood disorder among Afro-Caribbeans. *P D Marsden, Wellcome Trust Tropical Medicine Resource*





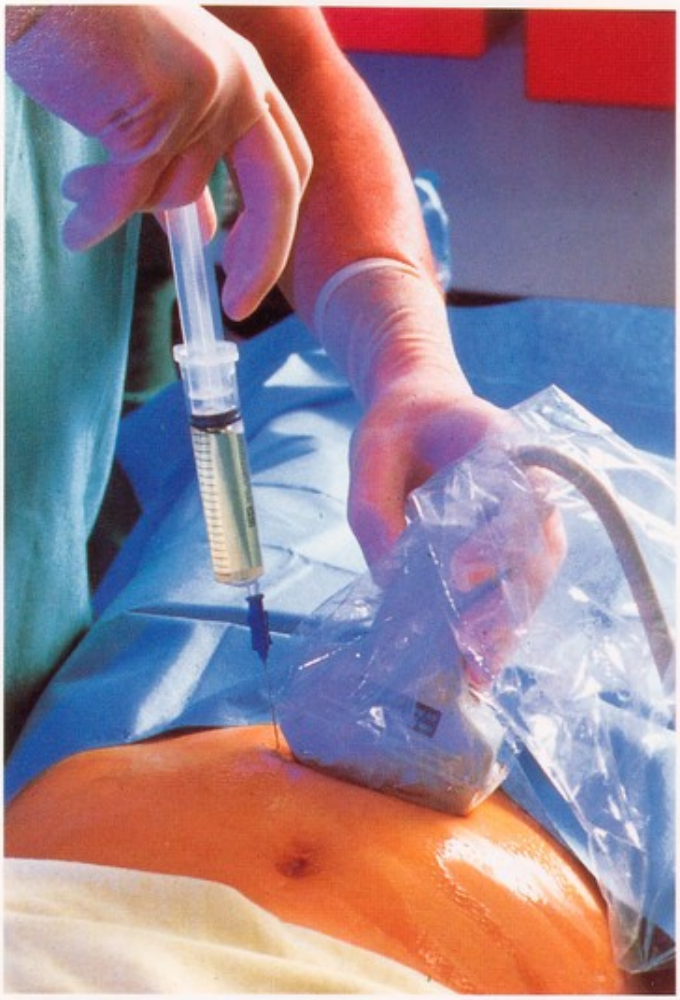
RIGHT: A family with two children with Down's syndrome (1930). *Eugenics Society*

BELOW: J Langdon Down who gave the syndrome its name.

OPPOSITE: Children with Down's syndrome – then called Mongoloids – in a children's home (c.1930). *Eugenics Society*

Mongol racial type, though his term 'Mongoloid' was eventually to yield to 'Down's syndrome'. For nearly a century, however, studies failed to produce a viable aetiological hypothesis. Then in the 1950s improvements in cell-examining techniques provided the solution. In 1959 three French cytologists announced that Down's syndrome children had an extra chromosome (chromosome 21).

Meantime a still more fundamental breakthrough had been achieved, concerning the nature of the genetic material itself. The Swiss biochemist Friedrich Miescher had discovered back in 1869 that the same substance occurred in the nucleus of every living tissue cell: this became called 'nucleic acid'. By the 1920s, two distinct forms of nucleic acid had been identified: DNA and RNA (ribonucleic acid).



ABOVE LEFT: Amniocentesis offers a route to screen for many inherited diseases. *SPL*

ABOVE RIGHT: The Eugenics Society promoted careful breeding to eliminate inherited disorders. *Eugenics Society*

It was believed that the DNA structure was simple and repetitive, and thus could not transmit information. Since chromosomes contained protein as well as DNA, scientists assumed that it was the protein in them that was the transmitter of inheritance, with the DNA simply holding the protein together. In one of the most spectacular episodes in modern science, however, that view was overturned. In 1953 Francis Crick and James Watson elucidated the double helical structure of DNA; it thereby became accepted that a complicated code could after all be contained in DNA.

This opened up a challenging new research field for genetics. Further advances occurred in the 1980s when it became possible chemically to read the genetic code in DNA and to isolate genes and clone (duplicate) them. These and similar developments had practical pay-offs. Thanks to biopsies and amniocentesis, clinicians were developing the capacity to screen unborn babies for genetic diseases. An increasing number of inherited and other congenital disorders became diagnosable before birth. Moreover, diseases and conditions caused by the absence of a specific gene product or a defective one could now – at least in principle – be treated by isolating the gene that encodes the protein and using it to produce large quantities of the desired protein.

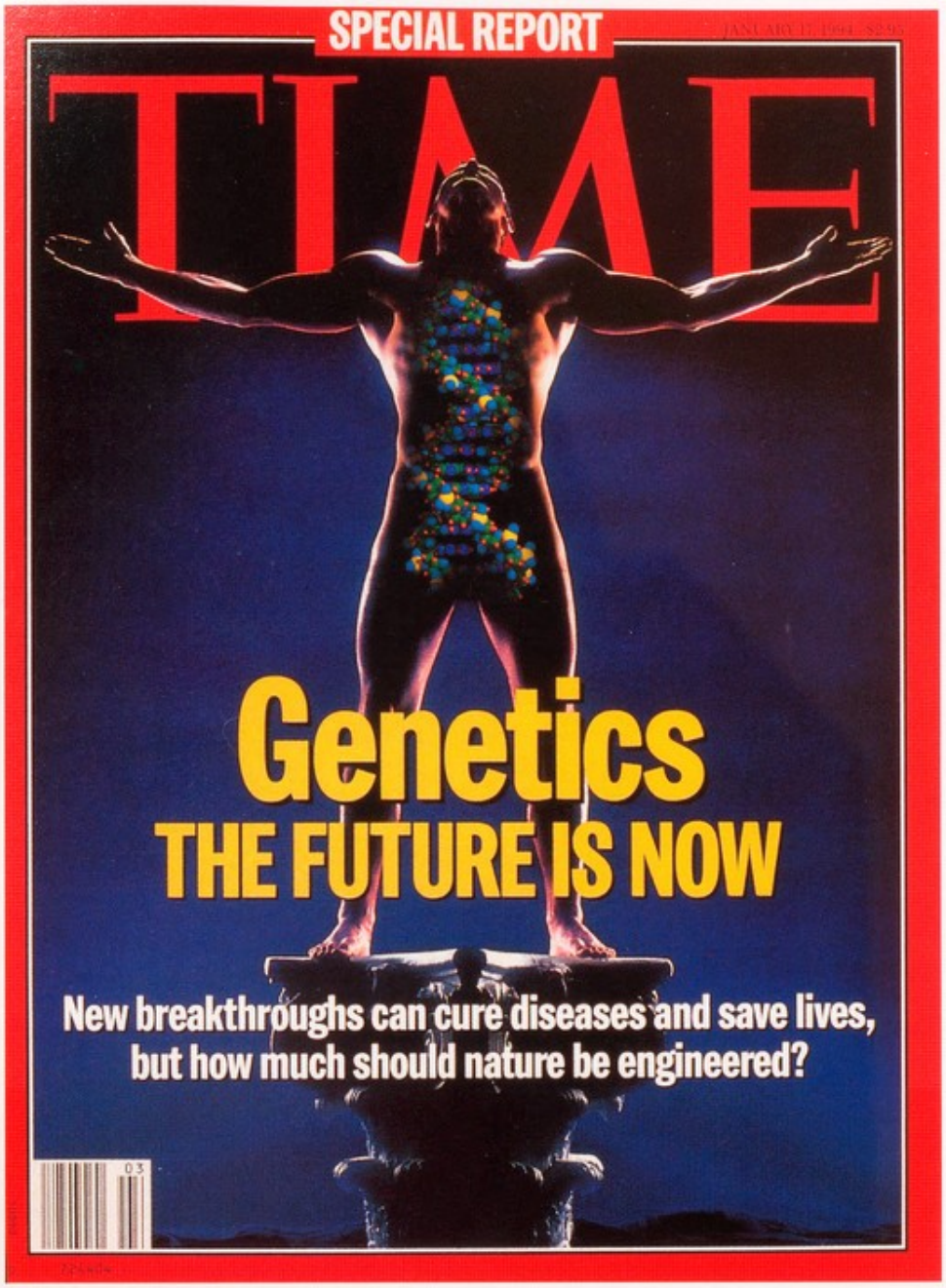
All this provides the backdrop to the launching in the mid-1980s of the international Human Genome Project, designed to sequence all human genes. James Watson, who became the chief spokesman for the enterprise, saw it in terms of a by now familiar project: it was "the ultimate tool for understanding ourselves at the molecular level". The locus of life had thus moved from humours to organs, to tissues, to cells, and finally to molecules.

The Project became the driving force for the promotion of large-scale genetic testing for inherited traits, with a view to gene transplantation as a means of overcoming inherited diseases. By the early 1990s researchers had labelled and decoded some 2000 genes, and identified a fair number of genes responsible for specific diseases, including Duchenne muscular dystrophy, cystic fibrosis, some cancers, inherited high blood cholesterol levels and inherited forms of Alzheimer's disease. In Bichat's time, 200 years ago, ever more was known about diseases which doctors could not cure. Now we are acquiring the ability to manipulate our own genes, the stuff of life itself.

In science, progress creates problems. The historical perspective on the rise of modern genetics offered here highlights three key problem areas. One centres on expectations. At least in the public mind, the point of the Genome Project is to prevent or cure diseases. But throughout medicine's development advances in knowledge have rarely led directly or rapidly to breakthroughs in health. Vesalius's discoveries cured no diseases. William Harvey's medical practice supposedly declined after his discovery of the circulation of the blood. Indeed, Thomas Jefferson, the third President of the USA, could reflect in 1806: "Harvey's discovery of the circulation of the blood was a beautiful addition to our knowledge of the animal economy, but on a review of the practice of medicine before and since that epoch, I do not see any great amelioration which has been derived from that discovery". The history of medicine teaches that the relations between scientific research and therapeutic benefit are not of the penny-in-the-slot kind.

This points to a second problem. A succession of visions have held the field as to the truth about disease: the anatomical, the physiological, the biochemical, the bacteriological – even the psychoanalytical. Now we have the genetic. Each time the temptation has been to declare – at least to the press, the paysters and the public: here lies the masterkey! The secrets of medicine are unlocked! History, however, shows the hubris in this. Illness has a multiplicity of causes and comes in many shapes. We may probably discover that many more diseases than once suspected turn out to have a genetic component. But disease is no more 'all in the genes' than it is 'all in the germs' – or for that matter 'all in the mind'. Scientific reductionism is a powerful tool but it can induce myopia. In understanding sickness and health we must continue to try to see the whole picture.

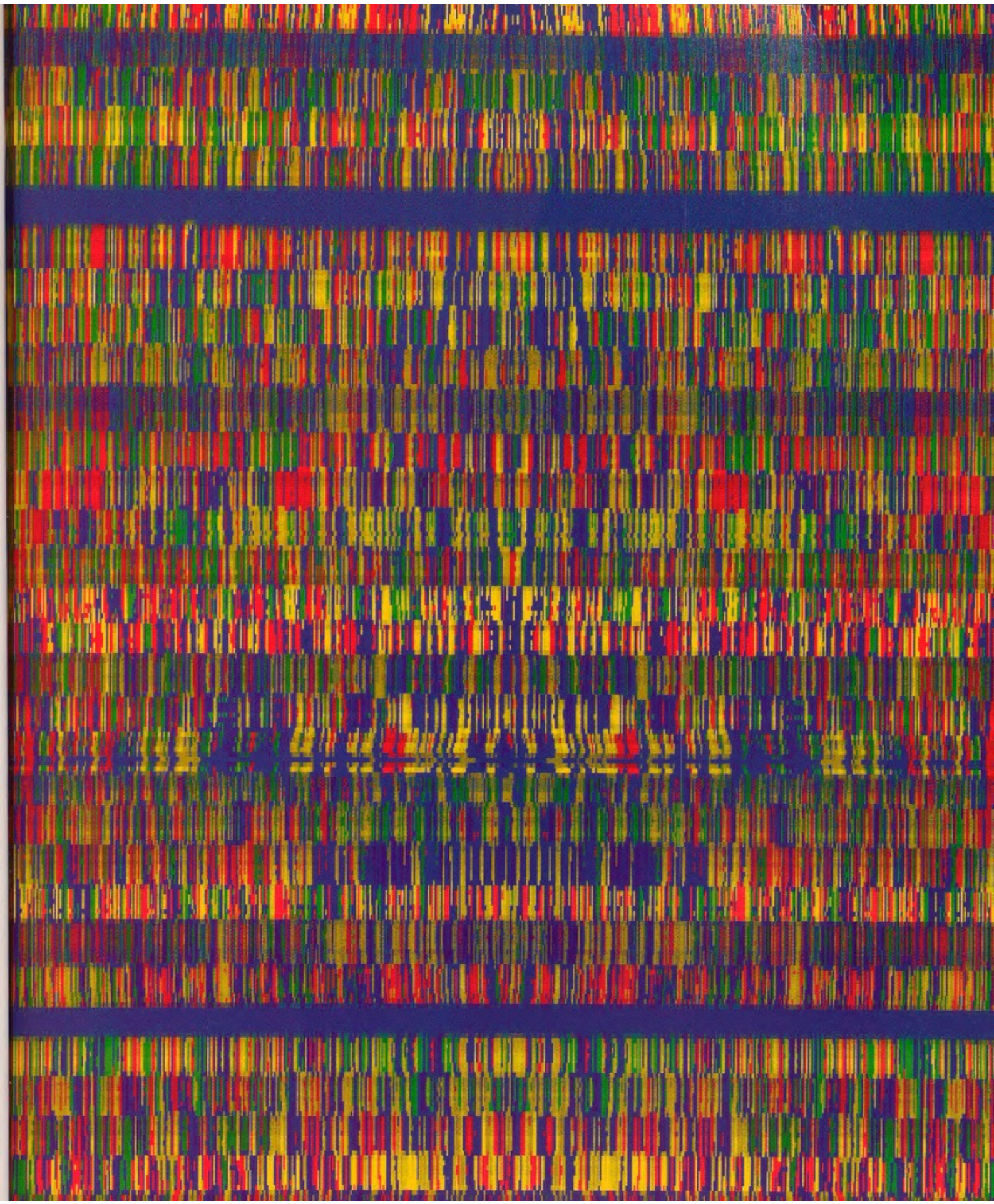
The third problem brings us back to the issue of knowledge and power. Western society believes in action, it embraces a 'can-do, will-do' mentality. This technological imperative has particular hazards with genetics, because of the boundless scope for genetic manipulation. Whether we like it or not, the knowledge derived from modern genetic research will force us and our successors to make decisions about the kinds of lives that are worth living. For the first time ever, it will be in our power, in theory at least, to determine the genetic make-up of future generations. We cannot turn our backs on these choices; our humanity and wisdom must match our technical skills. The Eugenic movement of earlier this century reminds us of the inherent dangers. Francis Galton, Darwin's cousin, promoted a science he called 'eugenism' which taught that progress lay in selective breeding. Nature counted for more than nurture, Eugenists maintained, and social evils were the results, not the causes, of biomedical defects. Such views were arguably taken to their logical consequence in the eugenic policies of the Nazis, which resulted not only in the extermination of six million Jews but in the sterilization or elimination of hundreds of thousands of schizophrenics, mental defectives and others



LEFT: The tantalizing promises of the new genetics are being realized today. But concerns over the consequences of some of its applications are also being raised. Time Magazine, *front cover, 17 January 1994*

whose genetic make-up meant that their lives were judged by medical experts as 'not worth living'.

So long as we heed these lessons, the prospects are hopeful and even immeasurable. We already have a sound grasp of the genetic basis of terrible disorders like muscular dystrophy, Tay–Sachs disease, Huntington's chorea and cystic fibrosis. There is every likelihood that other crippling and fatal conditions, perhaps even some cancers, will turn out to be genetically programmed. As in every other department of medicine, understanding is sure to lead to therapeutic action. Medicine has relieved mankind of many scourges; helped by the Genome Project, the twenty-first century seems set fair to be the age when the burden of genetic disorders is finally lifted.



A Quest for the Code of Life

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