
150 Years of UK Medical School Achievements
improving lives

MEDICAL SCHOOLS COUNCIL

The **Medical Schools Council** is the representative body for the UK's 32 medical schools. It works to ensure that the UK – and indeed the world – benefits from the contributions of the hugely talented teams of doctors, student doctors and colleagues who are working in medical schools to improve patients' lives.

To that end, we present here a selective overview of the impact – nationally and internationally – of individuals and teams who have worked in the UK's medical schools, universities and hospitals over the past 150 years.

Their efforts have not only transformed the quality and quantity of our lives, but have immeasurably changed society for the better.

Katie Petty-Saphon
Executive Director, Medical Schools Council
October 2008

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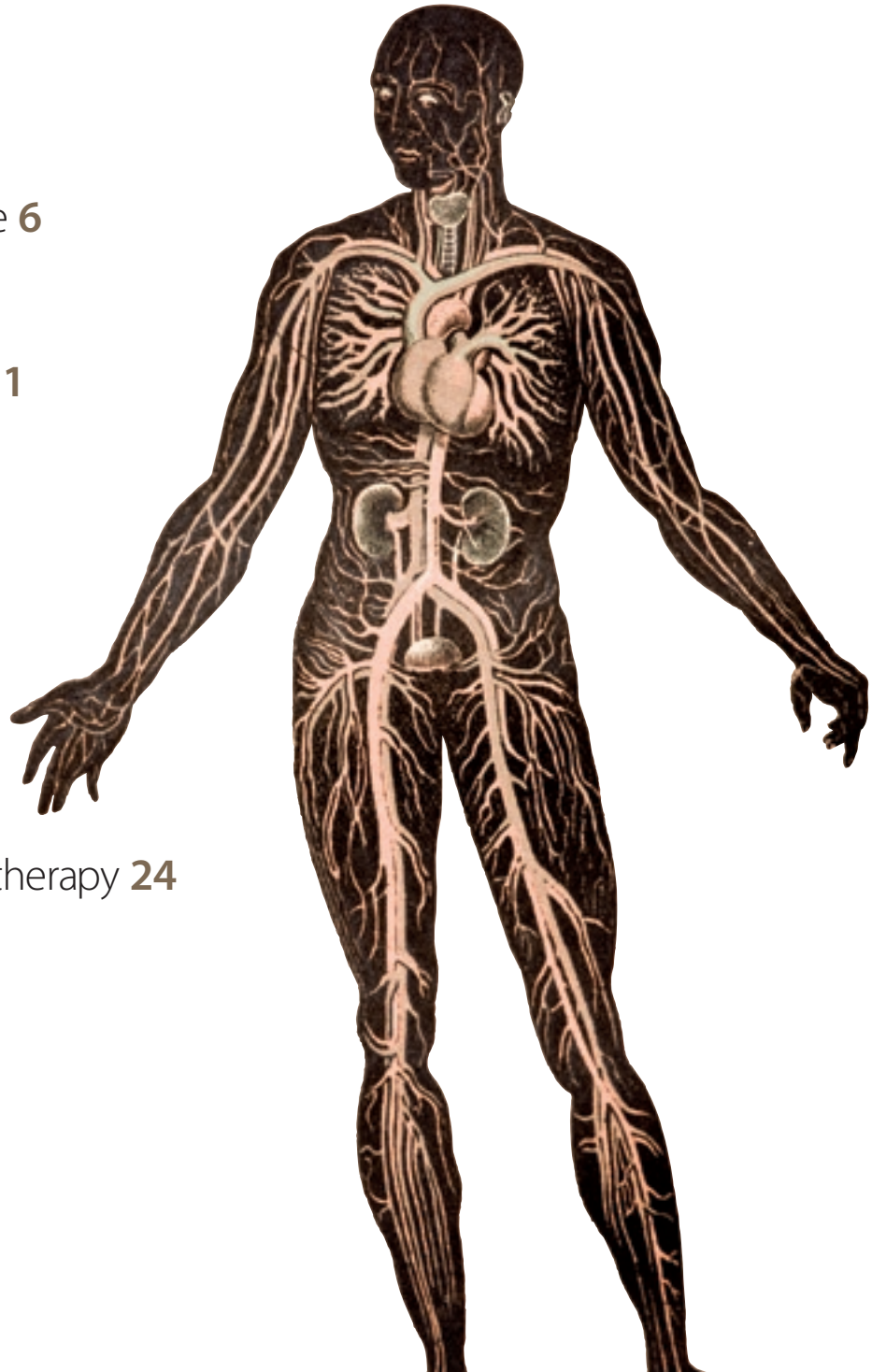


The modern era of UK medical schools began in the mid-19th century.

150 years of innovation

INTRODUCTION

It is difficult to be certain which medical school can lay claim to being the UK's oldest – although Oxford has the first record of a medical graduate in 1312. St Andrews University's Foundation Charter issued in 1412 lists the subjects to be taught as 'divine human law, medicine and the liberal arts' and Aberdeen appointed the UK's first medical professor in 1497 – indeed, Scotland was an early focus of medical education. Cambridge was teaching medicine by the 16th century (albeit with a maximum of four students) but medical schools did not truly blossom until the Victorian era when schools were established in Belfast, Birmingham, Bristol, Leeds, Liverpool, London, Manchester, Newcastle, Sheffield and Wales.

Thus the modern era of the medical school can be dated to the mid-19th century. It was not until a century later, when the Todd Report led to a wave of new schools in the 1970s, that their numbers increased significantly. With further expansion in the 1990s and early 21st century, the UK now has 32 medical schools as well as three partner schools in Derby, Durham and Lancaster.

The Victorian boom owes much to the professionalisation of medicine during the 19th century. By setting up its own education systems, codes of conduct and forms of governance, medicine established its authority as the trusted agency for protecting health and curing disease – a counterpart to the assorted quacks, charlatans, snake-oil salesman and others to whom members of the public might otherwise turn.

Medical education was crucial to this professionalisation. It ensured that only suitably able candidates could enter the profession. It also, of course, provided a way for aspiring physicians to acquire the necessary skills, knowledge and behaviour.

Crucially, though, from the Enlightenment on, medicine had ceased to be a static, backward-looking discipline. New knowledge was constantly being acquired. So, as well as acquiring existing knowledge, physicians were also generating new knowledge of their own. Sometimes they may have been motivated by their own innate curiosity, a desire to understand better the natural world. Often, they were driven by medical needs, to be able to do more for patients.

NEW KNOWLEDGE

The Victorian era was a time of explosive growth in understanding of the body and of the nature of disease. The emergence of germ theory transformed thinking about infections. The development of anaesthetics revolutionised surgery. Key physiological concepts were established. So, as well as being centres in which established knowledge was passed on from generation to generation, medical schools were hotbeds of discovery and innovation. The speed of advance could be breathtaking. Within months of Roentgen's discovery of X-rays, for example, a radiology unit had been established at Glasgow.

Why were medical schools able to be such drivers of change? Partly it was down to the nurturing of enquiring minds, essential in both science and medicine.

Perhaps most significantly, though, the juxtaposition of medical delivery and academic endeavour created an environment in which research could be allied to the realities of disease and medical needs. Even now, while research in medical schools is often curiosity-led, it is rooted in the potential for medical intervention.

Hence research in medical schools spans a spectrum, from highly goal-oriented studies that seek to improve healthcare in the short term through to more speculative work that may take decades or more to come to fruition. And that balance is important: too much focus on the here and now and the flow of medical innovations will dry up; too much emphasis on blue skies and patients will never derive any benefits.

While the links with medical service delivery are obvious, the importance of the connections with university academic networks should not be underestimated. The rise of biochemistry in the early years of the 20th century provided new routes by which knowledge could be translated into medical benefits. So too has the emergence of molecular genetics in the late 20th century. Engineering has contributed hugely to the development of medicine, particularly imaging technologies and replacement parts. Crucially, it took medically qualified individuals to spot the potential of new technologies and to devote the time and energy to turn them into tools of widespread practical value.

SOCIAL ROLES, POLITICAL INFLUENCE

Doctors have traditionally been recognised as the archetypal pillars of society, a position reinforced by polls confirming that they remain the most trusted group in UK society – the latest poll reveals that 90% of people trust them to tell the truth (compared with 78% for judges, 44% for civil servants and 18% for politicians).

In part this reflects the intimate nature of the doctor–patient relationship and the trust that must go along with it – it is literally our life in their hands. Partly, though, it also recognises a long history in which physicians have worked or campaigned for the public good.

It was doctors who identified the links between smoking and disease and led public health campaigns against smoking. It was doctors who promoted legislation to enforce wearing of seatbelts, which has saved thousands of lives. Invaluable resources such as the blood transfusion service and organ donor system owe their origins to the tireless work of doctors.

Internationally, British doctors are working in numerous developing countries, aiming not just to deliver medical care where it is needed but also to develop the capacity of countries so they are better equipped to tackle their own health problems.

In the UK, doctors are delivering the vaccines and public health programmes that help keep the public healthy. They are also at the forefront of surveillance for the appearance of new threats to health or the re-emergence of old ones. By feeding into the policy-making process, doctors can ensure that the country is prepared for the new challenges to health that will inevitably appear.

Above: Doctors have played a crucial role in creating the blood transfusion service.

Scientific training has also proven invaluable in the growth of population-based studies and randomised clinical trials. As well as shedding light on key public health issues, such work has established an evidence base to support rational healthcare delivery and policy making.

The roll call of Nobel Prize winners, and the stream of other innovations emerging from UK medical schools, is testament to the success of this model. Medical schools are not just training the doctors of tomorrow – they are also laying the foundations of the medicine these doctors will deliver.

A RECORD OF SUCCESS

The past 150 years have seen huge improvements in length and quality of life.

Life expectancy has leapt from 40 to 76 for men and from 42 to 81 for women, and continues to increase by five hours every day.

Infant mortality has been slashed – from more than 100 to fewer than 5 deaths per 1000 live births.

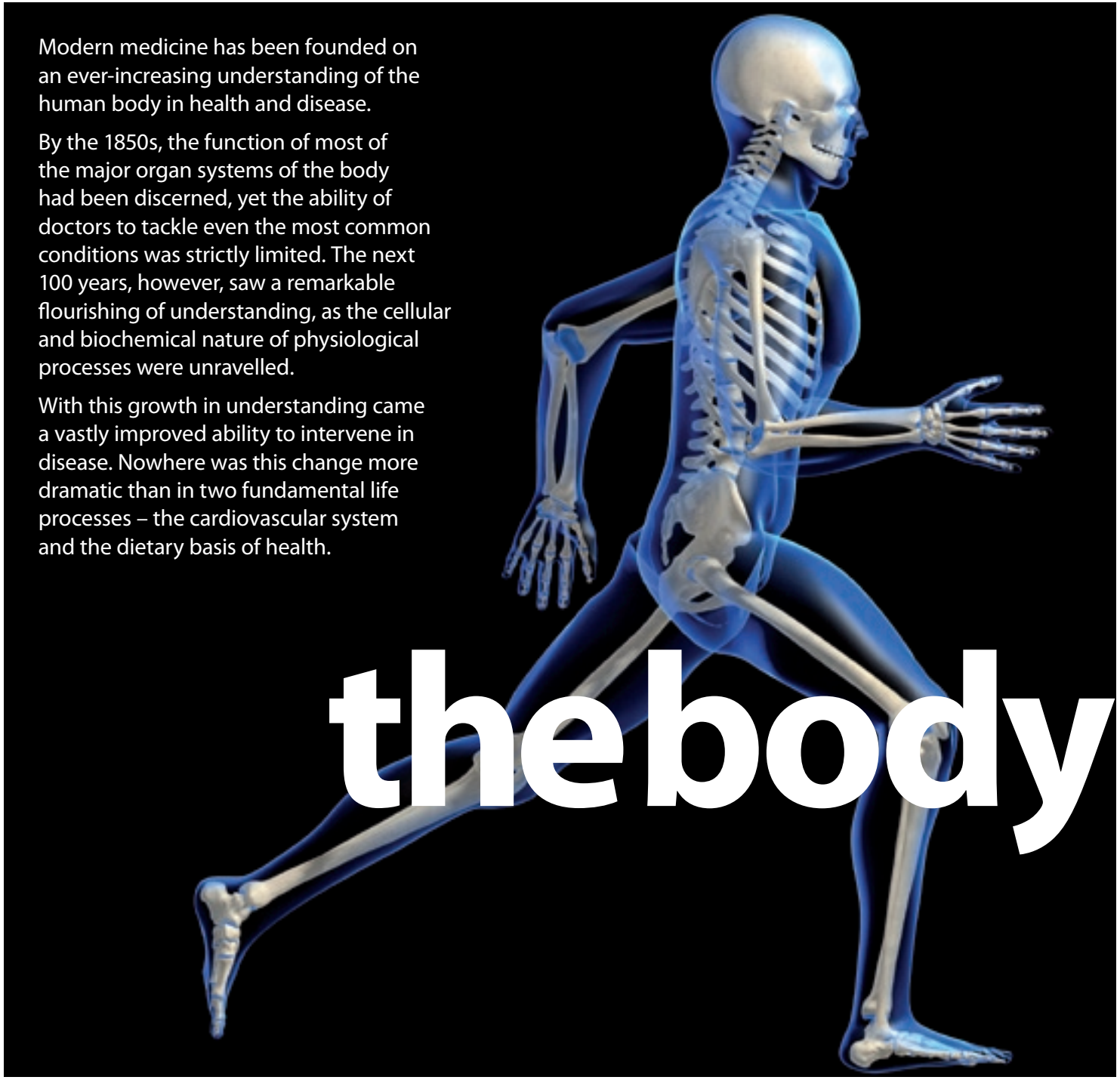
Women were not allowed on the Medical Register 150 years ago – but now make up 58% of the undergraduate population.

Antibiotics and vaccines have turned many infectious diseases into distant memories.

Dietary deficiencies are now rare. Organ transplants routine. Previously unimaginable surgical procedures are an everyday occurrence. Chronic conditions such as diabetes, if not cured are often at least adequately managed.

These advances were driven by a new awareness of the causes of ill-health and the development of new interventions to prevent or treat disease. While challenges still remain, the first 150 years have been a period of sustained success.

Above: Newborn baby in incubator.



Modern medicine has been founded on an ever-increasing understanding of the human body in health and disease.

By the 1850s, the function of most of the major organ systems of the body had been discerned, yet the ability of doctors to tackle even the most common conditions was strictly limited. The next 100 years, however, saw a remarkable flourishing of understanding, as the cellular and biochemical nature of physiological processes were unravelled.

With this growth in understanding came a vastly improved ability to intervene in disease. Nowhere was this change more dramatic than in two fundamental life processes – the cardiovascular system and the dietary basis of health.

the body

THE HEART AND CIRCULATION

Blood and its circulation has been widely recognised as a fundamental aspect of life – indeed, perhaps the fundamental aspect: the lack of a beating heart spelt death.

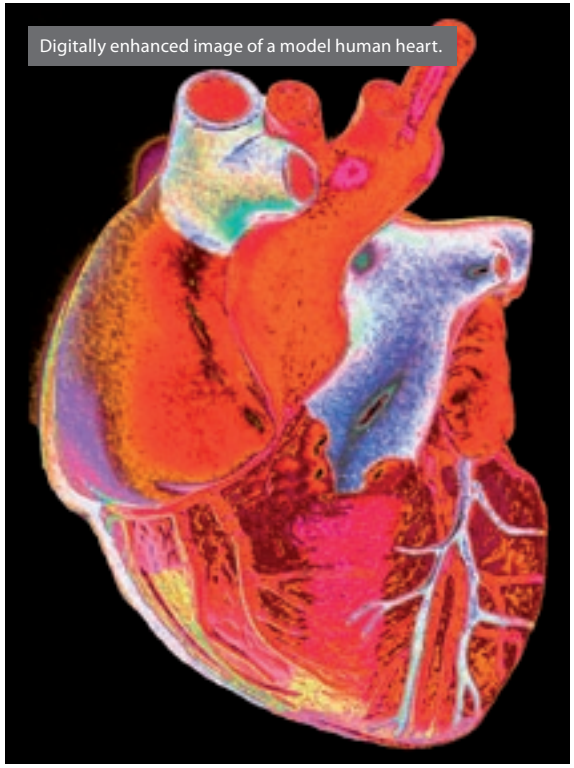
Not surprisingly, then, the heart and circulation have figured strongly in the development of modern medicine.

The pulse has been central to medical practice for centuries. The electrical innovations of the late 19th century were soon being applied to provide a more systematic assessment of heart function.

In 1872, while studying for his Doctor of Science degree (in electricity) at St Bartholomew's Hospital, **Alexander Muirhead** attached wires to a feverish patient's wrist in order to record his heartbeat. Later, **Augustus Waller**, working in St Mary's Hospital in London, was the first to tackle the heart systematically from an electrical standpoint. Making ingenious use of a toy train, his electrocardiograph (ECG) machine produced a trace that was projected onto a moving photographic plate. This allowed a heartbeat to be recorded in real time.

Ironically, Waller could see little clinical application for his work – unlike **Thomas Lewis** at University College London, who pioneered the use of ECG in clinical settings, founding a field crucial in cardiology to this day.

The pumping action of the heart was also yielding to intensive study. In 1915, **Ernest Starling** at University College London made the important discovery that the amount of blood pumped by the heart depended on the volume entering its chambers on relaxation – the so-called 'law of the heart'. Such insight provided a basis for understanding the nature of heart failure.

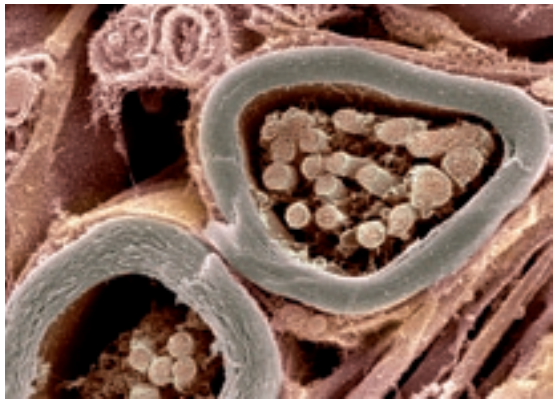


Digitally enhanced image of a model human heart.

By the post-war years, ultrasound was emerging as a potentially valuable imaging technique in medicine. It rapidly found application in cardiology, while **Aubrey Leatham**, with the assistance of **Graham Leech**, pioneered the use of sound-based imaging, echophonocardiography, at St George's Hospital.

New therapies also began to appear. The artificial pacemaker has saved many lives. The idea of using artificial electrical stimulation goes as far back as the pioneering work of Aberdeen's **John Alexander MacWilliam**, who in 1889 published his findings on human heart stimulation. Later, the inventive work on heart pacemakers and plastic heart valves by **Leon Abrams** of the Queen Elizabeth Hospital and the Birmingham Medical School in the mid-1950s led to their widespread use internationally.

On the drug front, the development of beta-blockers by **James Black** and ACE inhibitors by **John Vane** (see page 9) provided enormous benefits.



NERVES AND THE NERVOUS SYSTEM

Many key aspects of nervous system function have been revealed by UK researchers.

Following a varied scientific and medical education in London and Cambridge, **Charles Sherrington** established his career in Liverpool and, later, Oxford. Sherrington – possibly the only Nobel Laureate to play football for Ipswich Town – was hugely influential in developing the modern idea of the nervous system as an integrated system for controlling the body's actions.

Sherrington shared the 1932 Nobel Prize with **Edgar Adrian**, who studied medicine at Barts and, while in Cambridge, carried out landmark studies characterising the electrical behaviour of isolated nerve cells. He also helped to develop the 'sensory map' in the brain.

The nature of nerve transmission remained controversial in the early 20th century, with two opposing camps: the electrical and the chemical. The issue was largely resolved, in favour of the chemical camp, by **Henry Hallett Dale**, who trained at Cambridge and University College London (UCL) and discovered the neurotransmitter acetylcholine.

How chemicals could trigger electrical impulses was brilliantly explained by **Andrew Huxley** and **Alan Hodgkin** in Cambridge, who developed mathematical models to describe the dynamics of nerve impulses. Their Nobel Prize was awarded in 1963.

The behaviour of individual neurones was also the focus of **Bernard Katz**, a German-born biophysicist who, after working with Hodgkin and Huxley in Cambridge, spent much of his career at UCL. Katz discovered that neurotransmitters were released in discrete packages, or 'quanta', at synapses (a term introduced by Sherrington). His work earned him a Nobel Prize in 1970.

A further step forward came in 1975 when **Hans Kosterlitz** in Aberdeen discovered that the brain produced molecules which bound to opioid receptors – the so-called endogenous opioids or endorphins. He went on to show their importance in pain perception, opiate addiction, learning and memory.

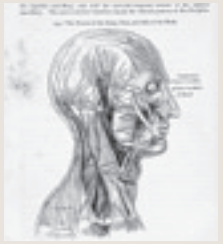
More recently, attention has focused on functional imaging, revealing insight into the brain in action. The UK again remains at the forefront of the field with groups such as **Ray Dolan** and colleagues at UCL and **Hugo Critchley** at Brighton and Sussex Medical School.

The great advances in our understanding of the nervous system in the 20th century led to a whole host of treatments based on pharmacological manipulation of nerve impulses – from beta-blockers to antidepressants. The remarkable progress in brain imaging promises to deliver equally significant advances in psychiatric and psychological conditions that are a growing cause of ill-health and distress.

Above: Colour-enhanced image of two myelinated nerve fibres.

1848
Alfred Baring Garrod at **King's College London**, who coined the term 'rheumatoid arthritis' and suggested use of lithium to treat mental illness, discovers increased levels of uric acid in the blood of patients with gout.

1855
Thomas Addison at **Guy's Hospital** describes Addison's disease, a skin condition caused by destruction of the adrenal glands.



1858
Henry Gray, a Lecturer in Anatomy at **St George's Hospital Medical School**, publishes *Gray's Anatomy*, probably the most famous medical textbook of all time.

1867
Clifford Allbutt, who studied at **York** and **Cambridge**, invents the clinical thermometer. Just 3 inches in length, it is a vast improvement on its predecessor, which was more than a foot long.

1891
Myxoedema is first treated successfully, using an extract of sheep's thyroid gland, by George Murray at **Newcastle's Royal Victoria Infirmary**.

1905
The first hormone, secretin, is discovered at **University College London** by William Bayliss.

1906
Sir Charles Sherrington publishes landmark findings on nervous system function while at **Liverpool**. He later moves to **Oxford** and is awarded a Nobel Prize in 1932.

1913
Thomas Lewis at **University College London** introduces the electrocardiogram (ECG) into clinical practice, laying the foundations of electrocardiography.

1915
Ernest Starling at **University College London** describes the 'Law of the Heart', an important step towards understanding heart function and the nature of heart failure.

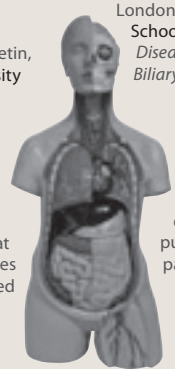
1923
John MacLeod, a graduate of **Aberdeen** University, is awarded a share of a Nobel Prize with Fraser Grant Banting for the discovery of insulin.

1952
Bernard Katz at **University College London** discovers the quantal release of neurotransmitters at synaptic terminals, for which he receives a Nobel Prize in 1970.

1953
Sylvia Simpson and James Tait at the **Middlesex Hospital** isolate the steroid hormone aldosterone.

mid-1950s
Inventive work on heart pacemakers and plastic heart valves by Leon Abrams of the Queen Elizabeth Hospital and **Birmingham** Medical School leads to their widespread use internationally.

1955
Sheila Sherlock, pioneer of hepatic medicine and first professor of medicine at London's **Royal Free Hospital School of Medicine**, publishes *Diseases of the Liver and Biliary System*.



1958
Aubrey Leatham at **St George's** Hospital, with Graham Leech, is the first to use echophonocardiography, publishing a landmark paper in the *Lancet*.

1961
The UK's first professor of nutrition, John Yudkin of **King's College London**, publishes *The Slimmer's Cookbook*, the first scientifically based book on slimming.

1969
Propanolol, the world's first beta-blocker, is launched, thanks to the insights of James Black.

1970
Graham Russell in **Sheffield** discovers the mechanism of action of bisphosphonates, drugs used to treat osteoporosis, Paget's disease and malignant bone disease.

1972
David Brock in **Edinburgh** finds that increased alpha-fetoprotein in the mother's bloodstream is associated with spina bifida and anencephaly, leading to prenatal screening tests.

1974
Graham Teasdale and Bryan Jennett in **Glasgow** develop the Glasgow Coma Scale, the standard method for assessing the conscious state of a patient.

1975
Hans Kosterlitz in **Aberdeen** discovers endorphins and goes on to show their importance in pain perception, opiate addiction, learning and memory.

1975
First ACE inhibitor launched, thanks particularly to the work of John Vane.

1989
David Barker in **Southampton** proposes the 'Barker hypothesis' – that poor maternal nutrition programmes a foetus for survival in a nutrient-poor environment.

1995
Jonathan Seckl and Brian Walker in **Edinburgh** identify steroid hormone metabolism in adipose tissue as a possible cause of cardiovascular complications linked to obesity.

1995
James Shepherd and colleagues publish the West of Scotland Coronary Prevention Study, the first demonstration that statins protect middle-aged men with high cholesterol levels and no history of heart attack.

1997
Stephen O'Rahilly and colleagues in **Cambridge** identify single-gene defects causing obesity in children, providing key insight into the nature of obesity.

1998
Researchers at **Oxford**, coordinated by Peter Sleight, show that a combination of aspirin with streptokinase is the most effective acute treatment after a heart attack.

1999
The Heart Protection Study, led by Rory Collins and Richard Peto, advocates widespread use of cholesterol-lowering drugs, even to those at low risk, as costs would be outweighed by savings on treatment.

2006
Andrew Hattersley and colleagues from **Peninsula College of Medicine and Dentistry** establish that patients with the most common genetic cause of neonatal diabetes could be treated with tablets, freeing hundreds of children from a lifetime of multiple insulin injections.

2007
Paul Thornalley and colleagues in **Warwick** discover that thiamine (vitamin B1) deficiency in diabetes is linked to abnormal metabolism in the kidney, leading to trials of thiamine supplementation to prevent vascular complications in diabetes.

CARDIOVASCULAR DISEASE

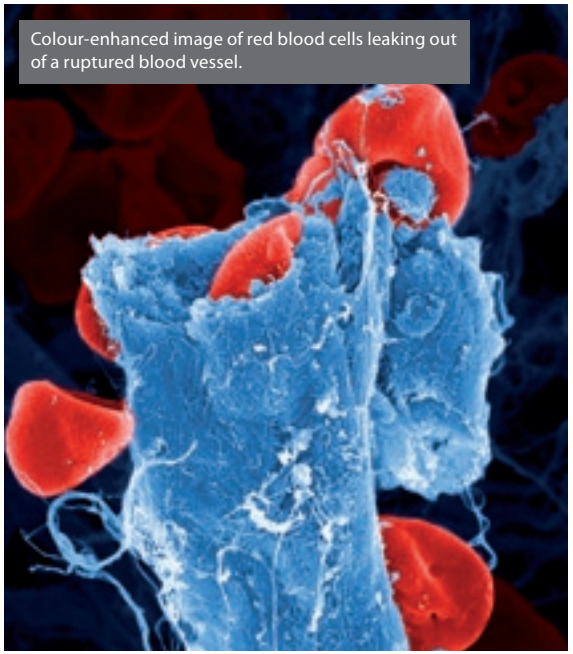
With people living longer, smoking and eating high-fat diets, coronary heart disease and related conditions were the UK's biggest killers.

One consequence was a significant shift towards cardiovascular disease epidemiology, and large-scale trials of treatments or preventive measures. Researchers at Oxford (coordinated by **Peter Sleight**), for example, showed that the 'clot-busting' drug streptokinase, in combination with aspirin, constitutes the most effective acute treatment following a heart attack.

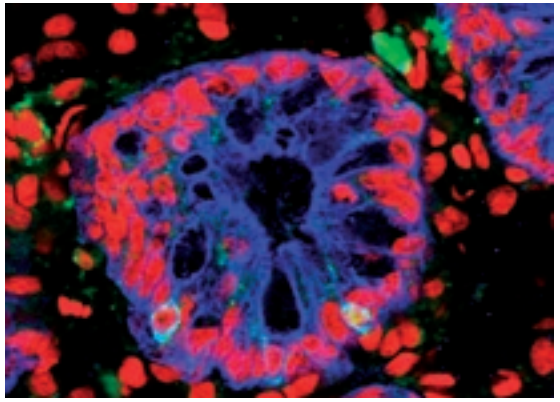
The Heart Protection Study, led by **Rory Collins** and **Richard Peto**, advocated widespread use of cholesterol-lowering drugs, such as statins, even to those with only a minor risk of heart attack or stroke. The cost of such an initiative, they calculated, would be outweighed by the savings made on treatment.

For those with acute coronary heart syndromes, **Keith Fox** from Edinburgh led studies precisely defining individual risk of heart attack and death and established the role of antiplatelet therapies such as clopidogrel in reducing mortality.

Although heart disease remains a major killer, mortality rates are falling. Patients are more likely to survive a heart attack and enjoy good quality of life afterwards.



Colour-enhanced image of red blood cells leaking out of a ruptured blood vessel.



HORMONES

Hormonal disorders have been known about for centuries – diabetes was described in the 11th century. While doctors did have some early success – **George Murray** at Newcastle's Royal Victoria Infirmary successfully treated myxoedema using an extract of sheep's thyroid gland in 1891 – the modern era really began in 1905, when **William Bayliss** and **Ernest Starling** at UCL discovered the first hormone, secretin. They introduced the term 'hormone' to describe the general class of substances that could act without physical connections between tissues.

The medical value of this area was vividly demonstrated by **John MacLeod**, a graduate of Aberdeen University, who received a share of a Nobel Prize in 1923 for showing that extracts of pancreas could control the symptoms of diabetes. The active principle was later identified as insulin.

Steroids became a mainstay of medical treatment in the 20th century, following extensive work on natural steroid hormones. The husband and wife team of **James** and **Sylvia Tait** (nee Simpson) at the Middlesex Hospital was notable for the isolation of aldosterone, part of the renin–angiotensin system, in 1953.

In 1989, **David Barker** in Southampton suggested that the roots of later-life metabolic conditions such as high blood pressure or diabetes might lie in the prenatal environment. In times of scarce nutrition, the metabolism of a foetus might be programmed for survival in a nutrient-poor environment. However, if food is plentiful, this adaptation stores up problems in later life. This influential 'Barker hypothesis' has received much attention with populations living longer in food-rich environments.

Another consequence of modern life is the dramatic rise in obesity. The physiological basis of this condition is being clarified, thanks to the work of researchers such as **Stephen O'Rahilly** and colleagues in Cambridge, who in 1997 identified defects in the receptor for the hormone leptin that cause obesity in children.

Steve Bloom at Imperial, meanwhile, has identified hormones signalling a sense of 'fullness' and is developing pharmaceutical mimics that might suppress appetite. Another promising lead, being pursued by **Jonathan Seckl** and colleagues in Edinburgh, is based on steroid hormone metabolism in adipose tissue, which may underlie the harmful cardiovascular complications of obesity.

The impact of genetics is also being seen. For example, a collaboration led by **Andrew Hattersley** and colleagues from Peninsula College of Medicine and Dentistry and **Mark McCarthy** and his team in Oxford has been dissecting the genetic causes of different types of diabetes. One consequence has been that hundreds of children can now be treated with tablets, freeing them from a lifetime of insulin injections.

Above: Neuroendocrine cells (light blue) in the human small intestine.

DIET AND HEALTH

As well as energy, our diet provides a suite of other molecules that are essential to life – the full range of which has gradually been identified over the past 100 years.

The early 20th century saw a profound change in medicine, with the emergence of the field of biochemistry and the realisation that disease could result from defects in biochemical processes. A key figure in this shift was **Archibald Edward Garrod**, the first director of Barts' Medical Clinic, who is generally considered the father of metabolic medicine. He also made the link with the emerging area of genetics, realising that some metabolic conditions could be inherited – coining the term 'inborn errors of metabolism'.

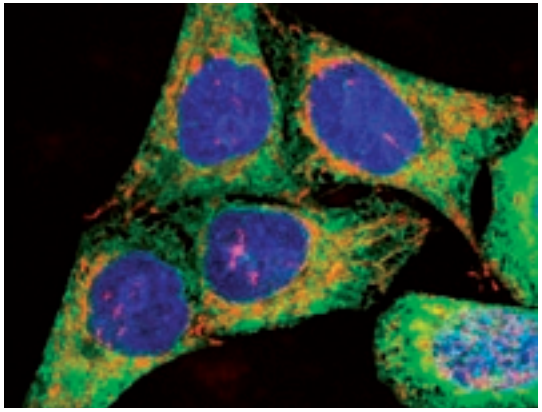
A second pivotal figure was **Frederick Gowland Hopkins**, who after studying in London moved to Cambridge and established its first department of biochemistry. He realised that diet was providing many trace elements, or vitamins – insight that led to a share of a Nobel Prize in 1929.

Further discoveries came thick and fast. Through studies on dogs kept in the dark and fed a restricted diet, **Edward Mellanby**, the first Professor of Pharmacology in Sheffield, established that rickets could be prevented by treatment with cod liver oil. He went on to contribute to the discovery of the role of vitamins such as vitamin D, the active principle in cod liver oil.

Following the work by **Norman Haworth** on vitamin C synthesis, for which he received the Nobel Prize for Chemistry in 1937, the pioneering Birmingham paediatrician **Leonard Parsons** was, in 1932, the first to use synthetic vitamin C to treat scurvy in children.

Vitamins were integral to the nutritional standards established by **Robert McCance** and **Elsie Widdowson** in Cambridge, who drew up guidelines on the nutritional needs of the population in wartime Britain – a time when the health of the population was remarkably good. Their iconic monograph, *The Nutritional Composition of Foods*, became the standard work on nutrition.

The potential ill-effects of modern diets were highlighted by **John Yudkin** of King's College London, who identified a link between sugar intake and coronary heart disease. The UK's first professor of nutrition, in 1961 he wrote *The Slimmer's Cookbook*, the first scientifically based book on slimming.



THE KREBS CYCLE

A protégé of Frederick Gowland Hopkins was German-born biochemist **Hans Krebs**. Krebs emigrated from Germany in 1933, to avoid persecution by the Nazis, and moved from Cambridge to Sheffield in 1945.

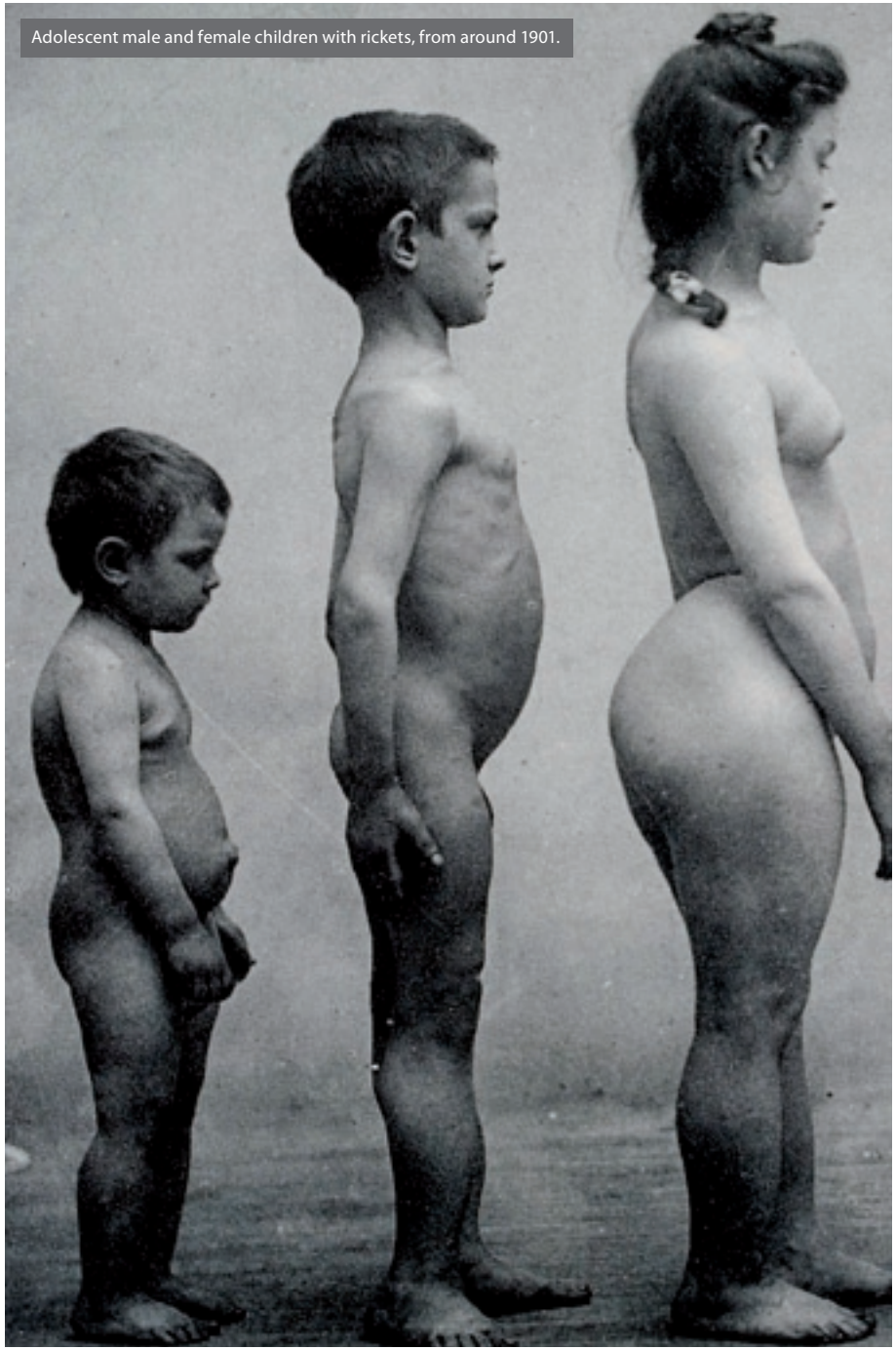
In Sheffield, he carried out a remarkable series of experiments that revealed the biochemical processes by which carbohydrate in food is metabolised in most living cells – subsequently named the Krebs cycle in his honour. This core biochemical pathway is found in nearly every living cell, from bacterium to human.

Hans Krebs was awarded the 1953 Nobel Prize in Physiology or Medicine for his work.

Above: Melanoma cells growing in culture.

In 1965, **Richard Smithells** at Leeds discovered that poor nutrition and vitamin deficiency, particularly of folate, in pregnant mothers was a risk factor for malformations of the spine and brain such as spina bifida. Folic acid supplements are now recommended for pregnant women. Later, in 1972, **David Brock** in Edinburgh noted that high levels of a foetal protein (alpha-fetoprotein) in the mother's bloodstream were associated with spina bifida and anencephaly, leading to the first widely used prenatal screening tests.

The recognition of the importance of dietary factors has almost eliminated several conditions from the UK. Scurvy and rickets are seldom seen, while spinal deformities are on the decline.



Adolescent male and female children with rickets, from around 1901.

Above: Growing crystals of a DNA repair protein bound to DNA.

structural

STRUCTURAL BIOLOGY

Knowing the structure of large biological molecules has opened up the prospect of tailored pharmaceuticals.

In 1962, **Watson**, **Crick** and **Wilkins** were awarded a Nobel Prize for the discovery of the DNA double helix. But they were not the only UK researchers receiving a Nobel Prize that year – so too did **Max Perutz** and **John Kendrew**, who were awarded the chemistry prize for their work on the three-dimensional structure of proteins.

Max Perutz established the Laboratory of Molecular Biology (LMB) in Cambridge and supervised the PhD studies of Watson and Crick. With John Kendrew, he pioneered the use of X-ray crystallographic approaches to study protein structures, working initially with the blood proteins haemoglobin and myoglobin.

Perutz was inspired by the father and son team of physicists, William and Lawrence Bragg, the latter being head of the Cavendish Laboratory in Cambridge. He also built on the work of **Dorothy Crowfoot Hodgkin**, who, under the supervision of J D Bernal, was the first to apply X-ray diffraction to the study of proteins. She solved the structures of penicillin, vitamin B12 (for which she was awarded a Nobel Prize in 1964) and, most momentously, insulin – after 35 years' toil.

Cambridge continued to excel in innovative structural studies. Another protégé of J D Bernal, **Aaron Klug** moved to Cambridge, combining electron microscope and crystallographic approaches to structure determination. He was able to look not just at single proteins but molecular aggregates – such as virus particles and complexes of DNA and protein and how they wrapped into nucleosome core particles. This work led to the award of a Chemistry Nobel Prize in 1982.

Klug went on to discover 'zinc fingers', characteristic protein structures that bind different DNA sequences with high specificity. There is growing interest in the design of novel zinc finger proteins to interfere with gene activity in disease states. Clinical trials are underway in which a tailored zinc finger protein is used to turn on a growth factor to stimulate blood vessel formation in peripheral arterial disease.

Another highly complex 'molecular machine' is the enzyme ATP synthase, the structure of which was solved by **John Walker** – yet another member of LMB who has been awarded a Nobel Prize (Chemistry 1997). This remarkable multimeric protein structure generates the cell's 'energy currency', ATP, driven by a stream of protons.

The structure of another important biological macromolecule – immunoglobulin – was determined by **Rodney Porter**, who worked at the National Institute of Medical Research, St Mary's Hospital Medical School and Oxford. With Gerald Edelman, he correctly proposed that antibodies form a characteristic Y-shape.

While it took Dorothy Crowfoot Hodgkin 35 years to determine the sequence of insulin, protein structures can now be determined in a matter of weeks or months. Indeed, recent years have even seen high-throughput approaches adopted, with international initiatives such as the **Structural Genomics Consortium**, partly based in Oxford.

The SGC is working out the structure of a range of medically important human and parasite proteins. Crucially, an understanding of how a protein's structure is linked to its function opens up the prospect of designing molecules to interfere precisely with a target protein.

engineering

RATIONAL DRUG DESIGN

Structural biology is a key technique in rational drug design, which has already given us important medications and is the basis of modern medicine.

For centuries, drug development was an empirical process – some successful drugs were developed but it was rarely clear how they worked. As an understanding of human physiology and biochemistry has improved, drugs can be specifically tailored to interfere with a biological process – rational drug design.

UK scientists played key roles in the early stages of this new approach to drug development. A central figure was **James Black**, who trained at St Andrews and Dundee before working in industry for ICI and Wellcome. Black developed analogues that were structurally similar to histamine and bound the histamine H2 receptor but did not trigger a cellular response. These 'receptor antagonists', such as cimetidine, inhibited gastric acid secretion and revolutionised the treatment of peptic ulcers.

Similarly well conceived was his pioneering work on beta-blockers. In the late 1950s, the standard way to treat angina and ischaemic heart disease was thought to be by boosting supply of blood to the heart by vasodilators. Black turned the issue on its head, reasoning that slowing heart rate would also protect the heart from reduced oxygen supply.

He drew upon a new theory that the effects of adrenaline, which boosted heart rate, were mediated by a specific receptor, the beta-receptor. Then at ICI, Black worked with medicinal chemists to invent a beta-blocking drug, eventually coming up with propanolol, the first successful beta-blocker – for which he was awarded a Nobel Prize in 1988.

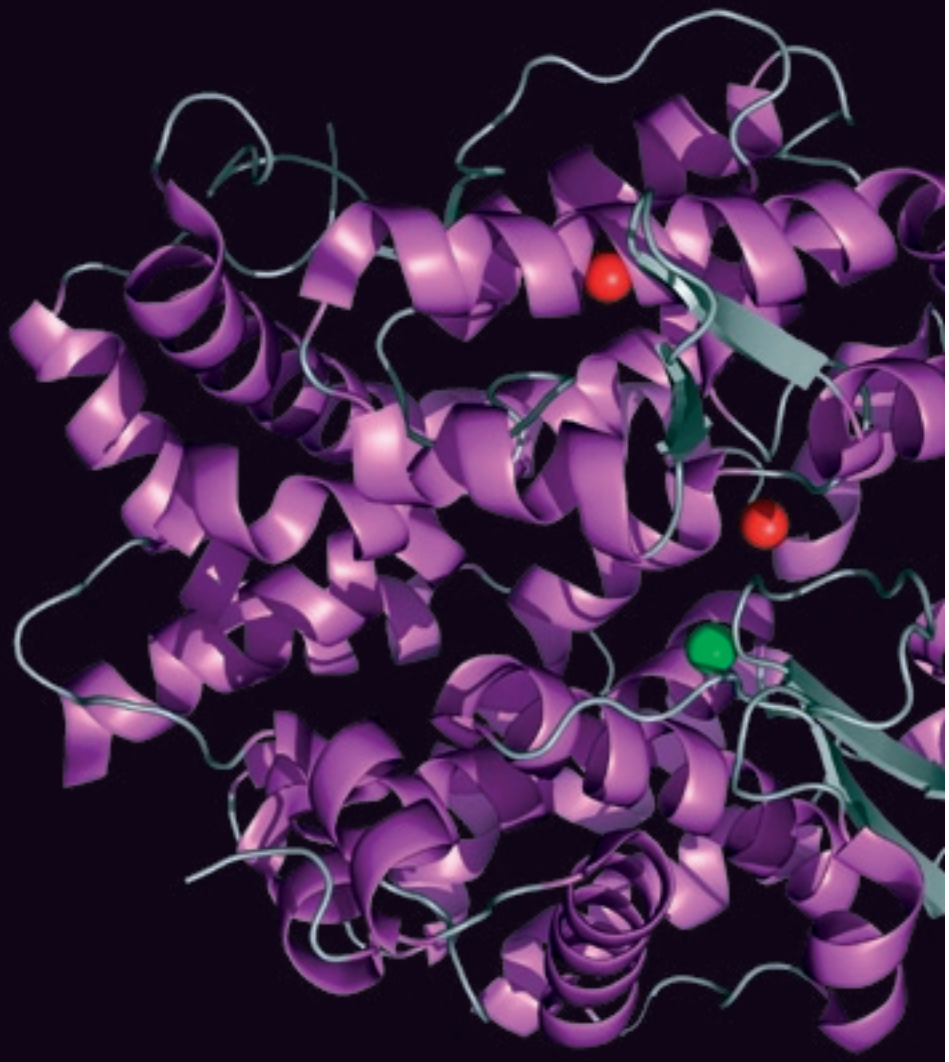
Launched in 1969, propanolol was spectacularly successful. Moreover, it led to profound changes in understanding of mechanisms of heart disease. Arguably his greatest legacy, though, was in defining the paradigm for modern pharmaceutical research: start with a clinical problem, define its mechanisms, investigate the potential of small molecules to interfere with these mechanisms in a desirable way.

SERVING AN ACE

The paradigm can clearly be seen in the work of **John Vane**, whose research led to the development of ACE inhibitors (blood pressure-lowering drugs that act on angiotensin-converting enzyme, ACE). A chemistry graduate from Birmingham, Vane moved into pharmacology at Oxford and later at the Royal College of Surgeons, testing the effects of peptides isolated from the venom of a Brazilian pit viper on ACE. This led to the first ACE inhibitor, captopril.

Vane is perhaps best known, however, for working out the mechanisms of action of aspirin, which turned out to be an inhibitor of prostaglandin synthesis. This understanding, which led to a Nobel Prize in 1982, has underpinned the widespread use of aspirin as a blood thinner. Indirectly, it also led to a new class of anti-inflammatory agent, the non-steroidal anti-inflammatory drugs (NSAIDs), which target the same processes but are designed to have fewer side-effects on the gut.

The examples of Black and Vane also illustrate how productive links between academia and industry can create medicines that benefit millions the world over.



Above: Molecular model of the testicular form of angiotensin I-converting enzyme.

Few areas have undergone such remarkable change during the past 150 years as surgery. Once the poor relation of medicine, in the 19th century surgery was losing its traditional association with the 'barber–surgeons' and becoming a highly skilled profession within medicine. Surgery is now one of the most sophisticated medical disciplines.

A significant factor was the introduction of anaesthesia in the mid- to late 19th century, which afforded surgeons precious time to perform more sophisticated operations.

At the same time, progress in infection control meant that patients were far more likely to survive surgical intervention.

The 20th century saw many innovations, from reconstructive surgery to minimally invasive techniques.

Then, in the second half of the 20th century, the ability to control tissue rejection spawned remarkable growth in the field of transplantation.

surgery and transplantation

SURGICAL STRIKE

The skill of surgeons came to the fore thanks to two advances: anaesthesia and the control of infection.

John Snow may be best known for linking the spread of cholera to contaminated water, but he has a second claim to fame as the first medical professional to anaesthetise a reigning monarch. At the suggestion of **James Young Simpson** – the Edinburgh professor who discovered the anaesthetic properties of chloroform – and **James Matthews Duncan**, Snow administered chloroform to Queen Victoria when she was in labour with her last two children.

If pain relief was a crucial advance in surgery so too was control of infection. In the mid-1800s, post-operative infection killed almost half of all patients undergoing major surgery. Pasteur, Koch and others were developing the 'germ theory', that infectious disease was caused by microorganisms. **Joseph Lister**, Regius Professor of Surgery at Glasgow, made the connection with wound sepsis and began to clean wounds and dress them using a solution of carbolic acid. In 1867, he was able to announce that his wards at the Glasgow Royal Infirmary had remained clear of sepsis for nine months.

In 1877, Lister moved to King's College London, going on to carry out pioneering brain surgery, improving mastectomy procedures, and developing a method of repairing kneecaps with metal wire.

The following decades saw many advances in surgery. In the 1880s, for example, the Birmingham Professor of Surgery **Lawson Tait** laid the foundation of modern gynaecology, including procedures for ectopic pregnancies which greatly increased survival. Tait did much to promote the idea of surgical removal of affected tissue.

Similarly influential was **Berkeley Moynihan**, a graduate of Leeds School of Medicine, whose book *Abdominal Operations* secured him an international reputation. Later, figures such as Geoffrey Keynes, a surgeon at Barts between 1946 and 1949, developed important ideas on surgical interventions for breast cancer and radium implantation.

A modern surgical team at work.

BRAIN SURGERY

British doctors have made key contributions to the development of brain surgery.

The modern era of brain surgery began with the realisation that the brain was functionally compartmentalised – different regions were responsible for controlling different parts of the body. Although German neuroscientists Fritsch and Hitzig first demonstrated this experimentally in 1870, it had already been surmised by **John Hughlings Jackson** of London Hospital Medical School.

Jackson, a graduate of St Andrew's, was the first to suggest that mental abnormalities were caused by structural damage to the brain. He was particularly interested in epilepsy, which affected both his wife and cousin, and drew an association between epileptic convulsions spreading through the body and electrical discharges spreading across the brain.

Jackson was a big influence on **David Ferrier**, an Edinburgh graduate working at King's College Hospital. Ferrier carried out the experimental work confirming Jackson's theories.

The medical implications of Ferrier's work were profound. If brain functions were localised, a patient's symptoms would provide clues to the location of brain abnormalities. Following this thinking, in 1876 Glasgow graduate and Lister disciple **William Macewen** predicted that a young boy had an abscess on his frontal lobe. However, his family refused permission for Macewen to operate, and the boy died. At post-mortem, Macewen's diagnosis was shown to have been correct. When Macewen did get to test his conclusions on patients, he met with dramatic success.

In recent years, a new form of brain surgery – deep brain stimulation – has been developed for Parkinson's disease patients who no longer respond to drug treatments. This approach owes much to the work of **Alan Crossman** in Manchester and neurosurgeon **Tipo Aziz** in Oxford, who in 1991 established that it reversed Parkinson's symptoms in animal models. Some 30,000 patients have now been treated, and the technique may also be of benefit in other conditions, including chronic pain and depression.

Heart surgery was advanced by innovators such as **Russell Brock** from King's College London, who in 1948 pioneered mitral valve surgery, as well as inventing new instruments to treat congenital heart defects.

In the 1960s, **Michael Tunstall** in Aberdeen improved control of pain relief in labour by developing 'Entonox', a mixture of nitrous oxide and oxygen still in use today.

The late 1980s saw a major advance, with the emergence of minimally invasive (keyhole) surgery, carried out for the first time in the UK by **Alfred Cuschieri** in Dundee. Most surgical procedures are now minimally invasive.

In Sheffield, **Alan Johnson** showed that surgical interventions could be compared with the same rigour and objectivity as pharmacological interventions in randomised control trials, in a pioneering study comparing conventional with laparoscopic surgery.

1853
Alexander Wood develops the hypodermic syringe, experimenting with a hollow needle to deliver morphine to treat neuralgia.

1853
John Snow is the first medical professional to anaesthetise a reigning monarch, administering chloroform to Queen Victoria during the birth of her last two children.

1876
William Macewen in **Glasgow** carries out groundbreaking brain surgery to treat abscesses and cancer.

1877
Joseph Lister moves to **King's College London** and is the first to carry out an operation under antiseptic conditions, driving huge change in surgical practice.

1883
In **Birmingham**, surgical pioneer Lawson Tait carries out the first surgical removal of fallopian tube to treat ectopic pregnancy, an approach that has subsequently saved many lives.

1905
Berkeley Moynihan, a graduate of **Leeds** School of Medicine, publishes *Abdominal Operations*, establishing his international reputation for surgical excellence.

1930
The first successful corneal graft is performed, after nearly a decade of work by the ophthalmic surgeon Tudor Thomas of **Cardiff** Royal Infirmary.

1946
Geoffrey Keynes, a surgeon at **Barts**, develops important ideas on the surgical removal of breast cancer and radium implantation.

1949
At St Thomas' Hospital, London, Harold Ridley of **King's College** performs the first cataract extraction combined with an artificial lens implantation, pioneering surgery that would restore the sight of millions around the world.

1953
Peter Medawar at **University College London** discovers immunological tolerance, the foundation for transplantation biology; he is awarded a Nobel Prize for this work in 1960.

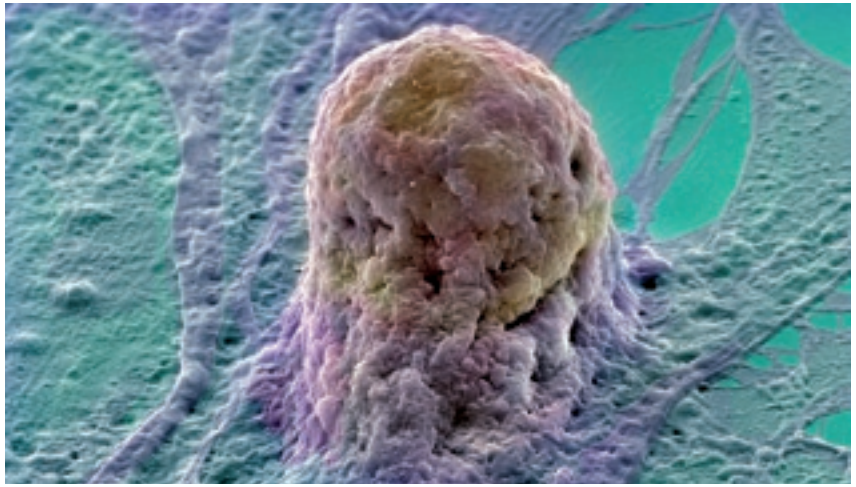
1962
John Charnley at **Manchester** carries out the first successful total hip replacement.

1962
John Gurdon in **Oxford** clones a frog, the first adult mammal to be cloned.

1963
Michael Tunstall in **Aberdeen** develops 'Entonox', a nitrous oxide/oxygen mixture for pain relief in labour.

1966
The association between dermatitis herpetiformis (a blistering condition of the skin) and intestinal abnormalities is first made by Marks and Shuster in **Newcastle**; small-bowel changes in dermatitis herpetiformis are later identified as coeliac disease.

1972
Andrew Wyllie and colleagues in **Aberdeen** describe and name apoptosis, programmed cell death.



STEM CELLS

A discovery from 25 years ago is turning out to have immense medical potential.

In 1981, **Martin Evans** (then in Cambridge, now in Cardiff) was, with Gail Martin in the USA, the first to culture embryonic stem cells. Evans went on to develop key techniques for manipulating mouse embryos, for which he received a share of a Nobel Prize in 2007. Engineering of mice is a valuable tool in medical research, particularly for developing mouse models of disease. And research on stem cells is offering many exciting new therapeutic opportunities.

Embryonic stem cells are exciting because of their pluripotency – their ability to turn into any of the many cell types of the body. New treatments may also emerge from research on adult stem cells. Generally, these cells are more restricted in the types of cells they can develop into, but are easier to obtain.

One hope is that stem cells will be able to repair damaged tissue (or stimulate the body's own repair mechanisms). **Anthony Mathur** at Barts, for example, is carrying out a clinical trial to test stem cell treatments for heart failure. It may also be possible to engineer new tissues – **Magdi Yacoub** and colleagues at Imperial have developed prototype heart valves based on stem cells.

To obtain embryonic stem cells, researchers turn to somatic cell nuclear transplantation – a technique pioneered in the UK. In the 1960s, **John Gurdon**, then in Oxford, was the first to clone a mammal – growing an adult frog by transferring a nucleus from a differentiated cell into an egg which had had its own nucleus removed.

This technique was famously used by **Ian Wilmut** and **Keith Campbell** in Edinburgh to clone Dolly the sheep. In humans, this approach can also be used to generate a supply of cells all sharing the same genetic defect, facilitating research on disease mechanisms. **Stephen Minger** at King's, for example, has created several such embryonic stem cell lines, including one carrying the most common mutation causing cystic fibrosis.

A particularly exciting goal is to understand the genetic and cellular programmes that control pluripotency – including the role of genes such as *Nanog*, named after the mythological Celtic land of the immortal, Tir na nOg, which was discovered by **Ian Chambers** and **Austin Smith** in Edinburgh. *Nanog* is one of a handful of genes that, collectively, can reprogramme cells into a pluripotent state.

The considerable advances being made in understanding the mechanisms controlling cell fate, and experience from early clinical trials, are combining to make stem cell therapy one of the most exciting areas of modern medicine.

Above: Human embryonic stem cell (gold) growing on a layer of supporting cells (fibroblasts).

REPLACEMENT PARTS

The idea that tissues or organs could be transferred between people, or other animals and people, has a long history. Yet most early experiments failed miserably, because of the recipient's rejection of donor tissue.

Some success was achieved in the eye, however, which is protected from the host's immune response. In 1930, the first successful corneal graft was performed, following nearly a decade's work by the ophthalmic surgeon **Tudor Thomas** at Cardiff Royal Infirmary. And in 1949, at St Thomas' Hospital, London, **Harold Ridley** of King's performed the first cataract extraction combined with artificial lens implantation, pioneering the surgery that would restore the sight of millions of people around the world.

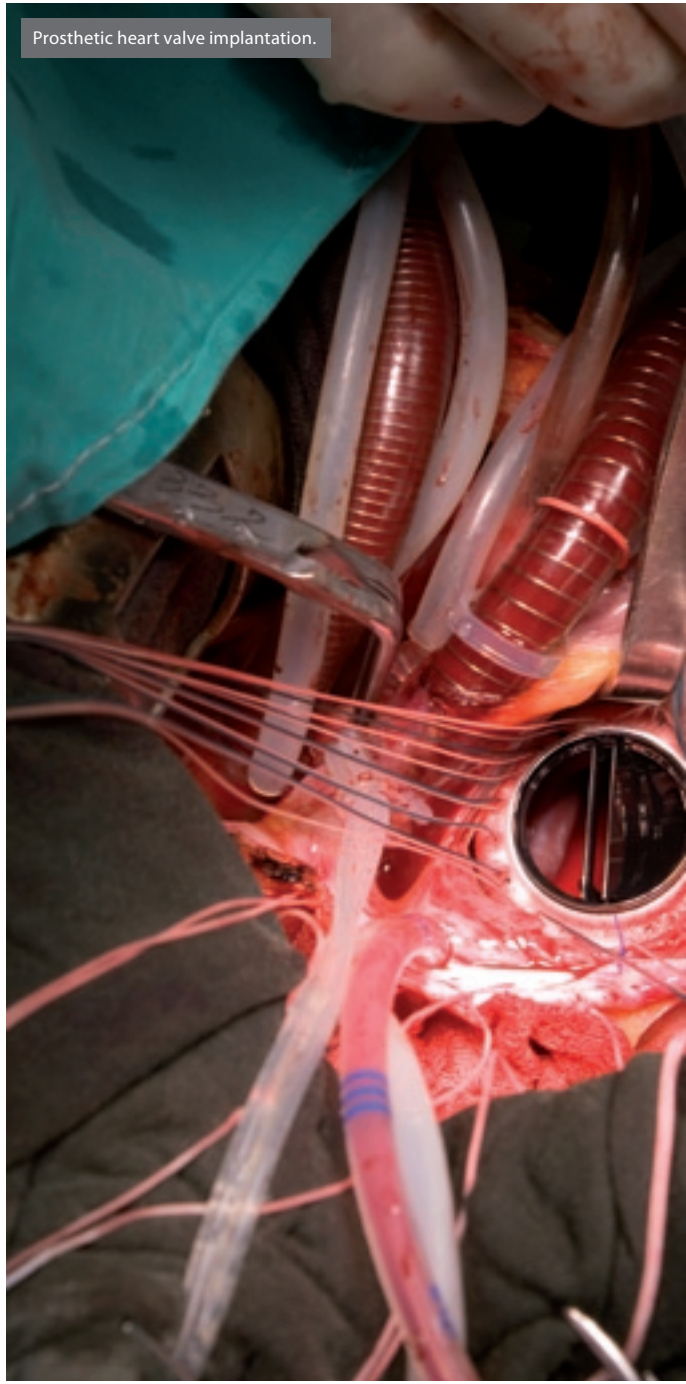
The explosive growth in transplantation owes much to the development and testing of novel immunosuppressive compounds by researchers such as **Roy Calne** in Cambridge. He was using drugs such as aziothioprine in kidney transplants, but it was his clinical work confirming the value of cyclosporine that turned an experimental technique into a routine procedure.

Calne worked with **Roger Williams** of King's College London on the UK's first liver transplants (Williams was later responsible for George Best's liver transplant). UK heart transplants were pioneered by **Magdi Yacoub** of Imperial College, who went on to perform more heart transplants than any other surgeon.

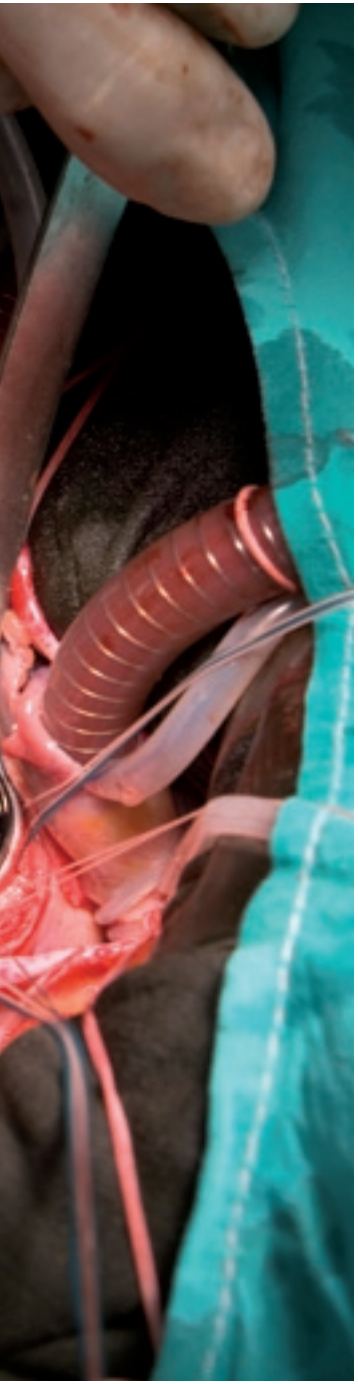
The clinical side of transplantation owed much to the ever-growing understanding of the immune system and its response to foreign tissue. A crucial contribution was made by **Peter Medawar**, who studied at Birmingham and UCL, and whose research revealed key insights into the nature of 'tolerance' to transplanted tissue – recognised by the award of a Nobel Prize in 1960.

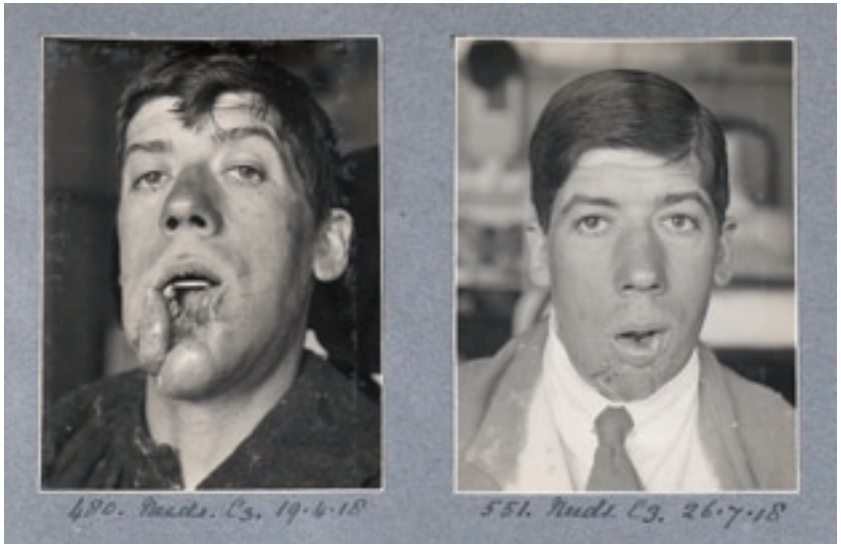
Medical innovations remain important, however, including the development by a team at Birmingham of the 'split liver' technique, enabling one liver to be transplanted to both an adult and a child.

A further key development has been the development of prosthetic body parts, notably the total hip replacement pioneered by **John Charnley** at Manchester and the Oxford Knee, developed by **John O'Connor** and **John Goodfellow** in 1976. Many thousands of children have benefited from cochlear implants, first launched in Nottingham in 1989.



Prosthetic heart valve implantation.





PLASTIC SURGERY

British doctors were pioneers of reconstructive surgery for injured servicemen.

War is a major driver of medical innovation. Reconstructive surgery, for example, was transformed during the First and Second World Wars – primarily thanks to two New Zealanders working in the UK: Harold Gillies and Archibald McIndoe.

Born in Dunedin in 1882, Gillies studied medicine in Cambridge before qualifying at Barts. A posting to France in 1915 converted him to facial surgery, and returning to the UK, he persuaded the Army to establish a treatment centre at Aldershot for troops with facial injuries.

The horrors of the Somme soon made it obvious that Aldershot's facilities were hopelessly inadequate, as soldiers flooded back to England with horrific facial injuries caused by shrapnel and sniper fire. Crucially, Gillies insisted that their treatment should be concentrated at one location – converting an old mansion house near Sidcup, Kent.

Unusually, Gillies drew together a multidisciplinary team, including artists, dentists, radiologists and anaesthetists as well as surgeons. They were responsible for numerous innovations, including the development of endotracheal anaesthesia by Ivan Magill. Gillies also placed great importance on the psychological welfare of soldiers.

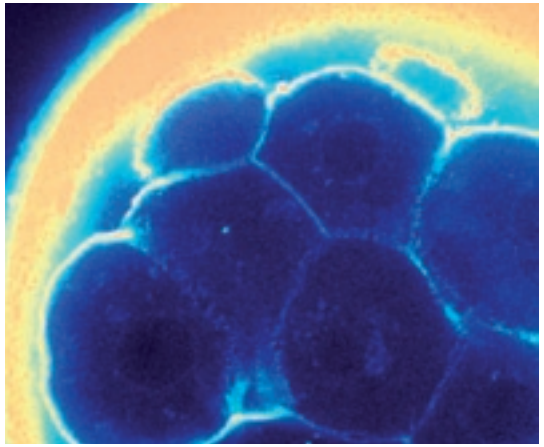
This concern was also notable in fellow New Zealander Archibald McIndoe. A cousin of Gillies, McIndoe studied medicine in New Zealand. He arrived in the UK in 1930 and secured a position in the plastic surgery department at Barts.

At the start of the Second World War, McIndoe moved to the Queen Victoria Hospital in East Grinstead. He was faced with new horrors: combustion of highly inflammable aviation fuel left many pilots with horrific burns.

With new techniques being pioneered, McIndoe's patients became known as the 'Guinea Pig Club'. As well as physical injuries, McIndoe paid equal attention to the potential psychological damage, integrating patients into local town life and emphasising the value of psychological rehabilitation.

Warfare generates many medical challenges, from unusual injuries to large numbers of casualties. Both Gillies and McIndoe are notable not just for remarkable surgical success but also the enlightened and humane way in which they cared for patients.

Above: Photographs of plastic surgery cases at the King George Military Hospital, 1916–1918.



APOPTOSIS: DEATH ON DEMAND

Understanding how cells commit suicide is leading the way to new treatments for cancer.

In 1972, Andrew Wyllie and colleagues in Aberdeen described and named the process by which cells deliberately and carefully dismantle themselves. A professor of Greek in Aberdeen suggested 'apoptosis', for 'falling off', as in leaves from a tree.

Apoptosis is important for removing cells in development (it creates the space between our toes, for example) but it also has a crucial role in preventing cancer – it eliminates damaged and potentially dangerous cells. If this process is disrupted, cells can multiply out of control.

Central to this system is *p53*, discovered by David Lane in Dundee. The 'guardian of the genome', *p53* monitors DNA for damage, triggering apoptosis when problems are detected. Mutations in the *p53* gene often lead to cancer – indeed, *p53* mutations are found in around half of human cancers.

Many insights into the molecular mechanisms of apoptosis have come from studies of the nematode worm *C. elegans*, including those of John Sulston in Cambridge, who received a share of a Nobel Prize in 2002.

Many agents targeting the apoptosis pathway in cancer are now in development.

Above: Confocal microscope image of a nematode worm (*C. elegans*).

1974
John Sulston and colleagues in Cambridge begin studies of cell death (apoptosis) in the nematode worm *C. elegans*.

1978
Roy Calne in Cambridge begins clinical trials on cyclosporine, a new drug preventing organ rejection. Success is an important step towards routine organ transplantation.

1979
David Lane in Dundee discovers the tumour suppressor *p53*.

1981
Martin Evans in Cambridge cultures embryonic stem cells for the first time.

1987
In Sheffield, Alan Johnson shows that surgical interventions can be compared with the same rigour and objectivity as pharmacological interventions in randomised control trials, in a pioneering study comparing conventional with laparoscopic surgery.

1989
The Nottingham Cochlear Implant Programme is established and provides the first UK child with a cochlear implant.

1991
Alan Crossman in Manchester and Tipo Aziz in Oxford show that deep brain stimulation corrects symptoms of Parkinson's disease in an animal model.

1996
Dolly the sheep is cloned by Ian Wilmut and Keith Campbell in Edinburgh.

2003
Ian Chambers and Austin Smith in Edinburgh identify a key pluripotency gene, *Nanog*.

2004
Stephen Minger at King's College London is the first to bank an embryonic stem cell line in the UK's national stem cell bank.

UK life science Nobel Prizes

Since Ronald Ross received the UK's first Nobel Prize in 1902, scientists based or trained in the UK have been regular recipients of these prestigious awards. While the Physiology or Medicine Prize recognises work of significant clinical importance, the Chemistry Prize has often also been awarded for achievements that have significant implications for medicine.

1902
Ronald Ross (P/M): Transmission of malaria

1922
Archibald Hill (P/M): Heat production in muscle

1923
John Macleod (P/M): Discovery of insulin

1929
Frederick Gowland Hopkins (P/M): Discovery of vitamins

Arthur Harden (C): Fermentation of sugar by yeast

1932
Edgar Adrian, Charles Sherrington (P/M): Function of neurones

1936
Henry Dale (P/M): Chemical transmission of nerve impulses

1937
Albert Szent-Györgyi (P/M): Chemistry of cell respiration

Norman Haworth (C): Structures of carbohydrates

1944
Herbert Gasser (P/M): Functions of single nerve fibres

1945
Ernst Chain, Alexander Fleming, Howard Florey (P/M): Discovery of penicillin

1946
Hermann Muller (P/M): Production of mutations by X rays

1947
Robert Robinson (C): Synthesis and analysis of alkaloids

1951
Max Theiler (P/M): Transmission of yellow fever

1952
Archer Martin, Richard Synge (C): Invention of partition chromatography

1953
Hans Krebs (P/M): Discovery of the citric acid (Krebs) cycle

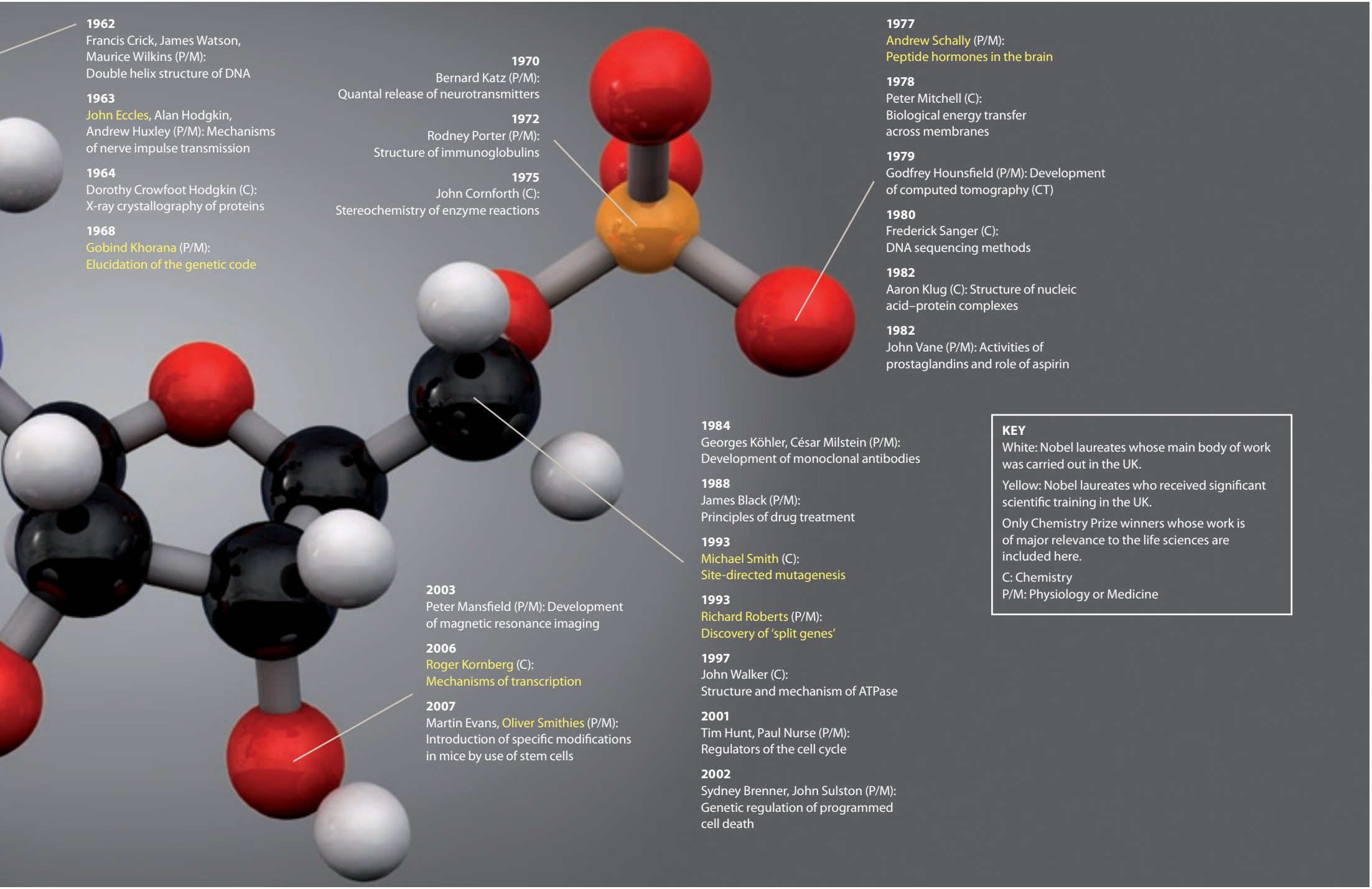
1956
Cyril Hinshelwood (C): Chemical kinetics of metabolic reactions

1957
Alexander Todd (C): Chemistry of nucleotides

1958
Frederick Sanger (C): Protein sequencing

1960
Peter Medawar (P/M): Acquired immunological tolerance

1962
John Kendrew, Max Perutz (C): Protein structures



1962
Francis Crick, James Watson, Maurice Wilkins (P/M): Double helix structure of DNA

1963
John Eccles, Alan Hodgkin, Andrew Huxley (P/M): Mechanisms of nerve impulse transmission

1964
Dorothy Crowfoot Hodgkin (C): X-ray crystallography of proteins

1968
Gobind Khorana (P/M): Elucidation of the genetic code

1970
Bernard Katz (P/M): Quantal release of neurotransmitters

1972
Rodney Porter (P/M): Structure of immunoglobulins

1975
John Cornforth (C): Stereochemistry of enzyme reactions

1977
Andrew Schally (P/M): Peptide hormones in the brain

1978
Peter Mitchell (C): Biological energy transfer across membranes

1979
Godfrey Hounsfield (P/M): Development of computed tomography (CT)

1980
Frederick Sanger (C): DNA sequencing methods

1982
Aaron Klug (C): Structure of nucleic acid–protein complexes

1982
John Vane (P/M): Activities of prostaglandins and role of aspirin

1984
Georges Köhler, César Milstein (P/M): Development of monoclonal antibodies

1988
James Black (P/M): Principles of drug treatment

1993
Michael Smith (C): Site-directed mutagenesis

1993
Richard Roberts (P/M): Discovery of 'split genes'

1997
John Walker (C): Structure and mechanism of ATPase

2001
Tim Hunt, Paul Nurse (P/M): Regulators of the cell cycle

2002
Sydney Brenner, John Sulston (P/M): Genetic regulation of programmed cell death

2003
Peter Mansfield (P/M): Development of magnetic resonance imaging

2006
Roger Kornberg (C): Mechanisms of transcription

2007
Martin Evans, Oliver Smithies (P/M): Introduction of specific modifications in mice by use of stem cells

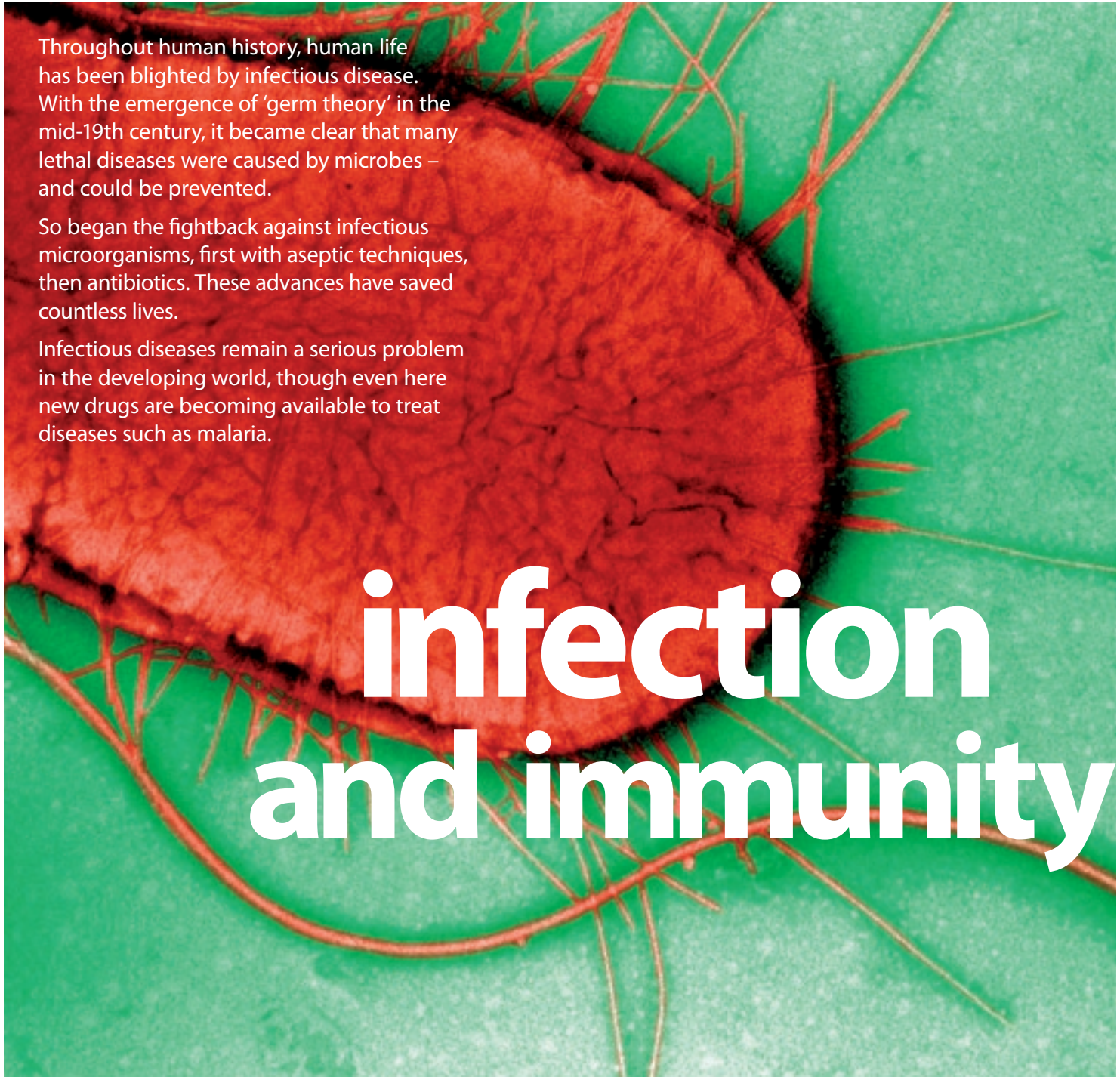
KEY

White: Nobel laureates whose main body of work was carried out in the UK.

Yellow: Nobel laureates who received significant scientific training in the UK.

Only Chemistry Prize winners whose work is of major relevance to the life sciences are included here.

C: Chemistry
P/M: Physiology or Medicine



Throughout human history, human life has been blighted by infectious disease. With the emergence of 'germ theory' in the mid-19th century, it became clear that many lethal diseases were caused by microbes – and could be prevented.

So began the fightback against infectious microorganisms, first with aseptic techniques, then antibiotics. These advances have saved countless lives.

Infectious diseases remain a serious problem in the developing world, though even here new drugs are becoming available to treat diseases such as malaria.

infection and immunity

RESISTING INVADERS

The origins of germ theory are generally credited to Louis Pasteur, but British doctors were quick to spot the medical possibilities of this new way of thinking.

Foremost among them was **Joseph Lister**. A dedicated medic – he spent three months of his honeymoon visiting medical centres on the Continent – Lister reasoned that chemical treatments could be used to rid wounds and surgical instruments of contaminating microbes. His use of carbolic acid and obsession with cleanliness radically transformed surgery.

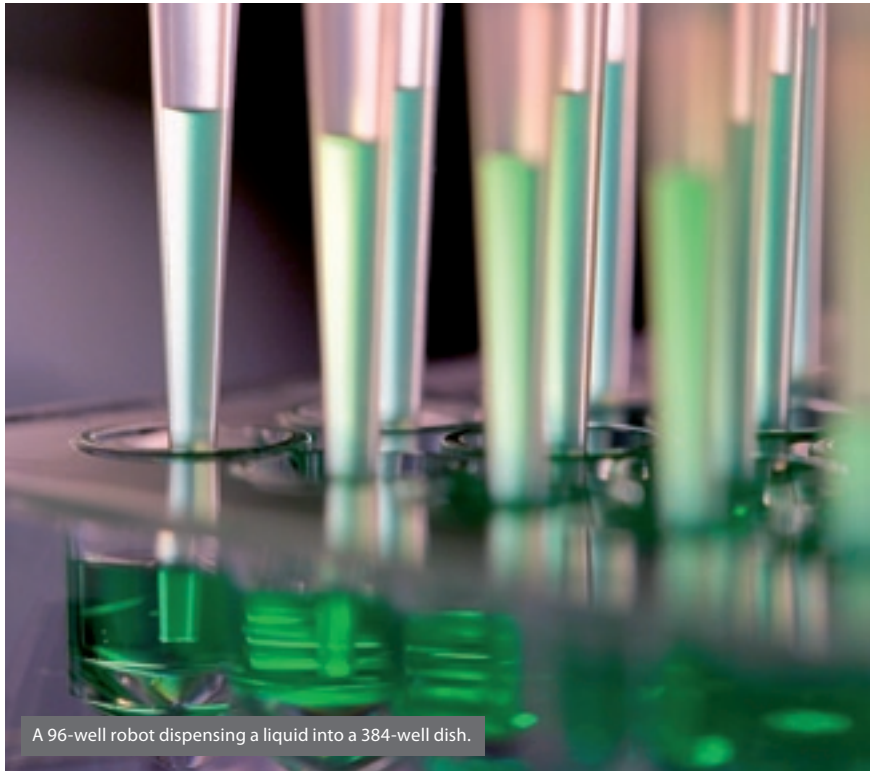
Antiseptic approaches prevented people from being infected. But if they did acquire infection, there was very little doctors could do. That all changed with the revolutionary development of antibiotics.

In 1928, while working at St Mary's Hospital, part of Imperial College, **Alexander Fleming** noticed that bacteria were not growing around mould colonies that had appeared on plates left exposed to the atmosphere.

He went on to discover that the active compound from his mould, penicillin, killed several disease-causing bacteria. However, he struggled to grow the mould and extract penicillin.

Turning the promise of penicillin into reality fell to a group of Oxford researchers, including **Ernst Chain**, **Howard Florey** (who shared a Nobel Prize with Fleming) and **Norman Heatley**, who made crucial contributions – including the inspired use of bedpans from the Radcliffe Infirmary to grow the mould.

Antibiotics are arguably the greatest ever advance in medical history. Their clinical value was confirmed by the Oxford team and others, including **Mary Evans** and **Wilfred Gaisford** at Dudley Road (now City) Hospital Birmingham, who ran clinical trials of the sulpha antibiotic M&B 693 (sulphapyridine) for the treatment of lobar pneumonia. This antibiotic was used to treat Winston Churchill when he contracted pneumonia in 1942.



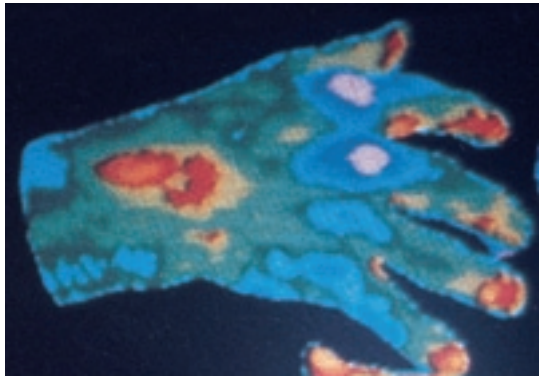
A 96-well robot dispensing a liquid into a 384-well dish.

DIAGNOSTICS

As well as treatment, diagnosis of infections can be crucial, helping to guide therapy. In 1951, **Frederick Heaf** in Cardiff developed a multi-puncture screening procedure which revealed whether someone had been exposed to TB. It subsequently became known world-wide as the 'Heaf test' and was in use in the UK for 50 years.

Several centres have made substantial contributions to detection methods, including **Anthony Campbell** In Cardiff whose assay technology based on chemiluminescence instead of radioactive labels is now used in over 100 million clinical laboratory tests per year, while in Birmingham, **Gary Thorpe** and **Tom Whitehead** pioneered similar tests to detect antioxidants and test water purity.

In the 1960s, **Peter Sneath** in Leicester developed computer-based methods for studies of microbial taxonomy and identification, ultimately leading to miniaturised biochemical test systems now used in virtually every hospital or diagnostic laboratory worldwide.



CALMING IMMUNITY

The immune system has evolved to defend us from microbial and other threats, but sometimes it turns on the body's own tissues, causing a range of autoimmune conditions.

A better understanding of the mechanisms of this immunological friendly fire can suggest new therapeutic options, as exemplified by the work of **Marc Feldmann** and **Ravinder Maini** at Imperial College. They targeted a key signalling molecule, tumour necrosis factor (TNF), which had been identified by Gordon Duff's group in Sheffield, developing new therapies for rheumatoid arthritis and other autoimmune diseases.

Their work is a notable example of translational research: taking a laboratory finding – that TNF is a key mediator in inflammation – and then developing and testing targeted therapies, helping to steer a drug through the drug approval process.

In Southampton, **Stephen Holgate** has adopted an analogous approach to block the action of the key inflammatory antibody IgE, leading to innovative biological approaches to treat respiratory conditions such as asthma.

Above: A thermogram revealing rheumatoid arthritis of the hand.

1832
John Snow enrols at **Newcastle's** medical school shortly after it opens in 1832, moving on to London to complete his degree. In 1854, he makes the connection between water and cholera transmission, halting a cholera epidemic in London's Soho.

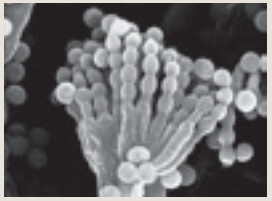
1867
Joseph Lister, Regius Professor of Surgery at **Glasgow** University, announces that his wards have remained clear of sepsis for nine months – testament to the success of his aseptic procedures.

1894
Patrick Manson, the father of tropical medicine, suggests that malaria is transmitted by mosquitoes.

1902
Ronald Ross, who studied medicine at **Barts** and later worked at the **Liverpool School of Tropical Medicine**, is awarded a Nobel Prize for his work confirming that mosquitoes transmit the malaria parasite.

1928
Alexander Fleming, of **Imperial College London**, makes his famous discovery of penicillin while working in the Inoculation Department at St Mary's Hospital.

1939
Mary Evans and Wilfred Gaisford at Dudley Road (now City) Hospital **Birmingham** begin clinical trials of the sulpha antibiotic M&B 693 (sulphapyridine) for the treatment of lobar pneumonia.



1945
Howard Florey, Ernst Chain and Norman Heatley, working at the Sir William Dunn School of Pathology in **Oxford**, demonstrate the therapeutic value of penicillin and develop ways to mass produce it, ushering in the age of antibiotics.

1951
In **Cardiff**, Anthony Campbell develops a novel biomedical assay technology based on chemiluminescence instead of traditional radioactive labels; the technique is now used in over 100 million clinical laboratory tests per year.

1951
Frederick Heaf in **Cardiff** publishes his work on a multi-puncture screening procedure for immunity to TB, subsequently known world-wide as the 'Heaf test'.

1952
James Riley in **Dundee** discovers that histamine is stored in mast cells, work that underpins much subsequent pharmacological and allergy research.

1965
Jenny Best and Jangu Banatvala at **King's College London** develop a technique for rapid diagnosis and detection of rubella, leading to the first characterisation of rubella virus by electron microscopy.

1969
In response to an outbreak of hepatitis that claims 11 lives, Ken Murray in **Edinburgh** develops the first diagnostic test for hepatitis B virus and later the first HBV vaccine.

1973
George Stevenson in **Southampton** isolates the first molecularly defined human anti-cancer antibodies, leading to the development of DNA vaccines for cancer.

1975
César Milstein and Georges Köhler in **Cambridge** develop a method for mass producing monoclonal antibodies, leading to a Nobel Prize in 1984.

1976
The World Health Organisation announces that smallpox has been eradicated, thanks to a concerted effort in which Allan Watt Downie at **Liverpool** has played an important role.

1982
Tony Pinching and Jonathan Weber of **Imperial College** establish the first UK cohort studies of people with HIV.

1983
Herman Waldman in **Cambridge** develops Campath-1 therapeutic monoclonal antibody, forerunner of alemtuzumab.

1984
Robin Weiss at **University College London** identifies CD4 as the cell surface receptor for HIV and develops the first serological test for the virus.

1985
In **Birmingham**, Gary Thorpe and Tom Whitehead pioneer the development and commercialisation of enhanced chemiluminescence, used in blood-borne disease analysis and water purity testing.

1986
Greg Winter in **Cambridge** develops techniques to humanise monoclonal antibodies.

1989
David Strachan from the **London School of Hygiene and Tropical Medicine** proposes the 'hygiene hypothesis', that lack of exposure to infections in early life underlies the recent rise in asthma and allergic responses.

1992
Marc Feldmann and Ravinder Maini at **Imperial College** develop treatments to block tumour necrosis factor, leading to new therapies for rheumatoid arthritis and other autoimmune diseases.

1997
Stephen Holgate, **Southampton**, pioneers anti-IgE therapy for asthma, leading to the application of innovative biological approaches to treat respiratory diseases.

1990s
Researchers at the **London School of Hygiene and Tropical Medicine** show in randomised controlled trials that mosquito nets impregnated with insecticides can block the spread of malaria.

2002
Mike Malim and his team at **King's College London** discover a human gene that inhibits HIV infection, opening up a new avenue of anti-HIV research.

2005
The Immunology and Infection Unit at **Hull York Medical School** opens, integrating the study of basic immunology, microbiology and parasitology.

2006
The WHO recommends use of artemisinin combination therapies, developed by Nick White and colleagues in **Oxford**, for treatment of malaria.

2006
Irwin Mclean in **Dundee** discovers that mutations of the fillagrin gene are present in many cases of eczema and asthma, providing new targets for treatment of these common diseases.

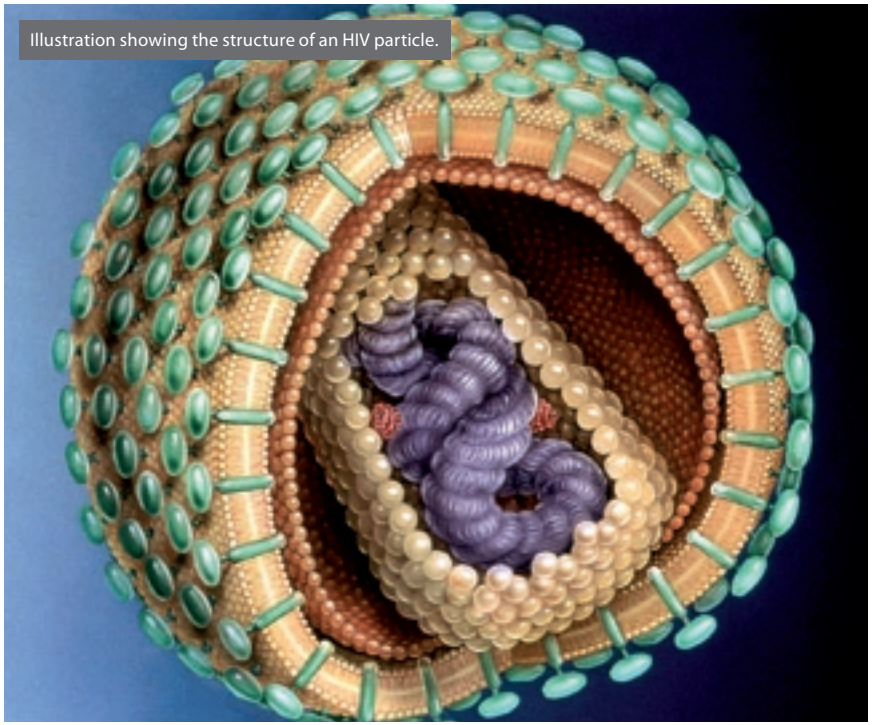


Illustration showing the structure of an HIV particle.

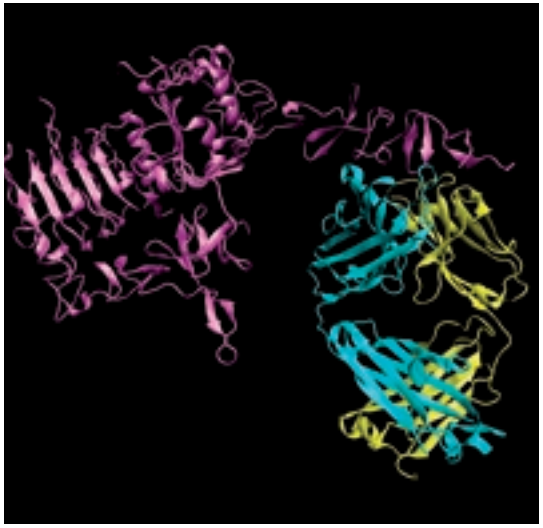
HIV

In the 1980s, a new devastating viral infection appeared: HIV/AIDS. Researchers in the UK made several important contributions in the early days of this new epidemic. **Robin Weiss** at University College London identified CD4 as the cell surface receptor for HIV and developed the first test for antibodies to the virus, used to identify those infected.

At Imperial College, **Tony Pinching** and **Jonathan Weber** established the first UK cohort studies of people with HIV in 1982, which generated important information on the progression of the disease.

Although effective drugs exist, there is still an urgent need for more and better treatments. Research continues into HIV at several centres, including King's College London, where **Mike Malim** and his team recently discovered a human gene that inhibits HIV infection, opening up a new avenue of anti-HIV research.

Meanwhile, groups such as that of **Andrew McMichael** in Oxford are attempting to understand the nature of the immune response to HIV and to develop effective vaccines.



MONOCLONAL ANTIBODIES

First created in the 1970s, monoclonal antibodies are invaluable in research and increasingly being used therapeutically.

The exquisite selectivity of antibodies makes them ideal tools in many areas, from detection and diagnosis to blocking of specific protein activity. In 1975, their use exploded when **César Milstein** and **Georges Köhler** at the Laboratory of Molecular Biology (LMB) in Cambridge developed a way of mass-producing identical antibody molecules – monoclonal antibodies.

One medical use is in cancer treatment, using antibodies targeted against structures found on cancer cells. An early example was the 'Campath-1' monoclonal antibody, specific for T cells, which was developed by **Herman Waldmann** and colleagues in Cambridge to treat forms of leukaemia and lymphoma.

Early medical use was hampered by the fact that monoclonal antibodies were based on mouse antibodies, and hence seen as 'foreign' by patients. A significant step forward was made by **Greg Winter** and colleagues, also at LMB, who replaced key mouse structures in the antibodies with their human counterparts – creating 'humanised' antibodies that now form the basis of therapeutic monoclonal antibodies.

This new class of therapeutic is becoming increasingly common, as researchers target molecules specifically implicated in disease processes. Examples include trastuzamab (Herceptin), alemtuzumab (the humanised form of Campath-1) and monoclonal antibodies against tumour necrosis factor (see page 17).

Above: Herceptin breast cancer drug, molecular model.

TROPICAL MEDICINE

The roots of tropical medicine lie in the UK and it continues to be a field in which the UK excels.

The field of tropical medicine was strongly influenced by the UK's imperialistic excursions overseas in the 19th century. Tropical diseases exacted a heavy toll on troops and government administrators stationed abroad.

A key figure was **Patrick Manson**, who trained originally in Aberdeen and made numerous discoveries about the causes and spread of tropical diseases. He helped to set up what is now the London School of Hygiene and Tropical Medicine.

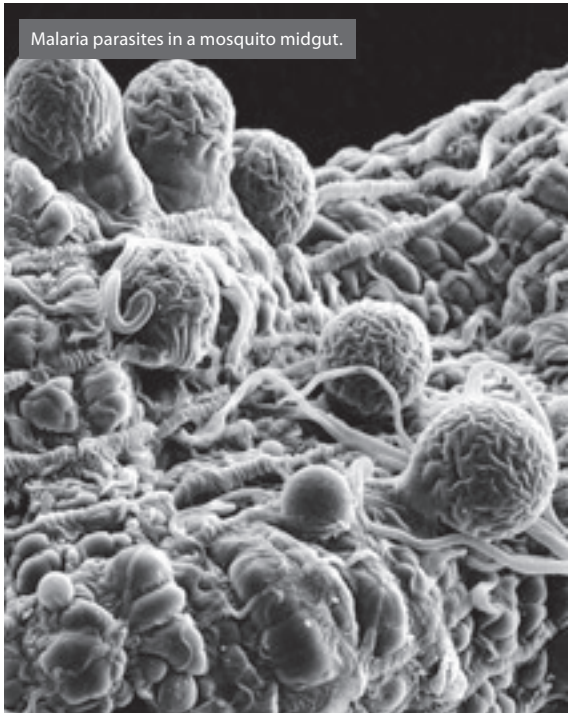
Possibly Manson's greatest contribution was to suggest that mosquitoes were responsible for the spread of the malaria parasite – a supposition proved by his protégé, **Ronald Ross**. Ross received the UK's first Nobel Prize in Physiology or Medicine in 1902. A medical student at Barts, Ross spent most of his career at the Liverpool School of Tropical Medicine.

Although malaria was banished from many regions in the 20th century – including England – it remains a serious global threat to health. Several effective drugs have been rendered next to useless because the malaria parasite has developed resistance.

Yet there have recently been encouraging signs of progress. Randomised controlled trials run by researchers at the London School of Hygiene and Tropical Medicine have shown that bednets soaked in insecticide are effective and cost-effective counters to malaria transmission. Their widespread use could save the lives of 400 000 young African children every year.

In a significant advance, **Nick White** and colleagues in Oxford, working in Thailand and Vietnam, have pioneered the use of artemisinin combination therapies for malaria, using derivatives of an ancient Chinese herbal remedy. Use of these drugs has dramatically cut deaths from malaria in South-East Asia and, globally, are the World Health Organisation's recommended drugs for malaria.

Postcard: mosquito net to be worn as a veil, early 20th century.



Malaria parasites in a mosquito midgut.

A mosquito (*Anopheles stephensi*) in flight with its abdomen full of blood.

an inside view

Being able to see inside the living body has revolutionised medicine.

For most of history, doctors were unable to see inside the living body, relying instead on outward signs of illness, poring over its emanations, or interpreting the pulse. The 20th century saw a flourishing of techniques for visualising living tissue, greatly extending medicine's diagnostic abilities.

The beginning of this new era can be traced back to Wilhelm Roentgen's discovery of X-rays in 1895. Remarkably, just months later **John Macintyre**, a nose and throat specialist in Glasgow with a particular interest in music – he also made phonographic recordings of famous singers and musicians – had opened the world's first radiology department. He presented his first X-ray images to the Royal Society in London in 1897.

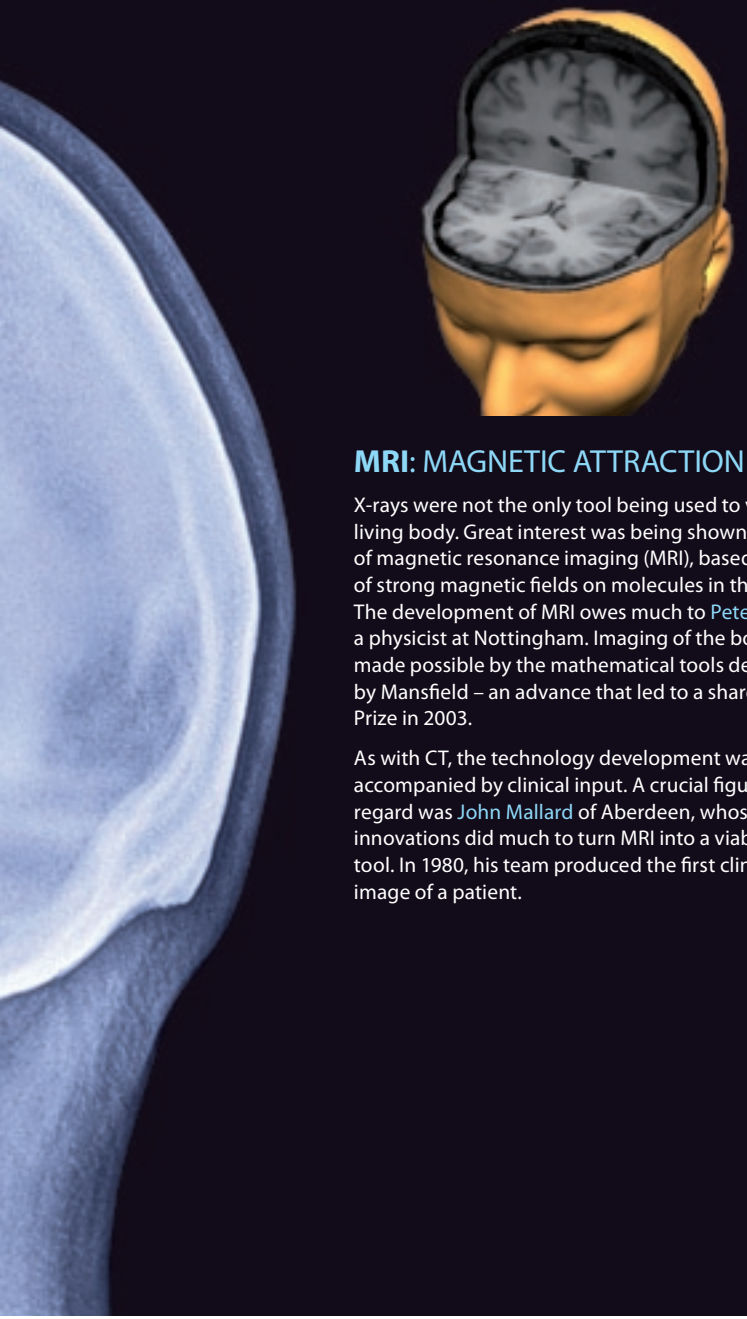
Above: Interior of the X-ray department at the Marie Curie Hospital for Cancer and Allied Diseases, 1934.

X-ray imaging is also at the heart of CT (computed tomography) scanning, developed by **Godfrey Hounsfield** at EMI in the UK and the US physicist Allan McLeod Cormack. By taking a series of 'slices' through the body, CT imaging provides a three-dimensional view of body structures.

Hounsfield tested his device on a preserved human brain and a fresh cow's brain, before in 1971 trying it out on a patient – a patient with a cerebral cyst. This work, carried out in conjunction with **Jamie Ambrose** at Atkinson Morley's Hospital in Wimbledon, part of St George's, was a crucial step in adapting the technology for medical practice.

In 1972 the first commercial CT scanner was pressed into service by **Ian Isherwood** and **Godfrey Hounsfield** in Manchester, with machines also being installed at Glasgow and the Institute of Neurology in London.

Below: MRI reconstruction of the brain, skull and face.

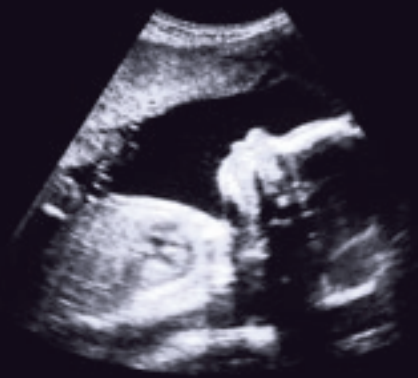


MRI: MAGNETIC ATTRACTION

X-rays were not the only tool being used to visualise the living body. Great interest was being shown in the use of magnetic resonance imaging (MRI), based on the effects of strong magnetic fields on molecules in the body. The development of MRI owes much to Peter Mansfield, a physicist at Nottingham. Imaging of the body was made possible by the mathematical tools developed by Mansfield – an advance that led to a share of a Nobel Prize in 2003.

As with CT, the technology development was accompanied by clinical input. A crucial figure in this regard was John Mallard of Aberdeen, whose practical innovations did much to turn MRI into a viable medical tool. In 1980, his team produced the first clinically useful image of a patient.

Below: Foetus ultrasound at 24 weeks.



ULTRASOUND: ENGINEERING MEETS MEDICINE

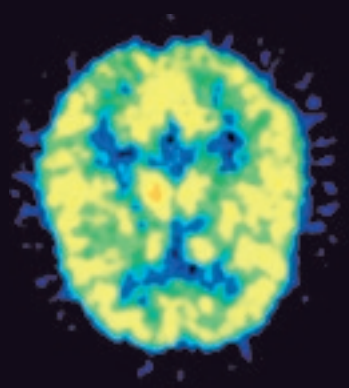
A further imaging technology, ultrasound, also owes much to UK researchers – in particular, Ian Donald in Glasgow. A former RAF medical officer and graduate of St Thomas', Donald arrived in Glasgow in 1954 with, in his words, "a rudimentary interest in radar… and a continuing childish interest in machines". Despite much scepticism he was convinced that echo sounding, or sonar, had great medical potential.

In 1955, Donald visited local boilermakers Babcock & Wilcox, at the behest of one of the directors, husband of a grateful patient. Two cars made the journey, their boots full of clinical samples. These were studied using an industrial ultrasonic metal flaw detector – along with a large steak as control sample.

Working with Tom Brown from the engineering firm Kelvin & Hughes, Donald refined the technologies for abdominal imaging, proving its worth with a series of spectacular diagnoses – including that of a woman with a history of fibrosis who was admitted with a suspected myoma. Ultrasound imaging revealed that she was actually pregnant. She went on to have a healthy baby.

By 1958, Donald had published the world's first ultrasound images of the foetus, and foetal imaging became one of the technology's main applications.

Below: Positron emission tomograph of the brain.



PET: FROM STRUCTURE TO FUNCTION

CT, MRI and ultrasound have provided a wealth of information on body structures and structural abnormalities. Recently, this structural insight has been complemented by a growth in functional information that can be obtained from the living body.

One key technology is positron emission tomography (PET), championed by John Mallard. The strength of PET signals from the body depends on metabolic activity, so PET imaging can reveal differences between structures that may be physically similar but very different in character – such as a cyst versus a cancer.

PET is now used for cancer detection and monitoring of responses to treatment, as well as for recording brain activity and tracing metabolism in the body. The availability of new forms of radiolabelled metabolite may significantly increase its potential medical uses. It may provide a way to diagnose early stages of conditions such as Alzheimer's disease.

The brain is also the target of a spinoff of MRI, functional MRI, which can be used to assess regional brain activation. It is based on the finding that blood flow in the brain increases with neural activity – a discovery actually made by Charles Sherrington in the 1890s.

fMRI is now widely used in research to identify areas of the brain active as particular tasks are undertaken, providing fascinating insight into the brain function. The technique is also revealing what may be going wrong in conditions such as schizophrenia, autism and attention deficit hyperactivity disorder.

doctor at large

A doctor is principally concerned with the health of his or her patients. Diagnosis and treatment of each individual patient is at the heart of medical practice.

Sometimes, though, physicians have the opportunity to have an even broader beneficial impact, by helping to safeguard public health.

The role of the doctor here can be significantly different – searching for the roots of disease outbreaks, identifying potential threats to health, or influencing health or social policy.

Through these kinds of activities, doctors are not only protecting the public from health dangers that are known about but also helping to identify where the problems of the future may lie.

DOCTOR AS DETECTIVE

Identifying the causes of diseases and how they are spread are fundamental steps towards prevention, and they often call for highly honed investigative skills.

One of the earliest and best known examples is that of **John Snow**, an early student at Newcastle's medical school, who made the connection between water and cholera transmission in 1854. He studied a cholera outbreak in Soho, London, and by mapping each case of disease, pinpointed a water pump on Broad Street as the likely source of contamination. By preventing the pump from being used, he also managed to halt the epidemic.

In 1894, the first UK Public Health lab was founded by **Sheridan Delepine** of Manchester. Delepine also successfully tracked down the causes of a poisoning outbreak in Derby in 1902, tracing its origins to a consignment of contaminated pork pies.

Monitoring of disease outbreaks in populations can also provide vital information on how a disease is spread within a community. An early example was the meticulous work of **William Pickles**, a graduate of Leeds Medical School, who followed an epidemic of catarrhal jaundice in Wensleydale, tracing the entire epidemic to one child and establishing the long incubation (26–35 days) of the disease. Pickles's careful and precise recording, published in his book *Epidemiology in a Country Practice*, provided a model for practice-based research.

Perhaps the most famous epidemiological study, though, was that of **Richard Doll**, who with **Austin Bradford Hill** of the London School of Hygiene and Tropical Medicine, showed that smoking caused lung cancer and increased the risk of heart disease. In the 1950s, the prevalence of lung cancer was rising inexorably, yet its causes remained a mystery. A popular idea was that road building might be to blame.

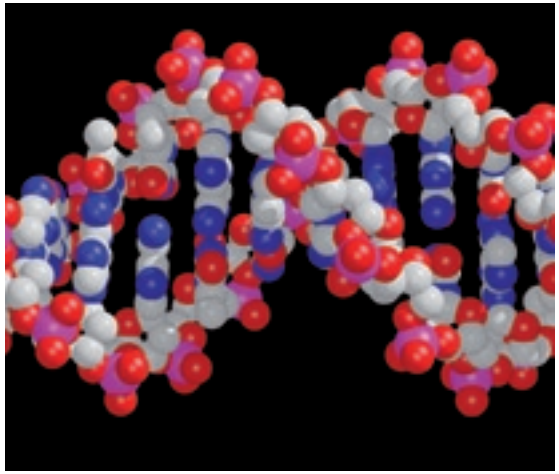
Ironically, it was through studies of general practitioners who smoked that Doll and Hill were able to link lung cancer to smoking. They confirmed the finding in other populations, ultimately leading to a profound change in attitudes to smoking and providing the evidence for a raft of public health measures.

Contaminants in the water supply, from a scientific report into the cholera epidemic of 1854.

Moreover, Doll and Hill's work laid the foundations of modern epidemiological practice, an area of profound importance to today's public health.

Evidence of the power of epidemiological approaches can be seen in the success of initiatives such as Bristol's **Avon Longitudinal Study of Parents and Children** (ALSPAC, also known as the 'Children of the Nineties'), which began with 14 000 pregnant women in 1991 and 1992. It has provided a wealth of information on the determinants of infant health and development.

And looking forward, the **UK BioBank project**, which is collecting health and lifestyle information from 500 000 people aged 40–69, in collaboration with centres throughout the UK, will provide valuable information on the causes of disease in middle and later life.



DNA AND MEDICINE

The second half of the 20th century saw a flourishing of DNA-based science, the fruits of which are beginning to be harvested in medicine.

The discovery of the double helix structure of DNA by **James Watson** and **Francis Crick** in Cambridge, aided by **Maurice Wilkins** and **Rosalind Franklin** at King's College London, is often heralded as the beginning of a new era in science. Equally auspicious, though, were the elucidation of the genetic code (to which Francis Crick, with **Sydney Brenner**, made important contributions) and the development of DNA sequencing technologies by **Fred Sanger**.

The emerging field of 'molecular biology' dovetailed with the traditional discipline of genetics. As well as providing molecular explanations for biological phenomena, the new field provided a suite of tools for studying living systems.

In medicine, a major goal has been to determine the role genes play in disease, harking back to Archibald Edward Garrod's 'inborn errors of metabolism'. In the modern era, pioneering work was done by **David Weatherall** in Oxford, whose group dissected the causes of thalassaemias, blood disorders caused by mutations in haemoglobin genes.

Genetic diagnostic tools emerging from the work have been widely adopted globally. In Cyprus, for example, testing for carrier status has reduced the number of affected children almost to zero, even though haemoglobin mutations are common.

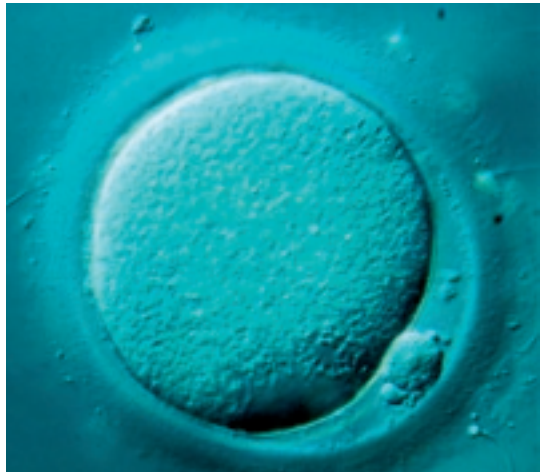
Single-gene disorders were soon being unravelled by new technologies – greatly helped by the Human Genome Project, to which the Wellcome Trust Sanger Institute at Hinxton made a major contribution. More common conditions – where genes and environmental factors combine to enhance the risk of disease – have proved trickier to unpick.

Within the past two years, this situation has changed dramatically, with a flurry of papers from the Wellcome Trust Case Control Consortium – a partnership between 24 leading UK groups – revealing a host of genes linked to a range of common diseases, from diabetes to Crohn's disease.

In general, psychiatric conditions have proven a tougher nut to crack. There have been some successes, such as a possible schizophrenia risk factor, DISC1, identified by **David Porteous** and colleagues in Edinburgh.

Although not of immediate medical benefit, identification of these genes opens up valuable new avenues of research for therapeutics.

Above: The DNA double helix.



IVF AND PGD

The birth of Louise Brown in 1978 was a landmark in reproductive medicine.

Infertility is common. For many couples the solution lies in IVF (*in vitro* fertilisation), first achieved in humans in 1978 by **Patrick Steptoe**, who trained at King's College London and St George's Hospital Medical School, and Cambridge physiologist **Bob Edwards**. More than a million babies worldwide have now been born via IVF.

As well as enabling couples to have the children they so desperately want, IVF has also opened up the possibility of prenatal genetic testing for parents known to be at risk of having children with serious genetic conditions. **Alan Handyside**, **Robert Winston** and colleagues pioneered the use of new DNA methods to identify harmful mutations in the cells of very early embryos – preimplantation genetic diagnosis (PGD).

In 2006, doctors at Guy's and St Thomas' Hospitals developed a modified procedure, preimplantation genetic haplotyping. This technique can identify more mutations than conventional PGD.

Above: Oocyte during *in vitro* fertilisation.

EFFECTIVE HEALTHCARE

The UK's medical infrastructure also owes much to the products of its medical schools.

Our highly effective national blood transfusion service, for example, is in large part due to the efforts of **Geoffrey Keynes**, a surgeon at Barts between 1946 and 1949. The UK was at the forefront of transfusion services, launching a national service in 1946.

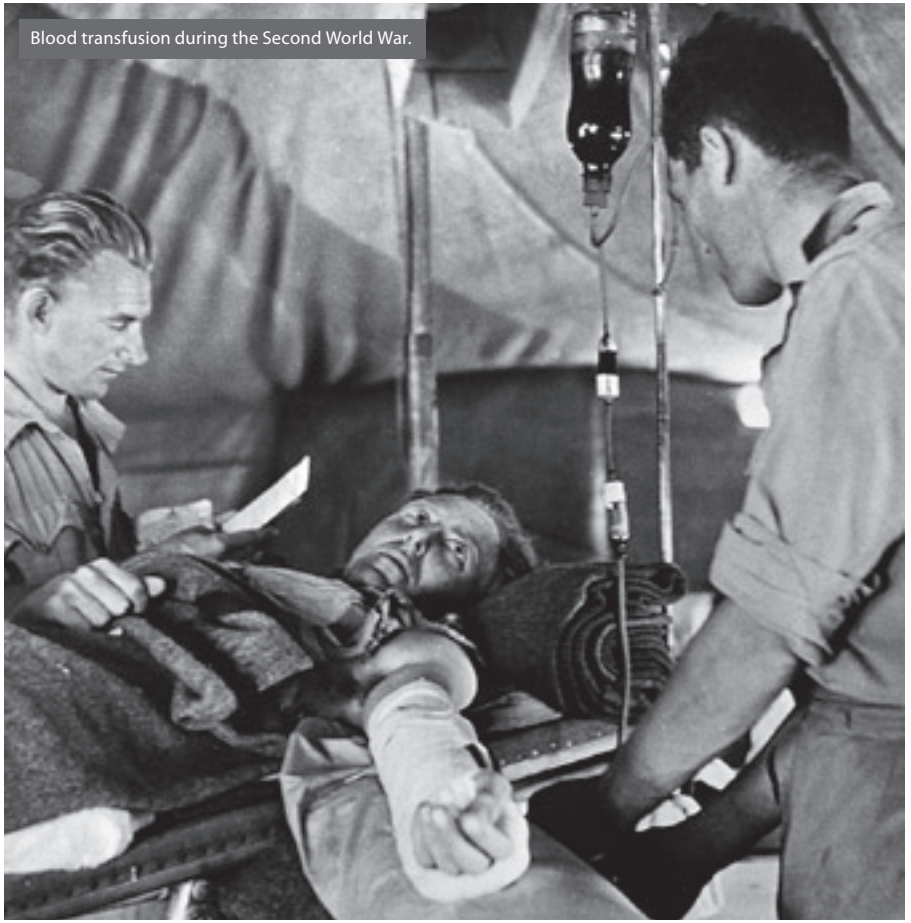
Two years later, the National Health Service itself was established – a process in which **Henry Cohen** (later Lord Cohen of Birkenhead) in Liverpool played a crucial role. Cohen was an exceptionally talented physician and teacher, and through his close association with **Aneurin Bevan**, the Minister of Health, he made a significant contribution to the planning of the NHS.

On the international stage, **Allan Watt Downie**, Professor of Bacteriology at Liverpool for over 20 years, provided expertise and practical assistance to the World Health Organisation in its efforts to eradicate smallpox, which was achieved in 1976.

In the latter part of the 20th century, the concept of evidence-based medicine gained ascendancy, emphasising the ability of medical research to identify effective (and cost-effective) treatments. The randomised controlled trial has become the gold standard by which therapies should be judged and has shown the value of numerous treatments now in routine clinical use, including statins and 'clot-busting' drugs (see page 6).

Other approaches have also yielded important information, however – including longitudinal studies which pinpointed babies sleeping on their front as a significant risk factor for sudden infant death syndrome.

The 2000s saw the continuation of large-scale clinical trials in primary care, such as those led by **Tony Kendrick** and **Paul Little**, involving a network of hundreds of general practitioners in Southampton, **David Mant** in Oxford and **Ann-Louise Kinmonth** in Cambridge. In Keele, **Elaine Hay** has shown how multidisciplinary health professional teams can use randomised controlled trials to identify effective primary care for people with common chronic disabling conditions such as back pain and osteoarthritis.



Blood transfusion during the Second World War.

Edzard Ernst at Peninsula Medical School has championed the rigorous appraisal of complementary and alternative medicines.

Evidence-based approaches to medicine have been energetically promoted by **Iain Chalmers**, who worked at the London School of Hygiene and Tropical Medicine and Oxford before establishing the Cochrane Collaboration. The drive for a rational basis for healthcare provision across the UK led to the creation of the National Institute for Health and Clinical Excellence in 1999.

COGNITIVE BEHAVIOURAL THERAPY

A 'talking therapy', cognitive behavioural therapy (CBT) offers a validated non-pharmacological approach for a range of disabling conditions.

CBT is a way of addressing distinctive thinking and behaviour patterns that negatively impact on a patient's mental state. Over the past 20 years, theoretical models have been developed for different conditions and used to create successful interventions.

The first CBT treatment approved by NICE was developed by **Chris Fairburn** and colleagues in Oxford for eating disorders such as bulimia nervosa. Researchers such as **David Clark** and **Anke Ehlers** at King's College London have shown that CBT is effective in post-traumatic stress disorder, helping survivors of the Omagh bombing in Northern Ireland, among others.

Notably, the success of CBT has been confirmed in randomised controlled trials, providing a firm evidence base for their wider rollout across the NHS – including a £173 million expansion of talking therapies announced in 2007.

Work continues to test the value of CBT in a wide range of conditions, including schizophrenia, being studied by, for example, **Doug Turkington** in Newcastle and **David Kingdon** in Southampton, and pain, the focus of **Simon Morley** in Leeds and others.

The computerised delivery of CBT also holds great promise. Beating the Blues for depression and FearFighter for phobias, developed by groups at the Institute of Psychiatry, have both received NICE approval.

Above: Talking therapies are effective treatments for depression.

SOCIAL FACTORS

An important role of doctors has been to highlight the health consequences of social inequities.

Even before the advent of the welfare state in 1948, **Dugald Baird**, Professor of Obstetrics and Gynaecology at Aberdeen, was highlighting the association between social circumstances and maternal and foetal health, promoting policies to reduce perinatal mortality, particularly among the poor, and to encourage planned parenthood.

Also influential was **Douglas Black**, a graduate of St Andrews and Professor of Medicine in Manchester. While on secondment at the Department of Health, he prepared what became known as the 'Black Report', the first major publication on the relationship between poverty and disease. Despite reputedly being suppressed by the incoming Conservative Government led by Margaret Thatcher, it later became a bestselling paperback and laid the foundations for much further work on the impact of social inequalities on health – still an issue, with male life expectancy differing by 10 years between affluent areas of London and Manchester.

Further evidence of the impact of social factors in health has come from the Whitehall study, led by **Michael Marmot** initially at the London School of Hygiene and Tropical Medicine and later at UCL. Looking at mortality rates among civil servants aged 20–64, the study found a clear link between civil service grade and mortality – those on the lowest grades were more likely to die early.

On a global stage, **Alastair Hay** of Leeds has been highly influential in his campaign for chemical agent disarmament, enshrined in the Chemical Weapons Convention adopted by 182 countries. Having seen the effects of Agent Orange in the Vietnam War, he has campaigned tirelessly against the use of chemical and biological agents in warfare.

Chart showing temperature and mortality of London for every week of 11 years, 1840-50, and 11-year average.

GENES AND CANCER

Numerous genes have been linked to cancer, including *MEN2* (causing multiple endocrine neoplasia, identified by **Bruce Ponder** in Cambridge), *p53* (discovered by **David Lane** in Dundee; see page 13), and the breast cancer gene *BRCA2* (isolated by **Mike Stratton** and colleagues at the Institute of Cancer Research).

Increasingly, it appears that cancer is genetically highly complex. Crucially, this complexity has important medical consequences. As the case of trastuzamab (Herceptin) illustrates, the causes of breast cancer will dictate whether a therapy will work.

More generally, the growing awareness of the links between genes (or their products) and risk of disease (and responses to drugs) is ushering in the field of pharmacogenetics or personalised medicine. While still in its infancy, treatments tailored to individuals' genetic make up will undoubtedly become more common in the coming decades.

Above: Colour-enhanced image of a breast cancer cell.

1854
John Snow makes the connection between water and cholera transmission.

1894
The first UK Public Health laboratory is founded by Sheridan Delepine of **Manchester**.

1919
Ethel Manson, a former Matron at **Barts**, succeeds in her campaign for the state registration of nurses. Manson is widely regarded as the founder of professional nursing and as a visionary, with ideas half a century ahead of her time.

1934
Henry (later Lord) Cohen becomes Chair of Medicine at **Liverpool**; an exceptionally talented physician and teacher, his close association with Aneurin Bevan, the Minister of Health, enables him to make a significant contribution to the planning of the National Health Service.

1939
William Pickles, a graduate of **Leeds** Medical School, publishes his book *Epidemiology in a Country Practice*, detailing his observations of an epidemic of catarrhal jaundice in Wensleydale.

1940s
Dugald Baird in **Aberdeen** highlights important role of social circumstances on maternal and foetal health, introducing the term 'perinatal'.

1946
Geoffrey Keynes, surgeon at **Barts** between 1946 and 1949, is instrumental in the establishment of a national blood transfusion service.

1950s
Richard Doll in **Oxford** and Austin Bradford Hill of the **London School of Hygiene and Tropical Medicine** show that smoking causes lung cancer and increases the risk of heart disease.

1967
Based at **London School of Hygiene and Tropical Medicine**, the original Whitehall Study begins; it uncovers a strong link between mortality and lower grades in the Civil Service.

1967
Cicely Saunders, of **King's College London**, founds the hospice movement and devotes her life to ensuring that terminally ill people can die with dignity and without pain.

1978
Patrick Steptoe, a graduate of **St George's**, is instrumental in work leading to the first 'test tube' baby, Louise Brown, born on 25 July 1978.

1984
Alec Jeffreys in **Leicester** develops the techniques for DNA fingerprinting and DNA profiling, which are now used all over the world in forensic science to assist police detective work and to resolve paternity and immigration disputes.

1997
The campaign of Alastair Hay of **Leeds** to outlaw chemical weapons is successful, with the creation of the Chemical Weapons Convention, since adopted by 182 countries.

2001
The world's first male fertility home test is developed in **Birmingham** Medical School, in conjunction with the company Genosis.

2007
In a newly built Clinical Research Facility and Trials Unit, University of **East Anglia** Medical School is coordinating a £4 million trial to determine the effectiveness of a screening programme for osteoporosis among 12 000 subjects in seven UK centres.

FUTURE CHALLENGES

Despite the major achievements of the past 150 years, significant challenges remain.

Many diseases remain difficult to treat, including Alzheimer's disease and other conditions that affect people in later life – which are growing in importance as the population ages. New therapies would also be valuable in other areas, including psychiatric conditions and management of chronic pain.

Although infectious diseases are not the major killers they used to be (in the UK at least), there is no cause for complacency. Antibiotic-resistant bacteria are a medical headache and new antibiotics are urgently needed. Globally, around two new human infections are appearing each year, mainly as pathogens jump species from animals to people. As HIV, SARS and avian flu illustrate, these infections can be highly dangerous. There is a need for ongoing surveillance to identify emerging threats, as well as for research to develop new and better treatments or vaccines.

Recent years have seen an alarming rise in obesity and associated health problems. Excessive weight gain is now common in young people, storing up potential health problems in later life. As a result, some fear that the century-long rise in life expectancy may stall or even decline.

On the international front, while some progress is being made, diseases such as HIV/AIDS, malaria and tuberculosis continue to kill millions every year. Even where infectious diseases are being brought under control, countries are beginning to feel the impact of the 'diseases of affluence' as heart disease, diabetes and so on take their place.

The developing world will also bear the brunt of climate change. But the UK will not escape its impact. The country can expect a future of increasingly turbulent weather, including heat waves and more severe weather events such as storms and floods. Respiratory complaints are likely to rise, particularly in cities. Food-borne diseases may well become more common.

More generally, the spiralling costs of healthcare are challenging the economic models on which medical care has been based for the past 50 years. Developing new, safe and effective drugs is becoming an increasingly expensive occupation, and much thought needs to be put into ensuring that the public can continue to gain access to the fruits of medical progress over the coming years.

OPPORTUNITIES

On the other hand, there are plenty of reasons to be optimistic about the future of medicine. The genetic revolution is transforming the way biomedical research is carried out. The Sanger Institute, which led the UK's contribution to the Human Genome Project, is now generating 10 billion base pairs of sequence information – the equivalent of three human genomes – every day. And productivity is continuing to rise exponentially.

This information is underpinning research into human biology and unearthing new leads for drug development. It is helping doctors dissect disease and offer treatments based on underlying causes rather than generic symptoms.

Pharmacogenetics, the use of drugs tailored to individuals' genetic make-up, is slowly infiltrating clinical practice. An early example is the use of genetic tests to identify those at risk of side-effects from antiretroviral drugs used to treat HIV infections. The clinical impact of pharmacogenetics is likely to be gradual, but it is already changing drug development, enabling companies to focus at earlier stages on responsive populations. It may also lead to new uses for old drugs, which have been shelved because of adverse reactions in a subsection of the population.

Progress in stem cell science is hugely exciting, particularly with the growing understanding of pluripotency – the ability of cells to generate all the other cell types of the body. There is a real prospect that adult cells could be converted into pluripotent stem cells, which could be used as a source of new cells for tissue repair or regenerative medicine. In fact, a significant challenge is to balance the urge to rush towards clinical application with the need to understand stem cells better, outside and inside the body.

The biology of ageing is another exciting area. With evidence growing that accumulating damage to cells underpins many of the diseases of later life, intervening in these processes could prevent a range of conditions.

More generally, disease prevention is emerging as a key aspect of public health. Many factors associated with healthy longevity have now been identified. Other dietary and behavioural information may be augmented by pharmacogenetic tests or genetic tests that identify risk factors for common diseases and suggest options for avoiding ill-health. It is feasible that supplements – dietary or pharmacological – could play an increasing role in keeping people healthy rather than treating them when they fall ill.

Another major opportunity lies in the gathering, sharing and analysis of health-related information. Large-scale epidemiological studies are already generating important findings. The UK has a great advantage in the shape of the NHS, and developing effective systems to draw on population data has to be a high priority.

Realising the benefits of the revolutionary changes in biomedical research of the past 50 years will call for some significant shifts. There is a widespread realisation – across the world – that more effort is needed to turn laboratory advances into practical medical innovations – the so-called 'translational research'. There is unfortunately no easy way to turn new knowledge into new products, and driving the process forward will have to involve major investment in people and facilities – a requirement that has been recognised and is being implemented.

So what of the doctor of the future? Increasingly he or she will be contributing both to treating illness and preventing disease; working locally but networking nationally (or internationally); listening to informed patients as well as dispensing advice and medicines. Medicine has been transformed over the past 150 years, and doctors have adapted too. Yet the principles that have governed doctors' behaviour and the importance of the trusting, therapeutic relationships with patients remain as valid today as they were a century and a half ago. Whatever changes occur over the next 150 years, doctors will undoubtedly be helping to drive and implement them in a way that benefits the public.

The preparation of samples for DNA sequencing.

UK MEDICAL SCHOOLS

Medical School	Council Member	Date Established
Aberdeen	Professor Mike Greaves	1497
Barts and the London	Professor Sir Nicholas Wright	1123 as St Bartholomew's, 1785 as the London Hospital Medical College
Birmingham	Professor Ian Booth	1825
Bristol	Professor Peter Mathieson	1833
Brighton and Sussex	Professor Jon Cohen	2001
Cambridge	Professor Patrick Sissons	1975
Cardiff	Professor Mike Owen	1893 (University of Wales, 2004 Cardiff)
Dundee	Professor Irene Leigh	1967
East Anglia	Professor Sam Leinster	2000
Edinburgh	Professor Sir John Savill	1720
Glasgow	Professor David Barlow	1637
Hull York	Professor Ian Greer	2001
Imperial	Professor Steve Smith	1997 as Imperial (1834 as Westminster and as Charing Cross)
King's	Professor Robert Lechler	1561 as St Thomas'
Keele	Professor Richard Hays	2004
Leeds	Professor David Cottrell	1831
Leicester	Professor David Wynford-Thomas	1975
Liverpool	Professor John Caldwell	1834
London School of Hygiene and Tropical Medicine	Professor Nick Black	1899
Manchester	Professor Paul O'Neill	1874
Newcastle	Professor Chris Day	1834
Nottingham	Professor Terence Stephenson	1966
Oxford	Professor Alastair Buchan	1312
Peninsula	Professor Sir John Tooke (Chair, Medical Schools Council)	2000
Queen's Belfast	Professor Patrick Johnston	1849
Sheffield	Professor Tony Weetman	1828
Southampton	Professor Iain Cameron	1969
St Andrews	Professor Hugh MacDougall	1413
St George's	Professor Peter Kopelman	1752
Swansea	Professor Rhys Williams	2004
UCL	Professor Ed Byrne	1828
Warwick	Professor Yvonne Carter	2000 with Leicester/2007 independent

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Editorial: Ian Jones, Isinglass Consultancy Limited.

Design: Jag Matharu, Thin Air Productions Limited.

TAP821/10-10-08/V3hc

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