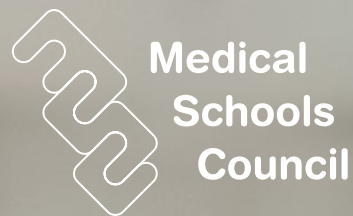


Health of the Nation

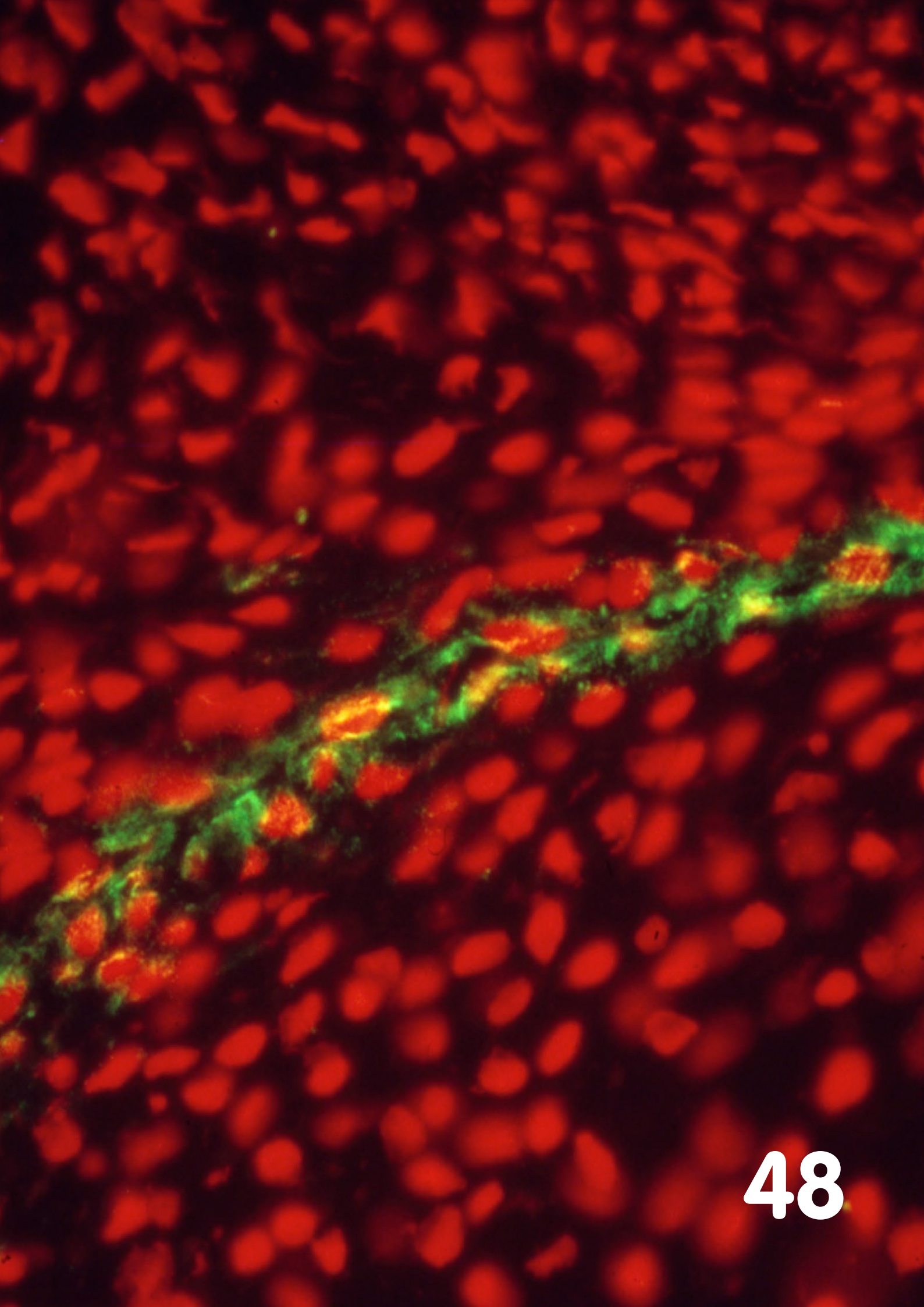
The impact of UK medical schools' research



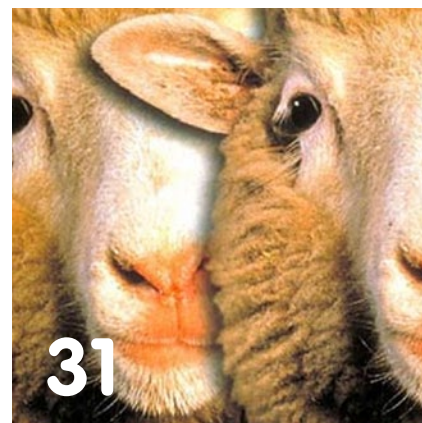
Medical
Schools
Council



**From discovery science to clinical impact –
health, wealth and societal gain**



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Cover image: Researchers working on Japanese encephalitis at the Institute of Infection and Global Health, University of Liverpool (see page 43). Photograph by Professor Tom Solomon





Introduction

Medical schools across the UK are producing world-class research to make patients and the country healthier and wealthier. The new system of assessing research quality in the UK, the Research Excellence Framework (REF), provides a fantastic opportunity to demonstrate the impact that this research is having.

Universities with medical schools sent 383 impact cases to REF Panel 1, 'Clinical Medicine', and REF Panel 2, 'Public Health, Health Services and Primary Care', for assessment. In this publication we have made a selection of 40 of UK medical schools' most impressive impact case studies, submitted in a host of subject areas.

The publication is organised into four themes:

1. Improving clinical practice

Case studies which are primarily about innovation, service redesign, patient outcomes, quality of care, changes to guidelines or clinical practice.

2. Boosting the economy

Case studies which have a primary or strong focus on economic growth (e.g. wealth creation, revenue through partnership with industry, cheaper treatments)

3. Delivering benefits to society

Case studies which are primarily focused on social policy issues and/or public understanding of health issues.

4. Beyond borders

Case studies which are primarily about improving healthcare internationally.

As you read the case studies, it will become apparent that there is a huge range of interlocking impacts contained within these developments. Indeed, many medical school researchers are also delivering positive impacts for the environment, culture and in other areas.

Choosing the top statements from each medical school was made exceptionally difficult by the wide variety of high-quality case studies received. This quality – consistently high across all medical schools – is evidence of a thriving UK academic life sciences sector. Collaboration between medical schools and movement of researchers from institution to institution are crucial elements of many of the case studies we have featured.

It is important to recognise that this excellent, collaborative research is facilitated by significant investment and infrastructure. The varied work of medical schools is supported through the National Institute of Health Research, Higher Education Funding Councils, the Medical Research Council (MRC), medical research charities and industry working together strategically. For example, the MRC's publication of outputs and outcomes of its funding¹ shows researchers receiving money from more than 1,000 different funders (as well as demonstrating impact of research conducted in many medical schools). The current UK biomedical research infrastructure is both an international success story and a delicate ecosystem.

The work of UK medical schools is also strengthened by the close relationship between universities and their partners in the NHS. Working with a national health system gives exciting opportunities in terms of data, access to patients and

¹ *Outputs, outcomes and impact of MRC research: 2013/14 report* www.mrc.ac.uk/news-events/publications/outputs-outcomes-and-impact-of-mrc-research-2013-14/

the potential to roll out innovative treatments, practices and ideas at scale. Close links between medical schools and their local primary, secondary and tertiary care organisations can help ensure medical schools are answering the right questions for the health service, and ultimately for patients.

At the individual level, the majority of the researchers leading the studies described in the following pages are 'clinical academics' who embody this close partnership. Clinical academics represent about 5% of the medical consultant workforce. They are university employees and, in addition to academic activities, they have honorary contracts with the NHS and spend about half of their week as practising doctors involved in patient care.² Their contribution to education, research and clinical service is immense.

Medical Schools Council members are united behind the principle that a research-rich environment is essential for high-quality medical education. Indeed, as shown by high-profile reports by Sir Bruce Keogh and in recent research,³ research active environments are not just good for students, they are also better for patients. Medical students themselves are making a growing contribution to these environments; efforts such as the Academy of Medical Sciences INSPIRE scheme will help support a long-lasting research culture.⁴

Our previous publication *Improving Lives – 150 Years of Medical School Achievements*⁵ said of medical schools that 'their efforts have not only transformed the quality and quantity of our lives, but have immeasurably changed society for the better.' This publication shows medical schools continuing to build on their inherited excellence to enhance life for all.

Health of the Nation oversight panel:

Professor Iain Cameron, Professor Chris Day, Professor John Iredale and Professor Paul Stewart

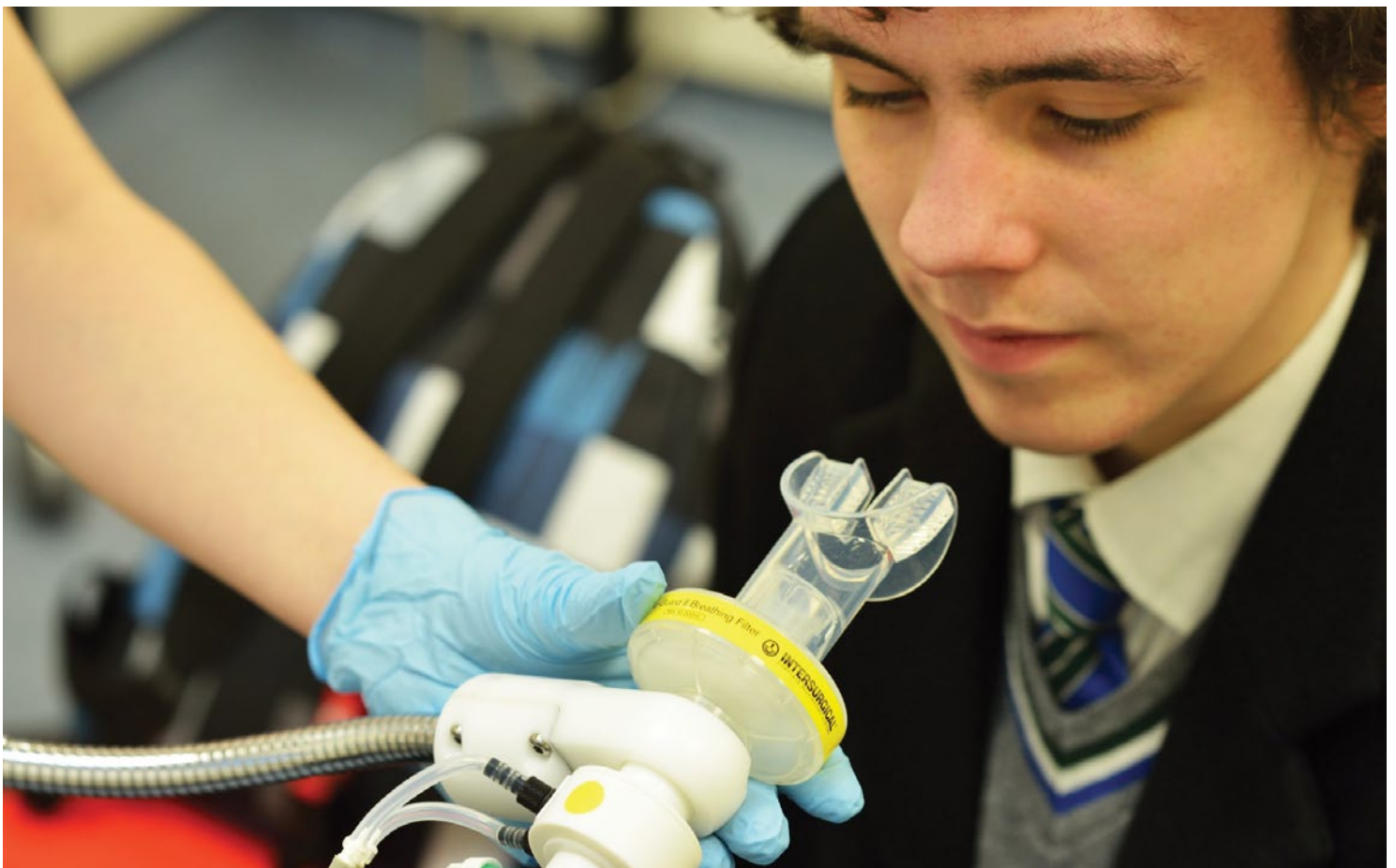
2 *Staffing Levels of Medical Clinical Academics in UK Medical Schools (2014)* www.medschools.ac.uk/Publications/Pages/Staffing-Levels-of-Medical-Clinical-Academics-in-UK-Medical-Schools,-2013-data.aspx

3 Sir Bruce Keogh's review of Trusts with high mortality showed that academic isolation can lead to Trusts being 'behind the curve' and stated that 'the best treatment is delivered by those clinicians who are engaged in research and innovation'. www.nhs.uk/NHSEngland/bruce-keogh-review/Documents/outcomes/keogh-review-final-report.pdf

Hanney et al (2013) found that when clinicians and healthcare organisations engage in research there is the likelihood of a positive impact on health-care performance. (Hanney S, Boaz A, Jones T, Soper B. Engagement in research: an innovative three-stage review of the benefits for health-care performance. *Health Serv Deliv Res.* 2013;1(8) <http://www.journalslibrary.nihr.ac.uk/hshr/volume-1/issue-8>)

4 More information about INSPIRE is available here: www.acmedsci.ac.uk/careers/mentoring-and-careers/INSPIRE/

5 *Improving Lives (2008)* www.medschools.ac.uk/Publications/Pages/Improving-Lives.aspx



Improving clinical practice

UK medical schools develop the doctors of tomorrow. Every year, approximately 8,000 UK medical students graduate and start working in the NHS. Through the leading research taking place at the medical schools that trained them, the way that these graduates go on to support good health and treat disease can be expected to constantly evolve and improve. Moreover, many will go on to undertake research to develop new treatments and improve care after they qualify as doctors.

Evidence-based medicine has been defined as ‘the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients’.⁶ Understanding the link between clinical practice and patient outcomes requires robust evidence. Without knowing why treatments work, there is a risk that inefficient and ineffective practice will occur. This would be to the detriment of the public health and public purse.

The case studies that follow demonstrate the action that medical school researchers have taken to improve the evidence base for medical practice thereby improving patient treatments and outcomes. More than just providing information, these researchers are often directly shaping guidelines and leading services themselves. With work ranging from the cellular level to the entire health system, the research displayed here is improving outcomes for patients and changing the way that medicine is practised for the better. In turn this is embedded in the culture of training tomorrow’s doctors.

Single gene diseases

**Barts and The London School of Medicine and Dentistry,
Queen Mary University of London**

Harlequin ichthyosis disease is a devastating and often life threatening skin disorder. At birth the whole body is encased in an armour of thick white plates of scale separated by deep red fissures. People who have this disease have skin so hard and thick that it cracks and are very vulnerable to infection because microbes can easily penetrate the cracks in the skin. Many babies born with Harlequin disease die within days of birth. The people who do survive into adulthood have to use vast quantities of moisturisers to soften their skin.



The disease is caused by a fault in the way that cells in the skin work. They do not move fats to the top layers of the skin and this stops the skin from working as a protective barrier against infections.

By comparing the DNA of Harlequin sufferers from many families and using a new method, called SNP array technology (single nucleotide polymorphism), the team discovered that recessive mutations in just one gene (ABCA12) on chromosome 2q35 are the major cause of harlequin ichthyosis. SNP array technology combines genetics with computing and can look at all an individual's genes in just two days.

The gene is recessive and so pre-natal diagnosis of more than 20 families found, as predicted, that in 75% of cases the child would not develop the disease

– thus providing profound reassurance to families. The team also performed the first case of pre-implantation genetic diagnosis for the condition, allowing a genetically unaffected embryo to be selected.

Another impact of a single gene mutation can be found on chromosome 13 where changes to GJB2 are a major cause of congenital hearing loss. The hearing ability of newborn babies is tested and for those who fail their blood can now be tested for GJB2 alleles in order to rapidly confirm the diagnosis. This permits early intervention such as with cochlear implants since delayed diagnosis may have a harmful effect on social, emotional, cognitive and academic development.

Researcher: Kelsell

Pulse oximetry screening to detect heart disease in newborn babies

University of Birmingham Medical School



Critical congenital heart defects (CCHD) are an extremely serious issue for newborns, affecting around 1600 cases annually in the UK alone. Up to one third of the defects are not detected in basic hospital screening practices, and these babies are at significant risk of serious health complications and death: risk of circulatory collapse is increased, and although surgery can greatly improve survival, poor condition at presentation increases surgical mortality. Timely diagnosis is therefore crucial for the best outcome for these children.



Only 35–50% of affected babies are identified before birth and around a third of babies with these potentially life-threatening defects in their hearts are discharged from hospital before diagnosis.

Blood oxygen levels are often low in CCHD. Pulse oximetry is a non-invasive method of measuring blood oxygen levels by placing a sensor on part of the patient's body. Although the technique itself was developed in the 1980s, and explored for CCHD identification in the 2000s, the results were inconclusive. In 2007, the National Institute for Health Research funded the PulseOx study which was run by the Birmingham Clinical Trials Unit. It was the largest UK study in this field, screening 20,055 newborn babies, and the first to assess the added value of pulse oximetry screening in modern healthcare systems where antenatal ultrasound screening was widely available. The study used robust methodology to generate clear supportive data around the accuracy, cost-effectiveness and acceptability of pulse oximetry and the value added to existing screening. These results demonstrated that the addition of pulse oximetry screening to existing screening tests resulted in 92% of babies with CCHDs being detected prior to discharge.

The work has had major impacts on international policy and practice across Europe, North America, Asia and Australia. It has also directly supported the affected children and their parents, and in particular lobbying groups internationally recognise the PulseOx study as one of 'the most compelling pieces of evidence' that 'should be part of any advocacy work'. The research was described in a Lancet editorial as 'a new milestone in the history of congenital heart disease'. A senior US cardiologist stated that the study had better design, appropriate reference and clarity of cardiac defect definition which meant that the Birmingham work 'tipped the balance of evidence towards universal screening in the USA'.

Researcher: Ewer

The Global Registry of Acute Coronary Events (GRACE) risk score for the management of acute coronary syndrome

University of Edinburgh Medical School

The GRACE registry, for the first time demonstrated that lower-risk rather than higher-risk patients with acute coronary syndromes (ACS) received more intensive medical and interventional treatment. To optimise the targeting of treatment for ACS and using data from the registry, the GRACE risk score provides clinicians with a powerful yet user-friendly means of identifying higher-risk patients at the time of their first presentation.

The independent predictors of outcome in 21,688 patients presenting with ACS were derived and the predictions validated prospectively in a further 22,122 patients, with the aim of predicting both in-hospital and six-month risk of death, and death or myocardial infarction. Nine factors independently predicted both death and the combination of death or myocardial infarction and conveyed more than 90% of the risk.

The GRACE programme identified that survivors of non-ST elevation ACS (previously perceived as minor or threatened heart attacks) had higher long-term risks of death and recurrent myocardial infarction and ST-elevation myocardial infarction (ST elevation refers to a finding on an electrocardiogram, wherein the trace in the ST segment is abnormally high above the isoelectric line). By identifying these patients, appropriate interventional strategies could be put in place and lives saved.

The GRACE risk score was made freely available to download to a mobile device. The app provides a user-friendly interface of the variables that convey 90% of the risk. Clinicians use this information alongside their own clinical evaluation to guide management of the patient. By facilitating appropriate treatment the GRACE risk score has contributed to a change in practice and improved outcomes saving 30 – 80 lives for every 10,000 patients presenting with non-ST elevation ACS.

Researchers: Fox and Gore

Stopping insulin: A life-changing therapeutic intervention for patients with neonatal diabetes

University of Exeter Medical School



Anthea Sieveking, Wellcome Images

Childhood diabetes usually requires life-long insulin injections and leads to a reduction in quality of life. This research revealed that around half of patients with permanent neonatal diabetes have mutations in a subunit of the pancreatic beta cell ATP-sensitive potassium (K_{ATP}) channel. For those with this mutation, the glucose sensing and insulin synthesis/secretion processes are intact, but insulin is not secreted because the channel remains open in the presence of ATP. Sulphonylurea drugs used to treat type 2 diabetes bind to the sulphonylurea receptor subunits of the channel to cause their closure, independently of ATP. The team proposed that sulphonylureas might close the faulty channels and facilitate insulin secretion when administered to patients *in vivo*.

This was found to be the case. Most patients with a K_{ATP} channel mutation are able to stop their insulin injections and achieve better blood glucose control on sulphonylurea tablets; glucose levels are within treatment targets and close to those in people without diabetes. More than 500 patients worldwide have had their diabetes therapy changed and very many more newly diagnosed individuals, who would have been prescribed insulin therapy, are being treated with tablets alone.

Diagnostic genetic testing is now available for all patients with neonatal diabetes. Of the 1,169 patients referred to Exeter from 77 countries, those diagnosed with a K_{ATP} channel mutation causing neonatal diabetes has increased from 10 reported in the first publication (2004) to 454 in October 2013.

Changing from insulin injections to sulphonylurea tablets improves quality of life by removing the many restrictions on life that are imposed by multi-injection or insulin pump therapy, stopping pain at injection sites, and reducing the need to tightly restrict the patients' diet. Patients also experience fewer hypoglycaemic episodes. The better glycaemic control achieved with sulphonylureas will reduce the future risk of diabetic complications including heart attack, stroke, kidney failure, blindness and neuropathy.

Many of the 20% of patients with neurological impairment have seen an improvement in their motor skills, cognitive function, speech, concentration, sleep and behaviour. Reports from parents have been substantiated by teachers and healthcare professionals. The early diagnosis made possible by clinical diagnostic genetic testing means that the maximum number of patients can benefit from improved neurological outcomes as well as better diabetes control and lifestyle gains. There have also been reduced healthcare costs due to the cheaper treatment, reduction in blood glucose monitoring and reduced risk of diabetic complications later in life. In the USA it is estimated that genetic testing followed by transfer to sulphonylureas and consequent improved glycaemic control saves \$12,528 per patient at 10 years.

Researcher: Hattersley and team

Use of Anti-Tumour Necrosis Factor in the treatment of chronic inflammatory conditions

Imperial College Faculty of Medicine

Rheumatoid arthritis (RA) is a costly and debilitating autoimmune disorder that is characterised by joint pain, stiffness, and impaired functionality. Symptoms arise from the inflammation and degradation of the synovial membrane, causing progressive disability in joint function.



Anthony Edwards, Wellcome Images

Work at Imperial College identified tumour necrosis factor (TNF) as a key therapeutic target in the abnormal joint lining in RA. As the disease progresses, patients require more frequent invasive procedures – joint injections, synovectomy etc – as well as the eventual replacement of affected joints.

The first clinical study, published in 1993, enrolled 20 patients with disease refractory to all existing treatment. They were given a single infusion of infliximab, a monoclonal antibody to TNF. Results were dramatic: the response rate with the highest dose of infliximab was 79% at four weeks in comparison to 8% with placebo. The success of repeated treatments was however less, partly due to the monoclonal antibody inducing an immune response to itself which limited its effectiveness.

Further studies of the mouse model indicated that combining an anti-TNF monoclonal antibody with a

therapy targeting the T cells of the immune system might improve response through synergy and a reduction in immunogenicity. This led to combining methotrexate, already established in the treatment of RA, with infliximab.

Full validation of TNF as a target came about in the form of clinical trials in man, which unequivocally showed significant benefit in most patients treated. Biologic inhibition of TNF, in combination with concomitant methotrexate (MTX), not only improved symptoms and signs of RA in many patients, but most dramatically halted the structural damage previously thought to be an inexorably progressive feature of the disease. Preservation of functional capability is a consequence of both reduction in disease activity and prevention of joint damage. The most impressive benefit of biologic TNF inhibitors has been demonstrated when therapy is initiated in the early stages of RA. Biologic anti-TNF therapies have set the height of the bar to which all biologics directed at alternative molecular targets have had to aspire to achieve the magnitude of improvement in symptoms and signs, prevention of joint destruction and preservation or improvement in function.

The work has had ongoing impact across the globe for the treatment of inflammatory diseases. Since 2008 Remicade® (infliximab) has been used to treat more than 1.3 million patients worldwide who have inflammatory conditions such as plaque psoriasis, rheumatoid arthritis, psoriatic arthritis, adult and paediatric Crohn's disease, ulcerative colitis, and ankylosing spondylitis. In 2012 Remicade was the 4th best-selling worldwide drug with total global sales of \$7.67 billion.

Researcher: Feldmann and team

Heart attacks: Improving therapeutic options for patients

University of Leicester Medical School



Professor Tony Gershlick

Coronary heart disease is the narrowing of the coronary arteries as a result of deposition of atherosclerotic plaque (hardening of the arteries). Every year in the UK, 150,000 heart attacks are caused by coronary artery blockage; worldwide, the figure is 17 million. The Leicester Interventional Cardiology group has been at the forefront of research to determine how best to manage such patients.

The first drug-eluting stent (releasing agents that inhibit the inflammatory over repair response) deployed in the UK was at University Hospital Leicester as was the first drug-eluting absorbable stent. The Unit's research has allowed stenting to evolve into an effective and safe procedure by testing the efficacy, safety and cost-efficiencies of stent designs and the drugs on them.

Initial pioneering work used thrombolytic ('clot-busting') drugs to proactively unblock the coronary arteries attenuating heart attack outcomes. Later work highlighted that thrombolytic agents were limited and could open only 65% of occluded arteries. The 'open artery hypothesis' proposed that the earlier and more completely the artery could be opened, the better the outcomes.

A question arose early on as to whether thrombolysis could be combined with angioplasty in heart attack victims and, if so, in which cohort. The REACT study established that viewing of the ECG 90 minutes after the thrombolytic treatment to see if the changes had resolved, was a good way of determining whether the vessel had been opened by a thrombolytic agent. This is still used worldwide. REACT also showed that those patients whose ECGs had not normalised at 90 minutes post-thrombolytic did much better in terms of major adverse cardiac events, with angioplasty. However not all patients are able to receive angioplasty in a timely fashion and so the STREAM trial (2009 – 2012) of 1,850 patients compared angioplasty for myocardial infarction with a strategy of thrombolytic plus REACT-based angioplasty, and showed that these were equivalent. This has enabled better outcomes for the 20% of patients in areas where there are geographical challenges to delivery of angioplasty for heart attacks.

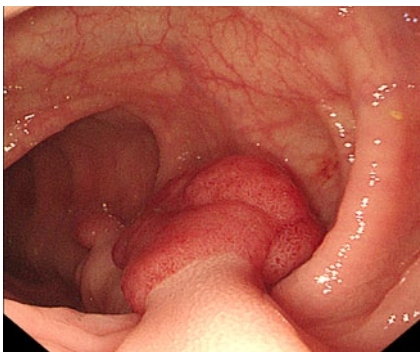
Across the world, patients are now managed according to a protocol that states that, if they receive thrombolysis, the ECG should be reviewed after 90 minutes and if the changes due to the heart attack have not resolved then they should have rescue angioplasty.

Researcher: Gershlick and team

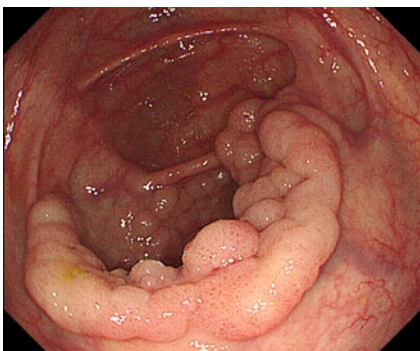
Saving lives through faecal occult blood (FOB) screening for bowel cancer

University of Nottingham Medical School

Types of polyps indicated by the screening:



a pedunculated polyp



a flat polyp

Around one in 20 people in the UK will develop bowel cancer during their lifetime. The disease kills around 16,000 people each year in the UK, and around 608,000 worldwide – mainly because it has non-specific symptoms and thus presents at a late stage. Bowel cancers tend to develop slowly from colonic polyps over a period of 10–15 years. Removal of these polyps at colonoscopy can prevent the polyp from becoming a cancer.

Furthermore, the slow development of bowel cancers means they can often be detected at an early stage, when they are easier to treat. These characteristics make bowel cancer an excellent candidate for a population screening programme. Faecal Occult Blood (FOB) testing can detect polyps on the lining of the bowel, and also early-stage bowel cancers.

The Nottingham trial randomised over 150,000 individuals (aged over 60) in the Nottingham area, by household, to receive either biennial FOB tests or no intervention. It showed a 16% reduction in bowel cancer mortality. The proportion of early-stage cancers detected in the screened groups was 26%, compared with 13% in the control population.

Population screening with FOB tests is simple, cheap and effective, usually detecting bowel cancers before they would present symptomatically. A guaiac-based test can be used in conjunction with an immunochemical test to help increase sensitivity of FOB screening. Furthermore, automation of the test allows manipulation of sensitivity and increased throughput.

As a consequence of this trial, the Department of Health launched two screening pilots and introduced a National Bowel Cancer Screening Programme (NBCSP), achieving national coverage in 2010. Since 2008, this has sent out almost 18 million invitations and detected 16,000 bowel cancers, of which 21.6% were early cancers with a 95% chance of cure. It is estimated that the NBCSP saves around 3,500 lives each year in the UK. International screening programmes modelled on the UK system will save many more. Since 2008, similar programmes of bowel cancer screening using FOB tests have either been rolled out or achieved national coverage in Northern Ireland, Scotland and Wales.

National bowel cancer screening programmes modelled on the UK system using FOB tests are also being developed and implemented in Canada, Denmark and Australia. Some of this commitment will undoubtedly have been influenced by the 'European Guidelines for Quality Assurance in Colorectal Cancer Screening and Diagnosis', which repeatedly cites the Nottingham research as evidence for the effectiveness of FOB screening.

Researchers: Hardcastle and Scholefield

Reduction of stroke risk by risk stratification and urgent intervention after a transient ischaemic attack or minor stroke

University of Oxford Medical Sciences Division

Transient ischaemic attack (TIA) and minor stroke comprise over 70% of all cerebrovascular events and about 90% of recurrent strokes occur in patients who previously had a TIA or minor stroke. The standard treatments aimed at preventing recurrent stroke include surgery to the carotid artery ('carotid endarterectomy') and medical treatments with drugs.



Funded by the Medical Research Council, research in Oxford has shown that the risk of a major stroke soon after a TIA or minor stroke had been greatly underestimated. Given this finding, it was important to identify who, amongst the 100,000 referrals with TIA per year in the UK alone, are at highest risk of an early major stroke. The group therefore also developed the 'ABCD system', a simple clinical tool to identify those people with a very high-risk of stroke in the next few hours and days.

Having shown that success in preventing major stroke after a TIA or minor stroke was likely to be undermined by the then commonplace delays to investigation and treatment, the group then showed that urgent investigation and treatment reduced the 90-day risk of major recurrent stroke by about 80%

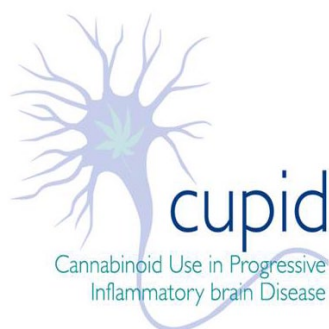
compared with standard care. Subsequent health-economic analyses showed that urgent intervention reduced the risk of disabling stroke and risk of hospitalisation, reducing overall hospital bed-days by over two thirds, generating savings of £624 per patient treated. Rolling the service out across the UK was estimated to prevent 10,000 strokes per year, saving the NHS up to £200 million annually in acute care costs alone. Daily emergency TIA and stroke clinics modelled on the Oxford system (i.e. ABCD-based triage and urgent treatment) were therefore mandated in the 2008 National Stroke Strategy and the NICE guidelines and are now standard across the UK and in many other countries.

In related work on the risks and benefits of carotid endarterectomy the group also found several important interactions between clinical subgroups and treatment effects, notably the rapidity with which benefit from surgery also falls with delay to intervention. The work also rapidly changed clinical guidelines, the 2008 National Stroke Strategy and NICE guidelines both substantially shortening the delay permitted prior to surgery. Repeated audits have shown that delays to endarterectomy have subsequently been substantially reduced across the UK. For example, in the early 2000s the average delay was over three months; by 2009–2010 it was 21 days; by 2010–2011 it had fallen to 15 days.

Researcher: Rothwell and team

Multiple Sclerosis: Developing treatment and improving outcomes measurement

Plymouth University Peninsula Schools of Medicine and Dentistry



Multiple Sclerosis (MS) is the commonest cause of neurological disability and death in young adults, with over 100,000 people affected in the UK. Treatments for the inflammatory phase of relapsing-remitting MS are increasing. However, despite many studies, no treatment has proven to alter the course of progressive MS.

Researchers at Plymouth believe the outcome measures used by these studies have contributed to this clinical scenario. They educated themselves in a little used but clinically meaningful measurement science and developed a suite of patient-reported clinical outcome assessment (COA) measures, or 'MS scales'. These scales are used widely in academic and commercial clinical trials, have influenced clinical research, and drug licensing in MS. The Researchers' applications of measurement science have also influenced other neurological diseases, including Alzheimer's disease.

The MS walking scale, a questionnaire measuring the impact of MS on people's walking, has been used multiple times in more than 9,000 people. Another longer MS questionnaire developed by Plymouth Researchers has been used over 30,000 times worldwide. Indeed, the MS scales have been translated into over 60 languages including French, Dutch, Russian and Spanish. Clinically useful scientifically sound measurement instruments enable effective treatment evaluations for MS, and other neurodegenerative disorders, from the patient-perspective. Indeed, their use has contributed directly to new drug licensing.

The Plymouth researchers' measurement science approach has been endorsed by the United States Food and Drug Administration for developing, evaluating, and modifying COAs. Their MS scales are in considerable demand by commercial organisations developing and evaluating new MS treatments. The measurement scales produced by these researchers have generated £437,000 of licence income for Plymouth University's trading company.

In parallel, Plymouth researchers have continued to evaluate the potential benefits and risks of cannabis for treating MS. Specifically, the Medical Research Council-funded the Cannabinoid Use in Progressive Inflammatory Brain Disease study (493 participants) which built on previous work and was the largest ever academic study of progressive MS, investigating the extent to which cannabis had an anti-progressive effect. Whilst results showed no overall benefit, they detected a possible effect in less disabled participants, and highlighted our limited understanding of progressive MS. The work, which has been extended to other neurodegenerative diseases, has been topic-leading and pioneered the evaluation of cannabinoids to slow neuro-degeneration.

Researchers: Zajicek, Hobart and team

Improving outcomes for patients with cystic fibrosis

Queen's University Belfast School of Medicine,
Dentistry and Biomedical Sciences

Cystic Fibrosis (CF) is the most common life limiting autosomal recessive disorder in Caucasian populations. There are over 80,000 people worldwide with the condition, with 10,000 in the UK. Researchers at Queen's University Belfast have made major contributions to the understanding of lung disease in cystic fibrosis.



This enabled the development of key outcome measures (lung function, exacerbations and nutritional measures) to be used in clinical trials to test new therapies. The research, which validated CF trial outcome measures, has had very significant impact on the management of people with CF because the early studies made multicentre trials more reliable, effective and efficient.

The trials have allowed optimisation of current anti-inflammatory and anti-infective treatments and have been a contributor to innovative transformative treatments for the underlying basic defect.

Queen's was selected to co-lead an international ground-breaking and landmark study using the first corrective therapy for the underlying defect in patients with CF. The

drug Ivacaftor corrects the function of a particular mutation in CF designated as G551D. This mutation in the CF gene affects 5% of people with CF worldwide but 10% of people in Ireland. The drug activates the mutated protein and restores significant function of the defective channel which causes CF in these patients. This Phase III study demonstrated a transformative impact on patients with very significant increases in lung function and quality of life with a concomitant reduction in pulmonary exacerbation. Ivacaftor represents a paradigm shift since for the first time not just the symptoms of CF are treated in the patients but treatment is aimed directly at the cause of the disease.

This therapy is an exemplar of personalised medicine and is prescribed for patients with the specific gene mutation on which this drug works.

Researcher: Elborn

The Moorfields Safer Surgery System: New techniques revolutionise glaucoma surgery

University College London Medical School

Glaucoma affects 70 million people worldwide, of whom seven million are blind. It is the most common cause of irreversible blindness in the world, and the most common neuropathy in the world. Based on relatively conservative figures, it is likely that more than 2% of glaucoma sufferers will require surgery during their lifetime, which is around 1.4m individuals.



Adrian Wressell, Wellcome Images

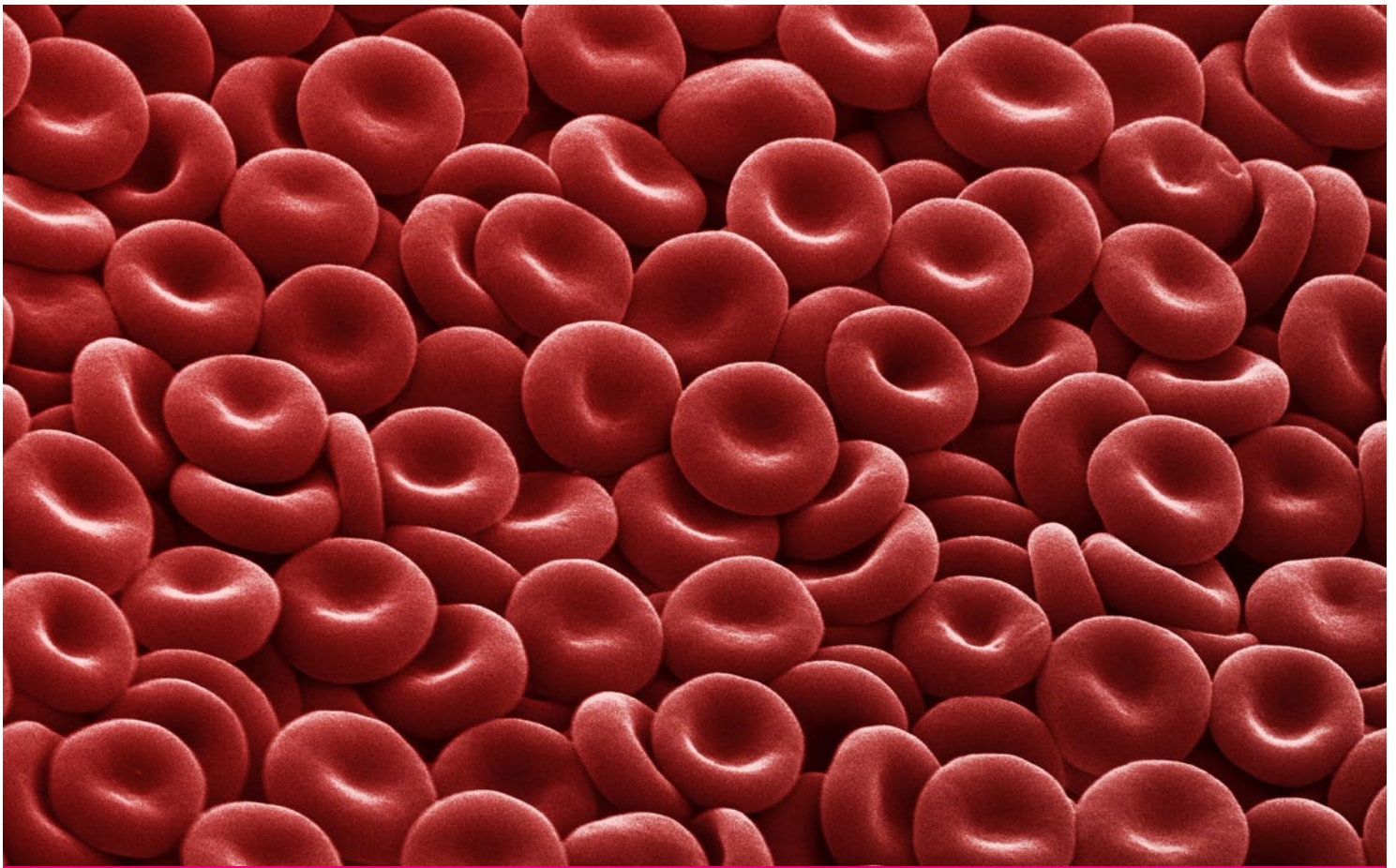
Research in the early 1990s at the UCL Institute of Ophthalmology developed *in vivo* cell culture models of the ocular wound healing process. This led to the discovery that very short (five minute) applications of anticancer agents including 5-fluorouracil (5-FU) and mitomycin-c (MMC) had long-lasting effects on ocular fibroblasts that were responsible for scarring after surgery. At that time, 5-fluorouracil was given clinically as a series of 14 painful injections around the eye in the first two weeks after surgery. Experiments suggested that an equivalent effect could be achieved with a single, inexpensive and painless exposure at the time of surgery.

We then developed a much more consistent and predictable model of glaucoma surgery in the rabbit, and this was carried into the world's first pilot human trials with five-minute exposures to 5-FU, which strongly suggested that this treatment (which costs just £1) is efficacious. The principles learned from research up to this point led to the development of the Moorfields Safer Surgery System. This consists of several simple changes to surgical techniques, and the development of improved components which dramatically reduced the incidence of potentially blinding complications.

Information about these techniques has been distributed free online and the system has reached all continents. In the UK, complications of trabeculectomy surgery have improved considerably since the national survey of trabeculectomy 15 years ago. Early complications occurred in 46.6% and late complications in 42.3% but, with the Safer Surgery System and anti-scarring

agents including 5-FU, complications such as blebitis, endophthalmitis, flat anterior chambers, hypotonous maculopathy, choroidoretinal detachment or visual loss are markedly reduced. Studies around the world have found similar improved outcomes using our protocols, which is of direct relevance to many hundreds of thousands of individuals worldwide.

Researcher: Khaw



Boosting the economy

The life sciences sector is recognised as a central pillar of the economy, with the UK among the world leaders in this area. It is estimated that the sector generates more than £50 billion in turnover, with approximately 176,000 people employed in 5,000 companies,⁷ which are geographically distributed across the whole of the UK.

The combined benefit of improving patients' lives and generating wealth is the result of an interdependent relationship between academia, patients, the NHS, medical research funders, and life sciences companies both big and small. While this network of different interests is complex and wide-ranging, patient care is at its core.

The case studies that follow demonstrate both huge savings to the public purse and new money being attracted to the UK. A striking feature of many of the studies is the global reach of the work. In an increasingly competitive world market, the dynamism of medical schools in starting new companies, supporting well established organisations, and creating jobs, contributes directly to the UK's place as a leader in this crucial sector.

⁷ https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/306854/bis-14-707-industrial-strategy-progress-report.pdf

Fuller Longer: Helping to develop a new health food range for Marks & Spencer

University of Aberdeen School of Medicine and Dentistry



Obesity and associated conditions are a major health concern. Helping people to make healthier choices is a priority for governments, health services, researchers and industry.

Research findings at Aberdeen have underpinned the development of the Fuller Longer range of products which are intended to support weight loss or weight maintenance diets. Aberdeen based studies conducted from 2008 onwards demonstrated that high protein and moderate carbohydrates sustain appetite control and weight loss. To come to their conclusions, the Aberdeen team conducted numerous studies with obese human volunteers which included psychological and physiological monitoring in and out of the laboratory. Researchers also used Positron Emission Tomography to understand how high protein moderate carbohydrate weight loss diets affect the brain. The findings showed that high protein moderate carbohydrate diets are as effective as diets that are high in protein, but low in carbohydrates. This means the valuable intake of fruit, vegetables and fibre can be maintained, unlike in other diets.

An interaction with Marks and Spencer (M&S) took the research findings through to the marketplace. Researchers worked closely with senior management and others within M&S to create an effective range of products. The Fuller Longer product range has represented a huge commercial success for the industry partner and is an established brand for the company's 20 million customers. Figures for sales in January 2012 indicate 1.5 million meals being sold in a week. This industry-academia partnership was a first for M&S, and has led to one of the UK's most popular retail healthy-eating food ranges.

As of 2015 the Fuller Longer range is rebranded to 'Balanced for You'.

Researchers: Johnstone and team

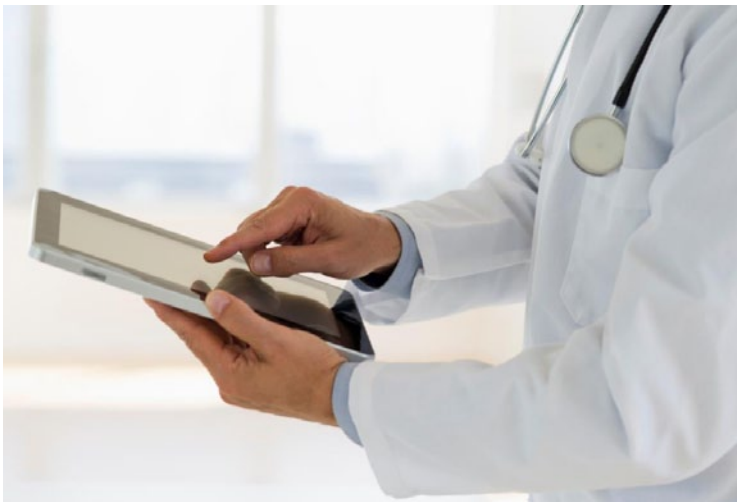


A new mobile application for detecting Alzheimer's disease

University of Cambridge School of Clinical Medicine



Detecting early memory problems in patients with Alzheimer's disease is an important step in ensuring the correct diagnosis is given. It also increases the potential for patients with this condition to be treated.



Researchers at Cambridge have developed CANTAB-PAL, a touchscreen test which assesses visual memory and new learning. This is used in a series of products developed by Cambridge Cognition, a spin-out from the University of Cambridge. These are essential tools for accurately assessing individuals with questionable dementia, mild cognitive impairment, Alzheimer's disease, and age-related memory loss. A mobile (iPad) application of the test has been created, which can be used in GP clinics. In addition, researchers have used neuroimaging methods to create results that will help in the development of drugs.

Tests from the CANTAB research suite have been used in 77 clinical trials since 2008. This has involved hundreds of sites world-wide, most of the major

pharmaceutical companies and also biotech, device and nutraceutical companies. It has been used in more than 1,000 departments in over 700 universities and clinical research institutions around the world. Six clinical commissioning groups in England are now using CANTABmobile to help implement the national initiative for early diagnosis of Alzheimer's disease.

Cambridge Cognition itself employs around 50 staff in Cambridge, with two US based business development staff. In 2012, the company was listed in the Top 100 fastest growing private technology firms in the UK on the back of revenues of £5.8 million that year. The benefit also extends to the health service as research evidence suggests that earlier diagnosis (facilitated by CANTAB) is cost effective due to more effective interventions and patients having prolonged independence.

Researchers: Robbins, Sahakian and team

Chemiluminescent technology underpinning global adoption of tests for infectious disease

Cardiff University School of Medicine



Research at Cardiff has led to the development of blood screening and clinical diagnostic nucleic acid amplification tests that have been adopted worldwide for the detection of infectious agents such as viruses and bacteria.

Researchers at Cardiff have investigated the light-emitting (chemiluminescent) properties of a family of chemical dyes and their use in biochemical analysis. Early research showing that the modified dyes could be used to develop clinical diagnostic tests formed the basis of patented inventions. By using two types of light-emitting dyes (one that flashes, one that glows) for the first time, it was possible to sensitively detect and quantify multiple biochemical targets (analytes) simultaneously.

Nucleic acid amplification test (NAAT) technologies have permitted the development of highly sensitive tests that are capable of detecting small quantities of nucleic acids in infectious agents and therefore small numbers of those agents. The superior analytical sensitivity can potentially produce a positive signal from as little as a single copy of the target DNA or RNA. However NAATs are prone to non-specific interference, potentially yielding incorrect results, particularly when conducted in automated, high-throughput systems.

The Cardiff research was transformative in providing a solution to the need for the internal control of nucleic acid amplification in high-sensitivity chemiluminescent *in vitro* screening and diagnostic assays. A novel, patentable solution was created with the development of 'second generation' flash/glow chemiluminescent technology. This allows the amplification of the nucleic acid target in the clinical sample (e.g. monitored by slow light emission) to be internally quality controlled by including a parallel amplification reaction for a known nucleotide sequence that can be independently monitored (using a fast light emitter). The technology also allows simultaneous detection of multiple, different analytes within the same sample.

The technology was adopted by the market leader in nucleic acid diagnostics in a range of tests for infectious agents, for example HIV, HCV and HBV, the detection of which is vital in maximising the safety of blood transfusions and blood products. Globally, the technology is used in more than 60 million *in vitro* diagnostic tests every year. Sales of the tests approach \$500 million per year and the company that adopted the technology was sold for \$3.8 billion. It has thus achieved worldwide reach and has yielded benefits both in clinical practice and commerce.

Researchers: Woodhead and Weeks

Progression of the Imperial College spin-out 'Circassia' to a multimillion pound specialty biotechnology company

Imperial College London Faculty of Medicine



Annie Cavanagh, Wellcome Images

Between them, asthma and allergic rhinitis affect an estimated 30% of the population of economically developed countries, and give rise to a global drugs bill in excess of £6 billion. These drugs are almost all focused on managing symptoms rather than being curative. Therefore, a large unmet medical need exists for a safe and effective treatment which prevents these conditions.

Between 1995 and 2004 researchers at Imperial College developed a T cell peptide allergy vaccine in an attempt to improve the quality of life for millions of allergy sufferers worldwide. Work has looked at vaccines for a range of allergies including house dust mites, ragweed, cats and grass.

An Imperial College spin-out, Circassia Limited, was founded to progress this work and was subsequently sold to Circassia Holdings Ltd, a clinical-stage specialty biopharmaceutical company based in Oxford. The company has developed a pipeline of products to treat common allergies through supporting a series of successful trials and accruing patents. Investment has been attracted from a range of partners including Lansdowne Partners, Tudor Capital, Goldman Sachs and Invesco Perpetual.

Circassia employs 25 people 'in-house' and supports the employment of an estimated 200 others through its outsourced business model. In 2012 alone, the company spent £23.6 million on R&D organisations. Since 2008, Circassia itself has raised £98 million to establish its viability as a spin-out company.

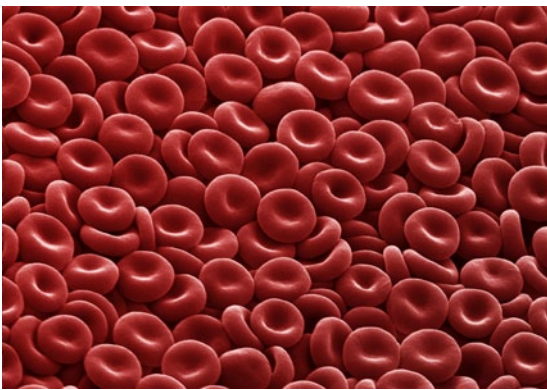
As well as creating this wealth, the vaccine approach taken has the potential for becoming the standard for allergy preventative treatment and may significantly reduce the global burden of this disease.

Researchers: Kay and Larché

Improving lives and transforming services for those with a life-threatening, disabling blood disorder

University of Leeds School of Medicine

Paroxysmal nocturnal haemoglobinuria (PNH) is a rare acquired blood disorder, in which the bone marrow cannot compensate for a massive increased loss of red blood cells. PNH affects approximately five people per million and frequently occurs in early adulthood. PNH is associated with severe life-long symptoms. In 1995, researchers at Leeds established that half of patients died due to PNH. Two years later, Alexion Pharmaceuticals developed eculizumab, a specific inhibitor of complement.



Annie Cavanagh, Wellcome Images

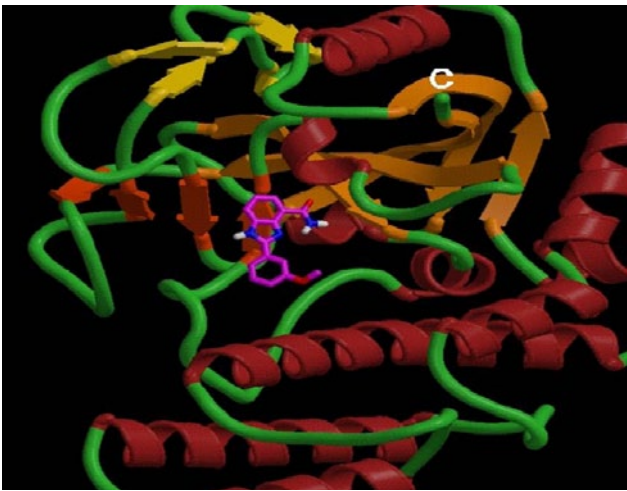
The potential of eculizumab in PNH was identified by the Leeds research team. It took over two years for researchers at Leeds to convince Alexion to permit them to perform trials in PNH. Alexion's reluctance was that the low numbers of patients with PNH would make drug development unviable. However, studies were approved, performed in the UK and showed that eculizumab immediately reverses the symptoms and complications of PNH, meaning that patients were able to return to work and stop supportive therapies, such as transfusions and painkillers. Further trials led by Leeds culminated in the approval of eculizumab in 2007 for clinical use.

Eculizumab has transformed the treatment of PNH with major economic impacts. The Leeds group recently published that the survival of patients with PNH receiving eculizumab is comparable with the normal population and that patients have a normal quality of life. Eculizumab is approved in over 40 countries and has been approved for another life threatening disease. Care services for PNH have been radically reconfigured globally and huge new pharmaceutical activity has been generated. In 2013, there were global eculizumab sales of \$1,551 million and Alexion Pharmaceuticals is worth over \$38 billion.

Researchers: Hillmen and team

The development of a novel class of anticancer drugs – attracting multi-million dollar investments in clinical trials by nine pharmaceutical companies

Newcastle University Medical School



X-ray crystal structure of a Newcastle inhibitor bound to PARP

Newcastle research selected the DNA repair enzyme poly(ADP-ribose) polymerase (known as PARP) as a promising target for cancer therapy. The research initiated in the 1990s not only led to the first in class trial of a PARP inhibitor, but also played a key role in establishing the translational research routes of drug development.

At the start of research, PARP was not considered a viable target, particularly by the pharmaceutical industry. The Newcastle team championed it and drove the project to clinical proof-of-principle. In collaboration with Cancer Research UK and Agouron Pharmaceuticals, Newcastle helped to develop rucaparib, the first PARP inhibitor to treat a cancer patient in a clinical trial.

The research has had a significant impact on the UK and global pharmaceutical industry, with a wide range of companies investing heavily in clinical trials and clinical PARP inhibitor programmes. Over 7,000 patients worldwide have been treated with PARP inhibitors in trials since 2008. The estimated investment by companies into these trials is around \$385 million.

The research has attracted investment due its huge potential to improve patient outcomes. Indeed, some patients involved in trials themselves who were originally diagnosed with an incurable disease and life expectancy of just a few months, have remained alive and in remission due to the intervention.

Researchers: Calvert and team

Economic and health benefits of novel light therapies for the treatment of skin conditions

Swansea University College of Medicine



Birthmark treatment, before and after

Skin conditions such as acne, sun-damage, pigment disorders and stretch marks can be debilitating and distressing. Research at Swansea on light therapy has contributed to an extensive market in laser and intense pulsed light (IPL) products for the therapeutic and cosmetic treatment of such skin conditions.

When research began, light therapy was being used to treat cervical cancer and reduce tumours. However, the broader potential of laser light was yet to be realised. Researchers at Swansea saw this opportunity and consulted clinical experts on how the use of laser and IPL products might affect different skin conditions. Insights from the research and experimental trials showed that light could be used safely and effectively to initiate wound-healing responses and suppress hair growth. The application of this research has created long-term health benefits for thousands of sufferers of distressing skin conditions.

Technology developed at Swansea through the course of studies has yielded several patents and the first FDA approvals for acne treatment, hair removal and skin rejuvenation. The market for light therapy for skin conditions and hair removal is estimated to reach \$3 billion by 2018.

Underpinning research from Swansea has spawned three spin off companies that develop laser and IPL products, employing approximately 150 people. Patents have been used to develop commercial partnerships with companies such as Procter & Gamble, Boots and Unilever. Work with Sony UK to manufacture laser and IPL products in South Wales has been described by the Welsh Government as an exemplar for the resurgence of UK specialist manufacturing. The research has made Swansea one of four global centres of excellence in light therapy alongside Boston, San Francisco and Tel Aviv. More than 1,000 person-years of employment around Swansea have been created due to this research.

Researchers: Clement and team

Gene therapy for immunodeficiency diseases

University College London Medical School

Primary immunodeficiency disorders are a diverse group of rare, inherited diseases where children are born with defective immune systems. In the most severe forms, children are unable to fight off even very mild infections, and without treatment, patients will usually die within the first two years of life. Finding the genes that cause these conditions gives potential for cheaper and more effective treatments to be identified.



Anthea Sieveking, Wellcome Images

Earlier clinical trials of gene therapy had largely been unsuccessful until researchers at UCL developed efficient methods for introducing therapeutic genes into haematopoietic stem cells. Since 2002, 32 patients with four different immunodeficiency disorders have been treated. Most are now at home, off all therapy. One parent said:

'Guy is now doing brilliantly; he can do all of the things his friends can do and more. He is able to play football and ride a pony. He wouldn't be here if it wasn't for the option of gene therapy treatment.'

The cost of gene therapy compared to other treatments is reduced because the patient has a significantly shorter stay in hospital (four to six weeks compared to eight weeks on average for other treatment option). Moving

patients away from costly enzyme replacement treatment has produced an overall cost saving of £5 million to date.

Researchers have been involved in creating the current guidelines for treating these diseases and advised the FDA, UK Gene Therapy Advisory Committee and other regulatory and expert bodies. In addition, collaboration with the 'Jeans for Genes Campaign', appearances in various media outlets including BBC Horizon and having work displayed at museums has helped engage the public in the science that has helped improve the lives of those with these rare conditions.

Researchers: Gaspar, Kinnon and Thrasher

Neurosolutions: A commercial partnership between academia industry to develop novel drugs for neurological disorders

University of Warwick Medical School



Electrophysiological research conducted at Warwick from 2000 has formed the basis for a spin out company called 'Neurosolutions'. The underpinning research for this company centred on the following areas:

- Central neural control of bodyweight and obesity.
- Spinal cord slice electrophysiology and the ability to probe the functional operation of neural circuits in normal and diseased states.
- Finding novel peripheral and spinal targets for treating pain.

To take this research to the pharmaceutical industry and promote interaction, Neurosolutions was created as a spin-out of Warwick University. As well as developing its own novel compounds, Neurosolutions provides specialised translational biomedical research services to the biotechnology and pharmaceutical industries to facilitate preclinical drug development.

The company has developed two novel compounds for treating pain in partnership with companies in Japan and the UK. Furthermore, Neurosolutions has a growing reputation and increased demand for its contract research services. Since the company was founded, expert translational neuroscience services have been provided to over 100 clients worldwide. Neurosolutions has earned around £7.5 million in contracts since its launch.

Patents, intellectual property and research publications by Neurosolutions staff (in collaboration with academic and industrial partners) have generated average annual revenues of £1.4 million per year. Five new biotechnology companies have sprung from provision of 'proof of concept' data by Neurosolutions. The company employs fifteen full-time staff based in the UK and Montreal.

In 2005, Neurosolutions floated on the Australian Stock Exchange to support the in-house development of compounds to treat neuropathic pain and dental pain. Work continues to collaborate with academia and industry across the world and provide services that support treatment of obesity, Alzheimer's, Parkinson's and many other conditions.

Researchers: Spanswick and team



Delivering benefits to society

Health remains a political priority for the UK public and few issues arouse more passion than the NHS. In the September 2014 Ipsos-MORI/Economist issues index, the NHS was seen as the third most important issue facing Britain today.⁸ In the context of this significant public scrutiny of healthcare, medical schools are helping to ensure that debates and discussions about health policy are better informed.

At an institutional level they achieve this with colleagues in hospitals and other healthcare settings, with staff such as clinical academics working for both medical schools and the NHS, carrying their experience from one sector to improve outputs in the other. At the individual level, research can work through different forms of public campaigning to reach those who may not otherwise be engaged, improving their understanding of the population's health issues, how these issues relate to society more broadly, and how the system can be best prepared for the health demands of the future.

The case studies that follow show medical schools conducting research that moves beyond the limits of the body and into the debates and priorities of society. As the stories reveal, the findings and work of UK medical schools have found practical solutions in fields as varied as gang violence and military fatigue.

⁸ <https://www.ipsos-mori.com/researchpublications/researcharchive/3455/EconomistIpsos-MORI-September-2014-Issues-Index.aspx>

Reducing violence to improve health, in the UK and internationally

University of St Andrews School of Medicine

The Public Health and Health Policy group at St Andrews University was established in 2008 and has become a leading centre in Violence Reduction Research. Its work includes evaluations of interventions and the study of factors that facilitate or prevent the adoption of effective violence prevention policies in the UK and internationally.



The team started by evaluating a gang member rehabilitation and violence reduction initiative, the Community Initiative to Reduce Violence (CIRV), in Glasgow in 2008. Motivations for positive change among gang members were explored and gaining work experience and obtaining and holding on to employment were identified as being particularly important. A detailed quantitative evaluation then demonstrated a fall of 52% in violent acts and a fall of 84% in knife carriage amongst those engaged in the programme.

Across 2009–2011 the group set about understanding factors that may underlie or precipitate violence, and they were able to show that young prisoners in Scotland have an excess of symptoms related to ADHD. It was found that the presence of these symptoms is predictive of

violent breaches of prison discipline. An innovative trans-dermal alcohol monitoring technology was piloted, allowing continual sobriety monitoring, as a possible means to reduce levels of alcohol-related violent reoffending.

Since the start of the 2008 evaluation and the publication of the 2011 results, we have changed police and social work in terms of attitudes, policy and tactics, substantially altering what these professional groups think is possible in dealing with violent young men. This work has changed the way social workers practise and how they are managed, and the Prime Minister and national newspapers cited it as a solution after the London riots. Its impact is a positive change in young people's lives, transforming their prospects from those of a lifetime of intermittent imprisonment to one of useful and meaningful societal involvement and contribution.

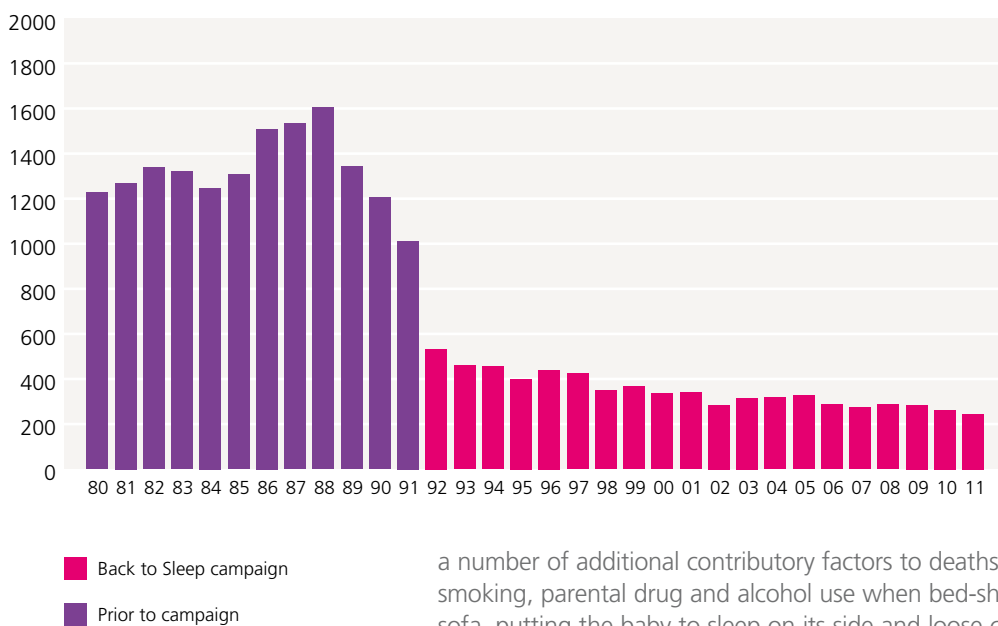
Researchers: Donnelly and team

Worldwide fall in the number of cot deaths

University of Bristol Medical School

University of Bristol research has led to a marked and persisting reduction in the number of cot deaths (sudden infant death syndrome, or SIDS).

SIDS deaths England and Wales 1980–2011



Studies published in the early 1990s were the first population-based investigations to document the importance of a number of factors (face-down sleeping position, wrapping infants too warmly and pre-natal smoking) that contribute to SIDS. Further data from the Confidential Enquiry into Stillbirths and Deaths in Infancy in 1993–1996 and the South West Infant Sleep Scene study in 2003–2006 identified

a number of additional contributory factors to deaths. These included post-natal smoking, parental drug and alcohol use when bed-sharing, co-sleeping on a sofa, putting the baby to sleep on its side and loose covering found over the infant’s head.

The Bristol approach to the investigation of unexpected infant deaths and the care of families was adopted by the Kennedy Committee which was set up by the Royal College of Pathologists and Royal College of Paediatrics and Child Health to improve the quality of such investigations and was subsequently incorporated into the Children Act 2004, becoming a statutory requirement throughout England from 2008. This process of child death reviews has led to a major change in the way medico-legal agencies involved in providing services to children interact, with a resultant improvement in the quality of such investigations and services to bereaved families.

The dramatic 67% fall in the occurrence of SIDS from 1988 to 1992 in England and Wales resulted from the identification of risks associated with putting babies to sleep face-down (prone). Nationally, death rates have more than halved again (54% fall) between 1992 and 2011. Tens of thousands of SIDS deaths worldwide have been prevented thanks to the team’s research, international collaboration and development of risk-reduction recommendations.

Researchers: Fleming, Blair and team

Negotiating human bodies and improving donation policies

Brighton and Sussex Medical School

Focusing on the experience of healthcare professionals and scientists operating in morally contested fields of biomedicine, the work underpinning this research has taken place at Brighton and Sussex Medical School since 2006.



Professor Bobbie Farsides

Over a range of funded research projects, the work has employed a novel interdisciplinary methodological approach entailing the combination of mixed empirical methods and philosophical/medico-legal analysis. A unique component of these projects was the use of Ethical Discussion Groups. This is an approach wherein practitioners who have previously been interviewed and observed in their professional setting are invited to participate in a group discussion facilitated by an ethicist. The data collected from these interventions have highlighted issues that needed to be addressed and have contributed to identifying workable solutions to complex ethical, legal and clinical issues identified as important by practitioners in the field who have valued the opportunity to reflect upon their practice, record their concerns and contribute to change in policy and practice.

Across a number of projects these methods were used to address questions of how and when to approach clients with regard to tissue and organ donation, how to define an embryo as 'spare', how to conceptualise and then acquire consent for the donation of embryos for treatment or research, and how best to construct robust regulatory and advisory frameworks. The work has influenced current practice and policy around consent and payment for donation, has influenced guidance relating to donation within the context of advanced cell based therapies and has prompted a re-assessment of guidance relating to donation and freezing policies.

Through its various aspects, the work on solid organ donation has also facilitated the resolution of ethical issues for clinicians caring for potential organ donors. In helping to clarify staff perceptions regarding the barriers to organ donation, and in informing the development of appropriate guidance, (for example the establishment of an ethical framework for caring for donors after circulatory death) the research has contributed to an increase of 50% in organ donations.

Researcher: Farsides

Dolly the sheep – the first cloned mammal

University of Edinburgh School of Clinical Sciences



This scientific breakthrough in regenerative medicine is widely recognised as the key stepping stone between earlier amphibian-based work and the reprogramming of adult human somatic cells to a stem cell state.

Researchers, led by Ian Wilmut (Inaugural Director of the Centre for Regenerative Medicine), with colleagues from the Roslin Institute (now University of Edinburgh), focused their scientific efforts on the manipulation of eggs (female reproductive cells), oocytes (egg precursor cells) and stem cells (cells that can divide and self-renew, but also differentiate into diverse specialised cell types). They were particularly interested in utilising somatic-cell nuclear transfer to produce viable embryos. This technique involves transfer of the nucleus from a somatic cell (any cell that is not a reproductive or stem cell) into an oocyte or egg deprived of its own nucleus (cytoplasm). Eventually this enabled the successful cloning of sheep from cultured cells derived from sheep embryos. Dolly – the first cloned adult mammal – was born on July 5, 1996, providing the first evidence that adult specialised cells are capable of driving the development of a complete and fertile animal.

Dolly has become a scientific icon, entering the public and educational lexicons in addition to scientific ones, stimulating rolling religious, ethical, cultural, political and scientific debates, and triggering public engagement with bioscience. For example, cloning principles are now part of high school education, including the International Baccalaureate, which is implemented in over 3,600 schools on five continents.

Dolly played a major role in clarifying the value of stem cell and regenerative medicine research to Government, contributing to the establishment of several high-profile initiatives, including the UK Stem Cell Initiative. In autumn 2012, the Chancellor of the Exchequer identified Eight Great Technologies of strategic importance to the UK and announced an additional funding of £600 million to help support their development. Regenerative medicine is placed among these great technologies.

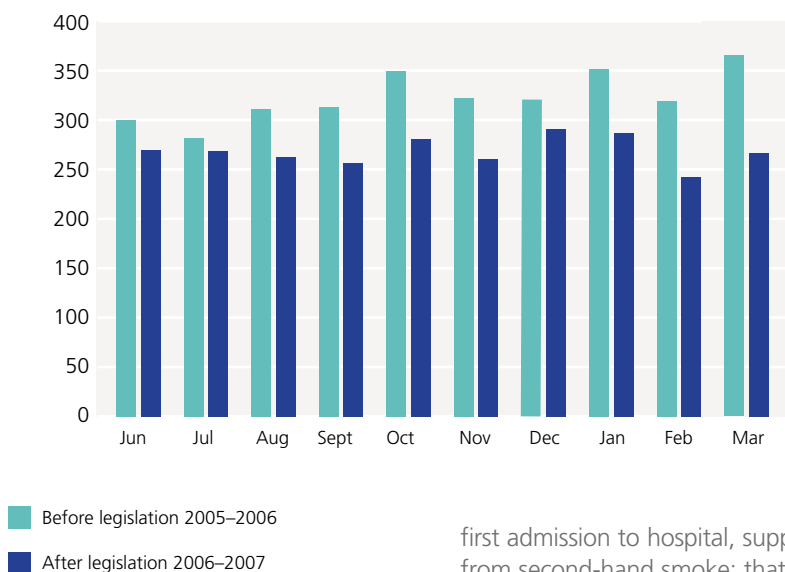
Researchers: Wilmut and team

The benefits of smoke-free policy in Scotland and worldwide

University of Glasgow School of Medicine

Since the end of March 2006, smoking has been prohibited by law in all enclosed public spaces throughout Scotland, with the specific aim of protecting non-smokers from the effects of second-hand smoke. Studies led by the University of Glasgow have provided the most robust available evidence that smoke-free laws have a significant impact on rates of heart disease, childhood asthma, complications in pregnancy, and stroke.

Admissions for acute coronary syndrome according to month before and after smoke-free legislation



From New England Journal of Medicine, Pell JP, Haw S, Cobbe S, Newby DE, Pell ACH, Fischbacher C, McConnachie A, Pringle S, Murdoch D, Dunn F, Oldroyd K, MacIntyre P, O'Rourke B, Borland W, *Smoke-free legislation and hospitalizations for acute coronary syndrome*, Volume 359, Pages 482-91. Copyright © 2008 Massachusetts Medical Society.

The Glasgow team was the first to perform a prospective study that linked reductions in admission rates to smoke-free legislation. For ten months before the enactment of the smoking legislation in Scotland on the 26 March 2006, and the same ten months in the year following legislation, patients admitted with acute coronary syndrome (ACS) to nine Scottish hospitals were recruited to the study. Over the period studied, the number of hospital admissions for ACS in Scotland decreased by 17%. By comparison, a 4% reduction was reported during the same period in England, where no such legislation had been introduced.

Further studies found that 'never smokers' who were exposed to second-hand smoke had a higher risk of adverse events (such as death or rehospitalisation) within 30 days of first admission to hospital, supporting the argument for protecting non-smokers from second-hand smoke; that childhood asthma admissions had been increasing by about 5% each year prior to the introduction of the smoke-free law, but were reduced by 18% per year following introduction of the legislation; that, for women who conceived between 1995 and 2009, there was a drop of more than 10% in the overall number of preterm deliveries, and significant drops of 5% and 8% in the number of infants born either small or very small, respectively, for their gestational age; that the incidence of cerebral infarction, which accounts for 50% of all strokes, was increasing at around 1% per year but, following introduction of the smoke-free law, reduced by around 9%.

This evidence has been used to support policy debate and decision-making in Scotland, the rest of the UK, and around the world. It has also provided a focal point for an extended and high profile global public debate over smoking legislation, and underpins health advice and campaigns published by the World Health Organisation, World Heart Federation and other international bodies.

Researchers: Pell and team

Improving health outcomes and primary care services for osteoarthritis in primary care

Keele University School of Medicine

Osteoarthritis affects 8.5 million people in the United Kingdom, accounting for a third of all years lived with disability. Keele's research has provided commissioners and third-sector organisations with accurate estimates of the size of the problem, policy-makers with evidence on groups at particularly high risk, and clinicians with original evidence on better approaches to assessing and managing osteoarthritis in patients presenting to primary care.



Keele's multidisciplinary team combined quantitative and qualitative methods with public involvement. This was used to describe the nature and scale of the problem in the population and how it is currently managed in primary care. Analysing routine recording in a network of general practices, in combination with new population surveys, provided accurate, national estimates of the burden of painful osteoarthritis and associated disability. The team identified possible contributing causes to osteoarthritis, focusing on lifestyle factors to discover several high-risk occupations (farming, mining, carpet-fitting) and demonstrated that prolonged kneeling and squatting were specific, potentially modifiable exposures associated with developing knee osteoarthritis. They developed and tested new methods for improving patient assessment in primary care, demonstrating that three simple questions asked by the GP during the consultation can improve their judgement of whose symptoms

are unlikely to respond to routine care.

The key insights from this research have led a shift in the concept of osteoarthritis from a structural disease characterised by changes on an x-ray to a clinical syndrome of persistent joint pain and disability, and provided rigorous evidence on the effective contributions of a range of active nonpharmacological treatments.

Research on the effectiveness of high-quality advice and supervised exercise programmes for osteoarthritis, and the researchers' commitment to seeing the implementation of these in routine primary care, contributed to exercise becoming a core treatment recommended in successive NICE and European guidelines for all persons with osteoarthritis and directly challenging both the belief that exercise is bad for joints with osteoarthritis due to accelerating 'wear and tear' and the idea that 'nothing can be done'.

Mental health consequences of deployment and overstretch in the UK Armed Forces

King's College London School of Medicine



Military personnel participating in King's research

Since 2003 the UK armed forces have had to cope with simultaneous major operations and to engage in intense, long-term combat operations. It has been claimed that this 'overstretch' may have effects on mental health.

In 2003, the 'Harmony Guidelines' developed by the UK Armed Forces assigned appropriate lengths of time for military personnel to be deployed on operations and optimal periods between deployments. These guidelines largely reflected opinion and experience rather than empirical evidence.

Based on a study involving 8,278 Regulars and 1,712 Reserves, KCL researchers established a

4.9% prevalence of probable post-traumatic stress disorder (PTSD), 13.0% for alcohol misuse and 19.7% for symptoms of common mental health disorders. Work from the US has consistently demonstrated a high prevalence of PTSD related to deployment in Iraq and Afghanistan and these rates continue to increase once personnel have returned home. KCL work with UK Armed Forces, however, found only a modest increase in the prevalence of probable PTSD with time since deployment, substantially lower than the rises reported from the USA. The most likely explanation is the shorter length of deployment, normally six months, in comparison to nine to 15 months in the US.

In 2011 the UK Armed Forces reviewed their policy on tour length to consider proposals for increasing tour length from six to nine months. Having been presented with KCL figures, the review accepted that increases in tour length might have a negative impact on mental health and may lead to rates of PTSD moving towards the much higher rates observed in the US, hence the proposals were rejected. KCL research also formed an essential part of the evidence that led to the US decision to reduce its tour length from one year to nine months.

In May 2011, the UK Government announced 'The Armed Forces Covenant' in which they stated a moral obligation to provide respect, support and fair treatment to members of the Armed Forces.

Researchers: Wessely and team

Introducing patient reported outcome measures (PROMs) into the NHS

London School of Hygiene & Tropical Medicine

Patients' views are essential to achieving high-quality care. Their perspective complements that of clinicians, providing unique insights into their own perceptions of health status and health-related quality of life. It is therefore important to find ways of involving patients in reporting on their own health outcomes.



The goal of research carried out by LSHTM since 1996 has been to develop and test ways of using Patient Reported Outcome Measures (PROMs) – measures of patients' health and health-related quality of life – collected before and after surgery in routine clinical practice.

The research fell into three phases: the development and psychometric testing of PROMs; methodological research to ensure accurate analysis and interpretation of these measures and then applied research which confirmed the feasibility of the routine use of PROMs to assess the quality of care of providers. This involved recruiting patients, following them up and making risk-adjusted comparisons of providers at reasonable cost.

The research into PROMs carried out at LSHTM has led directly to their introduction across the NHS in England for four elective surgical procedures. It is the first time that such measures have been introduced on a nationwide scale with the aim of

comparing the performance of hospitals. The NHS Management Board decided that from April 2009 it would be mandatory for all NHS patients undergoing the designated operations to be invited to complete pre- and postoperative PROMs questionnaires. Despite the change of government in 2010, there has been seamless political support for the use of PROMs. The value of PROMs for more sophisticated estimates of NHS productivity has been recognised by the Office of National Statistics and the National Audit Office. Since April 2010, PROMs data have been published online for the use of clinicians, managers, commissioners and the public. The huge scale of the programme is indicated by the 515,000 patients who participated over the first three years (over 70% of those eligible).

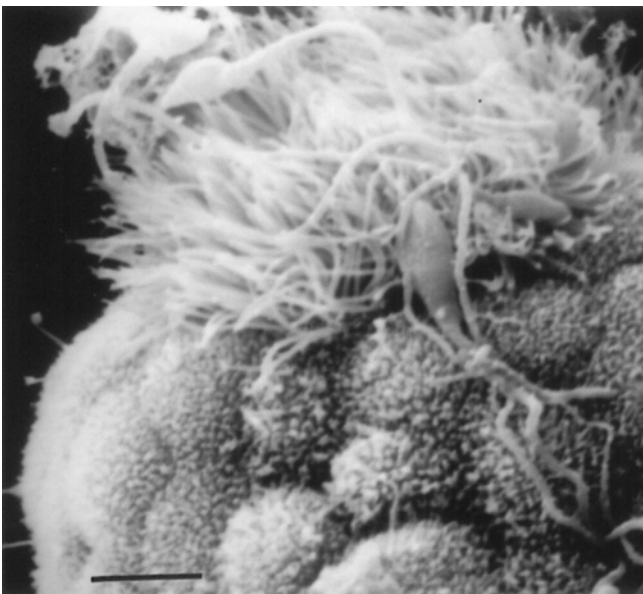
The President of the Royal College of Surgeons stated that 'the introduction of PROMs has been a major development in the history of surgery'. Professor Sir Bruce Keogh, Medical Director of the NHS, has said he hoped PROMS 'would shift the focus among doctors [away] from technocratic results, where an operation was deemed a success regardless of whether the patient remained in pain'.

Researcher: Black

The Great Sperm Race: Encouraging public understanding of human reproduction

University of Sheffield School of Medicine

The team at Sheffield undertook research focused on the basic biological processes of human sperm transport through the male and female reproductive tracts, and on the molecular and cellular basis of sperm function and male fertility.



The interaction in vitro of human spermatozoa with epithelial cells from the human uterine (fallopian) tube. Pacey AA, Hill CJ, Scudamore IW, Warren MA, Barratt CL, Cooke ID. *Hum Reprod.* 1995 Feb;10(2):360–366.

They used a tissue-culture model to show that the secretions from the inner cell layer of the Fallopian tube helped to prolong sperm survival beyond that normally seen in tissue culture. They went on to show that the sequence of fluids from the female reproductive tract, which sperm have to pass through on their journey, are critical to ensuring that the successful sperm have optimum physiology by the time they reach the egg.

A further project investigated how the human Fallopian tube might act as a sperm-storage site in the pre-ovulatory period. Using tissue culture and electron microscopy, the very first descriptions were made of the physical interaction between human sperm and the cell layer that lines the inside of the Fallopian tubes, showing that the part of the Fallopian tube closest to the uterus (called the isthmus) potentially stored the most sperm. It was found that, to release themselves from this storage site, sperm must exhibit a characteristic and particularly vigorous form of movement called hyperactivation.

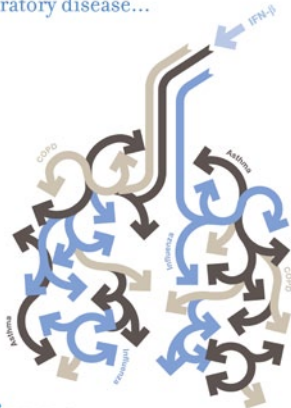
This research, conducted between 1992 and 2006, was developed into a film, *The Great Sperm Race*, which was shown on television in twenty-two countries between 2009 and 2010. The film was nominated for a Royal Television Society award in 2010 and won a Canadian Society of Cinematographers award in 2009 for the best 'Docudrama Cinematography' and an Academy of Canadian Cinema and Television, Gemini Award in 2010 for the Best Science Documentary. Online resources developed to support the film are still being used today and the game produced as part of these resources has been played nearly 10.5 million times since March 2009, with excellent feedback about its educational value.

Researchers: Pacey and team

Breathing new life into the treatment of respiratory illnesses

University of Southampton Faculty of Medicine

Targeting the causes of respiratory disease...



synairgen

The British Thoracic Society reported in 2006 that respiratory disease kills one in four people in the UK and costs the National Health Service £2.6 billion each year. Of 5.2 million people in the UK receiving treatment for asthma, around 2.6 million live with symptoms classed as severe, and around 500,000 of these experience severe symptoms because treatments currently available are incapable of bringing the disease under control. In addition, acute chronic obstructive pulmonary disease (COPD) attacks are the most common cause of hospitalisation in the country.

Through controlled infection of human volunteers, research at Southampton found that the airway epithelium plays a pivotal role in acting as a 'host' for common cold viruses, and that rhinoviral infections of the lower respiratory tract are directly linked with asthma exacerbations. This stimulated the discovery of a deficiency in the production of anti-viral interferons by bronchial epithelial cells grown from asthmatic donors. Crucially, the cells could be protected against virus infection by adding exogenous interferon beta (IFN- β), a breakthrough in the search for therapy. Follow-up studies into COPD showed that bronchial epithelial cells from long-term smokers are highly susceptible to rhinoviral infection but, as in asthma, are protected by exogenous IFN- β , a drug already used systemically to treat multiple sclerosis.

These novel mechanistic findings were the subject of a patent filed by the University of Southampton for the use of inhaled IFN- β for treatment of virus-induced exacerbations of asthma and COPD. This was licensed to Synairgen, a spin-out company set up by the University in 2004. Since 2008 Synairgen has concentrated its effort on the clinical development of inhaled 'IFN- β 1', and Phase I and Phase II clinical trials have been highly successful.

Further work undertaken by Synairgen internally and in collaboration with Public Health England has shown that IFN- β has utility against established influenza (swine flu, avian flu, and seasonal flu) infection. In 2010 this resulted in the filing of a patent for the use of inhaled 'IFN- β 1a' against influenza, attracting the US Department of Defense's interest in its applicability for combating bioterrorism.

Researchers: Holgate and team



Beyond borders

In 2013 the UK spent £11.5 billion on overseas development assistance with nineteen per cent of that budget devoted to health, more than to any other sector.⁹ The UK also has a strong track record in funding and delivering medical research in the developing world through the vital work of bodies such as the Wellcome Trust. This demonstrates the UK's commitment to the global health agenda and an understanding that global biomedical knowledge must be connected with the health systems of individual nations – as has been so graphically demonstrated with the 2014 Ebola outbreak.

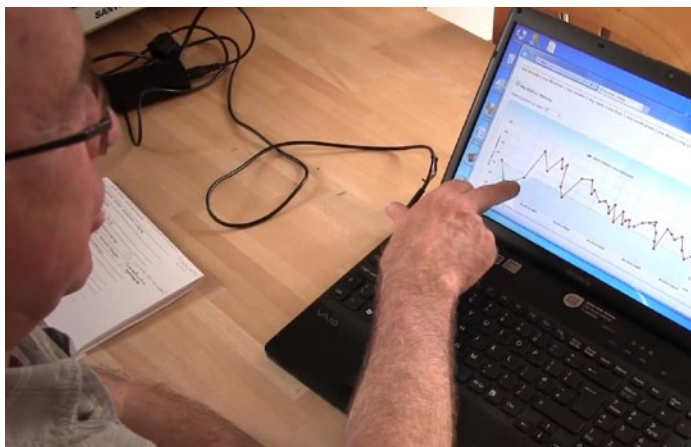
The UK's long and complex relationships with many parts of the world, for which the development of health provision has always played a part, have today moved into an awareness of the mutual benefits of working together and fostered an eagerness to engage which can be seen in different aspects of society, from the establishment of the NHS International Development Team to the work of private individuals: Médecins Sans Frontières UK estimates that it sends between 175 and 200 UK staff to the field each year.

As the case studies that follow show, UK medical schools are at the forefront, moving beyond their own borders to work in partnership with health systems and institutions around the world. They are showing that geography is no barrier to tackling lethal infectious diseases and also the global health challenges we all have common.

⁹ https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/368798/SID-2014a.pdf

Biomedical informatics transforming the care of people with diabetes, and with chronic diseases internationally

University of Dundee School of Medicine



Diabetes is a global health problem which poses severe risks for the world. The number of people living with diabetes is estimated to be 500 million by 2030. In response to this, researchers at Dundee developed a health informatics platform supporting chronic disease management nationally and internationally, along with a new record linkage tool for drug safety.

Initially, the Diabetes Audit and Research in Tayside, Scotland (DARTS) study tested the hypothesis that record linkage of routinely collected NHS data sources was

an efficient and accurate methodology to create a regional diabetes register. The study linked information from the community health index (health identity number), hospital clinics, pharmacies, laboratories, and the retinal screening service. The Government commissioned further informatics research at the University of Dundee to develop DARTS into a national technology product, the Scottish Care Information-Diabetes Collaboration (SCI-DC). Its roll out to the whole of Scotland has allowed the study of the epidemiology, pharmacovigilance and outcomes research on a national basis. Since 2004 SCI-DC has been implemented in all 14 Scottish Health Boards, and since 2008 it has been used in 1,038 general practices and 38 hospitals, monitoring the care of over 271,000 people with diabetes. It represents the most comprehensive clinical information system for the care of people with diabetes internationally.

SCI-DC has supported the evaluation of improved regional and national health outcomes, such as a 40% reduction in amputation rates and a 40% reduction in sight-threatening retinopathy from 2003–2009. The associated recruitment of individuals to large genomic studies (over 40,000 subjects), and the linkage of phenotype to genotype, has been of great importance. This linkage between research, informatics and healthcare led Sir Mark Walport, then Director of the Wellcome Trust to write (*The Times*, 30th May, 2011) 'If you live in Dundee and suffer from diabetes, you have recently been taking part in a medical revolution'.

Researchers: Morris, Leese and McDonald

The development of a European Action Plan for strengthening public health capacities and services

Durham University School of Medicine,
Pharmacy and Health



Durham University's Centre for Public Policy and Health (CPPH) has worked closely with the World Health Organisation's (WHO) Regional Office for Europe to help design the *European Action Plan for Strengthening Public Health Capacities and Services*. The European Action Plan draws extensively on three major CPPH research projects on the nature and governance of the public health system in England.

Through the first project, research was commissioned employing a complex systems approach, not previously applied to the topic, to identify the particular nature of, and challenges facing, public health policy and practice and to provide a conceptual framework for understanding and exploring possible ways of meeting these. The framework is generic and may be applied to public health systems in different countries. The second project found that partnerships in public health were more complex than those in health and social care services. Collective leadership emerged as vital, and, within complex partnerships, relationships were more important than structures. It identified the skills and competencies required to make partnerships more effective, and its originality and contribution to knowledge lay in bringing these findings together within a framework derived from systems thinking. The third research project focused on the relationships between governance, commissioning and public health, and developed the concept of 'public health governance'. It demonstrated the complexity of the governance landscape for public health, the leadership qualities required to negotiate it, and contributed to understanding the processes involved in addressing a governance deficit in public health.

The European Action Plan was endorsed by all 53 WHO member states in September 2012. The WHO describes it as constituting 'one of the main pillars of Health 2020', the WHO health policy framework and strategy which aims to support action across government and society to 'significantly improve the health and well-being of populations, reduce health inequalities, strengthen public health and ensure people-centred health systems that are universal, equitable, sustainable and of high quality'.

Researchers: Hunter and Marks

Global adoption of statins for cardiovascular disease prevention

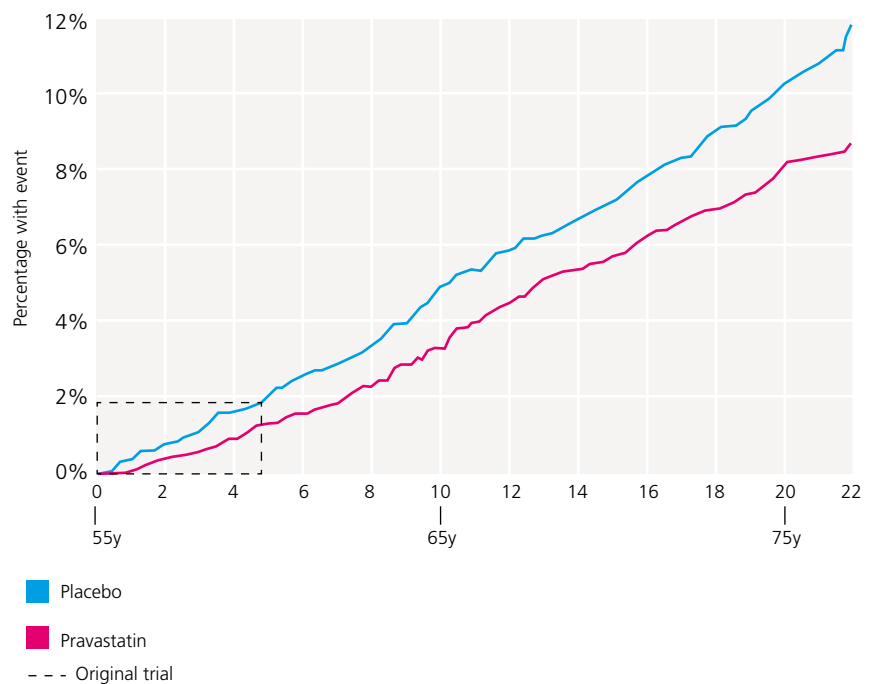
University of Glasgow School of Medicine

More than half of UK adults aged over 45 years have high cholesterol levels, the major modifiable risk factor for cardiovascular disease (CVD). Current estimates suggest that more than 7,000 European and US adults die of CVD each day. Internationally recognised clinical trials conducted by the University of Glasgow have provided the cornerstone of the evidence base supporting lipid lowering as a strategy to reduce CVD risk.

This landmark research drove the global adoption of statins as the first-line medical option for prevention of CVD and continues to shape modern day lipid-lowering guidance and practice worldwide, with associated benefits for patients and healthcare systems. Statins offer major benefits for patient outcomes, including reduction in mortality and major CVD events.

The ground-breaking West of Scotland Coronary Prevention Study (WOSCOPS) was a clinically driven *primary prevention* randomised controlled trial (RCT): the researchers purposely targeted individuals with no history of heart attack who were apparently healthy yet were at a high risk of having a heart attack in the near future based on their cholesterol levels. The team randomised 6,595 men (aged 45–64 years) with raised low-density lipoprotein cholesterol levels to treatment with pravastatin or placebo and participants were followed for an average of five years. Pravastatin reduced the risk of a first-time heart attack (myocardial infarction, MI) or

Long term follow up in statin studies: WOSCOPS 20-year experience CHD mortality
27% risk reduction over entire period $P < 0.001$



death from coronary heart disease (CHD) by 31% and was well tolerated. WOSCOPS therefore set the stage for statins as a safe primary prevention therapy for reducing CHD risk and provided conclusive evidence in support of the hypothesis that a raised blood cholesterol level is a modifiable risk factor for CVD.

The University of Glasgow led/steering committee involvement in RCTs on lipid lowering dominates the evidence base in current, high profile clinical guidelines on lipid lowering. 2011 ESC/EAS guidelines on the management of dyslipidaemias state that 'not only should those at high risk be identified and managed; those at moderate risk should also receive professional advice regarding lifestyle changes, and in some cases drug therapy will be needed to control their plasma lipids'. The guidelines also underscore the

need to promote primary prevention efforts. Adults with a 20% chance of developing CVD within a 10-year timespan should be offered a statin for primary prevention. Furthermore, statins are unequivocally recommended for individuals considered to be at very high risk; namely, patients with diabetes (if aged over 40 years), chronic kidney disease or peripheral arterial disease, as well as those who have previously experienced a CVD event.

WOSCOPS continues to impact prevention strategies with the recently announced 20-year follow up (presented at the American Heart Association 2014) showing clear long-term efficacy and safety. This evidence lays to rest many current concerns concerning the widespread use of these drugs in the population.

Researchers: Shepherd and team

Improving primary care for depression

Hull York Medical School



Wellcome Library, London

Depression is the second leading cause of global disability. The research generated evidence to help tackle depression at a population level and to improve the organisation of primary care services by integrating psychological and pharmacological management.

It showed that screening is unlikely to deliver benefits, but that organisational enhancements lead to clinical improvement and return to economic productivity. This provides the evidential basis for the flagship NHS policy for depression – Improving Access to Psychological Therapies (IAPT). York developed a computer case management system (PCMIS) allowing patient reported outcomes to be monitored in real time. It has recorded over 3 million episodes of care in the NHS.

Prior to the conduct and dissemination of the work, guidance issued by NICE and international bodies such as the US Agency for Healthcare Research and Quality had been supportive of screening for depression. In the UK, since 2005 GPs were paid to screen for depression in certain populations under the Quality and Outcomes Framework. The York research showed that this strategy was ineffective and inefficient. The outputs generated debate both nationally and internationally, prompting editorials in the BMJ and the Canadian Medical Association Journal.

Depression is the most common mental disorder and the second most common cause for consultation in primary care. Estimates

of the incidence of depression range from 36% of adults. The research addressed two major issues: (a) screening for depression and (b) organisation and delivery of primary care for management of depression. The Cochrane review, which pooled data from 16 randomised controlled trials including 5996 patients, reported that screening had no clinical impact on quality of care or depression outcomes. A meta-analysis (36 RCTs, 12,355 participants) found that average depression outcomes in primary care improved when services were managed in a 'collaborative' fashion by the use of trained case managers who deliver evidence-based psychological and pharmacological treatments. The greatest improvement in depression outcomes was found where case managers received rigorous training and supervision and used computer-decision support systems.

NICE revised its guidelines on the management of depression in 2009 and 2011 citing the York research 47 times in the most recent guidance as evidence of the effectiveness of collaborative care as an organisational model. There has also been NHS-wide improved access to psychological therapies for depression as a result of this major UK policy shift. The research is also cited in international guidelines in the US, Canada, Europe and Australia where practice has changed as a result.

Researchers: Gilbody and team

Control of Japanese encephalitis

University of Liverpool School of Medicine

Globally the most important cause of encephalitis (inflammation and swelling of the brain) is the mosquito-borne Japanese encephalitis virus (JEV), responsible for an estimated 70,000 cases annually across Asia.



Wellcome Trust Research Fellow Dr Lance Turtle, who is working with Professor Tom Solomon on Japanese Encephalitis in India. Photograph by Professor Tom Solomon

Although vaccines were developed years ago, their uptake in Asian countries has been hampered through several factors including lack of disease burden data, a consequence of poor surveillance, complicated diagnostics, and insufficient knowledge about disease outcomes. Research at the University of Liverpool has addressed each of these areas in turn, to overcome the roadblocks in vaccine implementation.

To strengthen surveillance the team demonstrated the wide range of clinical presentations the virus can cause, including a previously unknown poliomyelitis-like illness. They had a leading role in the development of the WHO Surveillance Standards, and showed they were effective. These Standards are now used across Asia. To improve diagnostics, the Liverpool team worked with colleagues at the University of Malaysia, Sarawak to develop and field-test prototype simple rapid kits for diagnosing JE in the rural field hospitals where it occurs. Similar kits are now used across Asia in the WHO Diagnostic Laboratory Network.

In 2003, the team showed with a randomised controlled trial that interferon treatment was ineffective, helping focus attention on the importance of disease control through vaccination. The Liverpool team developed the online e-learning tools for Clinical Assessment of Children with JE, and for using the disease outcome score which they had developed (2008–10) – now known as the Liverpool Outcome Score. This Score is now used in many Asian countries to help assess disability in JE. Although approximately 20% of children with JE die, the greater socio-economic burden is caused by those that survive with severe disability.

The impact of this research can be examined through the new University of Liverpool-supported vaccination programmes across Asia. By the end of 2013, vaccination had begun in 11 new countries, and the vaccine had reached more than 200 million people. The estimated public health benefits, derived from a health economic modelling study, indicate there may be up to 854,000 cases and 214,000 deaths avoided, with an associated saving across Asia of up to \$1.024 billion.

Researcher: Solomon and team

Improving outcomes for children with leukaemia internationally

University of Manchester School of Medicine

Researchers at the University of Manchester have made a significant impact nationally and internationally on improving the outcome for children with acute lymphoblastic leukaemia (ALL).



Royal Manchester Children's Hospital

Work in the period 1993–2003 led to the routine use of dexamethasone (instead of prednisolone), mercaptopurine (instead of thioguanine) and pegylated L-Asparaginase (instead of native asparaginase) in childhood ALL in the UK and elsewhere. Incorporating these drugs, researchers developed a new concept for the treatment of relapsed ALL. The trial introduced minimal residual disease (MRD) based risk stratification to select for patients to either receive chemotherapy or an allogeneic transplantation and was the first randomised international trial for relapsed ALL. A bespoke remote entry clinical trial management system was constructed indigenously.

This system permitted remote registration and data entry, provided decision support and standardised the reporting of MRD across all recruiting centres. This approach allowed countries including the Netherlands, Australia and New Zealand to adapt the study rapidly for their patients at all centres. A centralised cell bank for the UK was developed in Manchester for this trial. Building translational research into clinical trials has also allowed the identification of previously unidentified mechanisms of therapeutic failure paving the way for novel therapeutic strategies.

The survival rates in newly diagnosed childhood ALL in the UK are now over 85%, among the best in the world, and the outcome for children with relapsed ALL is improved by 10% in the UK, Netherlands, Australia and New Zealand. Changes in clinical practice based on this research are now national standards of care for children with *de novo* and relapsed ALL in the UK and Ireland. Other international groups have adopted key findings from the results of the frontline trials and the relapse protocol for childhood ALL now underpins European and North American strategy for the management of relapsed disease.

Researchers: Eden and Saha

Influencing international health policy to reduce acute waterborne diarrhoeal disease

Norwich Medical School, University of East Anglia

Diarrhoeal disease is the world's second most common cause of death in children under five years old, killing 760,000 children each year, and microbial contamination of drinking water is one of the most important causes. In England and Wales, acute diarrhoeal disease is estimated to cost the country £1.5 billion annually. Recreational water quality is a related issue and it is estimated that, globally, over 120 million gastrointestinal illnesses per year are caused by swimming and bathing in wastewater-polluted coastal waters.



Photograph by Jo Geere

UEA researchers completed a large cohort study demonstrating that children under 10 years of age in England who are reliant on contaminated private small water supplies have more than five times the risk of diarrhoea than children whose water is not contaminated. They have also shown that a high proportion of such water systems suffer from microbiological contamination, which is much worse than in large, mains drinking water systems. Economic analyses of water interventions to improve small-scale water supplies in developed countries showed that they reduce the direct and indirect costs of illness, outweighing the costs of improving the supplies. Epidemiological modelling research quantified the impact of community water systems on health in developing countries and highlighted the problems caused

by the unreliability of these supplies. For recreational water, methodological research showed that the statistical methods used by regulatory agencies to assess compliance with bathing water quality standards were flawed.

This research has led to changes in national and international health policy, including policies of the World Health Organisation (WHO), and it has influenced the recommendations of international expert groups and task forces, leading to changes in policy. Research was used specifically to underpin the WHO guidance documents on classification of bathing water quality. These WHO guidance documents form the basis of current European Union Bathing Water Directives, consequently enacted into UK law in 2008.

Researchers: Hunter and team

Exposing a treacherous trade

University of Oxford Medical Sciences Division



Genuine blister pack



Falsified blister pack

Falsified medicines in Africa: All talk, no action, Newton PN, Taberner P, Dwivedi P, Culzoni MJ, Monge ME, Swamidoss I, Mildenhall D, Green MD, Jähnke R, dos Santos de Oliveira M, Simao J, White NJ, Fernández FM. *Lancet*. 2014 Sep;2(9):e509–e510

Falsified (aka counterfeit) antimalarial medicines have a devastating effect on malaria-related mortality and morbidity on a global scale. Primary investigations led by researchers at the University of Oxford into this extremely dangerous trade have prompted criminal investigations, fake medicine trafficking arrests, interventions from the World Health Organization (WHO) and other international organisations, and have also led to new screening facilities and mobile screening technology in affected areas.

Investigations since 1999 identified an epidemic of fake antimalarial drugs in Asia and analysed the packaging, the banned substances they included and even the types of chalk and pollen within the tablets. These research data strongly suggested that they were being produced in southern China and, when these data were provided through INTERPOL to the Chinese Government, criminal investigations led to arrests and the seizure of 24,000 blister packs of fake antimalarials, potentially saving thousands of lives.

Subsequent research demonstrated that fake antimalarial drugs were widespread across malarious Africa. International organisations such as the World Health Organisation, INTERPOL, the Global Fund and the President's Malaria Initiative have launched a series of investigations, reports and interventions prompted by this evidence. These have, in turn, enhanced regulatory systems, improved medicine quality surveillance and increased co-operation between national drug regulatory authorities. The Worldwide Antimalarial Resistance Network (WWARN) based at the University of Oxford has developed an online platform for the collection, tabulation and mapping of reports of poor quality antimalarials globally (www.wwarn.org/aqsurveyor). This freely available resource is developed for public health organisations, governments, policy makers and researchers.

In addition, the underpinning research from the University of Oxford Medical Sciences Division has inspired the creation of networks in Africa that allow consumers to verify that their medicines are genuine using mobile phone free text messaging.

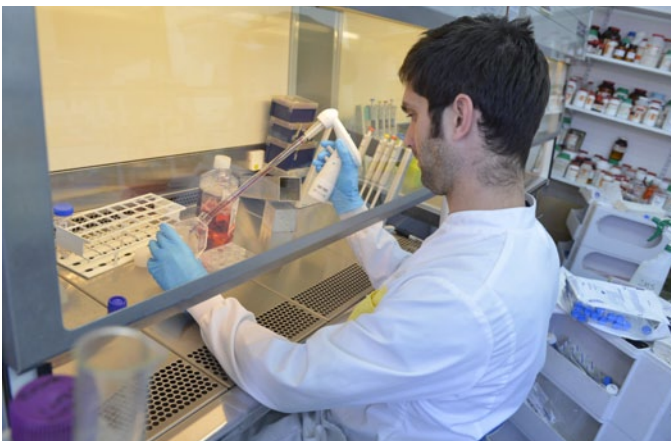
The work of these researchers, funded by Wellcome Trust, French Ministry for Foreign Affairs and International Development, and the Bill and Melinda Gates Foundation, has been widely publicised around the world. It has helped provide much-needed evidence to inspire ongoing action from global leaders, medicine regulatory authorities, criminal investigators and international health organisations.

Researchers: Newton

Discovery and development of thalidomide analogues for treatment of myeloma and other cancers

St George's, University of London

Following the serendipitous observation of improvement in leprosy in a patient taking thalidomide in 1965, a number of clinicians reported beneficial effects of this drug on certain steroid-resistant diseases including graft-versus-host disease following organ transplantation. Researchers at St George's postulated that thalidomide had immunomodulatory actions in addition to its well-recognised sedative action.



A trial in HIV-positive patients demonstrated potentially important immunomodulatory effects however it was clear that its widespread use was likely to be impaired by its association with birth defects, significant neuropathy in some patients, and its tendency to induce somnolence.

A programme to develop a thalidomide analogue was proposed and lenalidomide and pomalidomide were developed in collaboration with the start-up company Celgene. A phase I study in solid tumours showed that both analogues appeared to be immunostimulatory, in addition to their anti-inflammatory properties. This was subsequently confirmed in humans in 2010 when myeloma patients on these drugs were reported as responding preferentially to pneumococcal vaccines. It is now apparent that lenalidomide is 50,000 times more potent

than thalidomide in inhibiting tumour necrosis factor-alpha, and has less severe adverse drug reactions. A second key insight was that the anti-inflammatory, co-stimulatory and anti-angiogenic activities of lenalidomide made it an ideal agent for combining with other classical therapies, such as Gemcitabine and Docetaxol, leading to clinical studies with these combinations in myeloma.

Whilst the immediate beneficiaries of lenalidomide have been patients who suffered from myeloma or myelodysplasia, this drug is now being found to be effective in chronic leukaemias and lymphomas. Pomalidomide, the second analogue originally developed by Dalgleish in conjunction with Celgene has a more potent immune co-stimulatory action than lenalidomide and received approval by the FDA in February 2013 for relapsed multiple myeloma. It is now being trialled for use in other tumours.

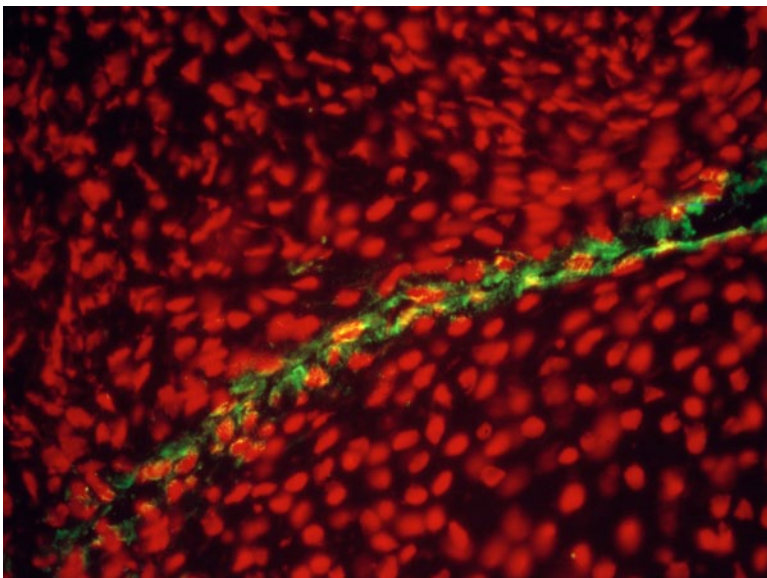
The development of lenalidomide has had a major impact on the growth of Celgene. From being a small non-clinical research organisation it is now a worldwide corporation based in New Jersey, USA, employing over 5,700 employees. Many of these employees are in Europe and the UK in particular, and this has led to the funding of many other research groups and clinical trials throughout the UK. Lenalidomide sales worldwide generated \$3.8 billion USD in 2012 and U.S sales have increased 16% this year and international sales 8%.

Researchers: Dalgleish and team

B cell depletion: an effective therapy in rheumatoid arthritis

University College London Medical School

In the 1980s and early 1990s it was a general view that rheumatoid arthritis (RA) was caused by T cells that attacked specific targets in joints. Yet, despite more than 20 years of research, no consistently autoreactive T cell had been identified. Research at UCL led to the hypothesis that B cells played an essential role in the pathogenesis of RA.



Section of foetal synovial joint showing CD16 expression on macrophages (green) almost entirely restricted to the separating tissue surfaces (intimal layer)

Following anatomical and immunohistochemical studies of normal and diseased human synovium they found that a receptor (CD16) was constitutively expressed on macrophages in synovial lining and to a lesser extent in other sites affected in the disease. The consequence of CD16 activation was to stimulate macrophages to generate TNF α , a powerful pro-inflammatory cytokine known to be involved in joint inflammation. CD16 appeared to be activated by soluble complexes of particular autoantibodies created through the expansion of B cells in a manner that avoided usual pathways to control their number. This led to the hypothesis that removing B cells would reduce the inflammatory stimulus and also break the vicious cycle of autoreactive B cell expansion. Proof of concept followed with the clinical success of a small trial of the B-cell-depleting agent, rituximab, in five patients with intractable RA in 1998–1999 by the UCL team, and confirmed by them in a larger cohort.

By the end of July 2013, Roche estimated that 228,801 patients have been treated with rituximab for RA, and a cost of £5,000 per annum less than other biologics, generating considerable savings to the NHS and even greater savings for low and middle income countries. Towards the end of 2006, a consensus statement and guidance document on the use of rituximab for routine care of patients with RA was issued by the European League Against Rheumatism (EULAR), describing the treatment as 'a major advance in the therapeutic armamentarium for patients with rheumatoid arthritis'.

Researchers: Edwards and Cambridge

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