The Medical Research Council is the UK’s leading publicly funded biomedical research organisation.

Our mission is to:

• Encourage and support high-quality research with the aim of improving human health.

• Produce skilled researchers, and to advance and disseminate knowledge and technology to improve the quality of life and economic competitiveness in the UK.

• Promote dialogue with the public about medical research.

“RESEARCH IS ABOUT PEOPLE – NOT JUST THE SCIENTISTS BEHIND DISCOVERY, BUT ALSO THE MEMBERS OF THE PUBLIC WHO HELP RESEARCHERS IN THEIR QUEST TO IMPROVE HEALTH AND THE MANY OTHERS WHO ARE AFFECTED BY THE FINDINGS.”

SIR LESZEK BORYSIEWICZ, MRC CHIEF EXECUTIVE
Medical research: benefiting people

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SINCE 1913 THE MEDICAL RESEARCH COUNCIL HAS MADE DISCOVERIES THAT HAVE IMPROVED THE HEALTH OF MILLIONS OF PEOPLE IN THE UK AND WORLDWIDE.
First and foremost in the MRC’s mission is supporting research with the aim of improving human health. Our scientists are behind some of the most important medical advances of the past century.

Our early work included tackling tuberculosis and rickets and developing antibiotics to treat bacterial infections — illnesses that blighted life for people in the early 20th century. Through the 1950s to 1970s we unravelled the structure of DNA, proved that smoking kills, began research that would quadruple survival rates for childhood leukaemia and invented MRI scanning. Over the next few decades MRC-funded science led to the development of monoclonal antibodies (which make up a third of all biotechnology products in development today) and effective drugs to delay the progression of HIV/AIDS, the discovery that statins cut heart attack and stroke risk and the sequencing of the human genome.

The past 12 months have witnessed more excellent results from our scientists in universities, hospitals and MRC units and centres. This Annual Review highlights a selection of these outstanding achievements and shows how the work of our scientists during 2007/08 is continuing to improve human health.

But research is about people — not just the scientists behind discovery, but also the members of the public who help researchers in their quest to improve health and the many others who are affected by the findings. This review focuses on them. For instance, five-year-old twins Isabella and Olivia Murphy gave samples of their blood for research that allowed MRC scientists to discover a new type of pre-leukaemic stem cell. Amanda Gill, teaching assistant from Sheffield, had two heart attacks before she reached middle age. Her heart specialist is also an MRC scientist, and what he sees in the clinic with patients like Amanda feeds directly back into his research in the lab. David Ward, who recently retired as a journalist, was enrolled in a study by his mother before he was born and has now been tracked for 62 years by scientists. The study is starting to yield important insights into ageing and health. Les Clarence, who turned 70 recently, had a stroke a year ago. During his recovery he has helped MRC researchers to test a new device aimed at helping stroke patients to overcome swallowing difficulties, a common and serious problem. By working with the many individuals who participate in MRC science, we are increasing our understanding of disease and helping to develop the treatments of tomorrow. And as this review shows, it’s a two-way process, where insights from our patients also feed back into our research.

Improving people’s health is the MRC’s priority and a focal point for our close relationship with the National Institute for Health Research (NIHR), the R&D arm of the NHS. The NHS turned 60 this year; its strong links with the MRC over the past decades are what have made possible much of our research. And our close relationship with NIHR is now helping us to make sure that discoveries by our scientists are even more quickly turned into health benefits. We’ve been working hard during the past year to put into place new funding programmes and initiatives to turn this into a reality — you can find out more about this in our 2007/08 Annual Report.

We hope you’ll enjoy reading about what our scientists have achieved during the past year and hearing the stories of just a few of the people who have helped to make their work possible.
The MRC supports a wide range of research into molecules, genes and cells, from developmental biology and genetics to cell biology and cancer. Priorities during 2007/08 included chemical biology – which uses chemistry to answer biological questions – and structural biology. A major focus was stem cell science and the MRC continued to support a wide range of initiatives in this area, including a five-year award to launch the MRC Centre for Regenerative Medicine in Scotland. In radiation and radiotherapy research, another priority, the new joint Radiation Oncology and Biology initiative was set up by the MRC, Cancer Research UK and Oxford University.

Maintaining a strong portfolio of molecular level research is very important to the MRC – as is continuing to encourage its translation into medical applications.
Olivia and Isabella Murphy, five-year-old twins whose blood samples enabled a major breakthrough in understanding leukaemia.

Olivia Murphy was diagnosed with acute lymphoblastic leukaemia in July 2005 when she was just two and a half years old. “She had been poorly for a couple of days and both my husband and I knew that something was not quite right,” recalled her mother, Sarah. “We took her to A&E and the first time they diagnosed gastroenteritis and the second time acute tonsillitis. So they gave her some antibiotics and, although she did seem to recover, she never fully regained her colour and she was still sleepy all the time. Then we noticed some bruising so we took her back to the hospital and they gave her a blood test – and that confirmed the worst.”

Olivia was put straight on intensive chemotherapy. “The first few days I thought she didn’t seem too bad, but then she went downhill rapidly, she lost her hair and was quite poorly. It was a 28-day cycle, so she had a lot of chemotherapy going through her little body. She also had to have blood tests taken constantly and had a catheter under her skin for injecting the chemotherapy drugs. For some reason her immune system suffered badly – she developed shingles and this led to her losing her sight in one eye. So she was in hospital quite often and for quite a long time.”

It was very hard for Isabella. “Previously, she and Olivia were together all the time and all of a sudden mummy and Olivia were away and Olivia was really poorly,” recounted Sarah. “Some of the drugs affected Olivia’s mood – Isabella would see her sister being happy and smiley one minute and then being violently ill and really bad tempered and crying the next. I think even now Isabella’s still suffering the effects of that.”

Sarah Murphy’s father was also a twin, which made her interested in twin research. When Olivia was diagnosed Sarah wondered whether Isabella had a higher risk of leukaemia as well and asked for her blood to be checked. That was when the researchers asked if they could use samples of both the girls’ blood for research. This led to the scientists discovering a new type of pre-leukaemic stem cell that had been present in both girls’ blood since birth. In Olivia, a second mutation meant the cells developed into leukaemia, but in Isabella they remained dormant.

Sarah said: “While the research was happening we were just getting Olivia’s results back. But when the findings came through, it was explained to me and I realised what a big deal it was. It made my husband and I and our family and friends realise how much work goes into finding treatments and cures and how much funding is needed. It opened our eyes to just how much effort goes into every little advance.”

Olivia still goes to have her blood tested every month and Isabella gets checked every couple of months. But it’s been a year since Olivia finished chemotherapy and her doctors are hopeful that they’ve beaten the leukaemia completely. The family is now getting on with their lives. Sarah said: “The girls love ballet, they look forward to it every week. They also love colouring in and drawing, especially Isabella – she’ll sit there for hours. Olivia has 20 or 30 Barbie dolls and she’ll play for hours with them in her bedroom. They’re very close but they are both very different.”
“WE HOPE THAT EVENTUALLY OUR WORK WILL LEAD TO THERAPIES TO TARGET BOTH THE PRE-LEUKAEMIC STEM CELL AND THE CANCER STEM CELL ITSELF, TO CURE LEUKAEMIA WHILE AVOIDING THE DEBILITATING AND OFTEN HARMFUL SIDE EFFECTS OF CURRENT TREATMENTS.”
 PROFESSOR TARIQ ENVER
Childhood leukaemia stem cells discovered

A team led by Professor Tariq Enver of the MRC Haematology Unit has for the first time identified pre-leukaemic stem cells, by studying blood from Isabella Murphy, whose identical twin sister Olivia had acute lymphoblastic leukaemia (ALL), the most common childhood cancer. Professor Enver explained: “Previously, no-one knew much about the nature or role of stem cells in childhood ALL in either its earliest ‘pre-leukaemic’ manifestation or in the fully transformed cancer state. Because pre-leukaemia changes in the blood are clinically silent, it was only by finding a twin of someone with the disease that it was possible to identify this early stage of disease before the cells turned cancerous.” In samples of Isabella’s blood, the researchers were able to identify cells in which abnormal fusion of two genes occurred during the mother’s pregnancy, to create a hybrid protein called TEL-AML1. Then, by studying Olivia’s blood, they were able to identify the cancer stem cells that the pre-leukaemic stem cells had turned into to cause and maintain leukaemia. The finding was confirmed when the scientists put the abnormal gene into human cells which were transplanted into mice with no immune system. This led to pre-leukaemic stem cells becoming established in the bone marrow of the mice. The work proved the ‘self-renewing’ nature of the cells and confirmed a direct link between the genetic malfunction and the generation of pre-leukaemic stem cells. The scientists are now trying to find out what triggers the pre-leukaemic stem cells to turn leukaemic, and to improve understanding of what regulates the cancer stem cells. Professor Enver said: “We hope that eventually our work will lead to therapies to target both the pre-leukaemic stem cell and the cancer stem cell itself, to cure leukaemia while avoiding the debilitating and often harmful side effects of current treatments.” The research was co-funded by Leukaemia Research.

“OUR FINDINGS ARE IMPORTANT BECAUSE THEY MIGHT ALLOW THE IDENTIFICATION OF GROUPS OF MEN AT HIGH AND LOW RISK OF PROSTATE CANCER AND ENABLE US TO BETTER CONCENTRATE SCREENING EFFORTS.” PROFESSOR DAVID NEAL

Targeting cancer-causing enzyme

Scientists at the MRC Laboratory of Molecular Biology have found a way to stop an enzyme that is involved in the uncontrollable cell division that occurs in many cancers. The enzyme is called phosphoinositide 3-kinase (PI3K). “The PI3K enzyme plays a key role in controlling how human cells behave and its mutation can lead to numerous types of cancers,” said Dr Roger Williams. Before the enzyme becomes active, it has to release a partner protein that acts as a molecular brake. Working with a colleague at the Albert Einstein College of Medicine in New York, Dr Williams and his team developed a three-dimensional model for how this brake is applied. They then made a mutated partner protein that acted as a brake for only the cancer-causing enzyme. “This intervention may be able to stop a cancerous cell from dividing uncontrollably,” he said. PI3K is already a well known target for cancer drug development, but the scientists hope that this extra insight into its structure and where the cancer-causing mutations occur might help with future drug development.

Prostate cancer markers to improve screening

Scientists have discovered new genetic markers that indicate predisposition to prostate cancer, the most common cancer affecting men in developed countries. The research might lead to more targeted screening for the disease. Professor David Neal of the University of Cambridge led the study of two groups of men, 1,854 with very low risk of the cancer and 1,894 with very high risk. By studying their genomes the scientists were able to identify areas on seven chromosomes that indicated a high risk of developing prostate cancer, as well as three genes within these locations. “Our findings are important because they might allow the identification of groups of men at high and low risk of prostate cancer and enable us to better concentrate screening efforts,” said Professor Neal. The work was carried out jointly with Dr Ros Eeles at the Institute for Cancer Research and Professor Doug Easton at the University of Cambridge, with funding from Cancer Research UK and the National Cancer Research Initiative.

Lung cancer stem cells make it hard to treat

For the first time, scientists have discovered that a common cancer of the lung, mouth, oesophagus and cervix contains a group of stem cell-like cells. Dr Sam Janes, an MRC Clinician Scientist at UCL, explained that this means the cells are capable of growing to form a new tumour, providing insight into why these cancers may be difficult to treat. “Future chemotherapy strategies for patients with cancer should consider identifying and targeting this population of stem cells alongside standard treatment,” said Dr Janes.
Quaternary structure of key cancer protein solved

Scientists at the MRC Centre for Protein Engineering at the University of Cambridge have uncovered the quaternary structure (the way several subunits of a protein fit together) of a protein implicated in 50 per cent of human cancers. The protein, tumour suppressor p53, provides our cells with key initial defence against cancer, but is inactivated by mutation in half of all cancers. The research should lead to the design of new anti-cancer drugs. Many important proteins involved in the cell cycle and signalling have ‘intrinsically disordered’ sections, with no specific folded structure. This allows them to bind to many different partner proteins. Solving the structures of proteins with intrinsically disordered components is currently a major stumbling block to structural research, which can provide insights into function. Professor Alan Fersht, Director of the centre, and his team used a battery of imaging techniques to solve the quaternary structure of p53, the first of such structures to be solved.

Pituitary stem cells may explain hormone changes

Scientists have discovered stem cells in the adult pituitary gland, which is located at the base of the brain. The work provides a possible explanation for the dramatic changes in populations of hormone-producing cells in this gland due to changing needs during our lives, such as growth, puberty, pregnancy and lactation. In a collaboration between two divisions headed by Professors Iain Robinson and Robin Lovell-Badge at the MRC National Institute for Medical Research and colleagues at the UCL Institute of Child Health, Teddy Faquier and Karine Rizzoti began by showing that SOX2, a protein often associated with stem cells, is present within immature cells in embryonic pituitaries. They then showed that cells with SOX2 still existed in adult glands. These did not make hormones themselves but had properties typical of stem cells. When isolated from the adult pituitaries and grown in the lab, the cells were able to divide and generate all the different hormone producing cell types present in the adult pituitary gland. Professor Lovell-Badge said: “These findings will help improve our understanding of the production of normal hormone-producing cells, as well as of medical conditions such as the loss of pituitary cells in patients with hormone deficiencies. Further study of these stem cells may point the way to reversing or replacing such losses in patients, as well as providing understanding of the formation, and eventually treatment, of pituitary tumours.”

Missing link discovered in stem cell science

Scientists are one step closer to understanding how stem cells work after discovering a new type of embryonic stem cell in mice and rats which is very similar to human embryonic stem cells. The discovery was made simultaneously by a Cambridge University team led by the MRC’s Professor Roger Pedersen and a team at Oxford University, under Professor Richard Gardner. The researchers derived mouse stem cells from the innermost cell layer (epiblast) of a one-week old rodent embryo, instead of the more usual early blastocyst (three to four days after conception). They found that these cells strikingly resembled human embryonic stem cells. The mouse stem cells from the later stage of development could be maintained using the same growth factors as those used to culture human embryonic stem cells. And, they looked very similar to human cells under the microscope. “The ‘epiblast stem cells’, as they have been named, constitute the missing link between mouse and human embryonic stem cells,” said Professor Pedersen. “On a molecular level, epiblast stem cells are more similar to human than to mouse embryonic stem cells. The differences between human and mouse embryonic stem cells that we have attributed to species differences may actually come down to the developmental stages from which the cells emerge.” The researchers say the finding is likely to accelerate understanding of stem cell development.
Newt protein offers clues to human regeneration

Adult salamanders have the ability to regenerate many of their body parts. The discovery of a key protein that helps salamanders to re-grow severed limbs may provide important insights into research into human regenerative medicine. MRC Professor Jeremy Brockes and his team at UCL uncovered a protein called nAG, secreted by nerve and skin cells after amputation of a newt’s limb. They found that this protein was key to producing a blastema – a mound of limb stem cells – which re-grows the missing part. The scientists were even able to induce regeneration of the limb when a nerve was severed below the stump tip by artificially making cells that produced the protein. By learning more about the molecular signalling that occurs in the formation of blastemas, they hope to eventually mimic the effects in mammals in non-regenerating body parts. However, Professor Brockes cautioned that such research is still a long way off: “While this is indisputably an important step forward, understanding how salamanders regenerate lost limbs does not necessarily mean that humans will be able to copy them and do the same.”

First common gene for height discovered

Although it’s well known that tall parents are likely to produce tall children, until now, none of the genes responsible for height was known. MRC, Wellcome Trust and Diabetes UK-supported scientists have identified a gene called HMGA2, a common variant of which directly influences height. They used data from the Wellcome Trust Case Control Consortium, the largest study ever undertaken into the genetics underlying common diseases, and the Diabetes Genetics Initiative in the USA. By examining DNA samples from 5,000 people the scientists found that a person carrying two copies of the variant gene was around 1 cm taller than someone with no copies. They believe the study may have major implications for helping scientists understand how common variants in human DNA actually affect us, especially in relation to growth and development. Dr Tim Frayling of the Peninsula Medical School in Exeter, one of the research leaders, said: “Height is a typical ‘polygenic’ trait – in other words, many genes contribute towards making us taller or shorter. Clearly our results do not explain why one person will be 6’5” and another 4’10”. This is just the first of many genes that will be found – possibly as many as several hundred.” The exact role that HMGA2 plays in height is unclear, but the researchers believe it is likely to be involved in increased cell production. This may have implications for the development of cancer, as tumours occur due to unregulated cells growth. Previous studies have shown tall people to be statistically more likely to be at risk of certain cancers.

The placenta acts like a parasite

The placenta uses a cloaking device similar to that used by parasites to avoid detection by the mother’s immune system, according to research by MRC scientists at the University of Reading. The researchers made the breakthrough when they were researching a diagnostic test for pre-eclampsia, a potentially fatal maternal illness. They believe the finding will revolutionise our understanding of the placenta and research into recurrent miscarriages and pre-eclampsia. It could even lead to new ways of avoiding immune system rejection, and be used in stem cell research and immune-related conditions like arthritis. Led by Professor Philip Lowry, the team discovered that a small protein called neurokinin B (NKB), which is secreted by the placenta, is raised in mothers who develop pre-eclampsia. While they were trying to translate this discovery into a way to diagnose the condition, they found that placental NKB contained a molecule that is used by parasitic worms to evade host immune systems. “Devising a mechanism by which you could make cells invisible to the immune system could lead to cures for a number of diseases and conditions,” said Professor Lowry.
The UK’s population is getting older, due to falling mortality and birth rates. The number of people aged under 16 is dwindling while the proportion of the population aged over 65 is increasing rapidly. Research into lifelong health and ageing is a priority for the MRC: our science covers a wide spectrum, from understanding the physiological changes that happen as people age to developing new treatments for conditions that affect older people.

Last year, the MRC opened a dedicated research unit to house the National Survey of Health and Development, a study started in 1946 which continues to follow more than 3,000 people who are now in their 60s. And as part of a major cross-council initiative, the MRC, the Biotechnology and Biological Sciences Research Council, the Engineering and Physical Sciences Research Council and the Economic and Social Research Council have funded three centres, in Edinburgh, Newcastle and London, that will study the ageing brain, frailty and health-related quality of life.
David Ward, retired journalist and member of the National Survey of Health and Development since his birth in 1946.

“They’ve tracked me for 62 years and know more about me than I do about myself,” said David Ward. Sitting in his converted loft on a drizzly morning looking out over a panorama of the Pennines, David talked about how it felt to be involved in a medical study for his whole life. “I’m fascinated by the idea of an alternative biography; the scientists have a completely different story about me, backed up by facts and figures from throughout my life, from the one I carry about in my head.”

David was enrolled in the National Survey of Health and Development by his mother when he was born and, for more than six decades, has joined thousands of others who have kept researchers supplied with facts such as whether they were born early, wet the bed, smoked, suffered from diabetes or died young.

The study began shortly after the Second World War in the run up to the founding of the NHS. The researchers approached the parents of every baby born in the first week of March in 1946 and asked them if they wanted to be involved. More than 3,000 are still on the books today.

“People were worried about the rapidly declining birth rate, but when the war ended and the soldiers came home, everybody started having babies again,” said David. So the study then moved on to investigate perinatal care – the period shortly before and after birth.

Assessments were carried out by health visitors and then by teachers at the schools of the children involved. “It made me feel singled out, but in a good way, a bit special. In my teens and at university, as well as the physical aspects of the research they asked me wider questions about my view of the world and my hopes and ambitions.”

David retired from The Guardian recently, where he worked as a journalist for 33 years. He’s written about his experiences in the study a couple of times. When he was 30, the researchers gave his eight-year-old daughter the same tests they had given him at eight. She did better. “I suppose many parents suspect their kids are brighter than they are, but they don’t always want it proved.”

Today, the participants are 62 years old and the survey is tackling what’s becoming an increasing issue in the UK: healthy ageing. The researchers are looking at the changes that happen as people grow older, and relating these to what they know about their childhood development.

Already the overarching finding seems to be that getting a good start is vital to having a healthy life. The mortality rate differs radically between those who get the best chances early in life and those who get the worst. Even so, there is also a group who didn’t get the best things in life but who still come out on top – the scientists want to know what makes these people so resilient.

“For me, the start was pretty good,” said David. “And being in the study all along has been good for me too. At the last thorough medical they took tubes of blood, swabbed my saliva, weighed and measured me, gave me an ECG and scanned my bones. The results came back; blood pressure, heart, cholesterol were all good. But they found some osteoporosis in my spine, something which I’d never have discovered otherwise. I don’t have any aches and pains but will be munching calcium tablets for the rest of my life.”

“IT MADE ME FEEL SINGLED OUT, BUT IN A GOOD WAY, A BIT SPECIAL.”
Adult education keeps brains sharp

Taking evening classes or other types of adult education or receiving job training in middle age helps people to keep their intellectual skills honed, according to MRC research. Although adult education is known to improve a broad range of life chances, little was known about its role in protecting intellectual skills in mid-life and beyond. Using data from the National Survey of Health and Development, Dr Stephani Hatch of King’s College London and Dr Marcus Richards of the MRC Unit for Lifelong Health and Ageing investigated the effect of adult education on tests of memory, word recognition and naming. People who continued to learn throughout life scored higher than those who finished their education in their 20s or earlier, irrespective of the intellectual ability or educational qualifications they already possessed. Dr Hatch said: “Much attention is now being paid to choices in adulthood that have long-term consequences for the protection of health and wellbeing – this is of growing concern in relation to the threat of Alzheimer’s disease in old age. Accumulating evidence suggests that intellectual skills are still flexible in mid-life, and that maintaining these can buffer the effects of Alzheimer’s disease in later life, and may even delay or prevent its onset.”

Breastfed women have later menopause

The National Survey of Health and Development also found that women who were breastfed or had higher cognitive abilities during childhood tended to have a later menopause than other women. Conversely, women who weighed the least at age two, had parents who divorced before they were 15, or who reached menopause before 50 years old were most likely to also reach menopause at 50. “It’s important to understand more about reproductive ageing given the increasing numbers of women having children later in life, and because menopausal timing is now recognised as an indicator of health in later life,” said researcher Dr Gita Mishra of the MRC Unit for Lifelong Health and Ageing. “Early menopause is linked to an increased risk of osteoporosis and heart disease, whereas late menopause is associated with an increased risk of breast cancer.”

Prions may prevent Alzheimer’s

Rogue proteins in the brain called prions are to be blamed for diseases such as mad cow disease and vCJD. But now, scientists have found that the normal type of prion produced by the body that doesn’t cause harm may actually play a role in preventing Alzheimer’s disease. Alzheimer’s follows a similar pattern of progression to vCJD and shares some genetic features, which prompted Professor Nigel Hooper of the University of Leeds to look for a link between the two. Together with colleagues at GlaxoSmithKline in Harlow, the Roslin Institute in Edinburgh and the Mayo Clinic in Jacksonville, Florida, Professor Hooper’s team used cells grown in the lab to look at the effect of high and low levels of normal prion protein on the formation of a protein called beta-amyloid, which binds with other proteins to form the plaques in the brain that are found in Alzheimer’s sufferers. They discovered that much less beta-amyloid was formed in cells with higher than usual levels of prion protein. To confirm this, they used genetically engineered mice lacking normal prion protein and showed that the harmful beta-amyloid protein could form again. “Our findings clearly identify a role for prions in regulating the production of beta-amyloid and in doing so preventing the formation of Alzheimer’s plaques. Whether this function is lost as a result of ageing, or if some people are more susceptible than others we don’t know yet,” said Professor Hooper. “The next step will be to look in more detail at how the prion protein controls beta-amyloid, knowledge that could be used to design anti-Alzheimer’s drugs.”

Vitamin D injections don’t prevent fractures

A four-year study by scientists at the MRC Epidemiology Resource Centre in Southampton and supported by NHS funding has found that annual injections of vitamin D do not reduce the rate of bone fractures suffered by elderly people. Vitamin D deficiency is common among older people and is thought to contribute to the risk of broken bones due to osteoporosis. Researchers led by Professor Cyrus Cooper and Dr Sarah Crozier gave almost 10,000 people aged over 75 an injection of either vitamin D or placebo at the same time as their annual flu jab for three years. They hoped that the vitamin treatment would reduce the number of broken bones. However, the results showed no difference between the two groups in the rate of fractures. The findings have influenced health policy, resulting in vitamin D injections not being recommended for all elderly people.

Anti-stress gene and Parkinson’s disease

Scientists have discovered a relationship between two cell enzymes and unravelled their roles in keeping the cell’s energy-generating machinery working smoothly. The research could provide a new target for development of therapies for Parkinson’s disease. Led by Dr L.
Miguel Martins of the MRC Toxicology Unit and Dr Julian Downward of the Cancer Research UK London Research Institute, the study has shown that the products of genes called HtrA2 and PINK1 co-operate in preventing breakdown of cell function. But if a person has an abnormal copy of the PINK1 gene, this affects the HtrA2 protein and contributes to development of Parkinson’s disease symptoms. Dr Martins said: “By protecting the mitochondria – the cell’s energy stores – PINK1 and HtrA2 help to limit environmental stress within the cell and maintain healthy function. Without these, the cell can’t function properly. This could explain cases of Parkinson’s disease that seem to arise sporadically. Overall, the description of the HtrA2 pathway in response to cell stress will lead to improved understanding of the development of Parkinson’s disease and in the long term hopefully to new therapeutic targets.”

Healthy living means living longer

A study of more than 20,000 people in the UK has shown that people who are physically active, eat five portions of fruit and vegetables a day, don’t smoke and only moderately live an average of 14 years longer than people who don’t do any of these things. The finding, which has informed UK Department of Health public health policy, comes from the EPIC-Norfolk study, a long-term collaboration between a national and international team of researchers. One of the principal investigators, Professor Kay-Tee Khaw of the University of Cambridge, said: “There’s lots of evidence for each of these four factors individually, but very little was known about their combined effect on health. In the hope of obtaining evidence to help persuade people to make behavioural changes to improve their health, we investigated the relationship between these specific health behaviours and the risk of dying.” She added: “These behaviours are entirely achievable, 30 per cent of the population already practise all four. Our results show that relatively modest changes to lifestyle can have an immense impact on health and life expectancy.

“OUR RESULTS SHOW THAT RELATIVELY MODEST CHANGES TO LIFESTYLE CAN HAVE AN IMMENSE IMPACT ON HEALTH AND LIFE EXPECTANCY.”
PROFESSOR KAY-TEE KHAW

Childhood abuse linked to later disease risk

It’s long been known that inflammation in the body is a key part of a person’s response to stress. Now, scientists have shown that the stress resulting from maltreatment as a child, defined as rejection by their mother, harsh discipline, disruptive caregiver changes and physical abuse, can raise levels of inflammation up to three decades later. Inflammation is a key risk factor for age-related diseases including heart and lung disease, diabetes and Alzheimer’s. Together with researchers at the Dunedin School of Medicine in New Zealand, Professors Avshalom Caspi and Terrie Moffitt of the MRC Social, Genetic and Developmental Psychiatry Centre at King’s College London studied more than 1,000 people for 35 years. They found that those who had been mistreated as children had significant increases 20 years later in C-reactive protein, fibrinogen and white blood cell count, all indicators of inflammation. Professor Moffitt said: “The study adds to evidence that health is not just a suddenly changed state but rather something that is achieved over a lifetime. To unravel complex disease processes we need to better understand exactly how psychosocial experiences ‘get under our skin’ and leave enduring effects on our health.”

Knee pain study leads to safer prescribing

Advice to use ointments or gels that contain non-steroidal anti-inflammatory drugs (NSAIDs) to be applied to the skin is just as effective as advice to use NSAID tablets for older people with knee pain. Furthermore, such topical treatments substantially reduce the risk of serious, sometimes even fatal, side effects and often cost the NHS less. The finding comes from a controlled study of 585 patients aged between 50 and 90 led by Professor Martin Underwood at Warwick University. The researchers recruited patients from the MRC’s General Practice Research Framework, a network of practices involved in clinical trials, epidemiology and health services research that was set up in 1973. The study showed equivalent knee pain outcomes from both types of treatment and that patients were very good at knowing what worked best for them. Its findings support new advice to GPs on the use of topical NSAIDs in guidelines on the management of osteoarthritis published by the National Institute for Health and Clinical Excellence.

Social deprivation and older people

Older people who live in deprived areas are more likely to have cognitive impairment and problems coping with daily life than those in wealthier areas, regardless of their own socio-economic status, Dr Fiona Matthews at the MRC Biostatistics Unit and colleagues studied 13,000 people aged 65 years and over. The finding has informed public health policy about the allocation of resources for the long-term care of the older population. The research is part of the MRC’s Cognitive Function and Ageing Study which looks at the health and cognitive abilities of older people across the UK. Begun in the 1980s, it has provided a wealth of information about the prevalence and costs of dementia, depression and physical disability, as well as healthy ageing.
Tackling global health issues is a continuing priority for the MRC. Although significant focus is on infectious diseases, global health also includes strengthening research into non-communicable diseases, such as heart disease and cancer, which are affecting more and more people in developing countries as lifestyles change and life expectancy increases.

In 2007/08 the MRC continued to work closely with partner organisations, including the Department for International Development and the European and Developing Countries Clinical Trials Partnership (EDCTP). The EDCTP involves 14 EU countries, Switzerland, Norway and a number of African countries, and has an overall goal of reducing poverty by improving the health of populations in developing societies. In partnership with EDCTP, during 2007/08 the MRC participated in and committed significant co-funding to eight calls for research proposals on vaccines and therapies to prevent and treat HIV/AIDS, TB and malaria.

And in 2007/08, funding was renewed for the MRC Tropical Epidemiology Group at the London School of Hygiene and Tropical Medicine. The group both leads and collaborates in research into public health problems in developing countries, with an emphasis on studies of potential therapies and preventative measures, particularly in infectious diseases. The group works closely with the MRC/UVRI Uganda Research Unit on AIDS and the MRC Laboratories in The Gambia.
Emma Durward-Brown, nurse at the Hospital for Tropical Diseases in London.

Emma Durward-Brown has worked in the emergency walk-in clinic at the Hospital for Tropical Diseases in London for about a year. She works in the triage department, running initial tests on patients who’ve come from overseas with illnesses they’ve picked up, giving treatment and referring those with more serious conditions to the doctors.

She’s been qualified as a staff nurse for six or seven years. “I was always interested in caring for people. When I was 18 I went out and worked with people who had Hansen’s disease – leprosy – with Mother Theresa’s nuns in India. It made me appreciate life – it really opened up my mind about other diseases and poverty.” The experience inspired Emma to work in tropical medicine – so she came back to England and went back to college and on to university.

In a typical day at the clinic, Emma sees a whole range of people. “We get a lot of people who have migrated to Britain and go back to Africa to visit family or friends, but they may not take malaria tablets. Sometimes it’s because they can’t afford them but often it’s because they never used to take them when they lived there, and think they’ve got immunity.” If someone has malaria, the blood sample confirming this can be back from the lab within an hour and Emma and her colleagues start further tests and treatment straight away. Around 2,000 cases of malaria and several deaths occur in the UK every year.

Emma works closely with lots of people in the hospital – other nurses, consultants, lab staff and even scientists. “I think research into tropical diseases is crucial. There’s still so much that can be done to find better ways to treat these problems. Although people from the UK can sometimes die from things like malaria, this is just the tip of the iceberg – malaria kills more than a million people every year, mostly in Africa.”

As well as people who’ve migrated here, the hospital also treats a lot of people who have gone to developing countries to volunteer, and backpackers returning from their trips. Alongside fever and diarrhoea, skin conditions are one of the most common ailments, including parasites that lay their eggs under people’s skin and then hatch into larvae.

“We’re lifelong learners in this profession; we get so many different people and illnesses coming through the doors – I find it fascinating,” said Emma. “Working with people from all walks of life, diagnosing and explaining what they have and making them feel better are the best things about the job. Every problem has a solution.”

“I was always interested in caring for people. When I was 18 I went out and worked with people who had Hansen’s disease – leprosy – with Mother Theresa’s nuns in India. It made me appreciate life – it really opened up my mind about other diseases and poverty.”
New biomarkers to distinguish severe malaria

In developing countries, infections like malaria, pneumonia and meningitis are common and deadly. Correct diagnosis of children with these illnesses is important to ensure that they receive adequate treatment, but the clinical signs and symptoms upon which diagnosis is made are often shared by several diseases. Now, scientists led by Dr Climent Casals-Pascual at the MRC Laboratories in The Gambia have identified four biomarkers – biological indicators – that can distinguish severe malaria from mild disease with 95 per cent accuracy. “Better clinical biomarkers will help us to optimise diagnosis of severely sick children and may eventually lead to improved treatment and reduced rates of illness and death,” said Dr Casals-Pascual. The next step for the scientists is to find out whether these biomarkers are also present in other severe infections, to differentiate malaria from these.

Mother’s diet affects child’s diabetes risk

For the first time, a study has linked nutritional deficiency in women during pregnancy to diabetes risk in the offspring. Dr Caroline Fall and colleagues at the MRC Epidemiology Resource Centre in Southampton studied 700 pregnant women in six villages in India and at 18 and 28 weeks gestation measured the levels of nutrients including folate and vitamin B12 in their bloodstream. They then measured the children’s height, weight, body fat and insulin resistance (an indicator of type 2 diabetes) at age six. They found that the combination of low vitamin B12 and raised folate levels increased the children’s risk of insulin resistance. “This research is new in showing that an imbalance of vitamins may be to blame for increased diabetes risk, rather than a simple deficiency,” said Dr Fall. “Vitamin B12 and folic acid are both required for the correct transmission of DNA molecules between generations and our findings provide evidence that maternal diet during pregnancy can influence the risk of diabetes in the next generation through effects on DNA.”

Combating TB drug resistance

University of Birmingham researchers have made inroads into understanding the precise mechanism of action of medicines used to treat drug-resistant tuberculosis. The findings may lead to the development of new drugs to treat what’s becoming an increasing problem worldwide. Professor Gurudyal Besra and his team worked with colleagues at Texas A&M University to study two drugs, ethionamide and prothionamide, that are used to treat infections including leprosy and TB. Despite their widespread use, the way in which the
drugs work was previously unknown. The scientists used a technique known as 'cell based activation' to study the crystal structures of the drugs inside a cell. This allowed them to see that the drugs bind tightly to a gene on the TB and leprosy bacteria that confers resistance to other drugs. Professor Besra said: "Knowledge of the precise structures and mechanisms of action of these drugs provides insights into designing new drugs that can overcome drug resistance."

**TB mutant that doesn’t cause disease**

There’s no completely effective TB vaccine and new drugs to tackle the disease are lacking. But research into the genetic and immune properties of the bacterium over the past three decades has opened up new avenues for therapy. Now, scientists at the University of Birmingham and the Albert Einstein College of Medicine in New York have created a mutant strain of TB that can infect mice but doesn’t cause the disease. The work has the potential to lead to the development of a live vaccine to prevent the condition. While working in the laboratory of Professor William Jacobs Jr in New York, Dr Apoorva Bhatt found that the resultant bacteria were able to persist in a mouse for up to 600 days without causing the disease. Dr Bhatt’s team at Birmingham now focuses on understanding why the bacterium doesn’t cause disease.

**India facing a million tobacco deaths by 2010s**

India’s smoking epidemic currently causes around a fifth of all male deaths in middle age, and will cause about one million deaths a year during the 2010s, research has found. Seventy per cent of these deaths will be in people between the ages of 30 and 69. The findings come from the first nationally representative study of smoking across the whole of India, a collaboration between scientists at the MRC-supported Clinical Trial Service Unit (CTSU) at the University of Oxford and colleagues in India and Canada. Sir Richard Peto of the CTSU said: “British studies show that stopping smoking is remarkably effective. At present, however, only two per cent of adults have quit in India, and often only after falling ill.” The study showed that smoking accounts for most of the difference in premature deaths between men and women in India. There were no safe levels of smoking, but while the risks from smoking just a few Indian roll-ups (bidis) a day were substantial, the risks from smoking a few cigarettes a day were even greater.

**Vaccine protects West African children from deadly meningitis**

A phase 2 clinical trial testing a vaccine to protect people living in Africa from a lethal and highly infectious form of meningitis has shown promising results. The vaccine is designed to protect children from a strain of meningitis known as serogroup A Neisseria meningitidis. Every eight to 10 years the infection sweeps through 21 sub-Saharan nations stretching from Senegal and The Gambia in the west to Ethiopia in the east. Along with the Centre for Vaccine Development in Mali, scientists working at the MRC Laboratories in The Gambia tested the new vaccine in 600 toddlers aged between 12 and 23 months. The results show that it is not only safe but generates up to 20 times more protective antibody against meningitis A infection than the vaccine currently in use. The key to the new vaccine’s efficacy is its structure. It is a conjugate vaccine, meaning that sugars from the meningitis bacterium are joined together with a protein designed to stimulate the immune system. Dr Brown Okoko, principal investigator at the MRC site in Basse, said: “We are all highly motivated and very proud to be able to contribute to the development of a vaccine that is critically needed in Africa.”

**WE ARE ALL HIGHLY MOTIVATED AND VERY PROUD TO BE ABLE TO CONTRIBUTE TO THE DEVELOPMENT OF A VACCINE THAT IS CRITICALLY NEEDED IN AFRICA.**

DR BROWN OKOKO
to the development of a vaccine that is critically needed in Africa.” The clinical trial was carried out by the Meningitis Vaccine Project, a partnership between the World Health Organization and PATH, a Seattle-based non-profit organisation that aims to help communities break long-standing cycles of poor health.

New cancer test could speed diagnosis in developing world

“The earlier a cancer is diagnosed, the greater the chance a patient will be cured. However, existing cancer screening tests are limited in their accuracy and ease of use,” said Dr Nick Coleman of the MRC Cancer Cell Unit in Cambridge. Now, Dr Coleman and his colleagues have invented a faster way to identify potentially cancerous cells in cervical smear samples. The technology relies on markers of cancerous and precancerous cells called MCM proteins. An automated test for MCMs would benefit women who live in the developing world by reducing costs and speeding up diagnosis. It could also be applied to other types of malignancy, as MCMs are over-abundant in a wide range of common cancers, including cervical, bowel and lung. The researchers tested the new diagnostic for cervical cancer in more than 2,000 women and have licensed the technology to TriPath Oncology (recently acquired by Becton, Dickinson and Co) for cervical screening and Cytosystems Ltd for detection of bladder cancer in urine. Funded by the MRC and Cancer Research UK, the work involved Addenbrooke’s Hospital in Cambridge, Homerton University Hospital in London, Kidwai Memorial Hospital in Bangalore and TriPath Oncology in North Carolina.

UK HIV transmission reasons haven’t changed

In the UK, men who have sex with men are the group most at risk of becoming infected with HIV/AIDS. Neil Macdonald of Imperial College London and Dr Barry Evans of the Health Protection Agency investigated whether the reasons significant numbers of these men are still acquiring HIV are the same as when the epidemic began. They studied 75 recently infected HIV-positive men and 157 men who’d stayed HIV negative. Both groups had received a previous negative HIV test within two years. “This work confirmed the role of unprotected anal sex with partners of known HIV positive or unknown HIV status in driving HIV transmission between men who have sex with men. Decisions not to use condoms were based on a multitude of factors, often including a desire for intimacy and trust,” said Neil Macdonald. The study also

“OUR FINDINGS HIGHLIGHT THE IMPORTANCE OF EXPLORING ALTERNATIVE WAYS OF COMBATING THE ANAEMIA OF HIV.”

PROFESSOR ANDREW PRENTICE

"THE RESULTS OF THIS RESEARCH ARE IMPORTANT FOR THE DESIGN OF GUIDELINES FOR COUNSELLING HIV INFECTED WOMEN, PARTICULARLY IF THEY DO NOT YET MAKE USE OF CONTRACEPTIVES OR IF THEY CONSIDER BECOMING PREGNANT.”

DR LIEVE VAN DER PAAL
highlighted the risk of using poppers (nitrite inhalants) during unprotected anal sex. The findings are helping to inform health promotion campaigns to try to reduce HIV infections among gay and bisexual men.

High iron levels predict death in HIV patients

Patients with HIV/AIDS are often prescribed iron to tackle anaemia, a common problem associated with the disease. But MRC scientists have now found that high levels of iron in the body can actually accelerate the progression of the disease. Professor Andrew Prentice of the MRC International Nutrition Group at the London School of Hygiene and Tropical Medicine said: “Our findings highlight the importance of exploring alternative ways of combating the anaemia of HIV.” His team worked with colleagues at the MRC Laboratories in The Gambia and at MRC Human Nutrition Research in Cambridge and retrospectively analysed samples from more than 1,300 HIV patients. They found that patients with high iron status had around twice the risk of dying during the time the samples were collected, compared with those with normal iron levels.

How sleeping sickness parasite evades immune defences

African trypanosomes are parasites that infect mammals, including humans, where they live in the bloodstream and tissue fluids. They are constantly exposed to the host’s immune defences, but elude these by a strategy called ‘antigenic variation’ where their protective surface coat constantly changes. This process involves turning on and off the genes that code for the ‘variant coat protein’ on their surface, so that what is expressed varies. Scientists led by Dr Richard McCulloch at the University of Glasgow have now worked out the fine details of this process in Trypanosoma brucei, the parasite responsible for African sleeping sickness. Dr McCulloch commented: “Trypanosoma brucei blights the economy and health of countries in sub-Saharan Africa. Biomedical strategies to tackle the parasite and the symptoms of the diseases it causes remain inadequate. Fundamental questions, such as precisely how the parasite avoids being killed by the host, are still unanswered. My group’s work has generated new insights into the way the parasite genome can be rearranged, which will allow us to address these questions in the future.”

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Dr Richard McCulloch

Pregnancy speeds up AIDS progression

Pregnancy accelerates the progression of HIV/AIDS, according to research by scientists at the MRC unit in Uganda. Paradoxically, fertile HIV positive women seem to have an immunological advantage over infertile women before they become pregnant. The researchers studied data about women with HIV collected since 1990, using decline in CD4 cells as an indicator of HIV progression. CD4 is a receptor on the outside of host cells that the HIV virus uses to get into the cell. As more and more host cells become infected, the number of cells left with CD4 receptors drops. The scientists discovered a steeper decline in the women’s CD4 counts after pregnancy. Dr Lieve van der Paal said: “The results of this research are important for the design of guidelines for counselling HIV infected women, particularly if they do not yet make use of contraceptives or if they consider becoming pregnant. Women who decide to become pregnant should be advised to do so only if their CD4 count is high, and should be given priority for antiretroviral therapy if they are eligible.”
In January 2008 the Department of Health in England launched a cross-Government strategy called Healthy Weight, Healthy Lives to try to make society healthier – from infant nutrition, to schools and food, from sport and physical activity to planning, transport and the health service. This followed publication by the UK Government of its Foresight report into obesity in October 2007, which highlighted the health threat from soaring levels of obesity. It suggested that, if current trends continued, by 2050 nearly 60 per cent of the UK population would be obese.

The MRC currently spends around £40 million a year on research into human nutrition and energy balance. This includes investigating the effect of diet on normal biological function and disease, the consequences of maternal diet and birth weight in later life, obesity and appetite control, gut function and gastrointestinal disease and the fundamental mechanisms underpinning these areas. In 2007/08 we began a strategic review of nutrition research to determine the national landscape for nutrition research and identify strengths, gaps and opportunities in our own portfolio. Other research councils, major charities, the Food Standards Agency, the Department of Health and the main universities with significant research investments have all contributed to this process.
Jim and Wendy Foster, avid gardeners, travellers, bird watchers, walkers and, between them, gym member, model builder, water colour painter, yoga and Pilates goer, local paper editor and tap dancer. And volunteers in MRC Human Nutrition Research dietary intervention studies.

“The first study I took part in looked at whether eating sugary foods increased the risk of diabetes. I came home and Jim had torn an ad for volunteers out of the paper. It got me interested as I wanted to lose a bit of weight and some people on the study had to diet so I thought, ‘what the heck’, and signed up for it.” Since then, Wendy Foster has taken part in several dietary studies: living on only milk and supplements for three months; taking fish oil capsules; having her bones scanned; and being hooked up to a calorimeter that precisely measures energy intake and output.

When he retired in 2004, Jim joined Wendy in one of these studies, known as Whole Heart. “I’ve been very lucky, healthwise. But my father, who looked the same as me and had an identical temperament, died of his third heart attack at the age of 73,” said Jim. “So by acting as a guinea pig for something that’s fairly innocuous, like changing from white bread, rice and pasta to wholegrain versions, I hoped that the results might help others, but might also help me.”

Jim and Wendy, who were married 40 years in August, squabble affectionately and chatter over the top of each other in their enthusiasm to talk about the part they’ve played in the studies. In 2006 they were both involved in Dr Susan Jebb’s RISCK study, in which participants were assigned to one of five regimes of dietary fat and carbohydrate. In their case, they were banned from eating potatoes for six months and had all their bread, rice, pasta, cereal, fat and oil supplied by the scientists. “The annoying thing was, I’d grown spuds in the garden for the first time that year and had to give them all to a neighbour,” said Jim.

The study was all about the effect of different types of fat and carbohydrate on a cluster of symptoms linked to heart disease and diabetes. Jim and Wendy had to go into the unit a number of times for tests of insulin sensitivity – an indicator of diabetes risk – and cholesterol levels. “The knowledge I took away from the experience was that my cholesterol levels were fine,” said Jim. “And that you really, really don’t like living without potatoes,” interjected Wendy.

Do they ever cheat? “No way! We get annoyed by people who sign up for something and then they slip up, saying ‘I had a piece of Easter egg. I couldn’t resist’. And if you go out for a meal but have been asked not to eat potatoes, you just don’t order potatoes.” But they concede that the RISCK study was easier to stick to than other studies they’ve done, because they were both following the same regime.

Through her participation in these studies, doctors discovered that Wendy had high blood pressure, which she now takes medication for, and intercepted what could have been a nasty case of anaemia. “We do it because it costs us nothing, we have the time, we give something back and, at the end of the day, it benefits us as well.”
Reducing diabetes RISCK

In one of the largest ever studies that’s had tight control over people’s diets for an extended period of time, researchers have shown unequivocally that reductions in saturated fat are linked to significant improvements in cholesterol levels. There are two types of cholesterol – high density lipoprotein (HDL) and low density lipoprotein (LDL) – sometimes referred to as good and bad cholesterol. The RISCK study, funded by the Food Standards Agency and carried out by MRC Human Nutrition Research, showed that reducing the intake of saturated fat cut levels of LDL cholesterol. Replacing saturated fat with monounsaturated fat lessened the reduction in HDL, or good, cholesterol. Saturated fat is found in foods like butter, red meat and dairy products, while foods such as nuts, avocados and olive oil contain monounsaturated fats. People following the low fat diet tended to lose weight. Even small decreases in weight were linked to improvements in insulin sensitivity. The scientists found no differences in blood pressure between volunteers on different diets. Dr Jebb said: “The overall results show that reductions in saturated fat are a key dietary strategy to lower cholesterol, while weight control is critical to reducing the risk of developing diabetes. Achieving these goals will significantly decrease risk of heart disease.”

New type 2 diabetes gene

Until recently, the genetic causes of type 2 diabetes were unclear, but the pace of discovery was accelerated in 2007 when the first results of studies examining whole genomes were reported. Using a different method, a collaborative team in Cambridge including the MRC Epidemiology Unit, the Sanger Institute and the University of Cambridge has found and confirmed another gene, WFS1. Their approach involved looking at the genes that are already known to play a role in the development of beta cells – which make and release insulin in the body. The team showed that variants of the WFS1 gene are linked to type 2 diabetes, and that mutant versions cause a more severe type of diabetes called Wolfram syndrome. The scientists then went on to work with a team of international collaborators to confirm the finding in European populations. Professor Nick Wareham, the Director of the MRC Epidemiology Unit said: “Understanding the genetic basis for type 2 diabetes may open up new approaches to treatment and the possibility of personalised approaches to prevention. Until recently, knowledge of the specific genetic variants was scarce; this work adds a new confirmed gene to the list of genes that may together or separately cause diabetes.”

Heart drugs could help most people with diabetes

Statins have long been known to benefit a wide range of people at increased risk of heart disease or stroke. Now, joint research by scientists at the MRC-funded Clinical Trial Service Unit (CTSU) in Oxford and the National Health Medical Research Centre at the University of Sydney has shown that people with diabetes could benefit too, even if they have normal cholesterol levels and no indicators of heart disease or stroke. The team examined the effects of treatment with statins in around 19,000 people with diabetes who had taken part in previous clinical trials, comparing them with results from 71,000 people without diabetes. The results showed that around a third of heart attacks and strokes could be prevented if people with diabetes regularly took statins. Professor Colin Baigent of the CTSU said: “A statin regimen sufficient to produce a substantial reduction in LDL cholesterol should be considered for most people with diabetes.” The research was jointly funded by the MRC, the British Heart Foundation and the National Heart Foundation in Australia.

Breakfast really is the most important meal

We’ve all heard the hype that breakfast is the most important meal of the day. Scientists at the MRC Epidemiology Unit in Cambridge have helped to show why, by demonstrating that people who eat a greater percentage of their total daily calories at breakfast time gain less weight than those who eat more later in the day. This was in spite of the fact that those who ate more at breakfast tended to eat more calories overall during the day. As part of the EPIC-Norfolk study, a long-term collaboration between an international team of researchers, almost 7,000 men and women aged between 40 and 75 were asked to complete a seven-day food diary. When the scientists weighed and measured the volunteers four years later, they found that people who ate between 22 and 50 per cent of their total daily calories at breakfast gained 0.79 kg during the follow-up, compared with 1.23 kg weight gained by those who ate between zero and 11 per cent. Dr Nita Forouhi said: "For every one per cent of greater energy intake at breakfast, with shifting
Looking at hungry brains

Scientists at the MRC Clinical Sciences Centre in London can now measure how full or hungry a mouse feels by looking at how the neurons are behaving in the part of its brain which regulates appetite. The scientists hope that the technique, which uses magnetic resonance imaging (MRI), will help improve understanding of why some people become obese but others do not. Measuring satiety – the psychological feeling of being full and satisfied rather than physical fullness – is difficult. In the past scientists have relied on asking trial volunteers how full they feel or watching how much food they eat, rather than more objective measures. The part of the hypothalamus that regulates appetite had already been identified, and Professor Jimmy Bell’s team discovered that they could see the neurons there firing by using a contrast agent of a manganese ion. The scans showed that when a mouse was hungry and the neurons increased in activity, the contrast agent was taken up and made the neurons light up. The intensity of this signal decreased as the mouse became less hungry and the neurons less active. The technique will allow researchers to objectively study how the ‘hunger neurons’ react in response to different stimuli. Professor Bell said: "We are now working on developing similar methods to study neuronal activity in the appetite centres in people."

Brain circuits that control how much we eat

MRC scientists have used brain scanning techniques to identify the brain circuits that ‘decide’ food intake in humans. They used PYY, a naturally-occurring hormone that regulates appetite, to investigate which areas of the brain are involved in controlling how much we eat. Eight normal weight men who had gone without food for 14 hours were given either PYY or a placebo while their brain was scanned continuously. Thirty minutes later they were offered an unlimited amount of food. PYY reduced food consumption in all eight men by an average of 25 per cent of calories eaten.

"This research highlights the added impact to obesity, even after taking into account things like smoking and previous illnesses. Dr Liu said: “This research highlights the added impact obesity can have on ill health. Effective strategies to reduce obesity in the community should lead to reductions in the load on health services.”"

Protein that may explain asthma link to obesity

Asthma and obesity are both increasing in prevalence in the developed world, and a link between them has been proposed. King’s College London researchers have now discovered a protein produced in the immune cells of people with allergic asthma that increases appetite, which may help explain the link. Inflammation in the lungs of people with allergic asthma is controlled by special immune cells called T-helper-2 (Th2) cells. Dr David Cousins and colleagues studied populations of Th2 cells in the laboratory and discovered a hormone called PMCH that has previously been linked to appetite regulation. "Our work provides a possible mechanism for the link between asthma and obesity. However, because not all people with asthma are obese, the next step is to look at different variants in the gene for the PMCH protein, to try and find out which ones are linked to being overweight.”
Heart and circulatory disease is the UK’s biggest cause of death, killing more than 200,000 people every year. It’s also a major cause of illness and disability. Lung disease follows closely behind, affecting one in seven people in the UK. In 2007/08, MRC research into heart and lung disease focused on building support for experimental medicine and associated discovery science. We continued a call for research proposals in respiratory medicine to strengthen the portfolio. Twenty-one new PhDs in respiratory science were funded, including projects that address the role of factors as diverse as fungi, viral infections, immune system reactions, the influence of maternal diet on asthma, and chronic obstructive pulmonary disease. An award was made to the University of Oxford for a whole body scanner to be used in cardiovascular research. And our new Ageing and Lifelong Health Unit was given funding specifically to collect data about cardiovascular, respiratory, musculoskeletal and mental health in older age.
Amanda Gill, sufferer of two heart attacks in less than a year.

Amanda Gill had her first heart attack last August and a second one nine months later. “I’ve been in excruciating pain for much of that time: it’s only in the last two weeks that it finally seems to have gone away,” she said. “It came out of the blue. I hadn’t given my health a second thought before and now I’ve been off work for nine months and in horrific pain for a lot of that time.”

After the first attack, Amanda was referred to Dr Tim Chico, heart specialist at the Sheffield Northern General and Hallamshire hospitals and scientist at the MRC Centre for Biomedical and Development Genetics. Tim put two stents – small tubes that open the artery back up and allow blood to flow through it again – into Amanda’s blocked right coronary artery.

But the pain didn’t go away and, after her second heart attack, she had another stent implanted. It wasn’t until further weeks of medication adjustment, even longer off work and continual anxiety about what was wrong with her that the pain finally went.

Some people – up to a third of the population – naturally develop collateral vessels. These are new blood vessels that grow and form connections to reroute blood flow around a blocked artery. Tim wants to find out why this happens in some people but not in others, and how to encourage the process in people like Amanda. He now wonders whether, when Amanda finally began to feel better, it was because her body had finally developed these collateral vessels.

How do the clinic and the lab feed into each other? “The research in my lab, although it’s basic science, is totally informed by what’s happening in the hospitals and by the needs and demands of patients with heart disease,” said Tim. “There have been massive improvements in the care of these patients, and yet it’s still the major cause of death in the developed world. And there are still a big proportion of patients who have symptoms which diminish their quality of life or even shorten their life, but that can’t always be addressed by conventional treatments. So while my patients are crucial to my research, the reverse is also true, in that looking for new and better treatments is very important to my patients.”

And how does Amanda feel about being treated by a doctor whose other love is science? “It’s great! Because Dr Chico doesn’t just see patients all the time, I think I get treated more like a person and not just another patient. But more importantly, the research has to be done – it’s one of the things that is absolutely necessary.”

“THE RESEARCH HAS TO BE DONE – IT’S ONE OF THE THINGS THAT IS ABSOLUTELY NECESSARY.”
Zebrafish earns its stripes with heart insights

Arterial occlusion – blocked arteries – is the cause of most heart attacks and strokes. A process called arteriogenesis – where so-called collateral blood vessels grow naturally and reroute blood flow around a blocked vessel – can reduce the consequences. Finding out more about how arteriogenesis works will help clinicians to find ways to enhance it in patients. But because it can only usually be studied post-mortem in mammal models, Dr Tim Chico’s team at the MRC Centre for Developmental and Biomedical Genetics in Sheffield has developed a zebrafish model to visualise the process. They study a type of the fish known as gridlock mutant zebrafish. These fish have a permanently blocked aorta – the blood vessel that takes oxygenated blood from their heart to the rest of their body – but it doesn’t cause heart attacks or kill them. The zebrafish embryos have transparent skin so scientists can watch the blood vessels under their skin without harming the fish or affecting the process. Dr Chico said: “Zebrafish are an important tool for studying this common and devastating human condition. As well as being transparent, zebrafish are easy to manipulate genetically and easy to test drugs on. So things I see in the clinic with my patients can give me inspiration for new research on my fish in the lab. We hope that this two-way feedback process will help to speed up the development of new therapies for people suffering from arterial occlusion.” The work was carried out jointly with Dr Thorsten Schwerte of the University of Innsbruck in Austria and co-funded by the British Heart Foundation.

Body’s daily rhythms controlled by timing of food intake

It’s long been thought that there’s a ‘master clock’ located in a part of the brain called the suprachiasmatic nuclei that controls daily rhythms in mammals and is set by light and dark cycles. But we also have clocks in other tissues, such as in the liver, that control things like metabolism and detoxification. MRC researchers at the University of Edinburgh have worked with colleagues at the MRC Laboratory of Molecular Biology and discovered that these rhythms can be set by the timing of food intake rather than being controlled by the master clock. Dr Tony Harmar and colleagues studied liver clock activity in mice lacking the master clock gene, and showed that it could be set by the timing of food availability. Because common cardiovascular events such as heart attacks and strokes are also subject to daily rhythms, often occurring at a particular time of day, the finding has implications for studying the daily variations that underlie these events. Dr Harmar said: “We hope that this research will lead to ways to reduce such risks, for instance, by optimising the timing of medication.”

Coping with stress cuts stroke risk

The ability to cope with stress can reduce stroke risk by around a quarter, according to research by MRC and Stroke Association-funded scientists led by Dr Paul Surtees of the University of Cambridge. The team studied ‘sense of coherence’ – a measure of a person’s ability to adapt to social stress – and stroke risk in more than 20,000 middle-aged and older men and women. They recorded more than 100,000 stressful life events, such as bereavements, divorces and separations. The results revealed that the men and women with a strong sense of coherence took less time to adapt to life events and had a 24 per cent lower chance of suffering a stroke during the seven-year follow-up. Dr Surtees said: “While many questions remain to be answered by further research, this evidence raises the possibility that improving our ability to respond to stress may have benefits for vascular health.”
Giving mice cold virus offers asthma treatment hope

Scientists have been able to recreate rhinovirus infection, the culprit behind most common colds, in a mouse for the first time. Discovered 50 years ago, rhinoviruses only usually infect humans and chimpanzees. There is currently no effective treatment for the virus, which can lead to more serious illnesses such as pneumonia and can worsen asthma in susceptible people. Professor Sebastian Johnston of Imperial College London, who led the research, said: “Until now it has not been possible to study rhinovirus infection in small animals. This has been a major obstacle to new treatments.”

The scientists discovered that rhinovirus can’t get into mouse cells because it can’t bind to their receptors. So they modified the mouse receptors to make them more like the human ones, and found that the virus could then infect the cells of the modified mice. Professor Johnston said: “These mouse models should provide a major boost to research efforts to develop new treatments for the common cold, as well as for more potentially fatal illnesses.” The research was co-funded by the MRC, Asthma UK and GlaxoSmithKline.

New hayfever vaccine stops itching and sneezing

Hayfever affects one in four people in the UK. But often the usual treatments of antihistamine tablets and nasal sprays don’t work well and the condition can seriously disrupt what’s for many the best time of the year. Professor Stephen Durham at Imperial College and the Royal Brompton Hospital has shown that a new treatment, a grass pollen vaccine in tablet form, significantly reduces symptoms and the need for other treatments and substantially improves patients’ quality of life. Previous immunotherapy vaccines have only been available as injections and carry a risk of severe allergic reactions, meaning they can only be given in a medical setting. Professor Durham led a multi-centre clinical trial testing the tablet vaccine in more than 600 people with hayfever in eight countries. “This tablet-based vaccine is an effective treatment for hayfever that can easily be managed by patients at home and has the potential to control symptoms and improve quality of life many years after therapy ends,” said Professor Durham. “Based on our knowledge of the way it works, we are now developing a test to predict whether the treatment will work in individual patients, when to start and stop therapy and how to predict relapse and the need for another course of treatment.”

Flu desensitises lungs to bacterial invaders

MRC scientists have discovered why people with flu often succumb to secondary bacterial infections such as pneumonia. Pneumonia, which is common during or after flu, is to blame for a large proportion of deaths from the illness. Scientists previously thought that the secondary infection occurred either because the flu virus breaks down the epithelial layer – essentially a barrier layer of skin – in the lungs, meaning that bacteria can get in more easily, or because flu increases the number of molecules available for bacteria to stick to in the lungs. But Professor Tracy Hussell’s team at Imperial College London found that, in actual fact, after flu the lungs become desensitised to the second invader and do not mount a strong immune response to kill off the bacteria. When they studied this phenomenon in mice, they found that this weak inflammatory response made the mice more susceptible to other infections for up to six months. Professor Hussell said: “Now we know that key cell types become desensitised we need to find out how and why. This will help us to develop better strategies to control secondary bacterial pneumonia during an influenza infection, which should alleviate symptoms and even reduce deaths.”
The MRC’s portfolio of neuroscience and mental health covers all areas of brain science, from basic neurobiology, including genetics, developmental biology and pharmacology, through to cognition, behavioural neuroscience, psychology and clinical treatment of brain-related conditions. During 2007/08, areas of particular focus were motor neuron disease, neuroimaging, autism, neurodegenerative diseases, brain tissue banks and strengthening links with industry.

The MRC held a workshop in partnership with the Motor Neuron Disease Association to agree future funding priorities, and a week-long course on the ‘biology of social cognition’ with the Cold Spring Harbor Laboratory in the USA. We joined two international partnerships, which will help us to coordinate research funding across Europe and to foster international activities in neuroinformatics, the scientific field which gathers and analyses the enormous quantities of information on this complex organ. Major investment included support for the MRC/University of Bristol Centre for Synaptic Plasticity, with an award of £7 million, and funding for a 7-Tesla MRI scanner at Oxford University to study the central nervous system. On behalf of the UK Clinical Research Collaboration, we convened an expert group on human brain tissue banking to consider future strategies for the collection and distribution of brain tissue to help keep the UK at the forefront of international research into disorders of the brain.
Michelle Wilks, teaching assistant, mum of two and epilepsy sufferer.

“I had my first fit at the age of 33 – I remember the day because it was the leap day of the leap year. It was a massive one – I was rushed to hospital and don’t remember anything. Luckily it was at 6am so Martin my husband was home. Alice and Molly, my two girls would have panicked and wouldn’t have known what to do.” Michelle Wilks had experienced unusual feelings of déjà vu several times in the days before her first big seizure, but not realising they were another type of mini-seizure, she dismissed them.

After the seizure she spent several days in hospital. Michelle was told she had either a brain tumour or a mini-stroke and had to wait for an MRI scan to find out which. “I don’t really know how I coped with the waiting, I just had to keep going so that’s what I did. Finally I went in for my tests – they gave me an MRI, an ECG, an EEG, blood tests, you name it, I had it.” She was diagnosed with epilepsy and put on a drug called Epilim, but the dose was too high – finding the right treatment at the right dose is a common difficulty with epilepsy. “The drug made my hair fall out in the shower, and then it grew back in massive curls! The drug also made it hard to lose the weight from having my children, which was very disheartening.” She went back to the doctor, had the dose adjusted and had a second drug added.

Next followed several years of adjustments to Michelle’s medication. “At one point I had 16 weeks to go of being seizure free before I could drive and then I had a massive one and had to go right back to the start. The thing I hated was having my choice to drive taken away, even more so than the actual driving.” The condition has also affected her memory:

“I always had a bad memory but now it’s terrible: I have to set alarms for everything! The first big seizure created a scar on my brain right by where memory is thought to be controlled.”

Michelle went through a time of feeling very depressed by it all. “But I went to a fantastic counsellor. He said it was like having a filing cabinet in my head that needed emptying out,” she laughed, repeating the counsellor’s analogy. “I hadn’t accepted that I had epilepsy.” But the drugs she’s on are working well now and any depression is clearly in the past. Michelle has been free of seizures for around 18 months and her bubbly chatty personality obscures the fact that anything was ever wrong.

How has the experience influenced Michelle’s opinion about medical research? “I had never really thought about it much before. But now I realise that it’s only because of research that there are drugs available that can help me and get my life back to normal. If you asked me before I would have said I wasn’t too keen on the idea of drugs being tested on animals, but I had never really considered the implications of this view.” And having personal experience of drug side effects and struggling to get a regime that controlled her condition properly, Michelle also recognises the need to continue this research. “Obviously, it’s important to find out more about how the current drugs work, and to work on developing new and better treatments.”
Epilepsy drug insights

MRC-funded scientists have uncovered important details about how a common anti-epileptic drug works, in research that may pave the way for the design of better drugs. Professor Annette Dolphin’s team at UCL worked with colleagues at the University of Innsbruck in Austria to investigate the mechanism of action of gabapentin, an anti-epilepsy drug that’s also one of the few effective drugs for alleviating chronic pain caused by damage to the nervous system.

It was previously known that the drug binds to a subunit called alpha-2-delta of calcium channels in nerve cells, which are required for passing messages between these cells. However, exactly how gabapentin works was unknown. Now the scientists have found that rather than directly blocking the calcium channel, gabapentin inhibits the ability of calcium channels to reach the nerve cell’s surface where they carry out their job.

Getting stroke drugs into the brain

Having previously shown that a naturally occurring protein called interleukin-1 receptor antagonist (IL-1Ra) protects the brain against stroke in animals, scientists have now shown that it’s possible to get the protein into the brain in humans. Nancy Rothwell, MRC Professor at the University of Manchester, said: “Getting drugs like IL-1Ra into the brain is a major challenge because large molecules do not pass easily into the brain. Here we’ve shown that IL-1Ra delivered intravenously does get into the brains of patients at levels which we think can reduce injury.” The team studied this may also be applicable to studying...
implants in both ears use different information to localise sounds than people with normal hearing. Instead of predominantly relying on timing cues between the ears, people with implants rely more on evaluating cues in the level of a sound. The finding is likely to have a big impact on how people with double implants hear things in environments where there are multiple sources of sound and reverberation. "Our research is the first step towards helping patients with bilateral cochlear implants – by learning how the brain hears sounds we build the base to develop innovative new technology," said Dr Seeber.

Stamping out the stutter

In the first study to combine structural and functional imaging in the study of stuttering, MRC researchers have discovered insights into brain irregularities in people who stutter. Dr Kate Watkins, of Oxford University, explained: "Brain imaging studies are starting to reach a consensus about the brain abnormalities related to developmental stuttering. By using these methods to look at brain activity during speech, we can see differences in these patterns of activity between people who stutter and those who speak fluently. Images of the brain's structure and connections help us to interpret why different brain areas function differently." In collaboration with Professor Peter Howell's group at UCL, Dr Watkins' team studied a group of young people who stutter and a group who didn't stutter. They used functional MRI scans and diffusion tensor imaging, which uses water molecules in cells to produce pictures of living tissues. The scientists discovered that those who stuttered showed different patterns of activity in their speech-motor system, with significant overactivity in the midbrain and underactivity in a region called the ventral premotor cortex. They also found differences in their white matter – the tissue through which messages pass in the brain. Dr Watkins said: "This work is helping us to gain a better understanding of the 'stuttering brain' that may eventually lead to explanations of the causes of stuttering and how treatments work."

"THIS WORK IS HELPING US TO GAIN A BETTER UNDERSTANDING OF THE ‘STUTTERING BRAIN’ THAT MAY EVENTUALLY LEAD TO EXPLANATIONS OF THE CAUSES OF STUTTERING AND HOW TREATMENTS WORK.”

DR KATE WATKINS

New target for MS found using old drug

Amiloride, a drug used to treat high blood pressure and heart failure, has been found to reduce symptoms of multiple sclerosis (MS) in mice. The discovery is that the drug can reduce nerve tissue degeneration suggests that it could be used to treat people with MS. The research was led by Professor Lars Fugger of the MRC Human Immunology Unit. He explained: "Looking for new ways to use established drugs is usually cheaper than starting the discovery process from scratch." The team began their search for therapeutic potential with studies of the role of a channel called ASIC1 that creates an opening in the cell membrane. It lets sodium and calcium molecules flood into a cell in higher than normal proportions. This can damage the long stems of nerve cells (axons) which carry messages from one nerve to the next. "Amiloride appears to work by blocking the action of the channel that lets sodium and calcium molecules into the cell. This suggests that drugs targeted at the ASIC1 channel could help reduce the level of nerve damage caused by MS," said Professor Fugger. The scientists are now planning a clinical trial testing amiloride in MS patients.

Sleep improves memory

Researchers at the MRC Anatomical Neuropharmacology Unit in Oxford have discovered that sleep is important for the stabilisation of memory. Led by Dr Jozsef Csicsvari, the team found that brain activity related to a person's recent waking experiences can be reactivated in the hippocampus during sleep, helping the formation of long-lasting memories. The scientists studied rats as they explored an environment and then as they slept and looked at the brief intervals in which pairs of neurons fired messages to each other. The results showed that the more frequently the neurons fired together during exploration, the stronger the correlated firing was during their sleep afterwards. Dr Csicsvari said: "Neuronal patterns during exploration can lead to changes in neuronal connections that temporarily store reactivated memory traces. The recurrence of these events was governed by where the animal explored and how long it spent there: factors which are required for autobiographical memory."

How what you see affects what you hear

For a long time experts have thought that our senses were kept largely separate in the brain, each with their own dedicated area in the cortex. But scientists led by Professor Jon Driver of UCL have discovered that brain areas thought to deal with a single sense can be strongly affected by what's happening in a different sense at the same time. This is due to feedback from the areas of the brain where the different senses meet. Professor Driver said: "Our research sheds light on how our different senses are combined to give a unified perception of the external world. In time, it may also reveal insights into various conditions, ranging from stroke to schizophrenia to autism, in which the normal mechanisms for combining information from different senses go awry." The next step for the scientists is testing how different forms of brain damage disrupt the process of integration between the different senses.
Mental health problems are among the most common of all health conditions. According to the Mental Health Foundation, they can affect almost a quarter of the population in any one year. Research into mental health and addiction is a priority area for the MRC. Our research ranges from understanding the effects on health of drug and alcohol misuse to studying conditions such as depression and schizophrenia, from their triggers to their treatments.
Robin Tyacke, research fellow in psychopharmacology, moderate social drinker and participant in a study of a new drug to block the effects of alcohol.

Robin Tyacke was working as a post-doc researcher when he responded to an advert for social drinkers. The scientists, led by Robin’s boss, Professor David Nutt, wanted to study a new drug to see if it could block the effects of alcohol. They wanted people who were used to drinking quite a lot – between 20 and 40 standard units of alcohol a week – so they could cope with the amount of alcohol they would need to drink for the research. “I wouldn’t consider myself a heavy drinker, more of a moderate social drinker. I think I’m probably quite normal in my drinking,” said Robin.

“Sometimes on a Friday after work I’ll have a few pints followed by a couple of rum and cokes – but that’s not unusual for many people my age.”

Robin and the other volunteers had to visit a clinical research unit jointly run by Bristol University and the NHS. “It was a small wind-beaten portacabin on the roof of the building, and we were either on our own or with one other person. It definitely wasn’t a social drinking scenario,” said Robin. “One of the times I was on my own. The other time I went in with another guy I didn’t know. Luckily he’d brought a set of Futurama DVDs so we just watched that!”

The participants were given either the drug or a placebo, and two hours later were asked to drink vodka mixed with orange juice every two minutes until they’d consumed around eight shots of vodka, depending on their body weight. “There were lots of shot glasses on a tray and we had to down them. Someone was looking at their watch saying you’ve got 10 seconds, and now the next one, and now the next one – it sounds like fun if you like drinking but actually wasn’t very pleasant! After about 10 shots I was given a rum and coke and a little plate of nuts. By then the room was moving, everything was spinning, much worse than after a few Friday night drinks.”

The volunteers repeated a barrage of tests they’d done while sober – motor function, blood pressure, heart rate and ability to recall a list of words – and were asked whether they felt sick, dizzy or sleepy and if they wanted to continue drinking. When the scientists collated all the results, they found that the drug made the men significantly better at recalling words on the list and made them feel a little less sleepy.

So what made Robin decide to volunteer and what was it like being on the other side of the research? “It wasn’t the first study I’d taken part in. It helps me when I’m recruiting people to my own studies to understand what people go through and what worries they might have about taking part in medical research. I think it gives me more integrity in my own research.” And would he do it again? “Without a doubt.”
Remembering what you did while drunk

In the first study of its kind in humans, scientists have discovered that a new compound can block the effects of alcohol that make people forget. Professor David Nutt's team at the University of Bristol tested the drug, known as a5IA, in 12 young men – post-grad students and post-doc researchers – who drank between 20 and 40 units of alcohol a week. Of the 12 volunteers, all but one scored on the threshold of a likely alcohol misuse disorder, an indication of hazardous drinking. The drug is thought to bind to a subunit of GABA, a neurotransmitter in the brain. Substances that act on GABA, such as alcohol and benzodiazepines (for instance, the sedative diazepam) often cause memory loss. The scientists contended that a5IA would block the effects of alcohol by making GABA unavailable for it to bind to. Half the volunteers were given a dose of a5IA and half were given placebo. After drinking a significant amount they were then asked to perform a number of tests, including recalling a list of words. The men who'd been given a5IA could remember an average of eight words, compared with only five among those who'd had placebo. The compound also seemed to make them less sleepy. However, it failed to reduce the 'urge to drink' that people feel after consuming alcohol, and did not block its effects on mood, motor coordination, dizziness or nausea. Professor Nutt said: "Finding ways to block or prevent the effects of alcohol could lead to new treatments for people with alcohol problems. Our next step is to look for similar molecules that can block the other effects, such as the pleasure people derive from drinking."

Social patterns of drinking and policy

To tackle the problem of binge drinking, the NHS and government departments involved in setting policy about alcohol use and alcohol-related harm need to know who drinks to excess and why. In a study co-funded by the Department of Health and the MRC, Dr Barbara Jefferis and her colleagues investigated social inequalities in drinking among British men and women born in the same week in 1958. They recorded the participants' educational qualifications and occupation at the ages of 23 and 33 as well as how much and how often they drank at ages 23, 33 and 42. The results showed that men with lower educational levels were consistently more likely to binge drink than men with more education. However, trends differed for women, with more educated women more likely to binge drink during their 20s than less educated women, and more likely to stop by 42 years. Less educated women were more likely to binge drink in their 40s. The overall prevalence of binge drinking declined with age, but nearly one in three men and one in seven women in their forties still reported binge drinking. The researchers also investigated non-drinking and found that non-drinking was consistently more common in men and women with lower educational levels. Dr Jefferis said: "This research helps to identify those at greatest risk of binge drinking. Policies aiming to reduce inequalities in health outcomes linked to drinking need to acknowledge that once inequalities in drinking patterns are set during young adulthood, they tend to persist into middle-age, with the exception of binge drinking in women where social trends reversed between young adulthood and middle-age. The study suggests that policies need to target middle-aged adults as well as the young adults who have the highest prevalence of binge drinking."

Marijuana might thwart babies’ nerve development

The endocannabinoid signalling system plays important roles in the adult brain. It not only produces the high induced by marijuana, but is also required for normal nervous system development. If a receptor in this system called CB1 is inhibited, developing nerves fail to establish their normal connections. The finding comes from Professors Anthony Graham and Pat Doherty and Dr Sheona Watson at the MRC Centre for Developmental Neurobiology and the Wolfson Centre for Age-Related Diseases at King’s College London. "This research has important implications for pregnant women, suggesting that marijuana use by mothers could have an effect on the development of babies' nervous systems from very early stages," said Professor Graham. "It also implies that pregnant women should not take the recently developed anti-obesity and addiction drugs that are designed to interfere with the endocannabinoid system, as these may also interfere with the development of their babies’ nervous systems."

Schizophrenia sufferers show increased fear response to benign faces

The amygdala is a region of the brain involved in detecting and responding to fear. Now, MRC scientists have discovered that patients with schizophrenia have over-activation of the amygdala when looking at faces that other people would consider neutral or benign. The results may help to explain the abnormal emotional responses that underlie psychosis. For the study, Dr Jeremy Hall's team at the University of Edinburgh studied 19 people with schizophrenia and 24 volunteers without the condition. Dr Hall suggested that the findings may provide a neural basis for understanding why people with schizophrenia often develop paranoid and persecutory beliefs about other people, as well as a target for measuring the effects of new treatments.

“FINDING WAYS TO BLOCK OR PREVENT THE EFFECTS OF ALCOHOL COULD LEAD TO NEW TREATMENTS FOR PEOPLE WITH ALCOHOL PROBLEMS.”

PROFESSOR DAVID NUTT
Hormone-driven changes in brain underlie PMS

Premenstrual syndrome (PMS) affects up to 80 per cent of women, making their lives difficult and affecting friends, family and work. The symptoms of other conditions, such as irritable bowel syndrome and panic disorder, can also worsen at this time. MRC-funded scientists at the University of Birmingham are studying how the hormone changes that induce PMS affect brain function. They discovered that falling levels of the sex hormone progesterone, which occurs at the end of the female cycle, can lead to increased production of certain subunits of a receptor for GABA – a chemical messenger in the brain that’s important in controlling anxiety. This may predispose women to the development of PMS by triggering anxiety-related behaviour and increasing pain sensitivity. Dr Thelma Lovick explained: “Our goal is to be able to stop these changes occurring by the development of new drugs and/or lifestyle changes to prevent the development of PMS.”

Unemployment raises self harm risk

One in 14 people will self harm at some point in their lives, and the rate is even higher among young people who are out of work, according to researchers at the MRC Social and Public Health Sciences Unit in Glasgow. They found that unemployment is an even stronger predictor of self harm among young people than the social class of their parents or their gender (young women are much more likely than young men to harm themselves). The survey of 1,258 18 to 20-year-olds investigated how gender, parental social class and current employment status related to reasons for starting and stopping self harm. The results showed that people who were unemployed were three times more likely to have self harmed at some point in their lives and up to seven times more likely to be self harming currently than those in work or full-time education. They were more likely to kill themselves too. The study also found that cutting or scratching were the most common methods, followed by taking dangerous tablets. Men were likely to use more violent methods than women. Dr Robert Young, who led the study, said: “The temporary nature of self harm in young people in employment or education suggests a better clinical outcome for this group, despite reluctance to seek help.” However, he added: “Some young people who are unemployed or sick are a cause for greater concern. They are more likely to be actively engaging in persistent self harm, and to be actively trying to kill themselves.”

Social adversity to blame for high psychosis rates

Social adversity throughout life is the most likely explanation of previously reported high rates of psychosis in UK Black Caribbean and Black African populations. The result comes from the MRC-funded AESOP (Aetiology and Ethnicity of Schizophrenia and Other Psychoses) study – a large investigation into first presentation of schizophrenia and other psychotic disorders. “The work has direct implications for public and mental health policy, service delivery and clinical practice, and suggests that more attention needs to be given to the impact of social adversity on serious mental illness and to the social needs of patients suffering a first episode of psychosis,” said researcher Professor Robin Murray of the Institute of Psychiatry at King’s College London. The scientists also found that features of the wider social environment, such as ethnic density and extensive social networks, help to explain the previously reported high rates of psychosis in densely populated areas.

Mothers’ anxiety can affect children

MRC-funded scientists at the University of Reading have shown that anxiety can be passed down between generations. Professors Lynne Murray and Peter Cooper and their team found that mothers with social phobia – an anxiety disorder that causes sufferers to fear social situations – have difficulty supporting their infants in social interactions with others. These difficulties can lead to the development of socially anxious behaviour in the infants. For the study, the researchers assessed 84 mothers with social phobia and 89 without the condition when they were interacting with their child and with a stranger. They found no differences between the mothers’ interactions with the children themselves, but the women with social phobia expressed more anxiety and were less encouraging of their child’s interaction with the stranger. This in turn made the children less socially responsive to the stranger. Professor Murray said: “This work shows the importance of the early environment in the intergenerational transmission of social anxiety. Interventions to support parents during this early period are crucial.” As a next step, the scientists are assessing the children when they make the transition to school, when clear signs of anxiety may become evident, and to see if their results are still apparent in the long term.
Developing medicines & technologies

Turning MRC research into health and economic benefits is one of the organisation’s key responsibilities. Over the past year we have worked closely with the National Institute for Health Research on a joint translational approach for UK health research, with several schemes now beginning to yield results. Priority areas in which we’ve set up new translational initiatives in the past year include stem cell science, toxicology and vaccine research. We’ve also put out calls for proposals to help speed the development of new therapies, for more research into improving methodologies and to set up cohorts of well-characterised patients for studying specific medical conditions.

MRC Technology (MRCT) is our technology transfer company. It facilitates the translation of cutting-edge scientific discoveries into commercial products. One of its roles is to identify and protect intellectual property developed in MRC institutes and units, usually through patents. These allow rights in the exploitation of the inventions to be licensed to companies. Income generated goes back to the MRC for further research. Licensing income from MRCT during 2007/08 was £85.4 million, bringing the total amount of cash generated in the past decade to £384 million.
Les Clarence is an articulate, spry man who turned 70 this year. But just over a year ago he woke up in hospital without feeling or control in his face and not remembering what had happened. He had lost the ability to speak clearly and to swallow. Les had suffered a stroke while he was out to dinner the previous night and had been rushed to hospital in an ambulance.

“That morning, the nurses asked me to swallow some water and I couldn’t. It knocked the air out of me – until eventually I brought it back up and could feel it dribbling down my chin,” said Les. “I felt like Quasimodo because I was walking sort of twisted, my face was twisted and I couldn’t talk properly. My wife had to do all the talking. It was very frustrating.”

The hospital arranged for a clinical psychologist and a speech therapist to help Les. He was also given regular physiotherapy sessions using a machine for assisted exercise – effectively a chair which moves different parts of the body for you. Les recounted: “Before my stroke when I was fit and healthy I’d be on the treadmill for about half an hour, and then I’d go on the bike and the cross trainer – I’d give the young ones a run for their money!” So after seeing physiotherapists at the hospital for several months, he decided to go back to his proper gym. “The physio department arranged for one of their staff to come with me the first few times. It gave me the confidence to think, ‘yes, I can walk down the street’. I’m still limited, physically, but I’m getting stronger. And I’ve always been optimistic.”

Not being able to swallow was one of the worst effects of Les’s stroke. “It affects you in so many ways. You can’t eat properly. You have to eat food that’s the consistency of mushy rice pudding but without the rice in it. It made meal times very boring and going out for dinner difficult. If you eat too much or too quickly you can choke. The danger is that even a little bit of food going down the wrong way can get into the lungs and cause pneumonia or other infections.”

That’s why Les volunteered to take part in a trial testing a new device to help people like him learn how to swallow again. The device consisted of a catheter with little electrodes on the outside that was put through his nose and into his throat. Les recalled: “I could feel the catheter in my throat, it was a little bit uncomfortable but not painful. When they first put the thing through my nose I gulped for air a bit, but the second time around it was fine and I got used to it. After using this to stimulate my throat, they took me down to the video fluoroscopy department and gave me food of different consistencies to try to swallow, while a camera watched the movement of my throat.”

Les noticed some improvement in his condition with the device. But this wasn’t the main reason he volunteered to take part in the trial: “In their minds some people see images of Frankenstein when they think of medical research. But it’s really not like that. My dad died of TB when I was only seven. The following year they found out how to cure it, and I’ve always thought, if only…”

“I volunteered for this research because even if it doesn’t help me, it might result in a treatment for someone else in the future. This is a completely new therapy, so I understand that it can take some time to find out how it works and how it should be used. It’s a learning curve and I’m grateful that my experience has been of some use in that.”
Innovative device to help stroke patients swallow

Up to 70 per cent of stroke sufferers have difficulties swallowing, putting them at risk of developing pneumonia or even choking. “Mortality is three times higher in stroke patients who have trouble swallowing and the problem increases length of hospital stay by an average of 20 days. There aren’t many motor problems that directly affect life expectancy in this way,” explained MRC researcher Dr Shaheen Hamdy. This led Dr Hamdy and colleagues at the University of Manchester to work on a device to help counteract this common problem. His patented invention, the first of its kind, has resulted in a University of Manchester intellectual property spin-out company. It’s now in the early stages of commercial production, initially to supply a large randomised controlled trial and gain regulatory approval. The device, called NutriStim, is battery operated and provides targeted stimulation to nerves in the throat. Its mechanism seems to occur at the cortical level, producing changes in brain regions related to swallowing. “There is a huge unmet need for a product like this one, with a very well defined customer group. Instead of having a standard feeding tube put through their nose into the throat, oesophagus and stomach, patients would use this device instead. It still works as a feeding tube but also has electrodes on the surface and is connected to a stimulator box. My team believes that this cutting-edge technology will have an enormous impact on patients’ quality of life, and will improve clinical outcomes and reduce the cost of care.” So far NutriStim has been tested on 60 stroke patients. More than 60 per cent of patients treated have responded positively. A larger-scale trial is now underway, with support from the UK Stroke Research Network.

Watching what goes on in infant brains

Researchers from UCL and Birkbeck College London have developed non-invasive optical methods to monitor what’s going on in infants’ brains as they interact with the world around them. The technique involves shining near infrared light into an infant’s brain to measure colour changes in the blood, which are associated with brain activity. For the research, Professor Clare Elwell of UCL led a multidisciplinary team of physicists, engineers and psychologists. Together they designed an ‘optical headpiece’ which allows 16 optical probes to be attached to an infant’s head to measure brain activity in different regions. They then collected data from four-month-old infants. “Our most recent studies have shown that localised responses in the brain of young infants to specific visual stimuli relate to social interaction,” said Professor Elwell. “Our long-term aim is to develop technologies to relate infant behaviour directly to brain function. This would help us to identify and treat infants with developmental disorders such as autism very early on.” Next, the scientists plan to enhance the monitoring system by enabling it to measure electrical signals from the brain at the same time.

Building designer proteins

Ribosomes are the machinery in cells that build proteins from DNA. Now, scientists have reprogrammed these so that they can incorporate designer amino acids into new proteins. In particular, Dr Jason Chin at the MRC Laboratory of Molecular Biology and his team have shown that it’s possible to create ribosomes that read the genetic code of DNA in a different way to usual. Dr Chin said: “The synthesis and production of many protein-based pharmaceutical products may benefit from the ability to incorporate designer amino acids with high efficiency. In addition, the tools we’ve created to do this may allow us to discover new therapies by looking at new amino acid sequences that natural biology has not yet explored.”

DNA damage gives clues to cancer drug effectiveness

Scientists have developed a new technology for testing the effectiveness of existing chemotherapy drugs. The technology will also help with developing and analysing future drugs. The team, led by Simon Reed at Cardiff University, have patented the technology, which is a method to determine how efficiently various cancer drugs damage the DNA of the cancer cells. Their work has also revealed important insights into one of the major methods by which DNA is repaired.

New cancer drug insights

Researchers at the MRC Toxicology Unit in Leicester have found that a potential anti-cancer drug that’s currently in clinical trials, known as TRAIL, might not act in the way previously thought. The discovery, funded by MRC Technology’s Development Gap Fund, might change the way patients are treated. TRAIL (tumour necrosis factor-related apoptosis-inducing ligand), causes cancer cells to die by binding to what are known as the ‘death receptors’, TRAIL-R1 and TRAIL-R2. These are receptors bound to the membranes of cancer cells. Previous research has suggested that TRAIL preferentially kills cancer cells by binding to the TRAIL-R2 receptor. But in their study of leukaemia cells the scientists found that TRAIL signalled to the cancer cells to die through the TRAIL-R1 receptor only. The finding has
implications for the use of TRAIL to treat cancer: several forms of both the drug and of antibodies to the R1 and R2 receptors are currently in clinical trials. Dr MacFarlane said: “Our findings highlight the importance of finding out, before patients start cancer therapy, whether cells from a particular tumour signal cell death via TRAIL-R1 or R2. This will help us to optimise treatment.” The scientists are now investigating how TRAIL interacts with primary epithelial tumours, such as breast and colon cancer.

Switching off kinases to stop cancer

Enzymes known as kinases normally play a critical role in preventing cancer, but mutations or overproduction of these can lead to the growth of tumours. Half of pharmaceutical industry research into new anti-cancer therapies is devoted to developing drugs that switch off particular kinases. Scientists at the MRC Protein Phosphorylation Unit at the University of Dundee have identified compounds that are very effective at switching off two kinases, called TBK1 and IKK, which are implicated in some types of cancer. The team’s work has led to a new drug discovery programme that is being run by MRC Technology’s Drug Discovery Group. A patent has been filed to protect these new compounds, which have received a lot of early interest from companies as potential anti-cancer and anti-inflammatory drugs.

New antibody blocks asthma

Researchers at the MRC Laboratory of Molecular Biology have found that blocking a signalling molecule that helps to control the immune system could be an effective way to treat allergic asthma. Allergic asthma is caused by a breakdown in the normal function of the immune system, where normally harmless stimuli such as pollen lead to uncontrolled immune responses.

The difficulty in breathing that follows is made worse by inflammation of the airway lining and build-up of mucus that further constricts the airways. The team designed a new monoclonal antibody that binds to interleukin-25 (IL-25), one of a family of molecules known as cytokines that are released by white blood cells and play a crucial role in immune reactions. In mice, this antibody completely prevented the narrowing of the airways, wheezing and lung problems involved in allergic asthma. The scientists worked with MRC Technology’s Therapeutic Antibody Group, who have successfully humanised the antibody. It’s hoped that MRC Technology will soon license the technology to a company for further development. Dr Andrew McKenzie, who led the research, said: “We don’t know if it will work the same way in humans. However, our results indicate that IL-25 could be playing an important role in allergic asthma, and that we have an inhibitor that works very effectively in experimental models.”

3D fruit fly images to benefit brain research

The fragile head and brain of a fly are not easy things to examine but MRC scientists have worked out how to make it a little simpler, in research they hope will shed light on human disease. They used an imaging technique called optical projection tomography (OPT). The OPT images could help to speed up genetic research into Alzheimer’s and other human diseases that affect brain cells. Dr Mary O’Connell of the MRC Human Genetics Unit explained: “Neurodegeneration isn’t a strictly human phenomenon. Insects are affected by it too. In the autumn, bees and wasps often develop erratic behaviour before they die... It’s already known that defects in the equivalent fly genes involved in human brain diseases cause brain cells in fruit flies to lose function as they age.” The team used OPT to image individual cavities within the brain of an ageing fly and see the brain deteriorate. MRC PhD student Leeanne McGurk, who captured many of the images, explained: “The dark colour of the fly exoskeleton prevents us from seeing inside it using a standard light microscope. Now, we have got over the problem by bleaching the fly exoskeleton. When the fruit fly becomes colourless it is possible to use imaging techniques not only to view its internal organs but to generate 2D and 3D images of the entire fly.” Using OPT images in this way allows the scientists to visualise where and how the products of selected genes are present in the fly. These patterns of gene expression in turn help to identify genes that control parts of the central nervous system and so provide detailed information about the human brain.

New malaria vaccine test heralds better prevention

There is a desperate need for new ways to prevent and treat malaria. Dr Tony Holder of the MRC National Institute for Medical Research has developed a practical way to test human antibodies against a human malaria parasite in a model system that can’t be easily replicated in a test tube. He explained: “It’s important to have good ways to test malaria vaccine candidates.

“Our findings highlight the importance of finding out, before patients start cancer therapy, whether cells from a particular tumour signal cell death via TRAIL-R1 or R2. This will help us to optimise treatment.”

Dr Marion MacFarlane

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before they go in to clinical studies in volunteers. Most of the tests used currently are carried out on parasites in test tubes and cannot mimic what is likely to go on in the body.” To overcome this problem, the scientists created mice with human antibody receptors and a rat malaria parasite modified to look like the human form. This allowed them to study human immune responses to components of the human parasite. Dr Holder added: “This approach can be extended to a range of malaria vaccine candidates to determine whether or not they might be effective in humans and to find out how to stimulate human immune responses to work against them.” The work was done in collaboration with Nottingham University, University Medical Centre in Utrecht and the Walter and Eliza Hall Institute in Melbourne.

**Targeting receptor in brain to improve treatments**

M1 muscarinic receptors receive chemical messages in the human forebrain. They are under investigation as drug targets for treating Alzheimer’s disease and schizophrenia. Scientists led by Dr Edward Hulme at the MRC National Institute for Medical Research are working with GlaxoSmithKline to find out more selective ways to target these receptors. They have used a method called ‘systematic mutagenesis’ to create mutations in many areas of a key part of the M1 muscarinic receptor – providing insights into exactly how the receptor binds to other molecules. Dr Hulme explained: “This work may lead to the development of new therapies for a number of devastating conditions, which are not available at the moment because of side-effects caused by a lack of selectivity of current drugs.”

**New use for common hypertension drug**

Researchers at the University of Newcastle have shown that a common drug widely used to treat high blood pressure – simvastatin – can reduce inflammation in lung transplant patients. The major cause of lung transplants failing is a condition called obliterative bronchiolitis (OB), characterised by severe inflammation and closing up of the small airways, eventually leading to death. Because statins such as simvastatin are known to reduce inflammation, Professor Paul Corris and Dr Chris Ward tested the drug on cell cultures taken from stable lung transplant patients. The results showed a significant drop in the presence of several molecules linked to OB when the cells were treated with simvastatin, indicating a reduction in inflammation.” This work will hopefully lead to better treatment of lung transplant patients. The lessons learned may also be applicable to other lung diseases,” said Professor Corris. The research was partly funded by GlaxoSmithKline.

**Promising new treatment for hepatitis C**

It is estimated that 170 million people worldwide are chronically infected with a virus that causes hepatitis C, but the majority of these are not aware that they’ve got the infection. In a high proportion of people, it can cause serious liver disease and even death. Transmitted mainly by blood, there’s no vaccine and the infection can be difficult to treat. Now, researchers from the MRC Virology Unit in collaboration with Nottingham University have demonstrated that a mouse monoclonal antibody (called AP33) that recognises the hepatitis C virus can effectively neutralise the infection. They worked with the Therapeutic Antibody Group at MRC Technology to produce a ‘humanised’ form of this antibody that could be used as a novel drug. Dr Arvind Patel from the MRC Virology Unit said: “The AP33 antibody has unique properties. It recognises a highly conserved region of the hepatitis C virus and therefore reacts with all major variants of the virus. We have shown that AP33 can effectively neutralise infection in cell culture experiments. Its special characteristics are of immense value to our ongoing research efforts into understanding how the hepatitis C virus gets into cells and how we can combat it.”

**“The AP33 antibody has unique properties… its special characteristics are of immense value to our ongoing research efforts into understanding how the hepatitis C virus gets into cells and how we can combat it.” Dr Arvind Patel**
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