MRC Annual review 2009/10: seven ages

Online version available at www.mrc.ac.uk/sevenages

Introduction

All the world's a stage
And all the men and women merely players
They have their exits and their entrances
And one man in his time plays many parts
His acts being seven ages

Shakespeare famously divided humanity into seven ages. The MRC Annual Review 2009-10 borrows this theme to show how MRC-funded research benefits everyone, at every stage of life.

The impact of medical research begins before we are even born, through research on genetics and fetal development. It improves health across the human lifespan from infancy to old age. Even after we die, research into tissues donated by volunteers is helping MRC scientists to unlock the causes of devastating conditions like Parkinson's disease.

Seven ages tells the stories of MRC scientists behind some of the most exciting discoveries from 2009-10 and of people of all ages who have benefited from their findings - along with a selection of the MRC's many research achievements.

1 – BEFORE BIRTH

FEATURE: Reproductive health decided early in fetal life

Dr Michelle Welsh is a Career Development Fellow at the MRC Human Reproductive Sciences Unit in Edinburgh, where research on sex hormones, infertility and diseases of the reproductive tract is carried out.

"Our team looks at how the reproductive system normally develops in the male fetus, and the effects that hormones have on that development. We also look at how those same hormones – called androgens – affect reproductive health and fertility later in adult life," explains Michelle.

When she was still a PhD student, Michelle discovered that there's a short time period in fetal life – around the end of the third trimester of pregnancy – during which androgens have to act in order to make a normal, healthy reproductive system.

By studying the effects of androgens in pregnant rats at different times, Michelle discovered that if androgens don't act during this time slot, the baby can be born with reproductive abnormalities. This 'masculinisation programming window' is so critical that even if the fetus is exposed to androgens at a later stage of development, it cannot be rescued from this fate.

Last year Michelle's team discovered that the action of androgens during the masculinisation programming window is also critical for determining penis length. Exposure to androgens after this time can speed up penis growth, but ultimately it cannot increase the size reached in adulthood.

"When people hear what I work on, it often raises a smile – in fact, without my knowledge, the research even ended up appearing in a men's magazine article on penis size," she says.

"But these reproductive birth defects are a very serious problem for men. For example, there's a disorder which affects almost one per cent of all newborn boys called hypospadias, in which the urethra doesn't open up in the correct place on the penis."

Michelle's findings suggest that reproductive birth defects might flag up an increased risk of more serious problems in later life. Research suggests that testicular cancers, reproductive birth defects and fertility problems such as low sperm count are all linked to the action of androgens during fetal development.

So what inspired Michelle to work in this field of research? "I've always thought how amazing it is that an entire person can come from just two cells – the sperm and the egg. And how so many tiny little signals all act together to create a person. It's not just that you have to have, for example, androgens – you have to be able to make them, to make enough of them, at the right time and they have to work in the right cells. And all of that has to come together."

Discovered: the gene which keeps females female

Scientists have discovered that ovary cells become more like testis cells in adult mice if the gene Foxl2 is 'turned off'. The landmark research by the MRC and the European Molecular Biology Laboratory (EMBL) has revealed that Foxl2, which is found on a non-sex chromosome, is solely responsible for keeping the ovary as an ovary in adults, acting by directly suppressing the male-promoting gene Sox9. The researchers created adult mice that lacked the gene Foxl2, and saw that this dramatically changed the cell types in the ovary. The cells began producing testosterone and organised into structures resembling those responsible for sperm production. These findings challenge several long-held assumptions about sex determination, notably that sex determination is fixed during embryo development and that female development happens by default. These findings might eventually help treat certain reproductive conditions, including some disorders of sex differentiation where there is a mixture ovary and testis cell types. Dr Robin Lovell-Badge of the MRC National Institute for Medical Research, who co-directed the research, said: "If these sorts of changes can be made in adult humans it may eventually remove the need for surgery in gender reassignment treatment. If this does become possible, it's likely

that while treated individuals would make the right hormones for their new sex, fertility would be lost".

Male fertility problems linked to maternal stress

Exposure to excess stress hormones in the womb combined with chemicals commonly found in the environment might increase the chance of boys being born with reproductive abnormalities. Scientists at the MRC Human Reproductive Sciences Unit and the University of Edinburgh looked at the effects of dibutyl phthalate, a chemical found in glues, paints and plastics, on fetal development in rats. Treatment of pregnant rats with dibutyl phthalate had some effects on their fetuses' reproductive development. These effects were markedly increased when the rats were also exposed to glucocorticoids – hormones produced in response to stress – although fetal development was unaffected by glucocorticoids alone. Birth defects seen in the rats included cryptorchidism, in which the testes fail to descend, and hypospadias, a mis-alignment of the urinary tract – both of which are on the rise in the human population. MRC Clinician Scientist Dr Mandy Drake, one of the scientists who led the research, said: "In most studies reproductive disorders are only seen with abnormally high levels of chemicals, which most humans aren't exposed to. Our study suggests that additional exposure to stress, which is a part of everyday life, may increase the risk of these disorders and could mean that lower levels of chemicals can cause adverse effects."

Early human development insights

Research has shed light on one of the earliest 'decisions' made by cells during human development. Scientists at the MRC Centre for Stem Cell Biology and Regenerative Medicine in Cambridge have demonstrated that a protein known as Smad Interacting Protein 1 (SIP1) plays a central role in influencing which type of cell embryonic stem cells will develop into. The scientists induced stem cells to form early specialised cell types and studied their responses at the molecular level. Findings showed that SIP1 encourages stem cells to develop into neuroectoderm, a type of cell that forms the nervous system, and that SIP1 discourages the development of the mesoderm and endoderm, which go on to form the heart, lungs and most other organs. The study also showed that a gene called Nanog is involved in maintaining stem cells' ability to transform into any cell type, by blocking the formation of SIP1. The findings could ultimately contribute to the development of stem cell treatments for diseases such as diabetes and Parkinson's disease. The research was led by Dr Ludovic Vallier, Senior Non-Clinical MRC Fellow, and Professor Roger Pedersen, who said: "Our findings show how human stem cells can improve our understanding of the key early events of human development, revealing the role of SIP1 and Nanog in these processes." The research was also supported by the National Institute for Health Research (NIHR) Comprehensive Biomedical Research Centre in Cambridge.

Low birth weight link to diabetes

Babies who are born small because of their mothers' poor nutrition during pregnancy are more likely to develop type 2 diabetes in adulthood. MRC-funded scientists at Cambridge University studied pregnant rats which were fed a low protein diet and as a result had offspring with a low birth weight. The baby rats were then given a normal diet during suckling to help them put on weight. The scientists looked at the cells in the baby rats' pancreas called islets, which are responsible for insulin production. Compared with the control rats, whose mothers were well fed during pregnancy, the rats with low birth weight showed damage to the DNA in their islets, as well as signs of stress and premature ageing in these cells. Type 2 diabetes occurs in adulthood when pancreatic islet cells malfunction and fail to make enough insulin. Therefore the research suggests a possible link between poor nutrition and growth in the womb and increased risk of developing diabetes in adulthood. Drs Susan Ozanne and Jane Tarry-Adkins, who led the research, explain: "In the offspring of poorly nourished rats we saw shorter than usual structures called telomeres in the islet cells. Telomeres protect the DNA in a chromosome from damage. This indicates premature ageing of these cells and a possible link with diabetes in adulthood."

Surviving the odds

Babies born very prematurely in the UK have a better chance of survival than ever thanks to advances in neonatal medicine. Understanding the factors that determine whether premature babies will survive is critical to deciding the best treatment. MRC-funded work has led to a new tool for assessing the chances that a baby born between 22 and 31 weeks of gestation will

survive to term – that is, the likelihood they will live to 40 weeks, the length of a normal pregnancy. Professor Tim Cole, from the MRC Centre of Epidemiology for Child Health at the UCL Institute of Child Health in London, developed the statistical model that underpins the new tool: the 'PREM score'. He says: "It's important that doctors can talk to parents of very premature babies with as much reliable information as possible. We've presented our data graphically, in a way that parents can understand as well as medical staff." The PREM score can predict survival to term even before a baby is born. Professor Cole adds: "Survival can be accurately predicted using gestational age and birth weight. But whereas clinicians usually count gestation in weeks, we found that every single day makes a difference."

Assessing pain in premature babies

Hospital staff caring for premature babies rely on signs such as crying or changes in facial expression to assess how much pain they are feeling, because infants aren't able to tell us when they are in pain. However, MRC-funded research has shown that premature babies aged under 32 weeks take longer to generate a change in facial expression after a painful event compared with older infants. Scientists analysed facial expression change in 95 babies aged between 25 and 44 weeks post-menstrual age when they had a routine clinical blood test, which involves a small cut to the heel. Infants aged under 32 weeks took 50 per cent longer to respond than those aged over 32 weeks. The effect was shown to be independent of brain damage, sleepiness or pain relief with morphine. Dr Rebeccah Slater from University College London, who led the research, said: "Premature babies can spend a long time in hospital after they are born and may undergo many painful medical procedures. Our findings suggest that following a painful event very young babies may take longer to mount a change in facial expression. This delayed response in younger infants should to be taken into account if pain assessment scores are to be accurately interpreted."

Solving the structure of the ribosome

Dr Venki Ramakrishnan became the MRC's 29th Nobel laureate in 2009 when he won a share of the Nobel Prize in Chemistry for his research into the structure and function of the ribosome. Ribosomes are molecular machines inside cells which make proteins by following instructions from genes. Virtually everything in a cell is either made by the ribosome or made by enzymes that were themselves made by the ribosome. Dr Ramakrishnan shared the prize with Dr Thomas Steitz of Yale University and Dr Ada Yonath of the Weizmann Institute of Science in Israel. Through many years of painstaking research, the three scientists used a visualisation technique called X-ray crystallography to map the position of each of the hundreds of thousands of atoms that make up the ribosome. The research has increased understanding not only of how the ribosome contributes to protein production but also to see directly how antibiotics bind to specific pockets in its structure. This could help researchers to design antibiotics to treat people infected with antibiotic-resistant strains of bacteria. Dr Ramakrishnan, of the MRC Laboratory of Molecular Biology in Cambridge, explains: "Many antibiotics work by blocking bacterial ribosomes, and this research make it possible to understand how antibiotics interact with the ribosome, and how it might be possible to design new and better antibiotics."

Unlocking the secrets of the developing heart

Research into a mysterious Dr Jekyll and Mr Hyde role-switching gene called Wt1 has shed light on how the embryonic heart forms. The research could pave the way to developing new cell-based treatments for the regeneration and repair of damaged hearts. Wt1 directly controls how genes are read by the protein-making machinery inside cells, sometimes activating different parts of the machinery and, conversely, sometimes switching them off. Professor Nick Hastie and his team at the MRC Human Genetics Unit in Edinburgh genetically manipulated early stage mouse embryos to remove Wt1 and looked at how this affected the developing embryo heart. They discovered that Wt1 played a crucial role in making sure that the embryonic heart stem cells gave rise to the correct cells to form a functioning heart. Without Wt1, some important parts of the heart - such as the cells which go on to form coronary arteries - failed to develop. The scientists were able to pinpoint that Wt1 works by controlling two agents involved in the gene-reading process called Snail and E-Cadherin. Dr Ofelia Martinez-Estrada co-led the research. She explains: "Professor Hastie's team now has evidence that Wt1 is vital for the maintenance of adult tissues and the repair of tissue damage. Ultimately this could help us to understand and treat common illnesses including cancers, heart disease and osteoporosis."

2 – BABY AND TODDLER

FEATURE: Protecting babies' brains
Lucas Macdonald took part in an MRC trial to test if body cooling can prevent brain damage in babies starved of oxygen during birth.

Four-year-old Lucas is at home in London playing with some garishly coloured plastic toys and chatting about his favourite TV programme, Roary the Racing Car. He's a typical lively and healthy little boy. But during his birth, there were complications. His mother Juliet recalls the moment when things started to go wrong:

"All had been going well with the labour, but at the eleventh hour Lucas started to get into trouble and the doctors got increasingly worried. I was rushed down the corridor into surgery and had an emergency caesarean. Because they had to do it so quickly, I was put under a general anaesthetic. And when I woke up Lucas was in special care."

The doctors suspected that Lucas had suffered birth asphyxia – which occurs when a baby's brain and other vital organs are starved of oxygen or blood, usually during labour or birth. Asphyxia can cause severe brain damage, cerebral palsy and even death in around half of the worst affected cases.

Juliet and her husband, Nico, agreed to enrol Lucas in an MRC-funded trial called Total Body Hypothermia for Perinatal Asphyxial Encephalopathy (TOBY) to test a new treatment for oxygen-deprived newborns.

"At that point we were in a bit of a tail-spin," explains Juliet. "I was recovering from the anaesthetic and feeling very groggy and I hadn't even seen Lucas at that point. We were feeling a bit unlucky. So when we agreed to take part in the trial and then heard an hour or two later that Lucas had been assigned to the treatment arm of the study we thought - well, that's our first bit of good luck".

Lucas's body temperature was cooled by three degrees to try and halt the progression of any brain damage he may have suffered.

Juliet smiles: "It looked a bit ridiculous because he was a full term quite chubby baby, so he looked like a giant next to all of the pre-term babies in the special care unit. They put him in an open cot with a special cooling mat under him and he stayed there for three days."

After that, Lucas had a brain scan – which showed no obvious damage – and Juliet and Nico were allowed to take him home. But then an anxious waiting game began.

"The doctors said we wouldn't know until he reached 18 months whether he was alright or not, so we couldn't really relax until then. But he seemed fine. We also had follow ups with the paediatrician who did developmental checks on him. He was behind on a few things for a while like gross motor skills – which basically means he couldn't be bothered to crawl – but he was ahead on cheekiness!"

At his 18-month follow-up, Lucas was given the all-clear. Not all babies in the trial were as lucky as Lucas, as unfortunately the treatment didn't work in every case. However, overall findings from the study showed that the cooling treatment reduced the likelihood of brain damage by 57 per cent. Since the findings were published last year, they've been adopted as an NHS guideline for treating all oxygen-deprived newborns.

"I couldn't help feeling a tingle of pride when the trial results got sent through to us and I realised that we had helped to advance medical knowledge," says Juliet. "Reading the results really transported me back to when he was born, and you do have a little tearful moment when

you think “Oh God, we were so lucky”. But that’s outweighed by feeling that it’s cool to be part of something that’s a success.”

Cooling prevents birth asphyxia brain damage

The MRC-funded TOBY trial (see profile) tested the theory that bringing about mild hypothermia in newborn babies with suspected birth asphyxia can reduce the brain damaging effects of oxygen deprivation. It followed 325 infants showing signs of birth asphyxia in hospitals in the UK, Ireland, Hungary, Sweden, Israel and Finland. The babies were randomly assigned to receive either cooling treatments (reducing body temperature to 33 to 34°C for 72 hours) or standard intensive care. Co-chief investigator Professor Denis Azzopardi, from Imperial College London and a member of the MRC Clinical Sciences Centre Neonatal Medicine Group, explains: “Although unfortunately it didn’t work in every case, our study showed the proportion of babies that survived without signs of brain damage went from 28 per cent to 44 per cent with cooling treatments. This provides irrefutable evidence that cooling can reduce brain damage after birth asphyxia.” The brain injury can go on for hours or days after oxygen deprivation first occurs, and this is the critical time when cooling is effective. Dr Azzopardi adds: “Lack of oxygen damages the mitochondria, the powerhouses inside cells. This sets off a chain of events which causes brain cells to go into apoptosis – programmed self-destruct mode. Cooling halts these processes, either by directly affecting apoptosis, stopping the chain reaction which begins it, or suppressing metabolism.” The TOBY children will be invited to take part in the next phase of the study which will assess them at age six.

Childhood brain infection guidelines needed

MRC-funded scientists from the Liverpool Brain Infections Group have highlighted the critical importance of guidelines for treating children suspected of having viral encephalitis. The current management of suspected cases is dangerously haphazard, the researchers say, after studying the situation at Alder Hey Children’s NHS Foundation Trust. Encephalitis is inflammation of the brain, often caused by the cold sore virus (herpes simplex type 1). Doctors can treat herpes simplex encephalitis with an antiviral drug, aciclovir, but if they delay patients can suffer brain damage or death. Because of this risk, children who come to hospital showing symptoms of herpes are often given aciclovir without proper investigation, even though the infection is rare. But aciclovir can also have serious side effects, including kidney damage, hepatitis and bone marrow failure. In the Liverpool study, which was based on a review of case notes over six months, the researchers found that almost a third of the babies and children who had received aciclovir had been given it without good reason. Furthermore, aciclovir was often given at the wrong dosage and the drug was stopped without explanation. Dr Rachel Kneen, who led the investigation, said: “Not only does this indiscriminate use of the drug put children unnecessarily at risk, it also involves the NHS in unwarranted costs in terms of longer hospital stays.”

Insights on how babies categorise

The ability to recognise different objects which belong to the same group is a critical part of how we make sense of our environment, and it’s thought that human infants can learn new categories from an early age. Research led by Dr Toby Grossmann at Birkbeck College, London, set out to understand how infants’ brains sort objects into basic-level categories (eg a bird vs a fish) or global level categories (eg an animal vs a vehicle) when they have little knowledge of the world around them. Six-month-old infants were video-recorded while they were shown images of either birds or fish during the learning phase of the experiment, and then tested with new images from the same category or images from a different category. The infants showed a preference for objects from the new, unfamiliar category by gazing at them for longer. A sensor net placed on the head showed that the infants used different parts of the brain at different times when they were categorising between birds and fish compared to when they were working out the difference between new examples of birds or fish. Dr Grossmann explains: “This early developing capacity to learn categories and to use this knowledge flexibly plays an important role in inference, prediction, decision-making, and learning language. It’s integral to all kinds of human behaviour.”

Newborns can hear danger

Babies are born with the ability to judge the size of a source of sound, MRC research has shown. We may have evolved this ability because it gives us the advantage of being able to detect

bigger, more dangerous predators, and larger, more physically able suitors, the scientists suggest. Using electroencephalography, which measures brain activity through electrodes placed on the scalp, teams at the MRC Cognition and Brain Sciences Unit in Cambridge and the Hungarian Academy of Sciences recorded the brain responses of sleeping newborn babies as they were played the sound of a French horn. The sound was played at the same level but at different resonances, to simulate different sizes of musical instrument. Alterations in the babies' brain activity showed that they were able to detect these size changes. In a separate study, adults were asked to watch a silent film and to ignore any sounds they heard while they were played human voices, unfamiliar animal calls and musical instruments at different resonances. Findings showed that their brains registered the size of all sources, despite their attention being focused on watching the film. Dr Martin Vestergaard, who led the research, explains: "Our results show that there is dedicated neural machinery in the human brain for detecting the size of sound sources, and that auditory size perception is an automatic, innate brain process."

Breastfeeding curbs obesity

Putting on weight rapidly during the first year of life is known to increase the risk of childhood obesity, but the influence of feeding practices on this is unclear. Researchers from the MRC Centre of Epidemiology for Child Health set out to discover if breastfeeding, breastfeeding duration and age of weaning each had any effect on weight gain from birth to age three. They did this by analysing data from 18,819 babies and their mothers who are part of the Millennium Cohort Study. Findings showed that breastfed infants gained weight more slowly than those who weren't fed breast milk. Infants who were breastfed for less than four months and therefore received formula or other milk from an early age were heavier and fatter at age three than those children who were breastfed for longer. This association remained even if age of weaning on to solid foods and height of the child was taken into account. Lead author of the study Dr Lucy Griffiths explains: "Although the effect of breastfeeding on reducing childhood weight gain was small, it could have a significant effect within the overall population. Better strategies to support mothers in breastfeeding their babies are needed."

No omega-3 link with childhood IQ

MRC and Food Standards Agency-funded research has proved that there is no link between infant intelligence and the amount of omega-3 fatty acids they are fed in breast milk or fortified formula. The benefits of omega-3 fatty acids, particularly docosahexaenoic acid (DHA) have been widely speculated because they are found in high concentrations in the brain and accumulate during the brain growth spurt that occurs between the last trimester of pregnancy and the first year of life. Studies in animals also suggest that a lack of DHA during periods of rapid brain growth may lead to problems in brain development. Scientists from the MRC Epidemiology Resource Centre in Southampton studied 241 children from birth until age four. They looked at the relationship between breastfeeding or the use of DHA-fortified formula in infancy and performance in tests of intelligence and other aspects of brain function. After the influence of mothers' intelligence and level of education had been taken into account, no relationship was found between the estimated total intake of DHA in infancy and a child's IQ. "Factors in the home, such as the mother's intelligence and what mental stimulation children receive, were the most important influences on their IQ," explains Dr Catharine Gale, who led the study.

Early walkers make more active teenagers

Babies who learn to stand and walk early are likely to participate more in school sports and get higher marks for physical education (PE) as teenagers. These first steps in life are partly genetically determined, but encouragement from parents may also play a part, the MRC-funded study suggests. Over 9,000 people in Northern Finland took part in the study, all of whom were born in 1966. Their parents were asked when they first stood up on their own and started walking. These dates were compared with their school grade for sports at the age of 14. Participants were also asked how many different types of physical activity they enjoyed and how often they played. Findings showed that those who walked earliest got a third of a grade higher for PE and participated in a third more sports sessions than those who first walked six months later. Although biology is partly responsible for these differences, as Dr Ulf Ekelund of the MRC Epidemiology Unit points out, there are ways parents may be able to help: "Data suggests that longer breastfeeding may lead to early development of motor skills, and standing with support can be encouraged by carers. So, socio-cultural factors also influence infant motor development."

Bottle feeding mothers neglected

MRC research suggests that the needs of mothers who bottle feed are being neglected, potentially putting their babies at risk. Scientists at the MRC Epidemiology Unit in Cambridge carried out a systematic review of 23 published studies on attitudes to infant feeding methods, involving more than 13,000 women. Results showed that most research on bottle feeding mothers to date had focused on why women choose this method in a bid to find ways of promoting breastfeeding. It also emerged that very little research has looked at how best to protect the health of bottle fed babies. Bottle feeding mothers frequently felt guilt, worry about what doctors and other healthcare professionals might say, and anger as a result of pressure to breastfeed. Some mothers had received inadequate information on how to bottle feed correctly, and mistakes in the preparation of bottle feeds were common. Incorrect feed preparation can increase the risk of milk contamination, undernourish a baby or lead to excess weight gain. “Evidence still suggests that breastfeeding is the best way of ensuring optimal health for mother and baby,” says Dr Rajalakshmi Lakshman, who led the research, “But the needs of bottle feeding mothers need to be better answered, because inadequate information and support for mothers who choose this method poses a risk to their babies’ health.”

Predicting mother-to-baby infection

One in twenty babies born to mothers with hepatitis C are also infected with the virus, research has shown. MRC-funded scientists have discovered a marker on cells of the immune system that may help identify those mothers with hepatitis C who are more likely to pass the infection on to their babies. The study, carried out at the Children’s Hospital in Trieste and elsewhere in Italy, set out to discover which factors influence transmission of the hepatitis C virus (HCV). HLA is a protein on our cells that flags up foreign proteins to the immune system in order to trigger an immune response. There are many variants of the HLA protein. By studying HLA variants in 384 mothers and their children, the scientists found that mothers with the HLA variant HLA-DRB1*04 were less likely to pass on the infection to their babies, while higher transmission rates were seen if the child had the HLA-DRB1*10 variant. They also found that if mother and child had different HLA variants there was a lower likelihood of the mother passing the virus on to her baby. Dr Antonio Amoroso, who led the study, said: "This is a step towards understanding HCV transmission rates and identifying those most at risk of passing on the infection, or of becoming infected."

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3 – CHILDHOOD

FEATURE: Battling muscular dystrophy

Jack and Tom Bosanquet are taking part in an MRC-funded trial of a potential new treatment for muscular dystrophy.

On first meeting Tom and Jack you wouldn’t suspect that they have a fatal illness. Tom is a bouncy seven-year-old with a cheeky grin who likes collecting football stickers. Jack, his ten-year-old brother is quieter and more thoughtful and has a passion for giraffes and dinosaurs. But both boys have Duchenne Muscular Dystrophy (DMD), an inherited muscle wasting disease which affects around one in 3,500 boys worldwide.

The disease is caused by a mutation in the gene which codes for dystrophin, an important structural protein in muscle fibres which acts like shock absorber to protect the muscle from damage. In boys with DMD, dystrophin is faulty, so over time their muscle tissue breaks down and is gradually lost. This causes progressive muscle weakness leading to paralysis and a shortened lifespan. The boys’ mother, Claire, explains how she and her husband Ian first realised something was wrong:

“When Jack was about two, we became a bit concerned that he wasn’t going up stairs as quickly as other children. The paediatrician referred us to a neurologist and shortly afterwards he was diagnosed. Then I was tested and found out that unfortunately I’m the carrier. But by that point we’d already had Tom, and before he’d reached his first birthday we found out that Tom had it too.”

Since then, the family have had to move to a new home that's suitable for wheelchairs to prepare for when the boys aren't able to walk any longer. Claire is on a long career break from her work as an occupational therapist to care for the boys full time.

"The boys get tired very easily, so even if they've had a good night's sleep it's as if they've run a marathon because of the damage to their muscles. Jack is fiercely independent and very determined to keep going. But often his legs ache and sometimes you have to cajole him to go out because he's just too exhausted to do anything. Soon they'll both need to use a wheelchair."

But Claire says the main impact of the disease on the family is emotional: "Ian and I know what's going to happen to them, even though the boys don't fully understand. You're constantly trying to do your very best for your children, but the whole time you're watching them gradually lose their ability to do things, which is obviously quite difficult."

In 2009, the family were invited to enrol the boys in a trial for a potential new DMD treatment, partly funded by an MRC Translational Research Grant awarded to Professor Francesco Muntoni of the MRC Centre for Neuromuscular Disease.

The regions of a gene which code for proteins are known as exons. Jack and Tom have a variation of DMD in which exons 45 to 50 of their dystrophin gene are missing. The potential new treatment, made by the US Biotechnology company AVI Biopharma, sits like a 'molecular patch' over the exon next to the missing part of the gene. The exon can then be skipped, allowing the gene's instructions to be partially read to produce a shorter, but semi-functioning dystrophin protein. It's hoped that this shorter dystrophin could prolong the life of DMD boys and improve their quality of life.

Jack and Tom had to travel down from their home in Nottinghamshire to London's Great Ormond Street Hospital once a week for three months to receive the drug, injected intravenously into their arms.

Claire thinks she's seen a subtle difference in the boys since they took part: "Tom doesn't fall asleep quite so much and he's got more energy. With Jack it's quite difficult to gauge – I think the treatment might have kept him at the stage he's at a little bit longer," she says.

But Claire is pragmatic about how much impact the trial will have on the boys' lives: "We understand that it's not a cure for DMD and that taking part in a trial is the first step in quite a long journey. But when Jack and Tom were first diagnosed there was absolutely nothing on the horizon and now several potential treatments may be out there. But Jack and Tom have been quite realistic that the drug probably won't be ready in time to help them."

"The overriding thing for me and Ian is that we've got two children with a life-limiting condition which you really can't do anything about. So being involved with the research trial, even though it may not lead to a cure, has been a very positive experience."

Hope for muscular dystrophy patients

Duchenne muscular dystrophy (DMD) is a fatal genetic disorder of childhood. It's caused by faults in the gene coding for dystrophin, an important structural protein in muscle. Professor Francesco Muntoni, an MRC scientist and Principle Investigator of the MDEX Consortium, is collaborating with US biotechnology company AVI Biopharma on the development of a potential new DMD drug called AVI-4658. AVI-4658 helps to correct the error in the faulty gene as it is read by the molecular machinery inside cells, allowing production of shorter, but partially-functioning dystrophin protein. The drug has shown promise in a first clinical trial in seven boys with DMD, funded by the Department of Health. A second study, partly funded by the MRC, was recently carried out in a group of 19 boys with DMD (including Jack and Tom Bosanquet – see profile). AVI-4658 was injected into muscle in the boys' arms. Findings showed that in seven of the ten boys who received the three highest doses of the drug more dystrophin was present compared with levels seen in muscle biopsies taken before treatment. In three of the boys, the change was particularly striking. Professor Muntoni said: "These results are promising. I believe

this drug shows the potential to slow down the progression of the disease. We're now planning future clinical studies with AVI Biopharma to further investigate this drug."

Simple solution to the spread of malaria

Although the number of cases of malaria is falling, it remains one of the world's greatest childhood killers. At the MRC Unit in The Gambia, scientists work on understanding the molecular basis of malaria and immune responses to it, and carry out field trials to test new ways of treating and preventing the disease. These can be new drugs and vaccines, but also include less technological approaches. Dr David Conway and colleagues in a research team led by Professor Steven Lindsay (now based at the London School of Hygiene and Tropical Medicine) showed that house screening was an effective barrier to the mosquitoes that carry the malaria-causing parasite. Screening either the ceiling or the whole house led to fewer children with anaemia, one effect of malaria infection in rural areas. Dr Conway said: "Malaria is on the decline in some parts of Africa where prevention is available through insecticide-treated bednets and artemisinin-based treatments. However, we need more ways of tackling it. This research showed that house screening by local workmen reduced malaria transmission – more work is needed to see if it is a sustainable and cost-effective way to reduce the burden of malaria."

Cell discovery sheds light on asthma

Asthma is common in childhood, and the number of children diagnosed with each year with the disease is on the rise. Scientists at the MRC Laboratory of Molecular Biology in Cambridge have discovered a new type of immune cell which could point the way to new preventative treatments for asthma. The cells, named nuocytes by the scientists, produce a chemical called interleukin-13 (IL-13). IL-13 is used in the body's immune defence against invading parasites and is also involved in causing inflammation of the airways in asthma patients – the symptom which causes breathing difficulties. The scientists hope that the discovery of nuocytes, a previously unknown source of IL-13, may improve our understanding of what happens in our immune systems at the beginning of an asthma attack. The research was co-funded by Asthma UK and led by Dr Andrew McKenzie. He said: "We have identified a new immune cell type, which is a major source of IL-13 – an important mediator in asthma. My group is now investigating the role of nuocytes in models of asthma with the goal of translating our research into new treatments."

Early sleep problems affect teenage brain

Researchers have uncovered a link between sleep problems in childhood and brain performance in adolescence. The MRC-funded scientists analysed data from a long-term study of over 1,000 teenagers in New Zealand who had been followed since birth. As part of the study, parents were asked to report any sleep problems the children had suffered at age five, seven and nine – for example, difficulty in falling asleep. At age 13, the study participants completed tests designed to measure different brain functions. Teenagers who had experienced sleep problems at age five and nine performed less well in two of the tests than their counterparts who hadn't had any sleep problems. One test asked them to a copy a visually complex picture and then draw it again from memory after a three minute delay. The other assessed information processing speed, hand-eye coordination and the ability to maintain two different trains of thought. The findings were independent of gender or socio-economic status. Dr Alice Gregory of Goldsmiths College led the research. She said: "This adds to the growing body of evidence suggesting that childhood sleep problems may be a risk factor for difficulties in later life. Children should be routinely assessed for sleep disorders and treated at an early stage."

Cereals may protect against heart disease

Folate is an important B vitamin found in fortified breakfast cereal and leafy vegetables, which prevents certain brain defects in the developing fetus. People who don't get enough folate in their diet end up with high levels of a chemical called homocysteine in their blood which is linked with heart disease; so folate and other B vitamins are also thought to play a role in combating heart disease by mopping up homocysteine. Research partly funded by the MRC looked at blood homocysteine levels in 2,127 children and teenagers aged between four and 18. They discovered that B vitamins in the body decreased significantly with age, with a corresponding rise in homocysteine levels. The researchers also found that children who ate fortified breakfast cereal had higher levels of B vitamins and lower homocysteine levels than those who did not. Dr Christopher Bates of MRC Human Nutrition Research in Cambridge, said: "Few studies have

looked at the importance of folate and other B vitamins in young people. The research shows that maintaining an optimal level of folate and the other B vitamins, B12, B6 and Riboflavin, in childhood and adolescence is essential for preventing build-up of homocysteine in the blood, and over a lifetime, this might be one of the factors which help to reduce the risk of heart disease. We suggest that age-specific guideline B vitamin levels should be drawn up for children, for use in a clinical setting."

'Resistance gene' offers insights into CJD

Strong genetic resistance to a fatal brain disease has emerged in a community in Papua New Guinea, MRC research has shown. The disease, kuru, is unique to the Okapa area in Papua New Guinea and, like Creutzfeldt-Jakob Disease (CJD) it is caused by infectious prions. Kuru devastated the affected population in the 1950s. The infection was passed on at mortuary feasts, where women and children consumed their deceased relatives as a mark of respect. Scientists from the MRC Prion Unit in collaboration with the Papua New Guinea Institute of Medical Research compared the genes of over 3,000 people from the valley and surrounding regions, including 709 people who had participated in cannibalistic mortuary feasts, 152 of whom later died of kuru. In the area where kuru had been most rife, they discovered a unique mutation in the prion gene called G127V, which protects against kuru. This gene has become frequent in this area through natural selection, in direct response to the epidemic. Professor John Collinge, director of the MRC Prion Unit, who led the research, said: "It's absolutely fascinating to see Darwinian principles at work here. Discovery of this powerful resistance factor against a truly terrible epidemic opens up new areas for research taking us closer to understanding, treating and hopefully preventing a range of prion diseases."

Fine tuning childhood cancer treatment

Survival from childhood cancers has increased dramatically in recent decades but research continues to improve the chances for children diagnosed with cancer. The MRC is funding a trial for acute lymphoblastic leukaemia (ALL), which affects around 450 children a year in the UK. The trial, called UKALL 2003, is using a new test to detect cancer cells in bone marrow after one month of chemotherapy. The number of cancer cells left at this stage – or 'minimal residual disease' – is linked to the likelihood that the treatment will cure the cancer. The new test is 500 times more sensitive than existing methods, so it allows doctors to assess very accurately how well a child with ALL is responding to treatment. Lead researcher Professor Ajay Vora, consultant paediatric haematologist at Sheffield Children's Hospital, says: "The treatment can be tailored to the minimal residual disease response. Children with a good response can be given less treatment to reduce the risk of side effects without affecting recovery, and those with a slower response may benefit from more treatment to improve their chance of cure. Research we published in 2009 showed this test made a real difference for infants under one year old. UKALL 2003 will determine if the same is true for older children – already, we're seeing that this test helps us provide the very best possible treatment for each child."

FEATURE: Homing in on brain tumours

Dr Nigel Davies uses sophisticated imaging techniques to increase our understanding of childhood brain tumours.

A physicist by training, Nigel works as a Clinical Scientist at Birmingham Children's Hospital. Here he's been using his knowledge of how the nuclei inside atoms behave to study brain tumours in children, using a technique called magnetic resonance spectroscopy (MRS). The aim of this work is to help develop more focused diagnostics and treatments for cancer, as Nigel explains:

"Traditional cancer treatment with chemotherapy and radiotherapy kills tissue indiscriminately. So, it blasts the tumour but has all kinds of unpleasant side effects on the body. We're working towards treatments which hit specific metabolic or genetic targets within each type of tumour – rather like a laser-guided missile which destroys the cancer and leaves healthy tissue unharmed."

Tumour cells behave differently to healthy cells, and their metabolism – the chemical reactions inside all cells which generate energy – is also different. Measuring and analysing the by-products of tumour metabolism (metabolites) can help scientists to identify the type of tumour

and even how quickly it is likely to grow and spread. The hallmark of some of these more aggressive tumours is a higher level of one of these metabolites, called glycine.

Nigel and his colleague, consultant oncologist Dr Andrew Peet have discovered a new and more accurate way to pinpoint glycine levels inside brain tumours. The technique is non-invasive and can be carried out while children are having their routine brain scans. Scanning the brains of children with MRS and using a special computer programme to analyse the results, Nigel and Andrew were able to separate out the overlapping signals from glycine and other metabolites with a similar 'fingerprint'.

"Using this technique we can identify the more aggressive tumours which need urgent treatment to keep them in check before they spread throughout the brain. In the long-term this might also shed light on a metabolic pathway in brain tumours which could be targeted with drugs," explains Nigel.

The technique is now being tested in a larger group of patients throughout the country, and Nigel's research was shortlisted for Children's Cancer and Leukaemia Group McElwain Prize. So is Nigel glad he made the leap from physics to medical research?

"The best thing about this job is the feeling that what I'm doing could have an impact on real people's lives in the future. Rather than just being interested in technology for technology's sake, I'm using physics and technology to affect people's lives at a very basic level."

Early screening detects pancreatic cancer risk

All of us have genes that regulate cell growth, which can malfunction and lead to tumours. In some people, malfunction of the MEN1 gene allows tumours to develop, particularly in the pancreatic neuroendocrine cells which make hormones that control cells of the stomach, pancreas and intestines. It's estimated that over 50 per cent of children with MEN1 malfunction will develop tumours by the age of 20, which is when screening currently starts. However, scientists funded by the MRC suggest that the real figure is much higher and recommend that the start of screening be brought down to age 10. Having found tumours in children as young as 12, their study argues that current figures don't take into account children with a faulty MEN1 gene who do not show any symptoms – either because the tumours are still small or they are inactive. The study, which involved 12 children with faulty MEN1 between the ages of six and 16, found that two had inactive pancreatic tumours that were larger than two centimetres. Five of the children had tumours of other endocrine glands. "These findings are important because these tumours are the commonest cause of death in patients with MEN1 and these deaths occur at a young age," says Professor Thakker of Oxford University who led the research.

Unsupervised kids move more

Lack of physical activity and rising obesity among British children is an increasing cause for concern. Although local authorities assess their neighbourhoods for access to recreational facilities, little attention has been paid to how much children can go out and about on their own. But freedom to go out unsupervised is strongly related to children's levels of physical activity, according to the Personal and Environmental Associations with Children's Health (PEACH) project which is run from Bristol University and part-funded by the MRC. The researchers found that children whose parents allow them out on their own, or with friends, have higher levels of physical activity than those who are allowed out less often unsupervised. Over 1,300 10- and 11-year-olds wore an accelerometer for a week, which measured their physical activity, and answered questions about when and where they were allowed out alone. One of the leaders of the project, Dr Angie Page, says: "Our research shows that there is a correlation between children's independence and their physical activity. Given the decline in children's independent mobility over recent years, we need to work on creating an environment where parents feel safe letting their children go out unsupervised."

Treating glue ear with steroids not cost effective

An MRC study shows that the practice of treating a childhood condition called glue ear with steroids is costing the NHS money to no effect, since most children recover naturally. Glue ear is a collection of fluid behind the eardrum, technically known as otitis media with effusion. It affects

80 per cent of children by the time they are four and is the commonest cause of surgery in children. The problem usually resolves itself but for a few children it can lead to deafness. Many doctors prescribe a steroid nasal spray to treat glue ear. However the study, involving 217 children being treated for glue ear, proves that using steroids is ineffective. One group of children were treated with a steroid nasal spray and another group with placebo for three months. After one month, 45 per cent of the children on the placebo were cured, compared with only 41 per cent of those on the steroid. After three months, the percentage of children cured went up to 52 per cent and 58 per cent respectively, a difference which is not statistically significant. Dr Ian Williamson, who led the research, said: “Otitis Media remains a very significant cause of child illness worldwide. New ideas to increase cost-effective management are still needed in primary care, where the majority of children are first seen.”

Early intervention improves life chances

Nearly 10 per cent of children aged five to 16 years have a clinically diagnosable mental health problem: evidence shows these problems have a serious impact on life chances and even life expectancy. Mental health problems at a young age not only affect our mental health as adults, but also our chances of doing well at school and in work, forming strong families and becoming good citizens. They also impose major costs on the individuals concerned and wider society. Research commissioned by the Sainsbury Centre for Mental Health, the Smith Institute and UNISON, and supported by the MRC, examined the long-term consequences of childhood and adolescent mental health problems. It showed the negative effects of mental health problems in childhood, particularly conduct problems such as persistent disobedience, fighting or bullying. For example, people who had conduct problems were more likely to have left school without qualifications and struggle with personal relationships as adults. Lead researcher Dr Marcus Richards, of the MRC Unit for Lifelong Health and Ageing, says: “A large amount of mental ill health among young people currently goes unrecognised and untreated. If we can address that, there is good evidence that early intervention programmes for childhood conduct and emotional problems can be highly effective in reducing these damaging consequences, and more than pay for themselves over the long term.”

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4 – TEENAGE YEARS

FEATURE: Improving teenage sexual health

Dr Katie Buston’s research focuses on sexual health in teenagers and young people.

Katie is a Senior Investigator Scientist at the MRC/CSO Social and Public Health Sciences Unit (SPHSU) in Glasgow. She began her research career with a PhD on media images of lone parent families. At that time, the early 1990s, such families were the focus of the government’s ‘back to basics’ policy – and the subject of many a tabloid headline. A seed was planted which led Katie to a career in research on young people’s sexual health and parenting. She’s worked at SPHSU for the last 14 years and recently she has been leading a study on young male offenders in Scottish prisons.

She explains: “I was interested in studying socially excluded young men, but it’s so difficult to recruit them to any kind of study – they don’t usually want to come in off the streets and talk to someone like me. So I came up with the idea of visiting them in prisons where you tend to get a selection of young men from socially deprived communities that you wouldn’t be able to access any other way.”

A group of 67 imprisoned young male offenders aged between 16 and 21 were asked to fill in a questionnaire about their sexual relationships, contraceptive behaviour and fatherhood. Katie followed this up with visits to the prisons to carry out in-depth interviews with 40 of them.

“One of the most interesting things that came up was the number of these young men who had been tested for Sexually Transmitted Infections (STIs). Ten or 15 years ago the general attitude among young men was that being tested for STIs would compromise their masculinity – but that wasn’t what I found. Also, many of them had been tested for STIs since they had been in prison and they seemed quite happy to go and get tested within that context.”

This got Katie thinking about the potential of using Young Offender Institutions as an easy and relatively inexpensive way to target and treat men in this high risk group, which could potentially lead to a reduction in the overall prevalence of STIs in the general population.

“If prisons were to offer screening programmes, perhaps even opt-out ones where everyone gets tested as a matter of course unless they object to it, you would probably get very high rates of take-up,” she says.

The findings also revealed that while many of the young offenders interviewed by Katie had had several sexual partners, often without using contraception, most didn’t intend to become a parent. But one in four young offenders in prisons are fathers – a relatively high figure considering that the men are aged between 16 and 21.

“Long term, we hope to develop parenting interventions for young men in prisons, especially the ones who are already fathers but also those who may become fathers in the near future. If we could work on their parenting skills like basic childcare and knowledge of child development, that could have a massive effect. Not just on their engagement with their children, but on their children’s health outcomes right into the future. Because the MRC is able to provide long-term funding we can plan for studies like this in the way that other organisations can’t,” says Katie.

Teenagers are often perceived negatively, but Katie feels a responsibility to defend teenagers against the bad press they get.

“We’ve all been teenagers, and I think at that time of life you have a lot of dilemmas and struggles to contend with. But I’ve yet to meet a teenager who isn’t just trying to go about their life and resolve those struggles. Even with the young offenders, by and large I found them friendly, helpful and happy to talk to me, and they even tried not to swear during the interview (though they didn’t always manage it!)”

“What’s been highlighted to me is the negative aspects of life that they’ve experienced and tried to get over – and how they’ve ended up where they are. If we can develop an intervention to break this cycle and see this make a difference to them and their children I’ll be happy.”

Testing in youth prisons could cut STIs

MRC research suggests that introduction of routine screening programmes for sexually transmitted infections (STIs) in young offenders’ institutions could reduce the prevalence of STIs in the wider community (see profile). Dr Katie Buston and colleagues from the MRC/CSO Social and Public Health Sciences Unit in Glasgow interviewed 40 young offenders (aged 16 to 20) in Scotland to better understand their STI testing behaviour and attitudes. Of the 40 individuals, 24 had been tested, and of these 16 had been tested within the young offenders’ institution, where the screening was convenient and readily available. Dr Buston explained: “Targeting male young offenders whilst they are inside may provide a rare opportunity to intervene in the lives of vulnerable young men. Most of those interviewed reported having had more than five sexual partners, with unprotected sex commonplace, yet only a handful of the men had undergone regular testing. A standard opt-out screening programme would enable the diagnosis and treatment of STIs amongst this group, as well as serving as an opportunity for sexual health promotion and perhaps contact tracing. This could reduce the prevalence of STIs in the community, in the medium- and longer-term, as many of those in young offenders’ institutions are released back into society in a matter of months rather than years.”

Cannabis linked to cancer risk

Scientists at the University of Leicester part-funded by the MRC have found convincing evidence that cannabis smoke may damage DNA in ways that could potentially increase the risk of developing cancer. Using a new highly sensitive method called liquid chromatography-tandem mass spectrometry, the researchers focused on the toxicity of acetaldehyde – a chemical present in both tobacco and cannabis smoke. They showed that exposing DNA to cannabis cigarette smoke produced similar levels of DNA damage as that seen after exposure to tobacco smoke. Lead author Dr Rajinder Singh said: “It’s well known that toxic substances in tobacco smoke can damage DNA and increase the risk of lung and other cancers. Cannabis, in contrast has not been

so well studied. It is less combustible than tobacco and contains toxic compounds which could potentially damage DNA and lead to cancer. Our findings have significant human health implications, especially as cannabis users tend to inhale more deeply than cigarette smokers, which increases respiratory burden. The smoking of three to four cannabis cigarettes a day is associated with same degree of damage to the lining of the bronchi, the air pipes which lead to the lungs, as 20 or more tobacco cigarettes a day."

Long term research

The MRC National Survey of Health and Development has been collecting a wealth of information about more than 5,000 people since they were born in March 1946 all around the UK. Now data on these individuals recorded in their childhood and adolescence are helping researchers in the HALCyon (Healthy Ageing across the Life Course) programme to investigate how cognitive performance in older people is affected by factors from across their whole lives. Previous research suggested that people with higher levels of neuroticism might be at increased risk of cognitive decline due to the effects of chronic distress on the brain. Using data from the 1946 birth cohort, the HALCyon researchers found that cognitive performance at age 53 was poorer in people who had scored higher in neuroticism in adolescence, but this was explained by the fact that these people had poorer cognitive ability in childhood. Dr Catharine Gale, of the MRC Epidemiology Resource Centre in Southampton, commented: "Intelligence in childhood is a powerful influence on cognitive function later in life. Children who perform less well on intelligence tests also tend to be higher in neuroticism. Once we took account of childhood intelligence, we found no evidence to suggest that being higher in neuroticism in adolescence had any long-term detrimental effect on cognitive performance."

Breaking down autism

Autism is a complicated condition. Different people experience it in very different ways. At the Institute of Education in London, psychologist Professor Tony Charman is working with a group of 100 adolescents with autism who have taken part in a battery of interviews, tests and assessments of their behaviour and cognitive abilities. Professor Charman says: "Autism research is usually based on studying a few characteristics in a small sample of individuals. By contrast, we're at the forefront of a new trend to look at a really broad range of factors in relatively large groups that will allow us to identify possible sub-groups in autism that just wouldn't have shown up in previous studies." For example, the research team found that about 20 per cent of the group were better at discriminating the pitch of sounds than their peers. Young people in this sub-group tended to take longer to start speaking as infants but now have good verbal abilities. Professor Charman added: "The findings from our approach are identifying potential sub-groups within autism that must now be investigated further. The aim is to develop more tailored ways of addressing autism based on cognition and perceptions in different individuals."

Disruptive teens don't recognise frowns

Adolescents with conduct disorder (CD) find it difficult to follow society's rules and codes of accepted behaviour. They show little concern for the feelings and rights of others and have a repetitive pattern of aggression and other forms of antisocial behaviour. Research funded by the MRC and the Wellcome Trust shows that teenage boys with CD find it difficult to recognise facial signals of anger or disgust. A group of 81 teenage boys with CD and 40 healthy volunteers were shown a series of pictures of faces with gradually changing facial expressions showing happiness, surprise, fear, sadness, disgust and anger and asked to identify the emotion being displayed in each image. Boys with CD showed a much poorer ability to correctly identify anger or disgust than their healthy counterparts. The research was carried out by Professors Ian Goodyear and Graeme Fairchild of Cambridge University and Dr Andy Calder of the MRC Cognition and Brain Sciences Unit in Cambridge. Dr Calder said: "Facial expressions are important social cues that can be used to reinforce socially acceptable behaviour and suppress inappropriate behaviour. Failure to correctly recognise these particular facial signals of social disapproval may contribute to the wider behavioural impairments shown by these adolescents."

'Good' values don't stop drug taking

Many people think that teaching traditional values at school protects teenagers against future smoking, alcohol abuse and drug use. However, research funded by the MRC suggests that trying to influence young people's values at school is unlikely to be effective. The study, which was

carried out by lead researcher Robert Young and Professor Patrick West at the University of Glasgow, involved over 2,000 school children, who were interviewed at age 15 and again at around age 18. Predictably, rebellious teenagers were more likely to be taking drugs. But teenagers who believed in traditional roles for men and women were also more likely to be taking drugs, which suggests that 'macho' stereotypes can lead to greater substance use. Teenagers who believed in hard work were more likely to be smokers, while individualists were less likely to smoke. However, none of the values that young people held at 15 was likely to predict whether or not they would be smoking, getting drunk or taking drugs at eighteen – at least for those who were not doing so already. "Our findings directly challenge the proposition that authoritarian or traditional values are necessarily better for health than liberal or individualist ideals," concluded Dr Young.

FEATURE: Growing up with research

Sunjay Singh is part of a long-term study of how genetics and environment affect health.

Sunjay has already packed a lot into his 18 years. He's just finished his first year at the University of the West of England studying genetics, he's a keen photographer and amateur actor, and he's currently filming a documentary for the UK Youth Parliament on extremism.

He's also one of over 10,000 Bristol-born teenagers who have been questioned, assessed, measured and monitored since birth in the Avon Longitudinal Study of Parents and Children (ALSPAC). ALSPAC aims to study the genetic and environmental factors which have an impact on development and health. Partly funded by the MRC, it's the source of many important research findings – for example that eating oily fish when pregnant can improve the baby's eyesight, or the discovery of genes linked with obesity. Sunjay's mother signed up to ALSPAC when she was pregnant with him in 1991, so he's been involved in the study for longer than he can remember.

"The earliest memory I have is when they asked me to draw a house. Some of those drawings obviously are going to be quite comical now. I think at the very beginning it was just easy things like that and then there've been questionnaires."

"We do clinics about once a year where they take different scans and measurements – of things like bones and muscles. You always get a scan of your entire skeleton and you get a little print-out of it, but they've done retina scans, eye tests and hearing tests and you get one of your leg, your heart, and your liver. So literally everything you can think of is put in there really," Sunjay explains.

"The best thing about it is the fact that you know you're doing something for a good cause, you're helping out – especially when you see the findings and you can read about them and realise 'yeah, I contributed to that'. And you get free biscuits as well, which is good!"

Not one for passive involvement, Sunjay is also a member of ALSPAC's teenage advisory panel which helps to shape and improve research studies carried out on the cohort.

"As we were growing up, the people that were writing the questionnaires or were trying to contact us were older than us – they weren't keeping up with us, basically. They wanted a group of people in the study that could advise them on things they could do better. So they come to us with questionnaires or ideas or study designs and they get our feedback on it. I think it's helped the organisation so much because it's now more accurately aimed at its audience."

Involvement in the longitudinal study helped to influence Sunjay's choice of degree, and now he's considering a career in science.

"I knew I wanted to study a science because I was always interested in it, so ALSPAC's definitely opened up different gateways. And I did my work experience in one of their labs so that's helped me too."

Would Sunjay recommend taking part in research to other teenagers? "Yeah definitely. It doesn't take a massive amount of your time, and you're helping out other people which is always good."

Diet beats genes in teenage obesity

Children who eat food that is higher in energy are more prone to be overweight as teenagers, regardless of whether they have the FTO 'fat gene', suggests research from the Avon Longitudinal Study of Parents and Children (ALSPAC) (see profile). The scientists looked at dietary energy density (DED), a measure of the amount of energy consumed per gram of food. High DED foods include dry foods such as sugar coated cornflakes, while lower DED foods tend to contain more water. The scientists studied the food intake of 2,275 children aged 10 and tested them for the FTO gene, which is linked with increased likelihood of being overweight. At age 13, the fat mass of the children was measured. Findings showed that having FTO and eating high DED foods were independently linked to being fatter during adolescence, but having FTO did not make children who ate a high DED diet any fatter. One of the study's authors, Professor George Davey-Smith of the MRC Centre for Causal Analyses in Translational Epidemiology and Scientific Director of ALSPAC, said: "This study shows that many different things contribute to obesity. Although FTO may put some children at greater risk of being fat, encouraging children to eat low DED foods might be an effective way to help all children avoid excess weight gain."

Clues for tackling cocaine addiction

One of the hardest things for people withdrawing from drug abuse is being reminded of their habit. Just seeing things they associate with drugs such as pubs, lighters or mirrors can be enough to make addicts relapse. This is because the brain learns to connect these drug-related cues with drug-induced pleasure so that eventually, the cues themselves become desirable. Research shows that much of people's susceptibility to this compulsive behaviour depends on their genetic make-up. MRC scientists have discovered that human cocaine addicts are more likely to have a particular variant of the gene GABRA2, which controls the transmission of signals through the part of the brain responsible for motivation and reward. Furthermore they've found that genetically manipulating mice to remove the gene stops the mice from exhibiting 'cocaine addict like' compulsive behaviour. In the study, groups of mice with and without GABRA2 were conditioned into associating a beeping noise with delivery of food. After a while they would push a button to activate the beeper even when food was not delivered, because they associated it with reward. When they were given cocaine, those mice with GABRA2 became increasingly 'addicted' to pushing the beeper, but the mice lacking the gene did not. Professor David Stephens of Sussex University says: "Our study suggests a new approach to identifying the genetic risk of addiction."

Social inclusion may reduce teenage substance misuse

Levels of smoking, drinking and illicit drug use amongst the UK's young people are among the highest in Europe. Research suggests that young people who feel included and engaged with school and education are less likely to use such substances from an early age. Dr Chris Bonell and colleagues from the London School of Hygiene and Tropical Medicine tested an intervention called the Healthy Schools Ethos (HSE) project in secondary schools in England, based on similar studies done in the USA and Australia. The research set out to explore whether and how HSE might work to reduce student substance misuse. Four schools were involved in the study, two of which implemented HSE over a year. A project facilitator helped staff and students in each school to form an action group and decide what local actions should be taken to improve inclusion and engagement. A survey of students was used to shape these decisions, which included actions such as re-writing school rules, introducing peer mediators and developing 'safe spaces' for younger students. Dr Bonell said: "Larger trials need to be done but our research suggested the work could have a big impact on students' engagement and attitudes to drugs, and there was also evidence of a reduction in violence."

How alcohol marketing impacts teenagers

The health and social costs of drinking have become increasingly prominent in recent years, and important policy steps have been taken in response. Central to the debate is alcohol marketing. With support from the partly MRC-funded National Prevention Research Initiative, Ross Gordon and colleagues at the University of Stirling carried out a study of the complex relationship between drinking and alcohol marketing. Nearly a thousand teenagers in the west of Scotland were interviewed at age 13 and again two years later. The teenagers showed a high level of awareness of alcohol marketing across a range of channels, including television adverts, football

shirt sponsorships, mobile phone covers and print media. They had well-developed attitudes to different brands of alcohol, showing a clear preferences for brands associated with a youthful image, or those marketed through references to youth culture. The brand image of the alcohol they drank was found to be strongly associated with self-image, and with peer group identification. Links between alcohol marketing and youth drinking behaviour were also discovered. Longitudinal data analysis found an association between alcohol marketing and youth drinking behaviours such as uptake of drinking and increased frequency of drinking. Dr Gordon said: “Our findings indicate that stronger regulation of alcohol marketing is needed to protect young people.”

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5 – ADULTHOOD

FEATURE: Probing the boundaries of consciousness

Dr Martin Monti’s research focuses on patients with severe brain injury, trying to find out whether or not they are conscious.

Martin’s research at the MRC Cognition and Brain Sciences Unit (CBSU) in Cambridge is trying to answer two questions: how much function is possible in a brain after severe injury? And what does it mean to be conscious?

Martin has had an unconventional career route. He started a degree in classics, switched to mathematical economics and finally ended up doing a PhD in cognitive psychology, grappling with how human language sets us apart from other species. From there it was a short hop to cognitive neuroscience research, and he’s been working at the CBSU for the past three years.

He explains what fascinates him about his research: “We all know what we mean when we talk about consciousness – but we have no real understanding, scientifically speaking, of what it is. We can more or less tell if somebody is or isn’t conscious – but there’s no measure of it. And yet it’s one of the most fundamental experiences of being human.”

By looking at brain activity in healthy volunteers, using an imaging technique called functional Magnetic Resonance Imaging (fMRI), Martin and his team think up ideas on how to test these questions. Once they’ve worked out what normal brain activity looks like on an fMRI scan and what it means, they can look for similar activity in the brains of patients with brain injury – which might indicate that they are conscious.

In February 2010, research led by Dr Adrian Owen and Martin became the focus of international attention when they showed that a man who was presumed to be in a vegetative state could communicate ‘yes’ and ‘no’ using just his thoughts.

“Our idea was that, even if somebody was completely unable to move their eyes, blink or move their hand in response to an instruction, they might still be able to think on command. If we could see the person thinking exactly what we asked them to think, then that would prove they were conscious,” says Martin

Using fMRI, the researchers were able to show that the man wasn’t in a vegetative state. The technique also gave him a way of communicating with the outside world for the first time in five years.

Martin says: “Now we have a way to ask questions that we couldn’t ask before. For example, patients who are aware but can’t move or speak could be asked if they are feeling any pain, allowing doctors to decide when painkillers should be administered.”

Now the scientists are looking at alternative ways of using this technique which are more portable, for example electroencephalography (EEG) – which involves detecting brain activity through electrodes placed on the head.

“We could envisage maybe giving this to a patient to bring home and use on a daily basis,” explains Martin. “Our fMRI technique works better than EEG, but an MRI scanner is very costly to operate, and it’s very big. Also, not all patients can go in an MRI scanner because they might have, for example, cardiac pacemakers. So we’re trying to fan out into all these alternative approaches that may have some advantage.”

More work needs to be done to find out how many other patients who are presumed to be vegetative are in fact conscious, but Martin says it’s unlikely to be many: “Just because we found these cognitive processes preserved in a small group of people, it doesn’t mean that all vegetative patients are like this – in fact, our research indicates that most of them really are unconscious.”

Martin’s now trying to find out whether vegetative patients can see or even recognise faces. Unlike coma patients, vegetative patients have their eyes open. “They wake up and fall asleep every day pretty much as you and I do,” says Martin. “That’s one of the reasons why it can be hard to believe they’re not conscious. Their eyes even wander a little bit, sometimes they even follow movement. But as yet it’s unclear if this is a sign of consciousness – and that’s what we want to find out.”

“My favourite part of the job is having the intellectual freedom to explore things that I just find extremely fascinating – consciousness and the mechanisms of the brain. And then figuring out how we can apply this knowledge to human health.”

“If I could look back at the end of my career and feel I’ve added my contribution to something that allowed us to have one little more bit of understanding of the human brain, I think I’d be very happy.”

Vegetative patient communicates by thought

Scientists led by Dr Adrian Owen and Dr Martin Monti at the MRC Cognition and Brain Sciences Unit in Cambridge have shown that a man presumed to be in a vegetative state could communicate ‘yes’ and ‘no’ using just his thoughts (see profile). Working with scientists at the University of Liège in Belgium, the team developed a technique in healthy volunteers to decipher whether people were responding ‘yes’ or ‘no’ to questions they asked. Patients imagined playing tennis if they wanted to answer ‘yes’ or imagined navigating around their homes for ‘no’ – activating different areas of the brain. The team then scanned 23 patients diagnosed as being in a vegetative state. Four showed signs of awareness, one of whom was a 29-year-old man who had sustained a severe traumatic brain injury in a road traffic accident five years before. The team mapped the man’s brain activity while he was asked questions such as ‘Is your father’s name Thomas?’ The scan showed that the man was able to communicate his answers by wilfully changing his brain activity. Dr Owen said: “We were astonished when we saw the results of the patient’s scan and that he was able to correctly answer the questions that were asked by simply changing his thoughts.”

Better cancer treatment decisions

Results from the largest ever clinical trial of treatments for advanced bowel cancer provide new information on the potential effects of different treatments that will help doctors make better decisions about how to fight the disease. The MRC COIN trial looked at whether these cancer patients could survive longer if a newer drug called cetuximab was added to their standard chemotherapy. Secondly, it tested whether taking breaks from standard chemotherapy could minimise side-effects, reduce time on treatment and improve patients’ quality of life without affecting how long they would live. It’s known that cetuximab only works in tumours with the normal form of a gene called KRAS. Adding cetuximab did not improve survival in these patients, but the results also showed that an alternative drug combination to standard chemotherapy, fluorouracil/oxaliplatin in combination with cetuximab, did show a trend to benefit. Results from the second part of the trial revealed that patients given intermittent chemotherapy suffered fewer side effects – but on average they survived for 1.4 months less than those who received continuous chemotherapy. Lead investigator Professor Tim Maughan, of the University of Cardiff, said: ‘‘Although these results don’t give a clear indication that one treatment option is better

than another, they will help inform patient-clinician discussions and ultimately decisions on individual treatment.''

Understanding cell death

Cells in the human body die continually, mostly through a process of self-destruction called apoptosis. The failure of apoptosis plays a role in many diseases including cancer and some immune system disorders, including autoimmune lymphoproliferative syndrome (ALPS). Apoptosis can be triggered following activation of molecules called death receptors, and the formation of a complex of proteins called the DISC. Paradoxically, the DISC has also been found to activate cell survival. Researchers at the MRC Toxicology Unit in Leicester have found that the DISC can trigger cell death or signal for cell survival by switching the activity of key death-promoting molecules. If the DISC is prevented from functioning properly, apoptosis fails to be carried out efficiently and the outcome is instead cell survival. Therefore, in diseases such as ALPS, where a crucial death-promoting protein is often not active, the DISC fails to function properly. A patent application protecting this discovery has now been filed by MRC Technology. Dr Marion MacFarlane of the MRC Toxicology Unit, who led the research, said: “This takes us a step closer to understanding how the DISC triggers cells to die. The challenge now is to try and use this fundamental knowledge to work towards developing better treatments for conditions which occur when DISC-mediated cell death goes wrong.”

Predicting cervical cancer

A study of 4,000 women with slightly abnormal cervical smear test results, most of which would never lead to cancer, has shown that a repeat smear is as good as a more invasive examination and biopsy. A smear test involves scraping cells off the surface of the cervix and looking at them under the microscope. Women in the MRC- and NHS-funded study were divided into two groups. One group had their initial smear test followed up with another smear test and the other group had a colposcopy – examination of the cervix with a microscope and a biopsy involving taking a small amount of tissue from the cervix for testing. Little difference was found between the two tests in being able to detect advanced changes within cells. But women who had smear tests suffered fewer adverse side effects, for example pain and bleeding, than the colposcopy group. A second trial also showed that colposcopy followed by recall if abnormalities are found is just as effective as the more radical approach of large loop excision (removing the whole zone of possibly abnormal cervical cells straight away). Principal Investigator in the study, Professor Norman Waugh of the University of Aberdeen, said: “The less invasive method of follow-up by repeat smear is as good as, but has fewer side-effects than, immediate colposcopy.”

Prioritising HIV therapy over testing saves more lives

Findings from a major MRC trial of HIV treatments in Africa show that by prioritising spending on anti-retroviral therapy (ART) rather than on expensive routine laboratory tests for HIV monitoring, more people could be effectively treated for no additional cost. Over six years, the MRC Development of Anti-Retroviral Therapy in Africa (DART) study aimed to find out whether the laboratory-based strategies used to deliver ART to people with HIV infection in resource-rich countries were essential in Africa, where around 4 million people still need ART urgently and resources are limited. Over 3,300 people took part in the trial, none of whom had previously had ART. All of them had severe or advanced HIV infection and their eligibility for receiving ART was assessed using tests such as CD4 cell count (a measure of immune system health). One group of trial patients received ART and their doctor was given the results of three-monthly blood tests to check for drug side-effects and measure CD4 cell count. People in a second group had the same ART and the same blood tests, but their doctors did not see CD4 count results and only saw the results of safety tests if they were seriously abnormal. Routine laboratory tests to monitor the effects of ART offered little additional clinical benefit to people with HIV in Africa compared with careful clinical monitoring. DART co-principal investigator Professor Peter Mugyenyi said: “We now have evidence that expensive blood tests aren’t needed routinely for HIV treatment to be successful and safe. It also means that treatment could be delivered locally to more people including those who live in remote villages far from the nearest laboratory, as long as healthcare workers have the right training, support and supervision. This could make a huge difference especially at this critical time when demand for treatment has increased while donor funds have declined.”

Cheap antibiotic halves HIV deaths

A new analysis of the MRC Development of Anti-Retroviral Therapy in Africa (DART) trial has shown that a safe, cheap and widely available antibiotic could save the lives of thousands of people starting anti-retroviral therapy (ART) for HIV in developing countries. The analysis of 3,179 trial participants, who were followed up for five years, showed that a daily dose of the antibiotic co-trimoxazole (trimethoprim-sulfamethoxazole) cut the risk of death by 50 per cent in the first 18 months of treatment in combination with ART. ART alone cut mortality risk by more than 90 per cent and cotrimoxazole provided additional benefit, halving the risk of death again. The antibiotic also reduced the occurrence of malaria by 26 per cent. Co-trimoxazole is used in countries with limited resources to treat and prevent common infections. In HIV patients, it effectively treats and prevents pneumonia, bacterial infections and the parasitic infection Isospora belli. Lead author Dr Sarah Walker from the MRC Clinical Trials Unit, said: “This compelling evidence reinforces the existing World Health Organization (WHO) guidelines, which have been variably implemented in developing countries. The benefits of this treatment far outweigh the risk of side effects, so healthcare workers can be confident in its effectiveness and help save more lives.”

DNA link to schizophrenia found

Schizophrenia is a devastating psychiatric disorder affecting around one per cent of the population. It’s often inherited, with around 85 per cent of schizophrenia sufferers having one or more parents who also have the disease. Now an international collaboration of scientists including a team from the MRC Biostatistics Unit in Cambridge has pinpointed the specific regions on the human genome which are linked with an increased risk of suffering from future schizophrenic episodes. The scientists compared the genomes of 9,294 people with schizophrenia with a control group of 20,050 healthy volunteers. Tiny changes to the DNA at certain locations on the human genome – at chromosomes 6p22.1 in Europeans and 3q26.33 in African-Americans – were found to be associated with schizophrenia. A gene called DNAJC19, which has previously been linked to neurological diseases, is found close to 3q26.33, so it’s thought that this gene might play a role in the disease. One of the scientists involved in the study, Dr Frank Dudbridge, said: “These results demonstrate that it’s possible to detect common genetic variants which are linked to increased risk of developing schizophrenia. Studying these signals should suggest important directions for research on susceptibility to these disorders.”

Treatment delay best for relapsed cancer

A protein called CA125 is released into the blood when certain cancer cells are present. Measurement of CA125 levels in the blood is a useful marker of tumour growth in ovarian cancer. Women who have been treated for ovarian cancer have regular blood tests for CA125 for several years after their first treatment to check for relapse. But new research shows that starting treatment early for an ovarian cancer relapse based on CA125 blood levels alone doesn’t improve chances of survival, compared with delaying treatment until symptoms arise. Scientists compared overall survival between 265 women with ovarian cancer in remission after initial chemotherapy who began second-line chemotherapy after a rise in CA125, and 264 women with rising CA125 whose treatment was delayed until relapse symptoms, such as pelvic pain, appeared. The early treatment group started second-line chemotherapy an average of five months before the delayed treatment group, but overall survival was the same for both, with poorer quality of life in the early group. Principal investigator Gordon Rustin, MRC Professor of Oncology at Mount Vernon Hospital, said: “Given our findings, patients may choose to avoid the inconvenience and anxiety associated with frequent retesting for CA125 levels as well as unnecessary early initiation of treatment for relapse.” The research was funded by the MRC and the European Organisation for Research and Treatment of Cancer.

‘Limpet like’ proteins provide secret to DNA repair

Research has found that a crafty family of ‘limpet-like’ proteins can play a crucial role in repairing DNA damage. This could pave the way to the design of new anti-cancer drugs which target this process. Two teams, one partly funded by the MRC, studied how cancer cells behave to better understand the ways in which cells respond to DNA damage. If this damage isn’t repaired accurately, cancer can be triggered. Both studies independently found that a family of Small Ubiquitin-like Modifier (SUMO) proteins could track down sites in the body where DNA damage has occurred, attach themselves to normal proteins, and then guide them in fixing the faulty

DNA. One of the teams also looked at the role of SUMO in relation to the breast cancer gene BRCA1 which, when faulty, is associated with a high risk of breast cancer. They discovered that after DNA damage, SUMO attaches itself to BRCA1 and 'switches it on', helping to prevent breast cancer from forming. Dr Jo Morris, of the Cancer Genetics Laboratory at King's College London, explained: "This new insight is the first step towards developing drugs which may protect normal cells from the side effects of chemotherapy, or improve the effectiveness of current breast cancer treatments."

Insights into cancer drug resistance

A gene which helps to determine whether cancer cells will respond to anti-cancer drugs has been identified by MRC researchers. Professor Ashok Venkitaraman and colleagues from the MRC Cancer Cell Unit in Cambridge looked at the effects of drugs which work by blocking the rapid division of cancer cells, such as taxol. Some cancer cells are resistant to these effects and continue to divide, but it's not understood how this resistance occurs. Using a technique called RNA interference, the research team tested the effects of over 500 genes on drug-treated cancer cells. They identified a gene encoding the protein UBE2S, which they believe is essential for cell division in drug-treated cells. Although UBE2S was not essential for cell division under normal conditions, once treated with taxol and similar drugs, the cells were unable to divide if UBE2S levels were reduced. Hence the amount of the protein present in cells may determine whether they're able to overcome the effects of drugs which stop cell division. Professor Venkitaraman said: "This discovery not only reveals a new mechanism that controls cell division, but also may help us to use taxol and related drugs more effectively by selecting the patients who are most likely to benefit."

Home treatment of HIV saves more lives

A study of HIV patients in Jinja, south-west Uganda, has shown that treatment of HIV patients at home is just as effective as clinic-based treatment. The study, funded by the MRC and the US Centers for Disease Control and Prevention, recruited 1,453 HIV patients at the same stage of illness and followed them over four years. Of these patients, 859 received anti-retroviral therapy (ART) at home from trained lay workers while the other 594 received ART in a clinic from doctors and nurses. During the first year, the proportion of patients who died was the same in both groups (11 per cent). At the end of the trial, virological failure (failure of ART to keep HIV at bay) was seen in 16 per cent of patients being treated at home compared with 17 per cent of those receiving facility-based care. The home-based model was slightly cheaper to run and much less costly for patients. Professor Heiner Grosskurth, Director of the MRC/UVRI Uganda Research Unit on AIDS, who led the research, said: "Our study shows that community-based treatment with ART can provide greater access to HIV treatment for all those who need it, including patients in remote rural areas who have to travel long distances – at considerable cost – to get to a clinic."

Nuclear protein could hold key to cancer progression

MRC research has discovered that a protein called germinal center-associated nuclear protein (GANP) could be involved in the development of cancers of the immune system such as lymphomas. Dr Vihandha Wickramasinghe and his team at the MRC Cancer Cell Unit in Cambridge found that in healthy cells, GANP is essential for acting as a courier for molecules of messenger RNA (mRNA), carrying them away from the nucleus of a cell to where they can be converted into working proteins. By removing GANP, this process, known as mRNA export, becomes severely disrupted and results in a build-up of mRNA within the nucleus, disrupting the production of proteins which carry out specific functions in the cell. As there are increased GANP levels in lymphoma cells, the findings suggest that there could be a previously unrecognised connection between mRNA export and cancer progression. Commenting on the findings, Dr Wickramasinghe said, "Working out how the GANP protein functions in mammals is an important step in identifying its potential role in cancer. Our results suggest that this process, mRNA export, may be involved in cancer development and progression. We hope that this work will lead to further insights into this disease and ultimately contribute to the creation of new cancer therapies."

Helping the immune system fight breast cancer

The body's own immune system can be a powerful tool in the treatment of cancer since it recognises and attacks tumours and foreign elements. However, the immune system is also

carefully regulated to prevent the body from attacking itself, but can inhibit our immune response to tumours. MRC-funded scientists have found that by stimulating a set of immune system cells that suppress tumours – natural killer T cells – and by depleting cells that inhibit the immune response – regulatory T cells – cancer patient survival rates go up dramatically. In a series of experiments in mice with mammary tumours, the researchers found that when they stimulated the natural killer T cells or depleted the regulatory T cells, survival rates went up from zero to 44 per cent. And when they combined the procedures, over 85 per cent of the mice survived. Furthermore, secondary tumours in the lungs were also reduced. Dr Xiaoning Xu of the MRC Human Immunology Unit in Oxford, who led the research, says: “Our results have shown that this dual treatment approach may have potential for cancer immunotherapy in humans.”

Hormone injections may reverse infertility

Twice-weekly injections of the hormone kisspeptin can restore fertility in some women, MRC-funded research suggests. The team from Imperial College London studied 25 women, 10 of whom had hypothalamic amenorrhoea – a common condition caused by sex hormone deficiency which prevents ovulation, resulting in infertility. The women received injections of kisspeptin or control injections of saline for eight weeks. Regular blood samples were taken to measure levels of luteinising hormone and follicle stimulating hormone, the two sex hormones essential for ovulation and fertility. Women with hypothalamic amenorrhoea remained sensitive to the effects of kisspeptin over the eight weeks of treatment. On the last day of the study, women who had been given kisspeptin injections showed a 16-fold increase in their hormonal response compared with controls. This is the first study to show that kisspeptin administration can lead to an increase in circulating sex hormones over the long term and it may lead to new therapies for women whose infertility is due to low sex hormone levels. Dr Waljit Dhillo of Imperial College London, who led the study, said: “These results are very exciting. Our next step will be to perform a much bigger clinical study with a larger number of participants to see if kisspeptin administration can enable women with hypothalamic amenorrhoea to regain fertility.”

Seeking out the cause of the cough

Research part-funded by the MRC has shown how environmental irritants like cigarette smoke trigger coughing – and how this trigger can be switched off. Scientists from Imperial College London and the University of Hull tested sensory nerves from rodents and humans. They showed that a type of receptor on the nerves, TRPA1, was activated by environmental irritants including acrolein, a key compound in cigarette smoke, and the chemical cinnamaldehyde. The scientists went on to show that inhalation of acrolein in guinea pigs caused coughing, and that the coughing worsened at higher concentrations. Blocking the guinea pigs’ TRPA1 receptors with a drug significantly reduced this coughing response. Professor Alyn Morice and his team at the University of Hull also tested the effect of inhaling cinnamaldehyde in 10 healthy, non-smoking volunteers and found that the chemical induced coughing in all of them. Professor Maria Belvisi, one of the study’s authors, said: “Many people say that certain things in the air can make them cough and we are very excited that we have shown, for the first time, what is probably happening inside the lungs. Now we can start investigating whether we can stop people from coughing excessively by blocking the receptor that triggers it.”

Pandemic over?

‘Swine flu’ was undoubtedly a genuine pandemic in 2009/10. More than 200 countries and territories around the world reported confirmed influenza A (H1N1) infections and over 160,000 deaths have been associated with the disease since the first reports in April 2009. However, it did not wreak the kind of havoc that was initially feared. The World Health Organization (WHO) has four Collaborating Centres for Reference and Research on Influenza, including one based at the MRC National Institute for Medical Research (NIMR) which has analysed more than 3,500 clinical specimens and virus isolates from 55 countries. Full genome sequencing has shown that the viruses are similar across the world, suggesting they are not mutating further. Dr John McCauley, Director of the Collaborating Centre at NIMR, says: “The majority of reported illness has been in people under 30 with relatively mild symptoms. Around two per cent of patients developed more severe illness, many having underlying medical conditions. Low levels of illness in the elderly are probably why we haven’t seen more deaths from this virus.” The Collaborating Centre and other groups at NIMR continue to research influenza. Their findings inform not only

our response to the evolution of the flu virus and possible further outbreaks, but also the way we prepare for pandemic infections in the future.

Unusual case of variant CJD

The brain disease variant Creutzfeldt-Jakob Disease (vCJD) is caused by infectious agents called prions and mainly affects people in their 20s or 30s. Scientists at the MRC Prion Unit have reported a vCJD case in which the affected person had a different variation in the gene coding for prion protein to that which is normally seen in vCJD cases. The finding comes from a Case Report on a 30-year-old man who died from vCJD in 2009. He had a small genetic variation at the PRNP 129 codon, which can code for the amino acids valine (V) or methionine (M). People can be VV or MM (homozygous), or MV (heterozygous). All 200 cases of vCJD identified since 1994 have been MM homozygous – but the man in this report was heterozygous. Professor John Collinge, director of the MRC Prion Unit, who wrote the report, said: "The majority of the UK population have potentially been exposed to Bovine Spongiform Encephalopathy (BSE) prions but the extent of clinically silent infection remains unclear. About a third of the UK population are PRNP codon 129 methionine homozygous. Individuals with other genotypes may be similarly susceptible to developing prion disease after BSE prion exposure, but with longer incubation periods. If so, further cases, which may or may not meet diagnostic criteria for vCJD, would be expected in these PRNP codon 129 genotypes."

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6 – MIDDLE AGE

FEATURE: Cutting cardiovascular risk

Dr Robert Clarke's work focuses on treating and preventing heart disease and stroke, which are still a major problem for people in middle age.

The Clinical Trial Service Unit (CTSU), which is part-funded by the MRC, is based in the elegant Richard Doll Building in Oxford, where airy walkways connect labs and offices. Here, Robert and his colleagues look at well known risk factors for heart disease like smoking and high blood pressure, along with newer risk factors like genetic make-up, in an attempt to better predict risk of cardiovascular disease.

Robert trained as a doctor in his native Ireland, and specialised in internal medicine and cardiology. But while attending a seminar in Cuba, he met the eminent epidemiologist Geoffrey Rose, who changed his career path for life:

"After ten days beside the beach learning from Geoffrey I knew I wanted to spend my life in epidemiology. He understood that even modest differences in the distribution of risk factors within populations can have a substantial impact on reducing the incidence of cardiovascular disease and the number of deaths from it. That was quite a radical concept at the time."

Geoffrey set up the Whitehall study, which tracked the health and lifestyles of 19,000 middle-aged male civil servants living in London. The study was set up between 1968 and 1970, at the height of the UK heart disease epidemic. Thirty years later, Robert and colleagues at CTSU, together with Michael Marmot and Dave Leon at the University of London, traced the records of 18,863 of the men and re-examined the 7,044 surviving participants. The re-survey provided invaluable information on risk factors for heart disease when measured in both middle age and in old age.

A recent analysis of the data led by Robert has uncovered the sobering finding that that middle-aged men who smoke, have high blood pressure and high cholesterol can expect to live 10 to 15 years less than men without these risk factors.

"Being able to communicate the risk as a 15-year difference in life expectancy associated with differences in a few key risk factors had a lot of currency for individuals. It means a lot more to people than it does to be told that you've got a doubling in risk of developing a certain condition," he explains.

Findings from the Whitehall Study and other research carried out at the CTSU have contributed to many public health policies on preventing cardiovascular disease, from banning smoking in the workplace to tackling high blood pressure by reducing salt in the diet. Robert is proud to have been part of it.

“Our work on highlighting the importance of cholesterol, blood pressure and smoking has saved millions of lives worldwide. I don’t claim any personal credit for any of that, but it’s been a privilege for me to be part of that team, and I see my work in that context.”

Heart risk factors can cut 15 years from life

Middle-aged men who smoke, have high blood pressure and high cholesterol can expect to live 10 to 15 years less than men without these risk factors (see profile). The finding is based on data gathered from 19,000 middle-aged male civil servants. The men were recruited to the study between 1967 and 1970, when the UK heart disease epidemic was at its peak. Participants, who were aged between 40 and 69 when they joined the study, filled in a questionnaire on their medical history, smoking habits, employment grade and marital status and had their height, weight, blood pressure, lung function and blood cholesterol and glucose levels recorded. With funding from the British Heart Foundation, the records of 18,863 men were traced and 7,044 surviving participants were re-examined in 1997. At the start of the study, 42 per cent were smokers, 39 per cent had high blood pressure and 51 per cent had high cholesterol. At the re-examination, about two-thirds had quit smoking and the differences in levels of blood pressure and cholesterol had also declined by two-thirds. Lead author Dr Robert Clarke of the Clinical Trial Service Unit in Oxford, said: ‘‘We’ve shown that if you stop smoking or take measures to deal with high blood pressure or cholesterol, it will translate into a 10-15 year increase in life expectancy.’’

Alcoholic disease insights

Scientists led by MRC Professor Ole Petersen have identified the critical proteins involved in alcohol-related pancreatitis which should make it much easier to develop a treatment. Pancreatitis is an inflammatory disease of the pancreas which is often associated with alcohol abuse. When alcohol is broken down, by-products called fatty acid ethyl esters are generated in the pancreas, which trigger excess calcium to be released within the organ’s cells. This in turn activates enzymes which are designed to be released into the gut to digest food. If the enzymes are prematurely activated inside the cell, they digest and damage the cell itself. Working with scientists at the RIKEN Brain Science Institute in Japan, the University of Liverpool team (now at Cardiff University) have identified the importance of a specific store of calcium in the cell to the development of pancreatitis. Their findings show that calcium moves out of this store into the cell through special calcium channels called IP3 receptors types 2 and 3. Professor Petersen said: “There’s currently no specific drug treatment for pancreatitis. Our research has identified the critical proteins responsible for the excessive calcium release, which is where the problem begins, so it will now be much easier to search systematically for specific chemicals for treating the disease.”

Aspirin bleeding risk

Aspirin helps prevent heart attack and stroke in people with established heart disease (secondary prevention), but these protective benefits don’t clearly outweigh the associated risks of bleeding in healthy people (primary prevention), MRC research has shown. Scientists at the Clinical Trial Service Unit at the University of Oxford analysed data from several primary and secondary prevention trials of long-term aspirin use. In the primary prevention trials, aspirin reduced the risk of non-fatal heart attack by about a fifth, or five fewer attacks each year for every 10,000 people treated. But this effect was offset by an increase in bleeds: one extra stroke caused by bleeding and three extra gastrointestinal bleeds each year per 10,000 people treated. In the secondary prevention studies, in which people had a much higher risk of having a heart attack, stroke, or dying from cardiovascular disease, aspirin reduced the risk of suffering these events by about a fifth (150 fewer events each year for every 10,000 patients treated). This major benefit far exceeded the risk of bleeding. Professor Colin Baigent, who led the research, said: “Aspirin clearly benefits people who already have cardiovascular disease, but this research doesn’t seem to justify general guidelines advocating routine use of aspirin in all healthy people with a moderate level of risk for heart disease.”

Nicotine products raise concerns

Nicotine-containing tobacco replacement therapies designed to help people kick their smoking habit could potentially cause mouth cancer, new research suggests. The research was co-funded by an MRC PhD studentship and the Institute of Dentistry, Barts and the London School of Medicine and Dentistry, Queen Mary University of London. The research team investigated the influence of the gene FOXM1 – a gene which is expressed at high levels in many forms of cancer – on mouth cancer and found that it was highly expressed in the progressive stages of the disease. They also studied the effects that different tobacco substances had on human mouth cells and discovered that nicotine – at the same levels as those found in tobacco replacement therapies – raised FOXM1 expression in the cells. Lead author Dr Muy-Teck Teh said: “We’ve shown the FOXM1 gene is activated by nicotine in human mouth cells in culture which raises the possibility that nicotine could potentially increase the risk of mouth cancer. We want to stress, however, that further research is needed to determine conclusively whether this is the case. There is no doubt about the harmful effects of smoking, so smokers should make every effort to quit.”

Improving survival in prostate cancer

Long-term findings from a clinical trial in prostate cancer patients have shown that the drug oral sodium clodronate improves overall survival in men with advanced (metastatic) prostate cancer, but does not benefit men with locally advanced (non-metastatic) disease. The MRC PR05 trial enrolled 311 men with metastatic prostate cancer who were starting or responding to hormone therapy for bone metastases. The men received either oral sodium clodronate or placebo for up to three years. In another trial, MRC PR04, 508 men with non-metastatic prostate cancer receiving standard care (usually treatment with radiotherapy, hormone therapy or both) took either oral sodium clodronate or placebo for up to five years. Findings from PR05 showed a 23 per cent relative decrease in deaths in the group allocated to clodronate. In contrast, PR04 found no evidence that sodium clodronate had any benefit as a treatment to modify the effects of other treatment in men with cancer that had not spread beyond the prostate. Matthew Sydes, Trial Statistician and Project Leader from the MRC Clinical Trials Unit, said: “Bisphosphonate drugs like sodium clodronate may be an important weapon against prostate cancer spreading to bone. We look forward to developing this work further with STAMPEDE, a follow-on trial that will assess zoledronic acid – a newer, more potent drug from the bisphosphonate class.”

Low IQ link with cardiovascular disease

Having a low IQ score is one of the strongest predictors of cardiovascular disease, second only to smoking, according to MRC research. Scientists at the MRC/CSO Social and Public Health Sciences Unit in Glasgow and the Centre for Cognitive Ageing and Cognitive Epidemiology in Edinburgh analysed data collected in 1987 from 1,145 men and women aged around 55 who were followed for 20 years. The participants were part of the West of Scotland Twenty-07 Study, a population study designed to investigate the influence of social factors on health. Data were collected for height, weight, blood pressure, smoking habits, physical activity, education and occupation, and general intelligence (IQ). Statistical assessment of the data showed that smoking was the strongest predictor of developing cardiovascular disease, followed by low IQ. Dr David Batty, who led the research, commented: “Our results suggest that intelligence might be linked with more healthy behaviour, such as taking exercise or abstaining from smoking. It’s also possible that environmental insults accumulated through life, such as illness or poor nutrition, take their toll on IQ. It may be worthwhile for health promotion campaigns to be planned with consideration of individual cognition levels.” Professor Ian Deary, psychologist in the team, added: “We also cannot rule out at this stage the possibility that intelligence and cardiovascular disease share some genetic determinants.”

DNA-repair proteins discovered

Scientists at the MRC Protein Phosphorylation Unit at the University of Dundee have discovered a group of proteins which act like a Swiss army knife to repair damaged DNA in human cells, therefore preventing mutations which can lead to cancer. It is known that cells are able to recognise and repair breaks in DNA, but the mechanisms behind this process aren’t fully understood. During the repair of DNA breaks, branch-points known as Holliday junctions are produced that must be cut in order for DNA repair to be completed. A team of researchers led by

Dr John Rouse has discovered a set of proteins in human cells called SLX proteins which tether together a group of enzymes. The enzymes can cut Holliday junctions during the repair of DNA – acting like a Swiss army knife with several blades. The research showed that cells which do not have the SLX proteins are unable to repair DNA breaks, leading to irreversible damage of the DNA and cell death. Dr Rouse said: “Now that we have identified these proteins and the role they play in repairing DNA we can start to develop drugs that target these processes. This could have a significant effect in cancer, primarily by helping to enhance the efficacy of drugs used in chemotherapy treatments.”

Screening halves aneurysm deaths

Abdominal aortic aneurysm (AAA) is a dangerous bulge in the lower part of the aorta, one of the major arteries which carries blood away from the heart. Results from a 10-year clinical trial has shown that screening men for AAA using ultrasound could prevent about half of all aneurysm-related deaths if screening were to be rolled out nationally. The study compared 67,770 men aged 65 to 74, half of whom were invited to a one-off ultrasound screening. The other half, the controls, were not offered screening. If the screening picked up an AAA, the affected men were monitored and were offered surgery if they met pre-defined criteria. Results showed that screening significantly cut the risk of death from AAA in the long-term, and that this benefit was maintained for up to 10 years. There were 155 AAA-related deaths in the screened group and 296 deaths in the control group. The screening programme was also shown to be highly cost-effective. Professor Simon Thompson, Director of the MRC Biostatistics Unit in Cambridge, who led the research, said: “As a result of these findings and the trial’s follow-up, a national screening programme for men aged 65 in the UK began in spring 2009, which should achieve full coverage of the country over the next few years.”

Kidney artery treatment ineffective

Revascularisation – a treatment which opens up blocked blood vessels – has no benefit for most patients suffering from the kidney condition atherosclerotic renal artery stenosis, research part-funded by the MRC has found. In this disease, fatty plaques develop on the inside of the main arteries to the kidneys, affecting blood flow and kidney function. The international Angioplasty and STenting for Renal Artery Lesions (ASTRAL) trial was the largest to date of treatments for this condition. It was coordinated by the University of Birmingham Clinical Trials Unit. The study investigated, in 806 patients, whether revascularisation treatment and medical therapy had any benefit compared with medical therapy alone. Findings suggested that revascularisation does not stabilise or improve kidney function and that the risks of using the treatment may outweigh the benefits. Professor Keith Wheatley, from the ASTRAL coordinating centre at the University of Birmingham Clinical Trials Unit, said: “This study clearly illustrates that patients with renal artery stenosis remain at high risk. During the course of the trial, a number of patients developed end-stage renal disease and needed dialysis, or had a heart attack or stroke, and almost half of the patients had died by five years. Therefore, more research is needed in this disease area to find more effective treatments.” The research was co-funded by Kidney Research UK and Medtronic.

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7 – GETTING OLDER

FEATURE: Unravelling the genetics of Alzheimer’s

Professor Julie Williams’ research has uncovered two new genetic links to Alzheimer’s disease.

Julie works in the MRC Centre for Neuropsychiatric Genetics and Genomics at the University of Cardiff. Here, scientists are trying to understand the genetic basis of neurological disorders which place a burden on society – from dyslexia to multiple sclerosis.

“Genetics has really taken off in the last 20 years and I was lucky enough to begin my research career just when things were really starting to blossom,” explains Julie. “It’s a very fast-moving and exciting field with new advances in technology almost every year, so it’s quite challenging to keep up with it all.”

One of Julie’s particular research interests is trying to understand and pinpoint the biological processes that go wrong in Alzheimer’s disease. As part of an international collaboration of

scientists, she has discovered two new genes, CLU and PICALM, which make people more susceptible to developing the disease.

“Over the years we’d found a few promising genetic variants, but we hadn’t been able to replicate the findings in other studies to prove there really was a link between the genes and Alzheimer’s disease,” explains Julie.

“So we bit the bullet and pulled together 16,000 cases of Alzheimer’s and a comparative group of healthy volunteers – the biggest ever genome-wide association study that had been done in this disease. And we found very strong evidence that two genes were associated with a risk of developing the disease, and that the pattern persisted across the very large sample we were looking at.”

So what was it like to make such an important discovery?

“We’re a pretty cynical lot in genetics, and having had so many disappointments in the past, you tend to disbelieve findings when you see them. So my first thought was to wonder what we’d done wrong,” says Julie. “But the penny finally dropped when we replicated the finding in other studies and also because the gene has a similar function to another Alzheimer’s-associated gene, ApoE. So the secret was, as we suspected, in having really powerful sample.”

Now that the genes have been identified, the scientists need to work out exactly how they contribute to the disease, which will eventually guide the development of treatments to slow down or prevent Alzheimer’s.

Julie explains: “One of the genes is centred on how the brain transports and processes cholesterol molecules. And since we did that study we’ve found two other Alzheimer’s disease genes associated with a process called clatherin-mediated endocytosis – which is basically a process the cell uses to bring large molecules into the cell and transport them to different parts of the cellular ‘machinery’ to be processed.”

“These findings give us a lot more focus for where we should be targeting drugs for Alzheimer’s disease in future. It also gives us the potential to reduce risk factors for the disease, so that we can reduce the number of cases of Alzheimer’s or perhaps delay its onset to give people another 10 years of healthy life.”

So what inspired Julie to take up a career in medical research?

“I’ve always wanted to do it. I remember having a bit of a nerdy moment at the age of about eight, going into WH Smith and buying a book on the jottings of Faraday and thinking wouldn’t it be great to find out something that nobody else knows – what a fantastic way to spend your time.”

“If one day I could see new understanding and knowledge coming from the genes we’ve discovered leading to a treatment that would be fantastic.”

Two new genetic links to Alzheimer’s found

Two genetic variants which appear to increase the risk of developing Alzheimer’s disease have been identified (see profile). A major international study analysed the genes of over 16,000 people over two years – the largest genome-wide association study (GWAS) of Alzheimer’s disease carried out to date. By comparing variations between the genes of Alzheimer’s patients and healthy volunteers on a mass scale, the researchers discovered the susceptibility genes CLU and PICALM. When these results were put together with another GWAS carried out in France, a third susceptibility gene, CR1, was also identified. Previously only one gene, APOE4, had been clearly identified as a potential genetic risk factor. Lead author of the study, Professor Julie Williams of the MRC Centre for Neuropsychiatric Genetics and Genomics in Cardiff, said: “This research is changing our understanding of what might cause the common form of Alzheimer’s disease and could provide valuable new leads in the race to find treatments. If we can combat the detrimental effects of these genes, we estimate it could reduce the chances of people

developing Alzheimer's by almost 20 per cent." The study was supported by several funders including the MRC, the Wellcome Trust, the Welsh Assembly Government and the Alzheimer's Research Trust.

FEATURE: Research into healthy old age

Eddie Holden, 84, is part of an MRC-funded study of older people, and has agreed to donate his brain to research when he dies.

Eddie is a retired cabinet-maker and celebrated his 60th wedding anniversary with his wife Mary this year. He's a loquacious man, full of tales of his time as a paratrooper during the Second World War, when he earned the nickname 'Fireworks Holden' for his habit of firing tracer bullets to find his way through the Malaysian jungle. He's a perfect example of healthy and active old age. Still firm on his feet, he regularly attends meetings with his old regiment and he's even got his own website full of musings and poems.

For the last 18 years, Eddie's been part of the MRC Cognitive Function and Ageing Study (CFAS) which looks at the health and cognitive function of older people. CFAS has collected a huge volume of data since it began in the 1980s, which allows researchers to study dementia, depression, physical disability and life expectancy in the older population. Eddie explains how he first got involved and what motivated him to do it:

"I got a letter in the post not long after I'd retired, so I phoned up to see what it was all about. My wife's mother had dementia and it's a terrible thing to see a person with a vibrant brain suddenly just go, so they don't know what they're doing anymore. So I thought if I could do something about it by signing up for a research study then let's go for it."

The research involves regular interviews and tests to measure Eddie's cognitive skills and to gather data about his lifestyle and health. He describes a typical visit:

"The interviewer brings a book with different pictures in it, shoes back-to-front and that sort of thing, and you've got to say what they are. Then she'll tell you a story and ask you about it a few minutes later – well, you keep thinking about it and you think what on earth did she tell me?"

"My worst thing is when she asks me to subtract seven from a number. But one thing I was good at is when she asked me to name as many animals as you can in a minute. I love African wildlife, so I went through the lot from elephants to wildebeest and she said she'd never heard anyone do so many!"

CFAS also includes neuropathology studies, aimed at improving the diagnosis of different types of dementia through looking at both diseased and healthy brain tissue. Eddie is one of many participants who have agreed to donate their brain to CFAS after death. Some may feel a little squeamish about the thought, but Eddie is matter of fact:

"I'm one of those practical people who thinks that when you're buried, all that's going to be left of you is your bones. The rest will go to waste. So why not let somebody have the body for research. That's the way I look at life – I've seen too much of life being wasted.

I'm in my 80s, but in by younger days people who worked on the land were old and dying at the age of 60. Now we've got 20 years extra in life because of all the medical advances that have happened. So I thought if someone can use my brain then I'd go for it – I wont know anything about it, I'll be dead."

Verbal fluency improving in the elderly

Elderly people in England are becoming more verbally fluent, and have the ability to recall just over one more word per minute than elderly people of earlier generations, according to research from the MRC Cognitive Function and Ageing Study (CFAS) (see profile). Results from a neuropsychological test which asks people to name as many different animals as they can within one minute were compared between two groups of people aged over 65. The first group, containing 9,458 people from the CFAS study, was tested in 1991, and the second group,

comprising 5,196 people from the English Longitudinal Study of Ageing, was tested in 2002. A group of 680 East Cambridgeshire participants aged 65 to 69 years in 1991 were also compared to an independent cohort of 600 people of the same age examined in 1996. Semantic verbal fluency increased by 1.1 words per minute in England between 1991 and 2002 and a similar increase was also seen between the East Cambridgeshire groups. Dr Fiona Matthews of the MRC Biostatistics Unit in Cambridge, who co-led the research, said: "Education and brain reserve are potentially important in protection from dementia in the older population. This evidence of a small improvement in fluency may provide some grounds for optimism about the potential to influence risk for dementia at particular ages. Whether this is the case will be tested in the new MRC CFAS II, which is now at the field work stage."

Preventing falls in dementia sufferers

Older people with dementia are eight times more likely to have a fall than their healthy counterparts without dementia, according to research part-funded by the MRC. They also recover less well after a fall. Falls not only cause injuries, but they also increase illness and deaths, and inflate the cost of care. In identifying the risk factors for falls, the study makes it possible to develop more tailored and effective ways of treating dementia sufferers. The research compared 140 people aged over 65 with mild to moderate dementia with 39 healthy volunteers. Both groups kept a diary of how many times they fell during the course of a year. Dr Louise Allan of the Wolfson Research Centre in Newcastle, who led the study, said: “In the light of our research, we believe that intervention trials to prevent falls in mild to moderate dementia should now be a priority. A different approach may be needed from the one used for people without dementia. Carers should focus on identifying risk factors for falls like orthostatic hypotension (dizzy spells) and depression and managing their treatment, as well as encouraging physical activity in people who do not have severely impaired gait and balance.”

IQ link between poverty and life expectancy?

Research has shown that IQ, a measure of a person’s ability to reason and problem solve, may have a role in the differences in cardiovascular disease and life expectancy seen between people from different socio-economic backgrounds. The scientists analysed data on IQ, socio-economic status and heart disease from a group of 4,289 former soldiers in the USA. They set out to pinpoint what it is about people of lower socio-economic status that confers a higher risk of cardiovascular disease and shorter lifespan. They found that IQ explained more than 20 per cent of the difference in mortality between people from disadvantaged backgrounds compared with those from more affluent backgrounds. This finding was independent of known heart disease risk factors such as smoking and obesity. The research was carried out by Wellcome Trust-funded Fellow Dr David Batty and colleagues from the MRC/CSO Social and Public Health Sciences Unit in Glasgow and the University of Edinburgh Centre for Cognitive Ageing and Cognitive Epidemiology. Dr Batty said: “Our findings suggest that measured IQ doesn’t completely account for inequalities in health, but it may strongly contribute to them. Public health messages on factors like diet, exercise and smoking – which are often conflicting and confusing even to knowledgeable people – could be simplified, and efforts to reduce socio-economic inequalities should continue in a broad way.”

Zebra finch earns its stripes

Sequencing the genome of a tiny songbird, the zebra finch, has shed light on the genetics behind human learning and memory, as well as fertility. The collaborative study involved experts from the MRC Functional Genomics Unit in Oxford, and from 24 other research teams from around the world. Songbirds share an important trait with humans: they learn to converse with each other. By comparing the genome of the zebra finch with that of the chicken, which does not learn to sing, the scientists were able to pinpoint the genes involved in vocal learning. One of the research team, Professor Chris Ponting of the MRC Functional Genomics Unit, said: “Normally we think of genomes providing a blueprint for making only proteins, but there are indications here that song stimulates the zebra finch to turn off the production of even more exotic molecules called RNAs.” The next stage will be to investigate the role of RNAs in learning and memory for the zebra finch, or even humans. The research has also revealed a genetic component to zebra finches’ sperm length and speed. It is now possible to identify genes that explain these differences in fertility, so the scientists think it is likely that the same genes will have similar effects in humans.

Maintaining brain power

Understanding what happens to brain cells as we get older is fundamental to tackling diseases such as Parkinson's and Alzheimer's. Like most cells in the body, brain cells get their energy from mitochondria – like tiny batteries, these parts of the cell store and release energy when it's needed. Researchers at the Centre for Brain Ageing and Vitality (CBAV), based in Newcastle University's Institute for Ageing and Health and funded by the cross-research council Lifelong Health and Wellbeing initiative, are studying mitochondria to see what role they play in ageing and related neurological diseases. Mitochondria are special because they have their own DNA, different to the DNA in a cell's nucleus. But mitochondrial DNA is just as prone to changes that can stop cells working properly. The CBAV team has identified the types of changes that occur in mitochondrial DNA in a part of the brain associated with Parkinson's disease. Lead researcher and CBAV director Professor Doug Turnbull says: "Changes in mitochondrial DNA can interfere with the way brain cells work. By looking at why and how these changes accumulate, we are learning what makes some cells particularly vulnerable. Our aim is to keep the batteries at full power and help prevent diseases like Parkinson's."

Understanding hearing loss

About one in five of us will experience some form of hearing loss in our lifetime, and it gets more likely the older we get. Technological advances of the last century have helped develop ever more sophisticated hearing aids, but there are many aspects to hearing loss and there are big differences in individuals' experiences. The MRC Institute of Hearing Research has a Scottish section based in Glasgow Royal Infirmary which is co-funded by Scotland's Chief Scientist Office. Research there concentrates on hearing impairment in adults, looking at what hearing loss means to someone and what benefits hearing aids can provide. Dr Michael Akeroyd and his colleagues study our ability to identify which direction sounds are coming from and how different kinds of background sounds affect this and other aspects of listening. Their research has shown that we struggle more to hear what someone is saying against a background of other voices compared to an equivalent background of noise. Dr Akeroyd says: "Interestingly, the effects were about the same for everyone. These findings are crucial in understanding how background sounds make listening harder and what distinguishes those situations that are difficult for everyone from those that are made worse by hearing impairment. This knowledge will help to inform the next generation of hearing aids."

Predicting Alzheimer's disease

MRC Senior Fellow Professor Nick Fox has used techniques he developed for measuring brain cell loss to predict whether people with mild cognitive impairment will go on to develop Alzheimer's disease. Using a series of Magnetic Resonance Images of patients created over time, Nick and his team at the Institute Of Neurology at University College London have shown that rates of brain loss correlated with clinical decline in these patients. People with higher rates of loss were shown to be more likely to suffer a decline in cognitive ability and to be diagnosed with Alzheimer's disease over the following year or two. The technique is now also being used to monitor the progression of brain loss in trials of potential treatments. Nick explains: "Healthy brains are very different from each other in terms of size and shape. However, increased losses over time appear to be a diagnostic marker of the onset and evolution of a neurodegenerative process such as Alzheimer's disease. The key to sensitive detection of these losses is to match each person's serial scans precisely. We hope that these techniques may help in the search for therapies which slow the disease's progression. Ultimately we'll need markers that can diagnose Alzheimer's as early as possible so that we can treat the disease in its earliest stages."

Mountain dwellers may live longer

A study of octogenerians in Northern Spain suggests that people living at higher altitudes may have genetically adapted to survive the harsher environmental conditions – and that this adaptation may also help them to live longer. The scientists looked at the DNA inside mitochondria – the power-houses which generate energy inside cells. Unlike the random mix of DNA in the nucleus of our cells that we inherit from both parents, mitochondrial DNA (mtDNA) is passed on unchanged from mother to child through the generations. mtDNA is also particularly susceptible to a type of damage called oxidative stress, and less of this damage has been linked with increased longevity. Two groups of over-85s of a similar genetic and cultural background

were studied– 69 people from villages in the Pyranees at around 1,400m altitude, and 69 from Ebro's Valley at around 300m altitude. Analysis showed that the Pyranees group were more likely to have a variant of mtDNA called haplogroup J2 than the Ebro Valley group, suggesting that it may provide a survival advantage. The mtDNA of the Pyranees group was also in a better state of repair than the Ebro group, suggesting that haplogroup J2 may protect mtDNA against oxidative stress-related damage. Dr Thomas von Zglinicki of Newcastle University, one of the authors of the study, said: "Our results suggest that a person's genetic background and the environment they live in may have an effect on longevity."

INDEX

The MRC Strategic Plan 2009 – 2014, Research Changes Lives, set out the direction for our research. Seven Ages, the MRC's Annual Review 2009/10, highlights some of the research discoveries we have made over the last year since the plan was launched.

This index show the stories of achievement selected for our 2009/10 annual review categorised by the MRC's strategic aims.

The achievements highlighted form a fraction of the many discoveries our scientists have made, but they give a taster of how the MRC is already delivering against its objectives.

Aim 1 – Picking research that delivers: Setting research priorities which are most likely to deliver improved health outcomes

Vegetative patient communicates by thought
Zebra finch earns its stripes

Aim 2 – Research to people: Bringing the benefits of excellent research to all sections of society

Aspirin bleeding risk
Assessing pain in premature babies
Breastfeeding curbs later obesity
Cooling prevents birth asphyxia brain damage
Fine tuning childhood cancer treatment
Hope for muscular dystrophy patients
Improving survival in prostate cancer
Kidney artery treatment ineffective
Pandemic over?
Screening halves aneurysm deaths
Solving the structure of the ribosome
Surviving the odds
Treating glue ear with steroids not cost effective
Understanding cell death
Unlocking the secrets of the developing heart

Aim 3 – Going Global: Accelerating progress in international health research

Cheap antibiotic halves HIV deaths
Home treatment of HIV saves more lives
Predicting mother-to-baby infection
Prioritising HIV therapy over testing saves more lives
‘Resistance gene’ offers insights into CJD
Simple solution to the spread of malaria

Aim 4 – Supporting Scientists: Sustaining a robust and flourishing environment for world-class medical research

Early sleep problems affect teenage brain
Heart risk factors can cut 15 years from life
Low IQ link with cardiovascular disease
Male fertility problems linked to maternal stress
Mountain dwellers may live longer
Verbal fluency improving in the elderly