

Max Perutz
 Science
 Writing
 Award 2014

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Christoffer van Tulleken – Winner
University College London

Ex Africa Semper Aliquid Novo

The most important chicken in medical history was a Plymouth Barred Rock Hen from New York. The chicken's name is not recorded but in 1911 she was brought by her owner to a young pathologist called Peyton Rous because of a large tumour growing out of her neck. Rous subsequently performed a series of experiments so elegant it is hard to believe he didn't know what he was looking for. He showed that the filtered extract from the tumour, containing no actual tumour cells, could cause more tumours in another chicken. Rous had discovered a type of virus that can cause cancer called a retrovirus.

At around the same time, in the dense tropical forests of the Congo Basin, another retrovirus managed to cross from a single chimpanzee to a single human and start a journey that would spread to 60 million people. This virus announced itself to science without fanfare: a brief report in 1981 documented five gay men from Los Angeles all with similar and unusual signs of immune system collapse, including cancers. The paper reads with the dispassionate tone characteristic of medical case reports, the deaths of two of the men are recorded with minimal eulogy, but it was to become one of the most significant medical announcements of the century. This was how the epic narrative of the Human Immunodeficiency Virus (HIV) began in our collective psyche.

But, while the virus had been crossing species and continents, science had also been making vast strides without any idea of how important those advances would be. When the epidemic exploded across geographical and social boundaries in the 1980s we had a head start, thanks to the work that started with Peyton Rous. Because we had gained an understanding of the biology of other viruses highly effective treatments for HIV were developed in less than 20 years from its discovery.

My research aims to contribute to this understanding of HIV biology which has so far been crucial in developing drugs. It takes place in small tubes and dishes in a lab and it's a long way from patients and from developing treatments.

It revolves around the unanswered question of how HIV destroys the immune system. Considering that HIV is probably the most studied and understood infection in history this is a huge gap in our knowledge.

Like all viruses HIV sits somewhere between a living organism and a collection of chemicals. It is a package of protein with a little bit of genetic code. Viruses can not reproduce by themselves, they infect other living cells and hijack their machinery to replicate. HIV specifically infects certain vital cells in the body's immune system and, over several years, as these cells die, the immune system weakens and patients succumb to diseases like the rare cancers and pneumonias first noticed in Los

Angeles. No one knows exactly how or why these immune cells, die but some preliminary data implicates the involvement of the machinery that human cells have for repairing damaged DNA.

This machinery, made up of proteins, is of great importance to HIV because, along with all other retroviruses, it actually inserts its genes into the DNA of the human cell. The viral genes become part of your own genetic code. In order to do that HIV needs to cut the long chemical string of the cell's DNA and insert its own. The cut is then repaired using the cells own DNA repair proteins. It may be these same DNA repair proteins which cause the cells to commit suicide leading to a gradual loss of the cells.

I am trying to understand how HIV interacts these DNA repair proteins by removing them one by one from cells and observing the effects. By getting rid of a protein interacting with HIV are we able to prevent cell death and if so might it be possible to design a drug that could perform the same task.

Superficially, the value of my research may be that it contributes to drug development which will better treat HIV. But justifying research by presuming the outcome is illogical almost to the point of absurdity. If I knew what was going to happen it would not be research. I may find that I am using HIV as a tool to better understand DNA repair in human cells and this may help with treating cancer. Or the results may have no applications in HIV or cancer, but prove vital for a new epidemic as yet unimagined just as experiments on the filtered extract of a chicken tumour have proved so directly important during the HIV epidemic.

Wiebke Nahrendorf – runner up
NIMR

Vaccines and volunteers- preventing malaria with a cup of mosquitoes

Nijmegen, The Netherlands. It is cold and a slight drizzle makes it uncomfortable to roam the campus of the Radboud University. It seems like an unlikely place to study a tropical disease. And yet behind the walls of the university medical centre an angry buzz emerges from cups, which look just like the ones for take-away coffee- only with a bit of white netting on top. The source of the buzzing: fifteen mosquitoes in each pot. These mosquitoes are infected with the deadliest parasite on earth: *Plasmodium*, which causes malaria. And they are hungry. For human blood.

In the waiting room two dozen volunteers are about to be called in to put their left arm on to a cup filled with these mosquitoes, which, while sucking blood, will infect them with malaria. - But HOLD ON! That seems like a terrible idea! Of course, these brave volunteers knew what they were in for and there is a whole battalion of dedicated doctors to check on them 24/7 and treat them if necessary, but still... Why are we infecting healthy Dutch people with malaria?

Malaria is a leading cause of death in many countries of Africa. Almost half of the world's population is at risk of getting the disease. The tiny, single-cell *Plasmodium* parasite is unfortunately very successful in evading drugs and efforts to get rid of the mosquitoes that pass it on, because it changes its shape and habitat all the time. After injection of a few parasites into the skin during a mosquito bite- *Plasmodium* first heads to the liver, where it cunningly hides causing no signs of illness. In the liver the parasite builds up strength to initiate the real threat: the infection of red blood cells. Parasite-infected red blood cells can cause flu-like symptoms: headaches, sweats and fever. Things also get worse quickly: many red blood cells get destroyed by the malaria parasite and infected red blood cells stick together and block blood vessels. These blockages, particularly in brain, kidneys and lungs, lead to seizures, unconsciousness and death. Parasites in the blood can also be taken up by a biting mosquito, ready to be passed on to another person, creating a cycle.

Malaria is most dangerous to the people who never had it before: especially for young children in Africa but also for travellers from Europe. The World Health Organization estimates that 482,000 children under the age of five died from malaria in 2012. Scientists all over the globe agree that the most effective way to wipe out malaria is to develop a vaccine. This has unfortunately been proven to be much more difficult for malaria compared to other less complicated diseases like Tetanus.

On our quest to find out how to make an effective vaccine against malaria, we need to understand how the immune system combats the disease. And this is where our brave Dutch volunteers come in; because we have found a way to protect them from malaria by exposing them to mosquito bites. Once a month our volunteers come into the clinic and put their arm on to a cup with fifteen malaria-

infected mosquitoes. At the same time we give them a tablet of an antimalarial drug, which kills the parasite as soon as it reaches the blood stream. After the third round of bites-and-drug we wait for five months, before infecting the volunteers again- this time without the drug as a safety net. And amazingly, they do not show any signs of illness from malaria and have no parasites in their blood stream! This means that *Plasmodium* was stopped in the liver. Why does this matter? If we could design a vaccine that protects in the same way, it would have a dual role in preventing malaria; keeping parasites out of the blood means the person will not get sick and there will be no parasites for a mosquito to pick up, breaking the cycle. So vaccinated people would not only protect themselves from the disease, but also help to reduce the amount of infected mosquitoes in their area. Both effects together would finally put a hold on malaria.

It is of course not very practical to ship millions of take-away coffee cups full of mosquitoes to protect everybody in Africa the way we did with our volunteers. But by studying how their immune system kills the parasite to protect them from malaria, we can take essential steps towards the development of a safe and effective vaccine.

So maybe it is not so crazy that Dutch volunteers put their arm on a pot with hungry mosquitoes, because they contribute to the huge efforts made worldwide to find a malaria vaccine and save millions of lives.

Edward Parker – commended
Imperial College London

Gut reaction: the impact of intestinal infections on polio vaccination

The Global Polio Eradication Initiative was never meant to last this long.

In 1988, when the campaign was launched, there was considerable optimism that polio would not see the end of the century. Although this deadline has long since passed, the progress made by the eradication initiative should not be underestimated: in what is arguably the greatest onslaught against a disease in history, polio has been reduced from an infection with a global distribution, responsible for 350,000 cases of paralysis each year, to one that is on the brink of extinction. Just 223 cases of the disease were reported in 2012 – the lowest number on record.

But polio is a wily foe. Despite exhaustive vaccination campaigns, the virus has never been eliminated in Pakistan, Afghanistan, and Nigeria. What's more, polio has recently been on the move. After cases in Ethiopia, Somalia, Cameroon, Equatorial Guinea, Syria, and Iraq, in May 2014 the World Health Organization declared the spread of polio to be an international public health emergency.

Why has polio proven so resilient in the face of eradication efforts? Certainly, the problem is far from straightforward. The eradication campaign has had to contend with huge logistical challenges, civil unrest, vaccine boycotts, and a recent upsurge in violence against healthcare workers.

There are also limitations to the key weapon of the campaign's armoury: the oral poliovirus vaccine (OPV). First developed by Albert Sabin in the late 1950s, OPV is, in many ways, an ideal vaccine. It is cheap, easy to administer (just a few drops on the tongue will do), and capable of protecting against each of the three types of poliovirus.

However, since the earliest trials of OPV, it has been apparent that children living in tropical, low-income countries are less likely to respond to immunisation than those in industrialised settings. While each dose of OPV will protect roughly 65% of children from type 1 paralytic disease in high-income countries, the same vaccine protects just 13% of children in India.

It is this phenomenon that my research is concerned with. Unfortunately, there is unlikely to be a simple explanation. Malnutrition, interference by maternal antibodies, and deficiencies in micronutrients may all contribute to the impaired performance of OPV in low-income countries. However, there is a good reason to suspect that intestinal pathogens may be important, and it is this possibility that I am investigating.

The hypothesis is certainly persuasive: infants living in tropical countries are exposed to a multitude of intestinal infections. If these infections activate the gut's immune system at the time of immunisation,

the vaccine viruses may be unable to induce a proper immune response. Like attempting to make a safety announcement at a rock concert, the message will simply be lost in the noise.

We are not the first group to consider the issue. In fact, at the First International Conference on Live Poliovirus Vaccines, held in 1959, Sabin himself presented several cases in which the response to his new vaccine seemed to be impeded in individuals infected with other intestinal viruses at the time of vaccination.

However, more recent studies have failed to paint a clear picture – while some have supported the interfering influence of intestinal pathogens, others have refuted these effects, and in the last decade or so, the question has dropped out of fashion.

But the tools of science are ever changing. Lab techniques developed in the last few years have opened up new ways of exploring the relationship between intestinal pathogens and OPV. With this in mind, I donned my lab coat and – working alongside collaborators in southern India – put to use a new molecular test that enables more than 30 different pathogens to be detected in stool samples in a matter of hours (to put this in context, in Sabin's day, the detection of a single virus could take up to 2 weeks).

Using this tool, we are examining the frequency of intestinal viruses, bacteria, and larger parasites (such as nematode worms) among Indian infants at the time of vaccination. In doing so, we hope to gain a detailed picture of the extent to which individuals who fail to respond to OPV experience a greater burden of infections.

The implications of this research extend beyond polio. Like OPV, oral vaccines against rotavirus and cholera have proven to be less dependable in low-income countries. Our immune response to these vaccines may well be shaped by similar factors.

More than half a century has now passed since the first doses of OPV were administered. Despite considerable effort, we remain unsure as to why the vaccine performs better in some regions than others. What is clear is that OPV and other oral vaccines face unique obstacles precisely where they are needed most.

Each step we make towards understanding the nature of these obstacles is a step towards overcoming them.

Jane Patrick – commended
Wellcome Trust Sanger Institute

Fishing for treatments for inherited muscle diseases

Which muscles are you using right now? Perhaps you're absent-mindedly shaking a leg or munching on food? At the very least, I expect you're breathing. The chances are you haven't even noticed your muscles working. Most of us take our muscles for granted, but for a child born with an inherited muscle disease, such as myopathy or muscular dystrophy, it isn't that simple.

These children have a faulty copy of a gene meaning their muscle doesn't develop or work properly, so they have weak or degenerating muscles from birth or a very young age and often developmental problems too. The problem is there is a vast number of different genes that can be affected, some unique to one patient, which gives a huge range of symptoms and makes it difficult to find an effective treatment. Recently scientists have used DNA sequencing technology to identify new genes linked to inherited muscle disease by looking for the faulty genes in affected children. The question is, how can we use this list of genes to help to find a treatment?

In my PhD research I'm trying to do this by using genomics, the study of all of the genes in an organism, along with zebrafish. You might be thinking that fish are nothing like humans, but actually zebrafish are extremely useful for research in genetics and ideal for investigating muscle. Unlike with mammals, the fish eggs are laid before fertilisation and develop entirely outside the mother. They have a transparent 'eggshell' meaning you can observe all stages of development without interfering, almost like having a window into a womb. Usefully, the muscle is very obvious during development. It forms evenly spaced chevron shapes down the embryo, like those lines on the motorway that tell you how big a gap to leave behind the car in front. When zebrafish muscle doesn't form properly this arrangement is disrupted and the pattern is often very obviously disorganised.

In my research, I'm trying to disrupt the same genes in zebrafish as those that are affected in children born with muscle diseases. Since the Human Genome Project sequenced, or 'read', the entire DNA sequence of humans many other organisms have had their DNA sequenced too, including the zebrafish. Most genes that cause muscle problems in humans have a partner in zebrafish and we can manipulate them to understand their function. I'm using a technique called CRISPR (pronounced "crisper"), which scientists developed from a mechanism found in bacteria. It involves targeting an enzyme to cut the DNA at a chosen position to prevent a specific gene from working. I inject the instructions to make this enzyme, along with directions to the correct DNA section, into zebrafish embryos just after fertilisation. At this point just one single cell has formed, so my injection mix is taken into the cell and passed onto subsequent cells as they divide to form the embryo. I use this to make zebrafish with the same faulty gene as human patients and then look at how their muscle develops, to model the human disease.

Zebrafish with muscle defects have moving problems as they develop, which you can see by poking their tail and watching how well they swim away. I also look at the arrangement of different muscle components using antibodies, which can attach to a specific protein and then fluoresce under a microscope, to highlight the arrangement of the protein within the muscle and show any differences from a normal healthy embryo.

As well as looking at the muscle structure I'm trying to probe deeper into the molecular changes in my fish by using the rapidly-advancing techniques of genomics. I measure how many products of every single gene are being made in my disease model fish and compare these to healthy fish, to look for differences that could be caused by the faulty gene. I'm hoping to identify genes that are used more or less by the embryo as the muscle development goes wrong. Some of these may be the same across a number of the model fish despite them having different faulty genes originally, which could reveal common features amongst the genetic spectrum of diseases. They could provide exciting new targets for treatment that would be effective for many patients, despite differences in the exact genetic cause of their diseases.

So why do I think my research is important? Inherited muscle diseases are rare compared to diseases such as cancer, heart disease and diabetes, but for the children and families affected by them the numbers don't matter. What matters is the difference between walking and being confined to a wheelchair, between breathing effortlessly like you or me and struggling with each breath, perhaps the difference between life and death. It's the difference between that absent-minded leg shake and a lifetime of struggling to move.

Thomas Hall – commended
Newcastle University

Brain-computer interfaces: science fiction or science future?

I visit Charlotte on a Saturday morning, arriving to the smell of fresh baking. After seeing her grandchildren, we head to the village hall for a surprisingly competitive monthly bake-off. But I'm not here just for tea and cake. A year ago, aged seventy-three, Charlotte suffered a stroke, leaving her wheelchair-bound and her right arm almost completely paralysed. One day she was working as a freelance architect; the next, she was unable to even write or dress herself.

But six months later, in 2034, Charlotte became one of around two hundred patients worldwide fitted with a revolutionary new medical device called a 'brain-computer interface', or BCI.

Back at home, she shows me the scar on her scalp where doctors implanted thousands of microscopic electrodes in the part of her brain that controls her right arm — the part that was 'disconnected' by the stroke.

A tiny cable runs from her scalp, under her skin, to the BCI, which appears as a bump on her chest, like a pacemaker. From there, a cable runs to another set of electrodes implanted in Charlotte's spinal cord.

The device charges overnight, but it's switched off now, and Charlotte's paralysed right arm lies awkwardly across her lap. She switches it on, and suddenly her arm comes to life. It's jerky for a moment, but the movement soon becomes quite natural.

She reaches for her tea, and explains how it works. The BCI records the tiny electrical signals produced by her brain when she 'thinks' about moving her arm. It translates this information into electrical impulses that are delivered, painlessly, to her spinal cord, activating the nerves to her arm and making her muscles contract.

The BCI has been life-changing. She's not yet back to work, but can dress herself, use a keyboard and bake again. She can't imagine what life would be like without it.

OK, so that was science fiction! But it's very possible that within 20 years Charlotte's scenario will be reality. Across the world, scientists are working hard to solve the remaining challenges.

As a neuroscientist, my research focuses on one of the key challenges: studying which brain signals would be best for controlling such a device.

The technology already exists to record brain signals from the motor cortex (the part of the brain controlling dexterous arm movements) over many months. But for most patients, a BCI needs to work for decades, otherwise the benefits don't justify the risks of surgery.

As well as having a long lifespan, the brain signals also need to be stable. If they constantly changed, Charlotte would wake up each morning not knowing how to control her arm.

The problem is that the brain reacts to having electrodes implanted in it. The 'foreign' material leads to microscopic scarring (called gliosis). Over time, this causes neurons to die, or be pushed away from the electrode. Currently, we can't record from individual neurons indefinitely.

With my supervisor, Andrew Jackson, I am studying a different type of brain signal, called the 'local field potential' or LFP, which includes very low-frequency patterns of brain activity.

Recording individual neurons is a bit like being at a noisy football stadium, trying to use microphones to record the voices of individual fans during the chaos of the match. Recording LFPs is like using the same microphones to record the chanting of the crowd, or the swell of the 'Mexican wave'.

Our research shows that we can make a reasonable estimate of what an individual neuron (football fan) is saying based on what these slower LFP signals (sounds of the crowd) are doing.

Importantly, these LFP signals appear to be stable over time. And they may have another advantage. BCIs need dramatic miniaturisation, but the major barriers are processing power and battery life. Our low-frequency LFP signals may help, because they can be processed efficiently with low-power electronics.

We made these discoveries in rhesus monkeys, who controlled an experimental BCI device using LFP signals. Monkeys are irreplaceable models in our research, because the neurons that control their arm movements are so similar to ours (whereas in rats, for example, they're very different).

In other work from our lab, Andrew Jackson and Jonas Zimmermann have shown that temporary arm paralysis in monkeys can be partially reversed by spinal cord stimulation — suggesting that a BCI like Charlotte's is achievable.

Our research matters because arm paralysis — from common diseases like stroke and spinal injury — places an enormous burden on individuals and on society. Arm and hand function is critical to people's independence and sense of identity.

I hope our work will contribute towards the development of a BCI like Charlotte's within 20 years: a fully implantable device that can reanimate a patient's own arm, and restore independence to many thousands of people.

Annelisa Sadler
University of Bath

Stress, depression and inadequate treatment; why are antidepressants failing teenagers?

Your teenage years are supposed to be some of the best of your life. You're young, carefree, with no responsibilities or commitments. But what if you feel like the whole weight of the world is on your shoulders? If you feel you're living in your own black bubble, away from your friends? If you struggle to drag yourself out of bed each morning and battle your way through each day? For teenagers who suffer with depression, this is reality.

The adolescent years are a time of huge change. Changes in body shape, social groups and increasing academic pressures are all normal emotional challenges of adolescence, but can make this a particularly stressful period of your life. Suffering from depression at the same time can make life unbearable. Depressed teenagers struggle to make friends and develop social skills, and can't concentrate well at school so often fall behind in their studies. Suffering from depression as a teenager makes you more likely to suffer from adult depression and to commit suicide. According to the World Health Organisation, around 1 in 20 people will experience a depressive episode each year. With depression often starting at a young age, the successful treatment of teenagers is essential.

Antidepressants used to treat depression may not always work that well in adults, but in teenagers they are particularly ineffective. Although there are several antidepressant drugs used to treat adults with depression, only one (Prozac) has been shown to have any benefit in teenagers. Even worse, antidepressants given to teenagers can increase the likelihood of the patient attempting suicide, a dangerous side effect which does not happen in adults. This is the central question in my research- why do teenagers not respond to antidepressants in the same way that adults do?

The answer may lie in the way teenagers and adults respond to stress. Stress is a major cause of depression, both in adults and in teenagers. Whether it is that deadline creeping up on you, trying desperately to make those last few pounds last until payday, or a blazing row with your best friend, all of us experience stress as part of our daily lives.

Our response to stress has evolved over thousands of years. For our cavemen ancestors, the sight of a sabre-toothed tiger on the prowl would switch on the hypothalamus in their brains activating the stress response. The sudden rush of the stress hormone, cortisol, into the blood helped them run faster, think faster, see more clearly, and listen more intensely than they did just moments earlier, priming them for the best chance of survival.

Today the tigers may be no more, but our response to stress, known as the hypothalamic-pituitary-adrenal (HPA) axis, remains. Increases in cortisol when stressed help us perform at our best in that important meeting or final exam, keep us alert and aware of the strange man lurking in the bushes, and even wake us up in the morning to start the day.

The HPA axis usually controls itself. Just like the thermostat which turns off your central heating system once it has reached the right temperature, your stress hormone system will switch itself off to stop it becoming overactive. Like most things in life, too much cortisol can be a bad thing. In some people, long periods of stress, with high levels of cortisol, can lead to problems with this off-switch and overactivity of the HPA axis. In the same way as a broken thermostat would cause the room temperature to rise, in depressed adults this leads to high levels of the stress hormone, cortisol, in the blood. Successful treatment of depression repairs the problems with the off-switch, fixes the thermostat, so the level of cortisol returns to normal.

In teenagers with depression, however, the stress hormone system reacts very differently to depressed adults. One idea is that depressed teenagers don't have problems with this off-switch, and so don't have a persistent increase in cortisol. Why is this? And could this be one of the reasons behind the lack of response of adolescents to antidepressant treatment?

My research aims to understand more about cortisol, and why the stress response is different in adults and teenagers with depression. The areas of the brain involved in the HPA axis are continually developing throughout adolescence, regulating the levels of cortisol in the blood. I study the changes in the HPA axis occurring after periods of stress, and what effects antidepressant treatment may have. By comparing what happens in the developing adolescent brain to the fully developed adult brain, we can better understand why current treatments are inadequate, and start to develop new successful treatments for the disorder.

So why does this matter? Not only is depression itself highly disabling, but suicide is the second biggest cause of death among 15-19 year olds, with 200 teenagers killing themselves each year in the UK and around 4000 attempting suicide. With current antidepressants failing teenagers, and the number of sufferers rising each year, the need for support among teenagers has never been higher. Developing effective antidepressant drugs could change the lives of teenage sufferers, their families and society as a whole.

Image of the Troubled Mind

Memories give our life a sense of meaning, a sense of community and family. We grow and learn as individuals based on our past experiences. Our minds are our moral guardians, which is why we are terrified of losing them. Yet there are millions of people who experience their fragility, as processes beyond their control dissolve their sense of self, in the neurodegenerative disease named after Alois Alzheimer. There are a few treatments for Alzheimer's disease that can reduce the effects of symptoms, but these are not cures: they can only delay the inevitable.

Contrast this with cancer, where in most cases we can see where it is early on and treat it. We can cut it out perhaps, give it a drug or blast it with radiation until it goes away. Why does this seem so much simpler? The key is the first part – seeing where the disease is, and early on. It seriously helps to have a target to aim at, and the sooner the better. Cancer diagnosis is relatively straight-forward, for reasons I'll come back to later.

With Alzheimer's and other types of dementia, we are still struggling to see what the disease does and at what time. This is due to many reasons, but the main one is that we are looking at the brain. You can't really cut it out, have a look at what you want and then put it back in. To me at least, a human brain looks like a wrinkled jelly, and I wouldn't be able to point at any bit and say, "there's the Alzheimer's".

It is only in the last few years that brain scans using Magnetic Resonance Imaging (MRI) have become advanced enough to reveal detailed 3D pictures of the whole brain inside a living person. We can get beautiful images of a person's brain structure down to sub-millimetre lengths. Right now research is at the point where we can see changes in brain structure between patients with late-stage Alzheimer's and healthy volunteers. It's through the imaging that we can see these differences, and get a better insight into what's happening when.

But is this enough? What we want is to be able to see differences in the brain before a patient gets confused or loses their memory. Whilst the brain might change in structure because of the disease, if this didn't have any effect on function then we wouldn't mind so much. The problem that patients, their relatives and the whole of society face is the loss of brain function, rather than changes in brain structure. Maybe brain activity can tell us something?

It's the difference between structure and function which makes Alzheimer's that much harder to diagnose than cancer. As soon as a cancer tumour forms, the structure changes immediately. We can image these structural changes almost straight away – we look for lumps, go for MRI or CT scans and we get a picture of a healthy organ with a blob where the tumour is.

What we do know is that Alzheimer's is linked with a build-up of chemicals called proteins in the brain. Proteins are coded in our genes and are essential for us to live, and each protein has a specific job to do. But sometimes they don't do what they are supposed to do. There are two different proteins that are being looked at: amyloid-beta proteins which form heaps called 'plaques', and tau proteins which form tangles. As the proteins build up they become toxic to brain cells. But understanding the interplay between these two proteins, and the subsequent changes in brain function and structure, is a tangle in itself.

When we see structural changes in Alzheimer's patients, there is already a loss of function. And we're not sure which aspect of Alzheimer's causes these losses. My research is looking at new ways to use an MRI scanner to image brain activity, rather than brain structure, and then see how this might be affected by the amyloid and tau proteins. The goal is to see if we can see any brain functional changes, and if they happen before the structural ones.

My research is aimed right at the heart of understanding why Alzheimer's disease has the devastating effect it does, and uses a healthy dose of physics combined with biology and neuroscience. The message is clear – if we can image the disease better, then we can design better treatments, and ultimately create what patients need the most: a cure.

Chris Smith

London School of Hygiene and Tropical Medicine

Mobile Technology for Improved Family Planning

“It is through journeys to the sick that we identify needs and problems” - the words of the public health pioneer Paul Farmer as he made a six-hour round trip to visit a patient with Tuberculosis. It was through my own journeys and conversations working on a health project in Samlaut, rural Cambodia, that I realised the importance of contraception. I met Thyda.

To my surprise, rather than medication to cure illnesses, Thyda spoke of need for contraception. Large families were difficult to support. Unintended pregnancy was common. Living two hours from the nearest big town, Thyda sought abortion from an unlicensed provider because she didn't know where else to go.

Working with local health workers, we started providing condoms, contraceptive pills and injections, but soon realised that we had to do more. People talked of side-effects, myths and rumours, such as *“Condoms cause burns.... or cancer!”* These fears led to discontinuation, and the risks of unintended pregnancy.

Contraception saves lives. Without contraception a woman could have 15 or more children in a lifetime. Contraception enables women to control their fertility. The benefits of contraception outweigh the risks, where the consequences of unintended pregnancies and unsafe abortion are a reality for women in developing countries.

If a jumbo jet with 400 young women were to crash every three days with no survivors there would be a global outcry. Yet women die from the consequences of unsafe abortions at the same rate: 47,000 deaths per year. What is clear is that abortion rates are lowest where contraception use is highest, yet 222 million women worldwide who want to avoid pregnancy aren't using effective contraception.

If contraceptive needs were met, this could dramatically reduce unintended pregnancies, unsafe abortions and maternal deaths. This would also lead to substantial social and economic benefits such as improved educational and employment opportunities, increased family savings and economic growth.

My research seeks to reduce barriers to contraception use. In Cambodia, many women like Thyda seeking abortion services don't use contraception, the most common reason: fear of side-effects. Compounding this, women returning to their villages lack access to good quality health information.

But technology offers hope. The global proliferation of mobile phones did not escape Cambodia, or Thyda. As over 80% of women seeking abortion services had a mobile phone, we realised a new possibility to maintain contact with clients. Even those living in the most far away villages. Could we use the mobile phone to provide health information?

MOTIF, MOBILE Technology for Improved Family Planning, is the name of my research project in Cambodia. A collaboration between Marie Stopes International, InSTEDD and the London School of Hygiene and Tropical Medicine. I have been working with a local Cambodian team to develop mobile phone support for contraception - mixing medical services with technology.

Many people we spoke to couldn't read so we developed voice messages. Women seeking abortion services could opt to receive a series of messages about contraception on their phone. The message is interactive. Women can respond to the message to request a call from a counsellor. Counsellors provide quality non-coercive support to enable women to choose a contraceptive method to suit their stage of life.

There's currently a buzz of excitement about using mobile phones for healthcare, or "mHealth", but also much uncertainty about what works. That's why we are evaluating MOTIF with a randomised controlled trial. In our study of women seeking abortion services, half receive existing face-to-face counselling and half receive this, plus the additional phone support. We then contact participants to compare contraceptive use between the two groups. This will allow us to really know if this support makes a difference.

Early indications are positive. As part of our evaluation, we visited Bopha, a woman who had received the voice messages and counsellor support: a 41 year old woman who happened to live in the same area of rural Cambodia I visited five years before. Already with four children, she discovered she was pregnant. She made a six-hour round trip on a motorbike in one day to have an abortion and joined the MOTIF study. She described how the messages and counselling reassured her when she was experiencing side-effects from contraception after her abortion.

Now imagine hundreds, thousands of Bophas and Thydas, not just in Cambodia but worldwide. Women wanting to avoid pregnancy, but with questions, concerns, and fears. Innovations like MOTIF could be scaled up at low cost to improve women's health worldwide.

For me, my return visit to Samlaut wasn't a journey to the sick. Fortunately Bopha was now healthy and happy. Making the six hour trip made me appreciate how far she had to travel to visit the clinic. However, maybe next time I'll just give her a call.

**names have been changed*

A short cut to better genes

“Is there really no cure?” he asks. Andy is my 15 year old patient who has aspirations to conquer the world as a photographer but is rapidly losing his eye sight. Life as a teenager is tough, but it is infinitely harder if, like Andy, you have the rare genetic condition Bardet-Biedl syndrome. Not only is he losing his sight; he is also facing the possibility of developing kidney failure and has struggled his whole life with an uphill battle against the bathroom scales. Like most genetic diseases there is no treatment for Bardet-Biedl syndrome.

Nearly 400 people are seen each year in the Bardet-Biedl syndrome clinic, all with similar health problems: failing eye sight, extra fingers and toes, kidney problem and obesity. While most people could live with an extra toe (easily treated with surgery or well-fitting shoes), losing your sight is, quite simply, devastating.

The explanation for the seemingly unusual combination of health problems in Bardet-Biedl syndrome is found in an unlikely place: our cell tails. Discoveries over the past two decades have revolutionised scientists’ view of the tails found on most of our cells. Previously regarded as evolutionary leftovers, we now know that cell tails, also known as cilia, play a key role in developing and maintaining almost every part of the body, including all the organs affected in Bardet-Biedl syndrome. Scientists have discovered that cell tails in people with Bardet-Biedl syndrome behave differently from those of a healthy person –they are shorter and the cells with diseased tails are slower to grow.

The problem *and* the solution could be found in our genes. Every person has around 25,000 genes in each cell in the body. Genes are packages of instructions that tell our bodies how to grow and develop. Most people with Bardet-Biedl syndrome (BBS for short) have a genetic fault in one of the 19 BBS genes. Genetic faults come in different shapes and sizes. Some are predicted to be mild whilst others are thought to be severe. My research shows that people with mild genetic faults, on average, keep their vision for seven years longer than people with more severe faults known as nonsense changes.

One group of drugs, known as read through therapy, has the power to ‘convert’ severe nonsense genetic changes to mild ones. In essence, it does what it says on the tin. It ‘reads through’ a severe nonsense mutation transforming it to a milder gene fault. Without this drug the cell discards the faulty gene product into a genetic waste bin. The hope is that this treatment could result in better eye sight and fewer kidney and weight problems in people with Bardet-Biedl syndrome.

The best way to assess how well these drugs combat blindness is to test them in eye cells. We are using a new technique that transforms skin cells from patients into eye cells through a scientific process known as *reprogramming*. A small skin sample is taken from a person with Bardet-Biedl

syndrome and transformed into a stem cell. This kind of cell has the potential to develop into any kind of cell in the body much like cells of a developing embryo. The stem cell is then encouraged to develop into an eye cell by growing in a highly specialised environment. This method allows us to see directly how well the drug works in the eye and to assess any side effects.

A major advantage of read through therapy is that it is already being used in clinical trials for other conditions. Most drugs take 15-20 years to develop, but a drug that is already licensed to use in clinical trials could be available in as little as two to three years. Around 14% of people with Bardet-Biedl syndrome have a nonsense gene fault that could benefit from read through therapy. The good news is that read through therapy works on nonsense gene faults in any gene. This means that if we can prove that this group of drugs can work in Bardet-Biedl syndrome, the wider implications could be even further reaching. It could benefit the estimated 600,000 people in the world suffering from a genetic disease caused by a nonsense gene fault. For people with Bardet-Biedl syndrome, as well as thousands of other people with a genetic disease, read through therapy really could be a short cut to better genes.

Felicity Hayball

MRC/CSO Social and Public Health Sciences Unit, Glasgow

Ignore the environment. It'll go away.

“Children see things in the environment that we may have forgotten how to see, let alone understand”

I want you to think about your childhood. How often were you outside? How often did you risk curfew to keep playing with friends? How often did you come home with grazes on your knees climbing up a tree?

Now think about children today. Children are becoming more concerned with their Facebook profile picture than with playing outside. The benefits of active children are numerous, ranging from positive physical health to mental wellbeing. Not interested in the benefits? What about the financial strain inactive children can place on the health care system? Childhood inactivity can result in a vicious cycle, where physical inactivity is a cause and a consequence of obesity, resulting in high blood pressure and cholesterol levels. Health problems such as these can carry through into adulthood manifesting into more serious conditions such as Type 2 Diabetes and coronary heart disease. Overall, obesity-related illnesses cost the NHS an estimated £4.2bn a year, with obese individuals estimated to have medical costs 30% higher than normal weight peers.

So of course, we want our children to be active and healthy. The question is how does our environment encourage or impede physical activity in children? Research suggests higher physical activity levels occur when children are outside. If the environment is appealing to children, the chances of time spent outside increases, potentially increasing children's overall physical activity levels.

It's a no-brainer that we want our children to be active, and a key step to ensuring this is to make the environment attractive to the children themselves. We could build enough playgrounds to keep the entire cast of Annie busy, but if playgrounds aren't what children want, we may as well be building motorways. This isn't a case of 'if we build it, they will come', but 'what should we build, so they will want to come'.

In May 2014 at the Global Summit of Physical Activity in Children, 15 countries presented report cards that gave an overview of how they were performing in relation to key physical activity indicators. Scotland received an F in overall physical activity, a lower grade than any other country; less than 20% of Scottish children achieved the international recommendation of 60 minutes of physical activity per day. Interestingly, Scotland did achieve a B in a 'community and built environment' variable. This variable included Scottish adolescent's thoughts on the perceived safety of their environment, access to facilities, and space for physical activity. My research seeks to understand the disparity between the two grades and the disconnecting evidence between Scottish children's perceptions and their

actual physical activity behaviour. I believe the key lies in understanding how children experience their environment, and more importantly, I want the children to tell me themselves.

In order to gain insight into how children feel about their environment, it's important to ask children how they feel about their environment. It may seem obvious, but it's often overlooked. Previous research concentrated on the 'where' and 'how often' of children's physical activity behaviour within their local environment, implementing devices such as Global Positioning System (GPS), accelerometers and measuring the number of physical activity facilities. Though this research is valuable, it does not offer an explanation for 'why'. It tells us numbers, geographical locations, percentages, it doesn't tell us why children interact (or choose not to interact) with their environment the way they do.

"One day, a teacher went over and asked a little girl 'what are you drawing', the girl said 'I'm drawing a picture of God'. The teacher asked 'but nobody knows what God looks like', the girl replied 'they will in a minute'"

Children are creative, imaginative, and visual; unique competencies reflected in how I will go about collecting information from the children. My research will ask children to choose between diary entries, drawing, and photography (or a combination) to express what they like and dislike in their environment. By permitting children to choose which method they would prefer to engage with, it increases the likelihood that the child will pick the methods they enjoy and (hopefully) be more willing to share their insights. Allowing children to choose the method aligns with my belief that we need to conduct research with children rather than on children.

My work will emphasize the importance of the local environment in shaping children's physical activity behaviours - to help policy makers create interventions that come directly from children themselves, in order to encourage and maintain active behaviour in our children.

Children's activity levels are declining and we are neglecting the influence of the environment. As Sir Ken Robinson has demonstrated; it should not be a case of only paying attention to children's minds; their bodies are more than a form of transport to get their heads into Math and Science lessons. We want children to be active, so we need to make sure they are growing up in an environment that not only allows it, but encourages it.

Obsessive-compulsive disorder — does age matter?

Have you locked the door this morning? Are you sure? If you feel the need to go back and check now, you are experiencing some of the key problems of obsessive-compulsive disorder (OCD): Doubt. Uncertainty. Worry.

The difference between you and a person diagnosed with OCD is that you will check the door *once*. Afterwards, you will continue with your day, satisfied and calm. Yet, despite having checked 20, 30, or more times, an OCD patient may remain deeply unsettled. Believing for example, that his parents will die unless the door is locked properly, he can't stop until it "feels just right".

We all obsess about things every now and then, but usually our worries serve a purpose. Not giving burglars a chance, for instance. Obsessions and compulsions in OCD, however, are irrational. They dominate patients' lives, cause distress and make most of them unable to study or work. Therefore, OCD is not just a personal issue; it is also an economic problem for society. Treatments are available, but they only work for about half of the patients. If we are to develop more effective therapies, we will first have to gain a deeper understanding of the disorder itself.

My PhD project focuses on how OCD starts in the first place. More than 80% of the patients experience their first symptoms before the age of 18. However, most of the research has focused on OCD in adults. This group is usually asked to complete a few computer based tasks. Designed as puzzles or games, they keep participants interested whilst producing important data that give us an insight into their abilities.

Researchers all over the world have identified key functions that are less developed in OCD. Suppressing a hand movement that has already started is one of them. If you were a participant in such a study, you would be asked to respond to an on-screen arrow by pressing a button as quickly as possible. However, when the arrow is followed by a "beep" you should not respond at all.

While this sounds easy enough at first, the beep is delayed until you can't help pressing the button incorrectly. Afterwards, we can measure how much time between the appearance of the arrow and the "beep" you needed to reliably stop your hand movement. For OCD patients, this time is a lot longer than for healthy people. They are what we call "disinhibited", which might explain their difficulties with control in general.

Next, we will ask you to play another game. You see two patterns and must determine which one is 'correct'. After a few attempts you may spot a rule that allows you to succeed every time, but again, there is a surprise in store. Each time you learn the rule, the computer will change it, making it a little

more difficult. Beginning as just purple shapes, the patterns become more complex as white lines are added. While irrelevant in the beginning, eventually you will need to learn a rule about these lines.

Healthy people are quite able to forget the old rules and to learn the new ones. However, OCD patients find it particularly hard to focus on the lines which they could previously ignore. They are stuck with the old solution to the problem and can't unlearn it. It might be the same kind of inflexibility in their every-day lives that requires them to check a door an excessive number of times to be sure it is locked...if they ever are sure.

There is a big controversy about whether adolescent and adult OCD are part of the same disease, or if they should be seen as two separate subgroups. The OCD symptoms reported in children and adults are similar and we treat them in almost identical ways: behavioural therapy and medication. Nonetheless, there are certainly more male than female adolescent OCD patients, whereas there is a gender balance amongst adult sufferers. Moreover, while many patients of all ages have other issues in addition to OCD, it tends to be ADHD in teenagers, but depression in adults.

This raises the question: are there fundamental differences between these two groups in terms of the OCD itself? Or do the adolescent patients grow up and still have the same less developed functions?

To test this, I will give the games you played in the fictional psychology lab to teenagers with OCD. If they are as disinhibited and inflexible as their adult counterparts, this suggests teen and adult OCD is the same mental disorder. If not, we might have to re-think our ways of treating adolescents with OCD and develop new therapies. Either way, we will understand how OCD starts in young people and what are the key functions patients lack.

And now go and check your door...once!

Rebecca Beresford

MRC Cognition and Brain Science Unit, Cambridge

Dementia

A word we've all heard; it's in the media all the time. We know it's scary, we know it's bad. But how can we help?

Beneath the umbrella term "dementia" there are many disorders; most share a common feature: memory problems. Alzheimer's disease is the most common dementia, comprising 70% of cases. There are 4.6 million new diagnoses each year; likely to triple by 2050. My research is focused on helping gain a diagnosis.

Diagnosis is important to enable patients to get treatment as soon as possible; and help them maintain independence and quality of life for longer. More sensitive tests that allow earlier diagnosis could provide better evaluation of potential treatment. Indeed, some of the recent failures of drugs during clinical trials may be attributed to the fact they were administered too late to have a beneficial effect.

Most of us have, unfortunately, had some experience of dementia. Like your colleague at work, Linda. She's always one for talking; unfortunately her husband passed away. She's looking good for her age at 66; still going strong as a part-time receptionist since leaving school early. But something has been off with Linda lately; she'd never had a great memory, now she forgets how much sugar you take in your tea...wait, coffee?

You hear that she's been to see her GP to discuss the things going on. Linda gets scared, she's heard of dementia and doesn't like the sound of it one bit! She's referred to a Memory Clinic and meets a lovely neurologist who asks about Linda's parents, their health etc... it seems pretty standard. Next she does some "tests". Linda is nervous and this affects her performance on some of the tests, but she soon realises some are easy! She has to copy an image and starts to think this may be a waste of her time. Then however, when the neurologist asks her to repeat the three words he mentioned earlier she doesn't have a clue. Next thing she knows, she's off for an MRI scan. She's seen these on Casualty. They don't show how noisy and claustrophobic they are on TV though.

Three years later you hear about Linda: she's got Alzheimer's disease. They couldn't tell at first, but she got worse at the tests she'd once found easy. Her first MRI scan was pretty early on in the disease, so the size of her hippocampus (part of the memory system) looked normal. But later on it'd shrivelled in size, and it became obvious that there was something wrong.

This leads to why my research is important:

In an ideal world, Linda wouldn't have had to wait so long before diagnosis. Perhaps she could have been sat in a chair, watching a screen, while sensors recorded her brain activity directly. This is possible with the relatively new technique of magnetoencephalography (MEG). She could have been doing a really simple task that couldn't be influenced by her education, IQ, or her mood that day. Even better if it were quick or if the machine wasn't really loud and intimidating, like that MRI scanner. Imagine if it could overcome differences in language, culture AND motivation. In particular, if it could be used to detect the really early effects of Alzheimer's on brain activity, like when Linda first went to the memory clinic.

This is what I aim to achieve during my PhD. And yes, it is as difficult as it sounds: Finding a task that activates memory systems that communicate with the hippocampus (the memory region, remember?) without the person realising that's what they're doing. First we need to know what the brain does when it's healthy. Following the many hours spent testing, twice as long is needed to analyse the complex brain signals. This is just step one! If everything goes to plan, three years from now, clinicians may have a new tool that contributes towards a more accurate diagnosis of Alzheimer's disease. This work is part of a national multi-laboratory project to evaluate the clinical use of MEG, supported by the MRC (Medical Research Council) and EPSERC (Engineering and Physical Sciences Research Council).

I've met so many lovely individuals; all generous enough to spend an hour or so sitting under a helmet while their brain activity is measured. It's often the way with research that you don't actually find what you thought you'd find. It takes hours of repeating things, tweaking, and going to enormous lengths to establish that the "squiggles" of data correspond to the brain activity relevant to memory. Yet throughout this painstaking process, I still hope that one day the findings will make a difference. That's one of the many reasons I love my job.

William Pembroke

MRC Functional Genomics Unit, University of Oxford

To sleep or not to sleep; revealing the rhythms of schizophrenia

It's funny how we instinctively trust our perception to reflect reality. One evening, you might be working on your laptop and, in an instant, the screen turns into a "multi-dimensional portal to another world." The text that you were *just* reading has now transformed into a "welcoming entourage of giggling, fancying pixies and elves"... Hallucinations like these are often described by patients with psychiatric diseases, such as schizophrenia. However, this particular fantasy world did not belong to a mentally ill patient. Instead, these were the delusions reported by Tony Wright, on the fifth day of his attempt to break the world record for sleep deprivation.

When I discuss my work, people often comment on how they know of someone with a psychiatric disease who suffers from insomnia. Others remark how "depressed" or "unstable" they felt after "pulling all-nighters" for those dreaded final exams. And it's true. Scientific literature supports a long-standing association between abnormal brain function and sleep disruption. Alterations to the body clock, or 'circadian rhythm', have been observed in up to 80% of schizophrenia cases, as well as in numerous other neurological disorders. But why is this? Current theory suggests that common brain mechanisms underlie both psychiatric disease and circadian rhythm disruptions.

To explore this hypothesis, I am investigating a mouse strain with altered cellular communication in the brain. Normally, one brain cell (neuron) releases a small chemical messenger, which tessellates onto a receptor of a closely neighbouring neuron. This binding transmits an electrical signal throughout the cell, which will generally release another chemical messenger to pass this signal on: a neurological domino effect. However, in the mice that I am studying, the 'dominos' required for transmission assemble more slowly, and when a cascade is set off, there are often not enough dominos standing to allow the cascade to complete. Overall, this leads to altered and decreased neurotransmission.

Interestingly, this mouse strain shares many behavioural and physiological characteristics with schizophrenia, making it a potent model for investigating the disease. However, perhaps even more interesting is the change in its circadian rhythm: these mice often wake early and have fragmented sleep patterns. I wish to identify genes that convert this broken 'neurological domino effect' into temporal changes in physiology. To aid my discovery, I focus on the suprachiasmatic nucleus (SCN).

The SCN is a tiny region of the mammalian brain, yet its impact on the body is huge, for it is the master of physiological time, the conductor of the greatest biological orchestra. Under its command are trillions of cells, each with different instruments essential for bodily function. Without the conductor, these 'musicians' will fail to keep the correct rhythm and harmony will turn to dissonance.

In many psychiatric diseases, this is precisely what we observe: desynchrony in the brain. My research involves searching for genes in this mouse model of schizophrenia whose activity in the SCN is abnormally altered over 24 hours. Only then, will I be able to tease apart the molecular relationship between circadian disruption and psychiatric disease.

Although this is exciting work, the clinical implications may not be immediately apparent. Currently, most disorders of the brain have no effective cure. Medication for schizophrenia can alleviate psychosis but it does not ease the burden of symptoms such as anxiety, apathy and depression. In fact, it may even intensify them. The lack of an effective treatment is likely due to psychiatric diseases being extremely complex: they are caused by a combination of numerous unknown genetic and environmental factors. This variety in the cause of the disease means its underlying molecular mechanisms are very difficult to unravel. My research will decipher current literature and offer missing pieces to the puzzle, potentially providing a platform for new evidence-based drugs to be used in these mouse strains, and eventually humans.

If you are among the 95% of the population without mental health problems, you may be wondering how my research affects *you*. Rather than being a mere side effect, circadian disruption is also a contributory factor to psychiatric disease and other disease-related symptoms. By understanding this relationship, we can provide medical advice based upon fact that will improve the quality of life for all: carefully deciding *when* to eat, sleep and exercise can have a beneficial impact upon mood, memory and cognitive skills. However, we now live in a changing society, where punishing work schedules and the distraction of iPhones can keep us awake to the early hours. These societal demands often conflict with our natural body clock, and we repeatedly find ourselves asking the question – to sleep or not to sleep? Perhaps it is time to listen to our brains before our brains stop listening to us.