



Max Perutz
Science
Writing
Award 2015

Winner

Emily Eisner, University of Manchester

Premonitions of Psychosis

I am lying on my office floor. Swirling vision and shimmering lights have just begun. These are warnings. I know that if I take painkillers and rest I can avoid the intense pain of a migraine headache. The trick is to intervene early.

My research is not about migraines, but the rationale is the same: you've got to spot the signs. Most people with schizophrenia recognise warning signs that they are getting unwell – for example poor sleep or increased anxiety. Intervening early can prevent a full-blown psychotic episode. Rather than just sidestepping an afternoon of discomfort, like my migraine, prompt assistance could avoid months of distress.

Each new episode of psychotic illness brings its own fears, costs and risks. Aside from the distress of the psychotic symptoms themselves, the disruption to an individual's work and social life can be huge. When you've been off sick for three months, revealing to your boss that you spent the time tormented by voices from the TV that commented on your every move and commanded you to kill yourself is tricky.

What if we could prevent new episodes before they started, using a device that's within your reach right now: your mobile phone? In the next two years I'll be trialling a smartphone app, "Express". Express helps people track their own warning signs of relapse. It asks them a series of personalised questions every week and sends this information securely to their care team. If warning signs increase above a critical level, the patient and their team take action to prevent relapse.

The mathematics of misery is economic as well as personal, so using an app like Express could save the NHS millions. Three months of relapse is four times more costly than three months of remission. With the average hospital stay costing £12,198, most of the NHS's £4 billion schizophrenia outlay this year will be spent managing relapses. This is life saving work. Suicide by people with schizophrenia accounts for more deaths per year in the UK than traffic accidents.

Other researchers have used warning signs to predict relapse, but doing this using a smartphone app is new. I have also extended the range of warning signs that people can monitor by adding a group of experiences known as 'basic symptoms'. If you've ever had *déjà vu*, that odd experience where something feels very familiar but you know that it can't be, you'll have some idea of what basic symptoms are like. One young lady I interviewed remembered that before her last psychotic episode the clock on the wall had looked a bit bent for a while. She was experiencing a basic symptom. Another noticed that colours seemed to be a bit brighter than usual. Both recognised that these odd experiences were just their mind playing tricks on them and, importantly, that they might mean they were getting unwell.

Basic symptoms have already been used to accurately predict the first episode of schizophrenia. Until now, no one has looked at whether they predict relapse. I interviewed twenty-three people who had recently had a relapse and asked them about their experiences beforehand. Strikingly, three quarters described basic symptoms. Some experienced as many basic symptoms as they did traditional warning signs such as insomnia. If we don't ask about basic symptoms, we are only getting half the picture. It's like monitoring the cholesterol of someone with heart disease but ignoring their blood pressure.

The next step is to ask people about basic symptoms right as they happen. Memories are imperfect – that's why some people keep a diary. It's easy to describe what happened today or this week, but if you asked me what I did three months ago it would be much hazier. I will invite people to use the Express app to keep track of their basic symptoms for six months. I'll then look at whether people who report increased basic symptoms tend to have a psychotic episode soon afterwards. This is more scientifically robust than simply asking people about what happened last time they got unwell. It should help me to answer an important question: could monitoring basic symptoms help predict and prevent relapses of schizophrenia?

Of my 421 Facebook friends, at least four will have an episode of schizophrenia in their lifetime, statistically speaking. They might be your friends or relatives too. Three of those four will have a relapse within five years, with most relapsing a second and third time. That's five years of disrupted work, interrupted friendships and unwanted hospital admissions. With early detection and prompt action they could rewrite that story. That is why my research matters – even if it sometimes gives me a migraine.

Runner-up

Alex Binks, University of Glasgow

Espionage, Martinis and Explosions: How Reprogramming Viruses can Help us Fight Cancer

As far back as the early 1900s, scientists have been hotly debating the age-old question of “who would win in a fight?” in regards to certain diseases. Over the years, these discussions gradually moved out of the pub and into the lab after numerous observations that certain cancer patients saw spontaneous remission following a naturally acquired viral infection. By the 1950’s, scientists were becoming bold enough to begin injecting cancer patients themselves with live viruses, and were doing so with remarkable success. In the modern genetic age, oncolytic (“cancer-killing”) viruses have become more targeted, more effective and more innovative than ever, and are close to becoming a real treatment option for many cancers.

Cancer forms when certain cells within our bodies gain mutations in their DNA blueprints that allow them to grow and divide uncontrollably. These cells can often break free from their surroundings and take a joy ride throughout the body, getting stuck in important organs, stopping them from working properly.

Viruses are lone wanderers, all they want to do is reproduce and create more copies of themselves, but they lack the ability to do this on their own. Therefore in order to continue existing, viruses have to sneak into cells and hijack their copying machinery, creating their own production line of new viruses which can go on to infect new cells. A virus doesn’t care too much for the fate of the cell it infects; a virus’s only concern is keeping the cell functioning long enough to get enough new viruses off the production line, and as a result the cell ends up knackered its resources and often dies. Oncolytic viruses can be made by taking a fully functional human virus such as herpes simplex virus, the causative agent of cold sores, and ripping out the genes required to cause disease. This leads to an “attenuated” form of the virus that is only able to infect cancer cells.

Let’s imagine the cell is a factory, and our virus is a secret agent trying to sneak in and switch out the factory blueprints for its own. A virus must do this without alerting the security within the cell to its presence, otherwise they can simply shut down the production line and stop the virus in its tracks. A normal unaltered virus can do this with no problem; years of evolution have given this virus all the secret agent training it needs to slip by security undetected. An oncolytic virus however, is more like an agent that’s had one too many martinis before beginning its mission. The once graceful virus now staggers its way through the factory, knocking over tables and making its presence known to the cell.

So these viruses are too sloppy to harm our healthy working cells, but cancer cells are sloppy too. In their quest to divide and conquer, cancer cells become highly deregulated; these are cell factories that have been turned into an all-night rave. While the cellular machinery may still be running, amid the chaos there’s no maintenance or quality control. Meanwhile, the cellular security is either non-existent or non-functional. This means that despite the sloppiness,

our oncolytic virus is still able to make it inside, start production, and watch the cancer cell fall to pieces without detection.

For my research, I'm interested in finding out how infection with oncolytic herpes virus leads to the death of a cell. The process of dying for a cell is less straight-forward than you might think, and in general a cell can die in one of two ways: apoptosis or necrosis. In apoptosis, the cell shrinks, breaks itself down and disappears without a fuss. You could compare this to our cancer cell rave simply shutting down, with everyone leaving in an orderly manner. However necrosis is more akin to the factory entering into self-destruct mode, the cell swells and bursts, going out in style with debris being flung across the entire neighbourhood.

In fact the difference between these types of cell death is incredibly important in how our bodies respond to cancer. Our immune cells actually play a big role in the body's fight against cancer; these are like circulating police, trying to shut down these cancerous cell raves where they can find them. As you can imagine, cells that die by messy, explosive necrosis attract a lot more attention from immune cells, which makes it easier for them to find other cancerous cells in the area and actually contribute to the cancer cell killing.

By trying to better understand how herpes virus is causing cancer cells to die, my hope is to find new ways to tinker with these viruses so that they induce more necrotic cell death, and develop better cancer treatments that work with our immune systems to help prime them in their fight against cancer.

Commended

Barry Bentley, MRC Laboratory of Molecular Biology

The Worm Wide Web: Mapping the Networks of the Brain

On a quiet morning in February 2003 the space shuttle Columbia started her descent into the Earth's atmosphere following a 15 day mission in space. Unfortunately, she never landed. Due to a heat shield that had been damaged during take-off, the space shuttle disintegrated in the intense heat of re-entry, tragically killing all seven astronauts on-board.

As investigators sifted through the wreckage, they found something remarkable. Amongst the experiments that had been sent into space were a number of microscopic worms called *Caenorhabditis elegans*. Amazingly these worms had survived the plummet to Earth, adding to a long list of achievements for this tiny species.

The worm has become something of a star in the world of science. As well as being able to survive extreme environments, worms have contributed to a number of important discoveries. They were, for example, the first animal to have their genome sequenced, and work on worms has contributed to three Nobel prizes.

Worms are a frequent visitor to space, where they are used to study the effects of micro-gravity, but as a neuroscientist my interest in the worm is closer to home. I am interested in how it can help us understand the brain.

The worm only has about 300 neurons, or brain cells, a great deal less than the 100 billion in the human brain. Despite this, worms have rich and varied behaviour. They can forage for food, sense and escape threats, form memories, find mates, and even perform some tasks we can't, such as sense magnetic fields.

Thanks to its small size, it has been possible to make a detailed map of how the worm's brain is wired — a task that is many years away for larger brains such as those of mice or humans. Due to our shared genetics, this map can shed light on how our own brains work.

The map of the worm's brain was completed in Cambridge in 1986 following a decade of painstaking work by a small group of scientists. These scientists carefully traced the tangles of nerve fibres, noting how they connected to one another. The map carried with it the expectation that we would soon have a complete understanding of the worm's brain.

While a lot of progress has been made since then, we have yet to achieve this understanding. There are numerous reasons for this. One is that neurons do not only communicate through the fibres that the map charted; they also communicate through an invisible network of chemicals that diffuse throughout the brain, similar to hormones. The most notable are a class of molecules known as monoamines.

Monoamines, which include dopamine and serotonin, play an important role in the brain. Psychiatric conditions, from depression to schizophrenia, have all

been linked to abnormalities in monoamine signalling; but we don't know how these systems work. It is here that the humble worm is once again becoming a pioneer.

For many years, scientists in labs around the world have been noting which cells in the worm produce monoamines, and which cells make receptors for them. This tells us which cells broadcast messages on the chemical network, and which cells receive them.

My work has been to collect this information together, to fill-in the invisible links that were left-out of the original map 30 years ago. To understand the role of these new connections, I am looking at their placement in the wider network of physical wiring. The techniques I use are the same ones used to analyse other networks, such as the internet or social networks. These techniques can help me to identify important cells, and patterns of connectivity which reveal their function.

Using these new techniques, we are making exciting discoveries about the monoamines. We have found that they form loops alongside the wires in the brain, which appear to regulate the flow of information. We are investigating whether these loops might play a role in learning or other high-level behaviours. We have also found that the control centres for the different monoamines are tightly connected to one another. This suggests that the different chemicals coordinate their action in ways that were previously unknown. Psychiatric conditions often involve multiple monoamines, and I am now working with psychiatrists to understand how my observations in the worm can be translated to humans, to shed light on mental health and brain disorders.

The idea that worms can help us understand mental illness is not as far fetched as it might sound. Worms have behaviours that mirror drug dependence and eating disorders, and much of their brain chemistry is similar to ours.

So next time you take a walk in nature, or look up at the night sky, remember the soil-dwelling, spacefaring heroes of science, who are helping us pave the way towards a happier and healthier future.

Commended

Stephanie Shoop, University of Manchester

Remission

Imagine sitting at your child's under-6s football match. Your hands cling to the seat in anticipation. You're terrified for your child, that she won't make that pass, that the team won't win, that that burly kid who frankly should be in the over-10s will knock her over. Looking up you see an even more involved parent or grandparent down by the pitch-side. Hopping and limping up and down the pitch, this elderly woman clearly has a joint condition, probably arthritis, but that isn't going to stop her. Your eyes focus on this grandparent as she hobbles her way cheering towards the other spectators. But actually, her proportions are all wrong for an elderly woman, even for a grown adult, and as you watch she shrinks and transforms into a six year old, cheering on her class-mates, baiting the opposing players. She should be on the pitch but her joints aren't up to it.

Remission.

This child has Juvenile Idiopathic Arthritis, or JIA. It is the most common arthritis diagnosed in children and the cause is unknown. She's also relatively lucky. JIA can be debilitating. It can cause fever, inflammation of the eye and even swollen liver and spleen.

Remission.

From the beginning, there was one word to cling to, one word that would mean riding her bicycle, climbing a tree and even donning the garish lime uniforms of the school football team. Remission. This has been her aim since she was diagnosed.

Remission: the absence of disease symptoms.

Whilst she sometimes thinks about remission, her parents, sat with the same expressions despite their child not actually competing, think about it constantly. They think about it when she's suffering and when she looks completely fine. They think about it at home and at work and at inappropriate times when hand-eye coordination should really take precedence. Please. Go into remission.

Remission.

For them, the word has developed a shape of its own. They dream of it settling over their daughter, enveloping her, healing her joints and removing her pain, taking away this old woman and giving them back their little girl. The word has a shape and a taste. But it can only be whispered.

Remission.

She remembers being diagnosed with JIA. The doctor mentions this ultimate goal, but also that half of children with JIA still have signs of disease into adulthood. He doesn't know how long her disease will last but getting into remission as soon as possible is important. As long as her JIA is playing up, she is at higher risk of long-term joint damage.

Remission.

He frowns before handing over a prescription. He has a lot of options to choose from and largely his own judgement to rely on. This is preposterous as before him sits a wealth of information in one child, information that could be useful in this decision. Is her gender, ethnicity, height or age important in deciding on treatment? What about family history? Is the number of swollen joints important? There is even more to think about. It had taken 18 months for her to be referred to this specialist clinic. Is this length of time important? What about the results of her blood tests? Should any or all of these be considered when picking a treatment? There is so little evidence on what predicts remission, it is hard to tailor treatment to this specific child. He sighs.

Remission.

This situation is repeated again and again and again for every child with JIA, at every hospital appointment. It doesn't have to be this way. If we knew what could predict remission in children with JIA, we could tailor treatments to each one and give them the best chance of achieving this important disease state. We could give parents back their children and children back their youth.

Remission.

Unfortunately, JIA is relatively rare and a large number of children would be needed to answer the question, 'What predicts remission?'. I have over 1500 patients with JIA to study. They have been recruited from hospitals all over the UK at their very first visit and have each been followed for up to 10 years. I have all of their information on age and gender, the form their disease has taken and blood test results. I also have highly detailed questionnaires on how each child functions in everyday life, with questions like can they get in and out of bed, or open a car door? I also know when each of them went into remission. By finding which patient characteristics combined with which treatments predicts remission, we could finally individualise treatment decisions. All of this so children with JIA can achieve their ultimate goal. No more whispers. Say it out loud:

Remission.

Commended

Clara Humpston, Cardiff University

Reconstructing Schizophrenia: Understanding the Unimaginable

Imagine a world so full of confusion and perceived hostility that you try to attribute meaning to everything you encounter, only to find there has never been any meaning from the very beginning. Imagine a fragmented consciousness where alien thoughts and voices constantly bombard your mind from unseen dimensions.

Imagine you have a diagnosis of schizophrenia and this is the only 'reality' you know.

Although it has been over 100 years since schizophrenia first became a psychiatric diagnosis, many fundamental questions about how its symptoms arise still remain largely unanswered. Psychiatrists define delusions and hallucinations – the hallmarks of a psychotic illness – as false beliefs and perceptions not based in external reality. Psychosis can have a severely negative impact on a person's wellbeing, especially when the disorder tends to strike in young adulthood. There are over 600,000 sufferers of schizophrenia in the UK alone, and their estimated life expectancy is 10 years shorter than that of the general population.

Psychosis also raises fascinating questions about how we experience everyday 'reality', something we all seem to take for granted. How do we know our brains are not playing tricks on us? How can we be certain that we are the 'normal' ones? What motivates me to dedicate myself to studying schizophrenia is the understanding that once a person's grip on reality is lost, there is very little left in their own sense of self. Psychosis, in other words, completely annihilates everything a person once knew about themselves. It is this immense suffering, this unimaginable pain and unspeakable fear that power me to further my own research, which focuses on how we might be able to disentangle the mechanisms of psychotic experiences.

Our expectations of how our inner experiences should turn out and how we actually perceive the world influence each other. When there is a mismatch between what we expect and we experience, our brain sends out an error signal (called a 'prediction error') so we can reconsider our position. This applies to how we sense our physical surroundings, how we learn new things and how we determine what we find rewarding. Previous research have found these different types of error signals to be very strong but inaccurate in patients with schizophrenia, with a tendency to disrupt the brain's usual functioning when there is no need to do so.

This could lead someone to form associations between irrelevant pieces of information or to mistakenly attribute their own inner speech to external sounds. Some think this may explain how certain types of delusions and hallucinations arise, but there is a huge knowledge gap in how error signals in the brain act together to distort a person's experience of reality. No one has to date linked all these different prediction error signals to first-person accounts of psychosis, but to me it is important to view the question under

investigation from multiple angles. This is why I believe my research could potentially fill this gap in knowledge.

I am carrying out studies in healthy individuals who have had benign experiences similar to psychosis, such as beliefs in telepathy and changes in the intensity of sound, and also in individuals diagnosed with schizophrenia. I will correlate their performance in behavioural tasks that tap into how the brain processes different error signals with their subjective report of unusual experiences. I also plan to do brain scans in some of these individuals, so that I can further investigate the 'patterns' in brain function. I am tremendously looking forward to interviewing patients with schizophrenia next year!

My prediction is that different levels of explanation will fall together nicely to form a much fuller picture of how the brain creates first-person experiences, how they in turn affect the brain and how these processes work differently in psychosis. In fact, some of the healthy individuals I am currently working with have had significant levels of psychosis-like feelings. Why do their experiences never become a problem? Perhaps the answer lies in how their brains process error signals, but I am more inclined to agree with the idea that psychosis itself is on a continuum with normal experiences. After all, where is 'normality' without the other end of the spectrum?

Still, even if my future findings will prove helpful to our scientific understanding of schizophrenia, they will only become truly useful when the patients themselves can benefit. I believe the very notion that psychosis is a part of human experience could offer comfort and resolution to the sufferers. Their brains are not 'defective' or 'abnormal', it is simply that many factors have contributed to a distressing way of thinking. This could mean patients with schizophrenia will no longer have to feel scared of themselves, and their new reality will be one of hope.

Evelyn Barron, Newcastle University

Quantity or Quality of Life?

How long would you like to live? If, like most people, you want to live to a grand old age then I have some good news for you – people today are living longer than ever before. But beware, there is no guarantee that we will spend these extra years in good health.

Finding ways to stay healthy will not just help us enjoy a better quality of life in older age. It will also help fix some of the challenges that a large proportion of older people in the population will present to society. As we age our chances of developing age-related diseases such as arthritis, heart disease and dementia increase. This costs the health service a lot of money, as does providing support for people in residential care or their own homes. There are also concerns about how our society will provide for older people financially, for example through pensions.

Researchers are designing studies to find ways to keep us healthier for longer. Some of these studies, called intervention studies, look at things that people can change in their everyday lives to help them achieve healthy ageing. These changes might be to people's diets, encouraging them to exercise more or spending more time with other people. To see if these changes work, researchers compare groups of people who have made changes with people who go about their lives as they normally would. If the people who make changes age more healthily than the others the intervention has had an effect.

The problem with these studies is that researchers have not yet agreed on what healthy ageing actually means. Different groups of researchers define it in different ways and how they define it depends on their academic background. There are also differences between what researchers and older people think is important for healthy ageing. Researchers focus on the presence of disease and disability, problems with brain function and how well we are able to take part in social activities. Older people also include these things when they define healthy ageing, but they include many more areas such as remaining independent, being able to adapt to change and having a good quality of life.

But why does it matter if researchers and older people think a little bit differently about healthy ageing? The answer is twofold. First of all, studying healthy ageing is very important for developing ways to treat the problems associated with ageing and to influence how governments plan for our future. We need researchers to agree on what healthy ageing is so that they are all measuring the same thing in their studies. In this way we will be able to compare the findings of different studies to see what works well and what does not work. Second, if researchers are asking people to change something about their lifestyle, we need to be sure that this change will lead to improvements in an aspect of healthy ageing that is really important to older people, otherwise why should people stick to the intervention?

In some of my research I am looking at the similarities and differences between what researchers and older people think is important for healthy ageing. I hope this will make researchers more aware of what older people think is important for later life so that future interventions can be designed accordingly. I am also investigating how researchers from different academic

backgrounds think about healthy ageing to encourage them to think in new ways about how they design their studies. For example, biomedical scientists focus on age-related disease, but if we encourage them to think outside of biomedical science they could target their interventions differently.

We know this has worked well from public health campaigns encouraging people to stop smoking. The anti-smoking messages on poster advertisements which showed the risk of developing lung cancer from smoking had an effect on people who score highly on a personality trait called conscientiousness, because these people were more tuned in to levels of risk. These same posters did not work as well on people with high levels of a personality trait called extroversion, because they were less tuned in to risk. Campaigns which showed a smoke free social lifestyle were more effective for extroverts because they were more interested in maintaining an outgoing lifestyle. Smoking is just one example, but it shows that targeting interventions based on what is important to different groups of people can make a big difference.

By encouraging researchers to consider new methods, we can make sure that interventions for healthy ageing appeal to older people and are relevant to their lifestyles. This will lead to more targeted, more effective interventions which will ultimately be more successful at promoting healthy ageing for the good of society and for each one of us as we get older.

Elka Humphrys, University of Cambridge

'It's not Fair': a Tale of Two Cancers

We learn from a young age that some things in life aren't fair. Most of the time we accept this fact and move on, but what if fairness wasn't a minor inconvenience but the difference between life and death? For thousands of people diagnosed with oesophageal (gullet) or gastric (stomach) cancer, this is the reality. Less than 20% of people with these cancers are still alive five years after their diagnosis, compared to over 80% of people diagnosed with breast or prostate cancer.

So why is there this difference in life expectancy between cancers? To answer that, we first have to understand how cancer develops. Cancer starts with a change in one or more of our cells, the millions of building blocks that make up the complicated structure of our body. Throughout our lifetime our cells work together, following instructions to grow and multiply at the right time, creating new cells to replace old, and fixing any damage that happens to our bodies. However, sometimes things don't go to plan and one or more cells create new instructions: growing and multiplying when they shouldn't be, forming structures that were never meant to be there, and creating a tumour.

Not all tumours are cancer, but the ones that are can grow quickly, expanding into the surrounding area, spreading to other parts of the body, and causing unusual changes to our body known medically as symptoms. For some types of cancer we are very good at recognising early symptoms, when it is still growing in one place, but for other types of cancer we are not so good at this. If cancer is diagnosed at an advanced stage, when it has already spread, it makes it difficult to give treatment, because even if the original tumour is removed there will always be many more cancer cells hiding in other parts of the body, waiting to grow and form new tumours.

It is this difference between diagnosing patients at an early treatable stage compared to an advanced untreatable stage that leads to the unfair difference in life expectancy between cancers. My PhD research aims to understand why oesophageal and gastric cancers are often diagnosed at an advanced stage, as this will help to identify how we could improve early diagnosis and therefore life expectancy.

I have discovered that research is a bit like trying to put a puzzle together when you don't have the picture and you know some of the pieces are missing. I started my PhD by collecting puzzle pieces from other people's research and I am gradually putting them together to find out what we already know about diagnosing oesophageal and gastric cancer.

So far I have found that patients do not necessarily recognise the seriousness of their symptoms and doctors sometimes misinterpret symptoms, meaning some patients see their doctor several times before they are sent to hospital for further tests. These 'delays' could mean the difference between an early and an advanced stage diagnosis. I have also found that people who are more deprived (less well off) are more likely to die from their cancer than people who are less deprived, a double disadvantage if paired with a cancer like oesophageal or gastric.

This gives us an idea of what is happening, but we are missing the pieces that tell us why it is happening, and that is what I hope to find out. I am not what you might expect from a cancer researcher. My research is not in a laboratory, but in the world of doctors and patients, learning about cancer from the people affected by it. This is the world of primary care research.

I aim to understand the experiences of oesophageal and gastric cancer patients, from when they first noticed that something was different, to when they decided they should see a doctor, and what happened when they did see the doctor. By comparing what people say and combining this with general information about them such as ethnicity, education level and income, I can find the missing pieces and start to see how the puzzle fits together.

My research will not complete the picture but it will move us closer to understanding what is happening and why, which in turn will reveal how we could diagnose these cancers earlier. Patients who take part in my research do so not for themselves, but to make a difference for patients in the future, a future where all cancer patients could expect to live for over five years regardless of the type of cancer they have. It's not fair right now, but it could be.

Helen Devine, MRC Centre for Neuromuscular Diseases

An Ode to the Androgen Receptor

Neurodegenerative diseases
Occur when nerve cells die
We certainly know that it happens
But we aren't quite sure how or why.
Parkinson's Disease would be easy
Alzheimer's or Huntington's too
They're probably near the top of your list
If I asked you to name me a few.

But Spinal Bulbar Muscular Atrophy?
Not heard of it before?
There's something special about it,
Let me tell you a little bit more.
Weakness in the arms and legs
Make it tricky for patients to walk
Weakness in the face and tongue
Make it hard to swallow and to talk.

The fault's in the Androgen Receptor
A particular genetic mutation:
Male patients have the disease,
Women pass it to the next generation.
When the Receptor binds testosterone
The troubles really start —
Patients get weakness, infertility
And problems in the heart.

The disease is slowly progressive
With no treatment and no cure
I'm hoping that might change
If I understand it a little bit more.
So I'm going on a journey
To explore why these cells die,
By searching out disease pathways
Using microscopes and dyes.

The first step is to find a way
To make a good human model —
Studies in other cells and mice
May not show the real disease problem.
Induced pluripotent stem cells
Are an exciting innovation
Stem cells from patient skin cells
Have the Androgen Receptor mutation.

From stem cells: motor neurons
I grow them in a dish
And after about twenty days
I see how they perish.
Stress, transport, mitochondria:
Possible avenues to pursue

In the course of my research
I may find something new.

Stress is hard to deal with
In research and in a cell
I can go for a little jog
But a cell can't in a well.
So they have a special mechanism
The "heat shock response" its name
If this isn't working correctly
Then this may be to blame.

Axons carry messages
From one end of the cell to the other
A traffic jam in this transport
Can lead to a spot of bother.
Motor nerves are very long
So they are at great risk
If blockages and hold ups
Mean transport isn't brisk.

Mitochondria provide the energy
A cell needs to survive
If the fuel supply is faulty
Then the cell can start to die.
So if their shape is distorted
Or they aren't working right
The cells start to malfunction
Pack up and say goodnight.

Cell death is like a puncture
Discovering it's not enough
The next job is to fix it
And that will be quite tough.
Motor neurons on a plate
Will be my way to screen
For a drug to reverse cell death;
That would be the dream.

SBMA is a rare disease
But patients still need a cure
I hope I can locate one
That's what my research is for.
The findings that I find
May also hold the key
To overall common pathways
In neurodegenerative disease

My research is for patients with SBMA
Who find everyday journeys are hard
And for whom it is a challenge
To read this poem out loud.

Thomas Crellen, Imperial College London

Beneath the Lake's Surface

Standing on the shore of Lake Victoria one is met with a peaceful scene. Pastel coloured boats drift by. Kingfishers emerge from lush foliage before hovering and diving at the water's surface. The lake sparkles a deep blue inviting you in. Don't be fooled though – the water is teeming with parasites.

Darting around beneath the shady banks are schistosomes. These tiny flatworms burst out of snails living in the lake and burrow through the skin of fishermen, women washing clothes, and children playing in the water. Once inside the skin the flatworms embark on a journey through the human body to their final destination, the veins surrounding the intestine, where they can live for years. The flatworms lay hundreds of eggs every day into the blood where they are then swept into the liver and spleen. As the eggs build up in these organs they cause a painful, chronic illness known as bilharzia.

More than two hundred million people worldwide are infected with bilharzia, the majority in tropical Africa. Despite this incredible number of cases, research on bilharzia has been a neglected area and so there is only one widely available treatment; a dose of the drug praziquantel is used to kill the adult worms. Countries such as Uganda are getting better and better at delivering praziquantel to schoolchildren in areas where the disease is rife. However, they lack the resources to check how well the treatment is working. If the parasites became resistant to the only drug available this would be a big blow to our efforts to control the disease. This is where my research comes in.

I have been working in Uganda with the Ministry of Health to test children for bilharzia in different schools. We treat the infected children and then return after a few weeks to check whether the drug has killed the parasites. Children in certain regions of Uganda have been treated every year since 2004, while others have never been treated before. By comparing how well the drug works against the parasites in these different areas I will be able to detect emerging drug resistance.

The second step involves the technology of DNA sequencing. Just as the Human Genome Project is revolutionising our understanding of our own genetics, my research on these parasitic worms is benefitting from the same technology.

In Uganda I extracted wriggling microscopic parasites from children's stool samples. This rather disgusting process took place in the school playground and so every time I looked up from the microscope dozens of curious children would be crowded around me. I took these parasites to the Sanger Institute in Cambridge where I am in the process of extracting and sequencing their genomes. My aim is to see if we can explain the differences in how children respond to treatment through the genetics of their worms.

An important missing part of this story is the genetics of the children themselves. Africa is the most genetically diverse continent on earth and so this study will miss any of the differences in the patients that make the drug more or less effective. Despite this limitation, the parasite genomes that I

generate will be freely available to other researchers and can therefore be used in future studies looking for new drug and vaccine targets.

On my flight to Uganda I happened to be sitting next to the Minister for Tourism. He complained bitterly that bilharzia was hindering development around the lake, denying the employment opportunities that watersports and cruises would bring. While the parasites and the threat of infection remains, tourists will be reluctant to dip their toes in the water.

I am hopeful that my research will play a small role in the efforts to control bilharzia. If we are able to avoid the threat of drug resistance then it is possible that the disease will be eradicated within my lifetime. In the future I hope that the people of Uganda and visitors to the country will be able to enjoy and prosper from Lake Victoria, safe in the knowledge that the waters are free of parasites.

Carolyn Nielsen, London School of Hygiene and Tropical Medicine

A Viral Spanner in the Works

It sounds like a bad science fiction plot, but sometimes it would be easier if everyone was identical.

I'm interested in how vaccines activate our immune systems and how this then works in the real world to protect us from dangerous infections. The problem is that not everyone's immune cells respond in exactly the same way, meaning vaccines often work better in some people than in others. This can be at a local level, such as between your colleagues at work, or on a grander scale with differences between whole geographical regions. For example we know that BCG, the vaccine for tuberculosis, is less effective in sub-Saharan Africa than here in the UK.

This is partially due to genetics- the genes for key molecules on immune cells have a huge amount of variation- while some is due to other factors you can't blame on your parents, such as ageing. Environmental influences, like nutrition or infection, can also affect your immune system. A perfect example of nature versus nurture.

My research at the London School of Hygiene and Tropical Medicine focuses on how one common virus, cytomegalovirus, contributes to this puzzle. Cytomegalovirus is a type of herpes virus that has co-evolved with humans for thousands of years. Our immune systems generally control it, but we can never entirely get rid of the virus. This constant pressure on your immune cells over time is like the cellular version of going grey- some types of cell in infected people become more mature and less responsive. This effect is similar to what is seen during normal ageing, but is unparalleled by any other infection.

In developing countries, including in sub-Saharan Africa, almost everyone is infected with cytomegalovirus. The prevalence varies in Europe or the USA but generally 30-50% of young adults have cytomegalovirus, not 100%. Cytomegalovirus could therefore be one of reasons why vaccines don't work as well in the developing world. Unfortunately, this is difficult to investigate as there are no uninfected people in these countries to participate in studies for comparison.

My project therefore looks at comparing immune cells from infected and uninfected people in the UK. I wanted to find out if there are any differences in responses when the cells are stimulated with vaccines, using whooping cough as an example. This involves mixing immune cells from previously vaccinated people with the whooping cough bacteria, then looking at how the cells react. Successful vaccination against whooping cough gives your body a sneak preview of killed whooping cough bacteria, triggering the build up of an arsenal of memory immune cells that can fight infection fast if you get exposed. Mixing your immune cells and whooping cough bacteria in the lab can give us an idea how well you might respond and be protected.

As immune cells activate, different molecules are sent to their surface which we can detect using fluorescent tags that stick only to these specific molecules. The number of cells that get labelled with the fluorescent tags tells us about how well that person has responded. This can be measured using a

technique called flow cytometry, which uses lasers to calculate what percentage of cells have been marked with each tag. The lasers allow us to count hundreds of thousands of cells per minute- a much faster and more accurate method than staring down a microscope!

So far, we've been able to show that people infected with cytomegalovirus have less powerful responses by a type of immune cell called natural killer cells. These cells don't have memory themselves, but they can respond very quickly to signals sent from other cells, like T cells, that do have memory and can recognise whooping cough bacteria. We're now trying to understand *how* cytomegalovirus has changed the natural killer cells to undermine the vaccine response.

It's not yet clear how large an impact these natural killer cell changes will have on the overall efficacy of a vaccine. We also don't know how important it is if you become infected with cytomegalovirus before or after vaccination. Additionally, since cytomegalovirus causes similar immune system changes to healthy, normal ageing, it is likely the relationship between infection and age is complicated. Interestingly, we have seen that natural killer cells in 10-year olds with cytomegalovirus infections in The Gambia (West Africa) have already undergone changes you wouldn't expect to see until late adulthood in uninfected people.

If future work builds on this and demonstrates there is a link between cytomegalovirus infection and poor vaccine efficacy, then the value of this research lies in helping to identify weak spots in vaccination programmes. Whether it's development of better vaccines with adjuvants (like an espresso for the immune system), or simply showing who needs the help of a booster jab, understanding why some people's immune systems respond half-heartedly to vaccines is crucial for guiding effective vaccination policies.

Vicky Stern, University of Sheffield

The Problem of Prematurity

This has been a good week. Today a patient brought her son back to visit us in the Preterm Clinic - born four months early, after a decade of gruelling fertility treatment, he's doing well. Yesterday we discharged another woman from hospital at 34 weeks after months of careful monitoring, finally able to look forward to the arrival of her baby after a long, anxious wait. These are the things I focus on during the bad weeks. But when a patient is enduring the heartbreak of her third late miscarriage, or a tiny 24 week baby loses their fragile grip on survival, the happy endings can seem all too distant.

Preterm birth is one of the biggest problems we face as obstetricians. Over a million babies die from complications of prematurity every year, often because they were simply born too soon. Specialist care for preterm babies is very advanced, but there are limits to what even the most sophisticated neonatal unit can do. Worse still is the situation for women who deliver early in low-income countries - limited access to maternity care means survival rates are dramatically reduced. The good news is that treatments to delay delivery do exist. Sadly, by the time many women come to hospital it is too late to try them. This is where my research comes in: we need to work out early on in pregnancy which women are at risk so we know who to monitor and treat.

We have some tests already: scans to measure the length of the cervix (neck of the womb) can look for signs of weakness and premature opening, swabs for infection and other indicators also help estimate the risk of early birth. Unfortunately none are 100% reliable and the consequences of falsely reassuring or worrying tests are serious, so we know there's room for improvement.

The mechanisms leading to premature birth are complex: different problems can trigger labour, including vaginal infections, an over-stretched womb or a weak cervix. However, regardless of what starts the labour, for birth to occur the cervix has to soften, shorten and open - it's an essential part of the process. Targeting our prediction tests at this step of the pathway should ensure that we pick up as many women as possible at risk of problems. We already know that the length of the cervix doesn't tell us everything. Some women seem to have a naturally short cervix, others have a shorter length because they've had treatment after an abnormal smear test, so results can be misleading. Our study is investigating whether a new test, designed to measure softening changes in the cervix, can tell us more about whether the womb is preparing for birth than current tests.

It's called electrical impedance spectroscopy (EIS) and works by measuring the electrical properties of body tissues. You might not think your body has electrical properties but in fact human tissue actually works a bit like a simple electrical circuit. Current can flow due to the movement of electrically charged particles such as salts, just as electrons travel round the wires of a circuit when it's connected to a battery. In the fluid spaces of tissue there are lots of charge carriers and current flows easily. In solid sections of tissue, the charge carriers are tied down and can only move a short distance so current flow is difficult. Measuring current flow can therefore tell us about the structure of the tissue - how much fluid around the cells there is, how tightly they are packed, what the solid bits are like and so on. These are all things which

change when the cervix softens before birth, so EIS measurements should be able to pick up softening early, before a woman develops symptoms.

You might think that electricity and the body don't mix – put them together in a word association game and many people's first thought would be shock or electrocution. In fact electricity has been used in medicine for decades. Dieters measuring their body fat on home weighing scales and pregnant women using TENS machines for labour pain relief are all using small electrical currents to gain information or improve symptoms. Electrical impedance has been used to design brain scans, detect cancer and to monitor the lung function of critically ill patients in adult and neonatal intensive care. The currents used in EIS are carefully calculated to ensure they don't harm the body at all. A hundred times weaker than those used in TENS pain relief, other than the touch of the instrument, there is no sensation from taking an EIS reading.

The technology is inexpensive, safe and easy to use. If our study shows it can accurately predict early birth, it could offer hope for those babies destined to arrive too soon, hopefully meaning our patients and clinicians will experience more good weeks than bad.

Anna Moon, Cardiff University

How WWII Can Help us Understand Schizophrenia

10th May 1940. Just one day in a conflict that was to last at least five more long and terrible years, a day nestled within ongoing confusion and devastation of a world locked in war. But an important day nonetheless.

It was the day that Hitler signalled the Nazi army to invade Holland, launching a full-scale attack that battered Rotterdam to the ground. The Dutch, hopelessly outnumbered and overwhelmed, surrendered within five days. It would take five years and over 200,000 casualties before the country was once again free. It was a terrible event on the course of a cruel decade of history.

With their invasion, the Germans caused a widespread and well documented stressful event that affected many, including expecting women who were abruptly forced to face the rest of their pregnancy in a war-torn country, many of them suddenly alone. Stress can wreck havoc on the functioning of the brain, thus it is perhaps not surprisingly that incidences of mental illnesses shot up all across Europe after WWII ended.

And when the fighting was done? When the next generation grew up away from the terror, in peacetime their parents had dreamt of, you might be forgiven for thinking these babies would grow up healthy. But that's not the case. Instead, researchers have found that rates of schizophrenia in the children of the Dutch mothers who were in their second or third trimester when the Germans invaded were increased significantly.

I am interested into how prenatal stress, such as what occurred in May 1940, can cause this increased risk of a child developing schizophrenia in later life. Schizophrenia is an illness where there is a breakdown in how your brain thinks, feels and how it responds to what you see and do. Sufferers resonate between depression and apathy to hallucinations and delusions, their mental thoughts fragmenting as they often struggle to tell the difference between reality and fantasy. Unlike other physical illnesses, you can't pop to the doctors for a pill that will certainly cure you or wait for it to go away on its own. It is dishearteningly common, affecting around 26 million people in the world. Ten percent, over two and a half million people, will die from suicide, and we still can barely make sense of how this disease works. Understanding how this disorder may be caused has to be one of our priorities, and this is where my research begins.

Rat models have been absolutely essential in understanding the effect this can have on the offspring's brain. One of the differences we see in children of stressed mother rats are alterations at the synaptic terminal. This is basically the bit at the end of the neurone before the synapse - the space where two neurones meet and communicate. The synaptic terminals dictate how electrical messages are transmitted through a complex and dense collection of protein structures that co-ordinate the first neurone to 'throw and release' the information via chemical messengers. The proteins on the surface of the second neurone then 'catch' them and allow the impulse to rush on towards the next synapse.

One important thing to understand is that structure at this synaptic terminal isn't static. Everything here is consequently rearranging, appearing and disappearing and shuffling around to allow for information transfer that allows for proper acquisition of memories and knowledge. This is known as synaptic plasticity. Receptor proteins, the *N*-methyl-D-aspartate receptor (NMDAR) and the α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA) receptor, are highly involved in this process. Imagine a child in school, memorising times tables. As they learn $2 \times 2 = 4$, the levels of NMDA and AMPA receptors at their synapses are shifting to allow them to learn the rules of mathematics, to form connections that could last a lifetime (or until their exams at least!) This process is also under strict control from other proteins and neurotransmitters in this complex network, such as activity-regulated cytoskeleton protein (ARC). ARC is known to affect both NMDA and AMPA receptors, giving it a key role in learning and memory.

Many mechanisms can cause abnormal regulation of this synaptic plasticity. This can cause widespread effects; information doesn't get transmitted appropriately, the right memories aren't formed, learning is altered – all things that build up to a schizophrenia like disorder. Prenatal stress has been suggested to alter ARC levels, which, if I can confirm and explore, may hint at a potential mechanism into how prenatal stress may contribute to schizophrenia through synaptic plasticity.

We may not be in the middle of a world war, but our society is under constant stress: work, inequality, terrorism. Studying how genetics and a stressful environment may work together to contribute to schizophrenia may be the first step in truly understanding this disorder, a first step in allowing us to treat sufferers with more effectiveness.

Daniel Yin, University of Oxford

The War on the War on the War on Bacteria

“That’s funny” certainly isn’t as memorable as “eureka” or “one giant leap for mankind”, but it was the utterance that started a revolution in medicine and health care during the 20th century. Like many hugely beneficial discoveries, Alexander Fleming discovered antibiotics by serendipity. Returning from holiday to find a population of his bacteria killed with a fungal contamination, he identified the key ingredient in the fungus that destroyed the bacteria and named it penicillin.

Previously, even the most innocuous cut or routine surgery could result in severe and even fatal infections. Following the first successful treatments with penicillin, the danger of bacterial infections was reduced significantly, allowing for ever-more complex surgical procedures and survival from illnesses that were formerly lethal.

Unfortunately, due to uncontrolled, unnecessary overuse of antibiotics in medicine and agriculture, bacteria have mutated and evolved to become resistant to even the strongest drugs. Once again a minor hospitalization may result in an incurable bacterial infection due to antibiotic resistance. The rise of these so-called “superbugs”—organisms resistant to all commonly-used antibiotics—poses a large and growing threat to human health. Can we find a way to combat this threat, and avoid living in a “post-antibiotic world”?

Alexander Fleming found the answer to a global health problem right in front of his eyes, and my research focuses on a type of molecule that is all around us, which can be found in places as diverse as alligator blood, wasp venom and even our own sweat; Antimicrobial peptides (AMPs) are exciting molecules with the potential to combat antibiotic-resistant bacteria as they function very differently from other antibiotics.

Most current antibiotics target specific biological machinery within bacterial cells, thereby killing them. Through random mutation and evolution, however, bacteria change the structure of this machinery to resist the drugs. In contrast, AMPs work by destroying a more fundamental part of a bacterium: the cell membrane. A membrane is a barrier that surrounds bacteria, letting in nutrients from the environment while expelling or blocking entry to toxins. Disruption of the membrane is lethal to a cell, and because membrane structure is so complex, bacteria appear to be unable to modify it in response to these AMPs.

My research aims to address a key problem hindering the development of AMPs as important future frontline antibiotics; the ability to tune their selectivity to kill antibiotic-resistant bacteria while leaving human cells unharmed.

Even if an AMP is an effective antibiotic, it is useless if it also endangers human cell membranes. After all, sulphuric acid is a superb antibacterial agent but it’s a shame it’s also a potent anti-human agent! It is still unknown exactly how these molecules work, so I am attempting to explain how the AMPs interact with cell membranes in more detail and understand why for example they don’t harm the alligator, wasp or human that produces them.

AMPs, like all peptides and proteins, are made up of building blocks called amino acids, of which there are around 20 found in nature. The exact sequence of these building blocks is intricately linked to how an AMP interacts with different cell membranes. Using a technique known as solid-state nuclear magnetic resonance (a process very similar to MRI imaging done in hospitals), I am trying to understand the link between the amino acid structure of an AMP and its ability to selectively destroy bacterial cell membranes.

Based on findings from these experiments, we are now attempting to exploit this by modifying amino acid sequence (and even using building blocks not found in nature for more diverse, non-natural structures) to produce man-made AMPs with selectivity greater than that found in nature, with the hope of eventually producing safe, resistance-proof antibiotics.

Of course, it's a foolish idea to think that AMPs will be a panacea to combat bacterial infections; nature has spent millions of years improving defence mechanisms, and it could be the case that resistance may eventually develop even to AMPs. However, it's clear that basic, fundamental research matters, as it underpins the development of drugs in a huge range of clinically vital areas. If Alexander Fleming has taught us anything (apart from the catchy one liner) it is that research of this kind can also sometimes unearth completely unexpected findings which could lead us into unknown realms of healthcare, that address the contemporary challenges to our survival.

Dan Craig, University of Birmingham

Fighting Flesh Poverty: an Apple a Day?

Just imagine. You're 80, and your walking stick now goes everywhere with you. Your mind's still sharp, and the family love your wise, experienced words. But what do you see when you look in the mirror?

It doesn't take somebody in a white coat to tell you that as we age our bodies get smaller, weaker and more frail. You've almost certainly already experienced this. Your grandma or grandpa. Your mum or dad. You may even be experiencing this first-hand. Either way, we all get old.

The natural process of becoming weaker and more frail as we age is a direct result of our muscles becoming smaller. In the 1990s, this process was given the name '*sarcopenia*', or literally '*flesh poverty*'. It's a condition that can have a severe impact on our quality of life, especially in our later years. It's also fast becoming a silent epidemic.

Why does it matter? Our muscles get smaller as we age...is that really so bad? Well, for starters, this loss of muscle size and strength is now known as a major cause of falls in the elderly. In addition, with loss of muscle usually comes loss of bone tissue. Couple this with the risk of falling, and you've got a recipe for disaster when it comes to bone fractures of all types.

On top of that, a lack of muscle mass and function can increase the risk of other diseases such as type II diabetes and heart failure. Perhaps the biggest problem of all is the impact it has on our level of independence, and the severe physical and emotional burden this often carries.

And yet...there is better news on the way.

Irrespective of age, the size of our muscles depends on two things: our bodies' capacity to build new proteins and their capacity to break them down.

Think of a wall of bricks. At one end, one person is laying new bricks and building the wall. At the other end, someone else is removing bricks and taking the wall down. The wall is your muscle, and the bricks are proteins. Fundamentally, this is how our muscle is maintained; through a dynamic balance of building new proteins and breaking down old ones. As we age, our bodies become less capable of building the wall, but better at breaking it down - and we start losing muscle.

One thing that can reduce the impact of this is our nutrition. When you tuck into your Sunday roast, the protein in the meal (from the meat and dairy products for example) is broken down into amino acids. These are the building blocks of the proteins. The amino acids are absorbed through our gut and filter into the bloodstream. Our muscles sense this and respond by building new proteins, which help our muscles grow.

As we get older, our bodies start becoming resistant to the protein and don't respond in the same way. As a result, we need nearly twice as much protein from our diets compared to when we were younger to maintain the size of our muscles. For some, a scientifically sanctioned reason to devour another steak

or guzzle more milk is a wonderful thing. For many others, eating twice as much protein every meal, every day is less appealing.

So, here's the good news. My research focuses on identifying smaller nutrients from common foods that could help keep our muscles in shape as we get older. There's one nutrient in particular that offers real hope, and it can be found in the lowly apple.

The nutrient – ursolic acid - is found in the skin and gives the apple its waxy, shiny appearance. It's also found in some herbal extracts, like rosemary. Ursolic acid has already been identified as a cancer-preventing nutrient. However, recent research in mice shows that it also has the ability to prevent muscle loss and even promote gains in muscle size. My work is aimed at finding out if this also happens in us humans.

I believe that ursolic acid works differently to protein when we digest and absorb it. That's why it could be used to help maintain our muscle size as we age. These smaller nutrients from common foods are sometimes referred to as '*nutraceuticals*', to reflect their potential medicinal (and *pharmaceutical*) qualities. Ursolic acid is an exciting new nutraceutical, because of its potential to reduce the natural muscle loss we currently experience with ageing.

You've heard the question asked... Can an apple a day keep the doctor away?

In the battle against flesh poverty, it's certainly clear that the foods we eat play a fundamental role. As for the humble apple itself, time will tell.

- End -