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Shortlisted essays

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[WINNER]

Putting Sleeping Sickness on the Radar

Amy Capes

It is the start of an invasion. There is no gunfire or explosions, just the mundane tickle of a fly landing on your skin. In Sub-Saharan Africa, this moment can be just as deadly as bombs and guns if that tickle is a blood-sucking tsetse fly. As the fly bites, the tiny protozoan parasites that cause sleeping sickness rush into your blood stream. What was a brief brush of legs and wings is suddenly a potential death sentence.

Your body is now a battlefield. The parasites begin to multiply and overwhelm your defences causing waves of fever as you try to fight back. If you are lucky, you get an accurate early diagnosis and access to one of the two drugs available for the first stage of the disease. If you are unlucky you are diagnosed late, when your brain is already crawling with the parasite and you begin to lose your mind. The most commonly used drug of the three licensed for the second stage was discovered 90 years ago and is based on arsenic. There is a 10% chance the drug will kill you because it is so toxic; but what choice do you have? It's a hopeless war; sleeping sickness invariably progresses to coma and death if you do not get treatment.

In Sub-Saharan Africa, the chances are you will not receive safe, effective drugs, and you will die from the disease or its treatment. The World Health Organization estimates that there are between 50,000 and 70,000 people with sleeping sickness in Africa, and that millions more are at risk. Even if a person isn't infected with the disease it still devastates lives, because it infects and kills livestock too. Sleeping sickness is a disease that is crying out for more research and better drugs. However, if we are to outwit the enemy, we need to understand what makes it such a lethal foe.

The sleeping sickness parasites are superbly designed for stealth; to succeed they must evade the defences of the human immune system. The shock troops of the innate immune system rapidly and indiscriminately attack foreign cells, while the adaptive immune system learns the signature of each invading pathogen, and launches powerful, surgical strikes. But the surface of the parasite bristles with an incredibly sophisticated coat of armour which is made up of millions of protein chains anchored to the cell surface. The armour repels the barrage of the innate immune system, and by the time the adaptive immune system has locked on to its target, the parasite has shed the old armour and replaced it with new, different proteins. The surgical strikes never find their target. The parasite flies under the immune system radar, allowing it to silently multiply and invade the body.

But what if we could strip the parasite of its armour? The parasites would be visible and vulnerable to the immune system. My research focuses on the anchor that holds the

armour's protein bristles in place on the surface of the parasite. If the parasite cannot make the anchor, then it cannot make its coat of armour. The parasite has a production line for assembling the anchor; it is built up, piece by piece, by a series of molecular machines known as enzymes. I design and synthesize molecules that mimic the anchor at a particular stage of its production. The mimics fit into the enzyme, but instead of allowing it to add the next piece of the anchor they jam the machine and stop it working. Once the anchor production pathway is shut down, the parasite loses its armour.

Making these anchor mimic molecules is slow and laborious because we do not know the structure of the enzyme we are trying to inhibit. It is like trying to guess the structure of a lock by making many different keys and seeing how they fit. But every molecule I make brings me closer to stripping the stealth armour from the sleeping sickness parasite, and finally letting the good guys win.

[RUNNER-UP]

Making statistical sense of an imperfect world

Michael Wallace

Hi there - I'm your friendly neighbourhood statistician, and I've got a few questions if that's alright. First up, how old are you? Ok, and how much do you weigh? Good, good, now how many calories do you eat on an average day?

If you're anything like me you'll have had a mixed response to that lot. It starts off ok - I'm pretty sure I'm 24 - but it goes downhill from there. I don't have a pair of scales to hand, and I can barely remember what I ate yesterday, let alone work out an average.

Welcome to the world of measurement error, a place I have lived for the last three years of my life whilst working towards a PhD in statistics. I'd come into it off the back of theoretical training, but then I found out about this pesky thing called the 'real world' where weighing scales aren't perfectly calibrated and people don't keep a record of precisely how many cups of tea they've drunk. Unfortunately, all the statistical models I'd studied relied on being fed data that are 100% accurate. For instance, when you see a headline about how eating red meat increases your risk of cancer by some percentage, this result will be (at least partially) based on asking real people how much red meat they eat. Unless you have a lot of money to spend it's unlikely your data will be perfectly accurate. If you blindly feed inaccurate data into statistical models you can end up coming to drastically wrong conclusions: the effectiveness of a drug could seemingly disappear, or we might mistakenly find something causes heart disease when it doesn't. It's important, then, to be aware of the problems measurement error can cause and, if necessary, take it into account.

So what can we do? As is so often the case in statistics, we collect more data. In some cases we might be able to stretch our resources to get some really precise measurements on a small group of people, or we could measure some people more than once. Both of these methods give us more information about the measurement error: if you measure someone's weight twice and get 79.5kg and 80.5kg that suggests the amount of error is pretty small, whereas if you got 60kg and 100kg you might think differently. The error is just another unknown in our equation, and by collecting these extra data we can learn more about it. From here, there are all sorts of algebraic tricks that help us turn this information into something we can reliably use, and it's at this point where I come in.

Despite being a relatively new area, there's already a mind-bogglingly large range of different models and methods for dealing with measurement error. As you may imagine, this can make it quite hard to know where to start if you've got measurement error and don't know how to deal with it. My work is, at its most fundamental level, about making

these methods accessible. I look at things from the perspective of the non-statistician, trying to answer the questions they would want answering, as well as making it easier to act on any recommendations I might have. Primarily this involves writing computer programs that make implementing these complex methods in a general setting more straightforward, but I also look at some specific types of scientific study to try and provide more tailored advice.

By this point you might be wondering exactly what it is I do all day, and I'm the first to admit that a statistician's life is as glamorous as, well, as glamorous as you'd expect. I spend most of my time at my computer either writing code or playing with datasets. If it's a really exciting day I might get some paper out and do a bit of algebra. My work may not appear as dramatic as that of my more practical colleagues, but my results have the potential to be just as significant. Statistics are the bedrock of almost every scientific study: get your stats wrong and everything else is basically useless. Measurement error is an often inescapable problem, and so a study that makes use of my results is one that can (I hope) stand up to greater scientific scrutiny.

So next time you see a headline about a groundbreaking medical discovery, spare a thought for the statisticians working behind the scenes. We might not be finding a cure for cancer, but we're the ones who can tell you if someone else has.

[HIGHLY COMMENDED]

Hunting out the enemy

Olly Donnelly

Sarah died at two in the morning, about three hours after I sent her parents home for the night - she was 19.

A couple of weeks before Christmas, completely out of the blue, she'd had a seizure. A CT scan of her head and a battery of other tests revealed widespread metastatic cancer. Metastatic melanoma is one of the most aggressive cancers and normally starts in the skin. In Sarah's case it had spread throughout her body, including her brain, before she'd ever known it was there.

The cancer in her brain made her have more and more fits. The fits weren't well controlled with medications and so Sarah had to come in and out of hospital to try and get on top of them. On one of those admissions I was working as a junior doctor in my second year. We gave the teenager more drugs to try and control the most recent fit and admitted her to the cancer ward for observation overnight.

I thought I was helping her parents by reassuring them that we'd look after their daughter and that nothing more was going to happen overnight. Sarah died on the ward, without her family, in that hinterland between Christmas and New Year's Day, less than a month after her first seizure.

Sarah had always been well, she had no other medical problems and like most other people who develop cancer, her immune system was perfectly normal. The cells of the immune system police the body, having evolved over a thousand millennia to tackle infection and parasites, but also possessing the potential to act against cancers. Our research looks for ways to trigger an immune response against cancer cells to help patients fight the disease.

If the immune system is the body's police force then melanoma is a very sophisticated and aggressive criminal. Melanomas, and other cancers, conceal their identity by reducing the number of molecules on their surface that normally provide information to immune cells - essentially a system of fake IDs and disguises. When an immune cell does recognise a cancer cell then it is prevented from triggering the alarm by a range of chemicals released by the cancer; akin to jamming the police radios. On the rare occasion that a cancer cell is successfully recognised and accosted it is resistant to the actions of the immune cell, as if the master criminal has already planned its jail break.

These barriers can be overcome. One approach we're trying is to use radiotherapy, a treatment to which melanoma in particular is considered relatively resistant. By giving radiotherapy to an area of metastatic melanoma we hope to generate inflammation not

just in the tumour cells but also in the nearby normal cells. This way even if the tumour refuses to release inflammatory signals then the adjacent healthy tissue will, which in turn will trigger an immune response. It's essentially calling the fire brigade when you need the police, but either way help is coming, and the cancer's ability to 'jam the radios' has been circumvented.

Another part of our work has been to use viruses chosen for their ability to infect and kill cancer cells. We've shown with a number of different viruses that the immune system is better able to recognise a virally-infected tumour cell. In fact having recognised a tumour cell riddled with virus the immune system is primed to better recognise other tumour cells too, overcoming the cancer's system of disguises.

With both of these treatments the therapy is confined to the area treated; you can't give radiotherapy to the entire body if the disease is widespread without doing more harm than good. Our aim is to find a treatment, or combination of treatments, that act on one area of disease but trigger an immune response to attack the cancer throughout the body.

Many have doubted that the immune system could ever play an important role in the fight against cancer but recent studies have debunked that. For the first time a drug has been tested in clinical trials that seems to have real benefits for patients with metastatic melanoma, and amazingly it has no direct action on the cancer itself. Ipilimumab acts on cells of the patient's immune system, not the tumour, and effectively takes the brakes off the immune system, unleashing it to attack the cancer. Like most cancer treatments there are side effects, but it is a huge leap forward for patients with melanoma and may have impacts for other cancers too. It is proof that the immune system can be harnessed - that it can be persuaded to join a fight it was previously blinkered to.

It feels a long time ago that Sarah died, but I still remember telling her parents to go and get some sleep, and still I think it's the worst mistake I've ever made. Since then progress is finally being made in the search for effective treatments for melanoma and hopefully there's more to come.

[HIGHLY COMMENDED]

A Volatile Pressure

Alastair Webb

As the blood pressure machine tightens on my biceps, cutting the blood flow to my hand, I nervously glance down at the small blinking heart on the screen. The uncomfortably youthful doctor taps away at his computer, giving off a sense of familiarity with the whole procedure, just shy of boredom.

beep...beep...beep. 170 / 95.

That's much higher than the last time.

"That's up a bit today, but I wouldn't worry. It was fine six months ago. Come and see the nurse next week and we'll check it again." Reassured, I head home.

I lie in my hospital bed 3 days later, someone else's arm hanging flaccidly from my body.

beep...beep...beep. 135 / 84.

The doctor leans over my bedside, his grim expression unable to provide the comfort I'm looking for. "I'm very sorry, you've had a stroke. Don't worry, we'll get you up to the Stroke Unit as soon as possible and get the therapists to see you." A psychiatrist's couch flashes through my mind before I realise that he means physiotherapy. He means rehabilitation. He means disability.

I've been on the other side of this conversation with my fictional patient many times, delivering the news that their life has changed forever, that independence has become dependence, that part of their brain will never work again. I've also reassured otherwise healthy people that their high blood pressure reading is just an aberration, or that it is the 'white-coat effect,' acknowledging my ability to cause stress just by being there. However I know now that I was wrong, as were millions of doctors just like me. A normal blood pressure reading doesn't cancel out a high reading found on another day, even when the average reading is 'acceptable.' We recently showed that people who have occasional episodes of raised blood pressure are more likely to have strokes, even if it is normal at other visits to the clinic.

This is a problem. For years doctors have taken the view that all patients have a 'true' blood pressure reading and that we need to estimate this by calculating the average of multiple readings. However, it is now clear that a volatile blood pressure is equally important in causing strokes, regardless of the average. This creates more questions than it answers: How many people have volatile blood pressure? How volatile does blood pressure need

to be to cause problems? What makes one person's blood pressure volatile whilst others are steady as a rock? What can we do about it? The beauty of science is that questions are never truly problems, however awkward or unpopular they may be. Instead they are opportunities to increase our understanding and hopefully make a difference to the person sitting opposite us in clinic.

We've addressed the last of these questions first. We combined the results from more than 600,000 people, having reviewed over 2000 clinical trials, to test if it is possible to treat volatile blood pressure with drugs that already exist. It is. Two types of medication reduce volatility in blood pressure and one type increases it, demonstrating the potential to prevent 1 in 10 strokes simply through choosing the correct drug. With more than 110,000 strokes in the UK per year causing over 50,000 deaths and more disability than any other condition, this could mean thousands fewer dead or disabled.

However, if we could understand why certain people have volatile blood pressure we might be able to prevent even more strokes. We are therefore examining people with small or 'mini' strokes who are at a particularly high risk of a stroke. By making careful measurements of their blood vessels we can assess how well their body controls their blood pressure and which of the many mechanisms involved is going wrong. By measuring their blood pressure, scanning their brain and monitoring them for the next five years we aim to identify which of these mechanisms is responsible for volatile blood pressure and how this causes strokes. Then, through working with groups around the world to combine data on individual blood pressure readings and the frequency at which strokes, heart attacks and other diseases occur, we will be able to determine which people truly need treatment for volatile blood pressure and which treatments work best.

I've stopped reassuring the person opposite me in clinic that their unusually high blood pressure is just a one off, instead I've started reassuring them that we can do something about it. Hopefully, the knowledge we are gaining from this work will tell us which tests are required to detect if someone has volatile blood pressure, how much of a problem it is and the best strategy to deal with it. Ultimately, this should mean that fewer people will have to hear me say 'You've had a stroke.'

Are You Chicken?

Samuel Bjork

It's amusing that one of the most persistent problems of human existence is so perfectly encapsulated by such a frivolous question: Which came first—the chicken, or the egg?

Philosophers as ancient as Aristotle made reference to this problem of circularity. Its variants bedevil any discussion of origins—of the world, of chickens, of life—to this day. It perhaps explains one draw of religious faith, for which this kind of circular questioning—if God created the world, did he also create himself?—is beside the point. Faith is justified by faith itself.

The "chicken-and-egg" problem, however, is an affront to science. We like to believe that science is justified not by theory or faith, but by fact. My graduate research has been guided by a pursuit of the chemical facts of the origin of life in the shadow of this overwhelming dilemma. Chicken? Or egg?

This search for the chemical origins of life begins with a basic observation: All living creatures are made of non-living materials. A complex interplay of inanimate chemicals forms the physical basis of life, yet the division between living cells and non-living molecules remains a hazy area of speculation. At the core of this speculation are the two questions I grapple with daily: when do chemicals come alive, and how do they do it?

There is a deceptively simple answer to this first question. In the stripped down framework of the primordial world, chemicals "come alive" when they are able to regenerate, replicate, and evolve. This is a primitive conception of life, one that we often use in colloquial speech. Ideas, we say, take on a "life of their own" when they arise with apparent autonomy, adapting and changing as they spread. The origin of life can be reduced to a similar ability to spread the information contained by molecules.

The theory that best addresses the second question—how such a "living" system may have arisen—is known as the RNA world hypothesis. RNA, like DNA, is a classic informational molecule. The four building blocks of both, called nucleotides, are arranged in sequences that determine nearly everything about us, from the color of our eyes to the way we think.

In modern cells, this information is encoded in discrete sections of DNA called genes. These genes are transcribed into RNA, which is then translated, with exquisite precision, into proteins. Proteins power most aspects of life by speeding up key chemical reactions, including the synthesis and replication of DNA and RNA, through a process called catalysis. Together, these three classes of molecules—proteins, RNA, DNA—form an efficient interlocking network.

Why, then, is RNA supposed to have come first? While RNA and DNA are equally capable of "encoding" information, RNA exhibits an additional property: unlike DNA, which relies on complex proteins to replicate, RNA can catalyze both its own replication and the reactions of other molecules.

It is this dual ability—to store information and produce it—that makes RNA so promising for the study of origins. It holds the possibility of resolving that most perplexing of paradoxes: Could RNA be both the chicken and the egg of life?

With three other chemists in my laboratory, I examine whether RNA can be coaxed into doing what it has, plausibly, spent millions of years teaching proteins to do for it. Can the four bases of RNA be assembled from the high-energy chemicals produced in the Big Bang? Once assembled, can these bases combine to form RNA capable of catalyzing other reactions, including its own replication? Can the process of replication, freed from the need for proteins, later usher those proteins back in as life marches forward? In my own research, I make short fragments of RNA and examine whether their three-dimensional shape is amenable to protein synthesis. I mix these fragments with high-energy protein analogues and look for some productive reaction, some hint of rudimentary information transfer.

I am, in short, a child cooking without a cookbook. And I'm cooking a ten-course meal. Let's assume there were only 30 different chemicals present on the early Earth. Suppose further that there is some combination of these chemicals—in some sequence, some proportion—from which life would emerge. It would take a lifetime to analyze even a fraction of the unfathomably large number of possible combinations.

Yet we still try. We try to tell a story, within the narrow realm of experimental inquiry, of how life might have begun—how we might have begun. Because the possibility of telling such a story is what science is all about. This is the chicken-and-egg problem writ large: we justify belief with experiment, and we experiment because we believe. Perhaps, in this way, the search for life's origins is not so different from life itself.

How to proof read a genome

Byrony Graham

The scribe sits scribbling furiously, sweat beading on his brow. He has to produce an entire copy of the text in front of him in a ludicrously short period of time, and he is feeling the pressure. He has no complex, automated technology to help him - just his own flesh and blood. Inevitably, he begins to make mistakes. He is only human, after all.

The text in question is the instruction manual which can build a human; it is your genome. Each individual on the planet has their own, unique text (with the exception of identical twins) and there is a copy inside every one of the thousands of cells which make up your body. These cells are constantly being replaced, and every time a cell divides it has to produce an exact replica of the genome - a text composed of 3 billion letters.

Clearly this is no mean feat. And the cell makes mistakes. But it also has the means to correct them, to proof read the genome. This process is critical to our health - if mistakes are allowed to accumulate, the cells become cancerous. Scientists now know that this accumulation is not specific to one type of tumour; it is the fundamental mechanism underlying every form of the disease. Understanding what causes these mistakes and why they are not corrected is therefore essential to the development of therapies which could potentially target not one, but many forms of cancer. And, during the course of my PhD, I am hoping to contribute to this understanding.

But I'm not actually interested in the mistakes in the text itself. I want to know what happens if someone tries to scribble all over it, or pull out a bookmark, or fold over the corner of a page. Even if the sequence of letters is identical, if the text is annotated differently – its meaning could be completely changed.

You see, although every cell in your body has the same copy of the genome, each cell bookmarks it in distinctively. It is these annotations, collectively referred to as epigenetics, which allow different cells in your body to have unique, specific functions despite having the exactly same copy of the instruction manual. So, when a cell needs to produce an identical copy of itself, it does not only have to copy the genome – it has to copy the bookmarks too. During the course of my PhD, I'm hoping to find out how a cell does this. How stable are these marks? How are they copied when a cell divides? What happens if cells make mistakes in where they put the bookmarks?

Using stem cells taken from mice and grown in a laboratory, I have identified tiny molecules inside cells which are passed on from a parent cell to its progeny. If these molecules aren't there when the cell divides, its descendents start to read all sorts of bits of the genome

they shouldn't; bits that should only be read in brain cells, or blood cells, or bone. So, these molecules somehow act to help the stem cell pass on its identity; to allow its progeny to remember their purpose in life. Are these molecules related to the bookmarks? Do they help tell the cells where the bookmarks are supposed to go? Or do they work in collaboration with the scribe directly, helping to copy the genome? I don't yet know. But what I do know, as a result of the work of other scientists, is that in tumours, these molecules are often changed or absent. So I'm pretty keen to find out.

Epigenetics is a new and exciting field which has not only revolutionised classical genetics, but could add critical information to our understanding of how and why, at the most fundamental level, we develop cancer. All over the world, scientists are working on different tumours from different parts of the body from different patients. But what is common to them all is that somehow, at some point, the scribe has messed up and a mistake has occurred in the genome. It could be a change to the sequence of the letters, a fold where there shouldn't be one, or a misplaced bookmark. I want to know what goes wrong to allow this mistake to be passed on to the next generation of cells. This could hold the key to understanding why tumours develop, and how we can treat them – even if we cannot stop the mistakes happening in the first place. We are only human, after all.

Risky pleasures in the bipolar brain

Liam Mason

You wake up feeling woefully low; thoughts plunged into deepest despair; unceasing hopelessness consumes your mind, your body and your soul. Not a week ago you had graduated with a degree to your name - the elation and enthusiasm that had burned with breathless ferociousness, now transformed into deepest apathy. A week of frenzied ecstasy, no need for sleep, those sky-high days of giddy recklessness and perpetual partying now so painfully regretted. As guilt and shame rack up, a trembled whisper escapes your quivering lips: "why did I do it..?"

Bipolar disorder (BD), formerly manic-depression, can be a devastating psychiatric disorder typified by a relentless cycle between the shrillest of emotional highs and haunting, rock-bottom lows. But what causes the 'normal' experience of emotion to go awry, as depicted above? More importantly, what can be done about these two opposing poles: mania and depression?

We generally feel low after experiencing loss or failure, such as losing a job, family member, or a relationship breaking down. People with BD may be particularly vulnerable to these experiences, provoking a loss of self-esteem and depression. On the flip side, success and achievement can be equally precarious; things like acing an exam or getting promoted can set in motion a terrifying upward spiral into mania.

The ascent into mania is initially typified by a bottomless supply of energy, creativity and confidence. As mood continues to expand and gather pace, a tidal wave of exuberance is accompanied with a voracious drive towards pleasurable – but often perilous – activities. Lavish spending sprees, uncharacteristic promiscuity and unprotected sex, as well as drinking and drug binges are greatly lamented pastimes, once the snowball of mania begins to thaw. New evidence suggests that these dramatic surges in mood, motivation and risk-taking could be due to hypersensitivity to sources of gratification.

The brain has evolved to reward us for choices that pay off using the 'feel good' neurochemical dopamine. Things like food, water, sex (and nowadays, cash) increased our ancestors' chances of survival and were therefore rewarded with a dopamine hit. Generally our sensitivity to rewards is pretty stable, but in BD the reward system see-saws: a blunted response to dopamine is thought to be the culprit in spells of depression, whereas heightened sensitivity to reward may be to blame in the manic brain.

So an imbalance exists in the brain's signalling of motivation and pleasure; but how can we better understand this 'spasmodic neurochemistry'?

The answer may be lying in the imaging facility at your local hospital. Functional magnetic resonance imaging is a technique allowing the pictures of the elusive mind (or more precisely, its thinking and feeling processes) to be quantified. Although the name may be long-winded, these scans can be obtained in minutes.

We hope to use this technology to better understand the brain networks underlying bipolar symptoms. Likely suspects include the ventral striatum, a part of the midbrain that codes the pleasure signal of experiences, and the amygdala, a part of the emotional brain relaying signs of threat. In mania it could be that the pleasure signal is exaggerated, or the warning signal is downplayed. Another idea is that the prefrontal lobe, the rational centre of the brain that normally mediates between these impulses, is out to lunch so to speak. This leaves the striatum and amygdala to battle it out in the heat of the moment, without the cooling voice of rational thought.

So, how is our research contributing to solving this puzzle? We wanted to find out whether a rewarding event; winning money on a gambling task, would trigger a greater dopamine hit in people vulnerable to BD. As well as taking greater risks on the task, there were clear differences in their brain waves: whilst the "woo-hoo"-factor associated with winning was enhanced as predicted, the "boo-hoo"-factor of losing was also found to be diminished. Maybe then, when people with bipolar disorder are faced with risky choices, they are not only more allured by the positives, but also more impervious to the costs.

As well as shaping future treatments for this devastating condition, we hope this research could benefit other clinical phenomena such as addiction, pathological gambling and binge eating, in which dopamine also features as a 'dark passenger'. Outside of the clinic, understanding how the brain interacts with reward is also applicable to those everyday instances in which the pull from immediate gratification diverts us from the path we'd rather walk. Whether it's succumbing to that chocolate muffin or topping up your glass of wine on a week night. Perhaps it's failing to keep Thursday's pay check away from that impulse purchase, or acquiescing to The Apprentice over your gym slot. In these ways we are all slaves to an ongoing tussle between the lustful ventral striatum and the more prosaic prefrontal lobe.

"All for one, one for all, that is our device".
Alexandre Dumas

The Power of One

Alice Neal

In the beginning there was one. From one cell came all cells, cells in numbers beyond imagining. Think about this, just for a moment. Every living thing that you see, from the fly that buzzes around your head to the plant on your window sill, all owe their very existence to an evolutionary journey that began with the same single cell. Now think about yourself. How your eyes move across these words, your hands that hold this paper, your self is made possible by the exquisite coordination of billions of cells. Yet you too, were once one cell, and your mother was once one cell, and her mother before that, all the way back until you reach that same cell that also gave rise to the fly that still buzzes around your head.

To make a new cell, a mother cell must pass on a copy of the instruction manual it uses to function: its DNA. In the case of complex life forms, you and me, yes, even flies, the manual is unimaginably enormous. Copying it is a serious undertaking. Sometimes small errors occur, letters get changed around, or repeated, or even missed out altogether. Replication errors (mutations) are the very coinage of evolution, they are responsible for all the beauty of the living world but equally they are responsible for all its cruelties.

Tim was a happy baby boy, though his mother recognised he had idiosyncrasies he was thought to be fairly normal. At age 4 however, he had abnormally large calves yet was weaker than his peers. He would fall several times a day, and had developed an unusual curve in his spine. By his 12th year Tim could no longer walk. At 15, weak neck muscles made it impossible for Tim to bend his head. At 17, due to a progressive weakening of the mouth and throat muscles, Tim required computer software to communicate, mechanical assistance to breathe and tube feeding. Tim died of heart failure at age 24.

Tim had Duchenne Muscular Dystrophy (DMD). His life course was simply due to the fact that his cells did not produce a protein called dystrophin, the molecular suspension that allows muscle contraction without damage. Tim's lack of dystrophin was caused by a genetic mutation that occurred during the division of his first few cells. If you could go back in time, and fix that one mistake, Tim's story would be very different. Unfortunately, time machines are beyond the realms of scientific possibility. Yet a cure for Tim is not.

Within all of us there remain cells that still possess the remarkable power of producing other cells: stem cells. When a stem cell receives distress signals from the body, it will emerge from hiding to divide sometimes hundreds of thousands of times to produce fresh new cells that can take over from old damaged ones.

The beauty of the stem cell is that we need only target one cell. Given time, a functional stem cell will give rise to millions of functional muscle cells. If I could have given Tim just a few of my stem cells, his muscle would have functioned just like mine. This is the vision that drives my research.

There is a type of mouse that suffers from a very similar disorder to Tim. I can take muscle stem cells from a mouse that does produce dystrophin and transplant them into this sick mouse. I am consistently astounded to see the emergence of dystrophin where there once was none. But it's not enough. Yes, we see dystrophin, but we need more of it. Is there something I can do that will encourage the transplanted cells to continue dividing? I want the very best cells for the job, I am not sure that I have them. Is there something special about the cells that survive transplantation? Can I identify and select for them? These are the questions that consume my working day and to which I passionately desire to find answers.

Increased understanding of stem cells has already led to astonishing places. We can make rats with no tails, mice that glow green, even flies that grow legs out of their head. These science fiction-esque feats, though they may seem alarming, are more than just trophies of intellectual accomplishment. For future generations of boys like Tim, the power of science to manipulate stem cells could be life changing.

This won't hurt a bit (...trust me, I'm a Nanotechnologist)

Frances Pearson

It's the day every new parent dreads. Anxiously glancing around the tense waiting room, eyes meet with shared trepidation whilst plump, rosy toddlers play with oversized building blocks, oblivious to their impending distress. A loud yelp, a millisecond of silence before a high-pitched wail reaches a deafening climax, and a red-faced child in floods of hot, wet tears is bundled back through the waiting room clutching his arm. It is vaccination day.

Babies aren't the only ones to hate injections – approximately 10% of adults also suffer from a fear of needles ranging from the mild to the debilitating. But what if there were another way to introduce vaccines into the body with the aim of stimulating protective immunity against infectious diseases, without the requirement for long, painful needles? My PhD research objective is to develop patches for the delivery of vaccines through the skin using arrays of tiny silicon microneedles. Made using the same micro- and nanotechnology techniques employed to manufacture computer chips, individual microneedles are only 100-300 μm in length - too short to reach the skin's pain receptors.

There's no doubt that injections are unpleasant, but needles carry far greater dangers than a simple 'sharp scratch'. Improper disposal of needles used to deliver medical injections accounts for up to 20 million new serious infections a year including Hepatitis B and C, and HIV through blood-borne transmission from person-to-person. Needles are an occupational hazard, and unless properly discarded could be re-used by injecting drug users, collected from waste sites by children, or even recycled for use in under-resourced hospitals or health clinics.

Before the risks associated with needle sharing were known, injecting many people with the same syringe was common practice in some countries, with disastrous effects. An attempt by the Egyptian Ministry of Health in the latter half of the twentieth century to control a parasitic disease affecting the liver aimed to provide populations living in high-risk areas with regular injections of anti-parasitic drugs. Though oblivious at the time, their re-use of needles to administer the drugs simply replaced one cause of chronic liver disease with another. Now, Egypt has the highest incidence of Hepatitis C in the world.

Put simply, needles are bad news, particularly in areas of the world where healthcare resources are in high demand. Despite this, they have been used to deliver vaccines since they emerged as a vital part of our defence against infectious disease. However, in the first demonstration that vaccination was effective in preventing disease by the English country doctor Edward Jenner in 1796, the vaccine was not delivered by hypodermic needle but instead scratched into the skin using an embroidery needle. This act not only gave birth

to one of the most effective public health measures of all time, but also would result in the first complete eradication of an infectious disease by man – smallpox. Though Jenner didn't realise it, depositing a vaccine just underneath the skin's surface is a particularly effective way of delivering it. This is because the skin (unlike the muscle where the majority of needle-delivered vaccines are placed) is packed full of immune cells, ready and waiting to face an opportunistic attack. I aim to take full advantage of this by placing vaccine amongst these skin cells using microneedle patches. Immune responses generated by vaccines delivered this way have the potential to be stronger than those resulting from delivery into the muscle, even when using a lower dose of vaccine.

I focus on malaria as an example of a disease that requires an extraordinarily high level of immunity in order to fight the parasite in its early stages to prevent symptoms from occurring, which can result in coma and death. These consequences are most common in children aged 0-5 years, with one child dying every 45 seconds from the disease. The first malaria vaccine is expected to reach licensure within the next 5 years. Currently, the diagnosis, treatment, and high mortality of malaria place huge burdens on a malarial country's economic growth, trapping it in a cycle of disease and poverty. Implementation of a simple method for delivering vaccines without costly personnel training (patches could potentially be self-applied) or provision for safe needle disposal would relieve some of these burdens. Patches are small and easy to distribute to those living in rural areas far from health clinics, which would make malaria vaccines more accessible to a wider number of people.

In mice, I have shown that delivery of a malaria vaccine using these patches was able to induce comparable immune responses as vaccination using a regular needle and syringe. This was assessed in terms of the number of activated immune cells able to secrete a substance known to kill cells harbouring parasites, preventing them from progressing to the symptomatic stage of malaria. These responses were equally as able to protect patch-vaccinated mice against acquiring the symptoms of malaria following infection with parasites, as those vaccinated by regular needle. Remarkably, this was with less than 10% of the dose that was required when vaccinations were given by needle, demonstrating the potential of the skin to induce stronger immune responses. This finding could translate to a reduced cost, and a wider distribution of vaccine doses.

Much work is still to be done before patches can replace needles altogether, particularly for the delivery of a vaccine against malaria, but with inspiration from Jenner and with cutting-edge technology as our tool, needle-associated pain and suffering may soon become history.

[SHORTLISTED]

In science no one can hear you scream

John Rushton

The microscope whirs into life. I turn out the lights, take a deep breath, and peer down the eyepiece. I adjust the focus, searching, hoping, and seeing... nothing. I am alone. I am in the dark. I am somewhere between despair and rage. It's all I can do not to bash my head on the desk in front of me. Maybe I should explain? Let's go back to the start...

In the late 1960s a ground-breaking approach to the treatment of disease was conceived – gene therapy. It seemed so simple. Genetic disorders (including well-known diseases such as Huntington's and sickle cell anaemia) are caused by genes, the blueprints for life, which have gone wrong. If you're trying to build a house, but the blueprints have had coffee spilt on them, you could end up with no windows, or an upside down roof, or something that wouldn't go amiss on Changing Rooms – the horror. The concept of gene therapy is that we can replace these faulty genes with working ones, and thus cure the disorder. Sounds easy enough, right? Wrong.

Nearly half a century later we are still a long way away from working gene therapy technology. That's not to say there hasn't been progress. Our understanding of the subject, and the technology and techniques used in the lab, has massively improved, along with the basic concept becoming widely accepted by scientific and medical communities. Public understanding and media depiction have also improved, even if films do repeatedly suggest that genetic experimentation will be the cause of zombie apocalypses and/or spider-man. There are still many problems left to solve, and that's where I come in.

The genetic disorder I study is Cystic Fibrosis (CF), one of the most common inherited diseases in the Western world, affecting over nine thousand people in the UK alone. CF is caused by a defect in a gene responsible for controlling sweat, digestive juices and clearing mucus. Without this gene thick, sticky mucus builds up in the lungs and digestive system, making it difficult to breathe and digest food. Worst of all, this mucus leads to a greater chance of contracting lung infection, almost always the cause of death. There are two copies of every gene in each cell in the body, and to suffer from CF both copies of the gene must be defective. If this is the case, you probably won't live past thirty. I want to be able to restore a working gene into the lung to treat this disease.

One of the biggest problems in gene therapy is getting the working DNA into a cell, a process called transfection. An obvious way of doing this is to use viruses, which have evolved over millions of years to enter foreign cells. However, the use of viral technology expensive and the immune response can make repeat dosage impossible. I'm trying to use a non-viral gene transfer agent, a chemical called polyethylenimine (PEI). Unfortunately

PEI-mediated transfection is much less efficient than viruses, so I'm creating a PEI which can target particular cells.

Think of the body as a street, each house being a different type of cell, with PEI as a burglar. The burglar tries to break into any house he can. Give him a key and he'll go to the house the key unlocks and walk right in. I've given him the key to the cells lining the lung – folic acid (aka vitamin B9). The doors to this house are the proteins which attach to folic acid and bring it into the cell – folate receptors. I have chemically attached folic acid to PEI, and I'm transfecting different cell types with a gene that makes them produce green fluorescent protein. If the transfection is successful then the cells will glow green under the microscope. Cell types which have folate receptors should prove easier to transfect.

I spend at least a third of my science time reading papers written by other scientists. I've been inspired by cancer research, virology, molecular genetics, chemistry and more. Newton said that scientists are standing on the shoulders of giants. In actuality, scientists are standing on the shoulders of a tower of other scientists who are all wearing a really long coat so that they look like a giant.

That's how it feels, at least – and it's no bad thing. So as I sit in my darkened room peering down the microscope at nothing, fighting that urge to scream at a failed experiment, I stop. I breathe. I remember the importance of the work I'm doing, and that even the smallest of results, negative or positive, is a step along the path of discovery. A path I am far from alone in walking. And I reach for the next plate of cells.

Racking our brains

Neshika Samarasekera

Two months ago I met Jane and her mother in the side room of our stroke unit. The day before, Jane had been due to meet her mother to go to a classical music concert. Her mother never arrived. When Jane reached her house she found her lying unconscious in the hall.

Every day about 400 people in the UK will have a stroke and instantly, their lives and those of their families are changed forever. Strokes happen when a blockage forms in a blood vessel that feeds the brain or when a blood vessel bursts (a brain haemorrhage.) I am researching brain haemorrhages and trying to work out what causes them.

So what do we know already? We know that various factors such as having high blood pressure can increase your chances of having a brain haemorrhage. However, when someone comes into hospital having had a haemorrhage, it is often very difficult to explain exactly why it has happened to them at that particular time.

The clue to unlocking these secrets may lie in examining the brain tissue itself. I am looking at a particular protein which deposits itself in the brain, called amyloid. In stroke, amyloid that finds its way into the blood vessels may weaken them and make them more prone to bleeding.

Some mysteries of the brain can only be illuminated by the microscope, and this is the case with amyloid. I am seeking consent from people who have had a brain haemorrhage or their families (if the person themselves is too unwell) to take samples of brain tissue after death and study the tissue for amyloid. This poses different challenges, both procedural and personal. In the late 90's public trust in doctors was eroded as the Alder Hey and Bristol organ scandals surfaced in which doctors had retained organs from those who had died without asking their families. This led to an overhaul of the framework governing the handling of human tissues and the creation of new laws which make explaining the tissue donation process and seeking consent paramount.

When I meet Jane, she is sitting by her mother's bed. Her mother lies peacefully with her drip removed and her paralysed side supported by pillows. The manicured nails on her limp left hand poke out from underneath the sheets.

'May I have a word?' I ask, and in the pit of my stomach I have that familiar feeling of butterflies. I usher her into an adjoining room.

During the course of the last year, I have gradually become accustomed to approaching families of people dying from brain haemorrhages to discuss tissue donation. I talk with Jane at length about the study and her mother's life. During the second world war she had been a prisoner of war in Poland and when the war ended, she came to England, meeting Jane's father and retraining to be a mental health nurse.

When families consider donation, there is a spectrum of personal and cultural beliefs that come to bear. 4-5 out of every 10 people I ask do give consent. Those who decline do so for a variety of understandable reasons. Some cite religious beliefs, others feel unprepared to make the decision, and sometimes the person asked would wish to donate their own tissue but feels that their relative for whom they are making the decision, would not.

Many relatives have questions: 'Will taking the tissue disfigure my father's or mother's face?' (It doesn't) or 'Will it delay the funeral?' (It doesn't since the sampling of the brain is done typically within forty eight hours of the person dying.)

When Jane phones later to say that she will give consent for tissue donation, she describes the need to balance her mother's wishes as a nurse who would wish to facilitate medical research with her troubled experiences during the war which led her to become intensely private and guarded.

I am constantly surprised by the generosity of those who give their consent in these difficult circumstances. The most common sentiment that families express is 'as long as it helps somebody else' but there have been a plethora of other responses, including interesting perceptions of tissue donation:

'My husband didn't want to complete the NHS Donor card because he thought that he would be 'bumped off' if he was then admitted to hospital. We now know that this was wrong and he would support tissue donation' or

'Is your role like being Nikki (Dr Nikki Alexander, forensic pathologist) in Silent Witness?!'

As we accumulate samples I hope that we can do justice to all those who have donated brain tissue by helping to find out more about what causes brain haemorrhages.

"So this will kill me then?"

Taming the Butterfly – Understanding treatment-resistant thyroid cancer

Neil Sharma

What do I say? Emma knows the answer, it's the third time she has asked the question and this will be the third time I answer it. We've been sitting talking for 20 minutes about the lump she found in her neck. About how it means that the thyroid cancer we cut out 12 months ago has come back. About how the fact it has survived being blasted with radioactive iodine means that we have used up our options. About how there is not much more we can do other than make sure she does not have too much pain. Emma is 29 years old; throughout the last 20 minutes she has not looked at me, focusing instead on Jack, her 2 year old son, playing with a squeaky toy. She looks at me now as she asks a fourth and ultimately final time. Again I tell her, "Yes, it will".

Emma has thyroid cancer, and although it is the commonest endocrine malignancy it is not as well-known as breast or lung cancer so does not get the coverage it deserves. Emma is in the usual demographic for the disease, young and female, and the fact that many of our patients will be mothers like Emma makes giving the diagnosis especially hard. Cancer is essentially caused by the failure of the "off switch" in a cell; the cell keeps multiplying despite the body's attempt to destroy it, eventually becoming the dreaded "lump". For most people with thyroid cancer, treatment will consist of an operation to remove the whole gland, followed by radioiodine to kill any remaining cancer cells. While for many this will be the only treatment they need, in a small number, such as Emma, the cancer does not absorb radioiodine. In these tumours, we are often lulled into a false sense of security, unaware that despite our best efforts some of the most hardy and untreatable cancer cells remain in hiding within the neck, multiplying and migrating, and that they may show themselves as a recurrence up to 30 years down the line. Or in Emma's case 12 months.

I work on a small protein called PBF, which although produced by pretty much every cell in our body, not much is known about. What we do know is that in a number of cancers, not only is it over produced but it also interferes with the cell's normal actions; the most significant of which in the thyroid is its ability to take up iodine. It is likely that PBF plays an important role in cancers such as Emma's, preventing them from taking up the radioiodine which would get rid of them once and for all. Unfortunately, we do not know enough about PBF to be able to stop it directly and it is here that my research comes in.

I use immortalised thyroid cancer cell lines to work out exactly how PBF causes these effects. The cells were taken from a cancer that killed someone years ago, then kept alive by scientists for decades to study how thyroid cancer behaves; in a way they are the ultimate double-agents. By examining the contents of these cells through a process called

mass spectrometry, I am identifying a number of the proteins that PBF interacts with. Hopefully one will be an "Achilles heel", another protein that we do know about and that we can target much more easily. By using a drug that inhibits this second protein, we hope to be able to prevent PBF blocking the uptake of radioiodine, making thyroid cancers much more susceptible to treatment.

Cancer research is a bit like a game of battleships in which PBF forms part of the vast, empty board of thyroid cancer. Laboratory research like mine hunts for targets; exploring the PBF corner of the board, searching for that elusive first strike. Once we get a hit, the next steps are to map out the rest of the ship. These are the clinical trials, the slow and steady process of determining whether the new treatment will be the magic bullet that sinks the battleship. Eventually, once all the trials are complete, once we know it is safe and once the treatment has been licensed, we can actually offer it to patients.

So unfortunately while this will all be too late for Emma, in years to come if a young woman sitting in front of me asks if her thyroid cancer will kill her, I hope to be able to say confidently "No, it won't."

More on the prize

Professor Max Perutz, who died in 2002, was a world-renowned scientist who helped to found the Medical Research Council's laboratory of molecular biology in Cambridge. He encouraged young scientists to communicate their research in plain language to the public.

The Max Perutz science writing award is aimed at supporting and rewarding scientists to convey the importance and excitement of their work in an accessible way.

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