



Max Perutz Essay Prize 2007: JOINT WINNER

Behind Enemy Lines: Discovering the Stealth Tactics of the Meningococcus

Anne Corbett

It's the kind of nightmare that all parents dread. Morning dawns like any other, accompanied by the usual frantic rush. The kids reach the school bus in the nick of time and are swept away, their minds already occupied with the serious business of playground politics. Your youngest, boisterous and vocal, just eighteen months old, remains in his high chair, clamouring for attention. He is the apple of your eye, your baby. You play happily together that morning, but by lunchtime you notice he is flushed and restless. As you put him down for his afternoon nap his temperature has risen and he has become feverish. The usual remedies don't seem to be working and after a couple of hours you become anxious. The flu-like symptoms have worsened and you decide to act. The doctors have taken samples, run their tests, and their faces are grave. You are joined at the hospital by the rest of your family. You huddle together, watching helplessly. By bedtime your healthy happy child is lost forever. How can things have changed so quickly?

Meningitis can kill its victims within just four hours. Symptoms vary between cases; often the telltale rash does not appear and the only signs of illness are a fever and headache. The most severe form of meningitis is caused by the bacterium *Neisseria meningitidis*, the meningococcus. It is not rare; in fact it lives in the nose and throat of up to 40% of the population. These hosts suffer no ill effects whatsoever, but pass the bacterium on to others by coughing and sneezing, or more directly by kissing. The trouble begins when the bacteria force their way through the tissues in the nose and throat, aiming for the bloodstream. They use the network of blood vessels as their own transport system, travelling throughout the body extremely rapidly, releasing potent toxins as they go. The immune system launches an all-out attack but by this point the damage is often too severe. The body is overrun with bacteria, and there is rapid swelling in the brain. Victims of meningococcal disease face mortality rates of up to 50%, and those who survive are often left with severe after-effects including deafness and paralysis. In order to tackle this disease we must understand how it is able to cause such devastation in such a short time.

The immune system is our key defence against infection. My research focuses on the role of white blood cells, neutrophils, in meningococcal disease. Neutrophils patrol our bloodstream looking for intruders. They are professional, voracious killers

that detect infection and arrive first on the scene, weapons primed for attack. Neutrophils engulf bacteria and use an arsenal of weaponry to launch the cellular version of chemical warfare. The potent chemicals degrade the bacterial cell, destroy its proteins, and attack its DNA, killing the bacterium very rapidly. We know that the meningococcus comes into contact with neutrophils during meningitis, but little is known about what happens when they meet. I study this interaction by extracting neutrophils from human blood and then infecting them. Usually bacteria are killed by neutrophils within thirty minutes. However, the meningococcus not only survives, but actually grows inside them. If it is able to stay alive inside neutrophils, this could be extremely important. Neutrophils can cross from the bloodstream into the brain and spinal cord. What if the bacteria hijack the neutrophils for their own gain? Not only would they be able to travel rapidly around the body and cross quickly into the brain, they would also be hidden from the rest of the immune system. It would be the ultimate stealth tactic – to remain under the enemy radar, using their vehicles as camouflage. My work is now exploring how the meningococcus is able to survive in the hostile environment within the neutrophil. I have found that the bacterium possesses a specialised repair system for preventing DNA damage, enabling it to withstand the neutrophils' destructive chemical attack far better than other species. I am also investigating how the meningococcus might use food sources available inside the host cell to its own advantage. It can divert its metabolism to strengthen its defensive structures when under attack. I believe it is likely that the bacterium scavenges inside the cell, bulking up its own defences whilst simultaneously depriving the neutrophil of its own precious resources.

If we are to tackle meningitis, it is imperative that we understand as much about the disease as possible. This is the route towards developing vaccines and improving treatments. The incentive is clear; meningitis develops spontaneously, and without warning. If the meningococcus is equipped to injure us by manipulating our own defences, we need to retaliate. Through better understanding of the disease we hope to find more effective ways to fight back.



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Pop-up proteins

Charlotte Rusby

Have you ever had one of those really complicated pop-up books? One where the dinosaur is coming out the page towards you in 3-dimensions and every last tooth and scale is separately attached in perfect and horrifying detail? Have you then tried to find out how the pop-up works? Peering between the pages as you open and close it, trying to see how everything is attached. Now imagine that you're trying to do this, but the book has shrunk 100 million times to the size of a protein molecule. Welcome to the world of protein folding!

Proteins are molecules indispensable in keeping the cells in our bodies working. They provide the rails and motor to 'trains' in the cell moving things from one place to another. They act as messengers allowing the cell to find out what is happening outside and taking messages from one part to another. They package the DNA so that parts that aren't being used are kept tidily away and ensure that the right genes are turned on at the right time. They also monitor what the cell is doing, and if something is causing trouble, they get rid of it. When the right time comes, they kill the cell.

Just as the pop-up book is made from pieces of card glued to the page in the right order, proteins are made from 'molecular card' (amino acids), glued together in the right order. If this gluing is done correctly, the protein will spontaneously fold to take up its completed 3D shape. Just like opening a pop-up.

Most of the time the protein pop-up works smoothly, but occasionally things go wrong. Changing one of the pieces might mean that the picture in the pop-up book isn't properly assembled, or isn't open all of the time. Likewise, a single mutation in the amino acid sequence can mean that a protein isn't folded properly, or isn't folded at body temperature – an amazing 80% of human disease-causing mutations have this effect. Proteins recognise each other and interact by shape, so the shape of a protein is imperative in ensuring that it works correctly. When a protein is unfolded or its shape is otherwise changed it can't interact and carry out its job properly. If that job involves killing misbehaving cells, those cells can proliferate uncontrollably – and that means cancer.

While many people have been working on ways to treat diseases by correcting the function of the proteins involved, my research looks at the fundamental question of

how proteins fold when they are working properly. If we want to understand complicated diseases, we need to understand how things work correctly. What I'm doing really is as basic as trying to understand how the pop-up book works.

A lot of the questions I'm asking are just the same as those you might ask about the pop-up book. What does the folded protein look like? What does the unfolded one look like? Is there a preferred order or logic to the self-assembly? Like the pop-up, the first question is much easier to answer than the others – as soon as you try and look at the unfolded protein, as soon as you fractionally open the book, the protein folds and the pop-up is complete.

Since the proteins I study are 100 million times smaller than the pop-up book – a hundred times smaller than a standard microscope can ever see – I can never 'watch' what I'm doing, I have to infer it by measuring other things. For example, by measuring the speed at which the protein folds, changing one amino acid – one piece of molecular card – and measuring the new speed I can find out which parts fold first. The next stage is to refine the general rules we have by comparing similar proteins and seeing how small differences in amino acid sequence – small differences in pop-up picture – affect the way the protein folds.

At the moment, if we design a new protein we can only guess what the final shape will be – but it is the final shape that dictates what the protein can or cannot do! Making new proteins is a bit like knowing what you want the pop-up to look like, but clumsily sticking pieces of card onto the book without really understanding how the process works. There are ways around this: if you take a protein similar to the product you want, you can make small changes and slowly build up something useful. A bit like changing the pop-up dinosaur into a dragon perhaps – although making an alpine meadow would be much harder. My hope is that one day we will fully understand the rules of our pop-up books – not only to understand disease but also to treat it by designing protein drugs that will do exactly what we choose.



Max Perutz Essay Prize 2007: RUNNER-UP

Flesh and Bone

Ruth Burnett

My friend Sasha is one of the few British women who are happy with their body. She's tall, naturally blonde, a size 8 and has men queuing up. She eats healthily, exercises regularly, doesn't smoke or drink excessively and takes delight in lecturing anyone who doesn't have her healthy lifestyle. But the low fat lifestyle, that is working so well for Sasha now, may hold a few surprises for her in the future and the beautiful figure she has may lead her to develop one of the major chronic diseases in the UK today.

I am talking about osteoporosis.

Until we reach around 30 years of age our bones are growing. At first we see this as a gain in height, but even after adult height is reached we continue building up bone by increasing the width of our skeleton. At around 30 years though, we have the most bone in our bodies that we will ever have. From this point onwards we start slowly losing bone as the natural processes that continually destroy it start to work faster than those that build it. As we age the bony structures are eroded and, like rocks in the sea, get thinner and the naturally tiny holes in them get larger and larger. This is osteoporosis. Eventually the bones don't support body weight so well any more and when weight is put on them suddenly, as in a fall or even standing up too quickly, they can break.

One in three women and one in twelve men over the age of 50 in the UK suffer a fracture caused by having fragile bones and this costs the health service billions of pounds each year. For the victims these fractures can mean dependency on others for life.

As with many diseases, lifestyle choices, such as smoking, heavy drinking, being inactive and having a poor diet, can increase the chances of developing osteoporosis. However, unlike most diseases, having a low body weight is one of the biggest risk factors for developing osteoporosis and determining its severity. This is because fat storage cells make a lot of different substances that protect our bones, such as female hormones. The more fat we have, the more of these bone-protecting substances are produced. So Sasha, with her low levels of body fat, can't be as assured of avoiding all chronic disease as she thinks.

Fortunately for her however there is the possibility of help on the horizon, in the form of the protein adiponectin. Adiponectin is a contrary protein: although it too is produced by the body's fat storage cells, it is unusual because less adiponectin is produced the more fat a person has. In other words Sasha will have a lot of adiponectin in her blood because she is thin.

Recently, scientists have started to think that adiponectin might affect the amount of bone mineral a person has and the speed at which it is lost. Experiments in laboratories have shown that adiponectin encourages the processes that build bone and slow bone erosion.

But how can experiments in laboratory test tubes show us what happens in our own bodies? In short, they can't. They can certainly give us an educated guess but the real test is what happens in real people.

In my research I am investigating whether adiponectin affects bone health in postmenopausal women, like Dorothy (whose name has been changed for confidentiality). Dorothy visited our suite, designed to make volunteers feel at home, and spent a day with me. During the day Dorothy had, amongst other measurements, scans taken of her bones that she could see displayed on screen. The results of those scans will tell Dorothy how healthy her bones are.

"When you get to a certain age you start thinking about osteoporosis and it's nice to know if you have a problem or not," comments Dorothy.

Together with the bone scans, I also measure the amount of adiponectin in Dorothy's blood, as well as the amounts of some other proteins in the blood that give me an idea of how quickly her bones are being eroded. When I put all this information together with that from other volunteers and take into account their body fat and muscle I should be able to see whether, in living people, adiponectin levels in the blood are linked to the health of bones.

If my friend Sasha is lucky I will be able to confirm that adiponectin is good for bones and in the future it will be possible to increase the bone strength of thinner people by making them more sensitive to this protein. Then Sasha will be able to return to her feeling of superiority over the rest of us and continue lecturing us mere mortals on how unhealthy we are.



Max Perutz Essay Prize 2007: COMMENDED

How We Know When To Quit

Daniel Campbell-Meiklejohn

It just slipped out. Across from me, horrified, my partner stared back over her breakfast. I hadn't meant what I said but if I simply admitted that, she would not let me forget it for a while. If I continued chatting on the other hand, I could stumble into a brilliant point or, even better, she might simply lose interest. I keep talking. Her brow is furrowing. I had seen this before. This was not good. However, I can still recover. I'm still talking. Her lips tighten. I up the tempo and look down to my bowl for support. My cereal, like my argument, is turning to orange soggy mulch. I look up. I have no previous experience with this particular expression, but I am pretty sure she is going to hit me with the toaster. Instead, she walks upstairs, leaving my cornflakes and I to review what had just occurred. Why didn't I just give up?

I could not have known precisely what would have happened if I had stopped or gone on, yet we all make these decisions every day without knowing their outcomes. We might decide to stay in a relationship or a job when things aren't their best, hoping that one day, it will be better. We could keep looking for our keys in the sand before calling roadside assistance or drive by the petrol station without getting direction because we might find our street sooner by chance. We might keep our money in a fund when our investments take a dive or perhaps send even more troops into Iraq. In all these cases, we take a risk in the hope of recovering our loss with the possibility that we could make things even worse.

Scientists call this 'loss-chasing.' Pathological gamblers have a particular problem with it and it is central to their disorder since they return often after losing to break even. If we know how these decisions play out in our brains, we can begin to understand why decisions go wrong in compulsive people, learn how we make these decisions ourselves and, perhaps with some ethical controversy, even predict the decisions people are about to make.

As I finish my breakfast, I think about the tug of war between the bliss of recovery and the bitter taste of losing more. These days, using new technologies like functional magnetic resonance imaging, we can virtually see into the brains of people when they make decisions. This year, we placed Oxford students into an fMRI magnet (resembling an oversized polo mint) and asked them to make

decisions to chase their losses or accept them. Inside their brains, we found a real life tug of war.

When things go wrong, the experience is said to leave a biological memory in our body. The next time we are about to make the same decision, a gut 'feeling' from our body's seemingly intuitive reaction to the familiar scene reminds us that we have made a decision like this before, and it did not go well. These feelings, are received in a brain area known as the anterior insula and cause other brain regions to think a little harder about what we are about to do.

We found that these brain areas are more active before a decision to quit the chase. At the same time, brain areas known to understand and expect the good things in life, rewards, reduce their activity. With this shift in brain activation, we will likely quit our chase. Without it, we will probably keep on chasing.

Interestingly, we also found that certain neurotransmitters in our brains can also affect how much we chase. If we lower serotonin levels, a chemical elevated by common antidepressants, we can cause healthy adults to chase their losses less. Alternatively, changing the workings of another chemical, dopamine, as is done in the treatment of Parkinson's Disease, increases the risk that we are willing to take to chase. This last finding helps us understand why some Parkinson's patients seem to turn to pathological gambling after treatment.

So, thinking back to our breakfast conversation, I can imagine the battle of brain activity in my head. Maybe my brain's response to a gut feeling was not strong enough to shut down my chat or maybe the tempting idea of a blissful recovery activated my brain's rewarding areas too much to resist. Perhaps a few brain chemicals shifted at an inopportune moment during breakfast. Today, we are closer than ever to figuring out how and why we make our decisions and it has been an eye-opening journey into the human mind during my doctorate at Oxford. One thing I realise now, on my way upstairs with two fresh cups of tea, I am about to cut my losses.



Max Perutz Essay Prize 2007: COMMENDED

Speechless

Vincent Deary

Leonard has no voice. Well, nearly none. If he tries, he can force out a cracked whisper. Mostly though, he has stopped trying and resorts to awkward mouthing and miming. His career as an actor is over. With friends and family, this once sociable life and soul now sits on the edges, wanting to be part of things yet dreading to be asked. It is his first visit to the Speech Clinic at the Freeman Hospital in Newcastle, and as he tells us his story, the effort it takes is palpable. This eloquent, intelligent man lived by his voice, loved words and conversation. Trying to convey his vibrant personality through this broken instrument both tires and embarrasses him. He gestures at his throat as he tries to speak, "this isn't me". He gives up. Then something gets him trying again – anger. For he was recently given some very bad news about his voice: there is nothing wrong with it.

Leonard is one of 50,000 people every year who suffers from a condition once known as hysterical dysphonia, now known as functional or psychogenic dysphonia. The nature and variety of the terms warns us that we are in the clinical and ideological grey area of "psychosomatic medicine". It's a big area. Every week, most of us will have a physical symptoms or two, usually pain or fatigue. For about a third of us, at some point in our lives, these symptoms will hang around, intensify and gather companions, and we will go to the doctor, only to be told, like Leonard, that there is nothing wrong. Such is the scale of the problem that the more pejorative labels, like hysteria, have had to go, now replaced by the more neutral "Medically Unexplained Symptoms" (MUS). For many specialist clinics, like ENT, Gastroenterology and Rheumatology, MUS account for close to half of their traffic. It's a hugely costly problem, but more than that, these symptoms are the point at which both lay and medical understanding of illness breaks down, leaving patients and doctors stranded in a kind of ideological no-mans land, where neither knows what to do.

Leonard's experience was typical. Finding nothing physically wrong, his consultant told him that his problem was "psychosomatic", and referred him for a psychological assessment. This is the current model in a nut shell. Both institutionally and ideologically, medicine splits the human being into two compartments, body and mind. If symptoms appear in the physical realm without physical cause, there is only one other place where they can originate. To link the

two realms, most physicians still rely on the psychoanalytic notion of “conversion”, where unacknowledged psychological distress gets translated into physical symptoms. Thus, after seeing the physician, the MUS patient will usually find themselves referred to the psychologist or psychiatrist. So it was with Leonard: “psychosomatic” he says, quietly furious, “is the word doctors use when they don’t know what’s wrong, and my subconscious is where they hide their ignorance”.

Recent research might serve Leonard better than this old paradigm. Based on the principles of cognitive behavioural therapy (CBT), its roots are in chronic pain research. Its starting position is that the patients symptoms are real, and that how they manage them can alter them, for better or worse. A typical response to pain is to use the affected part less, to become generally less active and more socially withdrawn. This is a good short term strategy. Long term, however, disuse often leaves the part weaker and more vulnerable to pain. The general decrease in activity leads to physical weakness, lethargy and tiredness, and more physical symptoms. Over time this can lower mood. Add to this medical uncertainty and personal anxiety about the cause or meaning of symptoms, physical tension, disturbed sleep, social withdrawal, loss of roles... The person with physical symptoms can become caught in various vicious circles, which can inadvertently make existing symptoms worse and create new ones. Using CBT to help patients out of these vicious circles has been shown to help people with other MUS. Will it also help Leonard and the 50, 000 like him?

Leonard recognises some of these patterns. He can feel the anticipatory tension any time he starts to speak, knows he is becoming more and more avoidant of using it. But it isn’t just his voice. He is exhausted, tense, frustrated, withdrawn and anxious about his future. We already know that speech and language therapy can help get his voice better, but that it probably won’t improve the other symptoms and feelings that have grown up around his condition. Our pilot study showed that giving a speech and language therapist a five day training in CBT improved the general well being of her patients, not just their voices. Now we are doing a larger trial to refine and test this intervention. Success could change practice across the health service, providing a model for training clinicians to deal with other unexplained symptoms. But, for the moment, we are hoping to give Leonard back not only his voice, but also his vitality.