



## Max Perutz Essay Prize 2008: WINNER

### Pain: it's all in your head

Michael Lee

You slip on ice and land heavily on your hand. The pain is instant. Soon, your wrist reddens and swells. It becomes painful to the touch. You rush to the A&E department of the nearest hospital and get an X-ray. Luckily, you haven't broken anything – merely sprained your wrist. It should get better in a few days. In the meantime, your wrist hurts and you wear a wrist guard to protect it from further strain. A week later, your wrist is back to normal. You soon forget that you were ever in pain.

What if the pain doesn't go away, though? Months pass. Your wrist gets worse. Now your whole hand hurts. Washing up and getting dressed becomes difficult. You start to worry and can't sleep properly. Doctors and painkillers become a part of your life. The pain is always there but your doctor can't find anything wrong. No one quite understands. You feel depressed. People seem to think you're making a big fuss. Maybe the pain is all 'in your head'.

The initial injury might have been different, but this story will be familiar to many chronic pain patients. Their pain persists long after the injury is healed. Without any injury to protect, such pain serves no purpose, and becomes crippling. Chronic pain is more common than we think. About a fifth of the world's population is believed to suffer from chronic pain. In Europe, chronic pain accounts for nearly 500 million lost working days and costs the European economy in excess of 34 billion euros every year.

Patients with chronic pain often complain of pain in areas where doctors find very little physical injury. These patients also suffer from anxiety and depression, both of which complicate and contribute to pain. This makes the study of any one cause of chronic pain very difficult. To get around that difficulty, some researchers simulate the symptoms that chronic pain patients feel in otherwise healthy volunteers.

I use capsaicin to increase pain sensitivity temporarily in research volunteers. Capsaicin is a chemical that comes from the chili pepper. When applied to the skin, it activates heat sensors found on nerve endings under the skin. These nerves generate signals that pass like electricity along a wire, up through the spinal cord and brainstem before entering the brain. As a result, pain is experienced. A large

area of skin surrounding around the spot where capsaicin has been applied also becomes sensitive. More pain than usual is experienced when a pin pricks the skin. Even a gentle caress can be painful.

What causes this increased pain sensitivity? One theory is that the nervous activity caused by capsaicin or by real life injury does not just get transmitted from the spinal cord to the brain, where it is experienced as pain, but also changes the nerve circuits through which it passes. These circuits get rewired as amplifiers and increase nerve activity so that more pain is experienced.

Brain scans can help locate these pain-amplifying circuits. Functional magnetic resonance imaging (fMRI) is a type of brain scan used in research. fMRI detects changes in magnetic fields that are related to brain activity. The big advantage fMRI has over other type of brain scans is that it does not involve radiation. I used fMRI to scan the brains of research volunteers whose skin had been sensitized by capsaicin and found increased activity in their brainstems. So perhaps the brainstem is an area where nerves get rewired to amplify pain.

Fortunately, the increased sensitivity caused by capsaicin is temporary. Within a few hours, all is back to normal for the research volunteer. The situation is of course quite different for the chronic pain patient. Their sort of pain doesn't go away. Have their 'pain amplifiers' become self-sustaining? If so, what has caused that to happen? Can these amplifiers be turned down? Perhaps these are questions that can only be answered by examining chronic pain patients directly.

Research like mine helps develop methods that allow us to look at what the human nervous system is doing when pain is felt. In future, these methods may help doctors figure out the source of pain in chronic pain patients. The pharmaceutical industry may be able to discover how existing painkillers work in patients themselves, not just in animals, and use that knowledge to develop better painkillers with fewer side effects. In the meantime, knowing that pain can be sustained by the nervous system in the absence of any detectable injury is changing the way doctors and society view and treat chronic pain patients. Chronic pain may well be 'in the head' but it remains very real to patients who suffer from it, and to the people who care for them.



## Max Perutz Essay Prize 2008: JOINT RUNNER-UP

# The Cold That 'Never Goes Away': Understanding Aspirin Sensitive Respiratory Disease

**Sophie Farooque**

Your nose is more congested than the M25 on Friday night. Your partner has kicked you out of bed for snoring. Running for the bus feels like an Everest ascent with a backpack. Your favourite pasta tastes like boiled cardboard. Innocent signs? Or is something more sinister creeping up, about to take over your life?

You are an adult in your prime but that's just when it strikes. You have ASRD. No you don't catch it from toilet seats; it stands for aspirin-sensitive respiratory disease, one of the most aggressive forms of asthma known. It can kill you within the hour, if you swallow something as seemingly harmless as aspirin. First you get a cold that never goes away then before you know it you are more breathless than Paula Radcliffe on the last lap - except all the time. But, it doesn't stop there. The disease destroys the lining of your nose and sinuses, filling them with fat slug-like polyps. Bugs cheerfully move into your blocked sinuses, and breed away causing pain, headaches and frequent trips to the doctor for antibiotics and painkillers. Except that you can no longer take painkillers.

Most of us swallow a couple of aspirin for a headache without giving it a second thought. The most widely consumed drug in the world, we use aspirin to prevent heart disease, eradicate hangovers, relieve colds and reduce DVT risk whilst flying. Now, if you take aspirin or ibuprofen, your chest shuts up tighter than a squeezed out dishcloth. Next thing you know, it's an ambulance, blue lights and a stay in your local intensive care unit. After a week of steroids, oxygen and bedpans, you decide that the description "aspirin-sensitive" is a tribute to English understatement: it's a death trap.

As ASRD progresses so does reliance on nasal sprays, inhalers and tablets. You are left puffing away, pockets more full of medicines than the average chemist, permanently having lost all sense of smell and taste. You are sent to the surgeon to clear out your nose: he snaps on his gloves and digs out multiple gelatinous polyps. Afterwards in an Alan Titchmarsh moment, he tells you polyps are like 'garden weeds' - easy to pull out but quick to grow back - sometimes within weeks. You both know that even the best 'weed killers', namely the medication prescribed just

does not work that well. A season ticket to the theatre (operating) has your name written on it.

Having made light of ASRD, as do some of my patients who use humour to bravely battle on against this disease - the grim reality is ASRD is a life sentence. As a specialist I do not exaggerate. Once diagnosed, you require lifelong medication but despite this will never have another symptom-free day. With over half a million fellow sufferers you are not alone, about 10% of the 5.2 million asthmatics in the UK have ASRD. I want to find new, effective treatments for these patients, and urgently. But how can we safely research this debilitating condition? Giving aspirin-sensitive subjects, aspirin to investigate its effects, is both unethical and dangerous.

In the last year, I have developed a test-tube (in vitro) model of ASRD. This is exciting because it allows me, at no risk to aspirin-sensitive patients, to recreate the inflammation found in their airways. I can conduct detailed experiments and try to understand why aspirin makes these individuals so ill. This model therefore unlocks the door to the mechanisms driving this condition, thereby opening the gateway to new treatments.

In our airways an enzyme called COX-1 manufactures chemicals called prostaglandins. Aspirin blocks COX-1 and inhibits prostaglandin synthesis. Some prostaglandins exacerbate asthma, but one called prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) has protective effects. It even protects ASRD patients, from the life-threatening respiratory crisis taking aspirin provokes. PGE<sub>2</sub> acts on four receptors called EP1-4 and levels of the EP2 receptor are far lower in the airways of aspirin-sensitive compared to aspirin-tolerant individuals. I believe it likely that aspirin-sensitive asthmatics make insufficient PGE<sub>2</sub> and after taking aspirin their PGE<sub>2</sub> levels drop precipitously lower. This would explain why their disease is worse in general and becomes far worse if exposed to aspirin. Another possibility is PGE<sub>2</sub> cannot protect these patients due to low EP2 receptor expression, even if adequate levels are produced. This newly developed model will allow me to determine if this is the case.

As well as sorting out these mysteries, I hope my work will translate into future benefits for aspirin-sensitive individuals because potential medicines which stimulate the EP2 receptor have already been identified. New treatments will reduce the significant financial cost this condition places on the NHS but most importantly will free patients from the life sentence that is ASRD.



## Max Perutz Essay Prize 2008: JOINT RUNNER-UP

# Every Little Helps: Promoting Physical Activity for Health

Clare Watkinson

We've all done it. The merest glimpse of summer, and we're frolicking half-naked in the chilly spring winds, loose limbs in all their goose-bumped glory. And then the full horror hits: shorts and swimwear that display our annual slippage as faithfully as Clingfilm on a Christmas Turkey. 'If only we'd done a bit more exercise!' we groan. But how? Getting into one of these industrial sports bras is strenuous enough, and without an advanced qualification in yoga it's all too easy to end up like a bondage display gone wrong. And as for the local pool, the last thing I want is to don the dreaded lycra - only to be mistaken for a stray jellyfish tangled in seaweed. So why not save ourselves the trauma, and park our trainers for good?

As Edward Stanley once remarked, 'Those who think they have not time for bodily exercise will sooner or later have to find time for illness' – although we don't necessarily need to stomach-crunch our way to good health either. Current guidelines recommend at least thirty minutes of moderate physical activity five days a week, and whether we're washing the car, chasing the kids in the garden, or simply taking the dog for a walk, we only need to move our bodies enough to breathe a little deeper and feel a little warmer for it to count.

But despite growing evidence that physical activity helps prevent obesity, heart disease, diabetes, stroke, cancer, osteoporosis and even depression, the number of people achieving minimum recommendations continues to fall. Over a quarter of the UK population are now classified as inactive, and recent estimates by the World Health Organization rank inactivity as one of the ten leading causes of death in developed countries. In a culture that places great importance on preserving youth and longevity, why do we continue to abandon the most potent anti-ageing treatment of all?

To estimate how potent these effects might be in the UK, I looked to data from the 1990 UK National Fitness Survey, which collected detailed physical activity reports from over 4000 men and women on the four weeks before their interview. Using tagged mortality records from the next sixteen years, I was able to show that even very modest amounts of reported physical activity – as little as one to four occasions of moderate or vigorous activity longer than twenty minutes – were

associated with a roughly 30% reduced risk of mortality. This was true for all age, BMI and socioeconomic groups.

Yet research shows that even among those who don't meet the recommended guidelines, 60% still overestimate their true level of physical activity, with many of us falsely believing we're doing enough already. And unless the inactive identify themselves as such, public health messages will only preach to the converted. But what if we simply measure people's physical activity using a scientific method and tell people the result? Could it make any difference?

This is the question behind my main research study, a randomized trial known as FAB (Feedback, Awareness and Behaviour). To measure the effect, we ask volunteers to wear a small device known as an Actiheart, a combined heart rate and movement sensor that attaches to their chest with the help of sticky electrodes. Weighing less than a few grams, it is a discreet device that allows us to record the volunteers' movement and heart rate over six days and nights, and to compute an overall physical activity score at the end. So that we can compare different kinds of feedback against a 'control' condition, volunteers are then allocated to one of four groups by chance, helping to make sure the groups are the same to start with. While one group receives a questionnaire only, the remaining groups receive one of three levels of feedback and the same questionnaire. A month later, we ask them to wear the Actiheart monitor again, enabling us to monitor any change in physical activity.

The results? Still eagerly awaited. But their importance lies not just in the possibility of a positive effect, but in the impact of 'desirable' results on behaviour too, about which we know very little. While some may be motivated to keep up the good work, others may be falsely reassured and perceive less need to stay active. And at the other end of the scale, undesirable feedback could result in worry or anxiety, prompting fatalistic attitudes and reduced activity. Only time will tell. But whatever the outcome, the hope is that it will lend just a little more evidence-based muscle to the ongoing campaign.



## Max Perutz Essay Prize 2008: COMMENDED

### How to grow a thymus

Adrian Fraser

A question. The thymus is:

- a) a small Australasian shrub with bright pink flowers, cultivated for its edible and nutritious berries;
- b) a rare, subtropical rodent, mostly nocturnal, noted for its burrowing habits;
- c) an organ found directly above the heart in mammals, where white blood cells develop?

The problem with working on a relatively obscure organ (the answer is c, by the way) is that whenever someone asks me what I study, I then have to spend some time explaining what a thymus is and why it is important. Sometimes I wish I'd chosen neuroscience, so I could just say "The Brain" and leave it at that: which is a shame, because the thymus really is a fascinating thing, berries or no berries.

At birth, our thymi (the slightly irregular pluralisation doesn't help much, but at least they're not pancreases. Pancreae? Pancreata?) weigh about 15 grams and continue to grow until puberty when they can reach 35 grams. The bad news is that after this it's all downhill, so that by the age of 60, they weigh as little as they did when we were born and are often almost entirely absent by 70. The ancient Greeks knew this, but they had even less idea about what the thymus does than most people I meet at parties. In the 60s, it was found to be involved in the immune response and since then many details of its structure and function have been uncovered. It turns out that the thymus contains lots of white blood cells called thymocytes or T-cells. The job of these cells is to circulate in the blood, recognising and attacking foreign or infected cells and the thymus is where they learn to do it.

When young T-cells enter the thymus, they rearrange themselves, so that each one develops a unique receptor on its surface which they use to recognise unwanted invaders. It acts like a lock which can only be opened by a specific molecular key, maybe a protein found on the surface of infected cells. The question is how do T-cells learn to recognise something that they've presumably never seen before? The answer is that the vast majority of them don't. Of all the T-cells that enter the thymus, only 2% survive to be released into the blood, making it a very harsh learning experience indeed. Immature T-cells are tested to make sure that their

locks will open when needed, then to make sure their particular keys don't belong in our bodies. If they fail an exam, they get weeded out, no re-sits permitted. Only those T-cells with working locks that don't open for any keys we already own get to graduate and, with the help of the thymus, become fully active immuno-police.

So if your thymus doesn't do its job right, you wind up unable to fight off diseases or with an over-eager immune system that turns on you. Neither of which is much fun. But didn't I already say that our thymi start shrinking just as soon as our lives are getting interesting? The *really* bad news is that I did and it does. It's one of the reasons that the elderly are more susceptible to diseases and less able to fight them off. And it's not just age that can lead to the loss of thymus function, some diseases and some treatments can take their toll, particularly in people closer to retirement than puberty.

The lab I work in focuses on the development of this under-appreciated organ and, in particular, on how a small number of cells manage to grow and develop into such a complex tissue. We have managed to separate out a specific group of cells in mice that are sufficient to create a thymus-like structure which can properly educate and activate T-cells. We can even get them to do this in a Petri-dish, which is great if you need a constant supply of mouse T-cells. The problem is that we can only do this with cells taken from early embryos, which isn't going to reassure any 70-year olds. I'm currently trying to figure out what these cells require to grow and to maintain their ability to form all of the important functional cell types in the adult thymus. This ultimately comes down to a combination of intelligent guesswork and trial and error but, along the way, my hope is to gain a better understanding of these early thymus cells and the environment that suits them. Eventually, I hope to apply this understanding to try isolating cells in adult thymi that can help regrow damaged or depleted tissue. For the meantime though, I'm busy trying to coax our cells into maintaining their thymic potential, which they seem unfortunately keen to lose. Still, at least I don't have to learn topiary.



## Max Perutz Essay Prize 2008: COMMENDED

# Resilience to suicide: Protective Barrier or Reduced Risk?

Judith Johnson

20<sup>th</sup> February 2008 dawned with sobering news: Jenny Parry had been found hanged in Bridgend. Her death was the most recent in a year-long spate of 17 suicides amongst the town's young people, which left Britain shocked. What was the cause of these tragedies? News reports were rife with speculation. Ideas of a local suicide cult were soon exchanged for a much more contemporary culprit, the internet. Before long social networking sites such as Bebo and Facebook found themselves fighting accusations, as the media labelled them the catalyst, the trigger and even the cause of the unfolding crisis.

Had the newspapers thought to consult suicide statistics, they may have found less cause for sensationalism. Though deeply saddening, when the figures are considered the deaths are not quite so shocking. For a start, suicide is the leading cause of death amongst 18-25 year olds. Further, suicide risk factors in Bridgend are all elevated above average levels. Amongst the counties of Wales it has the second highest rate of binge drinking, and the third highest rate of both substance misuse and unemployment. It also has one of the lowest rates of disposable income in England and Wales, and a higher than average rate of mental illness. Couple these facts with suicide cluster theory, which states that knowing someone who has committed suicide increases risk and a more grounded explanation is found; Bebo walks free.

And yet this is strangely unsatisfying, for one obvious reason: the vast majority of Bridgend's young people will not die by suicide. It could be argued that perhaps the individuals who died were those experiencing the highest level of risk. Maybe they were those who were unemployed, with substance addictions and mental health problems. It is hard to assess the strength of this argument as there seems to be little support for it, with news reports failing to report excessive substance misuse or mental health issues amongst those who died. This then prompts the question, what distinguishes those who died from the many who survived?

Conventional research has approached this question by studying mechanisms associated with suicidality. It has described a pathway to suicide which is marked by certain negative thoughts, feelings and behaviours. The pathway is unarguably dark, and its full distance is travelled by few. But what if this approach has simply

missed the point? Perhaps we should not be investigating why individuals die by suicide but ask how so many survive, despite risk. Instead of describing the pathway into suicidal behaviours, this is equivalent to scanning it for potential protective barriers. These barriers, if they exist, may prevent individuals from ever passing a certain point on the journey. Indeed, they may be as critical to the understanding of suicidality as the pathway itself.

This, in essence, is the exploration of resilience to suicide. It suggests that suicidal behaviour results not only from the risk that is present, but from the barriers that are absent. However, it is a relatively uncharted area of research which has not yet found evidence for one foundational issue. This, crucially, is the assumption that these barriers exist at all.

This is not to say that factors which reduce suicide risk have not been studied - to some extent they have. But what these studies have failed to deduce is whether these protective factors act as barriers on the pathway, or merely steps backwards. Say, for example, that a person is facing two known risk factors, such as unemployment and divorce. This person starts to experience suicidal thoughts, and enters the pathway towards suicidality. However, this person is also protected by the resilience factor of social support. The issue raised here concerns *how* this social support has its impact. Does it simply encourage the individual to retrace their steps on the pathway, or does it act as a barrier preventing them passing a certain point, regardless of the risk factors?

This issue is key to understanding the importance of resilience to suicidal behaviours. To return to the person in the example, if social support is a barrier then this individual would be able to withstand suicidality even if they became exposed to additional risk factors, such as depression. Theoretically, this would imply that resilience and risk are not simply separate ends of the same spectrum, but separate dimensions which may interact. If this is the case, the development of resilience could enable an individual to withstand suicide, even when risk factors are elevated.

Unfortunately it is too late for the young people who died in Bridgend, but we have a responsibility to explore interventions for the future. Building resilience may offer a potential prevention method, but before we can examine resilience factors we need to understand whether they exist separately to risk. This, is the first aim of my research.



## Max Perutz Essay Prize 2008: COMMENDED

# Up close and personal with a herpesvirus

Rebecca Robey

Recently, my best friend's husband of three years developed a nasty rash. His GP took one look at it and immediately diagnosed it as a herpesvirus infection. I can still hear my friend's resonating response to this news: "You've got WHAT???" Fortunately, it wasn't nearly as bad as it sounds. Herpesviruses carry with them something of a social stigma, and are widely associated with sexual promiscuity. Their name conjures up images of the unpleasant and unsightly rash of genital sores commonly known as herpes, which can be spread by sexual contact. But the truth is, most of us are riddled with herpesviruses and never even know it – and that is what makes them so fascinating.

Herpesviruses are, in fact, a large family of viruses one of which – Herpes simplex 2 – causes genital herpes. The other family members include Herpes simplex 1, the virus responsible for cold sores, Varicella zoster virus, which causes chicken pox and shingles (it seems only fair at this point to clarify that this is what the husband in question was actually suffering from), and Epstein-Barr virus, which is usually unnoticed, but can cause glandular fever and, rarely, certain types of cancer. What all herpesviruses have in common is that they have evolved cunning and complex ways of living undetected in their human host. They often lie dormant in their host's body, displaying no outward signs of infection. They are experts at avoiding the attention of the immune system, which seeks out and destroys invading pathogens. And leading the pack is Kaposi's sarcoma-associated herpesvirus (KSHV), arguably the most silent and stealthy of all the herpesviruses.

KSHV causes Kaposi's sarcoma, a cancer characterised by multiple purple-brown lesions on the skin. It was once a rare cancer, seen only in isolated demographic pockets – elderly men of Mediterranean origin and younger people of both sexes in parts of sub-Saharan Africa. For the most part, KSHV infection remains asymptomatic and goes undetected. But in the early 1980s, an unusual epidemic of Kaposi's sarcoma among young men in San Francisco and New York alerted medical practitioners to a new, devastating phenomenon – the outbreak of HIV and AIDS. In AIDS patients, who have severely damaged immune systems, KSHV no longer lies dormant, but frequently results in an aggressive case of Kaposi's sarcoma.

The association of Kaposi's sarcoma with AIDS has taught us a fascinating thing about KSHV. It has not just evolved to hide from its host's immune system, but has developed a fine balance of host-virus interaction. By provoking a low-level of immune response, KSHV helps its host keep its own infection under control. In this way KSHV can persist at low levels in the host for the duration of their life – it is not in the virus's best interest to replicate uncontrollably, resulting in a cancer that may kill the host it relies on to exist. And this is where my research comes in. The question I am addressing is how the immune system, when it is functioning correctly, is able to control KSHV infection.

Specifically, I am interested in the T-cell immune response against KSHV infection. T cells are the foot soldiers of the immune system. They are specialised into regiments, each one of which is programmed to recognise and destroy one specific invading pathogen. After an infection is cleared, just a few members of that regiment remain in the body and are called 'memory T cells'. If the body comes under future attack by the same pathogen, these memory T cells are on hand to react, and proliferate massively to create a defending army to clear the infection again.

I am investigating this system by isolating T cells from blood samples donated by patients who have recovered from Kaposi's sarcoma. These patients have, through chemo- and antiretroviral-therapy, boosted their levels of memory T cells that recognise KSHV, so bringing their infection back under control and clearing the cancer. I take a panel of different KSHV proteins that make up the virus as a whole, and test which of these proteins are recognised by the patient's memory T cells, prompting them to proliferate. If we can begin to understand this, then we have taken the first steps towards developing new therapies to boost the immune response to KSHV infection and potentially even a vaccine against it.

Kaposi's sarcoma has declined in the West since the introduction of antiretroviral therapies but it remains one of the most common cancers in sub-Saharan Africa, accounting for as much as half of all cancers in some countries. This is pretty shocking for a cancer that is almost unseen in the developed world. There is a desperate need for a cheap, widely available treatment or prophylaxis, and I hope my research will contribute towards its development.