



Max Perutz Essay Prize 2009: WINNER

The Best a Man Can't Get

Jacqueline Maybin

*I know I have the body of a weak and feeble woman, but I
have the heart and stomach of a king.*

Queen Elizabeth I, 1588

When addressing her troops before they faced the Spanish Armada, Queen Elizabeth I identified the exceptional ability of women to overcome their natural disadvantages. From birth Elizabeth was a disappointment to her father Henry VIII because of her sex. Yet, despite her “week and feeble” body, good queen Bess became one of England’s most popular and successful monarchs.

Without doubt, the average male is physically stronger than the average female. This is due to higher levels of the male hormone testosterone. Nevertheless, as I stumble through life I’ve noticed that strength does not always equate to physical power. The female hormones have ingenious ways of compensating. They give women an understated but enviable form of strength. Ironically, despite her exceptional “heart and stomach”, the most remarkable organs Elizabeth possessed were the ones that made her female.

The uterus, or womb, is the organ par excellence. It functions so efficiently that a full understanding of its processes may lead to novel treatments for a plethora of medical disorders. The inner lining of the womb is the endometrium. This lining responds to the female hormones and is shed monthly in a “period”. During bleeding the endometrium is red and inflamed and looks very similar to a wound on the skin. In contrast to the skin however, the endometrium has the extraordinary ability to rapidly repair without scarring. This efficient monthly repair is unparalleled in the male or outside the reproductive system. Severe inflammation in other organs leads to suboptimal healing, scar formation and disastrous consequences. A scarred organ does not function properly and loss of function equals illness. Patients in this situation require regular medication, surgery or even transplantation of a new organ.

So how does the endometrium do it? What unique processes are at play allowing the female system to withstand repeated inflammation on a monthly basis? The answer is that the endometrium is sophisticated, complicated and not fully

understood, i.e. typically female! Endeavouring to solve the mysterious workings of the endometrium will certainly be worthwhile. By defining what happens in an efficient system we hope to be able to convert abnormal "diseased" states back to normal. Or better still; prevent damage from occurring in the first place.

So what have we uncovered so far? It is clear that repair is highly co-ordinated and that any deviation from the tightly regulated sequence leads to inefficient healing. Just before a period, white blood cells pour into the endometrial tissue from the blood stream. These cells release enzymes that breakdown tissue and cause bleeding. As well as initiating the injury, these cells also mop up dead tissue and remove debris. White blood cells are a fundamental component of the healing process but if they hang around too long they cause problems. Therefore, the switch from "attack" to "retreat" has to be well timed. By examining tissue from women having a hysterectomy, I'm trying to identify control mechanisms for white cells in the endometrium. If identified, a factor that clears these cells could be harnessed as a treatment for inflammation anywhere in the body.

Subsequently, formation of new tissue must occur to repair the ragged surface left after a period. In addition, it allows regeneration of the lining in preparation for a potential pregnancy. A host of growth factors drive the production of new tissue. A master regulatory protein is likely to co-ordinate these factors. I study one such protein; Hypoxia Inducible Factor (HIF). My research has shown that HIF is produced in endometrial cells when oxygen levels are low. Right before a period the endometrial blood vessels constrict, meaning less blood and oxygen reaches the tissue. This fall in oxygen activates HIF, which leads to increased production of repair factors in the endometrium. I have also discovered that HIF levels vary from woman to woman. High levels of HIF lead to increased repair and might explain why some lucky women have very light bleeding. Conversely, low levels of HIF may equate to less efficient repair and longer, heavier periods.

Studying the extraordinary workings of the endometrium is exciting stuff. Not only is there potential to develop new treatments for gynaecology disorders but also for serious pathology elsewhere in the body. Undoubtedly Queen Elizabeth's men involved in battle in 1588 would have appreciated therapies that maximised wound repair and minimised scarring. Even today, our hospitals are full of people with problematic scarring and persistent inflammation. We still have a long way to go but I hope my work will take us one step closer to providing treatments that really are "the best a man can get".



Max Perutz Essay Prize 2009: RUNNER-UP

Blind Ignorance

Alastair Denniston

Two weeks ago Anna could see.

Two weeks ago Anna drove to work, glanced over her morning post, winked at Paul, gathered the team around her for the morning briefing and, looking at each of them in turn, gave them their instructions for the day. As usual Anna's enthusiasm filtered through their apathy, and even Paul hit the shop-floor with slightly more dynamism than a state funeral.

Today Anna is blind. In the last two weeks the trajectory of her life has ricocheted off at right-angles to the world of sales targets and everything else she had ever worked for. On that day – *day zero* she calls it - she left work early with a headache. Later that evening the vision in her left eye went blurred. Her sister drove her to the Accident and Emergency Department. As Anna moved through a quick succession of doctors, the working diagnosis in her notes was refined from 'eye problem' to 'ocular inflammation' to 'uveitis'. *Sounds unpleasant, but at least if they know what it is they can probably treat it*, she thinks.

The last doctor in the chain – the eye specialist or 'ophthalmologist' – examines Anna using a modified microscope known as the 'slit-lamp'. Despite its ancient and unwieldy appearance, this instrument allows spectacularly beautiful and detailed views of the delicate structures of the eye. I have been using it for over ten years but am still mesmerised by the sight of individual blood cells racing along the microscopic vessels of the surface of the eye, and never tire of watching the magnified pupil's microsecond adjustments to every tiny fluctuation in light.

But today Anna is in trouble. Her own immune system has turned against her. White blood cells known as leucocytes have infiltrated most of the major structures of the eye. There are so many that I cannot see 'in' much more than Anna can see 'out'. At the back of the eye, the critical light-sensitive retina resembles the victim of a microscopic paint-ball competition. Clusters of leucocytes choke the retinal vessels and spill over into the surrounding tissues. The immune system is running riot.

The strange thing is that these are the 'good-guys'. We normally rely on these cells to respond to outside threats such as infection. Indeed the immune system is often

described in heroic terms as an 'army' which defends us against 'hostile invaders'. But today as I look at Anna they seem more like a bunch of vigilantes who have taken to beating up innocent bystanders.

Most of the time our eyes live in their own protected little world. They travel in the 'quiet coach' of the human body in which the most dramatic thing that should ever happen is a change in the view. It is a civilised place in which even the immune system is on low volume. Most of our research underlines the ways that the immune system is kept in check within the eye. Inflammation inside the eye should not happen. But sometimes, as with Anna, the eye's immune system ramps up the volume releasing the destructive inflammatory process of uveitis.

Most uveitis is unexplained. We are good at describing it, reasonable at classifying it, moderate at treating it and, as yet, terrible at understanding it. In our research we probably get closest to what is going on through taking precious fluid samples from the front of the inflamed eye. Detailed study has allowed us to start building an accurate picture of the types of white blood cells involved during an attack of uveitis. We only have snap-shots, but from these images we are steadily working backwards towards the key events that kick this whole process off. Uveitis should not happen. But it does, and it can blind people.

I want to know why uveitis happens. I want to know because Anna is sitting in front of me in clinic, and we've been filling in the forms that will officially register her blind. I want to know because she can't go back to her job. I want to know because the best treatments we had weren't good enough. And I want to know so that, next time, I have something more to offer.



Max Perutz Essay Prize 2009: COMMENDED

Will it be Worth it?

Nicola Harris

Have you ever read the 'possible side effects' bit of a drug information leaflet and been horrified by the list? Even a common, over-the-counter medication such as paracetamol carries warnings that you may suffer skin rashes, blood disorders or even a swollen pancreas! Thankfully such side effects are extremely rare, but this leads to the question, if these effects are so rare, why do they exist at all? Why might I be fine with paracetamol but you might end up in A & E? At least we can always choose not to take the paracetamol, but removing the risk entirely like this is not always an option.

When a young child or teenager is diagnosed with cancer, for the parents who have to consent to any treatment, the more they read the worse it seems. Which treatment to go for first? How to know which will have the greatest benefit whilst causing the least additional pain and discomfort? Statistics can try to help with this decision making process, as a drug where only 1 in 100 patients suffer as a result of the treatment would obviously be preferable to one where 99 out of 100 patients suffer – or would it? What if that drug that is only beneficial for 1 in 100 patients results in a complete cure for that one child, whereas the 'safer' drug only offers a temporary remission to the 99 out of 100 patients who are able to complete the course? As a parent how on earth can you make that sort of decision?

What you really need is a lot more knowledge. If you knew why the drugs had different effects in different people, you could work out in advance whether your child was the 1 who would benefit or 1 of the 99 who would not – hey presto the decision's made for you – no agonising sleepless nights, no anxious waiting to see how ill your child gets, and no guilt if their suffering outweighs the benefits.

There are two key issues to consider. The first is what the body does to the drug. This is known as pharmacokinetics (PK). This deals with what happens to a drug once it enters the body, how it is metabolised, how long this takes and what metabolites (by-products) are produced. The second factor is what the drug does to the body. This is known as pharmacodynamics (PD), for example will it shrink or eradicate the tumour, or will it damage the kidneys?

Perhaps a good analogy is the effect alcohol can have on you and a friend on a night out. The alcohol is broken down by the liver to turn it into a series of non toxic compounds which can easily be excreted from the body via the kidneys. The speed of detoxification and elimination will vary from person to person (PK). The same quantity of alcohol may help you to have a good time, but leave your friend unable to stand and slumped in a corner (PD). Both factors may also explain why ironically your hangover lasts longer than your friend's!

I am working on the pharmacokinetics of a drug called fenretinide for the treatment of two cancers, neuroblastoma, which is a neuronal cancer mainly seen in children under 5 years old, and Ewing's sarcoma, which is a bone cancer mainly affecting teenagers. Cells from both these types of cancer have been shown to be very sensitive to fenretinide treatment when grown in the lab.

One of the interesting things about fenretinide is the products of its metabolism. Fenretinide is an 'active' drug, meaning it is able to kill cancer cells directly in the form it is given. It has two major metabolites; one is active and the other inactive. Clinical trials have shown that fenretinide undergoes significant metabolism to both of these metabolites when given to patients.

My work involves identifying the enzymes responsible for this metabolism so that I can try ways to alter it. If I can modify the metabolism so that the drug either remains as fenretinide or is only metabolised to its active metabolite, this should greatly improve the benefit seen in patients. Identification of the enzymes involved will also enable us to screen patients for the activity of these enzymes prior to treatment. We can then give a higher dose to those who would otherwise not have enough active drug present to gain a beneficial effect, or reduce the dose for those who would metabolise the drug too little and end up with active drug concentrations high enough to cause severe side effects.

Think about it - reading about that possible swollen pancreas wouldn't be so scary if you knew for certain it wasn't going to happen to you – or your child.



Max Perutz Essay Prize 2009: COMMENDED

Head Above Water: Pitting Peptides Against Asthma

Karen Mackenzie

“You’re being held under water and you just have your nose above the surface and you can’t get enough air.” A drowning? No, this is a young child’s description of an asthma attack.

Working in paediatrics I can appreciate why a child may feel this way. Take “Jack”. A toddler brought to Accident and Emergency (A+E) by his mother. He’s upset but true crying has been tempered by the increasing natural drive to inhale more and more oxygen. Mouth open, leaning forward on his mother’s lap, with every breath the muscles on his lean torso contract displaying each rib in turn. A+E staff move around him with calm efficiency administering medication and adjusting equipment, but beneath the calm everyone, particularly his mother, is aware of the urgency of the situation.

As his medication takes effect, Jack’s breathing gradually becomes less laboured and his tense face relaxes. He starts interacting with mum, pointing to objects around the room. Within a couple of hours he is back to his mischievous self, tipping the contents of the toy box onto the hospital floor.

The rapidity in which asthma medication can be effective has always impressed me but this means that the onset is often equally rapid. To appreciate this you need only look at the parents’ faces. It turns out that Jack was completely well that afternoon until an allergy to his cousin’s dog triggered his asthma and left him struggling for breath.

Allergic asthma is the most common form of asthma and now affects around 20% of children. Asthma symptoms occur when the airways constrict making breathing difficult. This happens when the body’s immune system mounts an allergic response towards an inhaled allergen – a protein such as pollen or animal hair. The particular allergen that triggers a patient’s asthma can often be identified by tests and then avoided. However, certain allergens such as pollen are impossible to avoid completely. Constant low level exposure can result in continual asthma symptoms impacting on the child’s daily activities and interrupting sleep.

Unexpectedly encountering an allergen, as in Jack’s case, can lead to an acute asthma attack. Current asthma treatments are vital but act either once symptoms

have already arisen or by generally dampening down immune responses. But what if allergic reactions could be specifically switched off even before asthma symptoms had developed?

One such treatment approach is to induce "tolerance" to the trigger allergen. Tolerance is the reason why not everyone is pollen allergic. If you are tolerant to an allergen it means that your immune system does not mount an allergic response to it. It is possible to give a protein allergen to an allergic patient in such a way as to induce tolerance. This can be an effective treatment but giving the protein allergen carries with it the risk of causing a severe allergic reaction. One way to reduce this risk is to use only a short fragment of the protein called a peptide. Using peptides to induce tolerance is known as peptide immunotherapy or PIT, and is potentially much safer. Some initial clinical studies have shown that PIT can improve allergic asthma but it does not work in all cases and the mechanisms involved are not yet fully understood.

I am studying the effects of PIT in the context of allergic asthma to help gain a better understanding of these mechanisms. Immune cells can express different molecules on their surface in different situations. This helps them interact with other cells and affects the overall type of immune response that occurs. By examining changes in the molecules expressed by immune cells during PIT, I aim to understand more about how tolerance occurs.

One reason why PIT does not always induce tolerance may be because the body is simultaneously fighting an infection. There is even a concern that giving PIT during an infection could actually make the allergy worse. It is therefore crucial to know whether viral infections such as "colds" affect PIT. This is especially important for children who usually have multiple viral infections each year. To address this I am also investigating how a common viral infection influences the outcome of PIT. Does viral infection prevent tolerance? Does the allergy become worse? If so, for how long after infection is this true?

I hope that results from my project together with other studies in the field may lead to the development of allergen targeted asthma treatments in the future. I believe that PIT has potential as a clinic-based treatment which could pre-empt the emergency scenario so familiar to Jack and his mother. Ongoing asthma research is needed to ensure that more asthmatics can keep their head above water.



Max Perutz Essay Prize 2009: COMMENDED

Memories of a brain cartographer

Alejandro Vicente Grabovetsky

Look. The world before you seems simple. It almost appears as though, somewhere inside your head, a cinema projector displays what your eyes capture and interpret. But that's not how we function. Instead, your brain is a cartographer, housing on its cortex a multitude of sensory, mostly visual, maps. Like regular maps, brain maps are drawn in a continuous and fluid way. Just as neighbouring countries are placed adjacent on a map, neurones that respond to similar visual locations are also grouped together.

Depending on the task at hand, our brains pick the best map to get the job done. When we talk about the Earth, depending on the context we interpret it in terms of political, geographical or weather maps, each with its rules and highlights. Just like a map maker, the brain interprets the world surrounding us by simplifying it: it splits it into categories, uses landmarks, and traces frontiers.

Over a dozen maps have recently been found in humans, spread about the brain's cortex. Some maps detect the edges and corners that delineate the outlines of objects. Others only take heed of movement or colour. Another few just seem to predict where you'll soon lay your eyes. Still others are centred on where your eyes are pointed, or relate to the position of your head or hands.

So, that variety is fascinating, but what does this add to science? Well, much of current brain science focuses on labelling a particular brain region with some function. Research programmes often try to find the "centre" for, say, envy, face perception or motivation. Remarkably few have actually explored how the brain manages to map and co-ordinate itself, that is, how it actually works.

My research focuses on learning more about visual maps, especially how they interact with attention and memory. Both are central to actual perception; for example, as you read this line you "see" the ones above and below, but ignore them; and if you close your eyes you'll find it hard to recall items around the paper or screen you read this from.

To find visual maps I use an fMRI (functional Magnetic Resonance Imaging) scanner to obtain 3D images of brain activity through time, while volunteers perform a visual task. In one such task, participants look at a computer screen split into

sectors, each sector filled with a pattern of waves changing in shape with time and disappearing. Their job is to pay attention to and then remember the patterns in some places while ignoring the rest. Then, I extract two different results. One contains the hot spots of activation during the attention and memory periods. The other, using a fairly new technique, finds chunks of brain where the pattern, not the general level, of activity, varies depending on the spatial location of stimulation.

In this way, I found that the occipital cortex, in the back of the head, showed much map-like activity when volunteers both paid attention to the visual stimuli and kept them active in memory. Interestingly, during the memory period the maps in occipital cortex were not active overall, but only subtly changed their pattern of activation. On the other hand, maps in parietal cortex, at the top and back of the brain, could be detected only during the attention period. Curiously, these same areas showed very high activation during memory, despite displaying no map-like responses.

The benefit of this increased knowledge becomes clear when we look at cases of brain damage that result in some form of visual deficit. Patients with blindsight are effectively blind, but can learn to navigate the environment. Visual neglect, on the other hand, affects attention such that patients can "see" but simply don't notice things happening in half of their visual field. Individuals with optic ataxia can describe how objects look, but find it impossible to interact with them. In contrast, those with visual agnosia are unable to name or describe objects, but can grasp them perfectly.

Many such syndromes can be better understood and treated if we know the precise properties of both the damaged and intact visual maps. We could guide rehabilitation by taking advantage of the plasticity of the brain. We might, thus, stimulate the activity of intact visual maps that communicate with the damaged ones, helping reactivate and regenerate them. This research hints at ways we might "encourage" brain cortexes to do this.

Even as my results add to our knowledge, though, they raise more questions. Why do brain areas sometimes act as maps and other times not? How do maps work when they are inactive? Much work remains to be done, but many benefits remain to be reaped. Still, one thing we can say for certain: there's much more to vision than meets the eye.