Transcript of JS’ Ockham’s Razor talk:

‘Life wasn't meant to be easy’  Old age, dementia and acquired resilience

Stress is something that has most of us in two minds. We all like to avoid conflict, danger and illness. We protect our young children from cold, hunger, infection, and bullying; we protect our teenagers – if we can – from themselves. This urge to protect expresses itself in communal ways, too; we provide pensions for the poor, medical care for the sick, compensation for the disabled, needle exchange for the addicted and retraining for the unemployed. The ideal of a society that provides for each citizen according to his need, and taxes him only according to his capacity, shaped much of the history of last century.

But this ideal of protection also gives us pause. The coddled child may, we fear, lack the gumption to meet life’s challenges; stress can strengthen you; welfare leads to dependency. And it is history that the dream a caring, communal life – the communist ideal – led to the misery of economic stagnation, bread queues and political oppression. It is a mistake, we say in this mood, to seek to protect everybody from every stress.

For those of us who study biology, there is no debate. Whether or not it was meant to be easy, life is stressful, from the womb to the grave. And the way we have evolved to survive stress has been to harness it – to use stress to trigger mechanisms which protect us.

Let me give three examples:

Late in the 19th Century, understanding grew that many diseases are caused by microscopic organisms; ‘germs’ they were called - bacteria and viruses and parasites that colonise the cells of our body with such efficiency that they make us ill, and kill us. By the middle of the 20th century, scientists had identified the immune system, a complex of cells and signals by which our body destroys the infected cells, preventing the spread of disease within our bodies. And from the 1980s, until new generation drugs curbed the HIV virus – which disarms our immune system - we witnessed an awful demonstration that we are all under a siege by a host of pathogens; a siege before which, without a functioning immune system, we become riddled with disease.

This immune protection - so critical to survival - is said to be acquired. For our immune system to protect us from a pathogen, we must each suffer exposure to it. There are exceptions to this rule: every baby is born with some immunity that comes from its mother, which for a few months protects it from diseases the mother has experienced. And, medical science has learnt to induce immune protection by exposing babies or kids or adults to fragments of viruses, in a process we know as vaccination. The fragments are engineered to activate protection, without causing the disease. The result – protection with minimal stress – was a major achievement of medical science last century. But these are exceptions that prove the rule; and the rule is that immune protection against a pathogen is acquired by an encounter with the pathogen. Our bodies have evolved to use the stress of that encounter to induce protection.

For animals that survive disease, predation is an equally inevitable, life-long stress. Predators must kill or starve; prey must flee or be eaten. To prime the body for the chase, the brain coordinates a complex flight/fight response. Adrenalin is released into the blood stream, to shift blood from the gut and skin to the muscles and to make the heart beat faster and harder. Our pupils dilate, our body hair lifts off the skin, we breathe more deeply; we are ready to chase or flee or fight off rivals. This reaction is essential to both predator and prey. But we cannot be constantly in this turbo-charged state. Again, the body has evolved to use the stress of hunger or danger or challenge to induce a complex response, critical for survival.
In recent years, a third system of body protection has been recognised. It protects our tissues, not from infection or predators, but from two ever-present dangers - toxins and the threat, especially for the heart and the brain, of an interruption to blood supply.

Somewhere in the 1980’s, researchers began to study ischemia – lack of blood supply - in heart muscle. Ischemia of the heart is a heart attack, usually caused by blockage to an artery. Pain, collapse, irreversible damage to the muscle of the heart follow quickly on each other; it was then – it is still - a very common cause of death. There were many outcomes of this work, one quite unexpected. Working in animal models, the researchers simulated a heart attack by closing off one of the heart’s arteries for just a few minutes. At some point they realised that a brief loss of blood supply changed something in the affected muscle – it became much more resistant to subsequent ischemia. It turned out that brief ischaemia upregulates – or turns on - mechanisms of anti-oxidant protection already present in the heart muscle cells. These mechanisms remain quiescent in the muscle cells until there is a crisis; this crisis, ischaemic stress, turns them on.

Now that first observation wasn’t very promising as a therapy. You can’t give people mild heart attacks in case they suffer a severe one. But laboratories all over the world have taken this striking finding in half a dozen directions.

It was shown, for example, that protective conditioning is not special to heart muscle; it has now been demonstrated in the brain and retina and lung. The genes that control the response are in every cell and therefore every tissue. Then, it was shown that if you make just a patch of heart muscle ischemic, the whole heart is protected; so the protection spreads. Next, it was shown that the protection spreads throughout the body, that heart muscle is protected by ischemia in even a remote part of the body. If you make one arm ischemic, for example, by putting a tourniquet on it and blocking its main artery, the heart survives better the stress of ischemia or of surgery; and the brain is protected from stroke. Called ‘remote ischemic conditioning’, this effect is now in increasing use clinically. And the scientists kept going. They showed that the ischemia doesn’t have to be experimental, as in clamping an artery or putting a tourniquet on a limb. Exercise induces muscle ischemia, creating the pain of strong exercise. I recall once asking my cardiologist why high blood pressure is bad for you, but exercise – which puts up blood pressure – is good for you. I did not know and she did not know; but that was years ago. Now we know skeletal muscle made ischaemic by exercise releases circulating factors that induce self-protective responses in probably all tissues. That’s why exercise is good for us. Further, the same response is induced by other forms of stress. We all experience low doses of gamma rays in sunlight, for example; well, low-dose gamma rays induce the same protective response as does ischemia. We all experience phytotoxins – toxins produced by plants to ward off insects. At high doses these toxins – like resveratrol, found in the skin of red grapes and therefore in red wine – can kill us. At low doses, plant toxins turn on the same protective mechanisms.

At some point, it became clear that we are dealing with a third system evolved to enhance our survival in a world full of stress. In this system, the experience of stress, usually ischaemia or a toxin, triggers resilience in the stressed tissue and throughout the body. And a good name for this response – taking example from acquired immunity – is acquired resilience. Perhaps the most familiar example is the decrease in morbidity and death associated with exercise; but it is a much broader phenomenon than that: body-wide resilience induced by exposure to a wide range of stresses.

None of this, by the way, was there when I was a student; then, the heart beat, the kidney filtered, the lungs exchanged gases, the liver metabolised, the muscles contracted, the skin enclosed it all. We had no inkling of this conversation between tissues, in which damage in one tissue induces a protective response throughout the body.

A few months ago, I had the privilege of time on this program, which I used to argue – on behalf of a team of researchers – an understanding of the cause of age-related dementia, of Alzheimer’s disease.
The dementia occurred, we argued, as a result of vascular ageing. Hardening of the great arteries makes the pulse steadily more intense with age, until the surge of blood with each heartbeat damages the brain’s blood vessels, causing small bleeds from small vessels. The bleeds are so small that they do not create acute symptoms; the patient is not aware that anything is amiss. But each results in the death of a small patch of brain tissue; each creates the plaque and tangle pathology which the German neurologist Alois Alzheimer described early last century, and the effect of many small bleeds becomes noticeable, first as a failure of memory, then as the slow loss of all mental function, the tragedy of dementia.

‘So, - all this tells us - if my heart stops I’ll die suddenly; if it keeps going, I’ll die slowly, as it beats my brain into a pulp’. It seems like – it is – an awful dilemma. And the point of my telling the story of acquired resilience is to say that – even in the face of so stark a dilemma – medical scientists aren’t done yet, not by a long way. Acquired resilience is already delaying dementia – in those who exercise, for example, or choose healthy diets and weight control. Many labs – my own is one -are exploring dietary supplements of highly anti-oxidant plants, or phototherapy or remote ischemia or phytotoxins, which all seem able to switch this protection on with minimal stress - the gain of protection without the pain. In our work on the brain, we are trying to understand whether these interventions are protecting the tissue of the brain; or are successful because they are making blood vessels resistant to the stress of the pulse. As always in science, there is a string of questions to answer. And our surgical colleagues are mulling ways of restoring elasticity to the ageing aorta, to soften the pulse to what is was in our youth.

With the better focus that comes from better understanding, dementia will be progressively delayed; our children will live longer than we will; the limit to longevity now set by the vulnerability of the brain to the aging pulse – this limit will be pushed back.

But we are not about to abolish mortality; as we delay dementia, a new limit to long, long life will emerge. I wonder what it will be, and whether the next generation of scientists and clinicians will be able to wrestle it to the ground.

**Guests**

Professor Jonathan Stone  
Professor of Neurobiology  
Director of the Bosch Institute for Medical Research  
University of Sydney

**Credits**

Presenter  
Robyn Williams  
Producer  
Tiger Webb