Company of Biologists Director Wins Nobel Prize

For Tim Hunt, October 8th was just a normal Monday, until the phone rang just after 10am. But this wasn't any ordinary phone call, it was the one that every scientist dreams of: he had won the Nobel Prize for Medicine and Physiology.

Hunt was told that he had been awarded it jointly with his Imperial Cancer Research Fund colleague Sir Paul Nurse, and Leland Hartwell, Director of the Fred Hutchinson Cancer Research Center in Seattle, Washington. Hunt, Nurse and Hartwell will be awarded with the prize in Stockholm on December 10th 2001, which is the 100th anniversary of the prize.

Hunt has been a Director of the Company of Biologists since company secretary, Richard Skaer, invited him to join in the early 1990s. They had known each other since they had taught together in Cambridge. At the time that Hunt joined the company, he was the Editor of Trends in Biochemical Sciences, and Skaer realised that he was an ideal candidate with his experience as a scientist and a publisher.

Since joining the company, Hunt has been a member of several committees, including the Charity Policy Development group and the Journal of Cell Science Advisory Committee. The Charity Policy Development group allocates the charity's funds to a variety of scientific good causes, including travelling fellowships for young scientists and larger endowments for more ambitious projects.

In the statement released by the Nobel Committee in Sweden, all three scientists have been recognised for their 'key discoveries of the cell cycle'. Hartwell and Nurse both studied cell cycle regulation in different species of yeast. In the early 1970s, Hartwell identified over 100 genes in the yeast, *S. cerevisiae*, that are involved in cell cycle regulation. He showed that one of these proteins, *start*, was involved in regulating a key step in the cell cycle, and Nurse soon found a homologue of this protein in another yeast, *S. pombe*. In 1987, Nurse found the same activity in a human protein, cyclin dependent kinase (CDK1) unifying eukaryotic cell division by showing that the same family of proteins in all eukaryotes regulate the complicated chain of events that govern the way a cell divides.

Tim Hunt's discovery of cyclin stemmed from his interested in protein synthesis, rather than curiosity about the cell cycle. While he was a research fellow in Cambridge, he began looking at the regulation of protein synthesis in a variety of cell types, including sea urchin eggs. But his work on sea urchin eggs didn't take off until he was invited to spend the summer at Woods Hole in the US to work on *Arbacia punctulata*, an Hawaiian sea urchin. Hunt explains that he decided to do a 'mad experiment', where he added radiolabeled methionine to recently fertilised sea urchin eggs and looked to see if he could find any differences in the proteins made in the fertilised cells, compared with the unfertilised eggs. When he ran the cell extracts out on an acrylamide gel, he noticed an enormous protein band that appeared while the cells were preparing to divide. As the cells divided the band vanished, but it reappeared once cell division was complete, and the cells had begun a new cell cycle. Hunt realised that the protein was being degraded, and later resynthesised. It was obvious to him from the way that the protein level varied periodically that it should be called cyclin. Hunt remembers that he was 'euphoric for a year' after the discovery, but getting the results published wasn't easy. The paper was initially laughed out of court by the referees who described the work as 'wild speculation based on faulty logic'.

The publication battle was the beginning of many years of work before Hunt cloned and sequenced the gene for cyclin, and even longer to prove that it regulated the kinase CDK1, which Nurse had discovered several years earlier.

Richard Jackson from Cambridge University collaborated with Hunt over many years and remembers when Hunt first told him about his break-through with the cell cycle. He says 'it was clear to Tim, but the rest of us took a little bit longer. He was very astute'.

Sir Paul Nurse (left) and Tim Hunt (right) shortly after hearing about the prize. Courtesy of the ICRF.

Has Malaria Met its Match? (p. 4157)

Anyone seeing the effects of malaria is left in little doubt that the parasite is efficient and deadly. One approach to controlling the parasite has been to wipe out its host, the mosquito. But DDT, the main weapon in man's anti-malarial arsenal, turned out to be a double edged sword, leading to its withdrawal. More recently, people have tried direct attack on the parasite. Helge Zieler and his colleagues at the NIH decided to target the parasite before it gets the chance to multiply, and have isolated a molecule that could revolutionise man's defences against malaria.

The malaria parasite takes up residence in two hosts, man and the mosquito, at different stages of its life cycle. A mosquito that feasts on an infected human gets more than just a blood meal: it picks up a dose of the parasite's gametes that will go on to produce the next generation. Once the gametes have mated, the fertilised cells, called ookinetes, bind to the insect's gut wall. At this point they begin the next stage of life where they multiply and produce sporozites that relocate to the insect's salivary gland, before infecting the next hapless victim.

Zieler figured that if he could prevent the parasite from binding to the gut wall, then he'd have a good way of stopping the parasite in its tracks. He decided to test a variety of enzymes that might bar the parasite from invading its insect host by degrading molecules in the mosquito's gut wall that the parasite needs to latch on to. He tested phosphodiesterase from two species: cow and the eastern diamondback rattlesnake. But only the snake phosphodiesterase sample disrupted the parasite's life cycle. So, it wasn't the phosphodiesterase that was disrupting the interaction. Zieler investigated further until he homed in on a 15 kDa contaminant protein that turned out to be the blocking agent: phospholipase A2 (PLA2).

Zieler believes that PLA2 could be a very powerful defence against malaria, but he accepts that there could be significant opposition. The only way that PLA2 can be delivered to mosquitoes in the field is if the insects themselves carry the gene. Of course a mosquito that produces a snake venom protein sounds like a deadly prospect, but it takes one mutation alone to neutralize the poison. Zieler has already tested mosquito guts with this non-toxic protein, and it is every bit as effective as its snake venom ancestor.

Marcelo Jacobs-Lorena, at Case Western University, is very enthusiastic about Zieler's results. He says 'this is a seminal finding!' Working in collaboration with Zieler, Jacobs-Lorena has created a transgenic mosquito that carries the PLA2 gene from bees. Early tests show that the PLA2 transgenic mosquitoes are 80 % resistant to the parasite, and Jacobs-Lorena is confident that a combination of similar approaches will be the most effective defence against malaria.

They both know that there are many problems yet to be overcome before this strategy can be released into the environment, but they are very optimistic that some time in the future transgenic insects will be at the forefront of man's campaign against the malaria parasite.

Hot Muscle (p. 4043)

It's been 400 million years since tunas and the lamnid shark family diverged from a common aquatic ancestor. But despite the long evolutionary separation, both groups happen to be the only fish that are warmer then their surrounding environment. Both species convergently evolved a specialised heat exchanger tissue called the retia that maintains an elevated body temperature as they descend and ascend through waters at different temperatures. Tuna fish also regulate their temperature in response to rapid changes in the environment's temperature. But it wasn't clear whether lamnids had convergently evolved a thermostat too. A team led by Jeffrey Graham from the University of California at San Diego has provided new evidence that lamnid sharks, such as makos and great whites, can regulate their body temperature in a similar way to their distant relative, the tuna fish.

But to do this, Graham's team had to make thermal measurements on sharks swimming in the lab. Everyone thought this would be impossible because of the obvious difficulties in working with lamnid sharks like makos: they're just too big to handle in the lab. The team decided to work with smaller, juvenile makos instead.

Diego Bernal and Chugey Sepulveda spent a couple of years searching the Pacific Ocean for the ideal specimens to test in the lab. Once they'd located a suitable fish, they rushed it back to the water tunnel in the lab, racing against time to implant the thermocouples and keep the fish alive while they collected the temperature data.

Bernal and Sepulveda saw that as they quickly warmed the water, the juvenile fish were able to regulate their retia so they rapidly gained heat from the environment. Then the team suddenly dropped the temperature, catching the fish in a situation that would make them vulnerable to rapid temperature loss. But instead of cooling, the fish were able to rapidly engage their heat exchanger, blocking heat loss and keeping the warmth in.

Both the lamnid sharks and the tuna have managed to solve the problem of keeping warm, but they've arrived at the solution by different routes. Differences in the way the retia are laid out, and their distant evolutionary relationship convinces the team that this is a case of convergent evolution. Bernal is very pleased that all the perseverance with the juvenile makos has paid off. He says 'it's not that it was too hard, it just took a long time!'

Diving to the Beat (p. 4081)

Manfred Enstipp is intrigued by animal behaviour, and more specifically, the limits that an animal's physiology set on the feats it can perform. For birds, their ability to dive is limited by the amount of oxygen a bird can load onboard, and how the bird consumes it once submerged. Birds that dive to different depths experience increased physical pressure, and Enstipp wondered how this would affect the bird's heart rate. Working with a team of hand-reared cormorants, he has found that the bird's heart rate can vary dramatically, and he believes that the drop is driven by the partial pressure of oxygen in the bird's blood.

Although cormorants aren't up there with the elite of avian divers, they perform much better than the least accomplished divers: ducks. Previous work with cormorants has found that just before a dive, the bird's heart rate is somewhere around 400 beats

per minute, but the instant that they descend beneath the surface, it plummets to around 250. During a shallow dive, the bird's heart rate continues to drop at a slower rate from 250 beats per minute, sometimes falling lower than their resting heart rate. Enstipp was intrigued by what was controlling the latter decrease in heart rate and whether the birds' heart would beat with the same rhythm during deeper dives.

Enstipp was lucky enough to join David Jones at the University of British Columbia, where he was the first person to have access to a new 12 m deep dive pool. He also had access to state-of-the-art heart monitoring equipment, designed by Russel Andrews, to check the bird's heart rate through each dive. Enstipp set to work with his cormorants to see just what their hearts would do.

Sure enough, the birds that skimmed 1 m beneath the surface showed the standard heart beat pattern. But the birds that swam to the bottom of the deep tank, did something that Enstipp hadn't expected. The secondary decrease in the heart beat rate that Enstipp knew happened when the birds were cruising 1 m beneath the surface failed to begin. Their hearts kept beating at 250 beats per minute throughout the deeper dive.

Why wasn't the heart rate dropping as the birds went deeper? Enstipp suspected that when the birds were diving near the surface, chemoreceptors in the bird's vascular system were sensing a drop in O_2 partial pressure as the bird consumed oxygen and dropped the bird's heart rate to conserve the oxygen that remained. But birds that were diving much deeper would not experience a decrease in the blood gas partial pressure, because at 10 m, their bodies would be under double the atmospheric pressure at the surface, raising the O_2 partial pressure, even as the bird used up its precious fuel.

Enstipp tested how the bird's heart rate behaved if he artificially elevated the O_2 partial pressure giving the birds an oxygen enriched air supply before shallow diving. Sure enough, their heart rates didn't decrease, just as if they had plumbed the depths. He believes that the chemoreceptors that reduce the bird's heart rate in response to a drop in O_2 partial pressure could be a crucial regulator of the bird's heart. However, he accepts that this reflex response isn't the whole story, and there are other modulating factors yet to be identified.

Enstipp is continuing to work with adult diving birds, but he says he's hoping to return to UBC to work with the cormorants again. He says 'the birds were fantastic, and so were the facilities!'

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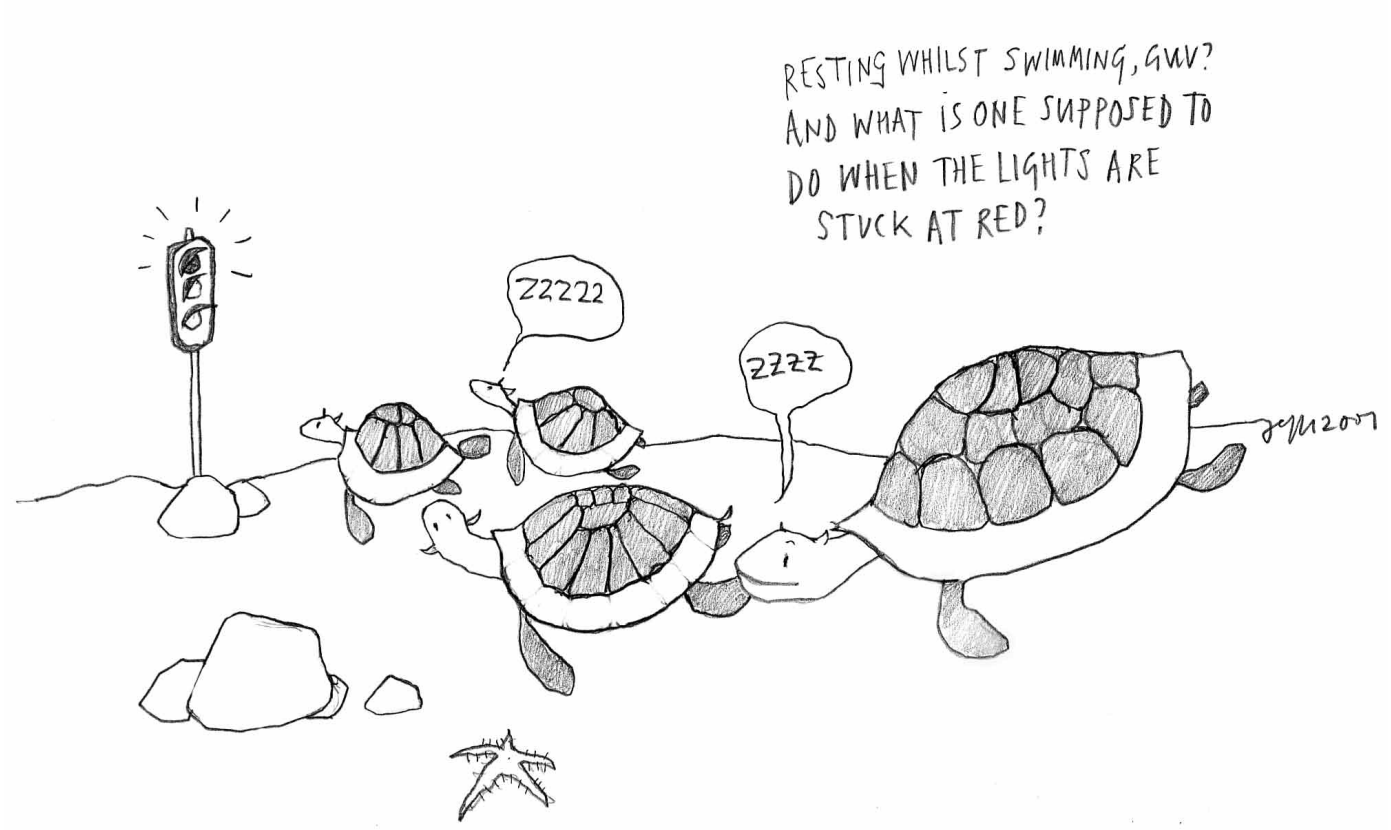
The Journal of Experimental Biology 204, i-iii (2001)



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