BIOLOGY

BALLOONING PARROTS AND SEMI-LUNAR GERMS

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Pillow talk first introduced me to *The Selfish Gene*. I remember the scene quite vividly, perhaps because of the weather. Sun was streaming into the room and it was exceptionally warm; in New Zealand's southernmost university town, such mornings were rare. I was a second year zoology undergraduate and my then girlfriend was majoring in English literature. I was a great deal more interested in her than in literature, but on this particular morning she told me about a weird biology book she'd had as a set text. I was surprised that a biology book would appear in a literature course, but she said that it was used to discuss the role of metaphor and then said, I believe without irony, that the author proposed that genes had emotions. We both laughed at this lunacy, and I suggested that she should read a sensible evolutionary thinker like Stephen Jay Gould.

Incredible as it now seems, my first physical encounter with the book was *after* I had finished my four year Zoology degree specializing in evolution, ecology, and behaviour. The limitations of my formal education were, I like to think, more than offset by the summer jobs I had with the New Zealand Wildlife Service on remote mountains and offshore islands. The best job came immediately after finals, when I had the extraordinary good fortune to work on the kakapo conservation program during a breeding season. Kakapo are the world's strangest and most fabulous birds. But to me then, as a budding evolutionary biologist, I came to see them as an intellectual affront. I just could not figure out how kakapo could be like they are; I couldn't even figure out how one might figure it out. Certainly, my extensive Stephen Jay Gould

collection was no help. My boss recommended *The Selfish Gene*, and this time, I actually read it. What a revelation. It didn't mention kakapo (of course), but here at least was a framework to explain them. I now spend my professional life thinking about infectious diseases the way *The Selfish Gene* taught me to think about kakapo. It turns out that selfish genery not only explains weirdoes like kakapo, but also makes insights possible that escape conventional biomedicine.

To explain why, I first need to describe kakapo. They are parrots which break all parrot records. They are the largest (big males weigh the same as a large cat) and the longest lived (an elderly bird found in 1975 is still alive). Beak and feet aside, they do not actually look like parrots: they have an owl-ish face framed with whisker-like feathers. They also do not behave like parrots: they are nocturnal, flightless, and meet only for sex, and then only every three to four years. And sadly, they are one of the world's most endangered parrots. At the time of writing, there are just eighty-six left, the majority of which are males.

Evolution has dealt kakapo an extraordinarily bad hand for life in the modern world. Until the last millennium, the only mammals in New Zealand were bats. Now, of course, there are humans, rats, cats, stoats, and dogs. Like so many of the endemic birds, kakapo were ill-prepared for mammalian hunters. When disturbed, kakapo freeze and hope to blend into the forest background. With their rich green coloration, this is visually very effective. But kakapo smell. They smell so strongly (of sweet hay), even I could sometimes smell them before I could see them. When the freeze routine fails with olfactory hunters, surviving kakapo can only run, climb, or jump away.

Their breeding system is just as hopeless. For most of their lives, kakapo are solitary, spending their time wandering about, grazing, and sleeping. In those rare years when they do breed, males aggregate in breeding arenas which are usually on high promontories. Here, they call out for females living in the surrounding valleys. Even the calling is weird. Males suck air into enlarged air sacs, blowing themselves up so they look like a balloon with a

beak. They then deflate themselves, the slow expulsion of air making a low 'sonic' boom. This inflation–deflation cycle, which takes a few minutes, is repeated from the same spot, all night, night after night for up to six months. The eerie boom can be heard for miles, attracting females—and predators. A single cat loose in one of these breeding arenas can wreak havoc.

Females come to these arenas ('leks') to mate, and then leave immediately to resume their solitary lives. Some miles from the leks, they lay eggs in nests built on the forest floor. Each night they go off on foraging trips of up to several kilometres. If the unprotected eggs manage to escape ground-hunting predators for a month, they hatch, only to produce completely helpless chicks. And now, because she has mouths to feed, mum has to spend even more time away foraging. After three months of this, the chicks are finally developed enough to leave the heavily scented nest for the relative safety of the open forest.

It is hard to imagine a lifestyle less suited to withstanding mammalian predators.[1] When I worked with kakapo in the 1980s, all we seemed to do was watch them die. Now they have been shuttled to predator-free islands where their future is brighter, but they will be heavily dependent on human management for some decades, if not in perpetuity.

I was part of a small research team in the south of Stewart Island, the southernmost of the large New Zealand islands, tracking females which had been fitted with radio devices. Alone in a tent on some exposed hilltop, often in the most appalling weather, each of us would take bearings on the handful of birds we were tracking every half hour, all night. Every two weeks the helicopter arrived bearing fresh meat and veg and, occasionally, rapidly melting ice cream and warming beer.

Mud was a feature of the place. The tracks we used to get to our tents were often knee-deep in the stuff. Lying in the tents was like being on a giant dirty waterbed. While we knew someone else was on another hilltop, radio contact was unreliable, and it was difficult not to go mad. Between half-hour telemetry readings we would read or doze (resetting the alarm every half hour). We

could only take it for a few nights before needing a break; we used to clamour for the job of sitting in hides at the leks, watching the balloon routine through the night-viewing scopes and, just like the male kakapo, hoping desperately that a female would arrive (in a region where predators had taken all the females, males copulated with fallen tree trunks and even a rolled up sweater). I never saw any females on a lek, but two hatched eggs that year. The chicks didn't last a month. In all of this, I kept asking, why? It is pretty easy to imagine that in a mammal-free world, flightlessness could evolve: flight is expensive so do without it if you can. The nocturnality (and associated owl-like features), green coloration, and freeze-responses we assumed to be essential adaptations to avoid visual hunters; large eagles existed in New Zealand until quite recently. But this crazy breeding system? Night after night I wondered how such a bizarre behaviour could have evolved. What a stupid thing for a species to do. Surely the males should help feed the chicks? What were they doing mucking around on leks?

In response to my persistent questioning, the scientist in charge, Ralph Powlesland, sent me a paper about other lek breeders which he thought might help. It didn't; it was full of inscrutable mathematics. But maths about breeding systems implied some kind of a theory. I demanded an interpreter and, much to my surprise, *The Selfish Gene* arrived on the next helicopter run.

Lying in my tented, muddy waterbed, I read it by torchlight between half hourly telemetry readings. In fact I read it three times, very slowly, trying to make sense of it all. Reading now the comments I then wrote in the margins, I must have been deeply sceptical (I guess in those days I valued the scientific opinions of English literature students). But there it was, clearly laid out. The good of the species was irrelevant! It was competition between strategies to maximize genetic representation that mattered. This competition could result in outcomes that were disastrous for all. Just as evolution could not have the foresight to arrange kakapo to be prepared for mammals, it could not arrange them to maximize the reproductive output of the species. Individual selfish genes

were maximizing their share of the gene pool, even if this meant fewer kakapo offspring overall. The kakapo males must have given up parental care because helping their chicks to survive was not the way for them to maximize their fitness. It didn't matter that the offspring of one mate mostly died: getting more mates must make up for it. And females mating on leks got to choose the best male genes going.

Of course, there in the tent, all this was hypothetical and to be fair, today we still do not fully understand the so-called 'lek paradox' for any species, let alone kakapo. But I think we all agree that the answer is somewhere among the ideas that flow from selfish genery. And what was clear to me then was that here was a framework which had tremendous explanatory power for all of biology. Evolutionary biology could actually *explain* organic diversity—really explain it in a predictive sense, not just describe it. Gould was wrong. Adaptationism could be rigorous, and generate testable ideas, some of which were clearly right. Gone in a stroke the intellectually barren 'it-just-is' hypothesis and woolly group selectionism.

I also drew another conclusion from the book. Much to my surprise, there were clearly people making a living ruminating about stuff I thought about in idle moments. I had already decided to be a career zoologist, but this made me think that perhaps I could—and maybe even should—do something other than applied conservation biology.

Sometime that autumn, a radio message arrived saying that I had a won a Ph.D. scholarship to Oxford. Over the next few years in Oxford, I learnt that many people worldwide were involved in working out the logical consequences of *The Selfish Gene*, and that in fact many had been doing so before the book had come out. Indeed, it turned out that the intellectual framework had already been in the air, but *The Selfish Gene* crystallized it and made it impossible to ignore. I learnt that most of the criticisms it attracted were intellectually boring or, worse, stupid. Other frameworks that people proposed as alternatives were either simple rebrandings or vacuous. This was the only show in town,

and it was a productive and exciting one. And I also learnt that the impact of the book on me was not unique. Many other students were doing what they were doing because they had chanced upon *The Selfish Gene*. It actually did deserve to be a set text in English Literature 101.

My Ph.D. was mostly concerned with how infectious diseases might be responsible for the bizarre songs, colours, and plumes of many male birds. While I was finishing my thesis, it occurred to me that we evolutionary biologists were fixated on hosts and inexplicably ignoring the infectious disease agents themselves. We had left them to microbiologists and parasitologists, who quite plainly did not think in selfish gene terms. Yet infectious diseases evolve on experimentally measurable timescales, so we could test theory, and because they make us sick, there must be money in it. Various epidemiologists had made forays into disease evolution (most notably Roy Anderson and Bob May, who had looked at the evolution of virulence),[2] and Paul Ewald had been using selfish genery to make controversial claims about the evolution of a swathe of human diseases.[3] But to me, this was but a drop in the ocean of possibilities, and none of it involved the sort of high-class experimental work that flowed from selfish genery, and which was by then captured in John Krebs' and Nick Davies' classic edited volumes and introductory text.[4]

Oxford was, and still is, capable of generating breathtaking intellectual arrogance. This must explain the belief that I developed towards the end of the 1980s that even though I knew absolutely nothing about how to do an experiment, or about any infectious disease, I could demonstrate that not only could selfish genery make sense of facts that biomedicine could not, it could even make novel quantitative predictions that would be turn out to be true.

The most heavily annotated part of my original copy of *The Selfish Gene* is Chapter 9, 'Battle of the Sexes'. It was this chapter that really convinced me that the adaptationist programme works. In it, Dawkins lucidly summarizes Fisher's gene-centred explanation of why 1:1 sex ratios are so common, even though

they clearly do not maximize the reproductive output of a species (just enough males to fertilize all the females would do this). Fisher's idea was that only a 1:1 sex ratio is evolutionary stable; all others can be invaded by a mutant producing slightly more of the rarer sex. This idea is so logically beautiful that no one bothered to test it experimentally until the 1990s: it simply *had* to be true (it was). Before then, the best evidence that it was true came from species without 1:1 sex ratios. In a 1967 paper, Bill Hamilton showed that where individuals are mating with very close relatives, the female-biased sex ratios which would maximize the number of offspring for a species as a whole would also be those that would maximize the fitness of individual genes.[5] That paper is to my mind the finest demonstration that the selfish gene framework is right. Hamilton's arguments makes quantitative predictions about the sex ratios that will be seen with different levels of inbreeding, predictions which he (and subsequently others) showed were true for many species of insect across a bizarre range of natural histories. I reasoned that if sex ratio theory is the empirical bedrock of selfish genery, then we should apply it to infectious diseases. If that didn't work, harder things like disease virulence would surely be beyond us.

Most infectious disease agents do not have males and females. Malaria parasites do. In malignant human disease, the malaria cells that infect mosquitoes have what Ronald Ross called a semi-lunar shape.[6] These have sex in the mosquito, and it is possible to distinguish the male and female forms in our blood. Females dominate, in contrast to 1:1 sex ratios in the vast majority of free-living species. I reasoned that this was a Hamiltonian bias.

I discovered I wasn't the first to think this (Michael Ghiselin and John Pickering had thought of it earlier), but encouraged by colleagues, particularly Anne Keymer and David Walliker, I pushed the idea harder. It turned out that we really could make quantitatively successful predictions. Karen Day and I measured malaria sex ratios in Papua New Guinea, and then, with Sean Nee, we used simple mathematical models to predict that at least

62 per cent of malaria zygotes in Papua New Guinea would be the result of mating among the same parasite clone.[7] At the time, conventional wisdom put the figure close to 0 per cent, though it had never been measured. Rereading our paper now, it is quite clear that we were worried about this wisdom, and I spent a great deal of the discussion describing why our estimate might be too high. I should have had more faith. Ric Paul and Karen Day subsequently used molecular genetic analyses to show that inbreeding rates in those malaria populations were in fact well in excess of 62 per cent.

This was the first scientific prediction I had ever made which had turned out to be right. Was it a fluke? Clearly we needed to do more, but with the best will in the world, no one was going to do lots of expensive molecular genetics just to test a fantasy of mine. So we needed a cheaper approach. I reasoned that sex ratios should be shaped by the rate at which people acquired new infections, and we could estimate that from the number of hosts that were infectious. Sean Nee and I formalized this mathematically, and then the search for data began. The data came in from collaborators over several years, mostly from populations of birds infected with malaria-like parasites. Each time we got data from a new population, I was shocked at the close fit between theory and observation. Eventually, we got data covering a large range of sex ratios and, staggeringly, *all* were as expected. Although it was published over ten years ago, I still consider that work to be my most philosophically satisfying.[8,9] From Chapter 9 of *The Selfish Gene*, it is possible successfully to predict previously unsuspected patterns for a group of organisms—and even a lifestyle—not featuring in *The Selfish Gene* or in almost any of the other work which flowed from it. This study relieved my physics-envy. For sure, not as impressive as predicting the existence of the planet Neptune in advance, but we evolutionary biologists can also make novel quantitative predictions that are right. And malaria is a damned sight more important to humanity than Neptune.

Of course, I failed to persuade anyone else that this was interesting. Evolutionary biologists already knew that sex ratio theory

worked, and biomedical types simply didn't care: sex ratio does not affect how sick we get and, worse, our arguments involved non-intuitive theory and equations. These days, my collaborators and I are applying selfish genery to malarial virulence and infectiousness, and at least some biomedical people are interested. Our controversial prediction that some vaccines could prompt the evolution of nastier pathogens is just a small logical step from the sex ratio theory of Chapter 9; our discovery that selfish strains dominate infections shows that the kin selection and relatedness of Chapter 6 apply to malaria too.[10,11]

My sense is that *The Selfish Gene* had a huge impact among evolutionary biologists, ecologists, and behaviourists, recruiting people to these fields and helping to get right the thinking of the less mathematically inclined. But in biomedicine, the largest and most well-funded area of biology, selfish genery has had negligible impact. This is in part because evolution is largely absent from biomedical training, and also because evolutionary biologists have been slow to leave the comfortable natural histories of birds and insects for the jargon-laden natural history of medicine. But it is also a consequence of the overwhelming dominance of a reductionism in biomedicine (ironically a criticism once levelled at Dawkins). Explanation of disease virulence and infectiousness is usually sought in terms of molecular interactions, cell signalling, and so on. Mechanistic description is of course fantastically important and it has yielded substantial insight and some clinical advances. However, such explanations are necessarily incomplete. To explain why something is like it is, we also need to ask about the evolutionary pressures. And this involves the thought processes laid out in *The Selfish Gene*.

Not thinking like this could even be dangerous. The conventional wisdom that infectious diseases evolve to be nice is hopelessly wrong. Evolution does not maximize longevity of an individual or the reproductive output of a species. If a virulent mutant competes more successfully with other parasites, that mutant will spread even if it is more likely to kill its host, its competitors, and itself. Had SARS persisted in the human

population, would it evolve to be nastier or nicer? Would the intervention measures we would be throwing at it alter this evolution for better or for worse? Such questions are very rarely even asked, and we do not know the answers.

For malaria, there are two questions I want answered. Why are strains that produce more of the semi-lunar cells needed to infect mosquitoes not more common? Broadly speaking, more transmission stages beget more transmission, yet most malaria infections contain barely any. Something very interesting must be going on for selection to favor reproductive restraint.[12] Second, why are malaria parasites killing so few people? Our experimental work shows that virulent strains have a fitness advantage; something is stopping them spreading. The chance of an African being killed by a single dose of malaria parasites is less than 1 per cent. Why should mutant parasites running a 2 per cent risk not spread?

A selfish gene perspective naturally begs such questions and, as Dawkins showed so clearly thirty years ago, provides a means to answer them. For malaria, some selection pressure is keeping the lid on transmission and virulence. Ideally we would like to use public health measures to screw that lid down tighter. We certainly do not want inadvertently to loosen it.

ENDNOTES

1 Indeed, if kakapo are the result of Intelligent Design, the designer was not very far-sighted.

2 Summarized in R. M. Anderson and R. M. May, *Infectious Diseases of Humans: Dynamics and Control* (Oxford: Oxford University Press, 1991).

3 Summarized in P. Ewald, *Evolution of Infectious Disease* (Oxford: Oxford University Press, 1984).

4 J. R. Krebs and N. B. Davies (eds.), *Behavioural Ecology: An Evolutionary Approach* (Oxford: Blackwell, 1978; 2nd edn., 1984); *An Introduction to Behavioural Ecology* (Oxford: Blackwell, 1981). Like Dawkins, Krebs and Davies were animal behaviourists, with the

consequence that the field came to be called *behavioural* ecology. This is something of a misnomer; selfish genery extends way beyond behaviour.

5 W. D. Hamilton, 'Extraordinary sex ratios', *Science*, 156 (1967): 477–488.

6 Winner of the 1902 Nobel Prize for his verification of Manson's prediction that mosquitoes transmitted malaria. R. Ross, *Memoirs* (London: John Murray, 1923).

7 A. F. Read, A. Narara, S. Nee, A. E. Keymer, and K. P. Day, 'Gametocyte sex ratios as indirect measures of outcrossing rates in malaria', *Parasitology*, 104 (1992): 387–395.

8 A. F. Read, M. Anwar, D. Shutler, and S. Nee, 'Sex allocation and population structure in malaria and related parasitic protozoa', *Proceedings of the Royal Society of London Series B*, 260 (1995): 359–363.

9 Things have moved on since this work; for reviews aimed at (i) evolutionary biologists or (ii) parasitologists respectively, see (i) A. F. Read, T. G. Smith, S. Nee, and S. A. West, 'Sex allocation in Microorganisms', in I. Hardy (ed.), *Sex Ratios: Concepts and Research Methods* (Cambridge: Cambridge University Press, 2002), 314–332, and (ii) S. A. West, S. E. Reece, and A. F. Read, 'Gametocyte sex ratios of malaria and related apicomplexan (protozoa) parasites', *Trends in Parasitology*, 17 (2001): 525–531.

10 The primary papers here are: (i) S. Gandon, M. J. Mackinnon, S. Nee, and A. F. Read, 'Imperfect vaccines and the evolution of pathogen virulence', *Nature*, 414 (2001): 751–756, and (ii) J. C. de Roode, R. Pansini, S. J. Cheesman, M. E. H. Helinski, S. Huijben, A. R. Wargo, A. S. Bell, B. H. K. Chan, D. Walliker, and A. F. Read, 'Virulence and competitive ability in genetically diverse malaria infections', *Proceedings of the National Academy of Sciences USA*, 102 (2005): 7624–7628.

11 For an overview of our virulence work, see (i) M. J. Mackinnon, and A. F. Read, 'Virulence in malaria: An evolutionary viewpoint', *Philosophical Transactions of the Royal Society of London Biological Sciences*, 359 (2004): 965–986, and (ii) A. F. Read, S. Gandon, S. Nee, and M. J. Mackinnon, 'The evolution of pathogen virulence in response to animal and public health interventions', in K. Dronamraj, (ed.), *Infectious Disease and Host-Pathogen Evolution* (Cambridge: Cambridge University Press, 2004), 265–292.

12 L. H. Taylor, and A. F. Read, 'Why so few transmission stages? Reproductive restraint by malaria parasites', *Parasitology Today*, 13 (1997): 135–140.