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Pathogen's progress: The digitally coloured scanning electron micrograph (SEM) shows a number of *Yersinia pestis* bacteria (yellow) that have gathered on the proventricular spines, a feature of the digestive system of its vector, the rat flea *Xenopsylla cheopis*. (Image: National Institute of Allergy and Infectious Diseases.)

species barrier in the early phase of farming and became less fatal when they established an equilibrium with their new human hosts (Curr. Biol. (2013) *23*, R667–R670), diseases like the plague do not depend on human hosts and are therefore able to maintain a high rate of mortality.

Thus, the present truce between *Yersinia* and our species depends heavily on the achievements of modern medicine, including antibiotics.

Future risks

The finding that *Yersinia pestis* only acquired the ability to use fleas as vectors fairly recently raises concerns as to what may happen if it picks up other virulence or resistance traits.

The spread of resistance to existing antibiotics and the shortage of fundamentally new ones becoming available is already a growing global crisis (Curr. Biol. (2013) *23*, R1063–R1065). Pathogens with dangerous resistance traits are frequently observed in hospitals, but, due to the excessive use of antibiotics in agriculture, they also occur in the environment. If *Yersinia* populations in the wild were to pick up effective multidrug-resistance traits, the containment of the disease could become a challenge.

Similarly, if the pathogen could harness new vectors that are more closely linked to humans than those that it uses at the moment, the third pandemic could run out of control. It is with such concerns in mind that researchers study the interactions of *Yersinia* with insect species like cat fleas (PLoS Negl. Trop. Dis. (2016) *10*, e0004413) and human body and head lice (Am. J. Trop. Med. Hyg. (2015) *93*, 990–993).

Even if the bacterium doesn't step up the threat all by itself, there is the danger that humans may intentionally make it more dangerous than it already is, in order to use it as a bioweapon. Apart from the crude precedent in the 14th century, plague was also developed as a biological weapon by Japan's 'Unit 731' in World War II (https://en.wikipedia.org/wiki/Unit_731). Japanese planes are alleged to have dropped plague-infested fleas over the city of Changde in China, sparking a disease outbreak that is estimated to have caused at least 200,000 deaths.

Even more worrying than the use of fleas would be the creation of an aerosol carrying the pathogen, which could be dispensed more easily and would cause pneumonic plague, leading to death much more rapidly, thus reducing the chances of treatment. This option has reportedly been investigated during the Cold War by both US and Soviet Union military researchers. However, due to the effective treatment options available with antibiotics, the threat was considered manageable.

Nowadays, as antibiotic-resistance traits are spreading in the wild and technologies are available for anybody to transfer such traits to a bacterial species of interest, one may have to reconsider the threat that weaponised *Yersinia pestis* may pose. Vaccination options have been investigated, but so far a vaccine that is effective and safe for general use has remained elusive (Infect. Immun. (2007) *75*, 878–885). A ruthless state or non-state force able to produce this sort of bioweapon could be tempted to use it for short-term benefits—and the events of the 14th century show us what the long-term fallout of this could be.

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Book review

The enemy of my enemy is my friend

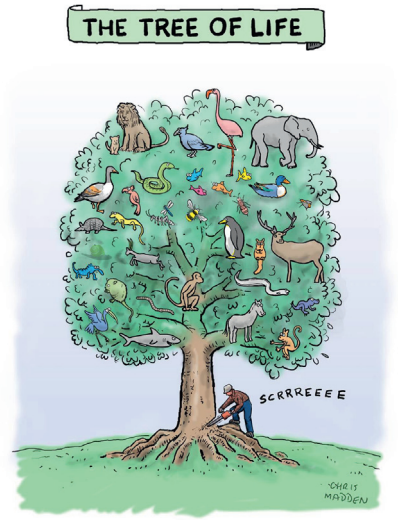
Peter A. Lawrence

The Serengeti Rules: The Quest to Discover How Life Works and Why it Matters
Sean B. Carroll
(Princeton University Press, Princeton, NJ; 2016)
ISBN: 9781400880263

We humans plunder our only home and we damage just about everything. In his new book, Sean B. Carroll, a research biologist who built his reputation by clever experiments with a small fly, turns his attention to greater matters. He points out that, like the knight in Bergman's *Seventh Seal*, our species is caught up in a game of chess with death and reminds us that the rules governing this game are the laws of nature. Carroll has two purposes in this book: to provide an entertaining read and to teach us about the interdependence of everything. He dips into his holiday trips and makes rather rushed stories from them through time, space and ideas. In this review, I will give you a taste of where he went and how far he has succeeded in his mission.

Carroll's story starts with a family visit to the Serengeti National Park, and springboards off that to a quick look at ecological principles, to how we are destroying sharks and on to overpopulation, to drug testing, to molecular biology. It is hard to keep up, but we are tugged along, at least for a bit. Then he comes clean and tells us he plans to give us "fresh insight and inspiration: insight into the wonders of life at different scales; inspiration from the stories of exceptional people who tackled great mysteries…whose extraordinary efforts have changed our world for the better."

The first of these exceptional people is Walter Cannon, who early in the 20th century made many contributions to our understanding of human physiology. Through a potted biography, Carroll wants us to know that Cannon saw clearly how regulation is crucial for the body to work and survive — without



Cartoon © Chris Madden

regulation, elemental processes go wild. The second is Charles Elton, the 'founder of modern ecology'. Elton, like Charles Darwin (and so many ecologists who came after), discovered general principles from thoughtful and patient observation of the natural world. In an entertaining and rambling biography of Elton, we learn about his expeditions and his observations of the interdependence of species and of food chains, a term invented by Elton. And from reading the work of Robert Collett, Elton thought about oscillations in populations, for example of lemmings and of how predators cycled in sympathy. And in one of his many interesting asides, Carroll tells us that Elton was mistaken because, relying on the unreliable reports of Collett, he launched the myth of the lemmings' periodic mass suicide. The problem was that Elton "had never seen a lemming". Carroll did not need to point out that the lemming myth is like many myths in science, where opinion and 'fact' are increasingly driven by reviewers who have themselves 'never seen a lemming'.

But whoa! We are off on a different tack, Carroll takes us into biomedicine to find "the logic of life" and tells us that "analogous rules and logic operate" in both ecology and molecular biology. Now we have a mini-biography of Jacques Monod to illustrate this claim. Carroll is at his best when he describes how Monod (with Francois Jacob and Leo Szilard) cracked a puzzle of genetic control in bacteria. Here he largely sticks to one storyline, and when he does, he makes it both exciting and clear.

Carroll is a geneticist, and I enjoyed it when he praised the value of the genetic approach, particularly as we geneticists are and have been subject to a prejudice that we find inexplicable: so often our papers are criticised and rejected because they "lack mechanistic evidence". By mechanistic evidence editors mean sequences, gels and pulldowns etc., as if these methods give more pertinent and foolproof evidence than genetics. I guess that Carroll would agree with me that while Nature can play the fool with geneticists, it can also make fools of molecular biologists. Genetics can "find mutations in genes of interest and is unbiased — it makes no assumptions about the number of players or what they do". And also the genetic approach is the best way to start solving a new problem — genetics has so often been the first explorer of a new country. At the end of this section Carroll points to how life "from the molecular scale all the way up to the ecological scale — is usually governed by longer chains of interactions than we first imagine, with more links in between". Quite so!

Then Carroll follows the life of Ancel Keys, a human epidemiologist who found the connection between heart attacks and cholesterol, and on to Mike Brown and Joe Goldstein, who consolidated that link in the lab, and whose results led to the development of statins. In this chapter, Carroll makes it clear that different individuals can together make a discovery that none of them alone could have imagined. In general, Carroll appears overfixated on Nobel Prizes, but he points out that deciphering cholesterol biosynthesis has "earned a total of eleven Nobel Prizes for a series of discoverers"; put like that it definitely sounds too many!

In yet another aside, he points out how Janet Rowley's important discovery of the role of chromosomal translocations in cancer was rejected by two successive journals, first on the ground that it was "unimportant" and second that it was just part of "normal variation". I like this story as it feeds one of my hobby horses that our present systems discriminate against the original and unexpected — first, because we don't risk funding people who want to try new things, and second, because we don't recognise and respect novel findings, precisely because they are new and unfamiliar. There's no more secure way to get a paper published in a vanity journal than to pin down what is largely expected in a field where there are many workers. Perverse, because what we need in scientific research is more originality, not less.

When Carroll tells one story, he does it very well, so that we can follow his plotline through the messy undergrowth of history. But this book is perhaps too much of a mix of short stories, each interesting in itself and each interconnected with some of the others. Some of these interconnections appear to be contrived, others convincing. A major thread is that everything is regulated: biochemical pathways, cell physiology, cell interactions during development as well as populations of animals and plants in the ecosystem. Carroll illustrates that regulation can occur directly when a process is limited by a negative regulator. But he also emphasises those many cases where a regulator represses another regulator and so acts on the end function in a positive way. In biology, two minuses often make a plus.

In the third part of this book, Carroll spells out the "Serengeti Rules" themselves, in which we leave molecules and cells behind and return to ecology, to interacting populations as exemplified in the African bush and elsewhere. Robert Paine did experiments in the field and explored regulation in the wild. Following on from Alfred Lotka and Vito Volterra, Paine found that population numbers and diversity were under the control of carnivores — without them, particularly the main 'keystone' species, the balance of nature was disturbed so that some herbivores took over to the detriment of others. The first of the Serengeti rules derive from this concept of keystone species — "not all species are equal". The remaining rules make his general point again, that in a place like Serengeti, all species are interconnected by competition for resources of all kinds. And "just as

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The interdependence of everything.
The bee depends on the flower for food, and the flower depends on the bee for pollination. The spider hides under the flower to catch the bee. Sean Carroll's new book focuses on the interdependence of life. Photo by Peter Lawrence.

with molecular rules, understanding these rules of ecological regulation enables us to diagnose what is ailing ecosystems, and potentially, to cure them". Here, one begins to lose the thread in a tangle of myriad examples and this reader began to skim a bit.

Nevertheless, one lesson is reiterated by Carroll and we are getting it: it is the double negative logic again — populations of baboons, or bay scallops or cancers are repressed by predators or 'tumour suppressors'. So when one sees baboons or scallops change in population numbers, the best advice is to look up the food chain to find the cause. In the case of scallops their predators (rays) increased… because their predators, the sharks decreased…because…well, you can guess who is responsible.

More short stories follow about the manipulation of populations in the wild: one example is the reintroduction of wolves into Yellowstone Park. The wolves were a success; paradoxically they helped aspen regrowth and boosted beaver numbers in the park. Food chains and population numbers are again the explanation. Then Carroll is back in Africa, reviewing personally the hugely successful restoration of wildlife in Gorongoso National Park by restocking and protection.

Here the account becomes even more discursive, as if whatever negative regulation that ought to be controlling Carroll's inherent tendency to ramble has been lifted further and we receive the full force of his stream of consciousness. Reading was a bit like watching many modern TV programmes on science, where the makers seem to be worried that we the public have a weak and limited concentration that cannot be kept active simply by the power of an argument, and that we need entertaining diversions. But ideas continuously built in front of us, piece by piece, can also grip a reader, and often Carroll demonstrates this by recounting his stories with clarity. Also the asides, the lives of some great scientists, have definite value, and even the diversions are sometimes diverting. But on balance, I would have urged more editorial discipline in the crafting of this book. Overall, as I read *The Serengeti Rules*, I was prepared to be captivated by Carroll's central idea that ecology, molecular biology, biomedicine and genetics all include a common logic, but for me that thesis flitted in and out of sight, like a butterfly in a sunlit glade.

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Q & A

Botond Roska

Botond Roska is a Senior Group Leader in Neuroscience at the Friedrich Miescher Institute (FMI) for Biomedical Research, and Professor at the Faculty of Medicine, University of Basel, Basel, Switzerland. He received an MD in Budapest, Hungary, and a PhD at the University of California, Berkeley. After being a Harvard Junior Fellow at Harvard University he started his research group, ten years ago, at the FMI. He investigates neuronal circuits in the retina, thalamus, and visual cortex; he is interested in using the gained knowledge to understand the circuit basis of neurological diseases and to design new therapies.

What turned you on to biology in the first place? I first studied medicine and mathematics. An unusual combination, so let me explain: I grew up in Budapest, Hungary. My father was a professor of computer science, working on nonlinear dynamics and its applications, and my mother is a pianist. For me, talking about and doing mathematics at home was as natural as for other kids watching TV or playing outside with friends. I liked mathematics a lot, but for idealistic reasons I started medical school. After a year, however, I felt that I needed to develop my thinking ability too, so I then started to study mathematics as well. I did the two in parallel. It was tiring but very rewarding. Towards the end of medical school, I wished to have a deeper understanding of living systems, especially to get insights into how the different parts of an organism are controlled and organized by a central unit, the brain. I did not feel ready to treat patients, as I did not have a coherent picture of the 'machine' I would be repairing. So I looked into ways of doing research in neuroscience.

And what drew you to your specific field of research? A dinner conversation with Frank Werblin, a neurophysiologist, later to be my PhD supervisor. My father was working on a computer structure that combined both analogue processing and logic. Frank and my father met frequently because they felt it should be possible to model the retina with such a computer. I was present at some of those