Taming Evolution

How best to manage the "natural" selection created by medical practice?

By Andrew Read

Evolution kills. Last year, about 100,000 Americans died of infections that were easily cured 20 years ago. That's more than twice the number killed in car crashes. The cures are failing because the germs are evolving. Pathogens bearing resistance mutations thrive when our medicines eliminate their competitors. Nowadays, pathogens can evolve around drugs faster than replacement drugs can pass through regulatory hurdles. In a few cases, resistance has evolved so far that some germs can be killed only with chemicals that also kill the patient.

The same evolutionary processes that produce drug-resistant "super-bugs" also are responsible for many of the complications of cancer. Chemotherapy very effectively removes drug-sensitive tumor cells, creating enormous opportunities for drug-resistant mutants to get more space and more nutrients. These mutants proliferate, creating untreatable tumors that can be fatal.

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"Unnatural" selection imposed by medicine shapes the evolution of disease-causing organisms, causing drugs, vaccines, and public-health insecticides to fail.

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The rapid evolution of cancers and infectious agents is typical of the incredible capacity of life to overcome environmental insults. Biologists know this process of genetic change as "adaptive evolution," and it is studied in organisms as diverse as Darwin's finches and slime moulds. One of the key medical and scientific challenges in the 21st century is adaptive evolution by the life forms we target with our pharmaceuticals.

Evolution Costs

The burden imposed on humanity by adaptive evolution can be guesstimated in particular contexts. Consider malaria, a disease now confined to the tropics where it sickens perhaps a quarter of a billion people a year and kills up to a million. The parasites that cause malaria have repeatedly evolved resistance to front-line drugs, and the mosquitoes that transmit them have evolved resistance to all classes of insecticides approved for malaria control. The standard response to this evolution is to search for new formulations and new active ingredients, with the expectation of replacing those products when they, in turn, fail. Even if we assume that an endless supply of effective products can be discovered, these evolutionary treadmills are expensive. It costs about $1 billion per decade for anti-malarial drug discovery to stay in the game. Bringing a new insecticide to market may cost up to $200 million. And it is impossible to put a cost on human suffering and death as interventions fail and national policies adjust.

These costs, and the prospect that we might be falling behind in the drug-bug arms race, have led to increasing interest in product "stewardship." The idea is that functioning pharmaceuticals are a common good for humankind, and so we should try to design and use them in ways that keep them working for as long as possible. Somehow, we need to to minimize the evolutionary forces that cause pharmaceuticals to fail, while still reaping the very health benefits that those forces generate.

Many medical professionals are engaged in trying to square this circle. Indeed, this enterprise is humankind's greatest attempt to deliberately shape the future evolution of any organisms. For example, very serious efforts are made to ensure that drugs are not used unnecessarily, on the theory that less drug use must equate to less evolution. This effort is why many drugs are available only by prescription, and why primary healthcare providers are implored to use antibiotics only when they are sure the patient is ill from a bacterial infection. Likewise, drugs against

One of the research aims of Andrew Read's lab, a collaboration with Professor Matt Thomas in the Department of Entomology, is to develop novel ways to kill mosquitoes resistant to chemical insecticides like DDT. One project is investigating a fungus that can be applied to surfaces where mosquitoes rest between hunting expeditions for blood. The mosquito at the top of this image has just ingested a blood meal; in the middle, a mosquito 24 hours after being killed by the fungus; and at the bottom, a mosquito, 48 hours after being killed by the fungus, is covered with it. Credit: Hugh Sturrock, University of Edinburgh, Scotland

TB, HIV, malaria, and leprosy are almost always used in combination because the probability of a single parasite being spontaneously resistant to two or more drugs is very, very much smaller than the probability of its being resistant to just one. Enormous efforts also are made to ensure patient compliance with treatment regimens, in the belief that incomplete drug treatment promotes drug resistance.

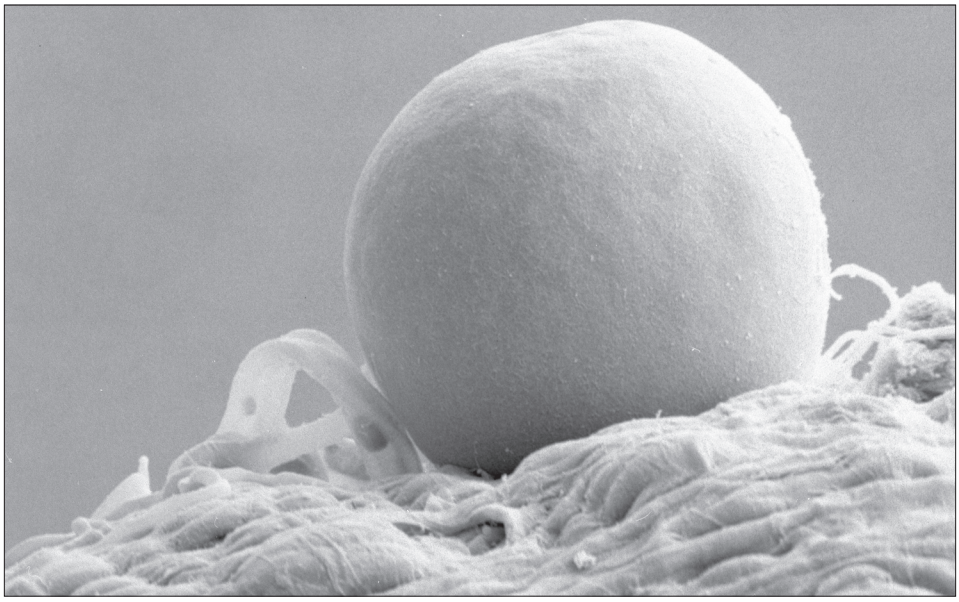
How much extra time on the evolutionary

treadmill do these policies buy our products? As an evolutionary biologist, I increasingly wonder whether we know enough to know — and equally, whether misunderstandings of how adaptation works obscure other strategies that might perform better.

Resistance Management

Step back a bit and think about what resistance evolution involves. As for all adaptive evolution, two elements are required. The first is genetic changes that can be passed to offspring and that protect otherwise susceptible germs from drugs. For simplicity, you can imagine that these changes are brand-new mutations, but there are other ways an individual pathogen can acquire resistance for the first time; for example, bacteria often acquire resistance genes from other species. The second element is natural selection, which is the main force that determines the fate of any genetic change. If there is no drug treatment at all, the new mutation is usually lost in short order — if it conferred evolutionary benefits beyond resistance, it would already have been favored by selection. On the other hand, if there is aggressive drug treatment, the new mutant is able to leave more progeny than its drug-sensitive progenitor. It then will become increasingly more abundant in the host in which it arose and so will have an increased likelihood of transmitting drug resistance to the next host, and the next . . . and so on.

So, to slow resistance evolution, we have two weak points to play with: the mutational inputs into the system (without resistance genes, evolution has nothing to chew on), and the selection on any resistant mutants that are present (without selection, resistance genes won't become common). My feeling is that the current thinking about resistance management focuses too much on mutational inputs and not enough on selection outcomes. This approach is like attempting to stop the horse from bolting by locking the gate, without preventing whatever might make the horse bolt in the first place. Locking the stable door is great if it works, but if you are too late, or there is another door, the horse has gone. The main problem with trying to limit mutational inputs is that resistant mutants might be quite frequently generated by chance — not least because there are usually billions of individuals in any pathogen species so, chances are, somewhere out there is a pathogen resistant to drugs we have yet to invent.



This electron micrograph is a very close view (magnified approximately 1,000 times) of the outer surface of the midgut of a mosquito that has been infected with the malaria parasite. The ball-shaped sack, an oocyst, is one of the life stages of the malaria parasite. When this sack ruptures, thousands of malaria parasites are released. These find their way to the mosquito's salivary gland. When the mosquito bites a human, the parasites are injected into the person's body along with the mosquito's saliva, causing the infectious disease malaria. Credit: John Findlay, University of Edinburgh, Scotland

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Research is providing the scientific foundation for more-effective 21st-century solutions for limiting the damage caused by pathogen evolution.

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This likelihood makes it impossible to assess in advance the effectiveness of strategies designed to suppress mutations. That does not mean we should not try. But, we should get very serious about finding treatment strategies that do not strengthen the evolutionary advantage for any resistant mutants that are lurking out there.

Curious Orthodoxy

Consider the exhortations by physicians, medical schools, drug companies, government health officials, and professional bodies that, to prevent drug resistance, it is essential that patients complete their drug courses even after they feel better. Can this be right? Continuing to treat the patient until every last sensitive parasite is dead simply maximizes the evolutionary advantage of any resistant parasites that are present. Aggressive chemotherapy could promote the very evolution it is intended to retard.

The main justification behind the exhortations to finish drug courses is that dead pathogens can't mutate to resistance — and this clearly is true. But that means aggressive chemotherapy is, from an evolutionary management perspective, a double edged sword. The good news is that it can reduce the chance of new resistance mutations arising in the first place. But the bad news is that, when an infection does contain resistant parasites (either a new mutation or a resistant parasite acquired from another patient), full-course chemotherapy ensures that those resistant parasites have the maximum evolutionary advantage.

How do these opposing evolutionary pressures play out? There will be situations where overwhelming chemical force retards evolution, and others when it drives things very rapidly. Perhaps for fast-mutating viruses like HIV, the mutation-suppression effect is beneficial. On the other hand, for diseases like TB or malaria, where most resistant pathogens are acquired from other patients, the

benefits of preventing mutations could be far outweighed by the immense selection pressures generated in the process. Chloroquine became ineffective against malaria when the highly-resistant progeny of a single parasite in Asia spread across Africa. Those resistant parasites enjoyed maximum evolutionary advantage in patients who took every last chloroquine pill they were prescribed.

Beyond Orthodoxy

How should patients be treated? I do not know. I think we lack adequate knowledge to decide for any infectious disease. It's a question of trying to balance the often conflicting requirements to 1) make the patient better, 2) prevent the patient infecting others, and 3) prevent the spread of resistance. My current thinking is that, among the various treatment regimens that can achieve the first two aims, we should use the one best able to achieve the third. Ongoing work in my research group, funded by the National Institutes of Health, is aimed at identifying that regimen in a mouse model of malaria. We are trying a variety of regimens, including reduced doses or intermittent treatment (once a week instead of every day, for example). All the regimens we have tried so far do better than standard practice at slowing the spread of resistance, and several do as well or even better at improving health and reducing infectiousness.

It is not out of the question that the ultimate heresy ("take pills when you feel sick and stop taking them when you feel better") might be best. But I doubt there will be generalities that will apply to all drugs and all bugs in all circumstances. My current preference is to try to prevent resistance mutations arising in the first place using combination drug therapy and then use 'light-touch' chemotherapy to minimize the rate of spread of any resistant mutants that are present. We may not need to use our chemicals to kill every parasite in order to achieve health. Often the immune system just needs a helping hand — and immunity is a lethal weapon against drug-resistant parasites. If there is a simple rule for managing the evolution of resistance, it is "impose no more selection than is absolutely necessary for patient health." If we want our drugs to last, we need to evaluate what we mean when we want to "cure" a patient.

Cancer

Analogous evolutionary processes occur in infections and in cancer tumors. Drugs select for resistance, and the more aggressive the treatment, the greater the evolutionary advantage enjoyed by resistant parasites or cells. This knowledge raises the possibility that light-touch chemotherapy might better prolong the life of the patient than the aggressive chemotherapy currently practiced. Very recent, path-breaking research by Robert Gatenby and colleagues at the Moffitt Cancer Center in Florida has suggested that it might be better to manage the size of tumors with chemotherapy, rather than using drugs aggressively to try to get rid of every last cancer cell.

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View a lecture by Andrew Read at

science.psu.edu/future-of-disease.

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In experiments with mice given tumors that normally are fatal, Gatenby's group found that the mice died from drug-resistant tumors if they had been treated "successfully" with aggressive chemotherapy. In contrast, when the researchers used the chemotherapy only when the tumors grew above a certain size, the mice survived to the end of the experiment. On days when drugs were not being used, sensitive tumor cells evidently outcompeted the resistant cell lines, so that the tumor as a whole continued to respond to chemotherapy. This approach is precisely analogous to what we are trying to do in my lab: use the drugs intelligently in order to give drug-resistant mutants as little advantage as possible.

Coda

In our work with malaria, and Gatenby's with cancer, there is a long way to go before we know how best to treat mice, let alone people. But I think our work illustrates the need for a rigorous, data-based science of adaptive evolution in the medical context. It might be, of course, that overwhelming chemical force has to be used to restore patient health or, in the case of infections, to prevent patients infecting others. If so, we might be stuck with evolutionary mis-management as an unavoidable side-effect. But I think it is worth asking if we can do better. We might discover treatment regimens that deliver the health that physicians and their patients want while, at the same time, mitigating as best we can the negative evolutionary impact of current medical practices. Perhaps my optimism is misplaced. If so, it is even more important to have a thorough understanding of the adaptive evolution that has escalated in recent decades. Medical practice is creating serious evolutionary problems for which we now need solutions.

***Andrew Read**, professor of biology and entomology, Eberly College of Science Distinguished Senior Scholar, and director of the Center for Infectious Disease Dynamics at Penn State, perhaps is best known for his research on how natural selection shapes the virulence of malaria.*

His current research focuses on understanding how the "unnatural" selection imposed by medicine shapes the evolution of disease-causing organisms, causing drugs, vaccines, and public-health insecticides to fail. One arm of his work is trying to determine whether some vaccines might drive the evolution of more-virulent pathogens.

His research is providing the scientific foundation for more-effective 21st-century solutions for limiting the damage caused by pathogen evolution in diseases including malaria and cancer-causing viruses of poultry. The thinking summarized in the accompanying article has benefitted from discussions with Troy Day, of Queens University, Ontario, and especially Silvie Huijben, a postdoctoral fellow in Read's group at Penn State. A video of Andrew Read's presentation during the 2011 Penn State Lectures on the Frontiers of Science is online at **science.psu.edu/future-of-disease.** *More information is online at* **www.thereadgroup.net/**