VICKI BARCLAY:

Enduring evolution

IMAGE: A.E. LANDES PHOTOGRAPHY

Barclay

In early June, post-doc Vicki Barclay came to work in the biology department with a broken rib and shredded knees and elbows. Her lab mates were mildly amused: as always, the injuries were self inflicted. On this occasion, Vicki had just finished 3rd among a nation-wide collection of professional women athletes in the seven day, 240 mile Trans-Sylvania Epic, the longest race in the U.S. endurance mountain bike calendar. She had fallen seven times, including a crash early on the first day that put her handlebar through her rib cage. Her competitors develop mental strength by training full time. Vicki does science.

Vicki was half way through her Ph.D. at the University of Edinburgh in Scotland, when her advisor, Andrew Read, was recruited to Penn State. Of the eight people that moved with Read in 2007, Barclay was the least enthusiastic to come. Her Ph.D. work was going well, and she was concerned about the down time. She planned to stay a year and be gone as soon as the thesis was finished.

She did finish her thesis on schedule, but by then she was hooked. First, she discovered what she calls the "endurance hungry State College community", a group of like-minded souls who enjoy the physical and mental preparation required to race bikes faster and faster over longer and longer distances. Second, the opportunity came up to do the killer experiment her thesis work was crying out for.

The evolution of disease-causing organisms in response to medical interventions is well known: witness the growing problems caused by drug-resistant microbes. Barclay's graduate work was trying to understand how a vaccine might drive the evolution of the parasites that cause human malaria. There currently is no approved malaria vaccine, but it seems likely there will be one day. Will malaria parasites simply evolve around the vaccine? Many people think so, but theoretical work by Read and others had raised the possibility that things might be even worse: the evolutionary process might generate parasites that were actually more deadly. Using rodent malaria, Barclay examined various assumptions of that theory in her thesis, and she had flown through her Ph.D. defense.

But hanging over it all was a nagging question. Could you directly test the theory by actually evolving the parasites in real time through populations of hosts immunized with vaccines currently in trials in humans? The experiment could not be done in people, but it might be possible in mice. Barclay and Read had discussed the critical experiments many times, but they were so large and so risky, and so logistically difficult, it was hard to imagine any grant agency would support them – or that any sane person would actually do them.

So when Read suggested that unconventional risk-taking science was precisely what unencumbered start-up funds should be used for, Barclay took a big gulp. The work would provide the means to stay in the State College cycling community. And she could not bear the thought that Read might persuade someone else to do the experiments. But could she handle the mental stress? They would need to run over many, many months, and could fail at any time. Twenty generations of infections were thought necessary to see an evolutionary outcome (though that was a guess). Successive generations of mice would need to be vaccinated and boosted weeks before they would be needed. There could be no mix-ups and particularly no contamination as the infections were passed from generation to generation. And the appropriate level of replication was scary: ten independently evolving parasite lines in vaccinated hosts, and ten in unvaccinated hosts, with each generation duplicated in case something went wrong, and every second generation everything frozen down in case of accidents. And then worse, Read got very keen on growing the experiment even larger after heated discussions in the Penn State Center for Infectious Disease Dynamics raised the reverse question. There was theory about what would happen in vaccinated (immune-enhanced hosts). But in contrast, how would parasite virulence evolve in immune-suppressed hosts? Figuring that out would add another ten duplicated lines, and the associated immune-suppression would require gallons of immunosuppressive antibodies. Barclay would have to make them herself as the experiment progressed. And throughout the whole process, it would be impossible to tell what was happening. There was the very real prospect that nothing at all would be gained—but that would not be clear for at least a year.

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IMAGE: VINCE M. CAMIOLO / RUNVMC.COM

Barclay racing in the Trans-Sylvania Mountain Bike Stage Race in State College with a broken rib. She finished 3rd overall in the pro woman's field.

Enduring evolution (continued)

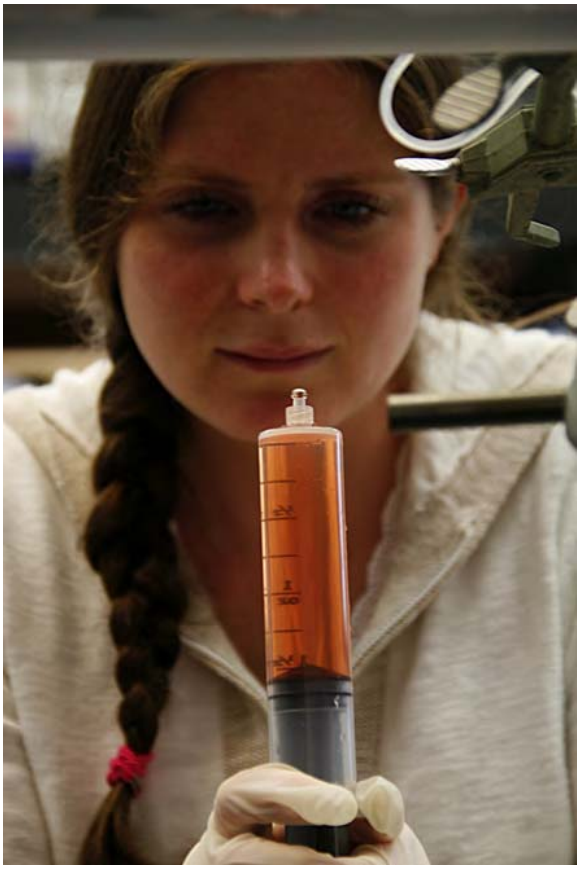
In the end it was two years. Barclay and Read dithered for months, examining the experimental protocols from all angles and consulting widely. Finally, Barclay took a deep breath and got going. It turned out to be much worse than she expected. Running hard, she was able to keep on top of the antibody production and the on-going vaccination protocols. But moving the parasites from one mouse generation to the next became a morale sink. Immunization did what it should do: suppress parasite numbers. Often this meant there were not enough parasites to pass to the next generation. Each week, more and more parasite lines were lost. For many months, the experiment was on the edge of complete failure. She came to dread Wednesdays, the day the parasites were moved to new hosts. But slowly, generation by generation, things eased, and eventually the evolutionary phase of the experiment was done. With the evolved lines safely in the freezer, Barclay went cycling in Scotland.

And then came the assay phase. What had evolution produced? Figuring that out took another five months of experiments, followed by months of statistical analysis and reanalysis....

And the answer? Striking differences in parasite virulence had indeed evolved. The parasites evolved in the vaccinated hosts had become nastier, as predicted. But so too had those evolved in the immune-suppressed hosts! The parasites that had evolved in normal mice were the least virulent. How could both immune-enhancement *and* immune-suppression have the same evolutionary effect? Barclay cannot find a plausible explanation that fits the data.

So she dodged the experimental blow out, but was not blessed with a sound-bite conclusion. The first of the resulting scientific papers on the evolutionary consequences of vaccination is now winding its way through the peer-review process. Given the emotions surrounding vaccines in the public arena, and political importance of malaria vaccines in the scientific community, the papers are likely to get a rough ride.

IMAGE: B CHAN / THE READ GROUP



Barclay purifies a cell culture to isolate antibodies to inject into mice to create 'immuno-compromised' mice.

It will be many more months before she knows whether the work will have impact. Asked recently what she found more grueling, endurance mountain bike racing or endurance science, Barclay answered without hesitation. "Obviously science. Your life doesn't depend on a bike race".

AROUND THE DEPARTMENT

Clockwise, Far Left: Stalked barnacles in the Lau Basin hydrothermal vent system in the southwest Pacific (approx. 3000m depth). The white "fuzz" is chemosynthetic bacteria growing on their cirri (foot-like appendages); Hydrothermal vent chimneys at the Mariner study site in the Lau Basin, Southwestern Pacific; Brisingid brittle starts in the Lau Basin. These animals do not live in areas of active venting but sometimes inhabit old extinct hydrothermal vent chimneys; Octopus in the Gulf of Mexico; Brittle stars hang onto coral branches taking advantage of the elevation from the seafloor to capture food (approx. 1000m depth).