other parts of the genome among these populations, suggesting that they do come into contact [14]. Unlike Wu's example of taxa infected with differing strains of *Wolbachia*, the scientific community considers these populations to be conspecific. Many other examples could be brought to bear where the BSC does not assume speciation is complete but 'loci of differential adaptation' exist.

Cases also exist in which the BSC would properly define taxa as species but in which Wu's genic concept would not. One example of nonadaptive speciation is polyploidy. Polyploidy causes speciation within a few generations, but there are no 'loci of differential adaptation' [15]. Hence, Wu's definition would consider diploids and resultant auto- or allotetraploids to be conspecific, whereas the BSC considers them to be heterospecific. Similar problems hold in cases where chromosomal rearrangements contribute to speciation [16]. In both of these scenarios, most evolutionary biologists adopt the BSC even though there is no indication of differential adaptation or even selection. Indeed, as several of the response papers noted, the community desires a species definition that is useful regardless of how species come to be [12,15], and the scenarios that Wu describes might not be universal [5,10]. The BSC is more generally useful, albeit imperfect, because all reproductive barriers have a similar effect in inhibiting gene flow, regardless of whether they originated by drift, meiotic drive, polyploidy, sexual selection, or natural selection.

Wu considers examples such as the above to be 'special cases' in the application of his concept [17]. He questions the frequency of cases of polyploidy, hence betraying an extensive botanical literature on its extreme commonality [18]. Why should Wu's concept be allowed such glaring exceptions, whilst the BSC must be employed in the strictest sense? There seems to be a double standard here, and when Wu's arguments encounter these special cases, he falls back on reproductive isolation [19]. Hence, Wu's concept provides only a very limited, if any, conceptual advance.

Finally, we are left with the question of where such a debate leads us. On the one hand, species concepts determine how the process of speciation is studied. Because it is arguably the fundamental step in cladogenesis and the generation of biodiversity, speciation has an indisputable role in evolutionary studies. On the other hand, only very limited scientific advances have emerged from the introduction of more species concepts, particularly when compared with the exciting empirical results of the past 15 years. Lineage-based species concepts could provide some advantage for conceptualizing and classifying species, particularly allopatric taxa, but no species concepts have facilitated research on the process of speciation like the BSC has. The words of Jerry Coyne on the subject summarize my perspective: 'It is clear that the arguments will persist for years to come but equally clear that, like barnacles on a whale, their main effect is to retard slightly the progress of the field. Ultimately, speciation will require less rumination and more perspiration' [20].

References

1 Dobzhansky, T. (1935) A critique of the species concept in biology. *Philos. Sci.* 2, 344–355
2 Mayr, E. (1942) *Systematics and the Origin of Species*, Columbia University Press
3 Hey, J. (2001) The mind of the species problem. *Trends Ecol. Evol.* 16, 326–329
4 Wu, C-I. (2001) The genic view of the process of speciation. *J. Evol. Biol.* 14, 851–865
5 Mayr, E. (2001) Wu's genetic view of speciation. *J. Evol. Biol.* 14, 866–867
6 Feder, J.L. (1998) The apple maggot fly, *Rhagoletis pomonella*: flies in the face of conventional wisdom about speciation? In *Endless Forms: Species and Speciation* (Howard, D.J. and Berlocher, S.H., eds), pp. 130–144, Oxford University Press
7 Mallet, J. (1995) A species definition for the Modern Synthesis. *Trends Ecol. Evol.* 10, 294–299
8 Rieseberg, L.H. and Burke, J.M. (2001) A genic view of species integration. *J. Evol. Biol.* 14, 883–886
9 Bordenstein, S.R. *et al.* (2001) *Wolbachia*-induced incompatibility precedes other hybrid incompatibilities in *Nasonia*. *Nature* 409, 707–710
10 van Alphen, J.J.M. (2001) Sexual selection, reproductive isolation and the genic view of speciation. *J. Evol. Biol.* 14, 874–875
11 Bridle, J. and Ritchie, M.G. (2001) Assortative mating and the genic view of speciation. *J. Evol. Biol.* 14, 878–879
12 Rundle, H.D. *et al.* (2001) Hybridization without guilt: gene flow and the biological species concept. *J. Evol. Biol.* 14, 868–869
13 Lewontin, R.C. *et al.* (1981) *Dobzhansky's Genetics of Natural Populations I–XLIII*, Columbia University Press
14 Schaeffer, S.W. and Miller, E.L. (1992) Estimates of gene flow in *Drosophila pseudooscura* determined from nucleotide sequence analysis of the alcohol dehydrogenase region. *Genetics* 132, 471–480
15 Orr, H.A. (2001) Some doubts about (yet another) view of species. *J. Evol. Biol.* 14, 870–871
16 Britton-Davidian, J. (2001) How do chromosomal changes fit in? *J. Evol. Biol.* 14, 872–873
17 Wu, C-I. (2001) Genes and speciation: a reply. *J. Evol. Biol.* 14, 889–891
18 Otto, S.P. and Whitton, J. (2000) Polyploid incidence and evolution. *Annu. Rev. Genet.* 34, 401–437
19 Shaw, K.L. (2001) The genealogical view of speciation. *J. Evol. Biol.* 14, 880–882
20 Coyne, J.A. (1992) Much ado about species. *Nature* 357, 289–290

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Imperfect vaccines and imperfect models

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A recent paper by Gandon *et al.* presents a model for how leaky vaccines can lead to evolutionary changes in the virulence of parasites. Whilst readers of some of the press reaction to this paper might be forgiven for thinking that it referred to certainties about actual malaria vaccines, there are currently no malaria vaccines beyond the early clinical trial phase, so the paper could in principle offer no more than theoretical predictions. The models might well be less appropriate for the chosen example of *Plasmodium falciparum* malaria than for other parasites. Critical review of the Gandon *et al.* paper highlights both the fact that the determinants of virulence in malaria are not well understood, and that monitoring of malaria vaccines should consider more than just the immediate effects on vaccine efficacy.

There is an important place in science for conjectures, and the example of malaria vaccines is justifiably topical. *Plasmodium falciparum* is the most important eukaryotic parasite of humans, with hundreds of millions of people infected at any one time, and at least 1 million people dying as a consequence each year. The need for a malaria vaccine is manifest, but none are currently registered for use, and

  PII: S0169-5347(02)02450-3

the complexity of the strategies used by the parasite to evade the host immune responses makes for major technical difficulties in designing one that is effective. It is likely that we will need to make do with an imperfect vaccine that allows some malaria parasites to survive, even in vaccinated hosts.

Much vaccination theory assumes the objective to be pathogen eradication. With malaria, this could well be an unrealistic goal, but the disease is so frequent that even a partially effective vaccine delivered via the less-than-optimal health systems available in sub-Saharan Africa could have a major impact on public health. To the epidemiologist, the benefits of such a vaccine would be obvious. However, the evolutionary consequences of selection induced by such vaccines are not at all obvious.

A new paper by Gandon *et al.* [1] represents an attempt to predict some of the consequences of such vaccines. The authors use a mathematical approach combining simple models of parasite transmission with a model for the evolution of virulence. The basis of this model is cost-of-virulence theory [2], one of several hypotheses for why host–pathogen interactions do not evolve towards symbiosis [3]. The theory acknowledges that killing the host is bad for the parasite, but that if more-virulent parasites have a higher transmission rate, competition among parasites for hosts will lead to tradeoffs with a stable state at an intermediate level of virulence.

Most effort in malaria vaccine research so far has been to develop vaccines to prevent infection, one of the kinds of vaccine considered by Gandon *et al.* An example is the RTS,S construct, which recently demonstrated some efficacy in The Gambia [4]. Gandon *et al.* suggest that the use of such a vaccine will lead to selection for reduced virulence. One way in which this could happen is if the virulent parasite has a high intrinsic growth rate. Competition among parasites leads to selection of more virulent parasites, because the faster growing parasites corner the resources of the host for themselves, pulling the evolutionarily stable state further towards virulence than in the situation without competition. A vaccine that reduces transmission will reduce competition among different malaria parasites and hence select for less virulent parasites.

However, natural immunity against *P. falciparum* does not prevent infection, and so it is unclear whether it is possible to completely block infection with a vaccine. Other vaccination strategies that mimic more closely natural immunity are therefore also being tried. These include vaccines that limit the multiplication of the blood stages of the parasite, thus preventing the parasites reaching densities at which they cause severe illness or death.

One evolutionary consequence of such a vaccine against a polymorphic parasite is selection in favour of pathogens expressing alleles different from those in the vaccine. There is ample evidence for such vaccine-induced selection from pathogens other than malaria and evidence for such selection has already emerged in one trial of a malaria vaccine [5]. Therefore, the vaccine must be designed to contain epitopes that cover a broad range of parasite types, including those causing severe disease. (Extending this idea, we can speculate that, if the specific factors affecting parasite virulence were understood, one might be able to induce immune responses that directly select in favour of less virulent parasites.)

However, Gandon *et al.* do not discuss this kind of selection, but rather the selection that occurs if the target epitope of the vaccine is not itself responsible for virulence. Within the cost-of-virulence model, the level of virulence results from a tradeoff between virulence and persistence, so the effect of any intervention that makes the parasite less virulent in practice is to generate selection in favour of intrinsic virulence until the equilibrium is regained. Any vaccine that slows parasite growth will lead to evolution in the direction of greater intrinsic virulence, so that unvaccinated individuals will be at greater risk than before.

The evidence for this cost-of-virulence model is limited. The theory assumes that the rate of parasite transmission from the human host increases with parasite virulence. This makes sense if virulence and transmission are simple functions of parasite multiplication rates. The Edinburgh group, where Gandon *et al.* are based, has shown that faster growing parasites are more virulent in the *P. chabaudi*–rodent model system. Chotivanich *et al.* [6] have elegantly demonstrated a relationship between the *in vitro* growth rate of parasites and the severity of disease in *P. falciparum* patients in Thailand (a country with relatively low malaria endemicity). However, this is only one group of patients, who are likely to be very different from the children in endemic areas of Africa who are the main victims of the disease. Even in the Thai study, there was considerable overlap in the growth rates of parasites in uncomplicated malaria with those of severe cases. Virulence in malaria is certainly not merely a matter of intrinsic growth rate, even in previously unexposed subjects [7].

In areas of endemic malaria in sub-Saharan Africa, in contrast to the infections in Thai patients, most *P. falciparum* infect people without causing many overt symptoms. The overall disease burden is enormous, but most of it occurs in specific sections of the population (young children, pregnant women, and short-term visitors). In the remainder, the parasites persist at low densities, but do not often cause acute illness.

In such a situation, competition among malaria parasites must be mediated by immunological mechanisms. Without immunological modulation, the progeny of a single inoculation would proliferate in an uncontrolled manner, killing the host within a few weeks. Persistence and transmission are mainly functions of how the parasite deals with this immune modulation, and the intrinsic growth rate is only one, probably rather minor, factor in this. But, although we have some idea about the strategies of immunoevasion (extreme polymorphism, antigenic switching, smokescreen effects etc.), we have very little idea about how these come together to define whether a given parasite persists in a given host, and even less how they affect transmission or virulence. There are many possible speculations about how immunity might affect the evolutionary biology of *P. falciparum*. For example, an attractive strategy from the point of view of a parasite already established within a host, and of the host itself, would be for the parasite to co-opt the host immune system to fight off potential competitors. There is some evidence that this happens. In particular, there is an upper limit to the incidence of malaria infections as the inoculation rate increases, and there is some evidence that the pre-existing infections might protect against superinfections in partially immune hosts [8].

Box 1. Superinfection: just one complicating factor

Gandon *et al.* [a] assume that an invading parasite immediately replaces the already resident parasite, so that, within their models, parasites compete for host occupancy. Within this model, any reduction in overall transmission level reduces the advantage to the parasite of exploiting the host rapidly, because the likelihood is reduced that an infection will be terminated prematurely by a superinfection.

The assumption that superinfections replace existing parasite clones was also made by many early malariologists [b], however, the orthodoxy on this issue for many years was the idea that superinfecting parasites behave independently of pre-existing parasite populations [c]. Now, although we can use molecular techniques to type parasites, it is clear that superinfection is frequent, but that the infections are certainly not independent of each other. Reality is somewhere between the two extremes. The resulting competition among malaria parasites within the individual host complicates any realistic model for the evolution of virulence.

References

a Gandon, S. *et al.* (2001) Imperfect vaccines and the evolution of pathogen virulence. *Nature* 414, 751–756

b Sergent, E, and Parrot, L. (1935) L'immunité, la prémunition *et al.* résistance innée. *Arch. Inst. Past. Alg.* 13, 279–319

c MacDonald, G. (1950) The analysis of infection rates in diseases in which superinfection occurs. *Trop. Dis. Bull.* 47, 907–915

What would be the implications of vaccination against blood-stage antigens if they play a role in cross protecting against invading clones? It is not easy even to predict the immediate consequences, which might well depend upon whether vaccination tends to eliminate the existing parasites, or to boost immune responses to the existing infections. The evolutionary implications are at least as unclear (Box 1).

It is commendable that Gandon *et al.* have stimulated thinking about the possible evolutionary consequences of malaria vaccines. But it is important to remember that their model is only one of many that are possible and that it might be a better model for simpler systems (such as viral pathogens) than it is for malaria. Unexpected effects of vaccination are probable when imperfect malaria vaccines are introduced on a large scale. The secondary effects of vaccination should certainly be monitored closely and, as Gandon *et al.* recommend, intrinsic growth rates of parasites are one parameter that should not be forgotten. But, it is not at all obvious that the predictions that they make will prove accurate.

References

1 Gandon, S. *et al.* (2001) Imperfect vaccines and the evolution of pathogen virulence. *Nature* 414, 751–756

2 Anderson, R.M. and May, R.M. (1982) Coevolution of hosts and parasites (Pt 2). *Parasitology* 85, 411–426

3 Ebert, D. (2001) The evolution and expression of parasite virulence. In *Evolution in Health and Disease* (Stearns, S., ed.), pp. 161–172, Oxford University Press

4 Bojang, K.A. *et al.* (2001) Efficacy of RTS,S/AS02 malaria vaccine against *Plasmodium falciparum* infection in semi-immune adult men in The Gambia: a randomised trial. *Lancet* 358, 1927–1934

5 Genton, B. *et al.* A recombinant blood-stage malaria vaccine reduces *Plasmodium falciparum* density and exerts selective pressure on parasite populations in a Phase I/IIb trial in Papua New Guinea. *J. Infect. Dis.* (in press)

6 Chotivanich, K. *et al.* (2000) Parasite multiplication potential and the severity of falciparum malaria. *J. Infect. Dis.* 181, 1206–1209

7 White, N.J. (1998) Malaria pathophysiology. In *Malaria: Parasite Biology, Pathogenesis and Protection* (Sherman, I.W., ed.), pp. 371–385, American Society for Microbiology

8 Smith, T. *et al.* (1999) Consequences of multiple infection with *Plasmodium falciparum* in an area of high endemicity. *Parassitologia* 41, 247–250

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Meeting Report

New advances in carbon cycle research

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The 6th International Carbon Dioxide Conference was held in Sendai, Japan, from 1–5 October 2001.

Although the Intergovernmental Panel on Climate Change (IPCC) Third Assessment Report (TAR) was published recently [1] with the latest assessment of our understanding of the global carbon (C) cycle, there is already a wealth of new information available. The 6th International Carbon Dioxide Conference provided a venue for scientists to present new findings that contribute to our understanding of the current and future C cycle.

Contemporary carbon sources and sinks: patterns

The Northern Hemisphere net C sink is currently relatively well constrained, but its longitudinal distribution is largely unknown. New analyses from multiple inverse models show that the Northern Hemisphere land sink during the 1990s was distributed quite evenly among North America (0.83 Pg C y^{-1}), Europe (0.62 Pg C y^{-1}) and Asia (0.61 Pg C y^{-1}). Surprisingly, boreal Asia accounted for a sink of 0.52 Pg C y^{-1} C, while boreal North America was a net C source of 0.26 Pg C y^{-1} (K. Gurney, Colorado State University, Fort Collins, CO, USA).

Less is known about the sink strength of the tropics, but it is thought to be large enough to counteract the 1.6 Pg C y^{-1} that are emitted because of tropical deforestation. Thus, inverse model calculations show a fairly unconstrained net balance of zero for the region between 15°N and 15°S. Even less is known about its longitudinal distribution, but ground-based estimates indicate that ~50% of the sink is in Amazonia (0.75 Pg C y^{-1}), and the other half is distributed equally between tropical Africa and south-east Asia (Y. Malhi, University of Edinburgh, UK).

The contemporary budget and distribution of C sinks and sources in the

  PII: S0169-5347(02)02451-5