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Discussion

Evolution and immunology of infectious diseases: what's new? An E-debate

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First question: When I read Steven's excellent book "immunology and evolution of infectious diseases" (Frank, 2002), I find that many basic concepts of immunology (nature of antigens, molecular structure of antibodies, mechanisms of humoral and cellular immunity) were already known when I was a medical student in the 1970s. Where do you think the main progresses have been done in this field since that time?

Response from Steven Frank

I often remind my students that the basic principles of genetics and evolution were understood before the description of DNA as the hereditary material in 1953. In the same way, the principles of immune specificity and memory were understood many years ago. So, it is interesting to take a step back and ask how the recent advances in immunology have changed our fundamental understanding of the host-parasite interaction.

Most immunologists would perhaps emphasize the advances in molecular understanding of the immune response. Those molecular details are indeed crucial, but to me the wonderful molecular work brings us just to the threshold of a new and exciting phase in the history of the subject. We are almost ready to understand what happens during an infection and how parasites evolve to escape host immunity.

Mims emphasized that "every infection is a race". Parasites divide rapidly and build up in numbers. The host, in response, builds up its populations of immune cells to fight the infection. The outcome turns on numbers and rates. If the host builds its numbers of immune cells fast enough, the infection may be cleared before the onset of symptoms. If the parasite builds its numbers too quickly for the host to control, then disease may develop and transmission is more likely.

The importance of numbers and rates may seem obvious, yet it has been rather rare for immunologists to consider whole systems as they actually function in real organisms. I think there was, however, some change in attitude in the middle 1990s that brought dynamics to the world of immunology. At that time, one of the great puzzles in biology concerned the long latent period during an HIV infection.

After the initial viremia of an HIV infection, the host has few free viral particles in the blood. Then, after perhaps 10 years of apparent inactivity, viral titers rise to high levels, CD4+ cell counts decline, and immunodepression follows. Everyone wondered: Where did the viruses hide for so many years during the latent period? Why were they not replicating?

The answer turned out to be that the viruses were replicating continuously and rapidly, killing host cells at a high rate, and also being cleared from the blood at an equally fast pace. The total observable population of viruses depends on the balance between the birth rate and the death rate. During the so-called latent period, HIV has a very high birth rate and a very high death rate. The net effect of these two rates is a low population number. The solution to a great puzzle of immunology depended on numbers and rates. Since that time, there has been a modest increase in interest in the quantitative factors that determine outcomes, although most work continues at molecular levels that remain unintegrated into the larger view of how the system functions.

The molecular level does, however, provide a wonderful foundation for future advance. Rates determine numbers, but it is the nature of molecular binding and specificity

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between host and parasite that determines rates. For example, structural and physico-chemical studies have established the nature of binding between host antibodies and parasite molecules (epitopes). The nature of that binding determines the speed at which antibodies clear parasites and how much parasites have to change to escape recognition by the host.

Structural studies show that about fifteen amino acids of the antibody surface contact about fifteen amino acids on a parasite epitope. Of the 15 or so amino acids in contact, about five contribute most of the energy of binding. Changes to one or two of the five key amino acids in the epitope are usually sufficient to greatly reduce binding and allow parasite escape. Physico-chemical studies can measure the binding affinity, which determines the number of free and bound antibodies and epitopes at equilibrium, and the on and off rates of binding that determine the kinetics of the antibody-epitope interaction.

For the first time in the history of biology, we have a glimpse of the whole from the level of molecular structure and binding, through the dynamics of biochemical reactions, to the numbers and parasite and immune cells and their rates of expansion and clearance, on to polymorphisms in populations at particular nucleotide and amino acid sites, through the fitness consequences of those polymorphisms and the patterns of evolutionary change over time and space.

Perhaps all of this extends a bit beyond the original question concerning immunology. But even within more traditional immunological subjects, there are signs of the same sort of potential. For example, Rao's lab has done some very interesting work on immunodominance—the tendency of the immune system to focus its response on very few epitopes in spite of the initial ability to recognize and respond to many different epitopes of a parasite. Rao has shown how the kinetics of antibody-epitope binding determine which immune cell lineages expand and dominate the immune response. Those studies show how molecular details of binding determine rates of cellular birth and death and consequently the numbers of immune cells and antibodies specific for particular epitopes. Binding, numbers, and rates—these are the advances in immunology that will tell us how systems function in real organisms and why different parasites follow their particular evolutionary paths.

Response from Sunetra Gupta

In my opinion, the main contribution of immunology over in the last decade or so has been to provide a sensible counterpoint to the excessive excitement surrounding the vast capabilities of molecular methods to provide detailed information on host–pathogen systems. The continued importance of 'traditional' immunological methods (although these too have undergone considerable refinement) has led us back repeatedly to the fundamental realization that how a substance is recognized and dealt with is far more critical than the correct 'description' of the substance itself. Steven's book abounds with such examples and very successfully demonstrates how immunological studies play a fundamental role at the interface between molecular biology and theory (by which I do not mean mathematical modelling, but the whole business of trying to understand what is going on!). Molecular methods such as high throughput sequencing can provide ways of rapidly testing certain hypotheses, but the generation of these hypotheses depends critically in the first place on information regarding how the immune system interacts with the pathogen, or indeed how various components of the immune response interact with each other. Clues can be found in laboratory studies, but also crucially from large scale population studies, and I would argue that the techniques that enable us to conduct these studies at the fine scale that we are now able to, constitute a major advance in the field since the 1970s. The accurate quantification of the various responses by new techniques such as flow cytometry or tetramer staining also provides the opportunity for exploring such systems using mathematical models as a tool, provided that we are careful to use numbers to illuminate rather than obfuscate the basic processes.

I do not entirely agree that there have been no major conceptual advances since the 1970s regarding the basic mechanisms of immunity (consider, for example, all the new insights that have been gained regarding antigen presentation) or that we have not added fruitfully to our catalogue of fascinating methods by which pathogens evade immunity (such as mimicry of complement regulators by Poxvirus). But I do feel that the main role of immunology at this point in time is to act as a strict chaperone to molecular biology, and pave the way for a more integrated approach to the study of infectious disease.

Response from Jean-Baptiste André

Progress in a discipline is often more a matter of slowly changing point of view than of specific new results. Hence, answering such a question pertinently requires to be a specialist of the discipline, which I am not in Immunology. I will thus only highlight, subjectively, a point I have been particularly interested in: the understanding of immune memory. Recent works indeed concur to substitute a naïve picture of memory as a static library of formerly activated lymphocytes with a more complex image of a maturing memory, optimized during primo-infection as well as at each new parasite encounter. I review non-exhaustively a few examples of such works.

(i) During an immune response, the lymphocyte population optimizes its affinity for the antigens through the selective expansion of cells with highest affinity (Busch and Pamer, 1999; McHeyzer-Williams et al., 1999; in the case of B cells hyper-mutation accelerates this process Nossal, 1992). (ii) Following the acute infection, remaining lymphocytes differentiate on a linear pathway from effector cells (slow replicating) to long-term memory cells (highly efficient to replicate when confronted to an antigen) (Wherry et al., 2003). The memory pool is hence

different from the naïve one, because of an increased frequency of antigen-specific lymphocytes but also because of a modification of their individual properties (see also Cho et al., 1999; Veiga-Fernandes et al., 2000). (iii) Thereafter, whether memory lymphocytes can be maintained in the long-run without any stimulation is a debated point (see Rocha, 2002 and references therein). Too much stimulation by the cognate antigen can lead to tolerance (loss of functional memory). However, stimulation by MHC seems necessary for the maintenance of efficient memory T cells, showing that the behavior of memory cells is permanently regulated by the organism. (iv) Following its initial formation during primo-infection, the memory pool can still be altered quantitatively and qualitatively as a result of the infection by different parasites (Selin et al., 1999). The high density of memory cells present after an infection is reduced when a response is mounted against a new infection. However, memory cells that can be cross-stimulated by the new parasite are selectively activated and thus not (or less) affected by this attrition. The high degeneracy of antibody recognition (a given antibody should recognize up to 10^6 different peptide sequences, see Steven Frank's book Chapter 4 and reference therein) might be used to optimize the efficacy of memory by selecting the most polyvalent cells.

I feel that such results, and perhaps many others on memory, yield a picture of immune memory that fits well an evolutionary thinking. The ontogeny of memory guarantees the protection against as many pathogens as possible with the smallest possible cost for the organism. Finally, this goes back to the emphasis of Steven Frank on rates and numbers. What ultimately matters for the coevolution of parasites and immunity is (i) rates and numbers during primo-infections, (ii) changes in rates and numbers owing to memory and (iii) costs of immunity (energetic and risk of self-damages).

Second question: Haldane (1949) has stated that infectious diseases have been the main selective force in the human species in the last 5000 years. Would you agree with this statement? Do you think it is still the case at nowadays?

Response from Steven Frank

Haldane (1949) explained why infectious disease is a major selective force on all organisms: "To put the matter rather figuratively, it is much easier for a mouse to get a set of genes which enable it to resist *Bacillus typhimurium* than a set which enable it to resist a cat". By this, he means that biochemical specificity mediates infectious disease, and small changes in genes can alter biochemical specificity. Thus, rapid genetic changes will often enhance the ability of hosts to recognize pathogens and to defend themselves. So, I do agree that infectious disease has been and continues to be a major force shaping the genetics of human populations.

Jared Diamond has argued convincingly that the rise of agriculture has greatly increased the influx of new diseases into human populations. Agriculture increases population density, which makes it much easier for new diseases to spread through populations and to be maintained endemically. With agriculture often comes the domestication of animals, which provides a large pool of infectious agents that may be introduced into human populations. Perhaps people now believe that SARS and HIV are aberrations of modern society and widespread travel. But most major human pathogens probably have spread widely in human populations only during the past several thousand years.

In a few cases, we know how particular human genes provide benefits against certain diseases. The CCR5 32 bp deletion that confers resistance to HIV provides a recent example; other cases include the association of particular MHC alleles with geographic regions that have intense infection with malaria. This must be just a fraction of the actual genetic effects; each major infectious disease probably alters gene frequencies of many human loci.

The known cases tend to focus on the spectacular examples of single-gene changes that provide great increases in resistance—CCR5 against HIV and the sickle cell allele against malaria. I suspect that polygenic, quantitative contributions to resistance are widespread in humans but difficult to detect with current methods. There is, for example, some evidence from pigs of high heritability in various measures of immune function.

I imagine that the immune system depends on many quantitative thresholds to determine the timing and strength of immunological response. Each threshold faces a strong trade-off between increasing the strength and rapidity of defense and the morbidity that often follows from a vigorous immune response. The costs and benefits for each threshold must vary over time and space and in response to different infectious agents. For these reasons, I believe that quantitative genetic variability in immune function will be particularly high and will explain much of the variation in individual response to infection. This is an understudied subject waiting to be discovered.

Response from Jean-Baptiste André

One of the major rationale of Haldane's (1949) statement is to me that, in the environment of our hunter-gatherers ancestors, the fastest changing factors should have been infectious agents. However this argument has restrictions. Adaptive immunity permits resisting new diseases without evolution and renders resistance to them, such as that to predators, also a matter of quantitative trade-offs, as mentioned by Steven Frank. Moreover, the "importance" of a selective force is measured by the intensity of positive but also purifying selection it yields (one cannot say for instance that the intensity of selection on housekeeping genes is weak only because they are rarely involved in selective sweeps), thus the fact to change is not a sufficient nor a necessary reason for a factor to exert strong selection. Finally, at least since the rise of agriculture, the social environment

of humans has also been changing fast, certainly exerting strong selective pressures.

However, even if I find it difficult to follow firmly Haldane (1949), it is undeniable that infectious environment is a major and rapidly changing determinant of one's fitness. As an illustration, one could list the numerous effects that past parasites have on our present phenotype. Infectious diseases have been responsible for the evolution of a complex and costly function of our organism: the immune system. The short generation time and consequent rapid evolution of most pathogens has shaped one of the main characteristics of this system (random antibody variations and clonal selection). Infectious diseases have molded many of our instinctive behaviors (repulsion for dirtiness, in water, food or even social relationships, . . .), as well as culturally transmitted ones (cook meat, wash hands, discover and consume antibiotics, do E-debates on infectious diseases, . . .). Resistance to infections and MHC-dependent body odors are used as criteria for mate choice. Psychology influences immunity and some infectious diseases can be said psychosomatic (warts for instance), infections may therefore be speculated to be also sender-controlled signals in social relations. The list is long of such influences of past infectious diseases.

However, do present infectious diseases still exert selection in developed countries? In a sense yes, because it keeps imperative to resist infections, as shown by the cost of being immuno-compromised. On the other hand, it is clear that the discovery of anti-infectious agents lessens the strength of selection for genetic resistance to new diseases. I would finally bet that, in a social world such as ours, selection on individuals due to diseases will not only exert on genetic resistance but also more and more on other features such as avoidance of "disease-generating" contacts, drug-consumption or drug-tolerance. Besides, the more resistance to infections become culturally transmitted (through learned behaviors or prescribed drugs) the more the pressure due to new pathogens is exerting on the whole social organization to provide rapid and efficient responses (drugs discovery and public health policies). Conclusively, the pressure exerted by infectious diseases on human species may have somewhat shifted recently but it is certainly still present.

Response from Sunetra Gupta

It is intuitively obvious that certain infectious diseases will impose selective pressure on human populations as there is nothing more definite—as selection goes—than dying before you have had the opportunity to reproduce. Then, of course, there are the other various ways in which disease could impair reproduction, care of offspring, etc. The mouse that has *B. typhimurium* may find it harder to protect itself or its young from a cat, so infectious disease can also act to enhance the force of other mechanisms of selection. This makes it difficult to disentangle infectious disease from other modes of selection in trying to answer the question—what has been the main mode of selection—and any opinions in this area are perforce impressionistic.

I think it was Steve Jones who suggested that we divide our evolutionary history into epochs governed by disaster, disease and decay (in that order) and I tend to agree with him. Although it is relatively easier to acquire the necessary mutations that protect you from *B. typhimurium* than that extra bit of running power that lets you slip away from the cat, the early stages of evolution are likely to have been dominated by larger predators than infectious pathogens, as well as other forms of physical disaster. As Steven Frank has already mentioned, the loss of hunter gatherer status probably tipped the balance in favor of the smaller predators (i.e. pathogens) by creating the conditions for the spread of infectious disease, as well as providing some protection from tigers and lions due to more advanced social organization and technology. Having dealt with the lions and tigers, we are now in the process of learning to combat our internal predators, and in many developed countries we have achieved enough success that our main concern is now 'decay' rather than 'disease'. Can genes that prevent 'decay' have an evolutionary impact? Only if you believe in grandparenting as a fundamental contribution to the survival of the second generation. So, even in this epoch of decay, the main selective force is likely to be disease, although its burden has clearly been considerably lessened (at least for the time being) in many developed countries. It goes without saying that disease continues to be a major selective force in many less developed countries. The distribution of percentage of total deaths is highly skewed in favor of infectious disease (mainly HIV) in Africa, whereas globally the biggest killers are ischaemic heart disease and cerebrovascular disease. The only major contribution to percentage of deaths that is neither an infectious nor a non-infectious disease comes from road traffic accidents—perhaps that is where we should be looking next for genetic associations!

Third question: Steven speaks about thresholds for immune response. I suspect that such thresholds act even more at a population level. Let's score individual immune resistance for a given infectious disease from 0 to 100. An individual scoring 100 will be totally resistant to this disease. However, in a population composed only of individuals scoring, let's say: 50, the spread of this infectious agent will be almost totally inhibited, so that it is useless for the individuals of this population to develop a costly 100. Does it make sense? Has it been modelized for precise examples?

Response from Steven Frank

The level of defense in the group is called herd immunity. The evolution of herd immunity concerns aspects of social behavior because the interests of individuals can differ from the interest of the group (Anderson and May, 1990). Defense not only protects an individual, but also protects neighbors by reducing the probability of transmission. So,

when neighbors defend themselves, selfish individuals can get away with little defense and avoid the associated costs. This divergence between individual and group interests causes problems with vaccine compliance–when most members of a group are vaccinated, then selfish individuals gain by avoiding vaccination and the associated risks. This selfish behavior lowers vaccine compliance and imposes a cost on the group.

In terms of costly immune defense, the optimal level expressed by an individual depends on the level of defense expressed by others in the population, the degree to which individual and group interests differ, and variation in the relative cost of defense for different individuals. I made a simple model to study these issues (Frank, 1998).

The conclusions from the model mostly show what one would expect. More intense risk of disease favors higher levels of defensive expression; greater cost of defense favors lower defensive expression. The gap between the level of defense favored by selfish individuals and the level that maximizes group success depends on the genetic relatedness between individuals and their neighbors. When relatedness between neighbors is high because individuals live near kin, individual interests come closer to those of the group, and the group benefits from a higher and more favorable level of defense. When relatedness is low, selfish tendencies cause lower defensive levels, and the group suffers a higher disease burden.

The most interesting conclusion from the model concerns variation in vigor among individuals. Those individuals in better health suffer less cost for expressing stronger immune defense. Given that stronger individuals tend to express powerful defense, this creates a level of herd immunity that favors weaker individuals to reduce their defensive levels. Thus, small variations in individual vigor lead to large variations in the levels of individual defense.

Response from Jean-Baptiste André

I do not have many things to add to what Steven Frank says. Two points only.

First, the "population threshold" that Michel talks about is when, owing to host resistance, the parasite's net rate of increase ($R0$) gets lower than one, the parasite becomes unstable, and disappears. However, as host resistance increases, $R0$ decreases continuously toward one and parasite's prevalence continuously toward zero, so I think we should not really talk about a threshold. But this does not change the heart of the question.

Second, concerning the evolution of host resistance, I think that the problem may change a bit if one considers the impact of herd immunity not only on parasite dynamics but also on parasite evolution. Indeed host resistance influences the optimal host exploitation strategy of the parasites (virulence for instance) which influences back the optimal level of resistance of the host (see, for instance, van Baalen, 1998). I briefly mention two potential consequences of this coevolutionary process. First, if herd immunity gets stronger, the parasites may be selected to be more aggressive, because they must counteract immunity and because they have fewer time to exploit the host (I built a model of acute infection which shows this: André et al., 2003, but see also van Baalen, 1998 or Gandon et al., 2001 for instance for general models). The consequence is that parasites become more virulent, especially against hosts with weaker immunity than the group average (roughly speaking). Parasite counter-evolution hence strengthens the selection favoring strongly immunized hosts, which reduces the effect of diminishing prevalence. A second consequence of coevolution is regarding situations where kin selection is operating on herd immunity. In such case indeed, host immunity should evolve as a natural tool of virulence management. One could imagine, speculatively, that different mechanisms of immunity (for instance, different kinds of memory) could have different consequences on parasite dynamics and counter-evolution. Avoiding infection in the short-term (with fewest energy expenditure as possible) might not involve the same mechanisms as reducing the parasite load (reduction of fitness owing to parasites) on the group in the longer-term. The question would then be whether our immunity has been more shaped by individual or by "group" (kin) selection.

Response from Sunetra Gupta

There are many sophisticated ways of answering this question as Steven has nicely demonstrated, so I have nothing more to say on that matter.

As regards the coevolutionary models that Jean-Baptiste mentions, I think we need to be cautious about adopting 'general frameworks'. Whether or not a parasite will evolve towards higher or lower virulence depends very much on whether there is a mechanistic link between virulence and transmissibility, whether the constituent pathogen types that differ in their virulence characteristics are in fact in competition with each other, and whether the antigens that are targeted in the development of immunity are involved in virulence. For example, the rise in frequency of the sickle haemoglobin gene does not appear to have resulted in increased virulence of *P. falciparum* malaria, probably because many of the severe symptoms are linked to its cytoaherence phenotype which involves an antigen that is not associated with the survival of the parasite within a sickle cell. I think that it is essential that evolutionary models are developed very closely in relation to some of the very precise (and also not so precise) immunological detail that is available to us currently, as well as the wealth of data on parasite diversity. And now that we have Steven's book to explain what it is all about, I am afraid we can no longer make the excuse that it is all totally impenetrable to us!

Fourth question: Selective pressure due to pathogens has literally carved our genetic background, which has conse-

quences, not only on our defenses against infectious diseases, but probably on many properties of our species. At least in the industrial world, this selective pressure has been now lowered since the vaccine and antibiotic era, and the progresses of hygiene. Do you envision that this could have drastic evolutionary consequences in the long term?

Response from Jean-Baptiste André

Reducing the pressure of infectious diseases on our genes would certainly have many consequences; but they are quite difficult to guess. They should be of two sorts. First as the selection (positive and/or purifying) due to infections would decrease, selection on other traits, associated with smaller fitness variances, would become possible. More generally, as the hazard of death due to diseases (or predators) is reduced, natural selection on any trait becomes more efficient. Second, and more importantly, lessening the pressure of infectious diseases should have large effects on traits that are advantageous per se but prevented by a trade-off with resistance to infections.

Making a caricature of Michel's question one can wonder what would be the consequences of a total removal of infectious diseases. Such an unrealistic situation would certainly not only yield the disappearance of our immune system or some energy reallocation but a global transformation of our organization. Numerous traits are indeed constrained by the need for resistance and also by the presence of immunity. It has even been hypothesized that the number of genes in our genome could be under the constraint of infectious diseases because having too many genes would render auto-immune avoidance too complicated (George, 2002). Our organization might be so much constrained by infectious diseases (skin, digestive tube, brain, behavior, pregnancy) that a world without them would be almost like a world without gravity.

However, a total removal of the selective pressure due to infections is not something one can envisage. The treatments we produce are designed for diseases against which we are poorly resistant; but we do not see the vast number of infections prevented by our natural resistance. Furthermore, the progress of hygiene might certainly yield the reduction of parasite virulence (because their survival in the environment is lowered) but I would not bet for their total eradication and immunity will remain for a long while a good "argument in the negotiation with parasites".

However, Michel is certainly right that the pressure due to parasites is decreasing in the industrial world. But I cannot answer his question! I cannot figure out a trait that would be quantitatively constrained by infections and only by infections (as clearly as the size of the head is constrained by natural birth for instance); nor can I guess which constraint would be mostly relaxed by a given reduction of infectious pressure. Maybe this is because infectious diseases are so important in our organization that I cannot even see what they do.

Response from Steven Frank

The scope of this question is so broad that is it hard to think about clearly. So, let's consider three particular issues.

Suppose that malaria were somehow brought under control throughout the world. Then the sickle cell allele would likely decline in frequency. This would be an interesting evolutionary consequence, but perhaps not of major significance. In general, various pleiotropic genes held polymorphic by pathogens may eventually move toward fixation. Each case of pleiotropy probably works more or less independently, so whether the total of all such pleiotropies would be somehow be more than the sum of the individual cases is hard to say.

Reduced pathogen pressure shifts mortality to later ages and different causes. This age shift of mortality causes survival to become less potent as an evolutionary force because mortality moves predominantly past the most fecund years. Differences in reproduction become more strongly influenced by variation in fecundity rather than survival. What does this mean for human evolution? Reduced viability selection and enhanced fecundity selection seem important changes, but the consequences are not clear. This is particularly so because culture strongly influences aspects of fecundity, perhaps more strongly than culture affects viability.

The reduction in the average intensity of pathogen pressure may decrease host immunity. This may occur by reduced exposure and immunological memory and by an evolutionary decline in the idle level of immune activity. Such reductions may make humans more prone to severe epidemics. So, the average consequence of pathogen pressure may be reduced, but severe bouts of selection may occur in a more episodic way.

This list makes clear that there can be many different consequences of reduced pathogen pressure. Each will likely have some effect, but whether changes in infectious disease patterns will play a key role in our evolutionary future remains to be seen.

Response from Sunetra Gupta

I assume that this will have evolutionary consequences, many of which have been discussed during the course of this debate, but it is interesting to further speculate how these may be drastic. The interplay between resistance to disease and other factors such as allergy will determine the long-term consequences of the removal of the former, and such intricate relationships are already the subject of current research. A more obvious consequence relates to the challenge of emerging disease in a context where exposure to natural related pathogens is much reduced. The reduction of herd immunity, and the obvious vulnerability it imposes on the human population, can be prevented by the continued imposition of vaccination, but good vaccines only exist towards a handful of diseases. They are those diseases whose threat has been greatly reduced without any

obvious intervention that pose the greatest problem here. While improved "living conditions" might have lowered our exposure to a range of pathogens, they may concommitently have increased our susceptibility as a population to their more pernicious cousins. This line of argument leads to the point already made by Steven that the population may become more prone to epidemics-leading to a more discrete pattern of selection than we have experienced so far.

In short, it is possible to speculate endlessly on this matter, but we can also be certain that the greater part of the answer is–like most of the future–utterly unimaginable.

Michel Tibayrenc

I thank you all three very much for participating in this very exciting E-debate.

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Jean-Baptiste André (France) is in PhD under the direction of Professor B. Godelle, he is studying the evolution of microparasites with a theoretical approach. He is in the "Laboratoire Génome, Populations, Interactions, Adaptations" in Montpellier, an important city for French Evolutionary Biology, in the sunny south of France. He is working on evolution of host exploitation strategies when both the individual-parasite and the whole-infection levels of organization are considered. He is interested both in dynamical aspects of the within-host level (evolution of virulence when intra-host dynamics are considered) and in evolutionary aspects (evolution of exploitation strategy when intra-host mutation and selection is occurring). He also works on the evolution of mutation rate in this two-level context. After PhD, and later, he plans to carry on his work in the field of parasites evolution, possibly with experiments also (such as in vivo evolution with bacteria), but also to start new modelling concerning the evolution of human cultural traits (gene/culture coevolution), especially while considering the class-structure of society.

Sunetra Gupta is a reader in the epidemiology of infectious disease at the Department of Zoology at the University of Oxford. She became interested in the mathematical modelling of infectious disease systems as an undergraduate at Princeton University under the influence of Lord Robert May, and continues to persevere to protect this holy subject from the invasion of the super-computer, and other unwanted technical advances.

Steven A. Frank began research in a radiation oncology laboratory studying DNA damage and repair. He found the science fascinating, but the intellectual and physical constraints of the lab too narrow. He next appeared in the Florida Everglades, studying the sex ratios of fig wasps as a way to gain insight into how natural selection shapes social behavior and adaptation. Like most students, he was testing a theoretical model taken from the literature. After collecting the data, he began to think more about the theoretical concepts that had led him to donate so much blood to the Florida mosquitos. Pursuing the theory, he spent many years studying models of sex ratios, social evolution, and natural selection. Eventually, that led to his first book, Foundations of Social Evolution (Princeton University Press, 1998). The work on social evolution turned him into a full-time theoretician, after which he moved onto theoretical work on another main interest, the dynamics of attack and defense. He then developed theories of genomic conflict, parasite virulence, resistance polymorphisms, and extensions into various studies of symbiosis. His most recent interests in problems of attack and defense are summarized in his second book, Immunology and Evolution of Infectious Disease (Princeton University Press, 2002).