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Pathogenesis: how far have we come?

Tremendous effort to understand how microbes influence health has brought fewer advances in treating and preventing disease than one might have expected.

On September 21, 2007 the biopharmaceutical company Merck announced the abandonment of phase II clinical trials of what until then had been touted as a highly promising vaccine to prevent HIV infection. What went wrong? Although it's too soon to say exactly, one possibility is that the strategy of the vaccine—to elicit $CD8^+$ T cell immunity to HIV proteins as a means to prevent or significantly reduce the chance of infection—won't work. That strategy was developed based on studies of HIV infection in experimental models, such as primates, and in patient cohorts, which suggested that cell-mediated immunity might be more effective than antibody-mediated immunity, the goal of most traditional vaccines, to combat HIV. Whether or not the strategy is ultimately successful, its appeal as a reasonable vaccine approach owes to the study of pathogenesis—in this case, HIV pathogenesis.

In this issue of *Nature Immunology*, we present a Focus on pathogenesis. We have commissioned three review articles that discuss diverse issues related to host-pathogen interactions, including lessons about immune memory learned from the 1918 influenza epidemic (Ahmed, Oldstone and Palese), cell-intrinsic immune subversion mechanisms (Roy and Mocarski) and the potential influence of commensal microorganisms in disease (Pamer). Three additional articles cover topics ranging from real-time imagining of host-pathogen encounters (Velázquez, Waite and Dustin), to 'high-grade' pathogens such as Ebola virus (Zampieri, Sullivan and Nabel), to 'natural pathogenesis experiments' that occur over time *in situ* in both individuals and populations (Quintana-Murci, Alcaïs, Abel and Casanova). We also provide an historical account of the work that led to understanding how cytotoxic T cells respond to peptide antigens in the context of major histocompatibility complex class I molecules (McMichael). A provocative overview summarizes key concepts in pathogenesis, important advances in the field, and challenges ahead (Virgin). The Focus website (http://www.nature.com/ni/focus/pathogenesis/) features more online content, including links to classic papers and to recent papers in the field published by the Nature Publishing Group and highlights of newly published papers that exemplify the current state of the field. We hope this special issue will convey the enormous possibilities in, and challenges of, pathogenesis research.

Pathogenesis of infection is variously referred to in the literature, but one of its principle features is the 'confrontation' of a pathogen with a host immune system. Integral to understanding the complexity of such confrontations is the adaptability of both pathogen and host. Some infections result in a 'stalemate' between the pathogen and host, leading to chronic or latent infection, whereas others lead to death of either the host or pathogen (see Zampieri *et al.*), but in both cases the outcome often is the dissemination of pathogen to other hosts. What then determines the outcome of infection, and how does the 'plasticity' of a pathogen in the face of an adaptive immune response alter the course of immune responses (see Virgin)? How does genetic variability within human hosts affect a pathogen's 'ability' to cause disease (see Quintana- Murci *et al.* and Ahmed *et al.*) and how do real-time microbe-host interactions occur (see Velázquez *et al.*)? Of particular importance to immune responses to infection are key features of pathogens: cell tropism, replication rate, expression of virulence factors and genome complexity (see Virgin and Zampieri *et al.*). Countermeasures by the host include many 'layers' of immune defense against invasion that not only block invasion but can dramatically alter the key features of pathogens in subtle ways (see Roy and Mocarski).

Importantly, adaptability of either host or microbe can ultimately lead to outcomes that are not necessarily predictable—such as the emergence of H5N1 bird flu. In some cases, however, the potential for adaptation is limited enough that relatively predictable outcomes allow for practical intervention. For example, interactions between the natural agent of smallpox and the majority of human hosts were sufficiently predictable that a vaccine was able to induce immunity that could withstand possible adaptations of the virus. Unfortunately, many other microbes are less predictable, as is the case for HIV (see McMichael). The very first trial to vaccinate against HIV sought (unsuccessfully) to induce the production of neutralizing antibodies—a strategy born from success in other cases, beginning with Jenner's use of dried cowpox as a vaccine against smallpox. That first HIV vaccine failure prompted calls for a new approach, which led to experiments indicating that an HIV vaccine to induce cell-mediated immunity might work—a possibility that, though unsuccessful in the Merck trial, may ultimately prove fruitful.

Although an increasing number of diseases are falling into the category of those whose pathogenetic history and properties are becoming clearer, if one were to perform a cost-benefit analysis of all the effort spent studying pathogenesis, what would the result be: a good return on investment? If not, why? What factors might explain the relatively slow pace of progress on some of the more vexing pathogenesis problems of our day, such as HIV vaccination? One may be in the conceptual frameworks and methodologies used to study pathogenesis. Reductionist approaches have long been the norm in pathogenesis studies, especially in immunology. Yet reductionist approaches have limitations (see Virgin), not the least of which is that redundancy of function in nature has shown that laboratory findings can be very different from what is important in real life (see Quintana-Murci *et al.*). Perhaps, then, more effort should be spent developing new approaches that draw broadly on advances made in specific fields to answer questions in pathogenesis—because in one sense the failure of the new HIV vaccine is a sign of how much we still do not understand about pathogenesis.