

interpret experiments in particle and in nuclear physics. Without the quark-antiquark pairs, it is impossible to quantify the associated uncertainty.

A breakthrough came 5 years ago, with the first wide-ranging calculations incorporating the back-reaction of up, down, and strange quark pairs (10, 11). This work used a mathematical representation of quarks that is relatively fast to implement computationally (12), and these methods enjoyed several noteworthy successes, such as predicting some then-unmeasured hadron properties (13). This formulation is, however, not well suited to the nucleon, and so a principal task for lattice QCD remained unfinished.

Dürr *et al.* use a more transparent formulation of quarks that is well suited to the nucleon and other baryons (hadrons composed of three quarks). They compute the masses of eight baryons and four mesons (hadrons composed of one quark and one antiquark). Three of these masses are used to fix the three free parameters of QCD. The other nine agree extremely well with measured values, in most cases with total uncertainty below 4%.

For example, the nucleon mass is computed to be $936 \pm 25 \pm 22 \text{ MeV}/c^2$ compared with $939 \text{ MeV}/c^2$ for the neutron, where c is the speed of light and the reported errors are the statistical and systematic uncertainties, respectively. The final result comes after careful extrapolation to zero lattice spacing and to quark masses as small as those of up and down (the two lightest quarks, with masses below 6

MeV/c^2). The latter extrapolation may not be needed in the future. Last July, a Japanese collaboration announced a set of lattice-QCD calculations (14) of the nucleon and other hadron masses with quark masses as small as those of up and down.

These developments are serendipitously connected to the work honored by this year's Nobel Prize in physics. The lightest hadron—the pion—has a mass much smaller than the others. Before QCD, Nambu (15) proposed that this feature could be understood as a consequence of the spontaneous breaking of chiral symmetry (16). In QCD, it has been believed, the spontaneous breaking of this symmetry by the vacuum predominates over an explicit breaking that is small, because the up and down quarks' masses are so small. Lattice QCD (4, 10, 11, 13, 14) simulates and, we see now, validates these dynamical ideas in the computer. Moreover, this success puts us in a position to aid and abet the understanding of the role of quark flavor (17), including asymmetries in the laws of matter and antimatter (18), for which Kobayashi and Maskawa received their share of the Nobel Prize.

Dürr *et al.* start with QCD's defining equations and present a persuasive, complete, and direct demonstration that QCD generates the mass of the nucleon and of several other hadrons. These calculations teach us that even if the quark masses vanished, the nucleon mass would not change much, a phenomenon sometimes called “mass without mass” (19, 20). It then raises the question of the origin of

the tiny up and down quark masses. The way nature generates these masses, and the even tinier electron mass, is the subject of the LHC, where physicists will explore whether the responsible mechanism is the Higgs boson or something more spectacular.

References and Notes

- H. Fritzsch, M. Gell-Mann, H. Leutwyler, *Phys. Lett. B* **47**, 365 (1973).
- D. J. Gross, F. Wilczek, *Phys. Rev. Lett.* **30**, 1343 (1973).
- H. D. Politzer, *Phys. Rev. Lett.* **30**, 1346 (1973).
- S. Dürr *et al.*, *Science* **322**, 1224 (2008).
- K. G. Wilson, *Phys. Rev.* **10**, 2445 (1974).
- M. Creutz, *Phys. Rev. Lett.* **45**, 313 (1980).
- D. Leinweber, “Visualizations of Quantum Chromodynamics (www.physics.adelaide.edu.au/theory/staff/leinweber/VisualQCD/Nobel).
- F. Butler, H. Chen, J. Sexton, A. Vaccarino, D. Weingarten, *Nucl. Phys. B* **430**, 179 (1994).
- A. Ali Khan *et al.* (CP-PACS Collaboration), *Phys. Rev. D* **65**, 054505 (2002).
- C. T. H. Davies *et al.* (HPQCD, MILC, and Fermilab Lattice Collaborations), *Phys. Rev. Lett.* **92**, 022001 (2004).
- C. Aubin *et al.* (MILC Collaboration), *Phys. Rev. D* **70**, 094505 (2004).
- C. Bernard *et al.* (MILC Collaboration), *Phys. Rev. D* **64**, 054506 (2001).
- A. S. Kronfeld, *J. Phys. Conf. Ser.* **46**, 147 (2006).
- S. Aoki *et al.* (PACS-CS Collaboration), <http://arXiv.org/abs/0807.1661> (2008).
- Y. Nambu, *Phys. Rev. Lett.* **4**, 380 (1960).
- J. Goldstone, *Nuovo Cim.* **19**, 154 (1961).
- N. Cabibbo, *Phys. Rev. Lett.* **10**, 531 (1963).
- M. Kobayashi, T. Maskawa, *Prog. Theor. Phys.* **49**, 652 (1973).
- F. Wilczek, *Phys. Today* **52**, 11 (November 1999).
- F. Wilczek, *Phys. Today* **53**, 13 (January 2000).
- Fermilab is operated by Fermi Research Alliance LLC, under Contract DE-AC02-07CH11359 with the U.S. Department of Energy.

10.1126/science.1166844

MICROBIOLOGY

Rogue Insect Immunity

David S. Schneider and Moria C. Chambers

Two recent studies have quietly and subversively broken the models we've used to describe insect immunity. Impressively, they've accomplished this by using gross observational studies rather than mechanistic approaches. On page 1257 in this issue, Haïne *et al.* (1) suggest that what we've considered the central pillar of insect immunity—antimicrobial peptides—may perform a “mopping up” role in clearing pathogens. Hedges *et al.* (2) show that heritable epigenetic properties can have as large an impact on insect immunity as any genetically encoded

pathway yet tested. Both studies teach us important lessons about the way a host organism interacts with microbes and may have immediate practical applications.

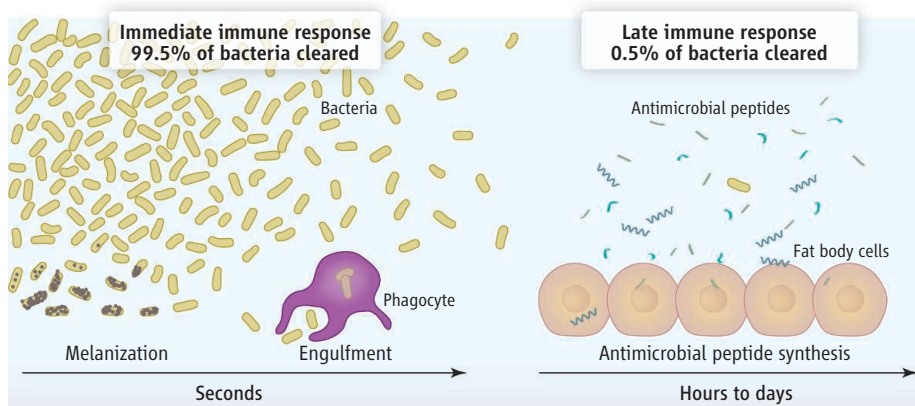
We often study host-pathogen interactions in insects to model human infections. A good illustration of this approach was the discovery that the immune-activated signaling pathway mediated by the Toll receptor in the fly *Drosophila melanogaster* is partially conserved by a family of Toll-like receptors in humans (3, 4). This is now a cornerstone of the field, and much of the recent work in insects has involved further dissection of the molecular details of the Toll pathway and the related Immune deficiency (Imd) pathway (5). When activated by microbes, these two pathways

Insects use a variety of strategies to fight pathogens at different stages of infection, which may guide antimicrobial development for human use.

induce the massive production of antimicrobial peptides by host cells, and the loss of signaling that is caused by mutations in pathway components deeply compromises the fly's immune response (6).

Haïne *et al.* show that the vast majority of bacteria are cleared from an insect before antimicrobial peptides are produced. In the mealworm beetle, *Tenebrio molitor*, immediate-acting immune responses, such as engulfment of bacteria by phagocytes (specialized immune cells) and melanization (in which bacteria are killed by reactive oxygen) likely do most of the heavy lifting when it comes to clearing microbes; more than 99.5% of injected bacteria are cleared from beetles, in the first hour of infection, before

Department of Microbiology and Immunology, Stanford University, CA 94305–5124, USA. E-mail: dschneider@stanford.edu



Clearing and mopping up. The majority of bacteria that infect an insect are cleared by immediate-acting immune responses, whereas the late-acting antimicrobial peptide immune response targets the few bacteria that are resistant to the early response.

any antimicrobial peptides are detectable. The authors hypothesize that the inducible antimicrobial peptide system removes residual microbes that are selected for resistance to the first wave of immune effectors.

The importance of this finding is that it provides a new logic for the order of immune events. The immediate-acting immune response followed by inducible antimicrobials in insects resembles the events that send a patient to the doctor—the patient’s immune system fails to clear some microbes and the doctor gives them antimicrobials to cure the infection.

This two-step approach to immunity works well for insects, but in the clinic, resistance is an inevitable outcome of antibiotic use. What is different between these two systems? In insects, we observe pairs of constitutive responses and subsequent “mopping up” antimicrobials that have been selected through evolution. By contrast, the drugs we use in the clinic are chosen because they are cheap, immediately effective, and cause few side effects, not because they prevent further resistance. Another possible difference is that insects produce dozens of antimicrobial peptides at once to fight infections, whereas a patient might be given one or two antibiotics. It may be difficult for microbes to evolve resistance to a large panel of antimicrobials. Haine *et al.* found that even though antimicrobial peptides are produced, and bacterial levels are knocked down about ten thousandfold, the beetles don’t clear the infections over the 2 week course of the experiment. This is a different outcome from what we demand of our doctors—a complete cure. That bacteria remain in infected bugs suggests that antimicrobial peptides aren’t just bacteriocidal. They may be functioning at low concentrations to alter the physiology of the bacteria and reduce pathology.

The founding principle of *Drosophila* immunogenetics is that genetically identical

flies have similar immune responses. Hedges *et al.* found that flies carrying a common bacterial endosymbiont, *Wolbachia*, had increased resistance to two insect viruses when compared to genetically identical flies lacking *Wolbachia*. Consider the following: When either the Toll or Imd pathway is disrupted through mutation, pathogens can kill mutant flies 10 times as fast as their wild-type parents. The loss of *Wolbachia* produces a similar phenotype during viral infections. This is terrifying; few, if any, insect immunology studies report the *Wolbachia* status of their flies (7). Apart from the obvious question, “How does this work?” the finding of Hedges *et al.* raises other questions: Does the presence of *Wolbachia* affect the ability of the fly to fight other infections (bacterial, fungal, parasitoid, or protozoan)? Is *Wolbachia* the only member of the native microbiota that has this effect? Recent work with herpesvirus in mice demonstrates a protective effect of persistent viral infection on subsequent bacterial infections. Together, the studies by Haine *et al.* and Hedges *et al.* promote the broad theme that our native microbes are symbionts that shape our immune response (8).

Even without knowing the mechanisms underlying these immune processes, it is easy to imagine their ecological impact. *Wolbachia* is transmitted maternally, through the germ line (9). *Wolbachia* could provide a fitness advantage to flies in the field if these flies face viral infections, providing a mechanism to drive *Wolbachia* into a naïve population.

What would happen if *Wolbachia* affects an economically important insect, like honeybees, the way it affects flies? If bees that normally harbor *Wolbachia* were cured of their infections, the epidemiological picture in the field would be hard to work out from scratch. We would find that bees lost one minor microbe and that many infectious agents could then produce stronger or different dis-

eases than were seen in the past. This could be confusing because our methods are optimized for identifying infectious diseases caused by the presence of single pathogens.

One might guess that an insect would be safe from having its microbiota altered. Honeybees are an exception, however, because we’ve been dosing commercial colonies of bees with antibiotics for decades (10). Before the rise of colony collapse disorder, one of the most important honeybee diseases was American foulbrood, caused by the bacterium *Bacillus larvae*. To deal with this threat, many beekeepers prophylactically treat their hives with tetracycline derivatives—the same antibiotics used to cure flies of *Wolbachia*. If these treatments cured queen bees, then all hives descending from these queens would also be *Wolbachia* free, because the microbe is transmitted maternally. A *Wolbachia*-virus sensitivity experiment may have already been performed on honeybees nationwide and may change the way bees interact with previously characterized pathogens.

The beauty of the studies by Haine *et al.* and by Hedges *et al.* is that they take simple observations and step beyond direct mechanistic questions like, “What does it take to turn on this immune pathway?” and lead us into new territory. In the past, our justification for studying insect immunity was that the molecular mechanisms of signaling were evolutionarily conserved and it is faster to work in systems where you can do rapid genetic screens. This new work shows how studying the progression of disease in insects can teach us the logic behind the structure of the immune response and promises to teach us how to avoid the evolution of drug resistance. The studies highlight the notion that our body is an ecosystem and that our microbiota are an essential part of our immune system.

References

1. E. R. Haine, Y. Moret, M. T. Siva-Jothy J. Rolff, *Science* **322**, 1257 (2008).
2. L. M. Hedges, J. C. Brownlie, S. L. O’Neill, K. N. Johnson, *Science* **322**, 702 (2008).
3. B. Lemaitre, E. Nicolas, L. Michaut, J. Reichhart, J. Hoffmann, *Cell* **86**, 973 (1996).
4. R. Medzhitov, P. Preston-Hurlburt, C. A. Janeway Jr., *Nature* **388**, 394 (1997).
5. M. M. Shirasu-Hiza, D. S. Schneider, *Cell. Microbiol.* **9**, 2775 (2007).
6. M. S. Dionne, D. S. Schneider, *Dis. Model. Mech.* **1**, 43 (2008).
7. M. E. Clark, C. L. Anderson, J. Cande, T. L. Karr, *Genetics* **170**, 1667 (2005).
8. E. S. Barton *et al.*, *Nature* **447**, 326 (2007).
9. L. R. Serbus, C. Casper-Lindley, F. Landmann, W. Sullivan, *Annu. Rev. Genet.* **42**, 683 (2008).
10. J. D. Evans, *J. Invertebr. Pathol.* **83**, 46 (2003).

10.1126/science.1167450