absorb 10 phonons before it reaches the top of the barrier at $m = 0$. At high temperature, phonons are in abundance, and the spins of the molecules frequently flip between $m = -10$ and $m = 10$, as in conventional paramagnets. At low temperature, however, phonons are scarce and the decay of the magnetic moment of the Mn_{12} crystal may take a long time (6). Under such conditions another mechanism of the magnetization decay comes into play: quantum tunneling between the m states.

Friedman *et al.* (*1*) found that, in contradiction with a commonsense interpretation, a weak magnetic field applied against the magnetic moment of the crystal slows down the decay of the moment. This remarkable observation helped them to understand the physics behind the stepwise hysteresis loop shown in the figure. According to quantum mechanics, the probability of tunneling must have maxima when the tunneling occurs between the m states of the same energy. This phenomenon is called resonant tunneling. In zero field the states with opposite projections of the spin, m and $-m$, have exactly the same energy, and the tunneling across the barrier occurs with the highest probability. A weak field applied in the positive z direction moves down all levels corresponding to positive m, while moving up all levels corresponding to negative m. This behavior breaks the condition of the resonance and suppresses tunneling. If the field in the positive z direction continues to increase, the positive m levels continue to move down while the negative m levels continue to move up. Quantum mechanics predicts that at about 5 kOe, levels with positive m will again come to resonance with negative m levels. The next resonance will occur at about 10 kOe, and so on. Altogether, there should be 21 resonances on the magnetic field, separated by 5 kOe, as the field sweeps from –100 to 100 kOe. Consequently, every 5 kOe, the rate at which the magnetization changes with time must have a maximum owing to the resonant tunneling. These maxima are responsible for the steps in the figure. Seven steps have been observed so far at the expected values of the field (*1*). As the field goes up, the energy barrier goes down, rapidly increasing the probability of the phonon-induced thermal over barrier transitions. For that reason, at 2.4 K the magnetization curve appears reversible above 15 kOe. Measurements down to 10 mK are needed to make all 21 magnetization steps apparent in high fields.

The possibility of quantum tunneling of a large magnetic moment has been intensively studied after it was suggested (*7*) that in magnetic nanoparticles quantum mechanics can reveal itself on a macroscopic scale. Experimentalists have been trying to manufacture a system of identical nanomagnets that would exhibit this effect (*8*). A crystal of Mn_{12} acetate is an ideal system of that kind: it consists of identical, regularly spaced, uniformly oriented, spin 10 magnets. Their magnetic moment is, however, intermediate between micro- and macroscopic. Being 20 times as great as the electron moment, it is sufficiently large to be treated macroscopically. At the same time, it is small enough to make its quantization noticeable in the magnetic hysteresis. This kind of behavior, which is intermediate between classical and quantum, makes the discovery of Friedman *et al.* (*1*) extremely interesting in the context of macroscopic quantum tunneling. After the finding was reported at the Magnetic Conference in Philadelphia in November 1995, it has been reproduced with high accuracy in other laboratories (*2*, *3*). There are now questions for the theorists. According to quantum mechanics, tunneling between the low-lying levels, such as $m = -10$ and $m = 10$, can occur only in a strong transverse magnetic field, which has not been the case in experiments performed to date. Apparently, much weaker fields resulting from interactions of molecular magnetic moments with each other, with nuclear spins, and so on, are responsible for the effect. In this case, tunneling can occur only from high excited levels for which the barrier height and the change in m are sufficiently small. Because these levels should be thermally populated, the observed Arrhenius-law temperature dependence of the magnetization reversal, which accompanies quantum steps, strongly supports this picture. Quantitative theory that would describe the resonant magnetic tunneling from excited levels is absent, however.

Research on magnetic molecules is in its infancy. As it advances, some practical applications of these systems may develop as well. Mn_{12} molecules have extremely high magnetic anisotropy. Well below 1 K the orientation of the molecular magnetic moment must be very stable. A system like Mn_{12} acetate can, therefore, provide the ultimate limit of high-density magnetic memory. Materials with even higher anisotropy would allow increased operating temperatures. Because molecules of that class can exist in a quantum superposition of "spin up" and "spin down" states, one can also imagine them as potential candidates for elements of quantum computers. In that instance, one could explore the fact that the probability of tunneling can be controlled with a magnetic field. Of course, the feasibility of devising materials and instruments that would allow the ability to read and write information at the molecular level has yet to be determined. The cooperation between chemists and physicists will be of primary importance for this exciting new area of magnetism.

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Lipid A: Target for Antibacterial Drugs

Martti Vaara

Bacteria are dangerously good at developing resistance to antibiotics. Thus the report on p. 980 of this issue by Onishi *et al.* (*1*) of a new antibacterial agent aimed at a previously unassaulted part of the bacteria (lipid A of the outer membrane) is especially welcome.

In the past, we have been able to introduce new antibacterial drugs at a pace sufficient to counter the infections caused by drug-resistant bacteria. Indeed in the 1980s, many people believed that bacterial infections were successfully controlled and that the era of bacterial diseases had passed. Many of the large U.S. and Japanese pharmaceutical companies reduced or stopped their efforts to find new antibacterial agents (*2*) and shifted their focus to antifungal and antiviral compounds. The rate of introduction of new antibacterial drugs with novel modes of action or genuinely different spectra of activity slackened. In the 1990s there was a worldwide resurgence of bacterial diseases, in large part due to the rapid emergence and spread of pathogenic bacteria resistant to multiple antibiotics. Indeed, bacterial strains resistant to all available antibiotics have emerged and

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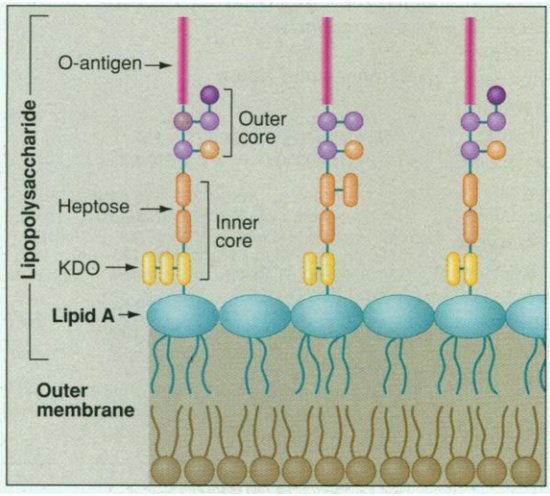
spread (3), limiting the therapeutic options for treatment of many severe bacterial diseases.

Therefore, we urgently need new antibacterial agents with truly novel actions. Unfortunately, finding and reporting of such agents is uncommon. Most new agents exert their action on classic targets and are just improved versions of existing drugs. Although there are some promising agents presently at the early stages of development, as reviewed in *Science* last year (4), others are desperately needed.

An attractive new target is the biosynthetic machinery of the unique lipopolysaccharide (LPS) constituent of Gram-negative bacteria. LPS is located in the outer monolayer of the outermost cell structure, the outer membrane, and consists of four domains (see figure): lipid A, the inner core oligosaccharide with two unusual sugars [3-deoxy-D-manno-octulosonic acid (KDO) and heptose]; the outer core oligosaccharide; and the O-antigen. LPS is a major structural component of the outer membrane and is responsible for the relative impermeability of the outer membrane to noxious agents, including many of those antibiotics that are effective against Gram-positive bacteria (5). This function as a permeability barrier is severely impaired by profound genetic defects in the inner core domains of lipid A (5, 6), as well as by cationic peptides and other agents that disorganize the LPS layer (7). Bacteria with defective or disorganized LPS are susceptible to the complement-mediated bactericidal activity of normal fresh serum (8). Furthermore, lipid A–KDO appears to be essential for cell viability: mutations affecting its synthesis are lethal (9, 10). Finally, lipid A is a potent toxin (also known as the endotoxin) and is responsible for the septic shock and high mortality associated with Gram-negative bacteremia. Accordingly, inhibition of LPS synthesis would be expected to be multiply beneficial in the therapy of Gram-negative infections.



Vulnerable point. A new antibiotic, which inhibits a deacetylase, prevents the synthesis of lipid A, an essential part of the bacterial outer membrane.

The first reports on antibacterial agents that inhibit LPS synthesis, published in 1987, described inhibition of the synthesis of KDO by dideoxyamino analogs of KDO in a cell-free system (11). To overcome the impermeability of the bacteria, the analogs were acylated with the dipeptide L-Ala-L-Ala, making them substrates for oligopeptide permease–mediated uptake through the cytoplasmic membrane. But these inhibitors were not therapeutically useful because the dipeptide is rapidly hydrolyzed in tissue.

Meanwhile, Raetz and his collaborators at the University of Wisconsin, Madison, discovered *Escherichia coli* genes such as *lpxA* and *lpxB* that encode some of the enzymes of lipid A synthesis and conducted systematic research on the biochemistry of various steps of lipid A synthesis (9, 10). Raetz, the internationally recognized leader in the field of lipid A biosynthesis, continued this work at Merck, Sharpe, and Dohme and successfully identified the enzyme defects in the lipid A mutants *envA* (*lpxC*) and *firA* (*ssc*, *omsA*, *lpxD*), which have a compromised outer membrane permeability barrier (10). Furthermore, Merck began screening for agents that inhibit LPS biosynthesis in living cells.

In this issue of *Science* (1), the Merck team reports that the function of one of the lipid A enzymes—the deacetylase encoded by *envA*—can be inhibited effectively by L-573,655, a synthetic hydroxamic acid that probably binds to a metal in the active site of the deacetylase. Some among the more than 200 analogs of L-573,655 subsequently synthesized at Merck are even more potent inhibitors. One of them, L-161,240, has considerable in vitro activity against wild-type *E. coli* (the minimal inhibitory concentration was about 1 to 3 μg/ml) and some activity against several other Gram-negative bacteria. No activity was detected at 100 μg/ml against two other Gram-negative species (*Pseudomonas aeruginosa* and *Serratia marcescens*), Gram-positive bacteria, yeast, or Chinese hamster ovary cells. Furthermore, L-161,240 and the analog L-159,692 were able to cure mice of an intraperitoneal *E. coli* infection.

Interestingly, the minimal inhibitory concentration of L-161,240 for the *E. coli envA* mutant was about 100 times as low as that for the wild-type *E. coli*. The authors offer two possible explanations for this greater sensitivity of the *envA* mutant: the target enzyme concentration could be much lower (that is, the concentration of *envA*-encoded deacetylase), or the defective outer membrane permeability barrier function could allow easier access of the drug. To distinguish between these hypotheses, one could test whether other mutants with defective outer membrane function, such as *lpxA* and *firA*, are similarly supersusceptible to L-161,240.

Future studies will elucidate the real clinical value of these new antibacterial hydroxamate compounds. They are not active against *Pseudomonas aeruginosa*, an often multiresistant, problematic bug, but more powerful analogs could potentially be made, as the authors speculate. The susceptibility of many other Gram-negative bacterial species and strains will be studied and extensive animal protection studies conducted to assess the future usefulness of these compounds in the treatment of infection. Furthermore, it will be important to know how effectively these compounds inhibit mammalian metalloproteases, and whether they are sufficiently nontoxic to be used in humans.

Promising new drugs can fail at any stage of development. We therefore need a continuing series of drug discoveries—from nonclassic sources such as plants and marine organisms, from basic bacterial physiology and molecular biology, from novel molecular screening approaches, and from optimally diverse combinatorial libraries of synthetic analogs (12). Reports like that of Onishi *et al.* (1) stimulate this search and are part of the drug evolution that balances the evolution of drug resistance.

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