in which they effectively observed a Q_φ of order 50. In the second implementation, the "flux qubit," the system is a superconducting loop, typically of size of the order of a few micrometers, subjected to a suitable external magnetic flux; in this case the S_x eigenstates correspond to different values of the circulating current and hence of the total flux, and the "magnetic field" is provided by collective tunneling between these two states. Fluctuations of the external flux ("flux noise") are a major source of decoherence, and the only experiments (*7*, *8*) to give evidence for quantum superposition in this system are indirect (spectroscopic) and suggest that the Q_φ of the particular systems investigated is too small to be useful.

In neither experiment reported in this issue is the system exactly a "charge qubit" or "flux qubit" as defined above. In the experiment of Yu *et al.*, it is a current-biased Josephson junction (which may be regarded as the system formed by breaking the flux-qubit ring apart and driving a fixed external current through the ends). More significantly, the two energy ("S_z") eigenstates are the ground state and first excited state that correspond to small oscillations of the Cooper-pair configuration (which in the flux-qubit geometry would be tied to the flux) around its metastable equilibrium value. It is thus plausible that the flux-noise problem (or its analog) should be less severe for this system. The experiment is of the Rabi-oscillation type (see the figure), with the probability of occupation of the upper energy eigenstate measured by its relatively rapid decay out of the metastable well. The Rabi oscillations persist for times of the order of 5 μs, thereby setting a lower limit on T_1; with the assumptions made in the paper it sets the same limit on T_φ, and because the Larmor frequency is 16 GHz this would then give a lower limit on Q_φ of ~2×10^5. However, the experiment does not measure Q_φ directly.

The experimental system of Vion *et al.* is a "hybrid" charge-flux qubit, cleverly designed so that during periods of free precession it is insensitive to both charge and flux noise, while at the readout stage the control parameters are changed so as to greatly increase the sensitivity to flux. In effect, it is a pure "charge" qubit during the free precession and a "flux" one at readout. Both Rabi-oscillation and Ramsey-fringe experiments were performed on this system, and the latter unambiguously gives a Q_φ of at least 2.5×10^4. It should be noted that the small decoherence rate applies when (and probably because!) the two superposed states are not distinguishable by the value of any macroscopic variable. When they are converted, by adjustment of the control parameters, into states of appreciably different flux, the rate increases dramatically (although even in the "worst" case Q_φ is still of order 50).

The most significant conclusion from these experiments is that whatever the difficulties that may be encountered in the attempt to build a quantum computer with Josephson circuits, the originally most feared one—an intolerable and ineluctable rate of decoherence—need not be among them. In addition, the fact that in the experiment of Vion *et al.* the factor Q_φ is large even when the superposed states differ markedly in flux value suggests that the fundamental test of quantum mechanics versus an alternative class of theories proposed in (*9*) may be feasible in the near future.

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PERSPECTIVES: MICROBIOLOGY

Subversion of Schwann Cells and the Leper's Bell

Peter J. Brophy

What! dost thou turn away and hide thy face?
I am no loathsome leper; look on me.
—King Henry VI, Part II: Act III, Scene II

In this scene, Shakespeare's Queen Margaret evinces the fear of leprosy widespread in medieval society (see the bottom figure). Her horror is particularly acute as the disease probably killed her husband's grandfather Henry IV in 1413. Elucidating the pathophysiology of leprosy is still an urgent matter, given that conservative estimates put the current number of people afflicted with this tragic disease at more than 2 million. Work by Rambukkana *et al.* (*1*), reported on page 927 of this issue, increases our understanding of how *Mycobacterium leprae*, the bacterium that causes leprosy, exploits the biology of peripheral nerves, enabling the colonization of host cells.

Leprosy, also known eponymously as Hansen's disease, was the first human disease shown to be caused by a bacterium. Peripheral nerves, and more specifically the Schwann cells that ensheath them in protective myelin, are the prime targets of this pathogen. Once *M. leprae* is established inside Schwann cells, there is often a strong cell-mediated immune response that causes extensive inflammation and peripheral nerve damage. The attendant paralysis and loss of sensation frequently lead to unintentional mutilation of the hands and feet. In this disease, the immune response is too much, too late.

M. leprae colonizes Schwann cells by attaching to both laminin-2, a protein constituent of the extracellular basal lamina, and its receptor α-dystroglycan, a component of the dystroglycan complex in the Schwann cell plasma membrane (see the top figure) (*2*). The bacterial ligand that binds to the laminin-dystroglycan complex is the PGL-1 glycolipid found only in *M. leprae* (*3*). Dystroglycan complexes link the basal lamina to the actin cytoskeleton of Schwann cells through membrane-associated linker proteins called dystrophins (*4*). They are believed to lend mechanical stability to Schwann cells and the nerve axons that these cells enfold, but they may also transduce signals from the exterior to the interior of the cell. In other tissues, dystroglycan complexes also seem to act as receptors for the hemorrhagic fever pathogens, lymphocytic choriomeningitis virus and Lassa fever virus (*5*).

Intracellular bacilli are readily observed in the Schwann cells that populate the peripheral nerves of lepers. However, Schwann cells are not all affected in the same way. Myelin-forming Schwann cells seem to be relatively free from *M. leprae* infection, whereas nonmyelinating Schwann cells are heavily colonized. The

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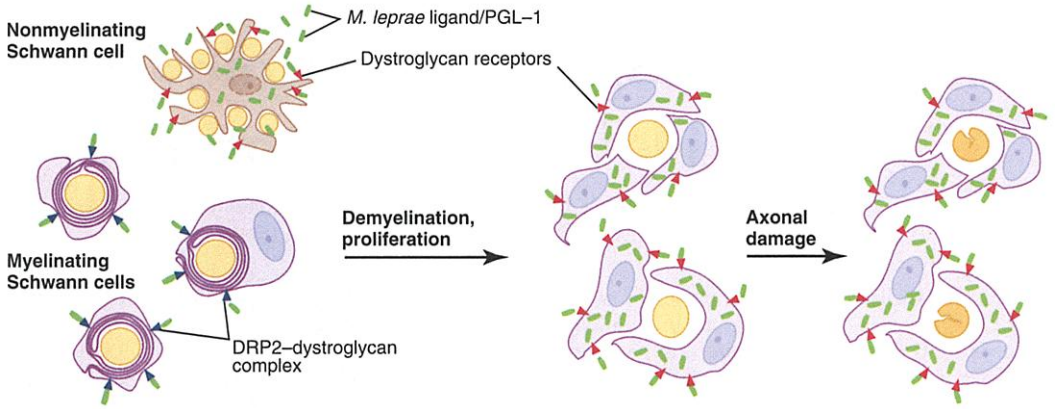
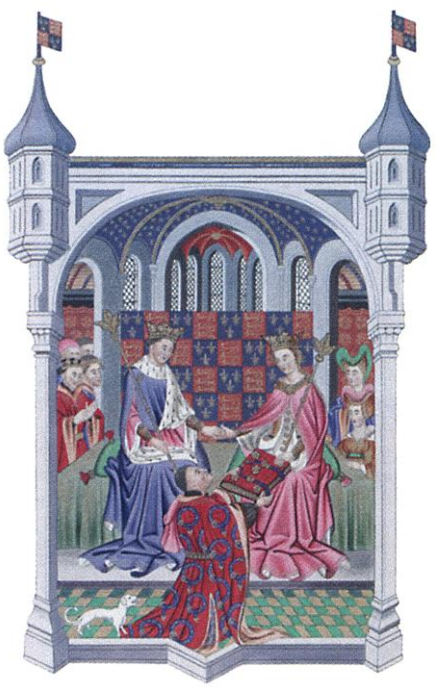
former make the myelin sheath that is essential for rapid nerve impulse conduction, whereas the latter normally surround bundles of small-diameter sensory nerve fibers. When myelinated nerve fibers are damaged by physical injury or immune attack, myelin-forming Schwann cells respond by first dedifferentiating and then proliferating (see the top figure). Normally, these cells are the source of new myelin sheaths following regeneration of injured axons.



An insidious subverter. Invasion of myelin-forming Schwann cells by *M. leprae*. Nonmyelinating Schwann cells are invaded by binding of the *M. leprae* glycolipid PGL-1 to dystroglycan receptors (red) in the Schwann cell plasma membrane. Simultaneously, *M. leprae* attacks myelinating Schwann cells and induces them to dedifferentiate, possibly as a result of the interaction of PGL-1 with the DRP2-dystroglycan complex (blue). Unlike complexes between dystroglycan and dystrophin or utrophin, dystroglycan-DRP2 complexes are concentrated in discrete patches where the Schwann cell plasma membrane approaches the outer surface of the myelin sheath (*7*). Dedifferentiation and proliferation of myelinating Schwann cells generates a pool of host cells susceptible to further colonization by *M. leprae*. Loss of myelin sheaths causes axonal degeneration.

Working in a Schwann cell–neuron coculture system in vitro, Rambukkana *et al.* confirm that *M. leprae* does not invade myelin-forming Schwann cells (*1*). However, the bacillus does affect these cells by inducing demyelination of the peripheral nerves with which they are associated. Demyelination activates Schwann cell dedifferentiation, making these cells more similar to their nonmyelinating counterparts and thus rendering them susceptible to invasion by *M. leprae*. The authors rule out involvement of the immune system in the nerve demyelination characteristic of leprosy. They infected the peripheral nerves of *Rag1*-deficient mice with *M. leprae*. These mice lack both B cells and T cells of the immune system, and so they cannot mount either a humoral or a cell-mediated immune response to bacterial infection. Demyelination induced by the bacillus was just as effective in these immune-deficient mice as in animals with a normal immune system. The authors reasonably conclude that binding of bacterial PGL-1 to α-dystroglycan on the surface of myelinating Schwann cells is sufficient to instigate dedifferentiation of these cells.



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King Henry VI (1421–1471) and Queen Margaret of Anjou (19th-century print by Henry Shaw).

But why do the dystroglycan complexes of myelinating and nonmyelinating Schwann cells mediate such very different responses to the PGL-1 of *M. leprae*? Most dystroglycan complexes depend on either an isoform of dystrophin or its close relative utrophin to link the transmembrane dimer of α- and β-dystroglycan to downstream signaling events. Schwann cells have both types of complex (*6*). Myelinating Schwann cells, additionally and uniquely, have a third dystroglycan complex in which dystrophin and utrophin are replaced by dystrophin-related protein 2 (DRP2) (*7*). Disruption of this complex causes demyelination of both mouse and human peripheral nerves (*7*, *8*). The fact that the dystrophin and utrophin complexes cannot compensate for the loss of DRP2-dystroglycan suggests that this complex constitutes a distinct signaling route from the basal lamina to the interior of the Schwann cell. This finding does not explain why *M. leprae* is unable to colonize myelin-forming Schwann cells. However, the existence of this essential complex may reveal why binding of *M. leprae* PGL-1 to α-dystroglycan at the plasma membrane causes a distinct response in myelinating Schwann cells. Chronic exposure of peripheral nerves to *M. leprae* could prevent remyelination by stalling Schwann cell differentiation and increasing the available pool of cells susceptible to colonization. Both the loss of myelin and the block in remyelination would contribute to the death of axons. It is now appreciated that the severe damage observed in a variety of human demyelinating peripheral neuropathies is the result of axonal damage attendant on the loss of the myelin sheath (*9*).

In the early 19th century, lepers were often kept in isolated colonies inhabited and in many cases run solely by themselves. It is instructive to remember that one such institution, the U.S. Public Health Service Hospital in Carville, Louisiana, only closed in 1999. Although leprosy is no longer a major health problem in the West, the World Health Organization reports about half a million *new* leprosy cases each year (*10*). Thus, clarifying the cellular and molecular pathogenesis of leprosy still remains an important task. The work of Rambukkana *et al.* is a significant contribution to achieving this objective.

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