and mathematics. Such programs are clearly needed and long overdue as a major focus for the nation's premier agency for the advancement of science. Colwell and Kelly cite four key areas for action: research on learning, coordinated K–16 requirements, improved teacher preparation and professional development, and improved instructional materials. "In each of these areas, active contributions by the scientific community are essential for success," they state. However, efforts in these areas will have little impact until the scientific community fully recognizes education as a task worthy of a scientist's time and focus.

Even at many colleges and universities where the declared core mission is the education of undergraduates, the hiring, promotion, and granting of other honors are based overwhelmingly on research accomplishments, with little consideration for the faculty member's educational achievements and skill. The reality of the scientific culture seems to be that educational work is not valued commensurate with laboratory work.

Colwell and Kelly state that "educational roles are no less important than our other responsiblities as scientists and citizens." How can this forward-looking policy be translated into substantive action?—by publicly respecting, valuing, and recognizing the teaching of science as separate from, but just as necessary and important as, scientific research. When the nation's premier scientific agency leads by example, valuing science education as a primary criteria in its own hiring, appointments to leadership positions and fellowships, and awarding of funds, the rest of the community will follow.

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Colwell and Kelly provide an overview of new efforts to improve science education. To make the story complete, I'd like to relate how the NSF is involving research scientists to help improve K–12 education.

For the past 15 years or so, the NSF has focused on workshop programs for teachers, to bring them up to speed in modern science. But it became clear that such relatively brief workshops did not change the classroom behavior of teachers as much as might be desirable. The NSF, therefore, developed a more intensive program, Research Experiences for Teachers and Students Projects. I direct one of these projects, where 40 biology teachers per year spend 6 weeks designing and carrying out research projects in the labs of university scientists and designing plans to implement components of these projects in their K–12 classes.

This new program appears to be doing wonders for science education. Teachers in the program direct the research projects of students in their classes with scientific know-how that could not be obtained from workshops. The teachers continue working with their research mentors, and the results of both the teachers' and students' research, in many cases, are publishable.

So, when Colwell and Kelly say that new NSF programs are working, from my experience they certainly are.

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Tuberculosis Vaccines

In their Report "Comparative genomics of BCG vaccines by whole-genome DNA microarray" (28 May, p. 1520), M. A. Behr *et al.* used genomic analysis to demonstrate genetic divergence of the Bacille Calmette-Guérin (BCG) vaccine for tuberculosis (TB)

that has occurred during its derivation and maintenance. They relate this genetic variation to the progressive decrease of the protective effect of BCG. However, there is another possibility for the declining efficacy of BCG that is not mutually exclusive from this explanation—concurrent evolutionary changes of the prevalent strains of *Mycobacterium tuberculosis*. The study by Behr *et al.* is unidirectional, looking only at deletions in *Mycobactrium bovis* relative to the recently sequenced *M. tuberculosis* genome.

Evolutionary divergence as a result of vaccination and herd immunity has been proposed as a model of vaccine-induced temporal changes of infectious pathogens. Comparisons of current circulating strains of *Bordetella pertussis*, isolated in the Netherlands, with isolates from the 1950s indicate that there have been antigenic shifts in two surface proteins, the S1 subunit of pertussis toxin and pertactin (*1*). These new variants have nearly replaced previously known wild-type *B. pertussis* in the highly vaccinated Dutch population.

Whereas BCG has undergone in vitro passage over many years, *M. tuberculosis* has likewise undergone in vivo passage in humans. The declining efficacy of BCG may be due, in part, to selective pressure

favoring adaptation of *M. tuberculosis* strains to BCG-induced immunity. Is it possible that genetic changes have occurred in *M. tuberculosis* strains as a result of the three billion doses of BCG administered over the past 80 years (*2*)? Are *M. tuberculosis* strains now better adapted, as a result of selection, to survive in and produce disease in immunized individuals?

We propose that the decreasing efficacy of BCG vaccine is a consequence of bidirectional divergence. As we seek improved tuberculosis vaccines, there should be a careful search for genomic homologies between strains of *M. tuberculosis* that currently cause disease and live vaccine candidates, whether BCG or attenuated *M. tuberculosis*.

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Tuberculosis remains one of the world's major killers, despite vaccination of 88% of newborns with BCG (*1*). Although it will be years before the total impact is realized, it is doubtful whether BCG is effective enough to eliminate TB in the developing world. It has been estimated from a meta-analysis that it is only about 50% effective (*2*). The analysis by Behr *et al.* shows that the efficacy of BCG has been attenuated through serial passage. They propose that pressure to minimize adverse effects of vaccination may have selected for less virulent, and therefore less effective, strains. Development of a new TB vaccine is of the highest priority (*3*), and more than 100 candidate vaccines are in different stages of development. In the choice of a new vaccine, the question arises, How effective does a vaccine have to be to eventually eliminate TB?

Some viral epidemics (for example, smallpox and polio), for which there are no effective antimicrobial therapies, have been controlled by highly effective vaccines alone. The control of TB differs because there are effective antibiotic treatments that are delivered to relatively large numbers of patients (50% of cases are treated in developing countries and 90% in developed countries) (*4*). Treatment of so many individuals benefits those treated, but it also decreases transmission rates in the entire community. Thus, TB vaccination programs, which are combined with antibiotic programs, have to be assessed differently.

We have extended our mathematical models of TB transmission (*5*) to evaluate vaccine programs and have derived a mathematical expression that allows us to predict the level of vaccine efficacy necessary to eliminate TB for any specified treatment rate and vaccination coverage level (*6*). For example, in the absence of treatment, a 95%-effective vaccine may be necessary to eliminate TB, but in the presence of 60% treatment, a 67%-effective vaccine would be sufficient (*7*). These results illustrate that if antibiotic treatment can be increased even moderately, we may not need the level of perfection (with respect to vaccine efficacy) that was achieved for smallpox and polio.

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7. Using the model in (*6*), we have derived the following expression. To ensure the elimination of TB, it is sufficient that the average number of new infectious cases caused by a single infectious case is less than unity, or $R_0(1 - F_T)(1 - F_VE) < 1$, where R_0 is the average number of infectious cases caused by a single infectious case of TB in the absence of vaccination and treatment, F_T is the fraction effectively treated with antibiotics, F_V is the vaccination coverage level, and E is the efficacy of the vaccine. Thus, the effect of treatment $(1 - F_T)$ and the effect of vaccination $(1 - F_VE)$ have a multiplicative effect on reducing R_0. For the examples in the text, we have assumed vaccine coverage of 88% (*1*) and an R_0 of 6.0 (*5*).

Response

We appreciate the letters by Ridzon and Hannan and by Lietman and Blower because they contribute further material to the discussion about BCG. The future of BCG vaccination is currently under siege, both because the TB community recognizes the need for a better vaccine against TB and because newer vaccines (for hepatitis B and *Haemophilus influenzae* B, for example) may compete for resources within vaccination programs.

Ridzon and Hannan postulate that wild-type strains of *M. tuberculosis* may have evolved under the select pressure of eluding the protective immunity provided by BCG. In such a situation, BCG vaccines of the 1920s may have provided protection against wild-type isolates of that era, but would no longer be protective against contemporary strains of *M. tuberculosis*. Although many theoretical arguments may support or refute this postulate, the only relevant data are the randomized controlled trials. In populations where BCG vaccines had not been previously used, there are numerous examples of trials where vaccination did not provide protection (*1, 2*).

Lietman and Blower extend their mathematical modeling to point out that the goal of an anti-TB vaccine need not approach 100% efficacy, because a less successful vaccine in conjunction with a treatment-based control program would provide important benefits. In this vein, it is important to reiterate the well-known strain variation between BCG vaccines and to recognize that the best BCG trials provided an efficacy on the order of 80% (*3*), well above the threshold of 67% described in Leitman and Blower's model. Although the search for an improved anti-TB vaccine is still the long-term goal, a thorough analysis of existing BCG vaccines may help uncover a sufficiently protective BCG strain among those already existing.

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CORRECTIONS AND CLARIFICATIONS

In the News article "Getting to the front of the bus" by Dan Ferber (3 Sept., p. 1514), the credit for the graphs on page 1515 listed the journal source but not the authors of the pertinent article. The full credit should have been, "C. C. Helbing, M. J. Verhoef, C. L. Wellington, *Research Evaluation* **7**, 53 (1998)."

The last letter in the 17 September issue, by G. Philip Robertson (*Science*'s Compass, p. 1852) should have stated that it was in regard to William H. Schlesinger's Policy Forum "Carbon sequestration in soils" (*Science*'s Compass, 25 June, p. 2095) and should have been entitled "Keeping track of carbon." The *Science* Online version reflects these corrections.

References and Notes

[3] **Bumps on the Vaccine Road**

Jon Cohen

Science, New Series, Vol. 265, No. 5177. (Sep. 2, 1994), pp. 1371-1373.

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[4] **Control Strategies for Tuberculosis Epidemics: New Models for Old Problems**

S. M. Blower; P. M. Small; P. C. Hopewell

Science, New Series, Vol. 273, No. 5274. (Jul. 26, 1996), pp. 497-500.

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