Fighting Antibiotic Resistance

In his letter about antibiotic resistance, H. L. Cooper (29 July, p. 590) advocates further study of the example set by Hungary, where the use of penicillin was considerably reduced in order to fight the spread of antibiotic-resistant bacterial mutants that survive when the wild-type strain is eliminated. It is expected that, in the absence of penicillin, the mutants eventually will be replaced by the competing, better-adapted wild types. While the minimal use of antibiotics is clearly desirable, the "asymptotic" success of such a strategy would depend on its acceptance on a worldwide scale and its extension to the great variety of antibiotics now in use. The use of antibiotics cannot be expected to reach zero.

One might consider a different approach, an attempt at a "Darwinian" reversal of fortune for drug-resistant mutants, which would seem to deserve a wider study, although it has been tried previously unsuccessfully in isolated cases. If this approach survives criticism and the necessary tests, it might complement other attempts that are not likely to lead to a complete solution to the crisis. Assume that a bacterium A, sensitive to an antibiotic α, mutates into bacterium A', for which there is no antibiotic (*1*). If a patient suffering from an A' infection could safely be "inoculated" with A, and if the competition indeed led to the elimination of A', one could then apply α to eliminate A in turn, although admittedly the situation is not simply "time-reversed" from the one which gave rise to the mutant. Success would depend on the relative viability of A and A' in that particular niche (*2*). One can envisage four investigative stages to decide for any (A, A') combination how well the competition works and in which success at one stage would encourage pursuit of the next one.

Stage 1: In vitro experiments carried out in a culture medium that approaches a natural niche, with A and A' injected in different amounts and in different order, with different time intervals between the injections. Thus, one could find to what extent A' loses out against A, with the results depending on their relative growth rates (*3*). It might be possible to replace A by a defective harmless pathogen of the same species, perhaps genetically engineered.

Stage 2: Studies with animal models to determine whether, after an A' infection, the addition of A, given at different times after the onset of the A' infection, succeeded in reducing A' below a threshold where it can be successfully fought by the immune system.

Stage 3: Inoculation with A of volunteer patients suffering from an A' infection that is not life-threatening and in whom suitable doses of A, routes of inoculation, and the time needed to eliminate an A' infection could be studied (*4*). The "age" of the A' infection might be important; it might be approximately deducible in some cases, for example, for patients infected in hospitals, for children infected by siblings, and so forth.

Stage 4: Patients suffering from a life-threatening A' infection might volunteer for inoculation by A, especially if it could be replaced by a harmless pathogen derived from it.

If inoculation with A should aggravate an existing infection unduly, the antibiotic α might have to be applied prematurely, aborting the attempt at a cure.

While some isolated, related procedures have been tried in the past (*5*), a systematic study (stages 1 and 2) of different (A, A') combinations seems desirable to find out whether there are some for which the approach discussed seems promising. A search for "Darwinian reversal" would also be of interest to evolutionary biologists.

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References and Notes

1. Although bacterial mutants usually arise spontaneously, some may be induced, for example, by diagnostic x-rays, which are copiously used for patients with lung infections.
2. The procedure may not work for those mutants A' that can transfer their drug resistance to A, depending on the rate of transfer.
3. Evidence of considerably slower growth of mutants than that in the wild-type strain is reported by M. Demerec [*Genetics* **36**, 585 (1951)] and by J. R. Saunders [*Brit. Med. Bull.* **40,** 54 (1984)].
4. Such "experiments" may have been unwittingly done when patients infected by A' were by chance infected later by A; if this indeed led to the elimination of A', one might have concluded that α, although ineffective at first, later became "miraculously" effective.
5. M. Scolaro, R. Durham, and G. Pieczenik chose a similar approach to treat a virus infection [*Lancet* **337**, 731 (1991)]. However, they took a bold shortcut, using blood from a patient infected with a nonpathogenic human immunodeficiency virus (HIV)–1 strain to inoculate HIV-infected volunteers.
6. I thank C. W. Anderson, D. M. Atwood, S. J. Gould, S. Lacks, A. D. Woodhead, and G. C. Williams for illuminating discussions.

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Women in Science

In their Policy Forum "The paradox of critical mass for women in science" (7 Oct., p. 51) Henry Etzkowitz *et al.* address the significant fact that academia's gender imbalance will not change solely by getting more women to enter science disciplines. They state, "[a] key factor in overcoming the problems posed by the paradox must be university-wide policies and programs. . . ."

This is a "paradox" that the Association for Women in Science (AWIS) has tried to overcome for 23 years. Etzkowitz *et al.* are on target in recognizing that increasing the