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Commentary

Disease transmission dynamics and the evolution of antibiotic resistance in hospitals and communal settings

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Despite the tremendous benefits of antibiotics for dealing with a wide range of pathogens, there is by now little doubt that their indiscriminate use has led to the emergence of novel resistant strains and a frightening new set of threats to public health. Hospitals and other community settings provide an especially fertile ground for the spread of those types; in particular, the recent emergence and proliferation of bacteria resistant to both methicillin and vancomycin has engendered serious concern, threatening the effectiveness of the last available options for treatment of potentially fatal *Staphylococcus* strains.

It seems clear that a considered and comprehensive strategy for antibiotic use is essential, permitting the intelligent deployment of antibiotics at rates that will not outpace our ability to develop new alternatives. Such a strategy should be built upon a quantitative theoretical foundation, derived from a firm understanding of how communal use of antibiotics translates into the emergence of resistant strains. Were such a theory available, one could base upon it a management strategy that would balance health costs and benefits in a way to make antibiotics available to those who most need them, without undercutting the long term community effectiveness of those drugs. Unfortunately, no such theory yet exists; but in this issue of the *Proceedings* Austin, Kristinsson, and Anderson (1) provide the framework for developing one. Their work, complemented by that of investigators such as B. Levin, Stewart, and others (2–6) provides the first such effort and a hopeful point of departure for future work. In this note, we summarize the main insights derived by Austin *et al.* (1) and indicate some further directions for investigations.

Transmission Dynamics and the Evolution of Resistance. The emergence of antibiotic resistance is a classic example of evolution in response to strong selection pressure, familiar to population biologists through phenomena such as selection for heavy-metal tolerance, or the protective coloration of the peppered moth *Biston betularia* in industrial regions of the United Kingdom. Indeed, standard population genetics theory allows for easy computation of the dynamics of resistance in the face of such selection pressures, and Austin *et al.* exploit this to derive initial estimates of the loss of effectiveness of antibiotic use. There is nothing new in this, a straightforward but important application of conventional theory. But the unique contribution of this work, and indeed of the remarkable body of work carried out by Anderson with May and other collaborators (7), is the placement of the problem within the context of an ecological perspective. The hospital or other communal setting indeed is an ecological community, in which multiple bacterial types are cocirculating and interacting with one another directly (through the exchange of plasmids) and indirectly (especially through interactions between patients and hospital workers).

The human body is home to a diverse microflora; some are beneficial, others are harmful, and still others live commensally, exercising little influence on their host under normal conditions. Antibiotics are typically introduced to treat the true pathogens, and for them the problem of resistance introduces questions concerning the length and intensity of treatment, multidrug strategies, and patient compliance. (See, for example, refs. 2–4). Commensals provide a different sort of problem, however. Under normal conditions, they live in such places as the skin or upper respiratory tract, causing little or no harm. On occasion, however, they become translocated to sites that are normally sterile, such as the blood or lungs, where they may have serious harmful effects (6). Many virulence factors, for example in *Staphylococcus aureus*, are carried on plasmids, and can be exchanged among different strains. Resistance-transfer factors, plasmids that confer resistance to antibiotics, are widespread. Resistance-transfer factors can be conveyed to sensitive strains by means of cell-to-cell contact. Undoubtedly, this is the principal mechanism for the rapid spread of multiply resistant strains (8).

Modeling of such situations has been carried out primarily by two groups (1, 5, 6, 9). Stewart *et al.* (6) and Levin *et al.* (5) develop models of within-host dynamics, providing expressions for the fraction of a host's bacteria that are resistant; but they either ignore the flow of bacteria among hosts or consider exchange only through an environmental reservoir. Austin *et al.* (1, 9) take a more explicit approach, keeping track of individual host organisms in an interactive population. Individual hosts are distinguished according to their disease status and whether they are under treatment with antibiotics. Austin *et al.* assume, for simplicity, that individuals can be colonized only by one strain. Thus individuals may either be susceptible (and either under treatment or not), colonized by the sensitive strain (and hence not under treatment), or colonized by the resistant strain (and either under treatment or not). Strains may transfer antibiotic resistance carried, for example, by plasmids through a mass-action process mimicking a superinfection; in particular, resistance is assumed to be conferred to sensitive strains at a rate that depends on the prevalence of resistance.

The commensal pathogens are characterized by long residence times, low transmissibility, and high prevalence. To describe the community level disease transmission dynamics of such a pathogen, Austin *et al.* (9) introduce a simple mass-action epidemic model with long infection period and low transmission rate. They further make the assumption that there is a cost to resistance. This somewhat debatable assumption (see, for example, ref. 10) ensures that relaxation of antibiotic use will lead to a loss of resistance. However, further data clearly are needed on this point, in particular concerning the transmissibility of resistant strains in host-to-host spread under field conditions.

The objective of the work of Austin *et al.* (1, 9) is to characterize the development of antibiotic resistance in com-

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mensal organisms as a consequence of drug therapy for other organisms within the hospital or community setting. Because the commensal is not the target organism, drug use is assumed to be independent of commensal prevalence. Hence, Austin *et al.* (1) assume that hosts receive treatment at a rate independent of their epidemic status, and they remain under treatment for a given average period. However, the introduction of antibiotics alters the transmission dynamics by reducing the reproductive rate of sensitive strains, as well as by providing (through clearance of sensitive strains) new hosts for resistant strains. These two effects both tend to enhance the reproductive rate (and hence the fitness) of the resistant strain relative to that of the sensitive. Austin *et al.* find that the transmission dynamics in itself can account for the slow rate of loss of resistance to reduced antibiotic load relative to the speed of its emergence.

Conclusions and Directions for Future Work. A key element in the framework of Austin *et al.* (9) is the possibility for direct transfer of resistance from one host to another by means of exchange of transposable elements. They also consider acquired resistance, whereby individuals who are colonized by sensitive bacteria are taken over by preexisting antibiotic-resistant mutants once treatment begins. Building on their dynamical description of the community dynamics, Austin *et al.* (1) demonstrate that, in the absence of such acquired resistance, the system may evolve to any of three states: domination by the sensitive strain, domination by the resistant strain, or coexistence, depending on the level of antibiotic consumption. Their analysis allows them to relate such outcomes and the level of resistance directly to the level of antibiotic use, providing a crucial tool for guiding management at the community level.

A principal finding of Austin *et al.* (1) is the existence of two thresholds involving antibiotic treatment, a_R and a_S. The thresholds are easiest to describe in the absence of acquired resistance. If the proportion a of individuals undergoing treatment at any time is less than a_R, then resistance will not emerge. For a above a_S, resistant types will displace sensitive ones. For intermediate levels of treatment, $a_R \leq a \leq a_S$, the two types will coexist, and there is a smooth transition from one extreme situation to the other as a increases from a_R to a_S. This middle region is broadened by plasmid transfer of resistance. The potential for conversion through acquired resistance increases the fitness of the resistant type, guaranteeing that it will always be present, and increasing its abundance under all circumstances.

There are few data yet available that would allow immediate implementation of the theoretical approach, though Austin *et al.* (1) point the way for such work through consideration of data from Finland and Iceland. In particular, the model's ability to track the response of resistance prevalence to changes in drug administration suggests the substantial potential of the model as a management tool. More generally, this work points the way for explaining patterns of antibiotic use and resistance across countries and for developing sound approaches to antibiotic management. Yet to be addressed are the more complex interactions that may exist among multiple interacting strains, whose interlocking transmission dynamics (11) are likely to play a crucial role in the rapid development of multidrug resistance. Second, the individual hospital or communal setting is too narrow a venue for studying global trends in antibiotic resistance; the model must be extended to consider multiple interacting populations. Finally, and related to this, the framework may be useful in studying the role of antibiotics in veterinary situations, a critical and neglected element of the total antibiotic picture (12). Thus, the very useful ecological approach of the authors for dealing with within-community dynamics suggests immediate extension to a broader setting. In summary, work such as this, complemented by the excellent investigations in refs. 5 and 6, provides hope for the essential comprehensive theory alluded to earlier.

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