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Genome Size and Antibiotic Resistance

I enjoyed the Guest Commentary by Dr. Steven Projan in the April 2007 issue of *Antimicrobial Agents and Chemotherapy* (3)—even though he took to task my quote, which headed the commentary, namely, that "laws of natural selection dictate that bacteria will eventually develop resistance to practically any antibiotic." Dr. Projan says "not necessarily so" and suggests that resistance emergence includes factors that we do not yet know. For one, he proposes that resistance is somehow linked to genome size, a concept that has not been described before. He infers that the larger the genome size, the greater the likelihood of developing resistance; therefore, the frequency of mutation to resistance will not be the same for all species. With this latter conclusion I agree, but the reasons are presumably more than genome size. His commentary, though, draws our attention to this correlation. I never meant that the rates of resistance emergence would be the same for each drug/bug combination. In fact, we have observed in *Streptococcus pyogenes* an absence of penicillin resistance, despite the emergence of isolates resistant to tetracyclines and macrolides.

But in the broader context, given enough time and drug, I do believe resistance will eventually emerge. But why should genome size matter? Dr. Projan suggests that organisms with larger genomes may more easily adapt to a "fitness burden" of acquiring new resistance determinants. Another possibility, especially among enteric gram-negative bacteria, is the major role of antibiotic efflux pumps. These are clearly important mechanisms for multidrug resistance and more numerous in the larger genomes. But resistance involves more than that which emerges via chromosomal mutation. *Staphylococcus aureus* has certainly accumulated a panoply of resistance determinants, but most of these are acquired. Transfer of extrachromosomal elements, like plasmids, impact resistance, as Projan also cites. I agree that too little attention is being paid to the commensal bacteria as reservoirs of these transferable resistance determinants (2). One could argue that if there were no plasmid-borne resistances or no mating potential among bacteria, resistance would be greatly reduced and take longer to appear. But then another question can be asked—how does genome size affect resistance gene acquisition? Is there an association? One explanation that Projan provides is that smaller genomes appear to have fewer genetic systems.

Projan suggests that his observation points to the larger genome species as the critical targets for "novel antibacterial agents." This conclusion bears great merit. Today these organisms are multidrug resistant, with no new drugs expected soon for their control. In this regard, perhaps these difficult-to-treat infectious disease agents require a totally new approach. Since resistance adaptation is easily attained, let's forget about targeting growth inhibition—let's enfeeble the organism so as to prevent its ability to cause infection. Such an approach can avoid the selection of resistance by growth-inhibitory agents and replace these with alternatives that allow growth but not infection (1).

I congratulate Dr. Projan on his commentary. In a way, he is challenging the extent of our understanding of resistance by putting forth a thought-provoking correlation not previously considered. He infers, and I concur, that we do not know very much about resistance, only that which is easily seen and surmised. We need to delve more deeply into the problem—the organisms, the conditions, the genes and the drugs, and how we affect these participants. His commentary sets a challenge to examine more closely this new observation, as well as to come up with other fresh concepts which probe the resistance problem. New ideas and revelations will aid in our quest to improve understanding of resistance and control its emergence.

Still, it must be emphasized that the gene and drug contribution to resistance appearance is only part of the equation. We do not have a problem if a single isolate in a hospital or community appears drug resistant. The true clinical significance of a resistance problem occurs when the numbers of resistant strains become great enough that an individual patient fails treatment. With appropriate awareness, surveillance, and coordinated containment measures, we can and should limit the increase and spread of such organisms when they first appear. These steps, combined with new insights into the genetics of resistance, will help us make inroads into solving and controlling the resistance problem.

REFERENCES

1. **Alekshun, M., and S. B. Levy.** 2004. Targeting virulence to prevent infection: to kill or not to kill? Drug Discov. Today Ther. Strategies **1:**483–489.
2. **Alekshun, M., and S. B. Levy.** 2006. Commensals upon us. Biochem. Pharm. **71:**893–900.
3. **Projan, S. J.** 2007. (Genome) size matters. Antimicrob. Agents Chemother. **51:**1133–1134.

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Ed. Note: *The author of the published article did not feel that a response was necessary.*