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Perspective

Humans live in a bacterial world. Throughout life, each of us carries a greater number of cells of our indigenous bacteria than of our own human cells, and the skin, respiratory, and gastrointestinal tracts are portals for the never-ceasing introduction of exogenous organisms. The current genomic revolution has produced important breakthroughs in our understanding of human diseases, based in part on the nucleotide and amino acid polymorphisms present in our outbred human population. The extent of the polymorphisms is such that except for identical twins, no two humans share the same genetic composition. However, the diversity in the bacteria to which we are exposed and that we persistently carry or become infected with is far greater than the variation between our own genomes. Why is this important? Clearly, exposure to exogenous pathogens is medically significant, and both preventive measures and therapies are aimed at minimizing their impact on human health. Colonization of humans by pathogenic bacteria is relatively common, but infection and disease follow in only a fraction of colonized persons. The differential risk for illness following infection is one of the central problems in understanding microbial pathogenesis. Most clinical investigators are well aware of the impact of the genomics revolution on our understanding of human disease. However, it is our experience that far fewer biomedical scientists are as informed [...]

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Humans live in a bacterial world. Throughout life, each of us carries a greater number of cells of our indigenous bacteria than of our own human cells, and the skin, respiratory, and gastrointestinal tracts are portals for the never-ceasing introduction of exogenous organisms. The current genomic revolution has produced important breakthroughs in our understanding of human diseases, based in part on the nucleotide and amino acid polymorphisms present in our outbred human population. The extent of the polymorphisms is such that except for identical twins, no two humans share the same genetic composition. However, the diversity in the bacteria to which we are exposed and that we persistently carry or become infected with is far greater than the variation between our own genomes. Why is this important? Clearly, exposure to exogenous pathogens is medically significant, and both preventive measures and therapies are aimed at minimizing their impact on human health. Colonization of humans by pathogenic bacteria is relatively common, but infection and disease follow in only a fraction of colonized persons. The differential risk for illness following infection is one of the central problems in understanding microbial pathogenesis.

Most clinical investigators are well aware of the impact of the genomics revolution on our understanding of human disease. However, it is our experience that far fewer biomedical scientists are as informed about the revolution that has occurred in the last 20 years that has transformed our thinking about bacterial pathogenesis. Historically, pathogenic bacteria were identified and classified on the basis of differences in relatively few phenotypic traits such as cell-surface antigens, biotypes, or chemotypes. With few exceptions, it was generally presumed that similarity in phenotypic traits was a reflection of underlying close genetic relationships. However, studies initiated by population geneticists and evolutionary biologists led to the realization that similarity or identity of phenotypic characteristics frequently does not indicate genetic identity, or even close phylogenetic relationships of strains (1, 2). The implications for our understanding of bacterial pathogen-host interactions

still are not widely appreciated and only now are being integrated into investigative strategies.

The nature and extent of genetic variation present in natural populations of most pathogenic bacteria differ considerably from those characterizing human populations. Most genomic variation in humans is attributable to single nucleotide polymorphisms (SNPs), where two alternate bases occur at one position. Comparison of any two human genomes reveals that there is approximately one SNP per kilobase (3). In contrast, for most bacterial species, comparison of any two isolates reveals a much higher rate of allelic variation. In addition, isolates of individual species can differ substantially in gene content, that is, presence or absence of genes such as those encoded by bacteriophages, plasmids, or so-called pathogenicity islands. The importance of these observations for understanding host-pathogen interactions is that consideration must be given to the genetic differences that exist among isolates of a species.

This issue is of more than academic interest to clinicians. Methicillin-resistant strains of *Staphylococcus aureus* contain a gene encoding an altered penicillin-binding protein that is absent in susceptible organisms, which has been acquired independently many times. Similarly, an important step in the evolution of many bacterial pathogens has been the acquisition of toxin-encoding genes by horizontal gene-transfer events occurring in natural populations.

For most chronic diseases of humans, both heritable and environmental factors play etiologic roles. Although most biomedical research now is focused on host polymorphisms in disease causation, in fact, environmental factors play the larger role in nearly every form of cancer (4). Since microbes are among the most important factors in the human environment, differential exposures likely contribute to differing rates of oncogenesis (5, 6). Our indigenous microbiota also perform a variety of functions, and in their entirety, represent a complex metabolic compartment within each of us that interacts in manifold ways with our own cells. We might easily ask: where do we (humans) start and they (microbes) end? The bacterial origin of the mito-

chondria found in most human cells illustrates the difficulty in providing a definitive answer to that question.

Not only is there variation amongst humans in the genera and species of the bacteria that invade or live within us, but the organisms themselves often are highly diverse. Thus, substantial polymorphism exists within exogenous organisms such as *Streptococcus pyogenes*, *Borrelia* species, and *Neisseria meningitidis*, and amongst indigenous bacteria such as *Escherichia coli* and *Helicobacter pylori* (7). Diversity per se is not an indication of virulence, since, for example, *Mycobacterium tuberculosis* is relatively clonal and *H. pylori* highly polymorphic.

How and why the bacteria that inhabit the human biosphere became so diverse is not fully understood, although the past 20 years have brought substantial advances (1, 8). As with all living creatures, each cell of each bacterial species is subject to natural selection. Variation reflects differences in both ancestry and in competition between closely related bacterial cells, in which certain individuals have survival advantages in particular environmental niches. Nevertheless, any such an advantage may be transient, as changing environmental conditions alternatively select for one trait or another. For organisms that live with or parasitize humans, human traits (whether common or polymorphic) can exert a strong selective force, narrowing and shifting the characteristics of the microbial population as the host milieu changes. Bacteria, with their large population size, elaborate mechanisms for mutation and genetic exchange, rapid multiplication rate, varied phenotypes, and ability to occupy diverse ecological niches, are ideally poised for environments in flux (9). Both de novo mutation and recombination help diversify bacterial populations.

However, from the perspective of biomedical scientists, a critical question is whether intrinsic or selected bacterial polymorphisms contribute to differences in clinical outcome. From classical microbiological studies, we already know that bacterial differences are important. For example, pneumococci with type III capsules and *Vibrio cholerae* cells that elaborate cholera toxin are more pathogenic than strains of these same species without these properties. However, more recent advances in genomics and experimental modeling allow us to discern more subtle variations that also make a difference, even among cells that are not gross-

ly distinguishable. That polymorphism even within a single conserved bacterial gene can result in clinical differences emphasizes the complexity of the interaction between host and microbe. Pathogenic bacteria are superb "cell biologists" and "immunologists," having long ago discovered the workings of their hosts at a molecular level. Clinicians now are using *Clostridium botulinum* toxins to correct muscular abnormalities such as strabismus, an unforeseen benefit of understanding the pathogenesis of botulism. Polymorphic bacteria, varying at single loci, become probes for our uncovering important cellular and immunologic processes in the host. In summary, everything present in humans has been discovered by bacteria long ago, either as our ancestors or as our cohabitators or parasites.

The present Perspective series introduces some of the biologically and medically relevant polymorphisms found in several species of bacteria, the basis of the genetic diversity in those populations, and its effects on human hosts. This dynamic area of inquiry combines the disciplines of genomics and informatics with the study of bacterial pathogenesis. Importantly, analysis of the molecular population genetics of pathogenic bacteria permits reconstruction of the phylogenetic history of organisms as they evolved toward states of altered virulence. The study of bacterial polymorphisms offers new insights into many evolutionary processes and will undoubtedly benefit several arenas of medicine, both predictably and serendipitously.

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