sist over long periods of time, and they cannot grow except by recruitment.

In short, populations differ from each other because many of their members tend to carry different mutants; furthermore, it is the non-uniformity of the individual members of a population which helps a population to function as an effective entity, and thereby to allow evolutionary competition. The situation is analogous to that of a complex organism which has different cells, but they collaborate and form a living unit. Many of the individual diversities in a population are genetically controlled, as are the different cells of a multicellular organism.

To allow evolutionary forces to favor, or to eliminate, either an individual or a population, there are two requirements applying to both these units of selection:

(1) The first requirement is the presence and function of cohesive forces; we are not surprised when the cohesive forces between the different cells of a multicellular organism allow this organism to act as an individual. However, we also have to accept the fact that there are inborn cohesive forces which cause the different individuals within a population to cooperate sufficiently for the population to function as one evolutionary unit.

(2) As a second requirement, there must be effective evolutionary differences between individuals which at the same time make every population different from other populations. The existence of mutations assures the occurrence of differences between individuals as well as between populations.

Important in the current context is the fact that it is genetic factors carried by individuals which make it possible for populations to function as different evolutionary units.

DUALITY OF INTEREST

None declared.

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Pharmacogenomics—Is there a role in antibiotic therapy?

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In its purest form, pharmacogenomics is defined as the functional linkage of the science of human pharmacology, toxicology and genomics. This link is somewhat artificial, and in its current usage, pharmacogenomics implies an association of some pharmacological agent with measurable host responses and possibly adverse events that vary with the host's repertoire of gene polymorphisms.[1] Several of the most obvious and well-discussed areas of pharmacogenomics potential have been oncology, CNS disorders, and inflammation, where a pattern of gene expression (up- or down-regulation) may be monitored in response to a given pharmacological agent. The ultimate promise of pharmacogenomics is of predictable outcomes from a study of human genomes and their responses *ex vivo* to a particular pharmacological agent.[2,3]

Treatment of infectious diseases is a bit of a therapeutic outlier. Ideally, one desires an agent that has no discernible effects on the host of an infection, while having lethal effects on the invading organism. Neither of these ideals is ever achieved. When one thinks of pharmacogenomics in infectious diseases, it is often in the context of drug effects (P_{450} interactions, etc) and seldom in terms of the microbial population that the drug affects. Usually this is couched in terms of a decision in prescribing of a drug to which the patient may be allergic or prescribing a drug to which the patient may have an adverse response due to aberrant metabolism because of, eg, polymorphic variations in the

expression of the repertoire of human cytochromes. If a pharmacogenetic, or pharmacogenomic evaluation was somehow instantaneously possible, the drug of choice would be matched against the maximum compatibility of the host and maximal effect on the infectious agent.

However, there may not be any more significant effector of human pharmacology than the microbial infection itself (bacterial, fungal and viral). The cascade of gene expression response to infection is diverse and immense, affecting numerous human host response genes including the complement cascade, general inflammation responses, febrile response, the numerous immune response systems, and likely additional factors yet to be uncovered. The human population heterogeneity can have an even more profound influence on the outcome of infection. Consider, for example, the presence of single-nucleotide polymorphisms in the human population; these minor differences in certain genes are known to affect the outcome of the events associated with the gene products. A recent, well-publicized example is that of individuals naturally resistant to HIV.[4] A mutation in the CD4 receptor prevents the virus from binding, thus preventing infection. Another example is the recent discovery of mouse polymorphisms in the *kif1C* gene that alter susceptibility of macrophages to anthrax toxin.[5] It is anticipated that this genetic basis for anthrax susceptibility will extend to man. The antimicrobials used to treat pathogens may also affect the 'pharmacogenomic' response in humans indirectly by affecting the presentation of a pathogen to the human host (eg modification of the pathogen surface or lytic events exposing bacterial intracellular content). Alternatively, the drug used to treat the infection can in itself affect host response by direct pharmacological action (eg, macrolides) or through effects on host gene regulation and/or expression.

Since pharmacogenomics deals with populations, one can perhaps likewise apply this approach of genomic population analysis to the infecting microorganisms. It has become clear that microbial populations, despite being largely clonal at the onset, can during an infection become heterogeneous in terms of, for example, antibiotic resistance. Let's consider the possible examination of antibiotic resistance by a pharmacogenomics analysis. There is evidence accumulating that differing environments (eg, in a host compartment) and stress (eg, antibiotic treatment) can increase mutation rates in bacteria.[6] This population heterogeneity, in turn, can lead to increased rates of resistance development and treatment failures. This heterogeneity of bacterial populations in an infection can become quite marked; for example, a very high percentage of mutators are found among *Pseudomonas aeruginosa* isolated from cystic fibrosis patients.[7]

The predictive nature of data from a pharmacogenomic evaluation of any given drug's effects on a pathogen could have a significantly greater impact than single point MIC measurements. That is, a MIC determines the ability of a drug to inhibit visible bacterial growth in a standard assay, but does nothing to predict resistance potential, mode of inhibition (bactericidal or bacteristatic), virulence, efflux, genes turned on or off—all 'genomics-measurable' parameters that may better predict the outcome of a given treatment regimen.

But how could this work? The most straightforward way to proceed would be a 'profiling' of gene expression in devising a pharmacogenomic evaluation, most likely established initially by whole genome microarrays with a significant contribution possible from proteomics. Effects normalized to drug-free controls and normalization to growth rates of a pathogen may provide data in which a rapid diagnostic test of gene expression (custom chip) and an algorithm designed to weigh factors beyond mere inhibition of visible growth are employed in the future. In addition, the effect of a pathogen on the up- or down-regulation of host defense function may also constitute a highly relevant measurement of the potential for success of the drug in the clinic.

Another important pharmacogenomic measurement is the pathogen's response to both the host immune response and the antibiotic used to suppress or kill it. The host response can be assessed by its ability to invoke a competent host immune response, both non-specific (ie RES system) and specific (antibody or T-cell response). Gene markers can quantitatively measure all of these responses, but none at present immediately help with diagnosis of infection or choice of therapy.

The bacterium's response at the genomic level, however, may be a very direct and quick indicator of the resistance potential. For example, the science of gene expression profiling (microarrays, etc) has evolved to the point that, within a day or two, a complete time-sequence-based expression pattern of gene products could be assessed in bacteria. This would allow for contrasting the 'normal' and 'drug affected' bacterium to see what effects drug treatment may have on the dynamics of the pathogen population. The ability of chips to detect single mismatches and expression levels of key resistance genes could be used both to detect resistance mutations, and measure expression levels of resistance genes. If a profile of relevant

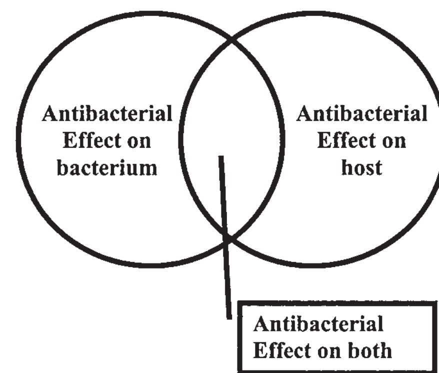

Figure 1 The key to the successful application of antimicrobial pharmacogenomics will be defining and exploiting the overlap 'pharmacogenomics' of the effects of antibiotics on both the bacterium and the host itself.

resistance markers or surrogate markers for resistance is available, it may impact on the selection of the drug for therapy. Specific examples would be the point mutations in key topoisomerase loci associated with quinolone resistance or the presence of the *mec* region or an *ermB*-bearing transposon. Another example would be type and expression levels of β-lactamases or drug efflux pumps. A 'profile' of resistant or resistance-prone strains may be ascertained, and this profile could emerge as predictive of the chance of resistance emergence in a particular pathogen population. A pharmacogenomics analysis of gene expression of a pathogen may provide a *predictive* outcome on therapy. At present, the methods are too costly and time consuming to contemplate this for routine analysis. However, it is not too early to begin to devise methods and gather data on these questions.

Pharmacogenomics offers the opportunity to exploit knowledge of the change in mRNA expression and the change in protein expression in response to a novel antimicrobial agent. These changes in expression can be in the host, in the pathogen, or even in an intermediary commensal organism (Figure 1). Knowing what genes are turned on, or which proteins' expression are changed in the pathogen upon infection provides additional targets for antimicrobial chemotherapy. Knowing that same information for the host offers additional targets that can be assessed to help the host fight off an infection, eg by regulating the innate immune response or blocking inappropriate inflammation. This knowledge will occur first in the laboratory, and the hunt for correlations will take time. Once correlations are established, though, there are two immediate paths available: screening to identify agents to stop the infection and development of rapid, highly specific diagnostics to assess the pathogen population.

Genomics, pharmacogenomics, and proteomics are technologies that offer tremendous promise in anti-infective drug discovery. The key to productively using these technologies is to think beyond the current research paradigm ie, identify a compound that kills or prevents the infective agent from growing. Instead, these technologies give us the potential for tens, if not hundreds, of novel anti-infective targets—from the pathogen's gene regulation and expression in response to therapy, to the host's gene regulation and expression in response to infection. We now have the opportunity to look deeper into the infective process and find other points at which to stop the pathogen. It is a tremendously exciting time to be working in anti-infectives: the promise is considerable, and the goal the best possible: saving millions of lives.

DUALITY OF INTEREST
None declared.

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The HUGO Mutation Database Initiative

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The human genome has somewhere around 30000 genes.[1] If we consider that some genes such as cystic fibrosis have nearly 1000 mutations causing this rare inherited disorder, it is possible that there may be up to 30×10^6 mutations causing single gene disorders if mutations in all genes cause disease. A more conservative figure is 3×10^6. If we consider also non-disease causing polymorphisms that are thought to occur every 200–1000 bases in the 3×10^9 genome, we arrive at 3–15 million possible polymorphisms. In the case of polymorphisms these are important in common disease, in variation in drug metabolism and as markers in linkage studies. When one considers single base changes in the 3×10^9 bases and that each of these can change to one of three others, there are potentially 9×10^9 base changes possible (without insertions or deletions). Thus it is clear that there are likely to be at least tens of millions of base changes that are important to human health. In the case of single gene disorders, each mutational event needs to be characterized by at least 10 extra pieces of data, ideally more like 50,[2] whereas polymorphisms perhaps need less. This means that there are at least hundreds of millions of pieces of data that are needed to fully record variation in the human genome. This is only one order of magnitude less