The host response to infection or immunization varies within a population. Historically, we have ascribed variation of response among individuals inoculated with identical vaccines to stochastic processes that could not have been predicted. Now that the human genome has been defined and extensive variation in the genome has been noted in both coding and regulatory regions, we can consider the hypothesis that some features of host response to infection or immunization are influenced by genetic factors. In a study in this issue of the Journal, Stanley et al. [1] show that haplotypes in the interleukin-1 gene complex and the IL18 gene are associated with an increased incidence of fever after vaccination of healthy adults with live vaccinia virus, the classic vaccine for protection against smallpox.

Recent trials of live smallpox vaccines, sponsored by the National Institutes of Health, have provided an ideal setting in which to explore the mechanisms underlying adverse events after vaccination with a live virus. Variola virus has not circulated for decades, and vaccinia virus immunization also has not been used for decades except in the military and in some laboratory workers. Recent political events led to the retesting of the safety and potency of vaccines that had been stored for many years, in case widespread immunization of the population became a necessity. Therefore, there have been clinical trials of primary infection with vaccinia virus enrolling hundreds of seronegative healthy adults. A significant proportion of the volunteers suffered some type of adverse event (most commonly fever). Severe adverse events have not been attributed to vaccine, which is to be expected given the moderate size of trials conducted to date and the expected rarity of these events. In very large vaccination programs, such as in the military, some severe adverse events have been noted, and the association between vaccinia inoculation and cardiac inflammation is of concern.

The relatively high frequency of individuals developing fever after primary inoculation with this vaccine provides a setting in which genomic and proteomic technologies can be brought to bear to explore mechanisms underlying adverse events. In studies recently published in the Journal [2, 3], high-throughput proteomic techniques were used in this setting to define alterations in cytokines and other soluble factors whose patterns were associated with fever, rash, and lymphadenopathy. The results of such studies are complex, revealing that a single cytokine does not account for the clinical phenotype of adverse events; rather, the patterns of multiple cytokines are the marker of the altered response. Soluble protein factors are difficult to study in this fashion, because each factor exhibits a distinct kinetics; measurement of cytokine levels at a single or limited number of time points may not detect the peak level of the factor in the weeks following immunization. Measuring systemic levels of proteins in the serum also may be misleading if the critical factor is the quantity of a cytokine in a local region of the body. Another approach to high-throughput analysis of the quantity of inflammatory mediators that is being used in similar studies is transcriptional profiling by means of microarrays to define the mRNA levels of thousands of factors. This technique is also susceptible to suboptimal sampling times and the limitations of the usual focus on the measurement of transcription in cells in the peripheral blood.

Genomic approaches, such as comparing polymorphisms in volunteers who experience adverse events with those in volunteers who do not, offer some advantages. If there is a genetic predisposition toward patterns of response, these genetic features do not change. Therefore, kinetics is not an issue, and genomic DNA can be obtained at any point during the study, even after a trial is completed. Stanley et al. chose an approach of studying a limited number of candidate genes that, prior knowledge would suggest, are associated...
with the induction of fever. The question here was whether the variation in the occurrence of fever was associated with individual variability at the genetic level (with the implication that the expression level or function of the gene product might differ between individuals with and without the polymorphisms). The investigators found that specific haplotypes were associated with fever, an important finding for understanding the variation in host response. We must consider the associations discovered by Stanley et al. to be preliminary, because emerging standards for genetic association studies will require replication in independent clinical populations. Many associations reported in the literature cannot be replicated when tested in independent populations. Nevertheless, the high biological plausibility of the role of these genetic features and the public health concern with respect to understanding the potential consequences of populationwide vaccination with vaccinia make Stanley et al.’s findings of interest.

Obviously, the long-term goal is to identify genetic features that could be determined before vaccination, allowing practitioners to modulate the vaccination plan according to risk. This type of practice—the goal of personalized predictive medicine—appears to be closer in terms of feasibility than ever, given the pace of genetic testing. Genomewide arrays testing for polymorphisms are now available in most academic medical centers for less than $1000 per subject. It is highly likely that widespread genetic testing will become a common feature of vaccine testing protocols. In fact, a testing sequence using genomewide arrays for genetic polymorphisms followed by transcriptional and proteomic arrays at multiple time points in association with sophisticated laboratory immunological assays and carefully graded clinical scores will likely become the norm. The guiding biological concept for interpretation of such massive sets of disparate types of data will be that all of the data should “tell the same story.” We can foresee a time soon when these data will not be interpreted individually; rather, integrated analytical tools will emerge to coordinate the use of genomic, proteomic, and clinical data from clinical trials. The potential for false discovery of associations is high, but new methods are emerging that will reduce such random associations. Interpretation must be guided by biological plausibility through the injection of expert knowledge into the analytical system. The proper development of such tools—and their efficient use—will require the close working of multidisciplinary teams of clinicians, laboratory scientists, bioinformatics experts, and statisticians.

References