

in rapid human to human spread due to the novel immunogenicity of this virus for the current world population.

Mathematical modeling of S-OIV transmission showed that, in a susceptible population, S-OIV infections generate approximately as many secondary cases as does a typical seasonal strain of influenza virus (7). However, due to the novel immunogenicity, the susceptible population is far greater for S-OIV infections than for the seasonal strains, perhaps explaining why S-OIV strains have outcompeted all the seasonal strains of influenza virus, accounting for over 99% of all influenza A virus infections reported to the Centers for Disease Control this year (8). Unexpectedly, 73% of all S-OIV infections have occurred in people under the age of 24 (3), contrasting with seasonal strains of influenza virus that produce only 23% of their infections in individuals under the age of 50 (9). However, individuals over the age of 60 produce antibodies that may react with S-OIV as a consequence of exposure to previously circulating strains of influenza virus, possibly explaining the enhanced incidence of S-OIV in children and young adults (10).

Since its emergence in 2009, S-OIV has been found in over 206 countries (11). It is likely that the virus will continue to circle the globe until exposure or vaccination renders the majority of the population immune, after which time new novel strains of influenza may out-compete S-OIV. Alternatively, S-OIV may remain endemic, with constant antigenic changes allowing for continued spread in the human population. The widespread presence of S-OIV, as well as its documented ability to replicate in the swine population, leads to the fear that another antigenic shift will occur, perhaps this time with an avian strain possessing markers for enhanced pathogenicity. However, the risk of such a reassortment between a highly transmissible human strain and a highly pathogenic avian strain has long existed. The current S-OIV pandemic has demonstrated the importance of influenza virus surveillance programs and the continuing development of vaccines and antiviral drugs, all of which should help to mitigate the consequences of the next influenza virus pandemic, however it may occur.

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Identifying Clinical Phenotypes of Asthma Steps in the Right Direction

Older concepts held that asthma is a relatively homogenous disease characterized by mast cell- and eosinophil-dominant inflammation and responsiveness to corticosteroids. Disease severity was classified primarily by measures of airflow obstruction, and severe asthma was considered a disease subtype with more severe allergic inflammation that required treatment with higher doses of corticosteroids. Patients with poor or absent responses to high doses of steroids were thought to have cellular or molecular defects in steroid responsiveness. The possibility that some phenotypes of asthma had airway pathology insensitive to steroids was not emphasized. Newer concepts of asthma view the disease differently, and asthma is now considered a heterogeneous multidimensional disease in which impairment (symptoms and functional limitations) and risk (likelihood of asthma exacerbations and progressive decline in lung function) are emphasized as the major determinants of disease severity (1).

Although eosinophilic asthma is an important clinical phenotype of asthma that is characterized by airway and systemic

markers of eosinophilia, subepithelial fibrosis, and corticosteroid responsiveness, there has been increased recognition of the importance of noneosinophilic asthma, which is characterized by the absence of eosinophilia and subepithelial fibrosis and poor responsiveness to corticosteroids (2, 3). T-helper type 2 (Th2) cytokines have been proposed as the upstream molecular regulators of eosinophilic asthma (4), but there are few clues about the molecular mechanisms responsible for noneosinophilic asthma. The change in thinking about asthma from a relatively homogeneous disease to a heterogeneous disease with different clinical phenotypes, explained by different underlying molecular mechanisms, has yet to greatly affect clinical management, but it has already changed how asthma research is conducted, and it will surely change how asthma will be treated in the future.

In this issue of the *Journal* (pp. 315–323), Moore and colleagues (5) analyzed multiple clinical variables in more than 700 subjects recruited by investigators in the NHLBI's Severe Asthma Research Program, and they used cluster analysis to

group together patients with similar clinical variables. Using this approach, they were able to identify five phenotypes of asthma that differed in multiple ways, including age of asthma onset, gender, body weight, degree of airflow limitation, reversibility of airflow limitation, and asthma exacerbation frequency. For example, one cluster was composed of patients with early onset atopic disease with normal lung function and little difficulty attaining asthma control; another cluster was composed of patients with an older age of onset, obesity, female gender, reversible airflow obstruction, and difficulty attaining asthma control. Yet another cluster had poorly reversible severe airflow obstruction, older age of onset, and a tendency to have systemic hypertension.

Although the authors used 34 clinical variables in their initial analysis, they showed that 80% of subjects could be assigned a cluster using just three variables: pre- and post-bronchodilator FEV₁% predicted, and age of onset of asthma. In all clusters it was possible to find subjects who would have been classified as severe or treatment refractory by current ATS criteria, highlighting the limitations of currently used classification systems. The implication of these findings is that we can do better in how we use clinical variables to categorize asthma and that these better-defined disease categories may ultimately be shown to have identifiable molecular underpinnings that can be specifically treated. Other groups have previously used similar analytic approaches to identify clinical phenotypes of asthma in research datasets. For example, among a group of difficult to treat subjects with asthma, Haldar and colleagues (6) also found multiple clusters, including one cluster with early onset of asthma and prominent symptoms but minimal eosinophilia, and another cluster with late onset of asthma and minimal symptoms but prominent eosinophilia.

In terms of advancing the concept of disease heterogeneity in asthma, the studies by Moore and colleagues (5) and Haldar and colleagues (6) are steps in the right direction. These studies begin to organize our thinking about how clinical heterogeneity should be tackled, but it is difficult to review the data without being reminded that major deficits persist in our understanding of mechanisms of asthma, and that much work remains to be done. In particular, faster progress is needed to understand the different molecular mechanisms underlying the multiple clinical phenotypes of asthma that are beginning to be consistently identified. To date, the studies that have tackled issues of clinical heterogeneity have been relatively small, have used research databases collected for other purposes, and have had limited ability to assign molecular mechanisms to clinical phenotypes. Now is the time to scale up this clinical research approach significantly. There is a great opportunity to use better methods of disease classification to identify asthma phenotypes that are likely to cluster by causative mechanism. If comprehensive biospecimen analysis is included in careful patient phenotyping protocols, then the heterogeneity of clinical phenotypes can be leveraged to match inflammatory/molecular signatures to specific clinical

phenotypes. This approach should at least point to underlying disease mechanisms that can be further studied in human studies or in disease model systems.

The chronic obstructive pulmonary disease (COPD) community in the United States is beginning a major new project: the NHLBI-sponsored SPIROMICS (SubPopulations and Intermediate Outcome Measures In COPD Study) initiative. This multicenter collaboration supports the prospective collection and analysis of phenotypic, biomarker, genetic, genomic, and clinical data from subjects with COPD for the purpose of identifying subpopulations and intermediate-outcome measures. A strong argument can be made for a similar initiative in asthma, which should include an assessment of the response to currently available asthma treatments. This discovery strategy will compliment other research approaches to uncover unsuspected mechanisms of disease and increase the likelihood that we can ultimately provide personalized programs of care for our patients with asthma.

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A Second Chance Setting a Protective Ozone Standard

On March 12, 2008, the United States Environmental Protection Agency (EPA) revised the National Ambient Air Quality Standard (NAAQS) for ozone. The new, stricter standard of

0.075 ppm per 8 hours replaced the older standard of 0.084 ppm per 8 hours. Although this stricter standard would provide the basis for requiring reduced ambient ozone levels, it did not, in