possible (1). This would involve the routine use of COPD "risk assessment tools" in primary care to identify those most likely to develop clinically significant COPD. These tools might include smoking and occupational history; history of infective exacerbations, lower respiratory tract infection, or pneumonia; symptom scores to assess exertional breathlessness, productive cough, and lethargy (Medical Research Council scale and COPD Assessment Test scores); spirometry to assess airflow limitation; and measurement of serum markers of inflammation (C-reactive protein, fibrinogen, or IL-6). In addition to smoking cessation, other interventions include regular exercise and, in those with systemic inflammation, anti-inflammatory treatments (e.g., statins) (4, 5). Other potentially useful interventions include a diet high in fiber, which has been shown to reduce the risk of developing COPD (6). We conclude that the call to research primary prevention interventions, aimed at maintaining lung health, is timely and founded on numerous epidemiological studies showing there are many potentially effective interventions, in addition to smoking cessation, that require further investigation. ■

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Reply

From the Editorialists:

We thank Dr. Young and Ms. Hopkins for supporting the National Heart, Lung, and Blood Institute (NHLBI) recent call to action to develop a research agenda for the study of primary prevention of chronic lung disease (CLD) and lung health (1). They refer to building evidence that chronic obstructive pulmonary disease (COPD) pathogenesis could be modified with therapies targeting systemic inflammatory processes. An important first step, they point out, is identification of those at greatest risk of developing COPD, so that risk-mitigation strategies can be tested. This is certainly one approach to pursue in this area of research.

The NHLBI is embarking on a strategic visioning process for heart, lung, blood, and sleep research, and compelling questions and critical challenges related to primary prevention of CLD will be key components of the process. We agree with Dr. Young and colleagues that the time is right for research in CLD primary prevention. As a first step, the scientific community identified a number of gaps, challenges, and opportunities, which have been published as a series of papers from the NHLBI Primary Prevention of Chronic Lung Disease workshop (2–8). A necessary step for the development of primary prevention interventions is to clarify what defines disease onset and/or the presymptomatic stages of disease to identify critical windows for primary intervention. The identification of risk factors for chronic lung disease permits risk stratification of populations for targeted primary prevention strategies to be tested. Robust measures of both lung health and disease need to be developed to provide biologic plausibility for the identification and validation of biomarkers that will distinguish among health, presymptomatic stages of disease, and disease onset. Novel technologies and approaches that can identify early perturbations in lung structure, function, and defense, as well as early integration of mechanistic and clinical studies, are necessary to identify modifiable intervention points in an efficient and timely manner.

We believe that with the joint efforts of the National Institutes of Health and the global research community, optimal and sustained respiratory health is within our reach, with the potential to improve the lives of millions of individuals. ■

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Two Faces of Vitamin E in the Lung

To the Editor:

The hypothesis for tocopherol isoform-dependent effects on asthma prevalence by Cook-Mills and colleagues (1) is derived in part from their important animal work, but also their interpretation of our own work with γ-tocopherol (γT) in experimental asthma. Although we have recently demonstrated that γT-enriched supplements can reduce endotoxin-induced neutrophil responses in human lung (2), we think the authors misinterpret our results in experimental asthma models when they conclude that γT was effective against neutrophilic, but not eosinophilic, inflammation. Both our results with antigen-induced asthma and rhinitis in rats (3) and ozone-induced exacerbation of allergic rhinitis (4) demonstrate 70–100% reduction in tissue or lavage eosinophils. We saw no effect of γT on any attendant neutrophil airway inflammation. Our results were also striking for the complete abolition by γT of mucous cell metaplasia in nasal and pulmonary airways, which is a key feature of clinical rhinitis and asthma.

Therefore, our results with the allergic brown Norway rats are opposed to the enhanced allergic responses associated with γT, as described *in vitro* and in BALB/c mice (5, 6). The use of different rodent species (brown Norway rat vs. BALB/c mouse) may contribute to the disparate observations in these animal models. Furthermore, we provided γT by oral delivery rather than by the subcutaneous route in mice, which would bypass liver metabolism. This is an important distinction considering that the anti-inflammatory metabolites of γT are known to be more potent than those of its precursor in inhibiting COX-2- and 5-LOX-mediated eicosanoids (7, 8).

Epidemiologic data suggesting positive correlations between plasma γT levels and diseases including lung disease are intriguing. However, there are many interpretations that can be made from these associations. One is, as the authors suggest, that γT promotes lung and inflammatory disease. A second is that these diseases result in an increase of γT as a response to ongoing disease. A third is that γT may be a co-nutrient with other agents that promote disease. Indeed, many plant oils that are commonly used in the United States but not Europe (such as corn oil and soybean oil) not only contain high levels γT but are also high in polyunsaturated fatty acids and n-6 fatty acids, which are known to contribute oxidative stress and promote inflammation. Thus, the apparent effect of γT may be a result of the polyunsaturated fatty acids and n-6 fatty acids contained in these oils. Interestingly, safflower and olive oils, which contain relatively high α-tocopherol levels and are commonly used in Europe, are rich in monounsaturated fatty acids, which are resistant to oxidative stress and inflammation.

Although animal studies and epidemiological studies provide important data regarding the actions of both γ- and α-tocopherol in inflammatory processes, only intervention studies can demonstrate the actions of these variants of vitamin E on inflammatory processes in humans. We have published two oral intervention studies in humans using a γT-enriched preparation. In these studies, we have shown that active treatment is associated with decreased *ex vivo* response of peripheral blood monocytes to LPS, as well as airway inflammatory response to inhaled LPS (2, 9). We have also shown that peripheral blood basophils recovered from allergic volunteers have inhibited degranulation responses to allergen *ex vivo* (10, 11). These observations, coupled with our animal data, strongly support the hypothesis that γT has anti-inflammatory actions against both allergic and nonallergic inflammation. We do not disagree that α-tocopherol has anti-inflammatory actions as well, especially in light of the intervention studies cited by Cook-Mills and colleagues.

Overall, we agree that nutritional and nutraceutical interventions represent exciting new and inexpensive approaches to decreasing allergic disease. We also agree that careful attention to dose, route of administration, duration of therapy, analyses of serum levels of tocopherols (and their metabolites), and clinical endpoints will be important in defining the role of tocopherols in asthma therapy. Thus, extending the investigation of the roles of α- and γ-tocopherol in the modulation of allergic and inflammatory disease into human populations is needed to fully understand the roles of these agents in allergic disease. ■

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