developed ones.[1] Even considering such study limitations as the small data sampling, the high prevalence of DM and IGT in community-dwelling older people in a developing country, Laos, is of particular note.

The high prevalence of DM in older people in a rural area in Laos could be associated with factors such as ethnic and genetic vulnerable factors, rapid economic development followed by nutritional transition, and other factors, such as the "fetal origins of disease" hypothesis, which postulates that early undernutrition increases the risk of certain chronic diseases in adulthood.[10] It will be necessary to investigate the causes behind the high prevalence of DM and IGT and their risk factors in Laos to prevent not only DM, but also related cardiovascular diseases, which are increasing in Asian countries.

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CARBOCYSTEINE THERAPY IN OLDER PEOPLE WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

To the Editor: As revealed by Yasuda et al. in their paper recently published in the *Journal of the American Geriatrics Society,*[1] the administration of the mucoactive agent, carbocysteine (S-carboxymethyl-L-cysteine), to patients with chronic obstructive pulmonary disease (COPD) may have additional beneficial effects on the reduction of common colds and episodes of exacerbation. Although, a statistically significant improvement was observed, there was, nevertheless, a range of interindividual variation apparent within their treated patient group.

Metabolism is usually a major factor influencing the efficacy of a therapeutic agent, and that of carbocysteine is known to be especially complex, with the pathways of decarboxylation, N-acetylation, sulfoxidation, and ester glucoronidation all being involved to differing degrees.[2–5] It is this consequent spectrum of metabolites to which an individual is exposed and not simply the administered parent compound. Several studies have indicated that the metabolism of carbocysteine varies widely within the same individual, with few sulfoxide (sulfur oxygenated) metabolites being produced after nighttime administration.[4,5] Such diurnal variation in metabolism, presumably under hormonal control, is overlaid on an underlying and apparently genetically determined ability to produce sulfur-oxygenated metabolites. This later spread of "sulfoxidation capacities" separates individuals with respect to their metabolic handling of the drug.[4,6,7] Clearly, the effects of this later inherent variation are phenotypically more pronounced after morn-

ing dosing and may even become undetectable after nighttime administration, when sulfoxide metabolite production is already at a minimum.

With a chronic dosage regimen, as reported in the study of Yasuda et al.,[1] steady-state levels will be readily established and maintained in all subjects. Nonetheless, subjects will display their own individualized profiles of metabolite levels, with some patients differing widely from others. This would be of little consequence if all the metabolic derivatives of carbocysteine behaved in the same or a similar manner, but this may be crucial. Various mechanisms of action have been purported for carbocysteine, including alteration of mucus composition and mucociliary transport.[8] Recent work suggests that this molecule acts as a free radical scavenger and that, in this respect, the sulfide (parent compound) is the active species, with the sulfoxide metabolites (already oxidized) being inactive.[9] With these underlying differences in metabolic handling, it may be reasonable to assume that a standard therapeutic dose of carbocysteine may be more effective in some patients than others and may even be ineffective in some. A simple shifting of dosing from morning to night may influence efficacy.

From the data collected by Yasuda et al.,[1] would it be possible to establish whether differences existed within the carbocysteine treated group? The authors have reported that, during the year of their study, 35 of these patients (45% of 78 total) had two or more colds per year (presumably 43 (55%) had one cold or none?), and 28 (36%) had one or more exacerbations of their COPD symptoms (again, presumably 50 (64%) experienced none). Bearing in mind the small number of patients and that the study was not designed for this purpose, would it be possible for the authors to examine their existing data to determine whether the responses of their carbocysteine-treated patients did indeed fall into a spread of responses that might be reflective of underlying differences in carbocysteine metabolism and hence exposure to differing levels of the therapeutic species? Was the shape of the spread (the key element) of responses different (could not be overlaid) from that observed with the placebo-treated patients?

It is recognized that further targeted studies almost certainly are required to answer these questions, but insights may be gained. It is also important to appreciate that an individual's pharmacokinetic profile will influence therapeutic efficacy, that the same dose may not be ideal for everyone, and that some drugs (carbocysteine included) may only be effective in certain patients. We would welcome correspondence concerning any marked variation in response to carbocysteine therapy.

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RESPONSE LETTER TO DRS. MITCHELL AND STEVENTON

To the Editor: We appreciate the thoughtful comments by Drs. Mitchell and Steventon on our previous article demonstrating that a mucolytic drug, carbocysteine, may have beneficial effects on the prevention of common colds and exacerbations in patients with chronic obstructive pulmonary disease (COPD).[1] Mitchell et al. demonstrated that metabolism of carbocysteine varies widely within the individuals and influences the therapeutic efficacy.[2,3] Therefore, they suggested that a chronic dosage and timing of drug administration of carbocysteine should be carefully determined on the basis of the interindividual metabolism of carbocysteine.

Various kind of viruses, including rhinovirus and influenza virus, have been reported to cause COPD exacerbations.[4] Furthermore, carbocysteine inhibits rhinovirus infections in human primary tracheal epithelium in a dose-dependent manner.[5] Therefore, the difference between blood drug concentrations regulated by drug metabolism may affect the effects of carbocysteine on the reduction in frequency of common colds and exacerbations of COPD, as they suggested. Unfortunately, we did not estimate the phenotype of carbocysteine metabolism in our previous report.[1] Therefore, we could not estimate the relationship between interindividual carbocysteine metabolism and the