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Since publication of their article, the authors report no further potential conflict of interest.

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Smoking-Related Mortality in the United States

TO THE EDITOR: The article by Thun et al. (Jan. 13 issue)[1] concluded that the risk of death from cigarette smoking continues to increase. Some issues, however, remain unclear. First, the effect of other risk factors that act in synergy with cigarette smoking has not been adequately weighted. Air pollution, for instance, may have finally contributed to bias in smoking-related outcomes, especially in relation to chronic obstructive pulmonary disease (COPD) and all-cause mortality.[2,3] It is also noteworthy that the makeup of cigarettes and the composition of cigarette smoke have changed remarkably in the past 50 years, such that a direct comparison of clinical outcomes may be misleading. In the United States, in particular, the sales-weighted average yields of "tar" (the residue produced by the burning of the cigarette) and nicotine have both declined from a high of 38 mg of tar and 2.7 mg of nicotine per cigarette in the 1950s to 12 mg and 0.95 mg, respectively, in the 1990s. The amounts and types of other harmful constituents of smoke have also changed since the 1950s.[4]

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No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: In his editorial on the article by Thun et al., Schroeder[1] notes that as smoking becomes less popular, those who continue to smoke will be increasingly marginalized. This is particularly true for patients with psychiatric disorders, who already undergo the stigma and marginalization associated with mental illness; these patients also have the highest prevalence of smoking among all patient subgroups. Approximately two thirds of patients with schizophrenia and half of patients with bipolar disorder smoke,[2] although, as with smokers who do not have a psychiatric disorder, most of them want to quit smoking.[3] Unfortunately, misperceptions about mental illness and tobacco use often prevent clinicians from offering evidence-based treatment for tobacco dependence to patients with psychiatric disorders,[3] despite the fact that life expectancy for these patients is approximately 10 years lower than that for the general population because of premature deaths from medical illnesses that are largely attributable to tobacco use.[4] The isolation, coexisting conditions, and lower life expectancy of persons with mental illness will not be lessened unless smoking cessation is made a top priority for this vulnerable population.

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No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: Surely Schroeder intended to attribute his pungent comment that "women who smoke like men die like men who smoke" to Joseph A. Califano, Jr., who said it on January 11, 1979, while serving as Secretary of the Department of Health, Education, and Welfare (HEW).[1] Califano's vigorous stance against smoking is generally considered to have been a major reason for his being fired from his HEW post that year by President Jimmy Carter,[2] so his blunt prophetic warning that the mortality from lung cancer among women who smoke would soon catch up with that of men who smoke has great historical significance.

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No potential conflict of interest relevant to this letter was reported.

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2. *Idem.* Obstacles to the prevention of teenage smoking: interview by Alan Blum. N Y State J Med 1985;85:360-2.

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THE AUTHORS REPLY: We thank Lippi and Mattiuzzi for their letter regarding the continuing increase in mortality from lung cancer and COPD that we observed among contemporary cigarette smokers in the United States. The increased risks cannot be explained by synergy between air pollution and smoking, since ambient levels of all so-called criteria, or principal, air pollutants established by the Environmental Protection Agency (particle pollution [$PM_{2.5}$], ozone, nitrogen dioxide, sulfur dioxide, carbon monoxide, and lead) have decreased in the United States since the 1960s.[1] The reductions in the tar and nicotine yield of cigarettes, as measured by machines that performed the cigarette smoking, obviously failed to prevent the continuing increase in risk to smokers. Although the main determinant of the increase was the generational shift toward persistent smoking beginning in adolescence, this trend was compounded by changes in cigarette design that increased exposure to tobacco-specific nitrosamines and promoted deeper inhalation of more dilute smoke, even though the cigarettes were marketed as being safer. These factors do not constitute biases in the usual sense. Rather, they represent at best imprudent modifications of exposure and missed opportunities to regulate the manufacture and marketing of cigarettes effectively.

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1. Environmental Protection Agency. Air quality trends. 2013 (http://www.epa.gov/airtrends/aqtrends.html).

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THE EDITORIALIST REPLIES: I am on record as agreeing fully with the sentiments expressed by Cerimele and Halperin.[1-3] In fact, our Smoking Cessation Leadership Center at the University of California, San Francisco, has been working in partnership with many groups, including the federal Substance Abuse and Mental Health Services Administration, to try to do just what they recommend: mainstream smoking-cessation programs among patients with mental illnesses and substance abuse disorders.[4]

Regarding Blum's comments: I did not reference former Secretary Califano because I was not aware that he had originated the phrase in question. Both Califano and the recently deceased C. Everett Koop, in his role as Surgeon General, courageously used their positions in the federal government to advocate for tobacco control at a

time when it was not politically safe to do so. They are true public health heroes.

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Since publication of his article, the author reports no further potential conflict of interest.

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Proteotoxicity and Cardiac Dysfunction

TO THE EDITOR: Willis and Patterson (Jan. 31 issue)[1] show that researchers can learn a great deal from the presence of a given disease pathway in seemingly unrelated diseases. In Parkinson's disease, as in many other neurodegenerative diseases, dysfunctional protein folding and degradation are key steps in a pathway that leads to protein accumulation, the formation of oligomers, and the spread of neurodegeneration.[2-4] We would like to add several points.

First, the authors refer mainly to macroautophagy when discussing autophagy, but there are other forms of autophagy, such as chaperone-mediated autophagy, that appear to play a particular role in the degradation of aggregate-prone protein species (e.g., α-synuclein in Parkinson's disease).[2-4] Second, mitochondrial integrity is critical in both heart and brain metabolism, and there is evidence that autophagy (or mitophagy) plays a role in impaired mitochondrial turnover in both neurodegenerative disease[3] and heart disease.[5] Third, Willis and Patterson highlight the detrimental consequences of a failure of autophagy, but with regard to evidence of maladaptive (overactive) autophagy in heart disease and neurodegeneration,[3] they could have commented on the dichotomous role of autophagy and the implications of modulating it for use as a novel therapeutic strategy.

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No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: Willis and Patterson discuss the direct role that misfolded proteins play in the pathogenesis of heart disease. The misfolding of cardiac proteins may also shed light on the growing evidence that autoantibodies targeting the heart can be associated with dilated cardiomyopathy and may contribute to the progression of cardiac dysfunction.[1] Studies on autoimmune disorders suggest that misfolded proteins can trigger autoimmunity through various mechanisms.[2,3] They can act as autoantigens and disrupt immune tolerance to native proteins; cause apoptosis, thus favoring the exposure of autoantigens; and induce the expression of heat-shock proteins (HSPs).[2,3] Chaperones in the HSP family are highly conserved immunogenic molecules[1] that send stimulatory signals to dendritic cells.[3] It has been proposed that antibodies against HSPs impair their function and hamper protein refolding.[3] A recurring anti-HSP60 antibody has been detected in patients with dilated cardiomyopathy.[1]

Further studies are required to clarify whether there is a link between protein misfolding and