ple, although the surveyed population (n = 1,647) in Tartu, Estonia had the highest rate of passive smoking (13.9% of never-smokers) and second highest rate of smoking (35.3%), it had the lowest prevalence of habitual snoring (12.0%). This geographical curiosity would be contrary to the author's conclusions about smoking or snoring. It may reflect the younger age of the population (and less exposure time) or indicate some local "snoring protective factor" worthy of further research. In addition, although we may have plausible explanations for the role of obesity and sex in the pathogenesis of snoring and sleep apnea, we really do not have a clue to explain the smoking association. Smoking-induced inflammatory damage to mucosal neural protective mechanisms against snoring is one possibility (9, 12). It is also possible that there may be developmental biological aspects to the smoking–snoring relationship. The passive smoking–snoring association is present in childhood (4–6) and maternal smoking influences airway development (13). It is entirely speculative, but possible, that the predisposition for snoring is preprogrammed during fetal development. However, this would not readily explain how current environmental tobacco exposure in adults would increase the risk of sleep-disordered breathing.

For the clinician, the data from Franklin and colleagues are timely and important. Too often, we pay little attention to lifestyle modification to treat snoring and sleep apnea and focus on mechanical therapies or surgery. In particular, as the authors suggest, smoking is often not acknowledged as a risk factor for sleep-disordered breathing. Smoking cessation will clearly be of general health benefit, and probably of specific benefit, in reducing snoring and sleep apnea, but objective data verifying this is needed. The dose–response relationship between smoking and snoring suggests this will be likely. Moreover, consideration needs to be given to urging the partner of a snorer to stop smoking. Snoring and sleep apnea have established adverse health effects, so the new data in adults presented in the current issue of the *Journal* add strength and rationale to government efforts aimed at reducing environmental tobacco exposure in the community. A "blast" of snoring should be matched by a "counterblaste" of prevention of royal proportions.

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Hunger Disease and Pulmonary Alveoli

Non omnis moriar
["*I shall not wholly die*"]
—Dr. Israel Milejkowski

"The time was 1940, the place the Jewish ghetto in Warsaw, Poland. The Nazis had sealed several hundred thousand people off from the outside world, determined to starve them to death" (1). Remarkable Jewish physician-scientists, themselves starving, conceived and completed a clinicopathologic study and smuggled the manuscript out of the ghetto to Professor Orlowski of Warsaw University. He buried it until it could be safely reclaimed (1). The diet in the ghetto was 800 calories per day (2), body temperature about 35°C, chests typanitic, chest X-rays showed hyperlucent lungs, O_2 consumption was diminished by 30 to 40%. Histologically, "emphysema" was diagnosed in 13.5% of cases examined (2).

In this issue of the *Journal* (pp. 748–752), Coxson and coworkers show that undernourished women with anorexia nervosa (AN) exhibit computed tomographic evidence of enlarged gas-exchange units (3). Their studies could have implications for the development of emphysema in humans. Indeed, they previously reported the presence of bullae and bronchiectasis in a woman with AN (4).

As an alternative to the hypothesis that undernourishment leads to the development of emphysema, they acknowledge (3) that the lung's response to calorie restriction could reflect an evolutionarily conserved adaptation to diminished O_2 consumption during food scarcity (5, 6). Although available evidence precludes a firm choice between alternatives, we favor the latter. Why? In part, because lung function studies in AN (7) do not support the presence of emphysema as the term is used clinically. In addition, a series of papers demonstrates that calorie restriction in rats, hamsters, and mice (5, 6, 8–11) causes gas-exchange unit enlargement and alveolar loss (5, 6); refeeding results in a decrease in size of the gas-exchange units (8) and alveolar regeneration (5, 6). Like Coxson and colleagues, the authors of the earlier papers considered that calorie restriction causes

emphysema (8–11). Even though such a conclusion about emphysema is literally correct, we do not believe it has the same meaning as used in pulmonary medicine because there was no evidence of alveolar destruction (5, 6, 8–11). However, we admit that studies of long-term calorie restriction in animals whose lungs have been appropriately fixed to enable detection of destructive emphysema are not available.

What is the basis for our "adaptative" interpretation of the findings? Periods of food unavailability occurred, and continue to occur, in the wild and to humans. Air-breathers have suffered episodes of diminished food intake since the Devonian, when lungfish estivated during periods of drought. Extreme food scarcity is life threatening, and the organism's metabolism adjusts, seemingly to diminish energy need while simultaneously maintaining the brain. During starvation, in addition to lowering body temperature (2), thereby decreasing heat loss and energy needed to maintain a higher temperature, the organism destroys unessential functional capacity and unneeded tissue. Tissue destruction generates substrate for gluconeogenesis, which provides glucose for the brain, and diminishes the cost of maintaining unneeded tissue.

O_2 need determines alveolar architecture. Calorie restriction diminishes organismal and lung (14) O_2 consumption and, in adult mice, causes loss of alveoli and alveolar surface area within 3 days (6); *ad libitum* refeeding increases O_2 consumption and induces alveolar regeneration (5, 6). Iguana shrink long bones during food scarcity; those that shrink the most have the greatest rate of survival (13). This loss presumably provides substrate for gluconeogenesis.

The lung's preferred substrate is glucose, but during calorie restriction the use of glucose by the lung is markedly diminished; lipid is used instead (14). Calorie restriction diminishes the rate of protein synthesis by lung, thereby lowering the lung's use of energy, and doubles the rate of proteolysis in the lung (15). The diminished use of glucose makes more glucose available to brain; doubling proteolysis provides substrate for gluconeogenesis and maintains muscle, another key organ for survival.

In animals with elastase-induced emphysema (16), and in human COPD, alveolar loss and diminished tissue elastic recoil persist after the initiators of these losses are gone; in neither is spontaneous alveolar regeneration known to occur. Calorie restriction does not diminish lung elastic tissue recoil (11, 12) and alveolar loss is regulated, ending after about 3 days even in the presence of continued calorie restriction (5, 6). *Ad libitum* refeeding after alveolar loss results in spontaneous alveolar regeneration (5, 6). Thus, regulated alveolar loss is followed by alveolar regeneration, whereas unregulated alveolar loss seemingly is not. Calorie restriction and refeeding of rats with preexisting elastase-induced emphysema results in a return of the size and surface area of the lung's gas exchange units but only to the dimensions present before the onset of calorie restriction (16). This suggests that, to the extent alveolar and extracellular matrix destruction are initiated in an unregulated manner by exogenous agents, spontaneous alveolar regeneration does not occur.

Molecular changes, which may mediate alveolar destruction during calorie restriction, precede the decline of lung (6), and organism O_2 consumption. Granzymes, produced only by cytotoxic lymphocytes (CTL) and natural killer (NK) cells, and caspase expression are elevated within 2 to 3 hours of the onset of calorie restriction (6); this indicates that calorie restriction activates these cells and initiates events resulting in regulated alveolar destruction. CTL and NK cells are thought to be involved in the alveolar inflammation of COPD. Explication of the signaling that activates and turns off these cellular populations in the lung during calorie restriction may shed light on the persistent alveolar inflammation and destruction in COPD. Understanding the signaling associated with alveolar regeneration, which *ad libitum* refeeding induces, may provide clues to the induction of alveolar regeneration in humans. Computed tomographic evidence of alveolar regeneration upon refeeding in AN would provide proof of principle in adult humans. Perhaps the lung "shall not wholly die" (1).

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