described. Her respiratory condition worsened progressively despite steroid therapy, until she died in 2008.

His maternal uncle was an ex-smoker of 45 pack-years with a previous history of atrial fibrillation and coronary heart disease. He worked as a carpenter with a significant exposure to wood dusts. In 2000, he presented with left pneumothorax, which led to the diagnosis of emphysema. In May 2010, he was investigated for breathlessness increasing over the last 3 years. HRCT showed CPFE with a definite pattern of usual interstitial pneumonia. FVC was 74% of the predicted value, FEV₁ was 84%, and DL_{CO} was 35%. He refused to be enrolled in a clinical trial and received an association of *N*-acetylcysteine, low-dose steroids, and oxygen therapy. He developed pulmonary hypertension and eventually succumbed to an acute exacerbation in May 2012.

His only younger brother was given a diagnosis of emphysema alone when he was 28 years old. At this time he used to smoke 20 cigarettes per day and mentioned premature hair graying. The most recent HRCT showed apical emphysema and mild pulmonary fibrosis of the lower lobes.

The proband, his uncle, and brother have a duplication of 22 nucleotides in the first exon of *TERT* at a heterozygous state (*TERT* reference sequences NM_, NP_: official nomenclature of the mutation NM_198253, NP_937983: c.22_43dup22, p. p.Arg15ProfsX). This mutation is not present in the Telomerase Database, nor in variant databases (Exome Variant Server, 1000 genomes) (4). His mother is an obligatory carrier. This case study supports the hypothesis that tobacco may trigger young-onset emphysema and pulmonary fibrosis alone or in combination in subjects with inherited mutations in telomerase, with a possible role of coexposures (1). The breadth of clinical features in multiple patients in this family demonstrates the need for further investigation of a possible genetic basis for CPFE. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

Hilario Nunes, M.D., Ph.D.
Assistance Publique-Hôpitaux de Paris, Hôpital Avicenne
Bobigny, France
and
Université Paris 13, Sorbonne Paris Cité
Bobigny, France

Isabelle Monnet, M.D.
Assistance Publique-Hôpitaux de Paris, Centre Hospitalier Intercommunal de
Créteil
Créteil, France

Caroline Kannengiesser, M.D., Ph.D.
Assistance Publique-Hôpitaux de Paris, Hôpital Xavier Bichat-Claude Bernard
Paris, France

Yurdagul Uzunhan, M.D.
Assistance Publique-Hôpitaux de Paris, Hôpital Avicenne
Bobigny, France
and
Université Paris 13, Sorbonne Paris Cité
Bobigny, France

Dominique Valeyre, M.D.
Assistance Publique-Hôpitaux de Paris, Hôpital Avicenne
Bobigny, France
and
Université Paris 13, Sorbonne Paris Cité
Bobigny, France

Marianne Kambouchner, M.D.
Assistance Publique-Hôpitaux de Paris, Hôpital Avicenne
Bobigny, France
Jean-Marc Naccache, M.D.
Assistance Publique-Hôpitaux de Paris, Hôpital Tenon
Paris, France

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Reply: Telomerase Makes Connections between Pulmonary Fibrosis and Emphysema

From the Authors:

I appreciate the opportunity to respond to the letter by Nunes and colleagues, which reports a family with a mutation in the telomerase reverse transcriptase gene, *TERT*, and several individuals with emphysema or the combined pulmonary fibrosis emphysema (CPFE) phenotype. The authors' observations follow on a study from our group that reported idiopathic pulmonary fibrosis, emphysema, and the CPFE phenotype in related individuals who shared a loss-of-function mutation in the telomerase RNA gene, *TR* (1). Our clinical report was in the context of observations in telomerase null mice that we had shown developed emphysema after chronic cigarette smoke exposure. We concluded that short telomere length is a genetic susceptibility factor for emphysema in mice and in some human cases (1).

Mutations in the essential telomerase genes, *TERT* and *TR*, underlie familial pulmonary fibrosis in up to one-fifth of cases and are its most prevalent genetic cause (2, 3). In these families, pulmonary fibrosis manifests as an autosomal dominant disorder with age-dependent penetrance. In some cases, pulmonary fibrosis is one of several manifestations of a telomere syndrome that includes bone marrow failure, cryptogenic liver cirrhosis, enteropathies, and certain malignancies (4). Mutations in the X-linked telomerase component *DKC1* also cause pulmonary fibrosis, underscoring the important role of telomerase dysfunction in pulmonary fibrosis pathogenesis (5).

The letter by Nunes and colleagues raises the question as to whether telomere syndromes are a cause of CPFE. Although it is still early, given that there are a number of cases now, the answer seems to be yes. However, I would like to make a case for using the

term “telomere syndromes” in reference to telomere disorders rather “telomeropathy.” Our group prefers the syndromic terminology because in individuals with telomerase mutations, there is often evidence of multiple organs affected outside the lung. The reference to “telomere syndromes” therefore reflects the fact that these patients do not have isolated lung disease but have systemic telomere maintenance defects that manifest in predictable patterns that are relevant for clinical decisions (4). For example, extrapulmonary degenerative disease may cause only mild blood count abnormalities *de novo*, but cytopenias may be significant and associated with morbidity in the lung transplant setting where myelosuppressive drugs are used. Telomerase mutation carriers often also have an increased predilection for rare medication-related toxicities. Such observations are the topic of ongoing work and highlight the importance of recognizing this entity in patients with lung disease.

I would finally like to highlight the opportunities that human genetics opens in considering the classification of lung disease. Although idiopathic interstitial pneumonias and emphysema have distinct physiologic and pathological classifications, it is clear from recent genetic studies that telomerase mutations are sufficient to provoke a broad spectrum of lung pathologies (reviewed in Reference 2). These often occur in the same individual, suggesting they represent differences in histology rather than pathophysiology *per se*. Such observations are important as we witness the twenty-first century revolution in genetic medicine. In this era, molecular medicine holds the promise to inform our understanding of disease mechanisms while opening possibilities for appreciating clinical patterns that may not have been imagined previously. The fact that telomerase mutations predispose to pulmonary fibrosis, emphysema, and the combined entity exemplifies such an insight because the mortality burden for these disorders is particularly devastating and because new approaches are very much needed. One thus wonders whether a day will come when we will refer to “telomere-mediated lung disease” rather than “emphysema” or “idiopathic pulmonary fibrosis” as the cause of a patient’s dyspnea, and hopefully, offer such a patient telomere-directed therapies. ■

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Mary Armanios, M.D.
Johns Hopkins University School of Medicine
Baltimore, Maryland

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Cognitive Decline in Patients with Pneumonia: A Role for IL-2?

To the Editor:

We read with great interest the contribution by Shah and colleagues (1). They demonstrated that study participants with pneumonia were subsequently at an increased risk of changes in cognition, such as dementia, and suggested that, after an episode of pneumonia, higher levels of systemic inflammatory markers may persist and accelerate time to dementia by causing neuroinflammation. However, they did not elaborate on how pneumonia may accelerate the progress of dementia. Thus, we would like to present a potential pathomechanism in the development of dementia in patients with pneumonia. According to a previous study by Moussa and colleagues (2), IL-2, a T helper 1 cell–derived glycoprotein with potent neuromodulatory effects, was increased in most patients (86%) with community-acquired pneumonia on admission. Denicoff and colleagues (3) studied the neuropsychiatric manifestations of treatment with IL-2. Cognitive tests and mood self-rating instruments were administered at the beginning and end of IL-2 treatment. Of the 44 patients studied, 22 patients (50%) had significant cognitive changes (all 22 became disoriented, and many also had psychometric evidence of cognitive deterioration). The neuropsychiatric adverse effects were dose and time dependent, becoming apparent more frequently at a higher dose and almost uniformly at the end of each treatment phase (3). Ellison and colleagues (4) also demonstrated that alterations of cerebrovascular permeability and morphology were evident after IL-2 infusion in animal experiments, and were accompanied by occasional axonal degeneration and demyelination. IL-2 crosses the blood–brain barrier to alter brain function. It exerts its effects on cognition by reduction of cholinergic transmission: Muscarinic receptor antagonists produce profound deficits in attention and memory through blockade of cholinergic neurotransmission (5). Null mutation of the gene coding the acetylcholine M1 muscarinic receptor in mice produced deficits in memory and a reduction in long-term potentiation in response to theta burst stimulation in the hippocampus (5). Hanisch and colleagues (6) demonstrated that IL-2 inhibited acetylcholine release from rat hippocampus by more than 50% of the control level, whereas other cytokines, such as IL-1, IL-6, and IFN- α , failed to modulate acetylcholine release. Therefore, there is a possibility that increased IL-2 in pneumonia might induce cognitive dysfunction by inhibiting acetylcholine release in the central nervous system. Further studies are necessary to test this hypothesis, as a confirmation could produce a target for the development of new pharmacological