Editorial

The changing natural history of COPD: summary from the American Thoracic Society Meeting 2016

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Notable Harvard professor and expert in chronic obstructive pulmonary disease (COPD), Dr. Bartolome Celli delivered a historical review about the origins of COPD and its natural history. In the historical perspective, Dr. Celli reminded the audience of the importance of respiration, commenting that respiration is the essence of life and that death is defined in part by the absence of respiration. During a 72-year lifespan it is estimated that a human breathes 223 million liters of air. Worldwide, biomass fuel exposure remains the most common cause of COPD (1). Biomass exposure has been present since 1.9 million BC and is nearly as old as human kind. Currently, however, people around the world continue to use biomass fuels quite commonly (1). Dr. Celli reminded us that tobacco smoking occurred in the Americas for thousands of years before the arrival of the Europeans, and that the tobacco plant was a gift of the Americas to the Old World of Europe. Despite longstanding exposures to biomass fuels and tobacco by humans, the first described patient with emphysema was in 1808 by Baillie where emphysema was noted in an autopsy specimen of a 74-year-old patient. Bronchitis was first described in 1814 by Badam which also coincided with the invention and utilization of the stethoscope. In 1846, spirometry was developed by Hutchinson, followed by the sphygmomanometer in 1893, ECG in 1903 and Chest X-ray in 1895. The definition of COPD was coined by Tiffeneau in 1947 with the familiar manifestations described in 1965 of emphysema and chronic bronchitis becoming integrally part of the pathophysiology of COPD. In 1964, Eriksson described for the first time, alpha-1 antitrypsin deficiency: a manifestation of autodigestion of the lung due to an imbalance of proteases of the lung.

Dr. Celli transitioned to discuss the natural course of the forced expiratory volume in 1 second (FEV1), reminding us, humorously, that COPD is defined as a disease that is not responsive to bronchodilators, but the treatment of choice remains bronchodilators. He highlighted the Fletcher and Peto curve, first published in 1977 (2), which is undoubtedly used quite often in clinics around the world to illustrate the importance of smoking cessation. The curve depicts the decline of FEV_1 over time. Various declining curves ensue depending on the smoking history of the individual, with the person with the most accumulated history of smoking losing lung function at the most precipitous rate. This popular, highly utilized graph was based on 792 men who were followed for 8 years. For non-smokers, FEV_1 declines 17.6 and 19.6 mL/year amongst females and males, respectively. In actuality however, for many smokers, lung function decline is not as dramatic as in the Fletcher and Peto graph. There are several important clinical outcomes of patients with COPD. Only 18% of the 792 followed by Fletcher and Peto exhibited a dramatic decline in FEV_1 (2), while, for others, FEV_1 does not worsen precipitously. In the Understanding Potential Long Term Impact on Function with Tiotropium Trial (UPLIFT), there was a post-hoc analysis done on 356 patients with COPD less than or equal to 50 years of age. These patients were considered to be in GOLD IV, with a mean FEV_1 of 1.24L (39% predicted) (3). There are also those who have lungs that are smaller in size than others in similar age cohorts but without COPD, a group Dr. Celli referred to as those in utero with developmental abnormalities leading to "poor assembly" of the pulmonary system. He posed the provocative question: is COPD a disease of infancy that one then diagnoses in adulthood (4)?

Dr. Celli then moved on to discuss the determinants

of gains and losses of lung function, e.g., lung function development in children and predictors of decline in adults. Low lung function in early infancy and during childhood years predicts decreased lung function in adulthood (5). Childhood disadvantages of having a predisposition for acquiring obstructive lung disease include a history of parental asthma, childhood asthma (6), and frequent childhood respiratory infections. In a *New England Journal of Medicine* article (4), long term improvements in air quality were associated with significant positive effects on lung function growth in children. Dr. Celli noted that current smoking, males with emphysema, a low BMI, lower CC16 (an anti-inflammatory protein) levels (7), lack of treatment for COPD, COPD exacerbations, particularly with a prolonged recovery (8), and environmental exposures portend a higher risk for larger declines in lung function. He went on to discuss the possibility of innate lung regeneration and challenged the dogma regarding COPD and the irreversibility of lung function decline. In some studies, GOLD stage of severity remained stable and some initially in GOLD IV even reverted to GOLD III, a less severe stage. In some COPD studies, between 8–30% of patients actually showed improvement in lung function. Thus, a significant proportion of patients enrolled in COPD trials do not have the originally accepted notion of ongoing precipitous lung function decline.

Dr. Celli then went on to describe the importance of co-morbidity in COPD and shared common pathways which he described as a comorbidome which consists of a genome with a transcriptome, proteome, metabolome that can then be separated into endotypes: an inflamed phenotype (blue bloater), or the implosive phenotype (emphysema), along with interactions with the environment. Dr. Celli highlighted the need to investigate the mechanisms of lung function improvement in those who had improvement in lung function. There has been an explosion of scientific literature on COPD. In 1973 there were 250 published papers, while in 2015 there were 6,000. COPD accounts for about 5% of deaths in the world (9). However, there is hope as worldwide smoking prevalence is decreasing. Dr. Celli cited the 10 COPD Commandments (10):

(I) Help to eliminate smoking and environmental pollution;
(II) Suspect COPD in cases of dyspnea, cough or chronic expectoration;
(III) Confirm the diagnosis. Perform spirometry;
(IV) Quantify dyspnea, BMI, functional capacity and exacerbation risk;
(V) Identify co-morbidities particularly heart disease, cancer, osteoporosis, depression, and gastroesophageal reflux;
(VI) Promote vaccination;
(VII) Promote exercise;
(VIII) Start patient-specific treatment;
(IX) Supervise the correct use of inhalers and other medications;
(X) Establish a follow-up plan and measure response to treatment.

Dr. Celli emphasized that COPD is here to stay but great advances have been made. Although accelerated loss of lung function is important in pathogenesis, there should be a new focus on determinants of lung function gain. Pharmacotherapy enables us to get the upper hand; however, it is clear that further research is needed. His analogy with art is illustrative: we as physicians are the artists of medicine. We paint our painting on our patients with the knowledge of the science. We can indeed strive to and continue to help our patients feel better.

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Footnote

Conflict of Interest: Dr. Liang is a sub-investigator for AstraZeneca, and Actelion however these relationships are not relevant to this article.

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