Is Chronic Obstructive Pulmonary Disease a Disease of Aging?

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Abstract

Chronic obstructive pulmonary disease (COPD) is a disease that usually presents clinically at an advanced age, after years of smoking cigarettes. It is usually believed that aging and its biological consequences are important mechanisms in the disease pathogenesis. This concept has maintained the focus of studies on COPD in old-age individuals. Here we analyze the possible role of aging from a different point of view and introduce different concepts that might be considered useful additions to the understanding of the disease. Essentially, we propose and show evidence that COPD is a disease of the young susceptible smoker that progresses over time and manifests in older age because we live longer and not so much because of the effect of aging itself; we examine the concept of cell senescence, the basis of tissue aging, and how stressors like the ones produced by smoking can accelerate cell senescence with all of its untoward consequences in COPD. We thus finally suggest that COPD might accelerate aging rather than be a consequence of it. In conclusion, we suggest that COPD could be considered a disease of the predisposed young individual that manifests clinically in old age because we live longer, with all of its consequences.

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Aging is currently, in a sense, a new and perhaps artificial phenomenon. We have, in Western countries, so effectively beaten nature, infections, bad hygiene, bad nutrition, and other factors so that our life expectancy has gone up from 49 years in 1900 to 78 years in 2010, and 20 years of this gain have occurred in the last 70 years (www.gapminder.org). It is difficult to say whether we are supposed to do this, i.e. age more than before, but we are certainly seeing the consequences. But what is aging? Evolutionary considerations suggest that aging is caused by a multiplicity of mechanisms, and it seems that a life-long accumulation of molecular damage underlies the aging process [1]. Such damage is intrinsically random in nature, but its rate of accumulation is regulated by genetic mechanisms for maintenance and repair. As cell damage accumulates, cells undergo a senescence that contaminates other nearby cells in the microenvironment, and this has effects on the body as a whole and is eventually manifested as age-related frailty, disability, and disease [2–4].

It is obvious that this biological aging affects all functions of the body, and the lungs are a perfect example. Respiratory function increases progressively from birth to early adulthood and then falls with age to values seen in youth. A fine example is provided by the values of the elastic recoil of the lung and obviously the FEV₁. Anatomically, air spaces enlarge, a change often thought to

represent old-age emphysema. However, authorities like William Thurlbeck [5], a studious investigator of emphysema, have maintained that this is not so, but that the alveolar ducts simply enlarge, a phenomenon which Thurlbeck [5] named duct ectasia.

Cells do not like aging either. They become senescent and go into cycle arrest or go into apoptosis easily and have difficulty being replaced [6]. Neither repair works well and obviously these changes (we should probably not call them abnormalities since they are part of the biology of 'normal' aging) exacerbate any insult or injury the lung, or any other organ, might suffer. Aging of the immune system, the so-called immunosenescence [7], is not helpful either since it induces a loss of protective immunity that is accompanied by a background of chronic inflammation probably induced by the senescent cells themselves. This inflammation causes more DNA damage, which in turn accelerates cell senescence and aging [4].

Similar alterations can be seen in other organs, probably accounting for the increased prevalence of one-time infrequent diseases. Obviously exposure to external agents (in part new ones like cigarettes or pollution secondary to industrialization, or excesses like richer, more elaborate foods) has not helped because stressors like the ones previously mentioned, acting through oxidative stress and/or inflammation, can induce and accelerate cell senescence with all of its consequences [4, 8].

Another important consideration is that chronic slowly progressing diseases, or diseases that necessitate long-term exposure to an agent in order to develop, were much less frequent when life expectancies were much shorter. Good examples of these diseases are chronic obstructive pulmonary disease (COPD) and cancer. Let us look at COPD. The age of the patients we see with COPD is high, i.e. 60–80 years if they are lucky, and the severity of COPD worsens as they get older, especially if smoking continues, hence the emphasis on COPD being a disease of aging. But is it due to aging, meaning the biological changes which accompany aging, or does it develop because we live longer? We would contend that there is a fine distinction between the two. By 'aging', we mean all of the biological changes that accompany normal aging. Living longer means that there is more time to do all kind of things, like take more trips, learn to play bridge, get married again, and smoke more, but it also allows more time for a chronic indolent progressive disease to manifest itself. Obviously the normal biological changes expected with aging are present and play a part, but living longer is probably just as important, if not more so, because it pro-

Fig. 1. Lung function decline vs. age in 3 hypothetical smokers. The FEV₁ values after ±40 years of smoking are shown. The loss of function/year in each case is indicated. The vertical lines represent the life expectancy in the year 1900 (48 years), the years 1970–1975 (58 years), and the year 2011 (78 years). The effect of 'living longer' on the FEV₁ can be appreciated.

vides time for the disease and the 'aging' changes to develop.

What do we mean by this? We mean that COPD is a disease that starts most likely soon after the initiation of smoking, in the susceptible smoker, and takes years to develop as a symptomatic disease that requires medical attention. Most likely the same smoker would not have developed a severe debilitating COPD 50, 70, or 80 years ago because they would not have had the time. They probably would have succumbed at a much younger age to other diseases, likely cardiovascular ones, which are prevalent among younger smokers (possibly also having mild unrecognized COPD) [9, 10], but, because they did not live long enough, they never developed the symptoms that would have brought them to seek medical attention and would have resulted in their eventual demise due to severe COPD.

Let us consider 3 individuals of the same age with the same smoking history and the same FEV₁ of 3.5 l at age 25 years (fig. 1). Now, at 65 years of age, patient 1 has an FEV₁ of 2.5 l, patient 2 has an FEV₁ of 1.9 l, and patient 3 has a FEV₁ of 0.5 l. Patient 1 has lost 25 ml/year, patient 2 has lost 40 ml/year, and patient 3 has lost 75 ml/year during 40 years of smoking. The fact is that it took patient 3 forty years to develop the severe disease, probably

because of a special predisposition, or other circumstances. The disease started years before medical advice was sought at age 65, but the patient lived long enough for the FEV₁ to fall low enough to become disabling. Can we call this a disease of aging, meaning secondary to the biological changes of aging? Should it not rather be considered a disease of the young that manifests itself late in life, if the patient lives long enough? It is now evident that in young adults a considerable percentage of subjects (3.5–5%) already has mild to moderate COPD, and this is evidence that the disease develops, in the young smoker, earlier than is usually believed [11, 12]. It should be pointed out that, when trying to diagnose possible COPD in young smokers, it is important to use the FEV₁/FVC percent predicted since using FEV₁/FVC <70% would undoubtedly underdiagnose the presence of airflow obstruction [13]. Furthermore, a proper diagnosis of obstruction is paramount since airflow obstruction in young adults (low FEV₁/FVC), in addition to smoking, is highly predictive of a low lung function in middle age [14, 15]. This concept is by no means new; Petty [16] and others have argued it for decades. However, it has been mostly forgotten and replaced by the new emphasis on aging. We believe that paying attention to the younger smoker should be a priority. It could teach us a lot about the pathogenesis and effective treatment.

It is thus clear that COPD is a disease that starts in the predisposed young smoker and manifests itself symptomatically in old age, if reached. It is the inexorable decline of lung function over many years, provoked by the constant smoking insult in the susceptible smoker, that eventually results, in the old smoker, in an irreparable situation, i.e. severe COPD, in which the lung is well beyond treatment or repair [17]. However, we keep on focusing on this terminal phase of the disease and devise treatments to improve the condition. We obviously have to do so in order to alleviate symptoms and, if possible, improve the mortality. But are these treatments effective? Several treatment trials with different drugs and drug combinations have been published showing that patients 'with COPD' have a lower number of exacerbations per year, an improved quality of life, and almost a reduction in mortality [18, 19].

For some reason, in these studies the assessment of the treatment response has been done in patients with COPD, according to the GOLD guidelines, but without considering separately the different stages (II, III, and IV) of the disease. The GOLD working group has made great efforts to classify COPD by its severity, which might imply dif-

ferent individual predispositions, risk factors, and abilities to dampen inflammation, promoting a total or partial evasion of COPD, as we recently discussed [20]. Can patients with COPD (previous) GOLD stages II, III, and IV be considered a single homogeneous population and be analyzed together? We do not think so. Furthermore, the conclusions of studies that consider mild, moderate, and severe COPD together can be misleading, as post hoc analyses of these studies seem to point out.

Post hoc analyses are usually concerned with finding patterns or relationships between subgroups of sampled populations that would otherwise remain undetected and undiscovered. Although post hoc analyses are sometimes called by critics 'data dredging', ultimately the information they provide could be essential for the formulation of better, more efficient a priori hypotheses and research designs. Regardless these possible limitations, post hoc subgroups analyses in these COPD treatment trials demonstrate that pharmacological treatments can improve the symptoms, exacerbation frequency, rate of FEV₁ decline, and mortality in individuals with stage II and stage III COPD, but in most cases not in patients with very severe stage IV COPD. These findings are not surprising since, as we pointed out before, the lungs of patients with very severe COPD are well beyond treatment or repair. However, it seems that our treatments can help in the milder, perhaps earlier stages of COPD, which is certainly an important message to take in account [21, 22]. Does this mean that a younger smoker who has reached moderate COPD, and could be losing function fast, would respond to treatment? Possibly, but we need to find out.

As has been said many times before, we pneumologists should follow the example of cardiologists. They do not treat terminal hypertensive heart disease and strokes, the final phase of severe hypertension. They identify and treat hypertension at the very early stages, hence preventing the terminal severe complications of chronic hypertension. Of course asymptomatic hypertensive subjects do not seek medical attention. Instead, good long-term studies about the development and early approach to the treatment of hypertension have been designed and have revealed how to treat and thus prevent many terminal life-threatening hypertensive events, saving lives and money.

We pneumologists are still trying new treatment approaches and even devising new drugs, at a high cost, and doing research on the severe stage of COPD in which the lungs are terminally destroyed and the small airways are gone or narrowed beyond repair, or combining all COPD

stages together. Obviously the results are not good in severe COPD cases, but these treatments seem to help in mild and moderate cases. It appears that the emphasis on the terminal stages of the disease has brought us to a sort of dead end. Maybe it is time to rethink our approach.

What can we do to learn more about the disease and possibly improve its treatment?

(1) The first step should be the identification of the population at risk in an earlier phase of the disease (think hypertension!). We know that smokers who develop COPD start losing function at a young age, soon after they start smoking, and this loss of function is highly predictive of airflow obstruction in middle age [14, 15]. Furthermore, the progression toward COPD in younger smokers is a continuous and gradual process [11]. The identification and study of this population would facilitate the understanding of the mechanisms of the disease at its beginning and the creation of more effective treatments.

(2) Maybe we should start thinking about the 'evasion' of rather than the development of COPD. It is well accepted that an abnormal inflammatory response with a strong adaptive immune component is an important pathogenic factor for COPD [23, 24]. However, most smokers evade the development of COPD, regardless of how much they smoke, via an active process that dampens this inflammatory response [20]. Obviously smokers that go on to develop COPD have been unable to dampen the cigarette smoke-induced inflammation. Perhaps it is time to put some money and effort into finding out why

some smokers fail to control the inflammatory response and go on to develop severe COPD.

(3) We might even look at aging and COPD from a different perspective. The 'disposable soma' theory of aging [1] considers that a life-long accumulation of molecular damage underlies the aging process. Keeping the soma going via constant repair requires constant effort, effort that in the long run is not warranted, and thus programming for survival ultimately fails and this results in aging. But stressors, like inflammation, oxidants, and others found in COPD, can directly induce and accelerate cell senescence with all of its consequences. It could then be argued that, due to the production of constant stresses that induce cell damage and eventual senescence, COPD might be directly responsible for accelerated aging, with all its untoward effects, rather than being a consequence of aging.

Perhaps it is time to change our strategy and pay attention to young/middle-aged smokers, try to find them, and learn about the disease at its beginning, while it is becoming established. We could learn a lot more about the disease mechanisms, its treatment, and even its prevention at that stage. Interestingly enough, at that early stage in the disease the maligned FEV₁ would still be the best predictor, or call it biomarker if you wish. Furthermore, the decrease or lack of a decrease in FEV₁ is the gold standard to find the biological biomarkers we all seek.

Thus COPD is, in our view, a disease of the young smoker, not a disease of aging. It is a disease of the predisposed young individual that manifests clinically in old age because we live longer, with all of its consequences.

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