# COPD 2020: changes and challenges

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### INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a major global health problem due to its high prevalence (about 10% of the adult population), rising incidence (related in part to the aging of the population) and very significant associated personal, social, and economic costs (23a). The World COPD Day (November 18, 2020) is organized by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) in collaboration with health care professionals and COPD patient groups throughout the world to raise awareness about COPD and to improve COPD care throughout the world (23a). To contribute to this goal, here we review the main changes that occurred over the past few years in our understanding of COPD to stimulate further research in the challenges that this new knowledge opens.

# THE STARTING POINT: THE FLETCHER AND PETO MODEL

More than forty years ago, back in 1976, Fletcher, Peto, Tinker, and Spizer published a book that presented the results of a population study with a stratified random sample of 792 men (mostly skilled manual or clerical) aged 30-59 years working in West London who were seen every six months during eight years (23). Results were summarized a year later by two of these authors in a brief review (22), in what came to be known as the "Fletcher and Peto model of COPD." According to this model, COPD was a self-inflicted disease by tobacco smoking that occurred in so-called susceptible smokers and was characterized by an accelerated lung function decline with age (22). Until recently, this model has constituted the "holy grail" of our understanding of the pathogenesis of COPD. Yet, as discussed below, it has several gaps that need to be considered to get to a better understanding of it (12). Each of them opens new questions that actually are opportunities for research with the goal to develop a new COPD paradigm.

### AN UPDATED PATHOGENIC PARADIGM

Epidemiological, clinical, translational, and basic research over the past decade or so has generated new knowledge that drives a new understanding of the pathogenesis of COPD (12). Below we review some of these research results with the caveat that this is not meant to be a systematic and comprehensive review. We selected those topics that, in our opinion (likely biased), may have a bigger impact on our understanding of COPD.

# COPD Beyond Smoking: A Dynamic Understanding of COPD (GxExT)

Epidemiological studies show that between 20 and 40% of all COPD patients in the world are never smokers (34) so, although smoking continues to be the main COPD risk factor, other conditions have to be considered too. Very recently, Kohansal et al. (16) reported in a large general population study in Austria that there are many other different environmental risk factors associated with low lung function, that they vary greatly in different age bins, and that they interact and accumulate with age in complex ways (Fig. 1) (15). These observations indicate that COPD (and most likely all human diseases) is not only the end result of geneenvironment interactions (GxE) but that the time axis also needs to be considered here (GxExT), since the same GxE may have different effects at different ages (8). As illustrated in Fig. 2, the dynamic interplay over a lifetime of two major biological phenomena-organ development, maintenance, and repair, on the one hand, and cumulative tissue injury and aging on the other-determines health, disease, and life expectancy (8). Of course, each of these two biological phenomena depends in turn on the GxE that occur in any particular individual at an specific age range, so their relevance (slopes in Fig. 2) can vary (for better or worse) in different individuals and in the same individual over time (8).

Of note here, COPD is not a monogenic disease and, as it is the case in all complex diseases, the genetic contribution is variable. Recently, Hobbs et al. (25) have reported the results of a genetic association study in a large number of COPD patients (n = 15,256) and controls (n = 47,936), with replication of select top results ( $P < 5 \times 10^{-6}$ ) in 9,498 cases and 9,748 controls. A combined meta-analysis identified 22 loci associated at genome-wide significance with COPD but their respective odds ratio (OR) was small (25), indicating that several of them have likely to co-occur to increase the risk of developing the disease when exposed to one or more environmental risk factor(s) at the appropriate time window (8) (Fig. 2).

### *Life Does Not Start at the Age of 25 Years: Lung Function Trajectories*

Traditionally, the Fletcher and Peto model has been interpreted as lung function decline starting at the age of 25 years

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Fig. 1. Environmental factors (represented here as first-neighbor networks) related to low lung function [as indicated by a forced expiratory volume in one second (FEV<sub>1</sub>) value < lower limit of normal (LLN); center yellow node in each network] at different age-bins. Each node represents one variable node size is proportional to the prevalence of that variable in that specific age- bin, and node color indicates variable category. Links between nodes indicate the existence of a significant (P < 0.05) relationship between them, thicker edges indicate lower P values and line type indicates whether the odds ratio (OR) is >1 (continuous) or <1 (dashed). For further explanation, see text. [Reproduced from Breyer-Kohansal et al. (15), with permission.]

(22). This has been a misinterpretation of their data since the authors themselves acknowledged that early life events resulting in a reduced peak lung function in early adulthood can also lead to COPD later in life with a normal lung function decline (22). However, this wise insight was basically ignored until five years ago when Lange et al. (27) showed in three large independent cohorts (Framingham Offspring Cohort, the Copenhagen City Heart Study, and the Lovelace Smokers Cohort) that about half of COPD patients followed the traditional enhanced lung function decline proposed by Fletcher and Peto, whereas the other half never achieved normal peak lung function at the age of 25 years and developed COPD with a normal rate of lung function decline, as hypothesized (and then forgotten) by Fletcher and Peto (22). More recent research showed that poor lung development is not a rare event since it occurs in 4-12% of individuals in the general population (9, 17, 28) and leads to the concept of lung function trajectories in COPD (9, 12). As illustrated in Fig. 3, in healthy subjects, lung function increases after birth due to lung growth and maturation (30), achieving a peak at around 25 years of age [earlier in females (26)] that is followed by a relatively short plateau and a mild decrease thereafter (7). This normal trajectory can be altered by changes occurring in each of these phases, development, plateau, and decline (9), for better or worse since it is also possible to identify a supranormal trajectory (17) (Fig. 3), whose implications are still unclear (12). Understanding how GxExT leads to different lung function trajectories is a colossal challenge and a great research opportunity for the young generation of scientists interested not only in COPD but in lung health in general. This is important because low lung function in early adulthood is not only a risk factor for COPD but it is also associated with a higher prevalence and about a decade earlier incidence of cardiovascular and metabolic diseases and premature death (Fig. 4) (13). This is why the European Respiratory Society has recently launched a Clinical Research Collaboration (CADSET) to investigate the biological basis and clinical consequences of different lung function trajectories through life (10).

# Heterogeneity of COPD: Endotypes, Biomarkers, and Treatable Traits

As its name indicates, COPD has been traditionally considered a "disease." However, it is now clear that there is ample heterogeneity in its clinical presentation (6) and pathogenic mechanisms (12, 20), so it is probably more appropriate to consider it a "syndrome" than a disease (19). To address this



Fig. 2. Interplay between two major pathogenic mechanisms of human diseases, including chronic obstructive pulmonary disease (COPD): organ development, maintenance and repair (green triangle) and cumulative tissue injury and aging (red triangle). Dashed arrows (green and red) indicate that the slope of these lines can vary (for better or worse) in different individuals. This interplay over a lifetime determines health and life expectancy (top triangle). For further explanation, see text. [Reproduced from Agustí and Faner (8), with permission.]

complexity, the concept of COPD "phenotypes" was proposed ten years ago (24). According to this proposal a "clinical COPD phenotype" would be single or combination of disease attributes that describe differences between individuals with COPD as they relate to clinically meaningful outcomes (symptoms, exacerbations, response to therapy, rate of disease progression, or death) (24). This proposal was later questioned because it does not really represent real life, since phenotypes are mutually exclusive whereas patients can simultaneously present one or more so-called "treatable traits" (1). This latter concept was



launched in 2016 as a precision medicine strategy for the management of patients with airway disease (not only COPD) that is "label-free" that is, it is agnostic of the traditional diagnostic labels of COPD, asthma, or bronchiectasis (5). It is based on the identification of "treatable traits" in each patient through "phenotypic" recognition or deep understanding of the critical causal pathways ("endotypes") (5). Importantly, treatable traits can coexist in the same patient and change with time (spontaneously or as a result of treatment) (5). There are pulmonary and extrapulmonary treatable traits as well as behavioral/social risk factors that merit individual attention and potential treatment (5). Elucidating the more relevant treatable traits in practice and their interactions, their biological basis, the biomarkers that can help to identify existing endotypes in each patient, and the tailored treatment for each of these traits requires further research (4, 11, 14, 21, 29, 32, 36, 37). For instance, circulating blood eosinophils have recently been identified as a reliable biomarker to guide treatment with inhaled corticosteroids in patients with COPD (35).

## A NEW INTEGRATED PARADIGM

The old view that COPD is a single disease caused by smoking and characterized by an accelerated rate of lung function decline that occurs in old (mostly) males (22, 23) is outdated and incomplete. The evidence briefly summarized above supports a different pathogenic paradigm that considers that COPD is a polygenic disease (25) with a significant epigenetic component (18, 31, 33), that there are multiple environmental risk factors (including smoking and many others) that interact and accumulate through life in complex ways (Fig. 1), hence modulating organ development, maintenance, repair, and aging (Fig. 2) and eventually determining a range of potential lung function trajectories through life (Fig. 3) and the occurrence of early multimorbidity and premature death (Fig. 4). This opens many questions that need basic, translational, clinical, and epidemiological research but also opportunities for a better prevention and management of the disease. Of particular relevance in our opinion is the need for preventing the disease (beyond smoking) by acting on many of the environmental risk factors depicted in Fig. 1, and, according to the lung function trajectories concept (Fig. 3), to intervene much earlier in life. It is likely that early interventions can be much more effective when the network of

Fig. 3. Lung function trajectories from birth to death. For further explanation, see text. [Reproduced from Agustí and Hogg (12), with permission.]

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Fig. 4. From left to right, prevalence and incidence of cardiovascular and metabolic diseases and all-cause mortality in participants in the Framingham Offspring Cohort stratified by their lung function [normal versus low (forced expiratory volume in one second, FEV1, <80% of the reference value in early adulthood)] at age 25. For further explanation, see text. [Reproduced from Agustí et al. (13), with permission.]

interactions that may develop through life is not fully developed yet (Fig. 1) (3).

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#### AUTHOR CONTRIBUTIONS

A.A., C.V. and R.F. prepared figures; A.A., C.V. and R.F. drafted manuscript; A.A., C.V. and R.F. edited and revised manuscript; A.A., C.V. and R.F. approved final version of manuscript.

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