

09 May 2019

COMMENT

THE LANCET RESPIRATORY MEDICINE

## DO WE NEED A NEW CLASSIFICATION OF AIRWAY DISEASES?

### THE CASE AGAINST

Alvar Agusti<sup>1</sup>, Ian D Pavord<sup>2</sup>

1. Respiratory Institute, Hospital Clinic, IDIBAPS, Univ. Barcelona and CIBER  
Enfermedades Respiratorias, Spain

2. Respiratory Medicine Unit and Oxford NIHR Respiratory Biomedical  
Research Centre, Nuffield Department of Medicine, University of Oxford,  
Oxford, UK

**Correspondence:** Dr. Alvar Agusti, Respiratory Institute, Hospital Clinic. Villarroel 170,  
08036 Barcelona. Tel: +3493 227 1701. E-mail: [AAGUSTI@clinic.cat](mailto:AAGUSTI@clinic.cat)

**Funding:** none

**Key-words:** Allergy, Asthma, Chronic Bronchitis, Emphysema, Precision medicine,  
Personalized medicine, Smoking, Taxonomy.

**Words** (excluding references): 913 words; **References:** 15; **Tables:** 0; **Figures:** 1.

How do we classify human diseases (i.e., its *taxonomy*) is at the core of clinical practice because it guides their diagnosis and treatment <sup>1</sup> The current classification of human diseases was proposed by Sir William Osler in the XIX century based on the main organ from which symptoms and signs originate and the histopathology findings in that organ. <sup>2</sup> This classification has been (and still is) useful in clinical practice but has a number of important limitations <sup>3</sup>. First, most human diseases are still diagnosed (and treated) as if they were homogeneous entities, which is clearly not the case <sup>4</sup>. For instance, the chronic airway diseases, asthma and chronic obstructive pulmonary disease (COPD) are now recognized to be complex and often overlapping diseases, that require a much more detailed pathogenic characterization in order to provide the best possible treatment to an individual patient <sup>1</sup>. A second concern is that the Oslerian classification of diseases does not take into consideration susceptibility states or preclinical disease manifestations. For instance, since the landmark study of Fletcher and Peto it is clear that not all individuals are equally susceptible to the damaging effects of smoking <sup>5</sup> and, more recently, it has become apparent that both asthma and COPD can originate very early in life. <sup>7-9</sup> The need for a more specific approach to the diagnosis and, above all, treatment of chronic airway diseases has become clearly apparent in recent years, particularly as we enter a new era of “biologic treatment” of these diseases, which, hopefully, will lead to a much more precise clinical management of these patients <sup>1,10</sup>.

For these reasons, some authors advocate that we need a new classification of human diseases for the XXI century. <sup>3,4</sup> Yet, it is not clear what this should look like. Loscalzo *et al* proposed that, in the post-genomic era, diseases need to be reclassified bottom-up

(i.e., from genes to symptoms) in contrast to the top-bottom Oslerian classification, which starts with their clinical presentation and then investigate the underlying biologic mechanisms to the extent possible<sup>3</sup>. They argue, compellingly, that the analysis of the complex molecular networks that underlie human diseases (i.e., network medicine) will help in this endeavour<sup>3,12</sup>. We fully agree that this strategy is likely to provide novel biological information, validate relevant biomarkers and provide novel therapeutic targets within a research framework. However, we doubt it will work in clinical practice. We argue that keeping the Oslerian classification, whose clinical utility has been clearly time-honoured, still provides the practicing clinician the necessary conceptual framework to establish an *initial syndromic* diagnosis from which to work up later the individual peculiarities of every patient<sup>13</sup>. In this context, the Oslerian diagnosis should be viewed as the *starting* point of the diagnostic process and not the final one.

Figure 1 compares the research and clinical practice approach to human diseases. From a research perspective, we can consider that the *Exposome* (i.e. the cumulative environmental exposures an individual encounters through life) interacts with the genetic background (*Genome*) of the patient through a number of multi-level, complex biological networks. As a result, one or more *Endotypes* (i.e., subtype of a disease defined functionally and pathologically by a molecular mechanism or by treatment response) might emerge or disappear dynamically through life, from pregnancy to death. The presence of these endotypes in any given individual may be revealed by one or more *biomarkers* (i.e., a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or

biological responses to a therapeutic intervention). Biomarkers do not necessarily need to be molecular markers. They can also be functional variables (e.g., lung function), imaging findings (e.g. presence of emphysema on computed tomography) or other clinically relevant measurements (please note that this is why biomarkers in Figure 1 are now positioned in between the research and clinical practice environments).

From a clinical perspective, the diagnostic process began by the process of *pattern recognition*<sup>19</sup>. Indeed, physicians have long been trained to integrate different levels of potentially relevant information (symptoms, signs, results from both biological tests and imaging techniques, among others) to identify different clinical patterns which actually form the basis of the current Oslerian classification of diseases<sup>2</sup>. For the reasons argued above, we believe that this is a necessary but insufficient step in the clinical management of patients with chronic airway diseases. The specificity of this step can be augmented by the use of validated biomarkers (see above) and/or the recognition of a *Clinical phenotype* (*i.e.*, a single or combination of disease attributes that describe differences between individuals as they relate to clinically meaningful outcomes<sup>20</sup>). Both lead to the final identification of so-called *Treatable Traits* (*i.e.*, therapeutic target identified by “phenotype” or “endotype” recognition through validated biomarker(s)<sup>10,21</sup>). We think that this approach will combine “*the best of two worlds*”, being of value to researchers and clinicians. On the one hand, clinicians will not lose our rich heritage of pattern recognition in practice, which greatly helps to start (not finish) the diagnostic process. On the other, patients will benefit from a more precise management thanks to the advances made in research, which will hopefully

92 help to estimate the risk-benefit ratio of any given treatment in an individual patient.  
93 These treatable traits can easily be presented in the form of a “control panel” to the  
94 practicing physician with the help of electronic medical records and artificial  
95 intelligence approaches <sup>22</sup> .  
96

97   **REFERENCES**

- 98    1.       Pavord ID, Beasley R, Agusti A, et al. After asthma – redefining airways diseases.  
99    A Lancet commission *Lancet* 2017; **391**(10118): 350-400.
  
- 100   2.       Vanfleteren LEGW, Kocks JWH, Stone IS, et al. Moving from the Oslerian  
101    paradigm to the post-genomic era: are asthma and COPD outdated terms? *Thorax*  
102    2014; **69**(1): 72-9.
  
- 103   3.       Loscalzo J, Kohane I, Barabasi AL. Human disease classification in the  
104    postgenomic era: a complex systems approach to human pathobiology. *Mol Syst Biol*  
105    2007; **3**: 124.
  
- 106   4.       Kola I, Bell J. A call to reform the taxonomy of human disease. *Nat Rev Drug*  
107    *Discov* 2011; **10**(9): 641-2.
  
- 108   5.       Fletcher C, Peto R. The natural history of chronic airflow obstruction. *Br Med J*  
109    1977; **1**(6077): 1645-8.
  
- 110   6.       Martinez FD. Early-Life Origins of Chronic Obstructive Pulmonary Disease. *New*  
111    *England Journal of Medicine* 2016; **375**(9): 871-8.
  
- 112   7.       Lange P, Celli B, Agusti A, et al. Lung-Function Trajectories Leading to Chronic  
113    Obstructive Pulmonary Disease. *New England Journal of Medicine* 2015; **373**(2): 111-  
114    22.

- 115 8. Agustí A, Noell G, Brugada J, Faner R. Lung function in early adulthood and  
 116 health in later life: a transgenerational cohort analysis. *The Lancet Respiratory*  
 117 *Medicine* 2017; **5**(12): 935-45.
  
- 118 9. Agustí A, Bafadhel M, Beasley R, et al. Precision medicine in airway diseases:  
 119 moving to clinical practice. *European Respiratory Journal* 2017; **50**(4): 1-13.
  
- 120 10. Barabasi AL, Gulbahce N, Loscalzo J. Network medicine: a network-based  
 121 approach to human disease. *Nat Rev Genet* 2011; **12**(1): 56-68.
  
- 122 11. Celli BR, Agustí A. COPD: time to improve its taxonomy? *ERJ Open Research*  
 123 2018; **4**(1).
  
- 124 12. Agusti A. The disease model: implications for clinical practice. *European*  
 125 *Respiratory Journal* 2018; **51**(4).
  
- 126 13. Han MK, Agusti A, Calverley PM, et al. Chronic Obstructive Pulmonary Disease  
 127 Phenotypes: The Future of COPD. *American Journal of Respiratory and Critical Care*  
 128 *Medicine* 2010; **182**(5): 598-604.
  
- 129 14. Agusti A, Bel E, Thomas M, et al. Treatable Traits: Toward Precision Medicine of  
 130 Airway Diseases. *Eur Respir J* 2016; **47**: 410-9.
  
- 131 15. Agusti A, MacNee W. The COPD control panel: towards personalised medicine  
 132 in COPD. *Thorax* 2013; **68**: 687-90.

133 **FIGURE LEGEND**

134 **Figure 1.** Comparison of the research and clinical practice approaches to human  
135 diseases. For further explanations, see text.

136