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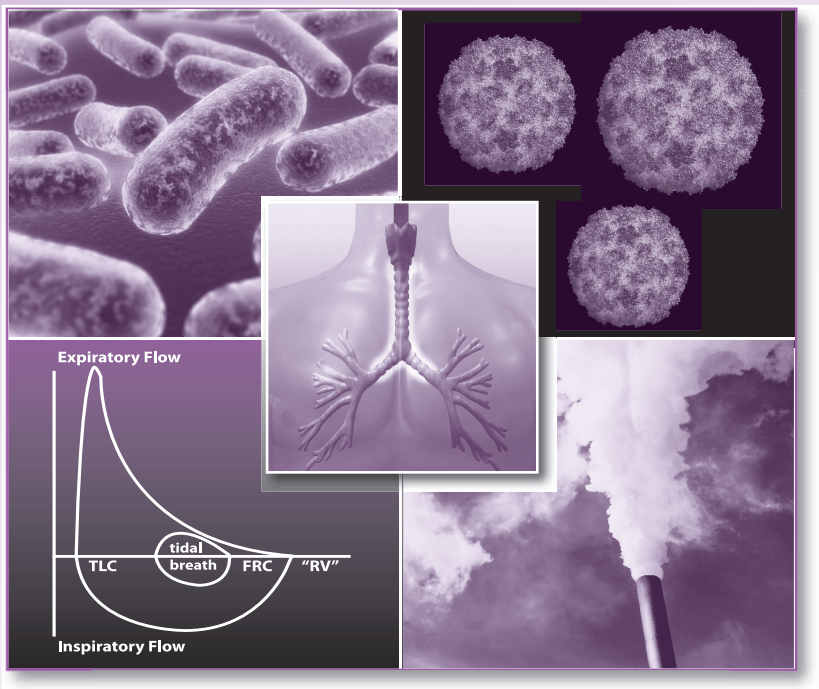
Chronic Obstructive Pulmonary Disease Exacerbations



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Chronic Obstructive Pulmonary Disease Exacerbations

LUNG BIOLOGY IN HEALTH AND DISEASE

Executive Editor

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Chronic Obstructive Pulmonary Disease Exacerbations

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Introduction

The first, or certainly one of the first, definition of chronic obstructive pulmonary disease (or chronic obstructive lung disease as it is also called) was proposed in the 1959 Ciba Foundation Symposium on "the definition and classification of chronic obstructive pulmonary emphysema and related conditions." Since, the journey of COPD (or COLD) has been remarkable; but the 1980s marked the beginning of a multinational research effort that has been most productive. Quite broad and diversified, this effort has focused on the pathology and possible treatments of this disease. Although it was recognized that the disease is irreversible and relentlessly progressive, delaying this progression and maintaining the best possible quality of life of the patients has been among the major goals.

As the editors of this volume point out in their Preface, it was reported "in the late 1990s that COPD exacerbations are an important determinant of health-related quality of life in COPD (patients)" and also of the speed and severity of the disease progression. Exacerbations are defined by a sudden worsening of the symptoms, and they may be life threatening in many instances. Yet, if appropriately managed, the patients may return to the same symptom and physiological levels as before the exacerbation. Much research at the fundamental as well as clinical levels has been conducted with the aim of understanding what triggers these exacerbations, how to prevent them, and how best to treat them. Indeed, much has been learned that can assist the practicing physicians and benefit the patients.

This volume titled *Chronic Obstructive Pulmonary Disease Exacerbations* and edited by Drs. Jadwiga A. Wedzicha and Fernando J. Martinez presents the most up-to-date knowledge about the mechanism and treatment of COPD exacerbations to the readership of this new volume. Contributors from North America, Europe, Asia, and the South Pacific report their experience on the basis of years of successful research and clinical care. All of the contributors to this volume are known and respected pioneers in their respective fields.

In their Preface, the editors predict that this volume will stimulate more investigations to better understand and manage COPD exacerbations. Of particular interest is the interdependency of COPD exacerbations and comorbid conditions. But, in addition, and most important, this book can help general practitioners make use of research outcomes, which can benefit their patients.

The series of monographs Lung Biology in Health and Disease has presented many volumes on COPD over the years, with the first monograph on this topic

published in 1978. Directly, or indirectly, the knowledge they have reported has contributed to better care of COPD patients. This volume, however, has very special messages that specifically address how to manage the worsening of the disease and, hopefully, maintain a better quality of life. As the Executive Editor of this series, I am grateful to the editors and the contributors for the opportunity to introduce this volume to our readership.

Claude Lenfant, M.D.
Vancouver, Washington, U.S.A.

Preface

It is now recognized that exacerbations are a major cause of the global morbidity and mortality associated with chronic obstructive pulmonary disease (COPD). They are also a cause of hospital admission and readmission and thus lead to considerable health care costs. Following the observation in the late 1990s that exacerbations are an important determinant of health-related quality of life in COPD, there has been considerable interest in the study of exacerbations. Over the last few years, studies have shown that exacerbations contribute to disease progression and mortality and that they are an important outcome for new therapies in COPD.

For this book, we have assembled international experts, both clinicians and scientists with an interest in COPD exacerbations, to review critically the current literature and provide up-to-date reviews on the various issues as well as highlight the many controversies and bottlenecks in the study of exacerbations.

COPD exacerbations are episodes of worsening of symptoms, accompanied by inflammatory and physiological changes. In this book, we have firstly covered issues of definition, diagnosis, and epidemiology and then presented a number of chapters on the many diverse mechanisms, including the role of bacterial and viral infection to the development of respiratory failure, associated with COPD exacerbations, which are heterogeneous events. It is now recognized that systemic inflammation and comorbidity play a prominent role in COPD and affect exacerbation outcome. Environmental issues, including air pollution, are difficult to study, but there is considerable recent information on their relation to COPD exacerbation in this book.

Both management of the acute exacerbation and exacerbation prevention have been addressed in separate sections. We now have a wide variety of pharmacological and nonpharmacological interventions to treat and prevent exacerbations, yet many clinicians are confused about how to use these therapies and for which patients. The section on exacerbation management will also cover new models of care for COPD exacerbations, integration of home and hospital care for these patients, and, importantly, end-of-life issues. Studies investigating new therapies for either reducing severity or frequency of COPD exacerbations have proved problematic to design and often conduct, with specific statistical considerations, and we have addressed these issues in the last section of the book.

We know that you will very much enjoy reading this book and that it will stimulate many of you to further study this fascinating and important topic. In view of their significance, COPD exacerbations will be the subject of much future research and clinical trial activity. The book will be useful as a reference to all clinicians involved in the care of patients with COPD.

Finally, we would like to thank all the authors for agreeing to write the chapters and contributing to this high quality book. We also express our gratitude to Sandra Beberman and her team for allowing us to proceed with this project and supporting us throughout the commissioning and production.

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Contents

Introduction Claude Lenfant . . . . . *iii*
Preface . . . . . *v*
Contributors . . . . . *vii*

Part I: Introduction

1. Definitions and Severity of Exacerbations ***1***
Stephen I. Rennard and Nancy Kline Leidy
I. Introduction ***1***
II. Definitions ***2***
III. Standardizing Measurement of Exacerbations ***7***
IV. Heterogeneity and Phenotypes of Exacerbations ***11***
V. Summary ***12***
References ***13***

2. Epidemiology of COPD Exacerbations ***15***
Andrea K. Johnston and David M. Mannino
I. Introduction ***15***
II. Methods ***16***
III. Exacerbation Frequency ***16***
IV. Frequent Vs. Infrequent Exacerbators ***18***
V. Lung Function Impairment ***19***
VI. Emergency Care ***19***
VII. Hospitalizations ***23***
VIII. Comorbidities ***23***
IX. Mortality ***23***
X. Conclusions ***24***
References ***24***

3. Differential Diagnosis of COPD Exacerbations ***27***
Peter M. A. Calverley
I. Introduction ***27***
II. Clinical Features of COPD Exacerbations ***27***

III. Principal Alternative Diagnoses 28
IV. Clinical Approach to Differential Diagnosis 33
V. Conclusion 35
References 35

Part II: Mechanisms and Pathophysiology

4. Symptom Changes at COPD Exacerbation 39
Terence A. R. Seemungal
I. Introduction 39
II. Common Symptoms at Exacerbation 40
III. Time Course of Symptom Changes 41
IV. Physiological Basis of Dyspnea and Symptom Recovery 43
V. The Concept of Recovery of Symptoms and Lung Function 44
VI. Changes in Symptoms and Airway and Systemic Inflammation 46
VII. Frequency of Symptom Changes and Recurrent Exacerbations 46
VIII. Symptom Changes and New and Colonizing Strains of Bacteria 46
IX. Symptom Changes and Viruses 47
X. Symptom Changes and Environmental Factors 48
XI. Symptoms and Treatment 48
XII. Conclusion and Recommendations 49
References 49

5. Airway Pathology at Exacerbations 53
Graziella Turato, Simonetta Baraldo, Kim Lokar-Oliani, Renzo Zuin, and Marina Saetta
I. Introduction 53
II. Airway Pathology During Exacerbations 54
III. Summary 58
References 58

6. Airway and Systemic Inflammatory Markers at Exacerbation 61
John R. Hurst
I. Introduction 61
II. Changes in Airway and Systemic Inflammatory Markers at Exacerbation of COPD 61
III. Utility of Changes in Airway and Systemic Inflammatory Markers at Exacerbation of COPD 67

IV. Summary *69*
Abbreviations *70*
References *71*

7. Pathophysiology of Acute Exacerbations of COPD *75*
Chris M. Parker and Denis E. O'Donnell
I. Introduction *75*
II. Pulmonary Function *75*
III. Dynamic Hyperinflation *79*
IV. Effects on Gas Exchange *80*
V. Cardiovascular Effects *82*
VI. Mechanisms of Dyspnea During Exacerbation *83*
VII. Conclusions *85*
References *85*

8. Systemic Consequences of COPD Exacerbations *89*
Scott S. Wagers, Karin Groenewegen, and Emiel F. Wouters
I. Introduction *89*
II. Systemic Inflammation and Oxidative Stress *89*
III. Skeletal Muscle Wasting *91*
IV. Exercise Intolerance *92*
V. Weight Loss *92*
VI. Osteoporosis *93*
VII. Diabetes *94*
VIII. Accentuated Thrombosis *94*
IX. Depression *94*
X. Summary *95*
References *95*

9. Mechanisms of Respiratory Failure in COPD Exacerbations *101*
Borja G. Cosio and Roberto Rodríguez-Roisin
I. Introduction *101*
II. Mechanisms of Hypoxemia and Hypercapnia *102*
III. Natural History of Hypoxemic Respiratory Failure *105*
IV. Effects of Oxygen Breathing *105*
V. Response to Bronchodilators *107*
VI. Response to Glucocorticoids *108*
VII. Conclusion *109*
References *109*

10. Role of Respiratory Viral Infection at Exacerbation *111*
J. K. Quint and Jadwiga A. Wedzicha
I. Introduction *111*
II. Detection of Viruses *111*

III. Mechanisms of Virus-Induced Exacerbations and Host Response . . . 114
IV. Susceptibility to Viral Infection . . . 114
V. Rhinovirus . . . 115
VI. Coronavirus . . . 115
VII. Influenza and Parainfluenza . . . 116
VIII. Adenovirus . . . 116
IX. Respiratory Syncytial Virus . . . 117
X. Human Metapneumovirus . . . 117
XI. Viruses in Stable COPD . . . 117
XII. Summary . . . 118
References . . . 118

11. Do Airway Bacteria Cause COPD Exacerbations? . . . 121
Himanshu Desai and Sanjay Sethi
I. Introduction . . . 121
II. Pathogenesis of Infectious COPD Exacerbations . . . 121
III. Role of Airway Bacteria in COPD Exacerbation . . . 122
IV. Conclusions . . . 127
References . . . 127

12. Interactions of Airway Pathogens and Inflammatory Processes . . . 129
Marco Contoli, Gaetano Caramori, Brunilda Marku, Alberto Papi, and Anita Pandit
I. Introduction . . . 129
II. Pathogens and Inflammation . . . 130
III. Conclusion . . . 135
References . . . 135

13. Comorbidity at Exacerbation of COPD . . . 139
David McAllister, John Maclay, William Macnee, and Roberto Rabinovich
I. Introduction . . . 139
II. Respiratory CoMorbidity . . . 139
III. Cardiovascular CoMorbidity . . . 140
IV. Anemia and Hyperglycemia . . . 143
V. Conclusion . . . 143
References . . . 143

14. Environmental Causes of Exacerbations . . . 147
Fanny WS Ko and David SC Hui
I. Introduction . . . 147
II. Environmental Factors Associated with AECOPD . . . 147

III. Summary 153
References 153

15. Exacerbations in Alpha-1-Antitrypsin Deficiency 157
R. A. Stockley
I. Introduction 157
II. Potential Role of the Neutrophil 157
III. Proteinase Cascade 158
IV. Alpha-1-Antitrypsin Deficiency 160
V. Management 164
References 165

16. Animal Models of COPD—Current Status of an Evolving Field . . . 169
Paul J. Christensen, W. Bradley Fields, Christine M. Freeman, and Jeffrey L. Curtis
I. Introduction 169
II. Murine Models of COPD 170
III. Genetic Models of Emphysema 175
IV. Autoimmune and Other Murine Models not Involving CSE . . 180
V. COPD Models in Nonmurine Species 180
VI. Summary and Future Directions 182
References 183

17. Comparison of Asthma and COPD Exacerbations 191
Joseph Footitt, Annemarie Sykes, Patrick Mallia, and Sebastian L. Johnston
I. Introduction 191
II. Epidemiology of Exacerbations 191
III. Etiology of Exacerbations 192
IV. Mechanisms of Exacerbations 195
V. Pathophysiology of Exacerbations 198
VI. Conclusion 199
References 199

Part III: Impact of Exacerbations

18. Risk Factors for Hospital Admission 203
Judith Garcia-Aymerich
I. Methodological Introduction 203
II. Risk Factors of Hospital Admission for a COPD Exacerbation 208
III. Conclusion 213
References 214

19. Effect of Exacerbations on Disease Progression and Mortality ... 217
James J. P. Goldring and Gavin C. Donaldson
I. Introduction ... 217
II. Studies That Have Investigated the Effect of Exacerbations on Disease Progression ... 218
III. Studies That Have Investigated the Mechanisms Behind FEV_1 Decline in COPD Exacerbations ... 221
IV. Evidence from Other Diseases That Lung Function Decline is Related to Infection and Inflammation ... 222
V. Effects of Exacerbation on Mortality ... 222
VI. Summary ... 223
References ... 223

20. Health Economic Consequences of COPD Exacerbations ... 225
Marc Miravitlles
I. Introduction ... 225
II. Costs of COPD ... 225
III. Economic Impact of Exacerbations ... 226
IV. Conclusions ... 230
References ... 231

Part IV: Management of the Acute Exacerbation

21. Use of Bronchodilators and Mucolytics at COPD Exacerbations ... 233
Wim Janssens and Marc Decramer
I. Introduction ... 233
II. Bronchodilators ... 233
III. Mucolytics ... 236
References ... 238

22. Corticosteroids in the Management of Acute Exacerbations ... 241
Dennis E. Niewoehner and Kathryn Rice
I. Introduction ... 241
II. Evidence for Clinical Efficacy ... 241
III. Dose, Duration, and Route of Administration ... 243
IV. Adverse Effects of Short-Term Systemic Corticosteroids ... 245
V. Mechanisms of Response to Corticosteroids in COPD Exacerbations ... 247
VI. Summary ... 248
References ... 248

23. Antibiotic Therapy at COPD Exacerbations *251*
Robert Wilson and Mitzi Nisbet
I. Introduction *251*
II. Meta-Analysis of Placebo-Controlled Antibiotic Trials in COPD *252*
III. Bacterial Infection Causing Exacerbations of COPD *253*
IV. Aims of Antibiotic Therapy at Acute Exacerbations of COPD *255*
V. Current Guidelines for Antibiotic Treatment at COPD Exacerbations *257*
VI. Patient Characteristics Which Might Influence Choice of Antibiotic *258*
VII. Other Issues *260*
VIII. Length of Antibiotic Course and Dosage *260*
IX. Biomarkers *261*
X. Atypical Bacterial Infections *261*
XI. Viral and Bacterial Coinfection *261*
XII. Future Research *262*
References *262*

24. Noninvasive Ventilatory Support in Acute Exacerbations of COPD *267*
Stanley D. W. Miller and Mark W. Elliott
I. Introduction *267*
II. NIV in Acute COPD *267*
III. NIV vs. IMV *268*
IV. Indications for NIV in AECOPD *268*
V. Where Should NIV be Given? *269*
VI. Contraindications *270*
VII. Choice of Ventilator Type *270*
VIII. Interfaces *271*
IX. Monitoring the Patient on NIV *271*
X. Predictors of Success and Outcome *272*
XI. Conclusion *274*
References *274*

25. Invasive Mechanical Ventilation and Weaning at COPD Exacerbation *279*
Antonio Anzueto, Andrés Esteban, and Fernando Frutos-Vivar
I. Introduction *279*

II. Impact of Exacerbations on Mortality 279
III. Physiological Impairment in Acute Respiratory Failure in Patients with COPD Exacerbation 281
IV. Respiratory Failure and Supplemental Oxygen 282
V. Weaning 287
VI. Conclusion 289
References 290

26. Oxygen Therapy and Exacerbations 293
A. G. Davison, Ronan O'Driscoll, and Luke Howard
I. Introduction 293
II. Blood Gas Pathophysiology in AECOPD 293
III. Critical Hypoxemia in Normal Subjects 295
IV. Levels of Hypoxemia Found in AECOPD 295
V. Hypercapnia 296
VI. Effect of Continuous High Concentrations of Oxygen in AECOPD 297
VII. Effect of Intermittent Oxygen Therapy or Stopping Oxygen in AECOPD 297
VIII. High-Flow Low-Concentration Oxygen Using a 24–28% Venturi Mask 297
IX. Use of Nasal Cannulae (Prongs) to Provide Controlled Oxygen 298
X. Recent Studies on AECOPD 298
XI. Oxygen Alert Cards and 24 or 28% Venturi Masks for COPD Patients Who have had an Episode of Hypercapnic Respiratory Failure 299
References 299

27. End-of-Life Issues and COPD Exacerbations 303
Anita K. Simonds
I. Mortality and Morbidity of Severe Acute Exacerbations 303
II. Symptom Burden 304
III. Conclusions 310
References 311

28. Novel Models of Care for COPD Exacerbations 313
Martyn R. Partridge
I. Introduction 313
II. Alternative Methods of Care That Have Been Described and Studied 315
III. Conclusion 322
References 322

29. Physiotherapy at Exacerbation of COPD *325*
Rachel Garrod and Christine Mikelsons
I. Introduction *325*
II. Positioning *325*
III. Breathing Techniques *326*
IV. Early Pulmonary Rehabilitation *327*
V. Early Rehabilitation of Intubated Patients with COPD *327*
VI. Airway Clearance Therapies *328*
References *330*

30. COPD Exacerbation and Pulmonary Rehabilitation *333*
William D-C. Man and Michael I. Polkey
I. Introduction *333*
II. PR in the Prevention of Acute Exacerbations *333*
III. PR in the Treatment of Acute Exacerbations *334*
IV. Summary *337*
References *337*

Part V: Prevention of COPD Exacerbation

31. Pharmacological Prevention of COPD Exacerbations *341*
Bianca Beghé, Fabrizio Luppi, and Leonardo M. Fabbri
I. Introduction *341*
II. Smoking Cessation *342*
III. Vaccines *342*
IV. Antioxidant and/or Mucolytic Agents *343*
V. Bronchodilators *343*
VI. Theophylline *345*
VII. Phosphodiesterase Inhibitors *346*
VIII. Inhaled Corticosteroids *346*
IX. Combination Therapy *347*
X. Importance of Comorbidities and Their Treatment *350*
XI. Conclusion *351*
References *351*

32. Self-Management in Prevention and Early Intervention of Exacerbations *357*
Jean Bourbeau, Erik W. M. A. Bischoff, and Maria Sedeno
I. Introduction *357*
II. Self-Management in COPD *358*
III. Self-Management to Prevent Exacerbation *360*
IV. Self-Management and Early Treatment *361*
V. Practice Advice in Using an Action Plan *364*

VI. Conclusion 365
VII. Needs for Research 365
References 366

33. Immunological Interventions 369
Phillippa J. Poole
I. Introduction 369
II. Influenza Vaccination 369
III. Pneumococcal Vaccination 373
IV. Haemophilus Influenzae Vaccination 373
V. Other Immunostimulants 373
VI. Conclusion 374
References 374

34. Oxygen Therapy and Home Mechanical Ventilation 377
Nathaniel Marchetti and Gerard J. Criner
I. Introduction 377
II. Oxygen Therapy 377
III. Home Mechanical Ventilation 380
IV. Conclusion 384
References 384

Part VI: Issues for Studies of COPD Exacerbations

35. Design of Trials for COPD Exacerbations 387
Fernando J. Martinez, Meilan Han, and Jeffrey L. Curtis
I. Introduction 387
II. Therapeutic Trials of AECOPD 387
III. Conclusions 400
References 400

36. Statistical Considerations for COPD Exacerbation Trials 407
Shawn D. Aaron
I. Introduction 407
II. Distribution of the Data 407
III. Approaches to Determining Rates 408
IV. Counting Individual COPD Exacerbations 409
V. Reporting Exacerbations 411
VI. Summary 414
References 414

37. Future Developments in Acute Exacerbations of COPD *417*
Peter J. Barnes
I. Introduction ***417***
II. Inflammatory Mechanisms ***417***
III. Novel Therapeutic Approaches ***420***
IV. Conclusions and Future Directions ***424***
References ***425***

Index 429

1
Definitions and Severity of Exacerbations

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I. Introduction

Acute exacerbations of chronic obstructive pulmonary disease (COPD) are relatively frequent events that have a major impact on patient well-being, both at the time of the event and in the long term. Recent observations have clearly shown that therapeutic interventions can, to some extent, prevent exacerbations as well as modify their course. This has created both the opportunity and the imperative to develop more effective interventions to mitigate the burden of acute exacerbations, which, in turn, has created a need for precise and operationally tractable definitions. Crucially, a definition of exacerbations is needed that permits the events to be adequately quantified, both in terms of frequency and severity. This has proven difficult for a variety of reasons. First, exacerbations are heterogeneous. In addition, they are primarily a patient-reported event. Objective confirmatory tests based on biomarkers have yet to be satisfactorily developed. The problem of definition is exacerbated by the distinction between definition and diagnosis. As pointed out by Prof. Gordon Snider:

> *It is important to realize the difference between the definition of a disease and its diagnostic criteria (1). The defining characteristics of a disease are the common properties specifying the group of abnormal persons on whom the description of the disease is based. The definition of a disease is important in communication.*
>
> *Diagnostic criteria are features of the disease chosen from its description that are found by empirical research to best distinguish the disease from others which resemble it. The diagnostic criteria may or may not include features of the defining characteristics and frequently include features that do not appear in the definition (1).*

Current efforts to establish a consensus definition of acute exacerbation of COPD have been primarily developed for one of three purposes: (*i*) understanding the etiology and mechanisms of exacerbations, (*ii*) determining the impact of exacerbations on the course of COPD, and (*iii*) determining if interventions alter the incidence or the clinical course of exacerbations. These studies are most often conducted in preselected populations that have a high incidence of events. Defining exacerbations in this population is a different problem

than that of diagnosis in a more general problem. Distinguishing between an acute exacerbation of COPD and events that may resemble it to varying degrees and in varying ways is a major clinical problem that has received very little attention (see chap. 3 for a more detailed discussion).

The current chapter will review the history of definitions of acute exacerbations of COPD, discuss the various types of definitions, and review current attempts to develop definitions that will facilitate the understanding of these events and expedite the development of therapies to mitigate them.

II. Definitions

Definitions can take various forms, reflecting their underlying purpose. Conceptual definitions are based in theory; while they may inform empirical and clinical practice, they often reflect a limited evidence-based understanding. Empirical definitions, in contrast, are operational. They permit development of quantitative instruments to describe events and are useful for hypothesis testing. In the case of exacerbations of COPD, which are patient-reported events, instruments to detect exacerbations should be based on the conceptual definition and patient descriptions and experiences of these events and show evidence of reliability, validity, and responsiveness. Practical applications in clinical settings require definitions that are empirically grounded and validated and applicable to individuals, in contrast to populations.

There are four dimensions of exacerbations to consider when defining exacerbations. Definitions that summarize the essential features of exacerbations inform the development of empirical methods for capturing the presence or *frequency* of these events. Descriptions of variability in magnitude inform operational definitions of *severity* and *duration*. Duration, in turn, involves two important components of exacerbation that are of clinical and empirical interest: *recovery* and *resolution*. Finally, the *impact* of an exacerbation includes its effect on health status, morbidity, mortality, and trajectory of disease.

A. Conceptual Definitions of Exacerbation

A number of groups and professional organizations have developed conceptual or working definitions of exacerbations on the basis of consensus in an effort to clarify the concept and guide research efforts to understand exacerbations and treatment effects and to inform clinical practice (Table 1). The definition proposed by the 1999 Aspen Lung Conference that refers to a *sustained* worsening of the patient's condition, implying an event that lasts at least 24 hours (2) while worsening *beyond normal day-to-day* variations, seeks to differentiate the severity of exacerbations from "bad days" or acute, short-term episodes of cough, breathlessness, or other manifestations within a given day. This group also proposed that mild exacerbations are characterized by an increased need for medication (which patients manage themselves), moderate are those for which the patients seek medical assistance, and severe are those in which the patient or caregiver recognizes clear and/or rapid deterioration and requires hospitalization.

The American Thoracic Society and the European Respiratory Society proposed definition was similar, specifying dyspnea, cough, and sputum as characteristic features (3). The first GOLD (Global Initiative for Chronic Obstructive Lung Diseases) report of 2001 did not define exacerbation, but described the signs and symptoms associated with the event (4). Breathlessness was identified as the main symptom, with wheezing, chest tightness,

Table 1 Consensus Definitions of Exacerbation

Source	Definition
British Thoracic Society, 1997	A *worsening* of the previous stable situation. Important symptoms include increased *sputum purulence*, *sputum volume*, *dyspnea or wheeze*, *chest tightness, and fluid retention.*
Aspen Lung Conference, 1999	A sustained *worsening* of the patient's condition, from the stable state and beyond normal day-to-day variations, that is acute in onset and necessitates a change in regular medication in a patient with underlying COPD.
GOLD, 2001[a]	*Increased breathlessness*, the main symptom of an exacerbation, is often accompanied by *wheezing and chest tightness*, *increased cough and sputum*, *change of the color and/or tenacity of sputum*, *and fever*. Exacerbations may also be accompanied by a number of nonspecific complaints, such as *malaise*, *insomnia*, *sleepiness*, *fatigue*, *depression*, *and confusion*. A *decrease in exercise tolerance*, *fever*, and/or new radiological anomalies suggestive of pulmonary disease may herald a COPD exacerbation. An *increase in sputum volume and purulence* points to a bacterial cause, as does a prior history of chronic sputum production
ATS/ERS, June 2004	An event in the natural course of the disease characterized by a *change* in the patient's baseline *dyspnea*, *cough*, *and/or sputum beyond day-to-day variability* sufficient to warrant a change in management.
NICE, Feb 2004	A sustained *worsening* of the patient's symptoms from their usual stable state, which is beyond normal day-to-day variations and is acute in onset. Commonly reported symptoms are *worsening breathlessness*, *cough*, *increased sputum production*, *and change in sputum color*. The change in these symptoms often necessitates a change in medication.
GOLD, 2006 (Rabe et al. 2007)	An event in the natural course of the disease characterized by a *change* in the patient's baseline *dyspnea*, *cough, and/or sputum* that is beyond normal day-to-day variations, is acute in onset, and may warrant a change in regular medication in a patient with underlying disease.

[a]Description rather than definition.
Italicized text highlights characteristic features.
Abbreviation: COPD, chronic obstructive pulmonary disease.

sputum tenacity, and fever as frequent accompanying features, with or without other nonspecific complaints. The description also pointed to reduction in exercise tolerance, fever, or radiologic anomalies as potential indicators of exacerbation onset. The most recent GOLD definition is similar to the 1999 Aspen Conference definition and again specifies changes in dyspnea, cough, and/or sputum as the characteristic or cardinal features of the event (5,6). It also specifies that the change *may* be sufficient to warrant a change in treatment, recognizing unreported events and permitting clinic contact for evaluation with an option to maintain current therapy.

On the basis of this work, there is consensus that an exacerbation of COPD is a state characterized by a worsening of the patient's underlying condition, including, but not limited to, an increase in respiratory symptoms. The requirement of a change in treatment varies across definitions and may actually reflect severity rather than define the event. With this definition in mind, how have exacerbations been measured in clinical research?

B. Empirical Definitions of Exacerbations

Event-Based

In epidemiologic studies and some prevention-targeted clinical trials, frequency of exacerbation has been defined in terms of health care utilization. This approach, often referred to as an event-based definition, operationalizes exacerbation in terms of the number of clinic visits, emergency room or urgent care visits, or hospitalizations for an exacerbation. These events are not only patient-initiated, but require action as determined by the physician. Time to first visit or hospitalization has also been used as an outcome in clinical trials testing interventions designed to prevent or reduce the frequency of exacerbations. The use of a change in treatment, generally oral steroids or antibiotics, as an additional criterion for the presence of an exacerbation has been varied.

Health care events have also been used as a proxy for exacerbation severity. It has been suggested, for example, that exacerbations requiring an unscheduled clinic or emergency room visit are "moderate," and those requiring hospitalization are "severe" (2,7). The addition of systemic corticosteroids and/or antibiotics to maintenance therapies has been used to signify the presence of an exacerbation or to rate an exacerbation as "moderate" (7).

There are a number of relatively serious limitations associated with an event-based definition of exacerbation. First, the initial clinic contact and visit is initiated by the patient on the basis of his or her assessment of the episode. With as many as 50% of exacerbations unreported (8,9), event-based definitions seriously underestimate exacerbation frequency. Admission to hospital is directly related both to the underlying health of the patient and to health policy or coverage within a given country or region. Patients undergoing treatment in regions with relatively liberal admission policies will have more frequent and more "serious" exacerbations, while those in regions with conservative admission policies will have less frequent and/or fewer "serious" episodes. This bias has serious implications for prevalence estimates in epidemiologic studies, effect estimates in studies examining the link between exacerbations and disease trajectory, and site selection and treatment outcomes in clinical trials. Finally, this definition does not take into consideration, standardize, or control for, the patient or physician assessment of exacerbation, including its elements or magnitude using the features outlined in the consensus definition. Symptom-based methods attempt to address these limitations.

Symptom-Based

Attempts at characterizing exacerbations for empirical purposes are often traced back to definitions used by Anthonisen et al., who used an empirical definition to identify and classify exacerbations in a clinical trial designed to test the benefits of antibiotic therapy (10). In this study, exacerbations were defined in terms of symptoms and classified into three types: Type 1—presence of dyspnea, sputum volume, and sputum purulence; Type 2—presence of two of these three symptoms; and Type 3—presence of one of these three symptoms, with at

least one of the following findings: upper respiratory infection (sore throat, nasal discharge) in the previous five days, fever without other cause, increased wheezing, increased cough, or increase in respiratory rate or heart rate by 20% over baseline. Patients who experienced an increase in symptoms were to notify the center and were examined by a nurse-practitioner who determined whether the symptoms fulfilled these criteria, indicating that the patient was eligible for intervention as outlined in the study protocol.

Seemungal et al. extended this definition for the East London (U.K.) prospective cohort study, designed to understand causes and mechanisms of exacerbations of COPD (9). These investigators defined exacerbation as two new symptoms of COPD present for two days, as recorded on a diary card, one of which must be dyspnea, sputum volume, and/or sputum purulence. Other symptoms could also be present and included cough, wheeze, sore throat, nasal discharge, or fever (9).

Diary Cards. The definition put forth by Seemungal requires the use of a daily reporting system, generally in the form of diary cards, to establish baseline levels for the patient's health status and to detect change indicative of an exacerbation. Diary cards have been used in a significant number of prospective clinical studies and trials to document symptom severity and to identify unreported exacerbations. Unfortunately, there is substantial variability in the content and structure of these diaries. Although most cards include dyspnea, cough, and sputum, the actual items used to capture these symptoms vary greatly. For example, some measures of dyspnea ask patients to rate their breathlessness with one or more activities while others ask them to rate their shortness of breath on a scale of "none" to "maximum," with no reference to activity. Similarly, cough has been assessed as frequent or severe, or the extent to which it interferes with activity or sleep, while sputum evaluations may include one or more items referencing color, consistency, volume, or difficulty, or a single item asking patients to rate their sputum "production" from none to severe. This measurement variability makes comparison of information across studies virtually impossible and may account for some of the inconsistency in findings across otherwise similar investigations.

Although cross-study comparisons are difficult, examining the general content of diary cards across studies contributes to the consensus-building process. Dyspnea, cough, and sputum production have been included in virtually all diary cards. Additional symptoms include chest tightness or discomfort, sleep disturbance or nighttime awakenings, fatigue (using terms such as weariness, tiredness, or faintness), and activity, including activities of daily living (ADLs) and work. Key questions include the following: What is the core set of clinical indicators of an exacerbation that are experienced by the patient and that should be assessed in order to determine the presence, severity, and recovery pattern of an exacerbation? What combination of these indicators constitutes or is consistent with an exacerbation, particularly those that are unreported? And finally, are exacerbations heterogeneous, and are there "phenotypes" of exacerbations that reflect different sets of features?

Identifying an exacerbation through diary cards requires an algorithm based on the definition of exacerbation and its clinical indicators, and an accumulation of data to create confidence in the sensitivity of the algorithm. In the absence of a standard, Seemungal et al. as described above, defined exacerbation *a priori* as the presence for at least two consecutive days of increase in any two "major" symptoms (dyspnea, cough, sputum) or increase in one "major" and one "minor" symptom (8). The first of the days was taken as the day of onset. Symptoms were binary coded and summed to give a daily symptom score.

C. The Patient's Perspective

Results from qualitative studies and patient surveys can provide important insight into patient perspectives of exacerbation and further inform definitions and measurement. Qualitative research is a hypothesis generating empirical method involving focus groups or 1:1 interviews in which the words and phrases of the study participants, recorded and transcribed, serve as the data (11,12). Systematic analytical methods are applied to identify and cluster information, formulate themes, and summarize the findings. In the case of exacerbations, qualitative research can provide a rich source of information about patient descriptions of their experiences, the terminology they use as they refer to these events, the manifestations or attributes that define them, and the actions they may or may not take when they occur. A limited number of studies using this methodology to understand and define exacerbations from the patient's perspective has been reported to date (13–15).

In a multinational cross-sectional interview-based qualitative study by Kessler et al. of 125 patients with moderate to severe COPD, the most common terms patients used when referring to a worsening of their condition were "chest infection" (16%; $n = 20$), "crisis" (16%; $n = 20$), or an "attack" (6.4%; $n = 8$) (13). Only two patients understood what the term "exacerbation" meant. Despite the varied terminology, patients clearly understood the concept and were able to identify and describe their exacerbation experiences.

The seriousness with which patients view an exacerbation is evident in their terminology (crisis, attack), the description of dread and fear related to their occurrence, and the anxiety and concern that accompany them (14). Patients participating in individual interviews in a qualitative study by Adams et al. (13) ($n = 23$) described a "frightening change" that led to consultation with a physician (13). Patients in focus groups of experiences with acute exacerbations of chronic bronchitis (AECB) associated panic and dread with the onset of the "attack" (15). The sudden and alarming nature of these events led Celli to suggest that the medical community adopt the term "lung attack" (Celli B, personal communication, 2005)(16).

Patients have described warning signs of an onset of exacerbation, including breathlessness, fatigue or tiredness, cough, or—in a relatively small number of patients (10%)—pain (14). When these warning signs occurred, they initiate various forms of self-care, including taking additional medication or resting, with relatively few patients (18%) in the Kessler et al. study indicating they would contact their physician (14).

Manifestations of exacerbation described by patients include respiratory symptoms (breathing difficulty, changes in phlegm, increased cough, difficulty coughing up phlegm, coughing up blood, runny nose, sneezing, and wheeziness), changes in daily activity (slower, difficulty performing), systemic signs and symptoms (anorexia, exhaustion, feeling weak, generally unwell, dizziness, sweating, cramping pain, and "other" ("grey" color, headaches, unable to speak) (13). A significant reduction in activity is also a characteristic feature of exacerbations. Nearly all of the patients (90%; $n = 107$) in the Kessler et al. study reported an adverse impact on ADLs, with half of these patients indicating that they required additional help with tasks during exacerbations (14). Forty-seven percent of the patients ($n = 59$) reported that all activities were stopped, and a third (38%; $n = 47$) could do nothing at all. Over a third (39%; $n = 49$) reported being bedridden.

There is also qualitative evidence to suggest that there may be within-patient consistency in how exacerbations are manifested. Most patients (85%, $n = 106$) in the Kessler et al. study reported consistency in symptoms from exacerbation to exacerbation. In

contrast, it is unknown if those who report varying manifestations are experiencing different types of events. Quantitative assessment of these qualitative findings could assist phenotyping and further clarify definitions and testing targeted treatment.

Patient surveys can also provide insight into patient perception of exacerbations and why they may go unreported. Miravitilles et al. for example, conducted a telephone survey of 1100 subjects reporting symptoms consistent with COPD and/or taking medication for a respiratory problem other than asthma (17). Symptoms of exacerbation with the greatest impact on well-being were increased coughing (42%), increased shortness of breath (37%), increased fatigue (37%), increased sputum production (35%), increased frequency of chest pains (20%), and fever (13%). Serious activity limitations were also reported, with nearly half (45%) reporting having to stay in bed or on the couch all day.

D. A Consensus Definition

Across all of the work outlined above, there is general agreement that exacerbations of COPD are events or episodes in which patients experience a remarkable, sustained worsening of the primary respiratory manifestations of the disease (dyspnea, cough, and/or sputum) beyond normal daily variability. There is also general consensus that a patient may experience a worsening of one or any combination of these symptoms, and that this respiratory symptom or symptom complex may be accompanied by other nonrespiratory symptoms or signs of exacerbation. Specifying these additional signs and symptoms is likely to contribute to a better understanding of the full range of attributes associated with exacerbations, the variability in presentation across patients, possible consistency within patients, and the role-specific etiologic or mechanistic processes may play in this variability. Standardizing the evaluation and scaling of exacerbations through a common tool and metric will help further characterize and perhaps classify exacerbations, including the prodromal, acute, and recovery phases.

III. Standardizing Measurement of Exacerbations

The consensus regarding definitions can inform the development and selection of measurement tools for various types of studies including large, population-based epidemiologic and economic studies estimating the frequency and burden of exacerbations in a population, as well as clinical studies examining frequency, quality, and impact of exacerbations and the effect of interventions to treat or prevent these events.

In the absence of a standardized metric or biomarker for exacerbations, the determination of whether or not an exacerbation is present in any individual patient is made by both the patient and the clinician. The patient's decision is first, as the individual experiencing the change in his/her condition must make a judgment that the change is sufficiently different or serious to warrant either a change in self-care practice or contact with a health care provider. The clinician's determination is based on the patient's report of his/her condition in the context of the consensus definitions outlined above, and any additional data gathered through physical examination or laboratory testing that may suggest alternative explanations for the patient's change in health state. Determining the severity and duration (resolution) of exacerbations are also left to the judgment and discretion of the clinician and

patient, who may have different opinions. Clearly, there is a need for a common definition and standardized tool for evaluating exacerbations of COPD.

A. Patient-Reported Outcome Tools

Because exacerbations are defined in terms of signs and symptoms experienced by the patient, and the event itself is initially recognized and treated by the patient, either independently or with the assistance of a health care provider, they come under the rubric of a patient-reported outcome, or PRO. In the United States, this means that any tool used in a drug registration trial to evaluate the effect of treatment on frequency, severity, and/or duration of exacerbations must meet the criteria set forth in the Food and Drug Administration (FDA) draft guidance on patient-reported outcomes. This includes making certain the instrument is grounded in the patient's experience, using data gathered through focus groups and/or 1:1 interviews, and assuring that patients understand the tool and interpret it correctly using cognitive interviewing methodology. The latter includes an in-depth 1:1 interview with patients to evaluate their understanding of the directions, recall period, item stems, and response options to make certain the respondents are interpreting the tool as it was intended and in a manner consistent with the underlying concept being measured. Empirical evidence of reliability, including internal consistency and reproducibility, validity, and responsiveness to change, is also required.

The EXACT-PRO (Exacerbations of Chronic Pulmonary Disease Test—Patient-Reported Outcome) initiative was developed to address the need for a standardized, validated instrument to evaluate the frequency, severity, and duration of exacerbations. This project brought together international experts in COPD, clinical trial design, and measurement and representatives from the FDA to discuss the key elements of a tool to operationalize exacerbations for use in pharmaceutical trials and regulatory submissions with the potential for more widespread use by the clinical research community. The initiative was launched in 2006, with unrestricted sponsorship from multiple pharmaceutical companies. It began with a large qualitative study involving over 70 patients with COPD in focus groups and 1:1 interviews to determine the essential attributes of an exacerbation from the perspective of the patients themselves and formulate the structure and content of the EXACT measure (18).

Figure 1 shows a heuristic for understanding the evolution of an exacerbation from the patient's perspective based on the qualitative work. This heuristic is consistent with the consensus definition in that it shows a sustained worsening of the patient's underlying condition with rising levels of breathlessness, cough, and sputum production together with other signs and symptoms that improve over time. According to the qualitative data analysis, exacerbations of COPD can be defined as follows:

> An event characterized by a rapid, persistent (at least two or three days), and disconcerting increase in the frequency and severity of symptoms, including respiratory symptoms (difficulty breathing, cough with sputum, chest discomfort), feelings of being weak or tired, and sleep disturbance, with a dramatic reduction in activity. Improvement or recovery is gradual and resolution is often indicated by the resumption of normal daily activities.

The qualitative data gathered during Phase I of the EXACT-PRO initiative were used to develop a pool of 23 items to evaluate exacerbations of COPD. These items were

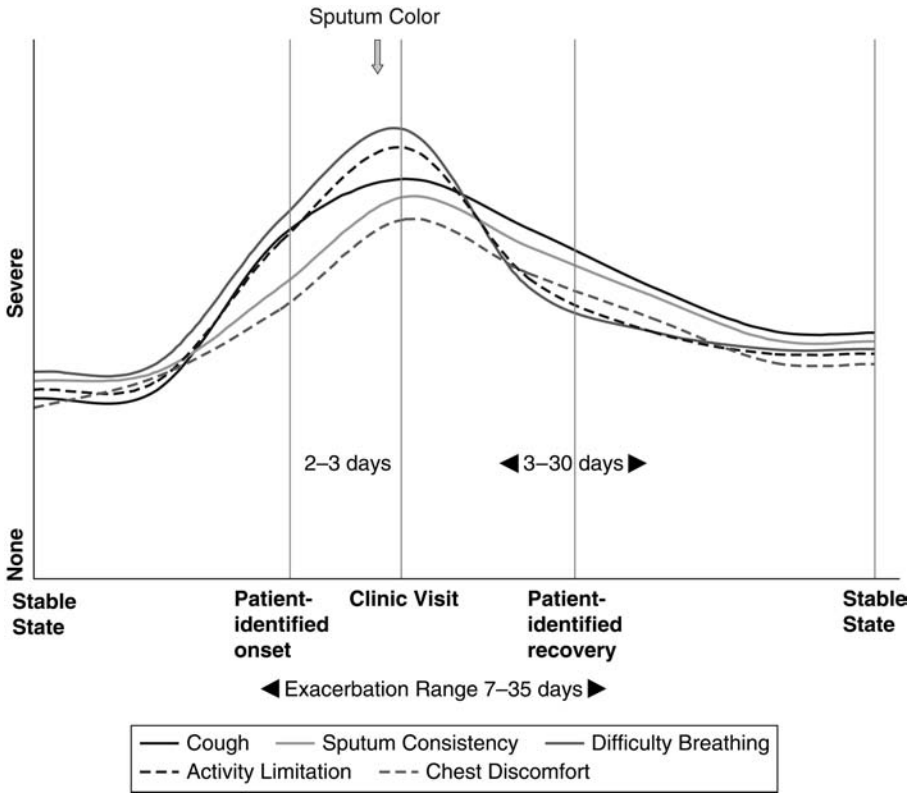

Figure 1 Qualitatively-based heuristic for depicting exacerbations of COPD.

subjected to an empirically-based item reduction process with reliability and validity testing in a prospective study. The study involved over 400 patients, 200 of whom experienced an exacerbation and 200 of whom were stable and had no clinic visit or hospitalization for an exacerbation during the previous 60 days. Patients completed the draft (23-item) tool daily using a personal data assistant (PDA). On the basis of this, nine items were eliminated. The final 14-item EXACT offers a comprehensive assessment during an exacerbation, evaluating breathlessness, cough and sputum, chest symptoms, difficulty with sputum, feeling tired or weak, sleep disturbance, and feeling scared or worried, and requires less than five minutes for patients to complete. A shorter tool made up of a subset of items from the EXACT is under development to ease patient burden during long-term prospective studies. This item subset is designed to signal the worsening of a patient's condition suggestive of an exacerbation and requiring a more comprehensive evaluation through the 14-item assessment. The entire process would be handled through PDA programming that would detect the signal and automatically display the additional items comprising the tool. Patients would complete the 14-item EXACT daily, until the score returned to the defined tolerance level, at which time the diary would convert back to the shorter subset of items. The PDA

could also be programmed to randomly administer the 14-item set to gather additional data throughout the study period.

The EXACT, therefore, is an instrument that is well designed to capture a patient-reported outcome dataset that can determine the incidence, severity, and duration of COPD exacerbations. The availability of a validated instrument with satisfactory measurement properties will greatly facilitate the evaluation of COPD exacerbations.

B. Laboratory Tests

While exacerbations are critically patient-reported events, the availability of laboratory tests for exacerbation would be a tremendous advance. There are several, nonexclusive uses for "tests" in the assessment of acute exacerbations of COPD. These include tests that could serve as defining features, as pathognomonic diagnostic points, and as gauges to quantify exacerbation severity. While no test currently available can be used for these purposes, much has been learned recently regarding the cellular and molecular mechanisms that underlie exacerbations and their physiologic consequences. These advances are reviewed in detail in other chapters (see chaps. 6 on inflammatory markers, 7 on physiologic changes, and 8 on systemic consequences). While all these represent potential objective tests for exacerbations, all share certain problems with regard to their use, which are highlighted here.

It is clear that acute exacerbations of COPD are, in most cases, inflammatory events. Increased inflammation can be gauged by increased neutrophils, cytokines, and inflammatory mediators in the sputum during exacerbations (19,20). Systemic inflammation is also supported by observation made in peripheral blood. Neutrophils show signs of activation and increased cytokines are readily observed (20–24). Importantly, the increase in cytokines is related to clinical features of the exacerbated patient (25). Moreover, the purulence of the sputum, which reflects local inflammation, is thought to be related to both clinical outcome and response to treatment (10,25). All these observations suggest that measures of inflammation have the potential to be useful biomarkers for COPD exacerbations. Unfortunately, many of these markers are also increased in stable COPD, with further increases during the acute event. As with symptoms, an acute event may be characterized by an increase from the "usual baseline." For these measures to be used to define events, it will be necessary to determine the magnitude of change that is meaningful. Similarly, it is likely that these measures are not specific to COPD exacerbations, as increased inflammation in the lung can result from other causes (e.g., pneumonia and systemic inflammation). This will complicate the diagnostic utility of inflammatory biomarkers. However, as current technology to assess inflammation provides readily quantifiable data, inflammatory measures are appealing as gauges of severity, if an event can be properly defined and diagnosed. Standardized PRO measures will facilitate the latter.

Increased respiratory rate in COPD patients can lead to dynamic hyperinflation (26). This may develop during an exacerbation due to an increased drive to breathe because of increased demand, anxiety, or other causes and may be independent of acute decrements in airflow, which would synergize to worsen the problem. Decrements in inspiratory capacity are likely to occur during acute exacerbations as improvement is observed with resolution (27,28). Thus, inspiratory capacity measurement is also an appealing "test" that could be used to assess exacerbations. As with measures of inflammation, however, dynamic hyperinflation is not specific to acute exacerbation; therefore, reductions in inspiratory capacity are likely to be more easily used as gauges of severity than as definitive diagnostic features.

Radiologic assessment has not usually been used to gauge COPD exacerbations. The major purpose of a chest radiograph in this clinical setting is to exclude another problem, such as pneumonia, which would preclude the diagnosis of an acute exacerbation (29). Advances in imaging of the lungs, however, have the potential to alter this approach. Aggressive diagnostic assessment has, in some studies, revealed the presence of pulmonary emboli in otherwise "unexplained" acute exacerbations (30). In addition, CT scanning can reveal evidence of pneumonitis when chest radiographs are normal, further confounding the distinction between an acute exacerbation and pneumonia (31). The ability of CT scanning to distinguish airway from alveolar disease (32) and to quantify dynamic changes on inspiratory and expiratory studies (33) suggests that this technology may have application to the assessment of acute exacerbations.

The application of "tests" to the assessment of COPD exacerbations is also complicated by the heterogeneity of exacerbations. For example, while most exacerbations are associated with inflammation, it is not clear that increased inflammation is present in *all* exacerbations. Of course, whether such "an-inflammatory" exacerbations are similar to or distinct from inflammatory exacerbations is also unknown. With the well-recognized etiologic and clinical heterogeneity of exacerbations, it seems plausible that biomarkers, physiologic, and radiographic assessments will be able to delineate among various types of exacerbations.

IV. Heterogeneity and Phenotypes of Exacerbations

Exacerbations of COPD are heterogeneous at several levels. The etiology may relate to viral or bacterial infection or to other causes (see chaps. 10 and 11). More importantly, individual patients may respond to an exacerbation differently. It seems likely that there will be underlying genetic differences that could contribute to clinical response, but few studies on this topic have been conducted. Patients also may respond differently because of their underlying pathophysiology. Individuals with greater heterogeneity in time constants (i.e., greater heterogeneity of obstruction across the various airways of the lung) should be more likely to develop dynamic hyperinflation and, therefore, should be more likely to experience dyspnea with increasing respiratory rate (34). Similarly, individuals with concurrent bronchiectasis may be expected to produce more sputum and be more likely to have chronic bacterial colonization, although this remains to be tested rigorously (20,35).

Patients with COPD are also heterogeneous with respect to their systems of social support. Those with able caregivers may have generally better care, particularly as their health status worsens. This may allow them to avoid some encounters with the health care system. Alternatively, better support may also allow patients to survive with otherwise more severe disease. Such individuals may necessitate greater intensity of intervention when an exacerbation occurs.

The heterogeneity of underlying disease can affect the assessment of exacerbations in several ways. First, patients with comorbidities may have conditions (e.g., congestive heart failure) that confound the diagnosis of COPD exacerbation. Second, many comorbid conditions may also confound the management of exacerbations. Diabetes, for example, may worsen in those in whom systemic glucocorticoids are required. The presence of these comorbidities may dramatically influence the impact of an exacerbation and may also affect the way in which therapy for exacerbation should be implemented. Unfortunately, many clinical trials systematically exclude individuals with serious comorbidities, and thus clinical information on concurrent management of comorbid conditions is often limited.