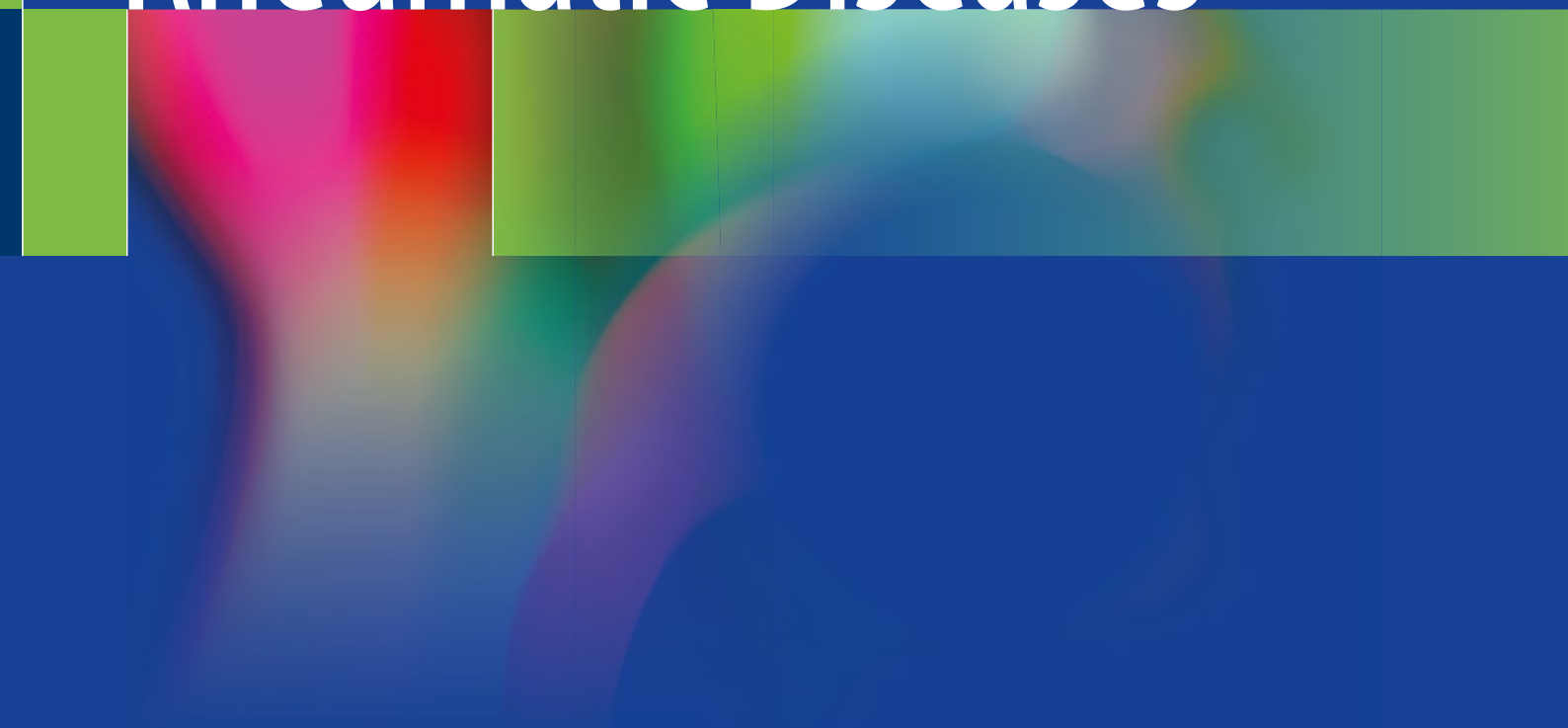
Luis R. Espinoza
Editor

Infections and the Rheumatic Diseases



Springer

Infections and the Rheumatic Diseases

Luis R. Espinoza
Editor

Infections and the Rheumatic Diseases

Springer

Editor
Luis R. Espinoza
LSU Health Sciences at New Orleans
Louisiana State University
New Orleans, LA
USA

ISBN 978-3-030-23310-5 ISBN 978-3-030-23311-2 (eBook)
https://doi.org/10.1007/978-3-030-23311-2

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Foreword

The intersection of infectious diseases and rheumatology has progressed at a torrid rate over the past generation; thus, it is timely to welcome such a comprehensive book as *Infections and the Rheumatic Diseases* for both the practitioner and for those engaged in basic and clinical investigations in this evolving field. Conceptually, the field can be viewed as a triptych painting, whereby in one frame infections are viewed as the etiology of rheumatic signs, symptoms, or as the cause of distinct nosological diseases (e.g., hepatitis C-associated cryoglobulinemia). Alternatively, in another frame, infections may represent formidable comorbidities to be dealt with by clinicians attempting to balance immunosuppressive regimens with a wide variety of chronic latent or persistent infections (e.g., hepatitis B or HIV). The final frame of this exhibit is the growing field of infections induced by our immune-based therapies which range from merely the frequent and mild ubiquitous respiratory infections observed to be increased in virtually every clinical trial of biologic and non-biologic disease-modifying antirheumatic drugs (DMARDs) or the increasingly recognized rise in zoster infections associated with Janus kinase inhibitors. At the extreme, we as rheumatologists are increasingly linked to the induction of rare yet potentially life-threatening opportunistic infections with pathogens such as mycobacteria, endemic fungi, and viruses. Furthermore, we are now being challenged by how to handle the identification of new microbes and assess their relationship to clinical diseases which no longer simply follow Koch's postulates which served us well over the first century of the microbial era. New pathogens are rapidly being discovered due to advances in diagnostic technologies such as next-generation sequencing and culturomics (an evolving field developed to culture and identify unknown bacterial members of our microbiota as a part of the rebirth of culture techniques in microbiology). Such advances once considered clinically arcane now must be understood by the rheumatologic community.

Advances in the field of rheumatology and infectious disease also include new syndromes such as acute and chronic inflammatory arthritis secondary to the epidemiologically emerging alpha viruses now invading the western hemisphere (e.g., chikungunya). In addition, there is also a new and complex area emerging, whereby our technology has helped us define the footprints of ubiquitous pathogens such as EBV, CMV, and others, yet we have not etiologically clearly linked them to emerging disorders such as chronic fatigue syndrome and other maladies which remain medically unexplained.

The care of complex rheumatic diseases is now more of an interprofessional team sport than ever before. We in the field of rheumatology are constantly challenged to keep pace with numerous related fields of which infectious disease is increasingly prominent. What practitioner has not cared for patients where infections have not served as the etiology of a rheumatic disorder, or a comorbidity or complication of our therapies? The need for staying abreast of new infectious etiologies, new diagnostics, and new ways to assess prognosis and of course new therapies mandates close rheumatology and infectious disease collaboration for both care and investigation. I will close by sharing that the first combined fellowship program in rheumatology and infectious diseases was launched at the Cleveland Clinic in 2015 and has already

produced the first of what is hoped to be a growing fraternity of clinician investigators with board certification both in rheumatology and infectious diseases. The interest is strong and the future is bright for this new and emerging field.

Leonard H. Calabrese, DO
Professor of Medicine, Cleveland Clinic Lerner
College of Medicine of Case Western Reserve University
RJ Fasenmyer Chair of Clinical Immunology
Vice Chairman, Department of Rheumatic and Immunologic Diseases
Cleveland, OH, USA

Preface

Infectious agents remain at the forefront of many maladies affecting mankind, despite the many advances in their therapeutic eradication. This has increasing relevance and importance when dealing with musculoskeletal disorders in which infections play an important role in causation, morbidity, and mortality. Old, newer, and emerging infectious disorders continue to affect populations worldwide, have a negative impact in public health, and also negatively impact the economy of afflicted countries.

The focus of this book is to highlight the relevance and importance of infectious agents in the etiology and pathogenesis of musculoskeletal disorders, as well as the role they play in affecting the natural course, disease expression, progression, and clinical response to conventional and biological therapy. There has been extraordinary development in biological therapies with the introduction of many types and classes of agents that possess excellent efficacy and safety. These agents are of particular importance to our topic because their use might be complicated by a variety of serious complications including opportunistic infections. An earlier version of this book was published over 30 years ago, and the editor of this work felt that the newer developments on this field merit an update.

The first section of the book discusses the role of bacterial infection. The opening chapter by Hudson and Carter discusses the role of the molecular biology of infectious agents in the genesis of inflammatory articular involvement. The potential role of ocular chlamydial infection and newer insights into chlamydial gene products into the pathogenesis of synovitis are discussed in depth. The next chapter by Attur and Scher provides an overview of microbiome and microbiota, which is a topic of great interest and relevance and is found to be a key element for hormonal, metabolic, and immunologic homeostasis for the host in health and disease states.

The next six chapters deal with the role of bacterial agents in the etiology, disease expression, clinical manifestations, and therapeutic management of common musculoskeletal disorders.

First, García-De La Torre and González-Bello present an update of gonococcal and non-gonococcal bacterial infection with emphasis on predisposing risk factors, clinical features, morbidity, and mortality and the use of newer agents in the management of septic arthritis. Septic arthritis in children is discussed further by Alarcón et al. The next two chapters by Tobón and Gotuzzo Herencia and Vega Villanueva, respectively, provide comprehensive reviews of specific infectious-related arthritides associated with *Salmonella* and *Brucella* infection, respectively. Next, Cohen-Rosenblum et al. provide an in-depth discussion of the etiology, clinical aspects, and management related to prosthetic septic arthritis. The last chapter in this section by Martín-Mola and Plasencia-Rodríguez provides an in-depth review of infection-related complications of the use of biologic agents in the therapy of rheumatic disorders.

The second section deals with the role of viruses in the etiology, disease manifestations, clinical complications, and therapeutic management of associated disorders. First, Reimold presents a comprehensive overview of the pathophysiology of viral disorders and vaccines. Viral and host predisposing factors that lend arthritogenic capacity to viruses and regulate viral growth and persistence such as genetic predisposition, innate and adaptive immune responses,

and host's comorbidities are discussed in detail. Perez-Alamino then presents an overview of the rheumatic manifestations associated with hepatitis B and C infection, as well as their therapeutic management recommendations. Vera-Lastra et al. next present an overview of chikungunya-associated arthritis. Chikungunya is a viral illness transmitted by the kind of mosquitoes that spread dengue and Zika virus. The most recent outbreak in the Caribbean and Americas is described. The next chapter focuses on arthritis associated with *Flavivirus* infections. Dr. Toloza and Agüero discuss emerging and re-emerging infections related to dengue and Zika. A comprehensive overview of the recent outbreaks is presented. Adizie and Adebajo next describe the inflammatory musculoskeletal manifestations associated with Ebola virus. Drs. Brom and Perandones describe the inflammatory musculoskeletal manifestations associated with parvovirus B19 infection. Characterization of its potential role in the pathogenesis of chronic arthritides and a comprehensive review of related literature are presented.

The next two chapters describe the clinical manifestations associated with retroviruses. First, Vega and Espinoza describe the inflammatory musculoskeletal clinical manifestations associated with HIV infection in the pre- and post-ART. Subsequently, Fuentes and Burgos provide a comprehensive overview of the clinical manifestations associated with HTLV-1 infection.

The final chapter in this section is devoted to rubella-related arthritis. Dr. Vega reviews clinical manifestations related to natural and vaccine-related inflammatory musculoskeletal manifestations.

The third section concerns with arthritis secondary to mycobacteria, fungi, and spirochetes. First, Oyoo and Genga describe the osteoarticular clinical manifestations associated with tuberculous and nontuberculous mycobacterial infections. This topic is of particular interest in view of its increased incidence associated with the use of biologic agents, especially in developing countries. Dr. Ribeiro et al. next discuss the clinical manifestations associated with leprosy as well as their therapeutic management. In addition, authors discussed newer insights on pathogenesis and autoimmune manifestations.

The next five chapters review musculoskeletal clinical manifestations associated with fungal disorders, some more prevalent than others, and with a geographic distribution. First, Dr. Echeverri presents an overview of coccidioidal arthritis, an endemic disorder in certain geographical areas of the world. Recent developments in epidemiology, diagnostic investigation, and therapeutic approaches are discussed. Histoplasmosis is discussed next. Dr. Pinto Peñaranda emphasizes the endemicity of this fungal infection and describes diagnostic pitfalls, as well as clinical and therapeutic considerations. Next, Dr. Restrepo-Escobar discusses another endemic disorder, blastomycosis arthritis, a prevalent disorder in northern United States and Canada. Its diagnosis, clinical manifestations, and therapy are discussed. *Candida* arthritis is reviewed by Drs. Alarcón and Bégué in a comprehensive manner including its epidemiology, clinical characterization, outcomes, and management. The final chapter on fungal-related arthritides is presented by Drs. Ramírez Gómez and Vélez Hoyos. They review a diverse group that includes *Aspergillus*, *Cryptococcus*, *Sporothrix schenckii*, paracoccidioidomycosis, and mucormycosis. Their diagnoses, clinical manifestations, and therapy are presented.

The chapter on syphilis-related musculoskeletal manifestations is discussed by Drs. Hajjaj-Hassouni and Rkain. This sexually transmitted infection remains relevant and important, in view of its increasing incidence among different populations. They present an overview of its epidemiology, clinical manifestations, and therapeutic management. Dr. Arzomand et al. next review another endemic disorder in the northeastern United States, Lyme disease, caused by *Borrelia burgdorferi*. Its pathogenesis, clinical stages, and therapy are well discussed.

Dr. Vega next discusses mycoplasma-related arthritis. These free-living microorganisms, primarily commensal residing on mucosal surfaces under certain conditions, may induce disease including arthritis in immunocompetent and immunosuppressed individuals. Its clinical characteristic, diagnosis, and therapeutic considerations are discussed.

Next, Dr. Márquez Hernández discusses parasitic-related rheumatic manifestations. This public health worldwide problem may at times involve the musculoskeletal system, and a high index of suspicion is necessary to arrive at proper and early diagnosis. Newest diagnostic techniques and more effective treatments are presented.

Finally, Drs. Cañete Crespillo and Ramírez García provide a comprehensive overview of Whipple disease, a rare infectious disease caused by *Tropheryma whipplei*. An excellent description of the localized and systemic forms of the disease is presented.

The next section of the book attempts to present a comprehensive review of the reactive arthritides in which genetic, immunologic, and environmental factors play a significant pathogenic role.

First, Drs. Naovarat and Reveille introduce the section reviewing the role that infectious microorganisms might play in the pathogenesis of spondyloarthritis. They provide an overview of potential mechanisms of action of a variety of microbial agents, especially gram-negative microorganisms. Newer insights are discussed in depth.

Rheumatic fever is presented next. This disorder is the prototype of reactive arthritis in which the host develops an immune response to streptococcal antigens. Newer insights into the pathogenesis, clinical manifestations, and therapy are discussed.

The pathophysiology of reactive is discussed next. Drs. Pathan and Inman described in depth newer insights into the pathogenesis of this disorder. Drs. Naovarat and Reveille next present an extensive description of the potential role of HLA-B∗27 and infection. This is followed by Dr. Espinoza's review of animal models of reactive arthritis. Development of animal models has facilitated a better understanding of the complex interaction between microbial agents, innate and adaptive immunity, and host responses. Drs. Carter and Hudson next present a comprehensive overview of the clinical manifestation and therapeutic strategies for reactive arthritis. Vasey and Espinoza next present an overview of the potential role of microbial agents in the pathogenesis of psoriatic arthritis. Lastly, Jatwani et al. discuss in depth the role of microbes in the pathogenesis of inflammatory bowel disease. They suggest that the use of new techniques focusing on molecular analysis of gut microflora in combination with genomic approaches is likely to further our understanding of the role that microorganisms play in the development of inflammatory disease.

The fifth and final section of the book discusses practical topics of great importance in the management of patients afflicted with rheumatic disorders. First, Jara et al. describe infections in patients with systemic lupus erythematosus, which, despite great advances in diagnosis and therapy, remain an important cause of morbidity and mortality.

The last two chapters of this book concern with vaccines in rheumatic diseases and climate change. First, Pineda et al. discuss the indications, contraindications, and efficacy of vaccines in patients with rheumatic disorders, as well as schemes to be used for patients traveling abroad. Lastly, Dr. Shellito presents an overview on the potential impact that climate change may have on the epidemiology of infectious diseases.

New Orleans, LA, USA Luis R. Espinoza, MD

Acknowledgment

This book is dedicated to the memory of John B. Zabriskie who was an inspiration to me in my formative years.

Special thanks go to the LSU Health Sciences faculty, especially the administration and Charles V. Sanders, Jr., Chairman of the Internal Medicine Department, who demonstrated resilience against the adversities caused by Hurricane Katrina and brought back our medical center to its present status.

I would also like to thank Luzlelia and Carmen Espinoza who provided me with guidance and support throughout the years.

My grateful thanks are also extended to Connie Walsh and Garth Haller, Springer, who provided significance assistance and encouragement for the completion of the book.

Finally, I extend my great appreciation to the many contributors without whose support, dedication, and work, this book could not have been possible.

Contents

Contributors

Adewale Adebajo, MBBS Faculty of Medicine, Dentistry and Health, University of Sheffield, Sheffield, UK

Tochi Adizie, MBChB The Royal Wolverhampton NHS Trust, Wolverhampton, UK

Santiago Eduardo Agüero, MD Centro de Rehabilitación Nivel II Ampliado, Province of Catamarca, Argentina

Andrés Esteban Alarcón, MD, MPH Department of Pediatrics, Children's Hospital New Orleans, Louisiana State University, New Orleans, LA, USA

Zuhal Arzomand, MD Rheumatology, Rhode Island Hospital/Brown University, Providence, RI, USA

Malavikalakshmi M. Attur, MD Division of Rheumatology, Department of Medicine, New York University School of Medicine, New York, NY, USA

Drexel University College of Medicine, Drexel University, Philadelphia, PA, USA

Scott A. Barnett, MD Department of Orthopaedic Surgery, Louisiana State University Health Sciences Center, New Orleans, LA, USA

Rodolfo E. Bégué, MD Department of Pediatrics, Children's Hospital, Louisiana State University Health Sciences Center – New Orleans, New Orleans, LA, USA

Martin Brom, MD Fundación Favaloro, Buenos Aires, Argentina

Hospital Italiano de Buenos Aires, Buenos Aires, Argentina

Paula I. Burgos, MD Departamento de Immunología Clínica y Reumatología, Pontificia Universidad Católica de Chile, Santiago, Chile

Juan D. Cañete, MD, PhD Arthritis Unit, Rheumatology Department, Hospital Clinic and IDIBAPS, Barcelona, Spain

John D. Carter, MD Internal Medicine/Rheumatology, University of South Florida College of Medicine, Tampa, FL, USA

Anna Cohen-Rosenblum, MD, MSc Department of Orthopaedic Surgery, Louisiana State University Health Sciences Center, New Orleans, LA, USA

Teresa Crout, MD Division of Rheumatology, University of Mississippi Medical Center, Jackson, MS, USA

María del Pilar Cruz-Domínguez, DSc Health Research Division, Hospital de Especialidades, Centro Médico La Raza, Mexico City, Mexico

Vinod Dasa, MD Department of Orthopaedic Surgery, Louisiana State University Health Sciences Center, New Orleans, LA, USA

Ryan Dewitz, MD Department of Orthopaedic Surgery, Louisiana State University Health Sciences Center, New Orleans, LA, USA

Andrés Felipe Echeverri, MD Internal Medicine, Rheumatology, Hospital Pablo Tobón Uribe, Medellin, Antioquia, Colombia

Luis R. Espinoza, MD LSU Health Sciences at New Orleans, Louisiana State University, New Orleans, LA, USA

Julio E. Figueroa II, MD Clinical Medicine, Louisiana State University Health Sciences Center, New Orleans, LA, USA

Alejandro Fuentes, MD Departamento de Immunología Clínica y Reumatología, Pontificia Universidad Católica de Chile, Santiago, Chile

Ignacio García-De La Torre, MD Department of Immunology and Rheumatology, Hospital General de Occidente and University of Guadalajara, Guadalajara, Jalisco, Mexico

Juan Esteban García-Robledo, MD GIRAT (Grupo de Investigación en Reumatología, Autoinmunidad y Medicina Traslacional), School of Medicine, Universidad Icesi, Cali, Valle del Cauca, Colombia

Abraham Gedalia, MD Department of Pediatrics, Division of Rheumatology, Children's Hospital, Louisiana State University Health Sciences Center, New Orleans, LA, USA

Eugene Kalman Genga, MBChB, MMED (Internal Medicine) Medicine and Therapeutics, University of Nairobi, Nairobi, Kenya

Ricardo Prado Golmia, MD Center Hospital AACD, Rheumatology, Hospital Israelita Albert Einstein, Advanced Center for Autoimmune Diseases Hospital BPMirante, Sao Paulo, SP, Brazil

Yelitza Concepción González-Bello, MD Department of Rheumatology, Centro de Estudios de Investigación Básica y Clínica, S.C. (CEIBAC, SC), Guadalajara, Jalisco, Mexico

Eduardo Gotuzzo Herencia, MD Department of Infectious, tropical and dermatological diseases, Cayetano Heredia National Hospital, Lima, Peru

Julio Granados, MD Immunogenetics Division, Department of Transplants, Instituto Nacional de Ciencias Medica y Nutricion Salvador Zubirán, Mexico City, Mexico

Najia Hajjaj-Hassouni, MD, PhD Department of Rheumatology, Mohammed VI University of Health Sciences (UM6SS), Casablanca, Commune Hay Hassani, Morocco

Alan P. Hudson, PhD Biochemistry, Microbiology, and Immunology, Wayne State University School of Medicine, Detroit, MI, USA

Robert D. Inman, MD, FRCPC, FACP, FRCP Edin University Health Network, Toronto, ON, Canada

Medicine and Immunology, University of Toronto, Toronto, ON, Canada

Toronto Western Hospital, Toronto, ON, Canada

Luis J. Jara, MD Education and Research, Hospital de Especialidades, Centro Médico La Raza, Instituto Mexicano del Seguro Social, Mexico City, Mexico

Universidad Nacional Autónoma de México, Mexico City, Mexico

Shraddha Jatwani, MD, FACP, FACR Rheumatology, St. Vincent Evansville, Evansville, IN, USA

Peter C. Krause, MD Department of Orthopaedic Surgery, Louisiana State University Health Sciences Center, New Orleans, LA, USA

Josehp Lira Tecpa, MD Clinical Research Unit, Hospital de Especialidades "Dr. Antonio Fraga Mouret" Centro Medico La Raza, Instituto Mexicano del Seguro Social, Universidad Popular Autónoma del Estado de Puebla (UPAEP), Mexico City, Mexico

Vikas Majithia, MD, MPH, FACP, FACR Internal Medicine, Division of Rheumatology, Department of Medicine, University of Mississippi Medical Center, Jackson, MS, USA

Bharat Malhotra, MD University of Mississippi Medical Center, Jackson, MS, USA

Javier Dario Márquez-Hernández, MD, MSc Internal Medicine, Rheumatology, Hospital Pablo Tobón Uribe – Universidad CES, Medellin, Antioquia, Colombia

Michel Augusto Martinez Bencomo, MD Research Division, Hospital de Especialidades Centro Médico Nacional La Raza, IMSS, Universidad Nacional Autónoma de México, Mexico City, Mexico

Emilio Martín-Mola, MD, PhD Rheumatology Unit, Universitary Hospital La Paz-Idipaz; Autonoma University, d-Medical Center, Madrid, Spain

Gabriela Medina, MD, MSc Clinical Research Unit, Hospital de Especialidades, Centro Medico La Raza, Mexico City, Mexico

Scott J. Melton, MD, PhD Department of Medicine, Section of Infectious Diseases, Louisiana State University Health Sciences Center, New Orleans, LA, USA

Benjamin S. Naovarat, MD Department of Internal Medicine, Division of Rheumatology, The University of Texas-McGovern Medical School, Houston, TX, USA

Ivana Nieto-Aristizábal, MD GIRAT (Grupo de Investigación en Reumatología, Autoinmunidad y Medicina Traslacional), Fundación Valle del Lili, Universidad Icesi, Cali, Valle del Cauca, Colombia

G. Omondi Oyoo, MD Clinical Medicine and Therapeutics, University of Nairobi, Nairobi, Kenya

Gabriel Pacífico Seabra Nunes Department of Medicine, Universidade Nilton Lins, Manaus, AM, Brazil

Ejaz Pathan, MD, PhD, MRCP Spondylitis Program, Toronto Western Hospital, Toronto, ON, Canada

Carlos Edgardo Perandones, MD, PhD, FACP Fundación Favaloro, Buenos Aires, Argentina

FLENI (Fundación para la Lucha contra las Enfermedades Neurológicas de la Infancia), Buenos Aires, Argentina

Rodolfo Perez-Alamino, MD Rheumatology Section, Department of Internal Medicine, Hospital Avellaneda, Tucumán, Argentina

Carlos Pineda, MD, PhD Division of Musculoskeletal and Rheumatic Disorders, Instituto Nacional de Rehabilitación Luis Guillermo Ibarra Ibarra, Mexico City, Mexico

Luis Fernando Pinto Peñaranda, MD, MSc Internal Medicine, Rheumatology, Hospital Pablo Tobón Uribe – Universidad CES, Medellin, Antioquia, Colombia

Chamaida Plasencia-Rodríguez, MD, PhD Rheumatology Unit, Universitary Hospital La Paz-Idipaz, Autonoma University, Madrid, Spain

Julio Ramírez García, MD Arthritis Unit, Rheumatology Department, Hospital Clinic, Barcelona, Spain

Luis Alberto Ramírez Gómez Rheumatology Department, Universidad de Antioquia, Medellin, Colombia

Anthony M. Reginato, PhD, MD Division of Rheumatology, The Warren Alpert School of Medicine at Brown University, Providence, RI, USA

Andreas M. Reimold, MD Internal Medicine, Rheumatic Diseases Division, Dallas VA Medical Center and University of Texas Southwestern Medical Center, Dallas, TX, USA

Mauricio Restrepo-Escobar, MD, MSc Section of Rheumatology, GRUA -Grupo de Reumatología de la Universidad de Antioquia, Department of Internal Medicine, GRAEPIC -Grupo Académico de Epidemiología Clínica, University of Antioquia, Medellín, Colombia

John D. Reveille, MD Department of Medicine, Division of Rheumatology, The University of Texas-McGovern Medical School, Houston, TX, USA

Sandra Lúcia Euzébio Ribeiro, PhD Department of Internal Medicine, Rheumatology Section, Medical School Universidade Federal do Amazonas, Manaus, AM, Brazil

Hanan Rkain, MD Faculty of Medicine and Pharmacy, Departments of Rheumatology and Physiology, Mohammed V University, Rabat, Agdal, Morocco

Miguel Angel Saavedra, MD Department of Rheumatology, Hospital de Especialidades, Centro Médico La Raza, Instituto Mexicano del Seguro Social, Universidad Nacional Autónoma de México, Mexico City, Mexico

Morton Scheinberg, MD, PhD Rheumatology Section, Orthopedics Department, Hospital Israelita Albert Einstein, Sao Paulo, SP, Brazil

Clinical Research Center Hospital AACD, Sao Paulo, SP, Brazil

Advanced Center for Autoimmune Diseases Hospital BPMirante, Sao Paulo, SP, Brazil

Jose U. Scher, MD Division of Rheumatology, Department of Medicine, New York University School of Medicine, New York, NY, USA

Jesús Sepúlveda-Delgado, MD Research and Diagnosis Division, Hospital Regional de Alta Especialidad Ciudad Salud, Centro Regional de Alta Especialidad de Chiapas, Tapachula, Mexico

Universidad Nacional Autónoma de México, Mexico City, Mexico

Judd Shellito, MD Medicine (Pulmonary/Critical Care/Allergy Immunology), Louisiana State University Health Sciences Center, New Orleans, LA, USA

Avinash K. Shetty, MD Global Health, Pediatric Infectious Diseases, Department of Pediatrics, Wake Forest School of Medicine, Winston-Salem, NC, USA

Carina Soto-Fajardo, MD Division of Musculoskeletal and Rheumatic Disorders, Instituto Nacional de Rehabilitación Luis Guillermo Ibarra Ibarra, Mexico City, Mexico

Lucilene Sales de Souza, MSc Dermatology, Fundação Alfredo da Mata, Manaus, AM, Brazil

Gabriel J. Tobón, MD, PhD GIRAT (Grupo de Investigación en Reumatologia, Autoinmunidad y Medicina Traslacional), Fundación Valle del Lili, Universidad Icesi, Cali, Valle del Cauca, Colombia

Sergio Miguel Angel Toloza, MD Health Statistics, Ministry of Health, Province of Catamarca, Argentina

Frank Barnett Vasey, MD Department of Internal Medicine, Division of Rheumatology, University of South Florida College of Medicine, Tampa, FL, USA

Luis E. Vega, MD Department of Medicine, Hospital Central de la Fuerza Aérea, Lima, Peru

Karen Isabel Vega-Villanueva, MD Department of Medicine – Section of Rheumatology, Cayetano Heredia National Hospital, Lima, Peru

Alejandro Vélez Hoyos, MD Department of Pathology, Universidad Pontificia Bolivariana, Medellín, Colombia

Hospital Pablo Tobón Uribe and Dinámica IPS, Medellín, Colombia

Olga Lidia Vera-Lastra, MD Internal Medicine Department, Hospital de Especialidades "Dr Antonio Fraga Mouret", Centro Médico La Raza, Mexico City, Mexico

Universidad Nacional Autónoma de México, Mexico City, Mexico

Matthew White, DO Rheumatology, Roger Williams Medical Center, Providence, RI, USA

Part I

Basic Aspects of Bacterial Infections

The Molecular Biology of Chlamydiae as Exemplar of Bacterial Pathogenesis in the Rheumatic Diseases

1

John D. Carter and Alan P. Hudson

Introduction

Along with small pox, tuberculosis, trachoma, and several other clinical entities, the rheumatic diseases are among the oldest known afflictions of mankind. For just one example, some observations suggest that rheumatoid arthritis (RA) has existed in North America for 3000 years or more [1]. From historical times, skeletal remains of the Medici family from the late Renaissance were examined recently, and they demonstrated evidence for RA, uratic gout, and diffuse idiopathic skeletal hyperostosis [2]. William Harvey was originally diagnosed with "gout," but recent thinking suggests that his problem probably was erythromelalgia [3]. In the mid-nineteenth century, Herman Melville was afflicted severely by what today would be diagnosed as ankylosing spondylitis [4]. In the late nineteenth/early–mid-twentieth centuries, August Renoir, Alexey von Jawlensky, Raoul Dufy, and Niki de Saint Phalle all suffered from RA [5, 6]. James Joyce probably suffered from *Chlamydia*-induced reactive (inflammatory) arthritis [4].

Interestingly, and not terribly surprisingly, most of the ancient scourges of mankind were of infectious origin, and as developed in this volume, the rheumatic diseases are not exceptions. For one currently interesting example, RA was first described in what can be considered the modern clinical literature by Landre-Beauvais in 1800; the clinical designation "rheumatoid arthritis" was coined by Garrod in 1859 [7]. However, as mentioned, the disease itself is unquestionably far older than its official clinical description. Because of its high incidence and critical clinical consequences for patients, RA has, of course, been the subject of intensive research for many decades. Some studies from earlier in the twentieth century suggested an infectious origin for RA, with more recent reports indicating that the pathogenesis characteristic of the condition is of genetic origin. However, neither infection nor genetics nor any other single factor currently is accepted as causative in RA. We have suggested that the etiology of RA actually is complex and not simply assignable to either infection or genetics [8].

Detailed discussion of the pathogenic mechanisms inherent in the many arthritides resulting from various bacterial, viral, and fungal infections is developed in detail in the following chapters, but while the molecular genetic/molecular biological specifics of each differ, one general theme that emerges among all of them is the elicitation of inflammation, often severe, in joint tissues. This is especially the case for arthritides elicited by bacterial infections. We have studied the lower body arthritis elicited by prior genital infection with *Chlamydia trachomatis* for nearly 30 years, and more recently the similar clinical entity elicited by its close relative the respiratory pathogen *C. pneumoniae*. Those studies and the work of many others have demonstrated clearly that several unexpected and unusual aspects of the biology of these pathogens are critical to their ability to elicit and maintain arthritogenesis. Importantly as well, interactions between the host and pathogen contribute importantly to pathogenesis.

In this chapter, we outline the molecular genetic/molecular biologic details underlying the pathogenesis process elicited by chlamydiae in the human synovium. For reasons developed below, the arthritis elicited by these organisms can serve in many ways as exemplar for pathogenic details characteristic of bacterially induced arthritis in general. Clinical details, epidemiology, treatments, and other aspects of *Chlamydia*-induced arthritis are developed in Chap. 28. The chapters surrounding the latter present information regarding arthritides related to *Chlamydia*-induced arthritis but which result from other bacterial infections. Over the last several years, a few papers have appeared concerning clinical and epidemiologic aspects of *Chlamydia*-induced reactive arthritis

J. D. Carter
Internal Medicine/Rheumatology, University of South Florida College of Medicine, Tampa, FL, USA

A. P. Hudson (✉)
Biochemistry, Microbiology, and Immunology, Wayne State University School of Medicine, Detroit, MI, USA
e-mail: ahudson@med.wayne.edu

L. R. Espinoza (ed.), *Infections and the Rheumatic Diseases*, https://doi.org/10.1007/978-3-030-23311-2_1

[e.g., 9–13], but it will be abundantly clear from what follows here that studies undertaken to elucidate the basic science underlying the pathogenesis characteristic of that clinical entity have been relatively scarce. For that reason, we provide several suggestions for areas of research that we consider important to support development of therapies to treat, and indeed to prevent, the arthritis.

Chlamydiae and *Chlamydia*-Induced Arthritis

Chlamydia trachomatis is an obligate intracellular bacterial pathogen that is the causative agent for important human diseases. In some regions of the world, well-defined strains (serovars) of the organism cause trachoma, which remains a significant cause of treatable blindness; other strains cause genital infections worldwide (for review see [14, 15]). In addition to these primary infections, it has been clear for many years that chlamydial infections frequently cause severe sequelae. These are foremost a function of genital infections with *C. trachomatis* and include fallopian tubule blockage leading to ectopic pregnancy, pelvic inflammatory disease, and other problems with the female upper reproductive tract. Importantly, another sequela is an inflammatory arthritis, which is the topic of this chapter and Chap. 28 (for review, see [14–19]). The arthritis is classified among the spondyloarthropathies, and it has been given several different clinical designations, including, originally, Reiter's disease [20]. Usually the arthritis has been referred to as reactive arthritis (ReA) and more recently simply as *Chlamydia*-induced arthritis [21].

Chlamydia pneumoniae is a respiratory pathogen first identified in 1986 and defined as a separate species a bit later [22, 23]. Infection with this organism apparently is common in all populations examined to date, and reinfection is frequent. Estimates indicate that pulmonary infections with the organism are responsible for perhaps half of all community-acquired pneumonia [23, 24]. Infections with *C. pneumoniae* also have been linked to severe sequelae, including asthmatic bronchitis, chronic obstructive pulmonary disease, atherogenesis, and an inflammatory arthritis similar to that elicited by genital infection with *C. trachomatis* (see [21, 25–27]). The clinical aspects of *C. pneumoniae*-induced arthritis mirror to some extent those characteristic of *C. trachomatis*-induced arthritis, although some differences are known.

The basic outline of chlamydial pathogenesis during primary infection of the genital tract has been defined through years of study. That process is a function of the biology of active infection by *C. trachomatis* – that is, it is a function of details attendant on the developmental cycle and later [28, 29]. The cycle is initiated by attachment of the extracellular form of the organism, the elementary body, to target host cells, upon which the organisms are taken into the host cell by an active process. The primary host cell type is epithelial, but other cell types can be infected as well [19, 30, 31]. The receptor to which chlamydiae attach on the host cell surface has been a target of research for decades, and a number of host surface molecules have been implicated (e.g., [32–34]). One report indicated that the receptor for *C. pneumoniae* attachment on endothelial cells is the lectin-like oxidized LDL receptor [35]. That observation is consistent with unpublished results from our group for attachment of either chlamydial species on epithelial cells [e.g., 36–39]). If these data are confirmed, it would provide some explanation for as yet unexplained aspects of chlamydial infection, such as how these organisms elicit phagocytosis in nonphagocytic cells. Once in the host cell cytoplasm, the organisms reside within a membrane-bound vesicle for the duration of their intracellular tenure. Within the inclusion, each elementary body undergoes a transcriptionally determined "differentiation" process that produces the vegetative growth form of the organism, the reticulate body. Each of these latter undergoes seven to eight cell divisions. Near the end of the cell division process for *C. trachomatis*, 80% or so of reticulate bodies dedifferentiate back to the elementary body form, and at about 48 h post-infection, those new extracellular forms are released to the external milieu by host cell lysis or exocytosis (for detailed review, see [19, 28, 39]). For *C. pneumoniae*, the cycle requires approximately 72 h for completion.

Studies from many groups have illuminated the means by which invading chlamydiae influence the host cell and its biochemical processes during active infection. Genome sequence data demonstrated that *C. trachomatis* possesses a type III secretion system, by which the organism injects effector proteins into the host cell at the attachment stage [40]. The total panel of injected proteins and their detailed functions in uptake into the host cells remain to be defined, but for one example, evidence for injection of a toxin encoded by the *C. trachomatis toxB* gene has been established [41]. Chlamydial TARP and other proteins function in the uptake/invasion process leading to sequestration of the organisms in their cytoplasmic inclusions [e.g., 42–45]. Interestingly, the gene designated CT622 on the genome sequence of *C. trachomatis* encodes a product which is injected into the host cytoplasm throughout the developmental cycle; loss of the encoded protein attenuates infectivity and intracellular development during the cycle [46]. Perhaps not surprisingly, chlamydiae manipulate host cell glucose transport via upregulation of *GLUT1* and *GLUT3*, and that upregulation is dependent on chlamydial protein synthesis [47]. Chlamydiae are dependent on iron acquisition from the host, and they have evolved unusual mechanisms to accomplish that uptake, although we do not fully understand those mechanisms, however [48]. Recent studies from several laboratories have demonstrated that chlamydial proteins strongly and directly influence host cell processes, to the advantage of the

pathogen. For example, the organism produces a protein designated CADD, which binds to host cell death receptors to influence the apoptotic process [49, see also 50]. Interestingly, a recent study identified a dual Lys63-deubiquitinase and Lys-acetyltransferase activities in the *Chlamydia* protein ChlaDUB1, and these activities lead to the breakup of the host cell Golgi apparatus [51]. All these manipulations of the host cell, either epithelial or monocytic, abet the ability of the pathogen to elicit joint disease. Reviews from a number of sources highlight these and other aspects of interaction with their immediate host cells by chlamydiae [e.g., 52, 53]. As developed in the following chapters, other bacterial pathogens also overt the host cell to their advantage.

Chlamydial infections elicit a strong inflammatory response, although that response is often more clinically apparent in men than in women, at least for urogenital infections. A major surprise from the various full-genome sequencing programs is that the chlamydial chromosome encodes not one, but three versions of the pro-inflammatory Hsp60 protein [40, 54]. The "original" gene, which is nearly identical to that from *E. coli* and other bacteria and which is well-known to be highly pro-inflammatory, is *groEL* (genome designation CT110), and it is found in an operon with groES, as in *E. coli* [40]. The other two Hsp60-encoding genes (CT604 and Ct755) are distantly linked to CT110. These three genes are the result of gene duplication events, although their sequences are not identical. The three Hsp60-encoding genes are expressed early in the developmental cycle, are transcribed fully independently of one another throughout that cycle, and show high levels of expression throughout the cycle [55]. These gene products are largely, although certainly not exclusively, responsible for eliciting the host inflammatory response, which includes high levels of production of IFN-γ, TNF-α, and other pro-inflammatory mediators. Host signaling pathways triggered during active chlamydial infection by other proteins from the bacterium have also been studied extensively [e.g., 56].

Strains/Serovars Involved in Arthritogenesis

As developed in Chap. 28, the incidence of *Chlamydia*-induced arthritis is relatively low following genital *C. trachomatis* infection; moreover, only about half of those who do develop the acute disease progress to chronicity (see [57–59]). *C. trachomatis* strains/serovars (originally defined serologically) are generally divided into ocular and genital groups. Serovars were differentiated as a function of the structure of the *ompA* gene product, and serovar-specific monoclonal antibodies to this protein were used to differentiate strains in infected tissue samples. More recently, serovars have been elucidated in clinical samples by DNA sequence of the cloned *ompA* gene, followed by in silico translation to determine the predicted amino acid sequence of the protein, [60, 61].

The ocular group includes serovars A, B, Ba, and C, and the genital group includes serovars D–K, plus the lymphogranuloma venereum group (LGV) [e.g., 19, 62]. The assumption has been that, since the inflammatory arthritis follows genital chlamydial infection, the inciting organisms must belong to the genital serovar group. We defined the DNA sequence of multiple cloned *ompA* genes from each of 36 patients with well-defined chronic *Chlamydia*-induced arthritis, in a study originally intended to assess sequence diversity at that locus within individual patient samples; as predicted, the diversity was low. We then asked which serovars were involved via comparison of our sequences to the known *ompA* sequences in the databases, and all sequences from each patient derived virtually exclusively from ocular group organisms [63].

We did identify a few cloned sequences in which some DNA exchange had taken place so as to give minor characteristics of genital serovar genome structure in the predominantly ocular serovar genome. The overall genome structure is somewhat different between ocular and genital group organisms at *ompA* and other chromosomal regions, and those differences are almost certainly responsible in some unknown fashion for the ability of ocular group organisms to disseminate from the genital system to the joint, once at that site to elicit severe inflammation. More detailed and extensive study of the genetic component of *C. trachomatis* infecting synovial tissue in additional patient samples must be done to elucidate the mechanism(s) underlying chlamydial dissemination from the urogenital system to the joint. Unknown attributes of the host genetic background must also influence dissemination to the joint in some individuals.

These differences either individually or in concert also must influence the remitting–relapsing phenotype of many patients with the chronic arthritis, again as developed in Chap. 28. The relatively low incidence of acute inflammatory arthritis among patients with a documented genital chlamydial infection may be a function of the presence or absence of ocular serovar organisms in the genital inoculum leading to infection. That is, infection of the human genital tract rarely if ever involves a clonal population of chlamydiae. Rather, the inoculum occasionally can include some serovar diversity, with a majority of such inocula including only one or more genital serovars and others, a minority, having a component (probably a small component) of ocular group organisms.

We suggest that the acute inflammatory arthritis develops only in that minority of patients whose genital inocula include ocular serovar organisms (for further discussion see [63]). However, this contention does not explain the observation that only approximately half of patients with the acute

disease progress to chronicity. The explanation for this almost certainly will be complex and center on genome sequence differences among the synovial population of infecting ocular organisms, as yet undefined aspects of the host genetic background, and the host–pathogen interaction that these genetic components engender. Elucidating these interactions and their genetic underpinnings will comprise experimental questions of significant interest for future studies. We note too that determination of whether cervical or urethral infections include a component of ocular serovar chlamydiae is one potentially useful approach to identifying patients at risk for development of the inflammatory arthritis.

Chlamydial Access to and Pathogenesis of the Joint

The elicitation of disease by a pathogen during primary infection often is just a preliminary for establishment of a longer-term relationship with the host [64, 65]. We and many and others have suggested that this is the case for genital infection by *C. trachomatis*, and it is also almost certainly true for ocular infections by this pathogen as well as pulmonary infection by *C. pneumoniae*. Production of chlamydial Hsp60 and other gene products during urethral or cervical infection elicits a number of responses from the host, including a Th1-type immune response [18, 19, 24, 62, 66–68]. Importantly, monocytic cells are attracted to the site of infection, where they take up elementary bodies with the purpose of disposing of them [e.g., 19]. However, following internalization of elementary bodies into the monocyte inclusion, the normal course of phagosome–lysosome fusion does not take place [26, 31, 69–73]. Instead, within the cytoplasmic inclusion, elementary bodies undergo the initial differentiation process to the reticulate body form; that is, transcriptome analyses over time during the first day post-infection of normal human monocytes in culture demonstrate that genes encoding products necessary for the differentiation to reticulate bodies are expressed as they are during the initial stage of normal active infection [19]. These include genes specifying components of the protein synthetic system, various transporters, proteins to be inserted into the inclusion membrane, the three Hsp60 proteins, and others. More than 200 genes encoding proteins, many of currently unknown function, are also expressed, and it is thought that many of these contribute to virulence and pathogenesis. Importantly, *Chlamydia*-infected monocytes are frequently extravasated from the genital tract, by which means they disseminate to other sites using the monocytes as a vehicle [26, 55, 67, 74].

During the hours after the differentiation process, chlamydiae within monocytic cells enter an unusual infection state designated "persistence" [26, 68, 75]. Data from patient samples and from studies of an in vitro model system of this state suggest that chlamydiae within the circulating monocytes reach the joint in the persistent state [26, 76]. That is, joint pathogenesis results from the biology of chlamydial persistence and the interaction of the organisms with the host cell in that infection state. Transcriptome analyses demonstrated that the transition from normal active infection to the persistent state often involves downregulated expression of many genes that are upregulated during the first 24 h post-infection, with adjustment of transcript levels for a panel of genes encoding lipid modification enzymes, ABC transporters, some components of the transcription and translation systems, and others [e.g., 70–72]. We identified no genes that were specifically or solely involved in transition to persistence for *C. trachomatis*; this is in contrast to the situation for other bacterial pathogens known to utilize a persistent infection phase, such as *Mycobacterium tuberculosis* and others [73].

Importantly, transcript analyses targeting the three Hsp60-encoding genes demonstrated high levels of expression for each during normal active infection, with expression levels of the CT604 and CT755 genes exceeding that of the authentic *groEL* (CT110) gene [55]. By contrast, studies of the monocyte model of chlamydial persistence demonstrated that transcript levels from CT604 were actually increased in that state, relative to their levels during active infection, but mRNA levels from CT755 were severely attenuated [55]. Indeed, even using extremely sensitive PCR screening systems, it was difficult to identify any transcripts from CT755 during established persistent infection. We confirmed that these data from the in vitro model system accurately reflected the situation in synovial tissue samples from patients with well-documented chronic *Chlamydia*-induced arthritis. Thus, the CT604 gene product probably functions in some manner to facilitate the transition to persistence, and attenuation of the level of the CT755 gene product during that transition indicated its possible function in maintaining the active infection state for chlamydiae [55]. These are contentions that must be demonstrated unequivocally.

Given that a significant host synovial inflammatory response is characteristic in patients with active chronic *Chlamydia*-induced arthritis, the CT110- and CT604-encoded Hsp60 proteins probably are involved in eliciting the synovial inflammatory response, whereas the CT755 gene product is not. Further, given the insertion of chlamydial proteins into the inclusion membrane and into host cell itself via the type III secretion system and other means during the infection process (see above), chronic synovial pathogenesis and its consequent inflammation must result from an extensive process of host–pathogen interaction. We view this interaction as a sort of molecular genetic conversation between pathogen and host cell that ends in a balance, which we understand as persistent long-term chlamydial infection of synovial tissue. We currently have little detailed understanding of that conversation,

but transcriptome analyses that are currently underway, and use of the new systems for modulation of chlamydial gene expression, will be critical in sorting out these details.

Remitting–Relapsing *Chlamydia*-Induced Arthritis

Many patients with chronic *Chlamydia*-induced arthritis display a remitting–relapsing disease phenotype, with quiescent periods of disease lasting for weeks to years in some cases [17, 18, 58, 59, 76; see also Chap. 28]. Virtually, all clinical samples that we and others have analyzed over many years were obtained from individuals in the active disease phase. We have, though, examined a small number of chlamydial and host gene expression issues during quiescence in samples from a few patients with documented chronic *Chlamydia*-associated arthritis [10]. We first asked if the organism is present in synovial tissue during quiescent disease, and quantitative PCR assays targeting the chlamydial chromosome in those samples indicated that the organism indeed is present; the bacterial load is several-fold lower during remission than during active disease. Interestingly, however, assessment of transcript levels from the three Hsp60-encoding genes in those samples showed that mRNAs from CT110 and CT604 were at or above levels seen in chlamydiae during active disease; transcripts from the CT755 gene were low in the quiescent disease samples, as in samples from those with active disease [10, 77]. Host cell mRNA encoding IL-10, IFN-γ, and TNF-α were below levels in synovial tissue samples from patients with active disease, but mRNA encoding MCP-1 and RANTES were either at about the same level as in active disease or in the case of the latter, significantly higher in some samples [10, 77, 78]. No data regarding the histopathology of the samples from patients in quiescent disease was available. While these data provide information regarding chlamydial and host genetic behavior during quiescent disease, they provide no insight into why remission was the case. Although the infecting organisms were present in the samples at relatively low levels in the quiescent disease samples, they were still producing high levels of mRNA encoding the two relevant Hsp60 proteins; the host response was not significantly attenuated from that reported in tissues from patients suffering active disease, at least in terms of messengers encoding pro-inflammatory cytokines and chemokines. Clearly, the simplest explanation of quiescence cannot be the case, i.e., that chlamydiae are in some dormant, totally inactive state during remission and that inflammatory molecules therefore are not present in the synovium. The true explanation for remission, and any strategy to exploit aspects bacterial or host behavior for therapeutic purposes, must await further investigation.

Summary

Significant progress has been made in understanding mechanisms of chlamydial pathogenesis during both primary active infection and persistent infection following dissemination to distant sites such as the synovium. As with the study of synovial pathogenesis elicited by other bacterial (and other) pathogens, much of this increased knowledge has resulted from studies of the basic biology of the organisms. In the case of chlamydiae, this includes elucidation of genome structure and differences in such structure among strains/isolates and among chlamydial species, which provides understanding that chlamydiae can and do sometimes exchange genetic information, accounting for some genome structure differences; detailed large-scale gene expression studies, extensive cell biological analyses to illuminate details of influences of the pathogen on its host cell, and vice versa will be required to provide a full picture of the pathogenesis process. It is clear that the host–pathogen interplay during both normal active and persistent infections is complex for chlamydiae, and we assume for other pathogens, and that further understanding of its complexities will be required before new avenues of therapeutic approach can be envisioned and productively pursued. Regarding *Chlamydia*-induced arthritis, the bacterial products that elicit the characteristic inflammatory response in the joint are being defined, and further insights into the nature and specific effects of those gene products on the host will inform current and future treatment options. Of potentially significant interest is the initial insight into the genetic behavior of pathogen and host during the remitting phase of the chronic arthritis, since if molecular details underlying the transitions between active and quiescent disease can be exploited, it should provide a means by which disease development or relapse can be manipulated to advantage. Progress has been made in treatment in terms of combination antibiotic therapy (again, see Chap. 28), as a function of identification of the nature of the chlamydial strains/serovars that appear to be the specific causative agents for disease development, and in terms of bacterial genetic and related strategies for entry into the persistent infection state [e.g., 73, 79].

A significant question at this point concerns the sources from which new insights will come vis-à-vis chlamydial pathogenesis and host–pathogen interaction. We contend that one potentially fruitful source will result from the development of systems for genetic manipulation of growing *C. trachomatis*, its related pathogens, and others [see 80–82]. Productive means of genetic manipulation of these organisms and others are becoming available, which will expand importantly our means of analysis of host–pathogen interaction [see e.g., 83]. Of course, a panel of well-developed genetic and biochemical methods already exist for the assessment of host cell responses to both active and persistent

chlamydial infection. Certainly, study focused on these aspects of host biology must be an integral part of any research program to develop new strategies for anti-*Chlamydia* therapies. Thus, given new experimental tools and the fresh points of view concerning pathogenesis that they provide, the control of both active and persistent chlamydial infections as they operate to induce inflammatory arthritis should be amenable to clinical control. We expect that these same strategies will be applicable to elucidation of the molecular details underlying joint pathogenesis elicited by bacteria other than chlamydiae, as well as other microbial pathogens.

References

1. Sangha O. Epidemiology of rheumatic diseases. Rheumatology (Oxford). 2000;39(Suppl 2):3–12.
2. Giuffra V, Minozzi S, Vitiello A, Fornaciari A. On the history of gout: paleopathological evidence from the Medici family of Florence. Clin Exp Rheumatol. 2017;35:321–6.
3. Hart FD. William Harvey and his gout. Ann Rheum Dis. 1984;43:125–7.
4. Ross JJ. Shakespeare's Tremor and Orwell's cough. The medical lives of famous writers. New York, NY: St Martin's Press; 2012.
5. Zeidler H. Great artists with rheumatoid arthritis: what did their disease and coping teach? Part I. Pierre-Auguste Renoir and Alexej von Jawlensky. J Clin Rheumatol. 2012;18:376–81.
6. Zeidler H. Great artists with rheumatoid arthritis: what did their disease and coping teach? Part II. Raoul Dufy and Niki de Saint Phalle. J Clin Rheumatol. 2012;18:431–6.
7. Landre-Beauvais AJ. The first description of rheumatoid arthritis. Unabridged text of the doctoral dissertation presented in 1800. Joint Bone Spine. 2001;68:130–43.
8. Stanich JA, Carter JD, Whittum-Hudson JA, Hudson AP. Rheumatoid arthritis: disease or syndrome? Open Access Rheumatol Res Revs. 2009;1:179–92.
9. Alvarez-Navarro C, Cragnolini JJ, Dos Santos HG, Barnea E, Admon A, Morreale A, et al. Novel HLA-B27-restricted epitopes from Chlamydia trachomatis generated upon endogenous processing of bacterial proteins suggest a role of molecular mimicry in reactive arthritis. J Biol Chem. 2013;288:25810–25.
10. Gérard HC, Carter JD, Hudson AP. Chlamydia trachomatis is present and metabolically active during the remitting phase in synovial tissues from patients with chronic Chlamydia-induced reactive arthritis. Am J Med Sci. 2013;346(1):22–5.
11. Bojović J, Strelić N, Pavlica L. Reiter's syndrome—disease of young men—analysis of 312 patients. Med Pregl. 2014;67:222–30.
12. Kumar P, Khanna G, Batra S, Sharma VK, Rastogi S. Chlamydia trachomatis elementary bodies in synovial fluid of patients with reactive arthritis and undifferentiated spondyloarthropathy in India. Int J Rheum Dis. 2016;19:506–11.
13. Baillet AC, Rehaume LM, Benham H, O'Meara CP, Armitage CW, Ruscher R, et al. High Chlamydia burden promotes tumor necrosis factor-dependent reactive arthritis in SKG mice. Arthritis Rheumatol. 2015;67:1535–47.
14. Whittum-Hudson JA, Hudson AP. Human chlamydial infections: persistence, prevalence, and prospects for the future. Nat Sci Soc. 2005;13:371–82.
15. WHO Department of Reproductive Health and Research. Prevalence and incidence of selected sexually transmitted infections. Geneva: WHO; 2011.
16. Sieper J. Pathogenesis of reactive arthritis. Curr Rheumatol Rep. 2001;3:412–8.
17. Zeidler H, Kuipers JG, Köhler L. Chlamydia-induced arthritis. Curr Opin Rheumatol. 2004;16:380–92.
18. Carter JD, Inman RD, Whittum-Hudson JA, Hudson AP. Chlamydia and chronic arthritis. Ann Med. 2012;44:784–94.
19. Ward ME. Mechanisms of Chlamydia-induced disease. In: Stephens RS, editor. Chlamydia –intracellular biology, pathogenesis, and immunity. Washington, DC: ASM Press; 1999. p. 171–210.
20. Carter JD, Gerard HC, Espinoza L, Ricca LR, Valeriano J, Snelgrove J, et al. Chlamydiae as etiologic agents for chronic undifferentiated spondyloarthropathy. Arthritis Rheum. 2009;60:1311–6.
21. Carter JD, Hudson AP. The evolving story of Chlamydia-induced reactive arthritis. Curr Opin Rheumatol. 2011;22:424–30.
22. Grayston JT, Campbell LA, Kuo CC, Mordhorst CH, Saikku P, Thom DH, et al. A new respiratory tract pathogen Chlamydia pneumoniae strain TWAR. J Infect Dis. 1990;161:618–25.
23. Kuo CC, Jackson LA, Campbell LA, Grayston JT. Chlamydia pneumoniae (TWAR). Clin Microbiol Rev. 1995;8:451–61.
24. Leinonen M. Pathogenic mechanisms and epidemiology of Chlamydia pneumoniae. Eur Heart J. 1993;14:57–61.
25. Schumacher HR, Gérard HC, Arayssi TK, Pando JA, Branigan PJ, Saaibi DL, et al. Lower prevalence of Chlamydia pneumoniae DNA compared with Chlamydia trachomatis DNA in synovial tissue of arthritis patients. Arthritis Rheum. 1999;42:1889–93.
26. Gérard HC, Whittum-Hudson JA, Carter JD, Hudson AP. Molecular biology of infectious agents in chronic arthritis. Rheum Dis Clin N Am. 2009;35:1–19.
27. Hahn DL, Azenabor AA, Beatty WL, Byrne GI. Chlamydia pneumoniae as a respiratory pathogen. Front Biosci. 2002;7:e66–76.
28. Abdelrahman YM, Belland RJ. The chlamydial developmental cycle. FEMS Microbiol Rev. 2005;29:949–59.
29. Witkin SS, Minis E, Athanasiou A, Leizer J, Linhares IM. Chlamydia trachomatis: the persistent pathogen. Clin Vaccine Immunol. 2017;24(10):e00203–17.
30. Gaydos CA, Summersgill JT, Sahney HH, Ramirez JA, Quinn TC. Replication of Chlamydia pneumoniae in vitro in human macrophages, endothelial cells, and aortic artery smooth muscle cells. Infect Immun. 1996;64:1614–20.
31. Dreses-Werringloer U, Gérard HC, Whittum-Hudson JA, Hudson AP. C pneumoniae infection of human astrocytes and microglial cells in culture displays an active, rather than a persistent, growth phenotype. Am J Med Sci. 2006;332:168–74.
32. Kuo CC, Lee A, Jiang SJ, Yaraei K, Campbell LA. Inoculation of Chlamydia pneumoniae or Chlamydia trachomatis with ligands that inhibit attachment to host cells reduces infectivity in the mouse model of lung infection: implication for anti-adhesive therapy. Microbes Infect. 2007;9:1139–41.
33. Su H, Watkins NG, Zhang YX, Caldwell HD. Chlamydia trachomatis-host cell interaction: role of the chlamydial major outer membrane protein as an adhesion. Infect Immun. 1990;58:1017–25.
34. Ting LM, Hsia RC, Haidaris CF, Bavoil PM. Interaction of outer envelope proteins of Chlamydia psittaci GPIC with the HeLa cell surface. Infect Immun. 1996;63:3600–8.
35. Campbell LA, Puolakkainen M, Lee A, Rosenfeld ME, Garrigues HJ, Kuo CC. Chlamydia pneumoniae binds to the lectin-like oxidized LDL receptor for infection of endothelial cells. Microbes Infect. 2012;14:43–9.
36. Gerard HC, Whittum-Hudson JA, Hudson AP. C pneumoniae utilizes apoE and the LDL receptor family for host cell attachment. In: Chernesky M, et al., editors. Human chlamydial infections. Proceedings of the 11th symposium on human chlamydial infections; International chlamydia symposium; San Francisco, CA, USA; 2006. p. 153–56.
37. Dautry-Varsat A, Subtil A, Hackstadt T. Recent insights into the mechanisms of chlamydial entry. Cell Microbiol. 2005;7:1714–22.