Introduction

Carolyn M. Black

Division of Scientific Resources, National Center for Emerging and Zoonotic Infectious Diseases,
Centers for Disease Control and Prevention, Atlanta, Ga., USA

Despite our knowing of it for centuries, chlamydial infection remains one of the most common bacterial infectious diseases in the world and its agent, *Chlamydia trachomatis*, is one of the most enigmatic pathogens known to medical science. This book was written to fill a dearth of books that are aimed at medical scientists and clinical practitioners who wish to delve more deeply into the clinical and public health aspects of chlamydial infection. The authors, all of whom are internationally recognized experts in this field, have provided information that is based on the latest research available at the time, in many cases including a summary of results of their own work. The book is structured in a logical fashion that begins with a description of the public health burden and epidemiology of chlamydial infections, moves through an overview of the biology and genomics of chlamydiae as they relate to the clinical spectrum and pathogenesis of infection, then reviews the topics of the immunological response, diagnosis and treatment, and finally addresses prevention with the status of current vaccine development research. We have also included a few sections on rarely presented information covering topics and populations of special interest to clinical and public health practitioners: pregnant mothers and their babies, outbreaks of a less common, invasive and systemic type of chlamydial infection known as lymphogranuloma venereum, or LGV, and chlamydial infections in men who have sex with men, gay and lesbian populations. The aim of this book is to cover clinical and public health aspects of sexually transmitted genital infections caused by *C. trachomatis* in humans and we have not attempted to cover infections caused by any other chlamydial species nor chlamydial diseases of the eye (trachoma) or respiratory tract, which have been richly described elsewhere in the literature.

To provide a backdrop for the main content of the book and for those who may be less indoctrinated in the field, the following is a short introduction on the history, biology and clinical spectrum of infections caused by *C. trachomatis*. Also, as a reference aid, it may be helpful to make note of some of the terminology used in the

field to refer to this organism and its infection. The genus and species name is *Chlamydia trachomatis* (italicized), but commonly the organism is referred to as 'chlamydia' in singular and 'chlamydiae' in plural, and 'chlamydial' as an adjective, for example, 'chlamydial infection'. Use of the term 'chlamydia' or 'chlamydiae' should refer to the bacterium only; when referring to the infection caused by this bacterium, 'chlamydial infection' or 'chlamydial disease' is the more appropriate terminology.

A Short History of *C. trachomatis*

Those with interest in chlamydiae and its diseases will find that learning about the history of what has been discovered and theorized in the past provides an intriguing foreshadow of the complexity of the organism's biology and ensuing disease. A search of the literature reveals that chlamydiae were 'discovered' in 1907 but chlamydial disease had actually been known of for centuries before this. References to chlamydial-like diseases of the eye appear in ancient Egyptian and Chinese texts as early as 15 BC [1]. In 1907, the German dermatologist and radiologist Ludwig Halberstädter (1876–1949), who was reportedly one of a small number of Jewish dermatologists able to leave Nazi Germany after 1933, joined a research expedition to Java to study syphilis. It was on this expedition, in the city of Jakarta, that he joined the Austrian bacteriologist Stanislaus von Prowazek (1875–1915; fig. 1) in conducting experiments that led to the discovery of chlamydial cytoplasmic inclusion bodies in the conjunctiva of the infected eye [3]. They named these newly found inclusions 'Halberstädter-Prowazek bodies' [4], a term which has perished from use, to the relief of many. A fascinating and enigmatic photograph taken of Halberstädter and Prowazek working with a blind man holding a baby orangutan makes us wonder whether the subject of experimentation was the man or the orangutan (fig. 2).

Chlamydiae were named for the word *chlamys*, the ancient Greek term for the short cloak worn by Greek military men draped around their upper shoulders and secured with a brooch on the right shoulder (fig. 3). It is believed that the chlamydiae were named thus because the intracytoplasmic inclusions formed by this agent inside host cells cluster around (are 'draped' around) the nucleus of the cell (fig. 4).

Because chlamydial disease was first discovered in the eye and has a broad range of symptoms (or lack of symptoms) that resemble other diseases or syndromes, the infection was not recognized as a sexually transmitted disease until 1976 [8]. Since *C. trachomatis* is an obligate intracellular parasite (i.e. grows only inside a host cell, cannot synthesize its own ATP or grow on any artificial medium), it was believed for a long period of time to be a virus. In fact, before it was considered a virus, the cytoplasmic inclusions of *C. trachomatis* were actually mistaken for a time to be a protozoan parasite. This was perhaps the first of a long series of false starts and misunderstandings about the nature and biology of this organism that have contributed

Fig. 1. Photo of Austrian bacteriologist Stanislaus von Prowazek, codiscoverer of chlamydial inclusion bodies and the cause of trachoma [2].

Fig. 2. Photo of Ludwig Halberstädter and Stanislaus von Prowazek (center) conducting an experiment during their research into cytoplasmic inclusion bodies of trachoma [5].

to the complexity and slow progress of research and, accordingly, the continued very high public health burden of disease [9]. Growth of the organism in embryonated eggs was first achieved in 1957 and in cell culture in 1963 – these achievements helped to finally resolve the question of whether chlamydiae were viruses or bacteria. Because of the unique developmental cycle of chlamydiae, which includes two highly distinct forms (fig. 5), the organism was classified taxonomically in a separate order (Chlamydiales).

Fig. 3. Statue of a chlamys-clad figure in the Louvre Museum in Paris [6].

Fig. 4. Photomicrograph of fluorescently stained chlamydial inclusions (green) clustered around the nucleus of a host cell [7].

Biology and Clinical Syndromes of *C. trachomatis*

The broad clinical spectrum of infections and sequelae caused by sexually transmitted *C. trachomatis* is summarized in table 1. The infection disproportionately impacts women and the highest prevalence of infection is found in adolescent female populations. The increased susceptibility of adolescent females to *C. trachomatis* is a result of their cervical developmental stage in which the columnar epithelium protrudes through the cervical os (cervical ectopy) [15], and also due to behavioral risk factors. There are a large number of factors that contribute to the pathogenesis of chlamydiae and this topic is expertly reviewed by Deborah Dean in her chapter in this book. Since the genome of *C. trachomatis* was first sequenced and advanced sequencing technologies have subsequently permitted completion of sequencing of many strain types, significant knowledge has accumulated on the genomic structure and the contribution of chlamydial genes to the nature of infection and disease, an overview of which is included in the chapter by Tim Putman and Dan Rockey.

Fig. 5. Developmental cycle of chlamydiae. The infectious stage, called the elementary body (EB), infects the host epithelial cell. The EB has been loosely compared to a spore since it serves to spread or disperse itself, is metabolically inactive and has a cell wall that allows it to persist in the environment. The EB enters the host cell by endocytosis and prevents fusion of lysosomes with the chlamydia-containing phagosome, thus permitting intracellular survival. Once the phagolysosome formation is stopped, the EB secretes glycogen which induces its transition into the vegetative and noninfectious form, called the reticulate body (RB). RBs divide approximately every 2–3 h by binary fission for 18–72 h, at which point they begin to fill the endosome and are detectable by antibody-specific stain in the host cell as inclusion bodies containing 100–1,000 RBs. After division and incubation in the cytoplasmic inclusion, the RB differentiates into new infectious EBs which are released either by rupture of the host cell or by exocytosis. The RB obtains energy through straw-like structures that extend through the membrane of the inclusion into the host cell cytoplasm. There is evidence that, under certain conditions, including a host inflammatory response that produces gamma interferon (IFN- γ), the intracellular development of chlamydiae may enter an alternate path in which it becomes nonreplicative while remaining viable, this is called the persistent phase [10, 11]. For example, IFN- γ induces the depletion of tryptophan that is required for chlamydial growth leading to the ‘arrest’ of the developmental cycle; however, the persistent phase chlamydiae can redifferentiate into the infectious EB form and reinitiate the cycle when IFN- γ is removed or when intracellular tryptophan levels are restored. Chronic states of chlamydial disease such as trachoma and reactive arthritis may be associated with the persistent phase of the developmental cycle [12, 13].

Table 1. The clinical spectrum of sexually transmitted *C. trachomatis* infections [information from reference 14]

Females		Infants ¹	Males
lower genital tract	upper genital tract		
Asymptomatic (up to 70%)	Pelvic pain, menstrual abnormalities	Conjunctivitis	Asymptomatic (up to 50%)
Cervicitis	Pelvic inflammatory disease	Pneumonia	Nongonococcal urethritis
Urethritis	Endometritis		Epididymitis
	Salpingitis		Lymphogranuloma venereum ²
	Pelvic peritonitis		Reiter's syndrome
	Lymphogranuloma venereum ²		Chronic conjunctivitis
Ocular	Sequelae	Sequelae	In men who have sex with men
Chronic conjunctivitis	Infertility		Proctitis
	Chronic pelvic pain	Abnormal pulmonary function	Proctocolitis
	Ectopic pregnancy		
	Perihepatitis (Fitz-Hugh-Curtis syndrome)		
	Reiter's syndrome (reactive arthritis)		

¹ Refers to infants born to infected mothers.

² Lymphogranuloma venereum (LGV) is a chronic infection of the lymphatic system that if untreated can result in complications involving the genital organs, joints, heart, liver, eyes or, rarely, the brain. LGV is sexually transmitted but caused by different strain types of *C. trachomatis* than genital infections.

The natural history of chlamydial infection is not well understood, but it is known that up to about 70% of genital infections in women and up to 50% in men are asymptomatic. The current belief is that while some genital infections resolve without treatment, some infections persist for months to a year or more, and some may progress to serious complications such as pelvic inflammatory disease, tubal pregnancy or chronic pelvic pain. The role of host factors in the course of infection and the outcome is not very well understood and this is an exciting area of research reviewed in the chapter by Dean.

We know that chlamydial infection begins at the cervix and the urethra where it can cause cervicitis and urethritis. From the cervix, the infection may move upward into the fallopian tubes and upper genital tract, possibly by the movement of infected host macrophages bearing chlamydial inclusion bodies. It is estimated that 10–20% of untreated cervical infections lead to pelvic inflammatory disease. The presence of infection in the fallopian tubes creates a significant inflammatory response that can result in serious scarring and adhesions that affect the patency of the fallopian tube, which leads to infertility. Chlamydial infections are highly prevalent in adolescent populations, who commonly become infected more than once, especially when their sexual partners are not treated. The epidemiology and control of chlamydial infections is described in detail in this book in the chapter by Catherine Satterwhite and John Douglas. The host response to infection is now understood as playing a critical role in the patho-

genesis of infection – this phenomenon and a detailed review of the immunology of chlamydial infection is included here in a chapter by Ray Johnson and Will Geisler.

Although there are sophisticated diagnostic tests available for chlamydial infections (described in detail in the chapter by Charlotte Gaydos), a large number of infected people do not present for medical care since they have no symptoms and are unaware of being infected. They are thus important sources of spread of infection to others. Laboratory testing followed by treatment is currently the best approach for the control of chlamydial infections. Investigations that seek to identify a virulence factor or factors that might prove to be effective vaccine candidates have been conducted for about 2 decades but have proved elusive to date (reviewed here by Joseph Igiertseme and Carolyn Black). Antimicrobial treatment regimens for chlamydial infection and its complications are generally considered to be effective and are described in the chapter in this book by Margaret Hammerschlag.

No treatise on the public health aspects of chlamydial infection would be complete without attention to some of the populations who are disproportionately or uniquely affected by this sexually transmitted disease. Toward this end, Ingrid Rours and Margaret Hammerschlag have contributed a chapter on complications of chlamydial infections in babies born to infected mothers, Henry de Vries and Servaas Morré have described an intriguing cluster of infections in men who have sex with men, and Devika Singh and Jeanne Marazzo have contributed a chapter on chlamydial infections in gay and lesbian populations.

Acknowledgments

I am grateful to the authors for their willingness to spend their valuable time and effort in making exceptional contributions to this work. Their passion for the often arduous and intricate work involved in the study of this pathogen is evident in their writing. I am also grateful to Dr. Claudiu Bandea for his insightful review, critique and suggestions for improvement. It is my hope that this book will not only inform and assist clinicians and public health providers, but also peak the curiosity of and inspire rich endeavors by the chlamydiologists of the future.

Disclaimer

The findings and conclusions in this report are those of the author and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

References

- 1 Taylor HR: Trachoma: A Blinding Scourge from the Bronze Age to the Twenty-First Century. Melbourne, Centre for Eye Research Australia, 2008.
- 2 Photo from Wikimedia Commons, a freely licensed media repository. <http://en.wikipedia.org/wiki/File:Prowazek.jpg>
- 3 Von Prowazek S, Halberstädter L: Zur Aetiologie des Trachoms. Dtsch Med Wochenschr 1907;33:1285–1287.
- 4 Whonamedit?: A Dictionary for Medical Eponyms: Halberstädter-Prowazek bodies. <http://www.whonamedit.com/synd.cfm/3980.html>.
- 5 Photo from Wellcome Trust Illustrated history of tropical diseases. Wellcome Images Ref No. GC LA/ Ill, <http://images.wellcome.ac.uk>. Wellcome Library, London.
- 6 Photo from Wikimedia Commons, a freely licensed media repository. http://en.wikipedia.org/wiki/File:Chlamys-clad_figure_Louvre_Ma305_n2.jpg.
- 7 Photo reproduced with permission from Prof. Dr. Thomas Miethke, Institut für Medizinische, Mikrobiologie, Immunologie und Hygiene, Munich, Germany.
- 8 Schachter J, Causse G, Tarizzo ML: Chlamydiae as agents of sexually transmitted disease. WHO Bulletin 1976;54:245–254.
- 9 World Health Organisation: World Health Report, 2001. Geneva, WHO, 2001.
- 10 Beatty WL, Morrison RP, Byrne GI: Persistent chlamydiae: from cell culture to a paradigm for chlamydial pathogenesis. Microbiol Rev 1994;58:686–699.
- 11 Morrison RP: New insights into a persistent problem – chlamydial infections. J Clin Invest 2003;111:1647–1649.
- 12 Beatty WL, Byrne GI, Morrison RP: Repeated and persistent infection with *Chlamydia* and the development of chronic inflammation and disease. Trends Microbiol 1994;2:94–98.
- 13 Villareal C, Whittum-Hudson JA, Hudson AP: Persistent Chlamydiae and chronic arthritis. Arthritis Res 2002;4:5–9.
- 14 Centers for Disease Control and Prevention: Recommendations for the prevention and management of *Chlamydia trachomatis* infections, 1993. Atlanta, MMWR, 1993.
- 15 Lee V, Tobin JM, Foley E: Relationship of cervical ectopy to chlamydial infection in young women. J Fam Plann Reprod Health Care 2006;32:104–106.

Dr. Carolyn M. Black
 Division of Scientific Resources, National Center for Emerging and Zoonotic Infectious Diseases
 Centers for Disease Control and Prevention
 Atlanta, GA 30333 (USA)
 E-Mail cblack@cdc.gov