Conferences and Reviews

Chlamydial Infections

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Chlamydiae are among the most common human bacterial pathogens. *Chlamydia trachomatis* has long been known as the causative agent of trachoma, the world's leading cause of preventable blindness.[1] Only in the past two decades have we realized that this organism is an important cause of genital tract disease. These infections are important not only because of their incidence but also because the infections result in long-term consequences such as tubal factor infertility and ectopic pregnancy. *C psittaci* is recognized as the cause of psittacosis, a relatively uncommon human infection acquired through exposure to infected birds. In recent years what was thought to be a variant of *C psittaci,* with no known avian reservoir, was recognized as a cause of atypical pneumonia in humans. This variant, originally called the TWAR agent, has now been placed in its own species. It, too, has been found to be a very common human pathogen. Both the clinical manifestations and epidemiology of this infection are currently being researched.

Taxonomy

The chlamydiae are among the more common pathogens throughout the animal kingdom. They are nonmotile, gram-negative, obligate intracellular bacteria. Their unique developmental cycle differentiates them from all other microorganisms.[2] They replicate within the cytoplasm of host cells, forming characteristic intracellular inclusions which can be seen by light microscopy (Figure 1). They differ from the viruses by possessing both RNA and DNA and cell walls quite similar in structure to those of gram-negative bacteria. They are susceptible to many broad-spectrum antibiotics, possess a number of enzymes, and have a restricted metabolic capacity. None of these metabolic reactions results in the production of energy. Thus, they have been considered as energy parasites that use the ATP produced by the host cell for their own requirements.

Chlamydiae are presently placed in their own order, the Chlamydiales, family Chlamydiaceae, with one genus, *Chlamydia.*[2] There are three species, *C trachomatis, C psittaci,* and *C pneumoniae.*[3] *C trachomatis* includes the organisms causing trachoma, inclusion conjunctivitis, lymphogranuloma venereum (LGV), and genital tract diseases (Table 1). There are three biovars within the species: the trachoma biovar, the LGV biovar, and the murine biovar. *C trachomatis* strains are sensitive to the action of sulfonamides and produce a glycogen-like material within the inclusion vacuole, which stains with iodine. *C psittaci* strains infect many avian species and mammals, producing the diseases psittacosis, ornithosis, feline pneumonitis, bovine abortion, and so on.[4,5] They are resistant to the action of sulfonamides and produce inclusions that do not stain with iodine. *C pneumoniae,* the most recently described species, has the same sulfonamide sensitivity and iodine staining characteristics as *C psittaci.* However, it has less than 10% DNA relatedness to the other species and has pear-shaped elementary bodies rather than round ones. It appears to be exclusively a human pathogen. *C pneumoniae* has been identified as the cause of a variety of respiratory tract diseases and has worldwide distribution.

Growth Cycle

Following attachment at specific sites on the surface of the cell, the elementary body (EB) enters the cell in an endosome in which the entire growth cycle is completed. Chlamydiae are ingested by susceptible host cells through a mechanism similar to receptor mediated endocytosis.[6] The uptake process is directly influenced by the chlamydiae, and ingestion of organisms is specifically enhanced.[7] The chlamydiae prevent phagolysosomal fusion. Once the EB (diameter, 0.25 to 0.35 μm) has entered the cell, it reorganizes into a reticulate particle (RB or initial body), which is larger (0.5 to 1 μm) and richer in RNA. After approximately eight hours, the RB begins dividing by binary fission. Approximately 18 to 24 hours after infection, some of the RBs become EBs by a poorly understood reorganization or condensation process (Figure 2). The EBs are then released to initiate another cycle of infection. The EBs are specifically adapted for extracellular survival and are the infectious form. In contrast, the intracellular, metabolically active, and replicating form, the RB, does not survive well outside the host cell and seems adapted for the intracellular milieu.

The chlamydiae appear to have evolved a unique structure consistent with the requirements of this growth cycle. Structural rigidity of the EB is not maintained by a peptidoglycan layer as is typical for bacteria. The rigidity of chlamydiae is based on cross-linking of three cysteine-rich proteins.[8] The most important of these is the major outer membrane protein (MOMP), which makes up 60% of the weight of the outer membrane.[9] MOMP is about 40 to 45 Kd in mass and contains serovar- and species-specific antigens.[10] In the EB, MOMP is bound to other MOMP molecules and to proteins of approximately 15 and 60 Kd by disulphide bonds. When reduced, MOMP forms porins, channels to allow entry of nutrients.[11] The more flexible outer membrane of the intracellular and metabolically active RB seems to be the reduced form.

History

Chlamydia trachomatis

Trachoma, one of the oldest recognized human diseases, was described in Egyptian papyri and in ancient Chinese writings.[1] The causative agent, *C trachomatis,* was first seen in stained conjunctival scrapings (see Figure 1). The diag-

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nostic intracytoplasmic inclusions were found first in specimens from experimentally infected nonhuman primates and then from humans. Shortly thereafter, the neonatal form of *C trachomatis* conjunctivitis (inclusion conjunctivitis of the newborn [ICN] or inclusion blennorrhea) and the related genital tract infections were recognized. For 50 years laboratory diagnosis was restricted to the search for inclusions in Giemsa-stained epithelial cell scrapings (see Figure 1). The agent was not isolated until 1957, when Chinese workers recovered the organism by inoculating conjunctival scrapings from trachoma patients into the yolk sac of embryonated hens' eggs.[12] Interest in *C trachomatis* grew with increased awareness of its role in genital tract disease.[13,14] Improved laboratory methodology—particularly tissue culture isolation procedures and the valuable epidemiologic tool of the microimmunofluorescence (micro-IF) test for measuring antibodies to *C trachomatis*—led to the elucidation of the wide clinical spectrum of this organism.[15,16] The most important revelation was the etiologic role of *C trachomatis* in acute salpingitis.[17] In many areas this is now recognized as the leading cause of pelvic inflammatory disease and the long-term consequences of tubal factor infertility and ectopic pregnancy.

In 1975, during a prospective study of inclusion conjunctivitis of the newborn, it was noted that some of the infants exposed to *C trachomatis* at birth developed pneumonia.[18] A characteristic pneumonia syndrome of infancy was then described and associated with chlamydial infection.[19] *C trachomatis* was quickly recognized as a major cause of pneumonia in the first six months of life.

A more invasive biovar of *C trachomatis* causes the systemic sexually transmitted disease lymphogranuloma venereum (LGV). This condition was first described in the late 1700s and the causative agent isolated in 1929.[1] *C trachomatis* biovars infecting humans have no known animal hosts.

Chlamydia psittaci

Psittacosis was first described in Switzerland in the 1870s.[1] Outbreaks of the disease were reported from a number of countries in Europe and the association with exotic or psittacine birds was recognized. The pandemic of 1929-1930 brought worldwide attention to the disease because of the approximately 20% fatality rates seen in the preantibiotic era. In the 1950s the importance of *C psittaci* infections (ornithosis) in poultry was recognized, and human psittacosis was described as an important occupational hazard to workers in poultry processing plants.[20]

Human psittacosis is a zoonosis, usually contracted from exposure to an infected avian species. *C psittaci* is ubiquitous among avian species. The birds usually have intestinal tract infections. The organism is shed in the feces, contaminates the environment, and is spread by aerosol.

C psittaci is also common in domestic mammals. In some parts of the world these infections have important economic consequences. *C psittaci* is a cause of a number of systemic and debilitating diseases in domestic mammals and, most importantly, can cause abortions.[5] Although human chlamydial infections resulting from exposure to infected domestic mammals are known,[21] they seem to be relatively uncommon.

TABLE 1.—*Natural Host Ranges of Chlamydiae and Human Diseases*

Species	*Natural Hosts*	*Human Diseases*
1. *C psittaci*	Birds, lower mammals	Psittacosis
2. *C pneumoniae*	Humans	Respiratory
3. *C trachomatis*		
a. Trachoma biovar	Humans	Trachoma, conjunctivitis, genital diseases, infant pneumonia
b. LGV biovar	Humans	Lymphogranuloma venereum
c. Murine biovar	Mice	None known

Chlamydia pneumoniae

During studies of trachoma performed in Taiwan and Iran, some apparent *C psittaci* strains were recovered from conjunctival swabs. Seroepidemiologic studies have suggested that infections with these strains (then called TWAR) are common in many parts of the world.[22,23] Age-specific prevalence rates suggest that transmission occurs in childhood and peaks early in adult life. *C pneumoniae* appears to be circulating among humans without an avian reservoir. It has been associated with a variety of respiratory diseases.[24]

Epidemiology

The epidemiology of chlamydial infections has some common characteristics. Because of the long growth cycle (48 to 72 hours), incubation periods are relatively long, usually on the order of one to three weeks. Persistent low-grade, clinically inapparent infections are common.

Chlamydia trachomatis

Trachoma. Trachoma is the world's leading cause of preventable blindness.[25] Approximately 600 million people are affected, with 10 million blinded. Trachoma is a major public health problem in many developing countries, particularly those in North Africa, sub-Saharan Africa, and Southeastern Asia. In these settings the infection is holoendemic, with virtually all members of affected communities acquiring the infection before they are two years old. It is a disease of families and of poverty, being found at highest rates and in the most severe form among the poorest segments of society. The prevalence of trachoma responds markedly to improving socioeconomic conditions. It has disappeared from some countries as a result of improved standard of living rather than of specific antitrachoma measures.

Young children with severe inflammatory disease are the main reservoirs for infection. Trachoma is a family disease, typically spread from child to child by direct personal contact. Flies can act as mechanical vectors because they feed on ocular discharges. Occasionally, adults may have active disease or may be inapparent shedders of the agent and therefore a source of infection for some children in the household.

Genital Infection. Genital infections are sexually transmitted. The proportions of society most affected are those at highest risk for other sexually transmitted agents.[13,14,26] Members of lower socioeconomic strata—particularly sexually active teenagers—have the highest prevalence of *C trachomatis* infection.[27] In industrialized societies, *C trachomatis* is now the most common sexually transmitted bacterial pathogen.[28] In the United States more than 3 million new infections are estimated to occur each year. (This may be compared with 1.8 million gonococcal infections and approximately 500,000 genital infections with *Herpesvirus hominis*).[29] Most prevalence and clinical studies have been done in the United States and in western Europe.

Sexually transmitted chlamydial infections appear to be just as important in many developing countries.[30]

Sexually transmitted chlamydial infections are widely distributed among the population. These infections are found at relatively high rates in populations that are at low risk for gonorrhea. For example, in higher socioeconomic groups gonorrhea is seldom encountered but chlamydial infections are common. In these settings, as exemplified by students being screened at private colleges, chlamydial prevalence often exceeds the gonococcal infection rate by a factor of 5- to 10-fold in symptomatic men or in asymptomatic women having routine pelvic examinations.[31] In general, it is only in the urban center venereal disease clinics that chlamydial and gonococcal infections occur at the same rate or in which, perhaps, gonococcal infections may be more common. In screening studies of women attending family planning clinics for birth control advice, chlamydial infection rates often exceed gonococcal recovery rates by a factor of 10.[27,32] Lower socioeconomic classes have higher infection rates, although the ratio of chlamydial to gonococcal infection rates in these populations tends to be lower than in the more affluent classes.

Age is the most important factor for *C trachomatis* infection. Younger women have the highest infection rates. In approximately one in six sexually active teenagers attending adolescent clinics, *C trachomatis* was cultured from the cervix during routine pelvic examinations.[27] Other risk factors have been identified. Use of oral contraceptives is associated with higher chlamydial infection rates.[34] Race (which may be a proxy for socioeconomic status) is also a risk factor: black women have been found to have higher infection rates. Sexual preference is another risk factor: *C trachomatis* is a more common cause of urethritis in heterosexual males than in homosexual males.

C trachomatis genital tract infections are widely spread in our society. Persons with *C trachomatis* infection, usually urethritis in men, differ from those with gonococcal infection in socioeconomic characteristics. They typically have higher socioeconomic status (i.e., higher income or education), are more likely to be white, and are usually less sexually active and less likely to have had previous gonorrhea. This depiction of *C trachomatis* as an upper-class STD is misleading. *C trachomatis* is more common than gonorrhea among socioeconomically disadvantaged persons. In fact, *C trachomatis* infections are more likely to occur in young black men and women. However, the "upper-class STD classification" is based on the fact that gonorrhea is less likely to occur in higher socioeconomic groups. *C trachomatis* affects all socioeconomic groups.

Neonatal Infections. Approximately 60% of infants exposed to *C trachomatis* during birth contract the infection.[35] Approximately one in three exposed infants develops conjunctivitis, and one in six develops pneumonia. The incubation period for conjunctivitis is approximately one to three weeks, while most of the cases of pneumonia occur in the second and third month of life. In the United States an estimated 5% of pregnant women have cervical chlamydial infection, placing their infants at risk.

Lymphogranuloma Venereum. Lymphogranuloma venereum (LGV), a sexually transmitted disease, occurs in most parts of the world.[36] In some countries, especially in Africa and Asia, it is a major cause of morbidity, as reflected in patient visits to venereal disease clinics. In the United States LGV is relatively uncommon; only a few hundred cases are reported each year. This statistic is somewhat misleading because the diagnosis is almost always established by positive complement fixation (CF) tests on young men with inguinal lymphadenopathy. In fact, the anorectal syndrome is probably more common in the United States than the bubonic form of disease. That diagnosis is seldom established except from specialized laboratories.

Chlamydia psittaci

This infection is usually spread by the aerosol route with human infection almost always occurring as a result of exposure to infected avian species.[1] Most human infections are attributed to exposure to infected pet birds, usually exotic psittacine varieties or parakeets. Infection in these birds may be symptomatic, or it may be inapparent. The birds usually have gastrointestinal tract infections. It is likely that infection is spread by aerosol from infective droppings. The human disease is also recognized as an occupational hazard within the poultry industry, particularly to workers in turkey processing plants. In Europe ducks are a common source of human infections. Although human-to-human transmission has been described—particularly in some very severe outbreaks of pneumonitis due to *C psittaci*—such transmission is uncommon. Some fatal secondary cases have been developed in hospital personnel attending severely ill patients with primary cases. However, such outbreaks occurred prior to the introduction of tetracycline therapy.

Occasional human infections occur with *C psittaci* derived from mammals.

Chlamydia pneumoniae

C pneumoniae infections may be cyclical in the population. Studies from Scandinavia have identified periodic outbreaks.[37] In military trainees in Finland there were four separate outbreaks of pneumonia over a 10-year period. Approximately 6% to 8% of the recruits developed relatively mild pneumonias. National laboratories in Scandinavia have noted periodic excesses of ornithosis as confirmed by CF test. Retrospective evaluation of the sera from those cases, using type-specific microimmunofluorescence tests, showed that in nonepidemic years approximately 10% of the seroconversions were due to *C pneumoniae.*[38] In contrast, in the years showing large increases in presumed ornithosis, approximately 50% to 70% of the sera showed type-specific increases in antibody titer to *C pneumoniae.*

Either asymptomatic or very mild infections with *C pneumoniae* must be common as judged by seroprevalence studies.[22,23] Infections appear to begin relatively early in childhood, rarely in infancy. The age-specific seroprevalence rates reach 30% to 40% of the population at approximately 30 years of age. In most areas studied, 40% to 65% of the overall adult population have shown evidence of *C pneumoniae* infection.

Most of the *C pneumoniae* infections that have been detected have been in young adults in whom the disease appears to be relatively mild and clinically indistinguishable from mycoplasma pneumonia.[22,37] These clinically apparent cases occur at rates similar to those seen for infections with *Mycoplasma pneumoniae* or influenza A virus. In older individuals with underlying illnesses, *C pneumoniae* can cause fatal disease[39] and, similarly, young children in the developing world may have fatal pneumonias due to this organism.[40] In the older individuals with underlying disease, approximately half of the diagnosed cases appear to be hospital acquired rather than community acquired. There are two possible explanations for this: (1) perhaps *C pneumoniae* is being transmitted from other infected individuals in the hospital, or (2) perhaps these patients are

long-term carriers of *C pneumoniae* in whom, as a result of intubation, manipulation, and general debilitation, the infection activates to cause pneumonia. All other chlamydiae are known to cause chronic and clinically inapparent infections. Thus it would not be surprising to see inapparent *C pneumoniae* infections that become clinically active.

Pathogenesis and Pathology

Chlamydial diseases affect diverse anatomic sites in a number of hosts. Although it is impossible to describe universal pathologic changes, some common features in the host response to chlamydial infections are noteworthy.[41] Typically in the early inflammatory reactions, polymorphonuclear (PMN) leukocytic infiltrates, particularly at the superficial epithelium, accumulate at luminal or surface sites. If there is a particularly exuberant acute response, pseudomembranes may form, as the cellular reaction is enmeshed within the fibrin that is deposited. Such lesions may be seen on the conjunctiva of infants with inclusion conjunctivitis or over the liver in perihepatitis in birds and humans. The inflammatory response soon changes to a mixed and even predominantly mononuclear cell response. Macrophages are particularly common in LGV and *C psittaci* infections. Lymphocytes and plasma cells are commonly found in human *C trachomatis* infections. Because chronicity is characteristic of chlamydial infection, there are often long-term persistent changes with low-grade inflammatory reactions.

Chlamydia trachomatis

The molecular basis of chlamydial pathogenicity is unclear. Studies in cell culture systems have identified a number of virulence factors that appear to be important in establishing infection.[42,43] These include the ability to recognize specific attachment sites, the ability to induce phagocytosis, and the ability to avoid phagolysosomal fusion.

Members of the trachoma biovar of *C trachomatis* are parasites of columnar epithelial cells and appear to cause disease in most anatomic sites where these cells are found. These organisms are primarily pathogens of the conjunctivae and genital tract, in which these cells predominate. The organisms can also be important pathogens in the lower gastrointestinal tract and respiratory tract. The LGV biovar has a broader host cell range, involving lymphoid and endothelial cells. It is more invasive and apparently capable of causing more tissue destruction as a result of the infectious process; late stages of LGV are often characterized by scar formation.

The trachoma biovar seems incapable of infecting enough cells to cause the tissue damage that appears in some of its diseases. Immunologic mechanisms for pathogenesis have been postulated.[14] More severe disease is often seen in secondary infection and in reinfection with heterologous biovars. A soluble extract from chlamydial particles can induce marked conjunctival inflammation in animals sensitized by a prior infection.[44] Thus, it seems that much of the pathogenesis of the trachoma biovar disease results from local hypersensitivity reactions.

The antigen responsible for the hypersensitivity reactions has been identified as a 57 Kd protein with genus-specific antigenic reactivity.[45] This leads to the speculation that prior chlamydial infection with any species could sensitize to a first infection with another species and therefore exacerbate its outcome.

With *C trachomatis*, that severe outcome is ultimately characterized by fibrosis. In trachoma the blinding lesion is scarring of the conjunctiva. Over time, contraction of these scars results in the lid distortion that causes corneal damage. In acute salpingitis the fallopian tube is scarred, leading to ectopic pregnancy or tubal factor infertility. In late LGV the genital and lower gastrointestinal tracts are extensively scarred.[36,46]

One common result of the trachoma biovar infection is the induction of lymphoid follicles.[1,41] Follicle formation in the conjunctiva is a hallmark of trachoma and inclusion conjunctivitis. Similar lesions have been observed in genital tract sites infected with the trachoma biovar.[47] These are true lymphoid follicles with germinal centers and a B cell predominance, although T cells are often found infiltrating the subepithelial spaces between the follicles.

LGV infection can result in giant cell and granuloma formation.[36,46] LGV lesions are also characterized by necrosis with formation of stellate abscesses. When an infection is restricted to the lymph nodes there is marked hyperplasia and transformation of macrophages into epithelioid cells. The entire process results in considerable necrosis, and large fluctuant bubos may develop.

The mechanisms involved in inducing conjunctival scarring are not clear, but it is thought to result from necrosis of follicles. It is interesting to consider that end-stage disease for LGV and trachoma biovars, in different anatomic sites, is a result of scar formation. Thus, the rectal strictures of LGV can be viewed in a sense to be analogous to the conjunctival scarring that ultimately results in blindness in trachoma and to the fallopian tube scarring that results in infertility after acute salpingitis.

Chlamydia psittaci

C psittaci is capable of infecting a wide variety of cells and of damaging most anatomic sites, probably due to the cytocidal effect of the infection. The typical sequence of acute and chronic inflammation occurs with *C psittaci* infections as well. Often the lung infections are complicated by secondary bacterial infections that obscure the characteristic pathologic picture. Inclusions of *C psittaci* can be demonstrated in alveolar macrophages and epithelial cells. The organisms can spread via the blood stream to involve many other sites.

Clinical Manifestations

Chlamydia trachomatis

Trachoma. Trachoma is a chronic keratoconjunctivitis caused by *C trachomatis.*[1,14,25] It may begin as a mucopurulent conjunctivitis and is often complicated by secondary bacterial infection. Marked follicular reaction and papillary hypertrophy develop. In hyperendemic areas most active disease is seen in young children. As the follicular reaction resolves, some focal necrosis may occur and scarring of the upper conjunctivae can develop. Over time, these scars contract and cause an inturning of the upper eyelids, so that the eyelashes abrade the cornea (Figure 3). These lesions (trichiasis and entropion) cause the blindness in trachoma. It takes many years for sufficient contraction of scars to occur to cause the lid distortion. Blindness therefore generally occurs more than 25 to 30 years after the peak of the active inflammatory processes. Mild cases of trachoma rarely lead to visual loss.

Inclusion Conjunctivitis. Inclusion conjunctivitis in adults or in newborn infants, also called paratrachoma, is usually relatively mild and self-limited. It results from inoculation of conjunctivae with genital tract discharges. Adults probably acquire the infection during sexual activity or by hand-to-eye transmission, while newborns acquire

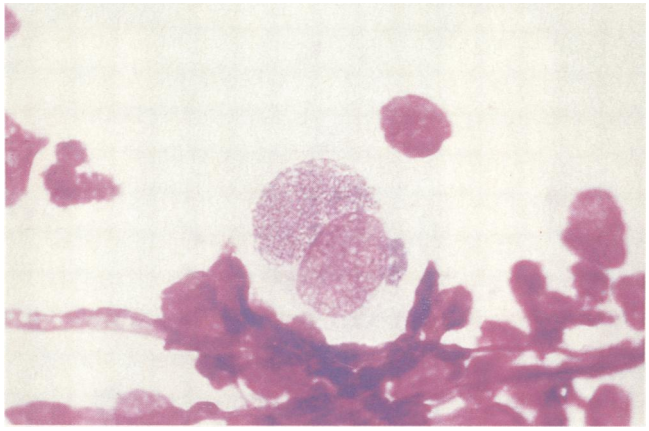

Figure 1.—Chlamydial intracytoplasmic inclusion in epithelial cell Giemsa-stained conjunctival scraping from a patient with trachoma.

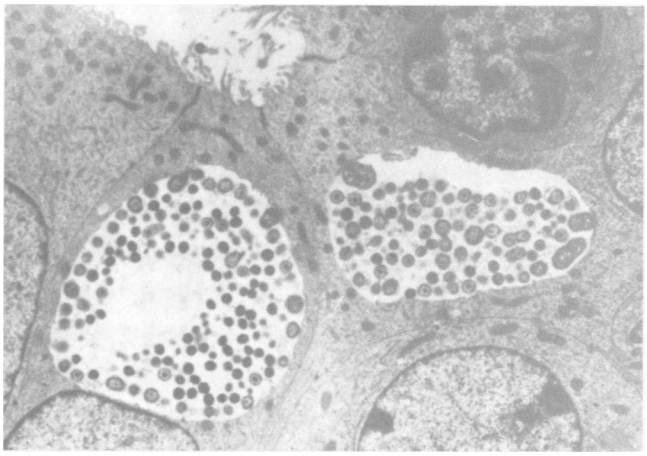

Figure 2.—Electron micrograph of *C trachomatis* inclusions in epithelial cells of mouse oviduct.[100] Note that inclusion contains both small elementary bodies and larger reticulate bodies. (Courtesy of D. Philips.)

the organism during birth.[35] The incubation period is typically between 6 and 19 days.[1] In adults the disease is follicular; infants, having a less developed lymphoid response, usually have mucopurulent conjunctivitis. Although micropannus and minor scarring may develop, severe disease with a poor prognosis occurs uncommonly.

Genital Tract Infections

Nongonococcal Urethritis. Nongonococcal urethritis (NGU) is probably the most common manifestation of *C trachomatis* infection of the genital tract[48] (Table 2). Approximately one third to one half of men with NGU have a demonstrable *C trachomatis* infection of the urethra.[49] Postgonococcal urethritis, a specific subset of NGU, occurs in men who have been successfully treated for gonorrhea.[50] Most had concomitant chlamydial infection. Gonorrhea is the major risk factor for *C trachomatis* infection of the genital tract. Approximately 20% of men and 40% of women who have *Neisseria gonorrhoeae* in their genital tracts will also have a concurrent *C trachomatis* infection.[51] Thus, the Centers for Disease Control recommend that heterosexual males and females with gonorrhea be given a course of antichlamydial therapy immediately after the β-lactam prescribed for treatment of the gonococcal infection. If this is not done, most of the men will develop postgonococcal urethritis. The women will develop postgonococcal cervicitis, but most importantly many will subsequently develop acute salpingitis.[52] An additional week of tetracycline therapy can prevent this.

Nongonococcal urethritis cannot be distinguished from gonococcal urethritis on clinical grounds. Men with gonorrhea are more likely to have a yellowish purulent discharge; men with nongonococcal urethritis tend to have a scant mucoid discharge that often can be elicited only by stripping the urethra. However, these statistical distinctions are not reliable in individual cases. It is beneficial to have a specific etiologic diagnosis for purposes of contact tracing and treatment, but urethritis in the male can be managed successfully without doing tests for *C trachomatis* (Figure 4). The approach is based on diagnosis by exclusion. To define the urethritis, a Gram stain smear of an endourethral swab or a discharge is made to see if polymorphonuclear

TABLE 2.—*Contribution of* Chlamydia trachomatis *to Selected Clinical Syndromes*

Men	Nongonococcal urethritis	30-50%
	Postgonococcal urethritis	70-90%
	Epididymitis (<35 years)	60%
Women	Mucopurulent endocervicitis	40-60%
	Acute salpingitis	25-50%
Infants	Conjunctivitis (<1 month)	25-50%
	Pneumonia (<6 months)	30-50%

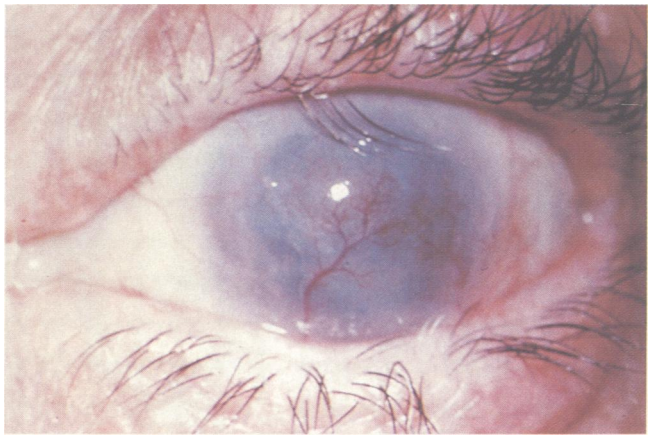

Figure 3.—Late stage of trachoma showing eyelashes abrading the cornea.

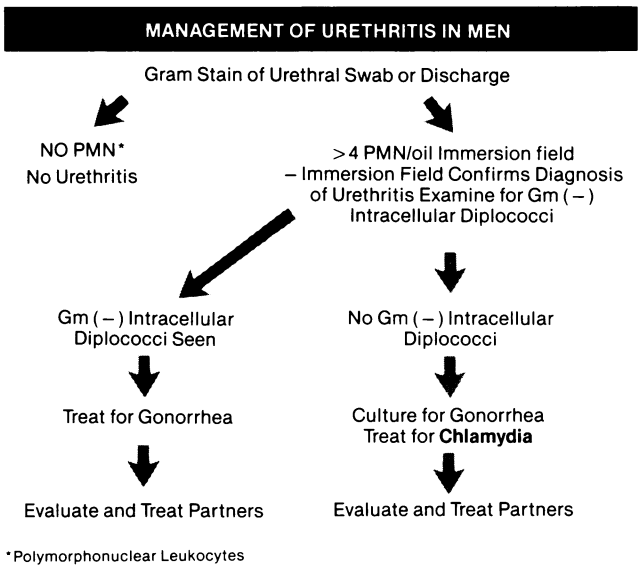

Figure 4.—Management principles of urethral infections of males.

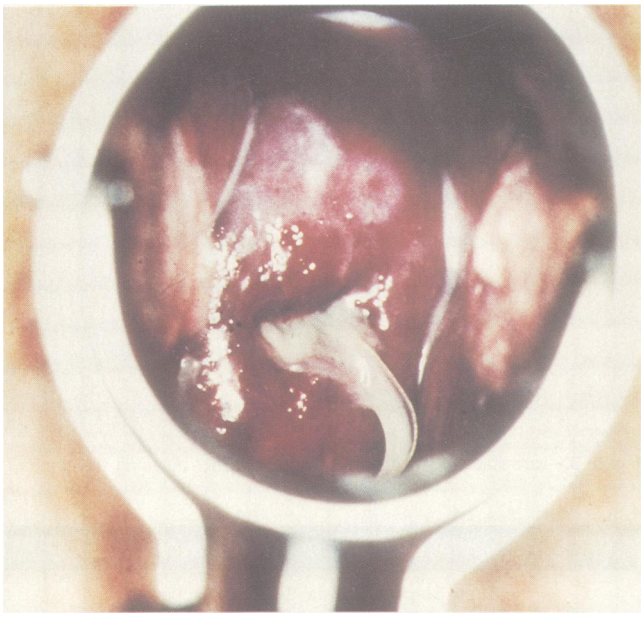

Figure 5.—Severe mucopurulent endocervicitis showing inflamed cervix with purulent discharge from the os. (Courtesy of E. B. Rees.)

leukocytes are present. If intracellular diplococci are found, a man should be treated for gonorrhea, followed by treatment for *C trachomatis*. If intracellular diplococci are not seen, culture tests for gonorrhea should be done at the same time that immediate treatment for nongonococcal urethritis is being given. In either instance partners should be examined and treated.

Approximately 1% to 2% of men with urethritis will develop epididymitis. *C trachomatis* and *N gonorrhoeae* are the usual causes of this condition in young, sexually active men.[53] Reflecting the relative prevalence of these pathogens, chlamydial epididymitis is about twice as frequent as gonococcal epididymitis.

A similarly small proportion of men with NGU will later develop Reiter's syndrome, or sexually acquired reactive arthritis (SARA). Many of the men with SARA have had chlamydial infection and increased immune responses to chlamydial antigens. Chlamydial antigens or particles have been found in joints of some of these men, but the true relationship of chlamydial infection to the disease is not yet clear.[54]

Cervicitis. C trachomatis causes a mucopurulent endocervicitis in women[55] (Figure 5), identified by: (1) the presence of a mucopurulent discharge from the endocervical os (by microscopy there should be more than 10 polymorphonuclear leukocytes per oil immersion field in a Gram stain smear of endocervical material), and (2) induced bleeding when a swab is rubbed against the wall of the endocervical canal. Swab tests can be used to demonstrate a purulent discharge (a white swab inserted in the endocervical canal will be colored yellow in the presence of a purulent discharge) or easily induced bleeding (a swab rubbed against the endocervical wall will be reddened by bleeding caused by pressure if the cervix is edematous and inflamed) (Figure 6). This condition is relatively common in patients attending STD clinics, and these diagnostic criteria have a predictive value for chlamydial infection of approximately 30% to 50% in that setting. Gonorrhea is the only other bacterial infection likely to be associated with mucopurulent endocervicitis. It has been suggested that presumptive treatment for a chlamydial infection should automatically be given when this syndrome is noted, with the expectation that the tetracycline regimens used for *Chlamydia* would be effective for most gonococcal infections.

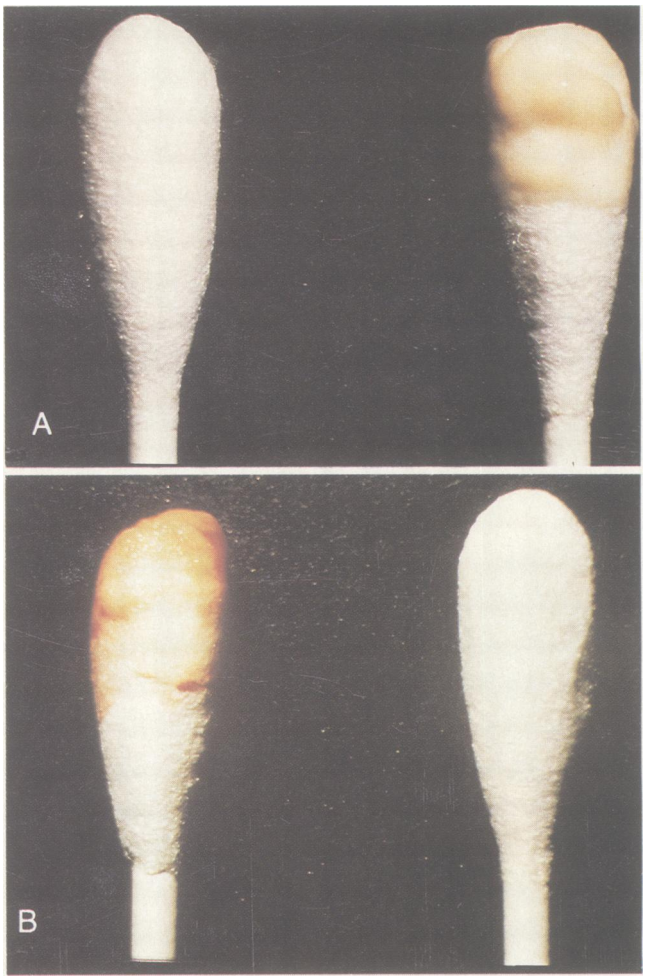

Figure 6.—Swab tests for mucopurulent endocervicitis. The swab is **(A)** colored yellow if there is pus in the endocervical canal; and **(B)** blood tinged after being rotated against the wall of the endocervical canal if it is inflamed. (Courtesy of J. Paavonen.)

Women with gonorrhea who have a mucopurulent cervical discharge tend to maintain that discharge if they also have a chlamydial infection and are treated with beta-lactam drugs alone. Thus, the same rationale and regimens for treatment of women with gonorrhea as were discussed above have been applied for men with gonococcal infection. The same regimens are used. It is even more important to treat women with gonorrhea for concurrent chlamydial infection on a presumptive basis. Women appear to have infection rates approximately twice as high as are observed with men. (35% to 45% of women with gonorrhea have concomitant chlamydial infection.) Eradication of the chlamydiae will reduce the subsequent development of salpingitis.[49]

Chlamydial cervicitis is serious in that it is a precursor for ascending infection. Many women who have *C trachomatis* in the cervix also have endometrial infection.[56] The rate at which infections ascend is not known, but in one study results in 25% of those women at risk for such an infection were positive. *C trachomatis* can cause either clinically overt salpingitis or an inapparent salpingitis. Fallopian tube damage, causing tubal factor infertility or ectopic pregnancies, can occur from inapparent infection as well as from a clinical episode of pelvic inflammatory disease.

Pelvic Inflammatory Disease. Women are most severely affected by infections with *C trachomatis* (Table 3). Pelvic inflammatory disease, the most important consequence of genital chlamydial infection,[57] has a broad clinical spectrum. The term pelvic inflammatory disease (PID) is preferable to the term acute salpingitis because the infection is not restricted to the fallopian tubes. Most women with salpingitis caused by either *C trachomatis* or *N gonorrhoeae* also have endometritis.[58] Inapparent salpingitis appears to be relatively common. The only truly reliable way of diagnosing acute salpingitis is by laparoscopy. Routine use of this procedure has helped to clarify the natural history of chlamydial salpingitis. Chlamydial salpingitis can have a milder clinical presentation than salpingitis caused by other microbes.[57] Indeed this has led to the introduction of more relaxed criteria for the clinical diagnosis for acute salpingitis (Table 4). Women with chlamydial salpingitis differ from women with gonococcal or nongonococcal, nonchlamydial salpingitis in typically being younger, having a longer duration of symptoms prior to seeking medical attention, and being less likely to be febrile. Paradoxically, the chlamydia-positive cases are more likely to involve an elevated sedimentation rate and severe inflammatory changes of the fallopian tube by laparoscopy. Thus, the picture which emerges suggests that while the clinical presentation may be mild, the tubal involvement may be severe. This conclusion is supported by the seroepidemiologic studies that show *C trachomatis* to be a major risk factor in tubal factor infertility and ectopic pregnancies and that most of the women with these complications do not have a prior history of a clinical episode of PID.[59]

Ascending genital infection is common. *C trachomatis* is found in the endometrium or fallopian tubes of approximately 25% to 50% of women with acute salpingitis in the United States and at higher rates in western Europe. *C trachomatis* is also associated with complications of salpingitis, such as the Fitz-Hugh–Curtis syndrome (perihepatitis).[60] Unfortunately, because chlamydial salpingitis can be clinically mild, or even inapparent, evidence of chlamydial infection is often first obtained retrospectively by serologic tests performed during evaluation of infertility.

TABLE 3.—*Impact of* Chlamydia trachomatis *in the United States*

Annual Infection: 4,000,000		
Men.....	1,000,000	Nongonococcal urethritis
	200,000	Epididymitis
Women.....	>250,000	Pelvic inflammatory disease
	50,000	Rendered infertile
	35,000	Ectopic pregnancies
Infants.....	60,000	Conjunctivitis
	35,000	Pneumonia
	20,000	Chronic lung damage

TABLE 4.—*Diagnostic Criteria for Acute Salpingitis*

All present:
1. Lower abdominal pain and tenderness
2. Cervical motion tenderness
3. Adnexal tenderness

Minimum of one present:
1. Temp >100.4°F (38°C)
2. WBC >10,000
3. ESR elevated
4. Inflammatory adnexal mass
5. Purulent fluid obtained via culdocentesis

Other Genital Tract Conditions. Approximately 6% of asymptomatic gay men attending venereal disease clinics were found to have *Chlamydia* by rectal swabs, as compared to a 12% recovery rate from men with proctitis.[61] *C trachomatis* can be recovered from the pharynx of sexually active males or females at risk for genital tract infection.[62] The role of this agent in causing pharyngitis is uncertain. Most of the evidence associating *C trachomatis* with pharyngitis was based on serologic tests. It is now thought that these were measuring cross-reacting antibodies to *C pneumoniae*.[63]

C trachomatis may also cause bartholinitis.[64] Urethral infections also occur in women, and chlamydial infection has been associated with sterile pyuria in some female populations.[65] This association of chlamydial infection with the urethral syndrome was shown in college-age women. It is probably unwise to generalize those findings to other populations of women.

The role of chlamydiae in complications of pregnancy is controversial. In some studies *C trachomatis* infection has been associated with stillbirths, prematurity, or small for gestational-age infants.[66-68] Other studies have found no effects, or very modest ones, of chlamydial infection on pregnancy outcome.[69,70] It is not clear whether these discrepant results reflect population differences or the confounding effects of other genital infections.

C trachomatis can cause postpartum complications. The organism has been associated with postpartum endometritis and salpingitis.[71] Women with chlamydial infection are at risk of similar outcomes after induced abortions. Testing women for chlamydial infection, and treatment with a tetracycline, of those infected, has been shown to reduce postabortal complications.[72]

Neonatal Infections

Approximately 5 to 21 days after birth, the infant with a chlamydial infection develops mucopurulent conjunctivitis.[35] Hyperemia and discharge are the most prominent findings. Follicles are not seen unless the condition persists for longer than a month. Inclusion conjunctivitis of the newborn (ICN) is usually self-limiting and will resolve in a few months without treatment. ICN is not considered to be a sight-threatening condition. Corneal damage is minimal, although some keratitis and micropannus can develop. Conjunctival scarring is relatively uncommon, although sheet scarring may follow the disease in infants who develop pseudomembranes.[1] These scars do not result in lid deformity. Occasional cases persist and severe disease that may threaten vision can rarely develop.

The incubation period for chlamydial pneumonia of infants is usually between 2 and 12 weeks.[19,35] The infants often have a prodrome of rhinitis and many have had conjunctivitis. Affected infants are usually afebrile, are markedly tachypneic and occasionally apneic, and have a staccato cough. They are hypergammaglobulinemic, particularly in the IgM class. A relative eosinophilia occurs in approximately one third of affected infants. Radiographs usually show hyperinflation.

The spectrum of chlamydial respiratory involvement in infants is quite broad. Nasopharyngeal infections are common.[19,35] Some infants develop severe rhinitis, without lower respiratory involvement, that can occasionally interfere with respiration.[73] The pathogenesis of chlamydia pneumonia probably reflects descending infection, and bronchiolitis can also occur.[74] Infants with chlamydia pneu-

monia typically fall into the category of "failure to thrive" and often have only mild respiratory distress, with tachypnea being the prominent finding. Occasionally these infants have severe respiratory problems and may become apneic and require respiratory assistance. Approximately three-quarters of the infants with pneumonia can be managed on an outpatient basis. The other infants are severely ill and must be treated in an intensive care nursery. This can be a life-threatening condition.

Serous otitis media is reported as a complication of the pneumonia and may occur independently. Infants with chlamydia pneumonia may subsequently develop chronic respiratory problems.[75] Severe rhinitis has also been associated with chlamydial infection in the newborn.[73] Gastrointestinal tract infections occur but no corresponding clinical manifestations have been described.[76]

Lymphogranuloma Venereum

This venereal disease is caused by three serovars within the species *C trachomatis.*[14] These organisms are also biovars, as they are more invasive and the disease is a systemic one. The LGV organism may be recovered from genital ulcers and may also be present in the cervix or urethra in an asymptomatic form. It is transmitted by sexual activity.

The incubation period is variable (usually one to three weeks, but it may be much longer). The first manifestation of the disease appears to be a primary lesion—a painless superficial ulcer or vesicle on the genitals. In temperate climes this lesion is often not apparent.[77] In tropical countries, the ulcerative form of the disease appears to be quite important. Within one to three weeks after the primary lesion appears, regional lymphadenopathy develops. Bubo development is known as the secondary stage of the disease and is typically seen in young men. Women probably have primary implantation of the organism within the vagina, where the draining lymph nodes are retroperitoneal rather than inguinal. Thus these women usually do not develop inguinal lymphadenopathy. The lymph nodes ultimately heal, often with some scarring, but the infection can persist and cause late destructive lesions involving the gastrointestinal tract and genitalia. Scarring can result in obstruction, and fistulas are common. Primary implantation within the rectum can result in a severe proctocolitis. This is not an uncommon condition among homosexual men in some parts of the United States.[36,78]

The anorectal syndrome can manifest itself in a number of different ways. There can be acute hemorrhagic proctitis or proctocolitis. Usually a bloody mucopurulent discharge is seen. The rectum and sometimes the colon are inflamed and often ulcerated. In another form of the condition the lesions are more proximal in the intestinal tract and rectal involvement is not obvious. For the diagnosis of proctocolitis, specimens are collected from the colon by a proctoscopic or endoscopic examination. Biopsies show giant cells and granuloma formation. The organism is found in subepithelial tissues. Men with this condition are often systemically ill with fever, chills, and weight loss. In 270 men examined for this condition in San Francisco and in whom typical causes of proctitis such as *Herpesvirus hominis,* syphilis, or gonorrhea had been ruled out, *C trachomatis* was isolated from biopsies of 24%, and 70% of the isolates that were typed were LGV strains. These patients tended to be quite ill and had been referred to gastrointestinal or infectious disease clinics for further evaluation. It is likely that this condition is not uncommon but that the diagnosis is often missed.

Although the primary sites involved usually are within the genitourinary tract, if the organism is implanted elsewhere, local disease may occur. For example, if the eye is the site of infection, a form of Parinaud's oculoglandular syndrome may develop. Implantation within the oral cavity may result in cervical lymphadenopathy. Systemic complications, including hepatitis, pneumonia, arthritis, and meningoencephalitis, have been described.

Chlamydia psittaci

Psittacosis is the name used for the human infection with *C psittaci.* In most cases, exposure to birds can be documented. The route of infection is via the respiratory tract. The incubation period is usually between 7 and 14 days, although a much wider range is recognized. The prodrome is relatively nonspecific. Infections are often subclinical and may be mild, resembling a common cold or a mild influenza attack, but severe pneumonitis may occur. In symptomatic cases fever, chills, and severe headache usually occur. Atypical pneumonia is a common presentation. Radiographs may show more extensive lung involvement than is expected on the basis of respiratory difficulty. The pulse rate may be lower than expected from the degree of fever and the general toxicity.

Alternatively, the disease may present with a general toxic, febrile state without respiratory findings. Overt clinical disease is almost always accompanied by fever and severe headache. Cough, when present, is usually nonproductive, but radiographs show extensive pneumonic involvement. Hepatosplenomegaly is common. Person-to-person transmission is uncommon. Prior to antibiotic therapy the case fatality rate was quite high ($> 20\%$), with most fatalities seen in those above the age of 50 years. Treatment of psittacosis with tetracycline is almost always successful and fatalities are rare, although the clinical response may not be rapid and recovery may be prolonged. Many complications are recognized, including meningoencephalitis, myocarditis, and hepatitis.

C psittaci can involve multiple organs. Although it has long been recognized that the agent can be associated with myocarditis in severe cases, there have recently been a number of reports of valvular involvement. In most cases the aortic valve has been involved and replacement has been required. The diagnosis in many of these cases has not been totally convincing. Pneumonia was not commonly found and *C psittaci* has not been isolated from specific lesions or the blood.

A number of pregnant women exposed to *Chlamydia*-infected sheep have had spontaneous abortions.[21] The organisms have been recovered from placental tissues and from other organs in fatal cases. Although the incidence of this infection is not known, *Chlamydia*-infected sheep clearly represent a threat to the health of pregnant women.

Chlamydia pneumoniae

C pneumoniae infections cause a variety of respiratory diseases,[24] typically a mild atypical pneumonia in young adults. The disease is clinically indistinguishable from pneumonias due to *Mycoplasma pneumoniae* or influenza viruses, even in older debilitated individuals in whom fatal outcomes have been observed. The diagnoses have depended upon specific microbiologic evaluations.

Diagnosis

The diagnosis of chlamydial infections is similar to diagnosis of other bacterial infections.[79] The organism can be

demonstrated in smears from infected sites; the agent can be isolated; and antibodies can be measured. Unfortunately, because chlamydiae are obligate intracellular parasites, they cannot be cultured on artificial media; cell culture systems must be used for isolation. These procedures require specialized laboratories and thus restrict clinicians' access to chlamydial diagnosis. Recently the revolution in biotechnology has resulted in the introduction of a number of nonculture tests for diagnosis of *C trachomatis* infection. Although these tests are not as sensitive as culture done under ideal circumstances, they are far more widely available and have greatly improved access to laboratory diagnosis of chlamydial infection. One major problem in the diagnosis of these infections is adequate specimen collection. A common mistake is to collect discharges from affected sites for laboratory tests. This is inappropriate. Chlamydiae are intracellular parasites. It is therefore imperative for most tests that an adequate specimen of the affected mucous membranes should be cleaned of discharge, after which specimens are collected by rubbing swabs briskly on the epithelial cell surfaces. For specimens from the female genital tract the use of cytobrushes is to be preferred over swabs.[80]

Although culture is clearly the most sensitive test, it requires maintenance of a cold chain to protect viability of the organism. The nonculture tests are better suited when transportation problems exist, or when a cold chain cannot be maintained, because they do not require viability for a positive result. The two most commonly used tests are a direct fluorescent antibody (DFA) test and an enzyme immunoassay (EIA) procedure.[81,82] They have comparable performance profiles, with sensitivity of 75% to 85% and specificity of 97% to 98%. The DFAs that provide the best morphologic identification use monoclonal antibodies against a species-specific epitope on the MOMP molecule.[83] They will stain only elementary bodies of *C trachomatis.* The EIAs are usually directed at the genus-specific lipopolysaccharide and thus should react with all chlamydial species. The DFA allows assessment of specimen adequacy. The EIA is more suitable for processing large numbers of specimens.

In general the test of choice for isolation of chlamydia involves inoculation by centrifugation of McCoy cells that are then treated with cycloheximide.[84] This antimetabolite favors the growth of chlamydiae in mammalian cells. Presence of the organism is demonstrated by specific staining for inclusions. It will take at least 48 to 72 hours for the laboratory to return a positive result. EIA and DFA results can be reported in less than 24 hours.

Chlamydia trachomatis

Trachoma. The diagnosis of trachoma is essentially made on clinical criteria.[85] Chlamydiae are difficult to detect in mild cases. In severe active cases, typically only 30% to 60% of conjunctival specimens will test positive for chlamydiae. The classical test, demonstration of inclusion by Giemsa stain, is now recognized to be insensitive.[86]

Genital Infection. Definitive diagnosis of genital infections is made by isolation of the agent in cell culture systems. Nonculture methods for chlamydial diagnosis are widely used. However, these tests, while being simpler and perhaps less expensive than cell culture systems, appear to be less sensitive. All of the nonculture tests have some false-positive results. Thus, they may not be suitable for use in low prevalence settings when the predictive value of a positive test will be low.[87] Nonculture tests should never be used when a result is being sought for legal purposes, such as in cases of rape or child abuse.

It should be stressed that some of the chlamydial diseases can be managed without a specific diagnosis. For example, urethritis in men can be managed easily on the basis of Gram stain (see Figure 4). In other instances, presumptive treatment is given based on clinical findings (Table 5). For example, women with mucopurulent endocervicitis or salpingitis should be automatically treated for chlamydial infection. Evaluation and treatment of sex partners is indicated in all of these conditions.

Serology is not useful in diagnosing uncomplicated genital tract infections, although the higher antibody titers seen by the microimmunofluorescence (micro-IF) test in complications (e.g., epididymitis, salpingitis, Fitz-Hugh–Curtis syndrome) may provide some support for an etiologic diagnosis.[88] Seroconversion may occur in a first infection with *C trachomatis,* but its detection will take several weeks and is therefore seldom clinically relevant.[89]

Neonatal Infections. Conjunctivitis can be diagnosed readily by any of the cytologic tests. Giemsa stain is adequate in diagnosing severe cases of conjunctivitis, while the DFA and EIA techniques are quite sensitive.[90] The agent can be easily isolated.

Although a specific diagnosis for pneumonia may be more difficult because of sampling problems, the organism can often be isolated from the nasopharynx or tracheobronchial aspirates.[19,35] Serology may be the test of choice in diagnosing chlamydial pneumonia because of the sampling problems.[91] Infants with chlamydial pneumonia almost always develop high IgM antibody levels. Because of their defined exposure (at birth), the diagnosis can be readily established on the basis of a single point titer of specific

TABLE 5.—*Treatment of Chlamydial Infections*

Organism and Condition	First Choice		Second Choice	
	Drug	Dose	Drug	Dose
C psittaci				
Psittacosis	Doxycycline*	100 mg b.i.d. × 3 wk	Erythromycin	250 mg q.i.d. × 3 wk
C pneumoniae				
Respiratory	Doxycycline	100 mg b.i.d. × 3 wk	Erythromycin	250 mg q.i.d. × 3 wk
C trachomatis				
LGV	Doxycycline	100 mg b.i.d. × 3 wk	Sulfamethoxazole	1 g b.i.d. × 3 wk
Trachoma biovar				
Genital tract infections (e.g., urethritis, cervicitis)	Doxycycline	100 mg b.i.d. × 1 wk	Erythromycin	500 mg q.i.d. × 1 wk
In pregnant women	Erythromycin	500 mg q.i.d. × 1 wk	Amoxicillin	500 mg t.i.d. × 1 wk
Infant pneumonia or inclusion conjunctivitis (infants)	Erythromycin	10 mg/kg q.i.d. × 2 wk	Sulfisoxazole	37.5 mg/g q.i.d. × 2 wk
Inclusion conjunctivitis (adults)	Doxycycline	100 mg/kg b.i.d. × 2 wk	Sulfisoxazole	37.5 mg/g q.i.d. × 2 wk

*Tetracycline 500 mg q.i.d. is considered to be the therapeutic equivalent of doxycycline 100 mg b.i.d. As doxycycline has become less expensive, it has become preferred because of potential advantages in compliance.

antichlamydial IgM antibodies, more than 1:32 in the micro-IF test.

Lymphogranuloma Venereum. LGV results in relatively high complement-fixing (CF) antibody levels and the CF test can be used to support a diagnosis. The micro-IF test can be used the same way, and very high titers of broadly reactive antibody are usually found.[92] Chlamydiae can be isolated from ulcers, lymph node aspirates, rectal swabs, or biopsies. DFA can also be used. In the past, the diagnosis was based on the use of a delayed hypersensitivity skin test (Frei test). This test is not recommended because of problems with sensitivity and specificity.[76] It is not available in the United States but is still available in some other countries.

Chlamydia psittaci

Clinical signs are not pathognomonic, although a relatively low pulse associated with a high fever and severe headache can be suggestive in a patient with pneumonitis. The physician's index of suspicion (asking questions about potential exposure to birds) is usually crucial to arriving at a diagnosis. Serodiagnosis is generally considered to be the method of choice because isolation of the agent is seldom achieved. Rising antibody levels can be demonstrated by CF or micro-IF tests.

Chlamydia pneumoniae

The diagnosis of *C pneumoniae* infection is relatively difficult. The organism does not grow well in cell culture systems. It can be isolated from throat swabs, and HeLa cells appear to be the most susceptible cell line. More often the diagnosis is established on serologic grounds. Approximately 50% of cases will show fourfold or greater rises in CF titers. Seroconversion, high ($\geq$ 1:512) IgG antibody levels, or IgM ($\geq$ 1:32) levels in the specific microimmunofluorescence tests are the usual diagnostic criteria.[24] Seroconversion may take four weeks.

Treatment

Chlamydia trachomatis

Trachoma. To prevent blindness in the hyperendemic areas, WHO recommends intermittent topical therapy with 1% tetracycline ointment.[93] In the typical setting this is given to all school children or young children in a village once or twice daily for six consecutive days on a twice yearly schedule. This regimen will not cure trachoma, but it will reduce the severity of the disease and thus prevent blindness. Oral therapy is appropriate for individual cases but cannot be easily administered on a mass basis in endemic areas.

TABLE 6.—*Syndromes Calling for Presumptive Treatment for C trachomatis*

Syndrome	*Expected Chlamydial Infection Rates*
A. Men	
Nongonococcal urethritis	25-50%
Gonorrhea	20%
Epididymitis (in young men)	60%
B. Women	
Mucopurulent endocervicitis	30-50%
Pelvic inflammatory disease	25-50%
Gonorrhea	35-45%
Partner with NGU	30%
Partner with *Chlamydia*	65%

Genital Infections. Treatment of uncomplicated genital tract infection is relatively easy with 2 g tetracycline/day for 7 days. This program results in cure rates in excess of 95%.[29] Upper genital tract infections require longer courses of therapy. Short-term therapy plays no role in management of chlamydial infections (Table 6).

Infant Infections. Chlamydial infection in the infant calls for systemic therapy with erythromycin (50 mg/kg in divided doses each day). Conjunctivitis will respond to 7 to 10 days of therapy, while pneumonia should be treated for 14 to 21 days. Topical therapy is not recommended for ICN because of relatively high failure rates and the fact that oral therapy will prevent subsequent development of pneumonia.

Lymphogranuloma Venereum. There are little data available from controlled treatment trials of lymphogranuloma venereum. Tetracyclines and sulfonamides have been used. The treatment of choice appears to be at least two weeks of tetracycline at 2 g/day. The response may be variable. In some instances, several courses of therapy appear to be necessary.

Chlamydia psittaci

Tetracycline, 2 g/day for at least two weeks, is considered the treatment of choice, with erythromycin being the alternative drug. Relapses are common if the patients are inadequately treated.

Chlamydia pneumoniae

These infections are treated as atypical pneumonias. The drugs of choice are tetracycline and erythromycin. No data are available from controlled treatment trials.

Prevention

There are no effective vaccines for human chlamydial infection.[1,14] The natural history of some of these infections, and the results of some experimental trachoma vaccine trials, suggest that a short-lived immunity can develop. Unfortunately, some vaccinees developed severe disease, and repeated infections are more likely to produce deleterious results. The importance of this evidence for immunopathology in chlamydial disease has been borne out with identification of a 57 Kd protein-sensitizing antigen.[45] Thus, there is now hope that modern techniques of molecular genetics will allow production of subunit vaccines free from sensitizing antigens.

Chlamydia trachomatis

Trachoma. Trachoma is a disease of poverty in developing countries. There are no control measures better than improvement in standard of living. Application of topical antibiotics will reduce severity of the disease and thus minimize the incidence of subsequent blindness. Corrective lid surgery is available to prevent development of blindness in those who already have lid deformity.

Sexually Transmitted Infections. Chlamydia control programs are only now being developed.[29] The Centers for Disease Control has recommended treatment guidelines for the management of chlamydial infections.[51] With the broader availability of diagnostic tests, the recommendation has been made that chlamydial infections be made reportable. Reporting of nongonococcal urethritis and PID (the former being the best proxy for chlamydial infections and the latter being the most important complication) should provide a firmer data base. In this way the prevalence and incidence of these conditions can be established. When high-risk pop-

ulations are better defined, control efforts can be implemented. It is likely that screening programs for asymptomatic sexually active individuals will yield higher rates of infection and be more cost effective for *C trachomatis* infection than they are for gonococcal infection. Routine treatment of all gonococcal infections with regimens effective against *C trachomatis* in heterosexuals will have some impact on the reservoir. About 500,000 of the 1.8 million annual cases of gonorrhea also involve chlamydial infections. The appropriate use of antichlamydial therapy on presumptive grounds in syndromes such as nongonococcal urethritis and mucopurulent endocervicitis will also have an effect. Contact tracing should be particularly productive in identifying new cases of *C trachomatis* infection because the reservoir is so large. The current efforts to promote condom use because of AIDS could benefit chlamydia control. Use of barrier contraceptives will reduce transmission.

In order to be effective, chlamydia control programs will have to attack the reservoir of infection. The interventions just described will help to reduce the reservoir but will leave many infected individuals untested. Even if routine screening for chlamydial infection is introduced for sexually active females at times when they have routine pelvic examinations, it will not address the issue of male carriers. Approximately 10% of asymptomatic, sexually active young men have urethral chlamydial infection.[94] It will require development of noninvasive tests that are acceptable to the asymptomatic males (urethral swabbing will not be) before screening programs can have a major impact.

Perinatal Infections. Infections in infants are preventable. A program of screening pregnant women and erythromycin treatment for those found to be infected will prevent perinatal chlamydial infection.[95] Use of topical erythromycin or tetracycline for ocular prophylaxis in the newborn may reduce inclusion conjunctivitis of the newborn but does not prevent it.[96] This regimen will not prevent pneumonia.

Chlamydia psittaci

Traditionally, the administrative method of controlling psittacosis derived from exotic birds has been by embargo. Importation of psittacine birds has been prohibited by many countries. Screening to select psittacosis-free birds for breeding has been used to establish uninfected flocks of those small birds that can be bred in captivity. Chemoprophylaxis for exotic birds has been developed.[97] If birds are held in quarantine and appropriately treated with tetracycline-containing feed, they can be cleared of *C psittaci* infection before they are introduced into normal distribution channels. When treated birds are introduced into commerce, clean premises can be maintained by keeping habitats closed and avoiding introduction of any untreated birds. Unfortunately, this approach will not work in the poultry industry because of potential contamination of premises by infected feral birds.[98]

Conclusions

As noted, chlamydiae are extremely common human pathogens, causing a broad spectrum of diseases. Human psittacosis, although long recognized, is probably the least important human chlamydial disease. It is not currently a major research area. *C pneumoniae* infections, on the other hand, have been described only in the last few years. This is the "hot" area in clinical research on chlamydial infections. It is obvious that this organism is widely distributed and that infection is common. This is a story that is unfolding.

In contrast, the torrent of new information on *C trachomatis* infections has slowed. After two decades of expansion of its clinical spectrum and increased awareness of the high prevalence of these infections, this is an area in consolidation. The application of techniques of molecular biology has rekindled hopes for a trachoma vaccine. There is need for such a vaccine. Trachoma remains the world's leading cause of preventable blindness. It has become obvious that the standard of living in many developing countries in which trachoma is endemic is not improving. With population growth, more people will be at risk of trachomatous blindness.

Sexually transmitted chlamydial infections remain a major public health problem. There is a clear need for an effective chlamydia control program.[99] The targets for reduction are well identified (see Table 3). These infections, and their consequences, cost billions of dollars each year. Thus control programs are almost certain to be cost effective. Given that reasonably accurate diagnostic tests are readily available and that these infections are easily treated, the lack of a control program is unacceptable.

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