Pneumocystis pneumonia (PCP) is one of the most common pulmonary infections in persons with impaired cell-mediated immunity, and particularly those infected with human immunodeficiency virus (HIV). Pneumocystis was first described in the lungs of guinea pigs, during experiments on American trypanosomiasis by Carlos Chagas in 1909 and by Antonio Carinii in 1910. Both considered the cysts of pneumocystis as part of the trypanosome’s life cycle. Shortly afterward the Delanoes found identical forms in the lungs of rats that had not been infected with trypanosomes and recognized the organism as a separate species. The name Pneumocystis carinii, was given to this organism as a generic name (Greek: pneumon, “lung”; kystis, “cyst”), honoring Carinii.

The organism attained medical significance, when van der Meer and Brug in 1942, and later Vanek, Jirovec, and Luke suggested it to be the cause of interstitial plasma cell pneumonia, a disease affecting premature and debilitated infants in central and eastern Europe. In the 1960s P. carinii was recognized as an important cause of pneumonia in immunocompromised adults on corticosteroids and cancer chemotherapy, in organ transplant recipients, and in children with primary immunodeficiency syndromes. The emergence of acquired immune deficiency syndrome (AIDS) in the 1980s thrust P. carinii to the forefront once again, as a leading cause of morbidity and mortality in immunocompromised individuals. Pneumocystis organisms infecting human beings have recently been named P. jiroveci.

The complete identification and classification of pneumocystis has taken many decades. Although initially considered to be a protozoan, it is now generally agreed that pneumocystis is a fungus. The ribosomal RNA is homologous to that found in fungi. A study of the small subunits of ribosomal RNA (16S-like rRNA) of P. carinii and the fungus Saccharomyces cerevisiae shows close evolutionary linkage between the two. The pneumocystis organisms also stain with methenamine silver stains, further supporting a closer link to fungi rather than protozoa. Recent molecular genetic studies that demonstrate the thymidylate synthase and dihydrofolate reductase genes to be similar to their counterparts in S. cerevisiae support the classification of pneumocystis as a fungus. Furthermore, ultrastructural studies have failed to show the cytoskeletal elements and complex organelle systems characteristic of protozoa.

Pneumocystis organisms are ubiquitous and globally distributed, having been identified in virtually every mammalian species including humans as well as rabbits, dogs, goats, cats, swine, chimpanzees, owl monkeys, and horses. The organisms have a wide range of genetic characteristics that are host specific. This observation was confirmed when polymerase chain reaction (PCR) applied to the human pneumocystis identified only P. jiroveci.

Epidemiology

The epidemiologic features of P. jiroveci are poorly understood. Experimental studies have shown that the infection is acquired by inhalation. There does not appear to be a natural transmission of P. jiroveci across species. Immunosuppressed rats and nude mice acquire the infection by direct and distant contact with infected animals. In humans, the major predisposing factor is impaired cellular immunity as seen in AIDS, protein-calorie malnutrition, primary immunodeficiency diseases, immunosuppressive therapy with corticosteroids or other agents, and prematurity. The organisms are present in practically every part of the world, including the temperate, tropical, and polar regions. The use of molecular technology through the dihydropteroate synthase (DHPS) locus analysis has facilitated epidemiologic study of the prevalence of P. jiroveci in the human population. Identical genotypes of P. jiroveci were found in...
the two groups of immunocompetent infants and adults with pneumocystis infection in a study from France, suggesting that the transmission cycles of infection in all individuals parasitized by P. jiroveci are linked with a common human reservoir.39,40

It is not clear whether there is an environmental reservoir for P. jiroveci, although mammalian lung appears to be a natural home.35 The isolation of pneumocystis DNA from rural outdoor locations and a seasonal variation in infection in patients suggest that there may be an environmental reservoir.41 Primary exposure to pneumocystis occurs early in life, so that most children have serum antibody by the age of 2 to 3 years.52-54 This is presumed to be an asymptomatic infection. The organisms remain latent within the host, and propagate when the host immune system becomes compromised. Several studies using PCR have found no evidence of pneumocystis DNA in the lungs of immunocompetent individuals, and do not support the latent reactivation theory.41,46-48 There are also experimental data in rat models that suggest that pneumocystis organisms do not persist in the lungs of immunocompetent individuals.49 Transmission of pneumocystis has been shown to occur animal to animal when they had a common air supply, in immunosuppressed as well as immunocompetent models, although the latter had a subclinical transient infection.41,50,51 Clinical studies have suggested the occurrence of human to human transmission of pneumocystis organisms.52-56

Acquired immune deficiency syndrome patients have been found to develop immunoglobulin M (IgM) antibodies with recurrent episodes of pneumocystis pneumonia.57 It has also been shown by immunoblotting that P. jiroveci (carinii) antigen recognition patterns in bronchoalveolar lavage (BAL) fluid can change with recurrent episodes of pneumonia.58 These findings may represent infections with different antigenic strains or antigenic changes in the existing strain of P. jiroveci. Recently, mutations in the DHPS gene of P. jiroveci were identified and used in epidemiologic studies of P. jiroveci. In one study of 139 HIV-infected patients with pneumocystis infection, 19% of patients with prior sulfa treatment had the gene mutation, compared to 4% of those without treatment.59 Co-infection with multiple strains of P. jiroveci was found in 20% to 30% of cases, suggesting that recurrent infections may be related to reinfection with a new strain rather than reactivation.60 The DHPS gene–type variation was related to the place of diagnosis and not the place of birth, suggesting the infection to be recently acquired. Additionally, 54% of P. jiroveci strains in newly diagnosed HIV-infected patients demonstrate DHPS gene mutations. Since these patients were not treated with sulfa drugs, such mutations suggest that the infection was acquired from patients who had received prophylactic sulfa. The authors therefore believed that these findings represent evidence for person-to-person transmission of pneumocystis. Person-to-person spread of P. jiroveci is also suggested by outbreaks of infection in malnourished infants in orphanages and in hospitals caring for immunosuppressed patients.37

Life Cycle

The major obstacle to study the life cycle and biology of pneumocystis is the inability to sustain propagation of the organism outside the lung.28 Our understanding of the life cycle of P. jiroveci derives mainly from detailed ultrastructural studies.61-65 Four developmental forms are described: trophozoites, cysts, precysts, and sporozoites (also known as intracystic bodies).66,67 All investigators have consistently identified the trophic (trophozoite) and the cyst stage, and also an intermediate precyst stage. Experiments using P. carinii from lungs of infected rats and human lung cell cultures have been partially successful in growing the organisms to study the life cycle.68 Based on the cell culture studies, it was proposed that several developmental pathways may exist.68 The environment may play a significant role in determining the predominant method of replication as it does in many yeast or other microorganisms.69,70 In tissue culture, at least two methods of development were proposed: an asexual cycle and a sexual cycle. Figure 13.1 shows the two cycles of P. jiroveci pneumonia development. The asexual cycle involves mitotic replication of the trophic forms. The sexual cycle involves the continued development of precyst stages to mature cyst forms, and the development of elongated daughter forms within the cyst, followed by excystation and collapse of the cyst.

The vegetative forms of pneumocystis, the trophozoites, are 2 to 8μm in diameter, and attach to type I alveolar epithelial cells. Although initially haploid, the trophozoites are believed to attain a diploid chromosomal number by gametic fusion.37 The trophozoites enlarge and develop into diploid precysts through a process of cell wall thickening.35 Sporozoites then develop within the precysts following meiosis and mitosis, a process referred to as asporogony.67,69 Mature cysts contain eight haploid sporozoites that become trophozoites, following rupture of the cyst wall, and recapitulate the life cycle.

The cyst is the largest and most easily recognized developmental stage of P. jiroveci. As demonstrated with Gomori’s methenamine silver (GMS) stain, the cysts are thick-walled spherules, 5 to 7μm in diameter, that assume a cup or crescent shape when collapsed. The cyst wall is trilaminar, 70 to 160nm in thickness, and shows a thick electron-dense outer layer, an electron-lucent middle layer, and a thin inner cell membrane.37 The cyst wall stains well with methenamine silver stain, cresyl echt