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PNEUMOCYSTIS CARINII PNEUMONITIS

Volume II

Walter T. Hughes

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DEDICATION

To Jeanette, Carla, Greg, and Chris.

PREFACE

A fascinating aspect of infectious diseases is the remarkable change that takes place over a span of several years. Within the past 50 years and within the lifetimes of many physicians practicing today, smallpox has been eradicated from the world; the incidences of tetanus, diphtheria, poliomyelitis, and pertussis have been greatly reduced through immunization programs; and, many younger physicians have never seen a case of measles, mumps, or rubella. Hospitals that were once dedicated to patients with tuberculosis have now been closed or used for other purposes. Scarlet fever and rheumatic fever have mysteriously diminished in frequency of occurrence. However, new entities have been recognized and previously unknown microorganisms have been discovered. Within the last decade, Legionnaire's disease, rotavirus enteritis, cryptosporidiosis, and human T-cell lymphotropic virus type III/lymphadenopathy-associated virus infection have become well-known diseases. Concomitant with such changes *Pneumocystis carinii* emerged from obscurity to take advantage of those immunosuppressed from advanced therapeutic modalities for cancer, organ transplant recipients, weakly infants, and victims of the acquired immunodeficiency syndrome (AIDS). In 1984 more people in the U.S. died from *P. carinii* pneumonia than from measles, mumps, varicella, gonorrhea, syphilis, leprosy, malaria, meningococcal infections, pertussis, poliomyelitis, plague, tetanus, rabies, rubella, rheumatic fever, scarlet fever, and typhoid fever *combined.*

In a sense *P. carinii* has served well as a modern ''diagnostician'' for congenital and acquired immune deficiency disorders. For many years the smallpox vaccine revealed congenital immunodeficiency disorders for the first time in infants who developed progressive vaccinia after receiving the live-virus vaccine. Since smallpox vaccination was discontinued, *P. carinii,* as well as other opportunistic organisms, have served in this respect. It was because of the fact that *P. carinii* pneumonitis occurred almost exclusively in the immunocompromised host that AIDS was recognized in 1981. Paradoxically, *P. carinii* infection is perhaps one of the most frequently encountered infections of man with three fourths of us becoming asymptomatically infected by the age of 4 years.

The intent of these volumes is to gather together information that has accrued over 75 years since the organism was first discovered. *P. carinii* has attracted the interests of a variety of professionals including parasitologists, pathologists, microbiologists, internists, pediatricians, surgeons, veterinarians, and others. Its cosmopolitan distribution has resulted in publications of its discovery in Brazil and France, of epidemics in infants in Europe, of sporadic disease in compromised patients in the U.S., Canada, Japan, England, Australia, Africa, India, the U.S.S.R., and other countries as well as high prevalence in animals throughout the world. Thus, our knowledge of this organism and the disease it causes comes from publications in many languages, often in journals with limited circulation and from physicians and scientists from widely diverse fields. I have attempted to review these data, often in great detail, sometimes briefly, but with sufficient documentation that the reader may search out references for his own review.

The disappointing reality of this undertaking is the fact that at the time of publication portions of the contents will be outdated and important recent developments will not have been included. It is also realized that despite diligent searching and a conscientious effort to be all inclusive some publications may have escaped review. This work was composed at a time when proliferation of publications abounded, primarily because of the AIDS epidemic, and greater scholarship could perhaps have been achieved by waiting until many interesting and important problems are solved. However, it was felt this compilation of data might in itself be useful to those involved in the care of patients with *P. carinii* pneumonitis and those involved in research with the organism and the disease.

The delightful reality of this undertaking was the association with many people who have

a common interest in this unique parasite, the disease, and the publication. Especially helpful to me over the years have been colleagues at St. Jude Children's Research Hospital. These include Warren W. Johnson, M.D., who was the first to teach me at the microscope about this organism and Donald Pinkel, M.D., who emphasized the importance of what seemed at the time to be an insignificant disease; Robert Price, M.D., who aided in histopathological studies; Linda Pifer, Ph.D., who spent several years as a colleague in our laboratory and subsequently established her own laboratory to further research efforts on certain aspects of *P. carinii,* and S.K. Sanyal, M.D., who contributed much to our understanding of the pathophysiology of the pneumonia. Especially important to clinical studies has been Sandor Feldman, M.D., whose attention to detail and completeness have added strength to our efforts. Martin J. Murphy, Ph.D., permitted us to visualize the organism through scanning electron microscopy. Postdoctoral fellows and trainees in infectious diseases who have elected an interest in *P. carinii* and contributed in a major way as co-investigators include Subash Chaudhary, M.D., H.K. Kim, M.D., David Grigsby, M.D., John W. Smith, M.D., Fred Cox, M.D., Paul McNabb, M.D., Thomas D. Makres, M.D., Frank Sisko, M.D., Samuel Havron, M.D., Michael Ossi, M.D., Richard B. Wilber, M.D., Douglas Bartley, M.D., and Haysam Tufenkeji, M.D. Relatively new investigators in our department who have had added a surge of enthusiasm to more basic research on this organism and its disease are Francis Gigliotti, M.D. and Dennis Stokes, M.D. In one way or another all of these colleagues have contributed to this volume.

Acknowledgement of other key investigators who through their research and their generous communications to me is indeed warranted. These include Peter D. Walzer, M.D., Lowell Young, M.D., Donald Armstrong, M.D., Harry Haverkos, M.D., John Mills, M.D., Constance Wofsy, M.D., Edward Pesanti, M.D., James W. Smith, M.D., Marylin S. Bartlett, M.S., Joel Ruskin, M.D., Sergio Stagno, M.D., Pieter J.A. Beckers, Ph.D., J.H. Meuwissen, M.D. and Werner Dutz, M.D., to mention a few.

If I am to make any prediction about *P. carinii* it will be that we have only begun to recognize the impact of the organism on man and that when the molecular biology is elucidated in detail it will be found to be remarkably unique.

Walter T. Hughes, M.D.

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Dr. Hughes received his M.D. degree from the University of Tennessee College of Medicine. He completed an internship at the Knoxville General Hospital and a pediatric residency at the LeBonheur Children's Hospital at the University of Tennessee. Following his residency he spent 2 years in infectious diseases research at the Walter Reed Army Medical Center and the Ft. Dietrick laboratories in Maryland. His first academic appointment was at the University of Louisville School of Medicine where he worked with Dr. Alex Steigman in clinical studies of the more common infections of children. In 1969 he moved to St. Jude Children's Research Hospital, an institute dedicated primarily to research in childhood cancer, to concentrate on infections of the immunosuppressed host. He soon became interested in a relatively new, and presumed rare, infectious disease caused by *Pneumocystis carinii*. During the past 2 decades his work has been directed to the elucidation of clinical aspects of this disease, to determining the natural habitat and mode of transmission of the infection, to the development of preventive and therapeutic modalities, and to characterize the biological features of the organism.

In 1977 Dr. Hughes joined the faculty at The Johns Hopkins University School of Medicine as Eudowood Professor of Pediatrics and Director of the Division of Infectious Diseases. Here he continued research in *P. carinii* pneumonitis and became actively involved in teaching clinical aspects of infectious diseases. In 1981 he returned to St. Jude Children's Research Hospital but continues to hold the faculty appointment of Lecturer in Pediatrics at The Johns Hopkins University. At this time *P. carinii* pneumonitis quickly gained notoriety because of its role in the acquired immunodeficiency syndrome (AIDS). Currently Dr. Hughes' research is aimed at methods to prevent, diagnose, and treat *P. carinii* pneumonitis. He has published over 250 scientific papers dealing primarily with infectious diseases in the immunosuppressed host.

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Chapter 8

CLINICAL MANIFESTATIONS

I. INTRODUCTION

The clinical manifestations of *Pneumocystis carinii* infection are limited almost exclusively to the respiratory tract. While tachypnea and dyspnea are common features of all cases of overt *P. carinii* pneumonitis, some variations can be categorized based on the age and condition of the host. The following scheme permits this categorization dealing with clinically distinct forms of the infection.

1. Subclinical infection
2. Infantile — epidemic interstitial plasma cell pneumonitis
3. Child-adult sporadic pneumonitis in the immunocompromised host
   A. Congenital and provoked immune deficiency disorders
   B. Acquired immunodeficiency syndrome (AIDS)
4. Unusual variants

II. SUBCLINICAL INFECTION WITH *P. CARINII*

By definition subclinical infection with *P. carinii* is not associated with discernible illness. However, no studies have investigated the primary, *de novo* infection in man. Since the majority of healthy individuals have acquired antibodies to *P. carinii* by 4 years of age the possibility exists, though not proven, that some subtle clinical expression of this "subclinical" infection may occur and has not yet been recognized. Details of the subclinical infection are given in the chapter on pathology.

III. INFANTILE (EPIDEMIC-TYPE) *P. CARINII* PNEUMONITIS

The first report of *P. carinii* pneumonitis in humans was from Amsterdam in 1942.[1] The organism was found infecting the lungs of a 3-month-old child with congenital malformation of the heart. The authors also found the organism in smear preparations from the lungs of 2 out of 104 autopsy cases examined, in a 4-month-old child and in an adult aged 21 years. Little information on the clinical manifestations of these cases was given in this landmark paper.

The first report providing comprehensive information on the interstitial plasma cell pneumonitis of infants caused by *P. carinii* came from Vanek et al.[2] in 1952. The observations were based on 32 autopsied cases in Czechoslovakia. They succintly described the clinical features. The onset was usually gradual with increasing tachypnea, dyspnea, and cyanosis. Fever and cough rarely occurred. The respiratory rate of severe cases reached 90 to 120 respirations per minute. Weight loss or failure to gain the expected weights was common. The physical findings were not striking. Infrequent crackling crepitations were heard over areas of consolidation. There were areas of dullness, usually paravertebrally, and areas of hyperresonance were encountered in some areas, probably due to compensatory emphysema. The duration of the respiratory symptoms (dyspnea, tachypnea, and cyanosis) in untreated cases was about 2 to 3 weeks. An additional 2 to 3 weeks was required to achieve complete recovery in those infants who survived. In 1957 Ariztia et al.[3] described similar cases from Chile. Of these ten cases all were considered to be undernourished and seven were premature infants. The clinical onset was difficult to determine since the signs and symptoms were

Table 1
CLINICAL SYMPTOMS IN INFANTILE *P. CARINII* PNEUMONITIS

Group	Patients	Cough	Chest retractions	Tachypnea	Cyanosis
I	6	6	6	6	6
II	14	14	14	14	3
III	8	8	6	6	3
IV	5	5	3	3	0

Modified from Dutz, W., Post, C., Vessal, K., and Kahout, E., *Natl. Cancer Inst. Monogr.*, 43, 31, 1974.

often mild and nonspecific. In six of the ten cases the onset was characterized by dyspnea, cyanosis, and loss of appetite. The temperature was never higher than 38°C. On examination the respiratory distress was marked and there was an anxious expression on the face. Moderate crepitations and rales were heard in only six of the cases. The blood count was not remarkable. Similar clinical features were reported from British infants in 1957.[4]

The most detailed information on the clinical features of infantile pneumocystosis comes from studies in Shiraz in South Iran. Endemic *P. carinii* pneumonitis was studied from 1961 to 1970 by a team of several pediatricians and pathologists.[5-9] The circumstances of the endemic in the Shiraz orphanage gives a clear understanding of the clinical aspects of the disease.[5] The institution in its early years of the studies operated under difficult circumstances. The nursing technique was poor, several children at times were fed with the same bottle. Fly control was very poor. Within 2 to 6 weeks after admission, even infants in good nutrition developed diarrhea from salmonellosis, shigellosis, enteropathogenic *Escherichia coli* etc. Even though the dietary intake of milk and formula was more than adequate to meet caloric needs and infants appeared hungry, taking formula in greedy gulps, most of them failed to thrive. A pattern of marasmus appeared after about 6 weeks of diarrhea. At 3 months of age most infants were less than birth weight. Infectious diseases "were rampant" among the debilitated infants, especially furunculosis and bronchopneumonia. The development of infants was severely hampered and almost none of the infants achieved the third percentile in weight and height for the first year of life. The author's state that "these children looked like skeletons; no trick of the pediatric feeding armamentarium helped to improve the nutritional status since atrophy of the intestinal mucosa by itself interfered with absorption."[9] It was under these adverse circumstances that symptoms of respiratory illness appeared, especially tachypnea, cough, cyanosis, and intercostal retractions. A summary of clinical symptoms from several groups of infants with *P. carinii* pneumonitis in the Shiraz orphanage is given in Table 1.

The sequence of signs and symptoms and pace of clinical manifestations has been expertly described by Gajdusek[10] in 1957 from a detailed review of the European epidemics in infants as well as his own observations of the infantile form of the disease. Usually the onset is slow and insidious and the earliest signs are nonspecific such as restlessness, languor, and poor feeding. An increased respiratory rate and a peculiar perioral and periorbital bluish cyanosis may be the first signs of respiratory tract involvement. At this time the lungs may appear normal to auscultation and percussion. Coryza, cough and fever may be absent as the respiratory rate increases and abdominal movements become associated with respiratory movements. After 1 to 2 weeks, dyspnea is more marked with flaring of the nasal alae, sternal retraction, use of auxillary muscle of respiration, increasing cyanosis, and extreme tachypnea. An anxious tortured-like facies with widely opened eyes and perspiration-covered head is characteristic. Abrupt episodes of coughing occur in some infants. The physical

findings are limited to fine crepitant rales and retractions of the chest wall. Even in the advanced stages of the disease the temperature remains normal or only slightly elevated. About one fourth of the infants may die. In those who survive, the course is usually prolonged over 4 to 6 weeks. In some infants the course is fulminating with death following only 2 to 3 days after onset of symptoms. The chest radiographic features are described in the chapter on diagnosis.

The infantile type of *P. carinii* pneumonitis is not limited to Europe or epidemic frequency. Several cases of the infection in Vietnamese infants have been described in refugees to the U.S.[11-14] These infants had clinical features similar to those described above.

IV. CHILD-ADULT (SPORADIC-TYPE) *P. CARINII* PNEUMONITIS

This clinical category of *P. carinii* pneumonitis refers to patients over approximately 6 months of age who are susceptible to the pneumonitis because of an underlying abnormality in the immune response. This includes individuals with congenital immune deficiency disorders, organ transplant recipients, patients with malignancies, and those receiving immunosuppressive therapy for other reasons. There are differences in clinical expression of the pneumonitis of this category when compared to the infantile type. Since patients with the acquired immunodeficiency syndrome (AIDS) may have some features of the infection that differ from the non-AIDS child or adult, this group will be considered separately.

A. Congenital and Provoked Immune Deficiency Disorders

Since the clinical manifestations of *P. carinii* pneumonitis are generally similar for individuals whose problem is malignancy, immunosuppressive therapy, organ transplantation, or congenital immunodeficiency disorders, these patients will be considered as a group. A special point will be made about the mode of onset in congenital immune deficiency disorders.

A report with clinical data on the largest number of patients with *P. carinii* pneumonitis is that of Walzer et al.[15] in 1974 from the Centers for Disease Control (CDC) in Atlanta. They tabulated the clinical features of 168 patients with confirmed *P. carinii* pneumonitis reported to the CDC from medical centers in the U.S. These data are summarized in Table 2. The majority (51%) of these patients had been symptomatic for less than 2 weeks prior to the diagnosis. The mean duration of symptoms was 19.7 days (median 13.6 days; range 3 to 120 days). This heterogenous group of patients was comprised of some infants with primary immune deficiency disorders and children and adults with malignancies, collagen-vascular disorders, organ transplant recipients, and a variety of other underlying abnormalities. The physical findings are summarized in Table 3. One must appreciate the fact that these clinical values were collected by many physicians at several medical centers over a period of a few years so some variations could be expected. Also concurrent infections were evident in about one fourth of the patients (Table 4).

Other studies have involved relatively large numbers of patients studied at single institutions. Some of these will be reviewed to indicate the consistent pattern of clinical manifestations. In children with cancer, 100 confirmed cases of *P. carinii* pneumonitis were studied sequentially at St. Jude Children's Research Hospital.[16] The clinical profile at the time of diagnosis is given in Table 5, 98 of these patients had bilateral diffuse alveolar disease discernible by chest radiograph. The fever ranged from 38 to 40°C and followed a persistent and spiking pattern. In 80 of these patients described in our earlier study the maximum respiratory frequency was determined.[17] This value taken as the least of the three highest recordings of respirations per minute, 4 or more hours apart, was greater than 40/min in 72 (90%) of the 80 children. The mean maximum rate was 68/min. In 7 patients the rate reached 100 respirations per minute. The cough was dry and nonproductive of sputum and was not paroxysmal. Cyanosis appeared after extensive infiltration became apparent on

Table 2
CLINICAL FEATURES IN 168 PATIENTS WITH CONFIRMED *P. CARINII* PNEUMONIA

Clinical features	No.	%
Symptoms		
Dyspnea	152	91
Fever	110	66
Cough	79	47
Productive cough	12	7
Hemoptysis	3	2
Chest pain	11	7
Night sweats	1	1
Signs (respiratory)		
Cyanosis	66	39
Rales	56	33
Breath sounds		
Decreased	22	13
Bronchial/tubular	14	8
Dullness	9	5
Rhonchi	7	4
Wheezing	2	1
Signs (other)		
Hepatomegaly	59	35
Splenomegaly	32	19
X-ray		
Infiltrate		
Diffuse and bilateral	164	98
Unilateral	4	2
Effusion	8	5
Adventitious air[a]	6	4

[a] Pneumothorax, pneumomediastinum, and so forth.

From Walzer, P. D., Perl, D. P., Krogstad, D. J., Rawson, P. G., and Schultz, M. G., *Ann. Intern. Med.*, 80, 83, 1974. With permission.

Table 3
QUANTITATIVE CLINICAL CHARACTERISTICS IN PATIENTS WITH *P. CARINII* PNEUMONIA

Characteristic	No. of patients studied	Mean value	Range
Physical findings			
Temperature (oral)	116	38.8°C	37.0—41.1°C
Pulse	125	129	84—200
Pulse (patients ≥ 10 years old)	75	118	84—180
Blood pressure (mmHg)	95	117/70	80—190/50—112
Blood pressure (patients ≥ 10 years old)	64	123/73	80—190/50—112
Respiration (no./min)	125	46	15—100
Respiration (patients ≥ 10 years old)	72	34	15—76

From Walzer, P. D., Perl, D. P., Korgstad, D. J., Rawson, P. G., and Schultz, M. G., *Ann. Intern. Med.*, 80, 83, 1974. With permission.

Table 4
CONCURRENT INFECTIONS IN 47 OF 194 PATIENTS WITH CONFIRMED *P. CARINII* PNEUMONIA

Systemic		
Bacterial		31
Pseudomonas	9	
Staphylococcus aureus	9	
Diplococcus pneumoniae	3	
Streptococcus	2	
"Gram-negative"	2	
Escherichia coli	2	
Proteus mirabilis	1	
"Mixed"	1	
Hemophilus influenzae	1	
Mycobacterium kansasii	1	
Viral		10
Cytomegalovirus	7	
Influenza A_2	1	
Herpes zoster	1	
Parainfluenza III	1	
Fungal		6
Candida	3	
Cryptococcus	1	
Aspergillus	1	
Histoplasma	1	
Mycoplasma		1
Local		
Candida		7
Herpes simplex		3
Herpes (? type)		1
Miscellaneous		
Otitis media		3
Abscess		2
Pyoderma		1
Peritonitis		1
Total		66

From Walzer, P. D., Perl, D. P., Krogstad, D. J., Rawson, P. G., and Schultz, M. G., *Ann. Intern. Med.*, 80, 83, 1974. With permission.

chest radiographs and was preceded by a period of ashen-gray appearance. When flaring of the nasal alae occurred there was almost always evidence of intercostal retractions. One of the most striking and consistent physical findings was the absence of rales on auscultation of the chest. This sign was absent even with extensive pneumonitis.

The temporal relationship of signs and symptoms is summarized in Table 6. Day 0 refers to the time of onset of the first symptoms from the infection. For example, 58 of the 80 patients had fever on the first day of illness. As can be noted fever and cough were the most frequent presenting signs and symptoms. Discernible pneumonitis by radiograph usually appeared after signs and symptoms had become recognizable. In 29 of the 80 patients pneumonitis was not evident by radiograph until 1 week or more after onset of the illness.

In a study at The Hospital for Sick Children in London 18 cases of *P. carinii* pneumonitis were reviewed.[18] All had either congenital immunodeficiency or a malignancy. The mean distribution of symptoms before presentation at the hospital was 2.5 weeks with a range