INFECTIOUS DISEASES OF CHILDREN

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To

SAUL KRUGMAN

with admiration and affection from his fellow authors and editors
who salute him on 45 years of contributions to
Pediatrics and Infectious Diseases

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PREFACE

The goals of this book have changed little since its first publication in 1958, edited in collaboration with the late Dr. Robert Ward. The preface to that initial edition stated that "the purpose of this book is to provide a concise and handy description of certain common infectious diseases of children. It is written primarily for pediatricians, general practitioners, and medical students who deal with children." We have resisted strenuously the temptation to enlarge the volume to become an encyclopedia covering extensively all aspects of all infectious diseases. This is done very well by a number of other more voluminous textbooks. Our goal has been to maintain this book as a handy, concise, practical reference used readily in the office, in the clinic, in the emergency room, and in the ward library.

This ninth edition has seen an augmentation of the numbers of contributors and authors. The four editors of the eighth edition have enlisted the support of talented colleagues who have brought their personal knowledge and experience to new chapters and to revisions of older ones. Infections caused by *Haemophilus influenzae* have merited the designation of a separate chapter as we enter a phase of successful immunization and the anticipation that invasive disease caused by this virulent organism may in the next few years become as rare in highly immunized populations as polio has become since the early editions of this textbook. Although it has not been proven that Kawasaki syndrome is an infectious disease, its epidemiology and clinical manifestations warrant its tentative inclusion under this rubric and therefore a new chapter has been added. We have always included rickettsial diseases among our topics, but the most prevalent tick-borne infection in recent years has become Lyme disease, which is now included with the rickettsial diseases in a new chapter on tick-borne infections.

In addition to acquired immunodeficiency syndrome (AIDS), which found its way for the first time into our eighth edition, the rapidly increasing numbers of children who are immunocompromised by other illnesses, medications, or suppression for the acceptance of organ or bone marrow transplants has prompted us to include a new chapter on infections in immunocompromised children. Although erythema infectiosum (fifth disease) had earned a few pages in previous editions, the great expansion in our knowledge of parvovirus B-19 and its effects has resulted in an expanded chapter including the new information relating to arthritis, aplastic crises in patients with chronic hemolytic anemias, and transmission of infection to the fetus. The virus responsible for roseola infantum (exanthem subitum) has been identified as human herpesvirus type 6 (HHV-6). New agents and new mechanisms of pathogenesis have been discovered for gastroenteritis. Viral hepatitis has been expanded with the identification of hepatitis virus C and E. To cover all the agents currently classified under the rubric "sexually transmitted diseases" (STD) is a monumental task that has been redone for this edition.

The foregoing as well as other additions and revisions have been integrated into the text to make it as current as possible at the time of publication. The cooperation of the publishers in bringing the book to press in a relatively short span is deeply appreciated by the authors and will be enormously helpful to the readers. Nevertheless, there will undoubtedly be new developments that emerge even in that hiatus of a few months, so the well-informed reader will continue to use this text as a base for clinical problem-solving but look beyond to journals and consultants for information not yet "in press." The editors remain deeply grateful to their respected colleagues who have added so much to this ninth edition.

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CONTENTS

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ACQUIRED IMMUNODEFICIENCY SYNDROME

WILLIAM BORKOWSKY
CATHERINE M. WILFERT

An outbreak of community-acquired *Pneumocystis carinii* pneumonia (PCP) was recognized in California and New York in 1980. Simultaneously, Kaposi's sarcoma occurred at 50 times the expected rate in male homosexuals. These events combined to define an immunodeficiency syndrome never before described. In addition, this syndrome soon was observed in intravenous drug users, recipients of standard blood products (both male and female), and non-drug-using female sex partners of individuals with the disease.

In 1982 an "acquired immunodeficiency syndrome (AIDS)" was recognized in children (Centers for Disease Control, 1982) and was described in New Jersey (Oleske et al., 1983), New York (Rubinstein et al., 1983), San Francisco (Ammann et al., 1983), and Miami (Scott et al., 1984). By 1987 AIDS had become the ninth leading cause of death for children between the ages of 1 and 4 years in the United States (Kilbourne, Buehler, and Rogers, 1990) and the third leading cause of death for black children and Hispanic children of this age in New York and New Jersey. The total number of cases of AIDS in children less than 13 years of age reported to the Centers for Disease Control (CDC) by the end of 1990 exceeded 2500. It is estimated that five to 10 times as many children may be infected by the agent that causes AIDS but have not yet fulfilled the clinical criteria established by the CDC for reporting the disease. AIDS has also become the seventh leading cause of death for adolescents and young adults (ages 15 to 24 years). It increased 100-fold between 1981 and 1987 (The Final Report of the Secretary's Work Group, 1988), and it is anticipated that this infection will be the leading cause of death for these populations by 1991. The most rapid increase in acquisition of human immunodeficiency virus infection is occurring in persons reporting that their risk behavior is heterosexual contact with an infected person. In 1989 as compared to 1988, a 36% increase in AIDS attributable to heterosexual transmission occurred (Oxtoby, 1991). In the same year an increase of 38% in reported pediatric AIDS cases occurred (Oxtoby, 1991; Fig. 1-1). Thus the acquisition of infection by heterosexual contact is reflected in the occurrence of AIDS in children who have acquired infection perinatally.

In less than a decade a previously unknown disease has ascended to become the single most important communicable disease in the United States and many other nations. Although pediatric HIV infection comprises only 2% of the total number of reported cases of AIDS in the United States, the rapid increase in reported cases in children and its emergence as a cause of death in young infants and children is clear.

ETIOLOGY

The causative agents of AIDS were isolated from the blood of patients and were described in both France (Barre-Sinoussi et al., 1983) and the United States (Gallo et al., 1984; Levy et al., 1984). They were referred to as the *lymphadenopathy-associated viruses (LAV)*, the *hu-*

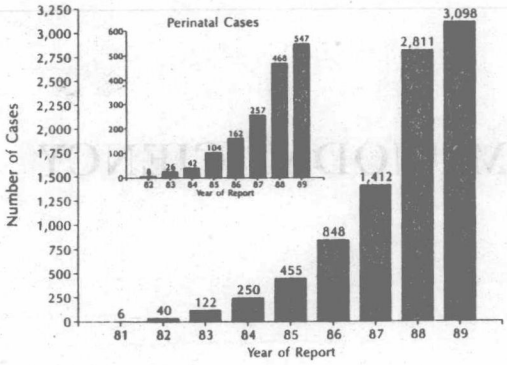

Fig. 1-1. AIDS in women of reproductive age (15 to 44 years) compared to perinatally acquired AIDS in children by year of report in United States through December 1989. (From Oxtoby MJ: In Pizzo P, Wilfert CM, editors. Pediatric AIDS. Baltimore: Williams & Wilkins, 1991.)

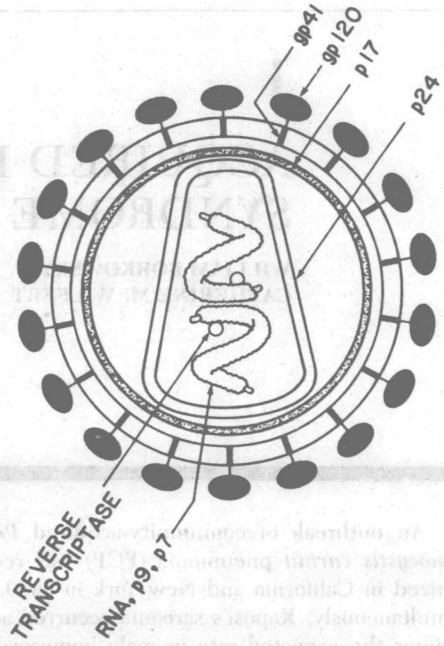

Fig. 1-2. Schematic representation of the morphological structure of HIV-1. ENV gene products, gp120 and gp41; gag gene products, p24, p17, p9, and p7; pol gene product, RT.

man T cell lymphotrophic viruses (HTLV-III), and the *AIDS-related retroviruses (ARV)* by the respective groups. By consensus, these agents now are termed the *human immunodeficiency viruses (HIVs)*. These enveloped RNA viruses are in the lentivirus subfamily of retroviruses and are 80 to 120 nm in diameter. Characteristics of HIV that resemble those of lentiviruses include (1) the long incubation period; (2) the ability to establish latent or persistent infection; (3) the ability to produce immune suppression; (4) tropism to lymphoid cells, particularly macrophages; (5) the ability to affect the hematopoietic system; (6) tropism to the central nervous system (CNS); and (7) the ability to produce cytopathic effects observed in appropriate cell types (Bryant and Ratner, 1991). The major targets of HIV include CD4-antigen–bearing cells, including helper T cells, monocytes and macrophages, Langerhans' cells, and glial cells of the CNS. HIV has also been reported as capable of infecting non-CD4–bearing cells such as enterocytes and certain neuronal cells.

HIV has a cylindrical eccentric core, or nucleoid, that contains the diploid RNA genome (Fig. 1-2). A nucleic acid–binding protein and reverse transcriptase are associated with the genome. Nucleocapsid structure is completed by the capsid antigen (p24), which encloses the nucleoid components. Surrounding the core of the virus is p17, the matrix antigen, which lines the inner surface of the envelope. Knoblike projections formed by the envelope glycoprotein, gp120, are on the surface of the virus. An associated intermembranous portion of envelope, gp41, anchors the gp120 component. The lipid bilayer of the viral particle is derived from the host cell plasma membrane as the virus buds from the cell. A portion of the gp120 domain of the envelope binds to the CD4 molecule of human cells with high affinity, and a segment of the gp41 plays a crucial role in the fusion of the viral envelope with the host cell (Fig. 1-3).

After viral entry and uncoating, the reverse transcriptase characteristic of all retroviruses produces double-stranded virally encoded DNA that enters the nucleus and integrates randomly in the host genome by using the long-terminal-repeat (LTR) segments that flank the other genes of the virus. The virus is then in a latent state in which it may remain indefinitely. A variety of stimuli, including antigens, mitogens, ultraviolet light, heat shock, hypoxia, and proteins derived from other viruses, are capable of ini-

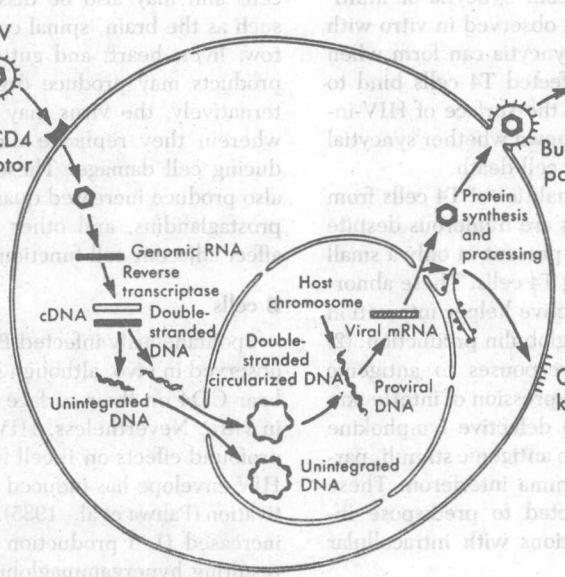

Fig. 1-3. The life cycle of the human immunodeficiency virus. (From Pizzo P, Wilfert CM, editors. Pediatric AIDS. Baltimore: Williams & Wilkins, 1991.)

tiating the transcription of HIV messenger RNA, which is first translated into complex spliced messages. These encode a group of regulatory molecules that ultimately govern the production of HIV messenger RNA capable of producing full-length transcripts and the associated structural proteins. The ribonucleoprotein core buds from the cellular membrane and acquires a coat of viral envelope glycoprotein and the lipid bilayer from the host cell. A viral enzyme (protease) completes the maturation of the virion by cleaving specific internal core components.

The individual isolates of HIV-1 from different persons vary a great deal. There is also considerable variation between sequential isolates obtained from the same person. HIV can spread from cell to cell independent of release of virus from the cell. This spread may occur through the fusion or syncytial formation of an infected cell with uninfected cell(s).

PATHOGENESIS

HIV infection in children is characterized by an incubation period or asymptomatic interval that is much shorter than it is in adults. The inevitable consequence of infection with the HIV is profound immunosuppression, which leaves the host susceptible to the development of infections and neoplasms.

T4 cells

The depletion of helper T cells (CD4) in symptomatic patients has been noted since 1981. HIV is capable of causing a profound cytopathic affect in T4 cells in vitro. However, only a small proportion of cells are infected with the virus, and not all are killed. Uninfected cells also die or are dysfunctional, perhaps mediated by the binding of gp120 to CD4 and thus interfering in its essential association with major histocompatibility complex (MHC) class II molecules. The virus is capable of establishing latency or a low level of replication in some cells.

T4 cell depletion is due in part to direct virus-induced damage, and there is some indication that "memory" helper T cells are more selectively depleted than "virgin" cells. The budding of large numbers of virus particles disrupting the external cell membrane contributes to destruction of the cell by creating osmotic disequilibrium. HIV replication results in the accumulation of a number of foreign products, including viral DNA, RNA, and core proteins, which may interfere with normal cellular function and con-

tribute to death of the cell. Syncytia or multinucleated giant cells are observed in vitro with HIV replication. Such syncytia can form when CD4 molecules of uninfected T4 cells bind to the gp120 expressed on the surface of HIV-infected T4 cells. It is unknown whether syncytial formation contributes to cell death.

The functional abnormalities of T4 cells from HIV-infected individuals are numerous despite the fact that the virus is present in only a small percentage of circulating T4 cells. These abnormalities include (1) defective helper interaction with B cells for immunoglobulin production; (2) defective proliferative responses to antigenic stimuli; (3) diminished expression of interleukin (IL-2) receptors; and (4) defective lymphokine production in response to antigenic stimuli, particularly of IL-2 and gamma interferon. These defects would be expected to predispose infected persons to infections with intracellular pathogens.

In the course of a normal immune response the CD4 molecule binds to the class II MHC molecules on the surface of an antigen-presenting immune cell. However, the CD4 molecule binds to gp120 of HIV with a greater affinity than for its normal ligand (class II MHC molecules). This high-affinity binding of gp120 to CD4 may contribute to the impaired T-cell responses and may also be the basis of autoimmune reactions destroying T4 cells. The gp41 of the virus possesses a region of homology with the class II MHC molecule. Anti-gp41 HIV antibodies from AIDS patients can react with class II MHC antigens and may therefore be involved in cytotoxicity or complement-mediated cell killing of uninfected target cells carrying only the class II MHC molecule.

Antibody-dependent cellular cytotoxicity (ADCC) may contribute to cell death of both infected cells and uninfected cells. If an uninfected T4 cell binds free gp120 to its surface, the cell can be mistakingly identified as infected and subsequently be destroyed by ADCC or by gp120-specific, CD4-positive cytotoxic T cells.

Monocyte and macrophage

HIV also infects cells of the monocyte-macrophage lineage. The virus is not cytopathic to these cells but may interfere in their ability to present antigens to helper T cells. Intact virus particles may replicate to high numbers in these cells and may also be disseminated to tissues such as the brain, spinal cord, lung, bone marrow, liver, heart, and gut where soluble virus products may produce organ dysfunction. Alternatively, the virus may be borne to tissues wherein they replicate directly, thereby producing cell damage. These infected cells may also produce increased quantities of IL-1, IL-6, prostaglandins, and other molecules that may affect adjacent cell functions.

B cells

Spontaneously infected B cells have not been observed in vivo, although some B lymphocytes bear CD4 on their surface and can be infected in vitro. Nevertheless, HIV infection results in profound effects on B cell function. In vitro the HIV envelope has induced polyclonal B cell activation (Pahwa et al., 1985). It may also produce increased IL-6 production by other cells with resulting hypergammaglobulinemia. In spite of the observed hypergammaglobulinemia that commonly is seen, both primary and secondary antibody responses to some antigens may be impaired (Bernstein et al., 1985), contributing to the high incidence of infection with common bacterial pathogens. The B-cell impairment often is observed in association with impaired T-cell responses to the same antigens (Borkowsky et al., 1987), and these findings are correlated with a poorer clinical outcome (Blanche et al., 1986).

Although neutrophils are not directly infected by HIV, autoimmune neutropenias have been observed, and neutrophil dysfunction has been described (Roilides et al., 1990). This defect may contribute to the immunodeficiency-related infections that occur.

PATHOLOGY

The primary pathological effects of HIV infection are seen in the lymphoreticular system in which marked cell depletion is the end-stage pathology. HIV probably infects the epithelial cells of the thymus, and thymitis has been described. This initial inflammatory response is characterized by multinucleated giant cells in the medulla of the thymus or by diffuse lymphoplasmocytic or lymphomononuclear infiltrates of the cortex and medulla. These changes precede the involution noted in end-stage disease. The involution is characterized by deple-

tion of lymphocytes, loss of corticomedullary differentiation, and microcystic dilation of Hassall's corpuscles (Joshi, 1991). In a few instances a reduction of Hassall's corpuscles has also been described, and this constellation is termed *dysinvolution*. The severe effects of the virus on the thymus of the young infant or fetus may contribute to the more rapid progression of the immunological compromise. It is likely that thymic dysfunction continues to contribute to illness in adult life.

Lymphoproliferation in lymph nodes, the gastrointestinal tract, and lungs is seen. Multinucleated giant cells are present. Late in the disease, lymph nodes are depleted of lymphocytes in the paracortex, ultimately progressing to marked lymphocyte depletion of the entire lymph node. Atrophic changes of the spleen, appendix, and Peyer's patches are also described in late stages. The pathological features in the brain include atrophy, sclerosis, microglial nodules, and necrosis with or without an inflammatory cell infiltrate, loss of myelin, vasculitis, and calcification of vessels and basal ganglia (Sharer, Cho, and Epstein, 1985; Sharer et al., 1986). The virus has been localized by in situ hybridization in macrophages, microglia, and giant cells and less frequently in glial cells and neurons (Shaw et al., 1985; Stoler et al., 1986). Opportunistic infections and malignancies of the CNS are infrequently seen in children.

Pathological findings associated with a broad spectrum of infectious agents, including *P. carinii* in the lungs, *Candida* of the mucous membranes, *Mycobacterium avium-intracellulare* of almost all tissues, and cryptosporidia of the gastrointestinal tract, are seen in biopsy and autopsy specimens. Viruses that are common causes of infection include herpes simplex, cytomegalovirus, Epstein-Barr virus, and varicella-zoster virus (VZV).

Other findings of undetermined pathogenesis appear frequently in tissue examinations. Dilated cardiomyopathy is observed with microscopic hypertrophy of myocardial fibers, focal vacuolation, interstitial edema, small foci of fibrosis, and endocardial thickening. Unusually sparse inflammatory infiltrates are seen.

Clinically important renal disease is accompanied by microscopic findings of focal segmental glomerulosclerosis and mesangial proliferative glomerulonephritis (Connor et al., 1988). Immunoglobulin and complement deposits are evident by immunofluorescence. It is speculated that circulating immune complexes may be contributing to the pathogenesis of the renal disease. P24 antigen has been demonstrated by in situ hybridization in tubular and glomerular epithelial cells in renal biopsy specimens of adults.

A variety of neoplastic disorders, including lymphoma, Kaposi's sarcoma (rarely), and leiomyosarcoma of the gastrointestinal tract, have been described. Longer survival of children may result in more frequent occurrence of malignancies.

Pathological studies of placentas are relevant because most pediatric HIV infection is acquired by maternal-to-infant transmission. Studies in Africa demonstrated chorioamnionitis in placentas of women who delivered infected babies. These women had more advanced disease, and it is not possible to determine whether this inflammatory response is a result of secondary infections or a direct consequence of the severity of the HIV infection. The detection of HIV in the placenta does not predict whether an infant has acquired infection. Recovering HIV from placental tissue has been difficult, but HIV has been found in placentas by in situ hybridization (Chandwani, 1991) and by the polymerase chain reaction (PCR) (Andiman and Modlin, 1991). HIV has been demonstrated in placental macrophages (Hofbauer cells) in fetal villi. These cells could serve either as a barrier to HIV or as a means of fetal HIV infection.

LABORATORY DIAGNOSIS

Antibody to HIV can be measured accurately and is the mainstay of laboratory diagnosis of HIV infection in adults, in children perinatally infected who are more than 15 months of age, and in children of any age who have acquired HIV infection through transfusion or blood products. Enzyme-linked immunosorbent assay (ELISA) and Western blot assays measure antibodies to the major structural proteins or antigens of the virus and are commercially available. A positive ELISA must be confirmed by a second determination plus a positive Western blot assay on the same specimen to reduce the rate of false positives to approximately 1 in 100,000.

Since all newborns receive maternal antibodies during the latter part of pregnancy through the placenta, any infant born to a mother with