Pathology and Pathophysiology of AIDS and HIV-Related Diseases

Edited by

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Preface

. . . knowledge brings with it the power to escape from the crippling stance of past generations, who were condemned to cower in ignorance before the Black Plague or the invisible menace of yellow fever.

Dr June E. Osborn
N Engl J Med, **318**, 444, 1988

In what has been but a few years the spectre of AIDS has intruded so pervasively that, in addition to medicine and the basic sciences, it has exerted a major impact in the fields of ethics, law, sociology, social behavior, psychology, economics, and has become an important issue in the arena of politics. In medicine, it touches upon every subspecialty area and requires a substantial fund of knowledge to address its implications. The diversity of this disease and the demand for a single source of detailed information on the pathology and pathophysiology of HIV infection provided the impetus for writing this book.

We decided on a organ-system format as the best and most comprehensive approach to the subject, as it is abundantly clear now that HIV exerts its deleterious effects on almost every organ of the body. The introductory chapters cover basic Epidemiology, Immunology and Virology of AIDS; and the concluding chapters are devoted to a variety of pertinent subjects such as HIV testing, AIDS in children, AIDS in Africa and immunodeficiency syndromes in non-human primates. Preventing HIV infection is emphasized in the Epidemiology chapter and specific preventive recommendations to health care workers in general and the pathologists in particular are summarized in the appendix.

The book is not meant to be an encyclopedia of gross and microscopic pictures of the pathologic lesions seen in AIDS. While the depiction of such lesions occupies a central point, there is a concerted effort made in each chapter to include useful ancillary data. Clinicopathologic correlation is emphasized and disease states occurring with AIDS are compared to those seen prior to AIDS. The book should thus appeal not only to pathologists but to physicians and investigators in other specialty areas of medicine and the basic sciences.

Much of the data are summarized in tables or presented diagrammatically. The references for each chapter cover pertinent publications from the beginning of the AIDS epidemic up to papers published in mid 1988, and, also some of the materials presented in the Fourth International Conference on AIDS, held in

Stockholm in June 1988. Given the constant influx of new data, keeping a book on AIDS up-to-date presents a major problem; however many of the findings in recent years pertain more to retrovirology, to the testing of new therapeutic drugs and to developing an effective vaccine. The Stockholm meeting emphasized the gradual plateau that has occurred in our knowledge of the various aspects of AIDS. It appears that for the coming years our insights into AIDS will assume a slowly incremented curve, in contrast to the dramatic advances made in the first five years of the history of this disease. Overall, the pathology in the various organ systems has been more or less the same, thus the material in this book will remain relevant for some time to come, and will serve as a foundation on which new observations can be added as they accrue.

It would not have been possible to illustrate adequately the spectrum of HIV-related diseases without the generosity of many pathologists, clinicians and investigators from the USA, Europe and Africa. We are thankful to these contributors as we are thankful to the behind the scenes effort of many secretaries and technologists.

We are particularly grateful to specific people who provided major help and support in this project. Ms Tracy Greene's typing, retyping (and typing again) of the text, tables and references during numerous weekdays and weekends proved to be pivotal in accomplishing this task. Mr. Al Waldstrom is credited for developing, printing and mounting many of the good photographs. We would also like to acknowledge the technical assistance of Mr Donald Delutis, and the constructive advice of Dr Micheline Federman.

We are particularly grateful to Dr Leonard S. Gottlieb who provided us with the opportunity to write this book and was a continuous and invaluable source of support throughout the project.

Sami J. Harawi
Carl J. O'Hara
Boston, August 15, 1988

Foreword

The advent of a newly recognized clinical disorder, AIDS, has mobilized the expertise of the clinical and basic science communities over the past seven years. The pathologist is positioned at a pivotal point in encompassing the pathophysiology of AIDS, having in hand material that is of critical importance to clinical investigators describing the spectrum of illnesses associated with AIDS virus infection as well as material that the cell biologist and molecular biologist can study to better understand HIV. This book is the first of its kind and stands as an important piece of work not only for the pathologist but for the general medical community.

AIDS was initially recognized in California and New York based on the unusual occurrence of *Pneumocystis carinii* pneumonia or Kaposi's sarcoma in young previously healthy homosexual men. In retrospect, similar cases had occurred in the USA and Europe in the late 1970s as well. Following the initial clinical reports of AIDS, we have witnessed an epidemic that can be likened to a mushroom cloud, beginning with what appeared to be a relatively small base in the male homosexual communities of the coastal cities of the United States, and then spreading out to become one of the most prominent, if not the most prominent, disease state before the public eye. Transmission of HIV by homosexual and heterosexual intercourse, contaminated blood products, parenteral drug abuse, and during the birth process, has resulted in an estimated million infected individuals in the United States, probably a similar number in western Europe, and estimates of 5 million in Central Africa.

It is also clear that the cell targets of HIV go beyond the helper T lymphocyte, and include the monocyte-macrophage and colonic epithelial cells. There may be other cells infected *in vivo* as well, with neurons and endothelium being possible targets. The clinical manifestations of HIV infection parellel to some degree the distribution of infected targets. Neurologic dysfunction has emerged as a prominent and particularly tragic complication. Its recognition by clinicians caring for AIDS patients was importantly refined by pathologists who described a variety of changes throughout the neuraxis. Pathologists provided molecular biologists with tissue that definitively demonstrated viral sequences within brain and spinal cord. Similarly, the recognition of non-Hodgkin's lymphoma in the AIDS population allowed detailed molecular study of tissue. In many, the Epstein–Barr virus appears to play an oncogenic role with attendant chromosomal abnormalities. Much of this work is based on the substructure of pathologic examination and characterization of the neoplasm.

Pathology plays a major role in the active care of patients with HIV infection, since biopsy is generally required to diagnose opportunistic infections and/or neoplasms affecting a variety of tissues, particularly skin, lymph node, lung and brain. Clinical decision-making is intimately tied to the accuracy of such pathological diagnosis, so

that it is incumbant upon all pathologists to incorporate within their knowledge base a clear and firm understanding of the manifold aspects of AIDS. Furthermore, as new and experimental therapies are attempted in AIDS, the pathologist is critical in assessing the benefit and toxicities of such treatments. Our own work on hematopoietic growth factors such as granulocyte-macrophage colony stimulating factor (GM-CSF) in the treatment of leukopenic patients with AIDS has been greatly assisted by detailed hematopathology. We have been able to understand the effects of these myeloid growth factors on target marrow progenitors, in part due to the expert interpretation of bone marrow aspirates and biopsies. It is likely that as future interventions unfold, the role of the pathologist will become increasingly important in our understanding of HIV biology.

The pathologist has had considerable concern regarding the appropriate safety and containment practices that should occur in the handling of tissue from the HIV-infected patient. Considerable thought has been placed in this area, and a series of recommendations have been formulated by the United States Public Health Service. Pathologists can feel comfortable in handling HIV-infected tissue in a safe fashion, protecting themselves and their staff, while providing important services to patients, clinicians and researchers.

Because the full spectrum of disease associated with HIV infection has not yet been manifest, it is likely that much of the new information and new insights which will be obtained over the ensuing years will be derived from pathology. This book serves as an important beginning in defining the state of the art and providing a complete knowledge base from which future work will emanate.

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Assistant Professor of Medicine, Harvard Medical School

Glossary

This section lists the abbreviations used in the book. When more than one designation is used in the literature, the one from this list has been chosen:

Ab	Antibody
AFIP	Armed Forces Institute of Pathology, USA
AFS	Acid-fast stain
Ag	Antigen
AIDS	Acquired immunodeficiency syndrome
ARC	AIDS-related complex
BBB	Blood-brain barrier
CAT	Computerized axial tomography
CD4	T-helper/inducer lymphocytes
CD8	T-suppressor/cytotoxic lymphocytes
CDC	Centers for Disease Control, USA
CMV	Cytomegalovirus
CNS	Central nervous system
EBV	Epstein–Barr virus
ELISA	Enzyme-linked immunosorbence assay
EM	Electron microscopy
FSGS	Focal and segmental glomerulosclerosis
GIT	Gastrointestinal tract
GVH	Graft-versus-host
HA	Hepatitis A
HAV	Hepatitis A virus
HB	Hepatitis B
HBV	Hepatitis B virus
HCW	Health care workers
H&E	Hematoxylin and eosin
HIV	Human immunodeficiency virus 1 and 2
HLA	Human leukocyte antigens
HPV	Human papilloma virus
HSV	Herpes simplex virus
HTLV	Human T lymphotropic virus I and II
HZV	Herpes zoster virus
IEN	Intraepithelial neoplasia
IFA	Immunofluorescence assay
IFN	Interferon
Ig	Immunoglobulin(s)
IL 2	Interleukin 2
IVDA	Intravenous drug addict(s)
JCV	Jacob–Creutzfeld virus
KS	Kaposi's sarcoma
LAV	Lymphadenopathy virus
LGV	Lymphogranuloma venereum
LIP	Lymphocytic interstitial pneumonia
MAI	*Mycobacterium avium-intracellulare* complex
MHC	Major histocompatibility complex
MTb	*Mycobacterium tuberculosis*
MRI	Magnetic resonance imaging
NHL	Non-Hodgkin's lymphoma
NIH	National Institute of Health, USA
NK	Natural killer (lymphocytes)
Pap	Papanicolaou Stain
PAS	Periodic Acid – Schiff
PCP	*Pneumocystis carinii* pneumonia
PGL	Persistent generalized lymphadenopathy
PML	Progressive multifocal leukoencephalopathy
PWM	Pokeweed mitogen
RBC	Red blood cells
SIDA	Syndrome d'immunodeficience acquise
SIV	Simian immunodeficiency virus
STD	Sexually transmitted diseases
STLV	Simian T lymphotropic virus
TOXO	*Toxoplasma gondii*
UK	United Kingdom
USA	United States of America
WB	Western blot
WHO	World Health Organization

Contents

1. Epidemiology

SAMI J. HARAWI

A new acquired immunodeficiency syndrome (AIDS) was recognized in the USA by the Centers of Disease Control (CDC) in the spring of 1981 when previously healthy homosexual men presented with Kaposi's sarcoma (KS) and *Pneumocystis carinii* pneumonia. In a relatively short period thereafter, a retrovirus was identified as the causative agent of AIDS, and sensitive and specific blood tests became available to identify infected persons. After a heated debate between French and American investigators regarding who discovered the virus first and the nomenclature to be used, an international committee adopted the Human Immunodeficiency Virus (HIV) as the most appropriate term for the AIDS virus. The major historical landmarks related to HIV infection are listed in Table 1.1. Table 1.2 lists some other related historical events:

(1) The association between KS and the immunodeficiency state became apparent a century after Dr Kaposi described the sarcoma. (2) Dr Robert Gallo and his co-workers discovered the first human retrovirus just prior to the onset of the AIDS epidemic [80]. (3) The 'sexual revolution' of the 1960s in the USA which involved a major change in the traditional attitudes towards sexuality, ushered in an era of increased promiscuity. These changes were also felt within the homosexual community, especially with the establishment of the 'gay liberation' movement. The revolt of the patrons of the 'Stonewall' gay bar in New York City in 1969 against the police who wanted the bar closed is considered by gay activists as the start of this liberation movement. In the late 1970s there was a sharp rise in the incidence of genital herpes (particularly among heterosexuals); there was also a concomittant sharp rise of a variety of sexually transmitted diseases among homosexual men (Chapter 19). All these events in a way heralded AIDS.

At the onset of the epidemic, AIDS seemed so confined to the homosexual population in the USA that a Danish investigator managed to correlate the decrease in number of the T-helper lymphocytes in homosexual men in Copenhagen with the frequency of their visits to New York City! Soon it became apparent in the USA that there were other groups at risk for AIDS, and AIDS cases began to appear in Europe and Central Africa. As of mid-1988, 100000 cases of

Table 1.1 HIV infection, historical landmarks

1952	Probable first case of AIDS (USA) [52b, 71b, 106a]
1959	Earliest HIV-positive sera, Zaire [72]
1966	Earliest (seropositive) cases, Norway [39a]
1969	Acquired immunodeficiency in Macaques Monkeys at the California primate center [50].
1975–76	AIDS cases traced in Zaire [12, 95]
1981, March	Transfusion-associated AIDS in a neonate (reported Dec. 1982) [20]
1981, Spring	First cases reported to the CDC, USA [39, 46]
1981, Late	African cases identified in Europe [28]
1982	European cases identified [28]
1982, Jan.	CDC task force [15] Case definition of AIDS
1982, July	Haitian cases reported [51]
1982, July	Hemophiliac cases reported [19]
1983, March	Request for voluntary refrain from blood donation by high risk groups
1983, Spring	Zairean cases reported [27]
1983, May	Isolation of AIDS virus (LAV), Pasteur Institute, France, Dr Luc Montagnier [5]
1984, May	Isolation of AIDS virus (HTLV III). National Institute of Health, USA, Dr Robert Gallo [40]
1984	WHO collaboration center on AIDS (Paris)
1985, March	Licensing of serologic tests Testing in Blood Banks
1985, June	First International Conference on AIDS, Atlanta (USA)
1985, June	1st revision of the AIDS case definition to include HIV antibody status [21]
1985, Nov.	First Conference on AIDS in Africa, Brussels (Belgium)
1985, Dec.	Report on HIV-2 antibodies in residents of West Africa [3]
1986, Winter	The AIDS virus designated HIV by an international committee [29]
1986, Spring	Staging/Classification of HIV infection CDC [13]; Walter Reed [85]
1987, May	AIDS-like disease in West Africans caused by HIV-2 [26]
1987, Summer	2nd revision of the AIDS case definition [23a]
1988, Jan.	First AIDS summit of health ministers (149 countries), London [48a]
1988, June	Two landmark reports on AIDS, USA [7a] 1. National Academy of Sciences 2. Presidential Commission on the HIV epidemic [7a, 98a]

Table 1.2 Historical events more or less related to the AIDS epidemic

1872	Description of the Sporadic (classical) Kaposi's sarcoma
1948	Kinsey *et al. Sexual behaviour in the human male* [58a]
1950	Penicillin effective against most sexually transmitted diseases
1960s	Birth control pill 'Sexual revolution' (USA)
1969	Start of the Gay Liberation movement (Stonewall Inn), New York City
1960s	Description of the Endemic Kaposi's sarcoma in Central Africa
1970s	Description of Kaposi's sarcoma in renal transplant recipients
1970s, late	Sharp rise in the incidence of genital herpes and of human papilloma virus-related intraepithelial neoplasia in female genitalia
1970s, late	Sharp rise in sexually transmitted diseases among homosexual men
1980	Discovery of the first human retrovirus, the Human T Lymphotropic Virus I [80]

AIDS have been reported to the World Health Organization (WHO) [66]. The cases were reported from 136 countries which was more than twice the number of countries that reported cases in the previous year. Twenty nine

European countries have reported 10 000 cases of AIDS and the WHO estimates that 500 000 to 1 million are infected with HIV [8a, 66, 79a]. Of the AIDS cases reported to the WHO, 60 000 were from the USA and in June 1988, during the 4th International Conference on AIDS, Dr James Curran, Director of the CDC, estimated that one new case of AIDS is diagnosed in the USA every 14 minutes! [29b]. In reality, however, the countries in Central Africa carry the heaviest burden of the AIDS epidemic, and the cases reported to the WHO seem to represent only a small fraction of the HIV-infected population in the world, which Dr Jonathan Mann, head of the WHO special program on AIDS, estimates to be 5–10 million people [66, 79a].

The discussion of the epidemiology and natural history of HIV infection in this chapter will focus predominantly on the disease pattern typical of industrialized countries. HIV infection in Africa will be discussed in Chapter 17.

1.1 HIV INFECTION OUTSIDE AFRICA

Risk groups and incidence

(a) USA

The number of AIDS cases has been steadily increasing worldwide, and in the USA, by extrapolating statistical data from 1986, it is expected to reach 270 000 cases by 1991 [4]. This approximation is based on the seroprevalence of HIV infection in the general population and in persons in the high risk groups. Tables 1.3a and 1.3b show HIV seroprevalence in various groups in the USA and include the data of the numerous studies on the rates of HIV infection that the CDC summarized for the White House towards the end of 1987 [7, 23b, 30a]. While at the onset of the epidemic the number of AIDS cases doubled every 5 months, at the last count in 1988, the doubling time was more than 15 months. Table 1.4 shows a steady decrease in the yearly increment of cases.

Over the 7 years that AIDS has been observed in the USA, it has affected predominantly the same groups that were at risk for the disease at its onset, and in roughly the same proportions

Table 1.3a HIV seropositivity in the general population in the USA [23b]

	HIV seropositivity (%)
Blood donors	
'Low risk' cities	0.02
'High risk' cities	0.11
Military (active duty and recruits)	0.15
'Sentinel' hospitals and prisons	0.30
Newborns	
Massachussetts [52a]	0.21
Inner City	0.80
Suburban/rural	0.09
New York State [24b]	0.80
Inner City (NYC)	3.0
Suburban/rural	0.2

Table 1.3b HIV seropositivity in the high risk groups in the USA

	HIV seropositivity (%)
Homosexual men	
Exclusively homosexuals	20–50
Bisexuals	5
Intravenous drug addicts	
'High risk' cities	50–60
Outside East coast	5
Heavy users (average)	25
Occasional users (average)	5
Hemophiliacs (A and B)	
Average	65
Range	60–85
Sexual partners of the above	10–60
STD clinic patients	
Homosexual men	24–73
Baltimore (45% homosexual men)	5.2
Military	1–1.5
Haitian – Americans (in the USA after 1977)	5

(Table 1.5). The majority of patients with AIDS are young men, and it is estimated that 1 out of 30 men between the ages of 20 and 30 is infected with HIV [30]. Over 50% of the cases have

Table 1.4 AIDS in the USA

	Increase (%)	Heterosexually transmitted (%)
1981	–	0.5
1982	259	1.0
1983	187	1.0
1984	116	1.3
1985	82	1.6
1986	60	2.3
1987	57	4

Table 1.5 Distribution of AIDS cases among various risk groups in Europe and the USA [24c]

	AIDS cases (%)	
	Europe	USA
Homosexual/bisexual men (with no drug abuse)	59	65
Homosexual/bisexual men (abusers of intravenous drugs)	3	8
Intravenous drug abusers (heterosexual)	20	17
Hemophiliacs	4	1
Transfusion (prior to 1985)	4	2
Heterosexual contact	6	4
Other/Undetermined	4	3

occurred in five major urban areas: New York City, San Francisco, Los Angeles, Miami and Newark. New York City carries the biggest burden of the epidemic [101] and patients with AIDS are predominantly homosexual men and Intravenous Drug Abusers (IVDA). In neighboring Newark (New Jersey), most of the patients are drug addicts. In San Francisco and Los Angeles, AIDS occurs predominantly in homosexual men. In Miami, Haitians who immigrated to the USA after 1977 account for a large proportion of the patients with AIDS. At the onset of the epidemic Haitians were thought to be at particular risk for AIDS, but it was found later that many of the HIV-infected Haitians have some other risk factors for the disease (e.g. bisexuality, or blood transfusion) [75]. It seems as likely now that HIV reached Haiti by way of homosexual men vacationing on the island as vice versa [78]. Although in absolute numbers there are more white patients with AIDS than Blacks and Hispanics, Blacks and Hispanics have a disproportionately higher incidence of the disease relative to the overall populations (Table 1.6).

Table 1.6 Race and ethnicity of AIDS patients in the USA [16]

	Whites (%)	Blacks (%)	Hispanics (%)
US population (for reference)	81	11	6
Overall incidence of AIDS	60	25	14
Male homosexuals	73	16	11
Heterosexuals	25	50	25
Race of IVDA (for reference)	32–41	40–50	9–28
AIDS in IVDA	20	50	30
AIDS in children	20	58	22

(b) Europe

The highest rates per population size of AIDS cases in Western Europe occur in France, Switzerland and Denmark [8a, 24d]. The apparent high rate of AIDS in Belgium is skewed by the fact that a large number of the cases (50% in 1986) came from Central Africa [34]. For the European Community as a whole, the estimated doubling time of AIDS cases has lengthened from 6.5 months to 9.4 months over a 2.5 year period from 1984 to 1986 [34].

Overall in Europe, the groups at risk from HIV infection and the relative incidence of cases in each group is comparable to the USA (Table 1.5). In Italy, Spain and Edinburgh (Scotland) however, the majority of AIDS cases occur in IVDA [8, 24d, 32, 34]. In this group, HIV infection is spreading more rapidly than among homosexual men, and at approximately the

same rate that it is spreading among IVDA in the USA.

Transmission [31a, 79a]

(a) Established routes

HIV has been isolated from practically all the body fluids: whole blood, plasma, semen, vaginal secretions, saliva, tears, urine, etc. However after close observation of the disease to date, there is no evidence of HIV transmission via food and drinks, casual contact or kissing [38]. Epidemiologic studies in Africa (Chapter 17), and a recent study in Belle Grade, Florida [14] ruled out transmission of HIV via arthropods. Clearly, as it has been since the onset of the epidemic, the main routes for transmitting HIV are through sexual contact (particularly if there is disruption of mucous membranes), or through blood and blood products' exposure. Recently, five cases of HIV infection have been reported due to skin or mucous membrane exposure to contaminated blood. The risk for such transmission is very low and it can be practically abolished if adequate precautions are taken in handling body fluids [23]. HIV is frequently transmitted transplacentally to the fetus, and a few cases of transmission via breast milk have been reported.

(b) Sexual transmission

Sexual contact has been the route for transmitting HIV in over 78% of all cases [76]. The chance for acquiring HIV from a single contact with an infected person is however estimated to be less than 1%. In comparison, transmission of infection after a single contact is estimated to be 25–50% for gonorrhea and 30% for syphilis [76].

In terms of routes of transmission, HIV is very comparable to the hepatitis B virus (HBV). Both viruses are transmitted through sexual contact, blood, needle sharing and perinatally. Evidence of past infection by HBV is prevalent among both homosexual men and IVDA. Table 1.7 compares prevalence and transmission of HIV and HBV. The main difference between the two viruses is that HIV is less infective (harder to acquire) but much more infectious (more deleterious to health) than HBV [76].

Table 1.7 Prevalence and transmission of Human Immunodeficiency and hepatitis B viruses [76]

	HIV	HBV
Seropositivity, USA	0.04%	5%
Risk groups		
Homosexual men (STD clinic)	20–70%	35–80%
IVDA	60–85%	60–80%
Transmission		
Household contacts	no	yes
Needlestick	<1%	30%
Sexual contact		
prolonged	50–60%	20–27%
single	<1%	?
Carrier state of infected individuals	100%	6–19%

(c) Heterosexual transmission

The incidence of heterosexual transmission of HIV outside the African continent was consistently low until 1985 (Table 1.4). In 1986 the increase in AIDS cases among heterosexuals in the USA was 130%, compared to a 95% increase in the 'undetermined' category, and a 56% increase in all categories [30].

Young (heterosexually active) military personnel [10] and military recruits [11] have an HIV seropositivity of 0.16 and 0.15% respectively. This seroprevalence is much greater than that of blood donors from cities in the USA who do not have a large population of HIV-infected persons (Table 1.3a). Heterosexual transmission among military personnel is evidenced by the crude male: female prevalence ratio of 2.7 [11].

Heterosexual transmission also underlies the prevalence of HIV infection in children (Table 1.6) and in women, particularly prostitutes. HIV seropositivity among prostitutes in the United Kingdom, France, and West Germany is negligible, while it may be as high as 78% among prostitutes using intravenous drugs in some cities in Italy and Switzerland [17]. In the USA [17], HIV seropositivity among prostitutes is