Volume 2

Advances in Pathology

Fenoglio-Preiser
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Advances in Pathology

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Preface

Volume 2 of *Advances in Pathology,* like its predecessor, is aimed at providing up-to-date information concerning various aspects of clinical pathology, anatomic pathology, experimental pathology, and forensic pathology. The current volume discusses several areas of current issues receiving a lot of attention. These include an approach to the diagnosis of human immunodeficiency virus infections and how to test for drugs of abuse. Many laboratories are currently beset by questions in both of these areas and it is hoped that both of these chapters will be helpful in providing basic information concerning them. Another area of current interest is pathologic changes associated with asbestos exposure, as we are often asked to address this issue with respect to occupational hazards. The subject is reviewed critically by Roggli.

The autopsy is suffering a decline in many institutions and yet it is the ultimate vehicle for quality assurance in hospitals. Drs. Anderson and Hill provide a discussion focused on understanding the discrepancies between premortem and postmortem diagnoses. This issue is central to the role of the autopsy and hospital quality assurance programs.

The knowledge of tumors is advancing rapidly at the research front and the information concerning genes and chromosomes associated with induction of cancer are expanding at a rapid rate. This information is also extending into the pathology literature. Yunis provides an outstanding review of chromosomal changes, particularly as they relate to hematologic malignancies. This information is currently of more than research interest and is being used routinely for diagnostic purposes in sophisticated reference laboratories.

The remaining three chapters relate to technical areas in the laboratory. These include the diagnosis of human tumors by immunohistochemistry, the use of genetic probes, and the use of nuclear resonance spectroscopy. Of these, the most commonly utilized is immunohistochemistry and the subject is surveyed in a review form for diagnosing tumors. Genetic probes have also been used increasingly in the diagnostic laboratory. The chapter included within this volume presents the first of a series of articles to appear in subsequent volumes. It deals with the concepts and techniques utilized in diagnostic laboratories when dealing with genetic probes. Subsequent volumes will include applications in microbiology, as well as other areas. Perhaps the most difficult to read article in this volume will be that concerning the use of nuclear magnetic resonance (NMR) spectroscopy in the pathology laboratory. This article is included, however, because there is an expanding pool of data concerning the usefulness of NMR spectroscopy in studying tumor biology, as well as in tumor imaging. The magnetic resonance imaging aspects of NMR spectroscopy are

already well established in the diagnostic workup of patients as provided by radiology services. However, there are applications for the technology to pathological tissues. Some of these are explored in the chapter by Halliday.

Cecilia M. Fenoglio-Preiser, M.D.

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Diagnostic Methods in Human Immunodeficiency Virus Infection

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The etiologic agent of the acquired immunodeficiency syndrome (AIDS) has been established to be the human immunodeficiency virus type-1 (HIV-1).[1, 2] The virus has been shown to be transmitted from person to person primarily through intimate sexual contact, contaminated blood or blood products, or perinatal infection. As such, laboratory methods for the detection of infected individuals can be utilized, with proper concern for patient confidentiality, to help prevent the further spread of the virus. This review will discuss current methodology commonly used for clinical labs in the United States for detecting infection by HIV. Newer methods in later stages of development will also be discussed.

HIV is a lentivirus in the family Retroviridae. This family of viruses shares in common a unique endogenous reverse transcriptase enzyme that, following penetration and uncoating of the viral genome, allows for transcription of the viral RNA into complementary DNA (cDNA). The cDNA is then integrated into the host cell genome. The integrated viral DNA can remain quiescent in a resting cell or be transcribed during cell activation to produce large numbers of viral particles. The initial event in the viral replication cycle is dependent upon attachment of the envelope glycoprotein gp120 of the virus, which enables HIV to bind to cells such as helper T lymphocytes and monocytes/macrophages.[3] These cells express on their surface the CD4 molecule, which is the high-affinity receptor for gp120. It is believed that with HIV infection of T helper lymphocytes, production of

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viral particles is related to the destruction of the host cell. The infection and subsequent destruction of the CD4+ T cells is one of the main causes of the immunodeficiency.[4, 5] Infection of monocyte/macrophages is not thought to result in death of this cell population. The chronic infection of the monocyte may contribute a large part to the dissemination of the virus throughout the body. In addition, chronic infection of monocyte/macrophages is associated with a number of functional immunologic defects that probably contribute to the immunodeficiency.[6]

During the course of infection by the virus there is a general serologic profile that many individuals follow (Fig 1). After initial infection with HIV, there is an incubation period in which no active viral replication can be detected. This lag period is highly variable among individuals. The virus then begins to replicate and high levels of viral products such as HIV p24 antigen may be detected in the circulation (see Fig 1).[7] Generally within 4 to 12 weeks after initiation of viral infection, antibodies to the various viral proteins (core, envelope, polymerase and regulatory) begin to appear. At this time, levels of viral antigens decrease and may become undetectable in blood. This situation may remain stable for months to years until viral replication again increases. At this time, HIV p24 antigen generally again becomes detectable and antibody to the p24 core protein decreases. This decrease in anti-p24 antibody correlates with or heralds a decline in the condition of the patient.[8] Exceptions to this general pattern do occur. For example, some individuals do not develop antibodies to the virus until long after exposure,[29] others do not lose anti-p24 antibodies in later stages of the infection,[10] and some individuals may not reexpress serum HIV p24 antigen.[11, 12]

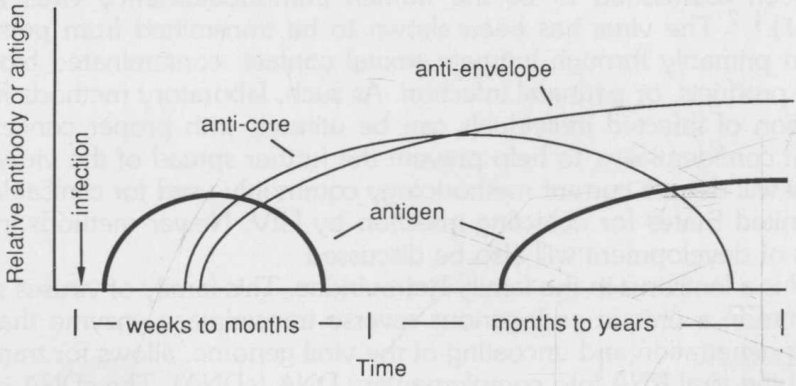

FIG 1.
Serologic time course of HIV infection. The figure illustrates a serologic profile commonly observed in infected individuals. After infection, antigen becomes detectable in blood. Four to 12 weeks after acute infection, antibody to both core and envelope proteins is detectable. The appearance of these antibodies correlates with the disappearance of viral antigens. This profile is stable for a variable period of from months to years after which the clinical condition of the patient worsens. This deterioration correlates with an increasing frequency of detectable viral antigen and a decrease in anti-core antibodies.

TABLE 1.
Methods for Detecting Infection by HIV

Anti-HIV antibody
Enzyme-linked immunosorbent assays
Western blot
Immunofluorescence assays
Radioimmunoprecipitation
HIV antigen
Enzyme-linked immunosorbent assays
HIV nucleic acids
Polymerase chain reaction
HIV culture
Detection of immunodeficiency
Flow cytometry for CD4+ cell number
In vitro mitogen or antigen responsiveness

A number of assays have been developed to determine infection with HIV (Table 1). The most commonly used tests detect antibody to HIV produced by the infected individual. These tests indirectly indicate the presence of HIV. Detection of viral antigen, viral nucleic acids (DNA or RNA), or isolation of the virus from the infected individual all directly indicate the presence of the viral infection. Other commonly used methods to indirectly diagnose the presence of HIV include tests that indicate a deficiency of the immune system such as the absolute numbers of helper T cells.

Currently Used Tests

Enzyme-Linked Immunosorbent Assay

Enzyme-linked immunosorbent assay (ELISA) is now the most widely used method for screening large numbers of individuals for either antibody to HIV or for direct detection of HIV antigen. HIV ELISA kits are produced by many companies and are relatively easy to use. Several of these kits have been licensed by the FDA for detection of antibodies to HIV. The principle of ELISA detection of antibody is to produce large quantities of virus in vitro and use the disrupted virus to coat a solid phase such as plastic beads or plastic microtiter plate wells. The solid phase is then incubated with the patient's serum followed by a secondary reagent that detects human antibody bound to the viral antigens on the solid phase. The second-

ary reagents are cross-linked to the enzyme, which when incubated with substrate results in a color change if antibodies to the virus are present.

Two concepts that are important for test evaluation are sensitivity and specificity. The sensitivity of a test is the probability that the test will be positive if the sample is truly positive while the specificity of a test is the probability the test will be negative if the sample is truly negative. Evaluation of the sensitivity and specificity of ELISA kits is important and several studies compare the commercially available ELISAs.[13–17] Overall the sensitivity and specificity of most of these tests have been reported to be greater than 99%.[18] However, the possibly serious psychologic damage inflicted by the report of a false positive antibody test makes even small error rates unacceptable. The viral antigens used to coat the solid phase are produced in cultured cells, usually the H9 human lymphoblastoid tumor cell line. This can result in false positive reactions if individuals produce antibodies to histocompatibility antigens present in this cell line (Table 2).[19, 20] These interfering antibodies can be produced as a result of multiple transfusions, in autoimmune disease, or after spirochetal or parasitic infection.[21] False negatives also can occur if infected individuals have not yet developed antibodies, as may occur early in infection or late in the infection when the immune system is depressed (see Fig 1).[18]

Western Blot

To minimize the reporting of false positive HIV antibody test results, a second antibody detection system is generally used as a supplemental or con-

TABLE 2.
Sources of Error in HIV-1 Testing by Serology*

False positive results	
Adult T cell leukemia/lymphoma	Cross-reactive HTLV-1 antibody
Autoimmune disease	Autoantibodies to nuclear and cellular antigens
Alcoholism	Immune dysfunction in liver disease
Hematologic malignancy	Hypergammaglobulinemia
Transplant recipients	Antibodies to HLA antigens
Multiparous women	Antibodies to HLA antigens
False negative results	
Acute HIV infection	Lack of detectable antibody for first 4–12 weeks following infection
ARC and AIDS patients	Loss of antibodies to viral proteins such as p24

*HTLV = human T cell leukemia/lymphoma virus; HLA = human leukocyte antigen; HIV = human immunodeficiency virus; ARC = AIDS-related complex.

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