IMAGING OF AIDS

TROTOT

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PIERRE M. TROTOT

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[redacted]

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Imaging of AIDS

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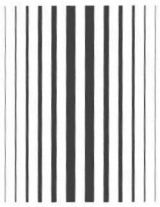


Foreword

> Knowledge of infectious illnesses teaches us that we are brothers and interdependent. We are brothers because we are menaced by the same danger, interdependent because the contagion most often comes to us from our fellows.
>
> Charles Nicolle
> *Destin des Maladiés Infectieuses*
> *(The Destiny of Infectious Diseases)*

It may seem unusual for a micropathologist to present a work written by radiologists.

Indeed, fifteen or twenty years ago, the work of the two fields did not seem to have much in common. It required the genius of a Benjamin Felson to create the model for a pathological reading of the thoracic radiograph. Everything has changed with the advent of sectional imaging: echography, computed tomography, and now magnetic resonance imaging.

The correspondence between the two morphological disciplines, pathology and radiology, has become obvious.

Still, they could just as easily enter into competition, with *in vivo* imaging tempting the practitioner to arrive at a diagnosis without the samples or punctures indispensable to pathology.

In fact, *in vivo* imaging is incapable of yielding an etiological diagnosis. The practitioner would be at a loss without histopathological data to guide the choice of therapy.

Therefore, for the past six years we have been pooling our data with Pierre M. Trotot in order to gain a better understanding of the different aspects of acquired immune deficiency syndrome.

AIDS appears to be a rather simple disease resulting from a virus whose elective target is the T4 lymphocyte. One might expect an unequivocal, indeed even stereotyped, clinical picture. As is now well known, this is not at all the case, since the immunodeficit resulting from this infection is the source of multiple opportunistic complications, both tumorous and infectious. This explains why, despite the ef-

forts of research teams around the world, numerous questions remain unanswered. More than ever, the work of these teams requires the juxtaposition of our two disciplines, as supported by the two examples which follow:

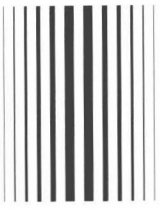
- Early diagnosis of pneumocystosis from the chest plate remains difficult; on the other hand, computed tomography in millimetric sections without injection of contrast medium is remarkably informative in its correspondence with the pathological image;
- Magnetic resonance imaging (MRI) permits the recognition of five types of individual images in subacute encephalitis. However, their etiological interpretation remains uncertain because of the interaction of pathogens at this advanced stage of the disease. Two approaches will, without doubt, provide clarification: observation from the initial stage onward of a group of seropositive patients and pathological comparisons.

I am happy to have participated indirectly in the production of this reference work for the practitioner confronted with the diverse clinical aspects of AIDS.

Professor R. Levillain
Chair of Pathological Anatomy and Cytology
Faculty of Medicine and Pharmacology, Besançon

Indeed, science strives to describe nature and to distinguish dream from reality. However, it should not be forgotten that human beings probably need dream as much as reality. It is hope that gives life its meaning. And hope is based on the prospect of one day transforming the present world into a possible world which seems better.

Francois Jacob
The Play of Possibilities
(Essay on the Diversity of Living Things)
Fayard, 1981, Paris



Preface

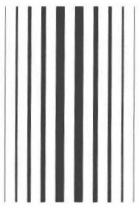
It has become very common to herald the progress of radiology. No one is unaware of the importance for medical practice of echography, the scanner, or of magnetic resonance imaging. It is therefore not surprising that a work would be devoted solely to the imaging of an infectious disease.

Infectious diseases, says Charles Nicolle, are constantly regenerating themselves. The acquired immune deficiency syndrome is a new embodiment of this idea. It represents the action of a microbial agent transmitted in certain epidemiological circumstances and is responsible for often fatal alterations in the infected organism. It also presents its own peculiarities: the most important one is, precisely, an immunodeficiency. Moreover, this characteristic had been recognized even before the causal agent was identified. Immunodeficit is responsible for the multitude of clinical pictures, resulting from opportunistic or tumorous infections, which the disease can take on. To recognize these complications, to follow their evolution, to distinguish them from direct attacks of HIV remains essentially the task of medical imaging. Indeed, it is clear that the difficulties of conducting a clinical study of patients with AIDS without medical imaging would be great. I therefore strongly encouraged Pierre Trotot when he informed me of his project to gather the different radiologic aspects of AIDS into one work.

This collection represents, on the one hand, studies ordered according to apparatus and, on the other, a few general chapters which place into an overall context the determinant aspects of the disease or its complications. In this way a double goal seems to have been achieved: the establishment of an atlas in which the practitioner will find images he needs, and the creation of a work in which these images are placed in their clinical context. Moreover, this book appears in a clinical collection which clearly sets a primarily medical tone.

It is with great pleasure that I wish this project the success it deserves, both with specialists in imaging and with practitioners of the various disciplines.

Professor Claude Lapresle



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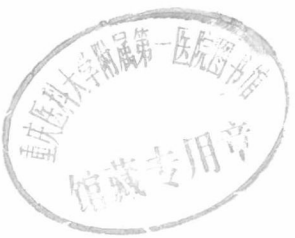

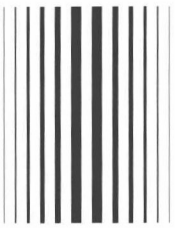

SECTION ONE

GENERAL CONSIDERATIONS

S. CHAMARET
L. MONTAGNIER

1

Retroviruses and HIV

Retroviruses are viruses whose genome consists of a single-strand molecule of ribonucleic acid (RNA) and which possess the enzyme reverse transcriptase. This enzyme, essential to viral replication, first transforms the RNA into a single strand of deoxyribonucleic acid (DNA) then synthesizes a second strand of DNA, forming a double helix of DNA in a ring structure, allowing the retrovirus to integrate itself into the cellular genome of the host cell. Viral DNA, integrated in this way, can remain in the cell in the form of a provirus and can be replicated with the cellular DNA. The viral DNA can also be expressed, in which case it is transformed into messenger RNA and in turn translated into viral proteins and completed copies of RNA. After its association with two complete copies of the RNA, the new virion leaves the cell by budding.

All retroviruses have this cycle of replication in common, and each possesses genes for the coding of different types of viral proteins:

- The gene *gag* (antigen group) codes for the internal proteins of the virus, associated with RNA, which constitute the nucleocapsid.
- The gene *pol* (polymerase) codes for inverse transcriptase and other enzymes necessary to its replication (e.g., endonuclease and integrase).
- The gene *env* (envelope) codes for a precursor that, after having undergone a complex process of glycosylation, is divided into a transmembrane glycoprotein and a surface glycoprotein that recognizes the receptor in the target cell.

Retroviruses can be distinguished on the basis of their morphology, as seen in the electron microscope, through supplementary genes, through their pathogenicity, and by the type of alteration in the host cells.

Three subfamilies are distinguished:

- *Oncoviruses,* characterized by their oncogenic power, are associated with some cancerous processes, chiefly lymphoma and sarcoma.
- *Lentiviruses,* associated with slowly developing diseases, are cytopathogenic for the infected cell.
- *Spumaviruses* are not at present known to be associated with any disease. The infected cells take on a foamy appearance and then degenerate.[22]

HUMAN RETROVIRUSES AND HIV

In 1980, the first human retrovirus known to cause leukemia and T-cell lymphoma was isolated by Robert Gallo and colleagues.[16] It was called human T-cell leukemia virus (HTLV), then HTLV-1 in 1982, when a second, antigenically similar virus, HTLV-2, was discovered by the same group.[10] HTLV-1 also seems to be associated with the etiology of a degenerative myelopathy, tropical spastic paraparesis.

In 1981, a specific clinical picture in the United States emerged that affected mostly homosexual men, intravenous drug users, transfusion patients, and hemophiliacs. These patients showed an immunodeficiency, and the new disease was eventually called acquired immunodeficiency syndrome (AIDS).

In 1983, Luc Montagnier and his collaborators at the Pasteur Institute, F. Barré and J. C. Chermann, isolated a new retrovirus from the lymph node sample of a patient afflicted with persistent generalized lymphadenopathy related to AIDS. The virus was named LAV (lymphadenopathy-associated virus).[2]

In 1984, R. Gallo and colleagues isolated a virus that they called HTLV-III, wanting to attach it to the HTLV family,[7] even though J. Levy and co-workers named a similar virus ARV (AIDS-associated retrovirus).[12]

Finally, with the consent of the discoverers, the International Committee on the Taxonomy of Viruses decided to name the retrovirus responsible for AIDS the human immunodeficiency virus (HIV).

In 1985, the team of Luc Montagnier,[4] in collaboration with physicians in Lisbon and at the Hôpital Claude Bernard, isolated another lymphocytic retrovirus from a patient infected with AIDS. The serum of this patient contained antibodies recognizing the internal proteins of the HIV prototype but not the envelope protein; however, the antibodies also recognized the envelope protein of the new virus. This virus was called HIV-2, and the first one, isolated in 1983, became HIV-1.

HIV-2 is very similar to a virus, isolated by R. Desrosiers, in macaque monkeys bred with AIDS.[6] This virus is now called simian immunodeficiency virus (SIV).

More recently, a retrovirus that is associated with immunodeficiency was isolated in cats.[15] All these viruses are similar to the lentiviruses that cause diseases in ungulates, such as visna in sheep, caprine arthritis encephalitis, and equine infectious anemia.[9] Only primate lentiviruses seem to have a definite tropism for T4 lymphocytes, although all lentiviruses are able to replicate themselves in macrophages.

GENETIC ASPECTS OF HIV

The nucleotide sequence of HIV-1 has been known since 1984.[1] A comparison between HIV and HTLV [HTLV-1] allowed complete differentiation between the two viruses and definitive inclusion of HIV in the group of lentiviruses whose prototype is visna, whereas HTLV [HTLV-1] belongs to the family of oncoviruses.[18]

The genome of HIV-1 is more complex than genomes of other retroviruses. In addition to the genes common to all retroviruses *(gag, pol,* and *env),* HIV-1 possesses five genes whose functions are not entirely known: *tat, rev* (also called *art* or *trs*), *vif (Q, sor), nef (F, 3'orf),* and *vpr (R).*

The gene *vif* codes for a protein that seems useful for the infectivity of viral particles. We do not know at the moment the function of the R gene product.

The product of *nef* is a protein that could act as an early marker of infection and is reported to have a negative regulating function, diminishing the expression of the provirus integrated in the cellular genome.

The *tat* (transactivator) and *rev* genes have a positive regulating function, acting in synergy. Their proteins amplify viral expression; thus, a large number of viral particles are made, the host cell is destroyed, and the virions infect other cells.

Although all the HIV-1 viruses have identical genomes, the comparison of complete sequences of several isolates reveals significant genetic variability. This variability is not constant throughout the genome; it is more significant for the relatively well-preserved *gag* and *pol* genes.

HIV-2 possesses the same biological properties as HIV-1. However, its nucleotide sequence reveals a supplementary gene, *Vpx,* which encodes a protein whose function is not yet known.[8] HIV-2 is closer to SIV than to HIV-1 (the gene *Vpx* is also present in SIV). The comparison of the sequences of several HIV-2 isolates shows a genetic variability, especially at the level of the *env* gene, and the variability of the total genome is still more significant among HIV-2 than HIV-1.[5,21]

DIAGNOSTIC TESTS

The discovery of the etiologic agent of AIDS permitted the rapid development of tests for the detection of the anti-HIV-1 antibody and more recently of the anti-HIV-2 antibody.

The most widely used techniques are the enzyme-linked immunosorbent assay (ELISA) and immunofluorescence. In case of a positive response, a confirmation test is carried out on a new sample. Confirmation tests identify the viral proteins recognized by the antibody. These are the Western blot test and the radio-immunoprecipitation assay (RIPA). Since RIPA involves the maintenance of infected cells and the use of radioactive metabolites, it is usually restricted to research laboratories.[2]

Now, in addition to the classical techniques for detecting antibodies, there is an ELISA for the demonstration of viral antigens in the serum by means of polyclonal and monoclonal antibodies. This test permits the detection of minimal quan-