The research basis for a crash 'BSDI' AIDS program

Why molecular biology alone cannot make the breakthrough, by Warren J. Hamerman, Director, EIR *Biological Holocaust Task Force.*

By far the most significant, although least generally commented on, section of the Oct. 29 report, *Confronting AIDS: Directions for Public Health, Health Care, and Research,* by the Institute of Medicine and Academy of Sciences, is a remarkably precise and scientifically honest 82-page chapter entitled "Future Research Needs."

Lest anyone maintain the dangerous illusion that there will be some quick and easy medical "fix" or "magic bullet" to halt the spread of AIDS, and that therefore we should not embark beginning the proverbial "yesterday" on a crash scientific program of unprecedented scale, the "Future Research Needs" chapter should be consulted very carefully.

Despite remarkable experimental work and scientific achievements over the past few years, what is *not* known about the virus and the disease far, far outweighs what is known. The Academy report states about already-accomplished scientific insights into the disease:

> Such insights, however impressive, are only the beginning of what promises to be a long and difficult path toward effective therapeutic interventions to minimize or eliminate the debilitating effects of HIV infection and toward limiting the spread of the virus by means of safe and effective vaccines.

The genetic structure and mechanical features of the infection have been well charcterized. However, science does not yet understand how the virus initiates infection, how it maintains infection, and what determines the triggering, progression, and diversity of the resulting disease complex. What are the co-factors—both external to the individual in the environment and endogenous to the living individual—to infection and subsequent disease activation? All of the questions relating to basic biological causality and dynamics of the viral infection, as opposed to the statics of the entities involved, are beyond our current scientific frontiers.

Therefore, a scientific crash research effort to conquer AIDS cannot succeed in time if it is only locked into the current mainline tracks of basic biomedical research grouped under the topics Molecular Biology or Biochemistry, Recombinant DNA, or Genetic Engineering technologies. We must encourage such mainline research programs to proceed as a necessary "component" of the Apollo-style AIDS program, and defend such experimental programs against those modern-day Jacobins such as Jeremy Rifkin who would guillotine the genetic engineers and experimental virologists as surely as their anti-science forebears beheaded Lavoisier.

Nonetheless, the inherent limitations of a unilinear or at best limited-track approach, wedded to more or less conventional state-of-the art molecular biology, will not succeed in generating the needed scientific breakthroughs. Second, despite all the engineering successes of molecular biology and recombinant work, the inherent reductionist character of this approach lends itself to knowledge about the "mechanics" rather than the "causality" of biological processes.

Configuration of BSDI

We need nothing short of a broad-based, international Biological Strategic Defense Initiative (BSDI), with the following salient general scientific traits:

1) Place the program in conjunction with the SDI laser and other energy-beam defense program so as to create maximum reverberation of ideas between research breakthroughs on "new physical principles" in the areas of the SDI, plasma physics and astrophysics, on the one hand, and the biomedical sciences on the other. In short, the program should be

FIGURE 1
HIV genome

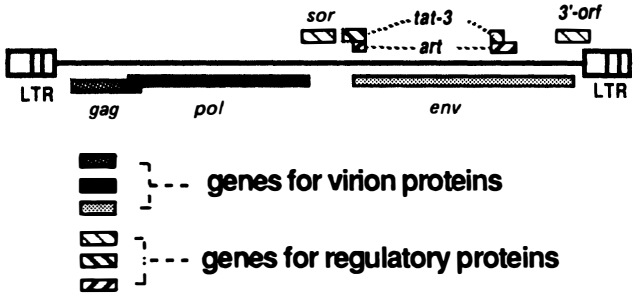


Diagram by Howard Temin, University of Wisconsin School of Medicine, Madison.

Source: Institute of Medicine/National Academy of Sciences: *Confronting AIDS.*

decisively *interdisciplinary*.

2) Nurture the areas of research variously known as *optical biophysics* or *non-linear biological spectroscopy*. This approach to biology was the intrinsic method of the groundbreaking discoveries on optical activity molecular dissymmetry of the great Louis Pasteur (1822-95). Optical biophysics is the study of the interaction of living substances with light—understood as electromagnetic radiation in the broadest sense—over the entire range of wavelengths from x-rays to radio waves. Today, these areas not only already provide and promise to give even more wonderful diagnostic and therapeutic methodologies to biology and medicine, but they also unlock the intrinsic means by which living processes are "tuned." Not only is there *inter*cellular communication through "bioluminescence" or photon emissions, but the *intra*cellular events from healthy mitosis to abnormal virus infection may well be ordered through coherent low-level biophoton radiation.

3) Eliminate the fetters on research which are imposed by so-called scientific managers, administrators, bureaucracies, and peer review committees which are inherently hostile to new, daring, and non-conventional ideas.

4) Encourage the broadest-based tackling of the scientific problems on the *international* level by promoting the creation of more and more scientific groups or research teams to become involved in productive experiments. Critical scientific capabilities exist from Indian biophysics, Japanese life science and Israeli basic biology to West German, French, and British biomedical and physics research. It is especially important to create such working scientific groups in Tropical belt nations. It should be recognized that the Soviet Union has extensive and field-leading classified research programs on non-conventional biophysics areas on electromagnetic radiation phase-shifts in biological systems under viral attack, which are critical components for science to find the means to stop the species-threatening disease AIDS.

FIGURE 2
Life-cycle of HIV

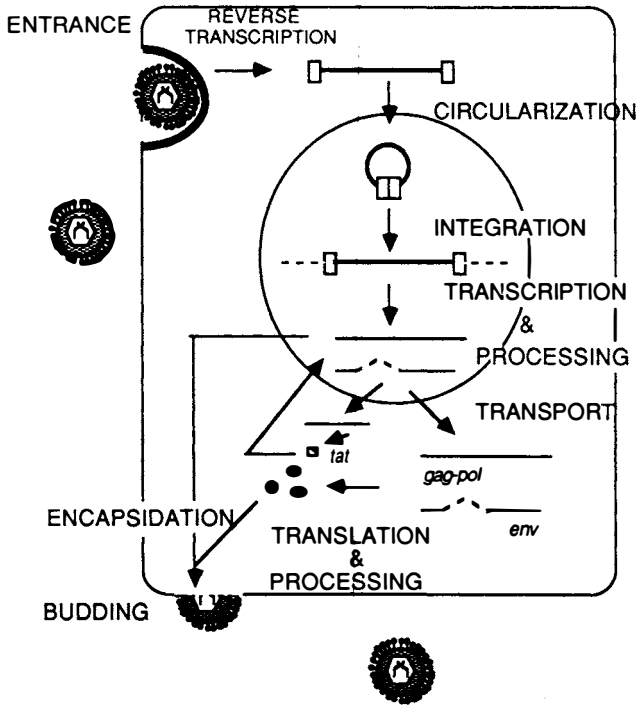


Diagram by Howard Temin, University of Wisconsin School of Medicine, Madison.

Source: Institute of Medicine/National Academy of Sciences: *Confronting AIDS.*

5) Foster an atmosphere which encourages "good scientific ideas and work" and not a pressure cooker for immediate applications and results. As the Academy of Sciences/Institute of Medicine correctly emphasized in *Confronting AIDS*, the progress achieved to date in identifying and characterizing the causative agent of AIDS would not have been possible without the scientific and medical knowledge achieved over the past 20 years in basic biomedical research. In that pursuit, the scientific investigator is rarely certain of when or if his research findings will be applicable to a disease.

6) Follow the model of the Apollo Moonshot program to initiate a crash effort to upgrade basic scientific education to create, and bring on-line, more scientific workers who will be necessary to complete the program.

What is not known

The Academy of Sciences report presents a straightforward briefing on the current state of our scientific knowledge about AIDS which should be read in its entirety by as many scientists and laymen as possible. The briefing is organized into the following sections: The Structure and Replication of HIV; the Natural History of HIV Infection; Epidemiologic Approaches to Understanding the Transmission and Natural

FIGURE 3
Structure of the HIV virion

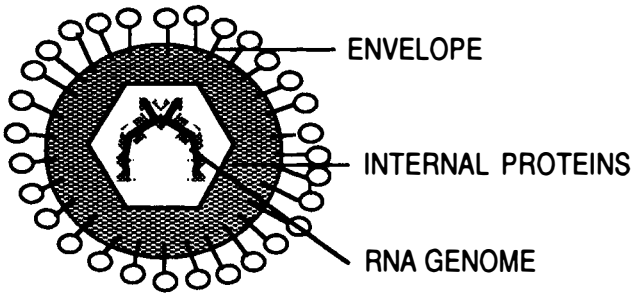


Diagram by Howard Temin, University of Wisconsin School of Medicine, Madison.

Source: Institute of Medicine/National Academy of Sciences: *Confronting AIDS.*

History of HIV Infection; Animal Models; Antiviral Agents; Vaccines; Social Science Research Needs; Funding for Research Related to AIDS and HIV; References.

There are many key scientific aspects of the disease which are currently beyond existing knowledge.

What are the unique features of the AIDS retroviral structure? Molecular cloning and nucleotide analysis of a number of independent isolates of HIV (Human Immunodeficiency Virus or the AIDS virus), have demonstrated that the virus has unprecedented complexity and marked diversity when compared with other known retroviruses. All previously known retroviruses depend on the protein products encoded by three viral genes known as *gag, pol,* and *env,* which specify the various structural and enzymatic functions required for viral infection and transmission. However, the HIV virus contains a minimum of four extra genes. At least two of these four additional genes correlate with functions which are *unknown* at this time.

What are the biologically causal dynamics in the entry of the HIV virus into the cell? The viral particle binds to a specific receptor molecule expressed on the surface of an appropriate target cell, enters the cell and uncoats in the host's cytoplasm. What causes each of these steps to occur? What coordinates this activity? The HIV envelope glycoprotein is unlike the similar components of most other retroviruses, both in its large size, and in the extent and pattern of its sequence variability. Under what conditions will cell entry occur and under what conditions won't it occur in a living organism (*in vivo*)? The Academy report emphasizes that the mechanism of attachment of HIV to its cellular receptor and its entry into the cell is as yet poorly defined. The entry and uncoating of the virus may or may not involve a membrane fusion event. In short, what are the co-factors for the initiation of the viral activity?

The retrovirus's single-stranded RNA is then transferred to a full-length linear duplex DNA intermediate by the activities of one or several enzymes known as reverse transcriptases. The linear intermediate is then transported to the nucleus, where it is circularized before becoming integrated in a stable manner into the DNA genetic material of the host cell itself. Once the virus's genetic information is integrated into the host's nucleus DNA, the retroviral genome is known as proviral DNA. How and why does the HIV genome migrate to the nucleus? How and why does its subsequent circularization occur? What are the causal and coordinating aspects of this integration activity? How does it precisely occur *in vivo*?

The provirus lies dormant, incorporated in the host cell's own nucleus. Under certain conditions after a prolonged period of time, the provirus is activated. Once activated, through a multi-step process, the provirus produces a messenger RNA which leaves the nucleus and causes the cytoplasm of the host cell itself to synthesize and assemble new viral particles, exact replicas of the original retrovirus, out of the cell's own protein. The new viruses are assembled near the cellular plasma membrane. The new retrovirus information proceeds through the cell plasma membrane, wrapping the information in a protein coat, as it buds from the cell. What factors initiate this process? What are the means for coordinating such an activation process? How do each of the individual steps proceed?

The HIV virus possesses an envelope with protruding spikes which surround a central electron-dense core. To fully understand the structure of the viral core, we need the methods of advanced physics to achieve the high-resolution of the structure of the viral proteins. Does the core resemble an electron-dense plasma? What are the locations and amounts of the various internal proteins and the nature of their interaction?

Why is there such a large rate of mutation (genomic variation) in the envelope glycoprotein of the HIV virus? Is this a direct feature of a genome which is composed of a single strand of nucleic acid (RNA in the retrovirus)?

The diversity does not appear to be random but occurs within several bands—"hypervariable domains." What are the means which cause the pattern of variability and the conservation of multiple variation domains?

Why has the virus so strongly selected for human cell infection? What are the unique features of *in vivo* viral expression?

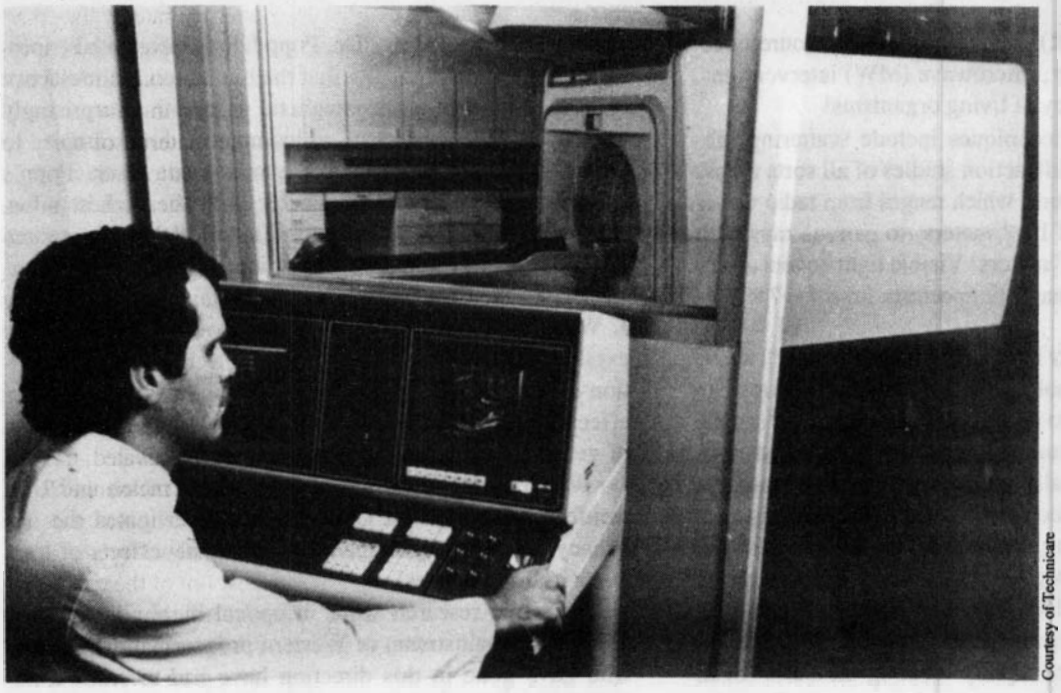
What are the different modes of the process of infection in the neurological as distinct from the immunological system?

What are the implications of these novel features of the AIDS virus for transmission?

What are the co-factors for transmission?

What are the subtle interactions between specific cellular immune response to HIV and the determinants of that response's success or failure?

What are the exact mechanism of cell killing by HIV?



Courtesy of Technicare

A Nuclear Magnetic Resonance scanner at the New York Hospital-Cornell Medical Center. NMR is a spectroscopic technique which allows detailed imaging of plant viruses, to determine how a virus affects the host cell. The method has great potential for study of the HIV virus in humans.

The Academy of Sciences draws the following conclusion from the current state of knowledge:

> In the past few years the techniques of molecular biology have provided the starting materials for a detailed evaluation of the replicative pathways of HIV and for the development of therapeutic strategies to inhibit those pathways. Although HIV was only discovered in 1983-1984, research has been so rapid and so successful that almost as much is now known about its molecular virology as about any other retrovirus. However, less is presently known about HIV-cell interactions than for many other retroviruses. As the pathogenesis of AIDS is clearly related to the interaction of the causative virus with the susceptible host, at the levels of both the target cell and the host organism, much more must be learned about the biology of HIV infection. Although an empirical approach to the development of prophylactic and therapeutic measures for HIV infection and AIDS may work, rational strategies are more likely to succeed, and these will require a good knowledge base.

Why optical biophysics?

There are several examples of the need to promote basic optical biophysics as an emphasized feature of the crash research program, which do not even get into the more restricted domains of advanced electromagnetic countermeasures for insect vector control and so forth.

At an international conference on "Magnetic Resonance in Biology Systems" two years ago in Goa, India, several interesting papers were presented.

A Dutch research team from the Agricultural University of Wageningen and the University of Utrecht presented a paper on "A Magnetic Resonance Approach of the Elucidation of the Molecular Mechanism of Virus Infection." The scientists used two plant viruses—the Tobacco mosaic virus (TMV) and the Cowpea chlorotic mottle virus (CCMV). These plant viruses, like the HIV virus, are composed of a protein coat surrounding RNA. TMV is shaped as a cylinder, 18 nanometers wide and 300 nanometers long, with a helical single strand of RNA inside. CCMV is shaped like a sphere with a diameter of 27 nanometers. Through the special application of advanced Nuclear Magnetic Resonance (NMR), the scientists were able to explore the very types of questions for the plant virus which must be studied for HIV: What are the processes by which a virus particle penetrates the host cell, dissociates, assembles, and leaves the cell.

A series of papers were presented by other scientists on frontier techniques of *in vivo* biological spectroscopy through NMR imaging.

A French biophysics research team based at the Pasteur Institute and National Research Labs at Saclay presented beautiful work on the mechanisms whereby the DNA helix shifts from a right-handed to a left-handed geometry. Another team of French biophysicists reported on a study of Transfer RNA structure and dynamics through NMR imaging of proton exchanges in the different nucleic acids.

NMR is only one technique of biophysics spectroscopy. Others include: Multi-parameter Light Scattering (MPLS) and its more specific form of Circular Intensity Differential Scattering (CIDS) based upon left and right polarized light; Biophoton multiplier counting; x-ray diffraction; Infared (IR) and Ultraviolet/visible (UV) spectroscopy; electron para-

magnetic resonance (EPR); Raman resonance; flouresence; scattering; optical activity; Microwave (MW) interventions; and soon x-ray microscopy of living organisms!

Thus, spectroscopic techniques include scattering, absorption, emission, and diffraction studies of all sorts across the electromagnetic spectrum, which ranges from radio waves with wavelengths around 10^{-1} meters, to gamma rays with wavelengths around 10^{-11} meters. Visible light covers a very small range in the electromagnetic spectrum from $4-7\times10^{-7}$ meters.

Light microscopes only have a resolving power well above the range of individual molecules. Electron microscopy can achieve higher resolution to about 2 nanometers but the sample must be studied in a vacuum and it must be first killed, then sliced very thin, and finally stained with a heavy metallic dye. Obviously such a technique cannot study living processes while they are living. Diffraction studies of crystals of pure macromolecules can give structural information to the atomic level (approx. 0.15 nanometers), but this technique requires crystals. Experimental programs in the United States and in West Germany are rapidly creating the basis for *in vivo* imaging with x-ray laser microscopy.

Pasteurian method

How are we going to expand our knowledge about the fundamentals of biological processes?

The real contribution of a Pasteurian optical biophysics approach to basic research, is that this method of investigation promises to reveal the most fundamental secrets of living processes. Approximately 10 million cells die in the human body every second, and with a few exceptions they are "normally" replaced within that same second. Genetic information theories, hormones, enzymes, and nerve-impulse signals are all too slow to coordinate such a turnover. Only bioradiation phenomena are quick enough to "tune" such a living orchestra.

Thus, a cell has two critical alternatives:

a) Mitosis or cell division as part of a heathy process of growth;

b) Viral replication and cell death as part of a diseased state.

Dr. Fritz-Albert Popp of the Technology Center at the University of Kaiserslautern in West Germany has devoted his life's work to studying coherent ultraweak photon emissions from living tissues. It is generally accepted that all living systems emit a very weak photon radiation of a few up to some hundred photons per second and square centimeter of surface area, ranging at least from ultraviolet to infrared. This low-level biophoton activity is not a mere biochemical luminescence. It corresponds to definite physiological and biological functions in cellular activity and strongly suggests a hypothesis that these biological photons or *biophotons* play a regulatory role.

Even more startling, Dr. Popp has demonstrated experimentally and theoretically that the biophoton luminescence originates from an electromagnetic field with a surprisingly high degree of coherence, as compared, for example, to technological fields such as the man-made laser. Popp's hypothesis is that the biomolecule with the highest information density, DNA, is the best candidate for the source of the biophoton regulatory radiation.

Dr. Popp is not the only worker in this domain. Sydney J. Webb of the University of Saskatchewan in Canada has explored the various "harmonics" of electromagnetic radiation signals in cell mitosis. In particular he has studied the effects of various microwave frequencies on the phenomena of genetic continuity and metabolic regulation.

W. Grundler of the Gesellschaft für Strahlen und Umweltforschung in West Germany has investigated the frequency-dependent biological (non-thermal) effects of low-intensity microwaves.

Since the research work in optical biophysics has not been in the mainstream of Western programs, the scientists who have gone in this direction have had to resist a tremendous amount of peer pressure. Their work has been underfunded and without adequate institutional backing.

In the United States, for example, biophysics was generally downgraded in 1968.

In the Soviet Union, on the contrary, this area of work has received intense support and classification.

The time has come for mankind to face scientific reality. We are faced with a species-threatening disease. Only a full-scale Apollo moonshot crash effort, mobilizing all the scientific capabilities at our disposal, and creating yet more tomorrow is appropriate. I propose that we give this crash effort the name: *The Pasteur Project.*

Ahead lies uncharted territory which will be characterized by an immense amount of hard work and an uncommon richness of scientific discovery. On with *The Pasteur Project!*

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