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AIDS RESEARCH

*Fundamental discoveries made in one area of biomedical research often benefit a wide variety of human diseases. Nowhere has this concept been more apparent than in the quest for a cure for AIDS. AIDS research has been a testing ground for new concepts and technologies in drug development, diagnostics, and prevention. Some findings have been immediately translatable, yielding new drug therapies for old diseases, including hepatitis and cancer. Others will require more time and applied research before their benefits can be realized broadly. Following is a summary of how research on HIV and AIDS is helping us all.*

# THE BROAD BENEFITS OF AIDS RESEARCH: An Update

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**1. I know how support for AIDS research benefits people with AIDS and HIV, but what about people with other diseases, such as cancer, heart disease, hepatitis, and Alzheimer's? Will the continued funding of AIDS research help people with those and other often life-threatening conditions?**

AIDS has a single underlying cause — a virus, HIV. This makes it easier to target than disorders with multiple and largely unknown causes. But AIDS research doesn't exist in a vacuum. Just as it was the federal virus-cancer program of the 1970s that paved the way to a better understanding of HIV, so has AIDS research become a gateway to the diagnosis and treatment of many diseases. For example, it has already led to a new drug for hepatitis B, the leading cause of liver cancer worldwide; for hepatitis C, a rapidly emerging, additional cause of chronic liver disease; and possibly for liver cancer. And it promises a great deal more. In "Cancer and AIDS," a recent article published in The Scientist, A.J.S. Rayl notes that "HIV/AIDS research has blazed trails empirically, politically, and even philosophically. Since this disease took hold some 15 years ago, new insights and understanding in immunology, antiviral research, vaccine development, and gene therapy have emerged from HIV/AIDS research laboratories and crossed over to cancer research," as well as to many other fields.

**2. What are some specific examples of those benefits?**

Recent therapies developed to combat HIV have had a profound impact on the quality of life of people with HIV/AIDS and, in many instances, have prolonged their survival. Less well known is how these drugs may be critical in the treatment of other diseases. For example, lamivudine (3TC), a drug that is similar to zidovudine (AZT) in its anti-HIV activity, has been found to block the growth of the hepatitis B virus. Now it is used to treat patients with chronic hepatitis who were untreatable by any other means. Adefovir, a very recent anti-HIV drug, also has been found to have marked anti-hepatitis B and anti-herpes virus activity in patients. Similarly, the success of the HIV protease inhibitors has spurred the development of similar inhibitors for use in treating other infections, such as hepatitis C and influenza, that rely on their protease enzymes to cause cell

damage. In addition, several drug companies are developing protease inhibitors for use in treating bone loss, or osteoporosis — a problem for a vast number of elderly people — and in limiting the heart muscle damage that results from a heart attack.

**3. What about breast cancer? It's a major cause of death among women, and current therapies have had only minimal impact on survival. Has AIDS research benefited patients with breast cancer?**

Yes. One promising experimental therapy for advanced breast cancer is high-dose chemotherapy, followed by a bone-marrow transplant. However, the profound immune suppression necessary for a successful transplantation often leads to devastating, even fatal, opportunistic infections, including cytomegalovirus (CMV), other herpes viruses, and pneumocystis pneumonia. These conditions are common in AIDS, too, and new drugs against CMV and other herpes viruses have come directly from AIDS-targeted research. New methods of preventing infections, such as pneumocystis, CMV, and toxoplasmosis, that threaten people with HIV, as well as those who are immune-suppressed because of organ transplants, cancer, severe autoimmune diseases, steroid treatment, or genetic disorders, have also come from AIDS research. These new prevention methods will have a direct impact on the survival of every person afflicted with an immune disorder, whatever its cause.

**4. Are there HIV-related advances that are useful in treating cancer itself?**

Absolutely. AIDS researchers have discovered antibodies and drugs that inhibit the activity of specific growth factors, or cytokines, which are the natural body hormones that promote the activity of HIV. Many of these hormones also accelerate the growth and spread of cancer cells. Inhibiting the essential cell receptors for such hormones, e.g., EGF (epidermal growth factor), prevents certain cancer cells from spreading. This strategy, which was used first in the experimental treatment of Kaposi's sarcoma, a cancer found in HIV-infected patients, is also being tested in bladder, vulvar, and breast cancers. Furthermore, small proteins and drugs that can block the growth of new blood vessels (which is critical to the survival of tumor cells) were developed to treat Kaposi's sarcoma, but are now being tested in many other cancers as well. Yet even as strategies to inhibit cytokines are being developed, their ability to promote the growth of certain normal body cells has focused interest on their potential for having a positive impact on specific conditions unrelated to AIDS. EGF-like molecules, for example, are being tested as treatments for spinal cord injuries and strokes.

**5. What about immune-based therapies for cancer and autoimmune disorders?**

Research on AIDS and HIV has stimulated interdisciplinary studies into the development of new treatments for both conditions. HIV-positive individuals often develop evidence of an autoimmune problem, such as a lupus-like blood abnormality, Sjogren's syndrome, rheumatoid arthritis, or psoriasis. For these autoimmune diseases, treatments developed in the context of AIDS should be directly applicable to the same conditions when they occur spontaneously, that is, apart from any association with an identifiable stimulus.

At the same time, treatments developed for other diseases have been applicable to AIDS and HIV; it is a reciprocal relationship. For example, the immune hormone IL-2 was first used almost a decade ago for the experimental treatment of malignant melanoma, a particularly devastating form of skin cancer, and for the treatment of kidney cancer. Now it is used to boost the T cell counts of people with HIV disease. Likewise, other hormones designed to modify immune cells in AIDS and now being tested — the most recent being IL-12 and TNF (tumor necrosis factor)-alpha inhibitors,

such as thalidomide — may also boost the immune systems of cancer patients. In those patients, the hormones assist in destroying the last vestiges of cancer, after most of the tumor has been removed surgically or reduced in size by radiation or chemotherapy. The TNF-alpha inhibitors may, in addition, be useful in combating the "body wasting" that accompanies AIDS, severe tuberculosis, and some forms of cancer.

Identifying the causes of various types of cancer is the only way to develop other new mechanism-based treatments. "We will probably learn more from HIV about indirect mechanisms that influence cancer than we have ever learned from combined research in all medical history," said Dr. Robert Gallo, who spent 20 years on "pure cancer research" before beginning his landmark work on AIDS.

**6. We hear a lot about testing procedures for HIV and for other infections associated with AIDS. Can these procedures help to improve the diagnosis of other diseases?**

Great effort has been expended in the development of better diagnostic tests for antibodies against HIV and for HIV itself. These tests are vital for following both the course of infection and the impact of various therapies. Extraordinarily sensitive techniques, capable of locating less than one molecule of HIV genetic material (DNA and RNA) among millions of particles of extraneous material, are now available and are known as PCR (polymerase chain reaction) and RT-PCR (reverse transcription PCR). Such techniques have made it possible to measure otherwise undetectable levels of cancer cells in individuals, who clinically appear to have been "cured," so that new therapy can be initiated or ongoing treatments continued, not inappropriately discontinued. Similar techniques applied to the rapid diagnosis of infectious diseases, such as tuberculosis, are also being perfected. Also of great importance is a capacity to search for the causes of cancer and other diseases and to detect at an early stage the probable emergence of new, unknown infectious diseases. The discovery of HHV-8, a herpes virus linked to Kaposi's sarcoma, was made possible by a new application of PCR. This technique is now being used worldwide to seek possible infectious causes for diseases of unknown origins.

The first medical application of an emergent technology, the "DNA microchip," is the detection of drug-resistant mutations in HIV. The ability to rapidly screen small quantities of blood for changes that are associated with resistance to specific antiviral drugs has enormous potential for use in HIV and, as new uses are developed, in biology and medicine.

**7. What impact does AIDS research have on Alzheimer's research? Alzheimer's may attack as many as one in ten individuals over the age of 80, and the incidence of this terrible disease will grow as the population continues to age.**

Alzheimer's disease is a progressive, global dementia of unknown cause. There are many theories as to how it occurs, including the autoimmune destruction of brain cells; the deprivation of nutrients to nerve cells secondary to the proliferation of a fibrous substance known as an *amyloid*; the growth of a unique infectious agent known as a *prion*; and others. Profound dementia is also an important component of AIDS in its late stages. Research has shown that HIV can cause dementia by interfering with the activity, nourishment, or interconnection of nerve cells and accessory cells of the nervous system through a process of cell injury known as *apoptosis,* or programmed cell death. AIDS dementia provides a test system, reproducible in monkeys infected with the simian AIDS virus (SIV), for studies of Alzheimer-like diseases. Drugs that are successful in ameliorating nerve damage and dementia in AIDS may thus have salutary effects in Alzheimer's.

**8. Aren't you reaching a bit when you talk about AIDS research benefiting patients with heart disease?**

Not at all. A substantial portion of HIV-positive children and adults suffer heart attacks and strokes. HIV appears to affect small blood vessels in the heart and the brain, rendering them vulnerable to spasm, blood clots, and early atherosclerosis. The small arteries of a two-year-old child with AIDS often resemble those of a fifty-year-old man. It appears that in HIV infection, apoptosis — the same condition mentioned above in regard to dementia — injures the cells that line the small blood vessels of the heart. This same injury occurs in HIV-negative people with atherosclerosis, where its origin is thought to be certain infections of the blood-vessel wall. Thus, the discovery of the means to block the apoptotic process may not only benefit those with AIDS, but everyone.

**9. One hears a lot about "AIDS activism." Has it helped anyone besides AIDS patients?**

Definitely yes. AIDS advocates have focused national attention on the high cost of new drugs and on the traditionally slow and cumbersome way in which drug development is regulated by federal agencies. The Food and Drug Administration has responded constructively to the urging of AIDS advocates and has instituted "fast track" procedures to review new treatments for *all* life-threatening conditions. Fast tracking has already been applied in the approval of drugs for treating Alzheimer's, AIDS, and other diseases, including cancer.

**10. What about costs? Should we compare the costs of different diseases? How cost-effective are AIDS treatments?**

If one simply counts deaths, then the number of people dying annually from either cancer or heart disease surpasses those dying from HIV disease. But statistics show that most of those dying from cancer or heart disease are much older than the average person dying from AIDS. In terms of years of productive life lost (i.e., when death occurs before age 65), AIDS is a much bigger threat and a much larger economic burden on society as a whole.

As one standard by which the cost-effectiveness of treatments can be measured, medical economists use $50,000, the cost each year of a life saved by kidney dialysis. Using this standard, the antiviral treatment of HIV/AIDS is an economical investment in life. It also compares well with some generally accepted interventions, such as heart surgery (e.g., coronary artery bypass) and blood screening for prostate cancer, each of which costs about $113,000 per year of life saved.

*In summary, HIV disease and AIDS need not — and must not — be viewed as distinct from other diseases. Education and "safer sex" messages, together with efforts to promote the treatment of substance abuse, will help to control current epidemics of sexually transmitted diseases and injection drug use. Basic and clinical research in AIDS, a disease for which the cause is known, is providing insights into immune, infectious, and cancerous diseases, their causes, and their treatments. Programs in immune system restoration, better diagnostic methods such as PCR, newer prophylactic antibiotics and drugs, and new therapies for infectious diseases and cancer — all developed in the course of AIDS research — are having a major impact on countless lives.*

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