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AIDS: Implications to Society and Approaches to Control

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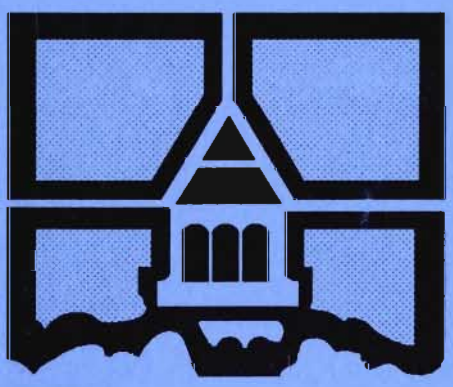
By
Robert W. Sidwell



76th Faculty Honor Lecture
November 6, 1990
Utah State University

November 6, 1990
Utah State University
Logan, Utah

Sponsored by the Utah State University **Quadrangle**

SEVENTY-SIXTH HONOR LECTURE
in the Natural Sciences

delivered at
UTAH STATE UNIVERSITY
Logan, Utah
November 6, 1990

A basic purpose of the Utah State University Quadrangle (formally the USU Faculty Association and Faculty Women's League) is to encourage the intellectual growth and development of its members by sponsoring and arranging for the publication of two annual faculty lectures in the fields of (1) the biological and exact sciences, including engineering, called the Annual Faculty Honor Lecture in the Natural Sciences; and (2) the humanities and social sciences, including education and business, called the Annual Faculty Honor Lecture in Humanities.

This seventy-sixth lecture, continues a tradition which began in 1942. Over the years this series has served to honor USU's most outstanding scholars from every college in the University.

Lecturers are chosen by a committee of the USU Quadrangle. Among the factors considered by the committee in choosing the lecturers are (1) creative activity in the field of the proposed lecture; (2) publication of research through recognized channels in the field of the proposed lecture; (3) outstanding teaching over an extended period of years; (4) personal influence in developing the character of students.

Dr. Robert W. Sidwell was selected by the committee to deliver the seventy-sixth Annual Faculty Honor Lecture in the Natural Sciences.

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By
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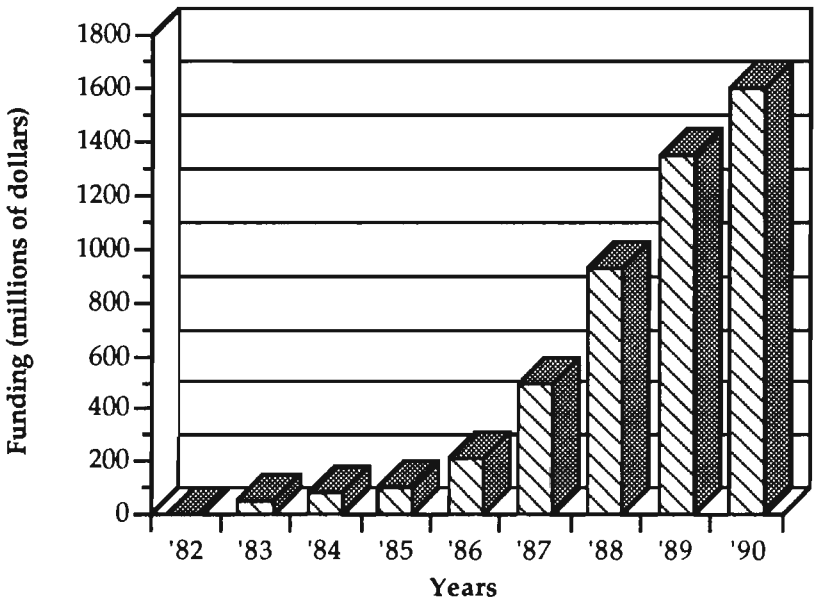
Introduction

It is perhaps a measure of today's society that a new disease of potentially world-wide implication does not gain national or international attention until a famous person contracts it. This was particularly seen with Acquired Immunodeficiency Syndrome (AIDS) when it became known that Rock Hudson of movie and TV acclaim was dying of it. By the time the celebrated pianist and entertainer Liberace died of AIDS, the various public health agencies around the world had begun to focus on the problem, and enormous sums of money were being committed toward its control. Today, more U.S. dollars are budgeted for AIDS than are being spent for any other disease, including cancer (Figure 1).

Figure 1. Federal Funding for AIDS (Combined Public Health Service, Federal Medicaid Share, Veterans Administration and Department of Defense)



Source: Office of Management and Budget

AIDS has caused major changes in the scientific and social perspectives of the people of the United States and, perhaps to a lesser degree, to public

perspectives throughout the world. This is a deadly disease caused by a new pathogen of a class which previously has never been conclusively shown to be a public health problem. We have had to adjust our scientific sights to focus on this new disease agent—an adjustment which has resulted in astonishing technological progress in learning of the etiology and means by which this new disease is spread. Such technological advancements, in addition to expanding our understanding of this new disease, may peripherally benefit the public in providing illumination on many other heretofore little known diseases. Unfortunately, science has thus far fallen short, however, of finding an acceptable cure for those with AIDS or of developing a vaccine for those who may be at risk.

The disease is making a major economic impact, both on increasing the demand for more research dollars and in escalating costs for medical treatment which has led to significant changes in insurance coverages and fees. Since a major means of transmission of the AIDS pathogen is through sexual contact, significant changes in human sexual behavior have been mandated.

It is the purpose of this lecture to provide a brief overview on AIDS: The disease, its etiology, some sociological effects and how our government is responding to the disease. I will end by reviewing some of the research being done at Utah State University (USU) toward control of this most significant new medical emergency.

The Disease

The disease of AIDS is not pretty, and people who die due to its effects usually do not do so quickly. The AIDS virus directly attacks several portions of the immune system. The primary target cell attacked is the helper T4 lymphocyte, a white blood cell required by the body to initiate the necessary immune responses to protect the body. The loss of these T4 cells results in a systematic failure of a large part of the immune system. The virus also attacks the macrophage, another important white cell which functions in a variety of ways to provide immunologic protection. The destruction of these immune mechanisms leaves the body open to attack by what are known as opportunistic infections, which are caused by viruses, bacteria, fungi, and protozoa (Table 1) which are of little significance in the healthy individual. In addition, the patient is highly prone to develop certain cancers; Kaposi's sarcoma, a cancer of the skin, and internal organs, is predominant.

The resultant opportunistic diseases are devastating, usually leading to a slow, and painful death.

The AIDS virus itself can cause clinical manifestations of disease. The macrophages infected by the virus migrate to many parts of the body and consequently are instrumental in the spread of the virus to cells of the brain, central nervous system, and spinal cord. The heart and blood-forming elements may also be attacked. Individuals infected in this manner often do

not display either the cancers or infectious diseases usually seen in AIDS patients. Instead, they exhibit dementia, severe emaciation, and occasional anemia, and are referred to as having AIDS-related complex (ARC).

Table 1. Opportunistic Infections in AIDS Patients

Organism	Common Clinical Manifestations
Virus	
Cytomegalo*	Retino-choroiditis, colitis, pneumonia
Herpes simplex	Mucocutaneous (mouth, rectum)
Herpes zoster	Dermatomal
Epstein-Barr	Hairy leukoplakia, possible neoplasia
Bacteria	
Hemophilus influenza	Pediatric upper respiratory, pneumonia, sepsis
*Mycobacterium avium-intracellulare**	Disseminated infection
Mycobacterium kansasii	Disseminated infection
*Mycobacterium tuberculosis**	Pneumonia, disseminated infection
Salmonella sp.*	Diarrhea, sepsis
Streptococcus pneumoniae	Pediatric upper respiratory, pneumonia, sepsis
Treponema pallidum	Neurosyphilis
Fungi	
Candida sp.	Esophagitis, stomatitis
*Coccidiodes immitis**	Disseminated infection
*Cryptococcus neoformans**	Disseminated infection, meningitis
*Histoplasma capsulatum**	Disseminated infection
Protozoa	
Cryptosporidium	Enteritis
Isospora belli	Enteritis
*Pneumocystis carinii**	Pneumonia
*Toxoplasma**	Encephalitis, retinochoroiditis

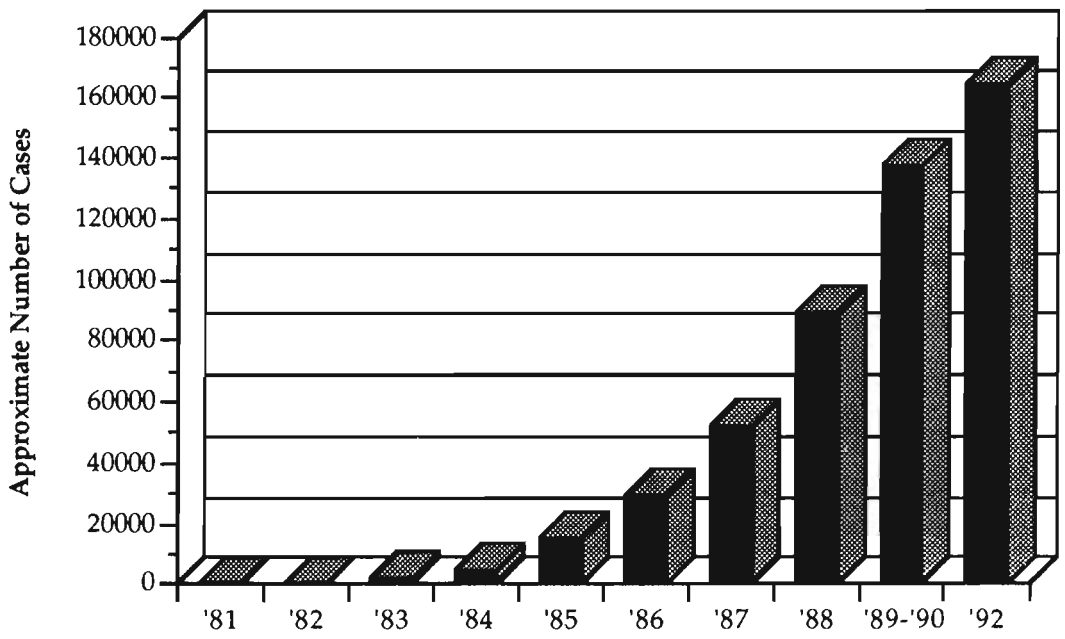
*Considered of major significance

Epidemiological Impacts

Probably the first case of AIDS in the United States involved a 15-year-old boy who died in 1969. The patient had small purplish lesions which were identified as Kaposi's sarcoma, and a major onset of chlamydia, a sexually transmitted viral disease. His immune system was functioning poorly at the time of his death. Samples of his body fluids and tissues were found 15 years later to be positive for the AIDS virus.[1] It is apparent that the virus present in this youth did not get widely spread, and no further cases of a similar nature were reported until 1981, when an immunodeficiency disease was seen in male homosexuals.[2,3] Since that time, the number of cases in this country has rapidly increased, to a total of 137,385 through June 1990[4] (Figure 2). By this latter date, 84,164 deaths have been attributed to the disease in the U.S.

By 1992, our public health authorities predict over 365,000 cases—at least 1,000 new cases for each day of the year.[5]

Figure 2. Increase in Clinical AIDS Cases in the United States, 1981 through 1992 (predicted)



Some even more sobering statistics also confront us. The numbers just cited are clinical cases of AIDS. If we also consider those who are seropositive but do not yet have symptoms, the numbers jump to over one and one-half million cases in the United States right now.[4] Thus the active cases are literally only the tip of the iceberg. By redefining of the scope of AIDS to include seropositive patients with those nearing death from AIDS as having "HIV disease," our medical authorities have then qualified the clinically healthy but seropositive patient for insurance benefits. This has subsequently raised the cost to care for such patients to an enormous extent.[6] Estimates of the cost for the lifetime care for an AIDS patient have ranged from $61,800 to $94,000.[6] Such marked increases in healthcare costs will ultimately affect us all in the pocket book.

None of the above figures reflects the incidence of AIDS outside of the United States. The disease is considered to be found in essentially all the nations of the world. In Africa, the World Health Organization has estimated that at least 400,000 persons have AIDS, and about 3.5 million additional Africans may be seropositive.[7] Most of these cases have been seen in central Africa, where literally entire towns have been decimated. We must recognize, too, that many countries in Africa are reluctant to admit the extent

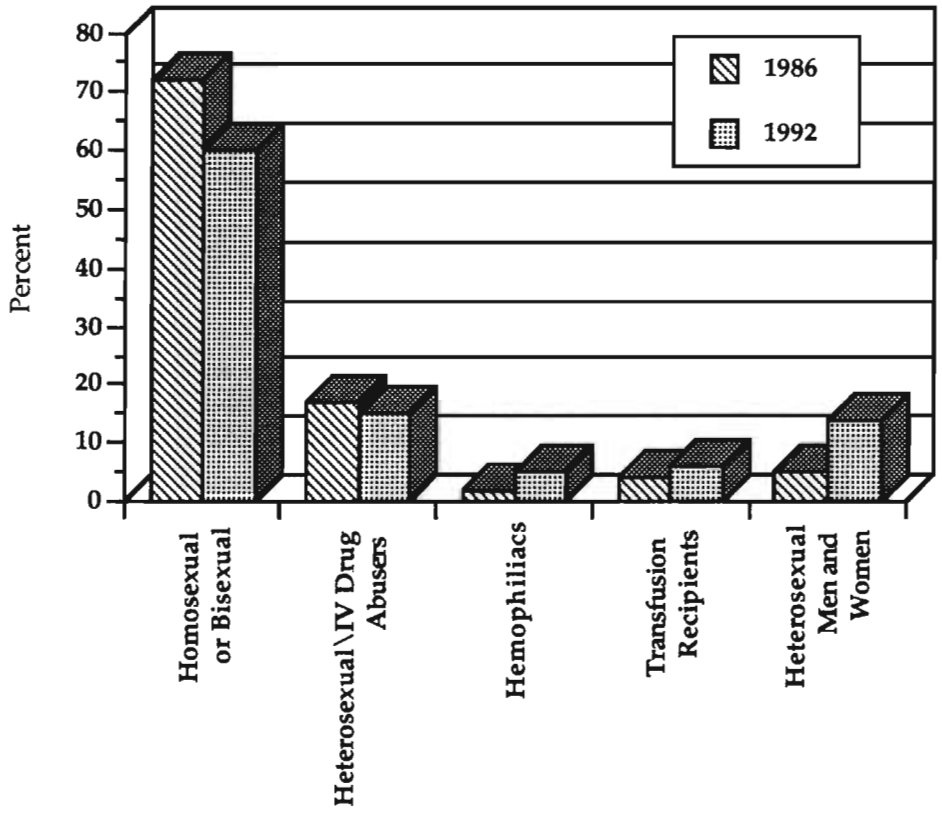
of the disease in their area, so there is little doubt the incidence of AIDS is much higher than now reported.

The AIDS nightmare in Africa and the response of some governmental officials there to it is illustrated in a recently described situation involving Tanzania.[8] Researchers at Yale University's international health program planned to determine the prevalence of HIV disease in pregnant women in that country. They were to look for antibodies to the AIDS virus in maternal and infant cord blood. Unfortunately, Tanzanian officials would not allow the women to be told either why the blood was being taken or what were the results of the testing. They were concerned that hysteria might develop among the women because there was no cure for AIDS. In addition, Tanzania's medical care system was unable to provide adequate supportive services. Because U.S.-associated trials require "informed consent," the study had to be abandoned.

The distribution of AIDS cases is interesting. Most of the infected patients are homosexual or bisexual men, followed by intravenous drug abusers (Figure 3). Hemophiliacs, transfusion recipients, and adults who participate in heterosexual activities are the primary other "at risk" groups. Note the information in the figure are 1986 statistics. Also shown, however, are the figures predicted for 1992, where it can be seen that a major shift occurs to sexually active women. We are already seeing this transmission of the AIDS virus from men to women occurring in much higher frequency.[9] Not shown on the graph is the predicted major increase of AIDS in the perinatal population. The current U.S. statistics indicate a 38percent increase of the disease among infants in the past year.[4]

The distribution of AIDS cases shifts dramatically in some other countries. In Africa, for example, women and children are now the hardest hit. Of the estimated 3.5 million seropositive persons in Africa, children under five constitute approximately 600,000.[7] Infections are almost non-existent in Africa among homosexuals. Thus, this is a disease which is not necessarily discriminating and is potentially capable of affecting many populations. One of the most touching photographs shown by an AIDS researcher at a recent medical conference was of an African hut with a girl about 12 years old standing in front of it holding a baby and with a toddler holding onto her leg. The researcher said that this was quite illustrative of the situation now occurring in Africa—both the parents had died of AIDS, and the baby eventually may as well. The entire burden of running the family had fallen to the 12-year-old.

Figure 3. Distribution of AIDS Cases in the United States, 1986 and 1992 (predicted)



The Virus

The causal agent of AIDS has had several names: lymphadenopathy virus (LAV), human T lymphotrophic virus III (HTLV-III), AIDS-associated retrovirus (ARV), and, finally, human immunodeficiency virus (HIV). The latter name, HIV, is in common use at this time.[10] It now appears that two types of HIV are responsible for AIDS. Type 1 (HIV-1) is the primary culprit, but recent evidences point to the emergence of type 2 HIV (HIV-2), which has similarities to simian immunodeficiency virus, an agent which causes an AIDS-like disease in nonhuman primates; HIV-2 has now been found in human populations in certain areas of Africa.[11]

HIV is a member of the Retroviridae family of viruses, and is thus often referred to as a retrovirus. Until the onslaught of AIDS, no retrovirus had been conclusively shown to be a cause of human disease. Retroviruses have RNA for their genetic material, from which DNA is made which is incorporated into cells, changing the cells' genetic makeup so that new viral RNA can be synthesized and assembled into new virus particles.

The viral DNA, once incorporated into the cell chromosome, may undergo a period of latency which can last years. Thus persons infected

initially with HIV may appear normal for long periods of time before the AIDS disease eventually develops. Despite the exposure to often very small amounts of virus through sexual contact, use of contaminated needles by drug abusers, or transfusions of contaminated blood products, an immune response to the virus is triggered. Antibodies to HIV subsequently appear in the blood and are used as an indicator of infection. Eventually, the latent infection is activated, and once this occurs, the virus will grow rapidly, and spread quickly to other cells throughout the body. The antibodies developed against the virus do not control the disease, which is in contrast to what happens in most virus diseases. The virus, in part, is transmitted cell-to-cell in a manner that it is not accessible to the antibody. Although HIV levels in the blood often decline with high antibody levels, considerable evidence is accumulating indicating that the anti-HIV antibodies may actually enhance the disease severity.[12] The later destruction of the other immunological components in the body by the virus then leads to further increases in disease severity and to the opportunistic infections described earlier.

The AIDS virus is an especially challenging entity. In addition to its effects on the immune system of the body, the virus also undergoes genetic variation, often in the same infected individual, during the period of infection.[12] This mutation of segments of the HIV genome occurs at a much higher rate than is expected to occur in human genes. Such variations may pose complications particularly in the development of viral vaccines.

A last point in this most simplified review of a highly complicated pathogen: HIV is relatively sensitive to destruction by normal conditions such as heat, light, and drying outside the body. Thus, transmission via casual contact such as on toilet seats, on lab benches, or breathing potentially contaminated air is unlikely and as yet has never been demonstrated. Although mosquitoes have been suspected of HIV transmission, considerable research has not shown this to occur. If it were not for the various exchanges of body fluids that occur in the human population, the spread of this virus would be no problem to us.

The United States Government's Response

The U.S. government's mechanisms for coping with the AIDS problem were both late in starting and slow to build up to render significant help. Today, however, as seen in Figure 1, the total dollar appropriation into AIDS research has reached major proportions. An initial review of the figure might incur the response that too much is being spent on this disease; the difference between AIDS and diseases such as heart disease, cancer, and stroke, which now kill many more persons than AIDS, however, is the fact that the incidence of AIDS is increasing at an extremely rapid rate and expanding into new populations, whereas the other diseases, while at a high rate, are not increasing in such a dramatic fashion.

The federal approach has been multipronged, involving a major Public Health Service task force including the Centers for Disease Control, the National Institute of Allergy and Infectious Diseases (NIAID), the National Cancer Institute, the National Institute of Mental Health, the National Institute of Drug Addiction, the Food and Drug Administration, the Department of Defence, the Veteran Administration, and the Health Resources Services Administration.

Within the NIAID, a new division has been formed, appropriately named the Division of AIDS. This Division has an Epidemiology Branch, a Biostatistics Research Branch, a Treatment Research Program, and a Basic Research and Development Program. These programs encourage and coordinate research involving much collaboration between medical workers and research scientists from the NIH itself, universities, nonprofit research institutes, pharmaceutical companies, and the rapidly multiplying biotechnology companies. With the innovative new National Cooperative Drug Discovery Programs, it is not unusual for one grant application to have many subapplications, each from a different institution.

A significant response by our government to the AIDS problem has been the literal "new age" of drug testing which aims to provide promising drugs to as many AIDS patients as possible. The drug testing concept, which has developed in part due to recommendations of AIDS activists, involves people with AIDS in the trial design, puts more emphasis on drugs for opportunistic infections, uses more flexible testing protocols and broader entry requirements, avoids the use of placebos, and involves the use of more sensitive disease parameters instead of death of the patient.[13] In addition, considerable flexibility is being displayed by the U.S. Food and Drug Administration to get more new drugs into clinical trials faster. Such monumental changes in drug testing may go beyond the treatment of AIDS to apply to testing of drugs against other life-threatening diseases.[13]

The AIDS research effort has begun to mature, and without question, no other virus has had so much learned about it so quickly. More is known about HIV than is known about any other virus. Unfortunately, as has been reviewed, the virus is so complex, and the disease manifestations so extensive and challenging, that much more needs to be learned before the disease can be controlled or adequately treated.

Treatment Difficulties

Treatment of AIDS patients is being approached from several directions. Before reviewing the approaches to AIDS treatment, which is the thrust of our USU research, we should first consider the challenges involved in attempting such treatments.

Since the AIDS virus becomes a part of the infected cell, often in a latent state for long time periods, the virus potentially may never be removed from the body by therapy, and treatments may need to be continued throughout the

lifetime of the infected individual. The occasional infection of brain tissues is a particular challenge to drugs, for they must cross the blood-brain barrier, which is high in lipid content and consequently almost impervious to any drugs not soluble in lipids. In addition, such therapies involving the brain should avoid having neurological effects, a complication difficult to avoid when drugs are found which can penetrate nervous tissue.

Since the host's immune response has been compromised or perhaps essentially destroyed by the HIV infection, the body cannot assist the antiviral therapy, which often acts by inhibiting the viral growth but by itself does not eliminate the virus; the sagging immune response may need bolstering by an immune modulating drug which may thus be required to be used in combination with more standard antiviral therapies.

The opportunistic infections which are usually the cause of death in the AIDS patient consist of a spectrum of disease agents, each requiring a different specific type of treatment. For some opportunistic pathogens, no therapies are yet known. Ideally, treatment may consist of therapy to stop the HIV combined with a drug or drugs to combat the opportunistic infection. Finally, the specter of drug-resistant viruses needs to be confronted. This is already beginning to be a problem.[14]

Treatment Concepts

Considering the above difficulties, treatment of AIDS can theoretically be approached by:

1. Anti-HIV therapy using a substance designed to attack the virus or to inhibit its growth (Table 2).

2. Anti-HIV therapy using cytokines, which are biological response modifiers produced by cells and which are becoming available in sufficient quantities to be of potential clinical use (Table 3).

Table 2. Substances Now in Use or in Clinical Evaluation as Specific Anti-HIV Therapies[15]

2',3'-Dideoxyadenosine (DDA)	D-Penicillamine
2',3'-Dideoxycytidine (DDC)	Dextran sulfate
2',3'-Dideoxyinosine (DDI)	Foscarnet
Acyclovir	Fusidic acid
AL-721	GLQ223 (Compound Q)
Amphotericin B	Glycyrrhizin sulfate*
Ansamycin	HOE/BAY 946
Avarol	Hypericin
Azidothymidine (AZT)	Lentinan
Carrisyn*	Peptide T
Cyanothymidine (CNT)	Ribavirin

*Also has immunomodulatory properties

Table 3. Cytokine Anti-HIV Therapies Under Clinical Investigation[15]

Anti-HIV antibodies	Leukotoxin
Colony-stimulating factor	Thymosin-a1
Gamma globulin	Transfer factor
Interferon a, b, g	Tumor necrosis factor
Interleukin-1, 2, 3, 4	

3. Anti-HIV therapy using materials that block viral entry into cells. These include peptide T, which is part of the envelope glycoprotein of HIV; CD4, the protein receptor on certain cells to which HIV binds; and the polysaccharide, polymannoacetate.

4. Stimulation of certain segments of the immune response using immunomodulators as a means of strengthening the system or to provide backup to any of the above HIV therapies (Table 4).

Table 4. Immune Stimulators Under Clinical Investigation as Anti-AIDS Therapies[15]

Ampligen	Imuthiol
AS-101	Isoprinosine
Azimexon	LF1695
Carrisyn	Methionine-enkephaline (MET-ENK)
CL246,738	Muramyltripeptide
Cyclosporin	Naltrexone
Imreg-1	Thymopentin

5. Specific treatment of the opportunistic infection(s) occurring in the AIDS patient, including anticancer therapy for Kaposi's sarcoma. These are too extensive to discuss in this overview.

6. Use of vitamins and appropriate diet to build up the patient.

7. Selective destruction of HIV-infected cells resulting also in the elimination of the virus. This approach to date involves the use of immunotoxins, which are combinations of antibody against the cell to be killed conjugated with a toxic substance. The toxic substance is harmless unless it can be taken into the cell—an event requiring the antibody to which it is attached.

8. Perfusion of the AIDS patients' plasma through a prosorba column which removes circulating immune complexes which are involved in AIDS pathogenesis, blocking normal immune responses.

9. Use of vaccines against all or part of the HIV genome. While not a treatment, it may be appropriate to include as the last approach in this review, although work with vaccines is literally the topic of a complete review in

itself. While early results with vaccines show some promise, much research remains to be done.

Utah State University Studies

The above review of the means to treat AIDS appropriately leads to a brief description of the AIDS research underway at USU. Our AIDS Research Group presently has two contracts with the National Institutes of Health; one is oriented toward developing therapies for a viral opportunistic infection associated with AIDS; in the other, research is being done into developing therapies for AIDS.

Therapy for opportunistic infections: The project to develop an agent for treatment of opportunistic infections is a collaborative study with chemists at SRI International (Menlo Park, California). Potential new drugs synthesized at SRI are evaluated against experimentally induced cytomegalovirus infections and for potential toxicologic effects in our laboratories. Two potential new drugs which are chemically related to ganciclovir, the only clinically approved drug for treating human cytomegalovirus infections, have been developed through this joint research effort. These substances are the phosphonate monoethyl ester of ganciclovir and the phosphonate diacid of ganciclovir.[16] Both new substances appear to be less toxic than ganciclovir, yet retain a strong antiviral potency (Table 5). Much is yet to be done in the development of these materials as drugs.

Table 5. Treatment for Opportunistic Infections: Human Cytomegalovirus Inhibition of Phosphonate Analogs of Ganciclovir

Compound	50% Cytotoxic Dose (μg/ml)	50% Cytomegalovirus-Inhibitory Dose (μg/ml)	Therapeutic Index*
Ganciclovir	1000	2	500
Phosphonate diacid of ganciclovir	~2000	2	1000
Phosphonate mono-ethylester of ganciclovir	~2000	4	500

*Cytotoxic dose + virus-inhibitory dose.

Studies with unique AIDS animal model: The research work to develop new therapies for AIDS underway at this university is involved particularly in the study of immunomodulators for the potential therapy of AIDS. Such research is challenging because we must use a small animal model which mimics, as much as possible, the AIDS disease in humans. The AIDS virus will not produce a disease in animals other than primates. A retrovirus of mice is thus employed, this being the Friend virus complex, which receives

its name from the scientist, Dr. Charlotte Friend, who originally discovered it. The Friend virus induces in mice a leukemia-like disease which will vary according to the genetic makeup of the animal. When special hybrid mice with the Rfv-$3^{r/s}$, H-$2^{a/a}$ and FV-$3^{r/s}$ genotype are infected, the resultant disease has many analogies to AIDS: in both infections, immunosuppression of the host occurs. Antibodies specific to the retrovirus occur in both the hybrid mouse and in man, yet both hosts are immunologically compromised if challenged by other disease agents. With the development of the antibody, only low levels of infectious virus can be found, yet the disease continues to progress.

Our laboratory is unique in using this special mouse with defined genetic characteristics for use as an AIDS animal model.[17] We have found the clinically useful HIV-inhibiting drug zidovudine (AZT), to markedly inhibit the AIDS-like disease in this mouse model. Of considerable significance, however, is our recent finding[18] that infected animals treated with AZT may appear to be "cured," i.e., free of all signs of the disease, including virus as sought by standard means. An apparently latent virus can still be seen, however, when extraordinary means are used for virus detection involving multiple co-cultivations of tissues from the animal with cultured cells of normal mice (Table 6).

Table 6. Detection of Persisting Retrovirus in AZT-Treated Mice

Treatment	Total Virus-positive Spleens Detected* by Standard Methodology	Total Virus-positive Spleens Detected* After Viral Amplification**
AZT, 80 mg/kg tid x 20	0/31	14/31
Saline tid x 20	6/10	10/10

*35 weeks after virus inoculation.

**Multiple co-cultivation with cultured indicator cells.

Such results lend credence to the cry for new, better drugs for treatment of AIDS. As mentioned earlier, a possible approach for improving the efficacy of an antiviral drug such as AZT is to use a second drug in combination with the original antiviral drug. Ideally, the second drug should have a mechanism of action quite different from the initial drug. This is where the immunomodulators enter the scene, for the mechanisms by which these materials act are to enhance or modify the host immune system. Thus, a drug like AZT may specifically inhibit the replication of the virus in the cell, while the immunomodulating drug acts to bolster the fading immunity which results from the HIV infection. Such combinations are beginning to be studied in the clinic; it is one goal of the USU AIDS Research Program to help identify which combinations may be best for use in those clinical situations.

Our studies to date indicate 3 immunomodulators have potential for use in drug combinations. These materials are recombinant human interferon a, pyran copolymer (also known as MVE-2), and imexon, which has the chemical name 4-imino-1,3-diazobicyclo-(3.1.0)-hexan-2-one.[19]

Use of genetically immunodeficient mice: A problem often encountered with potential immunomodulating drugs is their failure to achieve in humans the significant immune modulation seen in lower animals such as mice. An approach being taken at USU is again to use a unique mouse model, in this case the Severe Combined Immunodeficient animal, usually referred to as the SCID mouse. These mice lack functional T or B cells, are hypogamma-globulinaemic, poor mitogen responders, and fail to reject allogenic skin grafts.[20] In short, the animals are so lacking in a functional immune system that they are unable to reject foreign tissues introduced into their bodies. Thus, portions of a human immune system, such as found in human lymphocytes, can be injected into the SCID mouse, and, rather than being quickly eliminated by the animal, grow in the animal, literally reconstituting the mouse with the human immunity.[21,22] We are using these human immunity-reconstituted SCID mice as a "next step" in the process of evaluating Biological Response Modifiers (BRM). It is most encouraging when a BRM will stimulate segments of the reconstituted human immune system in the SCID mouse in a similar manner to what is seen in regular mice.

The immunological deficiencies of the SCID mouse have been shown by our group[23] to allow the animals to become infected by *Cryptosporidium*, a serious parasitic infection afflicting AIDS patients. Until this infection was demonstrated in the SCID mouse, researchers have had difficulty finding an acceptable model which could be used to study this disease and the effects of possible therapies upon it.

Transgenic animal research: A last challenge being targeted by our research program is how to deal with the latent virus or portion of the HIV genome which is being continually passed from one cell to its offspring. Again, a model is needed. In this case, we are collaborating with researchers at the Roche Institute of Molecular Biology (Nutley, New Jersey), and at the National Institutes of Health (Bethesda, Maryland) in the development of transgenic mice.[24] Noninfectious segments of the HIV gene are inserted directly by micromanipulation into the fertilized mouse embryo, which in turn is transplanted into a healthy female mouse. The subsequent offspring are born with the HIV gene segment being expressed in certain of its tissues and are referred to as transgenic animals. The HIV gene segment is expressed in immune cells of the skin and can be activated to be expressed in lymphocytes and macrophages by factors known to activate the virus in HIV-infected people. The offspring born later to these HIV gene-expressing mice similarly express the same gene, somewhat analogous to what occurs in man. We now have small colonies of these transgenic animals which are being used for the study of potential anti-AIDS drugs and BRMs.

Conclusions

This brief overview has hopefully shown that AIDS is a most serious affliction which is spreading rapidly, and, as yet, is not readily controlled. The government's massive basic and clinical research response to this disease has yielded dramatic advances and will benefit us in control of other illnesses. Many approaches are being taken to the treatment of AIDS, and numerous therapies are under evaluation. The much sought-after cure of this deadly disease is probably still much into the future, however.

The USU research programs I have described are a result of a truly collaborative effort involving scientists of many disciplines both from within the university as well as from highly regarded outside institutions (Table 7). Indeed, collaboration in research is the key for success in the battle against a most formidable and serious new plague, the disease of AIDS.

Table 7. Senior Researchers Involved With the Utah State University AIDS Research Program

USU Researchers

Robert W. Sidwell	Thomas Bunch
John D. Morrey	Mark C. Healey
Reed P. Warren	Kevin Jackson
John H. Huffman	Michael Arrowood
Donald F. Smee	Jan Mead
Dale L. Barnard	Kathleen Rasmussen

Outside Collaborators

Michael Hogan, Baylor College of Medicine
Malcolm Martin, National Institutes of Health
Elmer Reist, SRI International
Craig Rosen, Roche Institute for Molecular Biology

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