Pathways to Progress

Fall 2003

FOR TODAY'S PATIENTS AND TOMORROW'S CURES

The Quarterly Newsletter of Americans For Medical Advancement and Europeans For Medical Advancement

Americans For Medical Advancement (AFMA) and Europeans For Medical Advancement (EFMA) is a mainstream science-based research and educational institute dedicated to improving policy and decision-making regarding the use of the animal model in biomedical research. AFMA/EFMA opposes animal-modeled research as a modality for seeking cures and treatments for human disease based on overwhelming scientific evidence that findings from animal models cannot be reliably extrapolated to humans. We seek to demonstrate, through rigorous research and analysis, that the reliance on animal-modeled research, as well as other pseudoscientific endeavors, harms rather than helps humans, and prolongs human suffering by inhibiting medical progress. In addition to conducting research programs, AFMA/EFMA communicates through books and other publications, as well as articles in peer-reviewed literature, the urgent need to focus on research modalities that truly advance the knowledge necessary to prevent and cure human disease and promote human wellness.

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Is Primate-Modeled Research *Crucial?*

A look at claims made in the NIH/NCRR *Full Scale Evaluation of the Regional Primate Research Centers Program*

By C. Ray Greek, MD
AFMA President and Founder

The theory behind the widespread use of animal models of human disease leads to the proposition that transgenic plants should be good models of fish disease: We should be able to learn how chosen genes operate in fish and how to influence the expression of chosen genes in fish—by studying tomatoes—because fish genes can be inserted into a tomato plant's DNA. The same idea motivates some researchers to insert human genes into mice with an expectation of learning about human disease by studying transgenic mice.

It can be argued that the genetic variation that has accumulated over time has resulted in such diversity, in already complex systems, that in spite of a few inserted genes, the disparate species' biological functions have become too varied to lend one as a good model of the other. It is this recognition of physiologic diversity that leads some researchers to claim that close evolutionary kin will be better models of each other. This is the theoretical foundation for the use of monkeys and apes as models of human disease and behavior.

Claims made by the National Institutes of Health (NIH) and the National Centers for Research Resources (NCRR)

NIH/NCRR has endorsed an expansion of primate-based biomedical research in the *Full Scale Evaluation of the Regional Primate Research Centers Program—Final Report* (Office of Science Policy and Public Liaison, National Center for Research Resources/NIH. 2000). The report states:

> By virtue of their genetic relatedness and biological fitness as a model for human disease, nonhuman primates are crucial for certain types of biomedical and behavioral research….Currently, more than 1000 investigators—RPRC-funded core and other staff scientists, affiliates, collaborators, visiting scientists from other institutions, and doctoral students—rely on the Center's nonhuman primate models to study HIV/AIDS, brain and central nervous system disease, heart disease, cancer, and a great variety of other human diseases and disorders.[i]

The above claims are testable.

In order for a biomedical research method or line of study to be characterized as *crucial*, we should be able to easily discern the method's extreme significance or importance, or its decisive or vital role in the resolution of a crisis. If the importance of the method is difficult to identify or if its role has been other than decisive or vital in the resolution of a crisis, then we are correct to question whether the method is indeed crucial. Further, if the method has been counterproductive, or simply unproductive, we should question the theory on which it is based and consider other theories that predict a failure of the method.

NIH/NCRR makes specific implicit claims regarding the crucial role of primate research.

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Is Primate-Modeled Research *Crucial?*

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The First Claim: *Primates are crucial for the study of HIV/AIDS.*

Since the appearance of a wasting disease that became known as AIDS, many discoveries have shed light on the disease and have resulted in treatments. Thousands of investigators in diverse disciplines have contributed to our knowledge of HIV/AIDS. More than 125,000 papers related to HIV and AIDS are cataloged in the PubMed online database of the National Library of Medicine. If primates have been crucial to the study of HIV/AIDS it should be a simple matter to document the method's importance.

Monkeys and SIV

In the 1998 fiscal year, the NIH Regional Primate Research Center System received $51 million in base grant support, including $19.4 million (38%) in AIDS research funding that went largely to study SIV in monkeys.[ii] It is clear that NIH/NCRR placed great hope on the use of monkeys as models of HIV/AIDS.

Margaret I. Johnston of the National Institute of Allergy and Infectious Diseases had this to say about the differences between SIV and HIV:

> Differences between HIV and SIV could prove important in vaccine evaluation. First, and perhaps foremost, SIV and HIV are distinct viruses. SIV and HIV envelope proteins, which are the key target of neutralizing antibodies, are considerably divergent. Antibodies directed against the envelope of SIV do not neutralize HIV and vice versa. Cytotoxic T lymphocytes (CTLs) specific for HIV do not recognize SIV-infected cells and vice versa. Thus, to utilize monkey models, an analog of the human HIV vaccine must be prepared. In terms of quality or efficacy, SIV analogs might or might not be comparable to vaccine candidates optimized and manufactured for human trials. Another difference is that SIV isolates use the CCR5 coreceptor for virus uptake into cells. In 40–50% of HIV-infected humans, HIV that uses CCR5 predominates early and throughout the asymptomatic phase of a typical HIV infection, but a shift of tropism to CXCR4 is observed as these humans progress to AIDS. This shift has not been reported in SIV-infected macaques."[iii]

Wade-Evans et al write:

> However, since it is known that minor species-specific sequence changes in CCR3 and STRL33 affect their ability to act as coreceptors for HIV-l, HIV-2, and/or SIV, it is important to ascertain whether the relevant receptors function as expected in the animal model of choice….The ability of both CCR3 and STRL33 to function as coreceptors *in vitro* has been shown to be species dependent. Rhesus macaque CCR3 is unable to facilitate entry of several SIV and HIV-l isolates, but can still function as a coreceptor for several HIV-2 isolates. Similarly, rhesus STRL33 cannot function as a coreceptor for a variety of SIV-1 isolates, whereas sooty mangabey STRL33 can. The species dependent ability to act as a coreceptor, in the case of STRL33, has been reported to be dependent on a single amino acid substitution.
>
> All three receptors, CCR3, GPR 15, and STRL33 cloned from cynomolgus macaque PBMCs showed amino acid substitutions compared with their human and rhesus macaque homologs…. There are 19 amino acid changes between the human and cynomolgus macaque STRL33 homologs.[iv]

The large public expenditure on the development of monkey models of HIV, based on SIV in macaques, has been less than crucial to HIV treatment, therapy, or vaccine development according to the evidence at hand.

Because SIV is so different from HIV and because nonhuman primates are resistant to HIV, the two viruses have been combined to create a chimera, SHIV. SHIVs contain the HIV env and associated tat, vpu and rev genes, along with the full complement of remaining SIV genes. SHIVs can infect macaques; some are pathogenic and others are not. To date, all pathogenic SHIVs are isolates, or virus quasispecies, isolated from an infected animal. By contrast, all SHIV constructs, defined as chimeric virus clones, are nonpathogenic.

McMichael and Hanke:

> Studies of vaccines that protect macaques against SIV infection indicate that antibody-mediated protection is possible. It has been shown repeatedly that vaccines based on the viral envelope can protect nonhuman primates challenged with homologous virus. But the numbers of animals used in such studies are small, and the studies may have limited relevance to humans. It was disconcerting to find that unlike viruses adapted to laboratory culture, primary HIV isolates from infected patients were resistant to neutralization. These isolates were

later shown to use different coreceptors, although this fact alone does not account for the difficulty in neutralization. Two recent studies have shown that neutralizing antibodies directed at the envelope are made during HIV infection, but as they appear they immediately select for viral escape mutants, thereby becoming irrelevant.[v]

The large public expenditure on the development of monkey models of HIV, based on SIV in macaques, has been less than crucial to HIV treatment, therapy, or vaccine development according to the evidence at hand. The evolutionary distance between monkeys/SIV and humans/HIV seems to have undermined the utility of the methodology and challenges the theory that *similar diseases in similar species* should be good models of human (or any other species') diseases.

Chimpanzees and HIV

The differences between HIV in humans and chimpanzees are significant. Louis R. Sibal and Kurt J. Samson wrote in *ILAR Journal*:

Although progressive infection with HIV-1 can occur in some chimpanzees, chronically infected animals usually maintain normal numbers of CD4+ T-lymphocytes and do not become immunodeficient. The one exception stems from a report that a chimpanzee [Jerom] infected with three different isolates of type-1-HIV over a period of 10 years revealed a persistent decline in CD4+ T-lymphocytes that progressed to AIDS or an AIDS-like disease. Blood from this animal that was transfused into an uninfected chimpanzee induced a rapid depletion of CD4+ T-lymphocytes but did not cause clinical disease. Without disease as an endpoint, researchers can measure only the infection-blocking effect of candidate vaccines.[vi]

Although the Samson and Sibal strongly support the use of chimpanzees for AIDS research, they also state, "However, because AIDS is a complicated disease involving many molecular events in several different cell types, a vaccine that works in NHPs [nonhuman primates] may not work in humans."[vii]

The vaccine made by VaxGen, AIDSVAX, showed promise when given to chimpanzees[ix] but failed when tested on 3,330 humans, mostly men. An equal percentage of those receiving the vaccine contracted HIV compared to the controls.[x] Donald P. Francis of VaxGen was confident of the vaccine's success based on research with chimpanzees. He stated:[xi]

The initiation of the Phase III studies is the culmination of over 15 years of work, started at Genentech and continued at VaxGen….These laboratory studies led to the key studies in chimpanzees that further stimulated the development of AIDSVAX.

The theory of similar diseases in similar species has not resulted in progress in treating or preventing HIV/AIDS. Progress has been made, but advancements have come *in spite of*, rather than *due to*, nonhuman primate models of HIV/AIDS. What has proven *crucial* in the search for treatment, prevention, and cure is the use of humans and human tissues. There is a competing theory that predicts the failure of animal models and the necessary reliance on methodologies based on humans and human tissues. This is the theory of *evolution.*

Evolution theory predicts that *in vivo* models of disease and toxicology will be productive models only when the model and the modeled are the same species. The theory of evolution predicts that monkeys and chimpanzees will be poor models of HIV/AIDS, and that human-based studies will be crucial to medical progress. As above, this prediction is testable.

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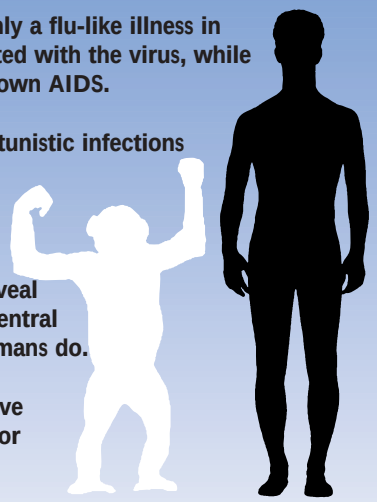
CONSIDER THE FOLLOWING DISPARITIES BETWEEN HUMANS AND CHIMPANZEES: [viii]

- **HIV does not reproduce well in chimpanzees.**
- **Chimpanzees have higher baseline levels of T8 cells, a greater proliferative response, and a lower ratio of T4/T8 cells. Considering the fact that T4 cells are selectively attacked by HIV, this difference is not insignificant.**
- **Unlike humans, chimpanzees do not drop their T4 counts to zero with infection. They do go down, but not as dramatically.**
- **Chimpanzees lack the "killer cells" which humans have. B-lymphocytes produce more antibodies in chimpanzees and they produce them earlier, thus stopping disease spread.**
- **Humans drop their antibody count prior to systemic illness; chimpanzees do not.**
- **Chimpanzees have HIV only in their red blood cells, while humans also have the virus in plasma.**
- **Chimpanzees exhibit only a flu-like illness in response to being infected with the virus, while humans go on to full-blown AIDS.**
- **Humans develop opportunistic infections and cancers associated with HIV, which chimpanzees do not.**
- **Chimpanzees do not reveal classic changes in the central nervous system that humans do.**
- **Chimpanzees do not have virus particles in saliva or cerebral spinal fluid.**



Is Primate-Modeled Research *Crucial?*

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Human-based studies' extreme significance and importance are easily discernable (see p7). The importance of primate-modeled research is difficult to identify. Its role has been other than decisive or vital in progress toward a resolution of the HIV/AIDS crisis. We are correct to question whether the method is indeed crucial. Further, the method has been unproductive and even counterproductive. We should question the theory on which it is based and consider other theories that predict this failure of the method.

The results of primate-modeled HIV/AIDS research suggest strongly that research methods based on the theory of "similar diseases in similar species" are not productive.

The Second Claim: *Primates are crucial to the study of brain and central nervous system disease.*

Though much broader than the specific claim regarding HIV/AIDS, this claim can be tested to some degree. If we consider two of the most well known diseases of the brain, Alzheimer's (AD) and Parkinson's disease (PD), and examine the progress that has been made in treatments, preventions, and cures, the importance of primate research should be easily discernable if the methodology has been crucial.

Alzheimer's disease

According to the Wisconsin National Primate Research Center, 111 primate research-based scientific papers addressing Alzheimer's disease were published between 2000 and 2003.[xii]

According to the NIH National Institute of Neurological Disorders and Stroke (NINDS),

> "There is no cure for AD and no way to slow the progression of the disease…. The NINDS conducts and supports research on neurodegenerative and dementing disorders, including AD. For example, although the cause of AD is still unknown, new research has shown that a vaccine, aimed at preventing or reversing the formation of AD-associated pathologic lesions, might be a useful therapy. Recent results using a transgenic mouse model suggest that immunological interventions may retard and even reverse the development of some of the pathologic changes associated with AD."[xiii]

In the case of Alzheimer's disease, it is apparent that primate research is not easily discernible as important or significant, and it has clearly not played a decisive or vital role in the resolution of this particular health crisis. It is indicative of the absence of the method's utility that NINDS cites a transgenic mouse study as the current best hope for sufferers of this disease. Primate research has not been crucial to the study of Alzheimer's disease.

Parkinson's disease

The Yerkes Regional Primate Research Center published a related claim in its 1989/1990 Annual Report, *The 60th Year, 1989-1990*:

> Yerkes studies with rhesus monkeys were the first to demonstrate the feasibility of surgically implanting dopamine-producing tissue into the brain as a treatment for Parkinson's disease. Research results were presented in 1985 by Emory neurosurgeon and initial Yerkes Affiliate Scientist Dr. Roy Bakay who conducted the studies and who has been performing the surgery on humans with Parkinson's disease at Emory University Hospital.[xiv]

A 1995 rebuttal to this claim remains valid today and is illustrative of the problems found in most claims of an animal model being crucial to medical progress.[xv]

> This claim is misleading because it confuses two different surgical procedures to treat PD; transplanting fetal tissue derived from a member of the same species (fetal homotransplantation), and non-fetal tissue (usually adrenal) from a human patient's own body (autotransplantation) to the defective brain area. Although Yerkes and other researchers have conducted extensive nonhuman primate fetal homotransplantation experimentation the first autotransplantation to treat PD had already been conducted in Sweden, in 1982, without prior nonhuman primate trials. The Swedish investigators used the patient's own dopamine-producing adrenal tissue.
>
> Bakay and colleagues stated their intention to demonstrate the clinical "feasibility" of their primate fetal adrenal tissue homotransplant work, but they never did apply their monkey findings to patients. In fact, the clinical transplants to which the Yerkes publication refers consisted of adrenal autotransplants. Bakay, Ray Watts and colleagues attempted to duplicate their human findings with adrenal autografts in nonhuman primates. However, the animal subjects were not suffering from PD, but rather from an induced Parkinson-like syndrome related to exposure to the neurotoxin MPTP. While this condition shares many features with PD, there are several important differences. PD is a progressive condition, while MPTP-induced Parkinsonism is not. PD patients characteristically show microscopic Lewy bodies in their brains whereas MPTP-treated monkeys do not. Also, the locus ceruleus of the brain is damaged in PD, but only older monkeys administered low-dose MPTP exhibit similar damage (possibly analogous to PD being found in older humans.)
>
> Given the cost of raising monkeys to old age, researchers generally use young adults. Bakay and colleagues have not specified the monkeys' ages, so they, too, likely have used younger monkeys [Watts RL, Bakay RAE, Herring Ci, et al.], further diminishing the probability that nonhuman primate experiments with autotransplants at Yerkes and elsewhere apply to human patients.

Primates seem not to have had a crucial role in the study of the brain and central nervous system diseases Alzheimer's and Parkinson's. We are aware of no disease of the brain and central

The theory of evolution predicts that monkeys and chimpanzees will be poor models of HIV/AIDS, and that human-based studies will be crucial to medical progress.

nervous system that has seen much progress as a result of primate research. In no case can we easily discern a crucial role. The claim that *primates are crucial to the study of brain and central nervous system disease,* is likely false.

The Third Claim: *Primates are crucial to the study of heart disease.*

The NIH CRISP (Computer Retrieval of Information on Scientific Projects) database is a "searchable database of federally funded biomedical research projects conducted at universities, hospitals, and other research institutions." [http://crisp.cit.nih.gov/]

The CRISP is a good sampling tool. The database catalogs grants, frequently including abstracts, from 1972 to the present. Though not an exhaustive listing of every federally funded study, (not included are intramural research, Department of Agriculture or Defense Department funded research grants) it provides an extensive sampling of historic and ongoing studies.

We conducted a search of the CRISP database, the specific details of which can be found on the AFMA/EFMA website. These results suggest that the NIH ranks the value of primate-based research on heart disease on a par with that of primate-based studies of cocaine use. It is not easily discernable from this data that primate research has been crucial to the study of heart disease or that the NIH has ever considered it to be so.

It is worth noting that the NIH Primate Research Center System was first organized under the auspices of the National Heart Institute (NHI). It is not unreasonable to imagine that heart disease research in monkeys would have been given a fair trial.

The claim that *primate research is crucial to the study of heart disease* appears to be false. [See Table 1.*]

The Fourth Claim: *Primates are crucial to the study of cancer.*

Note what Beniashvili says about nonhuman primates in cancer research in the text *Experimental Tumors In Monkeys* published by CRC Press in 1994:

> "Attempts to obtain malignant tumors in monkeys failed, since primates turned out to be highly resistant to certain blastogenic agents, carcinogenic for other animals."
>
> "Spontaneous tumors in monkeys are very rare…Many researchers believe that monkeys have an inherent specific resistance to malignant tumors. The low incidence of spontaneous tumors in monkeys has been associated with difficulties in experimental induction of tumors in these animals." "Thus unlike humans…in monkeys lung tumors are extremely rare."
>
> "…spontaneous tumors of the respiratory organs and mediastinum in monkeys, unlike in man, are extremely rare."
>
> "…spontaneous tumors of skin and soft tissue in nonhuman primates are comparatively rare."
>
> "For spontaneous skin tumors in monkeys, recurrences and metastases were not characteristic." They are in humans.
>
> "The above findings show that at present there have been just a few successful cases of the induction of soft tissue tumors in monkeys."

In fact, there is little evidence that primate research has played much of a role, even in the history of animal-based cancer research, at all. In modern textbooks of animal models of human cancer, primate research is rarely, and usually never, mentioned or even referred to. For instance, the *Handbook of Laboratory Animal Science*[xvi] includes a chapter entitled "Animal Models in Cancer Research." No mention is made of primates either in the text or in the titles of the referenced works (mice or rats are referred to in 23 out of 40 titles.)

The claim that *primates are crucial to the study of cancer* is far-fetched and amounts to little more than the wild assertion that *any* progress made in combating *any* disease is due to the *crucial* contribution of primate research. The transparent falsity of this claim should be an embarrassment to NIH/NCRR, but few people outside the industry are likely to have seen and considered the report. [See Table 2.*]

Implications

The claim that *nonhuman primates are crucial for certain types of biomedical and behavioral research…[such as]…to study HIV/AIDS, brain and central nervous system disease, heart disease, cancer, and a great variety of other human diseases and disorders* has been easily demonstrated to be false. If the claim were being made by anyone but an official policy recommendation committee, it could be dismissed as the pure

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Is Primate-Modeled Research *Crucial?*

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drumbeat of propaganda heard so frequently from public relations departments and paid lobbyists.

Unfortunately, the recommendations included within the *Full Scale Evaluation of the Regional Primate Research Centers Program* were uniformly endorsed by NIH/NCRR. [See: Profile of the Expert Panel.*]

Eight of the 12 members of the panel have a vested interest in primate research. In the case of one member, Dr. David Amaral, this interest amounts to over $2 million in proceeds from his federal grants. Regarding the four members with no clear primate experimentation experience, Stephen Seidel of NCRR, explained, "Drs. Eisen and Paterson are both immunologists, which is a key research focus of several of the NPRCs. Dr. Crawford had previous experience reviewing the computing systems of the NPRCs. Dr. Weisbrod brought to the process his skills as an economist."

It appears that public policy has been controlled by the industry and that little to no outside, independent experts in medical research policy were consulted prior to the NIH/NCRR endorsement of the panel's recommendations. Briefly, the recommendations were to increase the availability of primates to researchers, to increase the funds available to researchers choosing to experiment on primates, and to advertise the increases to the animal research community all because primate research has been so "crucial."

***References contained herein can be found on the AFMA/EFMA website at www.curedisease.com**

California Medical School Abandons Required Animal Model Course

In a victory for patients everywhere, the University of California San Diego School of Medicine has dropped its required (core) introductory canine-based physiology/pharmacology courses.

Resulting from a six-year campaign led by AFMA/EFMA science advisors, Dr. Lawrence Hansen and Dr. Nancy Harrison, UCSD Medical School students will no longer be required to take a course using dogs as surgical and drug effects models.

Surveys of medical schools around the country had revealed that UCSD was the only medical school in the state, and one of only a few in the country, that expected students to take the course. In spite of the industry-wide trend and the strong scientific evidence against the value of such models, Dr. Igor Grant, chairman of UCSD's Faculty Council, said that, "The main concern was that this issue had become so heated, it was impairing both the ability of students to learn and faculty to teach … clearly we didn't feel that it was so vital we couldn't do without it."

"We're delighted and ecstatic. The clear message is that it's not necessary, which we've been saying for a long time," said Hansen, a UCSD professor of neuroscience and pathology.

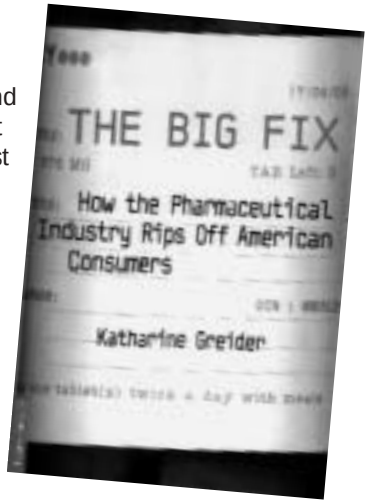
ARMA/EFMA science advisors Dr. Lawrence Hansen and Dr. Nancy Harrison are members of Doctors Against Dog Labs, a group of physicians and physician researchers at UCSD and in private practice around the country.

For more information, visit their web site at www.doctorsagainstdoglabs.com

New Book Puts Big Pharma Under the Microscope

AFMA is pleased to recommend *The Big Fix: How the Pharmaceutical Industry Rips Off Consumers* by Katharine Greider (Public Affairs Books 2003).

In this new book, the author examines the issue of corruption in the drug industry fairly and without bias. She introduces the reader to the history of the drug companies, how they interact with Congress and the FDA, how much pull they really have compared to other special interest groups, how much the medications they make actually cost and how much they sell for, and other key issues.



The Big Fix is not anti-drug; it is anti-greed and anti-corruption. Among other topics, Greider explains how the drug companies get their patents extended to the harm of patients, how they use advertisements to sell a disease that can be cured by taking their drug, and how many physicians are complicit in the drug industry's efforts.

The Big Fix is relatively short and an easy read. If you wish to learn more about the pharmaceutical industry, other informative books include *Bitter Pills* by Stephen Fried (Bantam Doubleday Dell Pub 1999) and *Prescription for Profits: How the Pharmaceutical Industry Bankrolled the Unholy Marriage Between Science and Business* by Linda Marsa (Scribner 1999).

Human-based discoveries and developments in the fight against HIV/AIDS

Human-based research has allowed us to gain more knowledge of HIV/AIDS. (Most of this data was taken from several review articles that appeared in the July 2003 issue of *Nature Medicine*. This review is an adaptation of the article "AIDS Summary" that appears on the AFMA/EMFA website.)

1981. AIDS was first noticed when homosexual men experienced an increased incidence of rare diseases, notably Kaposi sarcoma and opportunistic infections such as *Pneumocystis carinii pneumonia*, as well as cases of unexplained, persistent lymphadenopathy. Physicians quickly revealed that these individuals had a common immunological deficit resulting from a significant decrease of circulating CD4+ T cells.

1982. Clinical evidence was all that was available initially as there were no diagnostic tests. Between the first analysis of patient samples in early 1983 and the determination of the sequence of HIV-1 in 1985, a vast amount of data was accumulated on HIV through the integrated efforts of clinicians, virologists, immunologists, molecular biologists and epidemiologists. These early years of HIV research quickly led to strategies for the diagnosis, monitoring and treatment of HIV/AIDs.

Clinical and epidemiological investigations had provided persuasive evidence that the disease was caused by an infectious agent, probably a virus, transmitted by sexual routes and in blood derivatives. But all initial attempts to establish a link between the epidemiological and clinical features of this disease and a known virus failed. The French working group became convinced that the cause was probably an as yet unidentified virus.

1983. HIV was discovered to be the causative agent. A blood test was developed to identify patients infected with HIV.

1987. The first effective drug against HIV was the reverse transcriptase inhibitor (NRTI) zidovudine, or AZT. A screening process using large numbers of compounds that had been already produced for other purposes identified it. (AZT was originally developed as an anticancer drug but did not prove effective in that capacity.)

1991. More NRTIs available.

1994. Zidovudine prescribed for mothers-to-be to prevent mother-to-baby transmission.

1994. Ineffectiveness of monotherapy noted.

1982. As with many emerging infectious diseases, the initial and most powerful tool to illuminate the etiology of the disease was classic epidemiology. Initial observations suggested that the disease might have a retroviral etiology. Two retroviruses, human T-lymphotrophic virus (HTLV)-I and HTLV-II, which had been recently recognized at that time, were the only viruses known to preferentially infect CD4+ T cells. The transmission pattern of HTLV was similar to that seen among individuals with AIDS; in addition, HTLV-I and related retroviruses were known to cause varying degrees of immune deficiency in humans and animals. Thus, the search for a new retrovirus was undertaken in earnest.

1995. More sophisticated science in the form of targeted drug design has been the rule as drugs have been developed to target specific vulnerable points in the virus replication cycle, providing a cogent example of the importance of the basic research endeavors in viral biology and the translational approaches in drug development. The prototype of this approach was the expression, purification and crystallization of the HIV protease enzyme to facilitate the tailored design of protease inhibitors—a class of antiretroviral drug that was first approved by the US Food and Drug Administration (FDA) in 1995.

1995. HAART (highly active anti-retroviral therapy) developed.

HIV was discovered to be composed of 9 genes. The structure of HIV was identified. Light was shed on the pathogenesis of AIDS such as CD4 depletion.

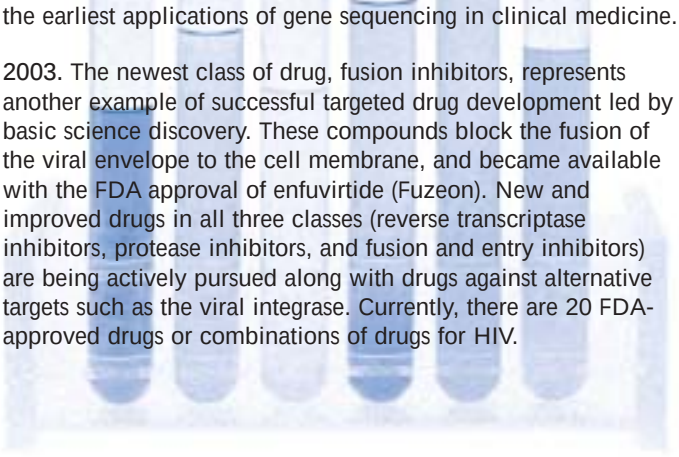
1996. First NNRTI (nevirapine) developed.

1996. A test to estimate viral load in widespread use.

2000. Lymph tissue was identified as the chief target of HIV. Other tissues were identified as reservoirs, thus making it hard to eradicate HIV from body. The treatment of HIV-1 is complicated by the existence of tissue compartments and cellular reservoirs. Much of the virus in the central nervous system and in semen evolves independently of virus found in blood cells. Latently infected, resting CD4+ T lymphocytes can survive for many years, and these lymphocytes can archive many quasispecies of virus that can re-emerge and propagate after the withdrawal of HAART. Macrophage populations can also express virus in HIV-1-infected individuals on virally suppressive HAART. Moreover, HAART does not inhibit all viral replication; low levels of viral replication occur "cryptically" below the limits of clinical plasma viral load detection.

Resistance testing of HIV isolates has become part of standard HIV-1 care. There are phenotypic and genotypic assays available to help predict which drugs are likely to have activity against HIV-1 and which agents are likely to fail because of resistance. Phenotypic assays measure drug susceptibility directly. Genotypic assays identify mutations in HIV-1 that are known to confer phenotypic changes. Genotypic testing, which is more widely used than phenotypic testing, is an example of one of the earliest applications of gene sequencing in clinical medicine.

2003. The newest class of drug, fusion inhibitors, represents another example of successful targeted drug development led by basic science discovery. These compounds block the fusion of the viral envelope to the cell membrane, and became available with the FDA approval of enfuvirtide (Fuzeon). New and improved drugs in all three classes (reverse transcriptase inhibitors, protease inhibitors, and fusion and entry inhibitors) are being actively pursued along with drugs against alternative targets such as the viral integrase. Currently, there are 20 FDA-approved drugs or combinations of drugs for HIV.



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Suggestions for Further Reading

For more information on why the animal model is an outdated and inadequate method of biomedical research, and how it harms humans, we invite you to consult the following print and online resources.

■ AFMA PAMPHLETS AND MONOGRAPHS

Of Mice, Money and Misconceptions: The Truth About Animal Experimentation. This 20-page booklet offers a comprehensive overview of the human costs of animal experimentation. The authoritative approach is suitable for the reader with a scientific background, yet understandable to the lay reader as well.

The Truth Hurts. This pamphlet presents a basic introduction to the issue of animal-modeled research.

Focus on the Future. This pamphlet describes a variety of human-based research modalities.

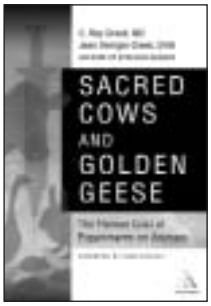
50 Deadly Consequences. This booklet presents startling facts about animal-modeled research backed by references.

The above publications are available through AFMA. Please contact us if you are interested.

■ BOOKS

Brute Science: The Dilemmas of Animal Experimentation, Hugh LaFollette and Niall Shanks (Routledge 1996).

Sacred Cows and Golden Geese: The Human Cost of Experiments on Animals, C. Ray Greek, MD, and Jean Swingle Greek, DVM (Continuum International Publishing Group, Inc. 2000).



Specious Science: How Genetics and Evolution Reveal Why Medical Research on Animals Harms Humans, C. Ray Greek MD, and Jean Swingle Greek, DVM (Continuum International Publishing Group, Inc. 2002).

The above books are available at your local and on-line bookstore.

■ ON-LINE RESOURCES

Americans For Medical Advancement and Europeans For Medical Advancement
www.curedisease.com

The AFMA/EFMA website provides a wealth of information on the failure of animal-modeled research, as well as an overview of the many other research modalities that have proven far more effective. It also provides an update on AFMA/EFMA activities, as well as back issues of our newsletter.

Medical Research Modernization Committee
www.MRMCmed.org

Pro Anima
www.proanima.asso.fr

National Anti-Vivisection Society
www.navs.org

***Pathways to* Progress**

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Americans For Medical Advancement is a national, not-for-profit organization incorporated in the State of California. Donations to AFMA are tax-deductible to the fullest extent allowable by law. A copy of AFMA's annual financial report is available by request. It is also available for viewing on our website, www.curedisease.com.

Pathways to Progress, the quarterly newsletter of Americans For Medical Advancement and its sister organization, Europeans For Medical Advancement (EFMA), is available in print free-of-charge to AFMA supporters. It is also available on-line at www.curedisease.com. The editors welcome article submissions of 500-1,000 words on topics related to the AFMA mission of advancing biomedical research that helps, not harm humans. Article submissions may be e-mailed to AFMA@curedisease.com.

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