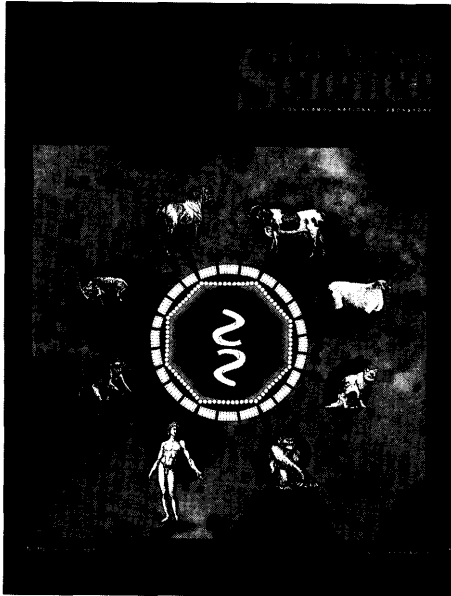


# Los Alamos Science

LOS ALAMOS NATIONAL LABORATORY





All the animal species surrounding the AIDS virus (center) are targets of AIDS-like diseases. The slow viruses, or lentiviruses, responsible for these diseases attack the cells of the host's immune system. In the background are T4 cells, the primary target of the AIDS virus. The cells are stained with toluidine blue to identify nucleoproteins. The black dots, produced by radioactive probes, show the location of viral RNA in these infected cells.

**W**hy AIDS research at Los Alamos? In 1981 when the first AIDS cases were publicized, Stirling Colgate, a physicist at Los Alamos, was among those who foresaw that a disease that undermines the human immune system and is transmitted through sexual contact could expand into a worldwide pandemic. The threat seemed to him nearly as serious as the threat of nuclear war, requiring the kind of conceptual and quantitative approach characteristic of research in physics.

Stirling explains: "Our dedication to understanding the growth of the AIDS epidemic received extra impetus in 1986 from the contrast between the popular view that the probability of progressing from infection to AIDS was as small as 10 to 15 per cent and the epidemiological evidence from Walter Reed Army Hospital and Germany that the conversion probability was at least 90 per cent, and more likely, almost 100 per cent. Another misconception at that time was that the slowing growth of the epidemic relative to the expected exponential growth was a sign that the epidemic was dying out.

"A quantitative understanding of the dynamics of the epidemic was desperately needed to develop a consensus among scientists. Only then could a rational national policy be established. Without knowing whether the number of AIDS cases in the United States would continue to increase, the dedication of resources required to defeat such a complex virus would be unlikely."

"AIDS and a Risk-Based Model"  
by Stirling Colgate, Ann Stanley, Mac Hyman, Scott Layne, and Cliff Quails

outlines the basic dynamics governing the epidemic in the United States. The model is based on two unique features of the AIDS case data from the Centers for Disease Control (CDC). First, the number of AIDS cases has not grown exponentially with time (as happens when all members of a population are equally at risk) but rather as the cube of time. Steady cubic growth between 1982 and 1987 has occurred not only among the total population but also among groups defined by sexual preference, race, and geographical origin. Second, the CDC data indicate that the average risk behavior (number of sexual partners per year) of those developing AIDS was extremely high at the start of the epidemic and has subsequently decreased with time.

The model reproduces both the cubic growth of AIDS cases and the progression of the disease from the highest risk individuals by assuming that people tend to choose sexual partners who are like themselves in sexual activity. Thus the model predicts that the disease will spread most rapidly among highly active high-risk individuals. However, because there is some mixing between risk groups, the epidemic will gradually spread to lower and lower risk groups. The authors hope that the pattern they have identified will dispel any wishful thinking that the threat of AIDS is not universal. The recent reports of HIV infection among college students (estimated to be 1 in 500) gives us reason to look carefully at the Los Alamos model.

All models of the AIDS epidemic are attempts to answer certain basic questions. How many people are infected now? How many will be infected in the next decade? What groups are most at risk? Where and what kind of intervention strategies will be most effective at stemming the course of the disease? Data to validate the epidemiological

models are sadly lacking and often hard to collect. Moreover, some data that have been collected are unavailable. Seeing this deficiency, the Los Alamos group suggested in a commentary in *Nature* that a national database of complete and unfiltered information from diverse sources be established and made available to researchers and health officials involved in surveying and forecasting the course of the AIDS epidemic. After the appearance of the commentary, Beverly Berger of the Office of Science and Technology Policy (OSTP) and Scott Layne of Los Alamos organized a workshop entitled "A National Effort to Model AIDS Epidemiology." The workshop brought together a diverse group of modelers, statisticians, biologists, clinicians, sociologists, and computer scientists to assess what is known and what needs to be known to make accurate predictions. Although the meeting started with some tension among participants from different fields, the interactive format of the workshop created an atmosphere that was described in a public letter by one participant as: "Above and beyond the immediate payoffs of the report on which we are working, we have created a critical mass of scientists from disparate areas who are now speaking to each other in a way that was not possible before." Unfortunately, no plans exist at present for continuing the type of interdisciplinary communication facilitated by the meeting. The flow of information among AIDS researchers is still reduced by sensitive political, legal, and ethical issues.

One of my observations at the OSTP workshop was the unfamiliarity of researchers from outside the hard sciences with the power of quantitative analysis.

The power of such analysis is evident not only in the opening article ("AIDS and A Risk-Based Model") but also in two other research articles in this issue. "Genealogy and Diversification of the AIDS Virus" by Gerry Meyers, Randy Linder, and Kersti MacInnes discusses a mathematical determination of the genetic distances among various HIV strains and between HIV and other immunodeficiency viruses. It traces not only the evolutionary history of the AIDS virus but also the present epidemiology of the disease. Gerry Meyers of Los Alamos started the Laboratory's effort to collect and analyze DNA sequences of these viruses in 1986. Through this unique effort we can monitor the mutations in HIV and identify unequivocally which strains are spreading and where. One important finding related to disease diagnosis is that the present test for HIV antibodies in the blood (the ELISA test) is based on a different strain of the virus than the one that may be most prevalent at this time. Although ELISA detects antibodies against new strains, we have an early warning that the test may have to be altered to keep up with the mutations of this virus.

The other quantitative article ("The Kinetics of HIV Infectivity") concerns a theoretical framework for interpreting viral infectivity assays. Such laboratory experiments are the principal means of measuring the virulence of different viral strains and the effectiveness

of various chemical agents designed to control the spread of infection within an individual. Until now, infectivity assays from different laboratories have been very difficult to compare to one another. The kinetic model developed by Scott Layne, Micah Dembo, and John Spouge describes the infection by free virus and other competing processes occurring in infectivity assays. It also defines standard experimental techniques for determining the rate constants of those processes from the assay data. The possibility of standardizing interpretation of infectivity assays and gaining more detailed knowledge of the kinetic processes is attracting the attention of laboratory scientists around the country.

One of those is Peter Nara of the National Cancer Institute. His quantitative HIV infectivity assay is particularly suited to validating the kinetic model. Peter, a doctor of veterinary medicine as well as a Ph.D. in virology, has been very generous in writing down for us his expansive view of where the AIDS virus fits into our understanding of viruses and their role in evolution and disease. In "AIDS Viruses of Animals and Man: **Nonliving Parasites of the Immune System**" we learn that the AIDS virus is one of a group of "slow" viruses whose strategy for survival is to develop slowly in the host and thereby assure continuity of the host-virus relationship. These lentiviruses have probably evolved over eons of time within the oldest and most crucial cells present in the immune systems of all vertebrate animals. As such, they have developed many deceptive strategies for outsmarting the immune system. After describing both clinical manifestations of disease and immune dysregulation caused by the lentiviruses, Peter reviews attempts (including his

own) to develop a traditional vaccine against the AIDS viruses. The conclusion he reaches is that such approaches have only a marginal chance of succeeding. He turns finally to animal models of host adaptation (such as those of the African green monkey and the chimpanzee) as a possible source of inspiration for developing a strategy against the AIDS and AIDS-like viruses. Another possible source of inspiration are isolated human populations in Africa that may have evolved and still are in equilibrium with the AIDS virus.

Our modern western culture has probably broken social and evolutionary barriers previously operative in culturally isolated populations that kept viruses, such as HIV, under control. In many such epidemics of the past, evolution has selected immunologically stronger hosts and less virulent mutants of the pathogen, but only through the toll of countless deaths. At present, AIDS is spreading rapidly among inner city populations in this country and is spreading in many areas of Africa. The World Health Organization estimates that between 5 and 10 million people are now infected worldwide. Are we to repeat the experiences of epidemics in centuries past? Are we, who have seen twentieth-century medicine conquer numerous infectious diseases, too confident or too complacent to see the extent of the threat? ■



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### AIDS and a Risk-Based Model . . . . . 2

*by Stirling A. Colgate, E. Ann Stanley, James M. Hyman, Clifford R. Quails, and Scott P. Layne*

A model that assumes people choose partners of similar sexual activity reproduces the observed cubic growth in AIDS cases, whereas most models predict exponential growth. A general distribution of sexual activity along with biased mixing are identified as the factors driving the epidemic from the highest to lower and lower risk groups.

Mathematical Formalism

*by James M. Hyman and E. Ann Stanley*

Numerical Results of the Risk-Based Model

*by James M. Hyman, E. Ann Stanley, and Stirling A. Colgate*

The Seeding Wave

*by Stirling A. Colgate and James M. Hyman*

### Genealogy and Diversification of the AIDS Virus . . . . . 40

*by Gerald L. Myers, C. Randal Linder, and Kersti A. MacInnes*

Comparison of the DNA sequences of HIV from various AIDS victims reveals a genealogy for the virus that agrees with the epidemiology of the disease.

Viruses and Their Lifestyles

An HIV Database

### AIDS Viruses of Animals and Man: Nonliving Parasites of the Immune System . . . . . 54

*by Peter Nara of the National Cancer Institute*

A class of "slow" viruses has evolved a full bag of tricks allowing them to use the immune cells of animals and man as a comfortable ecological niche and then to outsmart vaccines designed to evict them from that niche.

The Search for Protective Host Responses

### The Kinetics of HIV Infectivity . . . . . 90

*by Scott P. Layne, Micah Dembo, and John L. Spouge*

A first attempt to model the kinetics of viral infectivity in culture should help standardize laboratory experiments and help evaluate various treatment strategies for AIDS.

Mathematical Considerations