# THE FUTURE OF AIDS

## New research suggests HIV is not a new virus but an old one that grew deadly. Can we turn the process around?

BY GEOFFREY COWLEY

Ten years ago, Benjamin B. got what might have been a death sentence. Hospitalized for colon surgery, the Australian retiree received a blood transfusion tainted with the AIDS virus. That he's alive at all is remarkable, but that's only half of the story. Unlike most long-term HIV survivors, he has suffered no symptoms and no loss of immune function. He's as healthy today as he was in 1983—and celebrating his 81st birthday. Benjamin B. is just one of five patients who came to the attention of Dr. Brett Tindall, an AIDS researcher at the University of New South Wales, as he was preparing a routine update on transfusion-related HIV infections last year. All five were infected by the same donor. And seven to 10 years later, none has suffered any effects.

THEO WESTENBERGER FOR NEWSWEEK

**BEATING HIV AT ITS OWN GAME: Yung-Kang Chow and assistant Debra Merrill**

The donor turned out to be a gay man who had contracted the virus during the late 1970s or early '80s, then given blood at least 26 times before learning he was infected. After tracking him down, Tindall learned, to his amazement, that the man was just as healthy as the people who got his blood. "We know that HIV causes AIDS," Tindall says. "We also know that a few patients remain well for long periods, but we've never known why. Is it the vitamins they take? Is it some gene they have in common? This work suggests it has more to do with the virus. I think we've found a harmless strain."

He may also have found the viral equivalent of a fossil, a clue to the origin, evolution and future of the AIDS epidemic. HIV may not be a new and inherently deadly virus, as is commonly assumed, but an old one that has recently acquired deadly tendencies. In a forthcoming book, Paul Ewald, an evolutionary biologist at Amherst College, argues that HIV may have infected people benignly for decades, even centuries, before it started causing AIDS. He traces its virulence to the social upheavals of the 1960s and '70s, which not only sped its movement through populations but rewarded it for reproducing more aggressively within the body.

The idea may sound radical, but it's not just flashy speculation. It reflects a growing awareness that parasites, like everything else in nature, evolve by natural selection, changing their character to adapt to their environments. Besides transforming our understanding of AIDS, the new view could yield bold strategies for fighting it. Viruses can evolve tens of thousands of times faster than plants or animals, and few evolve as fast as HIV. Confronted by a drug or an immune reaction, the virus readily mutates out of its range. A few researchers are now trying to exploit that very talent, using drugs to force HIV to mutate until it can no longer function. A Boston team, led by medical student Yung-Kang Chow, made headlines last month by showing that the technique works perfectly in a test tube. Human trials are now in the works, but better drug treatment isn't the only hope rising from an evolutionary outlook. If rapid spread is what turned HIV into a killer, then condoms and clean needles may ultimately do more than prevent new infections. Used widely enough, they might drive the AIDS virus toward the benign form sighted in Australia.

## I. Where did HIV come from?

Viruses are the ultimate parasites. Unlike bacteria, which absorb nutrients, excrete waste and reproduce by dividing, they have no life of their own. They're mere shreds of genetic information, encoded in DNA or RNA, that can integrate themselves into a living cell and use its machinery to run off copies of themselves. Where the first one came from is anyone's guess, but today's viruses are, like any plant or animal, simply descendants of earlier forms.

Most scientists agree that the human immunodeficiency viruses—HIV-1 and HIV-2—are basically ape or monkey viruses. Both HIVs are genetically similar to viruses found in African primates, the so-called SIVs. In fact, as the accompanying tree illustrates, the HIVs have more in common with simian viruses than they do with each other. HIV-2, found mainly in West Africa, is so similar to the SIV that infects the sooty mangabey—an ash-colored monkey from the same region—that it doesn't really qualify as a separate viral species. "When you see HIV-2," says Gerald Myers, head of the HIV database project at the Los Alamos National Laboratory, "you may not be looking at a human virus but at a mangabey virus in a human." HIV-1, the virus responsible for the vast majority of the world's AIDS cases, bears no great resemblance to HIV-2 or the monkey SIVs, but it's very similar to SIVcpz, a virus recovered in 1990 from a wild chimpanzee in the West African nation of Gabon.

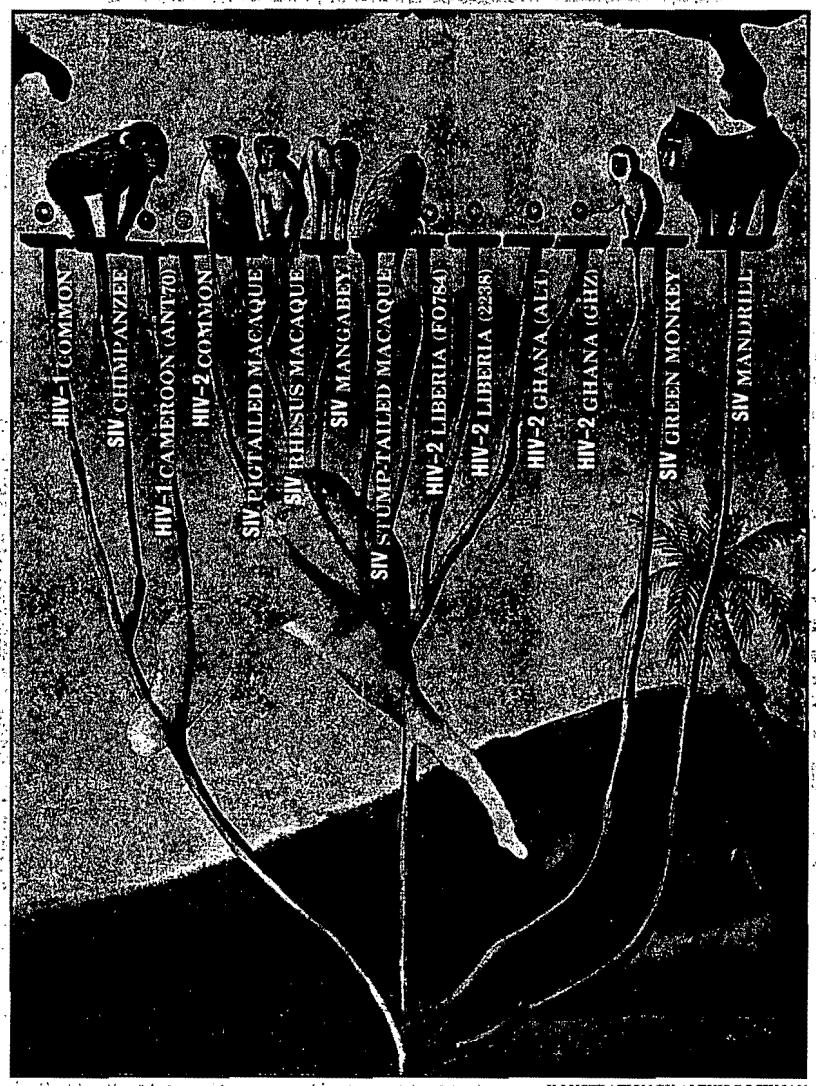



ILLUSTRATION BY ALEXIS ROCKMAN

**HIV'S EXTENDED FAMILY: Today's viruses are descendants of earlier forms. This family tree shows that the human AIDS viruses, HIV-1 and HIV-2, are more closely related to viruses found in primates (the SIVs) than to each other.**

The prevailing theory holds that humans were first infected through direct contact with primates, and that the SIVs they contracted have since diverged by varying degrees from their ancestors. It's possible, of course, that the HIVs and SIVs evolved separately, or even that humans were the original carriers. But the primates-to-people scenario has a couple of points in its favor. First, the SIVs are more varied than the HIVs, which suggests they've been evolving longer. Second, it's easier to imagine people being infected by chimps or monkeys than vice versa. Humans have hunted and handled other primates for thousands of years. Anyone who was bitten or scratched, or who cut himself butchering an animal, could have gotten infected.

Until recently, it was unclear whether people could contract SIV directly from primates, but a couple of recent accidents have settled that issue. In one case, reported last summer by the Centers for Disease Control, a lab technician at a primate-research center jabbed herself with a needle containing blood from an infected macaque. The infection didn't take—she produced antibodies to SIV only for a few months—but she was just lucky. Another lab worker, who handled monkey tissues while suffering from skin lesions, has remained SIV-positive for two years. In a recent survey of 472 blood samples drawn from primate handlers, health officials found that three of those tested positive as well. No one knows whether the people with SIV eventually develop AIDS, but the potential for cross-species transmission is now clear.

Far less clear is when the first such transmission took place. The most common view holds that since AIDS is a new epidemic, the responsible viruses must have entered humans within the past few decades. That's a reasonable suspicion, but it raises a sticky question. Why, if people have been handling primates in Africa for thousands of years, did SIV take until now to jump species?

One possibility is that humans recently opened some avenue that hasn't existed in the past. Some theorists argue, for example, that AIDS was spawned by a polio-vaccination program carried out in Africa during the late 1950s. During that four-year effort, 325,000 Africans received an oral polio vaccine produced in kidney cells from African green monkeys. Even if the vaccine was contaminated with SIV—which hasn't been established—blaming it for AIDS would be hasty. For the SIVs found in African green monkeys bear too little resemblance to HIV-1, the primary human AIDS virus, to be its likely progenitor. In order to link HIV-1 to those early lots of polio vaccine, someone would have to show that they contained a monkey virus never yet found in actual monkeys.

The alternative view—that the HIVs are old viruses—is just as hard to prove, but it requires fewer tortured assumptions. Dr. Jay Levy, an AIDS researcher at the University of California, San Francisco, puts it this way: "We know that all these other primates harbor lentiviruses [the class that includes the SIVs and HIVs]. Why should humans be any exception?" If the HIVs were on hand before the AIDS epidemic began, the key question is not where they came from but whether they always caused the disease.

## II. Was HIV once less deadly?

If HIV had always caused AIDS, one would expect virus and illness to emerge together in the historical record. Antibodies to HIV have been detected in rare blood samples dating back to 1959, yet the first African AIDS cases were described in the early 1980s, when the disease started decimating the cities of Rwanda, Zaire, Zambia and Uganda. When Dr. Robert Biggar, an epidemiologist at the National Cancer Institute, pored over African hospital records looking for earlier descriptions of AIDS-like illness, he didn't find any. It's possible, of course, that the disease was there all along, just too rare to be recognized as a distinct condition. But the alternative view is worth considering. There are intriguing hints that HIV hasn't always been so deadly.

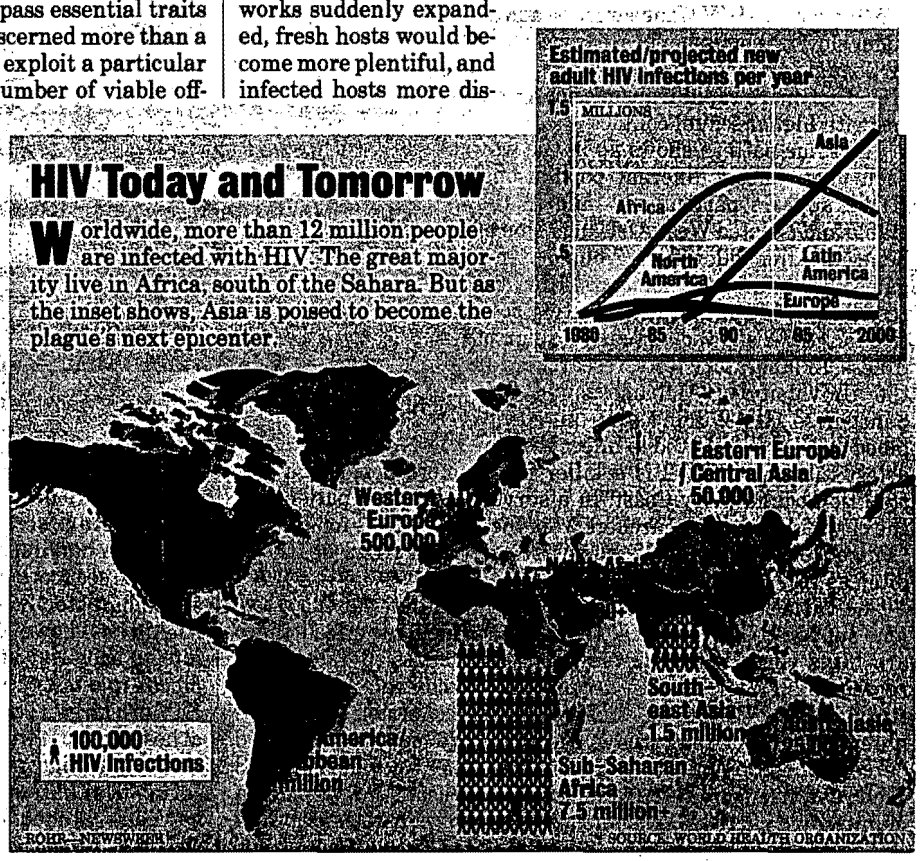
Any population of living things, from fungi to rhinoceri, includes genetically varied individuals, which pass essential traits along to their progeny. As Charles Darwin discerned more than a century ago, the individuals best designed to exploit a particular environment tend to produce the greatest number of viable offspring. As generations pass, beneficial traits become more and more pervasive in the population. There's no universal recipe for reproductive success; different environments favor different traits. But by preserving some and discarding others, every environment molds the species it supports.

Viruses aren't exempt from the process. Their purpose, from a Darwinian perspective, is simply to make as many copies of themselves as they can. Other things being equal, those that replicate fastest will become the most plentiful within the host, and so stand the best chance of infecting other hosts on contact. But there's a catch. If a microbe reproduces too aggressively inside its host, or invades too many different tissues, it may kill the host—and itself—without getting passed along at all. The most successful virus, then, is not necessarily the most or the least virulent. It's one that exploits its host most effectively.

As Ewald and others have shown, that mandate can drive different microbes to very different levels of nastiness. Because they travel via social contact between people, cold and flu viruses can't normally afford to immobilize us. To stay in business, they need hosts who are out coughing, sneezing, shaking hands and sharing pencils. But the incentives change when a parasite has other ways of getting around. Consider tuberculosis or diphtheria. Both deadly diseases are caused by bacteria that can survive for weeks or months outside the body. They can reproduce aggressively in the host, ride a cough into the external environment, then wait patiently for another host to come along. By the same token, a parasite that can travel from person to person via mosquito or some other vector has little reason to be gentle. As long as malaria sufferers can still feed hungry mosquitoes, their misery is of little consequence to the microbe. Indeed, a host who can't wield a fly swatter may be preferable to one who can.

These patterns aren't set in stone. A shift in circumstances may push a normally mild-mannered parasite toward virulence, or vice versa. One of the most devastating plagues in human history was caused by a mere influenza virus, which swept the globe in 1918, leaving 20 million corpses in its wake. Many experts still regard the disaster as an accident, triggered by the random reshuffling of viral genes. But from an evolutionary perspective, it's no coincidence that the flu grew so deadly when it did. World War I was raging in 1918. Great numbers of soldiers were huddled in the European trenches, where even the most ravaged host stood an excellent chance of infecting many others. For a flu virus, the incentives favoring restraint would have vanished in those circumstances. Rather than rendering the host useless, extreme virulence would simply make him more infectious.

Ewald suspects that HIV has recently undergone a similar transformation. Unlike influenza viruses, which infect cells in the respiratory tract and spread through coughs and sneezes, the HIVs insinuate themselves into white blood cells. Infected cells (or the new viruses they produce) can pass between people, but only during sex or other exchanges of body fluid. Confined to an isolated population where no carrier had numerous sex partners, a virus like HIV would gain nothing from replicating aggressively within the body; it would do best to lie low, leaving the host alive and mildly infectious for many years. But if people's sexual networks suddenly expanded, fresh hosts would become more plentiful, and infected hosts more dispensable. An HIV strain that replicated wildly might kill people in three years instead of 30, but by making them more infectious while they lasted, it would still come out ahead.




Is that what actually happened? There's no question that social changes have hastened the spread of HIV. Starting in the 1960s, war, tourism and commercial trucking forced the outside world on Africa's once isolated villages. At the same time, drought and industrialization prompted mass migrations from the countryside into newly teeming cities. Western monogamy had never been common in Africa, but as the French medical historian Mirko Grmek notes in his book "History of AIDS," urbanization shattered social structures that had long constrained sexual behavior. Prostitution exploded, and venereal disease flourished. Hypodermic needles came into wide use during the same period, creating yet another mode of infection. Did these trends actually turn a chronic but relatively benign infection into a killer? The evidence is circumstantial, but it's hard to discount.

If Ewald is right, and HIV's deadliness is a consequence of its rapid spread, then the nastiest strains should show up in the populations where it's moving the fastest. To a surprising degree, they do. It's well known, for example, that HIV-2 is far less virulent

than HIV-1. "Going on what we've seen so far, we'd have to say that HIV-1 causes AIDS in 90 percent of those infected, while HIV-2 causes AIDS in 10 percent or less," says Harvard AIDS specialist Max Essex. "Maybe everyone infected with HIV-2 will progress to AIDS after 40 or 50 years, but that's still in the realm of reduced virulence." From Ewald's perspective, it's no surprise that HIV-2, the strain found in West Africa, is the gentle one. West Africa has escaped much of the war, drought and urbanization that fueled the spread of HIV-1 in the central and eastern parts of the continent. "HIV-2 appears to be adapted for slow transmission in areas with lower sexual contact," he concludes, "and HIV-1 for more rapid transmission in areas with higher sexual contact."

The same pattern shows up in the way each virus affects different populations. HIV-2 appears particularly mild in the stable and isolated West African nation of Senegal. After following a group of Senegalese prostitutes for six years, Harvard researchers found that those testing positive for HIV-2 showed virtually no sign of illness. In laboratory tests, researchers at the University of Alabama found that Senegalese HIV-2 didn't even kill white blood cells when allowed to infect them in a test tube. Yet HIV-2 is a killer in the more urban and less tradition-bound Ivory Coast. In a survey of hospital patients in the city of Abidjan, researchers from the U.S. Centers for Disease Control found that HIV-2 was associated with AIDS nearly as often as HIV-1.

RICHARD HOWARD

**A NEW VIEW: Ewald argues that a Darwinian perspective can enrich our thinking about AIDS**

The variations within HIV-1 are less clear-cut, but they, too, lend support to Ewald's idea. Though the evidence is mixed, there are hints that IV drug users (whose transmission rates have remained high for the past decade) may be contracting deadlier strains of HIV-1 than gay men (whose transmission rates have plummeted). In a 1990 study of infected gay men, fewer than 8 percent of those not receiving early treatment developed AIDS each year. In a more recent study of IV drug users, the proportion of untreated carriers developing AIDS each year was more than 17 percent.

Together, these disparities suggest that HIV assumes different personalities in different settings, becoming more aggressive when it's traveling rapidly through a population. But because so many factors affect the health of infected people, the strength of the connection is unclear. "This is exactly the right way to think about virulence," says virologist Stephen Morse of New York's Rockefeller University. "Virulence should be dynamic, not static. The question is, how dynamic? We know that a pathogen like HIV has a wide range of potentials, but we can't yet say just what pressures are needed to generate a particular outcome."

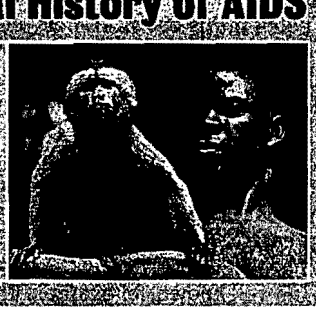
The best answers to Morse's question may come from laboratory studies. A handful of biologists are now devising test-tube experiments to see more precisely how transmission rates shape a parasite's character. Zoologist James Bull of the University of Texas at Austin has shown, for example, that a bacteriophage (a virus that infects bacteria) kills bacterial cells with great abandon when placed in a test tube and given plenty of new cells to infect. Like HIV in a large, active sexual network, it can afford to kill individual hosts without wiping itself out in the process. Yet the same virus becomes benign when confined to individual cells and their offspring (a situation perhaps akin to pre-epidemic HIV's). With a good animal model, researchers might someday manage to test Ewald's hypotheses about HIV with the same kind of precision.

## III. Can HIV be tamed?

Until recently, medical science seemed well on its way to controlling the microbial world. Yet after 10 years and billions of dollars in research, HIV still has scientists over a barrel. The secret of its success can be summed up in one word: mutability. Because HIV's method of replication is so error prone (its genes mutate at a million times the rate of our own), it produces extreme-

## A Hypothetical History of AIDS

**Why did HIV suddenly emerge as a global killer? According to one theory, the virus has infected people for centuries, but recent social changes have altered its character.**



**BEFORE 1960** Rural Africans contracted benign ancestral forms of HIV from primates. Because the viruses spread so slowly among people, they couldn't afford to become virulent.

**1960 TO 1975** War, drought, commerce and urbanization shattered African social institutions. HIV spread rapidly, becoming more virulent as transmission accelerated.

ly varied offspring, even within an individual host. Whenever a drug or immune response successfully attacks one variant, another arises to flourish in its place. Even when an AIDS drug works broadly enough to check HIV's growth, it rarely works for long. AZT, for example, can help prevent symptoms for a couple of years. But people on AZT still get AIDS, as the viral populations in their bodies evolve toward resistant forms.

There may not be a drug or vaccine on earth that could subdue such a protean parasite. But from a Darwinian perspective, killing HIV is not the only way to combat AIDS. We know the virus changes rapidly in response to outside pressures. Logic suggests that if we simply applied the right pressures—within a community, or even within a patient's body—we might begin to tame it.

It's well known that condoms and clean needles can save lives by preventing HIV infection. From an evolutionary perspective, there is every reason to think they could do more. Used widely enough, those same humble implements might push the virus toward more benevolent forms, simply by depriving virulent strains of the high transmission rates they need to survive. Gay men are already engaged in that exercise. Studies suggest that, thanks to safer sex, the rate of new infections among gays declined five- to tenfold during the 1980s. There are tantalizing hints that HIV has grown less noxious in the same population over the same period. In a 1991 study, researchers at the National Institutes of Health (NIH) calculated the rates at which infected people from different risk groups were developing AIDS each year. They found that as of 1987, the rate declined sharply among gay men, suggesting the virus was taking longer to cause illness. Part of the change was due to AZT, which can delay the onset of symptoms. But when the NIH researchers corrected for AZT use, there was still a mysterious shortage of AIDS cases. From Ewald's viewpoint, the shortfall was not only unsurprising but predictable.

How far could such a trend be pushed? Would broader, better prevention efforts eventually turn today's deadliest HIV-1 into something as benign as Senegal's HIV-2? No one knows. But the prospect of domesticating the AIDS virus, even partially, should excite public-health officials. Condoms and clean needles are exceedingly cheap medicine. They can save lives even if they fail to change the course of evolution—and judging from the available evidence, they might well succeed.

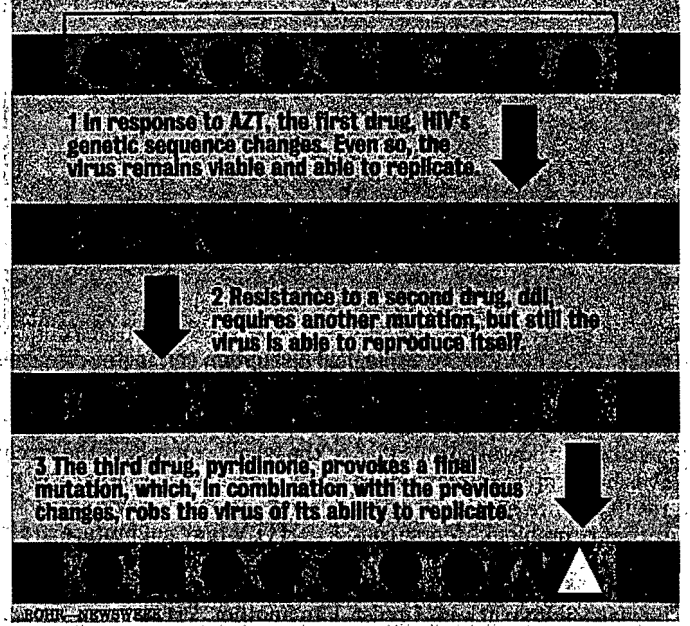
In the meantime, more than 12 million people are carrying today's HIV, and those who get AIDS are still dying. Fortunately, as Yung-Kang Chow and his colleagues at Massachusetts General Hospital showed last month, there's more than one way to manipulate viral evolution. The researchers managed, in a test-tube experiment, to outsmart HIV at its own game. Their trick was to combine three drugs—AZT, ddI and pyridinone—that disarm the same part of the virus (an enzyme called reverse transcriptase).

Any of those drugs can foil HIV's efforts to colonize host cells. When HIV encounters them individually, or even in pairs, it gradually mutates into resistant forms and goes on about its business. But each mutation makes the virus slightly less efficient—and as Chow's group demonstrated, there comes a point where mutation itself hobbles the virus (chart). By engineering an HIV mutant that contained three different mutations (one in response to each of the three drugs), the researchers ended up with a virus that was too deformed to function at all. If virgin HIV can't function in the presence of the three drugs—and if triply mutated HIV can't function at all—then the three-drug regimen should, theoretically, do wonders for patients.

It's a long way from the test tube to the clinic; many treatments have shown great promise in lab experiments, only to prove ineffective or highly toxic in people. Upcoming clinical trials will determine whether patients actually benefit from Chow's combination of drugs. The beauty of the new approach, however, is that it's not limited to any particular combination. While the Boston team experiments with drugs directed against reverse transcriptase, researchers at New York's Aaron Diamond AIDS Research Center are trying the same tack against another viral target (an enzyme called protease). "This virus has impressed us again and again with its ability to change," says Dr. David Ho, director of the Aaron Diamond Center. "It always has a new strategy to counter

## Harnessing Evolution in the Lab

Because HIV mutates so rapidly, no single drug subdues it for long. But in test-tube studies, researchers at Massachusetts General Hospital used a combination of three drugs to force it to mutate until it could no longer function.

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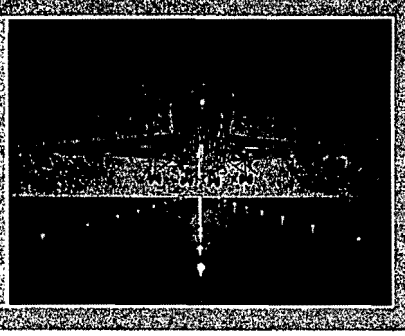
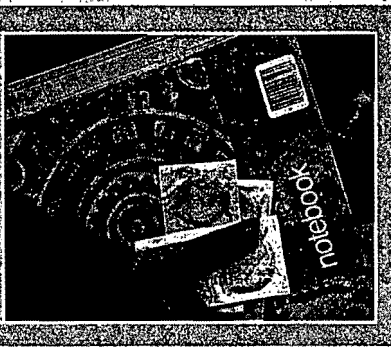


**1975 TO PRESENT.** Global travel placed HIV in broader circulation. Shifting sexual mores and modern medical practices, such as blood transfusion, made many populations susceptible.




**THE FUTURE.** If social changes can turn a benign virus deadly, the process should be reversible. Simply slowing transmission may help drive fast-killing strains out of circulation.

our efforts. Now we're asking it to make a trade-off. We're saying, 'Go ahead and mutate, because we think that if you mutate in the right place, you'll do less damage to the patient'."

## IV. Can the next AIDS be avoided?

The forces that brought us this plague can surely bring us others. By encroaching on rain forests and wilderness areas, humanity is placing itself in ever-closer contact with other animal species and their obscure, deadly parasites. Other activities, from irrigation to the construction of dams and cities, can create new diseases by expanding the range of the rodents or insects that carry them. Stephen Morse, the Rockefeller virologist, studies the movement of microbes among populations and species, and he worries that human activities are speeding the flow of viral traffic. More than a dozen new diseases have shown up in humans since the 1960s, nearly all of them the result of once exotic parasites exploiting new opportunities. "The primary problem," Morse concludes, "is no longer virological but social."

The Ebola virus is often cited as an example of the spooky pathogens in our future. The virus first struck in August 1976, when a trader arrived at a mission hospital in northern Zaire, fever raging and blood oozing from every orifice. Within days the man died, and nearly half of the nurses at the hospital were stricken. Thirty-nine died, and as hospital patients contracted the virus, it spread to 58 neighboring villages. Ebola fever ended up striking 1,000 people in Zaire and nearby Sudan, killing 500. Epidemiologists feared it would spread more widely, but the outbreaks subsided as quickly as they had begun. From a Darwinian perspective, that's no great surprise. A parasite that kills that rapidly has little chance of sustaining a chain of infection unless it can survive independently of its host.

SILVESTER—RAPHO-BLACK STAR

**CULTIVATING CONTAGION: Ecological disruption can foster disease**

More worrisome is a virus like HTLV, a relative of HIV that infects the same class of blood cells and is riding the same waves through new populations. Though recognized only since the 1970s, the HTLVs (HTLV-1 and HTLV-2) appear to be ancient. About one in 20 HTLV-1 infections leads eventually to leukemia, lymphoma or a paralyzing neurologic disorder called TSP. The virus is less aggressive than HIV-1—it typically takes several decades to cause any illness—but its virulence seems to vary markedly from one setting to the next. In Japan, the HTLV-related cancers typically show up in 60-year-olds who were infected by their mothers in the womb. In the Caribbean, where the virus is more often transmitted through sex, the average latency is much shorter. It's not unusual for people to develop symptoms in their 40s.

HTLV may not mutate as readily as HIV, but it is subject to the same natural forces. If human activities can turn one virus into a global killer, it's only prudent to suspect they could do the same to another. "HTLV is a threat," says Ewald, "not because it has escaped from some secluded source, but because it may evolve increased virulence." HTLV-1 is only one tenth as prevalent as HIV in the United States, but it has gained a strong foothold among IV drug users, whose shared needles are a perfect breeding ground for virulent strains.

No one knows whether HTLV could cause an epidemic like AIDS. Fortunately, we don't have to wait passively to find out. We're beginning to see how our actions mold the character of our parasites. No one saw the last epidemic coming. This time, that's not an excuse. ■

## As Human Habits Change, New Viruses Emerge

| VIRUS, DISEASE | SYMPTOMS | ORIGIN | STATUS |
|---|---|---|---|
| JUNIN<br>Argentine Hemorrhagic Fever | Fever, muscle pain, rash, internal bleeding and, sometimes, tremors or convulsions. Mortality rate: 10 to 20 percent. | First recognized in 1953, Junin has emerged as a result of an increase in corn cultivation in northern Argentina. Carried by mice. | A rodent-control program brought the virus's Bolivian cousin, Machupo, under control, but Junin has expanded its reach in recent decades. It strikes 400 to 600 people annually. |
| EBOLA<br>African Hemorrhagic Fever | Fever, vomiting, rash, muscle pain, gastrointestinal bleeding, shock. A deadly virus, Ebola kills at least half its victims. | Virtually identical to Marburg, a virus found in Germany in 1967, Ebola was first reported in 1976. Its origin is unknown. | An outbreak in Africa killed 500 in 1976. Philippine monkeys sent to a Reston, Va., research lab brought a related—but not lethal—virus here in 1989, leading to curbs on monkey imports. |
| DENGUE<br>Dengue Fever | Headache, fever, muscle pain, chills. More severe dengue hemorrhagic fever can cause internal bleeding and death. | Dengue has long plagued tropical Asia, South America and the Caribbean, favoring densely populated, mosquito-infested areas. | Infects more than 30 million people annually. Rare in U.S. but could spread more widely since a shipment of used tires brought virus-transmitting Asian tiger mosquitoes ashore in 1985. |
| HTLVs<br>Leukemia, TSP | Leukemia is a cancer of white blood cells which can spread to other organs. TSP is a degenerative neurological disorder. | HTLV-1 was first reported in 1980, but studies suggest that it and the related virus HTLV-2 have attacked humans for millenniums. | HTLVs are transmitted in the same manner as HIV but, so far, appear less deadly. One recent study found that up to 20 percent of IV drug users in Los Angeles are infected. |

SOURCE: STEPHEN S. MORSE—THE ROCKEFELLER UNIVERSITY; PAUL EWALD—AMHERST COLLEGE

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Little Rock, Arkansas 72201

February 18, 1993

Ms. Carol Rasco
Assistant to the President
Domestic Policy
The White House
Washington, D.C. 20500

Dear Carol:

I sincerely appreciated your call yesterday offering to set up a roundtable meeting at the White House between Mr. Stephens, myself and those key Administration officials who will be leading the fight in the area of AIDS research. As I mentioned, we have made good progress at both the NIH and FDA and would like to maintain our momentum under the new Administration.

As you requested, we will be collecting our thoughts over the next couple of weeks regarding which of those health officials should be included in this meeting. After that time I will call you or Ms. Kelly to see what dates will be open for you. We will arrange our travel schedule accordingly.

Mr. Stephens admires the President's committment to winning the war against AIDS. We sincerely appreciate your enthusiasm in setting up this meeting.

Thanks again.

Sincerely,

Gary R. Faulkner
STEPHENS ENTERPRISES, INC.

GRF: mc

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**December 16, 1992**

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## FOR IMMEDIATE RELEASE

### Stephens Releases Test Data On AIDS Antiseptic .

**Little Rock, Arkansas, U.S.A.** Jackson T. Stephens, Jr., reports that the National Institutes of Health has just completed a series of pre-clinical tests that demonstrate Exact™ is effective in killing clinical isolates of HIV-1 in serum. Exact™ is the trade name for two enzymes-- Myeloperoxidase (MPO) and Eosinophil Peroxidase (EPO)--that have previously been documented to kill the AIDS virus *in-vitro* , and could be used in a vaginal or anal suppository, or cream to prevent the spread of HIV and other Sexually Transmitted Diseases (STDs).

"Just as important as the fact that Exact™ kills HIV-1 in serum, is that there was no cytotoxicity, and the animal studies indicated no inflammation or irritation. We are very pleased with the support and efforts of the NIH to help us through this initial pre-clinical test stage, and we hope to begin human clinical trials in the first part of 1993."

"We will take every precaution to insure the safety and efficacy of our product both here in the U.S. and abroad," said Stephens, commenting from his office in Little Rock. "All of our work to date has shown that Exact™ is both safe and effective. We are grateful for the government help in expediting testing."

Stephens said: "The low cost of Exact™ makes it affordable for consumer use in suppositories, topical creams, lozenges, or lubricants. Use of Exact™ enhanced

products could make a significant contribution in the prevention of AIDS and other Sexually Transmitted Diseases (STDs)."

Because of the prohibitive cost of manufacturing even low concentrations of MPO and EPO, large clinical studies and commercial applications of the enzymes have, heretofore, not been possible. ExOxEmis has developed a proprietary manufacturing process which makes wholesale distribution of Exact™ viable.

## "Scorched Earth Versus Smart Bombs"

To date, other antiseptics and topical anti-viral agents are effective against infectious microbes only at concentrations that damage surrounding tissue and the immune system. In 1918, Alexander Flemming, the inventor of penicillin, documented this problem; Exact™ solves it.

Exact™ has a very high affinity for pathogens, but does no harm to surrounding tissue or helpful bacteria which naturally occur in the body. Stephens calls it the "smart bomb" of antiseptics.

Exact™ uses a chemical called singlet molecular oxygen which occurs during a high energy reaction. The "killing" properties of this oxygen are restricted by its short lifetime. The region of singlet molecular oxygen killing is about the width of a bacteria wall, so only organisms to which it binds are damaged.

ExOxEmis discovered and documented Exact's™ unique ability to bind primarily to harmful or pathogenic microbes without harming the normal flora.

## More About MPO and EPO

Myeloperoxidase (MPO) and Eosinophil Peroxidase (EPO) are the two primary killing components of a group of white blood cells known as neutrophils and eosinophils. These cells are considered the foot soldiers of the human immune system because there are so many produced by the body and they are the first component employed by the body's defense mechanism.

For many years, medical researchers have known these enzymes were effective microbe killers. What was not known was their selective ability to bind primarily to pathogenic organisms. Exact™ employs MPO and EPO in this unique and previously undiscovered method of selective binding.

ExOxEmis has completed the research, development, patent filings and manufacturing scale-up to supply Exact™ for commercial use.

## Exact™ Has Many Consumer Applications

The most immediate benefit of Exact™ to the general public can be its application in the prevention of AIDS and other STDs. When fully developed as a suppository, Exact™ can provide an effective barrier against infection. Exact's™ addition to donor blood bags to kill HIV and other blood transmitted diseases is a high devlopment priority with ExOxEmis.

Because Exact™ can kill a variety of pathogenic bacteria, viruses, yeasts, and molds, it has the potential for wide spread application in a diverse range of products -- these include: ophthalmic solutions; infant and enteral formulas; burn ointments; urinary tract lavages; feminine hygene products; surgical and consumer antiseptics; skin care products and cosmetics.

ExOxEmis is now offering commercial licensing and distribution agreements to major companies for Exact™, as well as bulk sales to academic and industrial researchers.

Jun 04 '92 09:55 REUTERS DALLAS

Mike Clancy P6/(b)(6)

1-AIDS

LITTLE ROCK COMPANY TOUTS AIDS DRUG
BY STEVE BARNES

LITTLE ROCK. ARK., JUNE 4, REUTER--EXOXEMIS, INC., a privately held medical company, said Thursday it has asked for federal assistance in developing what it describes as the only topical antiseptic known to destroy the AIDS virus.

Company officials said the enzyme-based formula, trade-named Exact™ is neither a cure for AIDS nor a vaccine against the viral disease, for which there is no known cure.

But they contended it promised significant protection against contracting the disease if employed as a prophylactic agent in vaginal douches, anal suppositories, mouthwashes or even hand soaps.

"We think we have something that has enormous implications for containing the spread of AIDS," said Jackson T. Stephens, Jr., of Little Rock, chairman of ExOxEmis, Inc.

ExOxEmis has laboratory and manufacturing facilities in San Antonio, Texas. Stephens Enterprises, Inc., of Little Rock is its owner.

Stephens said Exact had demonstrated laboratory effectiveness against other sexually transmitted diseases as well as a range of other infectious diseases.

Stephens said the company will present its preliminary findings to the Advisory Council of the National Institutes for Health in Washington September 15.

It is seeking as much as $50 million in federal research funds to move the evaluation process through animal and, ultimately human testing.

Every other pharmaceutical or biomedical company that has entered the AIDS research arena has, to our knowledge, focused exclusively on either a cure for HIV infection or a vaccine," Stephens said, "as opposed to our development of a topical prophylactic."

Stephens said scientists had long known that Myeloperoxidase (commonly called MPO) and Eosinophil Peroxidase (EPO), both naturally occurring enzymes in mammals, were extremely potent anti-viral agents.

He said the company's research team had made a trio of scientific breakthroughs which led to its present application for assistance from the National Institute of Health and the U.S. Food and Drug Administration.

The first such breakthrough was the development of a process by which MPO and EPO could be extracted from cattle and swine in sufficiently pure, ample quantities to be extensively tested and commercially viable.

Stephens said the company had elected not to patent the extraction process but to safeguard it as proprietary data.

The second watershed discovery, Stephens said, was that MPO (MPO and EPO are used interchangeably in biomedical parlance) would attack a pathogen such as the AIDS virus without first bonding to a molecular "carrier."

"We learned it has a natural affinity for pathogens," Stephens said. "It binds directly to the target cells."

"But perhaps the most significant finding, according to Stephens, was that it binds to and attacks only pathogens, leaving untouched healthy cells and beneficial, naturally occurring microbes, such as those which promote digestion and fight minor infections.

"It's a 'smart bomb,'" Stephens described Exact™. "It has a very narrow kill zone."

Stephens said ExOxEmis had not known of MPO's effectiveness against HIV until it learned of research being conducted by Drs. Seymour Klebanoff and Albert Coombs at the University of Washington School of Medicine.

In a study published in the July 1991 Journal of Experimental Medicine (Rockefeller University Press), Klebanoff and Coombs wrote that an MPO-based formula could serve to "deactivate" HIV infection in laboratory tests.

Stephens said ExOxEmis previously tested Exact™ against more than 40 other pathogens and discovered that it successfully attacked the harmful bacteria without disturbing adjacent, normal tissue.

"Soon enough, we concluded Exact™ could be the perfect antiseptic," Stephens said.

Solutions such as household bleach, while widely recommended to intravenous drug users as a method of selectively disinfecting hypodermic needles of the AIDS virus, damages human tissue, and is therefore without value as a surface antiseptic.

The company said it is prepared to begin large-scale production of Exact™ and apply for certification by Federal regulatory authorities, a process Stephens said would take from one to two years.

Stephens said ExOxEmis, created in 1987, was originally engaged in developing a process for detecting salmonella bacteria in poultry when its scientists, led by Dr. Robert Allen, noticed the specificity with which MPO attacked pathogens.

The company has since obtained one patent for MPO test applications and has a second patent pending.

Stephens said ExOxEmis is already offering licensing agreements to manufacturers of ophthalmic solutions, infant formulas and cosmetics, promoting the antiseptic and supplemental immunological benefits of Exact™.

REUTER MC

Arkansas Democrat
ARKANSAS' NEWSPAPER
LITTLE ROCK, JUNE 5, 1992

AP&L, agencies te
readiness below da
with mock emerge
— Arkansas




Opponent challenges
Walker to hold debate,
release tax records
— Pulaski Page



# Stephens firm testing drug to fight AIDS

BY ANDREW MOREAU
Democrat-Gazette Business Writer

A medical research company founded by Little Rock businessman Jackson T. Stephens Jr. is seeking federal aid for an antiseptic that an independent study shows destroys the AIDS virus.

The formula, developed by ExOxEmis Inc., is neither a cure nor a vaccine for the deadly virus. Rather it acts as protection against contracting the disease. The product is a topical prophylactic.

"This stuff has great promise," Stephens said in an interview Thursday.

ExOxEmis, owned solely by Stephens, is scheduled to go before the National Institutes for Health on Sept. 15 to ask for up to $50 million. The money would be used to test the drug on animals and would move to humans if initial testing is successful.

"We have several avenues to finance the clinical development of this and NIH is one of them," Stephens said. "They've so far indicated a willingness to help us. They will help us get off on the right foot with FDA, which has the ultimate approval."

The Food and Drug Administration would have to approve any product before it could be sold commercially.

Exact, the trade name of the enzyme-based drug, has shown potential to kill the AIDS virus and other sexually transmitted diseases when used in a vaginal douche, anal suppository, mouthwash or hand soap. "What we did was make this available to be put in humans in solutions," Stephens said of the product.

The enzymes, Myeloperoxidase (MPO) and Eosinophil Peroxidase (EPO), have had high manufacturing costs and as such have prevented clinical studies. The enzymes are produced naturally by mammals.

Another problem has been that antiseptics, in general, have been effective against pathogens only at large concentrations that also damaged tissue.

ExOxEmis was able to counter both problems, according to Stephens. "What we added to the equation was, we noticed our product had a natural affinity for pathogens and left normal flora alone," Stephens said. "That's essentially what our proprietary information is and we're going to protect it like the formula for Coke."

In addition, the company developed a process to produce the enzymes at a cost that could be affordable for commercial uses. "We figured out how to produce this in bulk in commercially viable containers," Stephens said. "It's the first time that's ever been done."

ExOxEmis has about 16 employees at its manufacturing

See EXACT, Page 6D

## Exact

• Continued from Page 1D

and research facilities in San Antonio and operates its business office in Little Rock.

The company can produce the product in gram quantities and has the capacity to produce in kilograms, according to Stephens, who said the San Antonio plant is 11,000 square feet.

Stephens founded the company in 1985, and in 1987 researchers began work on the product that developed into Exact. The product was intended for general antiseptic uses until a study in 1991 by the University of Washington found it could be used to prevent transmission of AIDS.

Seymour Klebanoff, a member of the National Academy of Science, and Robert Coombs, an ex-officio member of the National Advisory Board to NIH, conducted the study.

"Their work was independent of ours," Stephens said. Their study was published last July in the *Journal of Experimental Medicine* at Rockefeller University in New York.

ExOxEmis has had success in other areas. The company was awarded a U.S. patent in April for its Axis product line, which is an automated instrumentation and integrated software that measures the systemic state of inflammation within 30 minutes using one drop of blood. That product is being sold to pharmaceutical companies.


**LR-based firm reveals development of drug to help combat AIDS**

– Page 1D


# Gazette

90 PAGES 9 SECTIONS 35¢

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
Bethesda, Maryland 20892

Solar Building
Room 2C22
(301) 496-0700

January 7, 1993

Jackson T. Stephens, Jr.
Chairman, ExOxEmis Inc.
1769 One Union National Plaza
Little Rock, Arkansas 72201

Dear Mr. Stephens:

As per our phone conversation of Tuesday, January 5, 1993, I want to re-emphasize that the importance of continuing research and development of HIV viricides, such as MPO and EPO, is acknowledged by us in the National Institute of Allergy and Infectious Diseases. I have discussed the present state of development with Dr. Anthony Fauci, Institute Director, Dr. Pat Reichelderfer, Program Virologist, and Dr. Chuck Litterst, Drug Development and Surveillance Chief.

As previously stated, we are committed to do animal efficacy studies in the guinea pig model of Herpes. We feel such animal model efficacy studies are a logical next step, and if these compounds prove positive in a Herpes model, would generate support and enthusiasm by the AIDS Clinical Drug Development Committee (ACDDC). We are prepared to initiate animal studies with an appropriate drug formulation provided by you that will ultimately be employed in clinical studies.

We are also in agreement with your Scientific Director, Dr. Bob Allen, that animal studies of local toxicity following vaginal administration are critical. As you are aware, increased transmission of HIV has been associated with conditions of abnormal vaginal epithelium. The pathology report on the rabbit toxicology studies has been completed and you should be receiving a copy of the report shortly from Dr. Nancy Alexander of NICHD. The report apparently describes considerable toxicity with the gel base alone. Dr. Alexander's group does not formulate compounds, but, Dr. Allen has stated that the product (Exact) could be formulated as a gel. It is unclear whether the formulation supplied to NICHD was tested in vitro for efficacy. Again, it will be important to perform toxicity trials with the compound and formulation to be used in the clinical trial.

Further testing can proceed as soon as we have received the revised compound. Once the various contractors have received this formulation, it will take approximately 3-4 weeks to complete the cell culture work, and 3-4 months to complete the animal efficiency studies. It is highly likely that the ACDDC will wish to evaluate the results of the animal efficacy studies before making a decision to proceed to clinical trials.

As we discussed, it is also important to continue the dialogue with the FDA to understand what other suggestions or requirements they may have prior to initiating clinical trials.

Again, I want to re-assure you that because this product and approach are very promising in preventing HIV-1 transmission, we remain committed to assisting ExOxEmis so that this concept and product are developed in a timely manner.

Sincerely,

Steven M. Schnittman, M.D.
Chief, Medical Branch
Division of AIDS
Clinical Research Program
National Institute of Allergy
and Infectious Diseases
National Institutes of Health

cc: Anthony S. Fauci, M.D.
Pat Reichelderfer, Ph.D.
Chuck Litterst, Ph.D.

MEMORANDUM OF CALL — Previous editions usable

TO: CR

☑ YOU WERE CALLED BY — ☐ YOU WERE VISITED BY —

Gary Faulkner

OF (Organization)

☑ PLEASE PHONE ▶ ☐ FTS ☐ AUTOVON

(501) 375-0940

☐ WILL CALL AGAIN ☐ IS WAITING TO SEE YOU

☐ RETURNED YOUR CALL ☐ WISHES AN APPOINTMENT

MESSAGE

WH Sheds Mtg. per fax

Private Meeting w/Mr. Stephens + himself? 30 minute

| RECEIVED BY | DATE | TIME |
|---|---|---|
| RB | 3-2 | 2:00 |

63-110 NSN 7540-00-634-4018 STANDARD FORM 63 (Rev. 8-81)
☆ U.S.G.P.O. 1992 312-070-40024 Prescribed by GSA FPMR (41 CFR) 101—11.6

Carol —

This meeting is 3/18 @ 3:00.

Gary says you talked about a private meeting to take place before this one w/Mr. Stephens & himself. Says they need 30 min... w/b in town beginning 3/16. Pls. Advise. for

Give them a Wed. morn. or aft. time. Block off an hour.

* I need cc of the 3/1 memo when I go to Shalala today.

**Stephens Enterprises, Inc.**
111 Center Street, Suite 1616
Little Rock, Arkansas 72201
Tel : (501) 375-0940; Fax : (501) 375-4171

# FAX-MEMO

TO : CAROL RASCO
WHITE HOUSE FAX# (202) 456-2878

FROM: GARY FAULKNER
L.R. FAX # (501) 375-4171

**********

**Stephens Enterprises, Inc.**
111 Center Street, Suite 1616
Little Rock, Arkansas 72201
Tel : (501) 375-0940; Fax : (501) 375-4171

# FAX-MEMO

Call & tell him I'm out the latter part of wk. of 8th, this requested meeting time. It is I understand easier for Jocelyn to be in DC in late week so is he interested in March 18 or 19?
CJR

TO: Carol Rasco
FROM: Gary Faulkner
RE: White House Meeting on AIDS
DATE: March 1, 1993

---

Susie Whitacre advises me that you are ready to move forward with our meeting at the White House. Below you will find the names of those individuals who are most familiar with our effort and who we would like to have included in the meeting.

Dr. Anthony S. Fauci
Associate Director
Office of AIDS Research
National Institutes of Health
9000 Rockville Pike
Room 7A03
Bethesda, MD 20892

Dr. Steven M. Schnittman
Chief, Medical Branch
Division of AIDS
Clinical Research Program
National Institute of Allergy
and Infectious Diseases
National Institutes of Health

Dr. Jocelyn Elders
Surgeon General-Designate
Arkansas Department of Health
4815 West Markham
Little Rock, AR 72205

Mr. William B. Schultz
Chief Counsel for Food
and Drugs
Subcommittee on Health
and Environment
U.S. House of Representatives

In addition to the representatives from our Company, we would be wide open to any other Administration Officials you may wish to include in this discussion.

We will be happy to arrange our schedule to meet yours, but would suggest that we set the meeting sometime during the week of March 8, preferably the latter part of that week.

I will follow-up this fax with a phone call later today. Thanks again for coordinating this effort.

EXOXEMIS INC.

18585 Sigma Road San Antonio, Texas 78258
1-800-527-3196 210-491-0757 FAX 210-491-0038

Arkansas Democrat Gazette
ARKANSAS' NEWSPAPER
LITTLE ROCK, AUGUST 25, 1992
54 PAGES
6 SECTIONS
35¢

# LR firm's anti-viral drug ready for foreign markets

BY ANDREW MOREAU
Democrat-Gazette Business Writer

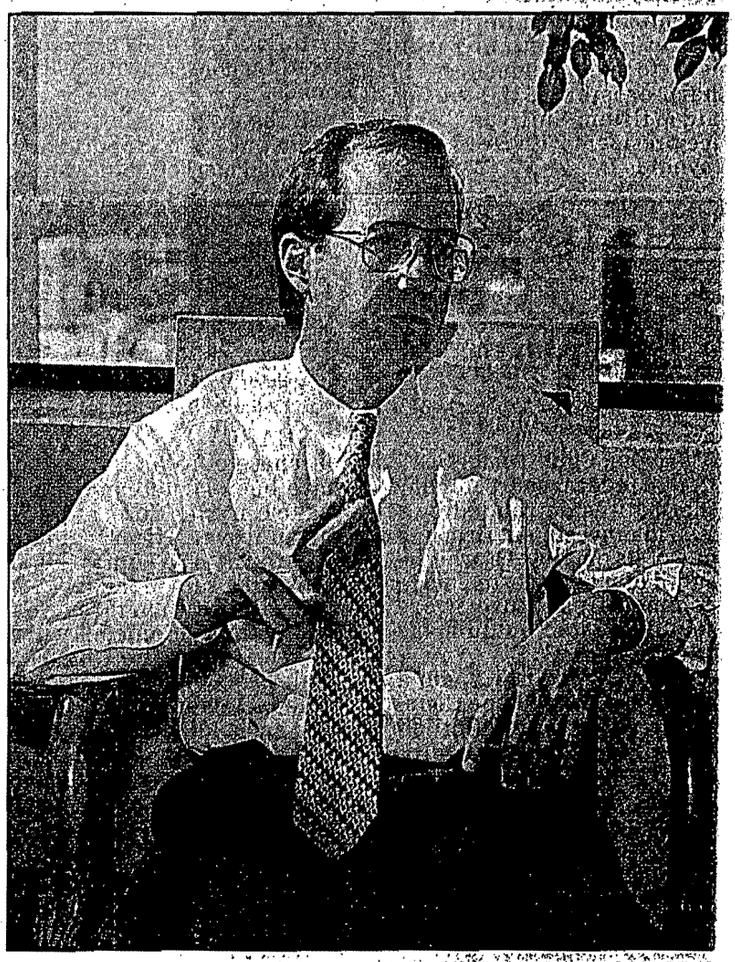
International markets may open soon for a Little Rock-based biomedical company that has developed a product it says can help prevent the spread of AIDS and other viruses.

In addition, ExOxEmis Inc. is near agreement with drug companies interested in licensing and distribution rights for the product, which will be marketed under the trade name Exact. The privately held company, which has its laboratories and manufacturing facilities in San Antonio, was founded by Little Rock investor Jackson T. Stephens Jr.

ExOxEmis is working with the National Institutes for Health to gain federal approval for the product, which is made up of the enzymes myeloperoxidase and eosinophil peroxidase. Four sites for experimenting in test tubes and animals have been set up, Stephens said. "Everything that has come out of that has been positive," he added.

Public sales in the United States could be about 18 months away, so Stephens said his company has been advised by the NIH to begin trying to get into international markets. "They said they thought it would be beneficial," he said Monday. "We have seen nothing that would temper our enthusiasm for the product."

International markets may not require the 18 months' approval time expected in the United States. "We may be able to beat that significantly by going to foreign markets," Stephens said.



Arkansas Democrat-Gazette/Mike St

**JACKSON T. STEPHENS JR.:** "It's hot right now and people want to kno there's something out there to combat AIDS."

More than two dozen countries, ranging from the African continent to Central and South America, are targets for the product. "We want to find out about the local customs and find out what would be the best way to use the product," Steph said. The enzymes, to com AIDS, can be packaged in m ways, including douch creams and suppositories. The product apparently

See STEPHENS, Pag

## Stephens

• Continued from Page 1D

gained some notice on its own without any benefit of aggressive marketing, according to Stephens, who said officials in Italy, Japan and the United Kingdom have contacted the company about the medication. "They contacted us to find out how to get it and how to use it," Stephens added. "It's hot right now and people want to know if there's something out there to combat AIDS."

Besides going public with its own product, ExOxEmis officials have been talking with drug companies about using the enzymes in their products. Those uses could range from infant formulas to eye-care solutions.

"We have a variety of companies that are interested in this," Stephens said.

Besides the primary focus on AIDS prevention, Exact could be used as a burn ointment, to treat acne or as an antiseptic. "There are lots of applications that we have yet to start with," he said. "But the ones we have tested, we have been tremendously successful."

The enzymes used in Exact have been known for years as effective anti-viral agents, but ExOxEmis is the first company to develop a process to produce it in bulk in a cost-effective manner. And Stephens said the company's goal is to keep costs down so the products can be sold to the general public. "It will be priced for over-the-counter use," he said. "Then we can make it well within the reach of everyone."

MEDIA WHO'S WHO

**BUYING POWER**

*Media Buyers Control Millions Of Dollars In Little Rock Ad Market*
*/ P. 18-19*

**AN EXACT SCIENCE**

*Jackson T. Stephens Jr.'s Company On Verge Of Drug Breakthrough*
*/ P. 14*

# ARKANSAS BUSINESS

VOLUME 9 NUMBER 35 AUGUST 31 - SEPTEMBER 6, 1992 1 DOLLAR

# An Exact Science

## Jackson T. Stephens Jr. And ExOxEmis On Verge Of Marketing Antiseptic Drug For AIDS Worldwide

**By Tim Taylor**
*Arkansas Business* Staff

ExOxEmis Inc.

You might as well learn how to pronounce it. It's going to be the talk of the medical world very soon.

ExOxEmis (*Ex-OX-amiss*) is a privately held biological company holding the key that could unlock the door to AIDS prevention.

The company, whose corporate office is in Little Rock, announced last week it would begin offering international distribution rights to two enzymes it markets under the trade name Exact.

Exact — the combination of myeloperoxidase and eosinphil peroxidase — has been documented to kill on contact the virus causing acquired immune deficiency syndrome. Besides being a preventive measure against AIDS, Exact is being promoted for its potential use in such applications as ophthalmic solutions, infant formulas, urinary tract lavages, burn ointments, feminine douches and suppositories.

"That's what we're excited about," says Jackson T. Stephens Jr., the chairman of ExOxEmis and founder of Stephens Enterprises Inc. "It has potentially widespread application. We think we have our hands around the most perfect antiseptic ever seen."

ExOxEmis, which has a laboratory and manufacturing facility in San Antonio, Texas, has approached health officials in several foreign countries including Zaire, Tanzania, Egypt, Saudi Arabia, France, Great Britain, Japan and Australia in regard to the distribution of the antiseptic.

While the two enzymes are currently being tested by the National Institutes of Health in Rockville, Md., for possible applications in three areas — human immunodeficiency virus, sexually transmitted diseases and respiratory ailments — ExOxEmis is pursuing domestic and international patents for the product.

Stephens expects approval on the patents within three months to a year.

The advantage Stephens and ExOxEmis have over possible competitors is the ability to produce the enzymes, very scarce until now, in mass quantities and at an affordable price.

The antiseptic properties of the enzymes have been documented for some time, but the extreme cost of manufacturing them on even a small scale has prevented any commercial or medical applications until now.

As a result of extensive research and development by ExOxEmis, founded by Stephens in 1987, a proprietary manufacturing process now exists that allows for the wholesale distribution of Exact.

Stephens' connection to the biological medicine field dates back seven years, when he was approached by Forrest Seale about financing the advancement of certain technologies Seale was scouting.

Seale, a San Antonio accounting executive with a background in marketing and manufacturing, and Stephens eventually formed MCLAS, a company designed to explore the technologies, which included an electronically activated penile implant and a bowling advertising and scoring system.

One of the technologies, a luminescent labeling system developed by the U.S. Air Force for diagnostic testing, was determined to be the most applicable. Although MCLAS was eventually dissolved, Seale and Stephens remained in a partnership and retained the rights to the luminescent labeling system.

ExOxEmis, short for excited oxygen emissions, was formed in October 1987 by Stephens and Seale, who brought aboard Robert C. Allen, then chief pathologist at an Army burn unit in San Antonio. It was Allen's research and documentation of the photon output of white blood cells during oxygenation that led to the production of Exact.

"Had we not gotten Dr. Allen, I probably would not have gone forward" with the manufacturing, says Stephens.


*Jeff Mitchell*

**LEAN AND CLEAN:** "We think we have our hands around the most perfect antiseptic ever seen," says Jackson T. Stephens Jr. of Exact, an anti-viral drug produced by his company, ExOxEmis Inc.

**Pathogen Killer**

Before Exact came on the scene, common household bleach was the only antiseptic known to kill the AIDS virus on contact. Other antiseptics, used in large enough concentrations, proved to damage both surrounding tissue and the immune system, making them useless.

Exact, using a chemical called singlet molecular oxygen that occurs during a high-energy chemical reaction, produces a "killing" property that is restricted by its short lifetime. Because of this, Exact's region of singlet molecular oxygen killing is restricted and thus damages only the pathogens to which it binds.

"It binds and kills specific pathogens while leaving normal tissue alone," explains Stephens, 40, the son of Little Rock financier Jackson T. Stephens.

"They're like smart bombs," he adds, "they go and kill pathogens preferentially," with various bacterium, viruses and yeast the targets of the "bombs."

Its ability to kill the AIDS virus will be a priority in discerning the various applications of Exact, Stephens says. The product could be developed as a douche or as an additive to creams, jellies or lubricants, and could also be used to coat donor blood bags as a means of preventing the spread of HIV and other blood-transmitted diseases.

"We plan to sell the enzymes to companies with existing product lines," says Stephens, referring to companies such as contact lens solution producers.

"We can use the enzymes in the solution to clean lenses," he says. "In the infant formula business, Exact may have a place as an additive to formula to help infants combat bacteria. And something we may do ourselves is manufacture the enzymes in suppository form or lozenge form, as a preventative to sexually transmitted diseases."

All of these markets could prove highly profitable for ExOxEmis and Stephens, who estimates having spent "well into eight figures" on the research and manufacturing of Exact and the company's other products.

With roughly $4 billion spent worldwide on ophthalmic products, more than $1 billion spent on infant formula in the U.S. and another $1 billion spent on condoms alone in this country, Exact could prove to be a boon to both the medical and business communities.

Exact is one of three product lines manufactured by ExOxEmis. Axis, already patented in the U.S., is a diagnostic testing system used to measure the systemic state of inflammation in the human body. Focus is a universal detection system for clinical chemistries, immunoassays and genetic probes.

But Exact is the company's present claim to fame. While ExOxEmis doesn't exactly roll off the tip of the tongue, Exact could very well become a household name. As part of the company's licensing arrangement, it will require each product using the enzymes to denote such with the Exact logo, just as Nutrasweet is in hundreds of products across the country.

"What we want to be is an enzyme supplier to companies in these markets," says Stephens. "It would be hard to sell this product if it wasn't 100 percent better than what they're using. And we believe it is." □

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
Bethesda, Maryland 20892

Solar Building
Room 2C22
(301) 496-0700

January 7, 1993

Jackson T. Stephens, Jr.
Chairman, ExOxEmis Inc.
1769 One Union National Plaza
Little Rock, Arkansas 72201

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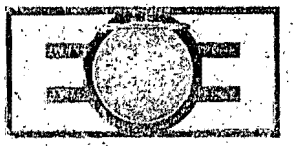
Sincerely,

Steven M. Schnittman, M.D.
Chief, Medical Branch
Division of AIDS
Clinical Research Program
National Institute of Allergy
and Infectious Diseases
National Institutes of Health

cc: Anthony S. Fauci, M.D.
Pat Reichelderfer, Ph.D.
Chuck Litterst, Ph.D.




J.T. Stephens, Jr.
*Chairman and Chief Executive Officer*

ExOxEmis, Inc.
18585 Sigma Road
San Antonio, Texas 78258

(512) 491-0757
FAX-(512) 491-0038
WATTS-1-(800) 527-3196

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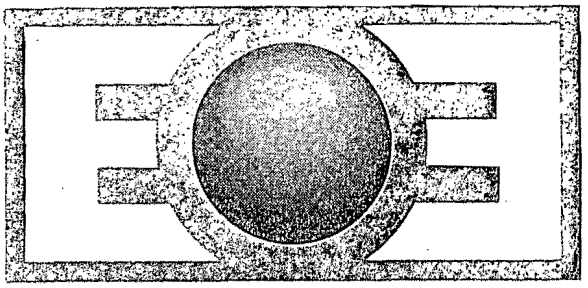

EXOXEMIS INC.