The Case of Missing Cofactors

"HIV is not the sole cause of AIDS" is an idea whose time has come and gone and come again. Now that the dream of eradication is dead, researchers are back on the cofactor scent. Bob Lederer reports.

April 1, 2000 By Bob Lederer

This spring, the protease era enters year five, and the bloom is off. While many people with AIDS are still flourishing on the drugs, dangerous side effects are popping up like mushrooms after a rainstorm, few promising treatments are in the pipeline, and even leading researchers have declared HIV eradication a mirage. Nagging questions from the earliest days of the epidemic are edging back into our consciousness: Why do some HIVers stay healthy for years, while others on the same meds get a major disease six months after HIV infection? And why do some people become infected the first time they encounter the virus, while others stay negative despite years of exposure?

Two books published this winter may bring some provocative answers into focus. Both Virus (W.W. Norton & Company), by distinguished French researcher and HIV co-discoverer Luc Montagnier, MD, and The Virus Within: A Coming Epidemic (Dutton), by award-winning medical journalist and ABC news producer Nicholas Regush, offer new evidence that AIDS may not be caused by HIV alone. Montagnier suggests that My- coplasma penetrans, a tiny bacterium, may play a central role in disease progression, while Regush points to reactivated hu- man herpes virus 6 (HHV-6). Both can in-fect the same CD4 cells as HIV and are just two of the many possible AIDS co-factors—microbes, nutritional deficiencies, psychological stresses and drugs—that may not only help establish the initial in- fection but spur HIV to reproduce and speed disease progression as well.

These books are unusual in an AIDS world that has largely adopted David Ho's slogan of "It's the virus, stupid" as its guiding principle. For years, the field has been polarized between establishment scientists who insist that HIV, time and perhaps your genes are all it takes to get sick and an increasingly shrill "AIDS dissident" movement, most famously re-presented by molecular biologist Peter Duesberg, PhD, whose adherents claim that HIV has nothing to do with AIDS, that the real culprits are recreational and prescription drugs, and that antiretrovirals are useless poisons (see "Don't Buy the HIV Lie").

"The debate has been cast in black-and-white terms," says Michigan State University physiology professor Robert Root-Bernstein, PhD. "HIV either is or isn't the cause, with nothing in between."

But Montagnier and several scientists cited in Regush's book are members of a third group that rejects the rigid positions of both sides. They accept that HIV plays a role in AIDS and welcome the advances of antiretroviral therapy, yet believe that the disease process is more complex than one virus killing CD4 cells. They argue that a small investment of funds to test their theories may set the stage for major treatment advances. And they are slowly gaining mainstream support.

back In 1981, after the first reports of rare infections and cancers in gay men, scientists were casting a broad net in search of explanations. No one model ruled. One theory for the immune problems was repeated exposure to sexually transmitted diseases (STDs); others ranged from cytomegalovirus (CMV) infection to the use, common among gay men, of amyl nitrites (poppers).

The first scientist to formulate a more comprehensive theory was Joseph Sonnabend, MD, a South African–trained physician with a distinguished background in microbiology and cancer research. By the late '70s, Sonnabend had become known to New York City gay men in the fast lane as a friendly, nonjudgmental doc willing to repeatedly treat STDs, often with fatherly advice about using condoms. Sonnabend drew from this experience to coauthor a May 1983 article, published in the Journal of the American Medical Association, that attributed AIDS—at least in gay men—to an overload of assaults on the immune system. His views were rooted in a long tradition of "multifactorial" medical theorists, who argue that the attack rate in all infectious diseases varies dramatically depending on multiple factors, including a person's immunity-injuring exposures. Among those Sonnabend cited in PWAs were repeated infections of CMV; reactivated Epstein-Barr virus (EBV), carried by most adults; and rectally deposited semen. Each factor fueled the others, Sonnabend proposed, creating a downward spiral that led to AIDS.

By this time, the immune-suppressive effects of CMV were well known to researchers, but throwing semen into the mix proved highly controversial within both the medical and gay communities. Researchers called the argument unfounded, and some gay writers branded Sonnabend homophobic. But several lab studies had recently found that semen, when enterring the bloodstream, could disrupt CD4-cell functioning, setting off autoimmunity—a kind of immune system civil war.

That year, two of Sonnabend's gay AIDS patients, singer Michael Callen and writer Richard Berkowitz, translated their doctor's multifactorial theory into a lay-language booklet, How to Have Sex in an Epidemic: One Approach. Coauthored with Sonnabend, the document laid the groundwork for the safer-sex guidelines that came to be universally accepted for AIDS prevention.

But as reports grew that the disease was striking such divergent groups as people with hemophilia, injection drug users, Haitian immigrants and Central Africans, funding was directed to uncovering a new infectious agent as the unifying cause. The same month in 1983 that Sonnabend's paper appeared, research teams led by Montagnier, a professor of virology at the Pasteur Institute in Paris, and by Robert Gallo, MD, then chief of the Tumor Cell Biology Lab at the National Cancer Institute (NCI), published evidence of just such a candidate in the blood of many PWAs. The following April, Gallo and federal health officials proudly announced that this new virus—later named HIV—had been found to be the "probable cause of AIDS."

Sonnabend publicly criticized the announcement as a rush to judgment. He argued that the virus was more likely an opportunistic infection in people whose immunity was compromised by other assaults. He expanded his own multifactorial model to include the hepatitis B virus, the bacterium that causes syphilis and immune-suppressive exposures to blood products, malnutrition and tropical diseases. “If you take the view that it’s just a germ, you don’t have to look at social conditions,” he said. “To make people well, you must eradicate poverty, hunger and ghettos.”

But HIV became king of the hill, and other AIDS theories were sent into exile.

Gallo’s patenting of the antibody test was quickly followed by the screening of the U.S. blood supply and the beginning of massive, worldwide HIV antibody testing. After a slow start, drug companies and the National Institutes of Health (NIH) began the drive—eventually a multibillion-dollar industry—to produce effective antiretrovirals. By early 1987, the Food and Drug Administration had licensed AZT and cofactor research virtually disappeared. “Orthodoxy can develop overnight,” Sonnabend says. “Once there, it usually stays for a very long time.”

The first challenge to that orthodoxy was quick in coming. In March 1987, Duesberg, a retrovirus specialist at the University of California at Berkeley and a former colleague of Gallo’s, jolted researchers with an article in Cancer Research laying out what he considered to be the serious flaws in the case for HIV’s causative role in AIDS. His argument exploited what then seemed to be a glaring weakness in the HIV advocates’ position: How could a virus kill so many CD4 cells when it seemed to infect so few of those cells? HIV, Duesberg concluded, was a “harmless passenger virus.” At a time when AZT was PWAs’ greatest hope, he called use of the drug unjustified and dangerous.

“The only cofactor is time,” Gallo responded flatly. “Everyone with HIV will eventually get AIDS and die.” When Duesberg testified before President Reagan’s AIDS commission in 1988, the only scientist on the panel called his statements “irresponsible” and accused him of “confusing the public.”

The commission appearance was Duesberg’s opening salvo in a new career of defiant public campaigning that inspired passionate support from some PWAs—and vilification by others. Activist Callen, a founder of several PWA organizations, synthesized Duesberg’s and Sonnabend’s arguments and became a tireless critic of the AIDS research establishment until his death in 1993. In the late ’80s and early ’90s, the debate roiled the gay press, and a variety of dissident thinkers—scientists, doctors and community advocates—became loose allies. “What united us then was a rejection of a categorical assertion that the cause of AIDS had been found,” Sonnabend recalls, “not a firm belief in some other theory.”

Sonnabend is referring to Duesberg’s 1990 declaration—now his mantra—that “the true causes of AIDS” are heroin, cocaine, poppers and AZT. All of these, Duesberg claimed, could sufficiently suppress immunity to cause AIDS, and every gay PWA, he insisted, had used at least one of them chronically. Most incendiary was his firm assertion that AIDS was not infectious. “Sex has never killed anyone,” he became fond of repeating.

Denunciations of Duesberg's views soon came from within dissident ranks. In 1992, at a well-attended Alternative AIDS Conference in Amsterdam, Sonnabend and Callen released a petition signed by prominent participants denouncing Duesberg for dangerously undermining safer-sex campaigns. Duesberg's supporters responded with a counterpetition. After that, the two factions went their separate ways.

Meanwhile, Root-Bernstein, the Michigan physiologist, was developing his own critique of conventional AIDS theory. The bookish lab scientist had been researching multiple sclerosis, an autoimmune disease, at San Diego's Salk Institute. He won a MacArthur "genius" award in 1981, which freed him to develop a general theory of autoimmunity.

Within six years, he says, it was clear that "the high rate of autoimmune diseases among PWAs meant that someone might have a good chance of figuring out autoimmunity by studying AIDS." In 1987, "frustrated by the fact that no one was doing the needed experiments," he began doing his own. In 1993, he published Rethinking AIDS: The Tragic Cost of Premature Consensus (Free Press), a 500-page, heavily footnoted review of the major cofactor theories, lauded by a then-dying Callen as "the most important AIDS book ever." Among Root-Bernstein's many arguments for investigating such theories is the extreme disparity in time periods from HIV infection to full-blown AIDS among different groups: for young hemophiliacs, 20-plus years; for gay men, 10 years; and for infants infected at birth, six months. "Each risk group has widely different exposure rates to infectious diseases, antibiotic use, immune-damaging drugs, nutritional deficiencies, blood products and semen," Root-Bernstein wrote. He called for tests to sort out the best theories, saying the results could pro-vide "the surprises that make doing science worthwhile."

One of those surprises is offered in the new book by Montagnier, the patrician French AIDS researcher who famously fought Gallo for shared credit for the discovery of HIV. In Virus, which came out in January, Montagnier explains that a newly discovered species of mycoplasma called penetrans may be a key cofactor in AIDS. First isolated by Shiyh-Ching Lo, MD, a researcher at the U.S. Armed Forces Institute of Pathology in Washington, DC, this tiny bacterium is present far more frequently in HIVers than in HIV negative people on three continents and can accelerate AIDS progression, according to 25 research papers cited by Montagnier.

In Virus, he writes that "a kind of synergy" between this mycoplasma and HIV may cause immune-system damage in PWAs—much as other virus-mycoplasma duos cause encephalitis in goats and leukemia in mice.

In 1990, when Montagnier an- nounced that tetracycline (a common antibiotic) had been shown in test tubes to inhibit HIV's killing effect by attacking this mycoplasma, he was widely ridiculed by leading AIDS researchers. Ultimately, his experiments with antibiotics in PWAs—which, he writes, "prevent mycoplasmas from multiplying but do not kill them"—helped only a few people. "As with other infections, if the immune system is incapable of finishing the job, antibiotics are not enough to fully eliminate a mycoplasma infection." So Montagnier's search for effective treatments continues, as do his broader epidemiological studies.

Montagnier emphasizes in his book that “it is quite possible that other cofactors, such as viruses and bacteria, are to blame” for disease progression in HIVers. One of those he cites specifically is HHV-6, which infects millions of people worldwide. Regush’s The Virus Within, out this month, presents growing evidence that reactivation of this virus—which, unlike HIV, has been demonstrated to directly destroy CD4 cells—may play a critical role in AIDS, chronic fatigue syndrome and some neurological conditions. “At the very least,” Regush writes, HHV-6 may “reawaken from dormancy to attack…components of the immune system, thus triggering, or contributing to, disease.” Regush narrates the medical detective story of two young Wisconsin pathologists, Donald Carrigan, PhD, and Konstance Knox, PhD, who, working on a shoestring budget, published numerous studies demonstrating HHV-6’s destructive power. Even though the virus has quite a pedigree, writes Regush, the two mostly labored in obscurity, as promising anti-HHV-6 drugs languished in the pipeline.

HHV-6 had been discovered in Gallo’s NCI lab in 1986, and the HIV maven quickly saw the new virus’ potential role as an AIDS cofactor. At a 1988 AIDS conference, he announced test-tube findings that HHV-6 killed CD4 cells more effectively than did HIV. By increasing HIV replication, “HHV-6 may accelerate progression of AIDS,” read a 1989 NCI press release. As Gallo’s lab continued to examine HHV-6, Carrigan and Knox picked up the trail. By 1995, they had accumulated a mountain of lab evidence of the virus’ destructive role in PWAs—not only killing CD4s, but also inducing fatal lung and brain infections and liver failure. In a presentation the previous year at Gallo’s annual research update, Knox said that if clinical studies backed up the lab data, AIDS might prove to be “a combination of HIV disease and HHV-6 disease.”

But, skeptics asked, couldn’t all this simply mean that HHV-6 was yet another lethal OI, rather than a cause of the immune destruction underlying AIDS? Furthermore, since HHV-6 was so widespread among people of all types, why would an AIDS-spe- cific role make sense? To answer these ques-tions, Knox and Carrigan built on 1995 NIH findings that a key marker of HIVers who progressed to AIDS was lymph node destruction. Despite HIV’s presence in lymph tissue, no evidence had ever been found that the virus was actually killing CD4 cells there, leading even mainstream researchers to speculate about indirect mechanisms of destruction. Carrigan and Knox compared lymph samples of nonprogressors to those from their own AIDS patients, including from autopsies. All 16 HIVers— whose health ran the gamut from 700 CD4 cells to full-blown AIDS to death—showed active replication of HHV-6 subvariant A, a strain found to be much more common among HIVers than among other groups. Knox says, “We found that the tissues with the most destruction had by far the most HHV-6A, and the tissues from the nonprogressors had very little.” Here, finally, was evidence that a virus other than HIV could directly damage CD4s.

The case for the role of HHV-6 and Mycoplasma penetrans as AIDS cofactors seems strong, and they are not the only candidates. (See “Just the Cofactors, Ma’am” below .) It is widely accepted that many viruses, bacteria and parasites present in HIVers cause the CD4-cell activation (stimulation) that can prompt HIV to replicate and do damage. While mainstream theorists argue that HIV can activate CD4s on its own, lab studies show that when CD4 cells from a healthy person are exposed to HIV, the virus quickly becomes latent or disappears. Only when other microbes—that is, cofactors—are added to the test-tube mix does HIV reproduce.

Along these lines, a prior history of syphilis was found in human studies to be the best predictor of both HIV seroconversionand disease progression. Root-Bernstein's theory, based on extensive lab work, is that a variety of microbe combinations (as well as someone else's blood or semen) confuse the immune system, triggering the autoimmune complications—nearly universal among PWAs—that kill CD4s.

Other researchers suggest that a number of cofactors—including many microbes, certain street and pharmacy drugs, and specific vitamin and mineral deficiencies—may promote disease progression by generating oxidative stress, a process by which the body produces "free radicals" (unstable electrons) that cause serious cell damage. Oxidative stress has been found to boost HIV replication and to lower CD4 counts. "Much of what we have taken to be evidence of immune impairment caused by HIV infection," Root-Bernstein says, "may in fact be the result of non-HIV processes."

Root-Bernstein radiates a kind of missionary zeal when he talks about the need for research to clarify the role of each proposed cofactor in HIV infection and AIDS. He recommends studies of people exposed to HIV without seroconverting and people exposed to immunosuppressive agents, as well as comparison studies of long-term survivors and HIVers who progress to AIDS.

He also proposes new research into antiretrovirals. Intriguing evidence from lab studies suggests that certain AIDS drugs, such as ddI and 3TC—whose benefits are thought to come from their anti-HIV properties—also block replication of hepatitis B and EBV. "That makes you wonder if the drugs are working by reducing the HIV viral load, the cofactor load or both," Root-Bernstein says. Most antiretrovirals have not been studied for their effects on potential cofactors, but he argues that quick, inexpensive lab studies could help doctors to choose more effective drug combos for their AIDS patients.

In the seven years since Root-Bernstein published his groundbreaking book, the AIDS landscape has changed dramatically. HIV research has produced significant evidence that the virus is the key player in AIDS. By the mid-'90s, new viral load tests found that large quantities of HIV predicted disease progression. Ho's theory, announced in 1995, that from the earliest days of infection billions of viruses battled billions of CD4 cells until the CD4s were exhausted, offered at least a partial answer to Duesberg's longstanding challenge about CD4 cell death. And strong evidence that protease inhibitors have rescued some PWAs from the brink of death was the icing on the cake.

All of these findings have led Root-Bernstein and many other cofactor theorists to move a bit closer to the mainstream position, and to further distance themselves from Duesberg and his allies. "People have pretty well demonstrated that HIV is an essential player in AIDS caus-ation," Root-Bernstein now says. Sonnabend agrees, adding with exasperation, "The 'AIDS dissidents' have become as dogmatic as the establishment people I criticized in the early '80s."

And ever so slowly, mainstream AIDS researchers are accepting the idea that some cofactors may play a role in disease progression. In an e-mail to POZ, a spokesperson for the Division of AIDS at

the National Institute of Allergy and Infectious Diseases wrote, “Some infections associated with ongoing immune activation clearly accelerate the progression of HIV disease.” The note went on to say, “Deficiencies of vitamins A, E, B6 and B12, as well as zinc and selenium, have been associated with increased risk of disease and death in HIV infection.”

Leading AIDS researchers at the Centers for Disease Control and Prevention now offer similar views, and even Gallo has lightened up a bit. He now says, “Some of Joe Sonnabend’s postulations catalyzed us to move faster” in studying the immune system’s response to HIV. As for his 1987 repudiation of AIDS cofactors, Gallo now says, “I was brasher and younger then.” He still argues that no cofactor is necessary for AIDS, but says he believes several may contribute to disease progression.

Still, there is a disconnect between the encouraging words of these leading scientists and institutional priorities, which have left most cofactor researchers high and dry. “Scientists generally do not change or broaden theories,” Regush writes, “in which they have invested so much effort.” For example, in June 1996, HHV-6 researchers Carrigan and Knox submitted their lymph findings to the prestigious British medical journal Lancet, “but our timing turned out to be miserable,” Knox recalls. Two weeks later, at the International AIDS Conference in Vancouver, the news of protease-based therapies—along with Ho’s prediction of imminent viral eradication—took the AIDS world by storm. “We ran full bore into the excitement over new HIV drugs,” Knox says. After an unusual four-month delay, the Lancet rejected the HHV-6 paper. Between the changing research climate and difficulties making ends meet, the two HHV-6 investigators shelved their AIDS research, setting up a research foundation partly funded by grants to study MS and chronic fatigue. Even Gallo has had trouble finding funds to continue HHV-6 research through his Institute of Human Virology, which now maintains only one half-time researcher in this area.

It is a pattern familiar in cofactor research. As Montagnier writes in Virus, “It is a deplorable fact that...the number of researchers interested in this line of investigation worldwide barely exceeds the number of fingers on both hands.”

A few doggedly persistent investigators have continued their probes, with exciting results. In 1998, Root-Bernstein and Steve Merrill, PhD, a professor of mathematics at Marquette University in Milwaukee, published a new mathematical model of the risk of developing HIV infection. That article concluded, “If cofactors are absent, no infection by HIV is possible if the dose of virus is small (such as via a needlestick). Moreover, with increasing cofactor load, susceptibility to HIV increases.” Sonnabend points to a 1999 study showing that many people exposed to HIV exhibit an immune response, yet never form antibodies or get sick, further supporting the notion that other factors determine infection. Another 1999 study found that degree of CD4-cell activation can predict death better than can viral loads, suggesting a role for CD4-activating cofactors. “If anything, the case has grown stronger,” says Root-Bernstein.

Knox says the time may finally be ripe, with the widespread antiretroviral-related problems of lipodystrophy, heart disease and viral resistance, to test the waters again for AIDS-related work on HHV-6. “We started thinking, ‘Gee, maybe now people will be more interested in coming at this

disease from another angle.' So we're dusting off our old data and preparing to submit it elsewhere."

Ultimately, the HHV-6 findings may open the door to an even more far-out theory of AIDS. According to Regush, several scientists have made discoveries suggesting the following scenario: Toxic attacks from microbes, drugs or other sources injure immune-system and brain cells, releasing into the bloodstream fragments of the body's internal retroviruses (genetic material, harmless in its latent state, born of ancient viral infections). HIV, the theory says, is one of those fragments—and once released, it begins to harm immune cells and perhaps reactivate powerful dormant viruses such as HHV-6. Investigation of this explosive theory is still in the very early stages.

Perhaps the release of Regush's The Virus Within will boost the efforts of cofactor theorists to attract funds for their AIDS research. That's certainly Root-Bernstein's hope. "Specific research protocols need to be set up to test the alternative theories and to compare their relative merits," he says. "So much effort has been put into understanding HIV that almost none has been put into studying how people survive or defeat it. I believe it is time to turn the tables."

JUST THE COFACTORS MA'AM

10 Steps You Can Take to Limit Immune Damage

Scientists are pushing for more studies of cofactors, but a mountain of evidence is already in: Microbes, deficiencies and stresses can all hasten progression to AIDS, while reducing them can do the opposite. Last year, in the first findings on a comprehensive "cofactor elimination" program, Jon Kaiser, MD, an AIDS physician in San Francisco, reported improvements in the lab numbers and health of patients for whom he diagnosed and treated immune-damaging exposures. The following come recommended by experts, but many may already be familiar to the HIV positive guy or girl on the go:

Follow safer-sex and clean-needle guidelines. This will help protect you from exposure or re-exposure to dangerous microbes, including HIV and a range of STDs, as well as to immune-suppressive semen and blood. Consistent practice has been found to decrease AIDS progression.

Use hygienic practices with food, water and sex. Intestinal parasites and food-poisoning bacteria can activate CD4 cells and speed progression (see "Bug Bugaboo, *POZ*, August '99; "Message in a Bottle," *POZ*, September '99). To limit exposure, handle food hygienically, choose water sources carefully and avoid contact with others' feces.

Test for and treat intestinal parasites. An estimated 40 percent of HIVers are infected with these immunity-damaging bugs, which require thorough testing to uncover.

Take preventive meds for opportunistic infections (OIs), if at risk. OIs heighten the risk of overall AIDS progression. Federal guidelines recommend preventive drugs for those whose CD4 counts fall

below a particular mark or who have had prior bouts of OIs. In addition, since uncontrolled studies show life extension for PWAs who take acyclovir (Zovirax), some doctors recommend all HIVers take this drug to suppress a variety of common herpes viruses.

Reduce or stop use of cocaine, heroin, poppers, alcohol and cigarettes. Cocaine and heroin, when used long term, are strong immune-suppressants and cause disease progression. Since the earliest days of AIDS, studies have indicated that heavy use of poppers correlates with high rates of Kaposi's sarcoma. Some evidence suggests that limiting intake of all of these toxins—which generate CD4-activating oxidative stress—may slow AIDS progression.

Improve diet and take nutritional supplements. Certain vitamin and mineral deficiencies—near-universal in HIVers—likely speed disease progression and death. Countering these shortfalls appears to extend lifespan, by supporting immune function and reducing oxidative stress (see "You Are What You Eat").

Supplement deficient hormones. DHEA deficiency may speed disease progression, and testosterone lack can cause some AIDS symptoms. Get both measured twice yearly and replace if needed.

Look after your mental health. Chronic psychological stress has been found to promote disease progression, damaging CD4 and other immune cells through hormonal pathways (see "Emotional Rescue," *POZ*, September '99). Several pilot projects using combinations of yoga, meditation, exercise, individual counseling and social support have found modest improvements in participants' immune status. Treating depression has been shown to improve survival odds for PWAs.

Minimize immune-damaging medical interventions. Various antibiotics, antiparasitics, cortisone injections, corticosteroids and tranquilizers are known to cause short-term immune suppression. While many medical interventions are unavoidable for HIVers, there are alternatives to some. Avoid chronic use of these drugs (except anti-biotics for prophylaxis). For less serious conditions, consider an alternative practitioner.

People with hemophilia: Change to high-purity or genetically engineered clotting factor. These products have been shown to stabilize or increase CD4 counts, probably by limiting exposure to harmful cytokines (immune-system messenger chemicals) produced when CD4 cells are activated by infections

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