Only weeks before the great conquistador Hernan Cortes seized control of Tenochtitlan (Mexico City) in 1521, his forces were on the verge of defeat. The Aztecs had repeatedly repelled the invaders and were preparing a final offensive. But the attack never came, and the beleaguered Spaniards got an unlikely chance to regroup. On Aug. 21 they stormed the city, only to find that some greater force had already pillaged it. "I solemnly swear that all the houses and stockades in the lake were full of heads and corpses," Cortes's chronicler Bernal Diaz wrote of the scene. "It was the same in the streets and courts.... We could not walk without treading on the bodies and heads of dead Indians. I have read about the destruction of Jerusalem, but I do not think the mortality was greater there than here in Mexico.... Indeed, the stench was so bad that no one could endure it ... and even Cortes was ill from the odors which assailed his nostrils."

The same scent followed the Spaniards throughout the Americas. Many experts now believe that the New World was home to 40 million to 50 million people before Columbus arrived and that most of them died within decades. In Mexico alone, the native population fell from roughly 30 million in 1519 to 3 million in 1568. There was similar devastation throughout the Caribbean islands, Central America and Peru. The eminent Yale historian David Brion Davis says this was "the greatest genocide in the history of man." Yet it's increasingly clear that most of the carnage had nothing to do with European barbarism. The worst of the suffering was caused not by swords or guns but by germs.

Contrary to popular belief, viruses, bacteria and other invisible parasites aren't designed to cause harm; they fare best in the struggle to survive and reproduce when they don't destroy their hosts. But when a new germ invades a previously unexposed population, it often causes devastating epidemics, killing all but the most resistant individuals. Gradually, as natural selection weeds out the most susceptible hosts and the deadliest strains of the parasite, a sort of mutual tolerance emerges. The survivors repopulate, and a killer plague becomes a routine childhood illness. As University of Chicago historian William McNeill observes in his book "Plagues and Peoples," "The more diseased a community, the less destructive its epidemics become."

By the time Columbus set sail, the people of the Old World held the distinction of being thoroughly diseased. By domesticating pigs, horses, sheep and cattle, they had infected themselves with a wide array of pathogens. And through centuries of war, exploration and city-building, they had kept those agents in constant circulation. Virtually any European who crossed the Atlantic during the 16th century had battled such illnesses as smallpox and measles during childhood and emerged fully immune.

By contrast, the people of the Americas had spent thousands of years in biological isolation. Their own distant ancestors had migrated from the Old World, crossing the Bering Strait from Siberia into Alaska. But they traveled in bands of several hundred at most. The microbes that cause measles, smallpox and other "crowd type" diseases require pools of several million people to sustain themselves. By the time Columbus arrived, groups like the Aztecs and Maya of Central America and Peru's Incas had built cities large enough to sustain major epidemics. Archeological evidence suggests they suffered from syphilis, tuberculosis, a few intestinal parasites and some types of influenza (probably those carried by waterfowl). Yet they remained untouched by diseases that had raged for centuries in the Old World. When the newcomers arrived carrying mumps, measles, whooping cough, smallpox, cholera, gonorrhea and yellow fever, the Indians were immunologically defenseless.
The Great Disease Migration

The disaster began almost as soon as Columbus arrived, fueled mainly by smallpox and measles. Smallpox—the disease that so ravaged Tenochtitlan on the eve of Cortes's final siege—was a particularly efficient killer. Alfred Crosby, author of "The Columbian Exchange," likens its effect on American history to "that of the Black Death on the history of the Old World." Smallpox made its American debut in 1519, when it struck the Caribbean island of Santo Domingo, killing up to half of the indigenous population. From there outbreaks spread across the Antilles islands, onto the Mexican mainland, through the Isthmus of Panama and into South America. The Spaniards were moving in the same direction, but their diseases often outpaced them. "Such is the communicability of smallpox and the other eruptive fevers," Crosby notes, "that any Indian who received news of the Spaniards could also have easily received the infection."

By the time the conquistadors reached Peru in the 1520s, smallpox was already decimating the local Incan civilization and undermining its political structure. The empire's beloved ruler, Huayna Capaj, had died. So had most of his family, including the son he had designated as his heir. The ensuing succession struggle had split the empire into two factions that were easily conquered by Francisco Pizarro and his troops. "Had the land not been divided," one Spanish soldier recalled, "we would not have been able to enter or win."

Smallpox was just one of many afflictions parading through defenseless communities, leaving people too weak and demoralized to harvest food or tend their young. Some native populations died out altogether; others continued to wither for 100 to 150 years after surviving particularly harsh epidemics. The experience wrought irrevocable changes in the way people lived.

Persuaded that their ancestral gods had abandoned them, some Indians became more susceptible to the Christianity of their conquerors. Others united to form intertribal healing societies and Pan-Indian sects. Marriage patterns changed, too. In North America most pre-Columbian Indians lived in communities of several hundred relatives. Tradition required that they marry outside their own clans and observe other restrictions. As populations died off and appropriate marriage partners became scarce, such customs became unsustainable. People had two choices, says University of Washington anthropologist Tsianina Lomawaima. They could "break the rules or become extinct." Occasionally, whole new tribes arose as the survivors of dying groups banded together. The epidemics even fueled the African slave trade. "The fact that Africans shared immunities with Europeans meant that they made better slaves," says anthropologist Charles Merbs of Arizona State University. "That, in part, determined their fate."

The great germ migration was largely a one-way affair; syphilis is the only disease suspected of traveling from the Americas to the Old World aboard Spanish ships (box). But that does not diminish the epochal consequences of the exchange. Columbus's voyage forever changed the world's epidemiological landscape. "Biologically," says Crosby, "this was the most spectacular thing that has ever happened to humans."

That isn't to say it was unique. Changes in human activity are still creating rich new opportunities for disease-causing organisms. The story of AIDS—an affliction that has emerged on a large scale only during the past decade and that now threatens the stability and survival of entire nations—is a case in point. No one knows exactly where or how the AIDS virus (HIV) was born. Many experts
suspect it originated in central Africa, decades or even centuries ago, when a related virus crossed from monkeys into people and adapted itself to human cells.

Like venereal syphilis, AIDS presumably haunted isolated communities for hundreds of years before going global. And just as sailing ships brought syphilis out of isolation during the 16th century, jet planes and worldwide social changes have unleashed AIDS in the 20th. War, commercial trucking and the growth of cities helped propel HIV through equatorial Africa during the 1960s. And when the virus reached the developed world during the 1970s, everything from changing sexual mores to the rise of new medical technologies (such as blood transfusion) helped it take root and thrive.

AIDS won't be the last pandemic to afflict humankind. As the Columbian Exchange makes clear, social changes that spawn one epidemic tend to spawn others as well. Researchers have documented outbreaks of more than a dozen previously unknown diseases since the 1960s. Like smallpox or syphilis or AIDS, most seem to result from old bugs exploiting new opportunities. "What's happening today is just what we've been doing for thousands of years," Crosby says. "Bit by bit by bit, we're getting more homogenized. In the Middle Ages the population got big enough to send out a boat and bring back the Black Death. Columbus brought together two worlds that were a huge distance apart. People were living side by side, then elbow to elbow. Soon we'll be living cheek to cheek. Everybody's diseases will be everybody else's diseases."