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Unintelligent Design

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A monstrous discovery suggests that viruses, long regarded as lowly evolutionary latecomers, may have been the precursors of all life on Earth

by Charles Siebert, Photography by Jörg Brockmann

Few things on Earth are spookier than viruses. The very name virus, from the Latin word for "poisonous slime," speaks to our lowly regard for them. Their anatomy is equally dubious: loose, tiny envelopes of molecules—protein-coated DNA or RNA—that inhabit some netherworld between life and nonlife. Viruses do not have cell mb embranes, as bacteria do; they are not even cells. They seem most lifelike only when they invade and co-opt the machinery of living cells in order to make more of themselves, often killing their hosts in the process. Their efficiency at doing so ranks them among the most fearsome killers: Ebola virus, HIV, smallpox, flu. Yet they go untouched by antibiotics, having nothing really biotic about them.

Bernard La Scola peers into an electron microscope in his laboratory in Marseille, France.

The existence of viruses was first surmised just over a century ago by Dutch botanist Martinus Beijerinck. He mashed up disease-riddled tobacco leaves and then passed the juicy pulp through a porcelain filter fine enough to trap everything down to the tiniest bacteria. When even that filtered fluid infected other plants, a world still acclimating to Louis Pasteur's germ theory now had an even tinier class of pathogens to contemplate. Here were entities so wraithlike that they remained unseen until 1935, when scientists armed with the newly invented electron microscope managed to take a picture of the "poison" lurking in Beijerinck's slime, today known as tobacco mosaic virus.

Less an organism than a jumbled collection of biochemical shards, the virus eventually yielded Wendell M. Stanley, the leader of the research team that exposed it, a Nobel Prize in chemistry rather than biology. The discovery also set off an intense scientific and philosophical debate that still rages: What exactly is a virus? Can it properly be described as alive? " 'Life' and 'living' are words that the scientist has borrowed from the plain man," the British virologist Norman Pirie wrote at the time. "Now, however, systems are being discovered and studied which are neither obviously living nor obviously dead, and it is necessary to define these words or else give up using them and coin others."

Seventy years later, the challenge continues to haunt science. So "other" are viruses that we're still trying to corral them with new metaphors: microzombies, pirates of the cell, submicroscopic hijackers. But even the more restrained characterizations betray a long-standing prejudice. Most biologists typically recognize three official branches of life: the eukaryotes, which are organisms whose cells have a nucleus; bacteria, the single-celled organisms that may or may not possess a nucleus; and archaea, an ancient line of microbes without nuclei that may make up as much as a third of all life on Earth (See "Will the Methane Bubble Burst?" Discover, March 2004). Viruses, being dependent on these organisms to host them, are viewed as evolutionary latecomers: genomic scraps that fell out onto the floor back when life was assembling itself into more complex arrangements.

Bacteriologist Bernard La Scola first identified Mimivirus, the largest known virus, in 2003. Although Mimi infects only amoebas, many of its kin pose a direct threat to humans.

The sheer prevalence of viruses, however, is forcing a reconsideration about how these entities fit into the biological world. Researchers have characterized some 4,000 viruses, from several dozen distinct families. Yet that is a tiny fraction of the number of viruses on Earth. In the last two years, J. Craig Venter, the geneticist who decoded the human genome, has circled the globe in his sailboat and sampled ocean water every couple of hundred miles. Each time he dipped a container overboard, he discovered millions of new viruses—so many that he increased the number of known genes 10-fold. Although we tend to think of viruses only in terms of the damage they do, a broader and more benign picture is emerging. Scientists estimate that they have discovered and documented less than 1 percent of all the living things on the planet. But for every organism in that unidentified 99 percent, at least 10 times as many unknown viruses are thought to exist—the vast majority of which are harmless to life and yet integral to it.

Now, with the recent discovery of a truly monstrous virus, scientists are again casting about for how best to characterize these spectral life-forms. The new virus, officially known as Mimivirus (because it mimics a bacterium), is a creature "so bizarre," as The London Telegraph described it, "and unlike anything else seen by scientists . . . that . . . it could qualify for a new domain in the tree of life." Indeed, Mimivirus is so much more genetically complex than all previously known viruses, not to mention a number of bacteria, that it seems to call for a dramatic redrawing of the tree of life.

"This thing shows that some viruses are organisms that have an ancestor that was much more complex than they are now," says Didier Raoult, one of the leaders of the research team at the Mediterranean University in Marseille, France, that identified the virus. "We have a lot of evidence with Mimivirus that the virus phylum is at least as old as the other branches of life and that viruses were involved very early on in the evolutionary emergence of life."

That represents a radical change in thinking about life's origins: Viruses, long thought to be biology's hitchhikers, turn out to have been biology's formative force.

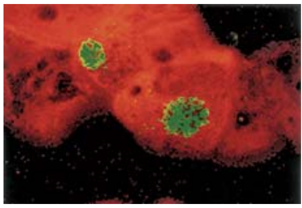
This is striking news, especially at a moment when the basic facts of origins and evolution seem to have fallen under a shroud. In the discussions of intelligent design, one hears a yearning for an old-fashioned creation story, in which some singular, inchoate entity stepped in to give rise to complex life-forms—humans in particular. Now the viruses appear to present a creation story of their own: a stirring, topsy-turvy, and decidedly unintelligent design wherein life arose more by reckless accident than original intent, through an accumulation of genetic accounting errors committed by hordes of mindless, microscopic replication machines. Our descent from apes is the least of it. With the discovery of Mimi, scientists are close to ascribing to viruses the last role that anyone would have conceived for them: that of life's prime mover.

The green hallways of the second-floor Rickettsia Unit at the Mediterranean University constitute what might be called an archive of agony. Stored there on freezer shelves behind a series of locked lab doors is an array of bacterial pathogens that have been caught and identified by the unit's crack detectives over the years. Rickettsia, the microbe that causes such diseases as typhus and Rocky Mountain spotted fever, resides there alongside many others, from Salmonella to strains of Legionella, a bacterium that causes a severe pneumonia-like disease in humans and was first identified following an outbreak at an American Legion convention in Philadelphia in 1976.

In the early spring of 2003, amid the familiar cast of microbial villains, Bernard La Scola, a bacteriologist at the unit, came upon something that none of his colleagues had ever seen. Focusing his electron microscope on a sample of what he assumed would prove to be an elusive new strain of Legionella, La Scola found himself staring instead at a viral monster.

"I went, 'Whoa,' " he recalls. On his computer he brings up an image, magnified 200,000 times, of the creature: a bug-eyed, hexagonal smurf with a head of electrified hair. That's but one of its looks. In three-dimensional imaging it appears more like a soccer ball. La Scola recognized both shapes as classically viral. Viruses seem to crave such crystal-like geometry, which is one of many reasons they've been thought of as more chemical than biological.

"I'm a bacteriologist," he says. "I don't think in terms of viruses, but this thing was way too big for that. So I called a friend of mine in the faculty of virology, and he came and looked at it and said, 'Oh, yes, it is a virus, but the size . . . ' "


Mimi, the largest known virus.

While there is some evidence to suggest that it may have once caused a type of pneumonia in humans, Mimivirus now seems to infect only amoebas. Until its positive identification in 2003, it was known as Bradfordcoccus and falsely suspected as the cause of a 1992 pneumonia outbreak in the West Yorkshire mill town of Bradford, England. That was where Mimivirus was first found, hiding inside an amoeba at the base of an industrial cooling tower. Cooling towers—along with evaporative condensers, riparian soil, tap water, showerheads, and treated sewage—are all hangouts of Legionella. And amoebas, as Timothy Rowbotham, a former disease detective with Britain's Public Health Laboratory Service, discovered back in 1992, are an ideal tool for collecting Legionella. In the ongoing to and fro between the world's microbes, amoebas are a nearly indomitable foe, gobbling up nearly everything in their path. Legionella, however, turns the tables on amoebas, rendering them both a food source and a perfect lab culture for microbe hunters.

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Rowbotham was unable to identify a number of the samples he collected in 1992, and he stored the mystery cultures in his lab freezer for future research. When budget cuts forced the closure of his lab in 1998, he had the presence of mind to call around and ask fellow scientists if they would be interested in any of the critters in his fridge. He had recently met Didier Raoult, he recalls, "and when I told him on the phone about the cooling tower cultures, he said he'd love those systems."

A student of Rowbotham's who had just accepted a postdoc position in Raoult's lab in Marseille took the samples south with him. Four new strains of Legionella would eventually be drawn out and identified at Raoult's lab, along with new bacteria closely related to Chlamydia, parasitic bacteria that, like Legionella, cause a variety of diseases. One last sample, however, defied all methods of examination for more than a year and a half, until La Scola turned his high-powered scope on the last Bradford holdout: Mimivirus.

In addition to its signature viral shape, Mimi exhibited what is known as an eclipse phase, a bit of telltale viral creepiness recognizable to any fan of sci-fi horror movies. When a virus penetrates a cell, it disappears inside the nucleus for four to eight hours, giving the outward appearance of complete normalcy. Then the viral particles that the cell has been coerced into making suddenly burst forth, shattering the host.

Still, it wasn't until Raoult sought the assistance of Jean-Michel Claverie, a bioinformatics specialist at the Institute of Structural Biology and Microbiology in Marseille, that the true weirdness and wonder of their monster was revealed.

At about a half-millionth of a meter across, Mimi is one of the few viruses visible under a standard light microscope. Its genome weighs in at a whopping 1.2 million letters: at least 10 times larger than a typical virus's; nearly triple the size of that of its largest viral counterpart, canary pox, in the smallpox family; and larger than the genomes of 20 or more parasitic bacteria. Moreover, within Mimi's outsize helping of genetic material, Claverie found genes for such things as the translation of proteins, DNA repair enzymes, and other types of protein. Those functions were thought to be the exclusive province of more complex cellular organisms. The boundary between viruses and complex bacteria had become officially blurred.

"We already had very large viral genomes in the database before Mimivirus," says Claverie. "But before we saw that the virus and bacteria groups could overlap, we never asked ourselves why some large viruses had, for example, 300 genes, while the typical virus only needs 10. Then we see Mimi, with over 1,000 genes, and we're thinking we have a problem with our whole concept of viruses."

Viruses come in all shapes, sizes, and degrees of sturdiness, and with all manner of strategies for getting at the cellular machinery they lack. Some batter-ram their way through the outer cell membrane. Some meld their membranes with a cell's and then suddenly revolve, like those faux bookcases in the movies, into the sacred chamber. Still others gain entry by disguising themselves as the sort of free-floating molecules that our cells routinely gobble up.

The manner of replication varies, too, depending on the virus's genetic identity. DNA viruses like smallpox, herpes, and now Mimivirus tend to be larger and more sophisticated genetically. They can exist for centuries outside a host and can afford to be more restrained when replicating inside one, making reliable, relatively error-free copies of themselves by hijacking the formula common to all life.

DNA makes a slight variant of itself known as RNA, which directs the production of the specific proteins of which all complex life-forms are composed. So-called RNA viruses are rogues: smaller, fast-replicating shape-shifters, descended from a time that evolutionary biologists refer to as the RNA world, back near the base of life's tree, before today's DNA-based organisms evolved. RNA viruses can direct the copying of their own proteins without using DNA—a shortcut that generates both more copies and more errors, or mutations. Although such activity might get you fired in the business world, in biology, mutations can offer a leg up. During unstable times—when environmental conditions shift or humans develop a successful vaccine—RNA viruses have the resiliency to adapt, outflank, and reemerge.

Influenza is the best known continuously morphing RNA virus. HIV is a particularly insidious RNA virus, known as a retrovirus because once inside the cell nucleus it reverses the DNA formula: a single strand of RNA manufactures its own double strand of viral DNA. That viral DNA is then directly spliced into the host cell's DNA and passed along with the cell's natural replication process.

There is even a newly discovered category of subviral agents known as viroids: naked snippets of RNA that lack even an outer protein coat and don't encode for anything. They are devoid of genes entirely, and yet they replicate and cause illness once inside a host. And then there are deeply derivative entities called satellites, metaviruses that can replicate only within a virus that is already busy inside a host.

Whatever neat conceptions and categorizations we develop, viruses have always found a way to poke holes in them. Scientists long assumed, for example, that viruses could only be made of DNA or RNA. Then in the late 1990s, a number of viruses were found to contain both. Retroviruses, meanwhile, were long thought to infect only animals. The only seemingly safe assumptions were that viruses will always be smaller in both physical size and genomic content than the simplest bacteria and that viruses had to have evolved after those same cellular organisms, on which their parasitism depends.

ow the discovery of Mimivirus has rendered even these two viral paradigms questionable. What Claverie calls "the final click" came after comparative analysis of Mimi's DNA with that of other organisms in life's three domains: the eukaryotes, bacteria, and archaea. Mimi, it turns out, belongs to its own distinct and extremely ancient lineage of large DNA viruses. Moreover, certain signature Mimi genes, such as those that code for the production of the soccer-ball shape of its capsid (an outer protein coat common to all viruses), have been conserved in viruses that infect organisms from all three of the domains, particularly in eukaryotes. The implications of that finding are truly radical: that Mimi, or a Mimi-like ancestor, emerged prior to the three other domains and played a key role in inventing the very cells of which humans and all complex cellular life-forms are made.

It is a difficult concept to get one's head around. Parasites, to us, are derivative, necessarily descendant from the biological entities they depend on for life. But simple does not always mean less evolved. Mimi's outsize complement of genes—so large that the virus is tantalizingly close to being an independent organism—suggest to many scientists that Mimivirus underwent reductive evolution early on and shed some of its genome, including the genes necessary to replicate on its own.

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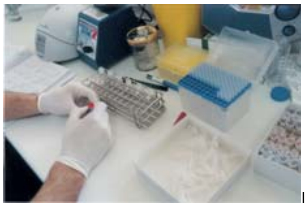
"With Mimi, we've captured by chance a picture of an organism that was undergoing such a reduction, evolving toward fewer genes," says Claverie. "This guy just retained more ancestral features than others." Biologists, Claverie says, can no longer view viruses as random assemblages of genes. "We have to confer to these guys a nobility, a genealogy. Not only a genealogy. They are very ancestral, and their ancestors are at least contemporary with ours and those of all present-day life-forms. Mimi is like the missing link."


In the lab, a virus must first be extracted from its holding vial before its genes can be extracted..

With the aid of advanced gene sequencing, comparative DNA analysis, and endless cross-referencing of the genomes of organisms from the three—or perhaps four—domains of life, a fuller concept of viruses and their role in evolution has begun to coalesce. In the mere year and a half since Bradfordcoccus's true identity was revealed, more genetically distinct and extremely ancient viruses have been found. All of them lead scientists to the same conclusion: Evolution's archvillain looks more and more like its vital and formative force.

Even as Darwinism has come under attack from the theology of the intelligent design movement, scientists have never been closer to divining life's origins. With DNA evidence as solid as that used to convict criminals, researchers can trace the shared genetic lineage of life's different branches back to the very base of the tree, some 4 billion years ago, when the interaction between primordial bacteria and viruses culminated in the "mother cell," the common ancestor of all life on Earth. Although the remoteness and complexity of those events makes them difficult to piece together, viruses like Mimi are emerging as the key players in the picture.

"We are now able to draw a tree of life for the first time that includes viruses as their own branch," says Patrick Forterre, a molecular biologist at the University of Paris-Sud.

Last July Forterre held a weeklong conference in Les Treilles, France, where two dozen of the world's leading microbiologists, cell biologists, and evolutionary biologists met to discuss "The Origin of the Nucleus." The nucleus, the command-and-control center of the eukaryotic cell, is ultimately what distinguishes a human from a bacterium. For eons prior to the emergence of the nucleated cell, life on Earth was essentially slime: vast, directionless mats of single-celled bacteria and archaea.

With no nucleus to further modify and craft gene expression and protein translation, life thrived but literally could not get hold of itself, could not assume new shapes or diversify. How the first nucleus came to be is a question that has intrigued scientists ever since Scottish botanist Robert Brown first detected a cell nucleus while peering at orchids under a microscope one day in 1824.

The discovery of Mimivirus lends weight to one of the more compelling theories discussed at Les Treilles. Back when the three domains of life were emerging, a large DNA virus very much like Mimi may have made its way inside a bacterium or an archaean and, rather than killing it, harmlessly persisted there. The eukaryotic cell nucleus and large, complex DNA viruses like Mimi share a compelling number of biological traits. They both replicate in the cell cytoplasm, and on doing so, each uses the same machinery within the cytoplasm to form a new membrane around itself. They both have certain enzymes for capping messenger RNA, and they both have linear chromosomes rather than the circular ones typically found in a bacterium.

"If this is true," Forterre has said of the viral-nucleus hypothesis, "then we are all basically descended from viruses."

Claverie says, "That's quite a big jump in our thinking about viruses—to go from their not even being organisms to being all life's ancestor."

Some scientists go a step further. They believe that viruses played a role even earlier in the evolutionary mix. The precise order in which the three domains of life evolved—whether, say, the eukaryotes emerged before or after the archaea and bacteria—is a much-debated subject. So is the identity of the progenitor of those different domains, the so-called last universal common ancestor, or LUCA, as it was dubbed by Forterre at the first Les Treilles conference in 1996.

"I'm probably one who has asserted most sternly that LUCA was viral," says Luis Villarreal, the director of the Center for Virus Research at the University of California at Irvine. "The genes and gene functions suggest that we're dealing with one of the earliest and oldest forms of life. Mimivirus really stretches our sense of scale of what a virus can be."

But just how far can that scale be stretched? David Prangishvili, a virologist at the Pasteur Institute in Paris and a colleague with Forterre in studying viruses that infect archaea, now thinks that viruses swam in the primordial soup prior to the emergence of cellular life of any kind and only later became dependent on cells. Forterre is less convinced.

"It is difficult for me to imagine," he says. "You need to have some type of closed system to be sure that the different reactants of the metabolism, or different mechanisms, can interact with each other and also have a kind of Darwinian evolution. You need to have individuals. I think there was an RNA world prior to the DNA world, when you had a lot of RNA cells. Maybe viruses originated at the time of the RNA cell. You need to have a cell to even obtain a virus."

Yet to virologists like Prangishvili and Villarreal, the concept of viruses as the primordial soup's first built-in stirrers seems to align perfectly with their nature: high creative replication, genetic reproduction, and sorting of gene fragments, not to mention their eerie biochemical straddle between life and nonlife.

"I think what confuses people is their assumption that parasites are only damaging things," says Villarreal. "How do you get creation and complexity out of them? You do because they persist, and to do that you have to take on all comers. You come up with inventions that prevent you from being displaced. It's no surprise that the number-one-selling software on the planet these days claims to be 'antiviral.' "

Information, whether biological or industrial, is passed along by replication. Create a new word-processing file and copy it: that's replication. But any replication process is susceptible to errors, which in turn can generate novelty. And novelty, especially in harsh, shifting conditions like those that prevailed on the newly formed Earth, is often an advantage: Some new life-forms will adapt better to the environment. To the utter abhorrence of the proponents of intelligent design, there is a certain randomness to evolution.

Some viruses, like Ebola or the new avian influenza, are basically runaway replicators, effectively burning their own life bridges in the process. But the majority, as Villarreal puts it, strive "to persist, not make a lot." Those that do persist eventually become both stable within, and staples of, evolution. The overwhelming majority of viruses are not harmful to their hosts. Each of us is infected with a huge array of viruses. The human genome, considered as a mass, contains more retrovirus sequences than actual genes.

"They're not doing anything," says Villarreal. "They're just persisting. And they were around long before humans evolved. The better part of the human genome is composed of viral DNA. That's true of nearly all eukaryotes, and the more complicated the organisms, the more of those sequences you have. We aren't sure exactly what they all do, but they are part of our genetic identity, this stuff we dismiss as junk. 'Junk' and 'parasite' are both words that will get you into a fight if you use them improperly. And yet they are where all life's creativity lies—its very origins."

What was the very first bit of life's biochemical code, and where did it come from? It may be no surprise to learn that viruses figure ever more prominently into this line of speculation. Some researchers go so far as to suggest that the very first life on Earth could have arrived in the form of a viral shard from afar, perhaps conveyed in the pore of a meteorite.

"Well, I used to laugh at the idea," says Mark Young, a Montana State University biologist who leads a research team that gathers new archaeal viruses from superhot aquatic environments in Yellowstone National Park and other places around the world. "But I wouldn't say it's absurd anymore. I think it has to at least be kept in the portfolio of the discussion."

Where researchers do agree is that a nearly immeasurable array of viruses remain to be discovered on this planet. A growing number of virologists and biologists are out to catalog them. Both Claverie's and Raoult's labs have already begun searching for more viruses like Mimivirus. Among the most likely sites are algae, the ocean, and of course, cooling towers. Claverie says he sees no good reason why there can't be viruses bigger than Mimi.

"I'm hoping Mimi isn't the only one of its kind on Earth," he says, "especially since that cooling tower in Bradford has been destroyed. But it can't be the only one. That would be ridiculously lucky for it to have just fallen into our lap."

Meanwhile, Young has been finding new archaeal viruses every time he looks for them. Asked why Mimivirus hadn't been discovered sooner, he says it may come down to the simple fact that we just haven't been looking.

"We haven't even begun to scratch the surface. The numbers are mind-boggling. If you put every virus particle on Earth together in a row, they would form a line 10 million light-years long. People, even most biologists, don't have a clue. The general public thinks genetic diversity is us and birds and plants and animals and that viruses are just HIV and the flu. But most of the genetic material on this planet is viruses. No question about it. They and their ability to interact with organisms and move genetic material around are the major players in driving speciation, in determining how organisms even become what they are."

We have been looking for our designer in all the wrong places. It seems we owe our existence to viruses, the least of semiliving forms, and about the only thing they have in common with any sort of theological prime mover is their omnipresence and invisibility. Once again, viruses have altered the way that we view them and, by extension, ourselves. As it turns out, they are not the little breakaway shards of our biology—we are, of theirs.