EMERGING VIRUSES

Chimpanzee Outbreak Heats Up Search for Ebola Origin

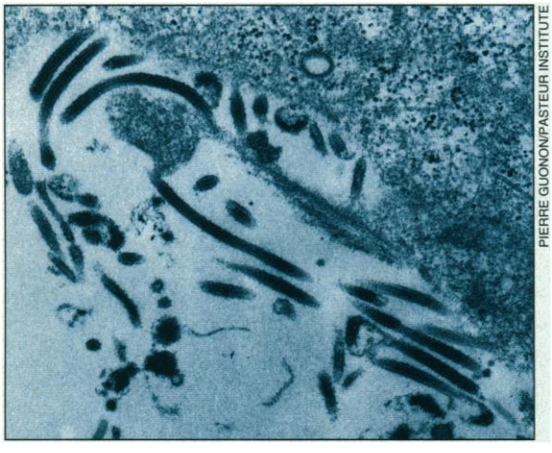
For the fifth time in 16 years, Ebola virus has reared its lethal head in equatorial Africa. At press time, some 60 people in four towns in Zaire had succumbed to the virus, which causes fever, diarrhea, and, in fatal cases, a breakdown of internal organs. As before, no one knows where the virus came from or what to expect of it in the future. But another, less heralded, Ebola outbreak may provide clues to those critical questions.

That outbreak took place last November, in the Ivory Coast's Tai Forest, and its primary victims were not humans but chimpanzees. As Bernard Le Guenno of France's Pasteur Institute and several colleagues report in this week's issue of *The Lancet*, the culprit was an entirely new Ebola strain, offering an unnerving glimpse of the virus's capacity for genetic change. What's more, the timing of the epidemic—just after the rainy season—raises suspicions that the virus normally lurks in an insect or some other arthropod and reaches its victims with the help of an intermediate mammalian host. Because both the reservoir and intermediate host must be hiding somewhere in the Tai Forest, a 4200-square-kilometer reserve, Le Guenno and his colleagues believe they may have a good shot at tracking down the virus's mysterious origins. Says Le Guenno, "Maybe this time we can find the natural reservoir for Ebola."

If so, the wild chimpanzees that Christophe Boesch had been studying since 1979 in the Tai National Park will have made a major, if tragic, contribution to virology. When the animals first began dying, the researchers had no idea that Ebola was involved. "All we knew then was that the chimpanzees had some disease and that it was killing many of them," says Boesch, a primatologist at the Swiss Institute of Zoology in Basel and a co-author of the *Lancet* report. Boesch initially thought that the chimpanzees were being felled by an illness introduced by humans, perhaps pneumonia or anthrax.

But when three of his field assistants did an autopsy on 1 ½-year-old Piment (French for "Hot Pepper") and found uncoagulated blood pooled around her internal organs, they began to suspect something more sinister. "I thought then it must be some hemorrhagic fever"—the kind of illness caused by Ebola and its relatives—says Pierre Formenty, the epidemiologist in charge of hemorrhagic fevers at the Ivory Coast's Veterinary Lab and another author of the paper.

Those suspicions deepened when one of the chimp watchers, who had taken part in the autopsy, fell ill only 8 days later. Feverish and suffering from acute diarrhea and a florid rash, she was taken to Abidjan and ultimately evacuated to Switzerland. There, she recovered—not from pneumonia but from Ebola virus, as Le Guenno discovered when he tested samples of the sick researcher's blood sent by Formenty's lab. Le Guenno, a specialist in filoviruses, the family of threadlike RNA viruses that includes Ebola, isolated the virus by inoculating Vero monkey cells with the researcher's serum. When he did immunologic comparisons between the chimp researcher's virus and known Ebola viruses, he discovered that the Ivory Coast Ebola was a new strain—the fourth to be discovered since 1976, when the first recorded epidemic broke out among villagers in the Sudan and Zaire.



PIERRE GUONON/PASTEUR INSTITUTE

A killer's mug. These threadlike particles of the Ivory Coast Ebola strain are magnified some 10,000 times.

Comparing the new strain's RNA sequence with those from earlier outbreaks reveals wide diversity, notes Anthony Sanchez, a research officer in the Special Pathogens Branch at the U.S. Centers for Disease Control and Prevention (CDC) in Atlanta. That's not surprising, he notes, because Ebola, like other RNA viruses, has an error-prone replication process, which would boost the frequency of mutations and thus the emergence of new strains. Sanchez says that the high mutation rate increases the chance that the disease could someday adopt a more contagious form.

But for now, as the Ivory Coast outbreak underscores, the virus is difficult for humans to contract. Only one of the three autopsy participants became ill. And while it is unclear just how she became infected, Le Guenno suspects that somehow—in spite of wearing rubber gloves—she came in direct contact with Piment's blood or tissue. That would be consistent with the evidence from the earlier epidemics, in which filovirus experts traced the spread of the disease to contaminated needles in missionary hospitals, and the current outbreak in Zaire, which has also primarily felled hospital workers.

CHRISTOPHE BOESCH

Early victim. Ebola virus killed 1 ½-year-old Piment; an autopsy then infected a researcher.

By establishing the first firm link between a wild primate and a case of Ebola in humans, the outbreak also supports a long-standing suspicion that outbreaks begin when the virus jumps the species barrier from wild animals. And it offers a hint of where Ebola's ultimate reservoir might be. It clearly isn't in chimpanzees, says Le Guenno, as the virus is lethal to them. In 3 weeks, it wiped out 12 of Boesch's 40 chimpanzees. In fact, the researchers believe that every infected animal died, because blood samples taken from three other chimps after the epidemic ended have tested negative for any exposure to the disease. "So the host is something else," says Le Guenno. Whatever it is, he adds, "it must be there in the Tai Forest."

Le Guenno and his colleagues think the occurrence of the outbreak at the end of the rainy season is a crucial clue. The timing seems unlikely to be a coincidence, they say: Only 2 years earlier, the same troop had suffered a similar die-off at the end of the rainy season, with eight animals succumbing in 2 weeks. Because no blood or tissue samples were collected from the dead animals, it's impossible to be sure that Ebola was to blame, but Boesch says that the disease looked similar to the recent outbreak. And that, says Le Guenno, implicates an insect or other arthropod that breeds in standing water. Tom Ksiazek, chief of the CDC's disease assessment section in the Special Pathogens Branch, agrees. "It may be that the virus's host is a seasonally abundant species,"

he says. Formenty and his assistants are now planning to trap a variety of blood-sucking insects in the Tai Forest and search them for the virus.

That's not the only search they are planning: They are also looking for a mammalian intermediary, on the assumption that Ebola employs the same modus operandi as many arthropod-borne viruses. Usually, such viruses infect an intermediate host mammal that allows the virus to reproduce en masse but is not itself harmed by the virus. That intermediate host, Formenty speculates, might be an unidentified species of rodent whose population has boomed since 1990, when Liberian refugees began streaming into camps near the park. The refugees may also have disrupted the forest ecology by illegally clearing and cultivating fields within the park, he says.

Formenty's group will search for an intermediate host by testing a wide range of the Tai Forest mammals for antibodies to the virus and for the virus itself. Other clues may come from the people in surrounding villages. Previous studies in Zaire have revealed isolated cases of Ebola among poachers and villagers who kill and eat monkeys, and any such cases near the Tai Forest could offer a glimpse of the virus's life cycle.

A close look at the chimpanzees' behaviors might also lead researchers to Ebola's mammalian host. Boesch is now reviewing the field records from the weeks preceding the epidemic, he says, "to figure out what other animals they came in contact with." Until the epidemics reduced the adult males in his study group from eight to two, Boesch's chimpanzees were well known among primatologists for their clever, cooperative hunting strategies. As a result, he plans to look into the possibility that the chimpanzees killed and ate some other species of mammal shortly before the outbreak.

Those studies, valuable as they may turn out to be, represent a sad turn for Boesch's research. Until the chimpanzees were decimated by Ebola, they were noted not only for their hunting skills, but their habit of using anvils and hammerstones to crack open palm nuts. Boesch had spent years getting the animals accustomed to people so that researchers could get close enough to observe such activities. "Sadly, now we will be studying the effect of [reduced] group size on these behaviors," Boesch says.

He suspects that his troop, lacking enough males for defense, will eventually be taken over by a neighboring group. And he worries about the long-term fate of the forest's entire chimp population, trapped in the reserve with Ebola virus and its mysterious host.

–Virginia Morell

ASTRONOMY

COBE Seeks Universe's First Blush

Three years ago the National Aeronautics and Space Administration's Cosmic Background Explorer Satellite (COBE) revealed the early moments of creation. By measuring and mapping the cosmic microwave background—a ubiquitous hiss that is a relic of the intense heat of the early universe—its detectors provided a glimpse of the nearly featureless sea of matter created by the big bang. Now COBE is flipping open the book of creation to a later page, perhaps a billion years into cosmic history, when the first stars and galaxies started to shine.

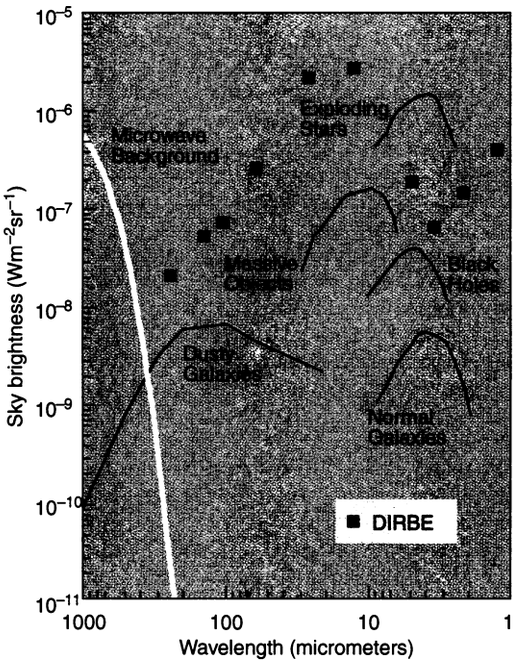
This new look at the early universe comes from another, less heralded COBE detector, one sensitive to the glow of infrared radiation known as cosmic infrared background. The infrared background, which astrophysicists believe is a relic of the universe's first light, is harder to identify and map than the microwave background because it has to be sifted from the much stronger infrared light emitted by nearby stars and dust. But little by little, investigators on COBE's Diffuse Infrared Background Experiment (DIRBE) have been uncovering the equivalent of a cosmic fossil bed, packed with clues about the galaxies and other objects in the primordial universe. "The data are starting to smell very cosmological," says DIRBE collaborator Alexander Kashlinsky, an astrophysicist at NORDITA in Copenhagen.

These cosmic fossil hunters haven't reached their goal yet, as they reported at a recent meeting.* It will be another 2 months or so before they can confidently say whether or not they have isolated an infrared signal with a cosmic pedigree. But as the background radiation's sketchy outline emerges, it is already having an impact on cosmologists' views of the first inhabitants of the universe. Gone are the massive black holes and swarms of the brilliant objects known as quasars that some theorists had envisioned in the early universe. "All those more exotic theories are in great trouble with the [DIRBE] upper limits," says University of California, Berkeley, cosmologist Joseph Silk.

DIRBE opens a window on this early era because it can detect a signal from stars and galaxies too faint to be seen by ordinary telescopes. Astrophysicists know that the most distant—and hence earliest—stars they can see directly can't be the first to have formed; they contain elements heavier than helium, which could only have been produced by nuclear fusion in a previous generation of stars. But the light from the first stars is lost in the glow of the night sky. It is dimmed not just by distance but also by the expansion of the universe, which shifts much of it into the near-infrared, and perhaps also by dust in the first galaxies, which would have absorbed light and re-emitted it in the far-infrared.

DIRBE investigators don't expect to resolve the ancient infrared glow into individual galaxies. The instrument essentially takes the temperature of wide areas of the sky, measuring the total amount of energy in the infrared background. But from that total, theorists hope to deduce how many stars populated the early universe and how bright they were. Meanwhile, the shape of the infrared background—its intensity at different wavelengths—should reveal clues to what early galaxies were like and when their first stars began to shine.

In search of these clues, DIRBE has scanned the infrared sky at 10 wavelengths ranging from 1.25 to 240 micrometers. Back on Earth, the DIRBE team at the NASA Goddard Space Flight Center and elsewhere has spent over 3 years trying to understand



Model universes meet data. Unpublished upper limits for the cosmic infrared background are now a factor of 10 lower than shown here, eliminating some scenarios for the early universe that invoke massive objects such as quasars and black holes.

* COBE Workshop on Unveiling the Cosmic Infrared Background, held from 23–25 April in College Park, Maryland. Principal Organizer: Eli Dwek, NASA/GSFC.