Gore's Fever and Dante's *Inferno*: Chikungunya Reaches Ravenna

Botticelli, Sandro (1444-1510) Canto XIX of Dante's *Inferno*. Snark / Art Resource, NY

So today, we dumped another 70 million tons of global-warming pollution into the thin shell of atmosphere surrounding our planet, as if it were an open sewer. And tomorrow, we will dump a slightly larger amount, with the cumulative concentrations now trapping more and more heat from the sun. As a result, the earth has a fever. And the fever is rising.

Al Gore (Nobel lecture), December 10, 2007 (1)

Warming of the deep ocean and ocean surfaces appears to be altering the natural cycles that help stabilize climate over decades to millennia . . .The explosive re-emergence of Chikungunya fever in 2004 is associated with intensifying weather extremes besetting Africa.

Paul R. Epstein (Harvard Medical School), March 2007 (2)

When they told us it was Chikungunya, it was not a problem for Ravenna any more. But I thought: this is a big problem for Europe.

Rafaella Angelini (Director of Public Health, Ravenna, Italy), December 7, 2007 (3)

FEVER PITCH

Last year, global warming stopped being a question of whether the ice caps were melting or polar bears were becoming extinct. The very week that Al Gore warned his Nobel audience that "the earth has a fever," two important studies showed how and why rising temperatures revamp the geography of infectious disease. Gore's inconvenient truth had hit the temperate zones.

In a *Lancet* publication, Rezza *et al.* (4) described the course of the first outbreak of Chikungunya fever in Europe. In August of 2007, a sudden epidemic of this tropical disease claimed more than 200 victims in and around Ravenna, Italy, a city lying on the same parallel as Bangor, Maine. Chikungunya fever is a bone-chilling, debilitating, sometimes fatal, viral illness, transmitted by the bite of an infected mosquito (5). Like several of its fellow arthropod-borne viruses (arboviruses), Chikungunya tends to affect the joints, sometimes chronically. Arboviruses launch mediators of inflammation (e.g., C3a) similar to those found in several rheumatic diseases (6). Indeed, the name "Chikungu-

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nya" derives from "kungunyala" in the Makonde language of East Africa, meaning "to double up or to become deformed" because of joint and muscle involvement (5). The Italian victims followed suit; one reported: "At one point, I simply couldn't stand up to get out of the car. . . I fell. I thought, O.K., my time is up. I'm going to die. It was really that dramatic" (3).

The Italian team that studied this outbreak identified the molecular structure of the virus and found it identical to one that caused earlier outbreaks in islands of the Indian Ocean. They blamed climate change for the spread into Northern Italy of the virus's favorite vector, the Asian tiger mosquito (*Aedes albopictus*) (4). R. K. Pachauri, Chairman of the Intergovernmental Panel on Climate Change, who shared a Nobel Prize with Gore, echoes that view. He warned that global warming has permitted the proliferation of weapons of mass infection and will affect "the health status of millions of people" (7).

AN INCONVENIENT MUTATION

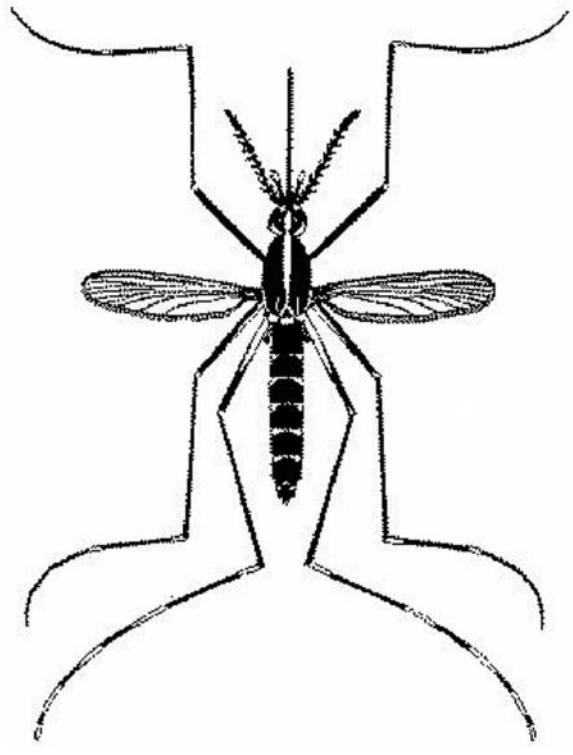
The second study to appear in December was from Stephen Higgs's group at the University of Texas Medical Branch in Galveston. They defined the molecular events that enabled the Chikungunya virus to hitch a ride in the organs of *Ae. albopictus* (8). Like the mosquito, the Chikungunya virus has also expanded its geographical range since it first appeared in Africa in the early 1950s (8). In East Africa, the virus was limited to the habitat of its traditional vector, *Aedes aegypti*. But, after finding a more accommodating host in the tiger mosquito, the Chikungunya virus sparked new epidemics in the Indian Ocean islands of Comorros, Reunion, and Mauritius. A violent outbreak of Chikungunya fever hit Reunion Island in 2005–2006. Of the island's population of 770,000 people, 265,000 took sick, and 237 died (9). World Health Organization (WHO) scientists soon found that these cases were caused by a strain of the virus that had undergone a specific mutation in the gene of an envelope protein (8, 9).

The Ravenna virus was carried in the blood of a South Indian man who was visiting relatives in Italy. Sure enough, the Italian doctors reported, he was infected by the mutant strain first identified in the Reunion Island epidemic (4). Reasoning that this mutation in Chikungunya might influence its fitness for different vector species, Stephen Higgs and his team at Galveston compared the behavior of the mutant virus in *Ae. albopictus*, the vector in Reunion, with its older West African vector, *Ae. aegypti*. They found that the mutant was not only happier in the organs of the tiger mosquito than in its traditional host but that the virus became more infective. They concluded that "the observation that a single amino acid substitution can influence vector specificity provides a plausible explanation of how this mutant virus caused an epidemic in a region lacking the typical vector" (8).

THE MOSQUITO COAST

For an arbovirus such as Chikungunya to enter a new zone, three elements are required: a change in the distribution and/or survival of the insect vector; a change in fitness and/or infectivity of the virus; and a human who carries the virus into an area deficient in mosquito control. Global warming, viral mutation, and air travel each played a role in the Ravenna epidemic, while lax insect control gave squatting rights to the tiger mosquito (10).

The tiger mosquito requires for its survival a mean monthly winter temperature greater than 0°C, a mean annual rainfall greater than 50 cm, and a mean summer temperature greater than 20°C (11). As more regions of the globe have met these criteria, the mosquito's range has expanded. The tiger mosquito is more aggressive than most of the other *Aedes sp.* and tends to outbreed them. Larvae of Asian tiger mosquitoes entered Italy in 1990, tucked into stagnant coils of used rubber tires from China, *via* Albania—just across the Adriatic from Ravenna. *Ae. albopictus* has now been reported in 10 Italian regions and 19 provinces. Since 1984, the tiger mosquito has also made its home in much of the United States (12). As U.S. imports of Japanese cars rose in the 1980s, so did the demand for their tires. As a result, larvae of *Ae. albopictus* arrived in the United States stowed in moist rubber tires destined for all those Camrys and Corollas (13). We've been warned that this stealthy invader, which is also the vector of dengue, West Nile virus, and eastern equine



The tiger mosquito: *Ae. Albopictus.* Image courtesy North Carolina Department of Environmental and National Resources, Division of Environmental Health.

encephalitis, has set up shop in Europe and the Americas for good (2). But why was Ravenna the first European site?

A GUELPH WAR CASUALTY

Ravenna lies in a marshy delta 13 feet above sea-level. In Roman times, Ravenna was only a few hundred yards from the Adriatic, but time and tides have moved the shores back by 6 miles. Effluvial reservoirs of stagnant water are guaranteed by the Corsini Canal, which connects the city to the sea, and by two small rivers, the Ronco and Montone. The site has for centuries been a safe haven for malarial mosquitoes less climatically fastidious than *Ae. albopictus* (14).

The most famous casualty of Ravenna's malarial mosquitoes was Dante Alighieri, the immortal poet of *The Divine Comedy*. In the summer of 1321, Dante died at age 56 of quartan malaria contracted in the marshes around Ravenna. His tomb in the city is a major tourist site. The poet and his contemporaries knew malaria well; it was the dreaded Quartan fever with temperature spikes every 3rd day, due to a cycle of pathology we now attribute to infection by *Plasmodium malariae*. Dante spelled out its vascular responses in the *Inferno*:

> *Like those who shake,*
> *Feeling the quartan fever coming on—*
> *Their nails already blue, so that they shiver*
> *At the mere sight of shade—such was I then. . .*
> Dante: *Inferno* Canto XVII (15)

Paradoxically, malaria, sometimes Quartan, sometimes not, was also responsible for the growth, survival, and artistic flowering of Ravenna. Since the days of the Romans, the malarial marshes formed a natural defensive perimeter for the city's inhabitants. The site attracted settlers: "There's only one reason anyone would choose to call such a dismal place home: it was 100% defensible. To the east were treacherous shoals and lagoons, to the west were malarial swamps that effectively cut the tiny encampment off from the rest of the continent" (16)—a marshy Gibraltar, as it were. Ravenna's location, facing the shores of Byzantium and straddling the northeast road to Rome, assured that waves of invaders would sweep over the land. In the millennium between 400 and 1500 AD, the town fell under dominion of Visigoth and Ostrogoth kings, of Byzantine and Lombard rulers, and of Venetian doges and Roman popes.

Dante, an exile from Florence, spent his last years in Ravenna under the wing of Novello da Polenta, the region's capo of the day (17). Dante's *Inferno* begins in 1300, "in the middle of my journey of life, I came into a dark wood. . ." (*Nel mezzo del cammin di nostra vita mi ritrovai per una selva oscura. . .*). Alas, he never made it to the end of the journey, which at the time would have been 70 years, at best. From 1302 to the day of his death, Dante was in exile from Florence, banished because of bitter factional strife that nowadays would be familiar to any observer of Middle Eastern politics—or a fan of the "The Sopranos." Medieval Tuscany was permanently divided between two rival factions, the Guelphs and the Ghibellines, and in turn, the Florentine Guelphs were further split by squabbles between White Guelphs and Black Guelphs. Conflict between the two Guelph parties turned to violence, and when the Black faction seized power, Dante's fate was sealed. As a sometime official under the White Guelphs, he was condemned to be burned alive if he ever returned to Florence (18).

Diplomacy and the mosquitoes did Dante in. In 1321, he was sent by Novello de Polenta to resolve a dispute between Ravenna and Venice over some salt flats. It was a mission of little consequence and less success. His historian notes: "On his way back to Ravenna by land, for the Venetians refused him the sea passage, he caught a fever in the marshes and returned to Ravenna only to die" (17). Dante had just finished the last verses of *Paradiso,* the apotheosis of the *The Divine Comedy*.

BEWARE THE AEDES OF MARSH

Mosquitoes bearing Quartan fever may have been the norm in 1321, but why were tiger mosquitoes swarming in the Ravenna of 2007? For reasons that remain unclear, mosquito control in the Ravenna region had lapsed back to medieval days. After World War II, energetic sanitary measures, the elimination of stagnant breeding sites, and discrete use of pesticides had driven malaria from the shores of Europe. The most effective pesticidal method was the application of 2 g/m^2 dichlorodiphenyltrichloroethane (DDT) to indoor surfaces once every 6 months. A review notes:

> The advent of DDT revolutionized malaria control. It enabled cheap, safe, effective treatments to be targeted at the site where most infections occur—in the home. . . The campaign was based on a careful application of scientific principles, meticulous planning, efficient administration, generous financing, and continuous emphasis on evaluation (19).

By 1975, the continent of Europe was finally declared free of endemic malaria.

A generation later, the mosquitoes were back. At the height of the Chikungunya epidemic in 2007, a Ravenna road-worker complained, "In the last three or four years, you couldn't live on these streets because the mosquitoes were so bad" (3). It's not unlikely that the vigorous anti-DDT crusades of Italy's Green Party have played a role. So influential has the movement become that the Greens are now part of the governing coalition (20).

Whatever the error was that permitted mass resurgence of mosquitoes in Ravenna, once Chikungunya struck, immediate counter-measures were taken. Italian public health authorities sprang into action, aided by the European branch of the WHO and molecular

biologists in Rome. Even before the exact pathogen was diagnosed, the public was warned to take precautions against mosquito bites, to expunge their breeding sites, and to use hot-lines for tracking new cases. Pesticides were unleashed; streets, parks, and public gardens were sprayed with permethrin, and larvicides, such as diflubenzoran or *Bacillus thuringiensis israelensis*, were added for door-to-door disinfection (21). So effective were these rigorous methods of mosquito control that a public health official could say, "by the time we got back the name and surname of the virus, our outbreak was over" (3).

Over for now, one might say. The summer epidemic may be over, but tepid tires are still being shipped around the globe, and the temperate zones are fertile breeding grounds for the tiger mosquito. Any one of this sturdy brood sits ready to spread the bad news of Chikungunya fever (22). There's a lesson for all of us to be learned from the epidemic in Ravenna, as Roberto Rosellini of the WHO told the *New York Times*: "Climate change opens the door to diseases that didn't exist here previously. This is a real issue. Now, today. It is not something a crazy environmentalist is warning about" (3). Gore was right. The effects of earth's fever are no longer limited to the Arctic and Antarctic regions. Global warming is no longer just a bipolar disorder. FJ

Gerald Weissmann
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