50 Years Ago

Normal tissue growth requires that cells should recognize each other and stop growing or moving at the right time and place. Understanding how this regulation is achieved is of fundamental importance. *A priori* one might expect that some kind of chemical signal passes from cell to cell. This is certainly the simplest explanation of the phenomenon of contact inhibition — cells stop moving and dividing when they come into contact with each other … Loewenstein and his collaborators … have shown that at regions of cell contact, junctional surfaces, in several tissues cellular substances diffuse rather freely from the interior of one cell to that of the next … Thus a quite large molecule could act as a signal for contact inhibition … These experiments … suggest that normal growth and differentiation of tissues depend on a flow of material from the interior of one cell to that of another.
From *Nature* 17 June 1967

100 Years Ago

M. G. Daressy has been writing concerning the long-disputed question as to the identity of one of the animals which the old Egyptians selected as the symbol of their malevolent deity, Set or Seth. Among creatures suggested as intended by the Egyptian artists have been the jackal, hare, oryx, and okapi, but all these assignments have been abandoned …
M. Daressy argues that the Set animal is really a creation of the imagination … so it is futile to search for the creature in either the existing or fossil fauna in Africa … It may be that the animal was very scarce, and that after its association with the detested deity it was exterminated by the Horus-following, orthodox Egyptians.
From *Nature* 14 June 1917

converges on South America. The groups sequenced Zika genomes from people and from *Aedes aegypti* mosquitoes, which carry the virus. Inspired by the success of real-time sequencing efforts during the Ebola virus outbreak[5], Faria and colleagues obtained several samples using a mobile sequencing laboratory deployed in Brazil. Together, these efforts produced more than 100 new genomes.

The groups used these genomes, along with some existing ones, to construct phylogenetic (evolutionary) trees of Zika in the Americas. In this way, they could reconstruct Zika's spread by following a trail of mutations — accumulated by virus strains that the authors sampled at different times and places — back to the outbreak's most recent common ancestor. These trees confirm previous evidence[6] that northeastern Brazil is the outbreak's hub.

The Zika strain that founded the American outbreak was evidently introduced from the Pacific islands[6], but the current studies cannot prove that transmission to Brazil was direct. Indeed, Faria *et al.* note that some of the deepest branches and earliest samples on the American Zika tree are from the Caribbean. Nonetheless, the collected genomes show that Zika was circulating in northeastern Brazil by late 2013 or early 2014 — more than a year before the first reported case in Brazil[7]. They also demonstrate that northeastern Brazil was the source of onward dispersal to several other countries, with an estimated 6–12-month lag between dispersal and initial detection in those regions (Fig. 1). These lag times are not unreasonable, given that it takes time for infection numbers to build up, and that the most obvious effects are seen in babies, born months after mothers have been infected.

It would be a mistake to dismiss these findings because of the 'small' sample sizes involved. Sample numbers in phylogenetic analyses are not the same as sample sizes in, for example, clinical trials. A single sequence can prove the presence of a viral strain at an early time. And, as in the current work, just a handful of strains showing substantial genetic differences can provide compelling evidence for years of undetected circulation.

Faria *et al.* and Metsky *et al.* thus provide time points from which to compare the pre- and post-Zika incidence of microcephaly — a condition in which newborns have abnormally small heads and brains — and other Zika-associated symptoms in each affected region. This comparison will allow a better understanding of the effects of the virus. The groups' work also indicates that successful jumps out of Brazil may coincide with times at which seasonal and environmental factors are optimal for viral spread by *A. aegypti*.

This last point resonates with Grubaugh and colleagues' paper[4] (page 401). These authors set out to determine how and when local transmission of Zika arose in Florida, again using phylogenetic trees from human- and mosquito-derived Zika genomes. They found evidence that Zika was introduced into Florida at least four times, several months before its presence was detected. The virus probably entered from Caribbean countries linked to Miami by substantial air and cruise-ship travel.

Miami may be unique among US cities in having the ingredients that favour Zika transmission: not only the presence of *A. aegypti*, which is found in many US cities, but also large numbers of people arriving from high-incidence Zika areas at times when the mosquitoes are prevalent. Nonetheless, Grubaugh and colleagues provide evidence that each 'successful' introduction failed to sustain a permanent infection in Miami. The transmission rate was below the crucial threshold of at least one secondary infection per primary infection, on average (a secondary infection being one contracted from another person in Miami, either through a mosquito or directly). By contrast, Faria *et al.* estimate that three secondary infections arose per primary infection in northeastern Brazil.

These papers, along with a report this year on Ebola[8], set a new standard for what can be achieved by studying disease outbreaks in tantalizingly close to real time, using rapidly obtained genome sequences analysed in a powerful computational framework[9]. Such work is possible mostly through the sustained efforts of a fairly small number of scientists supported by modest grants from a few enlightened funders. These breakthroughs not only are impressive in themselves, but also expose large gaps in current approaches to detecting and responding to potentially catastrophic disease outbreaks. Systematic pathogen surveillance is within our grasp, but is still undervalued and underfunded relative to the magnitude of the threat.

A virus-as-wildfire metaphor comes to mind in this context (possibly because I used to be a forest firefighter). In fire-prone areas of North America, lightning is expected, storms are tracked and each strike is pinpointed. Planes fly out at first light to look for smoke near each strike point, and firefighters are on site the same morning. This mentality needs to be applied to emerging infectious diseases. The responses to the recent Ebola and Zika outbreaks undoubtedly involved great courage and ingenuity, but they have looked too much like valiant bucket brigades organized after the fire is out of control. We should be detecting such outbreaks within days or weeks through routine, massive, sequence-based approaches — not months or years later, when clinical symptoms have accumulated.

To do this will require investment in more-comprehensive screening and archiving of animal and human biological samples (perhaps piggybacking on the millions of samples collected for other purposes worldwide each year, then discarded). It will involve developing better ways to recover and amplify viral genetic