Royal Society of Edinburgh

Science and Society Book Discussion

The Invisible Enemy: A Natural History of Viruses

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Tuesday 26 January 2010

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Viruses might be small, but they can be deadly. Light on their feet and quick to adapt, they constantly try to evade man's best attempts to keep them down. From smallpox to HIV, from flu to ebola, Professor Dorothy Crawford reminded us why we should take viruses seriously – and why we should respect them too.

Professor Crawford began by discussing her book, *The Invisible Enemy: A Natural History of Viruses*. Seven years in the writing – largely because the field moves so quickly – it provides a scientific account of viruses.

Viruses are tiny, but they are abundant, diverse and ubiquitous. She is often asked, she said, why she illustrated the book with a tulip. This was because of tulip mania, which gripped Holland in the 17th Century. When tulips were imported to Holland, the Dutch created new varieties which were variegated, with breaks in the colour. These became hugely desirable. But, as it turned out, the 'breaks' were caused by a virus (brought by aphids from surrounding fruit trees), which stopped the affected cells developing colour. The tulips cost up to the equivalent of £400,000 in today's money, being so expensive because they were weak and unreliable due to the virus infection.

The second question she is asked is why she wrote the book. She was "irritated with the press", she said, because they persistently use the term 'virus' for all sorts of "nasties", routinely mixing it up with bacteria; *E. coli*, for example, which is a bacterium, but is regularly called a virus.

There are huge differences between the two, she says, and not only the size (bacteria are much larger). Viruses are unique, because they are particles, not cells – "a piece of bad news wrapped up in protein", to quote Sir Peter Medawar. They have no molecular machinery for generating energy or making proteins so, in order to survive and reproduce, they rely on host cells, which they invade. Although she often uses the terms 'smart' and 'clever' to describe viruses, Professor Crawford stresses that they have no brain, and there is debate over whether they can be considered 'alive'.

Nevertheless, they are the most abundant form of life on the planet – or 'virosphere' – have been around since ancient times, are ubiquitous, and there are more than 100 million different types. Just one litre of sea-water contains 10 billion viruses and, laid side by side, the viruses in the ocean would span 10 million light years or six galaxies. "The stupidest virus is cleverer than the cleverest virologist," said George Klein. That's because viruses are so quick to evolve. Over the years, host species have evolved immune mechanisms to combat virus attack, but viruses have evolved ways of evading host immunity. In this 'arms race' the viruses have the advantage of being able to evolve faster.

Viruses have evolved to spread in any number of ways – through skin-to-skin contact, in water, from animals, in food and in the air, to name a few.

To illustrate, she quoted an example from her book, which involved a dinner at the elite Apothecaries' Hall. Two weeks later, the chef, a waiter, and 50 distinguished guests went down with jaundice caused by hepatitis A virus. The finger was eventually pointed at the raspberry *parfait*, specifically at the raspberries, which had been picked near Dundee two years previously, and frozen. The case uncovered some unsavoury practices by berry-pickers, including the habit of urinating in the buckets of fruit to save the walk to the loos – and to increase the weight of the fruit (they were paid by weight).

Factors which aid viruses to infect and spread among humans include exposure to animal viruses, crowding and poverty, and travel. This is illustrated by HIV, the 'killer' virus, which has been responsible for more than 25 million deaths so far, mostly in the developing world. The source of HIV has been traced to a chimpanzee subspecies, *Pt troglodytes*. A technique called 'molecular clock' has shown that it is a hybrid virus, probably a combination of viruses from two monkeys.

Although HIV probably first transferred to humans in 1900, it took around 60 years before it began to take off. By 1959 it had spread from rural Cameroon to the over-crowded city of Kinshasa. From there, it travelled to Haiti, possibly with a single infected traveller, then, in 1969, to the US, where it began to spread through the population and the world.

Crowding and poverty are dream conditions for viruses, whether that be in a poverty-stricken shanty town or a luxury cruise ship, some of which have been hit by epidemics of gastroenteritis caused by norovirus.

Smallpox too, the world's most deadly virus to date, probably passed to man from gerbils or camels and probably took hold when man moved from the 'hunter-gatherer' phase and started to live closely with domesticated animals. And, as travel times have collapsed, it has become much easier for viruses to go global. It now takes under a day to reach Australia from the UK, whereas it would have taken a year in the 18th Century.

Persistent viruses, such as those which cause warts, were inherited from our primate ancestors. They rarely cause serious illness, and have a survival strategy designed to cause long-term infection in an otherwise healthy host. The herpes virus family, for example, dates back some 400 million years. It has co-evolved with its hosts, showing remarkable adaption, and it doesn't go away. The chicken pox virus stays in the body once the actual disease has passed, hiding in the nerve cells in the spinal column and sometimes being reactivated in the form of shingles – which can, in turn, pass on chicken pox to a new generation.

Professor Crawford spoke a little about her latest book, *Deadly Companions: How Microbes Shaped our History*, which was published in 2007. This covers a wider range of microbes, and looks at why epidemics and plagues happened at certain points in our history, and whether our lifestyle was to blame. She concluded that the great epidemics of the past were caused by much the same factors which help viruses spread, that is, animal microbes, crowded living, travellers and poverty.

And it is still happening. In 2003, there was an outbreak of monkey pox in the US, which affected 71 people before it was controlled. The finger was eventually pointed at the exotic animal trade, which had imported it in a giant Gambian rat. This spread to prairie dogs in a pet shop, which in turn passed it to humans. "How mad is that?" concluded Professor Crawford.

Questions
The talk was followed by an extremely lively question and answer session, chaired by RSE President, Lord Wilson of Tillyorn. It covered issues ranging from whether viruses were alive to which viruses Professor Crawford respected most.
Asked if journalists who misused the word 'bug' should be fined or otherwise punished, Professor Crawford said she did not feel as strongly about that as the questioner clearly did. She had even, she admitted, used it herself.

One member of the audience described how he had been taken to hospital more than 20 years ago, having fainted in the night, and been diagnosed with a virus. Doctors told him they didn't know what the virus was, but said that didn't make a difference to the treatment, and he made a full recovery. Would treatment be so haphazard now, he asked. Professor Crawford said he was lucky to survive, because we knew far less about viruses then, and there were few antiviral drugs. Today we can diagnose more quickly and have more drugs at our disposal.

Asked how the virus in the frozen raspberries had survived, Professor Crawford said that freezing does not kill viruses – indeed, the viruses used in her research are stored at -20C "and they thaw all right".

Given that America had been essentially divided from the world until 1492, she was asked, were the persistent viruses found now the same as in other parts of the world? They hadn't really diverged, said Professor Crawford, which shows that they were very ancient and stable viruses.

Asked the question she had herself invited, that is, "are viruses alive?", Professor Crawford responded by asking for a definition of what it means to be alive. She believes that viruses are pieces of DNA which hijack cells, so "does that mean living?" Lord Wilson asked the audience to vote, and, fairly overwhelmingly, the audience decided that viruses were not alive.

Before the evolution of bacteria, how did viruses reproduce themselves? Professor Crawford said there was a theory that viruses might have degenerated, and might have once been free living bacteria. In any case, as soon as an organism developed, viruses would be quick to take advantage.

Given that the story of viruses keeps changing, does Professor Crawford plan to write another book? 'Yes', she said. She is planning one about the origins of HIV, in the style of a detective story – the work done to trace the spread is fascinating, she said.

Asked if we should still live with domestic animals, including birds, Professor Crawford said they were a threat (because they pass on viruses). Swine flu was a reminder of that, she said. We're never going to conquer viruses, so we have to think about how we live, she said.

Would it be possible for man to bring back viruses from outer space? There's a possibility, but there's no scientific evidence so far, she said.

Asked about resistance to drugs, Professor Crawford said that viruses were already becoming resistant to antivirals – because viruses have the ability to evolve so quickly.

The *Epstein-Barr* virus, and other herpes viruses, are the viruses she works on and are most respected by Professor Crawford, she said. Most human bodies are infected with *Epstein-Barr* and, in most cases, it doesn't make them ill. These viruses don't want to make the host ill; they want it to survive so they can survive, she said, and *Epstein-Barr* "has it taped".

Viruses can already be used as technical tools, as vectors to take DNA into cancer cells, for example, she said, when asked about their possible use in medicine.

Asked if we can synthesise viruses, Professor Crawford said we could do so if we knew the DNA sequence. Making a new virus would be risky, however, as you wouldn't know how it would act. There was a story some years ago, she said, that the USSR was manufacturing a combination between smallpox and ebola, but fortunately there was no evidence that this had happened.

She was asked several questions about what we could do about viruses. We already are fighting back, she said. For example, viruses used to be transmitted via blood transfusions, but these are now much safer. Working towards eradicating poverty would also be good, she said.

Asked if we need viruses to keep our immune system in good shape, Professor Crawford replied that that is a theory, but she is not convinced, since vaccines also stimulate the immune system.

Part of her work is looking at why viruses hit people differently at different ages, but she doesn't have a definite answer yet, she said in response to another question. It might be that people who, for example, develop glandular fever become ill because their immune system over-responds to the virus and causes the symptoms. Perhaps the response is less strong in a child because the immune system is less developed.

Finally, Lord Wilson, feeling sorry for the animals being blamed for passing humans viruses, asked if it was a two-way street. Yes, we pass viruses back and forth with animals, said Professor Crawford. But naturally we pay more attention when animals pass them to humans.