

Is SARS Genetically Engineered?

By Mae-Wan Ho

In the weeks that the allied forces were wreaking destruction and death in Iraq to hunt down Saddam Hussein and his elusive weapons of mass destruction, a SARS epidemic has been criss-crossing continents carried by air-passengers and spreading like molecular cluster bombs that explode to liberate further millions of infectious particles soon after a target is struck.

SARS Severe Acute Respiratory Syndrome is a completely new infectious disease spread by human contact, and kills about four percent of the victims.

The epidemic originated in Guangdong Province, South China. The Chinese authority has admitted mishandling the crisis and to have been slow to inform its citizens.

The disease first struck last November. In March, Liu Jianlin, a 64 year-old medical professor who was involved in treating patients, went from Guangdong to Hong Kong to attend a wedding. He was taken ill soon after arrival and admitted to hospital. He asked to be put into quarantine, but was ignored; nor did the hospital warn his contacts. As a result, nine guests in the hotel where he stayed caught the disease and carried it to Singapore, Canada, Vietnam and other hospitals in Hong Kong.

On 10 February, news of the disease was posted on ProMed, an international email notification service for infectious diseases outbreaks. The next day, China informed the World Health Organization (WHO), but refused to let the WHO team into Guangdong until early April.

A palpable sense of panic has gripped the health authorities around the world. Mother nature is the ultimate terrorist says an editorial in the journal Nature. Powerless to stop the spread, says New Scientist magazine, whose editor decries the lack of international control when it comes to disease epidemics: The international community has weapons inspectors poised to force entry into a country at the first hint that it may possess chemical weapons. But when it comes to disease, we have no international body empowered to take charge, even though the disease may be vastly more dangerous.

Eleven laboratories around the world participated in the hunt for the disease agent, a collaborative effort organized via teleconferencing, since March 17, by virologist Klaus Stohr at the WHO headquarters in Geneva.

The journal Science says that Malik Pieris of the University of Hong Kong was the first to identify coronavirus (which causes colds and pneumonia) just four days later. This finding was replicated in other laboratories. The virus and antibodies against the virus were detected in many, though not all infected patients, but were not found in more than 800 healthy controls tested.

The New Scientist says it was the death of Carlo Urbani, the WHO doctor who first recognized SARS as a new disease, that led to the discovery of coronavirus. It was isolated from his lungs and sent to Joe DiRisi in University of California at San Francisco who made the identification. The virus has since been named after Urbani. The World Health Organization, which played the key role in coordinating the research, formally announced on 16 April that a new pathogen, a member of the coronavirus family never before seen in humans, is the cause of Severe Acute Respiratory Syndrome (SARS).

The pace of SARS research has been astounding, said Dr. David Heymann, Executive Director, WHO Communicable Diseases programs. Because of an extraordinary collaboration among laboratories from countries around the world, we now know with certainty what causes SARS.

But there is no sign that the epidemic has run its course. By early summer, nearly 10,000 people had been infected in 25 countries with more than 750 dead. The worst hit regions are China, Hong Kong, Toronto, Canada.

A cluster of SARS patients in Hong Kong with unusual symptoms has raised fears that the virus may be mutating, making the disease more severe. According to microbiologist Yuen Kwok-yung, at the University of Hong Kong, the 300 patients from a SARS hot spot, the Amoy Gardens apartment complex, were more seriously ill than other patients: three times as likely to suffer early diarrhea, twice as likely to need intensive care and less likely to respond to a cocktail of anti-viral drugs and steroids. Even the medical staff infected by the Amoy Gardens patients were more seriously ill.

The Complete Story

John Tam, a microbiologist at the Chinese University of Hong Kong studying the gene sequences from these and other patients suspects a mutation leading to an altered tissue preference of the virus, so it can attack the gut as well as the lungs.

There is some remaining doubt, however, whether the coronavirus is the complete story. John Tam, director of virology at Prince of Wales Hospital in Hong Kong, found another virus, the human metapneumovirus in 25 out of 53 SARS patients, as have laboratories in Canada and Germany. Metapneumonovirus belongs to the family Paramyxoviridae, which includes viruses responsible for parainfluenza, mumps, and measles, as well as the Nipah and Hendra viruses in recent outbreaks.

Coronavirus showed up in only 30 patients tested while the bacterium Chlamydia has been identified in all samples in Hong Kong, through that strain of Chlamydia is not known to cause disease.

Could it be that both viruses are bystanders of the disease while an as yet unidentified virus could be responsible for SARS?

The coronavirus was atypical. It rapidly infected cells in culture dishes, something that other human coronaviruses do not do. Viruses from the lung tissue in Toronto patients readily infected monkey kidney cells, and no known human coronavirus infects that cell line.

DiRisi's laboratory has a virus detector chip capable of screening for 1200 viruses all at once. When samples sent from the Centers for Disease Control and Prevention in the United States (CDC) were screened, several species of coronaviruses lit up, the strongest spots indicating the closest identity were the avian bronchitis virus and a bovine coronavirus. This appears to fit China's statement that the earliest cases were in bird handlers.

However, more detailed analysis using polymerase chain reaction (PCR) by two groups who just published their results online in the *New England Journal of Medicine* indicate that the new virus is not closely related to any known virus at all human, mouse, bovine, cat, pig, bird, notwithstanding.

Further, the virus was isolated from cell cultures only, and not from the tissues of patients. The PCR fragments of the new coronavirus were not detected in any healthy subject tested so far. But not all patients with SARS tested positive for one of the PCR fragments. Where did this new virus come from?

Genetic Engineering Super Viruses

While the epidemic has still to run its course, a report appeared in the *Journal of Virology*, describing a method for introducing desired mutations into coronavirus in order to create new viruses. A key feature of the procedure is to make interspecific chimera recombinant viruses. It involves replacing part of the spike protein gene in the feline infectious peritonitis virus (FIPV), which causes invariably fatal infections in cats, with that of the mouse hepatitis virus. The recombinant mFIPV will no longer infect cat cells, but will infect mouse cells instead, and multiply rapidly in them.

These and other experiments in manipulating viral genomes are now routine. It shows how easy it is to create new viruses that jump host species in the laboratory in the course of apparently legitimate experiments in genetic engineering. Similar experiments could be happening in nature when no one is looking, as the SARS and many other epidemics amply demonstrate.

Where does the SARS virus come from? The obvious answer is recombination, which can readily occur when two strains of viruses infect a cell at the same time. But neither of the two progenitor strains is known, says Luis Enjuanes from the Universidad Autonoma in Madrid, Spain, one of the world leaders in the genetic manipulation of coronaviruses.

Although parts of the sequence appeared most similar to the bovine coronavirus (BCV) and the avian infectious bronchitis virus (AIBV), the rest of the genome appear

quite different. Could genetic engineering have contributed inadvertently to creating the SARSvirus? This point was not even considered by the expert coronavirologists called in to help handle the crisis, now being feted and wooed by pharmaceutical companies eager to develop vaccines.

Coronaviruses have been subjected to increasing genetic manipulation since the late 1990s, when P.S. Masters used RNA recombination to introduce changes into the genome of mouse hepatitis virus (MHV). Since then, infectious cDNA clones of transmissible TGEV, human coronavirus (HuCV), AIBV, and MHV have all been obtained.

It is not even necessary to intentionally create lethal viruses, if one so wishes. It is actually much faster and much more effective to let random recombination and mutation take place in the test tube. Using a technique called molecular breeding, millions of recombinants can be generated in a matter of minutes. These can be screened for improved function in the case of enzymes, or increased virulence, in the case of viruses and bacteria.

In other words, geneticists can now greatly speed up evolution in the laboratory to create viruses and bacteria that have never existed in all the billions of years of evolution on earth.

Controlling Bio-terrorism

John Steinbruner, University of Maryland arms control expert, has been calling for mandatory international oversight of inherently dangerous areas of biomedical research, specifically, an international body of scientists and public representatives to authorize such research.

He has taken the proposal to meetings of the American Association for the Advancement of Science and the World Medical Association in recent months, and in April 2003, to a London bio-terrorism meeting, sponsored by the Royal Society of Medicine and the New York Academy of Medicine.

The oversight system would be mandatory and would operate before potentially dangerous experiments are conducted. Access to results could also be limited to those who pass muster.

Requiring scientists, institutions and even experiments to be licensed would have a devastating chilling impact on biomedical research, said American Society for Microbiology (ASM) president Ronald M. Atlas. His answer is self-regulation, already in line with ethical requirements to prevent the destructive uses of biology.

The ASM orchestrated and supports a statement released February 15 by a group of major life sciences editors and authors, acknowledging the need to block publication of research results that could help terrorists.

Critics say even the self-censorship espoused by the journal editors and authors group is an impediment to the rapid progress of science, which is the best way to defuse the lethal potential of some biological research. But Steinbruner fears that self-regulation does not go far enough to head off terrorists.

Who needs bio-terrorists when we've got genetic engineers?

But what caught the attention of the mainstream media was the report in January 2001 of how researchers in Australia accidentally created a deadly virus that killed all its victims in the course of manipulating a harmless virus. Disaster in the making: An engineered mouse virus leaves us one step away from the ultimate bio-weapon, was the headline in the *New Scientist* article. The editorial showed even less restraint: The genie is out, biotech has just sprung a nasty surprise. Next time, it could be catastrophic.

The SARS episode should serve as a reminder of some simple facts about genetic engineering. In the first place, genetic engineering involves the rampant recombination of genetic material from widely diverse sources that would otherwise have very little opportunity to mix and recombine in nature.

In the second place, disease-causing viruses and bacteria and their genetic material are the predominant materials and tools of genetic engineering, as much as for the intentional creation of bio-weapons.

Finally, the artificial constructs created by genetic engineering are designed to cross species barriers and to jump into genomes, i.e., to further enhance and speed up horizontal gene transfer and recombination, acknowledged to be the major route to creating new disease agents, possibly much more important than point mutations which change isolated bases in DNA.

With genetic engineered constructs and organisms routinely released into the environment, we hardly need the help of terrorists. That may be why we are coming up against new epidemics of viral and bacterial diseases with increasing regularity. Mother nature is not the ultimate terrorist, we are.

A list of sources and references for this article is posted at www.i-sis.org.uk

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