



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

COMMENTARY

Comparative analysis of the SARS coronavirus genome: a good start to a long journey

See page 1779

Published online May 9, 2003

<http://image.thelancet.com/extras/03cmt124web.pdf>

Severe acute respiratory syndrome (SARS) is the latest in a long list of emerging infectious diseases to gain the attention not only of the scientific community but also of the general public. SARS is characterised by symptoms that include a temperature over 38°C, dry cough, myalgia, and mild sore throat, which progresses to atypical pneumonia. The disease is unusual in its high morbidity and mortality rates; and it mimics and indeed rivals the 1918 influenza pandemic, which still stands as the worst pandemic in history.¹ More disturbingly, SARS seems to transmit through direct contact and extreme infection-control measures are thus needed in affected areas.²

Although SARS currently has no absolutely confirmed cause, a first approximation of Koch's postulates has been satisfied for a newly discovered virus within the family *Coronaviridae*.^{3,4} This newly identified virus has been designated SARS coronavirus (SARS-CoV).⁵ Coronaviruses are large enveloped viruses with a positive-sense RNA genome ranging in size from 27 to 30 kb, the largest of any of the RNA viruses. Clinically speaking, coronaviruses are usually associated with the common cold in human beings, but in animals the virus can lead to highly virulent respiratory, enteric, and neurological diseases as well as hepatitis.⁶ Human coronaviruses are usually difficult to culture in vitro, whereas most animal coronaviruses and SARS-CoV can be easily cultured in Vero E6 cells.⁷

Recently, in a Canadian collaborative tour de force, the Michael Smith Genome Sciences Centre in Vancouver, British Columbia, and the National Microbiology Laboratory in Winnipeg, Manitoba, were the first to obtain a full sequence of SARS-CoV.^{8,9} With 29 751 bases, the genome, denoted Tor-2, possesses a classic coronavirus complement of 11 open-reading frames, S and E glycoproteins, and the matrix, replicase, and nucleocapsid proteins. However, at the aminoacid level, SARS-CoV has minimum homology with any of the three classes of coronavirus; SARS-CoV thus lies in its own group.⁹

In today's *Lancet*, Yijun Ruan and colleagues take the sequences of five SARS strains of known passage history in human beings and compare them with the Tor-2 sequence as well as other fully sequenced SARS-CoV strains from China and Vietnam. In addition to identifying small clusters of inherited mutations that are lineage-specific and can be used as molecular signatures to track transmission, the results suggest a remarkable genetic conservation of the virus since the outbreak was first documented in February, 2003. Although there are a handful of mutations between isolates, they may be due to adaption in culture. Previous experience with the evolution of influenza A virus shows

that such "end-of-lineage" changes are due to mutations selected in laboratory culture.¹⁰ In Ruan's study, most of the mutations in the SARS-CoV sequences probably represent adaption to Vero cells during propagation before sequencing. It can therefore be concluded that as the virus passes through human beings, SARS-CoV is maintaining its consensus genotype and is thus well adapted to the human host. This finding may indeed be a double-edged sword.

SARS-CoV is not likely to change rapidly and thus may not readily mutate to a benign infection, as seen with most other infectious agents transmitted by direct contact and where patients' mobility is crucial to facilitate transfer of disease. Any disease property that enhances transmission to new hosts will be the subject of positive evolutionary selective pressures.¹¹ Experimental analysis of viral evolution shows that genomic stability in a specific host is a function of viral population size—passage of large populations results in increased replicative fitness and virulence due to the competitive selection of optimising mutations.¹² By contrast, passage of limiting dosages results in decreased replicative fitness and attenuation due to the adventitious trapping of deleterious mutations. The hope with SARS-CoV is that it will attenuate its properties in human beings. Sadly, Ruan and colleagues' results suggest that this attenuation does not seem to be happening at a rapid rate and may indicate a worrisome epidemiological trend.

Yet, there may be a bright side to the evidence reported by Ruan and colleagues. The apparent genetic stability makes a vaccine seem more achievable. However, coronaviruses can transduce genes from foreign genomes, recombine with other coronaviruses, and mutate to drive rapid and extreme evolution—presumably SARS-CoV is a product of such evolution. Furthermore, SARS-CoV was found in the faeces of patients,³ which indicates more than one tissue tropism. This discovery also raises the slight possibility of transmission through water in which the property of high virulence can be maintained under conditions that allow untreated sewage contamination of surface and ground waters.¹¹ In addition, animal and human experiences with coronaviruses have illustrated a range of problems, including a lack of protective immunity, persistent infection, and immune enhancement (in which antiviral antibodies increase disease progression). This latter problem may explain in part the relatively high mortality rate. If a vaccine is possible, there is a long way to go.

There is also one more very puzzling aspect to the SARS story, which comes to the heart of the confusion and concern in the scientific and medical communities. Where and how did SARS arise? A great deal of retrospective isolation and genomic sequencing of human and animal

coronaviruses, especially in the virological hotbed of southern China, is required for the molecular sleuthing needed to solve this puzzle. SARS-CoV possesses a novel organisation of five open-reading frames that encode proteins with as yet unknown functions which, from experience with other viruses, may encode antagonists of innate and adaptive immunity.¹³ Much like the human genome, the SARS-CoV genetic code charts a detailed roadmap through unknown territories. Molecular virologists now need to interpret gene function from this genetic sequence, which will not be easy given that single aminoacid changes can dramatically affect biological function.

As the SARS outbreak looks to be contained in the more technologically advanced regions of the world, complacency must be avoided. That a coronavirus with high virulence has arisen should not be a surprise, because historically the worst epidemics of respiratory disease have come from the influenza A viruses, which ominously share several biological features with coronaviruses. Both viruses are zoonoses, both have instances of dual tropism for respiratory and gastrointestinal tissues, and, most importantly, both possess mechanisms for the generation of extreme genetic variability. Models of influenza might guide the understanding of the SARS coronavirus.¹⁴

There is a short period of grace in which to combat SARS. The major questions about SARS-CoV control and biology, such as mode of transmission, spread, and mechanisms of virulence, need answering—before the next time SARS rears its ugly corona.

*Earl G Brown, Jason A Tetro

Department of Biochemistry, Microbiology and Immunology,
Faculty of Medicine, University of Ottawa, Ottawa, Ontario,
Canada K1H 8M5
(e-mail: ebrown@uottawa.ca)

- Luk J, Gross P, Thompson WW. Observations on mortality during the 1918 influenza pandemic. *Clin Infect Dis* 2001; **33**: 1375–78.
- World Health Organization. Hospital infection control guidance for severe acute respiratory syndrome (SARS). April 24, 2003: <http://www.who.int/csr/sars/infectioncontrol/en/> (accessed May 2, 2003).
- Peiris JSM, Lai ST, Poon LLM, et al. Coronavirus as a possible cause of severe acute respiratory syndrome. *Lancet* 2003; **361**: 1319–25.
- Ksiazek TG, Erdman D, Goldsmith CS, et al. A novel coronavirus associated with severe acute respiratory syndrome. *N Engl J Med* 2003; **348**: 1953–66.
- World Health Organization. Update 31: coronavirus never before seen in humans is the cause of SARS. April 16, 2003: http://www.who.int/csr/sarsarchive/2003_04_16/en/ (accessed May 2, 2003).
- Lai MMC, Holmes KV. Coronaviridae: the viruses and their replication. In: Knipe DM, Howley PM, eds. *Fields virology*, 4th edn. London: Lippincott Williams & Wilkins, 2001: 1163–86.
- Drosten C, Günther S, Preiser W, et al. Identification of a novel coronavirus in patients with severe acute respiratory syndrome. *N Engl J Med* 2003: <http://content.nejm.org/cgi/content/abstract/NEJMoa030747v2> (accessed May 6, 2003).
- Rota PA, Oberste MS, Monroe SS. Characterization of a novel coronavirus associated with severe acute respiratory syndrome. *Science* 2003: <http://www.sciencemag.org/cgi/rapidpdf/1085952v1.pdf> (accessed May 6, 2003).
- Marra MA, Jones SJM, Astell CR, et al. The genome sequence of the SARS-associated coronavirus. *Science* 2003: <http://www.sciencemag.org/cgi/rapidpdf/1085953v1.pdf> (accessed May 6, 2003).
- Bush RM, Smith CB, Cox NJ, Fitch WM. Effects of passage history and sampling bias on phylogenetic reconstruction of human influenza A evolution. *Proc Natl Acad Sci USA* 2000; **97**: 6974–80.
- Ewald PW. The evolution of virulence and emerging diseases. *J Urban Health* 1998; **75**: 480–91.
- Brown EG, Liu H, Kit LC, Baird S, Nesrallah M. Pattern of mutation in the genome of influenza A virus on adaptation to increased virulence in the mouse lung: identification of functional themes. *Proc Natl Acad Sci USA* 2001; **98**: 6883–88.
- Seo SH, Hoffmann E, Webster RG. Lethal H5N1 influenza viruses escape host anti-viral cytokine responses. *Nat Med* 2002; **8**: 950–54.
- Fields BN. AIDS: time to turn to basic science. *Nature* 1994; **369**: 95–96.

Poststroke depression: getting the full picture

Since the 1970s, debate has raged over the origin of poststroke depression. Is it a reaction to the catastrophic onset of disability and all its attendant life changes, or is it the organic result of structural or biochemical changes in the brain resulting from neurological damage?

Reports in the 1970s and early 1980s suggested that poststroke depression was more common in left-hemisphere lesions.^{1,2} As routine CT scanning allowed more precise localisation, depression seemed to be related not only to lateralisation but also to proximity to the frontal pole.^{3,4} However, Gainotti et al⁵ pointed out that a significant proportion of left-sided strokes was excluded because of severe language problems, and when this selection bias was corrected, left frontal lesions were no longer a major determinant of depression. Other investigators^{6–8} were also unable to confirm the association with localisation of damage. A systematic review⁹ of the importance of lesion location in poststroke depression revealed the usual methodological limitations. None of the studies were completely comparable in timing, sampling, analysis of CT scan, or psychiatric evaluation. However, the reviewers concluded that there was insufficient evidence to associate poststroke depression with location of the lesion.

In the 1990s, further development of techniques (eg, positron-emission tomography) allowed exploration of biochemical and neurophysiological changes in the brain, such as binding of serotonin receptors.¹⁰ These results, together with the reported efficacy of selective serotonin-reuptake inhibitors in the management of poststroke depression,¹¹ supported the notion that biochemical change, rather than localised structural damage, led to the alteration of mood state after stroke.

Ivo Aben and colleagues¹² recently compared the cumulative incidence of depression during the first year after stroke and first-ever myocardial infarction. They demonstrated that, although the stroke patients seemed on first sight to have a higher incidence of depression (39% vs 28%), this difference disappeared once non-specific factors such as age, sex, and level of handicap were taken into account. This result suggests that poststroke depression does not in fact reflect a specific pathogenic mechanism. As the investigators point out, however, there are several potential weaknesses in their design—one of the most significant being that stroke patients with aphasia and severe cognitive deficits were excluded because they were unable to complete the self-assessment questionnaires used to measure depression. In all, 44% of the total population were excluded in the stroke group, compared with only 23% in the myocardial infarction group. These exclusions might have had an effect on the results.

Dysphasia is predominantly associated with left-hemisphere lesions. However, the resulting inability to communicate can rapidly lead to social isolation and breakdown of relationships. Thus dysphasia also ranks highly in the order of deficits likely to be associated with reactive depression. In studies of this sort, therefore, it is vitally important to include these patients when possible to ensure unbiased representation. The Beck Depression Inventory and the Hospital Anxiety and Depression Scale used to assess depression in Aben's study are useful and widely evaluated tools in the general population, but pose certain difficulties for stroke patients. Fairly sophisticated language, reading, and cognitive skills are required to complete these scales reliably.

Several techniques have been developed to overcome these difficulties. Gordon et al¹³ developed a structured