Rev. Med. Virol. 2013; **23**: 211–212.
Published online 21 May 2013 in Wiley Online Library
(wileyonlinelibrary.com)
DOI: 10.1002/rmv.1748

EDITORIAL

Editorial: an anniversary and a new member of the family

How rapidly a decade flashes by! Was it really 10 years ago when we heard, bit by bit, about a new disease with frightening, even apocalyptic potential? When tales of heroism were supplanted, temporarily, by fears of bioterrorism as the ominously numbered room 911 of the Metropole Hotel accommodated the first case to come to widespread attention in the West? The true origin turned out to be nature, not man, acting as a malign force to create a novel pathogen. And now, we have another virus from the same family affecting the same body system as the one from a decade ago. Will it stay localised to small pockets of infection or cause another pandemic like its cousin?

The story of Severe Acute Respiratory Syndrome (SARS) is given in standard textbooks [1]. The first cases appeared in Guandong, China in November 2002, but were not widely reported. Dr Carlo Urbani identified a case in Hanoi in February 2003 and urged the WHO into action, but soon succumbed to SARS himself. SARS coronavirus (SARS-CoV) was identified as the causative agent [2] and the palm civit the offending mammal vector that facilitated transfer from bats [1]. The cellular receptor was identified as angiotensin converting enzyme 2 [3].

Koch's postulates were fulfilled when virus derived from cell culture produced pneumonia in macaques from whom SARS-CoV could be re-isolated [4]. SARS-CoV was not highly contagious early in the disease course but, once the viral load peaked around day 10 of illness, the scene was set for transmission, especially when respiratory secretions were manipulated during clinical care. Standard precautions for control of infection, coupled with restrictions on international travel, were effective at terminating transmission and ending the pandemic, but left behind a case fatality rate of approximately 10% among the more than 8000 people affected [1]. Many treatments were tried in sick patients but without the controls necessary to determine if any intervention had beneficial or detrimental effects. Indeed, a systematic review, requested by WHO, commented that there was no evidence of efficacy, whereas several studies showed possible evidence of harm from the treatments offered, including ribavirin and steroids [5].

Starting in June 2012, cases of severe respiratory disease were reported in patients originating from the Arabian Peninsula, together with cases transferred to the UK and to Germany [6]. A novel coronavirus (nCoV) was identified which is also termed hCoV-EMC for Erasmus Medical Centre [7]. Four individual isolates have been sequenced and all appear very similar to each other [8]. The cellular receptor is dipeptidyl peptidase 4 (DPP4) [9]. Macaques were again used to satisfy Koch's postulates and prove that nCoV causes pneumonia [10]. Laboratory assays for both virus detection and serology have been produced and evaluated [11].

The disease presentation of pneumonia, sometimes with renal failure, is supported by finding dipeptidyl peptidase 4 receptors in both bronchial epithelium and kidneys [9]. Interestingly, in organ cultures, nCoV infected endothelial cells, type II pneumocytes and non-ciliated bronchial epithelium as well as the ciliated cells that respiratory viruses normally prefer [12]. In epithelial cell cultures, the nCoV disrupted the host transcriptome more than did SARS-CoV; specifically, nCoV downregulated both Class I and Class II major histocompatibility complex genes [13]. These components of the antigen presentation system were targeted by known inhibitors of signalling pathways, with corresponding reductions in viral titres shown for at least one compound [13]. In Vero and rhesus monkey kidney cell cultures, virus replication was inhibited by ribavirin and interferon, with evidence of an additive effect of the combination [14]. Genetic studies point to a bat origin for the virus [7] with speculation that animals found in the Gulf, such as camels and goats, might provide the link to humans [15]. As of 25 April 2013, there have been 17 cases with 11 deaths [8]. The median age of the patients has been 45, with an excess of males. They are grouped into four clusters; a healthcare facility in Jordan, two

separate families in Saudi Arabia and a family in the UK with a member who had travelled from Saudi Arabia [8]. So far, there is only limited evidence of person-to-person transmission [16,17].

Although there are striking parallels here with the aetiology and clinical severity of SARS, it is impossible to predict how the nCoV will affect the next editions of virology textbooks; will it become an important pathogen justifying a whole section or will it be a damp squib warranting merely a footnote? We are fortunate to have access to molecular biology to track the evolution of this virus, but the sensitive assays that are now available may be equally able to monitor the evolution of viruses that are failures as well as their close relatives that successfully adapt to infect humans. Only time will tell which direction this new virus will take and it will be interesting to look back in 2023 for a ten-year perspective on this latest member of the *Coronaviridae*.

P. D. Griffiths
p.griffiths@ucl.ac.uk

REFERENCES

1. Peiris PS, Poon LLM. Coronavirus and Toroviruses. In *Principles and Practice of Clinical Virology*, 6th edn, Zuckerman AJ, Banatvala JE, Schoub BD, Griffiths PD, Mortimer P (eds). Wiley-Blackwell: Chichester, 2009; 511–531.
2. Peiris JS, Lai ST, Poon LL, *et al*. Coronavirus as a possible cause of severe acute respiratory syndrome. *Lancet* 2003; **361**(9366): 1319–1325.
3. Li W, Moore MJ, Vasilieva N, *et al*. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. *Nature* 2003; **426**(6965): 450–454.
4. Fouchier RA, Kuiken T, Schutten M, *et al*. Aetiology: Koch's postulates fulfilled for SARS virus. *Nature* 2003; **423**(6937): 240.
5. Stockman LJ, Bellamy R, Garner P. SARS: systematic review of treatment effects. *PLoS Medicine* 2006; **3**(9): e343.
6. Bermingham A, Chand MA, Brown CS, *et al*. Severe respiratory illness caused by a novel coronavirus, in a patient transferred to the United Kingdom from the Middle East, September 2012. *Euro Surveillance* 2012; **17**(40): 20290.
7. Van-Boheemen S, de Graaf M, Lauber C, *et al*. Genomic characterization of a newly discovered coronavirus associated with acute respiratory distress syndrome in humans. *MBio* 2012; **3**(6): pii: e00473-12.
8. World Health Organization. Novel coronavirus summary and literature update – as of 25 April 2013. Global Alert and Response (GAR). Online Source [http://www.who.int/csr/disease/coronavirus_infections/update_20130425/en/index.html]
9. Raj VS, Mou H, Smits SL, *et al*. Dipeptidyl peptidase 4 is a functional receptor for the emerging human coronavirus-EMC. *Nature* 2013; **495**(7440): 251–254.
10. Munster VJ, de Wit E, Feldmann H. Pneumonia from human coronavirus in a macaque model. *The New England Journal of Medicine* 2013; **368**(16): 1560–1562.
11. Corman VM, Muller MA, Costabel U, *et al*. Assays for laboratory confirmation of novel human coronavirus (hCoV-EMC) infections. *Euro Surveillance* 2012; **17**(49): pii: 20334.
12. Chan RW, Chan MC, Agnihothram S, *et al*. Tropism and innate immune responses of the novel human betacoronavirus lineage C virus in human *ex vivo* respiratory organ cultures. *Journal of Virology* 2013; [Epub ahead of print].
13. Josset L, Menachery VD, Gralinski LE, *et al*. Cell host response to infection with novel human coronavirus EMC predicts potential antivirals and important differences with SARS coronavirus. *MBio* 2013; **4**(3): mBio.00165-13.
14. Falzarano D, de Wit E, Martellaro C, Callison J, Munster VJ, Feldmann H. Inhibition of novel beta coronavirus replication by a combination of interferon-alpha2b and ribavirin. *Scientific Reports* 2013; **3**: 1686.
15. Enserink M. Emerging diseases. New coronavirus reveals some of its secrets. *Science* 2013; **340**(6128): 17–18.
16. Buchholz U, Muller MA, Nitsche A, *et al*. Contact investigation of a case of human novel coronavirus infection treated in a German hospital, October–November 2012. *Euro Surveillance* 2013; **18**(8): pii: 20406.
17. Health Protection Agency. Evidence of person-to-person transmission within a family cluster of novel coronavirus infections, United Kingdom, February 2013. *Euro Surveillance* 2013; **18**(11): pii: 20427.

DOI: 10.1002/rmv