LESSONS FROM PRIOR CORONAVIRUS EPIDEMICS

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The coronavirus causing the COVID-19 epidemic, SARS CoV-2, was first detected in Wuhan, China on December 12, 2019, although the epidemic was not disclosed to the World Health Organization until December 31st. SARS CoV-2 was named because of its close relationship to SARS CoV-1 (Severe Acute Respiratory Syndrome Coronavirus-1) that caused a more limited epidemic in 2003. That coronavirus infected 8,098 individuals and caused 774 deaths for a mortality rate of almost 10%. That epidemic ended because the virus was much less transmissible than the coronavirus causing COVID-19 (see below for more on this). No effective vaccine or antiviral therapy was developed during the epidemic or in the ensuing years.

Another coronavirus epidemic was recognized in 2012. This was caused by the MERS-CoV (Middle Eastern Respiratory Syndrome Coronavirus) and infected 2,494 individuals, many in Saudi Arabia, and caused 858 deaths, a 34% mortality rate. Camels were the intermediate host for the virus, and camel-to-human transmission exceeded the rate of human-to-human transmission except for healthcare workers treating infected patients. No vaccine against MERS CoV has been developed, but several protease inhibitors originally developed to treat the AIDS virus have shown some clinical benefit in a limited number of MERS-CoV-infected individuals. Like many other viruses, the coronaviruses reproduce by making long precursor proteins that are not functional until they are cut into smaller units by proteases (enzymes that act like scissors). Protease inhibitors prevent this cleavage and let the larger, non-functional proteins accumulate. Protease inhibitors have been used in a few individuals with COVID-19 disease with a possible antiviral effect, but these are anecdotal reports, not carefully controlled clinical trials.

Genetic sequence analysis has revealed that the current SARS CoV-2 epidemic represents the third zoonotic transmission of coronaviruses from bats to humans, with each transmission involving an intermediate host (thought to be civets for SARS CoV-1, camels for MERS, and perhaps chickens for SARS CoV-2). What is so dangerous about the COVID-19 coronavirus is the ease with which it is transmitted between humans. The most likely explanation for increased transmission is the observed changes in the coronavirus spike protein that mediates binding to human cells. The SARS CoV-2 spike protein is predicted to bind to the cell receptor for the virus much better than SARS CoV-1 and MERS based on differences in the critical receptor-binding region of the spike. This change would be analogous to having a key that perfectly fits the door lock instead of one that only partially fits and works part of the time after a lot of jiggling.

Entry inhibitors that block receptor binding have been developed for the AIDS virus, but mainline therapy depends on small molecule inhibitors that block proteases and other critical components of virus replication. There are a host of candidate inhibitors to try with the COVID-19 virus, and many laboratories in the US are working as fast as possible to identify the best inhibitor (or combination of inhibitors) and get them into clinical trials. Unfortunately, there will be no shortage of infected patients to enroll in these trials.