Pulmonary Perspective

Severe Acute Respiratory Syndrome and Influenza
Virus Incursions from Southern China

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Only when we are at peace with nature will disease begin to melt away.

The eminent sinologist and historian, Joseph Needham, writing with his colleague Lu Gwei-Djen in the sixth volume of his mighty tome "Science and Civilization in China," emphasized the long held Chinese conviction that "the best medicine is preventive medicine," a conviction that goes back to the Warring States period (475–221 B.C.) when there was a flowering of philosophy and medical understanding. A Han Dynasty (206 B.C.–220 A.D.) writing concludes "A skillful doctor cures illness when there is no sign of disease, and thus the disease never comes" (1, 2). This component of the "Chinese Hippocratic Corpus," as Needham calls it, holds just as true in today's modern world and may be simply summed-up in one word: "awareness." In the case of emerging infectious disease, this means "preparedness," giving rise to "reaction."

Two thousand or so years onward in the China of today, this conviction is being sorely tested by nature with incursions of respiratory viruses from its southeastern province of Guangdong adjacent to Hong Kong. In 1997, the world was thrown into a state of alarm and high alert arising from the emergence of a potentially new influenza pandemic caused by the transmission of a highly pathogenic H5N1 influenza virus (H5N1/97) of avian origin from chickens to humans in Hong Kong (3–5). On that occasion, a pandemic was only one or two mutational events away. H5N1-like viruses were recognized in chicken and other land-based poultry in Hong Kong in 2001 and 2002 before they could infect humans (6, 7). Probably three or four mutational events from generating a pandemic influenza virus, these more recent incidents upheld the ancient ideal of preventing disease before it appears. In these cases the virus did not "escape" from Hong Kong almost certainly because of its having had sound human and animal disease and virus surveillance systems in place for some time. This led to the recognition of the source of the virus and its removal by the slaughter of poultry in live markets and on farms, or a combination of slaughter and ring vaccination on farms (6–8).

Over the years, Hong Kong essentially functioned as an influenza sentinel post for the wider region, stemming from the hypothesis that southern China is an epicenter for the emergence of pandemic influenza viruses (9). This hypothesis drew its strength from an earlier hypothesis generated from the 1968 H3N2 (Hong Kong) pandemic virus that pandemic influenza viruses have an animal origin (10). Consequently, a blueprint evolved to provide baseline preparedness at the human–animal interface in the epicenter for an inevitable influenza pandemic (11). The lack of signals indicating the emergence of the 1968 pandemic prompted Stuart-Harris to write soon after "Those who have spent their lives in attempts to further the conquest of infectious disease are humiliated by the contrast between the success of the astronauts and the failure to control acute respiratory disease" (12). Understanding animals and the ecology of their viruses might prove to be a positive, if not decisive, contribution in dealing with known and yet-to-be-revealed zoonotic situations.

In mid- to late-February 2003, the alarm of 1997 verged on panic in some areas of the world after the international seeding by air travel of a hitherto unrecognized coronavirus (SCoV), possibly of animal origin, which was isolated in Hong Kong from cases of severe atypical pneumonia (13). The disease was designated severe acute respiratory syndrome, or SARS (14), coming on the heels of an outbreak of severe atypical pneumonia with a reported case fatality rate around 4% some 3 months earlier in Guangdong Province (15). These circumstances, along with the clinical similarity between H5N1 "bird flu" and SARS (13), triggered the World Health Organization (WHO) Global Influenza Surveillance Network's reaction against SARS (16) in a manner befitting a newly emerging pandemic influenza virus. All the more so since the SCoV originated in the pandemic influenza epicenter as had the influenza H5N1/97 virus previously (4, 8) leading to a new level of international cooperation and collaboration within and outside the Network (16, 17) to stem the further spread of SARS. This splendid interaction gave rise to a series of reports confirming the isolation of a novel coronavirus from SARS patients from a number of centers (e.g., 18–21), wider aspects of the disease, its epidemiology, and its transmission (e.g., 22–24).

While many experts were primed for dealing with this newfound situation, the WHO played a leadership role in coordinating the multilevel activities involved. National health authorities in 30 countries reporting SARS cases reacted vigorously in their control measures (25), and in early July, WHO declared that the SARS outbreak had been contained worldwide (26); a great achievement. The virus had been dealt with decisively at the many focal points around the globe. Nonetheless, WHO issued a caveat of the need for continued vigilance worldwide for the possible reemergence of SARS (27) arising from, say, previously undetected, long-term carriers or fresh infections arising from contact with infected animals.

Because the earliest SARS cases in Guangdong Province reportedly occurred in restaurant workers handling wild animals as exotic food (28), and early phylogenetic analysis indicated

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that the SCoV was of novel zoonotic origin (13), wild mammals found in live retail markets supplying the restaurant trade were examined for the presence of the SARS virus. SCoV-like viruses with 99.8% genetic homology with the SCoV were isolated from Himalayan or masked palm civets (*Paguma larvata*) and a raccoon dog (*Nyctereutes procyonoides*) and neutralizing antibody detected in them and a Chinese ferret badger (*Melogale moschata*) (29). The human and wild mammal isolates could be distinguished phylogenetically within the nucleotide polymorphism of the spike gene, the gene encoding the protein responsible for the virus's coronal appearance. These and other data strongly suggested that the human SCoV is unlikely to have been the product of a recent intercoronaviral, recombination event (30) given the propensity of coronaviruses to recombine (31), and that index infection was from an established animal virus resident in animals (29).

Just as pandemic influenza is now considered a noneradicable zoonosis, the question arises whether SARS is, too. This begets the central question whether the civet cat is the prime host of SCoV-like viruses and whether human infection was the result of an enzootic or epizootic. Much work now needs to be done to understand the ecology of the virus. Studies of this kind may provide insight into the extent and diversity of coronaviruses in the animal kingdom; studies, which over the next decade, will have the value-added effect of improved understanding of common cold coronaviruses and their likely control by antiviral agents.

While the domestication of the duck 4,500 years ago brought influenza viruses into the "farmyard", leading to the emergence of epidemics and pandemics (32), information of the involvement of wild, exotic mammals in the SARS outbreak as it presently stands (28, 29) suggests that outbreaks of SARS-like illness may have occurred in times past in the countryside. Such outbreaks may have been just as severe as the recent episode but probably would have died out because of limited opportunity for the virus to spread from village focal points. Bringing exotic mammals, presumably stressed and shedding increased levels of virus, into densely populated centers contrives an artificial setting ideal for exposing animal handlers and the public to the virus. Burgeoning national and international travel exposed the existence of the SARS disease and its causative agent.

It remains to be seen whether SARS has a parallel with pandemic influenza in which domestic animals act as an intermediate or amplifying host for viruses originating from the wild. Here, it should be noted that duck-raising practices were modified at the start of the Ching Dynasty (1644 A.D.) by moving the birds from river banks and tributaries onto flooded rice fields as an adjunct to rice farming. This beautifully balanced ecosystem led to a permanent gene pool of avian influenza viruses in southern China (and other parts of east Asia) in close proximity to humans (9, 32, 33). In city markets, the continuity of SARS-like and avian influenza viruses depends greatly on the mix of animals, their duration in the market, how they are held after trading, and hygienic handling practices. The worth of systematic virus surveillance as a preventative measure against pandemic influenza has been established (34). Now, surveillance will need to be vigorously pursued to define the ecology and the most important source(s) of SCoV-like virus(es) for humans to this end. This task may take some time. Basic studies on the nature and distribution of virus receptors in the intestinal and respiratory tracts of representative wild and domestic and domesticated animals may give an early guide to this task.

Given the diversity of coronaviruses in domestic animals and the demonstrated ability of some to recombine (31), the possibility exists that the host range and pathogenicity of the civet cat and raccoon dog SCoV-like viruses could alter should they recombine with other coronaviruses. Were an SCoV or SCoV-like virus to recombine with a human coronavirus, known or as-yet unidentified, changes in host range and pathogenicity of each virus might ensue. These are uncharted waters.

The association of southern China with the emergence of respiratory virus infections raises the question of why this is so. H5N1/97 virus, its precursor viruses H5N1, H9N2, H6N1, and H5N1-like viruses have been isolated from domestic poultry in the region (e.g., 5, 35–37), and now there is the SCoV-like virus from the civet cat and raccoon dog (29). Live retail markets are the common denominator for this. Consequently, attention has focused on this type of market as a breeding ground for infections that affect humans (38). Chinese generally prefer food as fresh as possible. Taste is the prime consideration, thus meat should be from freshly killed animals. This particularly applies to poultry, giving rise to the existence of live-poultry markets. Poultry comprise two groups: major poultry, chicken, duck and goose, the chicken being the most important; and minor poultry, including pigeon, quail, pheasant, chukar, partridge, Guinea fowl, and waterfowl. Avian influenza viruses have been isolated from all of these birds.

The southern Chinese have a more marked preference for fresh food (of all kinds) nurtured particularly in the southeast corner by fertile land. Yet despite this, economic hardship persisted. Much of what was raised or grown was sold or traded, leaving poorer quality food for family consumption. The housewife ingeniously used all parts of an animal. Meat that was not produced had to be hunted, valued as much for its nutritive value as for its added taste. The scarcity (and seasonality) of such animals enhanced their value. There was also the belief that just as "like-healed-like," certain parts of the animal would enhance the human equivalent. For example, brains were cooked and given to scholars, feet/trotters were thought to enhance speed or other athletic performance, and so on. A main meat dish would only appear on the table for celebrations or feast days (39).

These traditions continue to the present, accounting for exotic food markets and, it appears, the SARS phenomenon. One of the intriguing aspects of the index case was that it occurred in mid-November (28), when snake meat and other snake parts are widely consumed to ward off the chills of the coming winter, raising the question of whether snakes are hosts to coronaviruses and what is the susceptibility of mammals, such as the civet cat, to infection by such viruses. The opportunity for exchange of viruses amongst different hosts, particularly from feces in cages, shop floors, holding pens, and killing rooms, would be considerable. Systematic virus surveillance of lower animals for coronaviruses is warranted.

Just as SARS investigations benefited from the ecologic studies on influenza viruses before it, so, too, influenza investigations stand to progress from the SARS experience. More than likely, the two fields will develop in tandem. It has often been said that influenza virologists should link hands with arbovirologists because of the overlapping interest in diverse nonhuman hosts. SARS investigations would benefit from this link, too, the spreading West Nile virus is a case in point (40). Such a conjoint relationship may offer a better prospect for infectious-disease intelligence (41). Although influenza-like viruses have been isolated from nonmammalian hosts (42, 43), probably more ecologically important is the recognition that a mammal, such as the mink, is susceptible to infection by the avian influenza virus H10N4 (44). On a personal note, the writer's interest in exploring animals as a source of pandemic influenza viruses was stirred by the detection of virus infectivity neutralizing activity for the reference H2N2 (Asian) influenza virus in the sera of two Asiatic black bears (*Selenarctus thibetanus)* and an orangutan (*Pongo*

pygmaeus) obtained in the mid-1960s from a zoologic collection (45). Although it was not possible to know whether these animals had been infected in the wild or in the zoo (as was more likely), the fact that the bears were subsequently traced back to a zoologic gardens in Hong Kong and that the sera were examined in the wake of the 1968 H3N2 (Hong Kong) pandemic was compelling.

Perhaps the greatest enigma about influenza is that pandemics occur on a time scale measured in decades rather than in years. This is despite the inestimable number of avian influenza viruses in southern China and the close association between humans and domestic animals in the countryside, facilitating exposure, as well as their presence in stressed poultry in live, retail markets. The possibility of infection through contact with wild animals in the countryside and city markets cannot be overlooked. More than likely, infection in the countryside is not uncommon (33), indicating how little is known about the genetic and molecular factors involved in the genesis of a pandemic virus in spite of recent advances (e.g., 46–48). While there may be only a limited number of hemagglutinin subtypes of virus with the hierarchic capabilities for sustained antigenic progression in humans (49), the odds for a subtype giving rise to a pandemic virus must be inordinately high.

The factors involved in the genesis of each pandemic virus are probably different. Thus, whereas the H5N1 virus must be the prime candidate for pandemicity at present (34, 50), unless these factors are in place, it is quite possible that another virus subtype could preempt it. Bearing in mind the awareness about H5N1, it would be a step forward if its incursions could be limited to brushfires (51, 52). Recent events in southern China have indicated that avian influenza H5N1 and H9N2 viruses can directly infect humans (4, 53, 54) without undergoing prior reassortment with a prevailing human influenza A virus, in which the pig acts as a genetic mammalian "mixing vessel" (55). Certain avian H9 influenza viruses in southern China are presently undergoing remarkable evolutionary changes as they move through aquatic and terrestrial poultry, resulting in changes that would seemingly facilitate human infection (36). The potential role of the pig in the genesis of a future pandemic virus cannot be underestimated. It hosts both avian H9N2 and human H3N2 viruses, and serologic evidence indicates its susceptibility to infection by avian H4, H5, and H9 viruses (56, 57). It is quite possible that had the H5N1/97 virus undergone prior reassortment in a pig, it could have given rise to a "full-blooded" pandemic virus at the outset with little or no warning, and the outcome would have been dramatically different.

Of recent respiratory virus incursions from southern China, influenza has an historic association with the region, whereas SARS apparently does not. This association linking China as a place of origin of influenza epidemics and pandemics goes back centuries (58), in keeping with a view in 1918 that "the great pandemics usually originated in the Far East, and gradually extended westward" (59). The first pandemic for which there is epidemiologically cogent data "narrowing" this down to southern China was that of 1889 (60). The pandemic that continues to arouse much interest is that of 1918, considered the deadliest in history, which was caused by an H1N1-like virus (61). This interest stems from a concern that a virus of the same order of potency could emerge in the future. Information on the genetic and molecular features responsible for this may be of prognostic value in examining avian and other influenza viruses in the influenza gene pool. At issue here is whether the 1918 virus arose from the gene pool in southern China (62). There are gaps in information, but it is the writer's view that the simple epidemiologic information available (63, 64) provides an indication that the virus may have arisen in southern China some years before 1918 (65). Outbreaks of influenza in Europe in 1916 are therefore of interest (66). The recognition of an incipient pandemic situation with the H5N1 virus in 1997 (8) and the isolation of H9N2 viruses from human cases in Hong Kong and China (54, 67) consolidate the importance of southern China as a region from which future pandemics might arise. Much effort in the influenza epicenter now needs to be directed toward getting ahead of the next pandemic virus. Surveillance of noisy objects for viruses might not be considered! (68).

It would be folly not to be aware of the possibility that an influenza pandemic could arise beyond the southern China epicenter. As recent pandemic viruses have been of the Eurasian lineage, avian influenza viruses on the Eurasian landmass, as well as in Africa and Australasia, may have a greater propensity for pandemicity than those of the North American lineage. The recent outbreak of highly pathogenic H7N7 influenza virus infection in chickens in The Netherlands, with cases of conjunctivitis and the death of a veterinarian, is of concern (69). The spread of H9N2 viruses mainly in chickens approaching panzootic proportions (70) indicates their potential for causing human disease beyond the epicenter. Influenza H6N2 viruses have recently been isolated from chickens in California whose H6 genes do not fit into clearly defined North American or Eurasian lineages, raising the question whether these (and perhaps other) Eurasian viruses are in the process of spreading to North America (71). Veterinary regulatory authorities and health authorities alike need to be aware of the wider dimensions of avian influenza viruses. The possibility of SARS emerging indigenously beyond southern China should not be overlooked. Surveillance of the civet cat, raccoon dog, and related animals for coronaviruses in and beyond China is of importance. This is particularly so in the case of the civet cat, which is raised commercially for the perfume industry.

In November 2002, the SARS genie escaped from the bottle in southern China. On July 5 2003, the WHO announced that, on available information, human chains of SCoV transmission appeared to have been broken globally (26). The question remains whether the genie has returned to the bottle. As respiratory virus infections are more prevalent in winter in temperate climates, the coming months could be a reasonable guide to the answer. Surveillance, surveillance, surveillance, clinically and virologically, as part of a wider initiative of infectious disease intelligence, holds the key to this answer for SARS and pandemic influenza, particularly in the southern China focus (41). As a backdrop to this question, the observation in one study in Hong Kong, that chronic hepatitis-B infection is an independent risk factor for progression to acute respiratory distress syndrome (22), warrants wider epidemiologic investigation. It remains to be seen whether the higher numbers of SARS cases in China, Taiwan, Singapore, and Hong Kong (25) are epidemiologically significant compared with the significance of hepatitis B in these places. Until the SCoV-like virus ecology is better understood, it will be important to minimize contact with exotic food animals (72) lest SARS makes a return in the short or long term (73).

The last thing the world needs is another problem. One of the many problems facing mankind is the continued existence of classical infectious diseases, including parasitic diseases and the emergence and reemergence of others over the last 30–40 years, with the prospect of more to come. There has been a zoonotic skew in recently emerged diseases—a trend that is likely to continue, largely due to human behavior (74). Introducing domestic and exotic animals into population centers artificially widens the human–wildlife continuum. On the plus side, smallpox has been eradicated (notwithstanding the holding of known reference stocks in two centers) and poliomyelitis stands to be eradicated within the decade. Pandemic influenza remains a noneradicable zoonosis, and SARS has made an unwelcome zoo-

notic incursion. It is as if nature will continue to test mankind, seemingly holding all the aces, in spite of the great advances in science and technology. It is the writer's view that mankind must take nature on board as an equal partner rather than as an adversary, the two working for the benefit of all, harnessing all that science and technology can facilitate. A world devoid of infectious diseases will be a great leap forward in human development.

The time is now ripe, particularly with the splendid collaboration and cooperation that were manifested during the SARS outbreak (16), for the Warring States conviction that "the best medicine is preventative medicine (1, 2) to complete the cycle of history" in China and for China to usher in a new era toward preventing the emergence of infectious respiratory virus diseases. Bridging gaps through an invigorated flowering in understanding and awareness and through the need to recognize, report, and react to untoward infectious respiratory (and other) diseases in China are paramount in this prevention and is dependent on sound political will (34). Such action will be beneficial for dealing with SARS should it recur and critical toward early preventative steps in handling a future influenza pandemic, the impact of which will surely be greater than that of SARS (75). Action of this kind stands to benefit not only China but the global community (76).

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