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Editorial

Breaking the species barrier

The years 1997–1998 brought climatic upheaval to Peninsular Malaysia in the form of a prolonged El Ni□o–Southern Oscillation-related drought together with months of ugly haze when unregulated slash-and-burn clearing of Indonesian forests darkened the sky [1, 2]. Fruit bat colonies found their food sources endangered and showed increased tendencies to migrate in search of new ones [3]. This was also a time of expansion of pig farming in Malaysia and export of pork to neighboring Singapore. Disaster came when an epidemic of a mysterious febrile illness, with minor respiratory and dramatic neurological symptoms, appearing first among pig farmers in the suburb of Ipoh, Perak on the northwestern Peninsular Malaysia. Early differential diagnosis included the mosquito-borne Japanese-encephalitis virus, but this proved incorrect [4]. Thus, early control measures, including anti-mosquito foggings and vaccination of pigs against JE, were ineffective. Farmers sold infected pigs to other farms across the county, often surreptitiously, causing spread of the disease. Conflicting governmental pronouncements that JE was the culprit delayed appropriate action for outbreak control [5, 6]. An entirely new virus, Nipah virus (NiV), related closely to Hendra virus that was already known in Australia for causing a deadly encephalitis in horses and several human deaths, was shown to be responsible for the Malaysian outbreak. Pteropid fruit bats were identified as the primary natural reservoir with the pig population as the secondary host [7]. The outbreak expanded with exported pigs to an abattoir in Singapore causing cases of infection and a death among workers there [8]. The Singaporean response was to prohibit the import of pigs from Malaysia, thus containing the outbreak. Over 100 people died in Malaysia because of the outbreaks and no effective treatment was known [9, 10]. A rapid scientific response by local and international experts soon discovered the transmission dynamics of NiV and how it managed to escaped its normal bat reservoir where it had survived undetected, for possibly decades. It was postulated that humans had altered the environment and that haze-related flowering and fruiting failure of forest trees in addition to increasing deforestation probably drove the migration of forest fruit bats to cultivated orchards. In Ipoh, there were numerous orchards surrounding piggeries and many fruit trees actually overhung pig-pens [3]. However, a retrospective diagnosis of human NiV encephalitis cases on the index farm in early 1997 suggests that bat-to-pig transmission did not directly result from the haze event. In particular, seven of the cases predated the rise in airborne particulate matter that is diagnostic of the haze event, which peaked in September 1997 [11]. The recognition of cases before the haze event refutes the hypothesis that the haze event drove initial cross-species transmission. Furthermore, at the time of the major outbreak in pigs and humans, NiV antibodies were found to be widespread in bat colonies within peninsular Malaysia [11], suggesting that the outbreak was not the result of a (recent) point source introduction of the virus into the fruit bat population, as previously suggested [3]. Pulliam et al. propose that repeated introduction of NiV from wildlife changed infection dynamics in pigs. Initial viral introduction was postulated to produce an explosive epizootic, which drove itself to extinction, but primed the pig population for enzootic persistence upon reintroduction of the virus. The resultant within-farm persistence permitted regional spread and increased the number of human infections [11]. Nevertheless, deforestation and the El Ni□o–Southern Oscillation that contributed to the haze event probably contributed to spread of NiV [3]. The issues involved are controversial [12-14].

NiV is named "Nipah" virus after the village of Kampung Baru Sungai Nipah in Negeri Sembilan State, Malaysia where the outbreak victim from whom the virus was first isolated lived [9]. The NiV is transferred by bat urine to the ground and pig feed, and from their saliva to fruit, whereby pigs became exposed to NiV [15, 16]. Pigs, by contrast with bats, which do not became significantly ill from NiV, developed a significant respiratory illness, characterized by coughing, sneezing, and expectorations, and exposed their human handlers to this potentially fatal and rapidly spreading encephalitis syndrome [6,9]. The eventual response to the NiV disease outbreaks was an ill-conceived, almost hysterical, effort to kill virtually every pig in Malaysia; more than a million in all. Doing this created a major

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economic disaster that required the army to implement. Large pits were dug and the pigs were bulldozed into them, and covered with quick lime and earth [6]. This was the response despite of knowledge that "it was pigs living underneath fruit bats" that had caused the epidemic. Destroying NiV infected pig colonies alone, and separating bats from pigs, was all that was initially needed to stop the epidemic [5].

The NiV outbreaks initiated a search in the Asian countryside to identify hitherto hidden bat colonies with a NiV reservoir. To no great surprise, our colleagues soon identified that we have been living with NiV in bats all over Southeast Asia [17, 18]. Fortunately, close cohabitation of the bats and pigs was previously rare and one reason for the long hidden nature of this hazard.

NiV-related deaths next appeared two years later in devoutly Muslim, and therefore virtually pig-free, Bangladesh and there was convincing evidence of human-to-human transmission, previously considered rare in Malaysia [19]. Bangladeshi scientists, with the help of international scientists eager to join the scene, discovered that local people were eating the popular raw date palm sap from the very trees inhabited by and fed on by fruit bats, who deposited their NiV contaminated saliva and urine [20, 21]. Close contacts of patients with NiV encephalitis, who did not partake of the date palm sap, also became infected [19]. NiV-related deaths were also discovered in neighboring Indian West Bengal; first as an unidentified illness that had been attributed wrongly to the Japanese encephalitis virus [22].

We now wonder what else is out there undetected among our animal neighbors that is waiting to climb the species barrier as dramatized in the 2011 film *Contagion* [23]. Fortunately, looking at hidden zoonoses has now become an encouraged endeavor. Hopefully, we may encounter surprises before they become epidemic outbreaks like NiV-related disease and develop rational contingency response plans. Progress in understanding the molecular biology of Nipah virus [24] as described in this issue [25. i.e., 703-08-12] will lead to a better understanding of the dynamics of Nipah virus transmission and has implications for disease management including the development of therapeutics and vaccines for this deadly pathogen.

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