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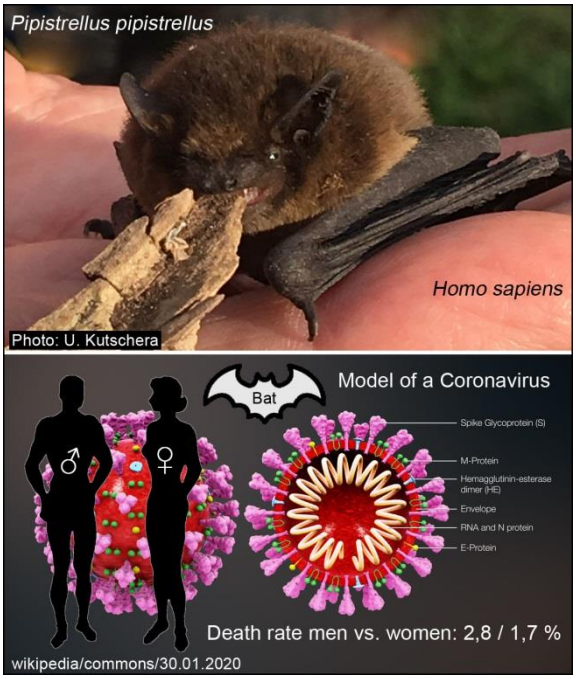
Gender-specific Coronavirus-infections in the light of evolution

In their *Report* "Cryo-EM structure of the 2019-nCoV" (Science 367, p. 1260–1263; 2020), D. Wrapp et al. write that "The novel coronavirus 2019-nCoV has recently emerged as a human pathogen in the city of Wuhan in China's Hubei province, causing fever, severe respiratory illness, and pneumonia." In addition, the authors refer to the rising number of deaths since the official outbreak on December 29, 2019.



However, with respect to mortality, this disease, recently named "Covid-19", displays a strong gender-specific occurrence that may be explained in the light of evolution. Four decades ago, A. D. Pickering and P. Christie published a remarkable article entitled "Sexual differences in the incidence and severity of ectoparasitic infestation of the brown trout, *Salmo trutta* L." (1). The authors reported that adult males of this fish species are more frequently (and severely) infested by a number of parasites than females of the same age. Remarkably, juvenile fish of both genders were found to be less attacked compared to sexually mature males (1). Numerous papers that were subsequently published "in the wake of Pickering & Christie 1980" have documented that there are gender-specific (or "sex-based") differences in immunological responses, both to foreign and self-antigens. As a result, in 2009, M. Zuk (2) labelled males as "the sicker sex".

In two recent *Review Articles* entitled "Sex differences in immune responses" (3) and "Sexual dimorphism in innate immunity" (4), the following facts were summarized. First, not only in fish (i.e., freshwater vertebrates) (1), but also in reptiles, birds, the house mouse and Rhesus macaques, immune responses are greater in females compared to males. In addition, three invertebrates species, the Sea urchin, the Fruit fly, and Scorpion flies, considerable "sex differences" in specific immune responses were documented – with a larger protective effect in females compared to males. Hence, the well-documented finding that women have a more

efficient immune system than men must be interpreted as an early "innovation" during the course of organismic evolution. When challenged by pathogens (bacteria, viruses etc.), female organisms can mount a much stronger immune response to the invading microbes compared to men.

Second, in our own species, over the life course (in utero, childhood, adulthood, old age) immune responses change and display the gender-specific pattern outline above: females have a stronger immune system than men, irrespective of the age of the individual (3, 4).

With respect to the "Covid-19"-pneumonia disease, it has been argued that "The coronavirus seems to hit men harder than women" (5). This conclusion is supported by the fact that, although both sexes have been infected in about equal numbers, the death rate in China was 2.8 vs. 1.7 % in men and women, respectively (n = 44.000 people). In other areas outside the epicenter of "Covid-19" (Hubei Province), a different pattern is documented. Despite lower mortalities, the infection rates of Chinese men were much higher than in the female sub-population (5). Moreover, in a report entitled "Analysis: Why have there been so many coronavirus deaths in Italy?", it was shown that, based on Government data, "The large majority of the deceased were male, and all were Italian citizens" (6).

Despite the fact that these "sex differences" in mortality rates may be, in part, due to gender-specific "life styles" (smoking etc.), there is evidence to suggest that the male vs. female-disparity with respect to "Covid-19" is an evolved feature related to bi-parental reproduction. In the house mouse, "Sex-based differences in susceptibility to SARS-CoV-infection" were detected (7). Under lab-conditions, the mortality rate in male mice was 90 %, compared to 20 % in females. It follows that, regarding coronavirus-infections, mice show a similar sexual dimorphic pattern in survival, as documented in humans (2, 3).

It is likely that the more efficient immune system in female vertebrates (fish, mice, humans) (1–4) may "confer a survival advantage to their offspring" (5), a feature that likely evolved under the selection pressure of continuous microbial pathogen attacks. Since males, whose reproductive role is to provide sperm for the fertilization of eggs, are unable to get pregnant and "become a mother", no such an "optimized immune response" developed in the "sicker sex" over evolutionary time scales.

Finally, it should be mentioned that recent research carried out by "China's Bat Women" (Zheng-Li Shi and coworkers) has shown that, like the severe acute respiratory syndrome (SARS)-virus, the novel coronavirus (2019-nCoV) originated in Chinese bats (Mammalia: order Chiroptera), from where they infected humans, which may be regarded as an "accidental host" (8). On illegal wildlife markets – a cultural tradition in Southern China,

where animals such as bats, pangolins, civets etc. are sold – coronaviruses can jump to humans directly or via intermediate hosts. However, bats (a natural reservoir for many viruses) eat insects and pollinate plants. Obviously, these flying mammals are not the problem for the outbreak of this zoonotic disease.

Unfortunately, in January 2020, the Chinese Communist Government suppressed the news about the occurrence of a highly infectious new virus that can cause, when transferred from bats to humans (zoonosis), a deadly pneumonia. As a result of this censorship of "politically incorrect infos" (and the open border-ideology of globalization), the coronavirus disease 19 (Covid-19) not only rapidly spread in China via human-to-human-transmissions: due to unrestricted travelling throughout Europe, the USA and elsewhere, it developed into a pandemic.

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