Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

operation to separate the water supply for the toilet and chlorinate it, perhaps with a hypochlorite generator. This could be prohibitively expensive. In these cases, using a disinfectant-releasing apparatus in toilet bowls may be more practical.

Locations that allow recirculation of lavatory air should be considered high-risk areas for infectious bio-aerosol exposure. The methods suggested by Immanuel et al[2] may be well suited for such areas in public restrooms, assisted living facilities, schools, and other buildings. Disinfecting toilet water in the manner suggested by the authors could protect people in shared residences where one or more residents are positive for COVID-19.

The COVID-19 pandemic is the third novel coronavirus outbreak of the 21st century, following on the heels of the severe acute respiratory syndrome coronavirus and Middle East respiratory syndrome coronavirus outbreaks. Still, little has been done to create preventive interventions in public health infrastructure. More research is needed to determine efficacy of the proposed approach against severe acute respiratory syndrome coronavirus 2 infection transmission, and such research is warranted in case of expected future similar outbreaks.

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COVID-19, the Female Immune Advantage, and Cardiovascular Impact

To The Editor: The article by Ritter and Kararigas[1] is a welcome addition to the coronavirus disease 2019 (COVID-19) medical literature, as significant physiologic variations across multiple systems exist between the sexes, yet are often neglected.[1] Although we applaud the hypotheses on differing male and female responses to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections, with emphasis on cardiac vulnerabilities, some additional key potential mechanisms with respect to the role of the "sex hormones" estradiol, progesterone, and testosterone require consideration.

Estradiol supports immune system modulation, amplifying innate and humoral immune responses, whereas testosterone is overall an immunosuppressant, in particular inhibiting differentiation of naive CD4+ T cells into T helper type 1 cells, impeding cell-mediated immunity. Estradiol helps initiate a robust innate immune response to pathogens via augmented toll-like receptor 7 (TLR7), an endosomal innate immune sensor recognizing RNA viruses such as SARS-CoV-2, inducing a type 1 interferon response, suppressing viral replication, and amplifying host antiviral response.[2] Subsequently, estradiol helps switch to a state of inflammatory resolution and healing. Progesterone also has substantial immunomodulatory effects on female immune systems.[3] These significant hormonal effects may result in dramatic sex differences in immune response to infection, and in turn, likely alter inflammatory-mediated cardiovascular impacts from SARS-CoV-2.

All immune cells have receptors for estradiol, enabling direct immunomodulation. This is complemented by the influence of estradiol on the renin-angiotensin-aldosterone system (RAAS), a second important immunomodulatory system.[4] Severe acute respiratory syndrome coronavirus 2 uses angiotensin-converting enzyme 2 (ACE2) as a functional receptor to infect cells, destroying its anti-inflammatory capabilities in the process. Females replete with estradiol have greater number and functionality of ACE2, likely a factor in their greater ability to handle SARS-CoV-2 infections. Additional estradiol-mediated RAAS modulatory actions provide further cardiovascular protection. Despite SARS-CoV-2–induced ACE2 deficiency, estradiol supports an anti-inflammatory state by facilitating angiotensin II

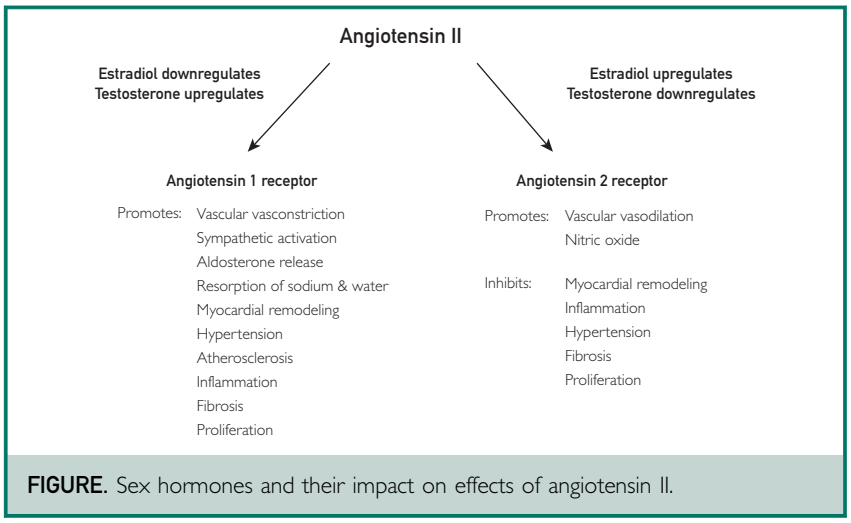

FIGURE. Sex hormones and their impact on effects of angiotensin II.

binding to the angiotensin 2 receptor, rather than the angiotensin 1 receptor. This alternative binding promotes vascular vasodilation and inhibits cardiac remodeling, in contrast to angiotensin 1 receptor binding that facilitates vasoconstriction and additional pro-inflammatory actions (Figure).

In addition to advantageous hormonal differences, females possess 2 X chromosomes, further contributing to the "female immune advantage." Although the "extra" X chromosome is deactivated, more than 10% of the second X chromosome genetic material, most related to immune function, stays active throughout a woman's life.[5] For example, the TLR7 gene is found on the X chromosome and escapes X inactivation, resulting in higher expression levels in females. Additionally, during embryonic times in females, both X chromosomes remain active for a short while, resulting in epigenetic modifications, further enabling females to better survive infections. Females likely evolved to better withstand viral infections, and understanding all contributing factors is essential to optimizing care.

We greatly appreciate this article's focus on the sex differences involved in immune responses and subsequent CV risk related to the current COVID-19 pandemic. Heightened awareness that such differences exist will hopefully foster expanded research into the significant inherent immune variances between males and females, and between reproductive and postmenopausal women, with the goal of pragmatically and successfully improving medical care.

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In Reply — COVID-19, the Female Immune Advantage, and Cardiovascular Impact

To The Editor: We thank Gersh and colleagues[1] for their letter in response to our article "Sex-Biased Vulnerability of the Heart to COVID-19."[2] In fact, we are pleased to see that our article is fulfilling its purpose of drawing attention to a topic little explored, putting forward notions and hypotheses for the field to contemplate.

We agree with Gersh and colleagues regarding the importance and relevance of the role of sex hormones beyond the reproductive system, particularly in the cardiovascular system as we have shown previously.[3,4] Given the importance of angiotensin-converting enzyme 2 in severe acute respiratory syndrome coronavirus 2 host cell entry, Gersh and colleagues accurately point out the influence of estradiol on the renin-angiotensin-aldosterone system (RAAS). In this context, we have recently discussed the modulatory actions of estradiol on RAAS in detail, thereby impacting several components of the cardiovascular system.[5,6]