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Bat Evolution, Demographic Data, and Pre-Existing Conditions Solve Mystery of COVID-19 Infection Severity

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Abstract

It is hypothesized that the reason behind coronavirus severity stems from the unique adaptations in bats, where the virus co-evolved, to accommodate flight which generates large amounts of oxygen free radicals. Oxidative stress, particularly through excess endogenous Nicotinamide Adenine Dinucleotide Phosphate Hydrogen (NADPH) oxidase production of superoxide, is the single unifying framework for explaining the large range of risk factors for severe coronavirus infection including aging, male gender, African-American race, cardiovascular disease, obesity, and diabetes. Evidence is presented that death rate as a function of age better resembles the near-exponential rise seen in cancer, where oxidative stress is high, rather than the historical W or U-shaped functions of pandemic or seasonal flu. In addition, consideration of more than 10,000 Center for Disease Control and Montgomery County, Pennsylvania publicly available cases suggested a deviation from an exponential rise in the oldest-old, consistent with lower oxidative stress levels reported in that group. Gender analyses unexpectedly found male-to-female risk of mortality to be an inverted U-shaped function peaking at nearly 2.5 times from age 30 to 50 and may reverse to half the female risk at the oldest ages, providing a good fit to known oxidative stress gender differences across the lifespan. Race data were consistent with higher mortality from COVID-19 and higher oxidative stress levels in African Americans. It is argued pre-existing conditions that increase risk all share high oxidative stress levels while, intriguingly, the possibly protective Inflammatory Bowel Disease and Lupus have low levels of NADPH oxidase-derived oxygen free radicals. Strategies for prevention and treatment that follow from the theory are briefly covered including N-acetyl cysteine in older men to restore glutathione levels to more youthful values and especially exciting, pursuing the inhibition of NADPH oxidases not only with well-known melatonin but also with less known compounds such as the naturally occurring apocynin, which is also inexpensive and readily available.

Keywords: COVID-19 • Oxidative stress

Introduction

Since the publication of the first genetic sequencing from WuHan, China of a novel lethal coronavirus [1] now known as SARS-CoV-2, the greatest global pandemic in a century has caused 1.4 million confirmed coronavirus infectious disease of 2019 (COVID-19) worldwide after 4 months and 33.7 million at 10 months. There were 200,000 deaths in the United States (US) alone over the same time period. There has also been a puzzle that persists: Why do some people have mild asymptomatic illness and others die?

It is hypothesized that the single unifying framework for explaining the seemingly puzzling range of risk factors for severe COVID-19 infection including aging, male gender, African-American race, cardiovascular disease, obesity, and diabetes is oxidative stress. It is further hypothesized that oxidative stress is not simply a useful construct, coincidence, or bystander but that its ability to explain differences in coronavirus severity stems from the known unique adaptations in bats, where the virus co-evolved, to accommodate flight which has the potential to generate large amounts of oxygen free radicals. Finally, the hypothesis particularly points to the relevant source of oxidative stress as not being environmental but rather self-produced excessive NADPH-oxidase which generates oxygen free-radicals, especially superoxide.

Following an explicit statement of how "oxidative stress" is used is the present work; the hypothesis is first evaluated by carefully considering demographic data for age, gender, and race. Publicly available information from global and local United States COVID-19 cases when analysed in detail provide evidence that differences in oxidative stress explains differences in mortality. Next, evaluation turns to individual differences in severity and pre-existing conditions-both risks and anti-risks of severe infection - which also raises in particular the role of NADPH oxidase in oxidative stress. The article then addresses why oxidative stress is relevant to the coronavirus at all with a brief mechanistic sense of "why" through angiotensin II and ACE2 followed, importantly, by the evolutionary sense of "why" in which genetic oxygen-related adaptations in the bat provide clues for the role of reactive oxygen species in humans. Implications of the hypothesis through brief discussion of prevention and the future close the article. Overall, a case is built that oxidative stress is an attractive framework for unifying the diverse findings on the risk factors for severe infection as well as why this came to be.

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Oxidative Stress in Brief

A Reactive Oxygen Species (ROS) are a byproduct of the use of oxygen during normal metabolism and respiration plus are generated by cellular Nicotinamide Adenine Dinucleotide Phosphate Hydrogen (NADPH) oxidases. ROS is not one thing and includes anion superoxide (O_{2-}), hydrogen peroxide (H_2O_2), singlet oxygen ($1O_2$), and hydroxyl radical (OH) but what they have in common is they are all unstable, at least to some degree, with the potential to damage anything in their path. ROS can damage proteins, lipids, and perhaps most consequently, DNA itself. ROS, however, are also important for cell signaling, thyroid function, and fighting pathogenic invaders. Thus, balance of ROS and antioxidant defense are critical for health. When ROS levels greatly exceed what is degraded by anti-oxidative defenses, a state of oxidative stress is said to ensue [2-5].

Age

Early in the pandemic, it became clear that age is a risk factor for serious infections, hospitalizations, and death. Ninety percent of all COVID-19 deaths in the US are in those over the age of 55 years. The rate of death in confirmed cases (number of deaths divided by number of cases) is shown in Figure 1 as a function of age at two points in time, 4 months and 10 months, after the initial Wuhan genetic case report. The regions used were local Montgomery County Pennsylvania (Montco) from data held at the county health department (https://data-montcopa.opendata. arcgis.com/pages/covid-19, through April 16 and Sept. 22, 2020 for early and late times respectively) and global for the entire US at 10 months from the CDC (https://covid.cdc.gov/covid-data-

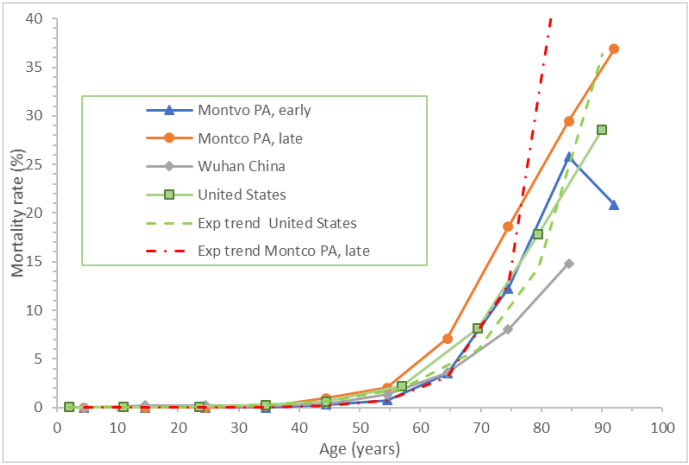

Figure 1. Mortality rates in coronavirus (COVID-19) confirmed infections as a function of age with exponential trendlines (up to 40%) at two times (4 months, number of infections=2,316 and 10 months, number of infections=11,715) since case 1 Wuhan China for Montgomery county Pennsylvania and at 10 months (number of infections=4,887,706) for all of the United States. The pattern including possible deviation from an exponential rise at old ages may better resemble cancer than the historic U or W shaped functions of seasonal or pandemic flu. Montco=Montgomery County. Exp=exponential.

tracker/#demographics, through Sept 22, 2020). The data are also shown with fitted exponential function trendlines and compared to mortality rates reported from Wuhan China. Note first that averaged across all ages, the rate of death is twice as high for current US residents and early Montco compared to Wuhan and three times as high for current Montco (mean rate=3.2%, 6.3%, 9.5%, 6.4% for Wuhan, early Montco, late Montco, and late US respectively). Further investigation is needed to tease apart any differences due to region, elapsed time, and viral strain.

As a function of age, the data verifies that mortality follows a near exponential rise for much of the lifespan (r2=.97 for US and .92 for late Montco) with near-zero risk early followed by dramatic escalation. By age 70, the risk of death in confirmed cases is nearly 18%, which is 80 times greater than the risk to life in the 30s. The rise in death rate with age is not an artifact of a greater number of coronavirus cases among the aged. The absolute number of cases instead peaks at a younger age within the 50th to 60th decade for early Montco and shows two peaks for late Montco and the US, with the second peak among twenty somethings (not shown). Rise of infection among the young may reflect this age groups' failure to withdraw from social interactions compared to remaining groups and a longer symptom-free interval from infection. Overall, the mortality rise with aging confirms at geographically local and global levels the increasing devastating consequences of infection with age.

We suggest the pattern of mortality rates as a function of age may better reflect that seen in cancer than flu which is one clue to the reason behind the coronavirus' severity. Influenza, another potentially serious viral disease, has historically been reported to have a U-shaped function with the very old and the very young at highest risk for severe complications [6]. This has been presumed to result from decreased immune responsiveness at the ends of the continua due to immunosenescence and immaturity respectively. Because the immune system of the very young resembles that of the very old, a hypothesis that decreases in immune responsiveness causes the age-effect in COVID-19 as well as flu predicts maximal severity at both ends of the continuum. Despite more recently emergent reports of a childhood Multisystem Inflammatory Syndrome following COVID-19, the rate of serious infection among the young remains low. In addition, a simple model of under-responsiveness would also predict greatest risk at the other end containing the highest-age individuals. As seen in Figure 1, however, death rates in the oldest-old may be less than predicted by an exponential rise, a potentially notable feature that will be elaborated below.

Moreover, catastrophic reaction to the coronavirus may involve too robust an immune response rather than too little [7]. This was also suggested for the 1918 pandemic of the Spanish flu which produced a different age-related morbidly and mortality than seasonal flu. It was characterized by a W-shaped function such that adults between 20 and 40 had unexpectedly high death rates peaking at age 30 [8,9]. Flu pandemics of 1957, 1968, and 2009 also had unexpectedly high deaths in people under age 65 [10]. Cytokine storm, in which highly responsive immune systems overreact to the virus to produce excessive proinflammatory signals leading to organ failure and death, has been considered as a possible cause of the unexpectedly high deaths in younger adults during flu pandemics [11] and in Severe Acute Respiratory Syndrome (SARS) [12] which is caused by coronavirus CoV-1, genetically related to the CoV-2 under consideration here. It has indeed also been suggested to be responsible for death in COVID-19 [13]. However, unlike flu pandemics, excessive COVID-19 deaths are not seen among adults in their prime with robust immune systems as would be expected. Overall, neither an over reactive nor underactive immune system under any simple model is a particularly good fit to the data.

On the other hand, it is intriguing to consider that cancer does share many of the age-related features seen for this coronavirus. A Cancer rate is very low in the young, rise after 40, and explodes after 60 [14]. We obtained data on cancer mortality per year from Cancer Research UK (https://www.cancerresearchuk.org/) which includes separate data for all age groups and we normalized the deaths to be out of every 100 people. Data was normalized to make them comparable in scale to the coronavirus data because there are currently approximately 30 times more deaths from cancer than coronavirus. The estimate of 30 times was obtained from US statistics of 8 million cancer deaths per year compared to 200,000 coronavirus deaths in the US over 3/4s of a year. Figure 2 shows the mortality rates as a function of age for both the coronavirus and cancer. Despite the fact that the coronavirus data are from the US and the cancer data from the UK, it is noteworthy that the shapes of the functions are similar.

Moreover, there is evidence that starting at age 80-85, there is a flattening and possibly even a reversal of cancer incidence [15]. This pattern has been reported for multiple cancers and in multiple countries. A notable feature of the coronavirus data considered above is what may also be describable as a flattening, and for early Montco possibly a reversal, of the rate of death at highest ages. That is, at advanced ages, the death rate may be lower than what would be expected based on an exponential fitted function (Figure 1). However, confirmation will require both larger numbers in the oldest age group (sadly) and, importantly, exact ages of cases and deaths in the oldest-old. Exponential functions yield big differences for even small changes to X when X is large; therefore, exact age value for X is critical for the oldest ages rather than bins such as "90+" that tend to be provided by public health repositories of data. For cancer, deviations from the exponential function led to the development of the beta distribution with three separate constants for different age ranges as a better fit than the historical exponential model of cancer [16]. This raises the possibility that this may be a better fit to the

coronavirus data as well.

We suggest the link between the cancer and corona age similarities are due to oxidative stress. Oxidative stress increases with age [4]. Experiments first with rats showed that by middle age, the balance between ROS and antioxidant defenses became difficult to maintain [17]. In humans, there is consistent evidence of ROS-induced damage to proteins [18], lipids (e.g. oxidized LDL-cholesterol [19]), and DNA (8-oxo-dG) in aged cells. Aging mitochondria produce higher levels of ROS [20]. Oxidative stress has also been a long-standing theory of aging in various incarnations in which damage from ROS accumulates and leads to loss of function [21]. Intriguingly, with continued aging, the levels of oxidative stress in the oldest-old may be equivalent to that of a much younger ager, possibly through a late-onset ability to boost levels of antioxidant enzyme activity and degrade ROS [22] Taken together, levels of oxidative stress across the lifespan-low rates in children, rapid rise in middle age, explosive growth in elderly, possible decrease from exponential prediction in the oldest-old - can account for the age-related function of the death rate in the coronavirus, just as has been suggested [23] to account for the shape of the function in cancer.

Gender

Male gender is another risk factor for severe outcomes that became apparent early in the coronavirus pandemic. Epidemiological analyses from China found overall mortality among men to be 2.8% and women 1.7%. Numerous suggested explanations for the gap have included differences in immune responsiveness, hormones, viral loads, bradykinin, and preexisting conditions and behaviors. We suggest that, as with aging, oxidative stress provides a good fit to gender findings. To determine any current gender inequity in the US, the same datasets as in the previous section can be considered. According to the CDC database, as of Sept. 22, 2020 in the US, 51.7% of confirmed cases are in women while 48.2% cases are in men. The slight edge for female incidence of infection is close to slightly greater population of women over men at 51and 49%-respectively in 2019 (https://www.statista.com/statistics/737923/us-population-by-gender/). A reversal in the incidence of death, however, verifies the male risk persists (46% women, 54% men). Calculating the rate of death in confirmed cases (number of deaths/number of cases) finds 2.5% in women and 3.2% men, a small difference similar to Wuhan, China and not detected in current Montco population (7.2% women and 7.0% men; early Montco data not available).

As would be expected by the oxidative stress model of coronavirus of gender differences, oxidative stress is higher in men than in women. Ide et al. was the first to explicitly compare levels across gender [24]. They used two established markers of oxidative stress, one of the aldehydes, which are generated by interaction between oxygen and lipid membranes, and urine 8-iso-prostaglandin F2α also present with ROS' damaging effects on lipids. Both were higher in healthy young men than age-matched pre-menopausal women. Although 8-iso-prostaglandin F2α has since come into question as reflecting oxidative stress [25], evidence has accumulated that males have higher ROS production while females have less oxidative stress and greater antioxidant potential [26]. The difference in genders may extend back through infancy where there was higher lipid oxidation in response to pain at end of pricking the heel of newborn boys compared to girls [27] suggesting a fundamental difference in the potential for ROS.

The gender difference also leads to a semi-quantitative prediction about gender and death rates in the coronavirus if the present oxidative stress hypothesis is correct. A review on the effect of gender differences in oxidative stress on the development of cardiovascular disease [26] points out the complicated relation of estrogen to oxidative stress including actually an increase in ROS production by mitochondria but nonetheless suggests the greatest difference in antioxidant properties between men and women is due to estrogen, with its ability to scavenge for free radicals as well as increase antioxidant enzyme defense Superoxide Diminutase (SOD) If estrogen contributes to the oxidative-stress difference in gender that we argue produces the coronavirus gender gap then the death-rate difference between males and females should be highest during times of the lifespan with high estrogen and lowest during times of low estrogen.

We therefore considered male and female mortality from coronavirus infection separately by age group. After calculating the ratio of number of deaths to number of cases for the death rate, the ratio of the male death rate to the female death rate was further calculated to yield a ratio of ratios. A value of 1 indicates equal incidence for both genders, values higher than 1 reflect greater death rate in males, and values lower than 1 would reflect greater death rates in females. The ratio of ratios as a function of age (Figure 2) finds a striking difference across the lifespan. There is little difference early in life rising to a peak in the 30s and 40s where the male risk is nearly 2.5 times higher than female risk and declines again thereafter. The bins of ages are too large for precise quantitative assessment but differences between pre puberty, adulthood, and post-reproduction years fit well with hormonal involvement in oxidative stress throughout life.

Intriguingly, there also appears to be a reversal such that in the extreme aged, the risk of death becomes higher in women than men, about twice as great. While greater numbers of patients are needed, and from different geographic locations. To confirm this as a general trend, it is notable that in women. Oxidative stress and oxidative damage rise with menopause [27-29]. It was also found that in older patients with cardiovascular disease, average age 69 years, oxidative stress as measured by serum hydroperoxides was now already higher in women than in men [30]. These researchers also note that women may be more subject to the damaging effects of oxidation when it is not degraded. Eventually, the risk of coronavirus death between genders may reverse due to changes in balances in redox.

Analysis of the gender gap by age revealed a highly changeable and important difference between men and women's risk at different ages which

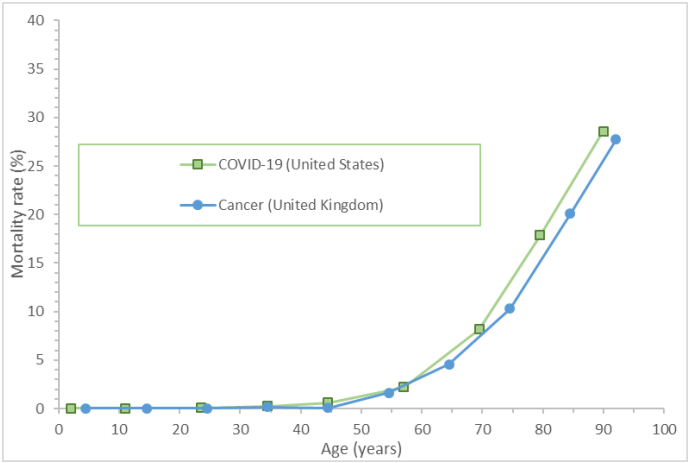

Figure 2. Mortality rate for COVID-19 infections in the United States shown against mortality rate per year for cancer per 100 people in the United Kingdom. The shape of the function across age is similar for the two diseases.

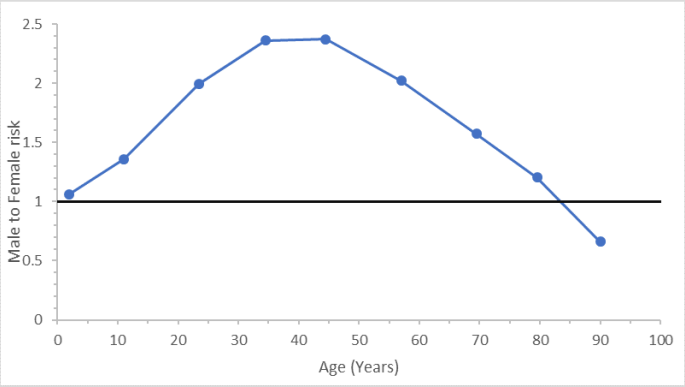

Figure 3. The ratio of the male mortality rate to the female mortality rate in United States COVID-19 infections. Values=1 reflect no difference between genders. Difference vary substantially across the lifespan with peak approaching 2.5 greater risk for men than women in the reproductive years that may correspond to peak differences in oxidative stress levels between genders A possible reversal at an advanced age suggest women's risk may surpass men which may relate to qualitative changes in oxidative stress for women following menopause.

is typically lost in news reports. The different pattern of oxidative stress across the lifespan, whether this proves to be caused by estrogen or some other factor, provides a good semi-quantitative match to the gender-age interaction in risk of coronavirus death.Note finally that it is also sensible in a model of oxidative stress and severe coronavirus risk that the difference in risk is several orders of magnitude smaller for gender than for age, even at the peak age of the gender gap. This is because the expected imbalances in ROS and antioxidant defenses, as well as the accumulation of its damaging effects, between men and women of the same age should be much smaller than between an older adult and a child of the same gender.

Race

The high rate of coronavirus infection in the US has brought to the forefront that there is also a racial disparity. Explanations suggested for the greater toll on African Americans have included poor access to and quality of medical care, as well as a high numbers of pre-existing conditions, social jobs, residential crowding, multigenerational living, and, too often dismissively, tobacco and drug use.Here too, oxidative stress can provide an explanatory framework for disease severity. It is now well known that there are racial differences in oxidative stress. For instance, African Americans have lower glutathione than white (European) Americans regardless of any presence of metabolic syndrome [31] and greater oxidative stress in response to exercise [32]. The racial difference may be so fundamental as to be apparent just in extracted cells from umbilical cords [33].

Calculating the current rate of death for COVID-19 in the US for African Americans (AA) and White Americans (WA), unexpectedly did not find a difference with an overall 5.1% AA and 5.4% WA mortality rate. However, race information is only available for 51% of cases but 82% of deaths which would inflate the numerator in unpredictable ways. In addition, further analysis by age finds a striking case-death reversal for the four age bins between ages 5 and 49. In each of these age categories, the number of cases is substantially higher in WA than AA yet the number of absolute deaths is higher in AA than WA. This suggests the rate of death (not just the number of cases) is indeed higher in African Americans, consistent with an oxidative stress explanatory framework. If this effect is limited to, or most apparent in, the child-to-middle age range as the data hint, it would be especially intriguing. However, at present we cannot rule out an artifact comprised of disproportionate data reporting between cases and deaths at different ages and genders. Clarification and comparisons with other racial groups such as non-black Hispanic patients, awaits higher quality data. Montco provides race information only for deaths and not cases thereby preventing the determination of mortality rates across race.

Individual Differences

Individual differences are only briefly raised in the evaluation of the hypothesis because there is currently an absence of data on whether healthy young individuals with unexpectedly severe virus infection have higher values on any markers of oxidative stress levels as the present hypothesis might suggest. It is not surprising; however, that any such differences have not been obvious because high oxidative stress levels are frequently invisible until accumulating damage eventually causes enough loss of function to produce symptoms of disease. Smoking is an oxidative stressor which metanalyses did find to increase severe outcome in hospitalized coronavirus infections [34]; however, oxidative stress markers were not obtained on any of the patients, In addition, there are also reports that smoking may prevent getting the infection in the first place; smoking as a risk factor may be complicated because of a potentially protective role of nicotine from an oxidative-stress perspective (see final section below) and warrants further investigation.

Less transparent causes than smoking for silent oxidative stress variation among individuals are numerous and include environmental stimulation of ultraviolet light, ionizing radiation, mercury. toxins, availability of the nutrients selenium, copper, iron, zinc, and manganese (cofactors for antioxidant production), and genetically, polymorphisms in at least 60 genes. Such as SOD2 [35], and even in DNA repair capabilities, such as levels of OGG1 gene expression. However, the environmental stressors are exogenous contributors to oxidative stress and there is reason to believe it is the endogenous NADPH oxidase-derived oxidative stress that plays a special role in coronavirus severity (See next section, Pre-existing Conditions). Nonetheless, the effects of these on individual unexplained cases and different markers of oxidative stress.Would be exciting avenues for future investigation. At present, the framework of oxidative stress currently receives neither support nor contrary data from differences in severity among apparently healthy individuals but has the potential to provide a unitary explanation that includes this variable as well.

Pre-Existing Conditions

The present hypothesis also maintains that all of the non-pulmonary pre-existing conditions reported to increase risk of severe complications and deaths from COVID-19 are precisely those conditions for which oxidative stress is well known to play a pivotal role [4], namely cancer, cardiovascular disease, diabetes, hypertension, obesity, chronic liver disease, chronic kidney disease, and neurodegenerative illness. The rate intensive care admissions ranges from 2 to 4 times greater with these conditions according to research conducted by the direct-to-consumer genetics testing company 23 and me (ttps://you.23andme.com/covid19/#severity-tool). Are these simply highly prevalent diseases in the US, Europe, and Asia and any comorbidity would increase vulnerability to a highly pathogenic virus? If an oxidative stress framework is applicable, then the converse should also be true. That is, low levels of ROS should be protective. We suggest that there are indeed hints of this in the literature.

While excess ROS as involved in disease development has received more attention, levels that are too low are also associated with disease. Insufficient

generation of ROS through genetic polymorphisms of the NOX2 NADPH oxidase complex has been found to predispose to Inflammatory Bowel Disease (IBD) [36]. Intriguingly, reports have found less than expected coronavirus infection in these conditions. In a paper entitled "Uneventful course in IBD patients during SARS-CoV-2 outbreak in northern Italy" [37], an observational study tracked all of the 529 IBD patients, 89% adults, at a hospital center for a month and found no apparent cases or hospitalizations including those both taking and not taking immunosuppressants. This contrasts with the 479 patients without IBD admitted to the hospital with severe infection and 21 individuals with IBD predicted to present with infection but did not materialize. It has also been reasoned that IBD should be a risk factor compared to the general population [38] because of increased expression of ACE2 in the gut, especially in Crohn's disease, yet as they discussed, did not appear to be based on their early literature search and lack of reports of IBD patients with COVID-19 in Wuhan China. They suggested that the unexpected finding may be because there are two types of ACE2 or because an additional receptor was required for viral replication, or because of the benefits of immunosuppressant treatment. Immunosuppressants seem unlikely as the sole factor mitigating risk as immunosuppressants in cancer do not appear to have a protective effect and IBD patients without them also appeared to have the protection. Oxidative stress considerations for the relative protection in IBD should be considered and also has the appeal as a single explanatory framework that ties together all the risk factors discussed previously.

Once IBD is established, it is true that increased levels of inflammation and ROS have been reported, which then might be expected to have the opposite result However, it has been found that states of ROS deficiency from decreased NADPH oxidase activity lead to compensatory changes such as exaggerated inflammation and immune responsiveness and as a result the ROS that is seen in established patients. But the case of IBD then may specifically implicate that it is ROS produced endogenously by NADPH oxidase that is of special significance for risk of coronavirus severity. Consistent with this is men's greater oxidative stress discussed earlier is at least in part due to greater NADPH oxidase activity [26]. We suggest excess ROS from increased NADPH oxidase activity is a risk factor while decreased activity confers protection.In addition, a similar situation may be present with other autoimmune diseases. The same NADPH oxidase deficiency also has been reported to increase autoantibodies and predispose to other autoimmune diseases, perhaps through compensatory changes for the ROS deficiency [39]. In particular, lupus has been implicated [40,41]. Consider that an early report conveyed that there were unexpectedly no cases of lupus presenting in the emergency room, which also interestingly as a historical note may to be why hydroxychloroquine was targeted as a possible treatment for coronavirus early in the pandemic [42]. Like IBD, lupus may be protective and in the present view, oxidative stress, and NADPH oxidase levels, may provide the link for the totality of factors affecting coronavirus severity and mortality.

Why: Angiotensin II, ACE2, RAAS

Why would oxidative stress have anything to do with COVID-19? For an answer to why in the sense of mechanism, note that oxidative stress increases angiotensin II [43] and vice versa [44]. Angiotensin II is part of the Renin Aldosterone Angiotensin System (RAAS) which is involved with coronavirus infection in humans. There was evidence early that viral load is higher with higher levels of angiotensin II [45]. In addition, it is now well known that another step in the RAAS plays a critical role in infection. SARS CoV 2) which produces COVID-19), as with SARS CoV 1, hijacks the angiotensin converting enzyme 2 (ACE2) receptor to gain entry into human cells [46], perhaps via the moderate amount of ACE2 expressed in the nasal mucosa [47]. Angiotensin II is degraded by ACE2, a gateway of the coronavirus. Because popular medications for hypertension work through the alteration of RAAS, there has been much interest in how exogenous ACE inhibitors and/or angiotensin receptor blockers may affect corona virus severity [48] as well as speculation on a seeming paradox of lower ACE2 in the elderly yet worse outcomes. While answers are still forthcoming, the involvement of RAAS components in coronavirus infection provides one possible mediator between oxidative stress and coronavirus. Others to investigate include heat shock proteins (see below), and NADPH.

Why: Bats and Viruses

But the most intriguing answer to the question of why oxidative burden has anything to do with coronavirus outcomes may be the evolutionary sense of "why". Bats are likely the natural hosts for coronaviruses [49,50]. We suggest the connection within humans between oxidative stress and severity of coronavirus infection lies within the unique characteristics of bats and the genetic adaptations that enabled them. Shen et al. [51] analyzed all genomes available on bats in 2010 for the Oxidative Phosphorylation (OXPHOS) genes, which are essential for the release of energy from double bonded oxygen to convert ADP to ATP, a vital part of metabolism. They found major changes in both nuclear and mitochondrial OXPHOS and argued that these enabled the greatly increased metabolism that is required for the demands of sustained flight in the bat, the only mammal capable of such activity. Thus, there may be a deep link between the unique oxygen demands of bat for flight and the oxygen free-radical vulnerability of humans to the virus.

Furthering the link, the increased requirement for oxidation in the flying bat is presumed to lead to a greater generation of destructive ROS [52] because the greater conversion from a stable double oxygen bond for the greater amount of energy also produces more of the unstable highly reactive oxygen free-radicals that are the by-product of the metabolism. Brunet-Rossonni [53] directly measured amount of free radicals and found that it was greater efficiency of oxygen use (low free radicals generated in relation to oxygen consumed) rather than absolute amount of free radicals that best distinguished at least one species of bat (little brown bat, Myotislucifugus) from other small mammals (white-footed mouse and short-tailed shrew). However, it is likely that an excessive amount of free radicals are also present and that efficiency reflects an additional oxygen-related adaptation for sustained flight; the study tested only one type of ROS (the relatively stable hydrogen peroxide) and did not consider the timing of flights in relation to testing. Whole genome sequencing of two distantly related bat species (fruit bat Pteropusalecto and insectivorous bat Myotisdavidi) [54] found expansion in genes responsible for DNA repair; the researchers believe these reflect the greater need to repair the damaging effects of all the ROS generated by flight.

These same researchers also looked specifically for genomic changes in the innate immune system because bats harbor many viruses and found numerous expansions and contractions of immune-related genes. Notably, genes that detect both viruses and endogenous damage to DNA from ROS were changed, including b-REL, AIM2, and If116, leading the researchers to suggest that accommodations for flight to ROS may have had far reaching implications to the immune system. Perhaps most strikingly, the entire PYHIN family (which includes AIM2 and IF116) was missing in both species of distantly related bats but present in all other mammals. Its absence has since been confirmed in 8 additional bat species [55]. If we complete the point, positive selection for the genes' elimination would prevent the inflammation that may result in excessive cell self- destruction in response to ROS damage but at the cost of eliminating the rapid detection and removal of foreign invaders, a task that is coupled with the self-destruction. (Note further this may be related to the bats' well-known tolerance to, and harboring of numerous viruses). There is a known shared mechanism for these two seemingly different tasks, the elimination of viral pathogens on the one hand and the repair of DNA from oxidative damage on the other [56]. This is also an important puzzle piece for human susceptibility to the coronavirus. The shared mechanism has been suggested to result either because of DNA damage from viruses or to reflect a direct antiviral weapon system [56]. The linkage may simply reflect the overarching shared goal: Good DNA: keep, bad DNA: destroy. The ethics and philosophy of the sources of the "bad DNA", be it viral or damaged self, may be of no concern for the purposes of fixing the problem. For our purposes, it further strengthens the plausibility that response to viruses can have a relation to oxidative stress.

Bat viruses evolved under unique conditions of high metabolism, free radicals and all the associated changes in efficiency, DNA repair, and immune

system. Since bats are not sickened by these viruses, shouldn't this unique evolution, if anything, make humans with high bat-like oxidative consumption and byproducts is less at risk rather than more? Not necessarily. Species that co-evolve are in an evolutionary arms race. This leads to seeming contradictions in which the same property is both weapon and vulnerability. For example, heat shock proteins kill viruses but also can greatly increase the replication of viruses. As a side note, a compelling study showed that increased heat shock proteins are another important unique adaptation for bat flight that enabled cell survival from the free radical damage and the increased body temperatures of high metabolism [52]. It is also worth noting that some heat shock proteins are also inducible by oxidative stress. Heat shock proteins role then in the coronavirus requires future investigation for potential mechanistic connection.

In general, the adaptations in the bat for flight with escalated oxygen use, increased DNA repair, and resulting alternations in immune defenses provide a unique battleground for the virus. From the virus" perspective, escape from rapid detection allows a prolonged period within which to develop stronger more effective weapons against this oxygen-driven environment. Transfer to humans with an oxygen free-radical environment familiar to the virus but who lack the specialized defenses is like unleashing a nuclear weapon on an enemy that is still using muskets and bayonets. It is likely not an accident that many of the viruses that pose an immense threat to modern humans even before SARS-CoV-2, such as the Ebola virus, are ones that are harbored by the bat. Exploration of the reverse may also have merit: The effects that long human co-evolved co-existing viruses, such as herpes simplex virus 1 and cytomegalovirus, have on bats. What at first may seem an arbitrary connection - oxidative stress and severe effects of coronavirus infection - turns out to reflect closely related issues of free radical generation, DNA repair, and anti-viral defenses. The coronavirus evolved to thrive in a battleground of abundant oxygen use that is now easily exploited in unlucky human enemies who have an abundance of the targets so familiar to the virus but in an enemy who lacks the equally formidable weapons that co-evolved in bats.

Prevention, Treatment, and Future

Approaching disease caused by oxidative stress is not a simple matter. Providing exogenous antioxidants can decrease the body's endogenous production of what may be more useful antioxidant enzymes [57] and may even increase mortality [58]. Vitamin C (ascorbic acid) in high doses produces, not reduces, ROS yet is effective in cancer and possibly coronavirus. Male and female systems differ in approach to oxidative stress with glutathione levels higher in the former and SOD in the latter which changes after menopause [26]. Therefore, men, premenopausal, and postmenopausal women may benefit from, or even require, different interventions to prevent severe outcomes from coronavirus infection. Despite the complexity, interventions for the coronavirus are emerging that we can see are ones that affect the balance between reactive oxygen species and anti-oxidant defense, such as melatonin, which decreases NADPH oxidase, and N-acetyl cysteine which overcomes the rate-limiting enzyme for the production of glutathione, and estrogen, which scavenges free radicals and increases SOD. We suggest further that if nicotine is protective against contracting symptomatic coronavirus, as has been suggested in the context of smoking (see above), it may be because nicotine has the potential to block NADPH oxidase activity [59]. Likewise, resveratrol then may be useful for the same reason, especially in early postmenopausal women because it also has estrogen-like activity on estrogen receptors [60]. Moreover, it follows from the present theory that other inhibitors of NADPH oxidase, many of which have been investigated in recent years to treat neurodegenerative disease, have the potential to treat or prevent severe coronavirus infection; for example, it would be exciting to pursue the compound apocynin, a naturally occurring inhibitor that is inexpensive and readily available now. Further research on NADPH oxidase as a therapeutic target, on oxidative stress markers, and even bat adaptations will likely help not only with the greatest pandemic of our lifetime but also with the many chronic diseases of our society and even human lifespan itself.

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