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Commentary

Does the hygiene hypothesis apply to COVID-19 susceptibility?

Abstract

In this commentary we argue that the hygiene hypothesis may apply to COVID-19 susceptibility and also that residence in low hygienic conditions acts to train innate immune defenses to minimize the severity of infection. We advocate that approaches, which elevate innate immune functions, should be used to minimize the consequences of COVID-19 infection at least until effective vaccines and antiviral therapies are developed.

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Currently, the world is experiencing a new coronavirus pandemic with no solution or end in sight. In some societies >10% of the population has been exposed to Severe Acute Respiratory Syndrome–Coronavirus 2 (referred to as COVID-19), but epidemiologists inform us that 60–70% need to experience the infection if protective herd immunity is to be established [1]. We could minimize the need for natural herd immunity by using prophylactic vaccines, but the prospects of developing vaccines that confer long term effective immunity against COVID-19 is uncertain. This new coronavirus is highly infectious with the outcome of infection extremely variable ranging from asymptomatic to fatal. However, the spectrum of disease in different societies varies markedly for reasons as yet not fully understood. For instance, in some developed countries, the reported fatality rate is far higher than in others. Also evidence shows that patients infected in low socioeconomic conditions suffer low rates of severe and lethal infection compared to those raised in more hygienic circumstances [2]. All infections have variable consequences and others and we have discussed the many factors that influence the outcome of infection with a virus [3–5]. These variables include age when infected, dose and nature of infection, presence of co-morbidities when infected such as immune suppression, metabolic disease and cancer, genetic and epigenetic variables, composition of the microbiome in different locations as well as past infection and environmental experiences. It is relevant to identify how these various factors come into play during COVID-19 infection since some are subject to manipulation by therapies that could lower the prospect of severe disease.

One susceptibility issue that has received minimal consideration is the immune status established as a consequence of past environmental and microbial experiences particularly early in life. In the early 90s, the so-called hygiene hypothesis was formulated to explain the rising incidence of diseases such as allergy and autoimmune diseases occurring in the developed world [6,7]. The hypothesis advocated that children exposed to certain environments such as farms, domestic pets and exposure to enteric parasites were less likely to develop allergies and some autoimmune diseases than those who experienced a more hygienic upbringing. Indeed, at least in some western societies well before COVID-19, the extensive use of hand sanitizers and frequent hand washings were encouraged in growing children. Added to this heightened concern for intense hygienic practices has been the frequent exposure of children to anti-biotics to ablate potential problems before they develop into clinical problems that most often amount to temporary inconveniences. The unintended consequence of these hyper-hygienic regimens was to change the basic status of non-specific immunity, perhaps in part a result of a change in the balance of commensal microorganisms in the gastrointestinal tract, skin and other surface locations [8]. The hygiene hypothesis has satisfactorily explained the increased frequency of some disease syndromes, but could it also explain why some individuals are more susceptible to the severe consequences of COVID-19 infection than are others? We suspect that the hygiene hypothesis is a viable concept that applies to COVID-19 susceptibility, but it could be a long time, even in this era of accelerated information gathering before epidemiologists could assemble evidence that early lifestyle can be related to later COVID-19 susceptibility. However, it does seem likely that extensive exposure to multiple microbes in the environment, food and water, as commonly occurs among those that reside in depressed socioeconomic circumstances, may render them resistant to the more severe consequences of COVID-19 infection.

Published data in the peer-reviewed literature provide minimal support for the contention, but newspaper articles in India and elsewhere have indicated that severe sometimes lethal effects of COVID-19 infection are uncommon in people living in the poorest communities. Moreover, spread and severe disease from such infection in densely populated and poor communities such as Dharavi in Mumbai appears to be limited [9,10]. Similarly, the numbers of recorded cases and deaths in other societies with low socioeconomic status have experienced far fewer cases than many.
developed countries [11]. Although the efficiency of recording all cases of COVID-19 infection and its consequence varies markedly between different countries, gathering evidence supports the idea that the outcome of infection is more likely to be asymptomatic or mild in developing countries and rarely has lethal consequences. Thus, the WHO statistics show lethality rates that vary from 0.3% to 10% with the latter occurring in some developed countries [2,11]. Severe disease necessitating hospitalization and oxygen supplementation is also more common in developed as compared to most developing countries. If as increasing evidence is showing COVID-19 infection is of less severity in developing countries, how can this be explained? Even more important, can the information be applied to reduce the consequences of infection in the developed world?

The most likely explanation for the different manifestations is that repeated exposure to unhygienic conditions exposes persons to microbes that express multiple so-called pathogen associated molecular patterns that activate one or more aspects of innate immunity. This changed activation state, which may persist for months but will not remain indefinitely [12], is often referred to as trained immunity and unlike adaptive immunity is not highly antigen-specific, is less robust and has minimal or no long-term memory [12,13]. However, the advantage of this type of immune response is that the response is general against one set of microbes can have bystander immune protection against other infections. This phenomenon was first advocated by the Mackaness and Nathan groups in the early 60s with the bystander immune effect being attributed to so-called activated or angry macrophages, terms seldom used these days [14,15]. We now realize that bystander immunity can be attributed to many cell types such as natural killer cells, dendritic cells, innate lymphocytes, gamma delta T cells in addition to macrophages [12].

The fact that trained immunity can be induced raises the prospect of its exploitation to raise the threshold of resistance to COVID-19 infection, a valuable maneuver during the time when we have yet to develop effective treatments or vaccines. The questions will include what approaches could be used to achieve trained immunity and how long they will be useful. Some studies have already shown that communities that still use Bacillus Calmette–Guérin (BCG) as a vaccine against tuberculosis may have lesser instances of severe COVID-19 infection than those countries that do not use BCG [16]. This notion has been complemented by advocating the use of BCG to vaccinate persons in an attempt to protect them against COVID-19 [16]. A recent letter by HIV pioneer Bob Gallo advocated using oral polio vaccine for a similar effect [17]. We consider that administration of galectin molecules, some of which can activate the innate immune system might also represent an approach to reduce the consequences of COVID-19 infection [18]. It is also worth noting that galectin therapy also has the potential to reduce the severity of COVID-19 once infected. Thus, galectins such as galectin-9 can reduce inflammatory cytokine production and change the nature of the inflammatory response caused by some viral lesions from a tissue damaging reaction dominated by pro-inflammatory T cells to one where counter-inflammatory regulatory T cells predominate [19].

For reasons still unknown, clinical disease following COVID-19 infection in children is uncommon in all communities. This might be linked to their having received multiple vaccines and their tendency to develop several minor infections which may have served to activate their innate immune systems. There also are recent claims that vaccination with MMR vaccines might confer protection against COVID-19 as it is claimed to do for Rubella because of cross-reactivity [20]. Other explanations for the apparent resistance of children to clinically evident COVID-19 infection could include lower levels of the viral entry receptor and the tendency of children to generate less tissue damaging so-called type I inflammatory reactions to antigens.

In conclusion, we surmise that frequent exposure of individuals to natural environmental microbes, live attenuated vaccines against other viruses or bacteria or certain natural ligands such as different types of lectins and saponins that can stimulate innate immune receptors all help to reduce the clinical consequences of COVID-19 infection. Moreover, we await with interest observations comparing the outcome of COVID-19 infection in adults raised as infants in environments that support the hygiene hypothesis compared to those raised in more hygienic circumstances. It seems relevant to us to employ innate immune activators in the face of infection at least until such time when effective vaccines are developed. Could it also be that constant hand washing, taking antibiotics whenever we endure minor infections and over-sanitizing our environs is not necessarily such a good idea?

Declaration of Competing Interest

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