

“Paradise lost” as many unknowns to be known to ensure “paradise regained” for Covid-19

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‘Paradise lost’ – the epic poem of the 17th century English Poet John Milton. It’s a story of fallen angel and loss of innocence of ‘Adam and Eve’ under the influence of Satan and their expulsion from the Garden of Eden. In the book of Genesis, God decrees them to suffer them from diseases. We are being enveloped in darkness of several extraordinary epidemics like plague, small pox, yellow fever, cholera, tuberculosis and flu from time to time. Germ theory established by the two giants ‘microbe hunters’ like Louis Pasteur and Robert Koch has changed our views about diseases. The microbes have all the attributes of Satan. The corona virus (SARS-nCov2, causing the disease, Covid-19) in the form of Satan pushed us in a new darkness as in William Blake’s poem “Sick Rose” arresting our image of a rose affected by disease. Very little is known about Covid-19 and our knowledge is beset with uncertainties and unknowns and demands in depth studies. Covid-19 altered us in strange way. It is a paradigm shifting event that divides life into a before and after. We do not know where we are in this drama. Is this the first wave or deadlier one waiting for us in the horizon? I recall watching the mural of Swedish painter Albertus Pictor applied to the white walls of the rustic Täby Church north of Stockholm and the movie “Seventh Seal” by Ingmar Bergman where the Knight while walking through the plague ridden Mediaeval Sweden, encounters the “Character of Death”. The “Death” invited the Knight to play chess knowing well that he only delay inevitable. In Edgar Allan Poe’s short story “The Masque of the Red Death” we see that our choice is limited. We are facing giant wave of anguish sitting in a row boat in a raging sea, like in Hokusai woodcraft painting of Japanese art. The “Book of Revelation” describes a war in heaven parallels as microbes wage war against host.

Paradise lost- a satanic influence on our immune system

The role of “Satan” as pathogens seeking to destroy the paradise of human health.

Our immune system - a holy trinity of three distinct cells, macrophages or phagocytes, T-lymphocytes and B-lymphocytes protects us against pathogens. At the later part of 19th century, Ilya Metchnikoff discovered phagocytic cells or macrophage and their role in immunity. Macrophages attained a prominent place in George Bernard Shaw’s, “Doctor’s Dilemma”. Bernard Shaw through his friend, bacteriologist of Guy’s Hospital, London, Sir Almroth Wright came to know about phagocytes. He wrote in his book that “----only one genuinely scientific treatment for all diseases, and that to stimulate phagocytes”. I think Shaw’s idea well ahead of his time in the light of today’s science. Phagocytes controls innate immunity-whereas T & B-lymphocytes dictate adaptive immunity. Our immune system can produce antibodies against any pathogen using limited gene pool.

Pathogen may have shaped the evolution of immune system

Though the opera “Carmen”, by French composer Georges Bizet introduced Roma or

Romani or Gypsies. They were originally from northern India, migrated to Europe more than thousand years ago. The researchers stumbled on an unusual immunological discovery. The Roma and European Romanians, were both exposed to the Black Death. Researchers looked for similarities in the DNA of Roma people and European Romanians that were also different from markers in the DNA of northern Indians, who did not face the Black Death. A cluster of genes in Roma and Romanians code for toll-like receptors proteins that are critical for defending the immune system were not found in north Indians, so natural selection must have favoured them in order for them to have survived in Europe after the Black Death. In another case, genetic differences that evolved to protect against past pandemics are still present at high frequencies in populations. The instance of this is deletion in the gene encoding the chemokine (family of proteins characterized by their ability to attract nearby cells) receptor CCR5, proposed to confer resistance to plague and small pox in Europe. It is important to study how the effect of such deletion, if any, on Covid-19 pathogenesis. In addition, one class of cell surface proteins of macrophages known as major histocompatibility gene (MHC) products play a critical role in resistance. Black rat populations of the central highlands of Madagascar are highly resistant to plague, whereas those from areas in which the disease is absent (low altitude) are susceptible which was attributed to cell surface protein and their variation known as polymorphism. MHC polymorphism may offer survival advantage for the species as a whole, where individual member may be susceptible. It will be of great interest to study how above genetic attributes in population can influence the outcome of Covid-19 pathogenesis?

Concept of “herd immunity” and can it stop subsequent infection?

During the Peloponnesian War, the plague killed nearly one-third of the Athenian population in 430BC. One of the important persons, the great philosopher Socrates who survived the epidemic said to have tended unscathed to the sick and dying. Socrates had evidently acquired immunity from his earlier exposure to the disease, just as Thucydides himself. Immune memory was first documented in ancient Greece by the historian Thucydides who noted that "the same man was never attacked twice". This was an astute observation, and probably the first to recognize the importance of immune memory. These cells are important to protect us from subsequent attacks. In the modern science, this is the most important area of vaccine research. There are basically three ways to stop the Covid-19 infection. One involves restrictions on movement and the second is a vaccine, but it still needs to be developed. A third is just wait until enough people get it. Vaccines create ‘herd immunity’ through memory cell, that’s how smallpox were eradicated. We do not know ‘memory cells’ status in the recovered Covid-19 patients. These cells are prerequisite for vaccine success.

Cloud in the horizon

Oddly enough, 15-20% of covid-19 patients show aggressive immune enhancement coupled with cytokine storm. Cytokines- a class of proteins molecules produced by immune cells, are of two kinds: the one increases the inflammation known as pro-inflammatory variety and the other does the opposite known as anti-inflammatory. Excess of pro-inflammatory cytokines do more harm than good causing multi-organ failure. Guarding against immune enhancement is one of the biggest challenges. Immunologists define the molecules that cause immune enhancement as “Superantigens”. Presence of “Superantigens” in Covid-19 is an open question. Covid-19 patients show spectrum of response. Chinese patients with mild symptoms, 70 percent developed strong antibody, but about 25 percent developed a low response and about 5 percent developed no detectable response. Mild illness, in other words, might not always build up protection. One important question is what would happen if we

vaccinate people those who have pre-existing propensity of immune enhancement. There is another concern that a subset of recovered patients come down with disease. It is unclear if this is reinfection or activation of latent infection.

Covid-19 vaccine

Development of an effective vaccine for COVID-19 to the control of the pandemic is of prime importance. But the road to get one is lengthy and bumpy. Currently such vaccine is not available. Vaccine researchers always they try to find out “the correlates of protection” from natural infection which is a key to vaccine development. Unfortunately, we do not know what are the “correlates of protection” against Covid-19 infection. The virus causing the disease is a RNA viruses more prone to mutations which compounds the problem further in vaccine development. Mere presence of antibody against virus never tells us that we are protected, all it tells us that we are exposed to the virus. It remains to be seen if protection is mediated through cellular arm or antibody or combination of both. Now there is a race to develop vaccine for Covid-19. There are many players in this endeavour. Most of the groups are using spike protein of the virus as antigen. Oxford University group is using chimpanzee virus as the carrier of spike protein nucleic acid. Other groups like, Moderna, US mRNA-giant and German giant, BioNTech teamed with Pfizer using mRNA to induce immune response against spike protein. The entire world is waiting to see success of such initiatives.

Paradise to regain through vaccination

“Paradise Regained” is another poem by Milton is the idea of reversals. Milton sets out to reverse the "loss" of Paradise. All said and done so far, the virus isn't well understood and we do not know who is most vulnerable and why? May be through appropriate scientific research, new vaccinations and new drugs will help to regain the Paradise. History need not simply recall the horrors of the past. It can guide us towards adopting precautions, remind us that accurate observation is vital to ensure a better response in future. New tools like early diagnosis, vaccines and drugs will offer good handle to resist the original sin to build up a new Eden in our planet.