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Wherever the art of medicine is loved,
there is also a love of humanity.
- Hippocrates

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Editorial

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Living on a Sick Planet

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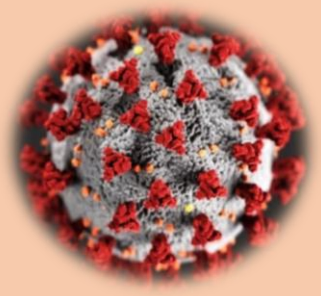

SARS-CoV-2 Virus: Courtesy CDC

When we develop land in a way that destroys biodiversity we create environments that are conducive to disease outbreaks. - Tom Ireland, Editor of *The Biologist*

Humanity's Fight Against Microbes: During the 18th century about 400,000 people were dying each year due to smallpox in Europe. In 1796 Edward Jenner, a country physician and a keen observer in England, successfully performed the world's first vaccination against smallpox. Taking pus from cowpox lesions on the hands of a milkmaid, Jenner inoculated an eight-year old boy. Six weeks later the boy was unaffected when variolated with smallpox on two sites. That simple procedure ushered the era of active immunization or vaccination. For the first time humanity learned how to protect itself against infections by microorganisms – bacteria or virus (Riedel S, 2005; Stern and Markel, 2005). Thanks to advances in microbiology, virology, cell and molecular biology, synthetic chemistry, synthetic biology, immunology, and artificial intelligence we have come a long way from that crude vaccine method used by Edward Jenner. We were able to develop potent vaccines and thus effectively controlled the spread of many bacterial infections (diphtheria, teanus, pertussis), and viral diseases (smallpox, polio, measles, mumps and influenza, including H1N1).

Challenges with Coronavirus Vaccines: When it comes to coronaviruses, it is not that easy to prepare reliable and long-lasting vaccines, because of highly adaptive evolution due to their rapidly replicable, and mutable nature with high genetic recombination as described by Dr, Malireddy S. Reddy in the following article. These led to emergence of novel pathogen variants of coronaviruses, which diversified into severe acute respiratory syndrome-related virues or the SARSr-CoVs of bat origin (Adachi et al, 2020). Thus, we entered the age of coronaviruses, and we do not know how long it will last. Despite these limitations, the scientific community and industry with the support from the US Government worked at a very rapid pace in bringing out candidate vaccines for COVID-19 in a record time using a variety of approaches. These are summarized in the April 2020 issue of the Nature under the title *The Race for Coronavirus Vaccines: A Graphical Guide* (Callaway E, 2020). Let us hope that these vaccines will at least contain the spread of infection, if not complete eradication.

Need for Averting Pandemics: Obviously, it is prudent to preemptively stop the infection by another novel type of SARS-CoV virus by means of preventive vaccination just like we do with influenza, rather than to fight against a pandemic as we are doing now with SARS-CoV-2. We cannot afford to act reactively and hastily after being hit with a pandemic every time. In this context, by hindsight we did not take the outbreak of SARS-CoV of 2003 infection seriously, and we failed to came up with a plan to prepare and face a similar viral infection turning into pandemic (Xu R, 2013). In fact, SARS-CoV had a higher case fatality rate (10%) as opposed to SARS-CoV-2 (2-3%), but it had very low reproductive rate (mitigated R_0 1.1; range 0.4 to 2.4) vs. SARS-CoV-2 (R_0 2.2; range 1.4 to 2.9) (Petersen et al, 2020). SARS-CoV of 2003 infected 8,422 people worldwide causing 919 deaths (10.9% case fatality rate) (Yang et al, 2020). In the United States 8 people were infected and none of them died. These numbers are very low as compared to annual influenza deaths in the United States. For instance, according to the CDC, the Influenza A (H3N2) infection in 2003-04 killed an estimated 14,114 to 16,342 people in the United States. This may be the reason we did not take SARS-CoV infection seriously. But, this taught us a costly lesson that we should not go by the number of deaths alone, but we should look deep into the nature of the virus and its family of related viruses. We were fortunate that the SARS-CoV-2 has low case fatality rate. If it had the same case fatality rate of SARS-CoV, 6.2 million people might have died worldwide (as against 1.45 million deaths reported so far). By the same token, 1.32 million people might have died in the United States (against 265,000 reported so far). These numbers exemplify the differences in the R_0 values and case fatality rates make at the ground level. Hence, we cannot take chances anymore, as we have no means or methods to predict the R_0 value and case fatality rate of the next SARS-CoV outbreak. ***We need to come up with a comprehensive plan to protect the entire humanity by nipping the pandemic in its budding stage.***

Nature of the Comprehensive Plan and Approach: Such a comprehensive plan calls for integration with concerted efforts among the biologists, clinicians and healthcare providers, public health officials, epidemiologists, vaccine industry, as well as the ecologists. One may wonder what ecologists have to do with the pandemics? In fact these zoonotic viruses come from the wild, often being displaced by rapid ecological changes due to shrinking forests, including rain forests, canopies, encroaching human activity into the wilderness among others. All these result in reduction in the populations or extinction of the natural hosts of coronaviruses, such as bats. In an ariticle published in the Aug/Sept 2020 issue of the Biologist, the voice of the Royal Society of Biology, United Kingdom, Professor Kate Jones, Ph.D., of the University College of London laid a clear picture of how intricately public health, biodiversity and ecological balance are related to outbreak of pandemics such as the COVID-19 (Jones K, 2020). Professor Jones, whose research investigates the interface of ecological balance and human health, with particular focus on emerging infectious disease from animals, says *a woeful lack of communication between public health bodies and ecologists is failing to prevent spillover of animal diseases into human populations*. She went on to add, *it is not one solution for wildlife and one solution for humans. It is the same solution.* According to Professor Jones, *there were at least three papers in 2019 that said coronaviruses might be a real problem in South China*. Before the emergence of SARS-CoV-2, Jones and her colleagues had repeatedly warned that environmental degradation around the world was increasing the likelihood of 'spillover' events and pandemics. ***It is time we start paying attention to such voices and act in the best interest of the humanity or we may have to live on a Sick Planet forever.***

The Solution: Soon after the 9/11 tragedy, the Department of Homeland Security was created to bring all federal and state departments and agencies entrusted with security of the nation, under one unbrella to deal with threats to the United States in an effective and comprehensive manner. That was a very appropriate response. The current COVID-19 pandemic is worse than the 9/11 incident in its magnitude in terms of toll of human lives and economic loss to the nation and the world. So, we should call for a similar initiative, such as creation of **National Institute of Epidemiology and Ecology** to integrate the work of physicians, biologists, public health officials, epidemiologists, and ecologists and focus at the interface of public health and ecological balance. Then only we can identify potential spillover of novel coronaviruses and other pathogens from animals to humans at a very early stage. That will markedly help us to contain those spillovers and thus prevent deadly pandemics. In fact this costs only a fraction of money the United States spent to control and contain the COVID-19 pandemic, exlcuding the stimulus package. ***It is time we need to take the war on pandemics to the very place where they originate.*** In parallel we should develops drugs that are effective against a wide range of coronaviruses. We already have scientific basis for at least two drug targets. All known disease-causing coronaviruses use ACE2 (angiotensin converting enzyme-2) for entry into the host cells, and RNA-dependent RNA polynerase (RdRP) for multiplication of viral genome. Drugs that block ACE2 or inhibit RdRP should be effective against all those coronaviruses including SARS-CoV-2.

References: Citations shown in the text are hyperlinks to their respective publications.

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Potential for Transmission of SARS-CoV-2 Infection through its Naked RNA:

Relevance to Healthcare Providers

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Prologue: Earlier I have published several articles pertaining to SARS-CoV-2, pathophysiology of COVID-19 disease, and possible ways and means to prevent or cure this viral pandemic (Reddy, 2020 a; Reddy, 2020 b; Reddy, 2020 c; Reddy, 2020 g). Here, I would like to put forward my conviction that it is possible for transmission of SARS-CoV-2 infection through its naked RNA after disruption of its external lipid coat. Although it may sound like a wild hypothesis, as the readers can soon find out there is enough scientific basis for my conviction, which may also account for rapid spread of the SARS-CoV-2 infection throughout the world in a short span of time. This hypothesis, which can be proved easily, has a significant relevance to healthcare providers and first responders of COVD-19 pandemic.

Mutation and Recombination of Viral Genome: Generally, viruses are continuously changing as a result of genetic selection. They undergo subtle genetic changes through mutation, and major genetic changes through recombination. Mutation occurs when an error is incorporated in the viral genome. Recombination occurs when coinfecting viruses exchange genetic information, creating a novel virus. The mutation rate of DNA viruses (not coronaviruses) is approximately those of eucaryotic cells, yielding in theory one mutant virus in several hundred to many thousand per virus genome copies, which is significantly low. Examples for DNA virus are Smallpox and Herpes etc. RNA viruses, such as coronaviruses (SARS-CoV-2), have much higher mutation rates, perhaps one mutation per virus genome copy, which is significantly higher. Mutations can produce viruses with new antigenic determinants.

Antigenic Drift and Antigenic Shift: Antigenic Drift involves the accumulation of a series of minor genetic mutations in genes of the same virus. Antigenic Shift involves mixing of genes from influenza viruses or other viruses from different species, such as pigs, birds, and humans. In simple terms, Antigenic Shift is intermixing of genes of several viruses (in the infected eucaryotic cell) from a wide range of viruses infecting both humans and animals. Antigenically altered novel viruses may be able to cause diseases in previously resistant or immune hosts. These major changes due to Antigenic Shift only happen so suddenly that human immune system may not recognize the novel virus. A classic example of Antigenic Shift is H1N1 influenza virus strain (Avian H1N1 strain mutation) responsible for 1918 pandemic that caused 50 to 100 million human deaths. The same virus also caused pandemic in 1934 and in 1947. The reappearance of virus strains, after a long absence, is believed to be the result of another recombination event involving the independent assortment of genes from two variant viruses rather than the Antigenic Drift due to the alteration of genetic material of the parent strain. This is exactly what is happening with SARS-CoV-19 virus. Perhaps it also happened in the case of H1N1 virus of 2009, where it was due to a combination of genes from pigs, birds, and humans. These changes result in viruses that spread more easily from animals to humans (zoonotic) and vice versa. On the other hand, virial mutants due to Antigenic Drift develop slowly over a time period and the mutated strain is somewhat similar to the parent strain, and infects only the same human species and not animals or vice versa.

Genetic Recombination and Creation of Novel Viruses: Recombination involves the exchange of genetic material between two viruses during coinfection of host cell. Thus, the current SARS-CoV-2 virus may once again gain or exchange genes from other influenza viruses or any other RNA viruses, resulting in a new sub-type with much higher pathogenicity, which can infect both humans and animals. However, fortunately so far mutations due to antigenic shift, unlike antigenic drift, do not occur that frequently. Alterations in the genetic material of virus (Antigenic Drift) may lead to changes mainly in the function of viral proteins. Such changes may result in the creation of a new viral strain of altered acute virulence in comparison to the parent, and unfortunately it does occur frequently. However, such new viral strain is species specific like its parent. An example of viral infection due to antigenic drift is influenza H3N2 variant in 2003-04 flu season, which was responsible for severe infections and lasted longer period than any other past flu seasons. This is the main reason for the

failure to develop 100% effective influenza vaccine, and consequently a new modified vaccine has to be developed every year prior to the flu season.

Genetic Mutations in Coronavirus: Coronaviruses are a large group of enveloped, single strand, positive sense RNA viruses. These viruses have the largest RNA genome, and thus have room for the insertion of large foreign genes, to amplify the rate of mutation due to recombination. The coronavirus, which enters into the host cell, when simultaneously coinfected by any other virus, can result in a new virus, with higher pathogenicity and can infect people who were resistant to parent virus and thus can cause uncontrollable pandemic. Thus, coronavirus SARS-CoV-2 can mutate once again through series of Antigenic Drifts or Antigenic Shifts or both and thus may cause some more uncontrollable pandemics in the future (beyond 2020). Currently this is the major concern of not only CDC and WHO, but also the entire world at large, considering the forthcoming flu season, while the COVID-19 pandemic is still active and spreading.

Naked RNA of SARS-CoV-2: What happens to coronaviruses when exposed to adverse conditions, when they are outside the human body? Indeed, some changes do take place in their morphology to make them less infective or totally non-infective. Now let us look into infective patterns and pathophysiology of disease caused by defective coronavirus or their naked RNA. What is naked RNA? The main genetic determinant of SARS-CoV-2, like any other coronaviruses, is its single standard RNA. When an intact SARS-CoV-2 virus is outside the human body, due to the adverse conditions, it may start to lose some of its structural components, such as spike proteins and other proteins like M (membrane), N (nucleocapsid), and E (envelop), and the protective lipid layer envelop. This is because of the disintegration of the viral particle. Under these conditions, the RNA which is enveloped and protected by the viral lipid layer will be liberated from the integral virus structure. Such an exposed viral RNA is scientifically termed as naked RNA.

Is Naked RNA of SARS-CoV-2 Infective? The first question here is, how long the naked RNA of SARS-CoV-2 stays intact and genetically functional when it is stripped off from the structured viral particle? The second question is, can such naked RNA with functional genetic determinants (viral genes) infect the susceptible human cell without the aid of its spike proteins and protective lipid layer? The popular and general answer is that it cannot, and according to the CDC the SARS-CoV-2 virus is ineffective after it has been outside the human body longer than 72 hours and at the most one week. However, CDC is silent about the infective capacity of the naked RNA. To the best of my knowledge there are no published articles on this important subject. However, extra precautions have been in practice in research laboratories, to prevent the contamination of work surfaces, and clothing of the researchers with naked RNA of viruses and thus to eliminate the potential for infection. Despite this known practice, surprisingly no attention has been paid to the prevalence of pathogenic naked viral RNA of SARS-CoV-2 in the households and public places, especially during pandemic times. It is perhaps due to the relatively recent emergence of the COVID-19 pandemic, although much has been published on COVID-19 disease and its lethal consequences (Connors and Levy, 2020; Huang et.al., 2020).

Hypothesis: Let me dwell into and hypothesize the fate of naked RNA of SARS-CoV-2 and its possible potential to infect and induce the COVID-19 disease. The general term used by scientists and CDC officials to describe ineffective virus is: "such a virus lost its ability to infect." Under the normal circumstance, the coronavirus infects susceptible human cells using its spike protein (S-protein), followed by integration of its membrane into the host cell membrane, thus gaining entrance into cell cytoplasm. Once inside the cells, it releases RNA to replicate and produce more infective viral particle and thus destroys cells and tissue and causing the disease. However, when it is outside the human body, the SARS-CoV-2 virus may start losing the surface viral proteins and the protective membranes, which are essential for the viral survival, and adsorption and penetration into the human cell. This is what is referred (non-scientifically) as "virus lost its ability to infect." However, in my opinion the functional naked RNA is still intact and has the capacity to replicate in the human cells, if it can be introduced mechanically through a vector. According to the literature, the naked RNA of MERS-CoV (related coronavirus) can stay intact for up to 16 weeks, even at room temperature, when it integrates with silica. Silica is a common dust component (Abdallah et al, 2020). These investigators were solely interested in stabling the naked RNA of MERS-CoV at room temperature, for the sake of sending samples economically to the testing laboratories at room temperature rather than shipping at minus 80° C. Their investigation proved that naked viral RNA can be stabilized at the room temperature using silica membrane (of spin columns) (Abdallah et al, 2020). Hypothetically, if such a naked RNA of coronavirus can adhere to mold hyphae (live or dead) along with fine silica (component of dust or dirt) it can get into nasopharyngeal orifices. Then the inflammation started by mold hyphae and perhaps also due to secondary pathogenic bacterial infection, the host cell membrane may be partially disrupted. If that happens, the naked viral RNA may enter into cell cytoplasm and thus allowing virial genome (naked RNA) to multiply within the human cells causing COVID-19 disease.

Relative Sizes of SARS-CoV-2 and the Potential Vectors: In this connection for the benefit of the reader, I would like to point out the relative sizes of the microscopic or submicroscopic single cell yeast (10 microns), mold hyphae (2,000 – 5,000 microns), mold spore (2-5 microns), spherical bacteria – diameter (1-5 microns), and single coronaviral particle diameter (0.02-0.10 microns or 20-100 nanometers). In contrast, naked RNA of SARS-CoV-2 cannot be over 2 nanometers in size. One micron is one millionth of a meter and one nanometer or millimicron is one billionth of a meter. Now one can see clearly that the coronavirus is 100,000 times smaller than a single mold hypha, and the naked RNA of the coronavirus is one million times smaller than one single mold hyphae. Even a single spherical cell bacteria or mold spore is 10,000 times larger than the naked coronaviral RNA. A single cell yeast is 50,000 times bigger than the coronaviral RNA, signifying that naked viral RNA or even intact coronavirus, including SARS-CoV-2, can be lodged onto the surface of these micro-organisms (live or dead) or even the smallest microscopic dust particle and thus can gain entrance into the human respiratory tract, buccal cavity, and eyes to start the SARS-CoV-2 infection.

Feasibility of the Hypothesis: This hypothesis is feasible because mechanical vectors such as mold hyphae (live or dead) may have cellulose as part of the cell wall which attracts the coronavirus or its naked RNA to stick to it and stay intact (without disintegration) for a long time at the room temperature. The same thing may happen when naked RNA attaches to silica present in dust or dirt in the indoors. Thus, by chance, if such a naked RNA (physically integrated with the mechanical vectors) gains entry into the nasopharyngeal orifice or buccal cavity it can cause disease, specifically if there are prior lung ailments or other comorbid conditions. Conversely, the injured coronavirus with defective RNA or even partially damaged RNA, after it is introduced into human cell (with the aid of mechanical vector) may integrate with other virulent coronaviruses or coinfected animal viruses through recombination and become a novel pathogenic virus. These can multiply and cause another severe pandemic. Perhaps in the past, such an integration might have created H1N1 virus in 1918 and other SARS-CoV and MERS-CoV viruses etc. Considering the high mutation rate due to Antigenic Drift or Antigenic Shift or both, even an effective vaccine may not give sufficient protection or immunity to prevent or eradicate the current and/or future lethal pandemics. It is an essential requisite that new and effective treatment modalities and drugs have to be developed to cure COVID-19 infection, in addition to the development of a successful preventive vaccine (if it can be developed).

Relevance of the Potential Spread of Infection through Naked RNA to Healthcare Providers: It has been reported from Wuhan, China that the COVID-19 infection was more pronounced in patients who were in the ICU, evidenced by increased concentration of proinflammatory cytokines in their blood than in patients who were not in ICU (Huang et. al., 2020). Thus, hospitals must take extra precautions to inactivate the SARS-CoV-2 naked RNA in their environment. In addition, other precautions such as effective filtration systems (to filter less than 30 nanometer size particles), sanitation of the healthcare providers must be strictly instituted. Hospital rooms must be sanitized periodically to eliminate mechanical vectors which can harbor not only the SARS-CoV-2 virus but also its naked RNA. In this connection, I would like to refer the reader to go through some of the articles written on coronavirus control in the food production facilities (Waltenburg et al, 2021; Nakat and Bou-Mitri, 2021). Even in China, the open food markets were closed to curtail the spread of SARS-CoV-2 (Huang et. al., 2020). In view of these published data, one can partly attribute the rapid progression and spread of COVID-19 in the world in the shortest time span to the potential of the naked RNA to cause infections through vectors. In January and early February 2020, the major COVID-19 problem was mainly in China with 70,000 people infected and the number of registered deaths were approximately 3,500. As of July 2020, more than 10.7 million people were infected with 516,000 deaths all over the world (Waltenburg et al, 2021; Nakat and Bou-Mitri, 2021). However, as of now (November 2020) globally, over 65 million people are infected causing more than 1.6 million deaths. Preliminary data indicate that SARS-CoV-2 can also infect domestic pets such as cats and dogs, thus promoting the unwanted spread of the pandemic due to reverse zoonosis (Sarkar and Guha, 2020). It is a must that we take extra precautions to curtail the spread of the SARS-CoV-2 virus pandemic.

Conclusion: In conclusion, it is highly imperative that we inactivate not only the intact or the damaged or injured SARS-CoV-2 virus but also its naked RNA in the households, and in public places (such as hospitals, nursing homes, offices, hotels including hospitality facilities, restaurants, class rooms, airplane cabins, airports, trains, and all other public transportation facilities etc., etc.) to eliminate further transmission of SARS-CoV-2 virus, This may prevent or reduce potential spread of infection through naked RNA aided by mechanical vectors. However further controlled studies are required in this arena to establish the role of naked RNA in the spread of SARS-CoV-2 infection. Pending those studies, it is prudent to care of ourselves.

References: Citations shown in the text are hyperlinks to their respective publications.

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A Synopsis of Fireside Chat with Dr. Anthony Fauci at the Annual Meeting of the American Society of Hematology

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The 62nd Annual Meeting and Exposition of the American Society of Hematology (ASH) held on December 5th to 8th, 2020 was no exception to rest of the world which has evolved and survived the effects of the pandemic. Like the elegant Red Blood Cell with its ability to maneuver through the intricate spaces of capillaries, valves and still come out unscathed, the organizers of the ASH have done a remarkable job in delivering the content i.e., the results of groundbreaking research, education and wellness sessions rather seamlessly in this one-of-a-kind all virtual meeting midst of peak of the pandemic.

One of the very informative sessions was the Fireside Chat with Dr. Anthony Fauci by Dr. Stephanie Lee, President of the ASH. Here is a compilation of few relevant excerpts from the session that I felt could be useful to oncologists treating cancer patients and the rest of the physicians caring for immunocompromised patients.

Dr. Fauci discussed the devastation caused by the COVID-19 explaining the chronology with the first case diagnosed on January 21, 2020 in the United States, which now became the worst devastation in past 120 years. This pandemic has caused more than quarter million deaths and resulted in 13 million infections in the United States. Explaining a few facts regarding the virus itself, Dr. Fauci mentioned that the immunity from the human coronaviruses infections lasts from months to years- NOT decades. Unlike the SARS-CoV-2, other coronaviruses never usually leave the upper respiratory tract. But the question which time has to answer is, can the way SARS-CoV-2 invaded entire organ systems induce a longer period of immunity? Similarly, we have to monitor the duration of immunity induced by vaccines.

Answering about the mutational changes of the SARS-Cov-2 virus which the scientific community is carefully studying, Dr. Fauci explained, the mutation of amino acid 614- change to D to G - increases the affinity of the virus to

ACE-2 receptor and thus increases transmissibility. There are not enough data to support whether these changes result in more virulence. There may be mutations which increase transmissibility but not virulence.

Dr. Fauci had shared his thoughts on the concept of long haulers. He opined that innocently this term leads to misperception – those who get infected and symptomatic with fever, cough and not that bad to go to hospital and take few weeks to recover. The other 25% or so of people are severely sick with thrombi and later cleared of the virus and come out of the hospital with lingering effects of end organ damage. Thus, there are two different cohorts. More research is needed to differentiate between those two groups.

On the important topic of vaccines, replying to Dr. Lee's question if people let their guard down after vaccines are available, Dr. Fauci hoped that would not be the case. He added, it may take months for people to develop immunity. There will also be some people who will refuse to be vaccinated.

Dr. Fauci shared his thoughts about the remarkable speed with which the process of development of the vaccine has occurred. He gave credit to the scientific community, federal funding program in purchasing the vaccine even before it was proven efficacious. Assuring the people who worry about the safety of the vaccine he shared the process of the safety monitoring and the role of the group of independent scientists from the FDA and oversight committees like VRBPA (Vaccine and Related Biological Products Advisory Committee). He said that independent safety monitoring scientists who do not have any skin in the game review the data and then the companies send those data to regulatory agencies to get approval, thus assuring an independent and transparent process.

ASH is an organization representing thousands of hematologists from all over the world who treat immunocompromised patients. In reply to the question can patients on chemotherapy and immunocompromised patients receive vaccine when available, Dr. Fauci answered that the physicians should recommend vaccination to those. They might not have a robust immune response, but some degree of immunity is better than none. This makes it even more important for healthy people to get vaccinated to provide herd immunity which benefits the immunocompromised patients.

It will be couple of years or more for the world to get back to its previous style of life. The vaccines for smallpox, polio and such viruses are successful stories of immunization programs. With billions of doses of COVID-19 vaccine available to immunize the entire world population, it should be possible to eradicate the SARS-CoV-2 virus. Three coronaviruses over the past two decades remind us to develop a generic vaccine in anticipation of a future pandemics due to coronaviruses. Public health systems need more support – and it is a cautious optimism that it will happen.

When asked about how Dr. Fauci takes care of himself, he said that he focuses on what to do. He is old enough to have seen many public health challenges and he got used to no limitation on work hours. He still thinks about himself as an intern of 1968 and works. He exercises every day and runs marathons.
In summary, Dr. Fauci reminded, that this pandemic is a serious problem, so we have no luxury to take a break - *it is a marathon not a sprint.*

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Diabetes Insipidus:

From Pituitary to the Kidney

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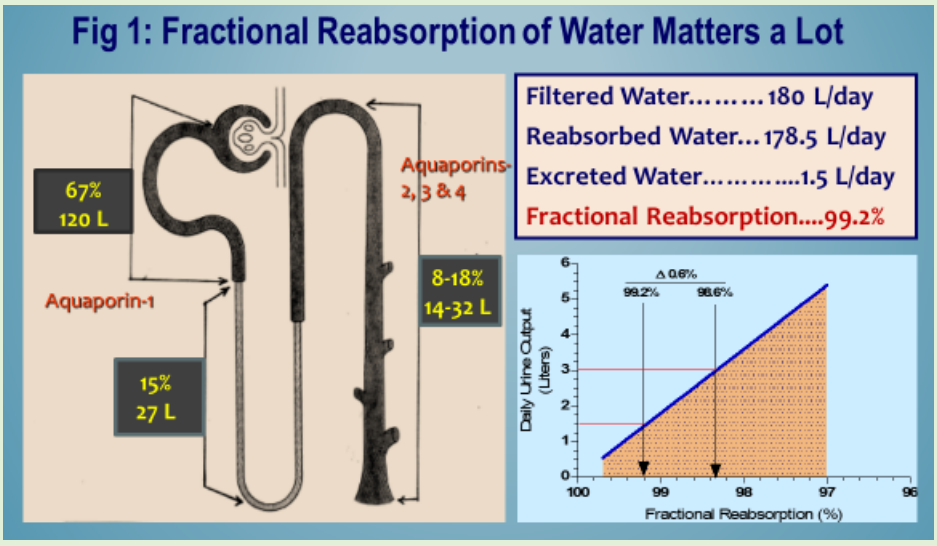
Introduction: In the November issue of Sushruta Medical News, we presented and discussed about the physiology and pathophysiology of aquaporin (AQP) water channels which play crucial roles in water homeostasis, and disorders associated with it. Here we will deal with Diabetes Insipidus, the collective term used for disorders of water homeostasis resulting in polyuria. *Diabetes* in Greek means *to pass through or to siphon*. It is a generic word that denotes increased flow of urine. It is the Latin word that follows it, such as *mellitus* (sweetened) or *insipidus* (tasteless), which differentiates between the two unrelated disease conditions, but sharing a common sign – increased flow of urine or polyuria. Diabetes mellitus or sugar diabetes, was known to humanity for a long time. However, it was only in 1670s Thomas Willis differentiated diabetes mellitus from other polyuric conditions, based on the sweetness of urine or lack of it. A major milestone occurred in 1913 when Farini successfully treated patients with diabetes insipidus with posterior pituitary extracts. In 1920s it was observed by De Lange that some patients with diabetes insipidus do not respond to treatment with posterior pituitary extracts. This led to Forssman and Waring in 1945 to identify and establish that kidney had a critical role in those patients with diabetes insipidus who did not respond to treatment with pituitary extracts. In 1955 Vincent du Vigneaud received Nobel Prize in Chemistry for the synthesis of arginine vasopressin (AVP) or the anti-diuretic hormone (ADH) (Vigneaud, 1954) elaborated by the posterior pituitary, thus ushering rational treatment of Central Diabetes Insipidus. In 1992 vasopressin V2 receptor was cloned (Lolait et al, 1992), followed by cloning of vasopressin-regulated aquaporin-2 (AQP2) water channel in the kidney (Fushimi et al, 1993). For further reading on the history of diabetes insipidus please refer to (Lindholm, 2004; Valenti and Tamma, 2015).

Renal Handling of Water: In order to better understand the nature of different types of diabetes insipidus, a basic knowledge of the current concepts of water handling by the nephrons and collecting ducts in the kidney is essential.



The average number of nephrons in one human kidney is about 900,000 to 1 million. But it can vary widely from 200,000 to > 2.5 million (Bertram et al, 2011). All of the nephrons are formed in the womb between 25 to 36 weeks of gestation, and nephron formation abruptly ceases at birth. So, premature babies have lesser number of nephrons, which may explain why they are prone to develop chronic kidney disease in adulthood (Crump et al, 2019). As shown in the Fig 1, every day, both kidneys in humans filter blood and form about 180 liters of filtrate. Of this about 178.5 liters are reabsorbed back into the blood, thus excreting 1.5 liters/day as urine. This amounts to 99.2% fractional reabsorption of water. The right lower panel in Fig 1 shows that if fractional reabsorption falls by 0.6% to 98.6%, then urine volume doubles to 3 liters from 1.5 liters per day, which is considered polyuria. Thus, in a healthy subject water

reabsorption by the kidney is regulated very precisely. This is achieved by both arginine vasopressin-dependent and independent mechanisms of water reabsorption by the nephron and collecting duct system. As shown in the left large panel of Fig 1, the proximal nephron starting from the base of Bowman's capsule to the tip of the loop of Henle expresses aquaporin-1 (AQP1) water channel. A large amount of filtered water (82% or 147 liters) is passively absorbed in this segment as a result of active transport of sodium. This represents isosmotic absorption of water as there are no osmotic gradients created in this part of the kidney. The ascending thick limb is impermeable to water, but actively transports a large amount of sodium. This creates osmotic gradients in the interstitium adjacent to the collecting duct system. The collecting duct system, which expresses vasopressin-regulated AQP2 water channel at the apical aspect and AQP3 and AQP4 water channels on the basolateral sides is the site of osmotic reabsorption of water. The water reabsorption in this segment shows a wide variation depending on circulating levels of vasopressin, being higher in the presence of higher levels of vasopressin. By virtue of expression of aldosterone regulated epithelial sodium channel (ENaC) on the apical side, collecting ducts also absorb 1 to 8% of filtered sodium. However, this small amount is responsible for salt-sensitive hypertension. **Collecting duct is unique in the sense it is the only tubular segment in the kidney where water and sodium absorption are "delinked" and are independently regulated by vasopressin and aldosterone, respectively.** From the clinical point of view, most disorders of water and sodium balance and salt-sensitive hypertension are due to defects in the transport properties of the collecting duct. Apart from these two circulating hormones, collecting duct transport of water and sodium are influenced by a variety of agents, such as alpha- and beta-adrenergic agonists, atrial natriuretic peptide, bradykinin, endothelin, epidermal growth factor, prostaglandin E2, muscarinic cholinergic agents, adenosine and extracellular nucleotides (purinergic agonists), which are produced locally in the kidney. These agents play critical roles in disorders of water and sodium handling by the kidney in disease states. Thus, from the clinical point of view, the collecting duct system is a very important segment in the kidney. So, let us examine briefly how water and sodium are handled independently in the collecting duct principal cell.

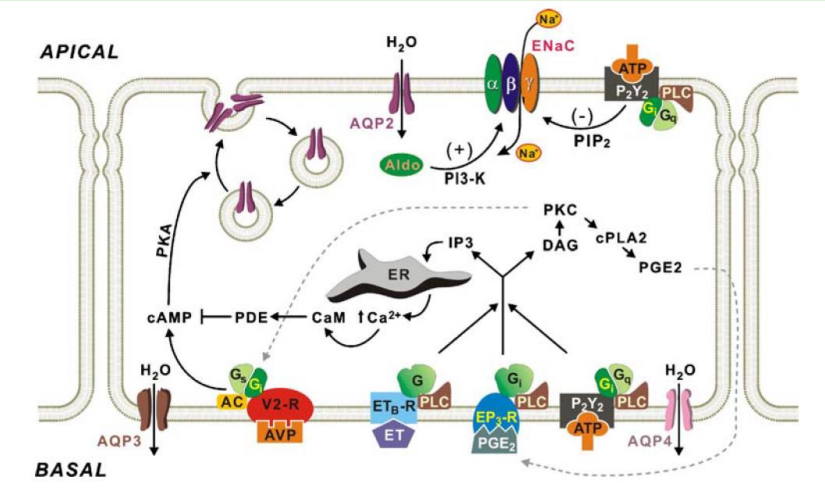


Fig 2: Schematic representation of independent regulation of water and sodium reabsorption in the collecting duct principal cell. Vasopressin (AVP) and its V2 receptor (V2-R) are at the basal aspect, and aldosterone (Aldo) and epithelial sodium channel (ENaC) are at the apical side of the cell. The scheme also shows AQP3 and AQP4 water channels constitutively expressed on the basal aspect, and AVP-regulated AQP2 water channel shuttling between the intracellular vesicles and apical membrane. *Reproduced with permission from Kishore et al, 2009 Purinergic Signalling 5:591-499*

In addition, the scheme depicts the interactions of prostaglandin E2 (through its EP3 receptor) and extracellular ATP (through P2Y2 receptor) with AVP and/or aldosterone in the collecting duct, making regulation of water and sodium handling by the kidney a complex phenomenon than what it appears superficially. Understanding of these complex mechanisms is crucial for the development of rational therapeutic approaches based on empirical science for the treatment of disorders of water and sodium homeostasis, such as acquired nephrogenic diabetes insipidus and salt-sensitive hypertension. Details of these interactions can be found in the review article cited (Kishore et al, 2009).

Types of Diabetes Insipidus (DI): The following are different types of diabetes insipidus.

Neurogenic Diabetes Insipidus: also called Central or Hypothalamic DI.	It is due to congenital deficiency of arginine vasopressin. This can be treated by the administration of vasopressin or its synthetic analogue, desmopressin.
Nephrogenic Diabetes Insipidus	It is due to resistance of the kidney to the action of arginine vasopressin (also called anti-diuretic hormone). It can be Inherited or Acquired. Inherited types may be due to genetic defects in the vasopressin V2 receptor or aquaporin-2 water channel. Acquired type, the most common one, may be due to a variety of causes (see below).

Gestational Diabetes Insipidus	It is a rare condition. During pregnancy, placental trophoblasts may elaborate an enzyme (vasopressinase) that breaks down vasopressin causing diabetes insipidus. It usually develops in the third trimester and resolves spontaneously 4-6 weeks post-partum. In patients with liver dysfunction, it may need treatment with desmopressin, as placental vasopressinase is metabolized in the liver. (Marques et al, 2015).
Dispogenic or Psychogenic Diabetes Insipidus or Primary Polydipsia	This condition is due to compulsive water drinking. Low dose intermittent administration of desmopressin may help in this condition. But caution needs to be exercised to avoid water retention.

Acquired Nephrogenic Diabetes Insipidus (NDI): This is the most common form of diabetes insipidus, and can be due to any one of the variety of causes, depending on the definition. If we apply a narrow definition, i.e., *water permeability of the collecting duct is not increased by vasopressin* -then acquired NDI is due to hypercalcemia, hypokalemia, post-obstructive uropathy, post-ischemic acute renal failure, and drugs, such as lithium, cisplatin, colchicine, demeclocycline, amphotericin B, methoxyflourane, dipheyl-hydantoin and alcohol. On the other hand, if we apply a broad definition, i.e., *defective medullary countercurrent function* - then we have renal failure (acute or chronic) or damage to renal medulla due to loop diuretics, sickle cell anemia and trait, amyloidosis, Sjögren syndrome, sarcoidosis, protein malnutrition and cystinosis.

Recent Advances in Experimental Therapies for Nephrogenic Diabetes Insipidus (NDI): In recent years several groups of investigators, including ours, reported novel experimental therapies for NDI, both inherited and acquired. These therapies are based on repurposing existing FDA-approved drugs used for other diseases, often called "off-label use". As such, these new therapies for NDI do not need approval by FDA, and physicians are free to try them in their patients at their own discretion. The following is a brief summary of those uses with references to published literature.

• **Metformin:** The widely used anti-diabetic drug metformin has been shown to improve urine concentration in animal models of defects in V2 receptor by activation of AMP kinase (Efe et al, 2016). About 90% of congenital nephrogenic diabetes insipidus are caused by defects in V2 receptor. Currently clinical trials are going on to evaluate the efficacy of metformin in central diabetes insipidus (ClinicalTrials.gov Identifier: NCT02460354). This is a significant development as children with this condition are prone to mental retardation due to cycles of dehydration-rehydration. In addition, at any age, this condition can cause chronic kidney disease due to urinary reflux.

• **Sildenafil:** Originally approved for erectile dysfunction sildenafil found a number of off-label uses (Smith and Babos, 2020). Sildenafil has been shown to reduce polyuria in rat models of lithium-induced nephrogenic diabetes insipidus (Sanches et al, 2012). Sildenafil increases apical trafficking of AQP2 water channel in the collecting duct principal cells and thus improves renal absorption of water. Recently a 4-year old boy with X-linked NDI resistant to conventional therapy showed substantial reduction in urine volume when treated with sildenafil (Assadi and Sharabaf, 2015).

• **Statins:** Recently it has been shown that statins exert pleiotropic effects and increase the expression of AQP2 water channel in the kidney, which is independent of their cholesterol reducing effect. This opened the possibility of treating nephrogenic diabetes insipidus by the administration of statins (Bonfrate et al, 2015).

• **Thienopyridine Group of Anti-thrombotic Drugs:** This group consists of clopidogrel bisulfate, prasugrel and related drugs, which irreversibly bind to platelet ADP receptor (P2Y12 receptor), thus prevent thrombotic episodes. We have shown that P2Y12 receptor is expressed in the kidney, especially in the collecting duct, and in the hypothalamus. We also showed that blocking P2Y12 receptor in rodents by the administration of clopidogrel or prasugrel increases urine concentration by increasing circulating levels of vasopressin, and by increasing the sensitivity of renal collecting duct to vasopressin. In addition, we showed that both drugs almost completely ameliorate lithium-induced NDI in rodents. Although not immediately translatable to the clinics due to the anti-thrombotic effects of these drugs, this concept opened the possibility of treating lithium-induced NDI by targeting purinergic signaling (Zhang et al, 2015; Kishore et al, 2015; Zhang et al, 2017).

References: Citations shown in the text are hyperlinks to their respective publications.

Disclosure: Author has patented technologies for the treatment of disorders of water balance, and co-founded a startup called ePurines, Inc to develop novel purinergic signaling based therapies for acquired NDI or dilutional hyponatremia or vasopressin excessive states.

Pioneers in Medicine and Healthcare

Edward Jenner, FRS

(1749 -1823)

Physician, Surgeon, Biologist, Geologist, Humanitarian, Who Experimented with Blood, Birds and Balloons

Contributed by: Bellamkonda K. Kishore, M.D.

In science the credit goes to the man who convinces the world, not the man to whom the idea first occurs. – Francis Galton

We all know that Edward Jenner was the Father of Immunization. But he was much more than that. He was a multifaceted genius with a very unusual track record of training and work. Born on May 17, 1749 in Berkeley, Gloucestershire, England, Edward was orphaned at the age of 5 years, and was raised by his elder brother. In the school, Edward developed strong passion for science and nature. At the age of 13 years, he started doing an apprenticeship with a country surgeon and apothecary near Bristol. It was during the apprenticeship Edward heard a dairymaid saying *I shall never have smallpox as I have had cowpox. I shall never have an ugly pockmarked face.* Later Edward went to do apprenticeship with George Harwicke and John Hunter, the famous surgeon. Both Jenner and Hunter had a natural love for biology and nature, and they worked together on those lines as well. Jenner also helped to classify the biological materials brought back by Captain Cook from his voyages. Jenner used to keep himself busy experimenting on a wide variety of subjects. He studied geology, and experimented with human blood. He built his own hydrogen balloon and flew several miles in the air in it. He did research on cuckoo and published a remarkable paper on this bird, for which he was elected as a Fellow of the Royal Society (FRS). Jenner pursued his passion for natural sciences lifelong, with his last work on migratory birds published posthumously. He also studied hibernating hedgehogs. As a clinician and surgeon, Jenner showed innovation in his work. He devised an improvised method to prepare tartar emetic (potassium antimony tartrate). In addition to publishing on medical topics, he used to play violin in a local club and composed poetry and light verse.

Although Jenner heard the dairymaid's words about her immunity against smallpox when he was a teenage apprentice, it was in 1796 at the age of 47 years he actually tested the claims of the dairymaid. He found a dairymaid Sarah Nelms with fresh cowpox lesions on her hands and arms. He took pus from her lesions and inoculated James Phipps, an 8-year old boy. The boy developed mild fever, discomfort in the axilla and loss of appetite, but recovered. Six weeks later, Jenner inoculated the boy with pus from smallpox lesions. The boy did not develop the disease. Edward Jenner concluded that protection was complete. Jenner submitted a report of his experiment and observations to Royal Society. It was rejected. Two years later, after performing the study on a few more subjects, Jenner privately published a small booklet entitled *An Inquiry into the Causes and Effects of the Variolae vaccinae, a Disease Discovered in Some of the Western Counties of England, Particularly Gloucestershire, and Known by the Name of Cow Pox*. Jenner called the new procedure as *vaccination* based on the Latin word *vacca* for cow, and *vaccinia* for cowpox. Unfortunately, Jenner's theory was discredited, and it was met with skepticism by the medical community. Jenner also found it hard to recruit volunteers for his work. Finally, in 1799 Drs. George Pearson and William Woodville supported Jenner by vaccinating their patients. By the year 1800 vaccination spread across Europe. Edward Jenner sent samples of his vaccine to Benjamin Waterhouse, a Professor of Physics at Harvard University. Waterhouse introduced the vaccination in New England, and persuaded Thomas Jefferson to try it in Virginia. Jefferson set up the National Vaccine Institute and appointed Waterhouse as its Vaccine Agent,

Edward Jenner received worldwide recognition and many honors for his work, but he never made money out of his innovative work. In fact, due to his intense research activities, his practice as a physician and his personal life suffered considerably. The British Parliament rewarded him with £30,000 in two installments. After retirement from his research on vaccines, Jenner settled down in the countryside as a practicing physician. On January 23, 1823 Jenner visited his last patient, a friend. The next day Jenner died of a massive stroke, thus ending a very illustrious and service-oriented life of extraordinary contributions to the humanity.

Source: Riedel S. Edward Jenner and the history of smallpox and vaccination. Proc (Bayl Univ Med Cent). 18: 21–25. 2005

An Observational Study of Out-of-Hospital Cardiac Arrests Reported in Indian Print Media

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Background: Newspapers in India often report incidents of cardiac arrest. Media reports are a source for raising awareness of cardiac arrest and cardiopulmonary resuscitation (CPR) among the public. This study is aimed at evaluating the reports of cardiac arrest published in Indian newspapers.

Materials and Methods: This is an observational study of cardiac arrests reported in Indian newspapers between January 2001 and June 2019. The study included reports containing the word "cardiac arrest" referring to a cardiac arrest event in India. Data of demographics, location, time, clinical characteristics, performance of CPR, and survival using the Utstein template were extracted from the newspapers. Reports of out-of-hospital cardiac arrest (OHCA) were selected for analysis.

Results: One thousand seven hundred seventy-nine reports of cardiac arrest were reviewed and 1703 reports were selected after excluding 76. Of these, 279 reports did not specify whether it was an in-hospital cardiac arrest (IHCA) or OHCA. Of the remaining 1424 reports, 377 reports were IHCA and 1047 were OHCA. One thousand forty-seven OHCA cases were selected for analysis. The study noted male preponderance and a median age of 51–60 years. OHCA commonly occurred in residential locations, followed by public buildings, other places, and street/highways. Prior risk factors, heart disease, and symptoms were reported in some reports. Of 15 subjects who received CPR, 11 were reported to have survived. Although demographic data are reported in the majority, there is poor reporting of clinical and resuscitation details.

Conclusions: The study gives a glimpse of OHCA in India and emphasizes the need for elaborate reporting of data on cardiac arrest. The crucial role of media is recognized.

AMERICAN ASSOCIATION OF PHYSICIANS OF INDIAN ORIGIN

December 14, 2020

Dear AAPI Friends,

In order to facilitate transition of the current Sushruta Medical News into a peer-reviewed Journal of the American Association of Physicians of Indian Origin (JAAPI), and for carrying out the groundwork needed for establishing a professional quality JAAPI, I hereby authorize the formation of an Ad hoc Editorial Advisory Committee with the following membership for the year 2020-21. This Committee will be responsible for the work needed to launch JAAPI and has the autonomy to take appropriate decisions as deemed beneficial for the entrusted work.

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Sincerely,

Sudhakar Jonnalagadda, MD
President, AAPI

Epidemiology of Out-of-Hospital Cardiac Arrests, Knowledge of Cardiovascular Disease and Risk Factors in a Regional Setting in India: The Warangal Area Out-of-Hospital Cardiac Arrest Registry (WACAR)

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Objective: Out-of-Hospital Cardiac Arrest (OHCA) is a global public health problem. There is inadequate data on OHCA in India. The Warangal Area out-of-hospital Cardiac Arrest Registry (WACAR) was planned to understand OHCA in a regional setting in India.

Methods: WACAR is a prospective one-year observational cohort study of OHCA in the Warangal area, Telangana, India. The study included 814 subjects of OHCA of presumed cardiac etiology brought to the Mahatma Gandhi Memorial Hospital during January 1, 2018, and December 31, 2018. The data collected included; standard Utstein variables with additional data on clinical characteristics (modified Utstein template).

Results: The majority of OHCA subjects were male with a median age of 60 years, and mostly occurring in residential locations within 1 h of onset of symptoms. Individuals with knowledge of CVD risk factors were more likely to report symptoms before OHCA. Data on resuscitation characteristics were inadequate.

Conclusions: The WACAR study provides baseline data regarding OHCA in a regional setting in India. The study demonstrated barriers involving data collection, patient knowledge of CVD risk factors and disease, and access to healthcare, which; impacted the data registry.