MEDICAL BITS FROM YOUR DOCTOR

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"Idealists are rebels that steer clear of the social dogma that constricts them."

Jose Ingenieros

"Idealists are the adversaries of mediocrity. They are those few enthusiastic, qualitative anarchist dreamers."

Jose Ingenieros

YOUR HEALTH!

Our Immune System

As most of you know, our immune system is necessarily complex and without defenses our survival on the planet would be very short!
Since many remain concerned about that minuscule particle of RNA, a few proteins and glycoproteins that make up SARS-CoV2, responsible for the outbreak of the COVID-19 Pandemic, we thought it would be timely to discuss how our immune system works and how we can harness the power of our immunity to promote the best possible defense against this challenge and others that will continue to defy humanity.

For most Homo Sapiens toiling about alongside the dwindling hundreds of thousands of other species on planet Earth, the last few months have offered a surreal journey and have reminded us that despite the transformation of our surroundings and the "control" we appear to exert over our environment, we remain at the mercy of Nature and the simple rules of biology.

Those rules also determine that solutions are slow to materialize. While we can achieve technological solutions or mathematical answers sometimes relatively quickly, biology moves at a slower pace and despite our impatience and anxiety to develop an efficacious and safe vaccine, we cannot expedite the body's response to diverse molecules and ascertain their protection unless testing, repeat testing, safety and efficacy are proven. Nevertheless, the speed of progress in this regard has been impressive! The typical timeline for development of effective vaccines is almost a decade. After 6 months from the time of discovery and sequencing the genome of SARS-CoV2, humanity has over 150 vaccine candidates and some are well advanced into phase III clinical trials which should be reason for optimism.

We have discussed in the past that without viruses and their ability to transfer genomic segments between species, evolution and our own existence would be unimaginable. At the same time, without effective and efficient defensive mechanisms, our survival would not be possible.

Immunity

The first reference to immunity was recorded by Thucydides during the plague of Athens in 430 BC. He noted that people who survived a prior epidemic could help the sick without becoming ill a second time, himself a survivor of the plague, went on to write one of the oldest accounts of human "disagreements": The History of the Peloponnesian War. We have reviewed on past **Newsletters** the importance of Edward Jenner, Joseph Lister, Louis Pasteur (and many others). We first learned of viruses behaving as human pathogens in 1901, through our Dr. Walter Reed and his work with Yellow Fever.

Our Defense System has many "layers" and is necessarily complex. Some parts of our defenses are easy to recognize. For instance, the integrity of our skin, teguments and mucosal surfaces is essential to keep "bugs" out of our sterile cavities and organs. An appropriate immune response implies the ability to recognize harmful and non-harmful micro-organisms while preserving health and homeostasis (normal function). This is a modest attempt to explain a very complex system and an oversimplification.

The Immune System has four main attributes:

- Ability to distinguish self from non-self.
- Specificity: Antigen – Antibody.
- Diversity: Ability to react to millions of antigens.
- Memory: leads to a rapid second response after exposure.

The Immune System		
Innate (nonspecific) defense mechanisms		**Adaptive (specific) defense mechanisms**
First line of defense	**Second line of defense**	**Third line of defense**
• Skin • Mucous membranes • Secretions of skin and mucous membranes	• Phagocytic cells • Antimicrobial proteins • The inflammatory response	• Lymphocytes • Antibodies • Macrophages

Our skin provides a physical barrier made of indigestible material. The sweat and sebaceous glands keep a low pH that keeps microorganisms at bay. Lysozyme in our saliva helps digest bacterial walls. The stomach with its low acidity decreases the chances that a bacterial load may overcome the defenses of our gut (and the reason anti-acids, H2 blockers and Proton Pump Inhibitors such as Prilosec or omeprazole or similar drugs may increase the incidence of infectious gastroenteritis, traveler's diarrhea and also Clostridium Difficile colitis).

The second line of defense is provided by our "innate" and non-specific defense system, mostly integrated by our "white cells" and antimicrobial proteins. The response is characteristically non-specific, there is no immunological memory and is found in nearly all forms of life.

Innate, of course, refers to features present from birth and not learned, which recognizes microbes through pattern recognition receptors (PRRs), specific for microbes.

Antimicrobial enzymes and proteins that use PRRs include lysozyme, complement components of our blood, C-reactive protein, lectins, defensins, cathelicidins and cell receptors such as toll-like receptors (TLRs) and are all part of a complex and intricate system of protection.
Cells from this second line of defense, such as neutrophils, eosinophils and macrophages are also able to release cytokines and other inflammatory mediators.

At the same time, our microbiome (bacteria, fungi and viruses that live in and on our bodies) impacts our mechanisms of defense and influences the maturation of our immune response. There is even a term to describe the alteration in composition and diversity of that collection of organisms: “Dysbiosis”. It can play a role in the development of obesity, food allergies, type II DM, asthma and other conditions.

The immune system has the ability to discriminate between “self” and “non-self” molecules. These “foreign” molecules are called antigens (***anti****body* ***gen****erators*) and have the ability to elicit an immune response and bind to specific immune receptors.

Our adaptive immune system developed over more than 500 million-years of evolution, likely from jawed vertebrates and cartilaginous fish. Sharks are the oldest living vertebrates with this plastic and adaptable immune system.

We have a specific and yet marvelously diverse defense system that can fend off countless pathogens and has the ability to “memorize” them which enables a rapid response to old challenges. Immune cells have the ability to reach all the confines of our bodies through blood, lymph and eventually tissues to encounter and fight off any would-be invaders.

These “learned” immune responses are continually refined and adjusted through our life and depend on our exposures and microbiologic challenges and are carried out mainly through lymphocytes, plasma cells and macrophages. Each T (for thymus) and B (for bone marrow) lymphocyte clonal populations acquire a structurally unique receptor during development which yields a large number of cells with high affinity to those specific antigens. We have learned of myriad and complex interactions between our innate defense mechanisms and adaptive “learned” immune responses over the past fifty years.

Newborns, of course, have no prior exposure to pathogens and therefore are vulnerable to infection. Mothers provide protection through transport of antibodies through the placenta. Breast milk also contains antibodies that are transferred through the gut of the infant in the first few months of life. After about 6 months, the bowel is no longer able to absorb large proteins like antibodies, as the digestive enzymes break them apart into their constituent amino-acids. This is called passive immunity because the baby “borrows” those antibodies and memory cells. The same principle applies if we inoculate antibody rich serum (the liquid part of blood and rich in antibodies) to a recipient.

Antibodies were discovered in 1890 when Drs. Von Behring and Kitasato showed that the transfer of serum from animals immunized against diphtheria could cure infected animals. Major questions pertaining their diversity were solved in the 1970's with the description of somatic hypermutations and variable-diversity-joining rearrangements (VDJ Rearrangement) of immunoglobulin or B cell receptor genes (BCR).

T cell receptors (TCRs) were discovered in the 1980's. They share a common ancestor with BCR genes based on a similar domain organization and rearrangement mechanisms to generate diversity. The evolution of our immune system goes back to the origin of cartilaginous fish and their components, such as pattern-recognition receptors (PRRs), Toll-like receptors (TLRs) nod-like receptors, (nLRs) and scavenger receptors (SRs) have remained very stable throughout the animal kingdom.

We breath and play in an environment full of microbes and pathogens, and yet, are usually completely unaware of most of the silent and automatic battles waged to prevent infection. Most of these battles are carried out by front-line and innate defense mechanisms which regulate and limit inflammatory responses.

Natural killer (NK) cells are lymphocytes closely associated with the innate immune system that do not attack microbes, but rather destroy our own compromised cells such as tumor cells or older cells that need to be eliminated. They are able to recognize such cells by detecting low levels of cell-surface markers called major histocompatibility complex I (MHC I). Normal cells are not attacked by NK lymphocytes because they have adequate expression of MHC antigens on their surface, putting the brakes on any further damage. The major histocompatibility system II (MHC II) is important for the recognition of antigens by T "helper" and "regulatory lymphocytes.

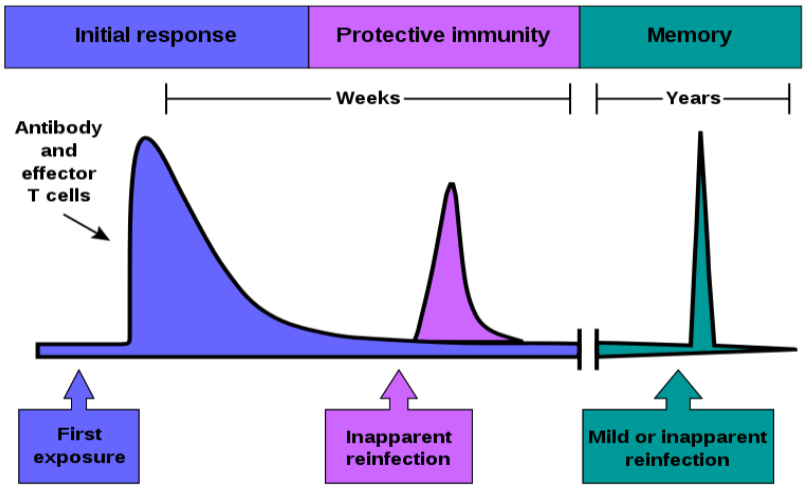
The NK cells are responsible for the clearing out of dying cells (apoptosis) and also tumor cells or "clonal populations" that develop routinely. Just consider that about 100 billion neutrophils leave the bone marrow, circulate and die each day. These dying cells and the trillions of cells that are recycled each day in our complex bodies would release cytotoxic and proinflammatory molecules into their microenvironments, were it not for the presence and function of NK cells, macrophages and dendritic cells that recognize and clear them in a process of apoptotic cell recognition and ingestion, reducing the risk of autoimmune and tumoral complications.

Heraclitus was right! "*No man ever steps in the same river twice, for it's not the same river and he's not the same man". "There is nothing permanent except change".*

The "adaptive" immune system, permits a strong response and immunological memory, where pathogens are "remembered" by a characteristic antigen previously presented and processed by our immune system.

The responses include the B lymphocytes (responsible for antibody generation) and T lymphocytes in charge of the "cell-mediated" immune responses. When these cells become activated and replicate, some of their offspring become long-lived memory cells that "remember" each specific pathogen and help mount a prompt and strong response when the same

antigens are detected again. This immunological memory can be induced by prior exposure to antigens, infection or vaccination.



(From Wikipedia – The Immune System)

In summary, the immune system works through the following steps:

1- Antigen (Ag) – pathogen, infects cells.

2- Macrophage (part of the innate immune system) ingests Ag and presents portion on its surface.

3- Helper T-cell recognizes Ag on the surface of macrophage and becomes activated.

4- Active Helper T-cell activates cytotoxic T-cells and B-cells.

5- Cytotoxic T-cells divide into active cytotoxic T cells and Memory T Cells

6- Active Cytotoxic T cells kill infected cells.

7- Simultaneously, B-cells divide into Plasma Cells and Memory B-Cells

8- Plasma cells produce antibodies that deactivate pathogen

9- Memory T and Memory B cells remain in the body to speed up the response if the same Ag reappears.

10- Suppressor T cells stop the immune system once Ag are destroyed.

It is also important to recognize that the immune system interacts with other organ systems such as the endocrine and nervous systems and plays an important role in tissue repair and regeneration.

For instance, estrogens are known immune stimulators (and probably the reason women have a lower mortality in the face of severe infections including COVID-19, but also are more likely to suffer from autoimmune conditions such as lupus and rheumatoid arthritis and others. Vitamin D is important to enhance T-cell driven immunity and this should serve as a reminder to take your multivitamins and your 1000-2000 IU of Vitamin D3 daily.

Rest and sleep are also important to ascertain adequate immune function. Sleep deprivation is known to be associated with a lower antibody production after immunization and lower protection.

If you want to learn more about this fascinating subject and the evolution of the immune system through the animal kingdom:

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3805090/ and for a summary of the function of our immune system:

https://en.wikipedia.org/wiki/Immune_system
https://www.slideshare.net/paigep/immune-system-63-and-111

And you have all read about the promise of “immunotherapy” to fight cancer, whereby our immune system is harnessed and recruited to fight malignant clonal cells. Of course, you know that as we age there is a process of “immune-senescence” that weakens our defenses against infection and allows for occasional mistakes in the constant surveillance that destroys malignant cells (and the reason cancer is more common as we age). Exercise, proper nutrition, adequate sleep and a positive attitude will help your immune system remain strong and vigilant!

Vaccines:

Everyone is now anxiously awaiting the development of effective SARS-Co-V2 vaccines to eradicate our most immediate foe: COVID-19.

The purpose of vaccination is to generate long-term active memory by activating B and T lymphocytes. Through immunization, an antigen (**anti**-body **gen**-erator) from a pathogen or artificially crafted, is placed into contact with our immune system in order to stimulate the development of specific T-memory cells and antibodies to confer protection against that pathogen.

Despite “fake news” and un-founded fears, vaccination is the most effective defense against myriad infections and after sanitation, the most important reason for the increased longevity in our modern world.

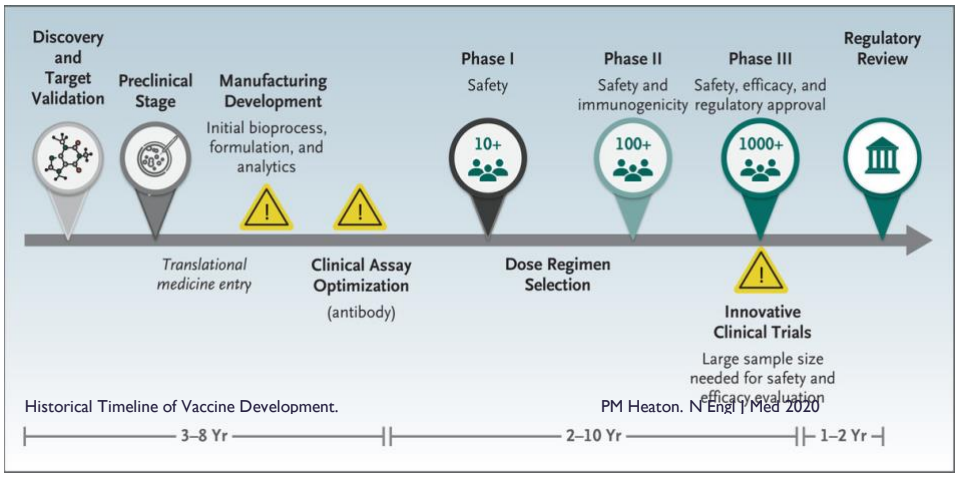
Historically, most viral vaccines were based on the introduction of attenuated viruses to prompt development of defenses without causing disease. Over the past three decades, genetic techniques have prompted the use of modified viruses as vectors for the introduction of the segment of DNA or RNA of interest that prompts the generation of an adequate immunologic response. More recently, genetic vaccines (which exploit part of the viral genome to stimulate a response) have become available and ten of the advanced vaccine trials against COVID-19 are using these newer technologies.

The first vaccine to launch a clinical trial and developed by Moderna, based in Cambridge, MA in collaboration with the National Institutes of Allergy and Infectious Disease (part of NIH) is now launching a phase III trial (proven to be safe and now analyzing efficacy) of a mRNA (messenger RNA) vaccine that uses a self-amplifying mRNA to produce immunogenic proteins and increase exposure to antigens.

MEDICAL NEWS:

SARS-CoV2 Vaccine Development

The most recent NEJM reports the results of the phase I clinical trial conducted by Moderna-NIAID (part of NIH). The accompanying editorial reports that “the rapid pace of development of vaccines against Covid-19 is enabled by several factors: prior knowledge of the role of the spike protein in coronavirus pathogenesis and evidence that neutralizing antibody against the spike protein is important for immunity; the evolution of nucleic acid vaccine technology platforms that allow creation of vaccines and prompt manufacture of thousands of doses once a genetic sequence is known; and development activities that can be conducted in parallel, rather than sequentially, without increasing risks for study participants”.



Historical Timeline of Vaccine Development. PM Heaton. N Engl J Med 2020

The study reports that the 100 ucg dose was safe and generated adequate antibody titers when two doses were administered a month apart. Of course, much work lies ahead after completion of promising clinical trials. Vaccine development and distribution for billions of people will provide another major public health challenge. And many questions remain, such as proper dosing for immunocompromised hosts, children, older patients. Also, do neutralizing antibodies to the spike protein of the virus predict efficacy? Studies in chimpanzees suggest that they do, but confirmation of correlation between antibody titers and protection needs to be confirmed and is the focus of these planned or ongoing phase III clinical trials. It is commendable to see that the usual decade of efforts and research have been compressed into 6 months and possibly, one or several of the candidate vaccines will make it to your clinic before long.

The Lancet today published positive results of the phase I/II clinical trial evaluating the recombinant adenovirus vaccine ChAdOx1nCoV-19 which was able to generate potent humoral (antibody titers) and cellular immune responses against the SARS-CoV2 spike protein in all participant.

I encourage you to read more about the subject in this interactive feature from the NYT that is updated frequently:

https://www.nytimes.com/interactive/2020/science/coronavirus-vaccine-tracker.html

As summarized by the Coronavirus Vaccine Tracker, there are now more than 137 vaccines in development with 4 in phase III, 11 in phase II and 15 in phase I clinical trials. There is one vaccine developed by CanSinoBIO, a Chinese company funded by the government and co-developed with the

Chinese military, that has been approved for administration to the military (not known if mandatory or optional).

Another excellent vaccine development update from Nature:

https://www.nature.com/articles/d41586-020-01221-y

DEBUNKING MYTHS: Q & A

1- **Vaccines may cause autism! Myth!**
Multiple studies have been conducted and there is conclusive evidence that vaccines do NOT cause autism. If interested in further reading, this Center for Diseases Control (CDC) reviews the literature here: https://www.cdc.gov/vaccinesafety/concerns/autism.html. and this study was conclusive: https://www.jpeds.com/article/S0022-3476(13)00144-3/pdf?ext=.pdf

2- **COVID-19 is associated with increased risk of clotting and therefore we should take aspirin or blood thinners. Myth!**
Patients who develop severe COVID-19 disease and usually those requiring ICU support, may go on to develop microthrombi and disseminated intravascular coagulation. For those patients, anticoagulation treatment is standard and decided by the ICU team at the time of care. Use of preventive blood thinners is unfounded!

3- **UV light / silver and copper-based agents destroy SARS-CoV2 and are effective preventive or treatment modes. Myth!**
While prolonged UV light may inactivate the virus, using UV light has no immediate effects and is potentially harmful. Metal-based products have no known effect on the virus.

Finally, we must continue to support the World Health Organization (WHO)! As you may have read, as of July 7th, 2020 the president of the United States, in his infinite "wisdom" and utilizing his unbounded "leadership" decided to withdraw the U.S. from the WHO. This is akin to dismissing your fire department as your house if going up in flames. Those of you who have been following the news realize that this is just another stratagem to blame a defenseless organization for the dismal response from the White House and the executive branch of our government.

The WHO is not perfect. It requires epidemiologic information from its member nations and needs invitations from those nations to carry out its work. It ensures drug safety and sets guidelines for treatments in nations that have more limited resources.
For a brief and insightful comment, read this: https://www.nejm.org/doi/full/10.1056/NEJMe2024894?query=featured_home

Of course, we should also recognize that humanity continues witness so many preventable deaths and so much avoidable suffering while at the same time we have the tools to do better and provide relief to Humanity!
Just think of the "malnutrition" pandemic afflicting the world. In most nations, obesity and its deadly complications. In a few, insufficient nutrition. And how about the constant drum beat of gun violence in America? And what about the "epidemic" of narcotic addiction and related mortality?

And what about the “silent killer”: TOBACCO! It remains the leading preventable cause of death which dwarfs the COVID-19 mortality. Cigarettes kill ½ million Americans annually and many millions worldwide. The pandemic has claimed 600,000 human lives.

In the meantime, keep cool, do not panic, eat a nutritious and diverse diet, stay active and be happy!

Use a properly fitted mask while in public **indoor** places.

Take a multivitamin daily and don’t forget your 1000-2000 IU of vitamin D3.

Be ready to accept vaccination as soon as it becomes available. Likely by early 2021.

And let’s try to make the best lemonade with the “lemons” nature has thrown our way!

Fear is not a rational response. This too shall pass! Do not anguish about rare problems unless you have won the lottery more than once.

Remember that the only certainty in life is… death… and the only fountain of youth proven by science, experience and millennia are exercise, laughter, humor and a good positive attitude!

Enjoy every minute of this most interesting JOURNEY and cherish this family time!!!

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References:

https://www.nejm.org/coronavirus
https://www.cdc.gov/coronavirus/2019-nCoV/index.html
https://www.who.int
https://clinicaltrials.gov/
https://www.nature.com/articles/d41586-020-00154-w]
https://en.wikipedia.org/wiki/Immune_system
https://www.nejm.org/doi/full/10.1056/NEJMe2025111
https://www.nejm.org/doi/full/10.1056/NEJMe2024894?query=featured_home
https://science.sciencemag.org/content/early/2020/05/12/science.abc5312
https://www.nejm.org/doi/full/10.1056/NEJMp2005630?query=featured_coronavirus
https://www.youtube.com/watch?v=-Gn8oJY1VHY&feature=youtu.be https://www.cfr.org/backgrounder/what-world-doing-create-covid-19-vaccine
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3805090/
https://www.nejm.org/doi/full/10.1056/NEJMcibr2009737?query=featured_coronavirus
https://jamanetwork.com/journals/jama/fullarticle/2767840

ANNEX: COVID-19 Timeline

From *Nature*:

https://www.nature.com/articles/d41586-020-00154-w

- 21 December, 2019, a few patients became ill with severe pneumonia in Wuhan, Hubei province of China.
- 31 December, 2019, a new virus is identified in samples from 4 patients with pneumonia of unknown cause. All patients had been present at the Huanan Seafood Market in Wuhan. Viral genome isolated and sequenced. Initially named 2019-NCoV (Novel Coronavirus 2019).
- 8 January, 2020 – ***Nature*** reports on the new virus, cause of mysterious "deadly pneumonia" in Wuhan, China.
- 21 January, 2020 - First US case confirmed in Washington State. 30 yo man returning from Wuhan, China.
- 23 January, 2020 – China closes Wuhan.
- 24 January, 2020 – Second US case. 60 yo woman returning to Chicago after visiting China.
- 28 January, 2020 - Human-to-human transmission confirmed in Germany.
- 3 February, 2020 - Study of live virus published.
- 6 February, 2020 – Retrospective autopsies completed in mid-April in Santa Clara, CA confirms that first deaths occurred in early Feb.
- 14 February, 2020 – Chinese authorities reveal number of infections in medical staff: 1,716 health workers had contracted the virus, 6 of whom died
- 17 February, 2020 - First case in Africa
- 25 February, 2020 - U.S. emergency funding for coronavirus response
- 26 February, 2020 - Brazil reports first case in South America
- 28 February, 2020 - Coronavirus spreads to sub-Saharan Africa
- 4 March, 2020 – Multiple drugs under investigation for coronavirus
- 5 March, 2020 - China study suggests children are as likely to be infected as adults, but most do not become ill.
- 11 March, 2020 - Transgenic animals for CV research in high demand
- 11 March, 2020 - Coronavirus becomes a pandemic, says WHO.
- 13 March, 2020 - US President declares "national emergency". It is no longer a "Chinese virus that will blow over by the spring".
- 17 March, 2020 - First vaccine clinical trials begin in U.S. (National Institute of Allergy and Infectious Diseases (NIAID) and Moderna (biotechnology company in Cambridge, MA) - "launched in record speed," 66 days from genetic sequencing of virus to the first human injection of the vaccine candidate.
- 18 March, 2020 – Deaths in Italy surpass those in China.
- 19 March, 2020 – No new cases confirmed in Hubei, China.

- 25 March, 2020 – Retrospective studies in Lombardy confirm that the virus was present in Northern Italy in early January 2020.
- 1 April, 2020 – Over 80% of ICU patients with COVID-19 have underlying medical conditions.
- 2 April, 2020 – Worldwide cases surpass 1,000,000.
- 7 April, 2020 – No new reported COVID-19 deaths in China
- 8 April, 2020 – Tracking App reveals lack of smell is key symptom.
- 15 April, 2020 – Trump – in his infinite wisdom and trust-worthy scientific knowledge – suspends WHO funding. Leonardo Da Vinci's birthday celebrated by "scapegoating" the WHO.
- 15 April, 2020 – Worldwide infections surpass 2,000,000.
- 21 April, 2020 – Mars probe HOPE ships from UAE to Japan for launch after July 15th when Mars and Earth are aligned. It should reach the Red Planet by 2021.
- 21 April, 2020 - https://1daysooner.org/volunteer launched. 15,000 people volunteer to be exposed to virus and accelerate vaccine development.
- 27 April, 2020 – The five ways Trump is undermining environmental protection under the cover of the Pandemic: https://www.nature.com/articles/d41586-020-01261-4
- 29 April, 2020 – Remdesivir speeds up recovery!
- 7 May, 2020 – First CRISPR testing kit approved in US. It works by programming the CRISPR machinery to detect snippets of the virus genetic material and expedites results to 1 hour.
- 15 July, 2020 – Only medications with proven efficacy so far: Remdesivir (antiviral) and dexamethasone, when used in patients with pneumonitis seems to expedite recovery, but not early on. In fact, it may worsen outcomes when used at the outset of disease. Non-Invasive oxygen delivery may be associated with better outcomes.
- 16 July, 2020 – mRNA vaccine able to generate adequate immunogenic responses and phase III clinical trial to begin soon.
- 20 July, 2020 – Recombinant Adenovirus vaccine that encodes SARS-CoV2 Spike protein is highly immunogenic on phase I/II clinical trials conducted in the UK and phase III trials to start soon.
- July 20, 2020 - *Over 14,300,000 cases and 600,000 deaths worldwide. Pandemic tracker: https://coronavirus.jhu.edu/map.html*