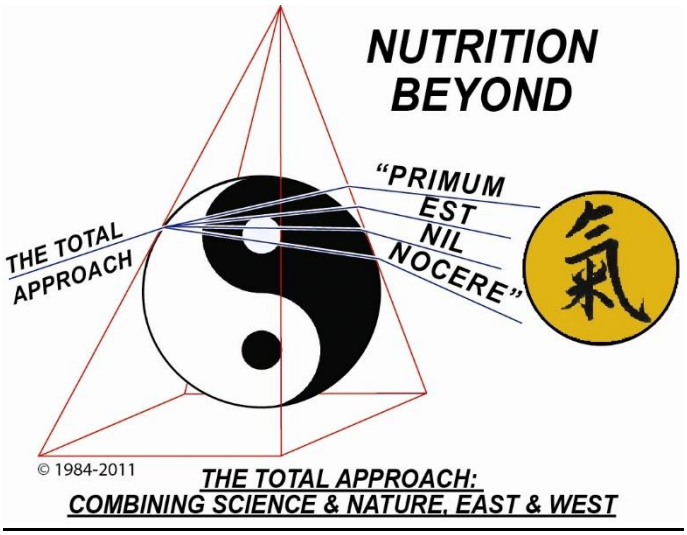
COVID-19: CONTAGION to Pathological/Lethal MORBIDITY to MORTALITY

THE Road to Perdition…and HOW to Avoid It:

The LAST WORD



Pt.2, Mar. 27, 2020: The "Tao" (Way) of Viral Warfare

Dear Patients & Friends,

We have to depart from our original intention today to have a close look at the components of the human Immune system because something more important has surfaced in the last 24 hours. This is quite ground-breaking & can give us a further clue as to the virus' other vulnerability....

Again, there are some "preliminaries" before I start on the subject-proper.

Respect & Tributes: In the last Instalment, I mentioned some old friends in the international world of medicine, advanced nutrition, & micro-biology.

These were people I had been, regretfully, out of touch with for a long time, simply because I got too busy. These are some of the very most talented members of the U.S. scientific & medical academia – the ***E****lite of the Elites*. Many of you here who have been with us since 2011 will remember them as I've featured these gentlemen here many a time. For the others, especially the relatively new ones here, some introduction to these leading lights from these leading U.S universities is in order:

First up, the 'Living Legend': a "*National Treasure*" in America. Nearly 60 years after his ground-breaking discovery, the "***Hayflick Limit***", Prof.Leonard Hayflick is still being

lauded, revered, acknowledged, celebrated.....The accolades & Awards they want to give him still continue to this very day.... 2 days ago, I sent him our last newsletter (Pt.1) on the COVID-19 Series. I wasn't sure IF I would hear from him again (after such a long absence of communications between us), but I have to tell you I **was** sure glad to hear from him early yesterday morning from San Francisco [he is Prof. of Micro-Biology at the Univ. of California at San Francisco]. This was what he had to say:

"Hi Lone,

Great to hear from you. I was worried by your long silence.

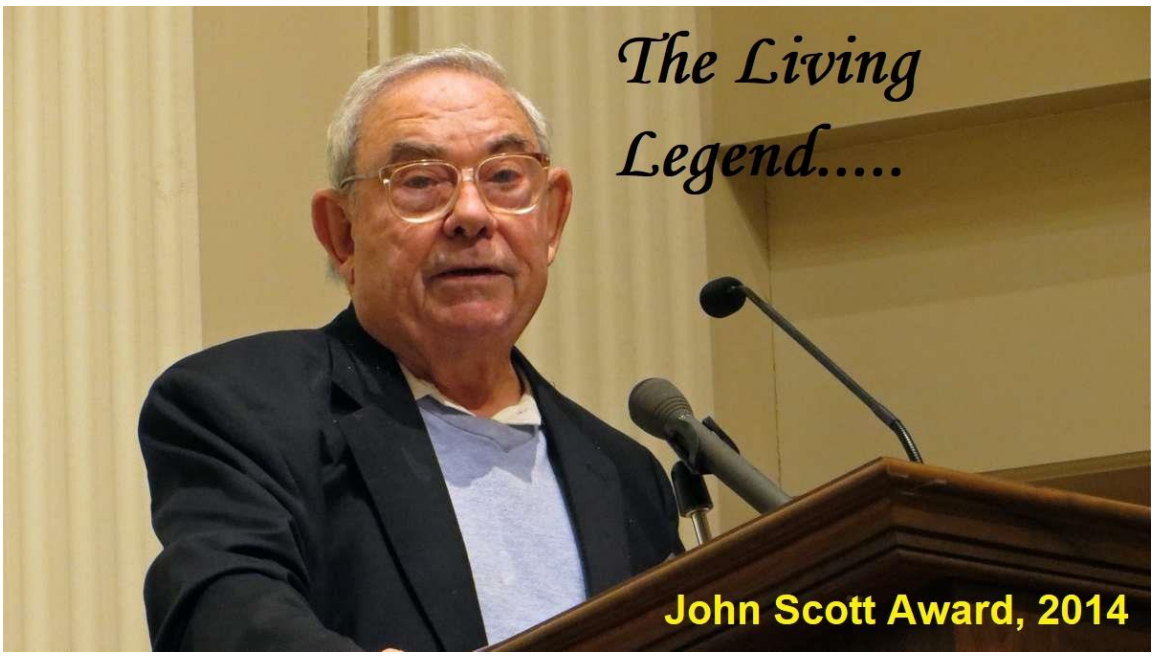
Your discussion of the coronavirus is a masterpiece. Thanks!

The event described in the attachment has been postponed until November.

Take Care,

Len "

The "event" referred to in his e-ml. is the ceremony awarding him the Univ. of Pennsylvania Perelman School of Medicine Distinguished Graduate Award. This Award honours alumni for their outstanding service to society & the profession of Medicine....This was scheduled for May 15, 2020, but obviously, it had to be postponed to this Nov. 2020. By normal reckoning, I should be in America in Nov. this year as I still have business to tend to in the U.S. However, most likely, because of the Virus, I **won't** be able to*. I attach here this letter of the award to him* so that you can see how this man continues to be recognised for what he did nearly 60 yrs ago!. Indeed, many a time in the past several years, I had been invited to attend several of the other awards accorded to him, but I hadn't been able. I would be determined to do so this time, but for the Virus... [In absentia, I will send our Logistics person on the ground, in New Jersey, Annie, to attend on my behalf; she lives only 20 mins. away from the University].



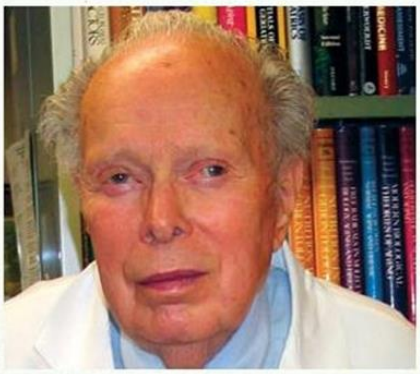
In the past, I had written about him here many times on different scientific/medical issues, and his own personal 'Trials & Tribulations'.... This is a rare human not often seen with the insight & qualities that set him apart from the rest of us mere mortals.... Several years ago, for a book I produced for limited circulation only [one copy landed on the desk of the President in the White House Oval Office], I wrote a couple of poetic tributes to him (see attached).

Next: Prof.Mike Holick, Boston (Prof. of Medicine at the univ. there). I didn't get a chance to tell you in the last newsletter: he IS the world's no.1 expert on Vit.D....Google his name & you'll see "tons" of YouTube videos of him being interviewed. Indeed, Vit.D is certainly essential for your Immunity (we'll discuss that later). Years ago (2012), at about the time I wrote the dedications to the gentleman above, I also wrote a poetic tribute to this icon (see attached).

Next up: 'Numero uno' in America in the world of Advanced Nutrition: Prof.Jeff Bland, from that massively COVID-19-battered state of Washington. For the last 50 years in America, he had "ruled the roost" in advanced nutrition there– the MOST formidable, authoritative expert in Nutrition in the world....I wrote a poetic dedication for him back in 2008 & included it in my book mentioned above. Check out this poetic-tribute (see attached).

All these gentlemen have now been invited onboard this Newsletter series on COVID-19, & the INVITATION to all of you to comment OR contribute insight on this subject (COVID-19) is now open (just via your e-mail back on this e-ml. address). Your contributions will be collated together into the body of the next sequence of newsletters.

Last is that gentleman who has "passed on" several years ago who I wish was here today so that he could perhaps contribute some valuable insight into our problem with COVID-19 & help us fight the fight. In his time, he was one of the most brilliant doctors ever to bless the human race with his insight, vision & knowledge: Denham Harman, Emeritus Millard Prof. of Medicine, Nebraska State Univ., Omaha:



Season's Greetings
and Best Wishes for a
Happy New Year

Denham 12/2-/09

While he was alive, I regret not having kept touch with him because, apart from being a great human being (he was also good friends with my other friend here, Prof.Hayflick), he had that unique medical insight that not many medical doctors of his time had....Yes, other than being the discoverer & developer of Free-Radical Medicine, he had a unique talent in Immunology... Attached was his last communique to me before he died.

Where are you, Denham, now that your country needs you?

Pt.2: some insight I didn't have 72 hours ago:

The Differential of World Contagion of COVID-19

Have you ever thought WHY some countries, despite their relative population sizes, have a far greater COVID-19 death rate than others? Let's consider an example: Italy (population: ~ 60.5m) vs. China (population: ~ 1.41b, more than 23 times!). Italy has now registered more deaths (nearly 8,300) than China (about 3,290). So has Spain (4,860 dead; total population: 46.7m)

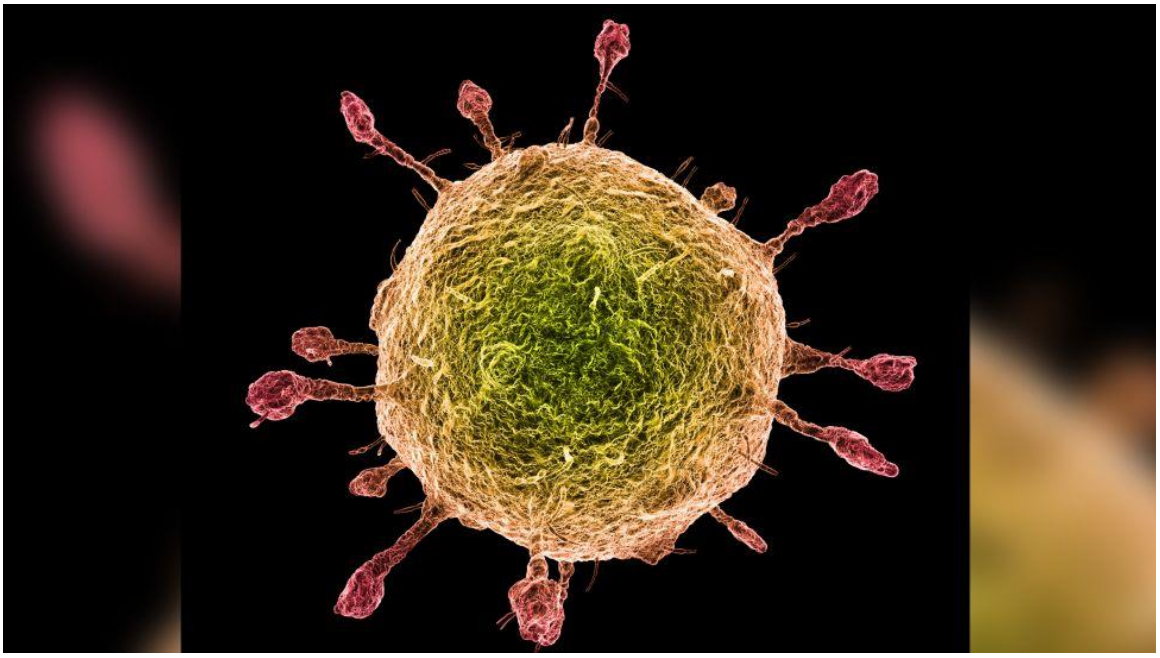
What about India, the 2nd. most populous country in the world (1.39b)? Its total no. of positive cases: 562; deaths: ONLY 11. NOW, mind you, in many parts of India, the basic hygiene in living standards is still ***very primitive***....(of-course, their extent of testing might been low due to low resources)

Italy has had ONLY a relatively (compared to China) short period of exposure to the virus. WHY has it been hit SO hard?? A country with a population much, much smaller (more than 23 times smaller!) than China HAS overtaken China in the absolute no. of deaths...., and yet India, the 2nd. most populous country on the planet has had only 11 deaths!

What's going on here??

My answer is only speculative....There is NO way to know the *rea*l answer...I doubt anyone has. [Maybe the ***WHO*** has done strain studies & correlated the different gene-sequences with degrees of virulence *and* death figures. IF they have, they're certainly NOT telling the world!!]

SO, what do I think the answer is? It IS the particular ***strain of the virus***, OR, more correctly, the ***mutational strain of COVID-19***...Remember how I've been stressing so much on the mutational aspects in the last 2 instalments of this newsletter? I think this ***is*** becoming more apparent.... DO you think the COVID-19 strain in northern Italy's Lombardo province IS the *same* as the one in Wuhan, China or even in India's Mumbai?? I DON'T think so. ***It just CANNOT be....***



The *"Tao"* (Way) of Viral Warfare

WHY we had diverted away from our original plan to dedicate this Instalment to discuss these further aspects of the viral behaviour instead of the promised treatise on the complex, intricate systems (3) of human Defences (**and** Offences) is very Oriental indeed, enshrined in *Bruce Lee's* fundamental philosophy:

The more you know & understand your Enemy, the easier you can defeat him....

So, I think it is worthwhile for us to take this viral behaviour "apart" further in order that we may understand its "idiosyncrasies" better....

Remember: the human vulnerability is NOT single factorial but multiple (see previous Instalment). Where the Wuhan, S.China strain may attack just the lungs, the Bergamo (Italian city in Lombardo) strain may go all out to strike, as well, all (or even some) of the human organs that are well "endowed" with the ACE2 receptors, like the: ***heart, kidneys, intestines*** (victims in Italy had complained of gut pains, urination problems & "shortness of breath" resemblant of a weak, struggling heart....).

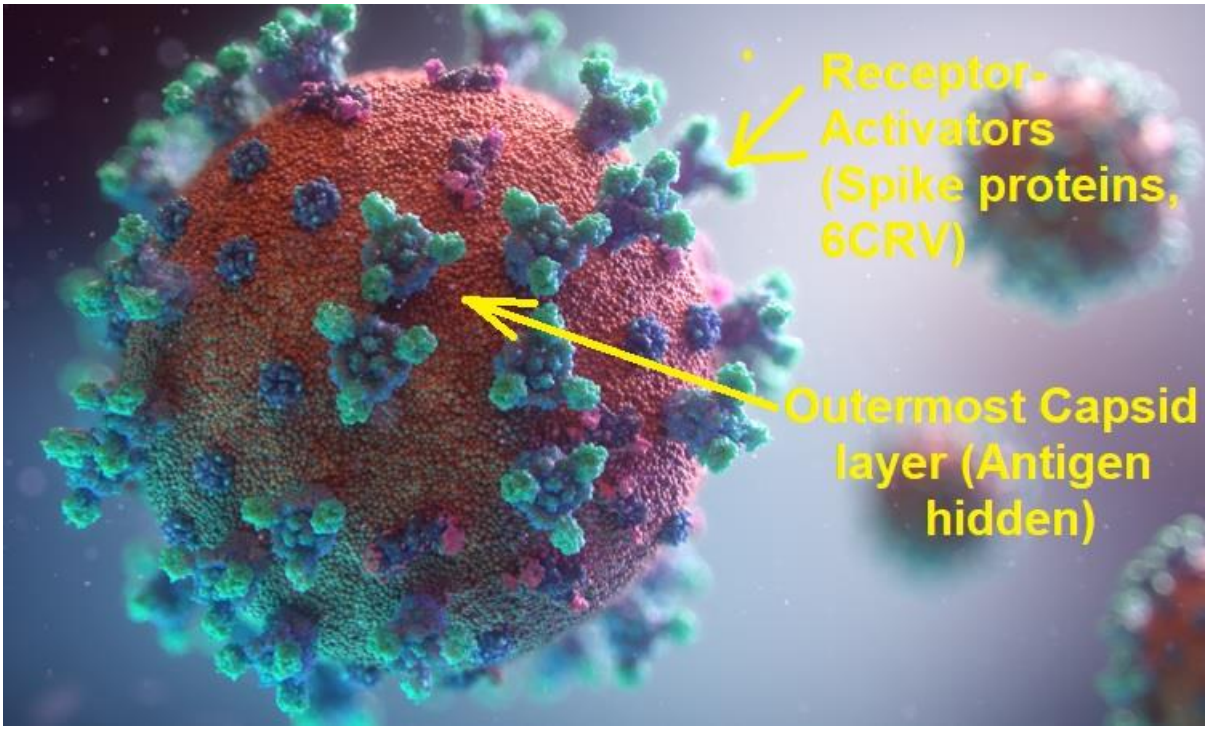
You will all remember, from the last Instalment, how we explained the fundamental mechanism by which **any** Corona virus "hooks" or "latches" itself to a human cell via the docking/fusion of its external Spike (S) protein with the ACE2 receptor in the bi-layer membrane of the target human cell [(1), (2), (3)] .

Already I've heard the Lombardo victims were having diarrhoea, & most victims world-wide, who did NOT hitherto have ***any*** diagnosed heart problems, are having severe breathing difficulties. These "breathing difficulties" are not just a consequence of the damaged alveoli-capillary junctions (interfaces) in the lungs, but also severely **damaged** cardiac muscles, valves, electrical nodes, etc.

THIS is scary...Let's talk about viral-damage to the heart system: you're talking about anything from myo-cardial ischaemia/infarctions, a complete disruption of the basic electrical node functions ---> atrial/ventricular ectopy/fibrillation, etc. In Wuhan, S.China, they found that extensive cardiac damage was seen in 19.7% of Px's (patients) of confirmed infections. Mortality amongst these COVID-19 +ve Px's with observed cardiac injury was 51.2%, compared to 4.5% amongst those **without** cardiac injury (Confidence factor, P<.001, which makes these figures pretty statistically significant!). In a Cox-regression model, Px's with cardiac injury had > 4X increased risk of death than those without observed cardiac injury from symptom(s)-onset to death [hazard ratio 4.26; 95% CI (Confidence Interval): 1.92-9.49)].

Of-course, cardiac injury was ascertained well beyond the "visuals" (ECG); there are many serological parameters that can shed light in a timely manner while the hapless Px's are bed-ridden, eg: **hs-TnI** (high-sensitivity Troponin), **hs-CRP** (hi-sensitivity C-Reactive Protein, an acute-Phase Protein; (I use this as a *"de facto" systemic marker of Inflammation*). ALL COVID-19 fatalities WILL eventually end up in a cardiac arrest....One of the most common aetiological antecedents to this, of-course, will be a high state of Inflammation. The spectrum of aetiological antecedents will span ramped-up clotting factors [elongated-time ESRs (Erythrocyte Sedimentation Rates), severely-

shortened PTs (pro-Thrombin Times), severely-raised INRs (International Normalization Ratios), etc.



Physicians here take Note: you DON'T have time to waste doing even the basic pathologics & Dx.... You CAN see what's happening with your Px: IF you have an emergency on your hand, just move with speed with the anti-Inflammatories to stabilize your Px's condition. IF you're not trained in the natural, phyto-medicine-based COX1, COX2, & LT (Leucotriene)-based techniques, just give your Px NSAIDs-based drugs....**Caveat:** many of you here who have been with me for a long time have NEVER seen me say this sort of thing before. BUT ***this*** is an emergency. IF you have a +ve infection case on your hands, you have NO time to "jerk around": that Px could be dead in 12 hrs.... IF all you know ***and*** have is NSAIDs, that **will** do – it's *better* than nothing.

How about this other salient fact:

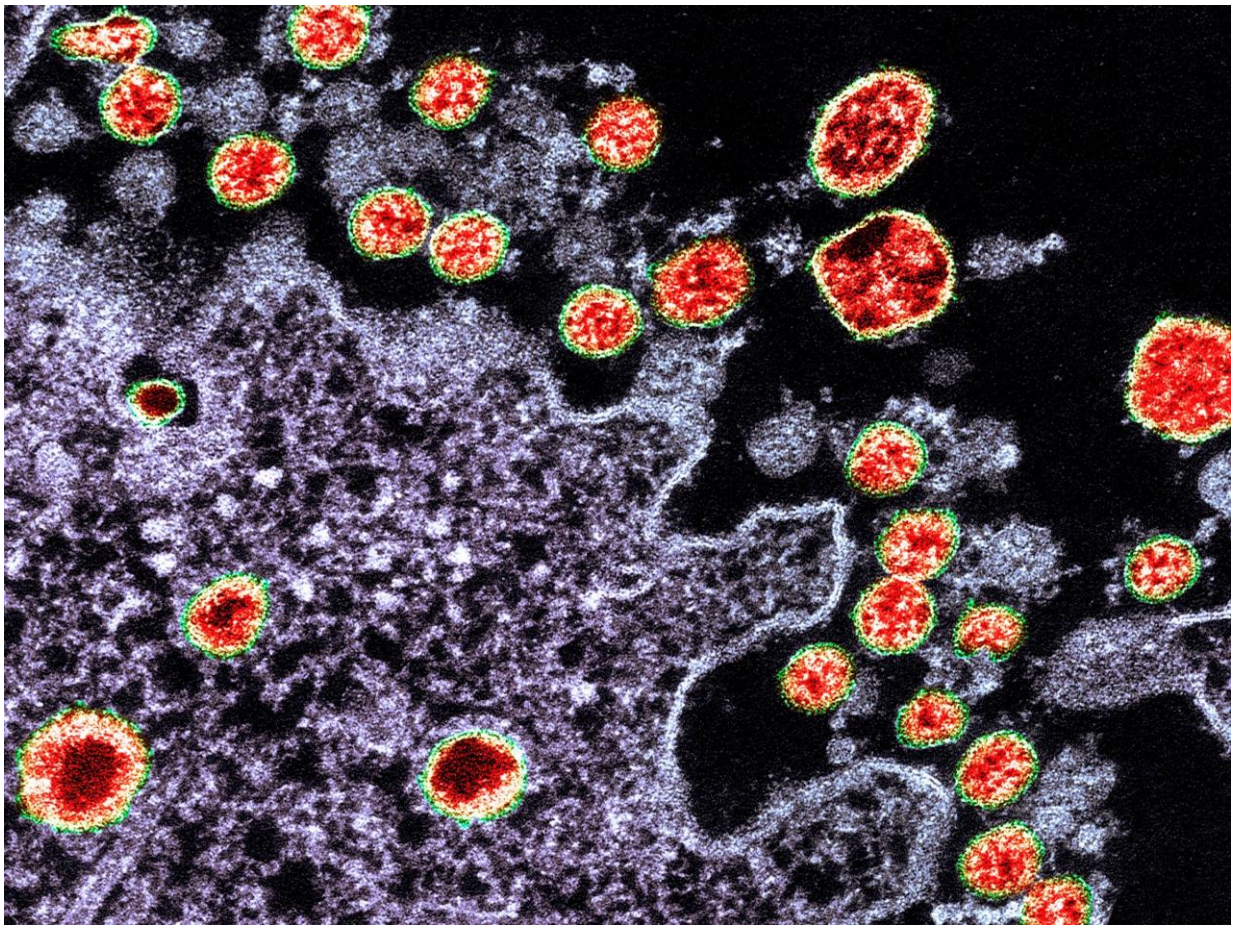
NOW, consider this: U.S, experts have frequently asked about:

WHY more men than women, in the SAME age group, world-wide, have died from COVID-19??....**WHY??**

Have a look at this table (based on overall world figures) [(4), (5)]: [**NOTE:** these stats. are from Feb.17 & 28, 2020; the current figures would definitely reflect the same bias]

SEX	DEATH RATE confirmed cases	DEATH RATE all cases
Male	**4.7%**	**2.8%**
Female	**2.8%**	**1.7%**

Let's look at the "confirmed cases": Male fatalities outnumbered female ones by nearly 68! What about "all cases" (some of which probably not recorded)?: male deaths outnumbered female deaths by nearly 65%. Whichever figure you look at, ***the difference is....staggering!***



You've seen the numerous White House COVID-19 Task Force daily press briefings, with the President flanked, on both sides by his top 2 Medical advisors, supposedly the top 2 experts in the U.S. on corona-viruses: Drs.Tony Fauci & Debra Birx. One of the commonest questions "thrown" at them by the feverish (NO pun intended here!) Press Corps. Is the question *WHY*. Sadly, none of them had an answer. In the last 3 days, **I think I found the answer**. And ramified from this answer would be some *ground-breaking implications from the stand-point of fundamentally inhibiting the virus' ability to "dock" with the ACE2 receptors in the human targets (the outer bi-layer cell membranes)* AND Prostate Cancer (PCa). WHAT?? Prostate Cancer, I hear you say?? Be patient: the explanation will come a little later.

THIS question (the above question) has been "thrown" ad infinitum "into the air" the last several weeks .... We, too, had originally postulated early in the piece: oh well, maybe men tend to be more overweight, smoke more, etc., etc, and, therefore, have inherently higher levels of Inflammation [ie. lower COX1 & PGE1, higher COX2 & PGE2, higher LTs B4, C4, D4, E4 (anti- & pro-Inflammation markers], etc, etc. The bio-chemistry logic here adds up, BUT there is NO epidemiological evidence out there! With people "dropping off like flies", of-course NO ONE with the resources has spared ANY resources to do such a field study... So, the above is still "speculative", with NO solid

clinical or epidemiological proof.... **I think *I know* the real answer to the original question though, after pouring over "mountains" of data....**

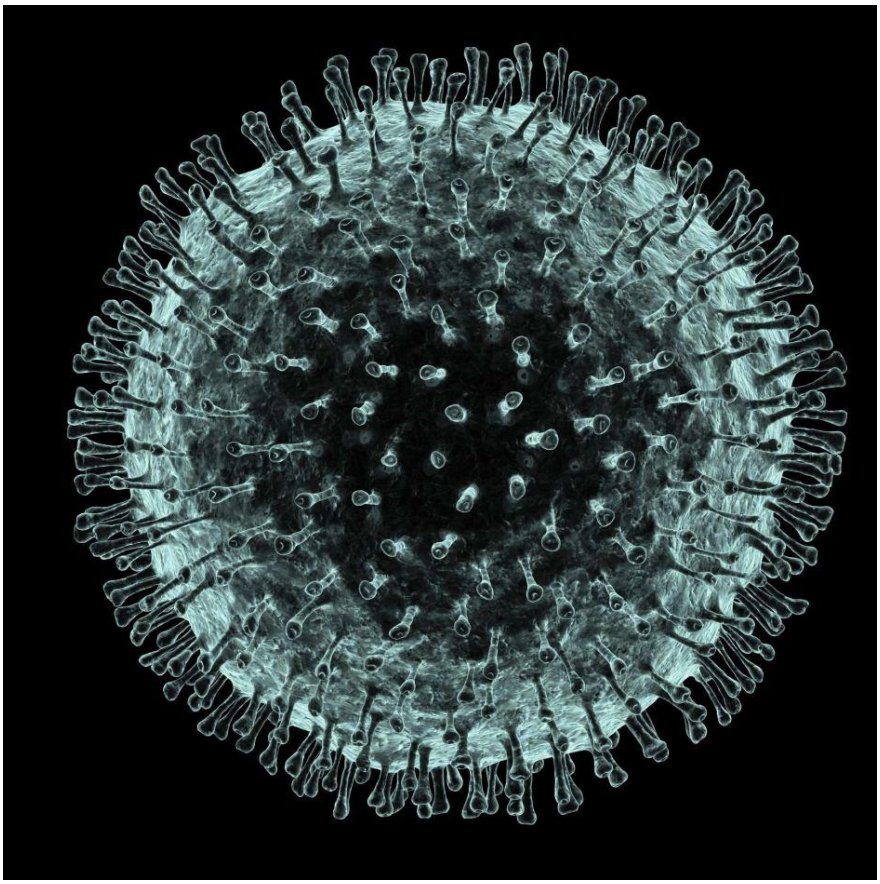
Remember what I said in my previous Instalment: the COVID-19 virus uses the m-RNA protein, **TMPRSS2 (T2), a trans-membrane Serine protease** in the outer bi-layer of the human cell to "prime" or activate its Spike (6CRV) protein – the very protein in the adversary's very 1st "line of strike".... What I had explained in the previous Instalment of this critical "interaction" was way over-simplified [this is not meant to be a univ. Biology lesson, but rather a "generalised" view to understand the basics of HOW you get infected]. There are actually a lot of bio-chemical reactions that go on the interface of the Virus' S protein docking with the host-cell's T2; this is the simplest way I can represent as to what happens at that critical interface:

T2 — cleaved (by Spike 'S') ⟶ S1, S2 sub-units

S1 [with RBD (Receptor Binding Domain)] binds ⟷ Peptidase Domain (of ACE2)

And voila!: you have an infected cell....

AND remember what else I said about this RNA protein, **TMPRSS2??** I said that this was 1 of 3 genes in a 3-gene test, Mi-PS, that we had been using for the last 10 years or more to test for Prostate Cancer (PCa) at the Univ. of MIchigan's MLabs.



Digression: Mi-PS stands for Michigan-Prostate Score. “Michigan” means the Univ. of Michigan, or, more specifically, its specialised prostate gene-testing lab., MLabs. The 3 genes measured in this test are: the TMPRSS2 (or **T2**), ERG (an oncogene family of Transcriptional factors regulating cell-proliferation, differentiation, angiogenesis, inflammation & apoptosis), and PCA3. Let me give a little background of all these 3 genes.

T2: This is Trans-membrane Serine Protease2. **Explanations:** the “membrane” here is the outer membrane (cell wall) of the human cell, target of the virus’ entry into the cell (see previous Instalment). Serine is an amino-acid (protein building block). Protease is an enzyme that can breakdown (or cleave) a protein into its component amino acids.

This gene (T2) is up-regulated by androgens [male hormones, eg. Testosterone (TT), its very 1st metabolite, 5-alpha di-hydro Testosterone (5α-DHT), DHEA (di-hydro-epi-Androsterone, etc.] in Prostate Cancer (PCa) cells[(2), (3)] and

Down-regulated in androgen-independant PCa’s [(2),(3).]

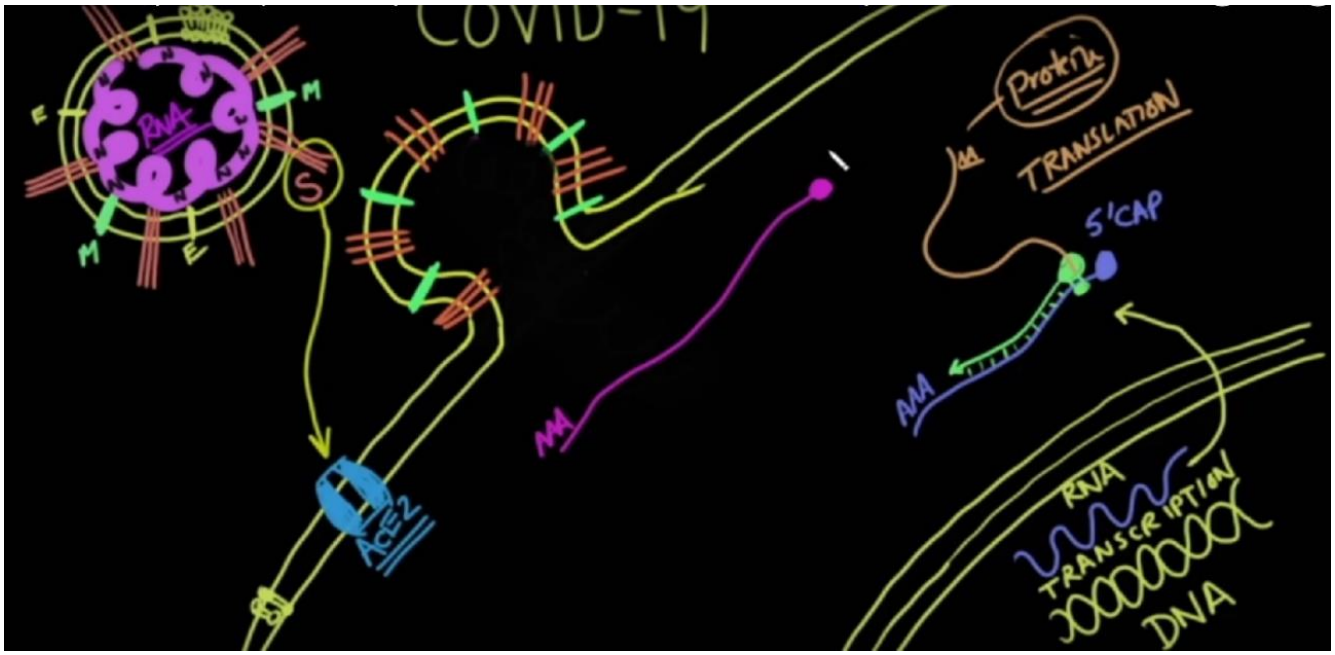
Let me put it for you schematically:

In the most common PCa (LnCAP gene line): T2 ↑ 5α-DHT also ↑

THIS is the most common type of PCa we encounter, the *most common* type we test with MLabs of the Univ. of Michigan. **This** type. This type of PCa is androgen-sensitive, ie. it responds to androgenetic-manipulations (specifically androgen-blockade of any type – take your pick!: the deadly drug-based or infinitely safer nutrition-based).

The other types (less common) of PCa: PC-3, DU145: T2 ↓

THIS type is basically androgen-insensitive (a little analogous to Breast CA estrogen triple -ve). This is fundamentally androgen-refractive, meaning it is refractive (“stubborn” or “unyielding”) to androgen-manipulations [I’m not going into the complexities here because it ***will*** take several pages].



(Acknowledgement: Dr.Seheult, MedCram)

Let's concentrate on ***most*** men, ie. the category of androgen-sensitive LnCAP type PCa. The 1 androgen that actively promotes it is the very 1st metabolite of TT, ie. 5α-DHT (5-alpha di-hydro-Testosterone). As a man grows older & older (from his early 40's onwards), his TT gets manufactured less & less (which is NOT good), & whatever TT he has, more & more of it is lost (by conversion) to 5α-DHT & the estrogens [especially the aggressive E2 (17β-Estradiole) & E1 (estrone)]. ALL these 3, in excess, are PCa- & BPH (benign prostate enlargement) promoting.

TT (or what's left of it) but mostly 5α-DHT up-regulate the TMPRSS2 (T2) gene....and hence the increased vulnerability to...COVID-19! (3)

Also, statistically, if you are a male in your 80's, your chances of getting PCa is 80%.... IF you're a male in your 90's, THAT statistic is 90%....

Let me recap: Bottom line: IF you are a male from your 40's upwards, your chance of getting PCa starts increasing exponentially (because of your androgen dynamics & the genes controlling them start "kicking in"). IF that happens, the older you are, the greater will be your vulnerability to COVID-19 infection because your m-RNA gene, TMPRSS2 (T2) has been up-regulated more.... (this applies to ANY Corona-virus)

Interestingly, IF you are an older man with diagnosed PCa in the less frequent category of androgen-independent (ie. androgen-refractory) PCa (eg. PC-3 or DU145, the supposedly "incurable" PCa), your vulnerability to COVID-19 (or ***any*** Corona-virus) is actually ***less*** because your T2 is down-regulated by the very refractory nature of your androgens(2).

Let me RE-cap 1 more time because THIS is so VERY important to the ageing male:

- IF you are an elderly male, your chances are much higher of getting androgen-sensitive Prostate Cancer (LnCAP type) **AND** heightened susceptibility & vulnerability to ANY corona virus (***these 2 factors ARE linked***).

- IF you're a much younger male, your TMPRSS2 (T2) expression will be much lower, and so will be your susceptibility to androgenetic-sensitive PCa ***and*** COVID-19 vulnerability.

The "mystery" about COVID-19 *is now unravelling*.....

[in a few Instalments from now, I will teach you how to reel back your T2 to reduce your chances of getting PCa, ***and***, in the process, how to make yourself LESS vulnerable to ANY Corona-virus]

OK, we had initially talked about the Mi-PS 3-gene test for PCa. SO, when the result of the test comes out, it is expressed as the ratio, TMPRSS2:ERG and an absolute value for PCA3, another incriminating gene in PCa.

The higher that ratio, TMPRSS2:ERG, the higher the probability of serious PCa, and, of-course the higher the vulnerability to...COVID-19 (or ANY corona-virus, like Ebola, SARS, MERS, etc.!).

What about the PCA3?

Many of our PCa Px's here know *this* Test well – they've done it! PCA3 is also a 'stand-alone' gene-test that, by itself, can predict, by its magnitude, the probability of the existence of PCa and its seriousness (staging). Although it has nothing to do with COVID-19 (or any Corona-viruses), I'll just briefly mention it here for the sake of other people here who might have suspicions of PCa:

It was the world's very 1st commercially-available PCa genetics test, with its reagent developed by Progensa, Santa Monica, USA. It was approved by the European Union (with a CE Mark) on Nov.14, 2006 & the FDA in Feb. 2012. We started making this test available nation-wide in 2008, in conjunction with our lab, NovioGendix (NG), in the Netherlands in competition with the giant Aussie pathology group, Douglas Hanly Moir (DHM) who were doing their assays thro' their sister lab, DHM, in London. Of-course, NG was the world's Reference Lab for PCA3, with the world's top PCA3 research scientist, Prof.Jack Schalken working from it (I knew Jack back then).

Then, of-course, Mlabs of the Univ. of Michigan then came along with the Mi-PS test for PCa several years later & we went onboard with them.

NEXT: we break down the Total human Defensive (and Offensive) Systems.

References

(1) Drug Target Review: Scientists demonstrate how COVID-19 infects Human cells, March 27, 2020

(2) GeneCards (Human Gene Database), 2020.

(3) M.Hoffman et al: *SARS-CoV-2 Cell-entry depends on ACE2 & TMPRRS2 & is locked by a Clinically-proven Protease-inhibitor",* **Cell** Journal, 181, 1-10, April 16, 2020 [A joint German-Austrian-Russian study].

(4) The Epidemiological Characteristics of an Outbreak of 2019 Novel Coronavirus Diseases (COVID-19) - China CCDC, Feb.17 2020.

(5) Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19) [Pdf] - World Health Organization, Feb. 28, 2020.

Dr.Lone S. Macloud, Ph.D., Cambridge Univ.,

(Chief Scientific Officer, NUTRITION BEYOND)