**NOTE 4 - Another complication is ARDS - leading to a *rapid* degradation and multiple organ failure (MOF). The cardiovascular, coagulation, neurological, and the other symptoms are linked to a *FAST* viral spread (viral sepsis). None of it is surprising, we have known this for years. Treating at community level BEFORE may avoid infected patients flooding the ICU's?**

While most patients will not develop any severe complications, some persons once they start to develop a deeper pneumonia, also develop **classical** complications seen with many other pulmonary viruses SARS-Cov2. The evolution of SARS is not new; its symptoms through the body have been studied in detail and can be found in excellent reviews (Gu et al. 2007). It starts by targeting the lung cells, then later goes deeper inside the bronchi, then penetrate in the blood and goes inside the cells in the blood vessels, the intestine, the kidney, and the brain. Lots of respiratory viruses do that actually – SARS just goes faster there. In some ways it resembles the RSV known in children. When the lungs are damaged, patients suffer what is called ARDS (Acute Respiratory Distress Syndrome). That is when they need respiratory assistance.

**Why is the SARS-2 virus more dangerous than others? *Speed, speed and speed.***

- First the rapidity of this process compared to the other viruses.
  In short, primary care givers do not have much time between the onset of a complication and the rapid degradation - if left untreated.
- Another danger is that the virus is 'stickier' than others (This helps getting it inside our cells)
- And an even more hidden danger is in the capacity of the virus to fuse the cells (see also Gu 2007) that it infects with each other, thus making giant distorted cellular blobs (plugs in the airways) and triggering a strong and inadapted immune response (a process called cytopathy). This happens in the majority of SARS patients with complications (Gu et al. 2007). In a lower number of patients with complications, the little lung structures where blood is being oxygenated (the alveolae) are physically breached and plasma and blood cells make the oxygenation impossible – even with respirators.

We will see below that none of those 3 dangerous features are specific to this type of virus, as many viruses fuse the cells (a process called "syncytial formation" and leading to super large cells called "syncytia"). The list includes Reoviruses, RSV, HIV, Dengue and many others… The same goes for the 'stickiness', it is linked to some special genetic sequences called PDZ (PDZ binding motifs). They are present in many viruses, including HIV and they just make those viruses stick more to cell membranes and their receptors, helping them getting INSIDE the cells.
**What is striking in SARS is its speed to complications in 2-3 days once they start in the minority of the cases.**

[Rem: A known French politician, P. Devedjian died in 2-3 days while being clinically stable and being an in-patient for just observation. At NO time he was put under therapy as he went from totally stable with fever and positive testing to the ICU]
[Rem: Prof Montagnier in France recently claimed that the coronavirus was a bioweapon because it contained genetic sequences present in HIV- sorry to mention that he should know better, those sequences are NORMAL in many viruses!]

In COVID19, the virus binds to the cells in the lung via a receptor (ACE2) (Gu et al. 2007). [A molecular receptor is like the mooring of a ship, it is a tight anchoring or binding]. This receptor is present in high concentrations in deep lung cells but also present in the blood vessels. It also explains why some people with heart diseases, hypertension, diabetes, are more susceptible to complications. Other receptors [anchors, cathepsin D being one] are also needed, but this is beyond the point of this note.

What is truly disturbing in the situation we are living now is ***the total disconnect with what was/is already known about the SARS of 2003, and the narrative of SARS in 2019.*** While there may be some subtle difference (between SARS 1 and 2), the mechanisms of action are fully similar. This should have helped clarify the situation, and it seems that it did NOT. A problem in this whole crisis is linked to scientific publications. Although a lot is already known, quite numerous authors get quick papers published as 'hypothesis' or as 'viral sepsis hypothesis'. While being incremental is a good scientific

quality, it does not help educate the authorities and the public during crisis – there is no need to re-invent the wheel just to fill in the gaps. It is obvious from all the clinical data that when a case becomes severe, and when the integrity of the air-blood barrier (the little alveolae in the lungs) is destroyed, oxygen does not help anymore, and this results in a vicious circle (see Gu et al 2007, but also in Li et al. in The Lancet 2020, and in Ling Lin 2020). In those rare patients with complications, after 6-7 days, the virus enters the blood and targets many systems (multiple organs failure situation) - this is NOT a hypothesis but a fact! Thus proposing more research (see 2 quotes right below) to be able to help with the understanding of how the virus kills – while a sound scientific proposal – is not a good message to authorities and the general public. ***Preventing the known complications known since 2003-2007 before they arise is key, and it is actually do-able by treating as early as possible.***

[Rem: Quote 1 "More immune-related research is needed to help us understand the pathogenesis, guide the treatment of the disease, and improve the prognosis". Quote 2 "Future basic science research is needed to explore whether SARS-CoV-2 directly attacks vascular endothelial cells, and to examine the effect of SARS-CoV-2 on coagulation and virus dissemination." ]

[Rem: When dealing with a fast-paced complex research effort, the press in search of a story but without the scientific training will report any new factoid as equally important and create the noise that prevent rational decisions and may even paralyze the health care workers and the MD's].

**Coagulation troubles.**

About the coagulation troubles, they are known since 2007, they come in LATE stages (when it is probably too late even), and it is both hyper- and hypo-coagulation at the same time. We can thus have strokes, blood clots, or blood not coagulating enough, but also micro-strokes in capillaries requiring even amputations (see Zhu Xu-You in 2010). Those are very complex situations, but they are NOT specific of the SARS – the cytomegalovirus (see Delbos et al. 2007) and the Herpes virus can do it too (see Gorek et al. 2007). Likewise it is known that the flu can do it in late stages of severe pneumonia (Yang et al. 2016). It is also known that this complex situation (called DIC – Disseminated Intravascular Coagulation) arises often in severe viral infections when they lead to septic shock, and is associated with high mortality rates around 50% (in Seki et al. 2013). Recent reports confirm that the coagulation troubles in SARS 2 like in SARS 1 may also lead **to permanent cardiovascular problems** – this makes the use of cardiac medications like chloroquine and its derivatives but also Statins (anti-cholesterol drugs used too frequently amongst the elderly) delicate as they may not be good to use for every patient during late stages.

So abnormal clotting is of course highly dangerous but *normal* once the disease becomes severe – (see Ref. Med page Today for a vulgarized perspective, and Giannis et al. 2020 for a more in-depth description) - like it is again the case with many other viruses. These severe coagulation problems occur in1 in 6 hospitalized patients (16% in Giannis et al, note: hospitalized COVID patients represent a minority of all the infected persons). But clinicians know this… and they know how to handle severe troubles of the coagulation, and they know how to treat patients. They should be allowed to work in peace, without non-contributing noise, or comments about *never seen before* coagulation troubles. Unfortunately, this expected complication of viral diseases was seemingly overlooked.

Coming back to the speed of SARS – which is the main cause of the ICU's being overwhelmed –

- It starts with very high and rapid viral multiplication in some patients (10-15%). This was already reported in 2004 for SARS1 and MERS (see CM Chu et al. in CMAJ. 2004) where it was seen that SARS gave higher viral loads. This meant more virus reproduction per unit time and volume and it was a bad sign (bad prognosis). This happens in the most severe cases, and not for the lighter cases. Same situation for MERS (see Oh et al, NEJM in 2016). See also Channapanavar in 2017, for a review about SARS more specifically.
  ***More viruses means FASTER disease (speed again !)***
- The more dangerous coronaviruses (like CoV1 and CoV2) infect the lungs at a deeper levels, this means where our airways have smaller diameters and thus can be more easily clogged. And this deeper infection with more cloggings leads to an abnormal immune response and then to Multiples Organ Failure (Channappavar et al. 2017).

**Why are those viruses "stickier"?** *(data from humans, animals and cell models)*

Apologies to all scientists for such a non-scientific term, but it is better understood by the non-biologists. A lot of viruses have some genetic sequences that makes their envelope a bit stickier – those are referred to as PDZ-binding motifs - this means that the protein of the envelope may interact and bind itself to numerous other proteins it can meet and can stick to the exterior of the cells it tries to enter (hence the term sticky!).

Those genetic sequences are not unique to this family of viruses but make them more effective at infection and entry inside our lung cells. This happens in humans and was proven in animals (see Jimenez-Guarden et al. 2014). In animal models, when such PDZ domains were removed, the virus became much more mild. **It is then understood that such domains are also targets for future medications.** This is also explained in an excellent review of the factors influencing the severity of the SARS family of viruses (see Fung et al. 2019).

Besides being sticky, this envelope protein is also essential for the virus entering our cells, and for the formation of the syncytia already mentioned. This protein is called a VIROPORIN because it forms holes in the membrane of the cell that is attacked (it actually forms what we call ion channels in biological jargon and - because of that - can also influence and control various processes in the cell).

These viroporins exist in many different viruses (see Chung et al. in 2015, also Farag et al. 2020) – like the RSV or the flu for example – and they are ALWAYS associated with the severity of the pneumonia and its side effects. They have many roles:

- Define the severity of the inflammation and of the immune responses (see Farag et al. 2020).
- They are also helping forming the plugs inside the bronchi (syncitya) (see Fung et al. in 2019).
- This viroporin type is important for the aggressive or for the benign character of the infection (viral fitness) (see Nieto-Torres et al PLOS One in 2014 & Farag et al. in 2020).
- In short those viroporins are essential for many aspects of the lifecycle of the SARS viruses (Schoeman et al 2019) and this was proved in cell models infected by the virus also (Li et al. 2020).

The viroporins are essential for many aspects that make those viruses fast and aggressive in some patients. **Medications that can block the viroporins are thus important to prevent the severe complications of ARDS.** (Alsaadi et al. 2019)

From the flu, we know that blocking its viroporin with AMANTADINE (a very old EMA and FDA approved medication) offers a relative preventive protection in humans. This is why amantadine was used and is still being used to protect both - in a preventive and curative manner - the medical personnel during flu pandemics. It costs nothing compared to Tamiflu. Amantadine has been shown in 1992 to block the pore of the viroporin (blocking the ion channel activity of this protein called M2 in the flu). More recent work has shown that amantadine may also interfere with the Viroporin of the SARS virus (Torres 2007). While this is not done *in vivo*, given the fact that amantadine is risk-free and has been widely used in the past, it would be worth considering it as prevention like in the flu. At least for the medical community.

This is a good example that it is possible to revisit the molecules that we have in our inventory to find specific and/or relatively specific therapeutic strategies against the virus. Designing NOVEL products makes commercial sense and should be encouraged, but NOT at the cost of existing knowledge that makes Public Health sense.

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