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EDITORIAL

Landing of the new Coronavirus to Italian shores: it is mandatory to make the most from the Chinese experience

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Worrying information on the ominous yet barely understood potential of Coronaviruses (Covs) is righteously overwhelming the mass media, which are forced to daily upgrade the death toll reports on the ongoing epidemics following the outbreak in Wu-Han, China. Recently published pieces of literature tell us the following story. In December 2019 an outbreak of severe viral pneumonia became evident to start from the province of Hubei, China.[1] Deep sequencing analysis led to identify a new Cov strain as the relevant pathogen, and to its identification as 2019-nCov. This agent soon proved rather diffusive, with viral pneumonia and respiratory failure as the main presentation.[2] The number of the affected subjects grew soon both in mainland China as well as abroad. At the time of this writing (February 23, 2020) the worldwide death toll is 2461, with some 80,000 contagions. Rewinding analysis of the affected cases, as reported in recent papers, has interestingly brought evidence that the virus can be transmitted in the incubation period,[3-5] thus contradicting the accepted tenet that asymptomatic subjects should be non-infectious. An answer to this question may come from deeper scrutiny of the 2019-nCov biology. This virus strain can probably infect and thrive in the cells of the upper lung airways, thus being released with the exhaled air early in the disease progression.[6] This piece of information is obviously crucial to understand the start of an outbreak from an apparently "negative" individual, but with a few exceptions like this one, our knowledge of Covs pathobiology remains fragmentary.

We are guessing that part of the difficulties originates from an inaccurate seek or release of information on the fine mechanisms of action of the Covs. The straightforward tenet that Covs are direct cytopathic viruses that will be halted when the properly formulated anti-nucleotide sequence is available, may be correct, but does not account for: 1) unpredictable outcomes; 2) worse prognosis in advanced age; 3) onset of deadly complications often in the late phases (recovering) of the lung disease.

We read a few papers in the light of our experience in hepatitis B/Delta virology and immunology,[7] gathering a few messages. A paper published back in 2009 was found to be particularly seminal. The authors used two mouse models permissive for a Cov experimental infection, fully simulating the spontaneous condition. Essentially, it was found that older but not younger animals responded with a "cytokine storm" including major pro-inflammatory cytokines and interferon (IFN), with the older succumbing to this mixture more than the younger.[8] In the following years, intense scrutiny of the IFNs, brought about the following evidence: 1) the IFN reac-

tion in some cases can alter the gut microbiome profile to reach dysbiosis, defined as a change to the composition of resident commensal communities, relative to the community found in healthy individuals;[9, 10] 2) such a response to IFN may become systemic, for example dampening gut immunity to *Salmonella* and permit clinically significant intestinal colonization.[11] Notably, today's reappraisals[12] are showing that respiratory infection can upset lung microbiome as well to ease bacterial superinfection, not only in initial but also in late recovery phases promoting unexpectedly fatal outcomes.

Thus, cardinal clinical findings seem all contained in three publications: disease behavior does mostly depend on host immunity, with full blown deadly reactions most probable in advanced age;[8] IFNs can impact gut microbiome causing gastrointestinal symptoms of a host, rather than a viral origin;[9] respiratory infections can so restrain lung microbiome as to propel secondary infections and causation of late symptom worsening.[12] In conclusion, intense translational investigation is required to correctly interpret symptoms in Cov infections, and begin timely, targeted, life-saving treatment.

While compiling these words, we are being informed that the outposts of the Cov troops have touched land on the Italian shores (with twelve fatalities and hundreds of infections so far) and seem to be here to stay and expand, thus giving us the chance to challenge knowledge and plans. From a strictly clinical point of view, the first note to be made is unfortunately a serious warning signal: since dealing with a "new" virus the never-exposed immune system is to be considered totally naïf, leaving people fully prone to unchecked infection. We thus attribute particular importance to the characterization of the antibody response in those who recovered; hopeful determination of neutralizing antibodies will warrant seeking of the corresponding antigen(s) as an initial step towards release of a vaccine. Secondly, intensive patient profiling should be pursued, with the hope to identify patient subgroups to be handled separately for, as the example: viral aggressiveness, ability to infect neighbors, or, importantly, ability of vertical transmission to the offspring. Thanks to these methods, we were able to show that carriers of the defective hepatitis Delta virus superimposed to the hepatitis B virus were to be handled separately to avoid deadly Delta hepatitis in the B carriers.[13] Identification of Coronavirus carriers with different infectivity or virus loads could allow for their precautious separation, and avoid massive shut-down of entire communities and plants. These policies are obviously at risk of generating mass psychosis and bankruptcy of economical systems.

In a word, this ultimate 2019-nCov outbreak can more-than-ever demonstrate the extent to which the future of mankind can be in the hands of science.

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