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EDITORIAL

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Coronavirus conversations, in a time of logarithm

On March 25, 2020, the Medical Exchange Club of Boston (MEC) convened a meeting of a kind and purpose unprecedented in its 100-year history, prompted by the SARS-CoV-2 pandemic. This, of course, was only one of such meetings of thought leaders that were taking pace all through the month and have continued. Here I wish to present some key points from that meeting. Readers should bear in mind that the US domain of the coronavirus pandemic was just moving into its most expansive phase at the time of this meeting and that none of us who participated claimed, then or now, to be prognosticators. This editorial is an account of just one gathering of minds around the pandemic. Nothing disclosed herein should be regard as proven science or therapy, and much of the breaking information conveyed at the meeting had not at the time been subjected to peer review prior to publication.

A point of nomenclature: in what follows, the virus is referred to by the accepted term SARS-CoV-2, while the infectious condition is referred to as COVID-19.

THE PANDEMIC'S PROFILE

The first speaker was Patrick Reeves, PhD (an instructor at Massachusetts General Hospital and Harvard Medical School and a team leader within Mass General's Vaccine and Immunotherapy Center). Dr. Reeves presented the latest data on the pandemic, pointing to Italy as a bellwether, noting that the United States would soon surpass Italy. He mentioned that IL-6 and C-reactive protein levels, both readily accessible by standard clinical blood assays, are emerging as markers for the infection's progression and strong negative predictors for outcome. He noted that preexisting cardiac comorbidity is a risk factor. He reported on the relative stability of the virus, based on recent genome sequencing comparing sequences between China and other sites. The SARS-CoV-2 spike protein is 76% homologous to that of SARS1, and searching back to the latter's neutralizing epitopes offers guidance for SARS-CoV-2. Dr. Reeves went on to emphasize some key clinical dimensions. Infections can exist for 5 days or more before symptoms present, and 30% of infected subjects are asymptomatic. He also reminded us that 40% of hospitalized patients are less than 55 years of age. Dr. Reeves cited a case in the UK just that morning in which a 21 year old became ill and died very soon thereafter.

The issue of viral entry was next discussed. Dr. Reeves pointed out that although there has been much talk about the ACE receptor, early reports indicate that the SARS-CoV-2 virus uses any of four, and he emphasized that the other three need to be brought into range. It is clear that COVID-19 progression is driven by an exuberant inflammatory cascade that culminates in T-cell exhaustion.

Dr. Reeves then discussed the interesting situation of moderate disease. He cited a case study in Australia in which samples from one such patient were used to take a deep dive into the acute immune response to the virus. There were elevations of antibody-secreting cells, of follicular helper T-cells, activation of both CD4 and CD8 lymphocytes, and increased levels of virus-specific IgG and IgM. During recovery, these antibodies remained elevated for 7 days after viral clearance. This study obviously bears on projections of herd immunity, with the caveat that moderate disease cases are only one segment of the affected and immunologically responding population.

Dr. Reeves next commented on the need for improved testing to detect both infected and seroconverted individuals. All evidence coming in from the field points to the superiority of nasopharyngeal swabs over oral, despite the increased logistics and some patient discomfort of the former. In one Wuhan, China study, rectal swabs remained positive for as long as 11 days after nasopharyngeal ones had been negative, raising issues of viral shedding and GI disease comorbidity.

Concluding, Dr. Reeves offered his perspectives about the vaccine frontier. A macaque study has recently shown that humoral protection can be durable, when rechallenged with the same strain. He cautioned against placing all bets on the spike protein, arguing for a diverse antibody repertoire against multiple viral proteins. He added that the recent evidence is that SARS-CoV-2 is not mutating as rapidly as seasonal flu, exhibiting minimal alterations when comparing sequences from China and other sites across the globe. This, of course, could be very favorable.

AT SEA WITH THE *DIAMOND PRINCESS* AND BOOTS ON THE GROUND IN WUHAN

The next to present was Michael Callahan, MD (Special Advisor to the Assistant Secretary of Public Health Preparedness and Response, HHS, and Director of Clinical Translation and Mass-Casualty Therapeutics in the Mass General Vaccine and Immunotherapy Center, and an infectious disease physician at Massachusetts General Hospital). He described his fascinating experiences around the not well-known epidemiological study done aboard the cruise ship *Diamond Princess* when it was hit by an outbreak. This was immediately recognized by health officials as a rare opportunity to study a hyperendemic setting. *Inter alia*, 76 cases were tracked to a 14th level toilet on the ship used by senior passengers attending a dance. Dr. Callahan emphasized the cooperation of the ship's personnel, including efforts to elevate the staterooms' humidity, as was becoming seen as beneficial in China in the early days of the outbreak. This unique shipboard study allowed each patient, or couple, to be tracked in close quarantine conditions.

In one of the most stirring moments of the meeting, Dr. Callahan reported the extraordinary levels of SARS-CoV-2 monitored in swabs taken from the protective suits of the *Diamond Princess* team, with values of up to 10 million viral particles per swab. He emphasized that in close quarters it appears to be among the most infectious of any respiratory virus ever seen.

Dr. Callahan then spoke about his experience in Wuhan as the first outbreak was occurring. Six risk factors emerged right away. One was age, not surprisingly. More unanticipated was gastrointestinal disease (ulcerative colitis, Crohn's). Chronic obstructive pulmonary disease and chronic renal failure have been revealed as the two most lethal comorbidities, the later something of a surprise. Hypertension has also emerged as a significant risk factor. As to chloroquine and hydroxychloroquine, Dr. Callahan said that a study of 2600 infected patients is underway is China. These drugs are extensively used there for rheumatoid arthritis and for *Plasmodium vivax* malaria in the south. As readers know, here in the United States there has been a rush on these drugs, leaving many lupus and rheumatoid arthritis patients at risk. There seems to be no consensus on their effectiveness for abating COVID-19 nor on any prophylactic potential.

PHARMACOEPIA PENDING

The third speaker was MEC member Edward M. Scolnick (former Director and currently Chief Scientist at the Stanley Center for Psychiatric Research at the Broad Institute and previously Director of Merck Research Laboratories. where he led many vaccine development programs). He began by addressing various efforts underway to potentially repurpose FDA-approved drugs, one of which is the antiepileptic lacosamide, which has an IC_{50} of 1 μM against SARS-CoV-2 in cell culture plaque assays. He went on to emphasize the importance of having rapid antiviral assays and deploying them intensively in advance of clinical studies, as was not done sufficiently in the development of the HIV protease inhibitors. If the repurposing efforts are unsuccessful, he believes the second most attractive opportunity would be antibody strategies such as one currently in development by Regeneron, in which a vast number of neutralizing antibodies from a humanized mouse model were screened. This has resulted in a cocktail of two antibodies that will enter early clinical trials in late May/early June. The company has US production capacity sufficient for the initial clinical studies. It has also provided the cell lines for the two monoclonals to Johnson & Johnson, which has massive scale-up capacity. Dr. Scolnick also pointed out the potential for this cocktail to be used prophylactically, in that these are fully humanized monoclonals and thus could be administered in repeated doses to maintain a protective state for several months. And it appears that SARS-CoV-2 is not rapidly mutating (*vide supra*), thus adding to the potential of this prophylactic concept.

Turning to vaccines, Dr. Scolnick emphasized that the pandemic has three populations: noninfected, infected and recovered, and infected and shedding. Clearly, if the level of social distancing and quarantine of infected individuals with mild symptoms were to be relaxed, the consequences would almost certainly be a recrudescence and a delay in the attainment of herd immunity.

Dr. Scolnik proceeded to discuss various vaccine approaches, stating that a macaque model for SARS-CoV-2 is now available that can be the preclinical theater for any of the vaccine efforts. Several companies are trying synthetic messenger RNA encoding the virus' spike protein, delivered by lipid encapsulation and intramuscular injection. The first out of the gate is Moderna, which at the time of this meeting had initiated a small trial on March 16. Pfizer, in collaboration its German partner BioNTech, is engaged in a similar project. Vector-based approaches are underway with the cold virus (Johnson & Johnson) and an oral adenovirus 26 approach (Ragon Institute, MIT-Broad Institute). Blackstone Health Sciences is funding a human cytomegalovirus-based vaccine approach to SARS-CoV-2 that is adjuvant-free, has no reported safety issues, and generates high titers of neutralizing antibodies.

OTHER WAYS TO CONTINUE THE CONVERSATION

In addition to keeping abreast of the rapidly moving science of SARS-CoV-2, researchers have a unique opportunity to utilize the pandemic to highlight the importance of federally funded basic research in understanding and treating infectious

diseases. Although travel restrictions prevent meetings with Congressional leaders in Washington, DC, advocacy can be just as, if not more, effective through virtual meetings with local offices and staff members. Long recognized as the voice of the biological research community, FASEB provides many online resources to assist scientists in their advocacy efforts, including a step-by-step tool kit,[1] legislative action center,[2] and, most importantly, data about National Institutes of Health and National Science Foundation funding in your state and congressional district[3] to demonstrate the positive impact of research on your region.

FASEB recognizes that this is a challenging and uncertain time for scientists; most laboratories have been temporarily shuttered or efforts redirected to support testing and rehabilitation of those affected by COVID-19. To facilitate rapid access to important guidance regarding agency flexibilities during this crisis, FASEB launched a Coronavirus Information webpage[4] that is updated several times a week. Similarly, staff meet regularly with agency and Congressional leaders to discuss policy gaps and ensure scientists needs are considered in recovery and stimulus supplements.

FASEB, and *The FASEB Journal*, are committed to doing all we can at this time. I have recently instituted expedited review of coronavirus-related manuscripts, and the editorial board is also granting generous extensions of time limits to authors for revisions that require additional experimental work. Meanwhile, we will support the US and international biomedical research communities in all the ways we can.

DISCLAIMER

Nothing in this editorial is to be construed as medical advice.

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