CORONAVIRUS

COVID-19: All the wrong moves in all the wrong places

Michael B. Yaffe, Chief Scientific Advisor and Academic Editor, *Science Signaling*, American Association for the Advancement of Science, Washington, DC 20005, USA. Center for Precision Cancer Medicine, Koch Institute for Integrative Cancer Research, and the Departments of Biology and Biological Engineering, Massachusetts Institute of Technology, Cambridge, MA 02139, USA. Divisions of Acute Care Surgery, Trauma and Surgical Critical Care and Surgical Oncology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA 02215, USA. Dr. Yaffe has patents pending related to the field of fibrinolysis and COVID-19 therapy. Email: myaffe@mit.edu

As the world continues to be ravaged by coronavirus disease 2019 (COVID-19), three major systemic failures appear to have coalesced to block progress in disease control, containment, and treatment. These failures reflect a "perfect storm" of governmental ineptitude, scientific ignorance/misprioritization, and the abdication of medical training to market-driven forces. Much has already been written about the dismantling of preexisting governmental panels and organizations charged with the oversight of emerging infectious diseases by the current administration, which, when combined with lies, denial, and willful disregard for the opinions of its own cadre of expert scientists, physicians, and public health officers, has resulted in regional pandemonium and the lack of a clear national health COVID-19 policy. Whether, as with the 1918 influenza pandemic, we will see a second wave of COVID-19 with a markedly increased killing power this fall remains to be seen, but wishful thinking that COVID-19 will mysteriously vanish is both unfounded and dangerous.

Unfortunately, blame for the poor response to the COVID-19 pandemic also resides with the scientific and medical establishments. A nearly monomaniacal focus on diagnostic testing using nucleic acid reagents and antibody-based serology tests reflects the current thinking of limiting transmission as the main mechanism for disease control. However, we know that some patients with clear symptoms of COVID-19 have one or two negative test results before testing positive, which is suggestive of intermittent viral shedding, whereas others may continue to test positively during convalescence due to shedding of degraded virions, when, in fact, they may no longer be contagious. This testing conundrum is not an indictment of the assays themselves. Instead, it reflects our basic ignorance of viral-host dynamics. More worrisome is the observation that, just like with the 1918 influenza, people infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can actively transmit the virus to others before they develop any particularly noticeable symptoms. These diagnostic difficulties, especially when compounded by the lack of a uniform national policy on quarantine, prevention, or risk that would actually make good use of these data, suggest that perhaps it is time to consider alternative measures for conquering the disease.

Indeed, as scientists, we should remember that COVID-19 victims are not dying of the beta-coronavirus infection per se, they are dying of the pneumonia, renal failure, and thrombosis that reflect the body's innate immune signaling response to the infection, an aspect about which we have been much less studious and scientific. Of the ~3.6 billion dollars that the NIH has reprioritized for COVID-19–related research (www.sciencemag.org/news/2020/06/nih-grapples-researchers-rush-claim-billions-pandemic-research-funds), about 40% has gone to NIAID with a diagnostic focus. Less than 3% of this money has gone to NHLBI, despite the fact that the lungs, heart, blood, and kidneys are the very organs responsible for COVID-19–related deaths! Some improvement in recovery has been seen in a subset of patients treated with the viral polymerase inhibitor remdesivir, but it does not appear, so far, to be the "wonder drug" that we need. Clinical trials targeting cytokine signaling (for example, anti–interleukin-6 therapy) are ongoing, but it is worth noting that monocytokine therapies have largely been catastrophic failures in treating other types of sepsis and multiorgan failure. Perhaps more global immune-modulating treatments, such as dexamethasone, which already looks promising, or multi-cytokine–directed cocktails, may prove equally or more effective. Clearly, however, studies examining signaling events in epithelial, endothelial, and immune cells are desperately needed for progress in COVID-19 treatment.

Despite this need, many universities and medical schools have actively discouraged research on the live virus, citing public health safety concerns and the lack of appropriate biosafety facilities. Yet, there has been no wholehearted effort to rapidly build such laboratories or to pursue a "Moonshot project" type of scientific program to better understand the pathophysiology of the disease. How does the virus cause such an unusual pneumonia that is noticeably different in many patients from other types of pneumonia and acute respiratory distress syndrome (ARDS)? Why is prone positioning so helpful in COVID-19 patients who are dying of hypoxemia? Why is renal failure so prominent? What is responsible for the profound thrombotic coagulopathy observed? How much of the disease is due to microvascular thrombosis and complement activation? Are there good animal models for COVID-19 disease? These obvious questions barely scratch the surface of our ignorance about how the virus causes critical illness. If it were possible, through such research, to prevent the hemorrhagic pneumonia, myocarditis, blood clots, and organ failure caused by the interaction between

the virus and the host, perhaps SARS-CoV-2 infections could be treated as we do adenovirus infections, a mere inconvenience for a few days. The fact that a large fraction of infected patients have a relatively mild clinical course, whereas others have either a severe acute response or a moderate persistent illness with a long protracted recovery (so-called "long-haulers"), provides a roadmap for just such types of signaling-based studies to better understand these different phenotypes.

Last, the medical profession as a whole also shares in the blame. In an age of unprecedented progress in basic science research, the gap between what we have learned from basic medical science versus our ability to apply this in daily clinical practice continues to expand at an ever-increasing pace. The decision by the Department of Health and Human Services that hospitals no longer have to have an autopsy program to qualify for Medicare reimbursement, despite the fact that undiagnosed diseases are discovered in up to 33% of autopsies, is a clear statement from federal officials that ignorance is good. Worse yet, many medical institutions have banned all autopsies on patients that died of COVID-19 because of the perceived infectious risk. How are we going to learn about this new disease if we are not even permitted to study it?

Scientists and clinicians have further contributed to the failure of the medical profession to provide anything better than supportive care to SARS-CoV-2–infected patients because of their inability to apply basic science rationale to a new disease entity. Instead, the last generation and a half of medical practitioners have been raised on a market-driven "clinical pathway" model of care. When one of us started medical school 35 years ago, physicians were expected to apply their own understanding of basic science—pathology, microbiology, physiology, and pharmacology—to diagnose and treat their patients on an individual basis. The success or failure of this approach is debatable because it placed the clear burden for good care on the intelligence, knowledge, and foresight of individual physicians, which may not have been the most universally equitable approach for patients. Instead, over the past 20 years, better uniformity in patient care was obtained by placing patients into "pathways." All patients with a particular subtype of disease are treated similarly using a proscribed written pathway guide for care. Market forces lauded the approach, and the physician's primary job became one of patient categorization. Those who could sort more patients into particular pathways the fastest received the greatest financial rewards. Insurance companies and for-profit medical centers loved the approach for its bland and monotonous efficiency. Physicians were now replaceable "cogs" in a giant medical machine. Somewhere along the line, our deep respect for hard thinking in clinical practice evaporated. Although the clinical pathways approach to care is a highly efficient and useful mechanism for ensuring standard-of-care treatment for well-studied diseases, it fails miserably when confronting a new disease like COVID-19. Consequently, many of our young physicians, uncomfortable without a guiding pathway document in front of them, now feel intellectually unmoored in the current pandemic, further contributing to their stress.

The response of the medical profession to this has been predictable and disappointing. Clinical unease has led to the creation of new COVID-19 clinical pathways within days of when the first infected patients arrive at hospitals, combined with an absurd demand that these pathways be based on data from randomized clinical trials. How, we would ask, is it possible to construct a pathway approach for treatment when we understand almost nothing about the basic or clinical science of the disease in the first place, and there are no randomized trials to reference? Is it not time to stop these reflexive responses to our collective stupidity and intolerance of ambiguity and uncertainty and reembrace old-fashioned, basic science–based medicine? Perhaps we might try to study the enemy in depth to discern its weaknesses, signaling and otherwise, before resorting to a series of rigid guidelines based, at this point, on the opinions of self-designated experts in the absence of any solid scientific foundation. Now is the time to devote ourselves to studying the science of this new disease and not just use PCR and antibody-based diagnostics to try and run away from it.

In 1910, Abraham Flexner decried the sorrowful state of medical education and academic medical practice in the United States and its divorce from fundamental scientific principles. This ultimately led to a complete revision of medical education and training based on the direct application of scientific research. More than 100 years later, the COVID-19 epidemic has only deepened his clarion call for reform.

–Christopher D. Barrett and Michael B. Yaffe

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Christopher D. Barrett, Center for Precision Cancer Medicine, Koch Institute for Integrative Cancer Research, and the Departments of Biology and Biological Engineering, Massachusetts Institute of Technology, Cambridge, MA 02139, USA. Divisions of Acute Care Surgery, Trauma and Surgical Critical Care and Surgical Oncology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA 02215, USA. Dr. Barrett has patents pending related to the field of fibrinolysis and COVID-19 therapy. Email: cdbarret@mit.edu

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