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Notes on the Pandemic #5
April 15, 2020

Dear DCI Community,

Can it really be that this is the fifth of these *Notes on the Pandemic*? At Stanford we are getting close to five weeks of sheltering in place since we began significant social distancing on Friday March 13th. As you know, social distancing has made a difference, especially when started early, impacting the number of cases and the number of deaths. Based on various tracking and modeling, around 17 countries have now seen declines in infection rates, which is encouraging. As of today, there are 2,008,850 confirmed cases globally with 129,045 deaths. In the US there have been 610,774 confirmed cases and 25,922 deaths of which 7,905 have been in New York City. While new cases continue to occur, some states, including California have had less confirmed cases and fewer deaths than originally projected thanks to the actions of state and local government leaders, health departments and medical centers. In states where shelter in place rules were delayed in their implementation (e.g., Connecticut, Florida, Georgia, Massachusetts, Texas), the peak surge is projected to April 26th which continues to affirm that COVID is impacting different regions of the country on different timescales and magnitude. Clearly this will make policies regarding return to work challenging since there will be no one model for all. But there will be guiding principles, some of which are discussed below in this letter. I know that along with the impact of COVID on our communities, concerns about the economy and return to normality is front and center for all of us. We are watching this debate unfold between and among states and the federal government so we will all be staying tuned. I felt that in this letter it might be helpful to review some of the science and public health issues that will impact on these policies.

Thinking About Immunity and Immunization and the Future

In *Notes on the Pandemic #3* I introduced some of the basic concepts of our defense system that protects us against microorganisms and other things foreign to our bodies (which can include organ transplants and even cancer). Immunity is highly conserved across evolution and species and, as we discussed, includes the "innate immune system," which might be considered the oldest and one that is found in all multicellular organisms, including plants, fungi and insects, and a number of its components are found in humans. In the simplest way, the innate immune system includes anatomic barriers (e.g., the skin and the linings of the various body cavities) that include adaptive machinery and mechanical forces to remove or expel microorganisms. These are aided by a broad repertoire of chemical mediators (including specific defenses against viruses, the interferons as well as the Toll-like receptors and other proteins) and, in some cases specialized cellular defenses (especially the white blood cells) that immobilize, inactivate or kill selected microorganisms. The innate immune system is our first line of defense but would not

prevent humans from becoming infected with a wide array of microbes. That is where the adaptive immune system comes in.

The adaptive immune system is also referred to as the acquired immune system and is more highly specific to particular pathogens and can provide long-lasting and in some cases lifelong immune protection. The two key features include so-called humoral immunity and cellular immunity, which have a number of interrelationships. Antibodies are the key component of the humoral immune system and their presence in our blood or at certain mucosal surfaces provide evidence of prior infection to a specific pathogen. For example, virtually all of us will have antibodies against influenza, although we all know that the simple presence of these antibodies doesn't provide complete protection against all future infections with influenza. In the case of influenza this is because the virus undergoes minor and sometimes more major shifts in its surface proteins each year, making yearly vaccination important. A question on all of our minds is whether antibody against SARS-CoV2, whether the result of prior infection or because of vaccination, will be protective. While we all hope for complete protection, the story is more complicated – in part because of the lack of data.

The Microbial Repertoire: First let's put COVID into a broader context. Upper and lower respiratory tract infections are frequent, often seasonal, and range from the "common cold" to other infections along the respiratory tract (e.g., sinusitis, bronchitis, pneumonia), some of which is related to a virus alone and others to viral infections that become complicated by secondary infections – often with bacteria. As it turns out there are more than 200 viruses responsible for respiratory tract infections. Rhinoviruses account for 30-50% of these infections and while a nuisance, they are rarely serious or life-threatening. As I have mentioned in earlier commentaries, coronavirus actually comprise 10-15% of respiratory infections, almost exclusively with the four species not associated with serious disease. The exception of course are the three coronaviruses that now all recognize have caused serious disease – SARS, MERS and, of course, SARS-CoV2, the cause of COVID. But it is also important to note that these are just some of the respiratory viruses that can cause serious disease. Other important ones include Influenza (A, B, C and D) as well as many different subtypes of influenza A based on variations of key antigens – which is why there is "antigenic drift" from year to year and why the influenza vaccine works with variegated success. Other respiratory viruses include parainfluenza, the respiratory syncytial virus, adenoviruses and enteroviruses.

Because it is associated with epidemics and periodic pandemics, including notable mortality, most of the focus regarding modern pandemics has been about influenza. In fact, Influenza has been responsible for four pandemics in recorded history – 1918, 1957-58, 1968 and 2009. Of these the most serious was the 1918 pandemic that resulted in at least 50 million deaths worldwide. There has long been a concern that a more serious influenza pandemic could occur if the avian strain (largely H5N1, as emerged in 2003) adapted to human-to-human transmission, which has not taken place on a larger scale – so far.

The Emerging Infectious Disease Pathogens. Beyond the respiratory viruses noted above, the National Institute for Allergy and Infectious Disease (NIAID) – the NIH institute that Dr. Anthony Fauci has directed for since 1984 – has a priority list of microorganisms that are threats because of natural events or because they could be engineered to cause mass destruction (see:

https://www.niaid.nih.gov/research/emerging-infectious-diseases-pathogens). Accordingly, NIAID has three categories of priority pathogens:

1. **Category A Pathogens** include organisms/biological agents that pose the highest risk to national security because they can be easily disseminated or transmitted from person-to-person and can result in high mortality. It is recognized that such infections could result in public panic and social disruption and thus would require public health preparedness. The organisms in this list include the bacteria that cause anthrax, botulism, plague and numerous viruses including those that cause dengue, Lassa fever, Ebola and others.

2. **Category B Pathogens** are microorganisms that are moderately easy to disseminate, result in moderate morbidity and (relatively low) mortality and which require specific enhancements for diagnosis and disease surveillance. There are some 39 organisms on this list that include bacteria, viruses, fungi and protozoa.

3. **Group C Pathogens** include those that could be engineered for mass dissemination because of their availability, ease of production and potential for high morbidity and mortality. There is a long list of microorganisms on this list which includes influenza and coronaviruses – although SARS-CoV2 wasn't known when this list was last revised, which underscores the importance of emerging organisms as a continuing threat to human welfare.

Because it has long been recognized that the risk of pandemics (or bioterrorism) are real potential threats, it is not a surprise that federal agencies have developed plans to prevent, control and mitigate the effects of a serious emerging infection. One example is the US Department of Health and Human Services **"Pandemic Influenza Plan"** that was originally formulated in 2005 and revised in 2017 to provide a roadmap of responsiveness (https://www.cdc.gov/flu/pandemic-resources/pdf/pan-flu-report-2017v2.pdf). Seven domains were identified, including:

1. ***Surveillance, Epidemiology, and Laboratory Activities*** – this includes better detection systems, many based on gene sequencing technologies. Candidate vaccines would need to be rapidly developed. And use of big data should facilitate surveillance and planning.

2. ***Community Mitigation Measures*** – use of community mitigation measures from the earliest stages of the pandemic would need to be deployed to slow the spread of a "novel" virus.

3. ***Medical Countermeasures: Diagnostic Devices, Vaccines, Therapeutics, and Respiratory Devices*** – this includes aggressive translation of applied research to mitigate the course of the pandemic.

4. ***Health Care System Preparedness and Response Activities*** **–** this recognizes the need to address the sharing of electronic health information, referral patterns, reimbursement models, business models and the need to prepare hospitals for surge strategies so that people can receive the level of care that they need.

5. ***Communication and Public Outreach*** – requires accurate, consistent, timely and actional communication using appropriate channels and spokespeople to deliver consistent and accurate information to multiple audiences.

6. ***Scientific Infrastructure and Preparedness*** – these are needed to develop new vaccines and therapeutics and to determine how well other control efforts are working.

7. ***Domestic and International Response Policy, Incident Management, and Global Partnerships and Capacity Building*** – Health and Human Services (HHS) will coordinate domestic and international pandemic preparedness and response activities, including rapid exchange of information, data, reagents and other resources needed domestically and globally to prepare for and respond to an (influenza) pandemic outbreak.

While this plan was developed for an influenza pandemic, which always seemed the more likely one to emerge (and which remains a major possibility for the future), it is clear that the plan developed by HHS in 2017 was well considered and highly applicable to other pandemics, including the current SARS-CoV2. So, the good news is that leaders knew what to do if the threat of a pandemic arose. The unfortunate news is that these recommendations weren't rapidly adapted to the coronavirus threat and, as we now know, we lost valuable time in all seven of these roadmap plans. A report by Amy Maxman in *Nature* on April 9th (https://www.nature.com/articles/d41586-020-01068-3) points out how fractured and sluggish our testing for SARS-CoV2 was and how this impacted on how we responded to the infection – even to date.

Even though there have been four pandemics with influenza as noted above, the yearly influenza season mortality ranges from 12,000-61,000 deaths in the US each year (and 290,000-650,000 globally). By way of comparison, with COVID-19 there have been 20,461 deaths in the US as of April 11th and 68,841 COVID deaths are projected by August 4, 2020 according to the Institution for Health Metrics and Evaluation (IMHE) (https://covid19.healthdata.org/united-states-of-america). Unlike influenza, the pace of the coronavirus infection, the surge on medical facilities and the early uncertainty on case-fatality rates all impacted the relative concerns about COVID versus annual influenza. And of course, unlike COVID but for influenza, there are available therapies for influenza as well as a vaccine which, even if imperfect, helps attenuate the course of infection.

Moving Beyond COVID: As of April 13th, the US has different time to peak surge across the US and has noted in the *Notes on the Pandemic #4*, different bed and ICU capacities. In a number of states and as noted above, the peak surge date has recently passed or could be later in April (as is the case in Arizona, Connecticut, Florida, Georgia, Kentucky, Massachusetts, Texas and others). I also mentioned the ***American Enterprise Institute*** *Roadmap to Recovery* in my last two communications which address in their Phase II the thresholds for graduated state openings, which will almost certainly vary around the US and world. As also discussed, key to this will be the ready availability of diagnostic tools for anyone suspected of infection or who had contact with someone infected as well as seroprevalence based on antibody testing. To that regard a number of institutions and companies are developing antibody tests. At Stanford a team led by

Dr. Scott Boyd developed a specific and sensitive ELISA assay that detects two types of antibodies: IgM antibodies that are made early after infection and then wane, and IgG antibodies that arise more slowly after infection but then persist, ideally providing long-term immunity. While it is clear that this new antibody test will delineate whether someone is newly infected or has had COVID in the past (although it could be negative if someone was infected around the time of the test before even an IgM response could occur). However, at this point, the presence of antibody *per se* does not necessarily mean that protection from future infection is conveyed. That will take time to discern and, of course, is highly relevant to whether an antibody-generating vaccine will provide protection to individuals exposed to or infected with SARS-CoV2. But even short-term immunity would be helpful in determining policies regarding reductions in social distancing.

And as that happens, it will also be important to have programs for COVID contact tracing and case finding in order to blunt rebound infections that are likely to occur when social distancing is relaxed (as has been seen in other countries). On April 10th The Johns Hopkins Bloomberg School of Public Health and Center for Health Security published online *"A National Plan to Enable Comprehensive COVID-19 Case Finding and Contact Tracing in the US"* (see: http://www.centerforhealthsecurity.org/our-work/pubs_archive/pubs-pdfs/2020/a-national-plan-to-enable-comprehensive-COVID-19-case-finding-and-contact-tracing-in-the-US.pdf). This plan is built on (1) ready access to rapid diagnostic tests for all symptomatic cases or those with a reasonable risk for exposure; (2) widespread serologic testing to understand the rates of infection and identify those who have developed immunity and could return to work, school etc.; and (30 the ability to trace all contacts of reported cases in order to carry out appropriate quarantine and reduce the spread of infection. This has been the approach employed in other countries that have had more successful responses to COVID than the US (including Singapore, South Korea, Taiwan, Germany) and that should be employed in the US – although that will require resources to do so. Ultimately the solution will be a build-up of immunity in the population (which may take time since significant portions of the population will remain unexposed to SARS-CoV2 because of successful social distancing) and thus they will remain susceptible to infections delaying "herd immunity." Alternatively, we can achieve herd immunity by a successful vaccine for SARS-CoV2. What will it take to get there?

The Path to a Vaccine. Vaccines and other immune-based therapies have transformative in reducing and even eliminating certain infectious diseases as well as impacting on other diseases, including cancer. Certainly, the eradication of smallpox (once the cause of pandemics) was commemorated on December 13, 2019, forty years after the last human infection with this once dreaded virus took place in December 1979. The last known human transmission took place in Somalia in 1977. This stands as one of the most extraordinary public health triumphs in history, thanks to a global collaborative effort initiated by the WHO. I am old enough to have received the smallpox vaccine as a child and I also remember the events that surrounded the development of the vaccine(s) for polio that took place in 1953-54. All of us have witnessed the discovery and implementation of other vaccines, some of which have worked extremely well and other which have not. Sadly, one of the great failures has been the inability to develop a protective vaccine for HIV/AIDS despite all that we know about that virus and the extraordinary efforts to do so since the 1980s. Hopefully that will not be the story with SARS-C0V2.

Vaccines against viruses are prepared in different ways. The overall goal is to induce an immune response, generally by antibodies, against key portion (or antigen) on the virus that produces a "neutralizing" impact and prevents the virus from getting a foothold in the body or at least in attenuating the course of the infection. Influenza vaccines fall into the latter category. Other vaccines, such as for measles, mumps, rubella and others, can be more fully protective although antibody can wane over time. Of special note to the changing demography in developed countries (of which we are members), is that the immune system becomes more diminished with aging. That is one of the reasons why people over 65 get a "double dose" of the influenza vaccine and even with that, it is generally only partially protective.

Vaccines can also be prepared in ways that make them live and attenuated (such as varicella, influenza, measles) or inactivated/killed (such as in the Salk version of the polio vaccine). There is also a live attenuated version of the polio vaccine that was formulated by Jonas Sabin. Some vaccines are prepared against a toxin produced by a microbe (e.g., the tetanus toxoid vaccine) whereas others are comprised of subunits of the organism (e.g., DPT vaccine) or through genetic engineering where the genes coding for the virus are inserted into a carrier (vector) virus – as is the case Hepatitis B vaccine. Genetic engineering has also led to the production of a vaccine against the human papilloma virus (HPV) and is being used to prevent cervical cancer.

It should not be overlooked that there are not vaccines against the coronaviruses that cause seasonal "colds" although there has been some work in developing a SARS vaccine (that was made less immediately relevant when that virus disappeared from the scene in 2004). It is also noted that vaccines for other respiratory viruses (RSV, adenovirus) have not been achieved but we need to be optimistic about a vaccine against SARS-VoV2. In fact, work is already underway, some using novel and even unique approaches.

Academic institutions, research labs and institutes, industry and international organizations, including NIAID, the WHO and regulatory agencies including the FDA, European Medicines Agency and others advocated or supported R&D for vaccine development and a number of approaches are being launched. As of April 10th the COVID-19 Vaccine Tracker (https://www.raps.org/news-and-articles/news-articles/2020/3/covid-19-vaccine-tracker) four vaccines moving to early safety (Phase 1) testing based on prior work with other coronaviruses like SARS and MERS. There are also vaccines against SARS-CoV2 in various stages of preclinical development and more that 26 that are exploring potential vaccine candidates. While there is understandable eagerness to move forward as rapidly as possible, the usual process for vaccine development includes the initial exploratory and preclinical stages which can sometimes be measured in years. Once it is deemed safe to begin studies in humans, the sequence of Phase 1 safety testing followed by Phase II testing to assess the candidate vaccines safety, immunogenicity, dose schedule, method of delivery and more. This is then followed by Phase III testing which generally takes place through randomized clinical trials that are usually placebo controlled. Clearly it is imperative that whatever vaccines come forth, that safety as well as efficacy be evaluated thoroughly and accurately.

At the same time, the federal government and regulatory agencies have some authorities to expedite promising vaccine development. For example, the Assistant Secretary for Preparedness and Response at HHS can invoke the Biomedical Advanced Research and Development

Authority to accelerate the development of new drugs and vaccines. Further the FDA has an Accelerated Path as well as the Critical Path Initiative. Hopefully these can help scientists, companies and the biomedical community to be as responsive as possible. But even in the best of circumstances, unless a candidate has already been studied for safety and efficacy which could still take 4-6 months for a new virus like SARS-CoV2, there is often an additional 4-6 months or more to produce and scale the vaccine. This is why most authorities have indicated that it could be a year or more before a vaccine is available. While we would all like such a forecast to be incorrect and for successful prevention to occur sooner, it is also plausible that it will take even longer, which makes the public health approaches noted above so important. Of course, if a drug or biological product is developed and effective, especially one that has already been approved for another disorder, that could add to the armamentarium and alter the coronavirus risk. That too is something worth hoping for – but not guaranteed. But there is an incredible amount of work going on in research laboratories around the world - so optimism is appropriate.

At a time where global collaboration is ever more important, the decision made yesterday that the US would halt funding for the WHO is disturbing beyond words. Not only could this impact our response to the pandemic, it also would cut off a lifeline to low-and-middle income countries and put hundreds of millions of people at risk. Such a decision at this time is truly beyond belief.

Reflections on Isolation, Improving Wellness and More

For most of us the term" shelter in place" has become synonymous with being isolated at home. The good news is that social distancing has had a positive impact on the course of the pandemic and an increasing number of nations appear to be moving through the most challenging phases of the pandemic. And while Zoom calls, meetings, online social engagements and religious services have become parts of our lives, even welcome ones, we are all cognizant of the loss of human contact and the value that comes from social engagement. That is one of the reasons why community and social engagement is one of the three pillars of DCI and why the data supporting its impact on positive longevity is so strong. While we have all marveled how technology has created opportunities that help breakdown physical social barriers, I am sure we would agree that a virtual world is not one that would welcome as a new normal.

And I suspect that many of us are feeling the pains of isolation and separation – influenced by the space we are in that the alternatives we have. In the first *Notes on the Pandemic* I concluded with a mention of Teddy, the teenager I cared for seven years, whose life was limited to a "protected environment" that was about the size of modern bathroom. As I noted, I often reflect on Teddy during challenges since his resilience gives me strength.

Over the last weeks I have also done "thought experiments" comparing the circumstances I experience (and expect you do as well) to individuals who have experienced much more profound isolation because of horrendous events like the Holocaust or being a political prisoner or victim of war and terrorism. In *Notes on the Pandemic #2*, I provided a list of books about pandemics. I am taking the liberty of now providing a list of books I have benefited from because of how they reflect on isolation under extraordinary and unfathomable situations. For me at least, these stories, including historical fiction, non-fiction and philosophical reflections along with beautiful literature, that I have read over the past couple of years offer perspective and

context for interpreting our own personal sense of isolation – at least through my personal lens. One or more might be of interest to you.

There is one caveat: the books by Harold Kushner are not about isolation per se but his writings have brought me comfort in difficult circumstances, particularly during my time as a pediatric oncologist or physician caring for children with HIV/AIDS. I hope some may be of help to you.

Following is a list of books I have been moved by. It would be great if our DCI Community recommended additional books or media that help them and which might be recommended to others.

1. *Chimamanda Ngozi Adichie*: ***Half a Yellow Son: A Novel***
2. *Anthony Doerr*: **All the Light We Cannot See**
3. *Nathan Englander*. ***What We Talk About When We Talk About Anne Frank: Stories***
4. *Victor Frankl*: ***Man's Search for Meaning***
5. *Ayelet Gundar-Goshen*: ***Waking Lions***
6. *Kristine Hannah*: ***The Great Alone***
7. *Kristine Hannah*: ***The Nightingale***
8. *John Hersey*. ***The Wall***
9. *Harold Kushner*: ***The Book of Job: When Bad Things Happened to a Good Person***
10. *Harold Kushner*: ***When Bad Things Happen to Good People***
11. *Harold Kushner*: ***Conquering Fear; Living Boldly in an Uncertain World***
12. *Primo Levi*. ***The Periodic Table***
13. *Bernard Malamud*: ***The Fixer: A Novel***
14. *Gabriel Garcia Marquez*: ***Love in the time of Cholera***
15. *Hisham Matar*. ***The Return: Fathers, Sons and the Land in Between***
16. *Hisham Matar*: ***In the Country of Men***
17. *Heather Morris*: ***The Tattooist of Auschwitz: A Novel***
18. *Lynne Olson*. ***Citizens of London. The Americas Who Stood with Britain in its Darkest, Finest Hour.***
19. *Isaac Bashevis Singer*: ***The Slave***
20. *Mark Sullivan*: ***Beneath a Scarlet Sky***

I also suspect that most of us are spending a lot of time on our computers with Zoom meetings and related activities. I seem to be averaging 10-12 hours per day with a blurring of weekday and weekend days. That could lead to a lot of sedentary behavior (to which my book list could add more unless you used audible books, as I do). The concern here is that unless we also prioritize the Wellness pillar of DCI we could come out of our social-distanced isolation less well than we entered. That is why exercise coupled with emotional and spiritual well-being are so important.

I would to share some encouraging data that has just been published by Dr. Tom Rando, who spoke at our fall quarter DCI Colloquium. Tom is a professor of neurology and neurological sciences and director of Stanford's Glenn Center on the Biology of Aging. Among many other contributions, Tom and his collaborators achieved notoriety for observing that when blood from a young mouse was infused into an old mouse, properties in the young blood conferred positive

benefits on stem cell renewal in the old mouse. In a study published on April 13th in ***Nature Metabolism*** entitled *"Exercise rejuvenates quiescent skeletal muscle stem cells in old mice through restoration of Cyclin D1"* Tom and his colleagues demonstrate a positive impact on stem cell renewal in older mice with an acceleration of muscle repair because of exercise. In these studies, the mouse exercise was voluntary wheel running (which I would like to equate with road running) and the impact was notable and related to the induction of Cyclin D1 (which normally declines with age) but achieved levels that accelerated muscle repair in older animals with exercise.

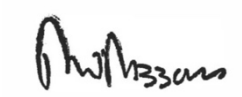
These data extend previous findings that indicate the benefits of exercise not only on muscles but on reducing the risk of dementia, improving cardiovascular health and more. Further, you can derive benefits from exercise on physiological health whether you start early in life, in midlife or older life. So, this is a good time to be sure that you are deriving those benefits – whether by walking around your living space or outdoors, or by doing other aerobic activities as well as strengthening exercises. The data to support the benefits of exercise continue to increase and even with our limitations due to social distancing, there are still plenty of opportunities. Also check out: https://arts.stanford.edu/arts-at-home/ for virtual arts and https://rec.stanford.edu/movementmotivation/ for virtual movement and exercise.

Some Final Thoughts

Last week our DCI 19 Class began spring quarter – the first done virtually and online – which is certainly not preferred. I know that everyone is working hard to accommodate to our new life order. On Wednesday evening, April 15th, we will resume our Life Transformation Reflections, one of the most important activities that takes place during the core DCI program. Since the inception of DCI in January 2015, these presentations have fostered bonding and community in extraordinary ways. Until now we never envisioned that we would (or could) do these presentations virtually but the closure of the university spring quarter left little choice, especially when the closure was carried to summer quarter. Not surprisingly our 2019 DCI Fellows have demonstrated resilience and creativity and have stepped forward to continuing sharing transformative aspects of their lives with their DCI cohort. It's a bit ironic that these transformative life reflections will take place in one of the most transformative times in history.

I am deeply grateful and appreciative of the continued engagement of our DCI Community – from alumni, current Fellows/Partners and future participants. Your commitment and support to each other and to future of DCI and, by reflection, higher education is deeply appreciated. These are challenging time across all sectors of the world as we knew it just months ago. We are experiencing first-hand the impact on higher education and also on healthcare and the impact beyond Stanford is extraordinary. Many of you will have seen the NYT article on April 15th "*After Coronavirus, Colleges Worry. Will Students Come Back*" (see: https://www.nytimes.com/2020/04/15/us/coronavirus-colleges-universities-admissions.html?referringSource=articleShare). The observations are ones we have been considering and discussing and, I believe, underscore the importance of continuing to explore the role of higher education across the lifespan. The disruptions that are now unfolding and the need for nearly all of society to think differently about the future make the connection between education, the workplace and society, ever more important. We all need to be part of this important dialogue.

Lots to think about as we look to a now uncharted future – but one where we can help provide a compass. I believe that our DCI Community can play a role in this navigation. Please share your ideas, recommendations and guidance.



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