

Thoughts of Thanksgiving

Covid Pandemic month 9 and the Community Actionable Intervention Screening Study (CAISS)

It is Thanksgiving week 2020. Covid-19 prevalence is now in exponential growth in North America as the annual US Thanksgiving Week holiday arrives. The respiratory transmission of this organism is now plainly appreciated and the changing season bringing Americans indoors plus the politicization of the measures to reduce person to person transmission are a perfect storm. Europe also has faced a similar cool weather and short light season blossoming of its disease prevalence, but parts of Asia remain better contained.

News of successful vaccine trails and introduction of several novel treatments suggests that the pandemic will be controlled by the middle of 2021. Faith in science and medicine is warranted once again. The dilemma now, however, is that for those acutely infected this holiday season, the respiratory spiral to failure that occurs in a predictable minority of acutely infected individuals still lacks an available actionable intervention. The numbers predict that the mortality of the next few months will be horrendous even as most afflicted individuals survive and recover. If prevalence of active disease elevates too high, the infrastructure to manage severe illness will be overwhelmed.

The IFN gamma signature associated with failure to control virus, and the activity of administered type I interferon in managing the disease still has me questioning whether the elephant in the room has less to do with the mechanisms of infectivity and viral proliferation than the readiness status of host defense in individual patients. There is a paradox between reductionist, mechanistic science executed to perfection with the barriers accompanying our biomedical infrastructure, and tolerance for outside the box innovation. Society desperately needs both. Every time “one models down or ratchets in” to create a manageable experimental system to generate the mechanistic data that is so useful in finding a cure, one deviates from the reality which is biology randomly at play in the community.

Last week, Regeneron was awarded emergency use authorization for its novel passive immunization monoclonal antibody cocktail. This formulation was administered to Donald Trump in combination with dexamethasone back in October. Dexamethasone is widely available, Regeneron’s monoclonal antibodies are being scaled up but not universally available, and if used late in disease can be disease aggravating.

I suggest that the “community level” question of whether the dexamethasone alone would yield indistinguishable results from the combination of dexamethasone plus Regeneron antibody, or antibody alone could be rapidly screened in a small CAISS model comparing interventions in early infected patients with emerging respiratory signs and symptoms.

My desire for a CAISS model, not surprisingly not embraced by in an era of incrementalistic, reductionist, perfectionist research since I first made my sirens call in late February 2020, will be brutally missed in the Christmas season ahead---The carnage from one more doubling in the exponential growth curve with the baseline where it is this week will be illustrative indeed.

The saeculum defines the process of societal evolution and change according to a seasonal pattern dictated by the dominant psychological character traits of the prevailing age groups (child, young adult, middle age, elder) in existence at any given moment in the cycle of the saeculum. I commend those interested to read Strauss's 1997 book, *The Fourth Turning*, to further explore this interpretation of the mechanism and pattern of societal change. I think there is an analogous process of social evolution within professional societies and institutions. The growth of institutional structure, the codification of process, establishes barriers in the name of quality. The process is predictable and dynamic. Linear thinking resists change and stifles eccentric thinking. However, the established system assures incrementalistic excellence --While the emerging solution to COVID-19 is unprecedented in its rapidity of its development and should be celebrated as a pinnacle accomplishment of modern reductionist biomedical research. It is also a feat of engineering. There is an analogy to progress in the war on cancer. My concern is simple. Structural rigidity of the system prevents alternative solutions from even being considered.

My reason for wanting a CAISS model was my reaction to the hazard of chasing anecdotes early in the pandemic. We have gambled that the definitive solutions to the pandemic will emerge in time, and it appears technology will deliver with unprecedented efficiency. Consider however that if indeed a safe and effect vaccine against covid -19 was not emerging with the new year, then the Christmas carnage of 2020 instead of being the final movement of this symphonic pandemic would prove to be only the prelude. Do also note that despite the promise of the new vaccines, possible negative consequences of immunizations with these novel agents in large populations over time remains an unknown and a calculated risk we must bear.

A CAISS model should be still be considered insurance against risk of an unanticipated bad outcome of the solutions now preparing to roll out. Availability of an actionable intervention at the community level could minimize the damage while we await the improved solutions that might be necessary and would follow.

I think a CAISS model should be written into the DNA of future pandemic preparedness—. I am confident Covid-19 is now in its final movement, but fear the price society will pay this winter of 20-21 will be severe.

A **Community Actionable Intervention Screening Study** is a proposed novel *clinical research institutional process that does not currently exist*. The model in its implemented form would adhere to all the safeguards that have been established to ensure adequate investigator and institutional oversight and individual study subject protections that are central to ethical and rigorous biomedical research. The model

would only be instituted in times of crisis at the direction of senior leadership of regional or International Institutes of Health and would allow for a streamlined process of central institutional review and data collection to make *triage tent community clinical interventional research* possible in rapid order despite the absence of formal research teams and expeditious institutional research processes in these outpatient environments. The process expedites participation in well-designed centrally directed projects with the intent to expedite priority screening evaluations of possible disease modifying interventions that are both readily available (thus actionable) and have established toxicity. Available technology to streamline the administrative, data collection process and provide centrally prepared & assembled simple instructions and treatments outpatient interventions, makes the process feasible for rapid implementation with minimalistic infrastructure and by-passes the delays caused by the daunting complexity of establishing a multicenter clinical trial at the community level. In a time of crisis, the community can be thus be mobilized to join the search for promising leads.

As a screening study, the model is intended to screen for large signals of clinical significance, that could be confirmed by a simple repetition and then used to justify traditional expensive and data intense prospective trials built off CAISS results. The premise is that modest treatment effects are not of significant impact to the community but identifying unanticipated toxicity or unexpected benefits might change the character and significance of a pandemic. The model is not intended to compete with the in-depth studies that will follow but permit identification of unanticipated signals. The Model should be adaptable to ideas emerging in the community and assess issues including specific agents, but also schedules of agents all of which may well defy preconceived expectations.

Meanwhile the teaching of the saeculum perhaps can deliver us from the divisive paralysis that of competing populist perspectives. Institutional and societal progress follows circular rhythms. We should make sure that rigid institutional process does not impair such cycling of ideas and innovation.

I share these thoughts because perhaps they can slowly reach the level of consciousness amongst increasing numbers of us, and a process of evolutionary improvement can bring us to a new level of accomplishment in the coming saeculum..

Thanks & Happy Thanksgiving 2020

Chris Nicodemus
Franconia, NH