From the Manhattan Project to COVID-19

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In March of 2015, Microsoft founder Bill Gates walked onto a TED Conference stage pulling a huge army-green nuclear war survival barrel filled with cans of food and water (1). He used this barrel to contrast the threat the world faced when he was a child and the threat the world now faced. The modern threat was not missiles but microbes. For Bill Gates, the world was not prepared for handling a pandemic resulting from a highly infectious virus. Technology could help contain the spread of the virus. To tackle a pandemic head on, governments needed to learn from how nations prepared for war. News agencies wrote stories of his talk and his prediction of a worldwide pandemic. Of course, Bill Gates was correct and is now considered one of the leading voices on the dangers of new diseases.

Not everyone has been considered in such high esteem after sounding the alarm about viral pandemics. In 2006, 9 years before Bill Gates delivered his TED talk, Dr. Michael Osterholm from the University of Minnesota spoke at a Nobel Conference, where he described a potentially dire real-life scenario resulting from the uncontrolled spread of a virus. Osterholm noted that he routinely received emails regarding his message about a lack of preparedness around the world (2). These emails fell into one of two categories, neither very complimentary. Half of them said that guys like him should be hung or at least be fired. He should be punished for scaring everyone needlessly. Guys like him were really bad. The other half said that Osterholm was part of a government cover-up. It was going to be much worse, and everyone was going to die. So why didn't he just tell the public that and be honest. But, like Bill Gates, Michael Osterholm was also correct and is now recognized as a leading voice on the dangers of new diseases.

Fifty years before individuals like Bill Gates and Michael Osterholm were spreading the word, Dr. Norman G. Anderson saw the future. Decades before the terms "proteomics" and "genomics" were introduced and long before the Human Genome Project and the Human Proteome Organization, this pioneer in 2D electrophoresis, the centrifugal analyzer, and gas and liquid chromatography techniques foresaw

Norman G. Anderson, 2006. Source N. Leigh Anderson with permission.

that we would be cataloging molecules in cells. In 1959, Anderson proposed the Cell Fractionation Project at Oak Ridge National Laboratory (ORNL), which would later become the Molecular Anatomy Program and which ultimately formed basis of the Human Protein Index (3).

But Anderson spent much of his time thinking about the problems associated with viruses, vaccines, and pandemics. His ideas about purification of viruses took root at ORNL, one of the Manhattan Project installations, in the immediate aftermath of World War II. Norman Anderson, however, did much of his thinking at a time when there were no 24-h cable networks. There was no Facebook, Twitter, Instagram, TED Talks, or YouTube, all of which were introduced in the 21st century. Looking back using today's standards, Anderson could be described as a visionary who lacked visibility.

After World War II, the nuclear weapons laboratories needed a new purpose. Norman Anderson had previously invented the zonal centrifuge at ORNL and in the 1960s proposed that this technology be adapted for another purpose. Researchers at multiple institutions were working on cancer viruses but were unable to successfully isolate them from culture. Anderson proposed the use of zonal centrifugation direct from tissues instead of growth in culture. If he could demonstrate the practicality of such an approach, it could be used for large-scale

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purification of a virus for a vaccine. Plus, the Food and Drug Administration required that any killed virus vaccine should contain no cancer cell DNA to ensure that the vaccine itself did not cause cancer. Even more important, the egg-grown vaccines during that time were often contaminated with egg proteins, which could result in anaphylaxis and even death—yet another need for virus isolation and purification. Norman Anderson to the rescue. He developed the K-II continuous-sample-flow-with-banding ultracentrifuge, which could handle 100 L batches of vaccine and which was able to almost completely eliminate contamination and the risk of anaphylactic reactions. This process is still used today.

Throughout his career, Anderson continued to believe that viruses, regardless of the source (i.e., bioterrorism, zoonotic, or natural mutation), constituted a major threat globally, yet there was no systematic approach to screening and surveillance for human viral pathogens (4). Anderson, his son Leigh Anderson, and John Gerin proposed a system for continuous surveillance of viral pathogens in human populations using large pooled samples of plasma or serum (5). Virions could be concentrated using the same ultracentrifuge technology developed at ORNL. Newly developed methods for amplifying and sequencing these viral mixtures could track the distribution of known viruses in the population, potentially detect outbreaks sooner, and identify novel or variant viruses. Norman and Leigh Anderson even considered it as a new Manhattan Project. This and other similar projects have carried on even after Norman Anderson's death in 2018 at the age of 99 years.

Norman Anderson once penned the following about a viral pandemic:

> *The current situation means that no one person or even a manageable group of persons is conversant with the basic problems and technical details of rapid detection and response to a new lethal infectious agent. Also lacking are free access to the relevant technologies, and an administrative authority with the talent and budgets now required to provide for our defense. A new agency is needed to spearhead the project, which would focus on three core objectives.*
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> *First, it must create and maintain the capability to detect and completely characterize any new virus infecting humans anywhere on the planet, and do so within days. This will require a revolution in virology, but one that is technically within our grasp. Second, it must assemble and update a comprehensive list of all human viruses (the human "virome") and determine how each functions in causing human disease. This provides a comprehensive foundation for understanding viral threats and anticipating the evolving capabilities of potential viroterrorists. Third, and most challenging, it must continuously produce and test subunit vaccines against all known human viruses, even if they are never used. Means must be developed for rapid scale-up of vaccine production on timescales commensurate with a real pandemic* (6).

At the age of 90, Anderson was asked during an interview what he would like to do. His answer:

> *What I'd like to do is ask this question. 'Why is it that if we have a new outbreak of a viral illness, say, a pandemic, there are no real plans for aborting it before it's over,' in other words, for making a vaccine in that short period of time? It can't be done now, but if it's ever going to be done, we've got to think about it very hard, and we've got to go through and say, 'do we have the technology for rapid virus identification, rapid virus isolation.' What are the barriers in making vaccines? Maybe all the hold-up is at some technological level, but it's also possible if it's all the FDA's problem, in other words, regulational—that if we have to run all the tests that are done, we simply will never get there. That's what I'd like to do, and that's actually what I am doing* (7).

If I didn't know better, I'd have thought that these words came from Bill Gates.

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