SARS-CoV-2 and How to Beat It

Dear Friends of Taconic Learning Center,

As promised, here are some of my columns on Covid-19. There were all published in the Lakeville Journal, The Berkshire Edge, and Norfolk Now. In putting them together, I realized they did not make a coherent story so I updated and modified them for clarity. It is still a work in progress and only a few of the images have been put in. I will show the rest in class.

My object is to show how science approaches such a disaster, where we succeeded and where we failed. There will be background on viruses and what they have in common. I will try to explain how our immune systems deal with them and in the case of Covid-19, why they can fail. Immunology is complex, but we will find a productive way through it.

There will be plenty of time for questions and discussion.

Best,
Rich Kessin

Some things to read:

The New Yorker, Jan. 5, 2021: *The Plague Year* by Lawrence Wright

CDC: https://www.coronavirus.gov

NIH: https://www.nih.gov/coronavirus

NCBI SARS-CoV-2 literature, sequence, and clinical content: https://www.ncbi.nlm.nih.gov/sars-cov-2/

AuthorHouse or Amazon: *The Famine of Men,* a novel about scientists who discover a new virus. It kills the cells that make testosterone. Is it all that bad really?

Our Coronavirus Pandemic

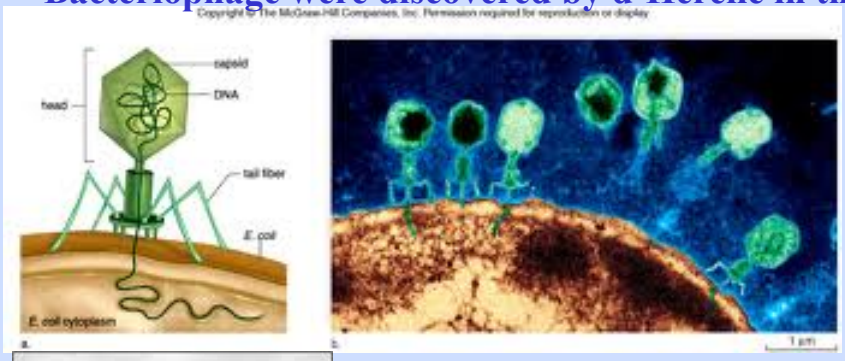
As an undergraduate I studied a virus called T4. That lab was my introduction to the power of viruses and molecular biology and working there remains one of my happiest memories. The lab was a refuge where I could do experiments that had never been done before. It had interesting people, as did the neighboring labs. My boss and mentor, Chris Matthews, was 28, barely older than I was but already an Assistant Professor at Yale. That was 1966, but all these years later Chris and I have avoided senescence or at least its worst effects.

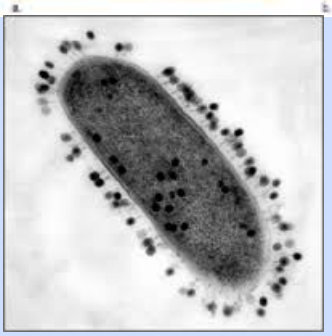
T4 has surreal form: under the lens of an electron microscope, it looks like the first moon lander and in fact it has a similar job: land on a surface and unload its cargo. It does not blast off, which would complete the metaphor, but its progeny do. This tiny beast has spindly legs and a spike that is essentially a syringe. Above the spike, where the lander's capsule would be, a hollow body contains the virus's DNA cargo. The tube contracts to blast that DNA across the cell wall and membrane and into a bacterial cell.

Despite its austere name, T4 virus has a certain cachet in the world of molecular biologists because of all the information and answers that scientists have derived from it. What is the genetic material? What are the physical properties of a gene? How do genes exchange pieces? How do simple machines like T4 turn on their genes in a particular order? T4 and similar viruses have never stopped giving answers or providing tools to study other fundamental problems in biology.

The wonderful thing about T4 is that it always worked and it worked fast: experiments lasted a day. It was perfect for an impatient undergraduate. When I added a few T4 viruses (or bacteriophage, officially) to a growing culture of *E. coli* and incubated the test tube at 98.6 degrees, nothing seemed to happen for a half an hour and then poof, the cloudy solution disappeared, leaving a slightly opalescent clear liquid. Two or three viruses per bacterial cell had become 100; and in an elegantly timed last act, the virus made an enzyme that dissolved the bacterial cell from within, liberating the new viruses. I was left with one milliliter in a glass tube. Chris noticed my astonishment and smiled. "Impressive, isn't it? How many viruses are in there, do you think?" About 10 billion, as it turned out.

Bacteriophage were discovered by d'Herelle in the 1920s





Bacteriophage were enormously important to molecular biology. The Hershey-Chase Experiment is one example.

All viruses are intracellular parasites and they have the same *modus operandi* or MO, as detectives like to say: bind to a cell, get their DNA or sometimes their RNA inside, make more viruses at the expense of the host cell, and get out. There are a few variations, but the virus has no intent or malevolence; infection is purely mechanical.

It does not matter whether the virus is SARS-CoV-2 infecting a lung cell or bacteriophage T4 infecting *E. coli,* the basic story is the same. The story gets more interesting when a virus confronts immune systems or other defenses, but in 1965, I was not concerned with the defense systems of bacteria or the immune systems of mammals. Much less was known about immunology then and we took pride in simple direct experiments.

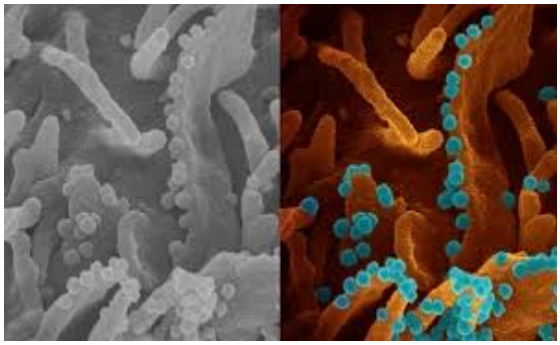
Viruses use our cells as factories to copy themselves; attempts to target them with drugs usually affect a vital function our own cells and fail. Antibiotics, then the glory of modern medicine, did not work. Still, by the 1950's and 1960's we had bested polio, measles, mumps, rubella, chickenpox, whooping cough, diphtheria and other virus diseases with vaccines. Smallpox has been eliminated. Since about 1995 new

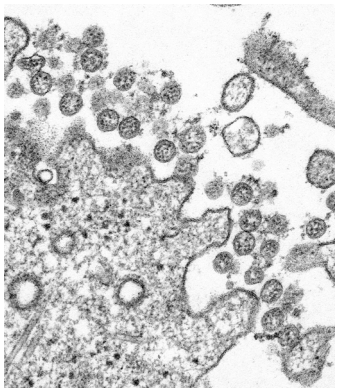
classes of drugs worked spectacularly against HIV and Hepatitis C, but these were unimaginable in 1966 as were DNA sequencing and other tools that are now routine.

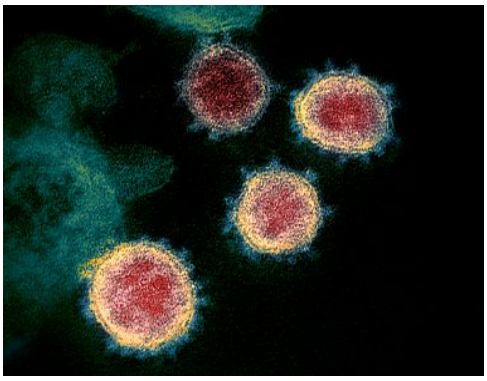
Since my column, *The Body Scientific*, began in The Lakeville Journal in 2010, there have been several viral pandemics, defined as vast infectious events covering continents. We had H1N1 influenza in 2009, H5N1 and several other flu viruses after that. We rediscovered Ebola, Zika, and Chickungunya in 2014 and 2015. Virologists thought that an influenza virus would drive the next big pandemic, chastened by the 1918-1919 flu epidemic, which is always in the background for microbiologists. We were well aware of coronaviruses because in 2003, we had SARS-CoV, which infected 8000 people and killed 800 and then disappeared. Coronaviruses also infect camels (MERS or Middle Eastern Respiratory Syndrome) and the people who handle them. MERS is exceptionally lethal to humans. Other coronaviruses just cause colds, an observation that may yet prove useful.

All human infections have a story. Diphtheria, yellow fever, anthrax and polio viruses have been fought by people like Pasteur, Salk, and Sabin. Scientists, physicians tend to be optimists, which can lead to a narrative that is triumphant: all problems can be solve. But that is never a given. We have failed so far, to make good vaccines for trypanosomes, malaria, amoeboid diseases, HIV, or Hanta virus among others.

This story of Covid-19 began with columns that I wrote from February to December 2020; I have not kept the columns intact in this narrative because with new information coming at fire hose speed, the story becomes confused. Still, some of the originals have been included in updated form, in if only to impose a sense of timing and to ask which of my assumptions or those of other people proved wrong. Errors and misconceptions are inevitable and when reconsidered they become a crucial part of science. The same thinking applies to after-action in the military after action reports and case studies in medicine. It helps to remember what we thought in January 2020 about SARS-C0V-2, if only to cheer us up about how much more we know now. That is the same experience Louis Pasteur had in the 1880's when he made vaccines to prevent anthrax, cholera, and rabies. We will meet Pasteur again.







Top Left: Coronavirus leaving a human cell. Note that the cell has many ruffles and the viruses leave from the ridges of these ruffles. The panel on the right is colored for clarity. Viruses are aquamarine. This is a scanning electron microscope image. The image on the extreme right is a transmission electron microscope image. The viruses are on the way out. Lower image is a computer colored image of SARS-CoV-2 itself. Courtesy of NIH.

A Strange Pneumonia in Wuhan

Feb 11, 2020

Of the scourges that the natural world can throw at us, a lethal new virus is one of the most frightening. At first we don't know where the virus came from, how many victims it will kill or leave debilitated, how to treat it, or how far and fast it will spread. Viral epidemics seem apocalyptic and the first response is often fear, or worse, panic. We are now in the fear stage for Wuhan coronavirus (as it was then

called), but science will chip away at its biology, while it also deploys to make vaccines.

The SARS (Severe Acute Respiratory Syndrome) infection of 2003 was kept secret for months by the Chinese authorities, giving it time to spread within China and abroad. Eventually, quarantine and public health measures suppressed it, but not before 800 people died of about 8000 diagnosed patients. The damage to trust between governments was severe. Openness is the first rule of public health otherwise no one has confidence.

Dr. Li Wenliang first noticed the "pneumonia of unknown origin" cases as part of an informal surveillance and reported these observations to his hospital colleagues in Wuhan. He was criticized by the police for spreading rumors and made to sign a confession. Such are the dangers of science in authoritarian societies. The Chinese scientists have been aggressive in efforts to study, treat, and contain the virus, but as I learned from Bob Woodward's book, *Rage,* CDC investigators were kept out despite repeated requests by Dr. Robert Redfield, the Director of our CDC to his counterpart in China, Dr. George Fu Gao. By this time in China the virus had begun to spread according to Lawrence Wright in the January 4 issue of the New Yorker, Dr, Gao was upset, some say in tears, that he could not invite the colleague we had known for a long time. By this time, Chinese and other scientists were learning that a new and very contagious virus was on the loose.

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Chinese scientists and physicians are not to blame, but rather security officials and other bureaucrats marinating in a suspicious authoritarian regime. I put the scientists in a different category; they know the problems of authority. Dr. Li Wenliang, an opthalmologist, died in early February of Covid-19 contracted while he was performing eye surgery on an elderly woman. If courageous people are silenced, it does not bode well for China, or any other country.

The treatments of the first 99 patients in Wuhan were described on January 29 in *The Lancet*, the British medical journal. Half of the patients worked in a live animal food market that was the immediate source of the epidemic, but not the original source of the novel coronavirus. According to Chinese authorities, by February, the virus has spread to all Chinese provinces. As of Feb. 4, 2020, there were 24,391 confirmed cases and 479 deaths, almost all in China. There were 1015 confirmed recoveries. There is person-to-person transmission, which is frightening. 2019nCoV (now SARS-CoV-2) is not as communicable as measles, nor as lethal as Ebola, MERS or SARS. It turned out to be bad enough.

Of the eleven Wuhan patients who died, most were older or smokers or asthmatic. The Lancet paper (a year ago now) described initial efforts to help the 99 original patients and they were extensive, including ventilation and the use of experimental drugs. The remaining patients either recovered or were no longer critical at the end of January, according to the Lancet article.

There is a lot to learn about the course of an infection; it is not a sudden event like a gunshot; Infection is a more gradual event, especially in the airways. The virus may be pushed up and disposed of by the cilia, millions of little waving oars that drive fluid upward. Virus entry may be blocked by a coating of mucous on the cells of the trachea, but sometimes the virus gets by the physical defenses. At that point the innate immune system responds, but no pathogen is without tools to battle the immune system. The virus responds by producing proteins that turn off the innate immune system.

The United States had 11 known cases as of Feb. 4, 2020—all people who had arrived recently from Wuhan and were isolated until they recovered. Local health authorities trace and talk to all contacts, providing food, thermometers, and other

necessities. Whether those 11 cases would give rise to new ones was the question at the time. [We know the answer; frankly I was hopeful at the time, but the CDC was not. They know more than I do.]. A good website to follow the epidemic is the Johns Hopkins University Corona Virus site and also The New York Times coronavirus tracker.

My late colleague, Anthony Piel, former counsel to the World Health Organization pointed out on February 6, 2020 that corona and other viruses can be detected and defeated if nations cooperate. The United States has always been a leader in Public Health and disease control, but our efforts have been curtailed. We had a government program called *Predict* that searched for novel viruses before they jump to humans, but that program has stopped, at least temporarily. We had a pandemic response plan that was shelved. We quit the WHO in an act of presidential petulance and blocked a long-standing cooperative effort that let an American lab collaborate with the Wuhan Institute of Virology with NIH support. These were mistakes. Other countries and organizations have taken up the slack.

Phylogeny figure
Wuhan caves

How We Got Here…

March 12, 2020

Caves shelter billions of bats, from Wuhan in China to Carlsbad in New Mexico, they fly out at night to feed on insects, fruit, or for vampire bats, blood. Their most extraordinary ability is echolocation; they listen in the dark and navigate by sonar, which allows them to find food, evade predators, and get back to their caves. They are mammals, warm blooded, fly long distances, leave droppings everywhere and some of them bite. We think of rabies as a disease of the past, but in the Amazon forests thousands of people die of rabies every year. There is a vaccine, but no treatment once symptoms have appeared.

Bats are also remarkable hosts for viruses and adept at spreading them. Many viral pathogens have been found in bats: Nypah virus, rabies virus, and coronaviruses, including SARS1 and SAR-CoV-2, to name a few. These viruses are often zoonotic, which means they have jumped from animals to humans through a bite, food contamination, or because humans eat bats in China and elsewhere. They are a good training ground for human viruses.

Bats hang from the roof of caves and hibernate in the winter. Their droppings accumulate as an ammonia-rich slush on the cave floor. It may sound revolting, but all that nutrient-rich guano harbors an extraordinary community of organisms, including coronaviruses and strange predatory amoebae. Scientists in Wuhan and elsewhere sample these environments, bring the samples back to the lab and determine the sequence of any viruses they can culture. They are always on the lookout for new respiratory viruses, as was Dr. Li Wenliang.

The March 12, 2020 issue of *Nature* has two dense scientific articles on the discovery of SARS-CoV-2. Though most of the data were already available, the narrative, all in one place, is gripping. The first article describes a 41-year-old man, straining to breathe, who was seen in The Central Hospital of Wuhan on Dec. 26, 2019. The second paper described four other cases and is confirmatory; they all had the same virus. The first patient had been sick for six days and reported fever, chest tightness, unproductive cough, pain, and weakness. He needed help breathing and had abnormal lungs on chest X rays and CAT scans (radiologists can see a wealth of detail in these images). Influenza was ruled out.

Twelve days after the appearance of symptoms, the patient landed in intensive care. His physicians put saline deep into one lung with a fine catheter and recovered 200 microliters of saline wash fluid— about four drops. The researchers hoped to flush out a virus, and they did—about 100 million particles. Virologists and biologists are used to large numbers, but 100 million in 4 drops (0.2ml) is a lot of virus. The paper did not say whether the patient survived.

Virus genomes are made of four nucleotide subunits: A, C, G, and U. In an a particular order they provide coded instructions for a cell to make the viral proteins. When virologists at The Wuhan Institute of Virology and another group in Shanghai sequenced the virus in their samples they found one virus with almost 30,000 nucleotides: A, C, G or U subunits. They learned that they had a new and possibly dangerous coronavirus that was related to the SARS virus of 2003, to MERS, a virus of camels, and a number of other coronaviruses viruses that harmlessly causes colds. In extensive computer comparisons—a kind of *23 and Me* for viruses—they learned that the new virus is more closely related to a bat coronavirus that they had found previously on expeditions to caves. The new virus was not identical to any known virus. On January 10 the sequence information that defines SARS-CoV-2 was deposited in a database called Genbank at the NIH and became available to the world. Dr. Barney S. Graham, working in the The National Institute of Allergy and Infectious Disease, headed by Anthony Fauci, immediately set about making a new vaccine. That work lead to the Moderna vaccine that is now being injected. (That is a good story and we will come to it.)

The physicians and scientists in China thought that the virus had made its way into a local indoor fish and seafood market where their patient and other infected people had worked. The market sold live hedgehogs, badgers, snakes, and doves, and the new coronavirus may have infected one of these species before it jumped to humans. That is still unclear.

By the middle of January the novel pneumonia had started to spread, affecting more that 100,000 people in Wuhan and had killed thousands. Hospitals were overwhelmed, despite the efforts of the authorities to build new hospitals and an enforced stay-at-home policy to break the chain of infection. At first there were not enough supplies, nurses, or physicians to treat all patients. A lockdown was declared and the contagion slowed. That is the situation that the United States and other countries may soon be in. [NB: It is *exactly* the situation we are in.] At the time, many of us realized that in most places in the United States, total lockdown would be almost impossible.

Epidemics and the speed at which a disease spreads have been studied for a long time and mathematics has made its contribution with a factor called R^0 (pronounced R naught). It describes the number of people a single patient infects, on average. With measles, R^0 is very high, 12 to 18—think of the measles infection in Disneyland a few years ago. SARS-Cov-2 is less infectious than the measles virus, and its R^0 is estimated to be 2-3. (The mutations from the UK and South Aftrica add about 0.4 to that number). R^0 for most influenza viruses is about 1.3. An R^0 value above 1 means that an epidemic will expand; reducing R^0 to 1 lets the infection smolder in the population. Reducing it to less than 1 drives the virus to extinction, as happened with the first SARS virus in 2003. Reducing R-naught is the idea behind sheltering in place, hand washing, and personal protective gear, including masks.

Most of the viruses that afflict us use RNA, not DNA, for their genomes. (I've read a lot of speculation but I do not know why.) No other pathogens use RNA and since the structure of RNA differs a little from DNA, the virus brings with it instructions to make enzymes that our cells do not have.

Enzymes are biological catalysts—one viral enzyme tacks the subunits of RNA together (an RNA polymerase). Another is a protease that cuts proteins into smaller functional units. Inhibitors that block the action of these enzymes stop the virus. Inhibitors of similar enzymes in HIV and hepatitis C, also RNA-based viruses, have essentially controlled these diseases. A recent report in the New England Journal of Medicine tested two inhibitors that block HIV but failed to stop SARS-Cov-2. Remdesivir, another drug, has been approved, but questions about remain about how well it really works. At the end of January, 2021, two new drugs that suppress inflammation have proved useful.

In March 2020, reports from China and France suggested that a combination of hydroxychloroquine, an antimalarial drug and azithromycin, an antibiotic, stops coronavirus reproduction. These reports described small tests and on closer examination the experiments proved to be a muddle. These drugs should not be promoted as an answer to the epidemic. The results are too thin a reed to grasp and their author has been called before French scientific authorities to answer questions about the reliability of his work. [In larger clinical trials the drugs have turned out to be useless.]

The ultimate preventative is a vaccine and a number have entered phase 1 trials, where they are tested for safety, dose, and the immune responses they provoke. They usually present humans with a coronavirus Spike protein, whose role is to bind to a known protein that protrudes from human cells. Starting in Spring 2020, it

will take at least a year to complete Phases 2 and 3. There will be intense pressure to speed the process up. That involves risks, but they may be inevitable. [The timing was right, and there was intense pressure, but risk was minimal, I think].

The Genome of SARS-CoV-2
Image and Legend
Important genes etc
CAVES, (WIV director portrait)
Dr. Graham

Why is this so hard?
April 2020

What the natural world can mount in the way of threats is greater than anything we could build ourselves. But when a new disease appears, we have a tendency to blame other humans, as if nature could not be so clever. The natural world creates new viral genomes by mutation or exchange between two viruses. Nature has the advantage of vast numbers of genomes, time, and selective pressure—if these viruses do not change they will be wiped out by immune systems. Joshua Lederberg, one of the founders of molecular biology, put it this way: *We live in evolutionary competition with microbes—bacteria and viruses. There is no guarantee that we will be the survivors*.

The genome of SARS-CoV2 is almost 30,000 nucleotides long and is arranged in a code that can be translated into the proteins of SARS-CoV-2. It had taken the scientists at the Wuhan Institute of Virology ten days to sequence and analyze the genome and it is all described in *Nature,* the British science journal. That the Wuhan Institute of Virology deposited the sequence so fast is not the act of people hiding information. Perhaps the functionaries of the Chinese Government, who threatened Dr. Li Wenliang after he described the disease, knew nothing about GenBank. Perhaps (my guess) the critical sequence information whizzed by them, like a fastball, low and away.

From that sequence, skilled virologists can make vaccines and begin other studies. The first to start was Dr. Barney S. Graham, who was already an expert on how to make a virus provoke the immune system. He had been working on RNA viruses for a long time and had created a vaccine against Respiratory Syncytial Virus, which causes a serious and common pulmonary virus in children. Having done the basic work, at the National Institute of Allergy and Infectious Diseases, he turned the project of to Moderna, a small company with expertise in RNA vaccines. A year later we have the results

○

- Barney Graham, MD, PhD,
- NIAID
- Vaccine and monoclonal antibody development for COVID-19, RSV, influenza, EV-D68, Nipah, Zika, HIV, Ebola, and other viral emerging pathogens
- virus neutralization
- Role of functional hierarchy and regulation of T-cell responses in immunity and pathogenesis of viral diseases
- Prototype pathogen approach for pandemic preparedness

Between now and the widespread use of vaccines, the best we can do, beyond testing and isolation, is to find drugs that slow the virus infection and protect front-line nursing and medical staff. There will probably be a new surge of virus in the fall [there is] and it would be criminal to ask nurses, doctors and critical medical staff to return to emergency rooms and intensive care units without much better protection than they have had. At this writing that supply is not assured.

Drugs that slow viruses similar to SARS-CoV-2 exist and are entering clinical trials. Remdesiver blocks the production of the RNA genomes for new viruses. More trials are necessary according to Dr. Anthony Fauci, for whom this is familiar territory from the battle against HIV. Tests of dosage and early use in the course of an infection may make remdesiver more effective, but at the moment, there are mixed

results. Another drug, baricitinib, blocks the cytokine storms and inflammation that occur days after infection. The NIH is beginning a clinical trial that asks whether the two drugs have additive benefits. Many such experimental treatments with other drugs are being done around the world including two that were announced in January 2021.

Prof. Arturo Casadevall of The Johns Hopkins Bloomberg School of Public Health speaks of layered defenses. What he has in mind is the convalescent antisera of people who have recovered from Covid-19. This approach to stopping the virus by supplying antibodies to the circulation has entered clinical trials in the United Kingdom and will soon be in double-blind trials in the United States. Anecdotal evidence (a scientific oxymoron) says that Italian patients benefitted from convalescent serum.

What seems to be happening is that post-immune serum and monoclonal antibodies work to mitigate the disease, but only if given early in the infection (January 2021).

Spread of SARS-CoV-2 in the United States

March 2020

In the United States there is increasing community spread of SARS-CoV-2 virus. Community spread means that the infection cannot be traced to a single source and that the virus is loose in the population. The first American fatalities came from a nursing home in Washington State, but the epidemic no longer has a single focal source. At the moment, growth seems to be exponential and tracks early events in Italy, which is in the midst of a crisis with 14,000 cases, 1000 dead and the country shut down. The US epidemic is at an earlier stage with more than 1629 cases and 41 dead according to the CDC. The numbers are increasing rapidly.

It is not enough to count sick people. Many people have subclinical infections and do not progress to symptoms, but are still capable of infecting others. Why such people are not seriously affected is a conundrum, or if you are an optimist, a clue. The human population is diverse, and some may have primed immune systems that protect them. An answer will eventually come into focus and it will be critical to stopping this and perhaps other epidemics. In the meantime, large swaths of the seemingly healthy population, especially in hard hit areas, must be tested for coronavirus to determine how many silent infections there are. Testing distinguishes coronavirus from other common infections and reduces hospital visits. Molecular testing also picks up the effects of hand washing and social distancing, and when drugs or vaccines become available their effects can also be studied without waiting for symptoms. There is a dire need for a reliable at-home test.

We have been monumentally bad at delivering these tests. It is not for want of scientific skill, but rather regulatory and other hurdles intrinsic to our decentralized medical system. Depletion in government agencies that normally prepare for such disasters has also had a serious negative effect. CDC made a critical error in preparing test kits. One of the reagents was contaminated by fragments of viral genome, which invalidates the test. No other tests were approved and the one was had had to be sent to CDC, which was a bad idea.. CDC is a diagnostic and a detection focused agency; they are not well equipped for large-scale manufacturing. Pharmaceutical companies have the facilities and expertise to do this. Mistakes and malfunctions will be sorted out in what I expect to be a damning after action report that also points a way forward.

An infection begins when people inhale droplets of mucus containing corona viruses, which populate the upper respiratory tract or sink more deeply into the lungs. If they survive the clearing power and barriers of the airways, they enter human cells and replicate. Their progeny descend to the throat and lungs, where they set off a strong innate immune response (see below).

For the severely sick, the task is to find hospital beds and medical staff. We need ventilators and oxygen to keep people breathing when their lungs are severely affected. Fatalities decrease when hospitals are not overwhelmed and the supportive measures of modern nursing and medicine can be brought to bear by rested workers. Exhausted nurses, physicians and staff are a recurring theme in this saga. There is not enough medical reserve of personnel in this country to deal with a pandemic such as this one. The Public Health Service has about 3500 doctors and nurses to deploy and that is not enough.

People can help decrease the rate of infection by avoiding crowds, hand washing, and other acts of hygiene, like mask wearing. Avoid surfaces that are coughed on or touched by many people: door handles, gas pumps, faucets, pens, handrails, and elevator buttons where the virus can last for days. These methods cut down the infection rate and void breaking the hospital system. It is inconvenient for everyone, but it works.

Masks, Mistakes, and Progress

July 29, 2020

We are currently arguing about masks and disease prevention. Virologists and others [including me] thought that because the Covid-19 virus is so small, it would pass through a normal surgical mask. We were wrong, fortunately. I should have known better since I used to work with a bacterial pathogen, *Legionella pneumophila* that comes packaged in membrane sacs with thousands of bacteria. That concentrated bacteria in the vesicle seem necessary for successful infection. Viruses also come in lipid droplets, which, from the point of view of the virus, may be adaptive, because they deliver a huge amount of bacteria or virus. Masks block droplets, if not single bacteria.

A review on airborne transmission by Drs. Kimberly Prather, Chia C. Wang and Robert T. Schooley was published recently in *Science.* They distinguish large infectious particles and small ones—both emerge from a cough or just breathing by asymptomatic individuals. The largest droplets, a tenth of a millimeter in diameter could contain millions of viruses but sink within the now famous six feet. These respiratory droplets contaminate surfaces where virus particles may remain infectious. These data, one must admit, are a bit fragmentary and perhaps dated, but they are helpful.

The small particles are about 1 micrometer in diameter and could contain up to 1000 viruses, which have a diameter measured in nanometers, or $1/1000^{th}$ of a micrometer [we calculated particle and virus diameters]. They accumulate in room air, are too light to sink and are easy to inhale. Minute floating particles, or aerosols, have a long history in microbiology. Louis Pasteur saw them on beams of light in dark rooms and knew in 1864 that they were a source of bacterial contamination. (Viruses had not been defined in 1864, although the word existed.)

Once a particle containing viruses enters cells deep within the lung or infects cells in the sinuses and throat, new viruses can be made immediately—lots of them. The virus contains messenger RNA that can be directly translated into new virus that come out of one cell and attack another. Think of a million virus particles attacking a small area of the lung surface, a form of viral Shock and Awe (immunology is vulnerable to military metaphors). Our immune systems, if unprepared, do not have much time to repel the attack. Remember the patient in

Wuhan who had hundreds of millions of viruses extracted from a site deep in his lung. A single cell produces thousands of viruses.

So wear a good mask and keep your distance. Clean your hands and the surfaces you touch. For the scientific paper behind these thoughts, enter: DOI 10.1126/SCIENCE.ABC6197 into any search engine. The information is readable and free to download. It is part of a movement for free access to scientific papers. DOI, by the way, stands for Digital Object Indicator—not poetic perhaps, but it gets you to the evidence.

Vaccines at Last!

July 2020

All vaccines, drug treatments, and therapies pass through clinical trials, which have many rules, derived from painful experience, to protect volunteers and patients. They have three stages. The first, which uses only a few volunteers, makes sure a vaccine or drug is safe and establishes a dose that provokes immune responses, in the case of a new vaccine. The second phase engages more volunteers and looks for adverse reactions and the activation of the immune system, but does not yet concentrate on efficacy, although with hundreds of people positive or negative effects may be obvious. The third phase tests protection from infection and requires thousands (30,000 in the current tests) of volunteers of all ages and ethnicities to get statistically significant answers. Neither physicians nor patients know whether an injection contains vaccine or placebo, hence the trials are called double blind. Well-designed clinical trials are the most critical part of solving Covid-19, but as one might imagine, they are expensive.

After a late start, the British are making progress. They have the advantage of the National Health Service and its hundreds of hospitals (one of which saved the Prime Minister, who seemed suitably grateful). The NHS uses one clinical trial protocol and a unified reporting system for several hundred hospitals that are equipped and trained to do this work. The British system is called RECOVERY (Randomized Evaluation of COVID-19 Therapy) and has already yielded results.

The NHS proved the value of dexamethasone, an anti-inflammatory steroid drug used for Covid-19 patients to control inflammation. Other data showed that hydroxychloroquine is useless. Several drugs that are useful against HIV and might have worked against SARS-CoV-2, even should have worked, did not help. According to *Science Magazine* reporter Kai Kupferschmidt, these three results changed the standard treatment of Covid-19 over a few weeks.

Interferon, a small secreted protein that affects inflammation and is induced by the innate immune system (see below), may help and is now being tested in various formulations. Like many therapies it depends on when during the infection it is given.

Monoclonal antibodies that bind to the SARS-CoV-2 virus and neutralize it are being tested, either for treatment or prevention. President Trump believes they cured him and perhaps they did, but proof awaits clinical trial completion. A recent

study (January, 2021), from Regeneron a pharmaceutical company, concluded that they are useful during the period before a patient makes his or her own antibodies, but not after.

At the end of July, the data from phase 1 and 2 trials of three vaccine candidates were released—one by Moderna, one by Pfizer, and the other by the Oxford/AstraZeneca vaccine team. All vaccines provoke a robust immune response in healthy volunteers. Both stimulated the production of circulating antibodies by B cells. They also induced T cells that recognize infected human cells and kill them. The two vaccines employ different strategies to provoke the human immune response and both have begun large phase 3 trials to determine efficacy. [Two have been approved for emergency use in the US, the UK, and other countries. The Oxford/Astrzenica vaccine is now being administered in the UK and other countries and will be available in the United States in April. There are many other candidates, but the important part of this process is the size and excellence of the clinical trials, including the power of their statistical analysis.

mRNA or Moderna and Pfizer
The adenovirus of Oxford
Virus map.
Schematic of infection
Photo of T-cell killing an infected cell.

October 26, 2020

The Ritual of Clinical Trials

On October 25, 2020, we were waiting for medical centers that administered Moderna vaccine or placebo in Atlanta, Houston or other hotspots of infection to report on the numbers of people in their trials had Covid-19. From my inquiries at the NIH, the Moderna vaccine is the only one in a Phase 3 trial that is fully subscribed—30,000 people have volunteered and have had both shots. The similar Pfizer vaccine was a little behind, but surged in the end and was approved first. Other vaccines, from Oxford/AstraZeneca, Novovax, from Johnson were all around the same stage in October 2020.

Before starting their Phase III trial, Moderna (and all others) had decided how many patients with Covid-19 had to be reported before the books were opened. At that moment investigators will know which patients had received the placebo and which the Spike coding mRNA. It was a surprisingly small number: 94 among 30,000 volunteers. As the trial went on, the number of Covid people with symptoms increased, but it was still a small fraction of 30,000. For those involved with the production of these vaccines, this is a bit of a nerve-wracking moment.

We need to know a lot about each patient. How sick are they? How long do they remain sick? Did anyone die? What is the viral load in each patient? Is the patient making antibodies? Are there side effects? Do tests in Atlanta, Toronto and Phoenix report comparable results? Have the data been checked and rechecked? A lot of information can be teased out of a well-designed trial, including fraud in reporting.

In the best of worlds, all of the sick patients would have received placebo and all of the people who received vaccine would be healthy. If both groups had an equal burden of disease, the vaccine fails. If the people who got vaccine had half the cases of the people who got placebo, that is defined as a success.

When the statistical analysis has been done and the vaccine has been shown to protect almost all of the volunteers who received active vaccine either completely or by restricting their disease to mild cases. Moderna and Pfizer prepare applications for emergency use. The FDA studies them and in mid December they say yes, both look good and give a temporary authorization.

The anxiety of waiting has historical resonance. Louis Pasteur and his colleagues made the first designed vaccine in 1879, for anthrax. There was a clinical trial at a farm in a town call Pouilly-le-fort, a village to the south of Paris. Patrice Debré a biographer of Pasteur and himself an immunologist, called it The Wager of Pouilly-le-fort. Twenty-five sheep were vaccinated and 25 were not. After two weeks the vaccinated sheep got a boost of vaccine (a lot like the coronavirus vaccine). Two weeks later all fifty sheep were given virulent *Bacillus anthracis*. Louis Pasteur was so overcome with anxiety that he could not bear to come to Puoilly-le-fort. He paced his laboratory while Emile Roux and Charles Chamberland, two of his best assistants, carried out the injections in front of a large crowd, that included a number of reporters. The world knew the importance of this bet. Success would change medicine and agriculture; failure would set back vaccines for decades. Two days later Roux sent a telegram saying, "Stunning Success!" Twenty-five sheep were dead or dying; 25 were perfectly healthy. A vaccinated cow, also survived.

At some point in the coronavirus test, the placebo arm of the study becomes ethically untenable and placebo treated patients will be notified and offered real vaccine. [a friend who was in this trial was notified and got the real vaccine in January 2021]. All treated patients, in the case of the Moderna and Pfizer vaccines, will be followed for two years to learn how long antibody and T cell responses last and to look for late side effects.

Imagine that it is early January and there is enough FDA approved vaccine to distribute. Some vaccines need to be frozen on dry ice, but Fed-Ex, UPS and other companies are prepared for frozen packages. Scientists and clinical labs know how to handle cold temperature—many of their supplies arrive on dry ice or even in liquid nitrogen. Soon the Oxford/AstraZeneca vaccine will be available and it requires only refrigeration. That will not be the rate-limiting step [it has not been so far]. The Johnson and Johnson vaccines should be ready shortly as will theNovavax vaccine, which is in Phase 3 trials. Distribution will be through established channels. I do not believe the military will be heavily used, except to vaccinate their own people and dependents (no small task) and perhaps for distribution in difficult places.

When will the general public get vaccinated? First in line are health care providers, who number between 17 and 20 million. That has started. There are 80 million essential workers and a lot of vulnerable people in nursing homes. We have a fluid situation but widespread vaccination should be available in May or June, as the CDC has been saying for some time. People may refuse to take a shot, but for the record, I

am planning to take the first one offered, as are many scientists and physicians. With Moderna and Pfizer reporting excellent phase 3 results, and other vaccines, all of which use the same Spike protein to provoke the immune system, are not far behind, May or June, may become April or May.

The worries about distribution and injection are real, but we have done this before. In 1947 a smallpox outbreak hit New York City. Within a week, millions of people had been vaccinated, an effort that remains a seminal moment in the history of public health. SARS-Cov-2 vaccination will also be such a moment. In the end, it is a question of national character. Great nations are resilient and recover from calamity.

Fortune Favors the Prepared Immune System

September 2, 2020

The first group to make a vaccine was led by Louis Pasteur who was already famous; he had a serious lab and excellent students. Pasteur had made the discovery years before that fermentation is carried out by minute organisms, either bacteria or yeast and without them wine cannot be made, bread does not rise, infections do not occur, and meat does not rot. There was extraordinary, even furious, objection, Pasteur was right in the end. Emile Duclaux, one of his students and later head of the Pasteur Institute, called the germ theory *fertile:* it gave rise to microbiology, sterile surgery, better wine and beer, and many other products. Fertile theories make people think.

The smallpox vaccine was an outlier, preceding others by about 80 years. Why the delay? It took that long to create the whole idea of microbiology and to create the germ theory of disease. Once Pasteur knew that a bacterium caused anthrax, he and his students managed to attenuate it and that gave rise to a vaccine against animal anthrax. Again the opposition was furious. Pasteur spoke and wrote beautifully and he was a battler. He knew the power of his ideas. One of his aphorisms was: *Fortune Favors the Prepared Mind.*

Fortune also favors the prepared immune system. So let's ask how that happens. Most of the Covid-19 vaccines are designed to present a SARS-CoV-2 Spike protein to the human immune system and provoke the production of circulating antibodies that bind to the virus or T-cells that recognize infected human cells and kill them. After a vaccination or illness, the immune response subsides, but many antibody-producing B cells and cell-killing T cells are banked to provide a memory of past infections. They are called memory B and T cells. When an infection with a previously encountered virus occurs, thousands or millions of banked lymphocytes start to divide and quickly produce enough antibody to block or minimize the infection. With some vaccines the banked cells last a long time (measles, yellow fever, smallpox, mumps and rubella), but with others, a few months or years (whooping cough, tetanus, influenza). Your cache of stored B cell and T cell reserves is the most important bank account you own.

The Spike protein is a long string of amino acids in a particular order. During its synthesis, the protein folds into a spike shape and is assembled into the SARS-CoV-2 virus, facing outward. The tip of the Spike protein grasps a protruding protein on the surface of human cells and the attached virus is pulled inside, where it unfolds and starts the production of more viruses. The protein that binds the viral Spike has a function of its own; it is part of a system that regulates blood pressure and is abundant in blood vessels. Injuring these endothelial cells causes blood clots, which are a major source of lethality.

The vaccines in Phase 3 testing are all products of genetic manipulation. The Oxford-AstraZeneca group uses a weakened chimpanzee adenovirus with an inserted Spike protein gene. Their Phase III trials have been completed in the UK, and the vaccine is in use. Let's hope that the NHS is good at distribution. The Chinese have four vaccines completing phase 3 and starting general use. There are many others, often with useful variations.

The Moderna and Pfizer viruses are RNA based and provide instructions for the synthesis of the Spike protein, but all in a test tube. The scientists wrap the coding mRNA in a lipid nanoparticle and inject it into human muscle, where it enters cells and uses their protein synthesis capacity to make Spike protein. The results have been published and summarized and are excellent.

All clinical trials must register with an organization at the National Library of Medicine at the NIH. Anyone can find the list of clinical trials for a disease or condition at www.ClinicalTrials.gov. If you are interested in joining a SARS-Cov-2 clinical trial, or any other, you will also find medical centers involved in the trials at that website (enter code identifier NCT04470427 for the Moderna vaccine). This site lists clinical trials for all diseases, drugs, devices, and conditions.

PfizerNBiotak results

January 2, 2021

Who Knew That Immunity Could Be So Complicated?

I can tell a good undergraduate student during a lecture on immunity, when in the middle of a complex explanation of clonal expansion of lymphocytes, a student in the second row, asks politely, "Dr. Kessin, are you sure? This sounds like bullshit to me." I have a procedure for such cases. I laugh. Then I agree with her. She was right, after all. I explain that immunology is confounding because it breaks so many conventions, that it *is* hard to believe. How is it possible that the immune system can recognize thousands or perhaps millions of individual chemicals? How can lymphocytes rearrange their genes like no other cells? The first vaccines and the idea that tiny bacteria can kill were also hard to believe in the 19th century. Immunity as a problem has taken more than two hundred years to work out and the results and ideas have been fertile along the way. We are nowhere near done yet.

Diagram of Clonal Expansion

Innate Immunity

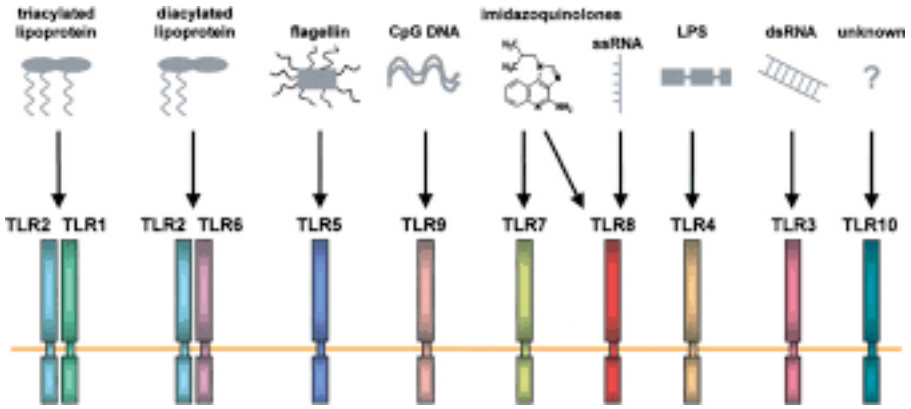
SARS-CoV-2 vaccines are on the move. I will breath easier when more companies produce vaccines, which should happen in the next month or two, turning a trickle into a healthy stream. The messenger RNA used in the first two vaccines was once an abstract concept, something that had to exist but could not be seen. That problem was solved and now we have mRNA vaccines. It's not a miracle, just hard work, imagination, and the money for basic science in universities and other elsewhere.

Where did all the money for basic science come from? In late 1944, President Roosevelt and his science advisor, Vannevar Bush, were thinking about the US government's vast wartime investment in basic science. Roosevelt asked what would happen to basic science when the war ended. Bush said it would collapse. That must not happen, Roosevelt decided, and it did not. Vannevar Bush was an engineer from MIT whose book about basic science inquiry *The Endless Frontier* became a seminal text in the history of American science and industry.

There was an enormous reorganization of government agencies after the Second World War, including of the military, intelligence agencies, diplomacy and a lot more. Sometimes lost in the bigger picture is the reorganization of science—The National Science Foundation was founded to do basic research, the NIH was organized. A huge amount of money was dispersed to universities and national laboratories, much of it for basic research, which has no immediate practical or commercial goal. If a young scientist has an idea—say, to find out what Toll Receptors do in fruit flies, there was a way (not easy to be sure) to apply to the NIH for money to test that idea and to train young scientists and undergraduates in the process. Some of the obscure titles of these projects could drive non-scientists like Senator William Proxmire a little nuts, but let's follow the idea of the once obscure innate immune system.

The innate immune system is ancient and protects even primitive cells against viruses and bacteria; it is present in amoebae, fruit flies and almost all nucleated cells. The adaptive immune system is essentially confined to vertebrates. (Bacteria have other mechanisms of defense, including CRISPR, which has recently been harnessed to cure sickle cell anemia and thalassemia).

The innate immune does not make antibodies or T cells and retains no memory of past infections. It does its best, so to speak, to contain threats and alert the adaptive immune system about pathogens roaming our airways or blood stream. In humans it is always present and a bit of a blunt instrument, but without it we are at risk because, if a person has never seen SARS-CoV-2 before, there are no memory B or T cells in the bank. The adaptive immune system requires almost 2 weeks to produce enough firepower to attack an invader with specific antibodies and T-cells.



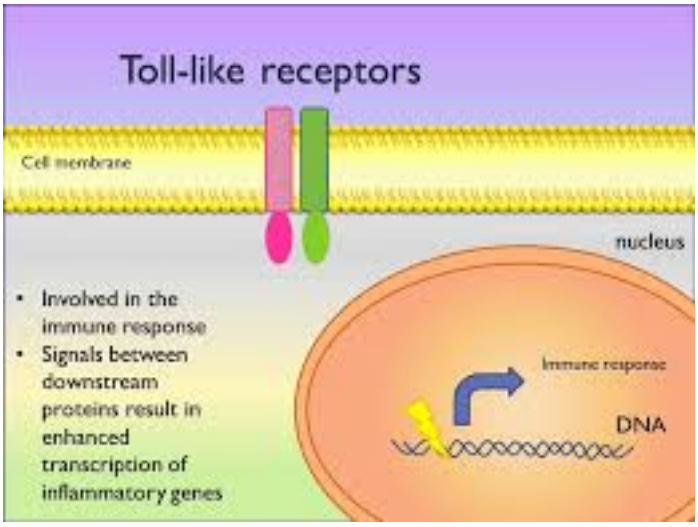
he moment, here is a large-scale effort to understand the biology of Covid-19 that might provide treatments that do not require vaccines. Is there some way to treat people who are in the early stages of infection, of even before they get infected, and stop Covid-19 from progressing? What is the difference between a few days of mild cough and a little fever and a serious respiratory infection? Could it be the innate immune system?

Imagine a lipid droplet containing thousands of virus particles inhaled by a victim. Those viruses will escape onto the mucous membrane cells in the nose, throat, or lung. The virus binds to a protein called ACE2, a landing site for the Spike protein and gets pulled into the cell, where it unwraps, and starts to copy its RNA. This sounds ominous and it may turn out that way, but in immune cells lining the throat and lungs, the alarms of the innate immune system have also sensed the invaders.

The innate immune system's antennae are 10 or 12 proteins called Toll-like receptors that face out of immune cells and sample the environment for viruses, bacteria, fungi, worms or other pathogens. Finding an RNA virus like SARS-CoV-2 sets the innate immune system off. (It hates RNA, to be anthropomorphic for a moment). The Toll-like receptor bound to the virus, tells the cell to turn on many genes involved in viral defenses. Once result is that defensive cells migrate to the site of the infection. This police force includes Natural Killer cells that attach to the

membranes of virus producing human cells and punch holes in them, which stops virus production.

When the innate immune system recognizes an RNA virus, it activates hundreds of genes that produce interferon and cytokines that limit viral damage to the host. If there is too much activation, a so-called cytokine storm can occur and that is destructive because many of these the recruited cells carry many digestive enzymes that are released, causing tissue destruction and inflammation. As part of inflammation the lung's blood capillaries leak and the lung's air sacs can fill with fluid and defensive immune cells. The process can leave a mess that one of our medical students described as the remains of a barroom brawl. Inflammation is the event that the dexamethasone treatment and other interventions, now part of Covid-19 therapy controls.



If the innate immune system functions properly in the week or two after SARS-CoV-2 infection, before the more specific antibodies and T-cells have produced enough cells or antibodies to enter the fray, it tends to limit early SARS and other infections. If that is the case, we might ask whether the DNA of very sick Covid-19 patients contains disabling mutations in genes of the innate immune system. There are hints that is the case, at least for some patients. Other patients have antibodies against their own interferon, a critical component of innate immunity and they also are more vulnerable. Do asthma patients, who have lung inflammation much of the time, do a little better with Covid-19? Perhaps, but it is a hint, not yet solid.

The dance between host and virus is complex. Viruses (measles is the best known) have genes that they use as weapons to turn off the host's immune response. SARS-CoV-2 certainly has such genes. All this viral offense can be circumvented if the victim has antibodies to the virus, such as our new vaccines are inducing.

Innate immunity is fascinating because it is ancient and present in non-vertebrates. It is *not* specific to a particular virus or bacterial infection. Is there a systematic way to turn lethal viral infections into a milder form of disease by controlling the innate immune system? That would be a fine thing for treating Covid-19 and let's hope, other infections. We do not want to go through the trauma of the past year with every epidemic.

Figure 1: Sensors of Innate Immunity: Certain proteins penetrate the membranes of immune cells. The horizontal line represents the membrane of immune cells; up is the outside of the cell, down is inside. The perpendicular lines show the Toll like Receptors, or TLRs, which bind and detect the RNA or DNA of viruses, the cell surface molecules of bacteria, fungi, or worms. All forms of nucleated cells have them; while the adaptive immune system is confined to vertebrates. The Toll-like receptors tell the adaptive immune system what is invading and give it a leg-up on the type of immunity to deploy. This image is from McInturff, Modin, and Kim, Journal of Investigative Dermatology 125:1-8, 2005.

Figure 2: When they detect a virus Toll-like receptors turn on cellular systems that induce inflammation causing the cells to produce interferon and cytokines. They bring defensive cells to the site of infection, some of which recognize virus-infected cells and kill them. This image is from picscience.net and is also available in animated form on U-tube.

Antibodies and T-cells

If the innate immune system functions during the first two weeks of an infection, it is not that adaptive immune system is doing nothing. Most B-lymphocytes in the blood, spleen, or bone marrow are dormant, their genomes are shut down, their DNA folded up. There are a lot of them and each cell has a different antibody protruding from its surface. One lymphocyte cell; one antibody, but billions of different lymphocytes.

Suppose we vaccinate the owner of these dormant B-lymphocytes with Spike protein. What happens? Mostly nothing, but among the billions of lymphocytes one or two bind a Spike fragment, like a baseball fits into a glove. A signal goes to the dormant nucleus, notifying the cell to unwrap its DNA, completely changing the look of the cell. Cells start to divide. Adaptive immunity functions by clonal expansion. In a week or more there are lots of lymphocytes, perhaps millions making antibody to the Spike protein. They are easy to spot, in lymph nodes.

There is a lot else going on. We cannot have antibodies or T cells reacting to our own proteins or we will get autoimmune diseases. Such lineages are killed off. For B cells this happens in the bone marrow, for T cells in the thymus. As the cells mature, rearrangements of DNA take place and regions of the gene are mutated to create greater antibody diversity. As B-cells mature, their antibody is released from the cell surface into the blood stream.

It takes a lot to become a decent B cell or T cell. Most of all it takes huge numbers and a great diversity of antibody. Readers may sympathize with that student who thought that immunity was all too weird. She was right, but two weeks after injection of Spike protein, we have lots of antibody and many T-cells. If the infection has not already caused terrible damage it can be controlled.

Figure: The Immune System and Clonal Expansion

Who Will Deal with a Pandemic in 2040?

Nov 22, 2020

Nothing is more valuable in the world of infectious disease than the human ability to watch for calamity coming over the horizon. That is what the CDC, the World Health Organization, various well-funded private agencies, and the specialists in the Department of Agriculture do. No organization or country is big enough to watch for all impending diseases and to do initial studies when they find one.

At this moment in the Covid-19 Odyssey, President Trump and his administration are lost on a wine-dark sea (November 2020). They have been infected but they do not know what to do or what the course of the disease will be—only that it is out of control. The administration has essentially given up without turning the matter over to the incoming Biden Administration. The Centers for Disease Control and Prevention has not been consulted in some time. CDC has taken a battering, but they know there are lives to be saved by simple public health measures before the vaccines arrive. My question here is what will happen the next time we face the next pandemic?

The scientists and physicians who will confront a new pandemic in 2040 are now in high schools around the world. Investment in people is what we did during and after World War II and after Sputnik—and that surely worked. There is nothing better to engage students in science and medicine and than a good story. I was attracted to science by a series of elegant medical detective stories by Berton Roueché, as were many other scientists and physicians. His bell-clear stories appeared in The New Yorker beginning in the 1940's and continued for decades.

The first Roueché story I read was *Eleven Blue Men.* It begins: *At about eight o'clock on Monday morning, September 25, 1944, a ragged aimless old man of eighty-two collapsed on the sidewalk on Dey Street, near the Hudson Terminal.* A little further on we learn that: *The old man's nose, lips, ears, and fingers were sky-blue.* Sky-blue? Not just a little blue, as in cold, but sky-blue? I needed to know what happened to this old guy and ten men like him.

Soon we meet Dr. Morris Greenberg and Dr. Ottavio Pellitteri of The New York Department of Public Health—the chief epidemiologist and a field epidemiologist. Dr. Pellitteri traced the blue men to bleak Bowery hotels and then to a restaurant

where they all ate. He discovered that all of these men had eaten oatmeal with sodium nitrite (used to cure meat) rather than sodium chloride (table salt). Ten of them recovered and the blue color gradually faded. One succumbed to tuberculosis, then very common. Berton Roueché's stories about health detectives from the New York Health Department and the CDC are extraordinary—there is a fine anthology called *The Medical Detectives.* If you are considering nursing, science, medicine, or journalism, or it you just like clear writing, read this book.

Decades after I read about Eleven Blue Men, I was teaching medical and Ph.D students at Columbia University's Irving Medical Center when a physician-investigator from the New York Department of Public Health called me. She needed reference for a young researcher from my lab; he had applied for a job as a disease detective on her service. We talked for a while (he got the job) and then I asked if it was true that the Health Department conference room was named for Berton Roueché. She seemed delighted that I asked. *It is*! *He is my hero. He changed my life!* She said. We talked for a while. It's good to have kindred spirits.

Mr. Roueché died in 1983, but CDC and the New York Health Department continued to solve cases and save lives. For example: *In April 1993,* a young Navaho woman on her way to a friend's wedding in Gallup, New Mexico developed trouble breathing. Physicians and nurses at the Gallup Indian Medical Center tried to help but she developed a devastating pneumonia and died. A week later so did her fiancé. Twenty-six people, Native American, Hispanic and white, most young and healthy, fell ill and thirteen died. The New Mexico Department of Public Health called the CDC.

The lungs of these patients were white with liquid that blocked X-rays. There was one clue: the X-ray looked like one from a Hantavirus patient seen years before in Korea. Hantavirus infections had never before been found in the United States but the CDC scientists knew that mice carried it and reasoned that mice around the victims' house might carry the virus. The ground under and around the house was loaded with mouse urine and feces, both with high levels of Hantavirus. When the ground dried, the wind whipped these leavings into an aerosol that the victims had probably inhaled.

I remember a seminar at Columbia University Medical Center in 1994 at which the CDC investigator explained how his team had solved the case. The lecture hall seats about 150 people, and it was packed with scientists and physicians, many standing in the aisles on the side and the spaces at the back. When the speaker showed X-rays of the victims' lungs, there was a gasp; one did not have to be a physician to

know that these people could not breathe and that Hantavirus was the cause. The case was solved in days by removing the mice and cleaning out the virus.

The novel Hantavirus was named *Sin Nombre* (no name). *Sin Nombre* virus is a nasty piece of work, one of our most worrisome, for which there is still no vaccine or treatment. Navaho elders had made the association between mice and pneumonia long before. CDC issues guidelines for diagnosis and provides training for physicians practicing in the Four Corners Region of the Southwest. Public health measures keep *Sin Nombre* at bay. Unlike SARS-CoV-2, *Sin Nombre* is not transmitted person to person. Imagine if it had been.

5 years ago, when he was 74 years old,
Fauci suited up for 2 hours each day to directly treat
Ebola patients during the outbreak.