I. LaRouche's Fourth Law

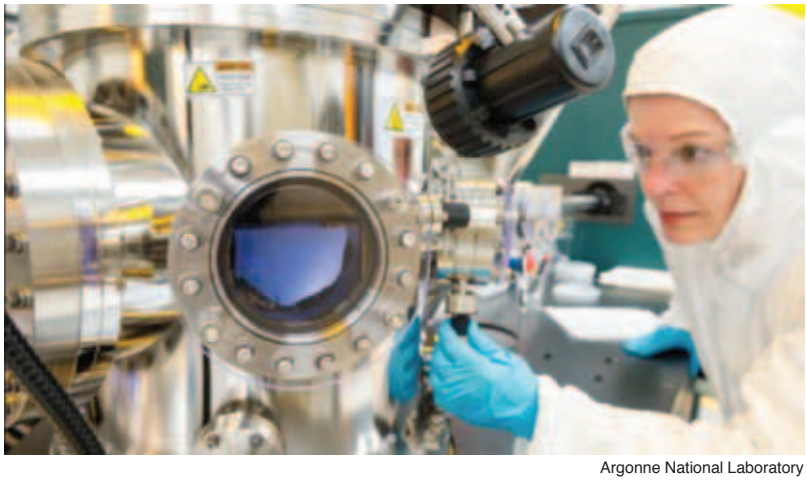
THE AMERICAN SYSTEM AT ITS BEST

Science Driver Medicine: RNA Vaccine Technology Expands Into Broader Disease Treatment

by Ned Rosinsky, M.D.

Aug. 7—COVID-19 has created a worldwide disaster of unprecedented proportions. If the onslaught of the epidemic is not checked, it may affect most the world's population, and cause tens of millions of deaths.

Yet, as frightening as this COVID-19 prospect is, there is a breathtaking worldwide surge of research currently underway to develop preventive vaccines, as well as treatments for active cases. This response to the epidemic has also been unprecedented.



Argonne National Laboratory

Ultra-high-vacuum scanning-probe microscopies, including scanning tunneling microscopy, tunneling spectroscopy, and atomic and molecular manipulation are used in the investigation of nanoscale phenomena. Here, a researcher at the Center for Nanoscale Materials at Argonne National Laboratory operates a synchrotron x-ray scanning tunneling microscope.

Some efforts are using traditional methods of extracting viral proteins and using them in a vaccine to stimulate an immune response. Some are using more advanced techniques such as taking a SARS-CoV-2 (the virus that causes COVID-19 illness) gene for a specific virus component, such as the spike protein, putting it into a harmless live virus, and using the virus to get the gene into the cells of the person. (The spike protein, on the surface of the virus, binds the virus to a receptor on the host cell.) The inserted gene is then used by the cells to make the coronavirus protein without the presence of the intact coronavirus, and this protein then stimulates an immune reaction that protects against the actual virus. And there are other advanced techniques in various stages of human testing, which I will describe below.

In the face of a general opposition to technological advance and basic science, begun with the environmental movement and accompanying anti-science Malthusianism in the 1960s, the medical research community is healthy and thriving in its response to the COVID-19 epidemic. Why are we apparently strong in medical research and so weak in other areas? It is fortunately due to a vital aspect of basic human nature. At this point in our development as a species, we all, each of us, will someday die. Our children will die. For those of us with living parents, we know that they will die.

Yet every year we read about progress in medical research. Sometimes it is agonizingly slow, sometimes it is surprisingly rapid. Currently we are going through a major transition in cancer treatment, using immune modulator mediations that improve the ability of the immune system to recognize cancer cells and attack

them, or medications that decrease the ability of the cancer cells to turn off the immune cell activity, or medications that decrease the ability of cancer cells to stimulate the growth of new blood vessels that feed the cancer, and so on. We now have hope for some tumors that previously were death sentences, such as melanoma, multiple myeloma, even lung cancer, and the field is exploding with potential new treatments.

We have not solved all the problems of cancer, heart disease, stroke, dementia, or the aging of body tissues generally, but there is a profound hope and expectation within the population that treatments, cures, and preventions for these major disorders is only a matter of time. After all, we have already seen a remarkable increase in life span in the U.S. over the past one hundred years.

This stubborn optimism is a thorn in the side of the oligarchs. They have tried to kill this optimism repeatedly, with HMO's making decisions for physicians on the basis of maximizing profits, with the right-to-die movement attempting to force through the idea that people who have a hopeless condition should be allowed to die, ravaging the medical ethic idea that every life is precious. And now we have the use of non-physicians practicing medicine independently, so potentially family practice physicians will no longer be needed.

Yet the optimism in the population continues, virtually unabated, and in the past several years it has been increasing to an unprecedented level, as the basic sciences of biochemistry, genetics, and physiology have ripened to the point that minor retooling of an established disease treatment may soon be all that is needed to produce a cure for even rare diseases, quickly and efficiently.

Yet the other problems in the economy persist, the destructive investments into derivatives, the trashing of the NASA and fusion budgets, the miserable state of our infrastructure, and the lack of a Hamiltonian type of national bank as a source of very long-term investments.

I propose that the COVID-19 epidemic and the astonishingly rapid vaccine and treatment research effort be used to spearhead a massive science driver for the economy. I propose that our weakened economy be returned to the American tradition of industrial and infrastructure development, new technology, Glass-Steagall banking regulation, and a long-term investment perspective of a Hamiltonian national bank.

These four measures will not function individually, but they are interdependent and must be accomplished simultaneously. Keep in mind, if our economy is robust, we can roll with the punches of future unexpected disasters such as COVID-19 without suffering the way we are now. This stubborn belief in the idea of progress is the characteristic feature of the anti-entropic nature of the human species, the idea that human creativity is the driver of universal progress. This idea is enshrined in our Declaration of Independence and Constitution, that we have inalienable rights, that government exists to promote the general welfare. Now is the time to bring these ideas to full fruition, to defeat the oligarchy once and for all, to finish what was started with the American Revolution against the British Empire.

The Chinese made people immune to smallpox by exposing them to small amounts of the scabs that arise over the smallpox pustules on the skin. This practice apparently goes back to the second century BCE.

Past Vaccines

Every human culture in recorded history has made attempts to prevent and treat human disease. Historical measures range from religious supplication, exorcising demons, and herbal remedies, to basic public health measures such as personal hygiene, clean water, a healthy diet, and safe working conditions. Among these efforts, the idea of providing immunity to a specific illness by exposure to a mild form of the illness dates back at least to the second century BCE.

There are indications that at that time, the Chinese were making people immune to smallpox by exposing them to small amounts of the scabs that arise over the smallpox pustules on the skin. The scabs are specific to the disease, with characteristic raised edges. The scabs were ground into a powder and inhaled through the nose. Alternatively, the material from a smallpox pus-

tule may have been taken and used for inoculation by scratching it into a person's skin. Either way would produce a smallpox infection, but it would be milder than the usual smallpox infection. Smallpox acquired naturally has a mortality of 10-30%, while smallpox acquired by exposure to the ground scabs or pustule material by skin scratch has a mortality in the range of 2%.

The Chinese Emperor K'ang, whose reign started in 1661 after he lost his father to smallpox, documented his own experience of supporting this vaccine treatment. The term "vaccine" generally refers to biological entities that produce active immunity against a particular infectious disease.

The smallpox vaccine approach used in China was further advocated in England by Mary Wortley Montagu, after she saw how effective it was in Turkey in 1717. Here she is portrayed by Jean-Baptiste van Mour.

Reports of the Chinese use of smallpox inoculation were received by the Royal Society in London in 1700, one from an employee of the British East India Company. The smallpox vaccine approach was further advocated in England by Lady Mary Montagu, daughter of an English duke, who lost two brothers to the disease and then contracted smallpox herself in early adulthood, but survived. Later in her life, while travelling with her husband in Turkey where he was British Ambassador, she happened upon a group of old women who annually inoculated large segments of the local population with smallpox pustule material either by scratching it into the arm, or making a hole in a vein with a needle and forcing the material into the vein.

Lady Montagu also noted that smallpox infection was almost unknown in that area of Turkey, and she documented her findings in a letter dated 1717. Soon afterward, her husband was recalled to England where smallpox was common, and she decided to have her 5-year-old son inoculated in Turkey. During a smallpox epidemic in London she had her second child inoculated, and she invited the king's physician to observe the procedure. The child recovered from the vaccination well and did not subsequently develop smallpox from the epidemic.

Lady Montagu discussed the vaccine procedure with the Princess of Wales, whose children were possible heirs to the throne. The Princess of Wales then asked King George I to have her children inoculated. The king agreed to the procedure for her female children but not the males, fearing that these possible future heirs to the throne might die from the vaccine. The inoculation procedure subsequently became widespread in England, and also in the American colonies.

Benjamin Franklin learned of the smallpox inoculation procedure and advocated the inoculation starting in 1730. Franklin suggested that his friend William Haberden, who was an English physician, write a pamphlet describing the procedure. The pamphlet was produced, although it was not signed by Haberden. It was distributed extensively in the American colonies as well as in England. The pamphlet provides a short list of the steps required to do the inoculation. Franklin was concerned that the vaccine was not being used widely enough, and he wrote a preface to the pamphlet in 1759, urging its use.

Benjamin Franklin, in a 1762 painting by Mason Chamberlin, an early promoter of smallpox inoculation.

Franklin on Smallpox

The pamphlet is titled, *Some Account of the Success of Inoculation for the Small-Pox in England and America. Together with Plain Instructions, By which any person may be enabled to perform the Opera-*

tion, and conduct the Patient through the Distemper.

The pamphlet then notes,

> Since at least 1730, Franklin has advocated inoculation for smallpox as "a safe and beneficial Practice." His suggestion for Dr. William Heberden's pamphlet and his own preface to it may be regarded as further efforts to persuade the people to use "a discovery God in his mercy has been pleased to bless mankind with."

Franklin's preface follows.

The Preface of Benjamin Franklin

Having been desired by my greatly esteemed friend Dr. William Heberden, F.R.S., one of the principal Physicians of this city, to communicate what account I had of the success of Inoculation in Boston, New-England, I some time since wrote and sent to him the following paper, viz.

About 1753 or 54, the Small-pox made its appearance in Boston, New-England. It had not spread in the town for many years, so that there were a great number of inhabitants to have it. At first endeavors were used to prevent its spreading, by removing the sick, or guarding the houses in which they were; and with the same view Inoculation was forbidden; but when it was found that these endeavors were fruitless, the distemper breaking out in different quarters of the town, and increasing, Inoculation was then permitted.

Upon this, all that inclined to Inoculation for themselves or families hurried to it precipitately, fearing the infection otherwise be taken in the common way; the infection inoculated in every neighborhood spread the infection likewise more speedily among those who did not choose Inoculation; so that in a few months, the distemper went thro' the town, and was extinct; and the trade of the town suffered only a short interruption, compar'd with what had been usual in former times, the country people during the seasons of that sickness fearing all intercourse with the town.

As the practice of Inoculation always divided people into parties, some contending warmly for it, and others as strongly against it; the latter asserting that the advantages pretended were imaginary, and that the Surgeons, from views of interest, conceal'd or diminish'd the true number of deaths occasioned by Inoculation, and magnify'd the number of those who died of the Small-pox in the common way; It was resolved by the Magistrates of the town, to cause a strict and impartial enquiry to be made by the Constables of each ward, who were to give in their returns upon oath; and that the enquire might be made more strictly and impartially, some of the partisans for and against the practice were join'd as assistants to the officers, and accompanied them in their progress through the wards from house to house. Their several returns being received, and summ'd up together, the numbers turned out as follows,

Had the Small-pox in the common way		Of these died		Received the distemper by Inoculation		Of these died	
Whites	Blacks	Whites	Blacks	Whites	Blacks	Whites	Blacks
5059	485	452	62	1974	139	23	7

It appeared by this account that the deaths of the persons inoculated, were more in proportion at this time than had been formerly observed, being something more than one in a hundred. The favorers of Inoculation however would not allow that this was owing to any error in their former accounts, but rather to the Inoculation at this time [of] many unfit subjects, partly through the impatience of people who would not wait the necessary preparation, lest they should take it in the common way; and partly from the importunity of parents prevailing with the Surgeons against their judgment and advise to inoculate weak children, laboring under other disorders; because the parents could not immediately remove them out of the way of the distemper, and thought they would at least stand a better chance by being inoculated, than in taking the infection, as they would probably do, in the common way. The Surgeons and Physicians were also suddenly oppress'd with the great hurry of business, which so hasty and general an inoculation and spreading of the distemper in the common way must occasion, and probably could not so particularly attend to the circumstances of the patients offered for Inoculation.

Inoculation was first practiced in Boston by Dr. Boylston in 1720. It was not used before in any part of America, and not in Philadelphia until 1730. Some years since, an enquiry was made in Philadelphia of the several Surgeons and Physicians who had practis'd Inoculation, what numbers had been by each inoculated, and what was the success. The result of this enquiry

was, that upwards of 800, (I forget the exact number) had been inoculated at different times, and that only four of them had died. If this account was true, as I believe it was, the reason of greater success there than had been found in Boston, where the general loss by Inoculation used to be estimated at about one in 100, may probably be from this circumstance; that in Boston they always keep the distemper out as long as they can, so that when it comes, it finds a greater number of adult subjects than in Philadelphia, where since 1730 it has gone through the town once in four or five years, so that the greatest number of subjects for Inoculation must be under that age.

Notwithstanding the now uncontroverted success of inoculation, it does not seem to make that progress among the common people of America, which at first was expected. *Scruples of conscience* weigh with many, concerning the *lawfulness* of the practice: And if one parent or near relation is against it, the other does not choose to inoculate the child without the consent of all parties, lest in case of a disastrous event, perpetual blame should follow. These *scruples* a *sensible Clergy* may in time remove. The *expense* of having the operation perform'd by a Surgeon, weighs with others, for that has been pretty high in some parts of America; and where a common tradesman or artificer has a number of his family to have the distemper, it amounts to more money than he can well spare. Many of these, rather than own the *true motive* for declining Inoculation, join with the scrupulous in the cry *against it,* and influence others. A small Pamphlet wrote in plain language by some skillful Physician, and publish'd, directing what preparations of the body should be used before the Inoculation of children, what precautions to avoid giving the infection at the same time in the common way, and how the operation is to be performed, the incision dress'd, the patient treated, and on the appearance of what symptoms a Physician is to be called, &c. might by encouraging parents to inoculate their own children, be a means of removing that objection of the expense, render the practice much more general, and thereby save the lives of thousands.

The Doctor, after perusing and considering the above, humanely took the trouble (tho' his extensive practice affords him scarce any time to spare) of writing the following PLAIN INSTRUCTIONS, and generously, at his own private expense, printed a very large impression of them, which was put into my hands to be distributed *gratis* in America. Not aiming at the praise which however is justly due to such disinterested benevolence, he has omitted his name; but as I thought the advice of a nameless Physician might possibly on that account be less regarded, I have without his knowledge here divulg'd it. And I have prefixed to his small but valuable work these pages, containing the facts that gave rise to it; because *facts* generally have, as indeed they ought to have, great weight in persuading to the practice they favour. To these I may add an account I have been favoured with by Dr. Archer, physician to the Small-pox Hospital here, viz.

There have been inoculated in this Hospital since its first institution to this day, Dec. 31, 1758, 1601

Of which number died, 6

Persons who had the Small-pox in the common way in the Hospital, to the same day, 3856

Of which number have died, 1002

By this account it appears, that in the way of Inoculation there had died but one patient in 267, whereas in the common way there had died *one* in *four*. The mortality indeed in the latter case appears to have been greater than usual, (one in seven, when the distemper is not very favorable, being reckon'd the common loss in towns by the Small-pox, all ages and ranks taken together) but these patients were mostly adults, and were received, it is said, into the Hospital, after great irregularities had been committed. By the Boston account it appears, that, Whites and Blacks taken together, but about one in eleven died in the common way, and the distemper was therefore reckon'd uncommonly favorable. I have also obtained from the Foundling Hospital, (where all the children admitted, that have not had the Small-pox, are inoculated at the age of five years) an account to this time of the success of that practice there, which stands thus, viz.

Inoculated, boys 162, girls 176, in all 338.

Of these died in Inoculation, only 2.

And the death of one of those was occasioned by a worm fever.

On the whole, if the chance were only as *two* to *one* [i.e., twice as many deaths from naturally acquired smallpox compared to the number of deaths from the vaccination—ed.] in favour of the practice among children, would it not be sufficient to induce a tender parent

to lay hold of the advantage? But when it is so much greater, as it appears to be by these accounts (in some even as thirty to one) surely parents will no longer refuse to accept and thankfully use a discovery God in his mercy has been pleased to bless mankind with; whereby some check may now be put to the ravages that cruel disease has been accustomed to make, and the human species be suffered to increase as it did before the Small-pox made its appearance. This increase has been more obstructed by that distemper than is usually imagin'd: For the loss of one in ten thereby is not merely the loss of so many persons, but the accumulated loss of all the children and children's children the deceased might have had, multiplied by successive generations.

B. Franklin,
of Philadelphia.

There are several aspects of this Franklin preface that are startlingly modern.

First, he gives the actual numbers generated by the studies, the cases of inoculation versus naturally acquired smallpox, and the outcomes, so the likelihood of effectiveness and adverse effects can be calculated.

Second, the numbers he accesses are in the hundreds to thousands, large enough to provide a reasonable determination of the strength of his conclusions.

Third, the gathering of the evidence of vaccination and outcomes in the initial Boston study was verified by municipal workers assigned to go door-to-door and interview patients and their families, an important attempt to eliminate bias in the reporting. They even recruited pro- and anti-vaccine citizens to accompany the municipal workers as they gathered the data.

Fourth, he contrasts the findings in Boston, where there was a major epidemic during the inoculations, and Philadelphia, where there was a less severe epidemic at the time. Both locations showed a strong effect of vaccination and a low number of deaths from the vaccine, but the results were more pronounced in Philadelphia. Franklin attempts to explain this discrepancy by pointing out that the urgency of the situation in Boston may have decreased the quality of patient evaluations prior to inoculation, as well as the quality of follow up after inoculation. Franklin thus analyzes potential weaknesses in the initial Boston study.

And fifth, by including the statistics on blacks as well as whites in the Boston study, Franklin, the political and philosophical father of the United States, more than 250 years ago demonstrated his concern for the lives, safety, and wellbeing of blacks as well as whites.

Franklin's focus on a potential weakness in his study, the discrepancy between the numbers in Boston versus Philadelphia, is a lesson sorely needed today, given the recent flurry of reports of vaccines and treatments for COVID-19 that are hailed as miraculous, prior to the completion of, or even attempt to do, competent, controlled double-blind studies. A double-blind study, considered the gold standard in modern research, involves providing the test treatment to some patients and an alternative treatment or "sugar-pill" to other patients, in which neither the patients nor researchers know who gets the treatment or the alternative until the study is over and the data is analyzed. This is done in an attempt to eliminate conscious and unconscious bias in doing the study.

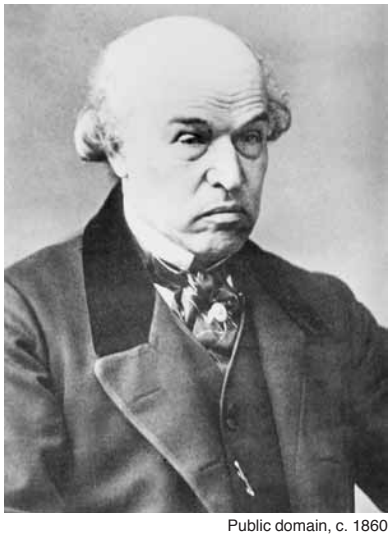
A potential weakness in the study is that the overall risk of not getting the vaccine is not addressed. This risk would be related to the likelihood of getting smallpox naturally during the individual's entire lifespan.

If smallpox were rare, then even if the chance of dying from the vaccine were much lower than dying from naturally occurring smallpox, that is, if they were both rare, that would have decreased the motivation for getting immunized. Franklin gets close to this point when he remarks that in Philadelphia, most of the naturally occurring cases were in children, because most of the adults were immune from frequent past epidemics. In contrast, in Boston the attempts to keep the disease out resulted in less frequent epidemics but the epidemics hit a larger proportion of the population when they did occur, due to decreased immunity in the population. The Philadelphia case indicates that the likelihood of getting smallpox naturally over one's lifespan is high, considerably over 50%.

Another way to approach this problem is to look at the total populations of Boston and Philadelphia during the time of the study.

Data recorded in the Johnson Cyclopedia from individual census studies, as well as estimates from the number of dwellings, put Boston at 17,000 in 1740; 15,731 in 1750; and 15,756 in 1760. The significant drop from 1740 to 1750 is discussed in the Johnson Cyclopedia, and is ascribed to smallpox and war. Philadelphia, in contrast, goes from 13,400 in 1750 to 18,758 in

Alchetron



Public domain, c. 1860

English physicians John Fewster (left) and Sir William Jenner were friends and professional colleagues.

1760, with no data from 1740. Now compare these total population figures to the total of naturally occurring cases in the Franklin tables. Boston had a total of 5,544 cases, Philadelphia a total of 3,856. Both of these numbers are a significant proportion of the total population, and they occurred during a single epidemic cycle. If naturally acquired smallpox is not rare, then Franklin's conclusions are valid.

Continuing Vaccine Efforts

The next step in the development of the smallpox vaccine came in 1768, when an English physician, John Fewster, was in the process of inoculating people with material from active smallpox cases. People who had survived an earlier smallpox infection were screened out and not inoculated, since they had acquired immunity. He expected that people who were inoculated would get the milder form of smallpox, and then would be immune to the disease.

On one occasion he inoculated a farmer, who did not have any response to the smallpox inoculation exposure. While discussing this with the farmer, the farmer said that he had in the past a severe case of cowpox. Fewster then questioned several other people who had no response to the inoculation, and he found that they all had a history of past illness with cowpox. The cowpox illness resembles smallpox, with skin abscesses and fever, but is very rarely fatal. Fewster then tried inoculating people with cowpox abscess material. He found that it was effective for causing immunity to smallpox, and was much safer than using smallpox material to do the inoculation.

This practice of using cowpox material spread rapidly in England and the American colonies. It is amusing that the English physician William Jenner, in 1798, published an article discussing the use of cowpox inoculation in a small number of patients, without reviewing any of the history of this practice in his article. When he died shortly after this publication, his biographer fabricated a story that Jenner had heard of the possibility of using cowpox from a milkmaid when he was 13, and that he got around to trying it out in 1798.

However, it is documented that Jenner had learned the practice of medicine from two physicians who were outspoken advocates of using cowpox to immunize against smallpox, so he would have been aware of the use of cowpox from his early training. Jenner was subsequently given credit for discovering the cowpox inoculation, and Fewster was forgotten, until the history was clarified several years ago.

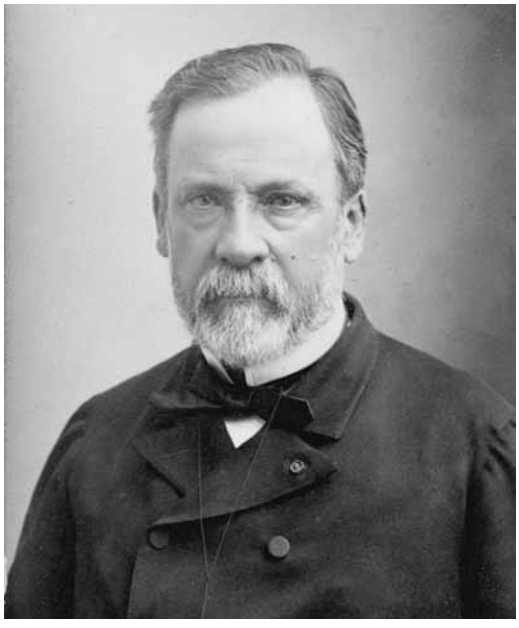
Such was the state of documentation and communication of medical knowledge in those days. Physicians kept each other informed of advances in knowledge at informal meetings in taverns. Franklin's beautiful study of the effectiveness and safety of cowpox inoculation would have been published today in a peer-reviewed medical journal, and the peer-reviewer would likely have raised the issue of the total population of the cities under consideration. Franklin, probably thinking that the total population numbers were well known at the time and not needing documentation when he wrote the pamphlet preface, would likely have complied with the peer-reviewer's comments and added the information, so that the conclusions would make sense wherever and whenever the article was read.

Of all the diseases affecting the human species, why would smallpox have been so early a focus for vaccine treatment? There are several issues that stand out in the case of smallpox.

First, it has a high mortality, and before widespread vaccination it was responsible for more deaths than any other infectious disease including the black plague.

Second, if an affected person survives the illness, he or she will never again contract the disease. Third, the distinct skin pustules and scabs are useful for identifying the disease, unlike diseases characterized by more general symptoms such as fever, cough, body pain, diarrhea, or more non-specific rash. Some diseases with non-specific symptoms may confer immunity, but since a similar-appearing disease may subsequently occur, the immunity to the first disease may go unnoticed.

Fourth, the skin pustules or scabs can be easily sampled, and therefore very small amounts can be given to healthy people in attempts to cause a milder illness which confers future immunity. Also, the samples can be manipulated, such as by drying, which may further weaken the smallpox severity with vaccination.



Louis Pasteur, as photographed by Paul Tournachon in 1878.

Pasteur

Louis Pasteur (1822-1895) initiated the next major developments in vaccine development. He was an artist as a child, preoccupied with sketching. His father urged him to enter a profession that would provide support for a family, and after some difficulties with early studies he became interested in chemistry. At age 24 he worked on the chemistry of tartaric acid, a naturally occurring substance found to be produced in the process of fermentation.

In 1815 the chemist Jean-Baptiste Biot had discovered that polarized light could undergo rotation when passing through organic substances. Biot did not draw any conclusions regarding chemical structure from these findings.

In his work with tartaric acid, Pasteur noted that tartaric acid from fermentation rotated polarized light, but tartaric acid produced from simpler substances in the chemistry lab did not rotate light. While examining crystals made from the lab-produced tartaric acid, Pasteur noticed that they were not all identical, but occurred in two forms. These two crystal forms were mirror images of each other—analogous to the difference between the right hand and the left hand—due to the angles of their characteristic facets. He separated the two groups of crystals, and he found that the two forms polarized light in opposite directions.

From this finding he developed his hypothesis that there were two chemical forms of tartaric acid, which were mirror-images of each other. Today, the property of a molecule occurring in two mirror-image forms is termed chirality. And in addition, he concluded that the tartaric acid produced in fermentation was only of one of the forms. He thus came across evidence that tartaric acid had a geometric structure which was of a form that it could demonstrate chirality, and this was before any specific knowledge regarding that form was known.

Keep in mind that at that time little was known about the geometry and structure of chemical compounds. There was no evidence that electricity is a flow of electron particles, and there was no understanding of molecular bonds between atoms.

It would have taken a visual artist such as Pasteur to appreciate and to be fascinated by this finding, someone with a strong, creative geometric imagination. This chirality may also have indicated to him that living processes were qualitatively different from non-living processes, which would play a role in his later arguments against spontaneous generation, as well as in his subsequent formulation of the germ theory of disease.

Informed by his impression of the potential complexity of living metabolism, derived from his extensive work on the chemistry of substances derived from living processes such as fermentation, Pasteur became opposed to the generally accepted idea of spontaneous generation of bacteria in rotting material. It was known that bacteria would not form in closed jars of material that were initially heated to kill any bacteria present at the start. The supporters of spontaneous generation held that the exposure to air was sufficient to generate

microscopic life, which was why the jars had to be open to promote bacterial occurrence.

To test this air-exposure hypothesis, Pasteur devised a flask containing heat-sterilized broth with a long, narrow S-shaped neck open at the end. He found that mold and other living microorganisms would not subsequently appear in the broth, even though it was exposed to the air through the long, twisted flask neck, likely due to any dust carrying microorganisms that entered the flask opening settling within the twisted neck and not traveling to the broth. This one experiment demolished the notion of spontaneous generation. Pasteur was the first to think of creating this experimental apparatus in the long history of the debate regarding spontaneous generation, and possibly it was his creative geometrical imagination that suggested using the long S-shaped flask neck.

Süddeutsche Zeitung

Dr. Robert Koch, the German bacteriologist and physician, in his laboratory, 1871.

Pasteur continued to study bacteria, in the context of an explosion of interest in microscopic life in the latter part of the nineteenth century. Pasteur became interested in the problem of the souring of wine and milk. He documented that the souring was due to microorganism growth, and he found that heating wine and milk, followed by keeping these liquids in air-tight containers, would prevent souring. This process, termed Pasteurization, became widespread throughout Europe.

Enlarging on his experience with microorganisms souring wine and milk, Pasteur developed an interest in the role of microorganisms in human and animal disease. In particular, he became interested in vaccine development. He studied the chicken cholera bacterial disease. He grew chicken cholera bacteria cultures in chicken broth, and he used these cultures to sicken chickens and study their reaction, which was usually fatal.

While Pasteur was on a month-long vacation, he assigned a research associate to continue the chicken inoculation, but the associate did not follow the instructions and went on vacation himself. When the associate returned, he used the old cultures to inoculate chickens, which caused disease but was not fatal.

When Pasteur returned, he used these recovered, healthy chickens to study inoculation from viable cultures, and he found that they were resistant to the disease. He reasoned that the failed cultures had weakened the bacteria to the point that they could not cause fatal disease, but they could still confer immunity on the host.

This was the first use of deliberately weakened microorganisms to confer immunity without causing disease. Unlike smallpox inoculation with scabs or pustule material, the chicken cholera inoculation did not cause a potentially life-threatening disease. And unlike the use of cowpox for smallpox inoculation, it was not necessary to find a similar, naturally occurring but less harmful microorganism to use for the vaccine. Pasteur presented these findings to the French Academy of Sciences in 1880.

This case of serendipity, the chance discovery that the spoiled cultures of chicken cholera would confer immunity without harming the chickens, illustrates a point that Pasteur made earlier in his career in 1854. On that occasion he had been appointed dean at the University of Lille, the site where he would be doing studies on the chemistry of fermentation. During the appointment ceremony Pasteur stated, "In the field of observation, chance only favors the prepared spirits."

Pasteur subsequently collaborated with bacteriologist and physician Robert Koch in studying anthrax, which was killing large numbers of sheep in Europe at

that time, and occasionally infecting humans. Koch identified the bacterium involved, and he gave samples to Pasteur. Pasteur weakened the anthrax bacteria with the chemical potassium dichromate, and he used the weakened bacteria to do a large experiment on sheep. He inoculated half the sheep with his vaccine, and then exposed all the sheep to anthrax. All the non-vaccinated sheep died, and none of the vaccinated sheep died. This experiment was widely publicized, and it was important for establishing Pasteur's credibility against his vociferous critics. Koch meanwhile became famous for discovering the bacteria that cause tuberculosis and cholera. He also developed techniques for pure cultures, using agar.

In a major advance, Pasteur then developed a vaccine against rabies. The causative agent is a virus, and not visible using the microscopes of that time. Pasteur modified his culture technique, using live rabbits to grow the virus, and then drying the affected rabbit nerve tissue to weaken the virus. The initial trials were controversial, but in 1886 Pasteur was able to do a trial on 350 people who had been exposed to rabies, and only one developed rabies. The success of this effort led to financial support for the creation of the Pasteur Institute, with the initial task of large-scale production of rabies vaccine.

In line with his broad experience with microorganisms causing disease, and using his personal credibility, Pasteur advocated public health measures to reduce bacterial contamination. He advised surgeons to wash their hands prior to performing surgery and between examining patients, measures that were accepted due to Pasteur's immense reputation. These measures greatly reduced surgical infections, and they also reduced puerperal fever, which can be fatal, in maternity wards.

Into the 20th Century

In the twentieth century, whole-organism vaccines continued to be developed, using either weakened or dead microorganisms. These vaccines were effective against measles, mumps, German measles, and diphtheria. The polio vaccine was developed in the 1950s, and an effective worldwide smallpox vaccine program eradicated this disease in the 1970s. The weakened live vaccines have the advantage that they can induce responses from several segments of the immune system: the host's white blood cells termed killer T-cells and helper T-cells, and the protein antibodies. The dead vaccines do not stimulate T-cell response, but do stimulate antibodies, so they are at times less effective than live vaccines. The problem with weakened live vaccines is that they may cause significant disease in people who are immune-compromised, such as people with AIDS or cancer.

To address these concerns, attempts have been made to use specific components of the offending bacteria or viruses, such as toxins or constituent proteins, which can generate a helper T-cell response as well as antibodies. These vaccines are termed second-generation.

It is important to keep in mind the progress of physics, chemistry, biology, and medical science generally, as the context for vaccine production, particularly in the nineteenth and twentieth centuries. There is also the political and philosophical climate, and the state of the cultural level. While the enormous extent of this historical field is beyond the scope of the present article, some highlights should be pointed out.

In addition to vaccines used to prevent infections, treatments for active disease using antibiotics were initiated in the twentieth century, including penicillin, found serendipitously in 1928, and tetracycline, discovered in 1957.

Before the development of antibiotics, there were no effective treatments for most bacterial infections, and bacterial infection was a major cause of infant mortality. Most combatant deaths in the Civil War were from wound infections, not from the wounds themselves. The great composers Schubert, Chopin and likely Mozart died early from infections which would today be eminently treatable—Schubert at 31, Chopin at 39, and Mozart at 35. The *Annals of Internal Medicine* published a study in August 2009 reviewing the historical data, including statements made by Mozart's contemporary family that he had a high fever and body swelling prior to death; the study concluded that he died of a Strep infection. And what a chunk of unwritten music died with him.

During the twentieth century, the physiology of many human diseases became increasingly understood, such as the discovery of insulin in 1921 and its first use in diabetes in 1922. Prior to the discovery of insulin, most childhood diabetics died in the first two years after the onset of the disease. We provide here a primer providing basic information regarding chemicals, catalysts and nucleic acids.

Continued on page 21

Chemical Reactions, Catalysts and Nucleic Acids

Chemicals are composed of atoms, and chemical reactions are changes in chemical composition. These changes may involve two chemicals combining to form one; a chemical breaking into two parts; or a part of one chemical transferring to another chemical. These chemical changes usually involve an intermediate state that has a temporary high energy level.

Think of playing catch with a football. Initially, one person holds the ball; this state is a stable low-energy state. That person then throws the ball, and while the ball is travelling through the air, the overall energy state is elevated. Then someone catches the ball, and the energy state returns to a stable low energy. Furthermore, if the thrower is standing at a higher elevation than the catcher, then the final energy state is lower than the initial state. The chemical reaction equivalent to the ball travelling in the air, is the activated intermediate state, a state of higher energy.

Now think of playing catch, where the passer and receiver are on opposite sides of a house that is located between them, and the passer and receiver cannot see each other. The passer has to throw the ball over the house, has to impart a significant energy to get the ball over the house, and has to do it in such a way that the ball ends up travelling in the correct direction, towards the receiver. If the house is more than 4 or 5 stories high, the game of catch may become impossible. This is where a catalyst comes into the picture. A catalyst lowers the required activation energy, lowers the height of the house.

In chemical reactions involving chemical changes in metabolism, an activation energy is frequently required, because the intermediate state has an imbalance in charge, a buildup of positive or negative charge, as in the process of transferring electrons between chemicals. The energy involved in this localization of charge can be lowered if, for example, the electro-negativity or electro-positivity can be dispersed over a larger area, so it is not so concentrated. Metals make good catalysts in industrial chemical processes because some of the electrons in a metal can move relatively freely, which is why metals conduct electricity easily. If a metal is in the presence of a chemical reaction, the buildup of charge in the reaction intermediate state can delocalize into the metal, so the reaction can go to completion more easily.

A related issue is that in the metabolism of living organisms, the geometries of the reactants can be quite complex, and the chemical changes are likewise geometrically complex. Using the football catch game analogy, if a set of goal posts is planted in the roof of the house, and the passer is required to throw the ball between the goal posts, then the receiver has an idea of where to expect the ball even though he cannot see the passer on the other side of the house, so the geometry is simplified. And just as in an actual football game, energy and geometry are both crucial in making a successful pass. Geometry includes orientation of the reactants, and also the shape and bulk of the reactants. In the football analogy, the position and mobility of the defense must be taken into account when the offense makes a pass.

In living organisms, the catalytic role is played by enzymes, which are generally large, specialized proteins. The proteins may have extended molecular electron orbitals that can diffuse the buildup of charge in chemical intermediates during the chemical reaction, and the proteins have specialized geometries that can fit like a hand-glove to choose the correct reactant chemicals from the biological environment, and then orient and hold the reactant chemicals in the correct positions for the reaction to occur.

The biological chemical reaction pathways function in the metabolism of the organism to utilize nutrients to extract energy, create the chemical building blocks used by the organism to grow and reproduce, and are involved in numerous other functions. The primary chemicals involved in metabolism are carbohydrates (such as sugars, starch, glycogen, and cellulose), lipids (fats and fat-soluble substances such as cholesterol), proteins, and nucleic acids. The primary elements composing these chemicals are carbon, hydrogen, oxygen, and nitrogen.

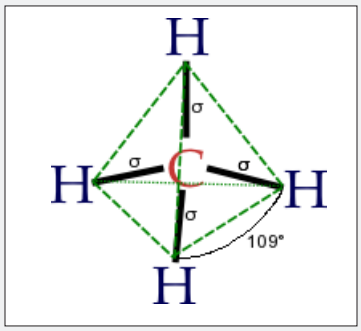
Dr. Robert J. Moon, the American physicist, chemist and engineer created a model of atomic nuclei in the 1980s using geometric symmetries based on the Platonic solids. These symmetries imply resonances that function to stabilize the physical entity. Similar geometric resonances appear to occur on the level of the atom and in chemical compounds.

The genetic material is made of DNA (deoxyribonucleic acid) both in the most primitive living organisms, the bacteria (prokariotes); and in the more advanced organisms, those with a nucleus in the cell (eukariotes). DNA is a polymer, a long molecule composed of subunits, termed monomers, which are nucleotides. A short gene may contain approximately 15 of these subunits, while a large gene may have 100 or more

subunits. Each nucleotide monomer subunit consists of one of four possible nitrogen-containing bases (think of the basic quality of the related ammonia, NH_3), a deoxyribose sugar molecule (a 5-carbon sugar), and a phosphate group (think of the acidic quality of the related phosphoric acid). The four possible nitrogen-containing bases are adenine, cytosine, guanine, and thymine.

The backbone of each DNA strand is held together by chemical bonds between the phosphate and sugar components, and the two strands are held together in the double helix by comparatively weaker hydrogen bond interactions between the pairs of bases, adenine from one strand matching with thymine from the other strand, and cytosine matching with guanine.

Methane, CH4, Tetrahedral Geometry



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A carbon atom forms 4 chemical bonds at the tetrahedral angle; hydrogen forms 1 bond.

The specificity of the gene is determined by the sequence of the 4 possible bases in the DNA polymer. DNA usually exists as a double helix of two strands of nucleic acid. The human genome consists of 3 billion pairs of bases, arranged in 23 pairs of chromosomes which are located within the cell nucleus. The DNA of bacteria ranges in size from 130,000 base pairs to over 14 million base pairs. For example, the genome of *E. coli* consists of 4.6 million base pairs arranged in a single closed loop chromosome. Most of the DNA in bacteria codes for genes, the rest being utilized for control of genetic expression.

In advanced organisms, the great majority of the DNA does not code for genes, but is involved in regulating the activity and timing of the expression of the genes. In the human, only 2% of the DNA codes for genes; the rest of the DNA is involved in gene control and expression.

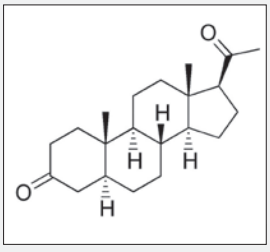
Each cell in the body has a complete set of genes, and in each particular cell only the genes that are needed for that cell type are active. You do not want fingernail genes active in your retina cells, unless you want to give someone the evil eye.

RNA (ribonucleic acid) is usually a single-strand polymer. RNA differs from DNA in several respects, with thymine replaced by another base, uracil; and deoxyribose replaced by another sugar, ribose. There is evidence that electrical currents may move along the strands of both DNA and RNA, which may have implications for enzymatic activity of these molecules, and these electrical currents may also support an antenna-like function for the molecules.

Although DNA is the genetic material in most organisms, RNA is also present in these organisms. The DNA genes, when activated, are used to create analogous copies of RNA, termed messenger RNA (mRNA). The sequence of bases in the DNA is mirrored by the base sequence in the messenger RNA. In eukaryotes this occurs in the nucleus. The mRNA then moves out of the nucleus to the cytoplasm of the cell, and it is utilized by structures in the cytoplasm, the ribosomes, to determine the production of proteins. The ribosomes are themselves composed of ribosomal RNA (rRNA) and proteins. The ribosome has an active site for the linking of protein building blocks, amino acids, to produce proteins. This active site has been shown to be portions of the rRNA itself.

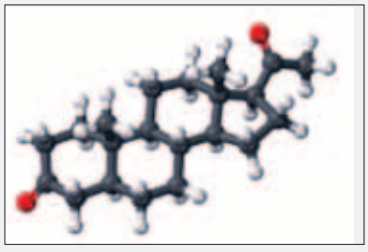
Therefore, these portions of rRNA are functioning

Three Visual Representations of the Same Chemical



Wikipedia/Jynto

Line Angle Representation



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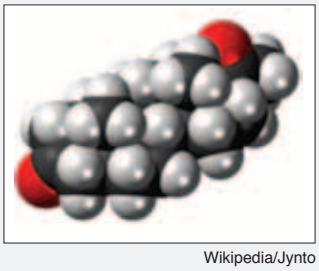
Ball and Stick Representation



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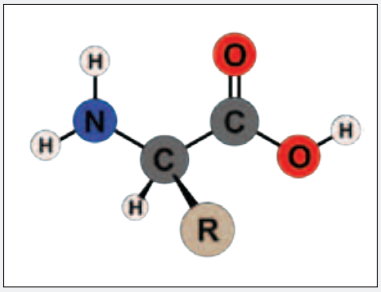
Spatial Extent of Atoms



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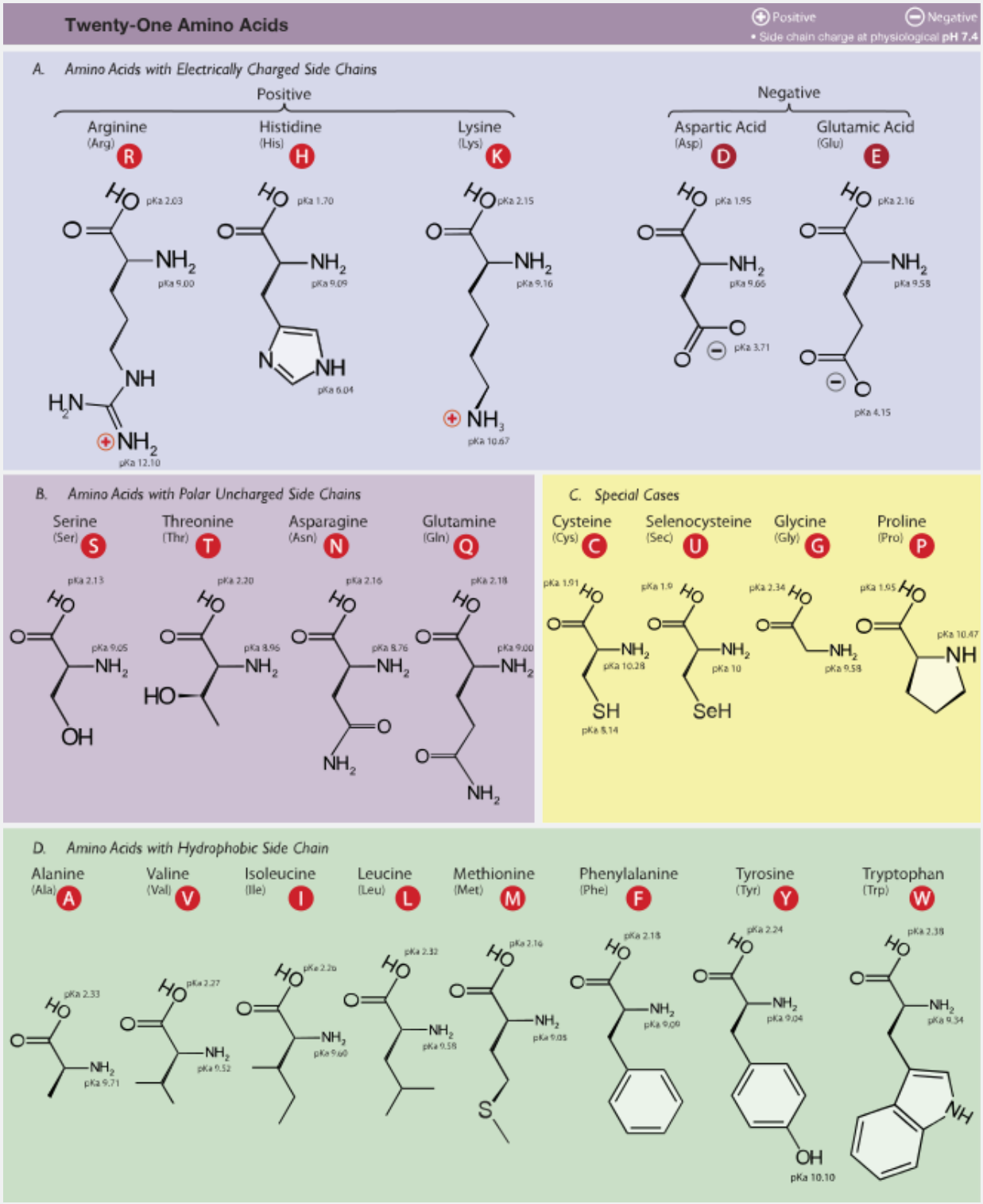
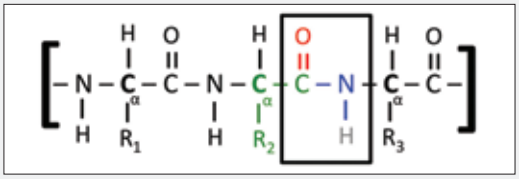
The Amino Acid Structure in Its Un-Ionized Form

The word amine refers to the NH_2 group attached to the left carbon. The acid arises from the loosely held H on the OH group attached to the right carbon. Nitrogen forms 3 bonds, oxygen forms 2 bonds. Carbon and oxygen may form a double bond, illustrated by a double straight line connecting them, which changes the tetrahedral 4-atoms bonded to carbon geometry to a flat 3-atoms bonded to carbon. The R represents the side chain, which is specific and different in each of the 21 amino acids that are the components of protein.



The 21 different amino acids found in organisms that have a nucleus in their cells (eucaryotes). These molecule diagrams use the line-angle representation. At the upper end of each molecule is the line-angle representation of the amino acid group. The R portion is the rest of the molecule, and the wide variations of the R portion are evident. Here the 21 amino acids are arranged in four groups according to the R portion chemical characteristics. These characteristics include acidity (pH), the tendency to expel a hydrogen nucleus (a proton); imbalance in charges carried (negative or positive); special cases such as cysteine that contains sulfur which can form a sulfur-ulfur bond with another cysteine in another part of the protein resulting in loops of the amino acid chain; and hydrophobic side chains which are electrically neutral over the broad extent of the R portion, so they are oil soluble but not water soluble.

Chemical Structure of the Peptide Bond



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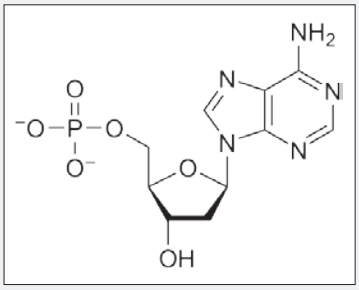
The amino portion of one amino acid attaches to the acid portion of another amino acid, and in the process an oxygen and two hydrogens are separated off.

Chemical Structure of a Nucleotide



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Nucleotides, the building blocks of DNA, have three subunit molecules: the phosphate group (at the left), which tends to liberate hydrogen nuclei into the surrounding environment and is therefore acidic; the deoxyribose sugar (in the middle) which forms a ring structure; and the nitrogen-containing base ring structure (at the right), which tends to grab hydrogen nuclei from the environment and is therefore basic.

in the role of enzymes in the production of proteins. In this case, there may be electrical currents in the rRNA that are lowering the required activation energy for the chemical reactions linking the amino acid building blocks in the formation of proteins. Again, this is similar to the use of metal surfaces in the industrial production of chemicals.

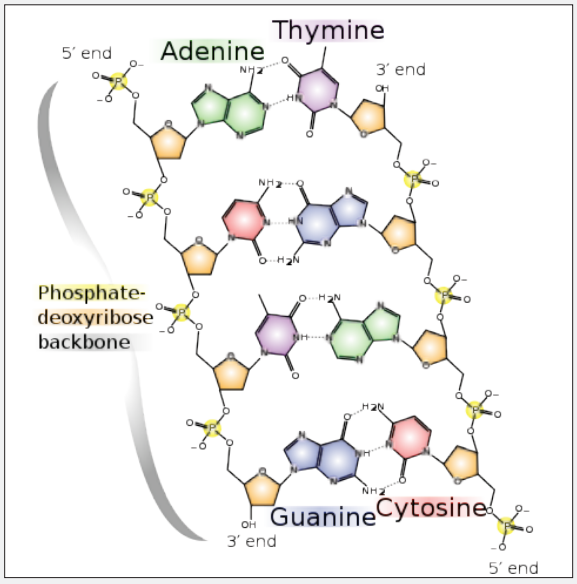
As indicated, proteins are polymers of amino acids. There are 20 different amino acids that are used as monomers in the production of proteins. In the sequence of bases in mRNA, each set of 3 bases codes for a specific amino acid. Since there are 4 possible bases, there are 4 x 4 x 4, or 64 possible sequences of 3 bases.

To implement this code, there is another type of RNA, called transfer-RNA or tRNA, which is present in the cytoplasm. Each type of tRNA has a region of the molecule that is specific for a triplet base sequence in the mRNA, and another region that is specific for a particular amino acid. Because there are more possible base triplets (64) than there are amino acids (20), some amino acids are coded for by more than one base triplet, and therefore have more than one tRNA associated with them. The tRNAs recognize specific amino acids in the cytoplasm and bring them to the ribosome. At the ribosome, the amino acids are arranged in a sequence that mirrors the base sequence code, and are linked together in chains to form proteins.

The proteins generated by the ribosomes function in numerous capacities, for example as enzymes, as structural components, as contractile components in muscle, as hormones, as antibodies in the immune system, and as immune modulators.

The amino acids are linked at the amino-acid-group end of the molecule, and the rest of the amino acid molecule projects outward from the polymer as branches

Chemical Structure of DNA



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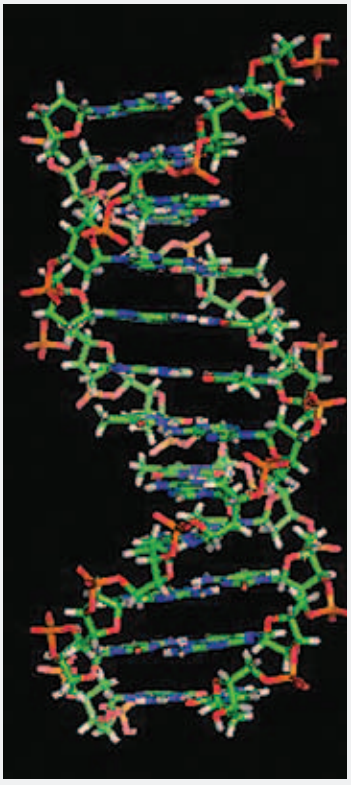
Each of the two main strands is composed of nucleotides. The nucleotides are held together by bonds between the phosphate group of one attached to the ribose of the next. The genetic code is represented by the sequence of bases. The two strands are held together by weak hydrogen bonds that link a base from one strand with a base from the other strand, shown as dotted lines. The bases can be single-ring or double-ring. There are two possible double-ring bases, adenine and guanine; and two possible single ring bases, cytosine and thymine. Due to the geometries of these bases, adenine pairs up only with thymine, and cytosine pairs up only with guanine.

A Section of Double-Stranded DNA



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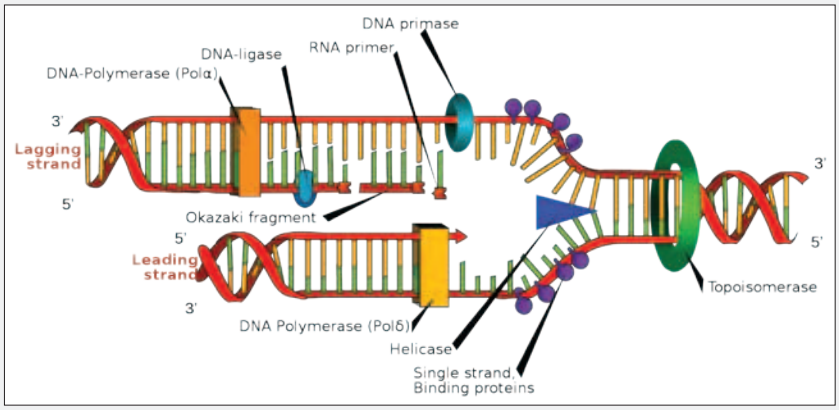
This shows the overall double helical structure.

Two DNA Strands Separating



Public Domain/ Mariana Ruiz

In the replication of DNA, the two DNA strands separate for short lengths to allow replication of the DNA, or to allow the production of mRNA for the purpose of protein production outside the nucleus on the ribosome. When the strands are separated, they are used to define the sequence of nucleotides that are brought in to form new DNA strands in DNA replication. The separated strands can also be used to define the sequence of nucleotides to form single-stranded RNA, which will be transported to the cytoplasm and used to guide the formation of proteins. RNA uses ribose as the sugar component, while DNA uses deoxyribose as the sugar component. The DNA base thymine is replaced by uracil in RNA.

from a central tree trunk. These 20 different types of molecular branches, termed side chains, have a variety of chemical characteristics. Some are acids, some bases; some are water-soluble, some are fat-soluble; some are large and bulky, some small; some are able to complex with metal ions, such as the iron in hemoglobin. One of the amino acids, cysteine, has a side chain that contains sulphur, and these cysteine side chains can form chemical bonds with each other, linking one part of the protein with another part, which changes the topology of the protein.

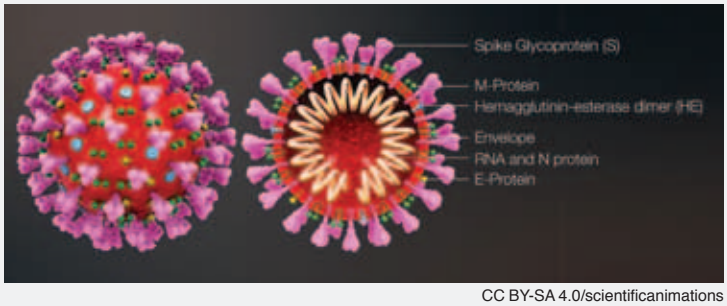
Each side chain has a specific geometric configuration. While being produced, and after being produced, the protein polymer chain undergoes further modification in the cytoplasm environment such as folding, forming helices, forming sheets, and complexing with other proteins, to assume the final geometrical functional form.

RNA is also involved in genetic regulation. It has also been found to complex with the genetic DNA to modulate the activity of the DNA genes in the nucleus.

There is some justification to hypothesize that in the early stages of the origin of life, RNA functioned as both the genes of the organisms, and as the catalysts used by the organisms for the chemical reactions involved in metabolism. The switch to DNA genes may have occurred due to the DNA being more stable in the presence of cosmic rays.

Cells contain within the cytoplasm, membrane-bound organelles. There are two important organelles within the eukaryotic cell that are relevant here—the mitochondria, which are the site of energy extraction from nutrients, and the chloroplasts, which use the energy from light to produce carbohydrates in plants by combining carbon dioxide (CO_2) and water. Both of these organelles have many characteristics of independently-living prokariotes, including the presence of their own DNA genetic material. These organelles use RNA in their own genetic expression. This is therefore yet another function of RNA in the eukaryotic cell. It appears likely that the eukaryotes started as interdependent, mutually collaborative arrangements of prokaryotes, a form of interaction which has persisted up to and including functioning in the cells of the human species.

Outside and Cross-Section Structural Views of a Coronavirus



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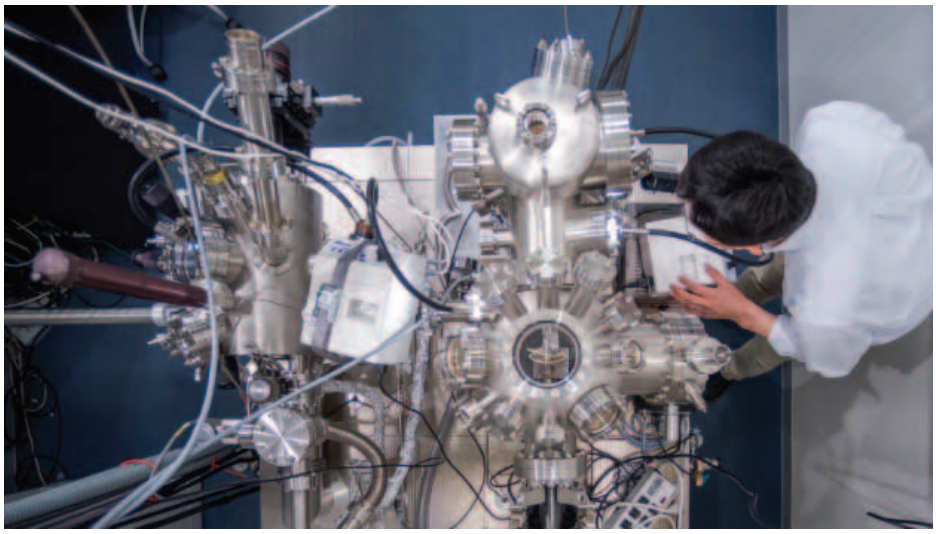
The spike proteins are labeled as spike glycoproteins because they are attached to oligosaccharides, which are short chains of sugar molecules. Other surface proteins identified are the E-protein and M-protein. The virus has an envelope, and within the envelope is the spiral representation of the viral RNA, which contains the viral genes. The spike proteins are involved in attaching the virus to the host target cell, and facilitating the entry of the virus into the cell. The spike protein forms an attachment to the lung cell at the site of the lung cell surface ACE enzyme (angiotensinogen converting enzyme). The spike protein can be used in vaccines, to trigger an antibody response to the protein, which then protects against an actual infection. The spike protein can be taken from killed whole viruses; it can be harvested from killed viruses; it can be produced in the host cells by inserting the virus gene that makes the spike protein into another virus such as an adenovirus and then infecting the host with the adenovirus to bring the gene into the host cells; or it can be produced within the host cell by inserting into the host cells lab-produced mRNA that codes for the spike protein.

Continued from page 15

DNA was demonstrated to be the genetic material in the 1950s, and the correspondence between a DNA's base sequence and the associated protein's amino acid sequence was worked out in the 1960s. Technologies for rapidly determining the sequence of bases in DNA and RNA, as well as for rapidly synthesizing DNA and RNA in the laboratory according to a specific required sequence, were developed and successively improved over the years 1960 to 1990. The human genome project, the sequencing of the entire human genome, was accomplished in an international effort from 1990 to 2003.

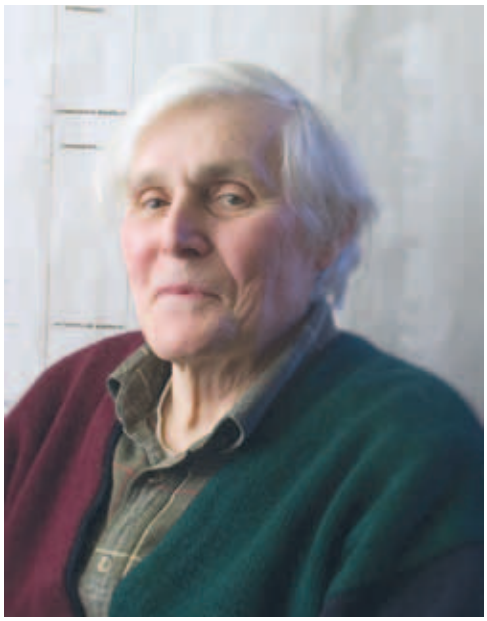


Argonne National Laboratory

At the Argonne National Laboratory Center for Nanoscale Materials, the Quantum and Energy Materials group paves the way for breakthroughs in new energy conversion and power-efficient energy technologies. Shown is a variable-temperature scanning tunneling microscope with atomic force microscopy capabilities.

The scanning tunneling microscope—enabling the visualization of individual atoms as well as the atomic structure of proteins and DNA—was invented in 1980. The scanning tunneling microscope is based on the quantum mechanics theory worked out in the early twentieth century, heralded by Einstein's paper on the photoelectric effect, which indicated that light has momentum despite not having mass, as well as Einstein's recognition that the energy in light occurs only in distinct amounts, termed quanta. Einstein's physics was heavily influenced by the work of nineteenth century mathematician Bernhard Riemann, who developed the concept of singularities, sources of input and sinks of output, determining fluid and potential flows in higher-level geometries.

Superconductivity, the flow of electricity with zero resistance, was discovered to occur in ultra-low temperature materials in 1911 by Dutch physicist Heike Kamerlingh Onnes, and has been used widely to produce the powerful electromagnets needed for MRI imaging, particle accelerators, beam spectroscopy, and magnetic confinement in the Tokamak and other experimental fusion energy machines. In 1924 Einstein collaborated with Satyendra Nath Bose to formulate a theory indicating that certain gases could condense at low temperatures to form a superconducting state. The first demonstration of this Bose-Einstein superconducting condensate took place in 1995.



CC/Don Hamerman, 2004

Carl R. Woese (1928-2012) formulated a theory of rapid initial origin of life based on the concepts of gene sharing among numerous species of primitive bacteria-like organisms.

In the later 1990s, Carl Woese, a geneticist with an interest in the origin of life, used the results of the genetic mapping of bacteria that had become available from the DNA sequencing technology, and the results of the Bose-Einstein superconductivity demonstration, to formulate a theory of rapid initial origin of life based on the concepts of gene sharing among numerous species of primitive bacteria-like organisms. The gene-sharing is modeled as a strongly collective effect in the early ecology, an effect that bears some resemblance to the collective effect in superconductivity. For example, if one species of

bacteria developed a gene that can perform photosynthesis efficiently, that gene could be transferred to other species rapidly, so the entire ecology would benefit, resulting in rapid collective evolution.

Recent, Current and Future Vaccines

Since 1997, DNA and RNA techniques have been developing that use the genes of the offending microorganisms in the vaccines. When used to produce immune responses, these are termed third-generation vaccines.

Furthermore, because RNA plays numerous roles in the normal functioning of cells, these genetic techniques provide opportunities to develop treatments for a wide variety of genetic-related disorders. Keep in mind that some cancers, heart diseases, and even longevity tend to run in families, indicating that there may be genetic factors involved.

There are three major types of RNA interventions. RNA may be given to inhibit specific DNA genes. RNA may be used to inhibit specific proteins. And RNA may be used to produce proteins directly by taking the role of messenger RNA (mRNA) on the ribosome.

There are two main types of genetic intervention that inhibit specific nucleic acids. The first is single-strand, short DNA, which is complementary to the targeted gene, termed antisense oligonucleotides (ASOs), consisting of 15 to 25 nucleotides (the units that make up DNA and RNA). The second is double-stranded RNA that interferes with DNA expression, and it is termed interference RNA or iRNA.

The ASO can stop naturally produced mRNA from being translated into protein by inhibiting the mRNA at the ribosome, or by causing the mRNA to degrade. In 2018 an ASO, inotersen, was approved by the U.S. Food and Drug Administration (FDA) for treatment of hereditary ATTR amyloidosis (familial amyloid polyneuropathy), a human disease characterized by the buildup of abnormal proteins in the nervous system, heart and other organs, which is progressive and may be fatal.

ASOs also operate by affecting splicing, which is the process by which an mRNA is changed to its final functional form. In 2016 two treatments of this type were approved by the FDA—nusinersen, which treats spinal muscular atrophy, a lethal inherited condition; and eteplirsen, used for treating Duchenne muscular dystrophy (remember the Jerry Lewis telethons of the 1950s-1960s). Eteplirsen blocks only a portion of the mRNA, which allows the production and normal activity of a part of the protein, but it blocks the production of the pathological portion. Eteplirsen is termed a morpholino oligomer due to modifications of the ribose sugar component in the RNA, which improves targeting and inhibits the cell's nuclease enzyme from degrading the medication. There are ASO medications in early clinical trials for the treatment of numerous other conditions, including Alzheimer's Disease, Huntington's Disease, and Amyotrophic Lateral Sclerosis (ALS).

CDC

A 26-year-old with Duchenne Muscular Dystrophy, a genetic disorder that causes muscle wasting. Children with DMD usually die of cardio-respiratory failure, but with stem cell therapy, this young man has not lost muscle power for five years and his heart and lung muscles and the upper half of his body are working well.

The iRNA involves double-strand RNA, which causes the degradation of the target pathological mRNA before it can be used to code for a protein. The iRNA complexes into a hybrid with the target mRNA, and activates an enzyme present in the cytoplasm, RNase H, which recognizes DNA/RNA hybrids in the cytoplasm and degrades the RNA. The iRNA is more difficult than single-stranded RNA to get into the target cell, but techniques involving packaging it in small membrane-bound vesicles have been effective. Another treatment for hereditary ATTR amyloidosis that was approved in 2016, patisiran, is of this type.

There are RNA treatments that use an RNA to target specific proteins. These RNAs are termed RNA aptimers. A treatment for age-related macular degeneration,

pegaptanib, uses this technique to decrease the activity of vascular endothelial growth factor (VEGF), a protein that stimulates the growth of blood vessels in the eye. Overactivity of VEGF causes blindness by the abnormally increased growth of blood vessels that interfere with retinal activity.

In the area of vaccines and cancer treatments, RNA therapies are used as mRNA to enter cells, engage the ribosomes, and produce specific proteins. This is a vast area of development over the past 10 years. RNA treatments of this type appear promising for the treatment of melanoma and other cancers.

Vaccines made from mRNA produce the antigens required for the stimulation of immunity indirectly, within the cells and utilizing the ribosomes in the cells. This process increases the speed of vaccine production because there is no need to grow the live microorganisms on cell cultures or fermentation processes, and then harvest the antigen from the virus, which requires extensive purification steps. The use of mRNA also offers increased reliability and scalability. The production platform is standardized, and all that is required for a change to another vaccine is the amino acid sequence of the new target antigen. This sequence is then used to produce the required mRNA, which is used for the vaccine. This eliminates the need for antigen-specific production facilities.

Other advantages of mRNA vaccines include post-translation natural modifications of the antigen in the cytoplasm, which mimic the situation in actual viral replication and increase the effectiveness of the antigen; and the use of multiple mRNAs in the vaccine for the production of multiple viral proteins that may be involved in multiplexing or consolidating into a single multi-protein antigen which is closer to the actual viral infection effect, and is therefore more effective as an antigen.

A COVID-19 Vaccine

There are currently three leading companies involved in clinical trials of SARS-CoV-2 vaccines using mRNA: Moderna in Cambridge, Massachusetts; BioNTech in Mainz, Germany in collaboration with Pfizer; and CureVac, in Tübingen, Germany. Moderna is in the lead, and it is now in Phase 3 testing, with possible final FDA approval for use by as early as November/December. BioNTech started an initial trial of its mRNA COVID-19 vaccine in April in Germany, and in May in the U.S. CureVac plans to begin Phase 1 in August. Since the start of its COVID-19 vaccine program, Moderna has been working directly with staff at the Institute of Allergy and Infectious Diseases (NIAID) at the National Institutes of Health (NIH).

Moderna has taken the lead by rapidly reformulating work that it used earlier on other viral diseases, which demonstrates the efficiency and flexibility of this approach. Moderna is now in Phase 3 testing of its vaccine, to evaluate safety, reactogenicity, and immunogenicity. Moderna's Phase 3 is placebo-controlled, and it will involve 30,000 participants. The endpoints of Phase 3 are the prevention of SARS-CoV-2 infection, the prevention of symptomatic COVID-19, and the prevention of hospitalization from COVID-19. Based on the Phase 1 and 2 trials, the dose of vaccine chosen to maximize effect and minimize adverse reactions is 100 micrograms (mcg), with a schedule of 2 doses given 28 days apart. Phase 3 participants will receive either two doses of 100 mcg, or two doses of a placebo.

Moderna has produced the required vaccine supply for Phase 3. With the 100 mcg dose, Moderna is on track to produce 500 million doses of the vaccine per year, and possibly 1 billion doses per year from its U.S. plant, in collaboration with the Swiss pharmaceutical company Lonza Group. Lonza has started manufacturing the vaccine.

The FDA requires 3 phases of testing to qualify for its approval of a new medical treatment.

The FDA defines Phase 1 as, "Researchers test an experimental drug or treatment in a small group of people for the first time. The researchers evaluate the treatment's safety, determine a safe dosage range, and identify side effects."

In Phase 2, "The experimental drug is given to a larger group of people to see if it is effective, and to further evaluate its safety."

In Phase 3, "The experimental study drug or treatment is given to large groups of people. Researchers confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow the experimental drug or treatment to be used safely."

The plan for each phase must be approved by the FDA prior to initiation. After the completion of Phase 3, the experimental data is presented to the FDA for final consideration of approval for use. The FDA may approve the use, delay decision and request additional data, or deny the request.

Funding for the Moderna COVID-19 vaccine devel-

opment includes support from the Biomedical Advanced Research and Development Authority (BARDA), a division of the Office of the Assistant Secretary for Preparedness and Response (ASPR) within the U.S. Department of Health and Human Services.

The Moderna COVID-19 vaccine utilizes mRNA-1273, which is an mRNA coding for a perfusion-stabilized form of the SARS-Cov-2 spike protein. This target antigen was selected by Moderna in collaboration with the Vaccine Research Center (VRC) at NIAID. The initial batch of mRNA was funded by the Coalition for Epidemic Preparedness Innovations, and it was produced on February 7, 2020. After analytic testing, it was sent to NIH on February 24, 2020, which was just 42 days after selecting the antigen. The Phase 1 testing started on March 13, 2020, which was 63 days after selecting the antigen.

Moderna currently has 9 viral vaccines under development. There are 6 vaccines for respiratory infections: respiratory syncytial virus (RSV) vaccine for older adults (mRNA-1777 and mRNA-1172 or V172 with Merck); RSV vaccine for young children (mRNA-1345); human metapneumovirus (hMPV) and parainfluenza virus type 3 (PIV3) vaccine (mRNA-1653); COVID-19 vaccine (mRNA-1273); and influenza H7N9 (mRNA-1851). There are 2 vaccines for infections transmitted from mother to baby: cytomegalovirus (CMV) vaccine (mRNA-1647); and Zika vaccine (mRNA-1893 with BARDA). There is 1 vaccine against a highly prevalent viral infection: Epstein-Barr virus (EBV) vaccine (mRNA-1189).

The current status of Moderna's vaccines in process are as follows: Phase 1 has shown positive results in 7 vaccines (H10N8, H7N9, RSV, chikungunya virus, hMPV/PIV3, CMV, and Zika). The CMV vaccine is currently in Phase 2 dose-confirmation study. The Zika vaccine, currently in Phase 1, was granted FDA Fast Track status in August of 2019.

In the area of cancer treatment, Moderna has the following studies in place. A cancer vaccine for melanoma is in Phase 2 (mRNA-4157), and this same mRNA is in Phase 1 in combination with pembrolizumab for inoperable solid tumors. For advanced solid tumors or lymphoma, Moderna has a Phase 1 with mRNA-2416, and for relapsed or refractory solid tumors, Phase 1 with mRNA-2752.

Moderna points out that there are 7,000 rare diseases affecting more than 300 million people worldwide, including 30 million people in the U.S. However, there are approved treatments for only 5 percent of the rare diseases. Many of the rare diseases are caused by defects or deficits of specific proteins produced by liver cells. Due to the low incidence of each of these rare diseases, there is insufficient research to address each of these conditions. The technique of mRNA greatly improves the efficiency of treatment, by providing the liver with the mRNA to produce the needed protein.

For example, for the treatment of the disease methylmalonic acidemia, which involves a missing normal enzyme, Moderna has a Phase 1-2 ongoing with mRNA-3704 and mRNA-3927 to produce the missing normal enzyme. Work is being done to produce other missing enzymes in the diseases propionic acidemia, phenylketonuria (PKU), and Fabry disease.

Moderna was founded in 2010 by Harvard scientist Derrick Rossi, who had an interest in stem cells and using mRNA to cause dedifferentiation of cells, followed by differentiation into various types of cells. Initial attempts to produce mRNA for chronic diseases in collaboration with major pharmaceutical companies were not successful, due to adverse effects of the mRNA and difficulties in getting mRNA into target cells.

In 2014, Moderna changed its focus to vaccine production. By 2018, the initial hurdles were largely overcome, and the current COVID vaccine development has passed NIH safety requirements for human trials. In December 2018, Moderna raised $600 million in an IPO for 8% of its stock, implying an overall valuation of $7.5 billion. In April 2020, BARDA allocated $483 million to support Moderna's COVID-19 vaccine program. In May 2020, Moderna board member Dr. Moncef Slaoui left the company and became the Chief Scientist for Operation Warp Speed, the Trump administration's leading effort to rapidly develop a COVID vaccine. If Moderna's COVID vaccine is successful, it will be Moderna's first finalized product to be approved for human use.

There are other COVID-19 vaccines that are in advanced states of development. The University of Oxford is working with AstraZeneca on a vaccine that uses a weakened adenovirus, which is a common cold virus. The researchers have put genes from the SARS-CoV-2 that code for the spike protein into the adenovirus. The adenovirus is modified so that it cannot replicate. The aim of the vaccine is to have the adenovirus bring the spike protein genes into the cells of the person vaccinated; the spike genes then produce spike protein, and

the spike protein initiates an immune response that is protective. President Trump has provided $1.2 billion to AstraZeneca to support this vaccine effort, through Operation Warp Speed. This development is now in Phase 2.

Johnson & Johnson is also working on a vaccine using an adenovirus to bring the SARS-CoV-2 spike protein genes into the host cell and produce the antigen that is intended to provoke an immune response. J&J has started Phase 1-2 testing in humans, and it anticipates starting Phase 3 in September. The testing involves subjects in the U.S. and Belgium, and it is being funded by Warp Speed.

Novavax and Sanofi/GlaxoSmithKline (Sanofi/GSK) are both using insect cells to manufacture spike protein by placing spike protein genes in the insect cells. The produced spike protein is then harvested, and it is then used directly in the vaccine to produce an immune response. Sanofi/GSK is adding an adjuvant to increase the immune response. Warp Speed has awarded Novavax $1.6 billion for late-stage trials and vaccine production. Operation Warp Speed has awarded Sanofi/GSK $2.1 billion for vaccine development and manufacturing.

Merck has started efforts to produce a vaccine using a weakened measles virus to transfer virus parts into the host cells. Merck has acquired Themis for this effort. Themis is a company in Vienna that was created from staff at the Pasteur Institute, and has previously used this technology to develop a vaccine against Chikungunya, a virus carried by mosquitoes. Merck says that this type of vaccine requires only one dose, which is more manageable than the spaced 2-dose regimen required by the mRNA vaccines and most of the other COVID-19 vaccines under development. The managing of 2-dose regimens is particularly difficult in areas with low living standards and marginal public health systems. The 2-dose vaccines are effective after a total of 6 weeks, while the single-dose vaccines are effective after 2 weeks.

Inovio uses DNA that codes for the spike protein. The DNA is incorporated into plasmids, which are microscopic, membrane-bound packets of DNA. The vaccine is given in the muscle or skin, and after it is given, a brief electrical pulse is administered to the area of the vaccination with a handheld device called Cellectra. The electrical pulse induces the cells in the area to open small pores, allowing the plasmids to enter the cells. The opening of the pores is reversible. Once inside the cell, the DNA is used to produce the spike protein, which stimulates the immune system against the SARS-CoV-2 virus.

Warp Speed recently funded the efforts of Regeneron, a company that produces an antibody to SARS-CoV-2 using the spike protein gene placed in mice. The mice produce large amounts of the antibody, which is harvested, purified, and administered to ill patients as a treatment. It is also planned for administration to people who have been exposed to COVID-19 but are not yet symptomatic or are mildly symptomatic, to prevent the development of major disease. Thus, it can be used for health care workers who have been exposed to COVID-19, as a preventive measure. This preventive use is similar to a vaccine, but it is immediately effective, though the effect is short-lived, approximately 1-3 months, due to the usual rate of breakdown of antibodies. BARDA announced funding of $450 million for Regeneron on July 7, 2020.

Chinese and Russian Efforts

A vaccine study conducted by the Jiangsu Provincial Center for Disease Control and Prevention and collaborators in Wuhan, China, is investigating the use of a weakened adenovirus to deliver genetic material that codes for the spike protein into host cells.

The host cells then produce the spike protein, which stimulates a host immune response, which is anticipated to protect against an actual SARS-CoV-2 infection. The results of the Phase 2 trial using this vaccine candidate were published in the journal *The Lancet* on July 20, 2020. The Phase 2 was randomized, controlled, and double-blind. It involved 508 healthy adult subjects, with 253 getting a high dose of vaccine, 129 getting a low dose, and 128 getting a placebo. Participants receiving the high and low dose vaccine had significant responses in antibody production, and in T-cell responses. None of the subjects getting the placebo showed an immune response. The test subjects were followed for 28 days after the test doses.

It is expected that the trial will soon move to Phase 3. Funding was provided by the National Key R&D Programs of China, National Science and Technology Major Project, and CanSino Biologics.

The Chinese have two other vaccines in development, both using inactivated SARS-CoV-2 viruses, and both are in Phase 3 testing. One is sponsored by the Chinese pharmaceutical company Sinopharm. Phases 1 and 2 were double blind and placebo controlled, and

completed in Jiaozuo, Henan Province. Phase 3 will be starting in Abu Dhabi, UAE, in collaboration with the Abu Dhabi government, and the Abu Dhabi-based artificial intelligence company G42 Healthcare. G42 noted that Sinopharm chose UAE for the Phase 3 trial because the nation houses more than 200 nationalities. The Abu Dhabi government plans the trial to involve 15,000 subjects.

The second Chinese trial of an inactivated SARS-CoV-2 vaccine, called CoronaVac, is being sponsored by the Chinese company Sinovac. The study has completed Phase 2 in China, and plans Phase 3 to occur in Brazil, at the Clinical Hospital of São Paolo. The trial is being done in collaboration with the Butantan Institute, a Brazilian public health research facility. The news release announcing the Phase 3 trial notes that Brazil has the second highest number of COVID-19 cases in the world, with 2.1 million confirmed cases, and 80,000 deaths as of July 20, 2020. It is also noted that AstraZeneca is collaborating with Brazil regarding a Phase 3 trial of another vaccine.

White House/Sheilagh Craighead

President Donald Trump formally announced Operation Warp Speed on May 15, 2020 in the White House Rose Garden.

Russian scientists at Sechenov University in Moscow, the top medical university in Russia, announced on July 15, 2020 that they have completed a Phase 1 study of a COVID-19 vaccine. The vaccine is described in the press release as using two types of adenovirus. The virus carries the gene for the spike protein into the host cell, which then produces the antigen in the host cell to stimulate the immune response. Phase 2 is planned for August.

The World Health Organization states that there are currently 25 vaccine programs worldwide that are in the stage of human testing. There are 139 vaccine programs in earlier stages of development, including additional programs at Sanofi and GSK.

Operation Warp Speed

The Trump administration initiated Operation Warp Speed in April 2020 to support and coordinate the research, production and use of vaccines, treatments, and tests for COVID-19. The program was announced publicly in May 2020. Operation Warp Speed is a public-private partnership. The federal agencies involved include DHHS, NIH, CDC, FDA, BARDA, DOD, Department of Agriculture, DOE, and the Department of Veteran Affairs. BARDA coordinates these agencies with private companies.

BARDA, the Biomedical Advanced Research and Development Authority, is a federal agency under DHHS, which develops medical defenses for the civilian population against attacks on the U.S. from chemical, biological, radiological and nuclear weapons (CBRN), and against other emergencies such as epidemics and toxic chemical spills. The DOD has parallel agencies to protect the armed forces. BARDA works with the Public Health Emergency Medical Countermeasures Enterprise, which coordinates responses to CBRN threats. BARDA provides funding to the private sector to support R&D for treatments, vaccines, and tests. As of January 2020, BARDA has facilitated FDA approval successfully for over 50 related submissions. BARDA oversees Project BioShield to fund R&D for treatments and vaccines that would defend against CBRN attacks. BARDA was created in 2006 by the Pandemic and All-Hazards Preparedness Act.

The U.S. Congress has authorized $10 billion for Operation Warp Speed this year, including $6.5 billion through BARDA for COVID-19 response measures, and $3.5 billion for NIH research.

To summarize, Operation Warp Speed is currently funding nine pharmaceutical companies engaged in COVID-19 vaccine development: Moderna, AstraZeneca/Oxford, Novavax, Johnson & Johnson, Pfizer/BioNTech, Sanofi/GlaxoSmithKline, Merck, Inovio, and Vaxart. Funding thus far includes $954 million for Moderna, $1.2 billion for AstraZeneca/Oxford, $1.6 billion for Novavax, $2 billion for Pfizer/BioNTech, $2.1 billion for Sanofi/GSK, $456 million for J&J, and $38 million for Merck.

Operation Warp Speed has been pushing for rapid vaccine development. The funding levels are high, there is a variety of vaccine approaches, and there is useful redundancy in several approaches, in which two companies pursue similar lines of research.

Merck is using the oldest and most successfully tried approach. The use of adenovirus as a carrier of the spike protein is a newer approach that has shown promise in the past, and it is being used by several companies.

There are two firms using the most advanced approach of mRNA, which has shown promise in Phase 1 and Phase 2 trials so far, but this technology has not been used in the past for a finalized, successful vaccine. Keep in mind that it has only been two years since Moderna solved the problems of getting the mRNA into the cells.

National Institute of Allergy and Infectious Diseases (NIAID) Director Anthony Fauci has remarked that Trump became enthusiastic about funding Moderna after he attended a presentation of their work. A member of the board of directors of Moderna was subsequently appointed to be the chief science advisor to Operation Warp Speed.

Trump appears to have been looking at the long term as well as short term regarding Moderna, since the mRNA, as indicated above, has much broader implication for disease treatment than just vaccines. This perspective is consistent with Trump's support of the Moon-Mars space colonization program. The creation of a Hamiltonian national bank would institutionalize this orientation more broadly, to cover fusion, maglev, and collaborative beam weapon defense for Mutually Assured Survival.

Another source of federal funding involved in therapeutics for infectious disease is from DARPA, the Defense Advanced Research Projects Agency.

DARPA was created in 1958 by the Eisenhower Administration in response to Sputnik. DARPA has invested heavily in military surveillance technology for anti-submarine warfare, for example. In the 1980s, DARPA was heavily involved in Strategic Defense Initiative technologies, including space-based surveillance systems and space-based high-energy laser beam weapons. DARPA has focused on both immediate military needs, and on basic science that may be useful at some time in the future.

In 2013, DARPA provided $25 million to Moderna to develop an mRNA platform that would be able to create antibodies quickly against novel biological warfare agents. Unlike vaccines, which stimulate the body to produce its own antibodies, the use of lab-produced antibodies would confer immediate immunity, and it could also be used to treat active disease. This early funding and subsequent support helped propel Moderna into the use of mRNA for infectious disease therapeutics, and that lead translated into it being the first to enter a Phase 3 study for a SARS-CoV-2 vaccine, which occurred in late July 2020.

A True Science Driver

It is important to locate the vaccine development efforts within the activity of science drivers more generally, as spinoffs. Going back to the beginning of the U.S. manned space program that got started after Sputnik, manned space flight required light-weight, small computers, not the bulky high-energy-consuming computers in use in the 1950s.

For this purpose, semiconductor technology was developed for computers in space flight, including landing a man on the Moon. This technology subsequently became the microchips that run the personal PCs that became widespread starting in the 1980s. The continued development of micro-circuits laid the basis for the inexpensive, powerful computer power that has been required for numerous scientific and other uses, such as the above-mentioned human genome project.

A more recent example of spinoff from the space program is a significant number of experiments on disease-causing bacteria that have been done in the conditions of microgravity on the orbiting Space Station.

It has been found that Salmonella and Multi-drug Resistant *Staph aureus* (MRSA) become more virulent, more harmful, in microgravity conditions. Keep in

mind that Salmonella is the third leading cause of childhood deaths in the underdeveloped countries, and MRSA is a leading cause of treatment-resistant, hospital-acquired infections. This increase in virulence under microgravity conditions is useful for understanding the genetics of virulence. Scientists have been able to identify unusually high expression of specific mRNAs in the high virulence state of these bacteria. The scientists can then identify the corresponding DNA in the bacterial genome, and specifically disable or knock out that DNA gene or genes, producing a harmless or minimally harmful variant of the bacteria. The resulting bacteria can then be used for vaccine production in its live form, or if preferred, in the dead form.

Looking back at the long history of vaccine development, we can see an approximately exponential rate of acceleration of progress.

The initial period of smallpox vaccine using small amounts of actual smallpox material stretches from the time frame of 200 BCE in China, to Dr. Fewster's cowpox finding in 1768, approximately a 2,000-year span.

From Fewster to the vaccines of Pasteur and Koch near the end of the 1800s is approximately 120 years. From Pasteur to the widening of vaccine use in numerous diseases brings us to the 1950-1960 time period, a 50- to 60-year jump, leading to the eradication of smallpox worldwide in the 1970s.

By 2003, we have the full human genome sequenced and mapped, and the stage is set for a vast explosion of research into the long-term chronic diseases that have up to now put a finite limit on human life expectancy: cancer, heart disease, stroke, dementia, and the aging of tissues more generally.

In the past twenty years, enormous technical advances in rapidly sequencing and reproducing nucleic acids has paved the way for not only the proliferation of vaccines, but also the wider use of genetic material such as mRNA in cancer and a large spectrum of rare genetic disorders.

The exponential rate of development entered a phase-change in the past ten years, as the various uses of mRNA and DNA in treating numerous diseases have taken off. This broad expansion of lines of research, emanating from the breakthroughs in basic sciences, is an example of a Riemann singularity operating in the realm of the human expansion of knowledge and associated increase in power over the universe. The singularity is a source, analogous to the source in a fluid flow or potential flow. It is not a point source in a Riemann mapping, but a state-of-existence source, a singularity in the state of the science.

We lived through the potential of such a source with the manned Moon landing under President John Kennedy, but it was thwarted by the international oligarchy using assassination and the crushing of the NASA budget.

We again lived through the potential of such a source in the development of the SDI and President Reagan's promotion of Mutually Assured Survival, but it was again thwarted by the oligarchy. Newly-anointed General Secretary Andropov turned the Soviet Union sharply against the Strategic Defense Initiative, which it had earlier been willing to discuss, at the time presumably due to his fear that the U.S. would make better use of spinoffs and leave the USSR in the dust. But Reagan offered to help the USSR with spinoff integration in the summer of 1983 and it was still refused, making it clear that a much fouler process was affecting the USSR, a process that was bent on maintaining divide and rule, was getting in the way.

Now we have the opportunity to use the magnificent singularity of the science pouring out of the vaccine research to treat and prevent many chronic genetic diseases, including possibly the aging process itself, and the oligarchy is stumped. They cannot stop this one, except by starting World War III in desperation and annihilating the planet.

With all these scientific efforts, it is highly likely that we will have a COVID-19 vaccine within a year, and very possibly by the last months of 2020.

Let us use the die-hard optimism of the population that expects progress in medical science, to revive the optimism that we have had in the past for other major science-drivers of the economy such as space exploration, and let us use this energy of optimism—to rid ourselves of the parasitical derivatives market with Glass-Steagall, to revamp our infrastructure, and to form a Hamiltonian national bank. The Golden Renaissance followed on the heels of the devastating bubonic plague. We can create another renaissance on the heels of the COVID-19 disaster. We only need to follow what we have done in the past, such as what President Franklin Roosevelt did to get us out of the Great Depression, with his programs such as initiating Glass-Steagall banking regulation, and massive infrastructure developments such as the Tennessee Valley Authority hydroelectric project.